ISSN 2218-6190 (online)

World Journal of *Dermatology*

World J Dermatol 2016 February 2; 5(1): 1-64

Published by Baishideng Publishing Group Inc

WJD World Journal of Dermatology

A peer-reviewed, online, open-access journal of dermatology

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2012-2016

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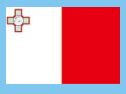

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World Journal of Dermatology

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Quarterly Volume 5 Number 1 February 2, 2016

World Journal of Dermatology
Volume 5 Number 1 February 2, 2016

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NAME OF JOURNAL
World Journal of Dermatology

ISSN
ISSN 2218-6190 (online)

LAUNCH DATE
June 2, 2012

FREQUENCY
Quarterly

Room 903, Building D, Ocean International Center,
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8226 Regency Drive,
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E-mail: bpgoffice@wjgnet.com
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PUBLICATION DATE
February 2, 2016

World Journal of Dermatology

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Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5314/wjd.v5.i1.1

World J Dermatol 2016 February 2; 5(1): 1-3
ISSN 2218-6190 (online)

EDITORIAL

Stress and quality of life in dermatological patients: Are out-patients' needs different?

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Author contributions: The author solely contributed to this paper.

Conflict-of-interest statement: There is no conflict of interest.

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Received: December 31, 2014
Peer-review started: January 1, 2015
First decision: February 7, 2015
Revised: September 30, 2015
Accepted: November 4, 2015
Article in press: November 3, 2015
Published online: February 2, 2016

Abstract

The debut, progression and maintenance of skin disease are related to stress (acne, alopecia areata, atopic dermatitis, lichen planus, psoriasis, urticaria, vitiligo, herpes, hyperhidrosis, pemphigus, rosacea or seborrheic dermatitis). Environmental, socio-professional, life events are representing external factors. Personality, previous experiences, traits of anxiety are individual factors influencing the state of stress. Perceived stress could be more harmful especially in "high reactors" to stress. Coping abilities to stress could be increased in social programs. There was a recent interest in measuring the quality of life in the last years. There are dermatology and disease specific questionnaires that could help. Out-patients have less time to wait for very sophisticated procedures. They expect faster results. For simple, acute diseases it is important to have a good communication and good understanding of the instructions to get results as soon as possible. For chronic diseases a strong long-term alliance is needed, so the patients should revisit for his benefit and not for giving up. Small questions regarding potential stressful events, impact on the quality of life, stigmatization, the level of symptoms (pruritus), psychiatric comorbidities (anxiety, depression), short questionnaires for quality of life give us a better picture, personalize the doctor-patient relationship and could influence the choice of treatment. Many skin disorders could be seen from a psychosomatic point of view and the final goal, especially for the chronic diseases, is to improve through our treatments the impact on the quality of patient's life.

Key words: Stress; Perceived stress; Quality of life; Out-patients; Dermatology life quality index; Children dermatology life index

Core tip: The debut, progression and maintenance of skin disease are related to stress. Besides external factors, individual factors could influence the state of stress. Perceived stress, high reactors to stress, coping abilities, quality of life questionnaires are some directions to discuss. Out-patients have different needs and expectations than in-patients. Good communication, empathy, personalized questions, short questionnaires could make a strong, long-term doctor-patient relationship with better results and satisfaction for both sides.

Manolache L. Stress and quality of life in dermatological patients: Are out-patients' needs different? *World J Dermatol* 2016; 5(1): 1-3 Available from: URL: http://www.wjgnet.com/2218-6190/full/v5/i1/1.htm DOI: http://dx.doi.org/10.5314/wjd.v5.i1.1

The interest for stress involvement in dermatological conditions and also for the impact of cutaneous diseases on the quality of patient's life increased in the last years. I have made an extended review[1] reporting that stressful events could induce, aggravate or maintain different skin diseases such as: Acne, alopecia areata, atopic dermatitis, lichen planus, psoriasis, urticaria, vitiligo. There were described such connections even with herpes, hyperhidrosis, pemphigus, rosacea or seborrheic dermatitis.

Other aspect is represented by the secondary stress induced by the skin disease itself, influencing the quality of life.

The impact of a stressful situation on patient's life (perceived stress) could induce more harm than the situation itself. There are patients "high reactors" to stress. For them it is a risk of developing psychosomatic diseases after some minor life situations perceived as stressful.

The state of stress could be influenced by external and individual factors. Environmental, socio-professional factors or different life situations are some of external factors. Major life events that appear in the list of Holmes and Rahe provoke important reactions to people. Serious illness of the patient or of beloved ones, death of family members or friends, separations or divorces are expected to induce anxious-depressive states with different psychosomatic appearances. Personal needs or previous experiences, personality and attitude facing different situations, family models represent individual factors that can also change the state of stress. For example reactions to exams, to quarrels, to changes of jobs, environment could be very different from a person to another. The psychological vulnerability of the person (ex high trait of anxiety) could change the appearance, the development and the progress of the psychosomatic disease.

There is a study[2] on out-patients with dermatoses that describes women having higher perceived stress. The perceived stress was higher in patients with psoriasis and acne than in tumors and was correlated to mental quality of life.

The reaction of the individual is an attempt to restore the balance and depends on the coping abilities. Social programs including stress management and psychological support are important in the achievement of coping abilities[3].

Persons with high stress resistance are characterized by a control on the events and life situations, acceptance of the responsibility of the facts that are happening. They are involved in everything they are doing and they accept the changes as natural.

More than 3000 of papers are studying the impact of skin diseases on the patient's quality of life and more than half have been published during the last 5 years, showing an increasing interest on this subject. For the measurement[4] there are generic instruments and also specific instruments (dermatology and disease specific). There are scales for adults, children, teen-agers, families, infants, *etc.*, in the need for more specific data.

After 15 years of working only with out-patients (more than 100000 consultations) in Romania, I think there are different needs for them. I know that there are different aspects regarding cultural habits, but people have general needs of care. I work with National Insurance System and patients have facile access to ambulatory after a reference from the general practitioner. In our country from Eastern Europe, people want and need to talk and to be listened. There is no intrusion in their intimacy if you ask personal aspects or if you try to personalize the doctor-patient relationship. Usually, there is a close relationship, because the patients are coming back for controls or for other acute episodes. Through years, if there is a good and trustful relationship, the doctors get to know the entire family.

Out-patients have less time to wait for results and other expectations than in-patients. Usually, in the ambulatory they are coming for common skin conditions and the alliance is very important. For simple diseases it is important to get results as soon as possible (ex: Impetigo, different kinds of superficial mycoses, contact eczemas, scabies aso), so, good communication and good understanding of the instructions will have the best benefit. They need detailed information and they should ask questions. For chronic diseases such as acne, psoriasis, atopic dermatitis, onychomycosis, chronic urticaria, warts, *etc.*, the alliance will represent the key point for the patient to return and not to give up with the long-term therapy.

In an era of fast movements and expectations, I consider that it will be very helpful for both doctor and patient to keep in mind small questions regarding potential stressful events, impact on the quality of life, stigmatization, the level of symptoms (pruritus), psychiatric comorbidities (anxiety, depression). Even they seem to be time-consuming this kind of questions will increase the trust and the satisfaction of the patient and will give us additional information and a more complete picture that could influence the choice of the treatment. Deeper, personalized questions will show to the patient the care and the empathy. For example, I use dermatology life quality index[5] and children's dermatology life quality index[6] for almost every patient with acne. There are 10 questions and it takes a few minutes to be filled in. The results of the questionnaires could give me information about the necessity of more aggressive lines of therapy in case of high impact on the quality of life and complex approach (for example, together with endocrinologist, psychologist or psychiatrist). On the other hand, if the impact on the quality of life is very low, even the lesions are important,

that could be a predictor that the patient is not ready for a long-time commitment in therapy.

Questionnaires are usually used in clinic for different types of studies. They are very complex and it takes a long time to be completed. In hospitals, where there are teams that work together they could be done by residents and there are not time-restricted.

But, a consultation for out-patient is short and short questionnaires are more convenient. They have to be very simple (a few questions), easy to be filled in by patients. Some of actual questionnaires have been already translated and used also for outpatients, but maybe it could be interesting to design some new ones especially for a facile use in ambulatories.

Many skin disorders could be seen from a psychosomatic point of view and the final goal, especially for the chronic diseases, is to improve through our treatments the impact on the quality of patient's life.

Questionnaires are not only for the clinics, doctors in ambulatories should be open to use them in daily practice as good instruments for measuring the severity and impact or the needs of patients. The short questions could point sensitive areas that could need deeper approach. Translations, validations and a wide use of questionnaires could give us new perspectives.

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DOI: 10.5314/wjd.v5.i1.4

World J Dermatol 2016 February 2; 5(1): 4-16
ISSN 2218-6190 (online)

REVIEW

Propranolol for infantile hemangioma: Current state of affairs

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Author contributions: Moyakine AV and van der Vleuten CJM contributed equally to this work; Moyakine AV wrote the majority of the original draft of the paper and approved the final version of this paper; van der Vleuten CJM devised the design of the study and participated in writing the paper; van der Vleuten CJM approved the final version of this paper and guarantees that all individuals who meet the journal's authorship criteria are included as authors of this paper.

Conflict-of-interest statement: Both authors have no conflicts of interest relevant to this article to disclose.

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Received: August 27, 2015
Peer-review started: August 31, 2015
First decision: September 28, 2015
Revised: October 19, 2015
Accepted: December 13, 2015
Article in press: December 14, 2015
Published online: February 2, 2016

Abstract

Infantile hemangioma (IH) is the most common benign tumor seen in infancy. This review provides up-to-date information on the pathophysiology, variations in clinical presentation, and natural history of IH, elaborating on associated anomalies, such as PHACE(S) syndrome and LUMBAR syndrome. Because of the benign and self-limiting characteristics seen in more than 90% of cases of IH, a conservative approach is usually chosen. However, some circumstances, such as ulceration, vision loss, breathing difficulties, or potential disfigurement, will require treatment during the proliferative phase. For decades, treatment of IH has primarily consisted of corticosteroids or surgery. Since 2008, propranolol has become the treatment of first choice. In this article, we bring to light the crucial changes in the treatment of IH over the past years. To date, there is still a lack of data on the possible long-term effects of propranolol treatment in young infants. A theoretical probability of the central nervous system being affected (that is, impairment of short- and long-term memory, psychomotor function, sleep quality, and mood) has recently been suggested. This review highlights research topics concerning these long-term adverse effects. Finally, information is provided on the potential instruments to measure IH severity and activity in clinical trials and/or in clinical practice and the recently developed and first-validated IH-specific quality-of-life questionnaire.

Key words: Infantile hemangioma; Propranolol; Beta-blocker; Adverse effect; Development

Core tip: The discovery that propranolol is efficacious in the treatment of infantile hemangioma (IH) has led to an upsurge in publications, increasing our knowledge of this subject. In this review, we provide the most up-to-date information on the pathophysiology, variations in clinical presentation, and natural history of IH. We look at possible working mechanisms of several treatments and the current concerns regarding the treatment of

first choice, propranolol. Finally, we provide an overview of instruments, measuring IH severity and/or activity and IH-related quality of life.

Moyakine AV, van der Vleuten CJM. Propranolol for infantile hemangioma: Current state of affairs. *World J Dermatol* 2016; 5(1): 4-16 Available from: URL: http://www.wjgnet.com/2218-6190/full/v5/i1/4.htm DOI: http://dx.doi.org/10.5314/wjd.v5.i1.4

INTRODUCTION

Infantile hemangioma (IH) is a benign vascular tumor caused by endothelial cell proliferation. With a prevalence of about 4%-10% in the first year of life, it is the most common benign tumor of infancy[1-4]. IHs may be located in any region of the body, including the internal organs, but are mostly (60%) located in the skin of the head and neck region[5,6]. The liver is the most common extracutaneous site of IHs. Hepatic IHs, which can be focal, multifocal, or diffuse, are the most common benign liver tumors of infancy[7]. IHs are seen 3-5 times more often in females than in males. Other risk factors for developing an IH [including their crude odds ratios (OR)] are: Caucasian race, low birth weight (OR = 1.8), prematurity (OR = 1.8), family history of IH (OR = 2.5), and being born from a multiple birth (OR = 2.2)[8-10]. Because of their benign and self-limiting character, no intervention is needed in more than 90% of cases. However, there are circumstances that will require treatment during the proliferative phase. These concern infants with IHs with a substantial morbidity, such as ulceration, vision loss, breathing difficulties, or potential disfigurement because of the tumor location. Until 2008, the treatment of IHs consisted of systemic or intralesional corticosteroids or surgery[11,12]. In 2008, treatment of IH with propranolol was reported for the first time[13]. After that, multiple publications followed, and the approach to IHs dramatically changed. This shift in the management of cutaneous IHs has also influenced the treatment of hepatic IHs[7,14,15]. Propranolol is currently considered to be the treatment of first choice for IHs.

Propranolol has been used for several decades to treat cardiovascular diseases, such as hypertension, ischemic heart disease, and arrhythmias in adults and children. Although there is an abundance of experience with propranolol in infants, responses to propranolol have been far better studied in adults than in children[16]. Propranolol has its side effects, although these are mild compared with previous IH treatments. The short-term side effects consist of hypotension, bradycardia, respiratory symptoms, hypoglycemia, gastrointestinal complaints, and cold extremities. The lipophilic nature of propranolol facilitates the crossing of the blood-brain barrier, causing adverse effects such as a sleepy and drowsy feeling during the day and restlessness at night[17]. Based on studies in adult volunteers and animals, it has been postulated that there may be long-term side effects of this drug, affecting the developing central nervous system, when given to infants[18].

Our review summarizes the discoveries that have been made since 2008 regarding the treatment of IHs with propranolol. It also highlights the most important areas that still remain unknown.

PATHOPHYSIOLOGY

Despite its high incidence, the pathophysiology of IH is still unclear. There is no universally accepted theory, and no single hypothesis is sufficient to describe and explain all of its features. The three most common hypotheses that partially explain development of IH are listed below.

Placental embolization theory

IH endothelial cells share immunohistochemical markers with the placental microvasculature. Both possess glucose transporter protein type 1 (GLUT-1), Lewis Y antigen, merosin, laminin, chemokine receptor 6, CD15, insulin-like growth factor 2 (IGF-2), and indoleamine 2,3-dioxygenase. This immunohistochemical profile differentiates IHs from other vascular birthmarks or tumors[19-22]. In addition, there is a high level of genetic similarity between the placenta and IH[23]. Therefore, it was hypothesized that embolization of placental endothelial cells to the fetus could play a role in the pathogenesis of IH. This hypothesis was strengthened by findings that transcervical chorionic villus sampling is associated with a threefold increased incidence of IH and that placental abnormalities, such as abnormal placentation, are associated with a higher incidence of IH[24-27]. However, the latter may also be explained by the hypoxia hypothesis. In contrast to the placental embolization theory are the failed attempts to detect the presence of maternal–fetal chimerism in IH tissue[28].

Angio- and vasculogenesis theory

Both angiogenesis (growth of new blood vessels from pre-existing vessels) and vasculogenesis (*de novo* formation of blood vessels from stem cells) are hypothesized to contribute to IH formation. IHs may result from somatic mutations in a gene mediating endothelial cell proliferation (growth regulatory pathways)[29]. Such mutations may alternate the vascular endothelial growth factor (VEGF) signaling pathway by reducing the expression of VEGF receptor 1 (VEGFR-1), which causes hyperactivity of VEGFR-2 and may induce IH formation through angiogenesis[30]. IGF-2 and basic fibroblast growth factor also stimulate angiogenesis and are upregulated in proliferating IHs[31,32]. Endothelial progenitor cells (EPCs), stem cells of vascular origin that are capable of differentiating into endothelial cells, seem to play a role in the development of IH through vasculogenesis[33]. EPCs possess the surface markers ($CD34^+$ and $CD133^+$) that are also found in endothelial cells of growing IHs, suggesting that these bone-

marrow-derived progenitor cells may play a key role in the pathogenesis of IHs by inducing postnatal formation of vascular tissue[34,35]. In 2008, Khan *et al*[36] injected immune-deficient mice with $CD133^+$ EPCs, which resulted in the development of GLUT-1-positive vascular tumors in these mice. These findings greatly supported the angiogenesis theory.

Tissue hypoxia theory

Hypoxia, either local or systemic, seems to be the most influential inducer of IH development. Hypoxia stimulates the proliferation of EPCs[24,37-41]. Transcription factor hypoxia-inducible factor 1α (HIF-1α) plays a key role in the tissue hypoxia theory. A hypoxic environment triggers the production of HIF-1α. HIF-1α in turn stimulates transcription of target genes, such as GLUT-1, VEGF and IGF-2[42-45]. These stimulations may take place either directly by HIF-1a signaling or by hypoxia-induced regulation of mammalian target of rapamycin (mTOR) complex 1 signaling. Deregulation of the mTOR pathway may lead to disorganized growth[46,47]. Overexpression of VEGF may also take place via the activation of the HIF-2α pathway as a response to the pathologic signal of a "dangerous hypoxic situation"[48]. It has also been demonstrated that the combination of hypoxia and an estrogenic environment has a synergic effect on IH endothelial cell proliferation, which may explain the greater incidence of IHs in girls[48].

As stated above, none of these three theories explains the pathogenesis of IH completely. Given the great variability of clinical presentations of IH, the uneven distribution of IHs over the body, the increased prevalence of IHs in Caucasians, and its familial occurrence, it is most likely that IH pathogenesis is not restricted to one factor, but to a combination of genetic predisposition and various environmental factors[48,49].

CLINICAL PRESENTATION

IHs develop in the first days, weeks, or months of life. They are not to be confused with congenital hemangiomas, which are fully developed at birth and either rapidly involute during the first year of life (rapidly involuting congenital hemangiomas) or do not involute at all (non-involuting congenital hemangiomas)[50,51]. Many children who develop an IH are born with a visible precursor lesion, such as a pale macule with telangiectasia or mottled vascular stain, at the future IH location[52]. Fully developed, an IH feels elastic and frequently warm. The tumor is not pulsating and is painless, except in the case of ulceration[48]. There is a great variation in size, but in most cases (80%), IHs are not greater than 3 cm in diameter[8]. Recognized risk factors for developing an IH include female sex, prematurity, multiple gestation, and low birth weight. Caucasians are at greater risk of developing an IH compared with individuals of Hispanic or African origin[5,6,53].

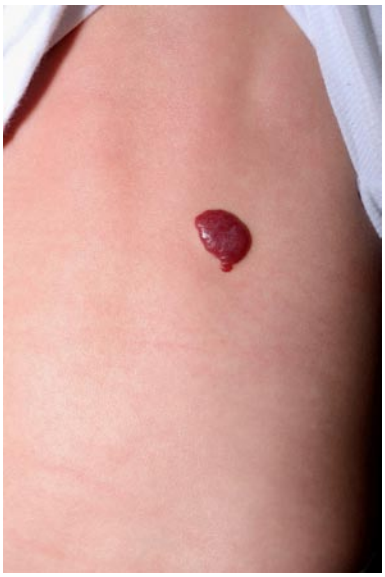

Figure 1 Superficial focal infantile hemangioma.

In the classification of the International Society for the Study of Vascular Anomalies (ISSVA), four different patterns of IH are described[54]. According to their pattern, IHs can be grouped into focal, multifocal, segmental (plaque-like, covering an embryologic segment), and intermediate/indeterminate[48,50]. Intermediate/indeterminate IHs show characteristics of both focal and segmental IHs. They do not entirely encompass an accepted embryologic segment nor do they arise from a single focus[48,51]. Segmental IHs have a higher complication rate and are associated abnormalities[55]. Apart from the pattern, the ISSVA classification makes a distinction between four different types of IHs, according to their clinical appearance: (1) superficial (50%-60%); (2) deep (15%); (3) mixed (25%-35%), which are distinguished by the layer(s) of the skin affected[55]; and (4) reticular/abortive/minimal growth, which is distinguished by its typical growth pattern[56,57].

Superficial IH

Superficial IHs are the most common type of IHs. They involve the papillary dermis and appear as bright red "strawberry" lesions in the case of a localized superficial IH (Figure 1) or as a plaque-like red lesion in the case of a segmental superficial IH (Figure 2). Segmental IHs are more often associated with complications, such as ulceration and associated anomalies, and more often require therapy[8,48].

Deep IH

Deep IHs involve the deep, reticular dermis and subcutis, resulting in a tumor with a bluish shine or (when deeper) normal skin color (Figure 3). Because of these characteristics, deep IHs may easily be misdiagnosed at first[55]. Deep IHs appear later than superficial IHs; typically around the age of 2 mo, and may have a

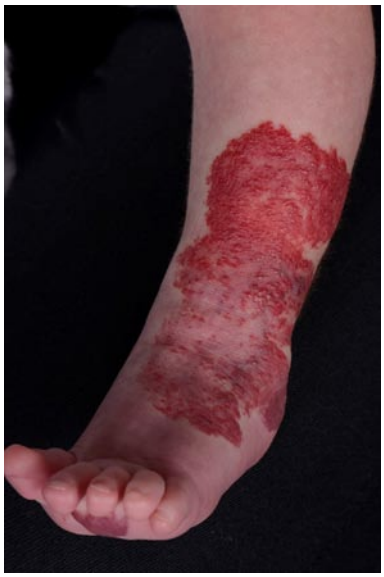

Figure 2 Superficial segmental infantile hemangioma.

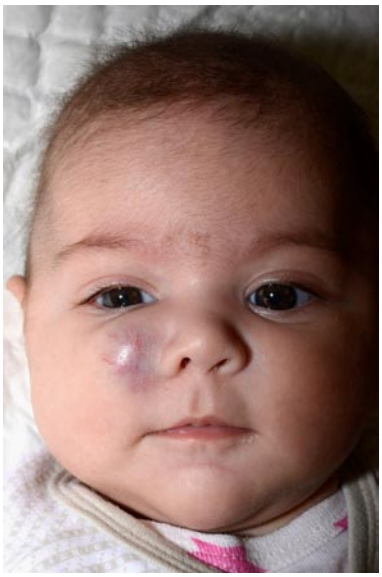

Figure 3 Deep infantile hemangioma.

longer proliferative phase compared with the superficial types[17,51,52].

Mixed IH

Mixed IHs have both superficial and deep components (Figure 4). The proliferative phase of the deep component in mixed IHs also stops later than in superficial IHs[17,48].

Reticular/abortive/minimal growth IH

A minority of IHs have arrested or minimal growth beyond the stage resembling the precursor lesions. Although their natural course is different from that of the other three types, these lesions do express GLUT-1 proteins and have similar other immunohistochemical characteristics (Figure 5)[56,57]. Several terms have been used to describe these in the literature. The most commonly used terms are reticular, abortive, or minimal growth IH. IHs of this type seem to have a predilection for the lower body[57]. The exact incidence of this type of IH is unknown, but it is believed to be relatively rare. However, a recent study by Munden *et al*[27] in which 578 pregnant women were prospectively enrolled and their infants followed up for 9 mo after birth, reports that of the infants with an IH, 20% had a reticular, abortive, or minimal growth IH.

Despite several hypotheses, the pathogenesis of segmental *vs* focal and superficial *vs* deep IHs remains unclear[19].

NATURAL HISTORY

IHs have a unique pattern of evolution. As stated above, IHs are not fully developed at birth, but start to grow shortly after birth (usually within a few days or weeks) from normal appearing skin or a precursor lesion[51]. This typical delay serves as a diagnostic tool, especially in deep IHs where the skin color may be bluish or even normal[48]. After a relatively short proliferative phase in the first 3-9 mo of life, the slow involution phase takes place between the median age of 2-4 years[8,48,58,59]. However, the proliferative phase may extend until 12 mo after birth, and in some cases, up to 24 mo after birth[48,60]. Approximately 25%-69% patients with IH may develop a residual lesion after complete involution of the IH. Residual lesions may consist of skin atrophy, skin surplus, telangiectasias, pigmentation, scarification after ulceration and/or fibrofatty tissue[3,58,61]. Epidermal invasion of an IH in combination with a deep component in the IH is most prone to residual lesions[58]. The difference in reported incidence of residual lesions in several studies may be explained by usage of different populations (*e.g.,* secondary/tertiary referral *vs* primary referral).

IH AND RISK OF ASSOCIATED ANOMALIES

There are two types of IHs that may be predictive of an underlying anomaly. These are (1) large, flat, segmental IHs of the face, which are associated with PHACE(S) syndrome and (2) IHs in the lumbosacral or perineal region, which may be predictive of LUMBAR syndrome [also known as Perineal hemangioma, External genitalia malformations, Lipomyelomeningocele, Vesicorenal abnormalities, Imperforate anus, and Skin tag (PELVIS) or Spinal dysraphism, Anogenital, Cutaneous, Renal and urologic anomalies, associated with an Angioma of Lumbosacral localization (SACRAL) syndrome].

PHACE(S) syndrome

The term PHACE was introduced in 1996 by Frieden *et al*[62], describing a combination of five anomalies: (1) posterior fossa abnormalities; (2) hemangioma of

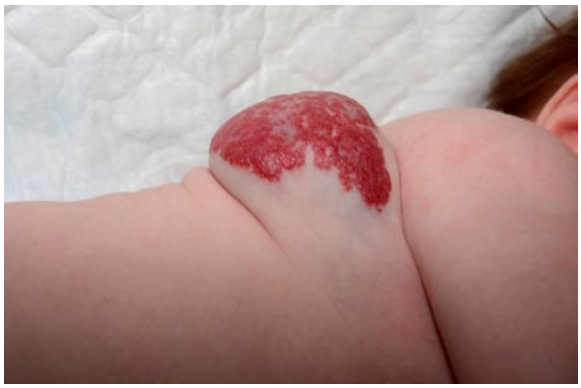

Figure 4 Mixed type infantile hemangioma.

