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Room 903, Building D, Ocean International Center, No. 62 Dongsihuan Zhonglu, Chaoyang District, Beijing 100025, China
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EDITORIAL

Steroid ulcers: Any news?

Mario Guslandi

Mario Guslandi, Gastroenterology Unit, S.Raffaele Hospital, Milan 20132, Italy
Author contributions: Guslandi M solely contributed to this paper.
Correspondence to: Mario Guslandi, MD, FACG, Professor, Gastroenterology Unit, S.Raffaele Hospital, Via Olgettina 60, Milan 20132, Italy. guslandi.mario@hsr.it
Telephone: +39-2-26432809 Fax: +39-2-26433491
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Abstract

Steroid ulcers, although a common feature in experimental studies, seldom develop in clinical practice, as observed by the meta-analyses carried out in the 90s. Corticosteroids alone become ulcerogenic only if treatment lasts longer than one month and the total administered dose exceeds 1000 mg. On the other hand concomitant intake of non-steroidal anti-inflammatory drugs results in a synergistic, highly damaging effect on the gastroduodenal mucosa. Thus, despite the survival of the steroid ulcer myth in the medical culture, pharmacological protection against steroid-induced peptic ulcers is a rare necessity while the best prophylactic strategy still remains to be determined.

Key words: Cortcosteroids; Peptic ulcer; Proton pump inhibitors

Core tip: Although the myth of steroid ulcers still survives among general practitioners, the incidence of ulcers in patients receiving corticosteroids is so low that concomitant gastric protection is not necessary except in patients on long-term, high-dose steroids or taking concomitant non-steroid anti-inflammatory drugs.

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STEROID ULCERS

The ability of corticosteroids to promote the development of peptic ulcers is an old concept, mainly based on the evidence provided by experimental and pharmacological studies, still widely accepted by clinicians.

A recent survey carried out in the Czech Republic has shown that 82% of physicians believe that cortisone is ulcerogenic[1].

From an experimental point of view, this has been clearly established and corticosteroids are known to inhibit the biosynthesis of gastric cytoprotective prostaglandins, while suppressing as well the production of gastric damaging leukotrienes.

In animal studies both gastric mucus production and gastric bicarbonate secretion are impaired by steroid administration, which results in a weakening of gastric mucosal defences[2]. In addition steroids impair both angiogenesis and epithelial repair mechanisms in experimental ulcers[3-5].

However, for reasons not quite clear, the real incidence of steroid-induced ulcers in the clinical setting is much lower than what could be expected on the basis of the experimental data.

In the past three different meta-analyses have been performed[6-8], the most recent and larger dating back to 1994[8] clearly indicates that steroid-treated patients have a relative risk for gastric and duodenal ulcers not significantly different from untreated controls. Unfortunately the quality of the clinical studies employed to perform the analyses was rather poor (no double blind conditions, no information about concomitant medications , no distinction between gastric and duodenal ulcers), which did not allow firm, definitive conclusions.

Thus, in spite of the "definitive" review articles ap-

peared on the subject[2,8] the myth of steroid ulcers still survives, also because, during the last twenty years or so, neither additional, perspective clinical studies nor other meta-analyses have been carried out. Admittedly, due to the low incidence of steroid ulcers in the clinical setting, it would be hard to conduct studies in this area unless an extremely large number of patients are recruited. This has not be done and most likely won't ever be done due to the lack of both sufficient interest by the scientific community and commercial motivation by the drug industry.

All in all, it would seem that corticosteroids rather than directly cause ulcers can, in keeping with experimental studies[3-5], hamper the healing process of ulcers caused by other agents, namely anti-inflammatory drugs (NSAIDs)[2,9].

Epidemiological studies have proved that NSAIDs are significantly more ulcerogenic than steroids but that the association of the two types of drugs has a truly synergic and lethal effect, increasing of 3 to 6 times the relative risk[10,11]. Yet corticosteroids themselves can become ulcerogenic if treatment lasts for more than one month, with a total intake higher than 1000 mg of prednisolone[6]. Elderly people (aged more than 65 years) seem to be more exposed to the risk of developing peptic ulcers.

A recent retrospective study examining the risk of gastrointestinal bleeding with low-dose aspirin alone and in combination with other drugs, has shown that the risk is increased when a high dose (but not low/medium dose) of corticosteroids is co-administered[12].

Pharmacological prevention of steroid ulcers in clinical practice does not seem, therefore, justified in the large majority of patients under corticosteroid treatment. Subjects undertaking a high-dose long-term steroid administration would deserve concomitant pharmacological "protection", but evidence-based information about the best therapeutic measures is wanting.

Proton pump inibitors (PPI) are often prescribed but no controlled studies in this area are available.

Indirect evidence, obtained by analyzing sub-populations in NSAID-treated patients suggests that the prostaglandin derivative misoprostol might be effective in counteracting the possible gastric toxicity of cortisone[13]. However this hypothesis, although consistent with the results of experimental studies on the effects of steroids on ulcer repair[3] remains largely unproven.

The results of the recent above mentioned survey[1] show that about 60% of gastroenterologists, compared with only 30% of the other physicians, refrain from prescribing any concomitant "gastroprotective" medication when low doses of steroids are employed. By contrast, when higher doses (*i.e.*, 1 mg/kg prednisone) are prescribed, more than 70% of gastroenterologists and about 90% of the other physicians also carry out empirical pharmacological prevention with PPI.

In conclusion, the body of knowledge on the possible ulcerogenic effects of steroid treatment in humans has grown very little in the last years. The more recent clinical studies (and subsequent meta-analyses) available in the scientific literature date back to the 90s and the experimental studies performed in the last two decades have added precious little to what was already known in the past.

Due to the apparent lack of interest by clinical researchers, the myth of steroid ulcers, although based on a very weak and disputable clinical evidence, still survives. In daily practice development of peptic ulcers in steroid-treated patients remains a very infrequent event, for which pharmacological protection is seldom required and the most effective drug prevention is still undetermined.

REFERENCES

1 **Martínek J**, Hlavova K, Zavada F, Seifert B, Rejchrt S, Urban O, Zavoral M. "A surviving myth"--corticosteroids are still considered ulcerogenic by a majority of physicians. *Scand J Gastroenterol* 2010; **45**: 1156-1161 [PMID: 20569095 DOI: 10.3109/00365521.2010.497935]

2 **Guslandi M**, Tittobello A. Steroid ulcers: a myth revisited. *BMJ* 1992; **304**: 655-656 [PMID: 1571634 DOI: 10.1136/bmj.304.6828.655-a]

3 **Carpani de Kaski M**, Rentsch R, Levi S, Hodgson HJ. Corticosteroids reduce regenerative repair of epithelium in experimental gastric ulcers. *Gut* 1995; **37**: 613-616 [PMID: 8549934 DOI: 10.1136/gut.37.5.613]

4 **Luo JC**, Shin VY, Liu ES, So WH, Ye YN, Chang FY, Cho CH. Non-ulcerogenic dose of dexamethasone delays gastric ulcer healing in rats. *J Pharmacol Exp Ther* 2003; **307**: 692-698 [PMID: 12966148 DOI: 10.1124/jpet.103.055202]

5 **Luo JC**, Shin VY, Liu ES, Ye YN, Wu WK, So WH, Chang FY, Cho CH. Dexamethasone delays ulcer healing by inhibition of angiogenesis in rat stomachs. *Eur J Pharmacol* 2004; **485**: 275-281 [PMID: 14757151 DOI: 10.1124/jpet.106.113035]

6 **Conn HO,** Blitzer BL. Nonassociation of adrenocorticosteroid therapy and peptic ulcer. *N Engl J Med* 1976; **294**: 473-479 [PMID: 173997 DOI: 10.1056/NEJM197602262940905]

7 **Messer J**, Reitman D, Sacks HS, Smith H, Chalmers TC. Association of adrenocorticosteroid therapy and peptic-ulcer disease. *N Engl J Med* 1983; **309**: 21-24 [PMID: 6343871]

8 **Conn HO**, Poynard T. Corticosteroids and peptic ulcer: meta-analysis of adverse events during steroid therapy. *J Intern Med* 1994; **236**: 619-632 [PMID: 7989897]

9 **Spiro HM**. Is the steroid ulcer a myth? *N Engl J Med* 1983; **309**: 45-47 [PMID: 6134237 DOI: 10.1056/NEJM198307073090110]

10 **Piper JM**, Ray WA, Daugherty JR, Griffin MR. Corticosteroid use and peptic ulcer disease: role of nonsteroidal anti-inflammatory drugs. *Ann Intern Med* 1991; **114**: 735-740 [PMID: 2012355]

11 **Aalykke C**, Lauritsen K. Epidemiology of NSAID-related gastroduodenal mucosal injury. *Best Pract Res Clin Gastroenterol* 2001; **15**: 705-722 [PMID: 11566036 DOI: 10.1053/bega.2001.0230]

12 **García Rodríguez LA**, Lin KJ, Hernández-Díaz S, Johansson S. Risk of upper gastrointestinal bleeding with low-dose acetylsalicylic acid alone and in combination with clopidogrel and other medications. *Circulation* 2011; **123**: 1108-1115 [PMID: 21357821 DOI: 10.1161/CIRCULATIONAHA.110.973008]

13 **Silverstein FE,** Graham DY, Senior JR, Davies HW, Struthers BJ, Bittman RM, Geis GS. Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1995; **123**: 241-249 [PMID: 7611589]

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EDITORIAL

Inflammatory bowel disease: An archetype disorder of outer environment sensor systems

Giovanni C Actis, Floriano Rosina

Giovanni C Actis, Floriano Rosina, Division of Gastro-Hepatology, Ospedale Gradenigo, 10153 Torino, Italy
Author contributions: Actis GC designed the study and drafted the paper; Rosina F chose and checked the references, and critically reviewed the final version to give his final approval.
Correspondence to: Giovanni C Actis, MD, Division of Gastro-Hepatology, Ospedale Gradenigo, Corso Regina 10, 10153 Torino, Italy. actis_g@libero.it
Telephone: +39-11- 8151250 Fax: +39-11- 8151388
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Abstract

The pathogenesis of the two inflammatory bowel disease (IBD) phenotypes ulcerative colitis (UC) and Crohn's disease (CD) has remained elusive, thus frustrating attempts at defining a cure. IBD often presents as a complex inflammatory process wherein colon lesions (UC) or widespread ulceration and fissure (CD) might be accompanied by ancillary extra-intestinal manifestations involving the eye, skin, joints or liver, but also by full-blown "autoimmune" disorders from psoriasis and multiple sclerosis to rheumatoid arthritis; attempts at unraveling a link or a hierarchical order in these entities have proven almost fruitless. More recently, the input of genetics has suggested that the IBDs might be multi-organ inflammatory processes, elicited by a large number of low-penetrance susceptibility genes, with environmental factors needed to induce full-blown disease. At a noteworthy exception to this rule, the description of the nucleotide-oligomerization domain (*NOD*) gene mutations in CD came at the beginning of the 2000s: the NOD-LRR are part of a highly conserved microbial sensor system which respond to bacterial peptidoglycans by mounting an inflammatory response. At least in Caucasian patients, the prevalently loss-of-function mutation of NOD permitted to unexpectedly define CD as an immune deficiency state, and upon its recent description in apparently unrelated disorders such as the Blau syndrome (a granulomatous pediatric syndrome), and perhaps in psoriasis and chronic obstructive pulmonary disorders, has contributed to revolutionize our view of IBD and CD in particular. The latter affection, together with psoriasis and chronic pulmonary disease can now be included into a newly identified category named "barrier organ disease", wherein a barrier organ is defined as a large mucosal or epithelial surface with an abundant metagenomic microbial population and an underneath reactive tissue, the whole structure being in contact with the outer environment and capable to react to it. Personalized treatments and empowerment of research across different disease phenotypes should be the advantages of this novel mindset.

Key words: Inflammatory bowel disease; Psoriasis; Chronic pulmonary disease; Innate immunity; Nucleotide oligomerization domains

Core tip: With its extended mucosal surface in contact with the environment, an overly reactive lymphoid tissue underneath, and an extraordinarily abundant metagenomic flora, the gut is in the position to play a central role in the pathogenesis of both its core disorders (inflammatory bowel disease) and remote autoinflammatory or immunopathic diseases. The IBDs have been listed as a "barrier organ dysfunction". We hereby focus on psoriasis, a barrier organ dysfunction which is often co-morbid with IBD, sharing with it microbial receptor genetic polymorphisms, and response to therapy. This comprehensive mindset shall boost science and drive our medical choices for immunoinflammatory pathology.

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INTRODUCTION

Perturbation of the intestinal homeostasis might be derived from any cause of breach of the active[1] and passive[2] barrier defense mechanisms of the lining epithelial cells, allowing contact of gut luminal contents with the overly reactive lymphoid tissue underneath. Despite the accumulating results of years of research in the field, the tenet of the need for a "sealed" epithelium as a primary means to restrain undue gut mucosal inflammation is still informing most of the currently active research. Basically, a perturbed mucosal permeability is thought to represent one of the shared features of the two officially recognized phenotypes of the inflammatory bowel diseases (IBDs), Crohn's disease (CD) and Ulcerative colitis (UC)[3], even though significant elements of difference between the two phenotypes are emerging from modern investigation, as discussed below.

Indeed, currently available evidence seems to best be interpreted by seeing the IBDs not as a dichotomy, but rather as a collection of discrete entities that, though sharing several similarities, do appear distinct enough as to call for a conceptual process of "splitting" over one of "lumping up". The conception of a genotype-serotype-phenotype axis might serve as the spine for such a way of thinking, as illustrated in a few examples that have recently been mastered in an authoritative review[4]. Polymorphisms of the nucleotide-oligomerization domain 2/caspase activation recruitment domain 15 secondary to mutation of their coding loci (*NOD2/CARD15*) (see below) would preferentially be expressed in ileal CD[5]; the *HLADRB1*0103* allele has been found to correlate with the severity of extra-intestinal disease in UC[6]; a whole range of anti-glycan antibodies including the widely used anti-saccharomyces cerevisiae antibody (ASCA) have been correlated with different CD behaviors in widespread geographical areas[7]; finally, racial factors conditioning for example the onset of peri-anal forms of CD have been described[8]. In the lines to follow, this non-exhaustive list shall be implemented by our own attempt to introduce a concept of the IBDs as centrally conditioned syndromes, insofar as being often diagnosed as co-morbidities of variegated bone marrow anomalies, often affecting the innate arm of the immune response. We shall further discuss that this "splitting drift", now somewhat prevailing in IBD nosography, can by contrast be mitigated by the breakthrough observation that the IBDs may be intertwined not only between themselves but also with other (apparently unrelated) disorders of remote systems (skin and respiratory organs) insofar as the gut, skin, and lungs are all lining territories between the outer and the inner environments (barrier organ diseases) (please see text below). We shall conclude by presenting evidence that this is not merely an academic exercise, but it can influence medical policies, and our decision making at patient's bedside.

AN UPDATED REAPPRAISAL OF THE PATHOPHYSIOLOGY OF IBD: CD

For several years, at the end of the last century, CD has been thought of as being derived from an unbalanced secretion of the pro-inflammatory cytokines tumor necrosis factor-α (TNF-α) and interferon (IFN)-γ, hence a Th-1 mediated disorder[9]. However, clinical and genetic data accrued early following 2000, have contributed to place the emphasis on phenomena of defective innate immunity, originating the novel concept of CD as an immune deficiency state. Central to this hypothesis were the observations of defective neutrophil accumulation in CD patients[10], with an impaired clearance of bacteria from tissues. The underlying problem appeared to be a defective macrophage which, though fully capable to form pro-inflammatory cytokines at the translational levels, erroneously trafficked them to premature lysosomal degradation[11]. Some 5 years before these clinical findings, a keystone genetic insight into the underlying innate immunity defects of CD had been released. Basically, some 40% of CD patients of a Western origin in both the European and American continents were found to carry at least one of three disease-associated variants (*L1007fsinsC*, *G908R*, *R702W*) of *CARD15*, consistently identified as a major susceptibility gene for CD in the caspase recruitment domain[12]. The intact *CARD15* encodes the NOD2 receptor, a member of a family of intracellular and host-specific cytosolic pattern-recognition receptors, containing a NOD and a leucine-rich repeat. Through this sequence, NOD2/CARD15 recognizes muramyl-dipeptide (MDP) a component of bacterial cell wall. The ensuing signal transduction cascade then culminates in the serine phosphorylation of the cytoplasmic inhibitor IκB (which then becomes ubiquitinated and tagged for proteosomal degradation) with following release and activation of NF-κB (previously inactive as sequestered in the cytoplasmic dimer). Translocated to the nucleus, NF-κB essentially de-represses the synthesis of several pro-inflammatory cytokines. CD-specific mutations of the *CARD* gene family hampers initial NOD-mediated recognition of MDPs, blunting the beginning of the response cascade[13]. Whether such genetic faults in fact lead to loss or gain of function has long been debated, with any interpretation being conditioned by the need to account for the excess (not the diminution as would be expected) of inflammation found in CD patients. This question mark seems to be partly met by the hypothesis that TLR-2 driven inhibition of Th-1 responses seems to be lost in *CARD*-mutated CD patients[14]. *NOD2* genes are also highly expressed in Paneth cells, where their mutations would cause decreased expression of antimicrobial peptides, including alpha-defensins[15]. Not less importantly, the Familial Mediterranean Fever genes (*MEFV*) have been shown to co-localize with *NODs* on chromosome 16, sharing with the *NODs* the same protein superfamily that regulates

apoptosis, cytokine processing and inflammation[16]. This might warrant envisaging a kind of a continuum between CD and autoinflammatory syndromes, providing arguments for the discussion below[17]. The NODs have most recently been shown to act in synergy with cell autophagy systems, a highly conserved chain that normally effects disposal of cell debris and intracellular bacteria[18]. Wild-type NOD proteins have been shown to serve as nucleating factors for the initiation of bacteria-induced autophagy, by recruiting the *ATG16-L1* gene product to coalesce on cell membrane at the point of bacterial contact. Cell bactericidal activity may be hampered both by a polymorphic NOD becoming incapable to accrue the autophagy proteins, and by mutations of the ATG16-L1 products themselves[19].

AN UPDATED VIEW ON THE PATHOPHYSIOLOGY OF UC

The demonstration of a role of innate immunity or of any of the immune effector limbs has been less immediate in the case of UC, lending limited help to the unraveling of its pathogenesis. A recent review[20] of the cytokine profile of UC has come to list a vast array of cytokines spanning from TNF-α and interleukin (IL)-6 up to IL-33; the lymphocyte subsets Th5 and Th17 seem to be the prevalent functional targets of this cytokine plethora. Of note, a rather robust experimental evidence indicates that the UC epithelial lesions could be derived from the pore-forming effects of IL-13, a secretory product of NK-T cells; in coherence with this tenet, recent experimental evidence has shown that in biopsy specimens of pediatric patients with early UC, STAT6, a transduction element that responds to IL-13, is in a prevalently phosphorylated state[21]. An interpretation of UC as a disease of increased permeability could be derived from the complex of these premises. If there is no convincing evidence for a role of innate immunity, UC could be most easily interpreted as a T-mediated disorder, considering its preferential response to the T cell modulatory drug cyclosporine[22].

IBD AND SOME (IMMUNE) DISORDERS SHARE GENETIC POLYMORPHISMS: THE BASIS TO PERCEIVE IBD AS A SYSTEMIC "SYNDROME"

If defects of the innate immune response have convincingly been described in CD, they have also been shown to be under a bi-directional influence: CD-like pictures have been found to often accompany disorders of innate immunity, and, the specific immune abnormalities that are present in CD have been described in other unrelated disorders. The literature on such topics is rather exhaustive. Among the examples of the former instance, chronic granulomatous disease[23] and glycogen storage disease type-1b[24] have been mostly characterized. Both disorders share an impairment of the respiratory burst, preventing neutrophil-mediated killing of bacteria and fungi. The underlying biochemical fault is the absence/malfunction of the nicotinamide adenine dinucleotide phosphate-oxidase oxidase enzyme complex. In-depth clinical and pathologic characterization of a subset of CGD patients has notably highlighted that their gut disease meets all of the criteria to make it indistinguishable from "idiopathic" CD[25]. *CARD15* gene mutations have been found in some cases of early-onset sarcoidosis, and, more strikingly, have been found to be responsible for the Blau syndrome, characterized by a granulomatous inflammation expressing mainly as arthritis, uveitis, and skin rash; the role of such mutations in infectious disease has been more controversial, but an association in patients developing gastric lymphoma during *Helicobacter pylori* infection has been suspected[26]; perturbed neutrophils but not mutated *CARD15* have been associated with the clinical expression of tuberculosis.

APPROACHING THE CONCEPTS: IBD-ALIKES AND IBD-SYNDROMES

These premises may generate the concept of an IBD-like picture, or of IBD-look-alikes, namely those conditions that mimic IBD, yet are still to be distinguished from so-called "idiopathic" IBD. The modes of this distinction must be conceived as being subject to the power of our diagnostic means, to the parameters being used, whether clinical, biochemical, endoscopic, histologic, and finally genetic; at which of these escalating grounds we decide to limit our escalation, and how high the bar is set within each ground.

To gain more insight into the issue, we searched the PubMed database mainly using IBD-likes, IBD-look-alikes, and IBD mimics as key words; the references of the articles that were retrieved were further manually scanned. This search disclosed an initial paper published in 1984[27], enumerating and recommending the pathologic features to distinguish true IBDs from so-called "impostors". This report was followed in 2006[28] by a rather extensive discussion of the IBD-like pictures that may accompany diverticular disease, the so-called segmental colitis associated with diverticular disease (SCAD). The authors emphasized that the contents of the several relevant articles were heterogeneous, with some of them finding morphologic features indistinguishable from CD or UC in a high proportion of the cases, others finding only a minority of such "IBD-alikes", and others denouncing a plethora of non specific lesions. As it is evident from the above paragraphs, a considerable literature has accumulated on this topic, and we have now attempted to identify a few common mechanisms in the genesis of these IBD-like diseases, gathering them in clusters.

We aimed to identify three main cluster mechanisms that are likely to generate an IBD-like picture: errors (often of pediatric relevance) of either of the two arms of the immune response; involvement of the gut from acquired

hematologic disorders or vasculitides; polymorphism of specific genes involved in the immune response, leading, through variegated pathways though, to the final common inflammatory imbalance that marks an IBD. We like to draw particular attention to the role attributed to the polymorphisms of pyrin, a protein domain coded for by chromosome 16 that, together with the TIR and CARD domains, is assumed to belong to the gene superfamily (often ill-defined as CATERPILLER)[29] of innate immune detection of micro-organisms in mammals. It has been shown that carriers of some pyrin mutations may develop not only familial Mediterranean fever, but, notably, a UC-like disease that turns out to resist conventional treatment, whilst showing response to colchicines[30].