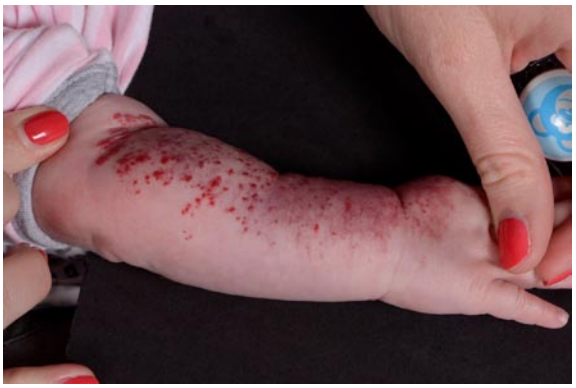

Figure 5 Minimal growth type infantile hemangioma.

the face (segmental); (3) arterial abnormalities (intra- and extracranial); (4) cardiac and aortic defects; and (5) eye anomalies. A sixth anomaly: Sternal cleft or supraumbilical raphe was added later[48]. PHACES syndrome is a spectrum of anomalies, because most affected children (70%) have only one extracutaneous manifestation[63]. The so-called "Dandy-Walker syndrome" is the most common brain involvement, followed by cerebellar hypoplasia or dysgenesia as a result of posterior fossa abnormalities[48,63]. Until 2009, a diagnosis of PHACES syndrome required the presence of a segmental, flat IH of the face in addition to one or more of the five anomalies described above[62,64]. In 2009, a consensus was reached defining PHACES as the presence of a characteristic segmental hemangioma or hemangioma greater than 5 cm in diameter of the face or scalp plus one major criterion or two minor criteria[65]. The exact incidence of PHACES is unknown. It has been postulated that in 20%-31% of children with segmental facial IHs, there is an association with PHACES[64,66]. A full workup for PHACES syndrome is suggested in every infant with a large (> 5 cm), segmental, facial hemangioma. This includes a complete physical examination as well as careful cardiac (including echocardiogram), ophthalmologic and neurologic (including MRI of the head and MRA of the entire head and neck area) assessments[67].

LUMBAR syndrome

IHs in the lumbosacral area or perineum are also associated with underlying structural anomalies. These IHs are also most commonly, but not exclusively, segmental[68]. A tethered cord in the context of spina bifida occulta should be considered, although more extensive associated morbidity may be the case. For these conditions, different acronyms have been suggested, such as SACRAL[69] and PELVIS[70]. The most recently proposed acronym, LUMBAR is preferred; it refers to the association of lower body hemangioma and other cutaneous defects, urogenital anomalies, ulceration, myelopathy, bony deformities, anorectal malformations, arterial anomalies, and renal anomalies[68]. There is no diagnostic consensus for LUMBAR, SACRAL, or PELVIS, such as for PHACES. Screening with ultrasound scanning of the spine, abdomen, and pelvis is suggested for all patients with a segmental IH greater than 2.5 cm in diameter of any lumbosacral or perineal region who are younger than 3 mo. For children older than 3 mo, MRI is indicated[68,71].

MANAGEMENT (PAST, PRESENT AND FUTURE)

The management of IHs has been changed drastically since the discovery of the efficacy of propranolol treatment for this indication in 2008[13]. Although there are no uniform international guidelines available for the treatment of IHs, propranolol is now considered to be the treatment of first choice. Before that, a whole range of treatments had been applied. Some of these treatments are rarely or no longer used (*e.g.*, X-irradiation therapy) because of their side effects and/or low efficacy.

Past

X-irradiation: Although there was already evidence that IHs involute spontaneously, X-irradiation has been widely used for two decades between 1930 and 1950, resulting in (unnecessary) radiation exposure and post-radiation skin atrophy, pigmentation, telangiectasia, contractures, and risk of skin cancer[72-74].

Vincristine: Vincristine is a vinca alkaloid that is widely used in cancer chemotherapy. Treatment of IHs with vincristine was first described in 1993[75]. This chemotherapeutic drug inhibits microtubule formation, causing arrest of mitosis and subsequent apoptosis[76]. Additionally, vincristine seems to affect angiogenesis[77]. Nowadays, it may only be indicated for severe IHs that are resistant to other therapies. The use of vincristine requires a central venous catheter for chronic administration. Furthermore, it has potential severe side effects, such as peripheral mixed sensorimotor neurotoxicity[78]. Other, less severe, side effects include rash, alopecia, and local reactions, such as phlebitis and necrosis[74].

Interferon: The use of subcutaneous interferon a-2a and -2b for the treatment of IHs was first described in 1989[79]. Its therapeutic effectiveness has been attributed to its anti-angiogenic properties. Interferon a induces apoptosis of endothelial cells, which might also explain the clinically and histologically observed involution without any sign of inflammation or necrosis[80]. Despite its high success rates, the use of interferon in the treatment of complicated IHs has been abandoned, because of its major side effects, such as spastic diplegia and blood abnormalities[81,82].

Topical corticosteroids: Potent topical steroids have been described for small, superficial, localized IHs[83]. Side effects include acne, perioral dermatitis, hypertrichosis, cutaneous atrophy, striae, hypopigmentation, and subcutaneous fat atrophy. Since the availability of topical b-blockers, with fewer side effects, topical steroids are less often prescribed in current practice[76].

Topical imiquimod: Imiquimod is an immune modulator. In 2002, the potential of imiquimod to shorten the involution phase of IH was first reported[84]. Due to its anti-angiogenic and apoptotic effects, imiquimod contributes to the regression of IH[85,86]. Its efficacy is equivalent to the efficacy of the topical b-blocker timolol (0.5% ophthalmic solution), which was first described a few years after the discovery of propranolol treatment for IHs[87,88]. However, timolol is more effective than imiquimod in terms of color involution and onset time[89]. Furthermore, imiquimod has a less favorable adverse-reaction profile and has never really become a very common treatment for IHs that are suitable for topical therapy[88].

Present

Watchful waiting: Knowing IH's natural history, it is justified to be restrictive in actively treating this self-limiting condition. Starting in the 1950s, physicians began to prefer this approach over the invasive X-irradiation and/or surgical removal[73]. At the present time, watchful waiting is still considered to be the best approach for the vast majority of patients with IH.

Systemic propranolol (first choice): In 2008, after the report of the very successful therapeutic effect of propranolol, IH treatment changed drastically[13]. Currently, propranolol has become the treatment of first choice for IHs. It seems that propranolol stops growth and induces an IH regression that is much better and safer than previous therapies[90]. Recently, Léauté-Labrèze *et al*[91], published a large-scale randomized placebo-controlled trial showing that propranolol is effective at a dose of 3 mg/kg per day for 6 mo in the treatment of IHs. This treatment resulted in a significantly higher success rate compared with placebo (60% *vs* 4%). These outcomes are in line with the results of the RCT conducted by Hogeling *et al*[92] in 2011. Earlier, Malik *et al*[93] had shown in their RCT that propranolol had a consistent, rapid therapeutic effect with a lower number of complications compared with prednisolone. They also demonstrated that a combination of both propranolol and prednisolone was not superior to propranolol alone[93]. An RCT carried out by Zaher *et al*[94] proved the superiority of oral admission of propranolol compared with topical and intralesional application. While the general mechanism of action of propranolol is well established as an antagonist of both b_1- and b_2-adrenergic receptors, the precise mechanism of action on IHs remains uncertain[19]. It is known that propranolol is effective in IH through vasoconstriction, inhibition of angiogenesis, induction of apoptosis, or dysregulation of the renin–angiotensin system (RAS)[95,96].

The most common serious adverse effects of propranolol are bradycardia, hypoglycemia, and hypotension. Other reported adverse side effects in adults and children include bronchospasms, congestive heart failure, hypothermia, somnolence, sleep disturbance, nightmares, depression, nausea, vomiting, diarrhea, hyperkalemia, gastro-esophageal reflux, psoriatic drug rash, and respiratory symptoms[92]. Because of the lipophilic nature of propranolol and the potential to penetrate the blood-brain barrier, the probability of affecting the developing central nervous system of infants with IH was postulated in a report in 2013[97]. This information was further elaborated by Langley *et al*[18] in 2015. In 2014, Gonski *et al*[98] showed no gross motor development problems in propranolol-treated children with IH. Recently, our group confirmed these findings. We not only looked for problems with gross motor development, but also included the fine motor/adaptation/personal social functioning and communication in our study[99-101], using the "van Wiechen scheme", a Dutch screening instrument based on the developmental model of an American developmental psychologist and pediatrician (A. Gesell). No signs of psychomotor developmental problems were found[101]. Despite these promising findings, it is still unclear what effects, either subtle or not, propranolol has on the developing brain. Future prospective studies on later age, using universal screening tools or more advanced neuropsychologic tests are needed to support these findings. Until then, propranolol should only be prescribed for children with IHs with current or impending complications.

Topical b-blockers (first choice): As an alternative to oral b-blockers, topical b-blockers have been used for superficial IHs. There are different forms of topical b-blockers, but timolol (0.5% ophthalmic solution or 0.1% gel), a non-selective b-blocker, is most widely used[76]. In 2013, a double-blind placebo-controlled RCT was published, comparing topical timolol 0.5% solution with placebo for superficial IHs. Timolol was shown to be safe and effective[102]. Recently, timolol 0.5% ophthalmic solution was compared with laser treatment, where timolol proved to be a safe, effective,

and painless alternative to lasers for the treatment of superficial IHs. In mixed IHs, laser treatment provided better results than timolol, because of its deeper penetration[103]. Comparison between timolol 0.5% ophthalmic solution and 5% imiquimod cream in 54 patients with IH (half of the IH was treated with timolol and other half with imiquimod) showed similar efficacy, but fewer side effects were seen in the timolol group[89].

Systemic corticosteroids (second choice): In the 1960s, systemic corticosteroids were found to be an effective treatment for IHs[104,105]. The mechanism of action is still not completely understood, but the main theory is that corticosteroids suppress the VEGF-A expression and therefore inhibit angiogenesis and/or vasculogenesis[106]. The usually recommended dose is 2-3 mg/kg per day, which is most effective in the early proliferating phase[107,108]. With a treatment response of 84%-90% and an overall rebound rate of 36%, this therapy became the first-choice therapy for severe IHs, requiring intervention[73,107,109]. The most common side effects of systemic corticosteroids are cushingoid facies (71%), personality changes (29%), gastric irritation (21%), fungal infection (6%), and diminished weight gain (42%) and height (35%)[110]. Other possible side effects were systemic infection, hypertension, increased appetite, aseptic necrosis of bones and cardiomyopathy[20]. Currently, systemic corticosteroids have become a little-used second-line option, because of the lower efficacy and less favorable side-effect profile compared with propranolol[76].

Intralesional corticosteroids (in specified indications): Intralesional corticosteroids (mostly triamcinolone 10 mg/mL) offer an alternative to systemic therapy for small IHs[76]. This therapy was initially used by ophthalmologists for periorbital IHs. Because of the risk of retinal artery damage and blindness, intralesional corticosteroids are no longer used for periorbital IHs[111-113]. The common side effects may include subcutaneous atrophy and hypopigmentation[76].

Surgery (in specified indications): Surgical treatment of IH is suitable in some specific cases. It is indicated in well-circumscribed, pedunculated, or ulcerated lesions that have failed to respond to medical treatment, grow rapidly, or cause significant deformity[114]. Although propranolol treatment has been a breakthrough in the management of IHs, many children still require plastic surgery after the involution phase. At the present time, most surgical interventions in IHs are used to treat those involuted IHs that have left residual lesions, such as skin surplus, scarification after ulceration and/or fibrofatty tissue[115,116].

Laser therapy (in specified indications): Pulsed dye laser (PDL) is the most commonly used laser treatment for superficial and ulcerating IHs and for residual lesions. The literature on the effectiveness of PDL in IHs is somewhat controversial. Some earlier studies suggest that early treatment of IHs with PDL prevents further growth, induces tumor regression, and improves cosmetic outcome, while an randomized controlled trial of 121 infants showed no significant difference in complete clearance or minimum residual signs between the PDL-treated group and the observational group[117-120]. Conventional PDL is ineffective in the treatment of deep IHs. Its penetration depth is limited due to the optical absorption and scattering in the epidermis and dermis[121]. Introduction of a long-pulse PDL in combination with an epidermal cooling system made a greater depth of vascular injury possible[120,122]. Additionally, the use of long-pulse PDL with an epidermal cooling system decreases the risk of scarring and induction of ulceration[122]. These types of laser treatment are not painless and may require anesthesia in infants.

The larger, deep IHs may also be effectively treated using the neodymium-doped yttrium aluminum garnet (ND:YAG) laser. However, due to greater risk of scarring or hypo- or hyperpigmentation, this therapy should be preserved for difficult, recalcitrant cases[121,123,124].

Therapy with the fractionated CO_2 laser is reserved for involuted IHs with residual fibrofatty tissue, atrophic plaques, or other textural changes[125].

Future

Other systemic β-blockers: Propranolol is a non-selective, lipophilic, b-adrenergic receptor antagonist, which binds to b_1- and b_2-adrenergic receptors[126]. The potential side effects of propranolol made physicians and researchers search for an alternative b-blocker that is as effective as propranolol, but with fewer side effects. It was suggested that a hydrophilic, selective b_1-blocker, atenolol, which occurs at lower concentrations in the brain, may have these characteristics[127,128]. A small randomized controlled trial showed no significant difference in effectiveness between atenolol and propranolol. However, no difference in adverse effects was demonstrated either[129]. In 2009, oral nadolol, a non-selective b-blocker, which is significantly less lipophilic than propranolol, was found to have a significant effect on IH growth, with a rapid reduction in size[130,131]. Recently, a small retrospective study of 48 participants showed effects of nadolol similar to those of propranolol. Although serious adverse effects were rare, side effects such as sleep disturbance, behavior problems, gastrointestinal symptoms, and cold extremities were still frequently seen[132]. In 2010, a case report suggested the use of acebutolol for the treatment of infantile subglottic hemangioma, because of fewer side effects on resting heart rate than propranolol, metoprolol, and atenolol[133].

In general, b-blocker lipophility and/or selectivity are factors that determine the efficacy and side-effect profile. It is unclear whether a degree of lipophilicity

may be required for tissue penetration and efficacy of IH treatment. It is also unclear whether b_{1}- or b_{2}-blockade or a combination of the two is needed to achieve a therapeutic effect. In conclusion, the search for a b-blocker with the best effectiveness and the most favorable side-effects profile, is still ongoing.

Rapamycin: Rapamycin, also known as sirolimus, is a bacterial macrolide that also has antifungal effects. Since rapamycin is an mTOR inhibitor, it inhibits mTOR signaling, an important regulator of growth and proliferation. By inhibiting the mTOR signaling pathway, rapamycin decreases the elevated VEGF and HIF-1 levels produced by endothelial cells, and reduces IH proliferation[134-136]. Rapamycin not only negatively affects cell proliferation, but also metabolism, as well as angiogenesis. Additionally, rapamycin seems to limit stem cell replicative capabilities, affecting vasculogenesis[137]. At this time, rapamycin treatment use is restricted to clinical trials until better safety data are available[20,76].

Angiotensin-converting enzyme inhibitors: With the expanding knowledge on IH pathogenesis as a result of the discovery of the efficacy of b-blockers for this indication, the regulation of hemogenic endothelium regulated by the RAS in IHs became a point of interest with possible therapeutic consequences[138]. A year later, expression of components of the RAS by the endothelium of proliferating IHs was shown[139]. The role of the RAS in IH is supported by the clinical observation of a higher incidence of IHs in premature infants, females, and Caucasians, since these groups have a higher renin level or activity than full-term infants, males, and black infants, respectively[139-142]. In connection with these findings, a clinical trial of eight patients with IH conducted in 2012 reported promising results for captopril treatment[143]. Shortly after that, it was contradicted by a small retrospective review from Australia, assessing patients with IH who had to discontinue treatment with prednisolone because of steroid-induced hypertension. Of the patients who received captopril after discontinuing prednisolone, 33% demonstrated no changes in IH and 58% demonstrated a worsening[144]. More prospective randomized studies are needed to confirm or disprove these findings.

Oral itraconazole: Recently, efficacy of oral itraconazole was reported in six infants with IH. An obvious clinical improvement was noted in all cases during a 3-mo period, with an improvement of 80%-100%. Side effects were mild and limited[145]. The exact mechanism of itraconazole effectiveness is not yet fully understood, but it seems that itraconazole has an anti-angiogenic effect by inhibiting the VEGRF-2[146]. The future will teach us what itraconazole adds to the therapeutic arsenal for IHs.

ASSESSMENT OF IH SEVERITY AND ACTIVITY

The number of prospective studies of IH and its treatment has increased rapidly. Especially since the discovery of propranolol for this indication, the need for validated and reliable instruments to measure IH severity and activity in clinical trials has become an important issue. In 2011, the Hemangioma Activity Score (HAS) was developed, which provided a total activity score by measuring the swelling, color, and ulceration of IH. HAS seems to be suitable for evaluating IH activity and response to treatment over time[147,148]. In 2012, the Hemangioma Investigator Group Research Core developed another scoring system, the Hemangioma Severity Scale (HSS)[149]. The HSS not only takes the objective items, such as size, location, and complications into account, but it also assesses the subjective items, such as pain and risk of disfigurement[149]. Recently, a group of Bulgarian dermatologists presented the Hemangioma Activity and Severity Index[150].

Time will tell which scoring system has the best qualities to be implemented in clinical practice and used for research purposes.

IMPACT OF IH ON QUALITY OF LIFE

It is well known that visible abnormalities, such as IH, may affect the quality of life (QoL) of children or their parents/caregivers. Several studies have tried to measure the impact of IH on children and their parents. Until recently, either validated non-IH-specific or non-validated but IH-specific questionnaires have been used, providing controversial information[151-153]. This controversy may be explained by the absence of attention to impact of IH-specific factors (*e.g.*, localization, size, and complications) in non-IH-specific questionnaires or by use of non-validated IH-specific questionnaires. Most of them measure the overall psychosocial well-being instead of measuring a specific IH-related psychosocial impact[151]. In February 2015, Chamlin *et al*[154] presented a validated IH-specific QoL questionnaire. It is only matter of time before the first reports of the impact of IHs on the QoL of children and their parents will appear using this validated, IH-specific questionnaire, giving more reliable information. These reports will be followed by studies on the effects of different treatments on QoL. This information will provide us with the tools to optimally deploy the therapeutic arsenal for IHs.

CONCLUSION

The discovery that propranolol is efficacious in the treatment of IH has led to an upsurge in publications, increasing our knowledge of this subject. In this review, we provided the most up-to-date information about the

pathophysiology, variations in clinical presentation, and natural history of IHs. We looked at possible working mechanisms of several treatments and current worries regarding the treatment of first choice, propranolol. Finally, we provided an overview of the instruments measuring IH severity and/or activity and IH-related QoL.

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P- Reviewer: Fernandez-Pineda I, Ji Y **S- Editor**: Kong JX
L- Editor: A **E- Editor**: Wu HL

World Journal of Dermatology

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DOI: 10.5314/wjd.v5.i1.17

World J Dermatol 2016 February 2; 5(1): 17-51
ISSN 2218-6190 (online)

REVIEW

Psoriasis treatment: Unconventional and non-standard modalities in the era of biologics

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Author contributions: Mahajan VK contributed to concept, literature review and analysis, drafting and critical revision, editing and final approval.

Conflict-of-interest statement: No potential conflict of interest.

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Received: August 17, 2015
Peer-review started: August 19, 2015
First decision: October 13, 2015
Revised: October 25, 2015
Accepted: December 17, 2015
Article in press: December 18, 2015
Published online: February 2, 2016

Abstract

Psoriasis is a potentially debilitating inflammatory dermatosis affecting 0.2%-4.8% of the population worldwide causing a significant occupational, personal or psychosocial morbidity to these patients for life. The basic aim of psoriasis therapy is to control the disease to maximum possible extent and improve the patient's quality of life. Management of triggers for flare-ups, lifestyle modifications, and dietary supplements are often recommended. Intermittent or rotational therapy with frequent alterations in treatment options is usually needed to reduce toxicity of anti-psoriatic drugs in the absence of safer alternatives. Currently, several biological agents categorized as either T-cell targeted (*e.g.*, Alefacept, Efalizumab) or cytokine modulating (*e.g.*, Adalimumab, Infliximab, Etanercept) are available for treating severe psoriasis. However, their high cost is often precluding for most patients. The usefulness of systemic (methotrexate, cyclosporine, acitretin or several other therapeutic agents) or topical (tar, anthralin, corticosteroids or calcipotriol ointments, phototherapy with or without psoralens) therapies has been well established for the management of psoriasis. The literature is also replete with benefits of less used non-standard and unconventional treatment modalities (hydroxycarbamide, azathioprine, leflunomide, mycophenolate mofetil, isotretinoin, fumarates, topical calcineurin inhibitors, peroxisome proliferator-activated receptors agonists, statins, sulfasalazine, pentoxifylline, colchicine, grenz ray therapy, excimer laser, climatotherapy and balneophototherapy, peritoneal dialysis, tonsillectomy, ichthyotherapy, *etc*.). These can be used alternatively to treat psoriasis patients who have mild/minimal lesions, are intolerant to conventional drugs, have developed side effects or achieved recommended cumulative dose, where comorbidities pose unusual therapeutic challenges, or may be as intermittent, rotational or combination treatment alternatives.

Key words: Acetretin; Azathioprine; Balneophototherapy; Calcineurin inhibitors; Calcipotriol; Calcium dobesilate; Climatotherapy; Colchicine; Cyclosporine; Dapsone; Excimer laser; Fumarates; Grenz ray therapy; Hydroxycarbamide; Ichthyotherapy; Isotretinoin; Leflunamide; Methotrexate; Mycophenolate mofetil; Pentoxifylline; Peritoneal dialysis; Phototherpy; Plaque psoriasis; Peroxisome proliferator-activated receptors agonists; Statins; Sulfasalazine; Tonsillectomy

Core tip: The clinicians must be aware of all available antipsoriasis therapies in view of variable therapeutic outcome(s) that may test one's ingenuity in managing some "difficult to treat" psoriasis patients. The non-standard and off-label therapies will remain an important alternative to more widely used measures in rotational/intermittent treatment(s) or until a therapy that is affordable, safe, effective, and more importantly, remittiv becomes available.

Mahajan VK. Psoriasis treatment: Unconventional and non-standard modalities in the era of biologics. *World J Dermatol* 2016; 5(1): 17-51 Available from: URL: http://www.wjgnet.com/2218-6190/full/v5/i1/17.htm DOI: http://dx.doi.org/10.5314/wjd.v5.i1.17

Table 1 Therapeutic options for psoriasis

Topical agents	Systemic agents	Phototherapy
Emollients	Methorexate	Natural
Tar and anthralin	Retinoids	Dead Sea Therapy
Dithranol	Cyclosporine A	and PUVA-Sol
Corticosteroids	Hydroxyurea	Artificial
Vitamin D analogs	Tacrolimus	PUVA, Bath PUVA,
Tazarotene	Mycophenolate mofetil	UVB and NB-UVB
Salicylic acid	Sulfasalazine	Newer
Tacrolimus/	6-thioguanine	Excimer laser, NB-
pimecrolimus	Calcitriol	UVB light enhanced
5-fluorouracil	Colchicine	Photodynamic
Ascomycin derivatives	Dapsone	therapy
	Azathioprine	
	Fumaric acid esters	
	Biologics: Etanercept,	
	Alefacept, Infliximab,	
	Efalizumab,	
	Adalimumab	

UV: Ultraviolet light; PUVA: Psoaralene ultraviolet A; Sol: Solar; NB-UVB: Narrow band UV.

INTRODUCTION

Psoriasis is a potentially debilitating inflammatory dermatosis affecting 0.2%-4.8% of the population worldwide and with an estimated prevalence of 2.2% to 2.63% in the United States with approximately 150000 newly diagnosed cases per year[1]. All its clinical forms may eventually evolve into chronic plaque psoriasis characterized clinically by well demarcated, erythematous, scaly plaques. Guttate psoriasis is often self limiting, lasting for 12 to 16 wk, without treatment. However, 1/3rd-2/3rd of these patients may later develop chronic plaque psoriasis. Spontaneous remissions in chronic plaque psoriasis, lasting for variable periods of 1 year to several decades, may occur in up to 50% patients. Erythrodermic and generalized pustular psoriasis tend to be severe and persistent. There is no evidence that the disease is anyway different in either gender. There is no known prevention for psoriasis and in most cases, it remains a life long disease manifesting at unpredictable intervals with weekly, monthly or occasional recurrences. Although not life threatening, psoriasis can significantly impair quality of life with as many as 79% of patients with severe disease reporting a negative impact on their lives, and nearly 5% of them had contemplated suicide in a survey by National Psoriasis Foundation[2].

A plethora of anti-psoriatic treatments, both topical and systemic, is available for the management of psoriasis (Table 1). During the past four decades or so systemic methotrexate has been used effectively to treat all forms of psoriasis, including erythrodermic pustular and chronic plaque psoriasis. Despite a major concern for hepatotoxicity associated with its long-term use, it is even indicated for long-term management of severe forms of psoriasis. Currently, several biological agents are being used or evaluated for treating severe psoriasis. The Food and Drug Administration (FDA) approved ones are broadly categorized as either T-cell targeted (*e.g.*, Alefacept, Efalizumab) or cytokine modulating (*e.g.*, Adalimumab, Infliximab, Etanercept). Except for being prohibitory expensive, these apparently have an advantage over current systemic therapies, as systemic adverse effects do not mar their efficacy.

The voluminous literature on treatment of psoriasis is itself indicative of limitations of any therapy. It is often confusing while selecting a treatment regimen as most treatment schedules are aimed to decrease disease severity and extent that it no longer interferes with occupation, personal or psychosocial well-being of the patient. However, the patient's own assessment for their current therapy may remain unsatisfactory. For instance, in two separate surveys 40%-42% of patients felt frustrated with the ineffectiveness of their treatments while 32% reported that treatment was not aggressive enough[2,3]. As psoriasis is a chronic life long disease, safety of a treatment during long-term use too is of major concern. To date there is no absolutely safe, simple and inexpensive treatment for psoriasis and the selection of various strategies has to be individualized. The basic aim of psoriasis therapy is to control the disease to maximum possible extent and improve the patient's quality of life. Although reduction of psoriasis area severity index (PASI) score to 50% is currently considered adequate, there is no clear association among illness impact, subjective well-being, and the disease severity[4]. The patients may also assess their psoriasis as more severe than physicians do necessitating the need for more patient centric therapies[5]. Intermittent or rotational therapy with frequent alterations in treatment options is employed to reduce toxicity of anti-psoriatic drugs while search for safer alternatives continues. This paper focuses and reviews the less used and unconventional treatment modalities which can be useful alternatives to treat psoriasis patients who have mild/minimal lesions, are intolerant to

conventional drugs, have developed side effects or achieved their recommended cumulative dose, where comorbidities pose unusual challenges, or may be as intermittent, rotational or combination treatment alternatives. As management of triggers for flare-ups, lifestyle modifications, and dietary supplements are recommended frequently, it will be prudent to briefly review them alongwith few first line therapies.

MANAGING TRIGGERS

Despite the knowledge accumulated during past few decades that psoriasis is an immune mediated, regeneration-like reaction of the skin in genetically predisposed individuals wherein various cells including keratinocytes, antigen presenting cells, and T-cells play a dominant role at different stages, the exogenous factors which trigger psoriasis or induce flare-ups are poorly understood. A variety of environmental factors such as physical trauma (scratching, insect bites, surgery, sunburn) causing damage to keratinocytes (Koebner's phenomenon), drugs (antimalarial, clopidogrel, beta blockers, angiotensin-converting enzyme inhibitors, lithium, gemfibrozyl, imiquimod, interferon (IFN)-α, IFN-γ, withdrawal of corticosteroids or cyclosporin), infections (bacterial, viral, and yeast), or metabolic disorders such as hypocalcemia (primary or secondary) are implicated triggers for exacerbations[6]. Exacerbation and persistence of psoriasis has been attributed to increased hyper-reactivity to superantigens that are usually viral or bacterial proteins[7]. Bacterial (*Staphylococcus aureus*, *Streptococcus* sp.) endotoxins act as superantigens and activate T-cells, macrophages, Langerhans cells and keratinocyte. Superantigens bind to class II major histocompatibility complex (MHC) molecules and Vβ segments of the T cell receptor resulting in its activation and cytokine release. Balci *et al*[8] found a high prevalence of colonization of skin lesions and nares of psoriasis patients by toxigenic strains of *Staphylococcus aureus* as compared to healthy controls. They also observed a significant relationship between PASI scores and toxin production and suggested association between psoriasis and non-classical superantigens such as *mecA*, *etb* and *see*. Although they did not elucidate on therapeutic implications of their findings, antimicrobial therapy may have some role in psoriasis treatment. Other suggested association between *Candida albicans*, *Borrelia burgdorferi*, and *Pityrosporum ovale* remains unsubstantiated[9-11]. HIV-associated psoriasis usually develop in non-terminal stages of AIDS that is frequently severe, recalcitrant to therapy and has associated arthritis six times more often[12]. Although zidovudine has not been found effective for psoriasis in HIV-negative patients, it reportedly improves HIV-associated psoriasis[13,14]. However, exacerbations in HIV-associated psoriasis were treated more effectively with triple antiretroviral therapy (stavudine 30 mg, lamivudine 150 mg, nevirapine 200 mg; all twice daily)[15]. The role of human papillomavirus type 5, demonstrated in scrapping of lesional skin in nearly 90% of a large series of psoriasis patients, in the etiology of the disease remains to be determined[16].

The association of psoriasis, pustular psoriasis in particular, with hypocalcemia, mostly from hypoparathyroidism (both idiopathic and familial), that resolved after treatment with calcium has been described by several workers[17-20]. Similarly, experimental and clinical demonstration of association between vitamin D deficiency and psoriasis has been further supported by the effectiveness of vitamin D analog (calcitriol) in the treatment of psoriasis[20].

MANAGING LIFESTYLE

Factors such as obesity, smoking and alcohol consumption, diet, and stressful life events have been suggested to affect the course of psoriasis. Although their exact role in the etiology of psoriasis remains unclear, being modifiable they may be important adjunct to the therapeutic management of psoriasis. Psoriasis patients have been observed to present more frequently with obesity than the general population and severe psoriasis, *i.e.*, PASI > 10 and > 20% body surface area involvement[21-23]. Duarte *et al*[21] considered obesity a risk factor for severe psoriasis by observing a strong correlation between PASI > 10 and all obesity parameters; waist circumference, waist hip ratio, and body mass index (BMI). Setty *et al*[22] examined data linking weight gain and incident psoriasis in 78626 women and observed that the relative risk of psoriasis increased with the rise in BMI during the study period of 14 years. The authors attribute this to the production of inflammatory cytokines by adipositis as a possible explanation. There are reports of improved psoriasis in patients who lost weight and after gastric bypass surgery[24-26]. Nevertheless, obesity does not appear to play a role in the new onset of psoriasis or affect the efficacy of adalimumab in the treatment of psoriasis[27,28]. However, prospective data is lacking specifically to evaluate the role of weight loss in psoriasis.

Smoking and alcohol consumption

Recent studies suggest that cigarette smoking increases oxidative damage, promotes inflammatory changes, and enhances expression of genes associated with psoriasis[29]. Several studies across countries have linked current and past smoking habits to the increased severity or new onset psoriasis[30-36]. Smoking > 20 cigarettes daily has been associated with more than two fold increased risk of severe psoriasis, whereas the association between smoking and psoriasis seems to be stronger in women[35,36]. Smoking can worsen severity of psoriasis and makes patients less responsive to therapy[33,35,37]. While non-smokers experience more frequent remissions than smokers, cessation of smoking leads to decreased severity and the excess risk of psoriasis also declines[33,36,38].

There is extensive published literature on excessive alcohol consumption among psoriasis patients in a recent systematic review[39]. Alcohol consumption appears to trigger, exacerbate and influence the severity and the progression of psoriasis and psoriatic arthritis[30,40-42]. The amount consumed and the type of alcohol seems to trigger development and/or exacerbation of plaque psoriasis. Qureshi *et al*[41] in a recent prospective study followed 82869 women for 14 years and showed that consumption of more then 2.3 alcoholic beverages weekly was an important risk factor for new onset psoriasis. They also deduced that consuming non-light beer is an independent risk factor for developing psoriasis in females. Similarly, alcohol consumption at levels higher then 100 g/d appears to be a risk factor for the development and exacerbation of psoriasis in males[40,43]. The exact pathomechanisms by which alcohol triggers or exacerbates psoriasis remain poorly understood. Immune dysfunction/immunosuppression and increased susceptibility for infections, excessive production of inflammatory cytokines, and epidermal hyperproliferation by cycle activators such as cyclin D1 and keratinocyte growth factor have been implicated[44,45]. Not the least, alcohol abuse in psoriasis patients too is associated with decreased response to treatment and has implications for interaction with antipsoriatic medication[43,46,47].

Diet and dietary supplements

Diet rich in gluten, polyunsaturated fatty acids, and alcohol has been implicated in the severity of psoriasis in a significant number of patients[48]. An increased incidence of psoriasis in patients with celiac disease has been suggested[49-51]. A gluten-free diet is also suggested to improve psoriasis severity in celiac disease and even in patients with no celiac disease but with immunoglobulin A and/or immunoglobulin G (IgG) antigliadin antibodies[50,51]. However, the link between psoriasis and gluten-intolerance remains poorly understood due to inconsistent data. Nonetheless, all psoriasis patients with celiac disease or gluten-intolerance should have a gluten-free diet for overall wellbeing. Polyunsaturated fatty acids, through overproduction of arachidonic acid derived eicosanoids, influence several inflammatory disorders including psoriasis. The outcome from studies on effect of diet rich in omega-3 polyunsaturated fatty acids remains inconsistent. However, intake of fish rich in omega-3 and vegetarian diets may benefit psoriasis patients, as there is decreased intake of arachidonic acid and consequent reduction in inflammatory eicosanoid formation. Omega-3 fatty acids, especially eicosapentaenoic acid and docosahexanoic acid, compete with arachidonic acid as substrates for cycloxygenase and lipoxygenase, which thereby reduces downstream proinflammatory cytokines in psoriasis plaques. Most studies performed to evaluate their efficacy or fish oil rich in omega-3 fatty acids as dietary supplements in psoriasis report improvement in mean PASI scores[52-57]. However, there is no agreement concerning the dose of oral supplementation to be effective and the outcomes of randomized controlled trials are less effective[55,56]. Parenteral infusions of omega-3 fatty acids has been reported beneficial in patients with acute psoriasis[57]. Systemetic reviews also advocates omega-3 fatty as adjuvant treatment of chronic plaque psoriasis in evidence-based clinical guidelines[58,59]

Although caffeine consumption has been observed to decrease the therapeutic benefit of methotrexate in rheumatoid arthritis[60], it does not appear to effect psoriasis or inhibit anti-inflammatory effect or therapeutic benefits of methotrexate in patients with psoriasis or psoriatic arthritis[61]. Low calorie diet in a study showed a significant improvement after 4 wk as compared to controls and oral vitamin D supplementation can be recommended in psoriasis patients who are not on topical treatment with vitamin D analogues. The reported beneficial role of probiotics in psoriasis needs evaluation[62,63]. Similarly, curcumin [1,7-Bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione], has been shown to resolve psoriasis by lowering phosphorylase kinase levels in psoriatic epidermis and decreasing Ki-67 cells, which are capable of division[64-66]. Psoriasis patients treated with topical steroid plus oral curcumin 2 g/d achieved best PASI 50, PASI 75, PASI 90 and PASI 100 than patients treated with topical steroids plus placebo in a recent controlled trial and perhaps best used as an adjuvant to other therpies[65]. This phytochemical is one of the curcuminoid extracted from turmeric (curcuma longa), others being demethoxy-curcumin and bisdemethoxycurcumin. It exerts anti-inflammatory activity by inhibition of cyclooxygenase, 5-lipoxygenase and glutathione S-transferase and a number of other molecules but lacks clinical data to support its recommendation as a part of psoriasis treatment. In general, there is no sufficient scientific evidence that any special psoriasis diet is beneficial and the influence of diet on the course of psoriasis remains controversial. Nevertheless, avoiding foods suspected of causing inflammation or flare-ups, and eating low energy diet, will reduce risk for psoriasis comorbidities including obesity, diabetes, and cardiovascular diseases.

Infections and antimicrobial agents

Streptococcal infection and onset of guttate psoriasis and exacerbation of chronic plaque psoriasis have been repeatedly linked so much so that some workers routinely treat exacerbations with antimicrobial agents[67-71]. Saxena *et al*[72] noted significant improvement in PASI score in 30 patients with chronic plaque psoriasis at 12 wk and excellent improvement at 2 years from treatment with intramuscular benzathine penicillin (1.2 million units) fortnightly for 24 wk initially and then given once a week for a 2-year study period. Later, in a single blind randomized case-control study they used oral azithromycin for 48 wk as a single 500 mg/d for 4 d with a gap of 10 d (total 24 such courses) and achieved PASI 75 in 80% patients in the treatment group[73]. No

significant change was noted in control group. However, 20% of treated patients experienced recurrence at the end of one-year study period. Polat *et al*[74] used erythromycin 1000 mg/d and topical corticosteroids in 36 psoriasis patients and only topical corticosteroids in 24 controls for 4 wk. They noted statistically significant difference between the mean PASI of the two groups at the end of the treatment. The treatment used for the study group was also more effective against pruritus. However, these effects were attributed to inhibition of the production of many proinflammatory cytokines, including interleukin-6 (IL-6), IL-8 and TNF-α, perhaps by suppressing NF-κB or activator protein-1, and reduced neutrophil activity by macrolides rather than to their antibacterial properties. It has therefore been suggested that macrolides might be candidates for adjunctive treatment of psoriasis[74,75]. It is always prudent to treat appropriately any suspected coinfection to reduce overall morbidity, although, intervention by antibiotics is not considered of significant benefit by some researchers[76,77].

ANTIMETABOLITES AND OTHER IMMUNOSUPPRESSIVES

The drugs like methotrexate and cyclosporine with their proven efficacy in psoriasis remain well-established thearpies of first choice for moderate to severe psoriasis. Methotrexate (0.2-0.4 mg/kg, 7.5 mg to maximum of 30 mg/wk), alone or in combination with other drugs, is highly effective for the treatment of all forms of psoriasis. Its efficacy almost equals that of cyclosporine A or fumarates but is superior to that of hydroxycarbamide or mycophenolate mofetil (MMF)[78-83]. The efficacy and safety of combination of methotrexate and biologic therapy using adalimumab, etanercept, infliximab, or briakinumab too has been demonstrated in several uncontrolled studies and case series involving patients with psoriatic arthritis as well, and even in patients without previous methotrexate therapy[84-93]. However, methotrexate induced hepatotoxicity ranging from an asymptomatic transaminasemia to hepatic fibrosis and cirrhosis remains the most important concern in addition to vast potential for drug interactions (Tables 2 and 3). Therapeutic guidelines and recommendations have been available from time to time for monitoring methotrexate induced hepatotoxicity (Tables 4 and 5)[94-96]. Unfortunately, the potential efficacy of a topical methotrexate preparation in palmoplantar or plaque psoriasis remains unexploited[97-99]. Drugs like hydroxycarbamide, azathioprine, leflunamide, 5-fluorouracil, paclitaxel, and MMF too have been used infrequently in spite of limited therapeutic benefit *vs* methotrexate.

Hydroxycarbamide

Hydroxycarbamide (hydroxyurea), an antimetabolite, inhibits DNA synthesis by interfering with catalytic activity of the enzyme ribonucleoside diphosphatase reductase during the S-phase of the cell cycle. It was reported to be effective in refractory psoriasis for the first time by Yarbo in 1969. Since then many reports have shown favorable but variable results[100-108]. However, it is probably difficult to evaluate efficacy of hydroxycarbamide from these studies as various workers have used different doses for varying periods of time and evaluated their patients by different criteria. For instance, Layton *et al*[102] in their study of 86 patient with extensive chronic plaque psoriasis treated with hydroxycarbamide (0.5-1.5 g/d given for 3-96 mo), observed satisfactory remission in 61% patients while other 39% patients had inadequate response or significant relapse during treatment. While Sharma *et al*[101] obtained 76% reduction in the mean PASI score with hydroxyurea (1-1.5 g/d) given for 12 wk. Moschella *et al*[103] administered intermittent courses of hydroxycarbamide over a period of 18 mo to treat 60 patients with severe or incapacitating psoriasis and noted good to excellent response in 63% patients in first 6 wk and in 50% patients in 18 mo respectively. Boyd *et al*[104] in their review summarized therapeutic experience with hydroxycarbamide as excellent in 18%-38% and poor in 15%-20% patients. Weekly doses of hydroxylcarbamide too have been tried with variable success[109]. Hydroxycarbamide, 3.0 or 4.5 gm administered in weekly doses, was found effective in small number of patients and devoid of serious side effects as compared to its reported safety profile of daily therapy in a comparative study[81]. Eight (53%) patients did not show adequate response (< 25% reduction in PASI) at the end of 4 wk and 8 (53%) patients had mild to moderate improvement (25%-75% reduction in PASI) at 8 wk of treatment. However, at the end of 12-wk study period only 2 (13%) patients achieved marked improvement (> 75% reduction in PASI), 11 (73%) patients had mild to moderate improvement (25%-75% reduction in PASI) and 2 (13%) patients did not respond at all. The mean percentage reduction in PASI score was 48.47% ± 26.53% at the end of 12 wk. However, methotrexate (15-20 mg/wk) was faster in clearing the lesions and associated with higher adverse effects than hydroxycarbamide. Cutaneous or nail pigmentation, diffuse reversible alopecia, gastrointestinal symptoms, hematological and liver function abnormalities are usual side effects reported in 33% and 43% patients while hematologic side effects comprised 21% and 35% after prolonged hydroxycarbamide therapy in two separate studies[102,103]. Kumar *et al*[110] reported side effects in their 65.5% patients, pigmentation of nails, skin or mucosa being the commonest one seen in 58.6% patients. Sharma *et al*[101] also observed post-inflammatory lesional and nail hyperpigmentation in all their 34 patients apart from hematological adverse effects and skin infections in 23.53% patients. More uncommon and severe adverse reactions necessitating discontinuation of therapy include "flu-like" syndrome, cutaneous

Table 2 Adverse effects of methotrexate therapy

System involved	Adverse effects
General	Fatigue, headaches, chills and fever, dizziness
Skin	Pruritus, pain and burning, urticaria, mild reversible alopecia, ecchymosis, acute ulcerations of psoriatic lesions, reactivation of phototoxic responses
Blood	Bone marrow depression, leukopenia leading to decreased resistance to infection, anemia, thrombocytopenia, bleeding, and megaloblastic anemia, Pancytopenia
Gastrointestinal system	Nausea and anorexia, diarrhea, vomiting, ulcerative stomatitis, pharyngitis, enteritis
Urinary system	Azotemia, microscopic hematuria, cystitis, nephropathy
Respiratory system	Acute pneumonitis, pulmonary fibrosis
Nervous system	Headaches, dizziness, drowsiness, blurred vision, acute depression
Reproductive system	Teratogenesis, defective oogenesis, menstrual dysfunction, reversible oligospermia, defective spermatogenesis
Uncommon side effects	Anaphylaxis, acral erythema, epidermal necrosis, vasculitis, osteopathy, lymphoma

Table 3 Methotrexate drug interactions of significance

Interacting drug	Mechanism/comments
Drugs that increase methotrexate drug levels and toxicity	
Salicylates	Decrease renal excretion, displacement from plasma proteins
NSAIDs	Decrease renal excretion, displacement from plasma proteins
Sulfonamides	Decrease renal excretion, displacement from plasma proteins
Dipyridamole	Increased intracellular accumulation of methotrexate
Probenecid	Increased intracellular accumulation of methotrexate, decreased renal tubular function
Chloramphenicol	Displacement from plasma proteins
Phenothiazines	Displacement from plasma proteins
Phenytoin	Displacement from plasma proteins
Tetracyclines	Displacement from plasma proteins
Drugs that simultaneously inhibit folate metabolic pathway-increase hematologic toxicity	
Trimethoprim	Inhibition of dihyrofolate reductase
Sulfonamides	Inhibition of dihydropteroate synthetase
Dapsone	Inhibition of dihydropteroate synthetase
Drugs that may synergistically increase hepatotoxicity-common target organ	
Systemic retinoids	Common target organ for toxicity-liver
Alcohol	Common target organ for toxicity-liver

NSAID: Nonsteroidal anti-inflammatory drug.

Table 4 Guidelines for monitoring psoriasis patients receiving methotrexate by utilizing PIIINP levels

Indications for considering withdrawal of methotrexate	Elevation of PIIINP above 10.0 μg/L in at least 3 samples in one 12-mo period
Indications for considering liver biopsy	Elevation of pretreatment PIIINP above 8.0 μg/L Elevation of PIIINP above 8.0 μg/L in 2 consecutive samples Elevation of PIIINP above the normal range (1.7-4.2 μg/L) in at least 3 samples over a 12 mo period
Remarks: Serum for PIIINP measurement should be collected prior to starting methotrexate and should subsequently be measured every 2-3 mo during continued treatment	

Table 5 Grading of Liver biopsy as per Roenigk scale and recommendations for further methotrexate therapy

Biopsy grade	Liver histopathologic findings	Recommendation
I	Normal; fatty infiltration, nuclear Variability and portal inflammation- mild	May continue methotrexate
II	Fatty infiltration, nuclear variability, portal tract expansion, inflammation and necrosis- moderate to severe	
IIIA	Fibrosis-mild	May use methotrexate with caution and repeat biopsy at 6 mo
IIIB	Fibrosis-moderate to severe	Should not be given except in exceptional circumstances
IV	Cirrhosis	

vasculitis, leukopenia, thrombocytopenia, and fixed drug eruption[103,104]. Side effects like lesional erythema and tenderness, lesional and nail hyperpigmentation, arthralgia, dryness of mouth, periorbital swelling and diarrhea 3 d after the weekly dose of hydroxycarbamide not warranting discontinuation of treatment were

observed by Ranjan *et al*[81]. This low incidence of side effects and particularly absence of serious ones like hematologic toxicity was attributed to less number of doses used for short period of 1 to 2 d in a week. It is also observed that some variants of psoriasis may respond better to hydroxycarbamide than others. A good clearance in pustular psoriasis patients treated with 1-2 g/d hydroxycarbamide has been observed in 45%-63% of psoriasis patients treated[105,107]. The response is slow in erythrodermic or guttate psoriasis and palmoplantar pustulosis[103,105,107,108]. Hydroxycarbamide and infliximab combination was more effective in treating a case of recalcitrant psoriasis who had failed therapy with acitretin, bath Psoralen ultraviolet-A (PUVA), narrow band ultraviolet B (UVB), topical tar ointment, diathranol, vitamin D analogs and steroids[111]. However, its use in combination with other psoriasis treatment remains understudied. Despite slow response, hydroxycarbamide appears a reasonable alternative to methotrexate in patients who either develop gastrointestinal or hepatotoxic side effects due to methotrexate, or have achieved its recommended cumulative dose.

Azathioprine and 6-thioguanine

Azathioprine, an analogue of physiologic purines (adenine, hypoxanthine, guanine), is approved for use in rheumatoid arthritis and renal transplant recipients for its immunosuppressive activity. It is also used in dermatology for the treatment of blistering disorders, parthenium dermatitis, atopic dermatitis or other inflammatory dermatoses. It is rapidly absorbed after oral ingestion and nearly 30% is protein bound. After absorption, azathioprine is converted *in vivo* to 6-mercaptopurine and then its active metabolite, the nucleotide thioinosinic acid. Its maximum effect is on rapidly dividing cells and it may block the active enzyme and antigenic sites due to its alkylating effect on sulfhydril amino groups. It inhibits mitosis, B-cell proliferation, suppresses T lymphocyte function, and antibody formation. It requires at least 6-8 wk for its onset of action. The recommended dose of azathioprine is 100-150 mg/d (1.5-3 mg/kg per day). Sufficient perspective data from randomized trials is lacking but reports have shown its efficacy in severe psoriasis. DuVivier *et al*[112] observed 75%-100% clearance of psoriasis in 13 psoriasis patients among 19 of 29 patients who had benefited from treatment with azathioprine. It was found effective in another 5 of 10 treatment-resistant psoriasis patients with $\geqslant$ 25% improvement[113]. Hacker *et al*[114] used azathioprine in a psoriasis patient who had failed conventional psoriasis therapy (methotrexate, etretinate, corticosteroids) because of inadequate response or adverse effects. Azathioprine was as effective as other drugs in the treatment of psoriatic arthritis as well in a long-term study[115]. Remissions for > 5 years have been reported in 10 psoriasis patients following treatment with azathioprine pulse therapy in a recent study[116]. The researcher used azathioprine "intermittent high dose" (500 mg on 3 consecutive days) repeated every month along with "continuous low dose" (100 mg daily) during the intervening period comprising "one azathioprine pulse" of treatment. The patients were treated in Phase-1 until clearance that occurred after 1-5 pulses (average 3.7 pulses). The responders were shifted to Phase-2 and received same pulse dosing for another 9 mo followed by Phase-3 of "continuous low dose therapy" for one year. The patients were followed up without any treatment (Phase-4). Additionally, patients were treated with oral methotrexate (15 mg weekly), topical tar ointment before starting azathioprine pulse therapy for faster clearance. However, gastrointestinal intolerance, and bone marrow and liver toxicity at high dose remain a major concern. Azathioprine has been used effectively to treat patients with concurrent psoriasis and bullous pemphigoid and seems to be a good choice for such patients during corticosteroid weaning[117-119].