We believe that from the above presented arguments it stems clear that a plethora of pictures that fit the requirements to be labeled as IBD may be derived from a vast array of factors; to signify this, the Greek-rooted term "syndrome" should be used to progressively replace the term "disease" and the acronym IBD. This change should adequately reflect the tapering of the list of the so-called "idiopathic" IBDs that is likely to occur as our causative knowledge becomes progressively refined[31].

RE-POSITIONING IBD INTO A BROAD CATEGORY: THE BARRIER ORGAN DEFECTS

If *CARD* gene sequences turn out to be embedded into a highly conserved domain complex that govern the response of mammalian cells to micro-organisms (The TIR, CARD and PYRIN triad)[32], it seems justified to expect that the clinical expressions of their eventual polymorphisms (*e.g.*, CD) will best be interpreted if contextualized.

Barrier organs and systems

The skin, gastrointestinal tract, and the respiratory epithelia constitute the main components of the barrier systems in the human body. Their structure mainly comprises an epithelial surface or a mucosa extensively interfacing the polluted environment, a basement membrane which, together with a wide array of cell-junction devices, serves to upgrade the sealing state of the system, and, typically, a highly reactive lymphoid tissue underneath, composed of antigen-presenting cells, often classified as dendritic cells, and various lymphocyte subsets capable to react with release of pro-inflammatory cytokines mostly including IL-1, TNF-α and IL-17. The surface of the barrier systems further harbors a huge variety of microbial species, which, at least in the case of the gastrointestinal tract, outweighs the number of somatic cells: this second cell universe within the body is sometimes called "metagenoma"[33]. When working properly, for instance at the gut level, the sensor machinery that was labeled as CATERPILLER above, serves to maintain the balanced co-existence between the local immune system at the barrier organ and the bacterial flora (with genetically-based mutations leading to undue inflammation up to the CD phenotype as discussed at the beginning); on the other hand, in the case of a full-blown outer infection, the CATERPILLERS will be called on the battleground to restrain a pathogen that has perforated the epithelial seals.

Two main phenotypes of barrier organ disease correlated with IBD

Representing an extended surface between the body and the outer world, being endowed with an overly reactive immune tissue, and harboring a large microbe metagenome, the skin shows a number of commonalities with the gut archetype. The development of its main disorder, psoriasis, is thought to initiate with a genetic/environmental breach of the sealing epithelium, causing substance loss and psoriatic plaques; this ends up with activating keratinocytes and inducing dendritic cells to produce pro-inflammatory mediators, fueled by degraded RNAs and DNAs as debris of massive cell wreck; in the presence of favoring genetic prerequisites and external factors (stress) the process may easily become chronic with the typical waxing-and-waning course that recalls IBD. Several observations of clinical and genetic orders suggest a link between IBD and psoriasis. Psoriatic skin lesions seem to occur seven times more frequently in CD patients than controls[34]; ten percent of patients with CD had a first-degree relative with psoriasis[35]; both disorders do respond well to the T-lymphocyte inhibitor drug cyclosporine. On genetic grounds, a susceptibility area for psoriasis, named *PSORS8* has been identified, in proximity with the CATERPILLER domain, on chromosome 16q21[36].

The mucosae of the airways represent a second example of obvious analogy, in terms of contact with outer antigens, and functional anatomy of their reactive tissue. To this end, chronic obstructive pulmonary disease (COPD) has received most of the attention[37]. Available studies have shown that COPD patients might be at an increased risk of developing CD[38], whereas IBD patients are notoriously prone to exhibit respiratory manifestations[39]. At a partial contrast with the generally shared opinion that smoking plays a crucial role in causing COPD, clinics do advise concern over several inconsistencies: (1) COPD severity varies widely irrespective of the number of pack years of smoking; and (2) full-blown COPD is found to develop only in 10%-20% of smokers[40]. Such observations have advised some investigators to focus on genetic studies of COPD, and their efforts have not remained fruitless. Recently, a loss-of-function conformational mutation of NOD2 has been described in COPD patients[41]. In this paper, non-COPD smokers were appropriately used as controls, in order to exclude a role of smoking per se in the distribution of the NOD2 variant (Figure 1).

CONCLUSION AND CAVEATS

We are excited and interested by seeing that part of our conclusive thoughts might coincide with those of other

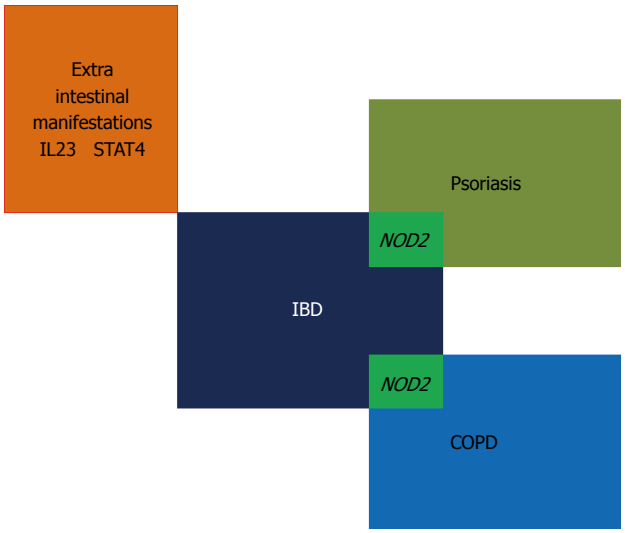

Figure 1 Morbid inflammatory bowel diseases galaxy. As barrier organ dysfunctions (see text) psoriasis and chronic obstructive pulmonary disease are supposed to overlap with inflammatory bowel disease (IBD) insofar as sharing mutations of nucleotide-oligomerization domain 2 (*NOD2*) genes; the so-called extra-intestinal manifestations of IBD might be mediated by interference with polymorphisms of the cytokine interleukin (IL)-23 or signal transduction systems 4 (STAT4); being not a topic in the present text, they are not further commented.

barrier disease researchers *e.g.*, psoriasis[36], in reckoning that intensifying attempts at modulating surface bacterial flora and unifying research on shared mediators of inflammation can be successful and cost-effective.

Conceiving IBD as a polyfactorial condition may make us more conducive to perceive the disorder hiding behind a given IBD-like picture; the possibly dramatic clinical counterpart of this changed mindset might be the identification of the patient's personalized treatment, or even the only causative treatment (as for example in the case of pseudo-UC incited by the mutated pyrin gene) that can save lives and financial resources.

Caveats

The above data and statements must still be interpreted with caution: it may still take a while before genetic profiling reaches its wide-scale clinical application; as of today, the described anomalies of innate immunity do more readily apply to CD than UC; CD is an extraordinarily heterogeneous affection, as shown for example by failure to detect *NOD* mutations in the disease subtypes that have been characterized in the Far East[42]. The latter observation has stimulated lively debate in the last several years. An interesting analysis of 2005[43] has hypothesized that in populations traditionally exposed to highly contaminated environments, defects of the innate immune response may confer a disadvantage and get selected out. However, progressive environment decontamination and use of "aseptic" industrial distribution food enriched in chemical additives yet virtually "sterile", may favor loosening of tolerance originating from continuous stimulation of sensors, thus allowing emergence of unchecked gut inflammation. Thus, one may cast the hypothesis that lifestyle rather than key genetic defects might drive the defective innate immune responses in Asians with IBD. With their accelerated pace of development, the Far East communities still represent a seminal area of interest and investigation, perhaps allowing to identify causative IBD factors and take preventive measures that in Western countries were not taken on time and got outdated.

REFERENCES

1 **Macpherson AJ**, Geuking MB, McCoy KD. Innate and adaptive immunity in host-microbiota mutualism. *Front Biosci* (Schol Ed) 2012; **4**: 685-698 [PMID: 22202085 DOI: 10.2741/s293]
2 **Gersemann M**, Wehkamp J, Stange EF. Innate immune dysfunction in inflammatory bowel disease. *J Intern Med* 2012; **271**: 421-428 [PMID: 22324936 DOI: 10.1111/j.1365-2796.2012.02515.x]
3 **Camilleri M**, Madsen K, Spiller R, Greenwood-Van Meerveld B, Verne GN. Intestinal barrier function in health and gastrointestinal disease. *Neurogastroenterol Motil* 2012; **24**: 503-512 [PMID: 22583600 DOI: 10.1111/j.1365-2982.2012.01921.x]
4 **Sachar DB**, Walfish A. Inflammatory bowel disease: one or two diseases? *Curr Gastroenterol Rep* 2013; **15**: 298 [PMID: 23250698 DOI: 10.1007/s11894-012-0298-9]
5 **Cuthbert AP**, Fisher SA, Mirza MM, King K, Hampe J, Croucher PJ, Mascheretti S, Sanderson J, Forbes A, Mansfield J, Schreiber S, Lewis CM, Mathew CG. The contribution of NOD2 gene mutations to the risk and site of disease in inflammatory bowel disease. *Gastroenterology* 2002; **122**: 867-874 [PMID: 11910337]
6 **Brophy S**, Pavy S, Lewis P, Taylor G, Bradbury L, Robertson D, Lovell C, Calin A. Inflammatory eye, skin, and bowel disease in spondyloarthritis: genetic, phenotypic, and environmental factors. *J Rheumatol* 2001; **28**: 2667-2673 [PMID: 11764216]
7 **Dotan I**. New serologic markers for inflammatory bowel disease diagnosis. *Dig Dis* 2010; **28**: 418-423 [PMID: 20926866 DOI: 10.1159/000320396]
8 **Hou JK**, El-Serag H, Thirumurthi S. Distribution and manifestations of inflammatory bowel disease in Asians, Hispanics, and African Americans: a systematic review. *Am J Gastroenterol* 2009; **104**: 2100-2109 [PMID: 19471256 DOI: 10.1038/ajg.2009.190]
9 **Brand S**. Crohn's disease: Th1, Th17 or both? The change of a paradigm: new immunological and genetic insights implicate Th17 cells in the pathogenesis of Crohn's disease. *Gut* 2009; **58**: 1152-1167 [PMID: 19592695 DOI: 10.1136/gut.2008.163667]
10 **Marks DJ**, Harbord MW, MacAllister R, Rahman FZ, Young J, Al-Lazikani B, Lees W, Novelli M, Bloom S, Segal AW. Defective acute inflammation in Crohn's disease: a clinical investigation. *Lancet* 2006; **367**: 668-678 [PMID: 16503465 DOI: 10.1016/S0140-6736(06)68265-2]
11 **Casanova JL**, Abel L. Revisiting Crohn's disease as a primary immunodeficiency of macrophages. *J Exp Med* 2009; **206**: 1839-1843 [PMID: 19687225 DOI: 10.1084/jem.20091683]
12 **Hugot JP**. CARD15/NOD2 mutations in Crohn's disease. *Ann N Y Acad Sci* 2006; **1072**: 9-18 [PMID: 17057186 DOI: 10.1196/annals.1326.011]
13 **Strober W**, Watanabe T. NOD2, an intracellular innate immune sensor involved in host defense and Crohn's disease. *Mucosal Immunol* 2011; **4**: 484-495 [PMID: 21750585 DOI: 10.1038/mi.2011.29]
14 **Zelinkova Z**, Stokkers P, Hommes DW. NOD2 in Crohn's disease--loss or gain of function mutations? *Neth J Med* 2005; **63**: 286-287 [PMID: 16186636]
15 **Koslowski MJ**, Beisner J, Stange EF, Wehkamp J. Innate antimicrobial host defense in small intestinal Crohn's disease. *Int J Med Microbiol* 2010; **300**: 34-40 [PMID: 19850516 DOI:

10.1016/j.ijmm.2009.08.011]
16 **Kuloğlu Z**, Kansu A, Ustündağ G, Birsin Özçakar Z, Ensari A, Ekim M. An infant with severe refractory Crohn's disease and homozygous MEFV mutation who dramatically responded to colchicine. *Rheumatol Int* 2012; **32**: 783-785 [PMID: 20049453 DOI: 10.1007/s00296-009-1326-4]
17 **McGonagle D**, Aziz A, Dickie LJ, McDermott MF. An integrated classification of pediatric inflammatory diseases, based on the concepts of autoinflammation and the immunological disease continuum. *Pediatr Res* 2009; **65**: 38R-45R [PMID: 19190531 DOI: 10.1203/PDR.0b013e31819dbd0a]
18 **Deretic V**. Autophagy: an emerging immunological paradigm. *J Immunol* 2012; **189**: 15-20 [PMID: 22723639 DOI: 10.4049/jimmunol.1102108]
19 **Nguyen HT**, Lapaquette P, Bringer MA, Darfeuille-Michaud A. Autophagy and Crohn's Disease. *J Innate Immun* 2013 Jan 15; Epub ahead of print [PMID: 23328432 DOI: 10.1159/000345129]
20 **Bamias G**, Kaltsa G, Ladas SD. Cytokines in the pathogenesis of ulcerative colitis. *Discov Med* 2011; **11**: 459-467 [PMID: 21616044]
21 **Rosen MJ**, Frey MR, Washington MK, Chaturvedi R, Kuhnhein LA, Matta P, Revetta FL, Wilson KT, Polk DB. STAT6 activation in ulcerative colitis: a new target for prevention of IL-13-induced colon epithelial cell dysfunction. *Inflamm Bowel Dis* 2011; **17**: 2224-2234 [PMID: 21308881 DOI: 10.1002/ibd.21628]
22 **Actis GC**, Fadda M, David E, Sapino A. Colectomy rate in steroid-refractory colitis initially responsive to cyclosporin: a long-term retrospective cohort study. *BMC Gastroenterol* 2007; **7**: 13 [PMID: 17389040 DOI: 10.1186/1471-230x-7-13]
23 **Marks DJ**, Miyagi K, Rahman FZ, Novelli M, Bloom SL, Segal AW. Inflammatory bowel disease in CGD reproduces the clinicopathological features of Crohn's disease. *Am J Gastroenterol* 2009; **104**: 117-124 [PMID: 19098859 DOI: 10.1038/ajg.2008.72]
24 **Lange AJ**, Arion WJ, Beaudet AL. Type Ib glycogen storage disease is caused by a defect in the glucose-6-phosphate translocase of the microsomal glucose-6-phosphatase system. *J Biol Chem* 1980; **255**: 8381-8384 [PMID: 6251055]
25 **Marks DJ**, Miyagi K, Rahman FZ, Grosvenor N, Bloom SL, Segal AW. Pathological features of inflammatory bowel disease in CGD are indistinguishable from those observed in Crohn's disease. *Gastroenterology* 2007; **132** Suppl 1: 156-157
26 **Henckaerts L**, Vermeire S. NOD2/CARD15 disease associations other than Crohn's disease. *Inflamm Bowel Dis* 2007; **13**: 235-241 [PMID: 17206682 DOI: 10.1002/ibd.20066]
27 **Rickert RR**. The important "impostors" in the differential diagnosis of inflammatory bowel disease. *J Clin Gastroenterol* 1984; **6**: 153-163 [PMID: 6371118 DOI: 10.1097/00004836-198404000-00011]
28 **Harpaz N**, Sachar DB. Segmental colitis associated with diverticular disease and other IBD look-alikes. *J Clin Gastroenterol* 2006; **40** Suppl 3: S132-S135 [PMID: 16885696 DOI: 10.1097/01.mcg.0000225505.67547.90]
29 **Lich JD**, Ting JP. CATERPILLER (NLR) family members as positive and negative regulators of inflammatory responses. *Proc Am Thorac Soc* 2007; **4**: 263-266 [PMID: 17607010 DOI: 10.1513/pats.200701-022AW]
30 **Sari S**, Egritas O, Dalgic B. The familial Mediterranean fever (MEFV) gene may be a modifier factor of inflammatory bowel disease in infancy. *Eur J Pediatr* 2008; **167**: 391-393 [PMID: 17520284 DOI: 10.1007/s00431-007-0508-x]
31 **Schölmerich J**. Evolving concepts in IBD therapy: What should be studied in the future? *Dig Dis* 2010; **28**: 472-477 [PMID: 20926874 DOI: 10.1159/000320404]
32 **Werts C**, Girardin SE, Philpott DJ. TIR, CARD and PYRIN: three domains for an antimicrobial triad. *Cell Death Differ* 2006; **13**: 798-815 [PMID: 16528382 DOI: 10.1038/sj.cdd.4401890]
33 **de Wouters T**, Doré J, Lepage P. Does our food (environment) change our gut microbiome ('in-vironment'): a potential role for inflammatory bowel disease? *Dig Dis* 2012; **30** Suppl 3: 33-39 [PMID: 23295690 DOI: 10.1159/000342595]
34 **Nair RP**, Henseler T, Jenisch S, Stuart P, Bichakjian CK, Lenk W, Westphal E, Guo SW, Christophers E, Voorhees JJ, Elder JT. Evidence for two psoriasis susceptibility loci (HLA and 17q) and two novel candidate regions (16q and 20p) by genome-wide scan. *Hum Mol Genet* 1997; **6**: 1349-1356 [PMID: 9259283 DOI: 10.1093/hmg/6.8.1349]
35 **Lee FI**, Bellary SV, Francis C. Increased occurrence of psoriasis in patients with Crohn's disease and their relatives. *Am J Gastroenterol* 1990; **85**: 962-963 [PMID: 2375323]
36 **Mattozzi C**, Richetta AG, Cantisani C, Macaluso L, Calvieri S. Psoriasis: new insight about pathogenesis, role of barrier organ integrity, NLR/CATERPILLER family genes and microbial flora. *J Dermatol* 2012; **39**: 752-760 [PMID: 22698089 DOI: 10.1111/j.1346-8138.2012.01606.x]
37 **Keely S**, Talley NJ, Hansbro PM. Pulmonary-intestinal cross-talk in mucosal inflammatory disease. *Mucosal Immunol* 2012; **5**: 7-18 [PMID: 22089028 DOI: 10.1038/mi.2011.55]
38 **Ekbom A**, Brandt L, Granath F, Löfdahl CG, Egesten A. Increased risk of both ulcerative colitis and Crohn's disease in a population suffering from COPD. *Lung* 2008; **186**: 167-172 [PMID: 18330638 DOI: 10.1007/s00408-008-9080-z]
39 **Storch I**, Sachar D, Katz S. Pulmonary manifestations of inflammatory bowel disease. *Inflamm Bowel Dis* 2003; **9**: 104-115 [PMID: 12769444 DOI: 10.1097/00054725-200303000-00004]
40 **Wang X**, Li L, Xiao J, Jin C, Huang K, Kang X, Wu X, Lv F. Association of ADAM33 gene polymorphisms with COPD in a northeastern Chinese population. *BMC Med Genet* 2009; **10**: 132 [PMID: 20003279 DOI: 10.1186/1471-2350-10-132]
41 **Kinose D**, Ogawa E, Hirota T, Ito I, Kudo M, Haruna A, Marumo S, Hoshino Y, Muro S, Hirai T, Sakai H, Date H, Tamari M, Mishima M. A NOD2 gene polymorphism is associated with the prevalence and severity of chronic obstructive pulmonary disease in a Japanese population. *Respirology* 2012; **17**: 164-171 [PMID: 21943069 DOI: 10.1111/j.1440-1843.2011.02069.x]
42 **Yamazaki K**, Takazoe M, Tanaka T, Kazumori T, Nakamura Y. Absence of mutation in the NOD2/CARD15 gene among 483 Japanese patients with Crohn's disease. *J Hum Genet* 2002; **47**: 469-472 [PMID: 12202985 DOI: 10.1007/s100380200067]
43 **Lanzarotto F**, Akbar A, Ghosh S. Does innate immune response defect underlie inflammatory bowel disease in the Asian population? *Postgrad Med J* 2005; **81**: 483-485 [PMID: 16085736 DOI: 10.1136/pgmj.2005.036590]

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EDITORIAL

Are medical ethics universal or culture specific

Furqaan Ahmed

Furqaan Ahmed, Department of Gastroenterology, South City Hospital, Karachi 75350, Pakistan
Author contributions: Ahmed F solely contributed to this paper.
Correspondence to: Furqaan Ahmed, MD, Department of Gastroenterology, South City Hospital, 128C KDA Scheme #1, Karachi 75350, Pakistan. furqaan@hotmail.com
Telephone: +92-3-8259667 Fax: +92-3-2788200
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Abstract

In our society and culture where family is of utmost importance, sometimes I wonder how much of a doctor's duty is to the patient and how much is to the whole family. As a medical student, I remember being told by my professors that we should treat the patient as a whole and not focus on just one problem or organ system. Similarly when practicing medicine in Pakistan, one cannot treat the patient alone and ignore the family. How much should relatives' wishes be taken into account when dealing with a patient? Don't patients have a right to their medical information? When, how, and by whom can that right be waived? What role does culture play when debating medical ethics?

Key words: Ethics; Culture; Pakistan

Core tip: This paper discusses to role of culture when debating medical ethics and wether cultural norms should be taken into account when applying the principles of medical ethics to a particular society. For example, in a society where the importance of family is paramount, how much should relativesi' wishes be taken into account when dealing with a patient?

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After graduating from the Aga Khan University Medical School in Karachi, Pakistan, I moved to the United States for postgraduate training in internal medicine and then gastroenterology and hepatology. Among the many things I learnt in those 10 years was that good medicine entails good communication with patients.

After completing my training in the United States, I began my practice as a gastroenterologist and hepatologist in my hometown of Karachi. One of the first patients I saw in my fledgling practice was a 65-year-old man with advanced esophageal cancer referred to me for palliative esophageal metal stenting. I spent a great deal of time explaining the nature of the disease to the patient and his family, as well as the somewhat limited options he had given the advanced state of his malignancy. I was greeted with blank stares and thought to myself "surely I am not the first one to explain these things to them and the doctor who sent him to me for a palliative procedure must have told them something". The patient and most of his relatives thanked me and left the consultation room. One son stayed back and then angrily asked me "Why did you tell him these things? He didn't know he has cancer! What right do you have to disclose this to him? As his family we know him best and know what is best for him and how much information he can handle." I was dumbfounded and mumbled some apologies. The patient never returned to me for esophageal stenting.

Sine this encounter, I have seen many patients who are unaware of their diagnoses - usually malignancies and occasionally chronic viral hepatitis. In the majority of these cases a relative will poke their head in the door before the patient enters to say that he/she does not know their diagnosis and please do not tell them. When I ask why, the answer I invariably get is: "The patient's spirit is too weak to absorb such news." I have learnt that arguing with such logic is futile. I have had only one rela-

tive ask me if they are doing the right thing in hiding the diagnosis from a patient. The daughter of a patient with stage 4 colorectal cancer asked what I would do if I were in her place and are they doing the right thing in hiding the true nature of her father's illness from him. She also said that I had recently returned from the United States and how are these issues handled in the West. As a doctor, I told her, I felt that it was my duty to tell patients the truth. I told her that if I were the patient, I think I would want to know if my days were numbered so that I could prepare myself, my family, and my affairs for my impending death. I also feel that patients probably know that they are dying and I don't see what avoiding the subject achieves. She listened to what I had to say but I doubt I changed her mind.