The major adverse effects of azathioprine include myelosuppression (anemia, leukopenia, thrombocytopenia, pancytopenia) that is more common among population having inherited deficiency of thiopurine S-methyltransferase (TPMT) activity. Liver toxicity (elevation of bilirubin, transaminases and alkaline phosphatase), and gastrointestinal side effects (nausea, vomiting, diarrhoea, oral ucers, esophagitis, steatorrheoa) are less common in recommended dosed. Nevertheless, patients should be monitored weekly for 1 mo, then every 2 weekly for 2 mo, and monthly or more frequently for hematologic or hepatic toxicity when dose alteration or other therapy changes are made/planned. Measurement of thiopurine methyltransferase levels can be used for guiding dosing pattern[120].

Six-thioguanine is the active form of azathioprine that works by inhibition of purine synthesis. It seems suitable alternative therapy for patients of who are failures or excluded for methotrexate, retinoids, or PUVA therapy. It is as effective or perhaps more effective in treating psoriasis than its parent drug. Zackheim *et al*[121] treated 48 patients having extensive plaque psoriasis with 6-thioguanine. They observed > 75% improvement as an initial response in 79%, > 50% improvement in 8% (including two patients with palmoplantar pustular psoriasis) while 13% had < 50% improvement. Almost 50% improvement continued in 65% patients during follow-up of 21 years (median 13 mo). The therapy was more effective, and better tolerated than methotrexate in majority of the patients who had changed from methotrexate due to inadequate response or side effects. Zackheim *et al*[122] made similar observations in their retrospective study of 81 patients with plaque psoriasis and five of palmoplantar pustular psorasis. A pulse-dosing schedule of 2 or 3 times per week showed marked improvement in 10 (71%) of 14 patients studied and maintenance dose varied from 120 mg twice a week to 160 mg 3 times a week[123]. Pulse dosing schedule

of 6-thioguanine is recommended to minimize its more serious adverse effects like myelosuppression, pancytopenia, and acute hepatitis but requires regular clinical and laboratory follow up[124]. Nausea, headache and fatigue occur less frequently.

Leflunomide

Leflunomide is an immunosuppressive disease-modifying antirheumatic drug. It is a prodrug and 70% of the drug administered converts into its active metabolite teriflunomide that inhibits mitochondrial enzyme dihydro orotate dehydrogenase (an enzyme involved in de novo pyrimidine synthesis). It is primarily indicated for treating rheumatoid arthritis and is found beneficial for the treatment of psoriasis with concurrent psoriatic arthritis. Kaltwasser *et al*[124] in a double blind, randomized placebo controlled study comprising 182 patients with psoriasis and psoriatic arthritis achieved a PASI 75 response at 24 wk in 17% patients in leflunomide group. While only 8% patients in placebo group had similar response. Similarly, psoriatic arthritis responded in 59% patients in leflunomide and systemic corticosteroids group *vs* 30% patients in placebo group.

Gastrointestinal irritation, elevated liver enzymes, leukopenia, drug eruption, headache, increased risk of infections, anaphylaxis, angiooedema, anaemia, agranulocytosis, eosinophilia, leucopenia, pancytopenia, vasculitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, oral ulcers, cutaneous lupus erythematosus, severe infection, interstitial lung disease, cirrhosis and liver failure, and teratogenicity are usual adverse effects[125]. Adequate contraception is recommended during leflunomide and additionally for 3 mo in males and 2 years in females after stopping the drug. Although combination of methotrexate and leflunamide is apparently more effective than either drug used alone (in rheumatoid arthritis), care should also be taken for concomitant use of methotrexate as combination may lead to severe or fatal hepatotoxicity[126]. Similarly, concurrent vaccination with live vaccines (like haemophilus influenzae type b vaccine and yellow fever vaccines) should be avoided due to the potential of severe infection because of immunosuppression from leflunamide.

Fluorouracil

Fluorouracil (5FU), an antimetabolite, acts principally by inhibiting thymidylate synthase leading to inhibition of pyrimidine thymidine synthesis. This anucleoside is important for deoxyribonucleic acid (DNA) replication. Thymidylate synthase catalyses methylation of deoxyuridine monophosphate to form thymidine monophosphate that is inhibited by 5FU therapy leading to cell death of rapidly dividing tumor cells and decreases epidermal proliferation[127]. Systemic fluorouracil is used for breast, anal, colorectal esophageal, pancreatic, gastric, and head and neck cancers. It is available as a solution, cream or a sustained-release preparation in various concentrations (0.5%, 1%, and 5%) for topical/intralesional use in actinic keratoses and Bowen's disease.

Due to its inhibitory effect on epidermal cell proliferation 5FU has been used topically, intralesionally or orally for treating plaque psoriasis[128-134]. As early as 1972, Tsuji *et al*[128] treated 13 patients with psoriasis using topical fluorouracil 5% ointment under occlusion. The treated lesions became necrotic followed by re-epithelization after stopping the ointment and complete clearance. Pearlman *et al*[129,130] used intralesional 1 mL fluorouracil (50 mg/mL) for 1-3 injections at 1- to 2-wk intervals (average 2 injections/patient) in 11 patients with psoriasis. The lesions improved in 2 wk and cleared completely in 4 wk. Subsequently, long remissions were observed in both the studies without significant systemic toxicity. Combining it with epinephrine for intralesional treatment showed improved response requiring single-dose treatment in 53 patients[132,133]. The combination was superior in improvement of psoriatic plaques than pulsed dye laser or betamethasone in a comparative study[133]. In a recent open-randomized-controlled study, 40 patients were treated with intralesional 5FU (0.1 mL/cm^2) weekly for three injections[134]. Total or near total clearance of lesions occurred in 35 patients at 12 wk. It was also effective for treating acrodermatitis continua of Hallopeau[135]. Gastrointestinal upsets, persistent hiccups, mucositis, headache, myelosuppression, photosensitivity, cardio toxicity, and mood alterations are common adverse effects of oral 5FU while pain, necrosis, and hyperpigmentation occurs from intralesional therapy.

Paclitaxel

Paclitaxel, a complex diterpene, is synthetic or derived from the bark of the Pacific yew tree (Taxus baccata). This chemotherapeutic agent demonstrates substantial anti-tumor effect in carcinoma of the breast, ovary, and lung, head and neck, bladder, testes, esophagus and endometrium. It has modest effect in Kaposi's sarcoma, lymphoma and carcinoma of the stomach and cervix. It has shown antiproliferative, antiangiogenic, and anti-inflammatory properties prompting a phase Ⅱ pilot study for its efficacy in 12 patients with severe psoriasis[136]. A dose-dependent decrease in PASI scores varying from 15% to 80% in different patients was observed. Higher dose (75 mg/m^2 every 4 wk for 6 doses) produced more significant results than lower dose at more frequent intervals; 37.5 mg/m^2 every 2 wk for 3 doses and 50 mg/m^2 for additional 6 doses. No patient had myelosuppression (usual with doses > 100 mg/m^2 every 3 wk), but hypersensitivity reactions occurred in two patients and another patient had flare up of Crh-on's disease. A new oral formulation, nanoemulsion of paclitaxel, has increased bioavailability in experimental animal models but needs evaluation for its clinical efficacy and safety among psoriasis patients[137].

MMF

MMF is an immunosuppressive drug used extensively in organ transplant recipients to prevent graft rejection prior to its usage for treating autoimmune blistering dermatoses (bullous pemphigoid, pemphigus vulgaris). It metabolizes to mycophenolic acid that inhibits de novo purine synthesis in B and T cells by inhibition of inosine monophosphate dehydrogenase enzyme for selective lymphocyte immunosuppressive effect. Haufs *et al*[138] reported first use of MMF for psoriasis leading to several case reports and uncontrolled studies demonstrating variable and beneficial effect of MMF for treating psoriasis[139-145]. Subsequent studies found MMF less effective as compared to methotrexate or cyclosporine but reported less nausea than methotrexate and renal toxicity than cyclosporine[82,146]. Beissert *et al*[146] observed a superior efficacy of cyclosporine as compared to that of MMF in a prospective, multicenter, randomized trial to treat chronic plaque-type psoriasis. However, there was no difference in time to relapse, side effects, and psoriasis disability index. As monotherapy, its overall PASI 75 achievement rate is less than 20% and PASI 50 is nearly 50%[144-146]. MMF also appears a reasonable alternative for patients with cyclosporine induced nephrotoxicity. Although PASI score increased in each patient treated with MMF after a 2-4 wk washout period of cyclosporine, the cyclosporine induced deranged renal function was significantly improved in a study evaluating switching from cyclosporine to MMF[147]. Regression of erythema, induration and scaling of psoriasis plaques has been reported from topical MMF but further evaluation is needed[148].

MMF has been also used successfully with cyclosporine minimizing toxicity of both drugs. Ameen *et al*[149] reported moderate to good improvement with cyclosporin (2.5 mg/kg per day) and MMF (3 g/d) in 3-11 mo among 78% patients with severe recalcitrant psoriasis. It also appear good choice in psoriasis patients having concurrent immunobullous disorders or HIV infection[150,151].

Severe gastrointestinal side effects (nausea, diarrhoea) and reversible hematologic toxicity are common. Hematologic malignancies, progressive multifocal leukoencephalopathy and serious infections have been reported in transplant recipients receiving MMF but are uncommon in psoriasis patients treated with MMF[152,153]. Nevertheless, all patients under treatment with MMF will routinely require evaluation for therapy-related complications by complete blood counts, hepatorenal function tests, and electrolyte estimation, and serious infections or neoplasia as per guidelines[142]. Despite unavailability of high-quality clinical trials, MMF in recommended doses of 1-1.5 g twice daily (maximum dose 3 g/d) appears a good alternative for the treatment of psoriasis in patients who are unable to take other drugs due to contraindication or toxicity or for maintaining disease control achieved from other therapies.

RETINOIDS AND RETINOID ACID METABOLISM BLOCKING AGENTS

Retinoids are synthetic and natural compounds that have biologic activity like that of vitamin A. Tretinoin and isotretinoin are the first generation retinoids while etretinate and acitretin are the second generation retinoids which are aromatic retinoids and supposed to be more effective in psoriasis and other keratinization disorders than first generation retinoids. Bexarotene and alitretinoin belong to third generation. The systemic retinoids, alone or in combination with other systemic (methotrexate, cyclosporine, hydroxyurea, PUVA) or topical agents (calcipotriene, coal tar ointment, steroids), or in rotational and sequential therapy constitute an important form of therapy in severe and resistant psoriasis. Retinoids are effective even as monotherapy particularly in exfoliative erythrodermic psoriasis and pustular psoriasis[154]. However, clinical data suggest that retinoid monotherapy may be less effective than other systemic agents in short term treatment of chronic plaque and guttate psoriasis. The advantage lies in their being not associated with immunosuppression or limitation of cumulative dose, and having no significant hepatic or renal toxicity. Therefore, they can be used alone or in combination with conventional therapies for psoriasis or biologic agents for treatment and maintenance therapy as well as in HIV affected patients with psoriasis. The exact mechanism of action of retinoids in psoriasis is not understood comprehensively. There are two families of retinoid receptors, a retinoic acid receptor (RAR) family and retinoid X receptor (RXR) family, each having three isoforms: α, β and γ. They perhaps exert their therapeutic effect by modulating three major pathogenic features of psoriasis, abnormal keratinocyte differentiation, keratinocyte hyperproliferation and tissue infiltration by inflammatory cells thus decreasing scaling, erythema and thickness of the plaques. They induce hypergranulosis and decrease number of tonofilaments and desmosomes, and widening of intracellular space causing a keratolytic effect. They inhibit neutrophil migration, alter cytokine production by T lymphocyte, interfere with keratinocyte responsiveness to cytokines or abolish resistance of keratinocytes to apoptosis[155]. However, isotretinoin has no clearly identified affinity for any retinoid acid receptor. Acitretin, an active metabolite of etretinate, is the most frequently used oral retinoid to treat psoriasis despite its lower efficacy as monotherapy *vs* methotrexate or cyclosporine. Its combination with UVB (reUVB) or PUVA (rePUVA) increases the responses of both modalities reducing the number and duration of therapy sessions needed to achieve clearance and decrease the cumulative adverse effects of ultraviolet (UV) radiation[156]. It can also be combined with other systemic agents like methotrexate, cyclosporine and hydroxyurea, biological therapies or with topical agents like calcipotriene and steroids in rotational and sequential therapy[157]. The efficacy of retinoids in

combination with biological therapies has been reported in several uncontrolled studies and case reports[158-167]. Ontheotherhand, other retinoids remain under evaluated for treating psoriasis.

Isotretinoin

Isotretinoin up to 2 mg/kg per day has been used in treating psoriasis[168]. Isotretinoin was first used in the treatment of psoriasis in 1973. Hotard *et al*[169] analyzed the medication prescribed to patients with a primary and only diagnosis of psoriasis spanning a period of 5 years. Out of 8.5 million visits, only 39% of the patients receiving systemic treatments were women. With respect to retinoids, it was observed that women received less etretinate (35% women among 100 patients on etretinate) than men but more isotretinoin (100% women) than men were, as all 9 patients who received isotretinoin were young females. Isotretinoin is considered more effective in pustular psoriasis than in chronic plaque psoriasis[170-173]. Moy *et al*[171] successfully treated 10 of 11 patients with pustular psoriasis using isotretinoin. Pustulation ceased after 3 to 5 d of treatment with daily dose of 1.5-2 mg/kg per day but recurrences were frequent on reduction of the dose. The pustulation subsided when the dose was increased again or most patients required additional agents to control their disease. Similarly, Al-Shobaili *et al*[174] found excellent outcome in a 16-year-old girl treated with isotretinoin for pustular psoriasis. Isotretinoin can be administered safely in patients who have developed adverse effects to etretinate. Marhold *et al*[175] reported a case of 29 years old female patient suffering from severe pustular psoriasis and had increased liver enzymes while on etretinate. Liver biopsy revealed changes of drug induced hepatitis. After normalization of the liver parameters following withdrawal of etretinate, isotretinoin was administered during a severe relapse. Contrarily, isotretinoin was well tolerated and resulted in a good therapeutic response. Vahlquist *et al*[176] also used isotretinoin in a patient of pustular psoriasis of palms and soles, who developed hepatitis after treatment with etretinate. However, they found it only marginally effective. Patients with plaque psoriasis can be treated with isotretinoin in a dose up to 1.5-2 mg/kg per day. Increasing small doses of isotretinoin are recommended initially while treating erythrodermic psoriasis in order not to provoke the disease[177,178]. Etretinate and acitretin has been shown to control chronic plaque psoriasis more effectively than isotretinoin when used as a single agent. Moy *et al*[171] compared isotretinoin with etretinate in chronic plaque psoriasis. Ten patients who had psoriasis affecting 20%-50% of their body surface area were treated with isotretinoin 1.5 mg/kg per day for at least 8 wk, and other 19 patients who had psoriasis affecting 40%-90% of their body surface area were treated with etretinate 0.75 mg/kg per day for the same period. Eighteen out of 19 patients treated with etretinate had either a complete or a moderate response, while only 4 of 10 patients treated with isotretinoin were moderate or complete responders. It showed a significant difference in efficacy in favour of etretinate. However, isotretinoin has shown equal efficacy to other retinoids when combined with psoralen photochemotherapy[179,180]. Combination of isotretinoin with PUVAsol was clinically more effective in clearing lesions of chronic plaque psoriasis and improved quality of life than PUVAsol alone in a recent study[180]. The mean percentage reduction in PASI score at the end of 12 wk was 51.92 ± 23.83 and 3 (27.27%) patients achieved marked to complete remission in a recent study comparing it with methotrexate[181]. Isotretinoin appeared less effective than methotrexate and only 4 (36.36%) patients had either mild improvement or were non responder in the first 8 wk.

Adverse effects of retinoids

Diffuse interstitial skeleton hyperostosis, premature epiphyseal closure, pseudotumour cerebri, severe headache and hepatotoxicity are potential important adverse effects. Musculoskeletal (arthralgia, myalgia, fatigue, muscle weakness, tendonitis), neuropsychiatric (mild depression, headache) and gastrointestinal (nausea, vomiting, abdominal pain) abnormalities may also occur. The retinoid tretogenecity remains the major concern and limitation for their use. When taken in the first trimester, they cause severe embryonic abnormalities in up to 50% and spontaneous abortion in up to one third of pregnancies. Malformations occur even with short periods of use, therefore no systemic dose of retinoids is considered safe during pregnancy. The most frequently described congenital malformation from isotretinoin is "the isotretinoin dysmorphic syndrome". It includes facial malformations (rudimentary external ears, absent or imperforate auditory canals, triangular microcephalic skull with large occiput and narrowing of the frontal bone, cleft palate, microphthalmia, depressed mid face), central nervous system anomalies (hydrocephalus, cranial nerve dysfunction), and cardiac malformations (over riding aorta, interrupted or hypoplastic aortic arch, atrioventricular septal defects, abnormal origin of the subclavian arteries). Limb reduction defects and thymic aplasia too have been described[182]. Hersh *et al*[183] reported that 10% of live birth records examined showed malformations of pregnancies occurring within 30 d after isotretinoin discontinuation. However, women who conceive one cycle after discontinuing isotretinoin are advised that their teratogenic risk is not higher than baseline[184]. The risk of retinoid embryopathy in fetuses fathered by men taking isotretinoin is minimal, if any.

Retinoids also adversely affect the skin (xerosis, palmoplantar and digital desquamation, retinoid dermatitis, photosensitivity, pyogenic granuloma, staphylococcus infections), the hair and nails (telogen effluvium, abnormal hair texture, dryness, fragility,

paronychia, onycholysis), the eye (dry eyes with visual blurring, blephrocunjunctivitis, photophobia), and mucous membranes (chelitis, dry mouth, sore mouth and tongue, nasal mucosa dryness, epistaxis). The majority of case control and other epidemiological studies have shown no association between mood change, depression, psychosis and suicide ideation, and isotretinoin use. Nevertheless, individual idiosyncratic psychological adverse response to the drug cannot be excluded[185]. Similarly, the current evidence is insufficient to establish a causal association between isotretinoin and inflammatory bowel disease[186].

New generation retinoids

Because of high selectivity for the β and γ subtypes of RARs the new generation retinoids have targeted action on psoriatic keratinocytes with minimum risk of adverse effects. They have better pharmacokinetics, and half-life of active metabolite of tazarotene (tazarotenic acid) is only 7-12 h. This imparts the advantage of contraception just being necessary for a few days after the last dose. The efficacy, safety and tolerability of tazarotene for psoriasis patients have been reported in phase Ⅲ trials[187]. It has been used safely for up to 52 wk without any significant increase in retinoid toxicities like hypertriglyceridemia, hypercholesterolemia, altered liver function tests, alopecia or conjunctival dryness. Several studies have also examined the safety and tolerability of topical tazarotene (0.1% and 0.05% gels), alone or in combination with topical corticosteroids (clobetasole, mometasone, flucinonide), calcipotriene or phototherapy for treating psoriasis[188-193]. Tazarotene 0.1% is generally more effective than the 0.05% cream. Tazarotene gel is non-sensitizer, non-phototoxic or non-photosensitizing, and treatment-related adverse effects like mild-to-moderate local skin irritation occur mainly from tazarotene 0.1% but systemic adverse effects do not occur.

Bexarotene, a synthetic RXR-selective retinoid, is an available treatment for cutaneous T-cell lymphoma. Antipsoriatic effect of oral bexarotene in doses up to 3.0 mg/kg per day during 12 wk of treatment has been evaluated on proliferation, differentiation, and inflammation parameters[194,195]. Smit *et al*[194] observed > 50% improvement in modified PASI, plaque elevation, and physician's global assessment in 22%, 52%, and 36% of patients, respectively, in a phase Ⅱ multicentric trial. No serious treatment related adverse events occurred. However, studies for the optimal dose and its potential as a new therapeutic modality are warranted. Similarly, therapeutic potential of topical bexarotene gel 1% in psoriasis needs further evaluation[196]. Oral Alitretinoin (9-cis-retinoic acid) 30 mg/d, alone or in combination with etanercept is another promising therapy for recalcitrant palmoplantar pustulosis or hyperkeratotic palmoplantar psoriasis but warrants confirmation of its efficacy and safety by controlled studies[197,198].

Contraindications, drug interactions and monitoring guidelines

Absolute contraindications for the use of retinoids are pregnancy or woman who is likely to become pregnant, non-compliance with contraception, nursing mothers, or individuals with known hypersensitivity. Relative contraindications include leukopenia, moderate to severe cholesterol or triglyceride elevation, and significant hepatic or renal dysfunction. Monitoring of concomitant medications that may interact with retinoids is required (Table 6). Pregnancy test in women of childbearing age, complete blood count, liver and renal function tests, complete lipid profile and urinalysis if indicated should be performed at baseline and repeated monthly for the first 3-6 mo, and then every 3 monthly. X-ray of wrist, ankle or thoracic spine at baseline and periodically are needed if retinoids are required for a long duration. Ophthalmologic examination is done as and when required.

According to iPLEGE program, the patient is advised to have a negative pregnancy test before isotretinoin use, every month during treatment, at the end of treatment and 1 mo after stopping treatment. The women must use two form of contraception for at least 1 mo prior to initiation of isotretinoin, during and one month after discontinuing therapy. Women of childbearing potential must access the iPLEDGE system at the time of first prescription and then at each subsequent prescription.

Retinoid acid metabolism blocking agents

Retinoid acid metabolism blocking agents, liarazole and talarozole, are retinoid mimetic drugs that act by blocking cytochrome P-450 dependent 4-hydroxylation of all-trans-retinoic acid. They modulate intracellular levels of endogenous retinoids and in turn normalize aberrant epithelial growth and differentiation. As the plasma all-trans-retinoic acid levels do not increase beyond physiologic levels, the retinoid-associated adverse effects are less frequent despite their efficacy similar to that of retinoids. Talarozole is a more selective inhibitor of the enzyme retinoic acid 4-hydroxylase and is effective in lower doses causing less side effects. Due to their rapid metabolism and clearance unlike synthetic retinoids, these drugs are safer for women and children. Liarazole was found effective for both palmoplantar pustular psoriasis and chronic plaque psoriasis in double-blind, randomized, placebo-controlled trials[199,200]. In a small pilot study, a noticeable improvement was observed in 4 of 7 patients with palmplantar pustular psoriasis treated with liarazole (75 mg, twice daily) as compared to 1 in 8 patients receiving placebo[199]. The lowest effective dose was 75 mg twice daily in a dose ranging, randomized, placebo controlled trial. A marked improvement occurred in 18% in liarozole 50 mg, 11% in 75 mg, 38% in 150 mg and 6% subjects in placebo group subjects, respectively[200]. Verfaille *et al*[201] treated 19 patients of psoriasis with talarozole (1 mg) for 8 wk and observed significant reduction in PASI. No formal

Table 6 Drugs interacting with retinoids

Interacting drug	Mechanism/comments
Drugs that may increase retinoids levels and/or toxicity	
Vitamin A	Induces hypervitaminosis A like toxicities
Tetracycline, doxycycline and minocycline	Increase pseudotumour cerebri risk
Macrolides, Azoles, *etc.*	Other CYP 3A4 inhibitors increase its level
Drugs that may reduce retinoids level	
Rifampicin, rifabutin	Induction of CYP 3A4
Anticonvulsants-phenytoin, Phenobarbital, carbamazepine	Induction of CYP 3A4
Drugs that may synergistically increase hepatotoxicity	
Methotrexate	Common target organ for toxicity-liver
Alcohol	Common target organ for toxicity-liver
Drugs whose levels are changed by retinoids	
Cyclosporine A	Cyclosporine A levels are increased *via* competition for CYP 3A4

announcement has been made for the results of phase II clinical trial for of its oral formulation, and phase I clinical trial for topical formulation[202].

FUMARIC ACID ESTERS

Althoguh fumaric acid was found effective in systemic treatment of psoriasis as early as 1959, the drug is licensed only in Germany and Netherlands for short-term (< 6 mo) use in patients with severe psoriasis when topical therapy is not indicated[203]. However, successful completion of a phase 3 study for use of its improved formulation in psoriasis has greatly renewed worldwide interest for this drug. The commercial preparations Fumaderm® initial and Fumaderm® have mixture of dimethylfumarate and three salts of ethyl hydrogen fumarate. (Fumaderm® initial contains dimethylfumarate 30 mg per tablet; Fumaderm® has dimethylfumarate 120 mg per tab).

The esters are used as fumaric acid itself is poorly absorbed after oral intake. They have almost complete absorption in the small intestines. The dimethylfumarate is rapidly hydrolyzed to more active metabolite monomethylfumarate by esterases. Dimethylfumarate and its metabolite monomethylfumarate are the principal active ingredients. Its interaction with intra- and extracellular thiols (glutathione) is considered the primary mechanism of action[204]. This inhibits NF-κB-mediated transcription of intracellular mediators (TNF-α or IL-8) and adhesion molecules (E-selectin, ICAM-1, VCAM-1). Other work suggests their therapeutic benefit by shift of the Th1-cytokines pattern towards Th2-type cytokine pattern associated with reduction in peripheral lymphocytes (primary T cells) inhibiting proliferation of epidermal keratinocytes in psoriasis patients[203,204]. Fumarates at higher concentrations inhibit induction of apoptosis and maturation of dendritic cells, which have an important role in immunologic reaction, and development and maintenance of an inflammatory response. These effects have been also demonstrated to be mediated by interference of the intracellular redox system.