There are limits to my concessions to these demands of secrecy. I refuse to do endoscopic procedures in patients who are unaware of the indication and potential risk of the procedure. I take informed consent seriously. Secondly, I refuse to initiate interferon-based antiviral therapy in patients who are unaware of their diagnosis of chronic viral hepatitis. I was quite taken aback the first time I was asked to start a patient on a six month course of thrice weekly interferon injections without telling the patient the true reason for the treatment. When I posited this dilemma to the relative making the request, I was told that the family would handle it and come up with a story to tell the patient. Furthermore, the entire family has to be on the same page. If there is disagreement within the family, then I feel the patient should be told the truth and the family can work out their differences later. I also try not to deliberately lie to patients. At their relative's requests I may be vague and not voluntarily divulge certain information but if asked directly I don't tell outright lies. What surprised me earlier on was how few of the patients would directly ask me about their diagnosis and life expectancy. As a result of needing self justification for dealing with patients this way, I tell myself that many of these patients themselves do not seem to want to know about their disease. I have yet to have a patient ask me directly what their disease is, saying they suspect their family is hiding something from them. However, I can not always be entirely sure of this. How does one know if a patient does not want to know the truth unless they explicitly say so?

In our society and culture where family is of utmost importance, sometimes I wonder how much of a doctor's duty is to the patient and how much is to the whole family. As a medical student, I remember being told by my professors that we should treat the patient as a whole and not focus on just one problem or organ system. Similarly when practicing medicine in Pakistan, one cannot treat the patient alone and ignore the family.

But I continue to feel conflicted about the issue[1]. How much should relatives' wishes be taken into account when dealing with a patient? Don't patients have a right to their medical information? When, how, and by whom can that right be waived? By hiding a patient's diagnosis, are we doing good or harm to a patient? Finally, what role does culture play when debating medical ethics?

REFERENCES

1 **Iyalomhe GB.** Medical ethics and ethical dilemmas. *Niger J Med* 2009; **18**: 8-16 [PMID: 19485140]

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MINIREVIEWS

Emerging causes of iron deficiency anemia refractory to oral iron supplementation

Sean Warsch, John Byrnes

Sean Warsch, John Byrnes, Sylvester Comprehensive Cancer Center, Miami, FL 33136, United States
Author contributions: Both authors contributed to data collection and writing of the manuscript.
Correspondence to: John Byrnes, MD, Professor, Sylvester Comprehensive Cancer Center, 1475 NW 12th Ave, Miami, FL 33136, United States. jbyrnes@med.miami.edu
Telephone: +1-305-2436611 Fax: +1-305-2435239
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Abstract

While oral iron supplementation is commonly used throughout many clinical setting, treatment with intravenous (IV) iron has historically been reserved for specific settings, such as chronic kidney disease, gynecologic issues, and anemia associated with cancer and its treatments. However, the use of IV iron has begun to gain popularity in the treatment of iron deficiency anemia (IDA) associated with two conditions that are being seen more frequently than in years past: patients who are status post gastric bypass procedure and those with inflammatory bowel disease (IBD). The Roux-en-Y procedure involves connecting a gastric pouch to the jejunum, creating a blind loop consisting of distal stomach, duodenum, and proximal jejunum that connects to the Roux limb to form a common tract. IDA occurs in 6%-50% of patients who have undergone a gastric bypass, the etiology being multifactorial. The proximal gastric pouch, the primary site of gastric acid secretion, is bypassed, resulting in a decreased ability to metabolize molecular iron. Once metabolized, most iron is absorbed in the duodenum, which is entirely bypassed. After undergoing bypass procedures, most patients significantly limit their intake of red meat, another factor contributing to post-bypass IDA. Chronic anemia occurs in approximately 1/3 of patients who suffer from IBD, and almost half of all IBD patients are iron deficient. IBD leads to IDA through multiple mechanisms, including chronic intestinal blood loss, decreased absorption capabilities of the duodenum secondary to inflammation, and an inability of many IBD patients to tolerate the side effects of oral ferrous sulfate. In this study, we reviewed the charts of all patients who received IV iron at Sylvester Comprehensive Cancer Center/University of Miami Hospital Clinic from January 2007 to May 2012. The most common indications for IV iron were for issues related to cancer and its treatment (21.9%), IBD (20.1%), and gastric bypass (15.0%). Of the 262 patients who received IV iron, 230 received iron sucrose and 36 received iron dextran. While doses of 100, 200, 300, and 400 mg of iron sucrose were given, 100 and 200 mg were by far the most common dosages used, 122 and 120 times, respectively. The number of dosages of iron sucrose given ranged from 1 to 46, with a mean of 5.5 and a median of 4 doses. The average dose of iron dextran given was 870.5 mg, with 1000 mg being the most common dosage used. Most patients (22 of 36) who received iron dextran only received one dose. While patients with traditional indications for IV iron, such as gynecologic issues and kidney disease, still were represented in this study, we expect to see a continued increase in physicians using IV iron for emerging gastrointestinal indications, especially considering the increased safety of new low-molecular formulations.

Key words: Anemia; Iron deficiency anemia; Intravenous iron; Gastric bypass; Inflammatory bowel disease; Crohn's disease; Ulcerative colitis; Chemotherapy-associated anemia

Core tip: Decreased absorption of oral iron leading to iron deficiency is a significant cause of anemia in several patient groups, including those status post gastric

bypass surgery and those with inflammatory bowel disease. In these patients, oral iron supplementation is unlikely to correct the deficiency. Intravenous iron is a safe, effective treatment strategy for overcoming the iron deficit seen in these patients, resulting in better outcomes and improved quality of life.

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INTRODUCTION

Intravenous iron has been available for medical use for over 60 years. Traditional indications for its use include medical conditions such as inflammatory bowel disease (IBD), chronic kidney disease (CKD), chronic inflammatory arthritis, congestive heart failure, pregnancy and postpartum state, and cancer, as well as orthopedic, cardiac, colorectal, and gynecologic procedures[1]. The development of recombinant human erythropoietin (EPO) in the late 1980's led to a renewed interest in its use as combination therapy in the setting of such conditions as CKD and malignancies. In a randomized study of 132 hemodialysis patients, the use of intravenous (IV) iron as an adjunct to EPO led to a greater increase in hemoglobin (Hgb) levels, the need for fewer doses of EPO, and less adverse effects associated with EPO use[2].

Iron dextran can lead to both local and systemic side effects. The most commonly reported local reactions include pruritus, pain, phlebitis, and muscle necrosis[3]. A retrospective study of patients who received IV iron for CKD compared the safety of the dextran to the sucrose preparation[4]. A total of 979 doses of dextran and 504 of sucrose were given, with 3 minor adverse events (AEs) occurring in the dextran group and 1 in the sucrose group. No serious AEs or anaphylactic reactions were reported in either group. Another retrospective study examined 619 patients who had received IV iron over a 2 year period[5]. Overall, there were 32 reported AEs, but no serious AEs or anaphylactic reactions. Larger retrospective studies have shown the rate of serious AEs with iron dextran to range from 0.0002% to 0.032%, with rates of serious AEs due to iron sucrose much lower[6]. The primary reason for the increased safety of iron sucrose is likely due to the fact that iron sucrose induces less sensitivity reactions that iron dextran does. A large safety review showed that sucrose induced 3.3 allergy episodes per million doses, while dextran led to 8.7 allergy events per million doses[7].

The Roux-en-Y procedure, the most commonly used method of gastric bypass surgeries, involves connecting a gastric pouch to the jejunum, creating a blind loop consisting of distal stomach, duodenum, and proximal jejunum that is connected to the Roux limb to form a common tract. A retrospective study of 150 patients who received gastric bypass found that 36.8% developed anemia[8]. The mean time from operation to the development of anemia was 20 mo. Almost 50% had a low serum iron concentration. A more recent prospective study followed 348 patients who had undergone gastric bypass for a 10 year period and found that 54% developed anemia, while 47% were iron deficient, with iron deficiency being much more common in women than in men[9].

While the etiology of iron deficiency anemia (IDA) in this population is often multifactorial, there are three causes that are cited most commonly: avoidance of red meat, diminished gastric acid secretion, and exclusion of the duodenum[10]. Red meat is the primary source of iron in North America, with heme accounting for two-thirds of total body iron, while molecular iron accounts for the other third[11]. Studies, as well as common experience, have shown that after patients undergo gastric bypass they are less able to tolerate the intake of red meat. One study of 69 patients found that 39% experienced emesis as a result of eating high fiber meats[12]. Molecular iron must be solubilized in an acidic environment before it can be absorbed[11]. In bypass procedures, the proximal gastric pouch, the primary site of gastric acid secretion, is bypassed. In a prospective study of eight patients who underwent a gastric bypass procedure, Behrns *et al*[13] demonstrated a marked decreased in gastric acid secretion in the stomachs of patients after they had undergone bypass, compared to pre-procedure levels. As a result of this lack of parietal cells, molecular iron is unable to get optimally metabolized. Once metabolized, most iron is absorbed at the duodenal brush border after it has been reduced from its ferric to ferrous form by ferric reductase[14]. However, in standard Roux-en-Y procedures, the duodenum is entirely bypassed, leading to marked decreased ability to absorb iron.

Other factors that may contribute to iron deficiency include gastritis involving the gastric pouch, esophagitis, and gastric ulcers[15]. While patients are recommended to take multivitamin supplements after undergoing gastric bypass to prevent nutritional deficiencies, patients may still be at risk for the development of IDA. In a randomized, blinded, prospective study of 56 menstruating women who had recently undergone gastric bypass, Brolin *et al*[16] found that twice daily ferrous sulfate, at a dose of 320 mg, was able to prevent iron deficiency. However, oral iron tablets are often difficult to tolerate, especially in patients who have undergone gastric bypass procedures, and there is still no consensus on the most effective method to limit the development of iron deficiency in this population.

Current guidelines recommend that patients who have undergone a malabsorptive procedure take 40-65 mg of oral iron daily to prevent the development of iron deficiency[17]. However, these guidelines acknowledge that patients may have difficulty tolerating oral supplementation and do not account for the fact that many patients

may be iron deficient prior to undergoing the procedure. The guidelines also state that once iron deficiency has developed, patients may be refractory to oral iron, requiring IV iron as a means to replenish their iron stores.

Anemia occurs in approximately 1/3 of patients who suffer from IBD, and almost half of all IBD patients are iron deficient[18]. Anemia in IBD is due to a combination of chronic intestinal blood loss, decreased absorption capabilities of the duodenum secondary to inflammation, the underlying inflammatory conditions that lead to anemia of chronic disease (ACD), and an inability of many IBD patients to tolerate the side effects of oral ferrous sulfate[18]. When patients are in an active inflammatory state secondary to their IBD, successfully treating anemia in IBD is significantly more difficult, making control of IBD paramount to the management of anemia in IBD[19].

Several randomized trials have evaluated the efficacy of iron versus oral supplementation in anemic patients with IBD. Lindgren *et al*[20] randomized 91 patients with IBD and anemia to receive oral iron sulfate or IV iron sucrose for 20 wk. The IV iron group tolerated the treatment better and saw a greater amount of patients increase their Hgb by > 2 g/dL (66% to 47%), have a resolution of their anemia (16% to 41%), and reach their reference Hgb level (42% to 22%). Another study randomized 200 patients with anemia and IBD to receive IV or oral iron in a 2:1 ratio[21]. The study met its primary endpoint, which was to prove non-inferiority of IV iron in increasing Hgb levels over a 12 week course. Of note, that rate of discontinuation of therapy due to AEs was 7.9% in the oral group compared to 1.5% in the IV group.

New guidelines recommend IV iron as first line therapy for IDA in patients with IBD. Absolute indications for the use of IV iron include a hemoglobin < 10 g/dL, intolerance or inappropriate response to oral iron supplementation, severe disease activity, use of EPO, and patient preference[22]. IV iron leads to a more rapid and prolonged response compared to oral therapy, and is better tolerated and leads to an improved quality of life. Furthermore, recent evidence has shown that oral iron can actually have a deleterious effect in patients with IBD, including an increase in oxidative stress, disease activity, and intestinal inflammation, as well as increasing the risk of colorectal cancer, as seen in animal models[22]. IV iron is beneficial even in cases where the anemia is attributable to ACD, which is defined as ferritin > 100 μg/L and transferrin saturation < 16% in the setting of anemia[23].

The combination of EPO plus IV iron has been shown to be an effective method to reduce the need for blood transfusion in patients with cancer who suffer from chemotherapy-induced anemia, as well as ACD. European Organization for Research and Treatment of Cancer (EORTC) guidelines recommend that patients receiving chemotherapy and/or radiotherapy who develop Hgb levels between 9-11 g/dL and display symptoms of anemia be considered for EPO treatment. Patients with Hgb < 9 g/dL will likely need blood transfusions, at least as initial treatment[24].

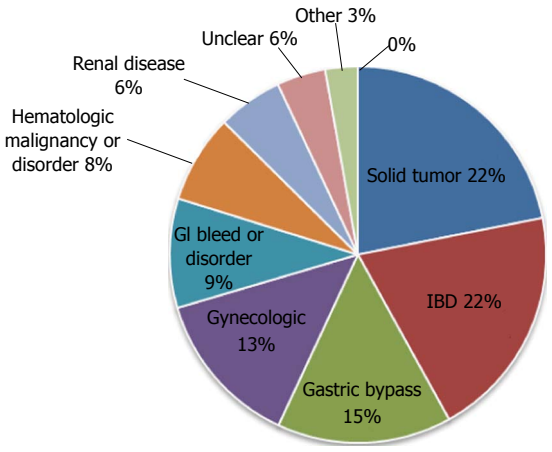

Figure 1 Indications for intravenous iron. IBD: inflammatory bowel disease; GI: Gastrointestinal.

In a randomized trial of 477 women with IDA secondary to heavy uterine bleeding, patients were randomized to receive either weekly IV iron or oral ferrous sulfate 325 mg three times a day for six weeks. Compared to those in the oral repletion group, more patients who received IV iron achieved a > 2 g/dL increase in Hgb (82% to 62%), a > 3 g/dL increase in Hgb (53% to 36%), and a correction of Hgb levels, defined as Hgb > 12 g/dL (73% to 50%), with no serious adverse effects reported in either group[25].

RESEARCH

After obtaining approval through the University Institutional Review Board, we searched Intellidose, the electronic program that records medication administration, for all instances in which intravenous iron was administered at Sylvester Comprehensive Cancer Center/University of Miami Hospital Clinic from January 2007 to May 2012. We documented the type of iron used, number of administrations, and dosages. We then searched UChart, an electronic medical record used by the university, to ascertain the indications for IV iron based on the patients' known diagnoses.

A total of 262 patients received IV iron. Several patients had multiple indications for IV iron. The most common indications for IV iron were for issues related to cancer and its treatment (21.9%), IBD (20.1%), and gastric bypass (15.0%). Other indications included gynecologic issues (13%), a gastrointestinal bleed or disorder other than IBD (9%), and hematologic malignancies or disorders (8%) (Figure 1 and Table 1).

Of the 262 patients who received IV iron, 230 received iron sucrose and 36 received iron dextran. While doses of 100, 200, 300 and 400 mg of iron sucrose were given, 100 and 200 mg were by far the most common dosages used, 122 and 120 times, respectively. The number of dosages of iron sucrose given ranged from 1 to 46, with a mean of 5.5 and a median of 4 doses. The average dose of iron dextran given was 870.5 mg, with 1000 mg

Table 1 Specific diagnoses that led to administration of intravenous iron

Gastric bypass	43
Inflammatory bowel disease (Crohn's disease, Ulcerative colitis)	58
Gastrointestinal bleed (ulcers, arteriovenous malformation, hemorrhoids, diverticulosis, Cronkhite-Canada syndrome)	16
Gastrectomy (secondary to gastric cancer, Mucosa-associated lymphoid tissue lymphoma)	5
Celiac disease	3
Pernicious anemia	1
Colectomy secondary to Familial adenomatous polyposis	1
Bulimia	1
Small bowel resection- reason unclear	1
Solid tumor (secondary to chemotherapy, due to disease infiltration/progression)	63
Gynecologic (menorrhagia, fibroids, endometriosis)	39
Hematologic malignancy (Hodgkin's, Myelodysplastic Syndrome, Post-transplant lymphoproliferative disorder, myelofibrosis, paraproteinemia, follicular lymphoma, Monoclonal gammopathy of undetermined significance, Acute myeloid leukemia, Chronic myeloid leukemia)	11
Lupus Anti-Coagulant on anti-coagulation, Antiphospholipid syndrome on anti-coagulation	4
Systemic lupus erythematosus	3
Anemia of chronic disease	1
Thallassemia	1
Sickle cell trait	1
Autoimmune hemolytic anemia	1
Jehovah's witness	4
Renal disease (polycystic kidney disease , chronic kidney disease end-stage renal disease)	16
Pregnancy	1
Rheumatoid arthritis	1
Skin wounds	1
Other indication, also on warfarin	5
Unclear on review of records (some have iron deficiency anemia as a diagnosis)	12

Note: Several patients had multiple indications for IV iron; all indications noted in chart are listed above. Data for 262 patients. Patients received treatment at Sylvester Comprehensive Cancer Center in Miami and Kendall.

being the most common dosage used. Most patients (22 of 36) who received iron dextran only received one dose.

CONCLUSION

While we expect IV iron to continue to be used for traditional indications, such as CKD and conditions associated with malignancies, we also expect to see a rise in its use for emerging indications, such as in patients status post gastric bypass procedures and in patients with IBD. Our study supports this claim, as 35% of the patients who received IV iron at our institution received it for one of these two emerging indications. Large studies have demonstrated the safety of iron dextran, and iron sucrose appears to be an even safer alternative. IV iron avoids many of the downsides of oral supplementation, such as decreased GI tolerance, absorption issues, and the ability to correct the deficiency with a short course of treatments, as opposed to long-term oral repletion. IV iron in combination with EPO has also been shown to decrease the need for blood transfusions. While oral iron remains front-line therapy for IDA, we expect to see IV iron used sooner in the course of treatment for GI-related deficiencies. This issue is likely to become more important in the future, as increasing numbers of patients undergo gastric bypass procedures and the prevalence of IBD continues to rise[26].

REFERENCES

1 **Muñoz M**, Breymann C, García-Erce JA, Gómez-Ramírez S, Comin J, Bisbe E. Efficacy and safety of intravenous iron therapy as an alternative/adjunct to allogeneic blood transfusion. *Vox Sang* 2008; **94**: 172-183 [PMID: 18069918 DOI: 10.1111/j.1423-0410.2007.01014.x]

2 **Kapoian T**, O'Mara NB, Singh AK, Moran J, Rizkala AR, Geronemus R, Kopelman RC, Dahl NV, Coyne DW. Ferric gluconate reduces epoetin requirements in hemodialysis patients with elevated ferritin. *J Am Soc Nephrol* 2008; **19**: 372-379 [PMID: 18216316 DOI: 10.1681/ASN.2007050606]

3 **Fishbane S**, Ungureanu VD, Maesaka JK, Kaupke CJ, Lim V, Wish J. The safety of intravenous iron dextran in hemodialysis patients. *Am J Kidney Dis* 1996; **28**: 529-534 [PMID: 8840942 DOI: 10.1016/S0272-6386(96)90463-1]

4 **Sinha S**, Chiu DY, Peebles G, Kolakkat S, Lamerton E, Fenwick S, Kalra PA. Comparison of intravenous iron sucrose versus low-molecular-weight iron dextran in chronic kidney disease. *J Ren Care* 2009; **35**: 67-73 [PMID: 19432851 DOI: 10.1111/j.1755-6686.2009.00099.x]

5 **Okam MM**, Mandell E, Hevelone N, Wentz R, Ross A, Abel GA. Comparative rates of adverse events with different formulations of intravenous iron. *Am J Hematol* 2012; **87**: E123-E124 [PMID: 22965928 DOI: 10.1002/ajh.23322]

6 **Wysowski DK**, Swartz L, Borders-Hemphill BV, Goulding MR, Dormitzer C. Use of parenteral iron products and serious anaphylactic-type reactions. *Am J Hematol* 2010; **85**: 650-654 [PMID: 20661919]

7 **Faich G,** Strobos J. Sodium ferric gluconate complex in sucrose: safer intravenous iron therapy than iron dextrans. *Am J Kidney Dis* 1999; **33**: 464-470 [PMID: 10070910 DOI: 10.1016/S0272-6386(99)70183-6]

8 **Amaral JF**, Thompson WR, Caldwell MD, Martin HF, Randall HT. Prospective hematologic evaluation of gastric exclusion surgery for morbid obesity. *Ann Surg* 1985; **201**: 186-193 [PMID: 3970598 DOI: 10.1097/00000658-198502000-00009]