Clinical studies from 1990s have reported a substantial reduction in PASI score following treatment with fumaric acid. Its efficacy and safety have been reported frequently and reviewed comprehensively[205-215]. Altmeyer *et al*[208,209] in two separate studies noted nearly 50% reduction in PASI in 50 patients with severe psoriasis and 80% in 83 patients respectively after 16 wk of treatment with Fumaderm®. Mrowietz *et al*[210] also reported 80% reduction in PASI after a 16-wk open-label multicenter study. The efficacy of fumarates is also confirmed in recent years. Litjens *et al*[211] reported nearly 53% reduction in PASI in 20 psoriasis patients while substantial improvement or clearance was observed by Carboni *et al*[212] in 71% of 40 psoriasis patients after 12-wk treatment with fumarates. Twenty percent patients achieved a statistically significant reduction in PASI from 13.9 ± 9.0 to 11.3 ± 9.2 in a single center study from United Kingdom[213]. The efficacy of fumaric acid ester in treating mild psoriasis too has been documented in a recent Italian study[214]. Reich *et al*[215] retrospectively analyzed the data of 984 patients with psoriasis for the long-term safety and efficacy of fumaric acid ester. Either the patients were on 24 mo of continuous treatment or at least 36 mo of intermittent treatment (mean duration 44 mo). Overall, 31%, 67%, 76%, 78% and 82% of the patients showed a substantial improvement or were clear of symptoms after 3, 6, 12, 24 and 36 mo, respectively, without significant laboratory abnormality or serious adverse effects. Although the efficacy of fumarates has been also demonstrated in psoriatic arthritis, nail psoriasis, and palmoplantar pustulosis, they are not recommended to treat psoriatic arthritis currently for lack of significant activity in arthritis, dactylitis, and enthesitis[216-219].

The therapy is usually initiated with low dose and escalated weekly until clinical response (usually observed in 4-6 wk) or a maximum dose of 1.2 g/d is achieved. Treatment with fumaric acid esters can be maintained for up to 2 years. Short-term intermittent therapy until major improvement followed by drug withdrawal is another mode of therapy. Although no rebound phenomenon or pustular exacerbation occurs, gradual tapering to minimal threshold dose is recommended to prevent relapse in patients with high disease activity.

The comparative efficacy of fumaric acid esters *vs* other systemic therapies remains understudied and so is that of their combination with other systemic therapies. Methotrexate and fumarates were equally effective without significant adverse events in the treatment of patients with psoriasis in a small, short-term study. Fallah Arani *et al*[83] in a first ever randomized controlled trial treated 60 patients with moderate to severe psoriasis vulgaris either with methotrexate (30 patients; 15 mg/Wk) or fumarates (30 patients; 30 mg, followed by 120 mg) for 16 wk. They reported 50% reduction in PASI at 12 wk of 42% and 60% patients in fumaric

acid esters and methotrexate group, respectively. PASI 75% was observed in 19% of fumaric acid esters and 24% of methotrexate group, respectively. Two patients in fumaric acid esters and 4 in methotrexate group dropped out due to adverse effects. Gollnick *et al*[220] found combination of oral fumaric acid esters and topical calcipotriol significantly more effective and faster acting than monotherapy with slight fumaric acid esters-sparing effect imparting a superior benefit/risk ratio. Combination produced higher and early mean reduction in PASI (76% *vs* 52%) and PASI 50 in 3 wk *vs* 9 wk. Fumarates can be combined with UVA or UVB during initial 3 wk of therapy[203]. There are reports of successful use in combination with methotrexate, acitretin, hydroxyurea or ciclosporin but combining retinoids have no additional benefit[221]. However, their combination with other systemic therapies is not recommended currently.

The fumaric acid esters are safe in inducing remission in a reasonable time and retain it through extended periods. Gastrointestinal complaints (nausea, abdominal cramps, or diarrhea) occur in up to 60% of patients in first few weeks of therapy. These symptoms can be reduced by dose reduction, taking the drug with milk, or addition of aluminium hydroxide, metoclopramide, ranitidine or pentoxifylline[222,223]. Flushing is seen in 30%-50% as feeling of warmth, facial flushing, and headache lasting for minutes to hours, and may be severe. It can be ameliorated with administration of acetylsalicylic acid. Leukocytopenia, lymphopenia, and eosinophilia can occur. The development of progressive multifocal leukoencephalopathy in two patients treated with Fumaderm® has been attributed to therapy associated prolonged severe lymphopenia[224,225]. Leukopenia below 3000/μL and lymphopenia below 500/μL, thus, need drug withdrawal or reduced doses. Eosinophilia is transient, seen in 4-10 wk of therapy, and improves after the drug withdrawal/reduction[226]. Occasional renal toxicity is observed and proteinuria when occurs will disappear following drug cessation or dose reduction[227,228]. Isolated elevation of serum bilirubin, hepatic enzymes, serum creatinine or potassium, and dyslipidemia may occur but increased susceptibility for infections or development of malignancies is not observed. Progressive multifocal leukoencephalopathy is a potentially severe toxicity. Discontinuation of therapy from adverse effects may be needed in 30%-40% cases.

CALCINEURIN INHIBITORS

Calcineurin or protein phosphatase 3, a calcium-dependent serine-threonine phosphatase, activates the T cells of the immune system and can be blocked by drugs called calcineurin inhibitors that include cyclosporine, tacrolimus, pimecrolimus and voclosporine. Both cyclosporine and tacrolimus are chemically distinct molecules. They bind to the intracellular immunophilins cyclophilin and FKBP-12 respectively. Both inhibit the phosphatase action of calcineurin required for the movement of nuclear factors in activated T cells to the chromosomes where subsequent cytokine synthesis occurs. They prevent IL-2 production in T cells and decreased secretion of IL-2 prevents proliferation of the inflammatory response *via* B cells and T cells. This attenuated inflammatory response greatly reduces the overall function of the immune system producing clinical response. Cyclosporine (cyclosporine A), a neutral cyclic undecapeptide, is derived from fungus *Tolypocladium inflatum gams*. It has been approved in the United States for 1-year and in Europe for 2-year of continuous therapy. Cyclosporine (2.5 to 5 mg/kg per day) has efficacy comparable to that of biologics in rapid control of severe, widespread, intensely inflammatory and erythrodermic psoriasis, cases resistant to other treatments, and nail psoriasis. Several studies have noted that 80%-90% of patients improve significantly after 12-16 wk of cyclosporine therapy[229,230]. The drug is also useful in treating childhood psoriasis with results and adverse effect profile similar to that is seen in adults[231-233]. However, early rebound flare up of psoriasis occurs after stopping the drug. Headache, tremors, and paresthesia/hyperesthesia are common adverse effects with short-term therapy. An irreversible nephrotoxicity and/or hypertension following long-term therapy especially in patients treated continuously with cyclosporine for > 2 years is of serious concern. Another major concern is almost six fold increased incidence of non-melanoma skin cancers like squamous cell carcinomas with long-term low-dose cyclosporine therapy especially when it is used in combination with PUVA (psoralen + UVA) therapy[234].

Voclosporine

This relatively new member of calcineurin inhibitors has higher affinity for calcineurin, faster clearance of metabolites from the body, high efficacy and a better safety profile as compared to cyclosporine. Nearly 67% patients receiving 1.5 mg/kg per day of voclosporine achieved PASI 75 in phase Ⅱ trial[234]. Similarly, 16%, 25% and 47% patients achieved PASI 75 response at 12 wk after voclosporine 0.2, 0.3, and 0.4 mg/kg, respectively, in a phase Ⅲ dose-finding placebo-controlled study comprising 451 patients with chronic plaque psoriasis as compared to 4% patients in the placebo group[235]. No significant adverse events or alterations in blood pressure, lipids or triglycerides were observed.

Topical calcineurin inhibitors

After noticing incidental improvement of psoriasis following systemic tacrolimus to prevent rejection in one heart and three liver transplant recipients, the researchers reported good response to the drug in other three patients with severe, recalcitrant and treatment resistant psoriasis[236]. Subsequently, European FK 506 multicenter psoriasis study group in a double-blind, placebo-controlled study comprising 50 patients with

severe recalcitrant plaque-type psoriasis randomized to receive treatment with either oral tacrolimus (FK 506) (*n* = 27) or placebo (*n* = 23) reported 83% PASI reduction in 27 psoriasis patients at the end of 9 wk[237]. Similarly, Rappersberger *et al*[238] used oral pimecrolimus with high clinical efficacy and good tolerability. The drug was well tolerated without clinically relevant laboratory abnormalities in a large, double-blind, dose-finding study[239]. Oral pimecrolimus, given as 20 and 30 mg twice daily in psoriasis patients, demonstrated a mean percentage reduction in PASI by 51.3% and 54%, respectively, at week 7 from the baseline. However, availability of topical formulations of tacrolimus and pimecrolimus (approved for atopic dermatitis) renewed interest for their use in the treatment of psoriasis as an alternative to topical corticosteroids. Mrowietz *et al*[240] used pimecrolimus (0.3% or 1%) to treat 10 patients with chronic plaque psoriasis in double-blind randomized-controlled study. Total scores decreased by 92% for clobetasol, by 82% for pimecrolimus (0.1%), by 63% for pimecrolimus (0.3%), and by 18% for control. They are most effective in recalcitrant psoriasis affecting the face, genitals, and intertriginous areas[241-245]. Tacrolimus (0.1%) ointment completely cleared psoriasis of face, intertriginous skin or both in 81% of 21 patients at end of study period of 57 d[242]. It also demonstrated complete clearing (24.8% *vs* 5.8%) in another randomized-controlled study at day 8, and 65.2% *vs* 31.5% at 8 wk in 80% of 167 patients with facial and intertriginous psoriasis[243]. Other researchers also made similar observations for efficacy and safety of topical tacrolimus with nearly 80% of patients having complete clearance of psoriasis on the face, genitalia, intertriginous areas, and corporal plaques[244]. Tacrolimus ointment improved plaque psorisis in a microplaque assay[246]. It has been also used with equal efficacy and safety in pediatric patients. Brune *et al*[247] evaluated tacrolimus 0.1% ointment in a single-centre open-label trial by treating 11 children aged between 6 and 15 years having psoriasis of face, folds or both. All patients had clearance or achieved excellent response within first 30 d itself. However, it is less effective for hyperkeratotic plaques involving back, trunk, elbows, and knees, perhaps from poor penetration[248]. Combining tacrolimus (0.1%) with salicylic acid (6%), or calcipotriene (0.005%) improves outcome in such cases[249,250]. Using tacrolimus or pimecrolimus under occlusion is also associated with improved efficacy in treatment of psoriasis[251]. Changing formulations for tacrolimus or pimecrolimus to improve its penetration and cutaneous bioavailability is another promising area for research. Topical liposomal tacrolimus was found nine times more effective than tacrolimus ointment in experimental studies[252]. Polymeric micelles- methoxy-polyethylene glycol-dihexyl substituted polylactide (MPEG-dihexPLA), a biodegradable and biocompatible diblock copolymer, as a nanocarrier was highly efficient for selective cutaneous delivery of tacrolimus experimentally[253].

Burning sensation and/or pruritus, usually in first few days of application of tacrolimus or pimecrolimus, is considered secondary to release of neuropeptides such as substance P[254]. Although United States FDA has issued "black-box" warning considering the risk for lymphoma and skin cancer, there is no convincing data for enhanced risk for the development of either cutaneous or systemic malignancy after topical use in large number of patients with atopic dermatitis for up to 4 years[255,256].

THIAZOLIDINEDIONES AND STATINS

Thiazolidinediones, pioglitazone, troglitazone, and rosiglitazone, are used for the treatment of non-insulin-dependent diabetes mellitus. They lower insulin resistance in peripheral adipose and muscle tissues, and decrease hepatic gluconeogenesis by binding to peroxisome proliferator-activated receptors (PPAR) γ. They also have cardiovascular benefits because of their property of lowering blood pressure, improving endothelial cell function/fibrinolysis, and increasing high-density lipoprotein. Increased expression of PPAR β/δ has been observed in activated T cells in human psoriatic lesions while experimental studies have shown that activation of PPAR β/δ in the epidermis could sustain a psoriasiform inflammation with keratinocyte hyperproliferation, accumulation of dendritic cells and endothelial activation[257,258]. Experimentally, topical PPAR β/δ antagonists effectively reversed PPAR β/δ activation triggered psoriasis-like changes[259]. The PPARγ agonists said to act *via* modulating anti-inflammatory actions by decreasing inflammatory cytokines like IL-2, TNF-α and IFN-γ, and down regulating the expression of adhesion molecules like VCAM-1[260]. They also inhibit the production of IL-17 by $CD4^+$ cells, and neoangiogenesis/angiogenesis both *in vitro* and *in vivo*[261,262]. Shafiq *et al*[263] in a double-blind randomized placebo-controlled clinical trial evaluated pioglitazone monotherapy in 70 patients with moderate to severe psoriasis. Three groups of patients received placebo, pioglitazone 15 or 30 mg/d, respectively for 10 wk. Psoriasis cleared or almost cleared in 40% of treated patients compared to 12.5% of patients in placebo group at end of the study period. The results were better with higher dose of pioglitazone and mean percentage reduction in mean PASI score was 21.6%, 41.1% and 47.5% in the pioglitazone 15 mg, 30 mg, and placebo groups, respectively. Adverse events like decreased hemoglobin in one patient and elevation of liver enzymes in two patients did not warrant withdrawal from study. In another open-label study, Bongartz *et al*[264] reported statistically significant reduction with pioglitazone 60 mg/d and non-steroidal anti-inflammatory drugs in average number of painful and/or swollen joints and a 38% reduction of PASI score in 10 patients after 12 wk of treatment. A 3-mo treatment period appears appropriate for any significant clinical response as most improvement occurred between 6 and 12 wk. The pioglitazone in combination with methotrexate or

acetretin seems more effective in improving plaque psoriasis in two recent studies than control groups receiving methotrexate or acetretin alone. Lajevardi *et al*[265] in a randomized controlled, assessor-blinded study compared the efficacy of methotrexate and combination of methotrexate and pioglitazone in 22 patients in each group. The PASI 75 was achieved in 63.6% with combination treatment as compared to 9.1% with methotrexate alone at end of 16 wk study period. Mean percentage reduction was 70.3% *vs* 60.2% in combination *vs* methotrexate alone group. Mittal *et al*[266] reported mean percentage reduction in PASI score of 64.2% in acetretin plus pioglitazone group as compared to 52.7% in acetretin plus placebo group after 12-wk study period. Its combination with other systemic therapy remains unevaluated. Troglitazone also normalized histological changes of psoriasis and reduced hyperplasia in experimental murine and human skin models. A substantial efficacy of troglitazone in psoriasis too has been reported in similar studies[267,268]. However, rosiglitazone was no more effective than placebo in a recent study[269]. Moreover, the drug has been withdrawn because of idiosyncratic hepatotoxicity.

Thiazolidinediones, due to their effect on lipid and glucose metabolism, appear to be therapy of choice for psoriasis associated with metabolic comorbidities like insulin resistance, obesity, dyslipidemia, or cardiovascular diseases. Pioglitazone 150 mg/d also led to complete remission of psoriasis in a 65-year-old man with non-alcoholic steatohepatitis and diabetes who had not responded to treatment with ursodeoxycholic acid[270]. However, topical formulations of these agents need further evaluation as no change was observed in PASI scores in a study comprising 8 patients with plaque psoriasis treated with topical 0.5% rosiglitazone[271]. Apparently, thiazolidinediones make useful therapeutic options for psoriasis and pioglitazone remains the most studied drug among its peers. Although more evaluation is needed for pioglitazone, alone or its combination with methotrexate, acetretin or other antipsoriatic drugs, it appears a relatively safe, convenient, and effective therapeutic option for psoriasis.

Statins

Statins include atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin. They were developed originally to treat lipid disorders in patients with hypercholesterolemia. They have significant immuno-modulating properties and studies have shown that they modify Th1/Th2 response to Th1 response, inhibit MHC-Ⅱ induction, cytokine release, inhibit mast cells degranulation, and induce apoptosis. CCL20/CCR6 interaction also plays an important role in the pathogenesis of psoriasis. Kim *et al*[272] investigated an inhibitory effect of statins on CCL20/CCR6 interaction and could demonstrate that IL-1β, TNF-α, and IL-17A significantly increased CCL20 production from HaCaT cells. Fluvastatin and simvastatin, but not pravastatin seemed to reduce this effect. Statins have shown to reduce inflammatory markers and when added to standard psoriasis therapy may improve disease severity. Statins show a hierarchy in their anti-inflammatory activity (cerivastatin > atorvastatin > simvastatin > pravastatin > lovastatin > fluvastatin)[273]. However, studies on their potential role in preventing psoriasis have yielded conflicting results. A decreased progression of psoriasis is shown to be associated with statin intake in several studies[274-279]. Contrarily, statins have been implicated for deterioration of skin lesions as well[280-283]. Shirinsky *et al*[279] in an 8-wk pilot study for the efficacy of simvastatin (40 mg/d) observed beneficial effects in seven patients with plaque psoriasis. Brauchli *et al*[275] observed no link between long-term use of statins and the decreased risk of psoriasis diagnosis in a case-control retrospective analysis of 36702 cases of psoriasis identified between 1994 and 2005 from United Kingdom based General Practice Research Database. However, they observed a reduced psoriasis risk for short-term statin users. Whereas, another retrospective cohort study assessed the relationship between adherence with statins and the risk of psoriasis among 205820 health plan enrollees in Israel (mean age 55 years; 54.1% female) and found that high and long-term adherence with statins is not associated with a meaningful reduction in the risk of psoriasis[280]. Another aspect of statins use is their combination with other antipsoriasis therapy. It showed a trend toward greater improvements in psoriasis severity in a study comprising 232 patients using topical corticosteroids, topical vitamin D, and some anti-ischemic treatments[274]. The patients on statins (n = 66) had more severe disease (BSA of 13.26%) before starting new psoriasis medication as compared with 12.25% for the patients in nonstatin (n = 166) group. Interestingly, the trend reversed after initiating medication, with a BSA of 5.21% *vs* 7.43% for the statin *vs* nonstatin users. There was overall 64% reduction in psoriasis severity in statin group as compared with 45% reduction in the nonstatin group. Although the difference was not statistical significance, trend for those treated with statins was toward greater improvement. Combined treatment with simvastatin and topical betamethasone also provided better clinical outcome in a double-blind study comprising 30 subjects with plaque-type psoriasis randomized to two groups[278]. Oral simvastatin (40 mg/d) combined with topical betamethasone (50% in pet) ointment in first group, whereas the second group received topical betamethasone (50% in pet) ointment and oral placebo. PASI score decreased significantly in both groups after study period of 8 wk. However, the reduction in PASI score was more expressed in simvastatin group patients. The potential efficacy of adding topical simvastatin to topical calcipotriol in plaque psoriasis also needs confirmatation[284]. Effects of combined treatment with atorvastatin (40 mg/d) *vs* placebo and keratolytics and/or corticosteroids were studied by Faghihi *et al*[276] in a prospective, randomized, double-blind, placebo-

controlled study. Oral atorvastatin was not associated with therapeutic benefit in patients with PASI scores < 12 points prior to addition of statin and the differences in mean PASI score were not statistically significant in two groups. Statins associated adverse effects like myopathy, proteinuria, elevated transaminases, or haemorrhagic stroke were not noted by these studies. Simvastatin presents the highest risk of toxicity *via* mechanism of CYP3A4 inhibition. It is not uncommon to find statins triggering/aggravating psoriasis. Cozzani *et al*[281] reported worsening of psoriasis in a patient 3 mo after atorvastatin and considerable improvement after discontinuation of atorvastatin. There is also report of exacerbation of psoriasis following pravastatin use[282]. Despite reduction in all-cause mortality among people without evidence of cardiovascular disease treated with statins, the major concern from wide use of statins in psoriasis is possible drug interactions between concomitant antipsoriatic or other therapies (methotrexate, cyclosporine, fibrates, macrolides, warfarin, digoxin, and azole antifungals)[285,286]. Potential interaction between fluvastatin and cyclosporine, primarily metabolized by CYP2C9 and not CYP3A4, is low[286].

It is perhaps too early to recommend use of statins in psoriasis as stand alone therapy as sufficient perspective data is lacking. The misinterpretation of available data is also possible as patients using statin are likely to change towards a healthier lifestyle as has been suggested by Brauchli *et al*[275]. Nonetheless, statins seems reasonable adjuncts to psoriasis therapy in view of the fact that psoriasis patients have a significant risk for metabolic disturbances and cardiovascular diseases.

ANTI-INFLAMMATORY AND OTHER DISEASE MODIFYING DRUGS

The utility of anti-inflammatory drugs as monotherapy is limited. While some of these agents like sulfasalazine have well identified advantage especially in psoriatic arthritis, others may perhaps have just more than a placebo effect. Nevertheless, their significance is perhaps in "add-on" therapy to ameliorate accompanying symptoms of inflammation and being sick.

Sulfasalazine

Sulfasalazine, a sulfa drug, is a derivative of mesalazine formed by combining sulfapyridine and salicylate with an azo bond. Sulfasalazine is primarily used for the treatment of inflammatory bowl disease including Crohn's disease and ulcerative colitis. It is also indicated for the treatment of rheumatoid arthritis or other inflammatory arthritis such as psoriatic arthritis. The recommended dose is 500 mg three times daily and increased as needed/tolerated. Sulfasalazine metabolizes to sulfapyridine that is responsible for some of the anti-arthritic effects and side effects of sulfasalazine from high serum concentrations of sulfapyridine and poor acetylation of the drug. Its other metabolite, 5-aminosalicylic acid (5-ASA), is considered responsible for its major therapeutic effect. However, its exact mechanism of action is not understood well but its anti-inflammatory effect is attributed to inhibition of dihydrofolate reductase and folate absorption. Sulfasalazine has been found effective in the treatment of psoriasis, spondyloarthropathy and psoriatic arthritis[287-299]. In a double-blind, randomized, controlled trial of sulfasalazine, intolerable adverse effects warranted discontinuation of treatment in 8 of 25 patients while other 7 of 17 patients, who continued treatment, showed 60%-89% improvement in their psoriasis[288]. In a small study, 3 of 8 patients in sulfasalazine group had moderate (50% to 70%) improvement of PASI score as compared 70% (very good response) improvement in PASI score in 6 of 7 patients in methotrexate group[293]. Significant improvement was observed in morning stiffness, number of painful joints, articular index, clinical score, and pain score, with the favourable response more pronounced in the polyarticular group and response became visible as early as 4 wk[289,297]. In a large double blind, placebo-controlled study 58% of 221 patients with moderate to severe psoriasis improved with sulfasalazine (2 g/d) over 36 wk and showed improvement in their psoriatic arthritis compared with 45% in the placebo group[290]. Rahman *et al*[295] treated 36 patients with sulfasalazine (3 g/d). One or more side effects warranted discontinuation of drug in 14 of 16 patients within 3 mo. A 50% reduction in actively inflamed joint count was noted in 7/20 patients at 6 mo and 11/15 patients at 12 mo as compared to 7/19 patients in the control group at 6 mo and 10/20 patients at 12 mo. Combe *et al*[299] also noted significant improvement in their study of 120 patients. Overall, the benefit remains marginal with no halt in radiographic progression in psoriatic arthritis and significant number of patients experience adverse effects. The axial disease also does not appear to improve significantly[294]. Comparatively, cyclosporine was more effective than sulfasalzine in the treatment of psoriatic arthritis in an open trial[298].

Although adverse effects are not serious, may occur in about 60% of patients requiring withdrawal from study in 15% patients[295]. Gastrointestinal intolerance (nausea, heartburn, vomiting, and diarrhea), malaise, headache, arthralgia, drug fever, and reversible oligospermia are common while leukopenia and agranulocytosis, and haemolytic anemia in G6PD deficient individuals are more serious adverse effects[296]. Skin eruptions can also occur and caused 4 of 23 patients receiving drug to drop out in a trial[288]. As the effect of sulfasalazine remains variable, its usage must be weighed against risk *vs* benefit of the drug. It must not be combined with methotrexate due to enhanced hepatorenal toxicity.

Colchicine

Colchicine, an alkaloid extracted from the plant

Colchicum species (*C. autumale*), has anti-inflammatory response by interfering neutrophil chemotaxis and inhibition of cell-mediated immune responses. It is mostly used to treat acute gout in a dose of 0.6 to 1.2 mg once or twice daily while its efficacy in psoriasis varies from being effective to having no effect on skin lesions. Wahba *et al*[300] observed significant clearing of skin lesions in 11 of 22 patients treated with colchicine (0.02 mg/kg per day) with symptomatic improvement observed in four patients with arthralgias. No significant difference was reported in 25 patients treated with colchicine (0.6-1.8 mg/d) or placebo at 23 wk in a subsequent placebo controlled study while colchicine was also associated with more adverse effects necessitating withdrawal from study in three patients[301]. Seideman *et al*[302] in a double blind, placebo controlled, and cross over study found significant improvement in joint pain and swelling, and grip strength in 10 of 12 patients after 16 wk treatment with colchicine (1.5 mg/d). Complete remission of pustular psoriasis occurred in 3 of 4 patients after colchicine treatment[303]. Palmoplantar pustulosis too has been treated successfully with some exceptions[304-306]. However, the potential efficacy of topical colchicine needs further evaluation[307]. Colchicine associated gastrointestinal adverse effects at doses above 2-3 mg/d are the major concern and may occur in 80% of patients and can be an indicator of maximum therapeutic dose. Myopathy and neuropathy may occur in long-term therapy while pancytopenia and renal failure results from overdose of the drug. Colchicine may be more useful in psoriatic arthritis, pustular psoriasis and palmoplantar psoriasis in a subset of patients, but more perspective data will be required to establish the role of colchicine in the management of psoriasis.

Dapsone

Therapeutic efficacy of this well-known antileprosy drug was first reported in a patient of generalized pustular psoriasis who was managed on a regimen of long-term systemic triamcinolone and dapsone[308]. Subsequently, several reports of its successful use in the treatment of childhood pustular psoriasis appeared[309-311]. An excellent response from dapsone was noted in 19 of 26 children while other five children had moderate response when treated with dapsone[310]. The response improved further when dapsone was combined with triptolide (the active ingredient in a Chinese herb) and erythromycin. Dapsone (100 mg/d) was also effective in treating inverse psoriasis involving genital skin fold[312]. The usual dose for pustular psoriasis in children is 1 mg/kg per day or 50-300 mg/d in adults and decreased to a low maintenance dose after effective control. The mechanism of its action in psoriasis has been postulated to be due to its anti-inflammatory effects by virtue of interference with neutrophil chemotaxis, blockage of prostaglandin- and leukotriene-mediated inflammation, and inhibition of myeloperoxidase in neutrophils and eosinophils, preventing tissue injury from oxygen radicals. Woolly headedness, anemia, dose-related methemoglobinemia, hemolysis in glucose-6-phosphate dehydrogenase (G6PD) deficient patients, agranulocytosis, hepatitis, dapsone hypersensitivity syndrome, peripheral neuropathy are some of its potential adverse effects requiring periodic evaluation. The utility of dapsone appears exciting but few well-controlled clinical studies are highly desirable to evaluate efficacy of this very versatile low-cost treatment in psoriasis.

Pentoxifyline

Pentoxifylline, a methylxanthine derivative, is a non-selective inhibitor that moderates the intracellular levels of cyclic adenosine monophosphate (cAMP) and cyclic guanisine monophosphate by decreasing their hydrolysis and augments cyclic nucleotide-dependant signal transduction leading to variable effects on inflammation[313,314]. It reduces blood viscosity, inhibits aggregation of platelets, erythrocytes and leukocytes, inhibits thrombus formation and improves microcirculation and tissue perfusion because of hemorheologic actions[315]. It also suppresses *TNFα* gene transcription, expression of TNF mRNA and secretion of TNF protein in macrophages and monocytes. The anti-TNF effect and antiproliferative effect of pentoxifylline is speculated to be responsible for its efficacy in psoriasis[293,316]. Magela Magalhães *et al*[317] in a randomized, placebo-controlled trial treated 61 patients with active psoriasis with pentoxifylline 400 mg/d or placebo. Clinicopathologic evaluation 8 wk after treatment showed no statistically significant differences from pre-treatment features between the two groups. el-Mofty *et al*[293] in a randomized controlled trial studied efficacy of sulfasalazine and pentoxifylline. They divided 32 patients in four groups treated either with sulfasalazine (group A), pentoxifylline (group B), both drugs (group C), or methotrexate (group D), respectively. Combination of sulfasalazine and pentoxifylline produced a better response than either drug used alone but methotrexate was superior in clearing the psoriasis at weeks 0, 2, 4, 6 and 8 of follow up. Its combination with fumaric acid esters is also said to reduce the severity and incidence of fumaric acid esters associated flushing and gastrointestinal side effects[224]. Similarly, use of pentoxifylline with cyclosporine might reduce later's nephrotoxicity[318]. Overall, its usefulness as monotherapy appears limited as compared to its combination with other antipsoriatic therapy. It is perhaps better to use it as only "add-on" therapy in the treatment of psoriasis[319].

PHOTOTHERAPY RELATED PROCEDURES

Phototherapy using UV light from sun or artificial source is a well-established treatment option in psoriasis of moderate severity, palmoplantar psoriasis, guttate and small plaque variety. UV light of both, broadband (BB) UV-B (290-320 nm) and narrowband (NB) UV-B (311-313 nm), and UV-A (320-400 nm) wavelength is predominantly used in psoriasis therapy. Comparatively, NBUV-B phototherapy is superior to BBUV-B in efficacy

and remission periods but is equal or less effective than PUVA therapy[320-325]. PUVA is useful in thick plaque psoriasis, palmoplantar psoriasis (particularly with topical psoralene), and for UVB phototherapy non-responders. However, UV-B phototherapy has added advantage of ease of administration and no psoralene toxicity (gastrointestinal intolerance, hepatotoxicity, phototoxicity, photodamage, premature aging, cataract, risk of skin cancers). Combination of PUVA or UV-B phototherapy has been used along with various topical (corticosteroids, calcipotriene, anthralin, tazarotene) or systemic treatments (methotrexate, retinoids) for enhanced therapeutic effect even at lower than recommended doses[326-329]. A combination of PUVA and UV-B has cleared psoriasis more effectively with an average of 11.3 treatments at doses much lower than needed for monotherapy[330]. The overall objective is to maintain minimum perceptible erythema for optimal dosing until 20-25 treatments, total or near total remission, or no further improvement is noticeable. The treatment is continued with reduced frequency to maintenance therapy once the remission is achieved. Nevertheless, the limitation is its contraindication in patients with erythrodermic or photo aggravated psoriasis, photosensitive disorders (systemic lupus erythematosus), personal or family history of melanoma or other skin cancers, and severe actinic damage. Eye protection is essential during UV phototherapy and ingestion of psoralene is contraindicated in children aged < 12 years.

Photodynamic therpay

Photodynamic therapy or photochemotherapy using topical aminolevulinic acid has been tried in psoriasis with inadequate clinical response in a randomized study comprising 29 patients[331]. Results have been discouraging in a recent randomized double-blind trial of this modality in 12 patients with psoriasis[332]. The therapy is frequently associated with severe pain and burning during and after treatment warranting its discontinuation. Topical hypericin, methylene blue, and systemic ALA and verteporfin are perhaps better tolerated photosensitizers for photodynamic therapy[333]. Like photodynamic therapy, photopheresis and extra-corporeal photochemotherapy are ineffective for skin lesions or psoriatic arthritis[334,335] and not prefered.

Grenz ray therapy

Grenz rays are essentially short-wavelength X rays with a wavelength of 0.07 to 0.4 nm, which is also in the range of long-wavelength ultraviolet radiation. They are produced at low kilovoltages with very limited penetration ability; up to the first half millimeter of the skin. Grenz ray therapy has been used effectively in many inflammatory dermatoses (eczemas, lichen planus, acne, Hailey- Hailey disease, mycosis fungoides) perhaps for their anti inflammatory effect and ability to decrease Langerhans cells in the epidermis[336]. Many researchers have reported good response from grenz rays (4 Gy weekly for 6 wk) therapy in psoriasis as well. Grenz rays therapy was effective in 14 of 16 patients with scalp psoriasis in a double-blind bilateral trial leading to complete clearing of scalp lesions treated with grenz rays for 6 wk and the remission lasted for 3 mo in 9 of these patients[337]. Grenz rays combined with topical corticosteroids cleared scalp psoriasis faster than topical corticosteroids alone in 17 patients with symmetrical scalp psoriasis lesions in a double-blind study[338]. The remission also lasted longer with combination therapy than when grenz rays were used alone. Lindelöf *et al*[339] compared grenz ray therapy alone with combination of grenz rays and topical betamethasone dipropionate in 40 patients with scalp psoriasis randomized into two groups. One group received 4 Gy of Grenz rays administered on six occasions at intervals of 1 wk and the other group was given the same Grenz ray treatment plus topical corticosteroid. The patients were assessed before and after Grenz ray therapy. Psoriasis cleared significantly in 16 out of 19 (84%) of the patients in the Grenz ray group, and I3 out of I8 (72%) of the patients in the combination group but the remission did not differ significantly between the two groups at end of follow-up of 6 mo. Remissions were longer with combination of grenz rays and selenium sulphide shampoo in combination as compared to placebo shampoo and Grenz rays[340]. Grenz ray therapy was also effective in a limited manner and appears to be a useful adjunct to other therapies for palmoplantar psoriasis and nail psoriasis particularly for nails with normal thickness[341,342]. The grenz ray therapy (4 Gy weekly for 6 wk) showed moderated but significant improvement of palmoplantar pustulosis in 15 patients in a randomized placebo controlled bilateral study[341]. The efficacy of grenz ray therapy was assessed in 22 patients with nail psoriasis in a randomized, bilateral controlled study[342]. One hand was allocated to treatment group receiving 5 Gy of grenz rays at weekly interval on 10 occasions. The placebo group received simulated therapy. The patients receiving active treatment showed moderate but significant improvement when psoriatic nails of normal thickness as compared to the control group. Overall, current evidence on its efficacy for psoriasis remains limited and development of non-melanoma skin cancers is a concern in the long term in addition to reported adverse effects of erythema and pigmentation[336,343].

Excimer laser

The monochromatic excimer laser used 308 nm xenon chloride light source and can deliver supra-erythemogenic doses up to 6 MED (2-6 MEDs) focally to the individual skin lesion for targeted phototherapy to minimize radiation and number of treatments. Initially used as three times weekly with an average of 10-12 treatments needed normally for improvement[344]. Asawanonda *et al*[345] reported at least 75% clearing of psoriasis in 72% of 124 patients after an average 6.2 treatments with excimer laser delivered twice

weekly. Higher response was noted with excimer laser in comparison with pulse-dye laser in a recent comparative study; few patients also responded better with the pulse-dye laser[346]. Patients in both the groups had remissions lasting more than 3 mo to 1 year. Blistering, burning and pain, and postinflammatory hyperpigmentation are potential side effects of excimer laser.

Climatotherapy and balneophototherapy

Exposure to sunlight is well known to improve psoriasis in majority. Daily bathing in Dead Sea water followed by exposure to sunlight perhaps remains the most studied mode of climatotherapy. The efficacy of Dead Sea climatotherapy has been attributed to the, high mineral contents, climatic conditions, and its location at about 400 m below sea level. Exposure to UV light through a mineral haze surrounding the beaches for 15 min daily to begin with is increased gradually depending on skin type to a maximum of 3 h/d for 3-4 wk. A 2 wk therapy is also considered optimal by some workers[347]. The therapy has been found effective in psoriasis decreasing PASI scores by 75% or more with long remissions[348-350]. Harari *et al*[351] observed 95.5% improvement of pre-treatment mean PASI score that decreased from 31.7 to 1.42 in 64 patients after 4-wk Dead Sea climatotherapy. All patients achieved PASI 50 and 75.9% of them reached PASI 75 during the same period. The median time of remission was 23 wk after a median duration of 33.6 wk. However, no long-term changes in psoriasis severity and quality of life were observed following Dead Sea climatotherapy in an earlier study[352]. Nevertheless, improvement is considered comparable to that from NB-UVB or PUVA therapy and other treatment modalities[351,353]. It was effective in psoriatic arthritis and has been used safely in pediatric patients[354-357]. Although considered expensive and time consuming, Shani *et al*[350] found it cost-effective considering the cost involved in travel, hotel accommodations, medical and laboratory charges, loss of productive days, adverse effects, and time taken for recovery of inpatient treatment. It has been combined safely and effectively with acitretin for psoriasis therapy[355].

Balneophototherapy involves salt-water baths and artificial ultraviolet radiation as an alternative to climatotherapy at the Dead Sea. Although high clearance rates have been reported with balneophototherapy[358,359], combination of Dead Sea bathing and sun exposure was more effective with 83% improvement as compared to 73% improvement with sun exposure alone and 28% improvement in psoriatics who only soaked in Dead Sea salts[360]. Climatotherapy is considered safe and adverse effects of this non-drug therapy such as sunburn, pruritus, folliculitis, solar elasotsis, solar lentigens, poikiloderma and wrinkles may occur[349,350,361]. Photodamage, malignant melanoma and non-melanoma skin cancer are other potential risks associated with long-term therapy.

Phototherapy for treating psoriasis, as standalone therapy or in combination with other modalities, remains as good an option as it was before therapies that were more effective became available. NBUV-B phototherapy is preferred being simpler and cheaper than all these procedures, virtually safer and free of adverse effects associated with psoralene ingestion.

PHYSICAL MODALITIES

Because of inherent complications, these physical treatment modalities should not be preferred to other therapeutic modalities or biologicals even in resistant debilitating disease.

Dialysis and related procedures

A report on incidental clearance of psoriasis lesions following haemodialysis in 1976 lead several small studies reporting a variable response[362-367]. Twardowski[363] also performed hemodyliasis for psoriasis in a non-uremic patient. A review of these reports reveals that peritoneal dialysis was more effective than hemodialysis. With 3-4 continuous ambulatory peritoneal dialyses per day, the psoriasis cleared completely in the two patients with renal failure and improved in the other two patients with normal renal function[368]. However, continuous treatment is perhaps required to prevent relapse. In a randomized double-blind crossover study treatment with sham and real peritoneal dialysis was performed in severe chronic plaque psoriasis unresponsive to conventional therapies including methotrexate[369]. Two patients cleared completely, two patients had more than 75% clearance and one patient had no significant response in peritoneal dialysis group while none of the 5 patients in the control group had any response. Sobh *et al*[370] treated 40 patients with severe psoriasis after their random grouping for haemodialysis (group-1), peritoneal dialysis (group-2), and treatment with modified Goeckerman (group-3). Ten dialysis sessions showed better response in peritoneal than haemodialysis, and both were better than Goeckerman treatment. There were no significant changes in plasma, or tissue zinc and copper levels while there was a significant decrease in IgG deposits after treatment in the three groups. Contrarily, Nissenson *et al*[371] in a randomized controlled trial of haemodialysis in seven patients with severe psoriasis observed no significant objective improvement. They performed a 24 h course of haemodialysis in three patients once daily for 4 d and repeat haemodialysis after 4 wk. Sham dialysis was performed in similar manner in four patients. In another study, 4/8 (50%) patients in haemodialysis group and 6/10 (60%) patients in peritoneal dialysis group, respectively, improved at the end of six months[372]. The benefit was temporary and one patient developed exfoliative dermatitis 11 d after haemodialysis. Three patients of Llewellyn *et al*[373] neither tolerated nor benefited from peritoneal dialysis. The exact mechanism of action of this procedure is poorly understood and is postulated to be from decreased IgG, increased fibronectin level, and postulated removal (from bloodstream) of growth-

promoting substances, psoriasis-related factors, activated polymorphonuclear leukocytes, interference with neutrophil migration[371,372].

While some psoriasis patients with renal disease may benefit from dialysis, the severe psoriasis itself independently predicts chronic kidney disease[374]. Haemodialysis may also cause relapse, worsening of pre existing psoriasis or trigger *de novo* psoriasis during chronic hemodialysis for renal disease. New-onset psoriasis may occur during both haemodialysis and peritoneal dialysis and factors implicated include dialysis-induced growth factor, cytokines, and chemokines in psoriasis development[375-377].

The outcome of hemofiltration, leukopheresis, cardiopulmonary bypass, and exchange with fresh frozen plasma in psoriasis treatment has been variable[378-381]. Plasma exchange gave no or only partial remissions but no controlled studies are available[382,383]. However, a controlled study noted no beneficial effect from sham and true plasma pheresis and leucopheresis[384]. Forced osmotic diuresis simply does not work[385]. Among all, peritoneal dialysis may favourably influence psoriasis outcome but never preferred unless it is required for its well-defined indications.

Tonsillectomy

Exacerbation, persistence or new onset of chronic plaques psoriasis within a subset of psoriatics is often attributed to hyper-reactivity to super-antigens, usually viral or bacterial proteins. Streptococcal infection has been the most implicated trigger in such instances. It has been suggested that some auto-reactive T cells primed against streptococcal proteins may cross react with keratinocytes (molecular mimicry) causing exacerbation of psoriasis. Molecular studies have suggested that auto-reactive T cells from tonsils can enter the circulation with homing to the skin triggering exacerbations/persistence of psoriasis. Tonsillectomy perhaps offer a valuable treatment option for such patients However, most reports in the literature on tonsillectomy comprise small case series or case reports pertaining to Japanese patients with acute guttate psoriasis, chronic plaque psoriasis or palmoplantar pustulosis. A complete clearance of guttate psoriasis and proteinuria was reported 2 and 6 mo after tonsillectomy in two patients, respectively[386]. Similarly, complete clearance of recurrent guttate psoriasis with remissions lasting for 16 mo was observed in two patients 1-2 mo after tonsillectomy[387]. Hone *et al*[388] reported complete clearance in 5 (83%) patients in a retrospective study comprising six patients with guttate psoriasis. However, the effect of tonsillectomy in guttate psoriasis remains poorly studied despite strong suggestion for its association with streptococcal pharyngitis. The clinical improvement in plaque psoriasis and reduction of circulating streptococcal and keratin peptide-reactive IFN-γ-positive CD8-positive skin-homing T cells is closely related[389]. However, the benefit of tonsillectomy in chronic plaque psoriasis remains ambiguous at best. In a questionnaire based retrospective study of 74 Danish patients with plaque psoriasis, 32% patients each reported complete or significant clearance of recalcitrant psoriasis vulgaris while 39% patients had some improvement[390]. Worsening of disease was reported by 7% and 22% experienced no improvement. There was also no statistical difference in the benefit of tonsillectomy for patients who reported flare up of their skin disease and who reported no effect from tonsillitis. Hone *et al*[388] reported complete or partial clearance of psoriasis plaques after tonsillectomy in 29% patients each, respectively; three of seven (42%) patients did not benefit at all. Recently, Thorleifsdottir *et al*[389] noted a significant reduction in PASI score ranging from 30%-90% in 86% of 29 patients *vs* 0% in controls in a randomized clinical trial of tonsillectomy in chronic plaque psoriasis. Nearly, 60% patients achieved PASI 50 and the improvement was apparent 2 mo after tonsillectomy that lasted for over 2 years. Rachakonda *et al*[391] also made similar observations in a recent systematic review of 20 publications of last 53 years comprising 545 patients with psoriasis who were evaluated for or underwent tonsillectomy.

The therapeutic efficacy of tonsillectomy was also analysed in 12 patients among 385 patients with generalize pustular psoriasis in a 1999 report by Ozawa *et al*[392]. The disease decreased in approximately 50% but only 2 (16.7%) patients showed clear-cut benefit. The exacerbation of palmoplantar pustulosis too has been imputed to acute tonsillitis pioneering its treatment with tonsillectomy[393-399]. Subjective marked or complete remission after tonsillectomy was reported by 89% of respondents to a questionnaire who had been treated for palmoplantar pustulosis by tonsillectomy[400]. Thirteen of 15 patients with palmoplantar pustulosis in another study reported effective to complete response 3 mo after tonsillectomy, no or partial response was also observed in one patient each[401]. Takahara *et al*[394,399] in two separate studies noted subjective improvement after tonsillectomy in 87% and 94% patients with palmoplantar pustulosis, respectively. Wu *et al*[400] have recently reviewed available evidence for the benefit of tonsillectomy in treatment of psoriasis. Overall, tonsillectomy may be useful for a subset of these patients in view of high rates of reported response to the procedure. However, additional well-designed studies including patients of diverse ethnicities will be needed for any recommendations. Moreover, the benefit must outweigh the risk associated with the procedure as disease remission after tonsillectomy was only for over two years or so in the reviewed reports. Long-term antimicrobial therapy will perhaps be more useful in such cases unless tonsillectomy is required due to its well-established indications[401].

Ichthyotherapy

Ichthyotherapy (Ichthys-Fish, Greek) means treatment

for skin by using fish *Garra rufa*, commonly known as "nibble fish" or "doctor fish of Kangal", which is a natural inhabitant of river basins in Central Eurasia. It is widely used in beauty and foot spas, and for the treatment of wounds or skin disorders like psoriasis and dermatitis that has made Kangal (Turkey) a popular health resort[402]. The treatment involves lying in the ponds/spas and let the fish nibble on the scales and loose skin on the affected areas. Although the utility of Garra rufa in the treatment of psoriasis was identified as early as 1989 by Turkish researchers[403,404], no controlled studies have been carried out for its efficacy. The two recent short-term, uncontrolled studies report beneficial effects of ichthyotherapy in psoriasis. Ozçelik *et al*[405] followed up 14 of 87 patients with chronic plaque psoriasis having prolonged immersion (mean 7.4 ± 1.1 h/d, mean 11.5 ± 6.6 d) in warm spring spas of Kangal containing *Garra rufa*. They reported complete clearance at 21 d in 8 (57.14%) and partial clearance in 6 (42.85%) patients, respectively. Two patients with erythrodermic or pustular psoriasis could not use this mode of therapy due to pain. Thirty-five of 87 patients experienced significantly longer remissions as compared to patients treated with topical corticosteroids alone. The overall beneficial effect was attributed to de-scaling of skin lesions by the fish, high selenium content and jacuzzi effect in spa water, natural sunlight, and reverse Koebner's phenomenon. Grassberger *et al*[406] used ichthyotherapy in a controlled medical setting to eliminate potential risk of infections associated with this mode of therapy. They evaluated its efficacy in 67 Austrian patients with moderate to severe chronic psoriasis who had undergone fish spa therapy for 2 h/d for three weeks in a tub containing garra rufa combined with short-term UV-A exposure and emollient application after each session. The tub and the fish were used exclusively for one individual patient. The bath water temperature was maintained at 36 ℃-37 ℃, filtered and disinfected constantly, and changed every 3-4 times a day. Overall, there was 71.7% reduction in PASI score and 87.5% patients reported a more favourable response *vs* other therapies. PASI ⩾ 75 and PASI ⩾ 50 were noted in 31 (46.3%) and 61 (91%) patients, respectively. Mean remission period was 8.58 mo and 65% patients reported decreased severity of relapse. They attributed beneficial effects to the relaxing effect of baths, decreased stress and psychological wellbeing contrary to the earlier belief.

Although no significant side effects were noted in these studies, pain, bleeding from nibbled skin lesions or transmission of viral and bacterial infections remains a potential risk[406,407]. The main concern about the use of fish spas involves the transmission of infectious agents such as *Mycobacterium marinum, M. fortuitum and M. chelonae, Aeromonas spp. (*Aeromonas folliculitis*), Streptococococcus spp*., *Salmonellae* (soft tissue infections, pustular dermatitis), *Vibrio cholerae*, *V. vulinficus*, or *Klebsiella spp* (wound infections) particularly among patients with diabetes, a common psoriasis co-morbidity, causing significant morbidity.

COMMENTS

The usefulness of various therapies, systemic (methotrexate, cyclosporine, acitretin or various biological therapeutic agents) or topical (tar, anthralin, corticosteroids or vitamin D analog ointments, phototherapy with or without psoralens) has been well established. The utility of vitamin D analogs (calcipotriol, calcitriol, tacalcitol, maxacalcitol, becocalcidiol) in psoriasis needs a mention here since these are important in sequential therapy as monotherapy or in combination with topical corticosteroids (halobetasol, clobetasol, betamethasone dipropionate) for added benefit and steroid-sparing effect. Over the years several clinical studies across the regions have demonstrated efficacy and safety of topical calcipotriene without tachyphylaxis or skin atrophy observed with topical corticosteroids[408-412]. Calcitriol is as effective as betamethsone propionate or short-contact dithranol therapy, and significantly more effective than calcipotriene for the treatment of facial, hairline, and flexural psoriasis with better tolerability. While several studies have demonstrated efficacy of tacalcitol in the treatment of mild to moderate plaque psoriasis, nail psoriasis and scalp psoriasis, maxacalcitol (25 μg/g) is considered more effective than once-daily calcipotriol[413-418]. However, noncompliance for vitamin D analogs reported in 12%-20% patients is due to lesional and perilesional irritation with accompanying perilesional erythema, stinging, itching, and/or burning following topical application[419-423]. Hypercalcemia, hypercalciuria and parathyroid hormone suppression are rare but potential systemic adverse effects and occur because of using more than recommended dose of 100 g/wk or in the presence of impaired calcium metabolism or underlying renal disease[424-428]. Relatively high cost of therapy is another reason for noncompliance.

Emollients, especially petrolatum-containing products, remain a main stay of any treatment. They retain moisture in the stratum corneum and increase local penetration of topical medications. Petrolatum ointment has an antipsoriatic effect while combination with salicylic acid (3%-6%) will have descaling effect on psoriasis plaques and enhance penetration of corticosteroid. Ichthyol pale (4% sodium shale oil sulfonate), a substitute for coal tar with conventional moisturizing properties, also offers anti inflammatory, antipruritic and antimicrobial actions because of high sulphur content[429,430]. All these can be used alternating with gradual withdrawal of topical steroids for the maintenance stage. Anecdotal efficacy of topical aminophylline 4% ointment could not be substantiated[431,432]. Changing topical formulations for improved drug delivery and cutaneous bioavailability appears another area for for future researchers.

Apremilast is recently FDA approved oral therapy of active psoriatic arthritis in adult patients. It was found superior over placebo in phase 3 randomised, placebo-controlled trial (PALACE 1-4 study) comprising patients with active psoriatic arthritis[433]. Overall, it was also

equally effective as monotherapy as in combination with existing DMARDs. There was also improvement in the PASI 50 (51% *vs* 19%) and PASI 75 (21% *vs* 5%) compared with placebo. Headache, nausea, and diarrhea were the only significant adverse effects reported. Apremilast 30 mg twice daily was also effective in chronic plaque psoriasis in a phaes 3 multicenter, randomized, placebo-controlled trial (ESTEEM 1 study)[434]. Its exact mechanism of action needs elucidation but said to regulate inflammatory mediators by inhibition of phosphosphodiesterase 4 enzyme in immune cells leading to increase in intracellular cAMP levels.