9 **Brolin RE**, Gorman JH, Gorman RC, Petschenik AJ, Bradley LJ, Kenler HA, Cody RP. Are vitamin B12 and folate defi-

ciency clinically important after roux-en-Y gastric bypass? *J Gastrointest Surg* 1998; **2**: 436-442 [PMID: 9843603 DOI: 10.1016/S1091-255X(98)80034-6]
10 **Love AL**, Billett HH. Obesity, bariatric surgery, and iron deficiency: true, true, true and related. *Am J Hematol* 2008; **83**: 403-409 [PMID: 18061940 DOI: 10.1002/ajh.21106]
11 **Conrad ME**, Umbreit JN. Iron absorption and transport-an update. *Am J Hematol* 2000; **64**: 287-298 [PMID: 10911382 DOI: 10.1002/1096-8652(200008)64]
12 **Halverson JD**, Zuckerman GR, Koehler RE, Gentry K, Michael HE, DeSchryver-Kecskemeti K. Gastric bypass for morbid obesity: a medical--surgical assessment. *Ann Surg* 1981; **194**: 152-160 [PMID: 7259341 DOI: 10.1097/00000658-198108000-00007]
13 **Behrns KE**, Smith CD, Sarr MG. Prospective evaluation of gastric acid secretion and cobalamin absorption following gastric bypass for clinically severe obesity. *Dig Dis Sci* 1994; **39**: 315-320 [PMID: 8313814 DOI: 10.1007/BF02090203]
14 **Fleming RE**, Bacon BR. Orchestration of iron homeostasis. *N Engl J Med* 2005; **352**: 1741-1744 [PMID: 15858181 DOI: 10.1056/NEJMp048363]
15 **Marinella MA**. Anemia following Roux-en-Y surgery for morbid obesity: a review. *South Med J* 2008; **101**: 1024-1031 [PMID: 18791538 DOI: 10.1097/SMJ.0b013e31817cf7b7]
16 **Brolin RE**, Gorman JH, Gorman RC, Petschenik AJ, Bradley LB, Kenler HA, Cody RP. Prophylactic iron supplementation after Roux-en-Y gastric bypass: a prospective, double-blind, randomized study. *Arch Surg* 1998; **133**: 740-744 [PMID: 9688002 DOI: 10.1001/archsurg.133.7.740]
17 **Mechanick JI**, Kushner RF, Sugerman HJ, Gonzalez-Campoy JM, Collazo-Clavell ML, Guven S, Spitz AF, Apovian CM, Livingston EH, Brolin R, Sarwer DB, Anderson WA, Dixon J. Executive summary of the recommendations of the American Association of Clinical Endocrinologists, the Obesity Society, and American Society for Metabolic & amp; Bariatric Surgery medical guidelines for clinical practice for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient. *Endocr Pract* 2008; **14**: 318-336 [PMID: 18463039 DOI: 10.4158/EP.14.3.318]
18 **Muñoz M**, Gómez-Ramírez S, García-Erce JA. Intravenous iron in inflammatory bowel disease. *World J Gastroenterol* 2009; **15**: 4666-4674 [PMID: 19787830 DOI: 10.3748/wjg.15.4666]
19 **de la Morena F**, Gisbert JP. [Anemia and inflammatory bowel disease]. *Rev Esp Enferm Dig* 2008; **100**: 285-293 [PMID: 18662081]
20 **Lindgren S**, Wikman O, Befrits R, Blom H, Eriksson A, Grännö C, Ung KA, Hjortswang H, Lindgren A, Unge P. Intravenous iron sucrose is superior to oral iron sulphate for correcting anaemia and restoring iron stores in IBD patients: A randomized, controlled, evaluator-blind, multicentre study. *Scand J Gastroenterol* 2009; **44**: 838-845 [PMID: 19330567 DOI: 10.1080/00365520902839667]
21 **Kulnigg S**, Stoinov S, Simanenkov V, Dudar LV, Karnafel W, Garcia LC, Sambuelli AM, D'Haens G, Gasche C. A novel intravenous iron formulation for treatment of anemia in inflammatory bowel disease: the ferric carboxymaltose (FERINJECT) randomized controlled trial. *Am J Gastroenterol* 2008; **103**: 1182-1192 [PMID: 18371137 DOI: 10.1111/j.1572-0241.2007.01744.x]
22 **Gasche C**, Berstad A, Befrits R, Beglinger C, Dignass A, Erichsen K, Gomollon F, Hjortswang H, Koutroubakis I, Kulnigg S, Oldenburg B, Rampton D, Schroeder O, Stein J, Travis S, Van Assche G. Guidelines on the diagnosis and management of iron deficiency and anemia in inflammatory bowel diseases. *Inflamm Bowel Dis* 2007; **13**: 1545-1553 [PMID: 17985376 DOI: 10.1002/ibd.20285]
23 **Auerbach M**, Coyne D, Ballard H. Intravenous iron: from anathema to standard of care. *Am J Hematol* 2008; **83**: 580-588 [PMID: 18273906 DOI: 10.1002/ajh.21154]
24 **Bokemeyer C**, Aapro MS, Courdi A, Foubert J, Link H, Osterborg A, Repetto L, Soubeyran P. EORTC guidelines for the use of erythropoietic proteins in anaemic patients with cancer: 2006 update. *Eur J Cancer* 2007; **43**: 258-270 [PMID: 17182241 DOI: 10.1016/j.ejca.2006.10.014]
25 **Van Wyck DB**, Mangione A, Morrison J, Hadley PE, Jehle JA, Goodnough LT. Large-dose intravenous ferric carboxymaltose injection for iron deficiency anemia in heavy uterine bleeding: a randomized, controlled trial. *Transfusion* 2009; **49**: 2719-2728 [PMID: 19682342 DOI: 10.1111/j.1537-2995.2009.02327.x]
26 **Molodecky NA,** Soon IS, Rabi DM, Ghali WA, Ferris M, Chernoff G, Benchimol EI, Panaccione R, Ghosh S, Barkema HW, Kaplan GG. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology* 2012; **142**: 46-54. e42; quiz e30 [PMID: 22001864 DOI: 10.1053/j.gastro.2011.10.001]

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BRIEF ARTICLE

Association of *ITPA* polymorphism with outcomes of peginterferon-α plus ribavirin combination therapy

Tatsuya Fujino, Yoko Aoyagi, Mariko Takahashi, Ryoko Yada, Naoko Yamamoto, Yuki Ohishi, Akihiko Nishiura, Motoyuki Kohjima, Tsuyoshi Yoshimoto, Kunitaka Fukuizumi, Manabu Nakashima, Masaki Kato, Kazuhiro Kotoh, Makoto Nakamuta, Munechika Enjoji

Tatsuya Fujino, Laboratory for Clinical Investigation, National Hospital Organization Nagasaki Medical Center, Ohmura, Nagasaki 856-8562, Japan
Yoko Aoyagi, MarikoTakahashi, Ryoko Yada, Naoko Yamamoto, Yuki Ohishi, Akihiko Nishiura, Motoyuki Kohjima, Tsuyoshi Yoshimoto, Kunitaka Fukuizumi, Makoto Nakamuta, Munechika Enjoji, Clinical Research Institute, National Hospital Organization Kyushu Medical Center, Fukuoka 814-0180, Japan
Manabu Nakashima, Munechika Enjoji, Faculty of Pharmaceutical Sciences, Fukuoka University, Fukuoka 814-0180, Japan
Masaki Kato, Kazuhiro Kotoh, Department of Medicine and Bioregulatory Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka 814-0180, Japan
Author contributions: Fujino T, Nakamuta M and Enjoji M designed the research; Fujino T, Kohjima M, Yoshimoto T, Fukuizumi K, Kato M and Kotoh K performed the research; Fujino T, Aoyagi Y, Takahashi M, Yada R, Yamamoto N, Ohishi Y and Nishiura A analyzed the data; Fujino T and Enjoji M wrote the paper; Nakashima M and Nakamuta M reviewed it.
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Correspondence to: Munechika Enjoji, MD, PhD, Faculty of Pharmaceutical Sciences, Fukuoka University, 8-19-1 Nanakuma, Jonan-ku, Fukuoka 814-0180, Japan. enjoji@adm.fukuoka-u.ac.jp
Telephone: +81-92-8716631 Fax: +81-92-8630389
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Abstract

AIM: To analyzed the association between inosine triphosphatase (*ITPA*) (rs1127354) genotypes and sustained virological response (SVR) rates in peginterferon (Peg-IFN)α + ribavirin (RBV) treatment.

METHODS: Patients who underwent Peg-IFNα + RBV combination therapy were enrolled (n = 120) and they had no history of other IFN-based treatments. Variation in hemoglobin levels during therapy, cumulative reduction of RBV dose, frequency of treatment withdrawal, and SVR rates were investigated in each *ITPA* genotype.

RESULTS: In patients with *ITPA* CC genotype, hemoglobin decline was significantly greater and the percentage of patients in whom total RBV dose was < 60% of standard and/or treatment was withdrawn was significantly higher compared with CA/AA genotype. However, SVR rates were equivalent between CC and CA/AA genotypes, and within a subset of patients with Interleukin 28B (*IL28B*) (rs8099917) TT genotype, SVR rates tended to be higher in patients with *ITPA* CC genotype, although the difference was not significant.

CONCLUSION: *ITPA* CC genotype was a disadvantageous factor for Peg-IFNα + RBV treatment in relation to completion rates and RBV dose. However, CC genotype was not inferior to CA/AA genotype for SVR rates. When full-length treatment is accomplished, it is plausible that more SVR is achieved in patients with *ITPA* CC variant, especially in a background of *IL28B* TT genotype.

Key words: Chronic hepatitis C; Interleukin 28B; Inosine triphosphatase; Peginterferon; Ribavirin

Core tip: Inosine triphosphatase (*ITPA*) polymorphism at rs1127354 is significantly associated with hemoglobin decline and reduction of ribavirin (RBV) during peginterferon-α + RBV therapy. However, the effect of the *ITPA* gene single-nucleotide polymorphism on treatment outcome is still unclear. In this study, *ITPA*

CC genotype (rs1127354) was not inferior to CA/AA genotype for sustained virological response rates although CC genotype was a disadvantageous factor for the treatment in relation to completion rates and RBV dose. When full-length treatment is accomplished, the SVR rate tended to be higher in patients with the CC genotype, especially in a subset of patients with the favorable TT genotype (rs8099917) of Interleukin 28B.

Fujino T, Aoyagi Y, Takahashi M, Yada R, Yamamoto N, Ohishi Y, Nishiura A, Kohjima M, Yoshimoto T, Fukuizumi K, Nakashima M, Kato M, Kotoh K, Nakamuta M, Enjoji M. Association of *ITPA* polymorphism with outcomes of peginterferon-α plus ribavirin combination therapy. *World J Gastrointest Pharmacol Ther* 2013; 4(3): 54-60 Available from: URL: http://www.wjgnet.com/2150-5349/full/v4/i3/54.htm DOI: http://dx.doi.org/10.4292/wjgpt.v4.i3.54

INTRODUCTION

Hepatitis C virus (HCV) genotype 1b accounts for around 70% of chronic hepatitis C in Japan[1,2]. A sustained virological response (SVR) in eliminating HCV RNA by peginterferon (Peg-IFN)α + ribavirin (RBV) combination therapy is attained in 40%-50% of individuals with HCV-1b[3-5]. Triple therapy using Peg-IFNα + RBV + telaprevir is anticipated to be effective for SVR in approximately 75% of patients with HCV-1b[6-8]. It is known that polymorphisms located upstream of the Interleukin 28B (*IL28B)* gene, encoding for λ or type Ⅲ interferon (IFN-λ), are major predictors of SVR in the Peg-IFNα-based combination therapies[9-12]. Two single-nucleotide polymorphisms (SNPs), rs8099917 TT genotype and rs12979860 CC genotype, have been independently associated with a higher rate of SVR following Peg-IFNα-based combination therapies in individuals with HCV-1b infection. IFN-λ is believed to upregulate the JAK-STAT (Janus kinase-signal transducer and activator of transcription) pathway through interaction with a cellular transmembrane receptor, resulting in antiviral activity. In Japanese individuals, strong linkage disequilibrium is recognized between the two *IL28B* SNPs, rs8099917 and rs12979860, and 99% coincidence has been reported[13].

The most important adverse events of Peg-IFNα-based combination therapies include RBV-induced hemolytic anemia, which is severe enough to require dose reduction of RBV in 10%-20% of patients, and which may affect overall efficacy[3]. RBV-induced ATP depletion in red blood cells is believed to be a primary mechanism for RBV-induced hemolytic anemia. A genome-wide association study has shown a strong association between SNPs of the inosine triphosphatase (*ITPA*) gene in chromosome 20 and RBV-induced anemia in patients infected with HCV-1b[14]. Two functional SNPs, a missense variant in exon 2 (rs1127354) and a splicing altering variant in intron 2 (rs7270101), independently reduce the expression of *ITPA*, leading to inosine deficiency and protection against RBV-induced ATP depletion[15-18]. Accordingly, the protective genotypes, rs1127354 CA and AA as well as rs7270101 AC and CC, are associated with decreased *ITPA* activity, which confers protection against RBV-related ATP depletion and hemolytic anemia. The Japanese have the AA genotype exclusively at rs7270101, therefore the CC genotype at rs1127354 is a major predictor of RBV-induced anemia during antiviral combination therapy in Japanese patients infected with HCV-1b[18,19].

However, it is controversial whether *ITPA* (rs1127354) CC genotype, which induces heavier hemoglobin decline, affects therapeutic outcomes. From the standpoint of health economics, it is important to examine the significance of factors predicting viral response to antiviral treatments and therapeutic outcomes. In this study, Japanese patients infected with HCV-1b, who had experienced Peg-IFNα + RBV combination therapy, were retrospectively analyzed. Patients were divided into groups according to genotyping of *ITPA* rs1127354 and *IL28B* rs8099917. Our primary analysis was focused on the quantitative change from baseline in hemoglobin levels and platelet counts, cumulative reduction of RBV dose, frequency of treatment withdrawal, and estimation of treatment outcome.

MATERIALS AND METHODS

Study patients

This retrospective cohort study was performed in 120 patients with chronic HCV-1b infection who were treated with Peg-IFNα + RBV combination therapy at Kyushu Medical Center Hospital between January 2007 and December 2009. The patients met the following inclusion and exclusion criteria. Inclusion criteria were: (1) baseline serum HCV RNA levels > 5.0 log IU/mL; and (2) Japanese patients aged 20-65 years at study entry. Exclusion criteria were: (1) decompensated liver cirrhosis; (2) serum hepatitis B surface antigen; (3) hepatocellular carcinoma or its history; (4) autoimmune hepatitis, alcoholic liver disease, hemochromatosis, or chronic liver disease other than chronic hepatitis C; (5) chronic renal disease or creatinine clearance < 50 mL/min at baseline; (6) hemoglobin < 12 g/dL, neutrophil < 1500/μL or platelets < 100000/μL at baseline; and (7) history of receiving IFN-based treatment. All patients gave consent for analysis of SNPs in *ITPA* and *IL28B* genes. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the Ethics Committee of Kyushu Medical Center. Written informed consent was obtained from each patient.

Antiviral treatment

Peg-IFNα2b (1.5 μg/kg) or Peg-IFNα2a (180 μg) was injected subcutaneously once weekly. RBV (600-1000 mg/d) was administered after breakfast and dinner. The RBV dose was adjusted by body weight: 600 mg for < 60 kg; 800 mg for 60-80 kg; and 1000 mg for > 80 kg. As a standard combination therapy, Peg-IFNα and RBV were continued for 48 wk. Treatment duration was extended up to

Table 1 Baseline characteristics of patients

Baseline characteristics	*ITPA* polymorphism (rs1127354)		*P* value
	CA/AA (*n* = 37)	CC (*n* = 83)	
Age (yr)	61 ± 8	59 ± 11	NS
Gender: male/female	18/19	37/46	NS
HCV RNA (log IU/mL)	6.2 ± 0.6	5.9 ± 0.5	NS
Hemoglobin (g/dL)	13.4 ± 1.5	13.8 ± 1.7	NS
WBC ($\times 10^3$/μL)	4.7 ± 1.2	5.0 ± 1.5	NS
Platelet ($\times 10^4$/μL)	18.0 ± 6.0	18.0 ± 7.0	NS
AST (IU/L)	56.8 ± 34.9	58.2 ± 42.3	NS
ALT (IU/L)	65.5 ± 40.0	68.4 ± 56.8	NS
GGT (IU/L)	56.1 ± 52.3	55.3 ± 49.4	NS
AFP (ng/mL)	5.3 ± 4.0	24.2 ± 61.8	NS
Staging: $F_{1,2}/F_{3,4}$	19/16	49/27	NS
IL28B: TT/TG + GG	29/8	53/30	NS

ITPA: Inosine triphosphatase; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: γ-glutamyl transpeptidase; AFP: α-fetoprotein; NS: Not significant; HCV: Hepatitis C virus; *IL28B*: Interleukin 28B.

72 wk in some patients in whom HCV RNA first became undetectable after week 12 but before week 48. SVR was defined as undetectable serum HCV RNA for 24 wk after treatment completion. Rapid virological response (RVR) and early virological response (EVR) were defined as undetectable serum HCV RNA at 4 wk and 12 wk of Peg-IFNα + RBV treatment, respectively. The RBV dose was reduced by 200 mg in patients receiving 600 or 800 mg (by 400 mg in those receiving 1000 mg) when hemoglobin decreased to < 12 g/dL, and by another 200 mg when it was < 10 g/dL. RBV was withdrawn or stopped temporarily when hemoglobin levels decreased to < 8.5 g/dL. Dose of Peg-IFNα2b (or Peg-IFNα2a) was reduced by 50% when the leukocyte count decreased to < 1500/μL, neutrophil count to < 750/μL, or platelet count to < 80000/μL; Peg-IFNα2b or Peg-IFNα2a was withdrawn when the above measures were decreased to < 1000/μL, < 500/μL or < 50000/μL, respectively.

Laboratory data

Hematological, biochemical, and virological parameters were determined by the clinical laboratory at Kyushu Medical Center. Serum HCV RNA concentrations were determined by the COBAS TaqMan polymerase chain reaction (PCR) HCV test (Roche Diagnostics, Tokyo, Japan). Genotyping for the *IL28B* (rs8099917) and *ITPA* (rs1127354) polymorphisms was performed by TaqMan SNP Genotyping Assays (Applied Biosystems, Branchburg, NJ, United States) that apply a PCR-based restriction fragment length polymorphism assay.

Statistical analysis

Statistical analysis was performed using JMP software (SAS Institute Inc., Cary, NC, United States). Differences between categorical variables were analyzed using Fisher's exact test or χ^2 test. Mann-Whitney *U* test was used for continuous variables. Multivariate analysis was used to identify factors independently associated with the achievement of SVR.

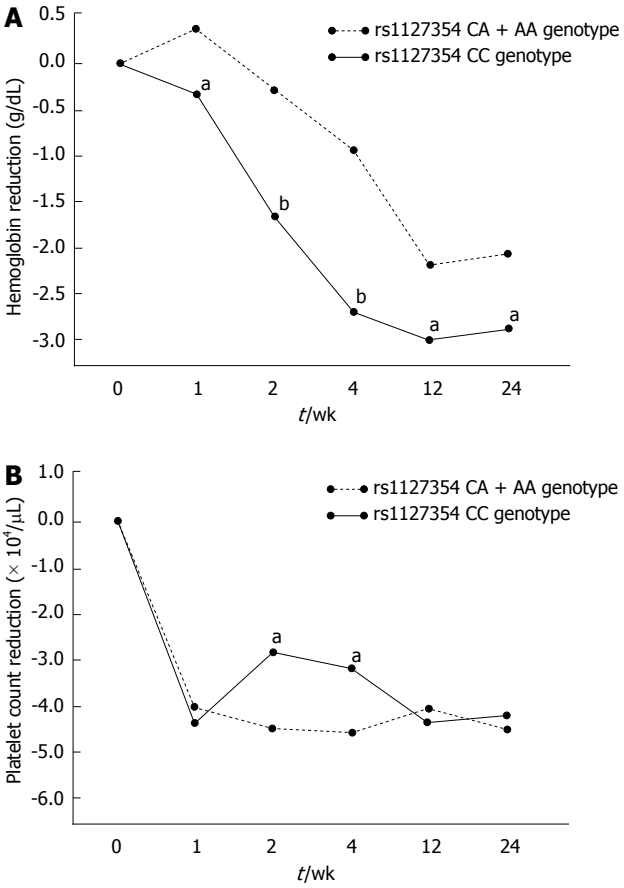

Figure 1 Chronological variation of hemoglobin levels (A) and platelet counts (B) in each inosine triphosphatase genotype at rs1127354. [a]*P* < 0.05, [b]*P* < 0.01 compared with CA/AA groups.

The OR and 95%CI were also calculated. $P < 0.05$ was considered to be statistically significant.

RESULTS

Association between ITPA deficiency and hemoglobin decline

Baseline characteristics of 120 enrolled patients are shown in Table 1. The study population included 83 patients with major (CC) genotype and 37 patients with minor (CA/AA) genotype of *ITPA* at rs1127354. Within listed items, no significant difference was seen between *ITPA* CC and CA/AA groups. Chronological variation of hemoglobin levels and platelet count during Peg-IFNα + RBV therapy is shown in Figure 1. As reported previously, hemoglobin decline was obvious in patients with *ITPA* CC genotype (rs1127354) and a significant difference was seen at week 1, 2, 4, 12 and 24 (Figure 1A), meaning that *ITPA* deficiency due to CA/CC genotype was associated with slower hemoglobin decline early in treatment. The greatest difference in mean hemoglobin reduction was found at week 4, while platelet reduction was temporally heavier in patients with *ITPA* CA/AA genotype at week 2 and 4 (Figure 1B). Leukocyte and neutrophil counts were equivalent between *ITPA* genotype CC and CA/AA

Table 2 Sustained virological response rates according to total ribavirin dose in each inosine triphosphatase genotype

ITPA genotype (rs1127354)	Patients with > 60% total RBV dose	Patients with < 60% total RBV dose	Total
CA + AA	48.3% (14/29)	12.5% (1/8)	40.5% (15/37)
CC	58.5% (31/53)	20.0% (6/30)	44.6% (37/83)

Each group includes patients in whom treatment was withdrawn. RBV: Ribavirin; *ITPA*: Inosine triphosphatase.

Table 3 Virological response according to classification by inosine triphosphatase and interleukin 28B single-nucleotide polymorphisms *n* (%)

Virological response	*IL28B*: TT		*IL28B*: TG + GG	
	CA + AA (*n* = 29)[1]	CC (*n* = 53)[1]	CA + AA (*n* = 8)[1]	CC (*n* = 30)[1]
RVR	3 (10.3)	10 (18.9)	0 (0.0)	4 (13.3)
RVR + EVR	18 (62.1)	35 (66.0)	1 (12.5)	8 (26.6)
SVR	13 (44.8)	29 (54.7)	2 (25.0)	8 (26.6)

[1]Inosine triphosphatase (*ITPA*). SVR: Sustained virological response; RVR: Rapid virological response; EVR: Early virological response; *IL28B*: Interleukin 28B.

groups during treatment (data not shown).

Treatment outcome in each genotype of ITPA

As a result of hepatocellular carcinoma, therapeutic inefficiency, or adverse events, such as depression, appetite loss, easy fatigability, retinal hemorrhage, and hemolytic anemia, Peg-IFNα + RBV therapy was discontinued in 18 patients with *ITPA* CC genotype (21.7%) and 6 patients with CA/AA genotype (16.2%). Moreover, serious reduction of RBV administration (< 60% of scheduled total dose) was compelled in significantly more patients with CC genotype compared with the CA/AA genotype. The percentage of patients receiving < 60% total RBV dose, including patients with treatment interruption/withdrawal, was significantly higher for the CC genotype (37.3% *vs* 21.6%, $P < 0.05$). To investigate the influence of dose reduction of Peg-IFN on treatment outcome, we also analyzed the dose of Peg-IFN administered for each rs1127354 genotype, and > 70% of the expected total dose was administered to all patients with treatment completion (data not shown). SVR rates were analyzed according to the total RBV dose and *ITPA* genotype (Table 2). In the whole population, SVR rates were higher in *ITPA* genotype CC than CA/AA genotype (44.6% *vs* 40.5%), although the difference was not significant. SVR rates tended to be higher for the CC genotype than the CA/AA genotype in patients with > 60% total RBV dose (58.5% *vs* 48.3%) or < 60% total RBV dose (20.0% *vs* 12.5%), but there were no significant differences between the *ITPA* genotypes.

SVR, RVR and EVR rates were determined for *IL28B* (rs8099917) and *ITPA* (rs1127354) genotypes (Table 3). In a subset of patients with *IL28B* TT genotype, RVR, RVR + EVR and SVR showed higher rates in patients with *ITPA* CC genotype compared with CA/AA genotype, although the difference was not significant. In a subset of patients with *IL28B* TG/GG genotype, SVR rates were equivalent between CC and CA/AA genotypes.