Peptide-T, tyrosine kinase inhibitors (Erlotinib), p38 mitogen activated protein kinase inhibitors, protein kinase-C inhibitors, nerve growth factor receptor blocker, rapamycin inhibitors (sirolimus, everolimus) constitute experimental therapies[435-441]. Alternative approaches (acupuncture, ayurvedic medicine, traditional Chinese medicine, homeopathic medicine, naturopathic medicine, *etc*.), and immunotherapy (heat-killed delipidated, deglycolipidated *Mycobacterium vaccae*, *Mycobacterium w* or anti-leishmania vaccines) forms other interesting area of research despite variable results[442-445].

It is also interesting to note the evolution of psoriasis and its therapeutic modalities. The concept of keratinocyte dysfunction led to treatment with phototherapy, methotrexate, and retinoids before 1980s, whereas, cyclosporine was introduced after it was considered an immunologic disease during 1980s. Alefacept, efalizumab, and TNF-α blockers were developed during 1990-2005 as psoriasis evolved as a disease of altered cytokine profile (IL-12/Th1-mediated). In recent years, ustekinumab and secukinumab have been developed in view of IL-23/Th17-mediated cytokine profile in psoriasis. Normalization of angiogenesis, an important pathologic component of psoriasis lesions, appears emerging concept for novel antiangiogenic agents for more targeted therapy; may be in combination or as an alternative to conventional therapies. Calcium dobesilate inhibits VEGF and interferes with fibroblast growth factor-induced neoangiogenesis; the efficacy of topical 5% cream in limited plaque psoriasis appears promising[446-448]. Neovastat, also a VEGF antagonist with anti-angiogenic and anti-inflammatory properties, has shown statistically significant reduction in PASI score in randomized phase Ⅰ/Ⅱ dose-comparison clinical trials comprising 29 patients with psoriasis[449]. More well designed studies are required before these drugs are approved for the treatment of psoriasis. Finally yet importantly, the clinicians must be apprised of all available antipsoriasis therapies in view of variable therapeutic outcome(s) that may test one's ingenuity in managing some of the "difficult to treat" patients. It seems that nonstandard and off-label therapies will remain an important alternative in rotational/intermittent treatment(s) or to more widely used and evidence based treatments until a therapy that is affordable, safe, effective, and more importantly, remittiv becomes available.

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P- Reviewer: Ayroldi E, Denadai R, Farkas A, Guslandi M
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DOI: 10.5314/wjd.v5.i1.52

World J Dermatol 2016 February 2; 5(1): 52-56
ISSN 2218-6190 (online)

MINIREVIEWS

Treatment of mycosis fungoides, in the era of stem cell transplantation

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Author contributions: All authors equally contributed to this paper with conception and literature review, and critical revision and editing, and final approval of the final version.

Conflict-of-interest statement: Authors declare no conflict of interests for this article.

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Received: September 1, 2015
Peer-review started: September 2, 2015
First decision: September 29, 2015
Revised: October 30, 2015
Accepted: December 9, 2015
Article in press: December 11, 2015
Published online: February 2, 2016

Abstract

Mycosis fungoides and Sèzary syndrome are the most common subtypes of cutaneous T-cell lymphomas. Even though, in early-stage disease, Mycosis fungoides commonly has a more indolent course, disease will progress in about 20% of such patients. About 30% of patients have been reported to develop advanced-stage disease and, at present, there is no cure for the disease. A number of systemic approaches have been used for advanced-stage mycosis fungoides (IIB-IV) and transformed disease. Aggressive approaches seem to be warranted in such patients. The scope of this review is the stem cell transplantation in mycosis fungoides and its leukemic variant, Sèzary syndrome.

Key words: Mycosis fungoides; Sèzary syndrome; Stem cell transplantation

Core tip: Some cutaneous T-cell lymphoma patients progress to advanced-stage disease or leukaemic stages. To date, there is no cure for those cases. In the last few years, several publications reported durable responses in some patients following allogeneic hematopoietic stem cell transplantation. Our aim is to define outcomes after hematopoietic stem cell transplantation for mycosis fungoides and Sèzary syndrome.

Patir P, Vural F. Treatment of mycosis fungoides, in the era of stem cell transplantation. *World J Dermatol* 2016; 5(1): 52-56 Available from: URL: http://www.wjgnet.com/2218-6190/full/v5/i1/52.htm DOI: http://dx.doi.org/10.5314/wjd.v5.i1.52

INTRODUCTION

Cutaneous T-cell lymphomas (CTCL) are amongst a group of malignancies of T-lymphocytes which primarily involves the skin. Mycosis fungoides (MF) and Sèzary syndrome (SS) are the most common subtypes of CTCL[1]. Based on the TNM classification, MF has four clinical stages, which has been translated further into early-stage and advanced-stage disease. Patients are considered to have "limited-stage" or "advanced-stage" disease if they have stage IA, stage IB, or stage IIA

Table 1 Summary of studies on auto hematopoietic stem cell transplantation and allo hematopoietic stem cell transplantation in patients with mycosis fungoides and Sèzary syndrome

Ref.	Year	Study location	Cases	Feature of study
AutoHSCT				
Bigler *et al*[11]	1991	United States	6	The first publication containing patient series with autoHSCT
Olavarria *et al*[9]	2001	United Kingdom	9	The analysis of autoHSCT with harvested cells post-T-cell depletion
Duarte *et al*[10]	2008	Spain	20	The use of auto and alloHSCT were summarized in this review
AlloHSCT				
Duvic *et al*[14]	2010	United States	19	The safety and efficacy of total skin electron beam with alloHSCT
Duarte *et al*[12]	2010	EBMT	60	The first large multicenter analysis of alloHSCT
Schlaak *et al*[15]	2012	Germany	-	To compare the efficacy and safety of conventional therapies with alloHSCT
de Masson *et al*[16]	2014	France	37	The largest multicenter analysis of alloHSCT for transformed MF
Duarte *et al*[13]	2014	EBMT	60	Updated with a prolonged median follow-up of 7 yr
Lechowicz *et al*[17]	2014	United States United Kingdom Australia	129	The largest reported descriptive cohort of patients receiving alloHSCT

HSCT: Hematopoietic stem cell transplantation; MF: Mycosis fungoides.

disease and stage ⅡB, stage Ⅲ, or stage Ⅳ, respectively. Even though, in early-stage disease, MF commonly has a more indolent course, disease will progress in about 20% of such patients[2]. About 30% of patients have been reported to develop advanced-stage disease and, at present, there is no cure for the disease[3]. In terms of outcome, the most significant predictor appears to be clinical stage of the disease.

In most of advanced stage CTCL cases, short-term clinical responses can be achieved with the use of various therapies, with a median survival time of 2.9 years. Patients with SS, on the other hand, have shorter median survival, approximately 13 mo[2,4,5]. A number of systemic approaches have been used for advanced-stage MF (ⅡB-Ⅳ) and transformed disease. These approaches include the use of retinoids, histone deacetylase inhibitors, interferon-α, bexarotene, the fusion toxin denileukin diftitox, extracorporeal photopheresis and chemotherapy without or in conjunction with stem cell transplantation. Despite of the limited data, the outcome is very poor in younger patients who have advanced-stage MF and are refractory to or relapsed after treatment with IFN-α, bexarotene, or histone deacetylase inhibitors. Aggressive approaches seem to be warranted in such patients[6]. The scope of this review is the stem cell transplantation in MF and its leukemic variant, SS.

HEMATOPOIETIC STEM CELL TRANSPLANTATION

Overview

Hematopoietic stem cell transplantation (HSCT) is a procedure in which hematopoietic progenitor cells obtained from bone marrow or peripheral or umbilical cord blood, either autologous or allogeneic, is administered to the recipient with the aim of recomposing the bone marrow. It has been shown that conditioning regimen composed of chemotherapy and/or radiotherapy combined with either autologous or allogeneic grafts was an efficient salvage treatment for a number of hematological malignancies that are unresponsive to conventional therapies. The most common indication for an HSCT in Europe is lymphomas. There has been an increase in the rate of allogeneic HSCT (alloHSCT) for lymphoma in recent years, largely owing to the introduction of reduced-intensity conditioning (RIC) alloHSCT[7,8]. RIC is a procedure to reduce the tumor size prior to the transplant to refrain from standard regimes of high-dose therapy. RIC appears to be as effective as standard conditioning regimens but with significantly less toxicity. Even though we have sufficient experience with HSCT in other types of lymphoma, there is only a handful of cases and series available with regard to CTCL (Table 1).

Autologous HSCT for mycosis fungoides and Sèzary syndrome

Results with autologous HSCT (autoHSCT) did not particularly meet the expectations[9,10]. As a matter of fact, autoHSCT is rarely, if ever, used for MF or SS. Bigler *et al*[11] published the first paper on the advanced-stage MF and autoHSCT in 1991 and reported the outcome of six patients after autoHSCT. Later, in 2001, Olavarria *et al*[9] published the analysis of autoHSCT with harvested cells post-T-cell depletion of nine patients with advanced-stage MF. Their data showed that complete clinical remission had been achieved in all patients and the median duration to achieve complete remission was 7 mo. However, the authors have reported that some of the cutaneous diseases relapsed, albeit in a less aggressive form. In 2008, the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation analyzed data of twenty patients with advanced MF/SS who received an autoHSCT since 1986 retrospectively. They calculated that the median estimated time to disease progression was only 2.3 mo[11]. Unfortunately, high-dose chemotherapy with

autoHSCT showed only short-lived responses.

Allogeneic HSCT for mycosis fungoides and Sèzary syndrome

AlloHSCT may be considered for patients with advanced disease (≥ stage ⅡB) whose disease fails to respond to all primary therapy options or who do not experience durable responses with any primary or salvage therapies.

The first large multicenter analysis of alloHSCT for advanced-stage MF came from the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation in 2010 that reported sixty patients with MF and SS. Data showed that, estimated overall survival (OR) in patients with advanced-stage MF/SS at 1 year and 3 years were 66% and 54%, respectively. In MF/SS patients, disease status, donor type and type of conditioning regimen have been identified as the main determinants of the outcome of alloHSCT, with the disease status having the highest impact across all outcomes. An earlier phase of the disease time course independently predicted both lower relapse/progression and higher progression free survival and overall survival. Neither the differences in outcomes between MF and SS patients or between TNM stages were significant. RIC protocols appeared to lower the risk of non-relapse mortality (NRM) below to that associated with myeloablative conditioning (MAC) without apparently increasing the risk of relapse/progression. RIC alloHSCT continued to offer a better OS than MAC alloHSCT. AlloHSCTs from matched HLA-identical related donors had a better outcome than alloHSCTs from matched unrelated donors. There are only 15 cases in a series on matched unrelated donor in MF/SS, which makes our experience very limited. It is possible that the outcome would be better as our experience builds up[12]. This original series were reanalyzed by the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation in 2014. New analyses revealed that OS at 5 and 7 years were 46% and 44%, respectively while PFS at 5 and 7 years were 32% and 30%, respectively, confirming that patients with advanced-stage MF or SS indeed benefited from alloHSCT. Data also showed that 27 patients (45%) had relapse or progression at a median of 3.8 mo after HSCT, indicating that disease relapse and progression comprised the main causes of post-transplant failure. It is worth noting that 8 of these 27 patients were alive at a median of 8 years after HSCT. This finding suggests that donor lymphocyte infusions (DLI) and/or other salvage therapies were very beneficial in rescuing some patients. At last follow-up visit, 27 patients were alive, and 26 of them were in CR. Seven year NRM was 22%, with the latest NRM occurring 14 mo after HSCT. Moreover, the risk of NRM is slightly higher if the patient has a poor performance score at HSCT (Karnofsky < 70) and the risk of relapse or progression is higher in patients who receive T-cell depletion. However, none of these alters survival significantly[13].

Duvic *et al*[14] reported the results of their prospective study on 19 patients with advanced stage MF who underwent total skin electron beam irradiation, followed by alloHSCT with conditioning with fludarabine and melphalan. The authors calculated the 2-year OS and PFS and reported them as 79% and 53%, respectively. The authors also reported that was the main cause of failure of treatment among their patients who had advanced phase disease was progressive disease.

Further, Schlaak *et al*[15] planned to compare in patients with advanced primary cutaneous T-cell lymphomas the efficacy and safety of conventional therapies with alloHSCT. Unfortunately, an updated literature search in January 2013 did not reveal any randomised controlled trials. Therefore, the authors of this study could not come up with a validated conclusion or propose recommendations for clinical practice.

A retrospective multicenter analyses has been carried out by de Masson *et al*[16] in 37 patients who had advanced stage CTCL and treated with alloHSCT. These patients included 20 cases (54%) with transformed MF. Best to our knowledge, this study is the largest multicenter retrospective analysis of alloHSCT for transformed MF. Therefore, the estimated 2-year OS rate of 57% in this study indicates that alloHSCT is suitable in advanced stage primary CTCL, including transformed MF. Nineteen (51%) patients experienced progression, which translates into 56% 2-year cumulative incidence of progression. The relapse rate was higher than other studies which could be explained by the fact that most of our patients had transformed MF, which is associated with a higher risk of relapse.

Lechowicz *et al*[17] conducted a study on the outcomes of alloHSCT in MF/SS, using the data gathered from 129 subjects who presented in 2014 to the Center for International Blood and Marrow Transplant Research. To our knowledge, this analysis is the largest descriptive study on patients who received alloHSCT for MF/SS. However, due to the fact that 39% of the patients had stage Ⅳ MF/SS, this cohort represents the minority of patients with MF/SS with very aggressive disease. The result of that study confirms that alloHSCT is useful, delivering acceptable NRM (19%-28%) in MF/SS patients and that patients benefit from the treatment.

CONCLUSION

Based on the publications with limited evidence, HSCT has the potential to increase response in advanced-stage MF and the results are especially consistent and promising for alloHSCT. However, autoHSCT is not devoid of any disadvantages, one of which is the possibility of an early relaps. This may be due reinfusing the malignant cells, which contaminate the graft. Hence, T-cell depletion to get the graft free from tumor cells before autoHSCT is a feasible and safe option[9]. Insufficient results achieved by autoHSCT means that alloHSCT should be listed as the treatment option for

advanced-stage MF. In contrast to autoHSCT, alloHSCT, which is obtained from a healthy donor, avoids the risk of tumor contamination of the graft and more importantly, has the potential to provide a ground for adoptive immunotherapy, leading to "graft-versus tumor-effect" (GVT)[18]. Based on previous reports, alloHSCT in advanced-stage MF appears to be superior to autoHSCT but relapse remains the major cause of mortality[9-11]. Even though relapse is not uncommon, the course of the disease varies and some relapse with more indolent disease than others. It is obviously easier to manage relaps with indolent disease by non-chemotherapeutic agents. Duarte *et al*[10] argued that DLI was beneficial in achieving complete remission after alloHSCT even if the patients had advanced-stage MF relapses and that this was an indication of the presence of GVT effect[10]. Even though high grade graft-versus-host disease (GvHD) following alloHSCT is one of the greatest challenges for a clinician, low grade GvHD is a desired situation as a positive relationship has been found between disease-free survival and low grade GvHD. Therefore especially low grade skin GvHD, which often involves the skin in MF might increase the effectiveness of alloHSCT in MF[19].

Limited number of studies in this area calls for caution while interpreting the results and implementing the findings in planning the treatment. To date, we have not been able to accumulate sufficient data from randomized controlled trials, which would otherwise clearly demonstrate the efficacy of alloHSCT in advanced-stage MF. We need more research, especially, prospective studies to enhance our knowledgebase in newer therapeutic modalities and establish a protocol on when to use alloHSCT.

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P- Reviewer: Chen GS, Cuevas-Covarrubias SA, Hu SCS, Kaliyadan F, Negosanti L, Vasconcellos C **S- Editor**: Qiu S **L- Editor**: A **E- Editor**: Wu HL

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DOI: 10.5314/wjd.v5.i1.57

World J Dermatol 2016 February 2; 5(1): 57-64
ISSN 2218-6190 (online)

Clinical pharmacokinetics profile of ivermectin 1% cream after dermal applications on the face

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Conflict-of-interest statement: All authors declared that they are employees of Galderma R and D, SNC. Galderma R and D was the sponsor and funded all the clinical studies presented in this paper.

Data sharing statement: No raw or individual data will be shared.

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Received: July 2, 2015
Peer-review started: July 6, 2015
First decision: July 31, 2015
Revised: November 2, 2015
Accepted: November 23, 2015
Article in press: November 24, 2015
Published online: February 2, 2016

Abstract

AIM: To investigate the pharmacokinetics profile of Ivermectin 1% cream after topical treatment in patients with papulopustular rosacea (PPR).

METHODS: Ivermectin 1% cream is a new, effective, and safe treatment for PPR. The human pharmacokinetic (PK) profile of ivermectin and its circulating metabolites were assessed following topical application of ivermectin 1% cream to the face. Clinical PK assessments were conducted after 4 wk of treatment using healthy volunteers and PPR subjects. Additionally, PK sampling was conducted up to 1 year of treatment in clinical phase 3 studies. Plasma concentrations of ivermectin and ivermectin metabolites were determined using high-performance liquid chromatography with fluorescence detection after a specific derivation to increase sensitivity.

RESULTS: Systemic exposure to ivermectin was quantifiable at low levels in healthy and moderate to severe PPR subjects following the first topical application of ivermectin 1% cream (mean C_{max} of 0.5 ± 0.2 ng/mL and 0.7 ± 0.5 ng/mL in healthy volunteers and PPR subjects, respectively). Ivermectin plasma levels reached a plateau after 2 wk of repeated topical application, indicating that steady-state concentrations had been reached. No further ivermectin plasma accumulation was observed during the long-term clinical studies that investigated ivermectin treatment up to 1 year. Investigation of ivermectin metabolites indicated that 2 circulating metabolites represented

more than 10% of parent drug systemic exposure at steady state. Repeated topical application of ivermectin 1% cream resulted in lower systemic exposure levels when compared with orally administered ivermectin, suggesting limited transdermal absorption of ivermectin. Topically applied ivermectin is cleared from the plasma slowly (with a prolonged plasma half-life when compared to the oral route).

CONCLUSION: Applications of ivermectin 1% cream result in low systemic exposure levels. Steady–state conditions are achieved by 2 wk without further accumulation under chronic treatment.

Key words: Ivermectin; Pharmacokinetic maximal usage trial; Metabolites; Plasma and rosacea

Core tip: Papulopustular rosacea (PPR) is a chronic skin disease affecting patients face, with a dramatic impact on social and professional interactions. Ivermectin 1% cream is a new effective and safe treatment for PPR recently approved in many countries. This article presents the clinical pharmacokinetics (PK) assessments conducted during the drug development of Ivermectin 1% cream. Usually, for topical products, PK assessments are incomplete due to the low systemic exposure. For ivermectin cream, a comprehensive PK and metabolism program was conducted in healthy volunteers and PPR patients up to 1 year treatment. These provided valuable information to better assess ivermectin safety profile.

Benkali K, Rony F, Graeber M, Jacovella J, Chappuis JP, Peirone MH, Poncet M, Delage S, Bouer R, Wagner N. Clinical pharmacokinetics profile of ivermectin 1% cream after dermal applications on the face. *World J Dermatol* 2016; 5(1): 57-64 Available from: URL: http://www.wjgnet.com/2218-6190/full/v5/i1/57.htm DOI: http://dx.doi.org/10.5314/wjd.v5.i1.57

INTRODUCTION

Ivermectin is a semi-synthetic derivative that belongs to the avermectin family of macrocytic lactones with anti-parasitic activities and is thought to have an anti-inflammatory effect by decreasing cellular and humoral immune responses[1]. The efficacy of oral ivermectin in human and animal demodicidosis and its anti-inflammatory properties suggest that ivermectin may also be effective in the treatment of papulopustular rosacea (PPR)[2,3]. Ivermectin 1% cream development has shown that this treatment is effective and safe in treating inflammatory lesions of papulopustular rosacea[4,5]. Therefore, ivermectin is now approved in the United States and in European Union member states as Soolantra® Cream 1% for treatment of papulopustular rosacea in adults[6].

Ivermectin pharmacokinetics (PK) data are well documented but mainly available for the oral marketed product for the treatment of onchocerciasis, strongyloidiasis of the intestinal tract and lymphatic filariasis[7]. In addition, ivermectin is indicated for scabies treatment in some countries[7]. After single or repeated oral dosing, peak plasma concentrations are achieved at approximately 4 to 10 h after dosing[8-10]. The plasma systemic exposures increase proportionally with doses between 6 and 120 mg[8,9]. After single 12 mg doses of oral ivermectin (tablet) in healthy volunteers, the mean peak plasma concentrations were from 23.5 to 50 ng/mL[10]. Ivermectin elimination curve might be subject to an enterohepatic recycling[11,12]. Ivermectin is widely distributed in the body with a volume of distribution about 3.1 and 3.5 L/kg, after ingesting 6 and 12 mg of ivermectin, respectively[13]. In addition, ivermectin is approximately 93% bound to plasma proteins, mainly to serum albumin[14].

Ivermectin is extensively metabolized in vitro by liver microsomal cytochrome P450 3A4 to hydroxylated and demethylated metabolites[15]. Ivermectin and its metabolites appear to be eliminated mainly in the faeces, with minimal urinary excretion (≤ 1% of the administered dose). The mean half-life of ivermectin when administered orally is ranging from about 15 to 20 h[9].

Recently, ivermectin has been approved for use in human as a topical treatment of head lice infestations with a short contact therapy (10 min application, single use)[16]. The ivermectin transdermal absorption was evaluated in a clinical study in subjects aged from 6 mo to 3 years after a single application of ivermectin 0.5% lotion on the head. The resulting systemic exposure levels after a single 10-min application were very low in comparison to the oral administration, the mean maximum exposure (C_{max}) being 0.24 ± 0.23 ng/mL[17].

The present work summarizes the human PK behavior of ivermectin and its metabolites following topical applications of ivermectin 1% cream as developed recently for the treatment of PPR. A comprehensive assessment of the clinical PK profile of ivermectin following topical application was performed in healthy volunteers and PPR subjects after 4 wk of treatment. In addition, due to the anticipated chronic use of this treatment, systemic exposure levels were further investigated in long term studies of up to 1-year treatment.

MATERIALS AND METHODS

PK study in healthy volunteers

A single-centre, open-label study to assess the pharmacokinetics and safety of ivermectin 1% cream has been conducted in healthy volunteers. Thirty-two male or female volunteers were enrolled in the study. A maximized dose (1 g of ivermectin 1% cream) was applied under nurses' supervision on the whole face as

a single application (Group 1: 8 subjects) or as repeated applications once (Group 2: 12 subjects) or twice (Group 3: 12 subjects) daily for 28 d. The treatment was followed by a 28 d or 56 d follow-up treatment-free period for the single and repeated dose respectively.

For the single application group (Group 1), blood samples for the determination of ivermectin plasma levels were collected over a 24 h period post dose and during a 28 d follow-up period.

For the repeated application groups [Group 2 (QD) and Group 3 (BID)], blood samples for the determination of ivermectin plasma levels were collected over a 24 hperiod on day 0 (first drug application), 14 and 28. In addition, pre-dose blood samples (residual levels) were collected on day 7 and 21. Blood samples were also collected during the 56 d follow-up period.

Maximal use PK study in subjects with severe papulopustular rosacea

This study was a multi-centre, open label study, involving approximately 15 adult male or female subjects with severe PPR, *i.e.,* with at least 25 inflammatory lesions and an Investigator Global Assessment (IGA) of rosacea of severe (score 4 on a 5-point rating scale from 0 to 4). Subjects were treated by nurses once daily on the whole face with 1 g of ivermectin 1% cream during a 4 wk period. The treatment was followed by a 28 d treatment-free follow-up period.

Blood samples were collected over 24 h in day 0 (first drug application), 14, and 28 to investigate the pharmacokinetics of ivermectin (and its related metabolites) in the plasma. In addition, pre-dose samples were collected at day 7 and 21. Blood draws were also sampled during the 4 wk following the last treatment application.

Long term use clinical studies

Two phase 3 studies of same design (Study #1 and Study #2) enrolled a total of 1371 adult subjects with moderate to severe PPR. The design of these studies has been previously described by Stein *et al*[4]. Overall, 1 group of subjects was treated with ivermectin 1% cream once daily for 52 wk, the remaining subjects were treated with the vehicle (during the first 12 wk of treatment) followed by an active treatment, azelaic acid 15% gel twice daily (from wk 13 to 52 of the study). Blood samples to assess ivermectin systemic levels were collected in a subset of subjects at approximately 12 h after the drug application at week 12, 32, 52 and at week 56 (4 wk after treatment stop).

Ivermectin and metabolites plasma concentrations measurement and PK analysis

In all clinical trials, ivermectin plasma concentrations were measured, after a solid-phase extraction, using the same validated high-performance liquid chromatography method (using fluorescence detection after a specific derivation to increase sensitivity). The limit of quantification of the method was 0.05 ng/mL. In addition, an estimation of concentration levels of the ivermectin metabolites was performed from the human plasma samples collected in the maximal use PK study.