Table 4 Comparison of profile between sustained virological response and non-sustained virological response patients

Factors	SVR (*n* = 54)	non-SVR (*n* = 66)	*P* value
Age (yr)	57 ± 12	61 ± 9	< 0.05
Gender: male/female	21/33	33/33	NS
Body mass index (kg/m^2)	23.5 ± 4.1	22.6 ± 3.3	NS
HCV RNA (log IU/mL)	5.9 ± 0.6	6.1 ± 0.6	< 0.05
Hemoglobin (g/dL)	13.7 ± 1.3	13.8 ± 1.8	NS
WBC (× 10^3/mL)	4.7 ± 1.3	5.1 ± 1.5	NS
Platelet (× 10^4/mL)	20 ± 7	17 ± 6	< 0.05
AST (IU/L)	46.2 ± 25.8	66.7 ± 47.1	NS
ALT (IU/L)	56.1 ± 33.3	75.1 ± 61.1	NS
GGT (IU/L)	39.8 ± 24.1	67.4 ± 61.2	NS
AFP (ng/mL)	8.3 ± 19.8	10.1 ± 24.2	NS
Staging: $F_{1,2}/F_{3,4}$	12/40	28/30	< 0.01
72 wk treatment: +/–	10/44	14/52	NS
Ribavirin dose (%)[1]	90 ± 35	76 ± 41	NS
ITPA: CC/CA + AA	38/16	45/21	NS
IL28B: TT/TG + GG	44/10	38/28	< 0.01

[1]Percentage of ribavirin administration to the scheduled total dose of full-length treatment (48 or 72 wk). SVR: Sustained virological response; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: γ-glutamyl transpeptidase; AFP: α-fetoprotein; ITPA: inosine triphosphatase; NS: Not significant; HCV: Hepatitis C virus; IL28B: Interleukin 28B.

Table 5 Multivariate analysis for predictive factors associated with SVR

Factors	Category	95%CI	*P* value
HCV RNA (log IU/mL)	≥ 6.0: 1.0 < 6.0: 3.94	1.42-10.95	0.008
IL28B (rs8099917)	TG + GG: 1.0 TT: 3.46	1.18-10.10	0.023

HCV: Hepatitis C virus; IL28B: Interleukin 28B; SVR: Sustained virological response.

When background of SVR and non-SVR patients was compared, there was a significant difference in age, HCV RNA concentrations, platelet counts, staging, and *IL28B* SNPs, but not in *ITPA* SNPs (Table 4). Table 5 shows the result of multivariate analysis for predictive factors associated with SVR. The multivariate analysis proved that viral load (HCV RNA < 6.0 log IU/mL) and *IL28B* TT (rs8099917) were independent factors for SVR.

DISCUSSION

It has been shown that the SNP (rs8099917) in the *IL28B* gene is strongly associated with response to IFN-based therapy for chronic HCV-1b infection, and the SNP (rs1127354) in the *ITPA* gene predicts RBV-induced anemia in the Japanese population[19-23]. In this study, patients with *ITPA* (rs1127354) genotype CC showed a higher degree of hemoglobin reduction in response to Peg-IFNα + RBV treatment at week 1, 2, 4, 12 and 24 compared

with those with the CA/AA genotype (Figure 1A). The greatest difference in mean hemoglobin reduction was found at week 4. These findings confirmed the reported evidence that *ITPA* deficiency (rs1127354 CA/AA variants) renders protection against the development of RBV-induced hemoglobin decline in Japanese patients infected with HCV-1b[20-23]. The exact mechanism by which *ITPA* deficiency protects against RBV-induced hemolysis has yet to be resolved. One postulated mechanism for the development of anemia is the accumulation of triphosphorylated RBV in erythrocytes, causing eventual oxidative damage to erythrocyte membranes, and *ITPA* deficiency may confer protection against RBV-induced ATP reduction by substituting for erythrocyte GTP, which is depleted by RBV in the biosynthesis of ATP[24-26].

Thrombocytopenia, which leads to poor treatment efficacy because of the initial or early dose reduction of Peg-IFNα, is one of the critical adverse events caused by IFN-based antiviral therapy. A previous study has reported that the *ITPA* (rs1127354) CA/AA genotype is independently associated with a greater reduction in platelet count as well as protection against the reduction in hemoglobin, whereas patients with the CC genotype have significantly less reduction in mean platelet count[27]. We also evaluated whether genetic variants in the *ITPA* gene were associated with IFN-induced thrombocytopenia. In this study, CC genotype showed lesser trend of reduction at week 2 and 4 compared with CA/AA genotype (Figure 1B). The result may support the association of *ITPA* gene SNP (rs1127354) with platelet decline in response to Peg-IFNα + RBV treatment.

Hemoglobin reduction often necessitates dose reduction of RBV and premature withdrawal from therapy, therefore the *ITPA* (rs1127354) genotype CC may be considered as a disadvantageous factor for Peg-IFNα + RBV treatment. However, although *ITPA* polymorphisms are significantly associated with RBV-induced anemia, their effect on therapeutic outcome is unclear. Some studies have shown no association[14,28-31], and others have reported a possible association with treatment outcomes in chronic hepatitis C patients[21,22]. In the present study, although there was no significant association between *ITPA* polymorphisms and treatment outcome, there was a trend towards higher SVR rates in patients with *ITPA* CC genotype, which seemed to contradict previous studies[21,22,28-31]. The different outcome among the institutes may be due to the difference of inclusion and/or exclusion criteria. In this study, the relationship between *IL28B* and *ITPA* variants were additionally analyzed on treatment outcome. When analyzed in the patients available for treatment outcome, all patients were administered > 70% of the scheduled total Peg-IFNα dose, but the incidence of RBV dose reduction (< 60% of the scheduled dose) and withdrawal was significantly higher in patients with the rs1127354 genotype CC. However, the rate of SVR tended to be higher in patients with the CC genotype, especially in a subset of patients with the favorable TT genotype at rs8099917 of *IL28B*, although the difference was not significant between the CC and CA/AA genotypes (Tables 2 and 3). Independent favorable predictors for SVR identified in multivariate analysis were low viral load (HCV RNA < 6.0 log IU/mL) and TT genotype at rs8099917 of *IL28B*, but not CC genotype at rs1127354 of *ITPA* (Table 5).

There were several limitations to this study. (1) Because of the small sample size which may have contributed to the loss of significance observed or some statistical errors, this study may be ranked at preliminary status; (2) Because of the retrospective nature of the study, enrolled patients may not represent the standard Japanese population infected with HCV; (3) Several other significant SNPs, which have been detected in *ITPA* as well as *IL28B*, may have influenced and distorted the results; and (4) Mutations in other genes and non-genetic factors that may affect response to antiviral therapy against chronic hepatitis C were not determined.

In conclusion, the SVR rates tended to be higher in patients with the CC genotype than the CA/AA genotype, especially in a subset of patients with *IL28B* (rs8099917) TT genotype, despite a higher rate of RBV dose reduction and treatment withdrawal. Multivariate analysis identified *IL28B* SNP (rs8099917) and HCV RNA as independent predictors of SVR. It is plausible that, in a background of *IL28B* (rs8099917) TT genotype, more SVR is achieved in patients with *ITPA* CC variant when full-length (duration of 48 or 72 wk) treatment is accomplished. These findings indicate that *ITPA* (rs1127354) CC genotype is by no means inferior to the CA/AA genotype for viral response to Peg-IFN + RBV combination therapy.

COMMENTS

Background

A single-nucleotide polymorphism (SNP) at rs1127354 of the inosine triphosphatase (ITPA) gene is associated with hemoglobin decline during peginterferon (Peg-IFN) + ribavirin (RBV) combination therapy in patients with hepatitis C virus infection. However, the effect of the ITPA gene SNP on treatment outcome has not been fully elucidated. Authors analyzed the association between ITPA (rs1127354) genotypes and sustained virological response (SVR) rates in Peg-IFNα + RBV treatment.

Research frontiers

ITPA CC genotype was a disadvantageous factor for Peg-IFNα + RBV treatment in relation to completion rates and RBV dose. However, CC genotype was not inferior to CA/AA genotype for SVR rates. When full-length treatment is accomplished, it is plausible that more SVR is achieved in patients with ITPA CC variant, especially in a background of Interleukin 28B (IL28B) TT genotype.

Innovations and breakthroughs

In patients with ITPA CC genotype, hemoglobin decline was significantly greater and the percentage of patients in whom total RBV dose was < 60% of standard and/or treatment was withdrawn was significantly higher compared with CA/AA genotype. However, SVR rates were equivalent between CC and CA/AA genotypes, and within a subset of patients with IL28B (rs8099917) TT genotype, SVR rates tended to be higher in patients with ITPA CC genotype, although the difference was not significant.

Peer review

The topic is interesting and relevant. The manuscript is well written and concise.

REFERENCES

1 **Enomoto N**, Takada A, Nakao T, Date T. There are two ma-

jor types of hepatitis C virus in Japan. *Biochem Biophys Res Commun* 1990; **170**: 1021-1025 [PMID: 2117923 DOI: 10.1016/0006-291X(90)90494-8]
2 **Hayashi K**, Fukuda Y, Nakano I, Katano Y, Toyoda H, Yokozaki S, Hayakawa T, Morita K, Nishimura D, Kato K, Urano F, Takamatsu J. Prevalence and characterization of hepatitis C virus genotype 4 in Japanese hepatitis C carriers. *Hepatol Res* 2003; **25**: 409-414 [PMID: 12699851 DOI: 10.1016/S1386-6346(03)00016-0]
3 **Fried MW**, Shiffman ML, Reddy KR, Smith C, Marinos G, Gonçales FL, Häussinger D, Diago M, Carosi G, Dhumeaux D, Craxi A, Lin A, Hoffman J, Yu J. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med* 2002; **347**: 975-982 [PMID: 12324553 DOI: 10.1056/NEJMoa020047]
4 **Hadziyannis SJ**, Sette H, Morgan TR, Balan V, Diago M, Marcellin P, Ramadori G, Bodenheimer H, Bernstein D, Rizzetto M, Zeuzem S, Pockros PJ, Lin A, Ackrill AM. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. *Ann Intern Med* 2004; **140**: 346-355 [PMID: 14996676 DOI: 10.7326/0003-4819-140-5-200403020-00010]
5 **Manns MP**, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, Goodman ZD, Koury K, Ling M, Albrecht JK. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet* 2001; **358**: 958-965 [PMID: 11583749 DOI: 10.1016/S0140-6736(01)06102-5]
6 **Hézode C**, Forestier N, Dusheiko G, Ferenci P, Pol S, Goeser T, Bronowicki JP, Bourlière M, Gharakhanian S, Bengtsson L, McNair L, George S, Kieffer T, Kwong A, Kauffman RS, Alam J, Pawlotsky JM, Zeuzem S. Telaprevir and peginterferon with or without ribavirin for chronic HCV infection. *N Engl J Med* 2009; **360**: 1839-1850 [PMID: 19403903 DOI: 10.1056/NEJMoa0807650]
7 **McHutchison JG**, Everson GT, Gordon SC, Jacobson IM, Sulkowski M, Kauffman R, McNair L, Alam J, Muir AJ. Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection. *N Engl J Med* 2009; **360**: 1827-1838 [PMID: 19403902 DOI: 10.1056/NEJMoa0806104]
8 **Akuta N**, Suzuki F, Seko Y, Kawamura Y, Sezaki H, Suzuki Y, Hosaka T, Kobayashi M, Kobayashi M, Saitoh S, Arase Y, Ikeda K, Kumada H. Determinants of response to triple therapy of telaprevir, peginterferon, and ribavirin in previous non-responders infected with HCV genotype 1. *J Med Virol* 2012; **84**: 1097-1105 [PMID: 22585728 DOI: 10.1002/jmv.23262]
9 **Ge D**, Fellay J, Thompson AJ, Simon JS, Shianna KV, Urban TJ, Heinzen EL, Qiu P, Bertelsen AH, Muir AJ, Sulkowski M, McHutchison JG, Goldstein DB. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. *Nature* 2009; **461**: 399-401 [PMID: 19684573 DOI: 10.1038/nature08309]
10 **Suppiah V**, Moldovan M, Ahlenstiel G, Berg T, Weltman M, Abate ML, Bassendine M, Spengler U, Dore GJ, Powell E, Riordan S, Sheridan D, Smedile A, Fragomeli V, Müller T, Bahlo M, Stewart GJ, Booth DR, George J. IL28B is associated with response to chronic hepatitis C interferon-alpha and ribavirin therapy. *Nat Genet* 2009; **41**: 1100-1104 [PMID: 19749758 DOI: 10.1038/ng.447]
11 **Tanaka Y**, Nishida N, Sugiyama M, Kurosaki M, Matsuura K, Sakamoto N, Nakagawa M, Korenaga M, Hino K, Hige S, Ito Y, Mita E, Tanaka E, Mochida S, Murawaki Y, Honda M, Sakai A, Hiasa Y, Nishiguchi S, Koike A, Sakaida I, Imamura M, Ito K, Yano K, Masaki N, Sugauchi F, Izumi N, Tokunaga K, Mizokami M. Genome-wide association of IL28B with response to pegylated interferon-alpha and ribavirin therapy for chronic hepatitis C. *Nat Genet* 2009; **41**: 1105-1109 [PMID: 19749757 DOI: 10.1038/ng.449]
12 **Kobayashi M**, Suzuki F, Akuta N, Sezaki H, Suzuki Y, Hosaka T, Kawamura Y, Kobayashi M, Saitoh S, Arase Y, Ikeda K, Chayama K, Miyakawa Y, Kumada H. Association of two polymorphisms of the IL28B gene with viral factors and treatment response in 1,518 patients infected with hepatitis C virus. *J Gastroenterol* 2012; **47**: 596-605 [PMID: 22438096 DOI: 10.1007/s00535-012-0531-1]
13 **Watanabe T**, Tanaka Y. IL28B: Drive the hepatitis C treatment setting toward a tailored approach. *Nagoya Med J* 2011; **52**: 51-56
14 **Fellay J**, Thompson AJ, Ge D, Gumbs CE, Urban TJ, Shianna KV, Little LD, Qiu P, Bertelsen AH, Watson M, Warner A, Muir AJ, Brass C, Albrecht J, Sulkowski M, McHutchison JG, Goldstein DB. ITPA gene variants protect against anaemia in patients treated for chronic hepatitis C. *Nature* 2010; **464**: 405-408 [PMID: 20173735 DOI: 10.1038/nature08825]
15 **Arenas M**, Duley J, Sumi S, Sanderson J, Marinaki A. The ITPA c.94C& gt; A and g.IVS2+21A& gt; C sequence variants contribute to missplicing of the ITPA gene. *Biochim Biophys Acta* 2007; **1772**: 96-102 [PMID: 17113761]
16 **Cao H**, Hegele RA. DNA polymorphisms in ITPA including basis of inosine triphosphatase deficiency. *J Hum Genet* 2002; **47**: 620-622 [PMID: 12436200 DOI: 10.1007/s100380200095]
17 **Stepchenkova EI**, Tarakhovskaya ER, Spitler K, Frahm C, Menezes MR, Simone PD, Kolar C, Marky LA, Borgstahl GE, Pavlov YI. Functional study of the P32T ITPA variant associated with drug sensitivity in humans. *J Mol Biol* 2009; **392**: 602-613 [PMID: 19631656 DOI: 10.1016/j.jmb.2009.07.051]
18 **Sumi S**, Marinaki AM, Arenas M, Fairbanks L, Shobowale-Bakre M, Rees DC, Thein SL, Ansari A, Sanderson J, De Abreu RA, Simmonds HA, Duley JA. Genetic basis of inosine triphosphate pyrophosphohydrolase deficiency. *Hum Genet* 2002; **111**: 360-367 [PMID: 12384777 DOI: 10.1007/s00439-002-0798-z]
19 **Suzuki F**, Suzuki Y, Akuta N, Sezaki H, Hirakawa M, Kawamura Y, Hosaka T, Kobayashi M, Saito S, Arase Y, Ikeda K, Kobayashi M, Chayama K, Kamatani N, Nakamura Y, Miyakawa Y, Kumada H. Influence of ITPA polymorphisms on decreases of hemoglobin during treatment with pegylated interferon, ribavirin, and telaprevir. *Hepatology* 2011; **53**: 415-421 [PMID: 21246582 DOI: 10.1002/hep.24058]
20 **Sakamoto N**, Tanaka Y, Nakagawa M, Yatsuhashi H, Nishiguchi S, Enomoto N, Azuma S, Nishimura-Sakurai Y, Kakinuma S, Nishida N, Tokunaga K, Honda M, Ito K, Mizokami M, Watanabe M. ITPA gene variant protects against anemia induced by pegylated interferon-α and ribavirin therapy for Japanese patients with chronic hepatitis C. *Hepatol Res* 2010; **40**: 1063-1071 [PMID: 20977565 DOI: 10.1111/j.1872-034X.2010.00741.x]
21 **Ochi H**, Maekawa T, Abe H, Hayashida Y, Nakano R, Kubo M, Tsunoda T, Hayes CN, Kumada H, Nakamura Y, Chayama K. ITPA polymorphism affects ribavirin-induced anemia and outcomes of therapy--a genome-wide study of Japanese HCV virus patients. *Gastroenterology* 2010; **139**: 1190-1197 [PMID: 20637204 DOI: 10.1053/j.gastro.2010.06.071]
22 **Azakami T**, Hayes CN, Sezaki H, Kobayashi M, Akuta N, Suzuki F, Kumada H, Abe H, Miki D, Tsuge M, Imamura M, Kawakami Y, Takahashi S, Ochi H, Nakamura Y, Kamatani N, Chayama K. Common genetic polymorphism of ITPA gene affects ribavirin-induced anemia and effect of peg-interferon plus ribavirin therapy. *J Med Virol* 2011; **83**: 1048-1057 [PMID: 21503919 DOI: 10.1002/jmv.22069]
23 **Osinusi A**, Naggie S, Poonia S, Trippler M, Hu Z, Funk E, Schlaak J, Fishbein D, Masur H, Polis M, Kottilil S. ITPA gene polymorphisms significantly affect hemoglobin decline and treatment outcomes in patients coinfected with HIV and HCV. *J Med Virol* 2012; **84**: 1106-1114 [PMID: 22585729 DOI: 10.1002/jmv.23302]
24 **De Franceschi L**, Fattovich G, Turrini F, Ayi K, Brugnara C, Manzato F, Noventa F, Stanzial AM, Solero P, Corrocher R. Hemolytic anemia induced by ribavirin therapy in patients

with chronic hepatitis C virus infection: role of membrane oxidative damage. *Hepatology* 2000; **31**: 997-1004 [PMID: 10733558 DOI: 10.1053/he.2000.5789]

25 **Russmann S**, Grattagliano I, Portincasa P, Palmieri VO, Palasciano G. Ribavirin-induced anemia: mechanisms, risk factors and related targets for future research. *Curr Med Chem* 2006; **13**: 3351-3357 [PMID: 17168855 DOI: 10.2174/092986706778773059]

26 **Hitomi Y**, Cirulli ET, Fellay J, McHutchison JG, Thompson AJ, Gumbs CE, Shianna KV, Urban TJ, Goldstein DB. Inosine triphosphate protects against ribavirin-induced adenosine triphosphate loss by adenylosuccinate synthase function. *Gastroenterology* 2011; **140**: 1314-1321 [PMID: 21199653 DOI: 10.1053/j.gastro.2010.12.038]

27 **Tanaka Y**, Kurosaki M, Nishida N, Sugiyama M, Matsuura K, Sakamoto N, Enomoto N, Yatsuhashi H, Nishiguchi S, Hino K, Hige S, Itoh Y, Tanaka E, Mochida S, Honda M, Hiasa Y, Koike A, Sugauchi F, Kaneko S, Izumi N, Tokunaga K, Mizokami M. Genome-wide association study identified ITPA/DDRGK1 variants reflecting thrombocytopenia in pegylated interferon and ribavirin therapy for chronic hepatitis C. *Hum Mol Genet* 2011; **20**: 3507-3516 [PMID: 21659334 DOI: 10.1093/hmg/ddr249]

28 **Thompson AJ**, Fellay J, Patel K, Tillmann HL, Naggie S, Ge D, Urban TJ, Shianna KV, Muir AJ, Fried MW, Afdhal NH, Goldstein DB, McHutchison JG. Variants in the ITPA gene protect against ribavirin-induced hemolytic anemia and decrease the need for ribavirin dose reduction. *Gastroenterology* 2010; **139**: 1181-1189 [PMID: 20547162 DOI: 10.1053/j.gastro.2010.06.016]

29 **Thompson AJ**, Santoro R, Piazzolla V, Clark PJ, Naggie S, Tillmann HL, Patel K, Muir AJ, Shianna KV, Mottola L, Petruzzellis D, Romano M, Sogari F, Facciorusso D, Goldstein DB, McHutchison JG, Mangia A. Inosine triphosphatase genetic variants are protective against anemia during antiviral therapy for HCV2/3 but do not decrease dose reductions of RBV or increase SVR. *Hepatology* 2011; **53**: 389-395 [PMID: 21274861 DOI: 10.1002/hep.24068]

30 **Eskesen AN**, Melum E, Moghaddam A, Bjøro K, Verbaan H, Ring-Larsen H, Dalgard O. Genetic variants at the ITPA locus protect against ribavirin-induced hemolytic anemia and dose reduction in an HCV G2/G3 cohort. *Eur J Gastroenterol Hepatol* 2012; **24**: 890-896 [PMID: 22584257 DOI: 10.1097/MEG.0b013e3283546efd]

31 **Doyle JS**, Hellard ME, Thompson AJ. The role of viral and host genetics in natural history and treatment of chronic HCV infection. *Best Pract Res Clin Gastroenterol* 2012; **26**: 413-427 [PMID: 23199501 DOI: 10.1016/j.bpg.2012.09.004]

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BRIEF ARTICLE

Outcome of patients with primary sclerosing cholangitis and ulcerative colitis undergoing colectomy

Sombat Treeprasertsuk, Einar Björnsson, Emmanouil Sinakos, Emma Weeding, Keith D Lindor

Sombat Treeprasertsuk, Division of Gastroenterology, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand
Einar Björnsson, Department of Internal Medicine, Section of Gastroenterology and Hepatology, The National University Hospital of Iceland, IS121 Reykjavik, Iceland
Emmanouil Sinakos, Emma Weeding, Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN 55905, United States
Keith D Lindor, Health Solutions, Arizona State University, AZ 85004, United States
Author contributions: Treeprasertsuk S designed study, interpreted data and wrote the manuscript; Treeprasertsuk S and Sinakos E collected data; Björnsson E, Weeding E and Lindor KD analyzed data; Björnsson E and Lindor KD revised the manuscript.
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Correspondence to: Sombat Treeprasertsuk, MD, PhD, Associate Professor, Division of Gastroenterology, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Rama4 Road, Pathumwan District, Bangkok 10330, Thailand. battan5410@gmail.com
Telephone: +66-2-2564265 Fax: +66-2-2527839
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Abstract

AIM: To study the outcomes of primary sclerosing cholangitis (PSC) patients with ulcerative colitis (UC) undergoing colectomy.