Pharmacokinetic parameters (C_{min}, C_{max}, T_{max}, AUC and $t_{1/2}$) were calculated for each subject using a non-compartmental method (Kinetica™ software, version 4.3, InnaPhase Corporation, Philadelphia, United States). Descriptive statistics were performed on PK parameters. In addition, selected PK parameters (from healthy volunteers and PPR PK studies) were transformed into natural logarithms (Ln) and submitted to an analysis of variance including subject and time as factors in the model to assess the steady state conditions. The statistical review of the study was performed by a biomedical statistician.

Table 1 Demographic characteristics of subjects enrolled in pharmacokinetic studies

	Healthy volunteers PK study (n = 32)	PPR subjects maximal use PK study (n = 17)
Age (yr)		
Mean ± SD	30 ± 8	54 ± 12
(Min-max)	(18-45)	(35–74)
Gender (male/female)	16/16	6/11
IGA score: 4 (n %)	NA	17 (100%)
Inflammatory lesion count		
Mean ± SD	NA	40.5 ± 14.3
(Min-max)		(27.0-88.0)

NA: Not applicable; PK: Pharmacokinetic; PPR: Papulopustular rosacea.

RESULTS

PK study in healthy volunteers

Thirty-two healthy volunteer subjects were enrolled. There was an equal repartition of males (50%) and females (50%) in each group. The mean age (± SD) was 30 ± 8 years (Table 1).

Single dose application

After a single topical application of ivermectin 1% cream, ivermectin plasma levels were quantifiable in all subjects (Figure 1). The mean values of $AUC_{0\text{-}12h}$ and $AUC_{0\text{-}24\ h}$ were 3.8 ± 1.4, 8.3 ± 2.5 ng × h/mL, respectively (Table 2). The mean maximum plasma concentration of ivermectin peaked at 9 h after dosing (mean C_{max}: 0.49 ± 0.15 ng/mL) and slowly decreased thereafter (Figure 1). The mean plasma terminal half-life was 45 h (range 32 to 130 h).

Repeated applications

Following repeated topical applications of ivermectin 1% cream, systemic exposure was higher than that found after a single application (Table 2 and Figure 1). However, ivermectin systemic levels reached a plateau at day 14 of treatment for both QD and BID dosage regimen groups (Table 2 and Figure 1). In addition, the

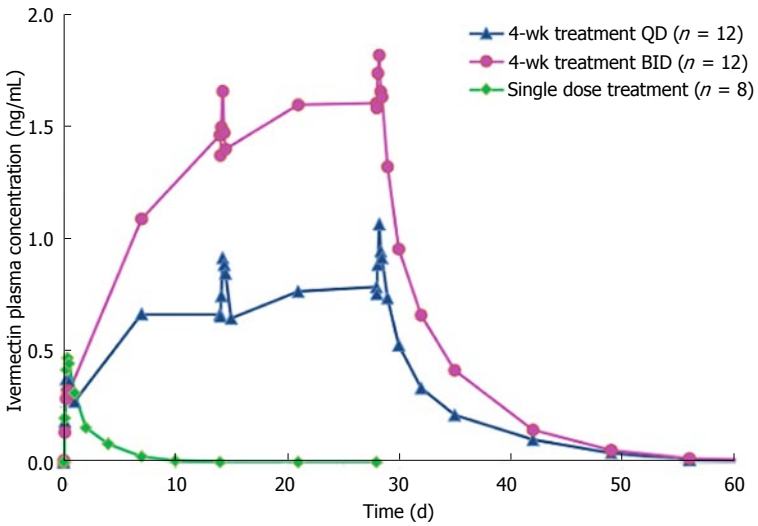

Figure 1 Plasma concentration-time curves after application of ivermectin 1% cream in healthy volunteers (means). QD: Once a day; BID: Twice a day.

Table 2 Pharmacokinetic parameters obtained after topical applications of ivermectin 1% cream in healthy volunteer subjects

Group	Time Point	C_{max} (ng/mL)	T_{max} (h)	$AUC_{0\text{-}12\ h}$ (ng × h/mL)	$AUC_{0\text{-}24\ h}$ (ng × h/mL)
1: Single dose	NA	0.49 ± 0.15	9 ± 3	3.8 ± 1.4	8.3 ± 2.5
2: QD 4 wk	Day 0	0.41 ± 0.17	10 ± 5	3.1 ± 1.5	6.9 ± 2.9
treatment	Day 14	0.93 ± 0.35	NA	9.8 ± 3.4	19 ± 7
	Day 28	1.08 ± 0.43	NA	11 ± 5	21 ± 8
3: BID 4 wk	Day 0	0.34 ± 0.16	11 ± 2	2.6 ± 1.5	NA
treatment	Day 14	1.70 ± 0.66	NA	18 ± 6	NA
	Day 28	1.90 ± 0.76	NA	20 ± 9	38 ± 17

NA: Not applicable; $AUC_{0\text{-}12\ h}$: Area under the plasma concentration-time curve from pre-application (T0) through to 12 h; $AUC_{0\text{-}24\ h}$: Area under the plasma concentration-time curve from pre-application (T0) through to 24 h.

comparison of PK parameters (AUC and C_{max}) calculated at d 14 and 28 have shown that there were no statistical differences in both dosage regimen groups, evidencing that the steady-state was already reached at day 14 (Table 2 and Figure 1).

After twice daily repeated topical applications of ivermectin 1% cream, the systemic exposure parameters (C_{max} and $AUC_{0\text{-}24\ h}$) were 1.8-fold higher than parameters calculated for the once daily dosage regimen, suggesting a dose proportionality trend with the applied dose (Table 2). In addition, no gender effect on PK parameters was observed in this study (data not shown). After the last topical application, ivermectin was slowly eliminated with a mean half-life of 87 h (range 28 to 180 h) and 97 h (range 55 to 163 h) for the QD and the BID groups respectively.

Maximal use PK study in subjects with PPR

From the 17 subjects enrolled, 2 discontinued the study prematurely, and 15 subjects completed the study. The mean age of all 17 subjects was 54 ± 12 years, and the majority of subjects were females (64.7%). All subjects presented a severe PPR with an IGA score of 4 and mean facial lesion count of 40.5 ± 14.3 (Table 1).

After 1 single topical application of ivermectin 1% cream, quantifiable ivermectin levels (> 0.05 ng/mL) were detected in the plasma of all subjects (Figure 2). Maximum plasma concentrations of ivermectin were observed within 9 h post dose with a mean C_{max} of 0.69 ± 0.49 ng/mL and then slowly decreased thereafter to 0.37 ± 0.21 ng/mL, 24 h post dose (C_{min}) (Table 3). After repeated topical application, ivermectin maximum concentration reached a plateau with a C_{max} of 2.10 ± 1.04 ng/mL and 1.74 ± 0.77 ng/mL at day 14 and 28 (Figure 2). In addition, residual concentrations (C_{min}) were also stable from day 7 to day 28 ranging from 1.17 ± 0.88 ng/mL to 1.36 ± 0.63 ng/mL.

Table 3 Pharmacokinetic parameters of ivermectin obtained after topical application of ivermectin 1% cream once a day in subjects with papulopustular rosacea (maximal use pharmacokinetic study)

Parameters Mean ± SD	Day 0[1]	Day 7[2]	Day 14	Day 21	Day 28
Pre-dose/C_{min} (ng/mL)	0.37 ± 0.21	1.17 ± 0.88	1.26 ± 0.53[3]	1.36 ± 0.66[3]	1.36 ± 0.63
C_{max} (ng/mL)	0.69 ± 0.49	NA	2.10 ± 1.04	NA	1.74 ± 0.77
T_{max} (h)	9 ± 6	NA	10 ± 8	NA	11 ± 4
$AUC_{0\text{-}24\ h}$ (ng × h/mL)	9.3 ± 5.4	NA	36 ± 16	NA	35 ± 14

NA: Not applicable; Pre-dose/C_{min}: Residual drug concentration (pre-dose level); $AUC_{0\text{-}24\ h}$: Area under the plasma concentration-time curve from pre-application (T0) through to 24 h; [1]*N*: 17; [2]*N*: 13; [3]*N*: 14.

Overall, all assessed systemic exposure PK parameters (C_{min}, C_{max} and $AUC_{0\text{-}24\ h}$) were stable through the treatment duration (Table 3). Indeed, after repeated topical applications of ivermectin 1% cream in subjects with severe PPR, exposure to ivermectin was similar at day 14 ($AUC_{0\text{-}24\ h}$ of 36 ± 16 ngh/mL) and at day 28 ($AUC_{0\text{-}24\ h}$ of 35 ± 14 ngh/mL), indicating that steady-state conditions were reached by 2 wk of treatment. Furthermore, the statistical analysis demonstrated that steady state conditions were achieved after 2 wk of treatment, as evidenced by the

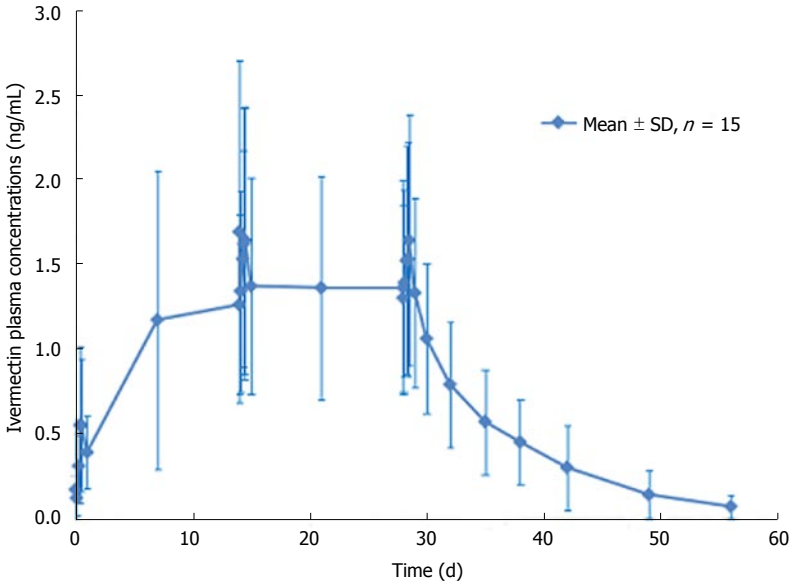

Figure 2 Plasma concentration-time curves after application of ivermectin 1% cream once a day in subject with severe papulopustular rosacea.

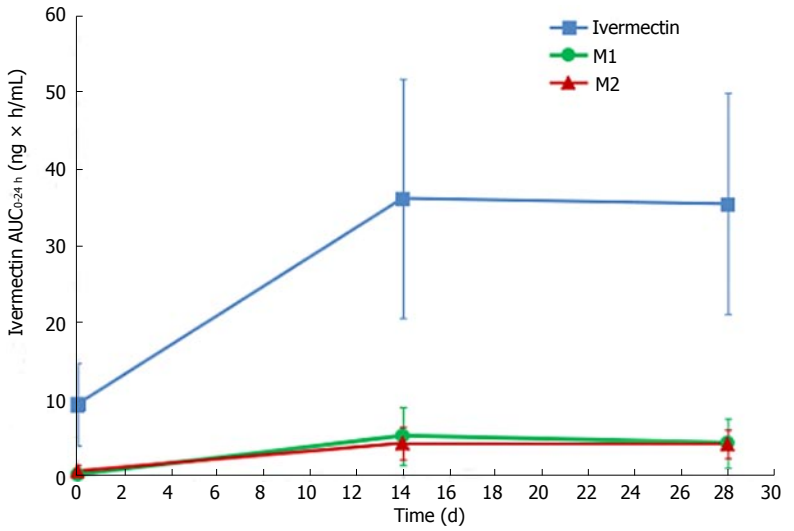

Figure 3 Mean $AUC_{0\text{-}24\ h}$ of ivermectin and its circulating major metabolites versus study days in subject with severe papulopustular rosacea. $AUC_{0\text{-}24\ h}$: Area under the plasma concentration-time curve from pre-application (T0) through to 24 h.

geometric mean ratio of $AUC_{0\text{-}24\ h}$ of day 28-14 (0.99, 90%CI: 0.82-1.18).

At the end of the 28 d application period, ivermectin was slowly cleared from the plasma (Figure 2). The mean value for the apparent terminal half-life was 145 h (range 92 to 238 h).

Ivermectin metabolites investigation has shown that 2 circulating metabolites represented more than 10% of parent drug systemic exposure at steady state. According to FDA guidance on safety testing of drug metabolites, these 2 metabolites are considered as major[18]. These 2 metabolites were identified as a 3" O-demethyl ivermectin (M1) and 4a hydroxy ivermectin (M2). The systemic exposures of M1 at day 14 ($AUC_{0\text{-}24\ h}$ of 5.2 ± 3.8 ng × h/mL) and at day 28 ($AUC_{0\text{-}24\ h}$ of 4.3 ± 3.2 ng × h/mL) were similar, indicating that steady state was already reached by day 14. The same tendency was observed with M2, which had similar systemic exposures at day 14 ($AUC_{0\text{-}24\ h}$ of 4.2 ± 2.1 ng × h/mL) and day 28 ($AUC_{0\text{-}24\ h}$ of 4.1 ± 1.8 ng × h/mL) (Figure 3). At the end of the 28 d application period, the metabolites were slowly cleared from the plasma, with the last quantifiable concentration being observed 4 to 8 d after the last application.

Long term use studies

Blood samples for the assessment of ivermectin levels were collected in 197 subjects in the 2 phase 3 studies (Study #1 and Study #2). Ivermectin concentrations were stable through the 1-year treatment duration with concentrations means ranging from 0.3-0.5 ng/mL (Table 4 and Figure 4). Four weeks after the last treatment application (at week 56), ivermectin plasma concentration had decreased to mean concentrations of 0.07 and 0.1 ng/mL in Study #1 and #2, respectively (Figure 4). In addition, only 26% of subjects still had quantifiable low levels of ivermectin 4 wk after the last application, ranging from 0.05-0.89 ng/mL.

Overall, ivermectin 1% cream was safe and well tolerated after repeated topical treatment in both healthy volunteers and PPR subjects after 4 wk or 1 year treatment periods. With regards to ivermectin

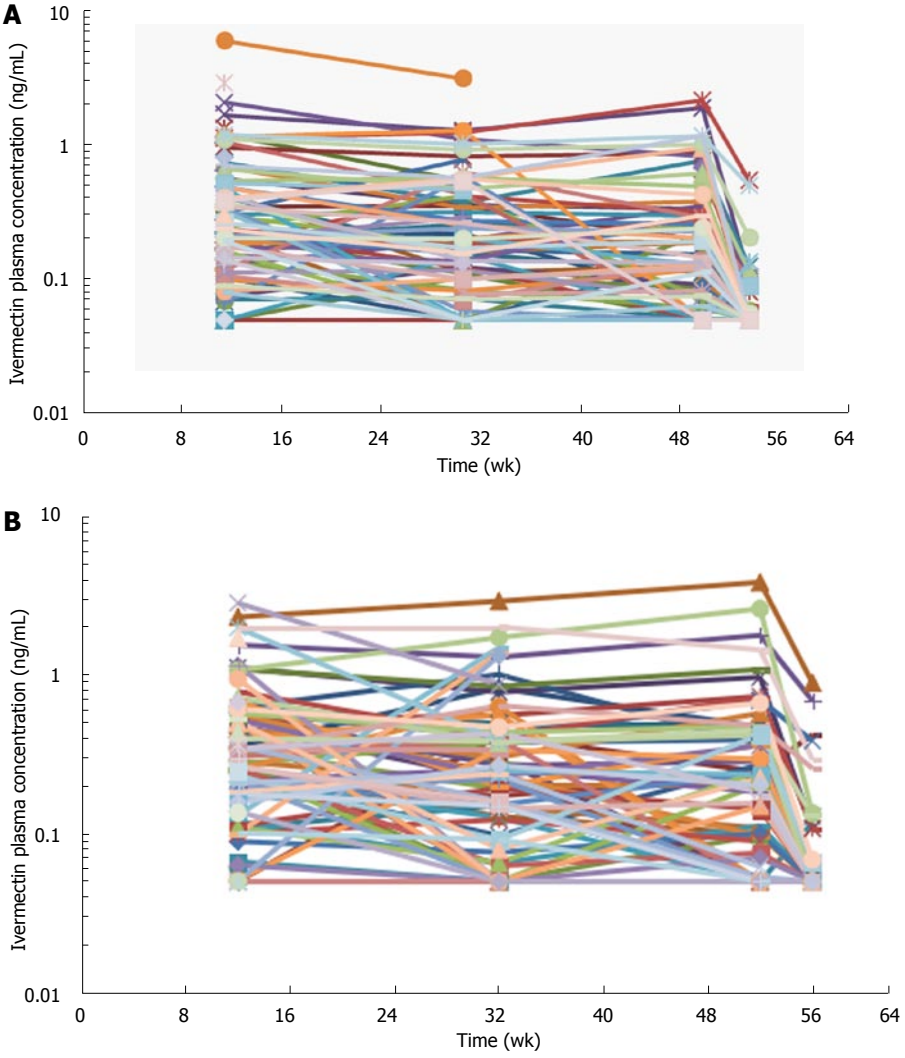

Figure 4 Individual ivermectin plasma profiles in a semi-logarithmic scale. (A: Study #1; B: Study #2) in subject with severe papulopustular rosacea.

Table 4 Ivermectin plasma concentrations (ng/mL) obtained after repeated topical applications of ivermectin 1% cream QD in subjects with papulopustular rosacea (maximal use pharmacokinetic trial and phase 3 studies #1, #2)

Treatment duration	Maximal use PK study[1]	Study #1[2]	Study #2[3]
Week 2	1.3 ± 0.5 (0.6 to 2.3)	NA	NA
Week 4	1.4 ± 0.6 (0.5 to 3.0)	NA	NA
Week 12	NA	0.5 ± 0.7 (< 0.05 to 6.0)	0.4 ± 0.5 (< 0.05 to 2.8)
Week 32	NA	0.4 ± 0.4 (< 0.05 to 3.1)	0.4 ± 0.5 (< 0.05 to 2.9)
Week 52	NA	0.3 ± 0.4 (< 0.05 to 2.2)	0.4 ± 0.6 (< 0.05 to 3.80)

PK: Pharmacokinetic; NA: Not applicable; [1]*N*: 14 (week 2), *n* = 15 (week 4); [2]*N* = 105 (week 12), *n* = 77 (week 32), *n* = 73 (week 52); [3]*N*= 92 (week 12), *n* = 84 (week 32), *n* = 65 (week 52); Note: Data represent Mean ± SD, and minimum to maximum, as available. BLQ data were imputed to the LOQ of 0.05 ng/mL for the maximal use PK study C_{min} concentration is displayed. For Study #1 and #2 blood samples were taken approximately 12 h after drug application.

exposure, systemic levels were low and stable through the 1-year treatment duration without any further accumulation.

DISCUSSION

The pharmacokinetics investigation of ivermectin 1% cream was conducted on both healthy volunteers and subjects with moderate to severe rosacea (PPR). In addition, to assess ivermectin systemic levels under chronic use conditions, blood samples were collected during a treatment period up to 1 year. The PK studies conducted in healthy volunteers and PPR subjects showed that after the first topical administration ivermectin was not completely eliminated at the time of the second application (24 h after the first dose when considering a once daily dosage regimen). Subsequently, ivermectin plasma concentrations were higher during the second dosing interval. However, after repeated topical application, plasma concentrations of ivermectin increased progressively until reaching a plateau after 2 wk (*i.e.*, steady state conditions)

(Figures 1 and 2). After repeated topical applications of ivermectin 1% cream in healthy subjects, the PK behavior of ivermectin could be accurately predicted from single dose data, confirming that the PK profile of ivermectin was not affected by the repeated topical applications (time stationarity). Moreover, systemic exposure in healthy volunteers increased proportionally to the daily dose of ivermectin (dose proportionality) (Figure 1 and Table 2).

The PK study in PPR subjects was conducted under maximal use conditions to ensure the assessment of the maximal exposure. Then, the maximum body surface area involved in the pathology (whole face) and the maximum therapeutic dose (1 g) were used. In addition, subjects with PPR presented the upper level of severity (at least 25 lesions and IGA score of 4 in all subjects). Overall, ivermectin systemic exposure levels obtained in PPR subjects under maximized conditions were much lower than those observed after oral administration. The mean C_{max} in PPR subjects treated under maximal use conditions was 1.74 ± 0.77 ng/mL after 4 wk treatment, while the means C_{max} after 12 mg oral dose were from 23.5 to 50 ng/mL[10]. Overall, these data evidenced the limited ivermectin transdermal absorption.

The repeated topical applications of ivermectin 1% cream in this study resulted in similar exposure after 2 or 4 wk of treatment ($AUC_{0\text{-}24\ h}$ of 36 ± 16 ng × h/mL at week 2 and $AUC_{0\text{-}24\ h}$ of 35 ± 14 ng × h/mL at week 4), confirming that steady state was reached by 2 wk as was observed in healthy volunteers. In addition, at steady state levels, 2 metabolites, 3''O-demethyl ivermectin and 4a hydroxy ivermectin, were considered as "major" because their systemic exposures were greater than 10% of ivermectin systemic exposure (parent compound)[18]. These 2 metabolites were previously characterized consecutive to oral administration of ivermectin[15]. In addition, these 2 metabolites were present in the same ratios (metabolite/parent) after oral ivermectin administration (data not shown).

With regard to impact of disease severity on ivermectin systemic exposure, no trend of correlation was observed between the number of inflammatory lesions and systemic ivermectin levels. From the maximal use PK study, the patient presenting the highest level of severity (subject with 88 inflammatory lesions) had a lower systemic level of ivermectin (C_{max} of 1 ng/mL and an $AUC_{0\text{-}24\ h}$ of 23 ng × h/mL) than the most exposed subject who had 35 inflammatory lesions at baseline (C_{max} of 4 ng/mL and an $AUC_{0\text{-}24\ h}$ of 75 ng × h/mL). In addition, the time to reach the peak of exposure (T_{max}) and the time to reach the steady state conditions were similar between healthy volunteers and subjects with PPR. However, ivermectin systemic exposure levels in PPR subjects were slightly higher than those observed in healthy volunteers (1.6-fold higher). Nevertheless, considering the high variability and the limited number of subjects, no firm conclusions could be drawn on the impact of rosacea skin on ivermectin transdermal penetration.

At the end of the 4 wk treatment period, ivermectin was slowly cleared from the plasma in both healthy subjects and subjects with severe PPR. Under maximal use conditions, the half-life ($t_{½}$) of ivermectin was approximately 6 d (range: 92-238 h), and the last quantifiable concentration was observed approximately 24 d after ivermectin application. This prolonged apparent half-life indicates that ivermectin was slowly cleared from plasma after the last treatment application. This terminal half-life is more prolonged than the one published for an oral administration of ivermectin oral tablets (15 to 20 h)[9]. This increase in terminal half-life observed by topical route suggests that absorption is the limiting step for ivermectin elimination. The term flip flop is used to describe this phenomenon[19]. Therefore, ivermectin elimination is limited by its slow absorption process through the skin (absorption dependent elimination): After the last application, ivermectin is slowly cleared from plasma, the low absorption phase becoming the limiting factor for its elimination. However, to confirm that no accumulation of ivermectin occurred in deeper body compartments and to confirm that steady state conditions are achieved, plasma samples were collected over longer treatment duration (up to 52 wk) in subjects with moderate to severe PPR. Overall, the ivermectin mean plasma concentrations measured at weeks 12, 32, and 52 were similar (Table 4 and Figure 4), supporting the assumption that steady state was achieved after 2 wk of treatment with no further accumulation.

Repeated topical application of ivermectin 1% cream resulted in lower systemic exposure levels in comparison to those observed after ivermectin oral administration, evidencing the limited ivermectin transdermal absorption. In addition, the steady state conditions were achieved by 2 wk of treatment and no accumulation occurred under chronic treatment as evidenced in long term use clinical studies for up to 1-year treatment. The pharmacokinetic behavior of ivermectin applied topically (prolonged plasma half-life) is consistent with a slow release of ivermectin from the skin rather than an accumulation in a deeper body compartment.

COMMENTS

Background

Pharmacokinetics investigations of topical drugs are of a high interest during drug development. The characterization of the transcutaneous penetration helps to assess the pathology effect of drug systemic exposure; and therefore, define accurately safety margins and the potential for drug-drug interactions.

Research frontiers

For a long time due to the limited sensitivity of analytical methods, the pharmacokinetics behaviors of dermatological drugs were not investigated thoroughly. Therefore, limited information on drug safety was available. However, recent technological innovations in the bioanalytical field now allow the accurate quantification of very low levels of circulating compounds. Then, pharmacokinetics of topical drugs and their metabolites became feasible.

Innovations and breakthroughs

This article describes the comprehensive assessment of the ivermectin's pharmacokinetics, a topical drug, recently approved for the treatment of papulo-pustular rosacea. This assessment includes metabolites investigation and the determination of the drug exposure in chronic use up to 1 year.

Applications

Pharmacokinetics results presented in this article will provide prescribers with valuable information about the systemic safety of this new treatment.

Terminology

Pharmacokinetics is the study of the drug absorption, distribution, metabolism and elimination. These information are useful to establish treatment conditions and bring important knowledge on the drug safety.

Peer-review

This is an interesting and well written article regarding the pharmacokinetics of 1% Ivermectin cream.

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