METHODS: We identified 193 patients with PSC and UC undergoing colectomy at the Mayo Clinic (Rochester, MN, United States), between January 1, 1995 and December 31, 2008 using a computerized record system. Eighty-nine patients were excluded due to unclear diagnosis, liver transplantation prior to colectomy, age less than 18 years, inadequate follow-up data or known cases of cholangiocarcinoma. We retrospectively reviewed data from patient medical records. Clinical information, date of colectomy, preoperative and follow-up liver tests and pathological findings of the colon were reviewed. The Mayo risk score at baseline was calculated to obtain survival estimates for up to 4 years of follow-up. The primary endpoint was defined by the presence of all-cause mortality and/or liver decompensation requiring liver transplantation. All patients who did not have a clinical note on December 31, 2008 were considered as patients with an incomplete follow-up unless they reached a study endpoint (death or underwent liver transplantation) prior to that date. The study was approved by the Institutional Review Boards of the Mayo Clinic.

RESULTS: Of the 2441 patients with PSC observed in this period, 104 patients (4.3%) had UC and underwent colectomy and were included. The median age was 43.2 years, and 67% were male. The leading indications for colectomy were severe colonic inflammation (49%), the presence of colonic dysplasia during routine surveillance (42%) and bowel perforation (3%). Twenty-six patients were lost to follow-up after a median duration of 3.9 years. The remaining 78 patients included 52 patients (66.7%) who were followed for a median duration of 5.5 years and 26 patients (33.3%) who developed primary endpoints including death (n = 13) or underwent liver transplantation (n = 13) with a median follow up of 2.6 years. For the secondary endpoint, the liver complications within 1 mo following the colectomy were found in 9 patients (8.6%) and included worsening liver tests (n = 3), liver failure requiring liver transplantation (n = 2), acute cholangitis (n = 3) and right hepatic vein thrombosis with hepatic infarct (n = 1). A multivariate logistic analysis demonstrated that only lower platelet count and lower albumin level preoperatively were significantly associated with more primary endpoints (OR = 0.99 and 0.05 respectively).

CONCLUSION: One third of patients with PSC and UC

undergoing colectomy died or underwent liver transplantation within 2.6 years. PSC patients with lower platelet counts and lower albumin levels were significantly more likely to have a poorer outcome.

Key words: Prognosis; Colectomy; Primary sclerosing cholangitis; Ulcerative colitis; Outcomes

Core tip: To study the outcomes of primary sclerosing cholangitis (PSC) patients with ulcerative colitis (UC) undergoing colectomy. We identified 193 patients with PSC and UC undergoing colectomy at the Mayo Clinic (Rochester, MN, United States), between January 1, 1995 and December 31, 2008. Eighty-nine patients were excluded. Of the 2441 patients with PSC, 104 patients (4.3%) had UC and underwent colectomy and were included. The median age was 43.2 years. One third of patients with PSC and UC undergoing colectomy died or underwent liver transplantation within 2.6 years. PSC patients with lower platelet counts and lower albumin levels were significantly more likely to have a poorer outcome.

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INTRODUCTION

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease and is associated with inflammatory bowel disease (IBD) in 60%-80% of patients[1-3]. Ulcerative colitis (UC) is more commonly prevalent than Crohn's disease (CD) in patients with PSC[4,5]. The colitis associated with PSC has unique findings and is usually extensive[4,6]. UC in patients with PSC is associated with an increased risk of colorectal neoplasia compared to patients with UC alone (OR = 4.8)[7]. The incidence of colorectal neoplasia at 5 years in PSC patients with IBD is significantly higher than in patients with UC alone (33% *vs* 13%, $P = 0.054$; borderline statistical significance by unmatched log rank test)[4].

A recent study reported that PSC was the third leading cause (15.4%) of abnormal liver tests among 545 patients with underlying IBD undergoing colectomy with ileal pouch-anal anastomosis (IPAA), after a transient elevation of liver tests (49%) and fatty liver (15.4%)[8]. Another study evaluated the progression of liver disease after proctocolectomy in patients with PSC and UC[9]. After proctocolectomy with IPAA, they found that 5 of 30 patients (16.7%) underwent liver transplantation at intervals of 1 to 11 years[9]. Previous studies have shown that patients with liver cirrhosis can experience worsening of their liver disease after surgery and poor outcomes[10,11]. Surgery may lead to severe complications such as decompensated liver disease, worsening of a pre-existing decompensation or even death. Very limited information exists on the prognosis of patients with PSC and UC undergoing colectomy[12]. We aimed to assess the outcomes and predictors of outcomes of PSC patients undergoing colectomy at the Mayo Clinic, Rochester, MN, United States.

MATERIALS AND METHODS

This was a retrospective study using a computerized record system of patients who had been diagnosed with PSC and UC and were undergoing colectomy at the Mayo Clinic, Rochester, MN, United States, between January 1, 1995 and December 31, 2008. PSC was defined as present when all the following criteria were met: (1) chronic cholestatic disease of at least six months' duration; (2) elevation of serum alkaline phosphatase (ALP) levels; (3) retrograde, operative, percutaneous or magnetic resonance cholangiography demonstrating intrahepatic and/or extrahepatic biliary duct obstruction, beading or narrowing consistent with PSC; and (4) exclusion of secondary sclerosing cholangitis or other causes of cholestatic liver diseases[3].

A diagnosis of PSC was made using the Hospital International Classification of Disease Adaptation (HICDA) codes of 05760310. A diagnosis of IBD was based on the following HICDA codes: cholangitis, sclerosing (05760310); disease, Crohn's, nos (05630110); enteritis, regional, nos (05630111); ileitis (regional)-see also enteritis (05630112); colitis, Crohn's (05630113); disease, Crohn's, recurrent (05630120); enteritis, regional, recurrent (05630121); colitis, ulcerative, chronic-cuc (05631110); colitis, ulcerative, nos (05631120); colitis, thrombo-ulcerative (05631121); colitis, ulcerative, acute (05631130); colitis, granulomatous (05632110); disease, granulomatous, colon (05632111); disease, inflammatory bowel, nos (05639212). HICDA is an adaptation of the International Classification of Diseases (ICD)-8 for hospital morbidity, which was used at Mayo Clinic to maintain continuity of the Medical Index and the Rochester Epidemiology Project for on-going longitudinal studies[13]. Of the 2441 patients with PSC, we identified 193 PSC patients with IBD (7.9%) who had undergone colectomy and retrospectively reviewed data from their medical records.

We retrospectively reviewed data from the medical records. A detailed history and physical examination was recorded by a health care provider using standardized protocols. Clinical information, date of colectomy, preoperative and follow-up liver tests and pathological findings of the colon were reviewed. The Mayo risk score at baseline was calculated to obtain survival estimates through up to 4 years of follow-up. The Mayo risk score calculations can be accessed from the web site: http://www.mayoclinic.org/gi-rst/mayomodel3.html, and the MELD

model/UNOS modification can be accessed from http://www.mayoclinic.org/ meld/mayomodel6.html.

Inclusion criteria

We included PSC patients who underwent colectomy and had results of preoperative liver tests and at least one post-operatively. Colectomy cases included open or laparoscopic colectomy. All included patients must have had at least one follow-up visit after the colectomy. The liver tests included total bilirubin, direct bilirubin, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and ALP levels in the serum.

Exclusion criteria

Of the 193 patients with PSC and UC undergoing colectomy, we excluded the patients with the followings: underwent liver transplantation prior to colectomy, inadequate follow-up data, CD, age less than 18 years and known cases of cholangiocarcinoma.

Follow-up data

The primary endpoint was defined as the presence of all-cause mortality and/or liver decompensation requiring liver transplantation and it has been measured at 1 mo and at the end of follow-up. All causes of death listed on the death certificates or pathological findings (underlying, intermediate, immediate and other major conditions) were recorded using the ICD-10 revision.

The secondary end point was defined as the presence of liver complications post-operatively occurred within 1 mo which included ascites, variceal bleeding, clinical hepatic encephalopathy or liver failure and required hospitalization. The worsening liver tests were defined as increases in AST, ALT or total bilirubin to at least 2-fold greater than the baseline values. Other information including the the length of hospital stay and general post-operative complications were recorded.

All patients who did not have a clinical note on December 31, 2008 (the end of follow up in this study) were considered as patients with incomplete follow up unless they developed an endpoint (death or underwent liver transplantation) prior to that date. The study was approved by the Institutional Review Boards of the Mayo Clinic, and all participants provided permission for their medical information to be used for research.

Statistical analysis

Statistical analyses were performed with SPSS version 15.0 software. Subjects were categorized by the presence or absence of primary endpoints. Continuous variables were presented as the mean ± SD or median [interquartile range (IQR)] as appropriate. Comparisons between the two groups were performed using independent *t* tests if values were normally distributed or by the Wilcoxon rank sum test if the distribution was not normal. Categorical data were presented as numbers (percentage) and were compared by Fisher's exact test or the χ^2 test where appropriate. All tests were two sided, and the chosen level of significance was $P < 0.05$. A logistic regression analysis was used to identify factors significantly associated with the presence of primary endpoints in PSC patients with UC undergoing colectomy. Only variables with a P value < 0.1 in a univariate analysis were included in the multivariate analysis. We estimated receiver operating characteristic (ROC) curves of related variables for detection of the primary endpoints in patients with PSC to maximize the area under the curve (AUC).

RESULTS

Clinical features at presentation

Of the 2441 patients with PSC, 193 patients with PSC and UC undergoing colectomy were identified. Eighty-nine patients were excluded due to liver transplantation prior to colectomy (n = 30), inadequate follow-up data (n = 35), CD (n = 16), age less than 18 years (n = 6) and known cases of cholangiocarcinoma (n = 2). The remaining of 104 patients (4.3% of 2441 PSC patients) were included in this study. The median age was 43.2 years, and 67% were male. The demographic and biochemical data of the 104 patients are shown in Table 1. The median (IQR) Mayo risk score was -0.05 (-0.7, 1.1) while the median (IQR) MELD score was 9 (6, 12). The leading indications for colectomy were severe colonic inflammation (49%), colonic dysplasia observed during routine surveillance (42%) and bowel perforation (3%). Most of the preoperative total bilirubin, direct bilirubin and albumin levels were within normal range, while the mean ALP value was two fold greater than normal.

Clinical outcomes

Table 1 summarizes the postoperative clinical outcomes of the 104 patients with a median (IQR) hospital stay of 7 d (6, 11). Of 104 patients with PSC and UC, 26 were lost to follow-up after a median duration of 3.9 years. The remaining 78 patients included 52 patients (66.7%) who continued follow up, with a median duration of 5.5 years, and 26 patients developed primary endpoints including death or underwent liver transplantation (33.3%), with a median follow up of 2.6 years (Figure 1). The causes of death of the 13 patients were liver-related complications: hepatocellular carcinoma, hepatic renal syndrome and/or liver failure (n = 4), metastatic cancer to the liver (n = 5), acute cholangitis (n = 1), amyloidosis (n = 1) and unknown causes (n = 2). Two patients died at 10 and 20 d following colectomy. For the secondary endpoint, the liver complications within 1 mo following the colectomy were found in 9 patients (8.6%) and included worsening liver tests (n = 3), liver failure requiring liver transplantation (n = 2), acute cholangitis (n = 3) and right hepatic vein thrombosis with hepatic infarct (n= 1) (Table 2). General postoperative complications were found in 36 patients (34.6%) within 1 mo. The most common complications were anemia or blood loss requiring blood transfusion (n = 11; 10.6%), intra-abdominal abscess requiring drainage (n = 4; 3.8%), acute bowel obstruction

Table 1 Baseline characteristics data, laboratory tests and clinical outcomes of 104 patients with primary sclerosing cholangitis and ulcerative colitis who underwent colectomy

Patient characteristics[1]	Total (n = 104)	Patients who continued follow-up or developed primary endpoints (n = 78)
Baseline characteristics data		
Age at colectomy (yr)	43 (30-53)	42 (28-52)
Gender, male	70 (67)	56 (72)
Race, Caucasian	98 (94)	76 (97)
Presence of advanced liver fibrosis at baseline	27 (32)	24 (39)
Mayo risk score at baseline	-0.05 (-0.7, 1.1)	-0.001 (-0.8, 1.4)
BMI (kg/m^2)	25 (22.6, 28.6)	24.7 (22, 27.4)
Previous use of immunosuppressive drugs	38 (36.5)	29 (37)
History of receiving ursodeoxycholic acid	33 (31.7)	26 (33.3)
Diabetes mellitus or impaired glucose tolerance	7 (7)	6 (7.6)
History of current smoking	2 (2)	2 (2.6)
Indication for colectomy		
Severe colonic inflammation	51 (49)	37 (47)
Colonic dysplasia	44 (42)	36 (46)
Bowel perforation	3 (2.8)	3 (3.8)
Other indications	6 (5.7)	2 (2.6)
Laboratory tests at baseline		
ALT (< 40 U/L)	70 (43, 113)	73 (43, 135)
AST (< 40 U/L)	50 (30, 96)	55 (32, 100)
Albumin (g/dL)	3.9 (3.5, 4.2)	3.9 (3.5, 4.2)
Total bilirubin (mg/dL)	0.7 (0.5, 1.5)	0.8 (0.5, 1.9)
Direct bilirubin (mg/dL)	0.2 (0.1, 0.7)	0.3 (0.1, 0.9)
ALP (U/L)	359 (194, 657)	385 (197, 839)
Glucose (mg/dL)	93 (86, 106)	93.5 (86, 107)
Creatinine (mg/dL)	1.0 (0.9, 1.1)	1.0 (0.9, 1.1)
CA 19-9 (normal < 55 U/mL)	17.2 (8.8, 51)	16.8 (8.5, 51)
Platelet (× 10^9/L)	289 (201, 350)	289 (205, 351)
INR	1 (0.9, 1.1)	1 (0.9, 1.1)
Clinical outcomes at the end of follow-up		
Undergoing Ileal pouch-anal anastomosis	78 (75)	58 (74)
Length of hospital stay (d)	7 (6, 11)	8 (5, 12)
New diagnosis of malignancy after colectomy	32 (30.8)	26 (33.4)
Colorectal cancer	19 (18.3)	13 (16.7)
Other malignancy	13 (12.5)	13 (16.7)
Pathological findings		
Colonic inflammation	62 (60)	45 (57.7)
Presence of colonic dysplasia	24 (23)	21 (27)
Colon cancer	19 (18.3)	12 (15.4)
Post-operative general complications within 1 mo	36 (34.6)	34 (43.6)
Post-operative liver complications within 1 mo	9 (8.7)[2]	9 (11.5)
Results of follow-up		
All-cause mortality	13 (12.5)	13 (16.7)
Liver transplantation	13 (12.5)	13 (16.7)
Continued follow-up	52 (50)	52 (66.6)
Lost to follow-up	13 (25.0)	-

[1]Median (interquartile range; IQR) or n (%); [2]Including worsening liver tests (n = 3), liver failure requiring liver transplantation (n = 2), acute cholangitis (n = 3) and right hepatic vein thrombosis with hepatic infarct (n = 1). BMI: Body mass index; ALT: Alanine transaminase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; CA 19-9: Cancer antigen 19-9.

requiring re-exploration (n = 4; 3.8%), bowel ileus (n = 4; 3.8%), high ileostomy output (n = 3; 2.8%), wound infection or delayed wound healing (n = 3; 2.8%) and other complications (n = 8; 7.7%) including urinary retention (n = 3), fever with unknown causes (n = 2), acute pancreatitis (n = 1), abdominal pain with unknown causes (n = 1) and portal vein thrombosis (n = 1).

By the end of the follow-up of patients with PSC and UC who underwent colectomy, 13 patients developed colorectal cancer (15%) and 13 patients (16.7%) were diagnosed with other malignancies. The primary location of the malignancies were cholangiocarcinoma (n = 6), hematologic malignancy (n = 4), gallbladder cancer (n = 1), hepatocellular carcinoma (n = 1) and intradural extramedullary spinal cord tumor (n = 1). Colonic dysplasia was found in 21 patients (21.2%) including low-grade dysplasia in 16 and high grade dysplasia in 5.

Predictors for primary endpoints (death or undergoing liver transplantation)

Table 3 shows the comparison of clinical characteristics of the 78 PSC patients with UC who underwent colectomy based on the presence of primary endpoints. Table 4 shows the results of 3 models from the multivariate analysis to identify the best-fit model for predictors of primary endpoints. Model 1 was the best-fit model, which found that only a higher platelet count and higher albumin level preoperatively were significantly associated with fewer primary endpoints (OR = 0.99 and 0.05, respectively; P < 0.05). Using the ROC curves for the detection of primary endpoints, we found that a preoperative platelet count of 194 × 10^9/L was the best cutoff value based on a sensitivity of 46%, a specificity of 88.5%, a positive predictive value (PPV) of 66.7%, and an negative predictive value (NPV) of 76.7% with an AUC of 0.67. The best cutoff value of the preoperative albumin level for the presence of primary endpoints was 3.7 g/dL with a sensitivity of 73%, a specificity of 82%, a PPV of 70%, an NPV of 84%, and an AUC of 0.80.

Figure 2 shows the survival curve of the 104 patients with PSC and UC who underwent colectomy. The smooth line represents median survival estimates calculated from the Mayo risk scores at baseline, and the stepped line corresponds to survival per the Kaplan-Meier method. The two survival curves were found to significantly differ over this time period (P = 0.01) which indicated that PSC patients with UC who underwent colectomy died or required liver transplantation more often than those PSC patients with UC who had no colectomy regarding to the same baseline calculated Mayo risk scores.

DISCUSSION

Our study indicates that one third of PSC patients with UC who underwent colectomy died or required liver transplantation within an average interval of 2.6 years. This result was similar to a previous study from the Cleveland Clinic showing that 38% of cirrhotic patients with PSC who underwent colectomy experienced early

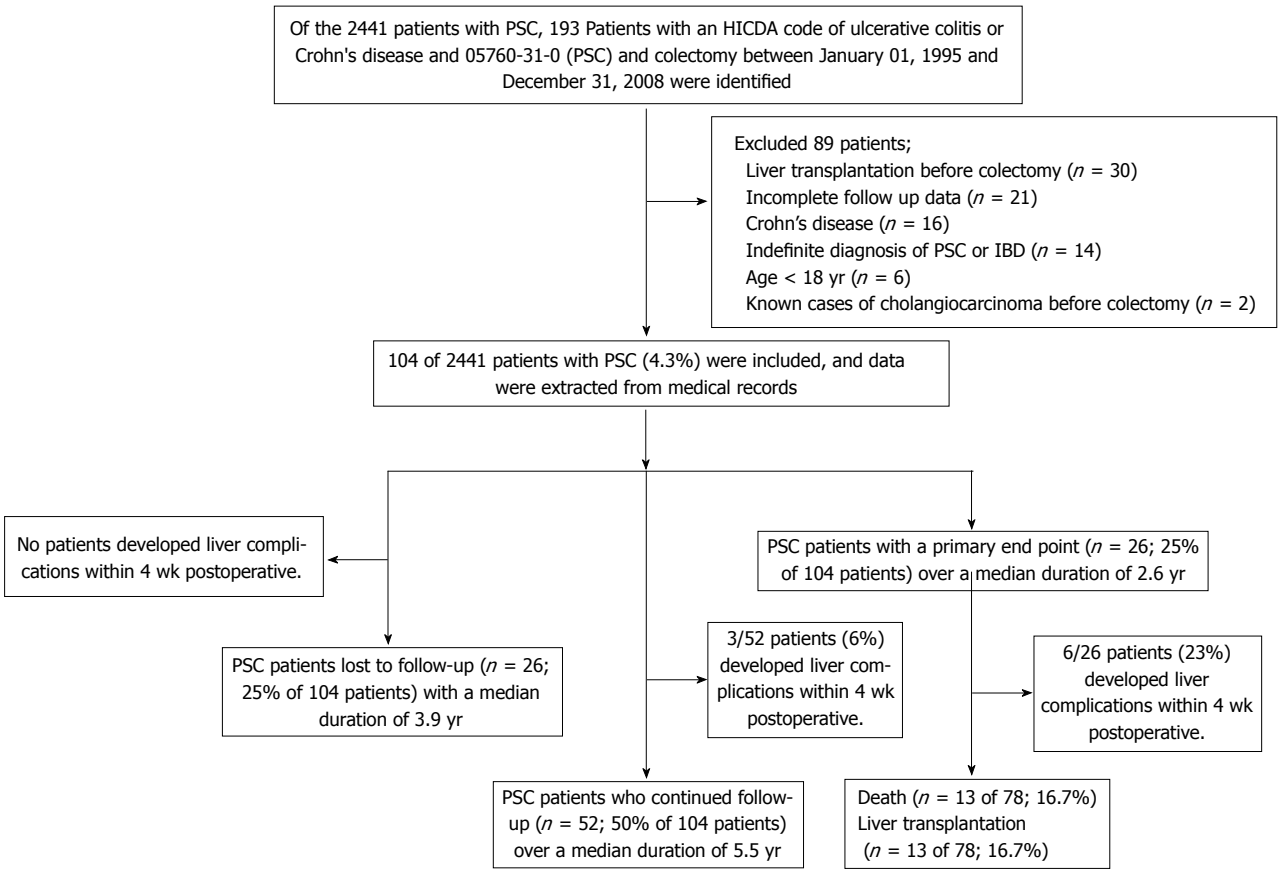

Figure 1 Outcomes of 104 patients with primary sclerosing cholangitis and ulcerative colitis who underwent colectomy. IBD: Inflammatory bowel disease; PSC: Primary sclerosing cholangitis; HICDA: Hospital international classification of disease adaptation.

Table 2 Nine patients with primary sclerosing cholangitis and ulcerative colitis who underwent colectomy had worsening liver tests postoperatively

Case, Sex	Age at colectomy (yr)	Presence of advanced liver fibrosis	Pathological findings in the colon	Blood loss requiring transfusion	Liver complications	Other complications	Length of stay (d)	Presence of primary endpoints	Duration of follow up (yr)
1, M	28	Yes	Moderate inflammation	No	Worsening liver tests	Abdominal pain, Dehydration	18	No	8.5
2, M	28	Yes	Transverse colon cancer grade 3/4 T3N2	Yes; 2 units	Worsening liver tests	High ileostomy output	15	Death; colon cancer metastasis to liver	1.2
3, F	52	Yes	Mild inflammation	No	Worsening liver tests	Delayed wound healing, Blood loss	8	Death; liver failure	0.3
4, M	32	No	Moderate inflammation	No	Acute cholangitis	None	9	Liver transplant	1.1
5, M	33	Yes	Moderate inflammation	No	Acute cholangitis	None	6	No	8.3
6, F	54	No	Mild inflammation	Yes; 6 units	Liver failure	Severe blood loss, shock	8	Liver transplant; liver failure	0.3
7, F	21	Yes	Necrotized distal ileum with perforation	Yes; 9 units	Liver failure	DIC, Respiratory failure, GI-bleeding	30	Death; liver failure	0.03 (12 d)
8, F	21	No	Moderate inflammation	Yes; 2 units	SMV and hepatic vein thrombosis	Anemia,	15	Death; liver failure	8
9, M	41	No	Moderate inflammation	No	Acute cholangitis	Wound infection	10	No	3.6

M: Male; F: Female; DIC: Disseminated intravascular coagulation; HCC: Hepatocellular carcinoma; SMV: Superior mesenteric vein.

Table 3 A comparison of the clinical characteristics of 78 patients with primary sclerosing cholangitis and ulcerative colitis who underwent colectomy categorized by the presence or absence of primary endpoints

Clinical characteristics[1]	Without primary endpoints (n = 52)	With primary endpoints (n = 26)	P value[2]
Gender, %female	11 (21)	11 (42)	0.05[2]
Age at colectomy (yr)	38.7 (27.8, 51.6)	45.8 (29.4, 52)	0.40
Presence of advanced liver fibrosis	12 (23)	12 (46)	0.03[2]
Pre-operative Mayo risk score	-0.1 (-0.9, 0.9)	1.3 (-0.2, 2.2)	0.01[2]
Pre-operative MELD score	7 (6, 9)	14 (11, 18)	< 0.001[2]
History of anemia or blood loss requiring a post-operative blood transfusion within 1 mo	4 (7.7)	7 (27)	0.02[2]
Post-operative liver complications within 1 mo	3 (5.8)	6 (23)	0.02[2]
Length of hospital stay (d)	7 (5, 10)	9 (7, 15)	0.07
Hemoglobin (g/dL)	13.1 (11.9, 14.4)	10.8 (9.8, 13.1)	< 0.001[2]
Platelet count (× 10^9/L)	296 (247, 357)	244 (126, 337)	0.02[2]
INR	0.9 (0.9, 1.0)	1.1 (1.1, 1.3)	< 0.001[2]
Total bilirubin (mg/dL)	0.7 (0.5, 1.3)	2.3 (0.6, 5.0)	0.001[2]
Direct bilirubin (mg/dL)	0.2 (0.1, 0.4)	0.9 (0.2, 3.5)	0.002[2]
ALP (U/L)	352 (180, 494)	709 (276, 1232)	0.003[2]
AST (U/L)	44 (31, 90)	80 (36, 129)	0.09
Albumin (g/dL)	4.1 (3.4, 4.3)	3.5 (3.3, 3.9)	< 0.001[2]
Duration of follow up from colectomy to the last follow-up (yr)	5.5 (3.8, 8.8)	2.6 (0.8, 5.6)	0.007[2]

[1]Median [interquartile range (IQR)] or n (%); [2]P value < 0.05 for primary sclerosing cholangitis patients with or without primary endpoints and those variables with a P value < 0.1 in a univariate analysis were included in the multivariate analysis. AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; MELD: Model for End-Stage Liver Disease.

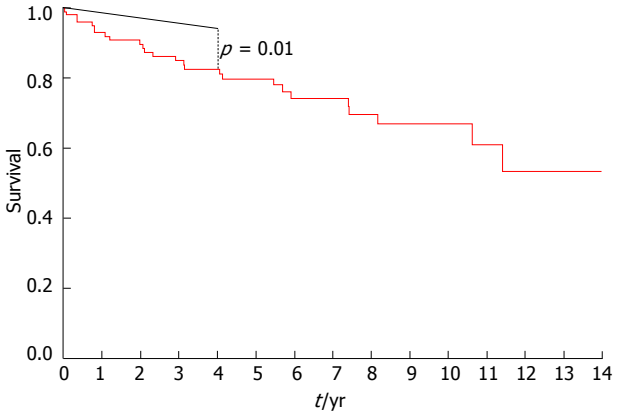

Figure 2 The survival curves of 104 patients with primary sclerosing cholangitis and ulcerative colitis undergoing colectomy. The smooth line represents the median survival estimate calculated from the Mayo risk scores at baseline, and the stepped line corresponds to survival calculated using the Kaplan-Meier method. The two survival curves were found to significantly differ over this time period (P = 0.01) which indicated that primary sclerosing cholangitis (PSC) patients with ulcerative colitis who underwent colectomy died or required liver transplantation more often than those PSC patient with ulcerative colitis who had no colectomy regarding to the same baseline calculated Mayo risk scores.

postoperative death compared to 0% of non-cirrhotic patients[14]. However, the previous study was limited by the small number of included patients with PSC who underwent colectomy (n = 24) and the need for a preoperative diagnosis of cirrhosis. The present study builds on previous reports from our center regarding the risk of colectomy in patients with PSC and UC[15,16].

However, three previous studies reported that proctocolectomy had little effect on the progression of liver disease in patients with PSC and UC and there was no significant difference in the survival of patients undergoing colectomy compared to unoperated patients[17-20]. A study from England showed that PSC patients who underwent colectomy prior to or concurrent with liver transplantation (n = 17) had a mortality rate of 12%, and they concluded that colectomy was a relatively safe procedure and believed that considering colectomy pre-, during, or shortly after liver transplantation in selected patients with risk factors for colorectal cancer would reduce the risk of colorectal cancer[19]. The low colectomy rate of 4% in our study might reflect the usually quiescent colitis in PSC. The majority of our patients were the large duct PSC which might have an impact on the poorer outcome from liver complications[9,21,22]. Recently, the outcomes after elective colectomy in patients with cirrhosis were examined and showed that cirrhotic patients undergoing colectomy had a 3.7-fold increased risk of death (HR of 3.7; 95%CI: 2.6-5.2)[23]. The in-hospital mortality (6%), length of stay (9 d), and total expenses of cirrhotic patients were significantly higher than for those without cirrhosis[23,24].

Our results showed that a lower platelet count and lower albumin level preoperatively were associated with poorer outcomes. Thus, using simple preoperative blood test screening may provide useful information for monitoring patients pre-operatively. The timing of colectomy is an important issue. Recently, a study from Italy[20] showed that eight of 16 patients with PSC and UC post-liver transplantation had active colitis despite immunosuppressive medications with a median interval from liver transplantation to colectomy of 6.5 years. Few studies showed that the colitis condition in PSC patients with UC remained inactive or under controlled of at least 60% of cases after orthotopic liver transplantation[25,26]. Another studied revealed that liver transplantation for PSC independently reduced the need for colectomy (HR = 0.43; 95%CI: 0.25-0.75; P = 0.003)[11] Additionally, the presence of colon carcinoma and high grade dysplasia were more frequent in the non liver transplantation group and this group of patient had increased inflammation of the colonic mucosa at histology (P = 0.011)[10]. Thus, the patients with severe progressive PSC requiring liver transplantation should proceeded for supportive care of colitis and listed for liver transplantation which might reduced the disease activity of UC and the need for colectomy[10,11].

About 17% of our PSC patients with UC developed colorectal cancer, which was similar to a previous report from England showing that the cumulative risks of developing colorectal cancer in patients with an intact colon and IBD were 14% and 17% after 5 and 10 years, respec-

Table 4 Multivariate analysis models showing the association between primary sclerosing cholangitis patients with ulcerative colitis who underwent colectomy and the primary endpoints

Multivariate analysis	*P* value	OR	95%CI
Model 1[1]			
Platelet (× 10^9/L)	0.030	0.991	0.98-0.999
Albumin (g/dL)	0.006	0.05	0.007-0.44
Model 2[2]			
Pre-operative Mayo risk score	0.390	1.2	0.77-1.97
Hemoglobin (g/dL)	0.010	0.6	0.45-0.91
Model 3[3]			
Pre-operative MELD score	0.090	18.6	0.6-567
Hemoglobin (g/dL)	0.090	0.03	0.001-1.9

[1]Model 1, to avoid overestimation of the model, we excluded the Mayo risk score and the Model for End-Stage Liver Disease (MELD) score from model 1; [2]Model 2, we included the Mayo risk score in the model and removed the individual variables used for Mayo risk score calculation; [3]Model 3, we included the MELD score in the model and removed the individual variables used for MELD score calculation. $P < 0.05$, all variables with $P < 0.1$ in a univariate analysis were included in the multivariate analysis models.

tively[19]. Recent study showed that the colonic neoplasms that developed in PSC-UC patients were spread throughout the colon on colonoscopy and they were found predominantly on right sided colon[5]. Thus, surveillance colonoscopy and biopsies should be performed in patients with PSC and UC at 1-year to 2-year intervals[3].

The main strengths of our study are the inclusion of a large number of PSC patients with PSC and UC and the available clinical data and pathological findings, which were useful for outcome assessment. However, our study is limited by its retrospective nature in a tertiary center, and it contains data derived from multiple physicians from 1995 to 2008, which may have resulted in a selection bias. Additionally, surgeons excluded the colectomy procedure for all patients with poor liver conditions. Second, we included all PSC patients who underwent colectomy and had results from preoperative liver tests and at least one post-operative test, which may explain the small number of patients with liver complications. Thus, further multicenter prospective studies of post-operative liver complications and poor outcomes in patients with PSC and UC undergoing colectomy should be performed to provide clearer guidance for the selection of patients to be referred for a liver transplantation and colectomy rather than colectomy alone.

Unfortunately, we had to exclude a number of patients (10%) who had incomplete data because they were lost to follow-up. Additionally, the Mayo risk score and MELD score could not be calculated annually from our retrospective data therefore the colectomy might changed the progression of the PSC severity which cannot be concluded. Last, we had only a small number of patients with liver complications, and we can therefore not draw a firm conclusion regarding the association between liver complications and poor outcomes.

In conclusion, one third of PSC patients with UC who underwent colectomy died or underwent liver transplantation within an average interval of 2.6 years. PSC patients with advanced liver fibrosis (lower platelet count and lower albumin level) and UC who underwent colectomy were associated with significantly poorer outcomes.

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COMMENTS

Background

The colitis associated with primary sclerosing cholangitis (PSC) has unique findings and is usually extensive. Ulcerative colitis (UC) in patients with PSC is associated with an increased risk of colorectal neoplasia compared to patients with UC alone. Previous studies have shown that patients with liver cirrhosis can experience worsening of their liver disease after surgery and poor outcomes. Surgery may lead to severe complications such as decompensated liver disease, worsening of a pre-existing decompensation or even death. Very limited information exists on the prognosis of patients with PSC and UC undergoing colectomy.

Research frontiers

Authors aimed to assess the outcomes and predictors of outcomes of PSC patients undergoing colectomy at the Mayo Clinic, Rochester, MN, United States.

Innovations and breakthroughs

One third of patients with PSC and UC undergoing colectomy died or underwent liver transplantation within 2.6 years. PSC patients with lower platelet counts and lower albumin levels were significantly more likely to have a poorer outcome.

Applications

PSC patients with UC who underwent colectomy died or required liver transplantation more often than those PSC patients with UC who had no colectomy regarding to the same baseline calculated Mayo risk scores.

Terminology

The primary endpoint was defined as the presence of all-cause mortality and/or liver decompensation requiring liver transplantation and it has been measured at 1 mo and at the end of follow-up. All causes of death listed on the death certificates or pathological findings (underlying, intermediate, immediate and other major conditions) were recorded using the International Classification of Diseases-10 revision. The secondary end point was defined as the presence of liver complications post-operatively occurred within 1 mo which included ascites, variceal bleeding, clinical hepatic encephalopathy or liver failure and required hospitalization To concisely and accurately describe, define or explain the specific, unique terms that are not familiar to majority of the readers, but are essential for the readers to understand the article.

Peer review

Few studies showed that the colitis condition in PSC patients with UC remained inactive or under controlled of at least 60% of cases after orthotopic liver transplantation. Another studied revealed that liver transplantation for PSC independently reduced the need for colectomy. Additionally, the presence of colon carcinoma and high grade dysplasia were more frequent in the non liver transplantation group and this group of patient had increased inflammation of the colonic mucosa at histology. Thus, the patients with severe progressive PSC requiring liver transplantation should proceeded for supportive care of colitis and listed for liver transplantation which might reduced the disease activity of UC and the need for colectomy.

REFERENCES

1 **Broomé U**, Olsson R, Lööf L, Bodemar G, Hultcrantz R, Danielsson A, Prytz H, Sandberg-Gertzén H, Wallerstedt S, Lindberg G. Natural history and prognostic factors in 305 Swedish patients with primary sclerosing cholangitis. *Gut* 1996; **38**: 610-615 [PMID: 8707097 DOI: 10.1136/gut.38.4.610]

2 **Wiesner RH**, Grambsch PM, Dickson ER, Ludwig J, MacCarty RL, Hunter EB, Fleming TR, Fisher LD, Beaver SJ, LaRusso NF. Primary sclerosing cholangitis: natural history, prognostic factors and survival analysis. *Hepatology* 1989; **10**: 430-436 [PMID: 2777204 DOI: 10.1002/hep.1840100406]

3 **Chapman R**, Fevery J, Kalloo A, Nagorney DM, Boberg KM, Shneider B, Gores GJ. Diagnosis and management of primary sclerosing cholangitis. *Hepatology* 2010; **51**: 660-678 [PMID: 20101749 DOI: 10.1002/hep.23294]

4 **Loftus EV**, Harewood GC, Loftus CG, Tremaine WJ, Harmsen WS, Zinsmeister AR, Jewell DA, Sandborn WJ. PSC-IBD: a unique form of inflammatory bowel disease associated with primary sclerosing cholangitis. *Gut* 2005; **54**: 91-96 [PMID: 15591511 DOI: 10.1136/gut.2004.046615]

5 **Navaneethan U**, Venkatesh PG, Lashner BA, Remzi FH, Shen B, Kiran RP. Temporal trends in colon neoplasms in patients with primary sclerosing cholangitis and ulcerative colitis. *J Crohns Colitis* 2012; **6**: 845-851 [PMID: 22398080 DOI: 10.1016/j.crohns.2012.01.012]

6 **Broomé U**, Bergquist A. Primary sclerosing cholangitis, inflammatory bowel disease, and colon cancer. *Semin Liver Dis* 2006; **26**: 31-41 [PMID: 16496231 DOI: 10.1055/s-2006-933561]

7 **Soetikno RM**, Lin OS, Heidenreich PA, Young HS, Blackstone MO. Increased risk of colorectal neoplasia in patients with primary sclerosing cholangitis and ulcerative colitis: a meta-analysis. *Gastrointest Endosc* 2002; **56**: 48-54 [PMID: 12085034 DOI: 10.1067/mge.2002.125367]

8 **Navaneethan U**, Remzi FH, Nutter B, Fazio VW, Shen B. Risk factors for abnormal liver function tests in patients with ileal pouch-anal anastomosis for underlying inflammatory bowel disease. *Am J Gastroenterol* 2009; **104**: 2467-2475 [PMID: 19550410 DOI: 10.1038/ajg.2009.343]

9 **Lepistö A**, Kivistö S, Kivisaari L, Arola J, Järvinen HJ. Primary sclerosing cholangitis: outcome of patients undergoing restorative proctocolecetomy for ulcerative colitis. *Int J Colorectal Dis* 2009; **24**: 1169-1174 [PMID: 19636573 DOI: 10.1007/s00384-009-0773-4]

10 **Marelli L**, Xirouchakis E, Kalambokis G, Cholongitas E, Hamilton MI, Burroughs AK. Does the severity of primary sclerosing cholangitis influence the clinical course of associated ulcerative colitis? *Gut* 2011; **60**: 1224-1228 [PMID: 21402617 DOI: 10.1136/gut.2010.235408]

11 **Navaneethan U**, Venkatesh PG, Mukewar S, Lashner BA, Remzi FH, McCullough AJ, Kiran RP, Shen B, Fung JJ. Progressive primary sclerosing cholangitis requiring liver transplantation is associated with reduced need for colectomy in patients with ulcerative colitis. *Clin Gastroenterol Hepatol* 2012; **10**: 540-546 [PMID: 22245961 DOI: 10.1016/j.cgh.2012.01.006]

12 **Lindberg J**, Stenling R, Palmqvist R, Rutegård J. Early onset of ulcerative colitis: long-term follow-up with special reference to colorectal cancer and primary sclerosing cholangitis. *J Pediatr Gastroenterol Nutr* 2008; **46**: 534-538 [PMID: 18493208 DOI: 10.1097/MPG.0b013e31815a98ef]

13 **Melton LJ**. History of the Rochester Epidemiology Project. *Mayo Clin Proc* 1996; **71**: 266-274 [PMID: 8594285 DOI: 10.4065/71.3.266]

14 **Post AB**, Bozdech JM, Lavery I, Barnes DS. Colectomy in patients with inflammatory bowel disease and primary sclerosing cholangitis. *Dis Colon Rectum* 1994; **37**: 175-178 [PMID: 8306840 DOI: 10.1007/BF02047543]

15 **Kartheuser AH**, Dozois RR, LaRusso NF, Wiesner RH, Ilstrup DM, Schleck CD. Comparison of surgical treatment of ulcerative colitis associated with primary sclerosing cholangitis: ileal pouch-anal anastomosis versus Brooke ileostomy. *Mayo Clin Proc* 1996; **71**: 748-756 [PMID: 8691895 DOI: 10.1016/S0025-6196(11)64839-8]

16 **Kartheuser AH**, Dozois RR, Wiesner RH, LaRusso NF, Ilstrup DM, Schleck CD. Complications and risk factors after ileal pouch-anal anastomosis for ulcerative colitis associated with primary sclerosing cholangitis. *Ann Surg* 1993; **217**: 314-320 [PMID: 8466305 DOI: 10.1097/00000658-199304000-00002]

17 **Martin FM**, Rossi RL, Nugent FW, Scholz FJ, Jenkins RL, Lewis WD, Gagner M, Foley E, Braasch JW. Surgical aspects of sclerosing cholangitis. Results in 178 patients. *Ann Surg* 1990; **212**: 551-556; discussion 551-556; [PMID: 2222020 DOI: 10.1097/00000658-199010000-00017]

18 **Cangemi JR**, Wiesner RH, Beaver SJ, Ludwig J, MacCarty RL, Dozois RR, Zinsmeister AR, LaRusso NF. Effect of proctocolectomy for chronic ulcerative colitis on the natural history of primary sclerosing cholangitis. *Gastroenterology* 1989; **96**: 790-794 [PMID: 2914641]

19 **Vera A**, Gunson BK, Ussatoff V, Nightingale P, Candinas D, Radley S, Mayer A, Buckels JA, McMaster P, Neuberger J, Mirza DF. Colorectal cancer in patients with inflammatory bowel disease after liver transplantation for primary sclerosing cholangitis. *Transplantation* 2003; **75**: 1983-1988 [PMID: 12829898 DOI: 10.1097/01.TP.0000058744.34965.38]

20 **Bosso MC**, Marchesa PE, Ricchiuti A, Giacardi A, Cocchis D, Campi M, Palisi M, Salizzoni M. Proctocolectomy for ulcerative colitis after liver transplantation for primary sclerosing cholangitis. *Transplant Proc* 2009; **41**: 1390-1392 [PMID: 19460568 DOI: 10.1016/j.transproceed.2009.03.027]

21 **Tischendorf JJ**, Geier A, Trautwein C. Current diagnosis and management of primary sclerosing cholangitis. *Liver Transpl* 2008; **14**: 735-746 [PMID: 18508363 DOI: 10.1002/lt.21456]

22 **Tanaka A**, Takamori Y, Toda G, Ohnishi S, Takikawa H. Outcome and prognostic factors of 391 Japanese patients with primary sclerosing cholangitis. *Liver Int* 2008; **28**: 983-989 [PMID: 18397233 DOI: 10.1111/j.1478-3231.2008.01726.x]

23 **Csikesz NG**, Nguyen LN, Tseng JF, Shah SA. Nationwide volume and mortality after elective surgery in cirrhotic patients. *J Am Coll Surg* 2009; **208**: 96-103 [PMID: 19228510 DOI: 10.1016/j.jamcollsurg.2008.09.006]

24 **Meunier K**, Mucci S, Quentin V, Azoulay R, Arnaud JP, Hamy A. Colorectal surgery in cirrhotic patients: assessment of operative morbidity and mortality. *Dis Colon Rectum* 2008; **51**: 1225-1231 [PMID: 18521677 DOI: 10.1007/s10350-008-9336-y]

25 **Navaneethan U**, Choudhary M, Venkatesh PG, Lashner BA, Remzi FH, Shen B, Kiran RP. The effects of liver transplantation on the clinical course of colitis in ulcerative colitis patients with primary sclerosing cholangitis. *Aliment Pharmacol Ther* 2012 Mar 19; Epub ahead of print [PMID: 22428731 DOI: 10.1111/j.1365-2036.2012.05067.x]

26 **Gelley F**, Miheller P, Péter A, Telkes G, Nemes B. Activity of ulcerative colitis before and after liver transplantation in primary sclerosing cholangitis: the Hungarian experience. *Transplant Proc* 2012; **44**: 2164-2165 [PMID: 22974943 DOI: 10.1016/j.transproceed.2012.07.098]

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META-ANALYSIS

Reduced esophageal cancer incidence in statin users, particularly with cyclo-oxygenase inhibition

Ian Leonard Phillip Beales, Abigail Hensley, Yoon Loke

Ian Leonard Phillip Beales, Department of Gastroenterology, Norfolk and Norwich University Hospital, Norwich NR4 7UY, United Kingdom
Abigail Hensley, Yoon Loke, Norwich Medical School, University of East Anglia, Norwich NR4 TJ, United Kingdom
Author contributions: Beales ILP and Loke Y jointly conceived the study; Beales ILP and Hensley A performed the searching and data extraction; Beales ILP wrote the initial and final versions of the paper and is guarantor of the paper; all authors performed the data analysis and have seen the raw data and agree with publication.
Correspondence to: Dr. Ian Leonard Phillip Beales, Clinical Senior Lecturer and Honorary Consultant Gastroenterologist, Department of Gastroenterology, Norfolk and Norwich University Hospital, Colney Ln, Norwich NR4 TJ, United Kingdom. i.beales@uea.ac.uk
Telephone: +44-1603-591003 Fax: +44-1603-593752
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Abstract

AIM: To examine the association between statin use and the development of esophageal cancer

METHODS: We performed a systematic review and meta-analysis. Multiple databases (Pubmed, EMBASE, Cochrane Library, Web of Science, Wiley Interscience and Google Scholar) were systematically searched for studies reporting the association of statin use and the development of esophageal cancer. Literature searching and data abstraction were performed independently by two separate researchers. The quality of studies reviewed was evaluated using the Newcastle-Ottawa Quality assessment scale. Meta-analysis on the relationship between statin use and cancer incidence was performed. The effect of the combination of statin plus a cyclo-oxygenase inhibitor was also examined.

RESULTS: Eleven studies met eligibility criteria, 9 high and 2 medium quality. All were observational studies. Studies examining adenocarcinoma development in Barrett's esophagus included 317 cancers and 1999 controls, population-based studies examining all esophageal cancers included 371203 cancers and 6083150 controls. In the Barrett's population the use of statins (OR = 0.57; 95%CI: 0.43-0.75) and cyclo-oxygenase inhibitors (OR = 0.59; 95%CI: 0.45-0.77) were independently associated with a reduced incidence of adenocarcinoma. Combined use of a statin plus cyclo-oxygenase inhibitor was associated with an even lower adenocarcinoma incidence (OR = 0.26; 95%CI: 0.1-0.68). There was more heterogeneity in the population-based studies but pooled adjusted data showed that statin use was associated with a lower incidence of all combined esophageal cancers (OR = 0.81; 95%CI: 0.75-0.88).

CONCLUSION: Statin use in patients with Barrett's oesophagus is associated with a significantly lower incidence of adenocarcinoma. The chemopreventive actions of statins, especially combined with cyclo-oxygenase inhibitors deserve further exploration.

Key words: Aspirin; Barrett's oesophagus ; Chemoprevention; Cancer risk; Esophageal carcinoma; Non-steroidal anti-inflammatory drugs; Statins

Core tip: Esophageal cancer remains a major burden upon health. The incidence of esophageal adenocarcinoma has increased dramatically in western countries. Experimental studies have suggested that statins may have useful actions against esophageal cancer cells. This systematic review and meta-analysis of observational studies shows that statin use was associated with a reduced incidence of all esophageal cancers (19% decrease). A more striking reduction in adenocarcinoma incidence in patients with Barrett's esophagus taking statins was seen (43% decrease) and this effect was

enhanced in those also taking cyclo-oxygenase inhibitors (74% decrease). This combination offers promise for chemoprevention and further interventional studies are warranted.

Beales ILP, Hensley A, Loke Y. Reduced esophageal cancer incidence in statin users, particularly with cyclo-oxygenase inhibition. *World J Gastrointest Pharmacol Ther* 2013; 4(3): 69-79 Available from: URL: http://www.wjgnet.com/2150-5349/full/v4/i3/69.htm DOI: http://dx.doi.org/10.4292/wjgpt.v4.i3.69

INTRODUCTION

Esophageal cancer remains an important worldwide problem with high rates of incidence and death as well as considerable morbidity and burdens of treatment[1,2]. In the developed world, the incidence of esophageal adenocarcinoma (EAC) has increased dramatically over the last 30 years and now outstrips esophageal squamous cell cancer (ESC) in some countries[3-7]. Although the incidence of squamous cancer appears relatively flat in the developed world it continues to be a major health problem in many places[2]. Despite improvements in the diagnosis, screening and treatment, the mortality and morbidity of these conditions remains substantial.

Chemoprevention remains one attractive way to reduce the incidence of esophageal cancer. Most of the attention has been devoted to EAC, as this appears to develop in most cases from a pre-malignant phenotype, metaplastic (columnar-lined) esophagus (Barrett's esophagus), providing both a means to study, and intervene in cancer development[8,9]. At present there are no proven chemotherapeutic agents, although aspirin appears to offer the most attractive combination of risks and benefits, and the results of the large United Kingdom (ASPECT) trial are awaited with interest[10].

Experimental laboratory studies have suggested that statins, hydroxymethylglutaryl-CoA reductase inhibitors (HMG-CoA), might have useful anti-cancer effects against the progression of Barrett's esophagus and EAC. In our laboratory we have shown that 4 different statins (simvastatin, pravastatin, lovastatin and rosuvastatin) inhibit the proliferation and induce apoptosis in both malignant EAC cell lines (OE33 and Flo-1) and non-malignant QhERT Barrett's cells[11,12]. These effects appear to be due to inhibition of HMG-CoA reductase, which not only reduces the intermediates which are required for the subsequent formation of cholesterol but also limits the availability for other metabolic intermediates that are required for the prenylation of signalling G-proteins. This prenylation of G-proteins, localises them to the cell membrane where there are key players in pro-proliferative and anti-apoptotic signalling[13]. We have shown than statins inhibit signalling *via* the ERK and Akt cascades in Barrett's cells, which contribute to the anti-proliferative and pro-apoptotic effects[11]. Similar effects, albeit with less detailed characterization, have also been reported in other EAC cells (simvastatin in OE19 cells[14] and simvastatin, and less so atorvastatin, in FLO-1 cells[15]). Experiments using pharmacological inhibitors and RNA interference have shown that the anti-cancer effect of statins in Barrett's cells seems to be separate from, but additive to, the effects produced by inhibition of the cyclooxygenase (COX)-2/prostaglandin E2 pathway[11,12]. There is a single laboratory study showing that lovastatin has some modest anti-proliferative and pro-apoptotic effects in TE-8 and SKGT-4 esophageal squamous cancer cell lines[16].

Although these experimental studies are clearly promising, it is important that these are correlated with clinical outcomes before embarking on either significant change in practice or even an adequately powered randomised trial to further explore these effects.

Although several studies have attempted to explore the association of statin use and esophageal cancer incidence: individually these have often been relatively small and underpowered[17,18]. To place this in context, a prospective study in patients with Barrett's esophagus would require approximately 4000 subjects followed up 5 for years, assuming a statin use rate of 40% and a cancer incidence of 0.5% per annum, to have 80% power to detect a 50% reduction in cancer incidence. A proportionately larger study would be needed based on the latest and more conservative rates (0.1%-0.3% per annum) of malignant progression in Barrett's esophagus[19,20]. No individual study has come close to this recruitment. Therefore to further explore the potential cancer-protective effects of statins in esophageal cancer we have performed a systematic review and meta-analysis of published literature examining the association of statin use and esophageal cancer, following the MOOSE guidelines[21]. Our review of the literature demonstrated two distinct categories of studies: those examining statin use in relation to malignant progression to EAC in Barrett's oesophagus and those examining statin use on a population scale which either combined or did not differentiate between EAC and ESC. We have analysed these separately.

MATERIALS AND METHODS

The Pubmed, EMBASE, Cochrane Library, Web of Science, Wiley Interscience and Google Scholar databases were searched for relevant publications, published in English up to February 1st 2013 using the search terms "esophageal neoplasm," "Barrett's esophagus," "esophageal adenocarcinoma," "statin" and "Hydroxymethyg- lutaryl-CoA reductase inhibitor." The reference lists of these papers were then hand searched for any additional publications. Randomised controlled studies, case-control studies and prospective cohort studies were eligible for inclusion. Two investigators (Beales ILP, Hensley A) independently reviewed the articles and extracted the data, differences were clarified by discussion and mutual agreement.

Data extraction

The following information was abstracted from the pub-

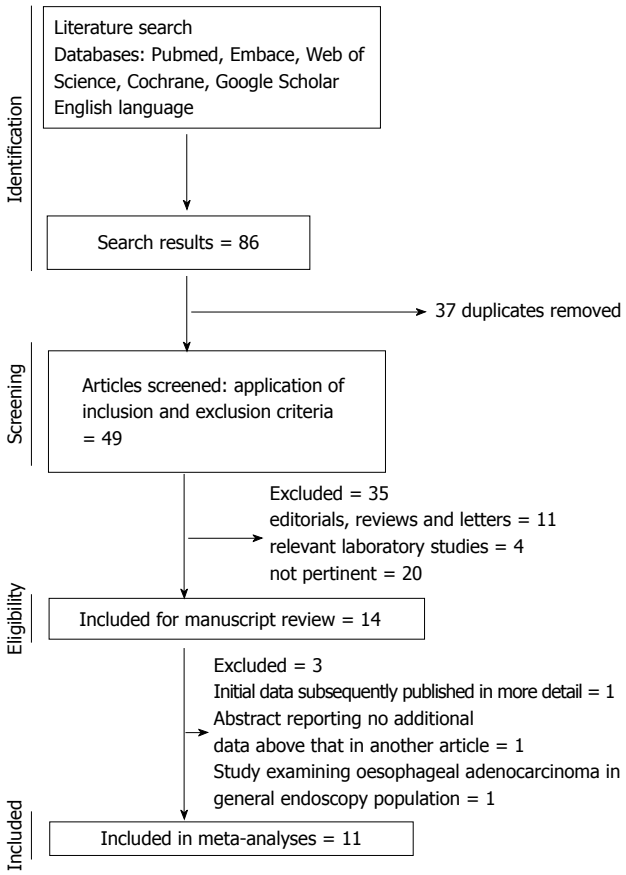

Figure 1 Flow chart showing process of study selection and data extraction.

lications: type of study, numbers of participants, raw data for ever or never use statins and unadjusted and adjusted risk estimates for statins (where available).

Study characteristics

A pre-specified protocol was used to record the following from the eligible studies: authors, journal, participant source, selection criteria, drug exposures of interest, ascertainment of drug exposure and outcome, and confounding factors adjusted for.

Assessment of risk of bias and study quality

We checked the validity of the included studies based on possibility of confounding and potential for misclassification of tumour pathology and/or drug exposure. Risk of bias assessment was focused on the selection of participants, comparability of cases and controls (with any adjustments for confounding), and methods used in ascertaining drug exposure and outcomes. The quality of all studies was assessed using the Newcastle-Ottawa Quality Assessment Scales for cohort and case-control studies using the star rated system as previously described[22]. In brief, this scores studies in each of 9 categories, with a star rating awarded for high quality in separate areas related to the selection of subjects, comparability of groups, reliability of outcomes and exposures. We regarded 9 stars as high-quality studies, 7-8 stars as medium quality, 5-6 stars as low quality and < 4 stars as very low quality.

Statistical analysis

Review Manager (RevMan) version 5.023 (Nordic Cochrane Center, Copenhagen, Denmark) was used to calculate the pooled risk ratio (based on ORs or hazard ratios from individual studies) using the inverse variance method, random effects model. Statistical heterogeneity was assessed using the Cochrane I^2 statistic, with I^2 > 25% indicating moderate statistical heterogeneity, and I^2 > 50% indicating a substantial level of heterogeneity[23]. A sensitivity analysis was performed by separately omitting one study at a time to assess if the pooled estimate had changed significantly compare to the results of all pooled studies.

RESULTS

The search yielded 146 potentially eligible publications, after exclusion of experimental and animal studies, reviews, editorials and other papers irrelevant to the current study, 14 relevant papers were reviewed and 11 were eligible for inclusion in the meta-analysis. The flow chart of study selection is shown in Figure 1. Of these 11 papers, 10 were published in full[17,18,24-31] and one only published in abstract form[32]. Of those excluded from the final analysis, one paper reported initial data[12] that were subsequently published in full with larger cohorts in 2 subsequent papers and one abstract reported on essentially the same cohort reported in another abstract but with insufficient extra information to be utilised in the meta-analysis (we attempted to clarify the data with the author but received no response)[33]. One further study was the only one which examined the association between statin use in EAC patients compared to all-comers without cancer[34], as all other studies examined either EAC in the Barrett's esophagus population or all esophageal cancers in general population, this paper was not analysed in the meta-analysis but the data were extracted for review. Two of the studies included in the meta-analysis involved different methodologies of interrogating the same research database and generated different data sets, hence both were included[28,31]. The studies reviewed are summarised in Table 1. No randomised studies were identified; 6 case-control studies and 5 cohort studies were included. There was heterogeneity in the methods of presentation of the results between the studies with reference to the adjustment for risk factors; therefore we performed separate meta-analyses on the adjusted and unadjusted ORs. Data on individual statins, dose or duration of exposure were reported too variably to be analysed robustly in the meta-analysis. Overall 9 of the papers were rated as high quality (9 stars out of a possible 9) and 2 of medium quality (7-8 stars out of a possible 9) using the Newcastle-Ottawa scale.

Statin use and esophageal adenocarcinoma

Five separate studies examined the association of statin use with the development of esophageal adenocarcinoma in patients with Barrett's esophagus[17,18,24-26]. Where high-grade dysplasia was reported as an outcome, this was

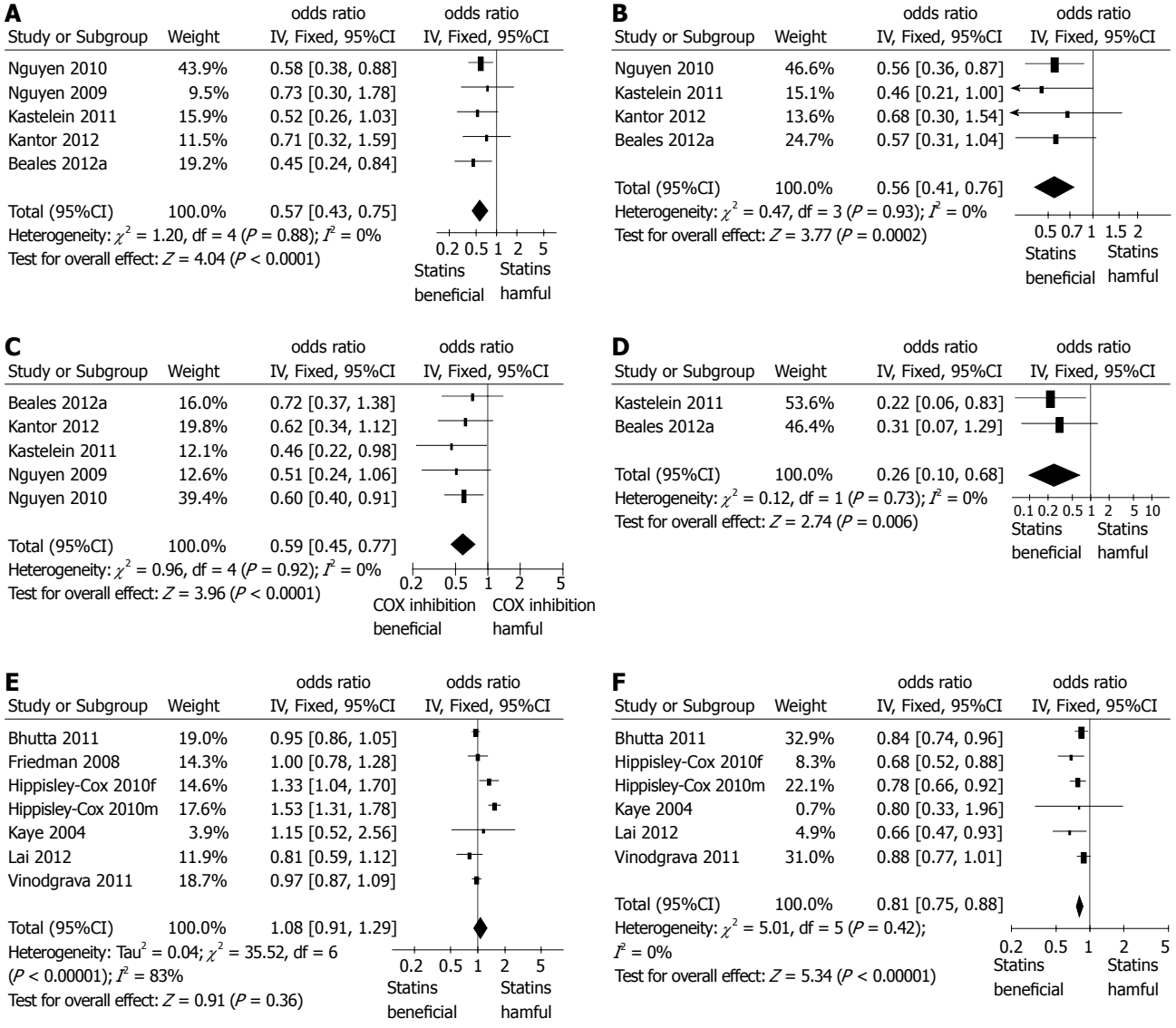

Figure 2 Meta-analysis. A: Meta-analysis of pooled unadjusted odds ratios for the effect of statin use on the development of esophageal adenocarcinoma in patients with Barrett's esophagus; B: Meta-analysis of pooled adjusted odds ratios for the effect of statin use on the development of esophageal adenocarcinoma in patients with Barrett's esophagus; C: Meta-analysis of pooled adjusted odds ratios for the cyclo-oxygenase inhibitor [aspirin, non-steroidal anti-inflammatory drug (NSAID) or coxib] use on the development of esophageal adenocarcinoma in patients with Barrett's esophagus; D: Meta-analysis of pooled adjusted odds ratios for the effect of combined statin and cyclo-oxygenase inhibitor (aspirin, NSAID or coxib) use on the development of esophageal adenocarcinoma in patients with Barrett's esophagus; E: Meta-analysis of pooled unadjusted odds ratios for the effect of statin use on the development of all esophageal carcinomas in population-based studies; F: Meta-analysis of pooled unadjusted odds ratios for the effect of statin use on the development of all esophageal carcinomas in population-based studies.

included with adenocarcinoma for analysis due to the indication for intervention at that stage. Data from a total of 317 adenocarcinomas and 1999 non-cancer Barrett's controls were included in the meta-analysis. In addition, one further study examined the association of statin use in patients with esophageal adenocarcinoma compared to cancer-negative a controls rather than just Barrett' s esophagus patients, this study was not included in the meta-analysis[34].

Meta-analysis of all the 5 studies providing crude, unadjusted ORs showed a significant negative association between statin use and the development of esophageal adenocarcinoma in patients with Barrett's esophagus (OR = 0.57, 95%CI: 0.43-0.75) without any significant heterogeneity in the results (Figure 2A). Very similar results were seen the meta-analysis using pooled adjusted ORs (combined OR = 0.56; 95%CI: 0.41-0.76), again without heterogeneity (Figure 2B). Sensitivity analysis showed that omitting any single study did not demonstrably alter the results. Interestingly in the additional study examining the association of statins and esophageal adenocarcinoma compared to endoscopy negative controls, not included in the meta-analysis, the unadjusted OR was very similar (adjusted OR = 0.52; 95%CI: 0.27-0.92)[34].

We also performed a meta-analysis of the relationship between cyclo-oxygenase inhibitor use and esophageal adenocarcinoma development reported in these studies. This showed that the use of aspirin or other cyclo-oxygenase inhibitors was associated with a significantly lower incidence of adenocarcinoma in Barrett patients (OR =

Table 1 The conclusion of the studies reviewed

Study	Setting	Studies	Participants	Ascertainment of statin use for inclusion	Risk estimates for statins (*vs* no statin) and factors adjusted for	Limitations, notes and quality
Kastelein *et al*[25]	Netherlands, hospital based	Prospective cohort	Cohort of 570 BO, 38 developed EAC or HGD	All statins, statin use during study period, patient interview and questionnaire, pharmacy records	Statin use = 1 mo HR = 0.46 (95%CI: 0.21-0.99); statin use = 5 yr HR = 0.51 (018-0.1.47); statin use = 5 yr HR = 0.49 (95%CI: 0.22-0.85); statin plus aspirin HR = 0.22 (95%CI: 0.06-0.85); adjusted for age, sex, length of BO, baseline histology and aspirin use	No adjustment for BMI or smoking; limited categorisation of duration-, and dose-relationship; Newcastle-Ottawa 9 stars
Nguyen *et al*[24]	United States, hospital based, veterans administration	Case-control	116 EAC, 696 BO	All statins, at least 1 filled statin prescription in study period, pharmacy database	At least 1 statin prescription HR = 0.56 (95%CI: 0.36-0.87); statin use < 12 mo HR = 0.63 (95%CI: 0.38-1.06); statin use > 12 mo HR = 0.52 (95%CI: 0.30-0.91); adjusted for race, out-patient encounters, non-cancer co-morbidity, use of other medications	97% male, veterans' population; Not adjusted for BMI, alcohol, smoking; no categorisation of dose-relationship; Newcastle-Ottawa 9 stars
Beales *et al*[26]	United Kingdom, hospital based	Case-control	85 EAC, 170 BO	All statins, statin use for > 6 mo prior to cancer diagnosis, questionnaire and clinical and prescribing records	Statin use OR = 0.57 (0.28-0.94); statin and aspirin combined OR = 0.31 (95%CI: 0.04-0.69); adjusted for age, sex, smoking, aspirin, NSAIDs, proton pump inhibitors, BMI, diabetes mellitus, metformin, alcohol; significant negative associations with statin dose and duration.	Cancers were a mix of *de novo* and screening-detected cancers; Newcastle-Ottawa 8 stars
Beales *et al*[34]	United Kingdom, hospital based	Case-control	112 EAC, 448 cancer negative gastroenterology outpatients	All statins, statin use for > 6 mo prior to cancer diagnosis, questionnaire and clinical and prescribing records	Statin use OR = 0.52 (95%CI: 0.27-0.92); statin and aspirin combined OR 0.27 (95%CI: 0.05-0.67); adjusted for age, sex, smoking, aspirin, NSAIDs, proton pump inhibitors, BMI, alcohol, diabetes mellitus, metformin; United Kingdom, population based	Controls were hospital outpatients; Newcastle-Ottawa 8 stars
Fang *et al*[12]	United Kingdom, hospital based	Case-control	EAC 63, cancer-negative gastroenterology outpatients 252	All statins, statin use for > 6 mo prior to cancer diagnosis, questionnaire and clinical and prescribing records	Unadjusted statin OR = 0.42 (95%CI: 0.19-0.89); unadjusted statin plus aspirin OR = 0.11 (95%CI: 0.01-0.82)	Controls were hospital outpatients. Unadjusted for any risk factors; not included in meta-analysis as more extensive dataset published subsequently; not quality rated
Kantor *et al*[18]	United States	Prospective cohort	BO 411 in cohort, EAC developed in 56	All statins, any statin use during study period, questionnaire	Statin use OR = 0.68 (95%CI: 0.30-1.54); adjusted for sex, age, smoking, NSAIDs	No adjustment for BMI; no data on dose or duration relationship. Included any use of statin, Relatively low incidence of statin use in BO population; Newcastle-Ottawa 9 stars
Nguyen *et al*[17]	United States, hospital based, veterans administration	Retrospective cohort	BO 344 in cohort, EAC or HGD developed in 33	All statins, any statin prescription during the period of study, pharmacy and clinical records	Statin use OR = 0.73 (95%CI: 0.30-1.78), unadjusted	94% male, veterans population. Incomplete adjustment for potential confounding factors; Newcastle-Ottawa 8 stars
Bhutta *et al*[32]	United Kingdom, population based	Case-control	4242 cancers, 17233 controls	All statins, statin prescription for 10 mo in the year preceding diagnosis of cancer; read codes within GPRD	Use of statins OR = 0.84 (95%CI: 0.73-0.95); adjusted for BMI, smoking, aspirin, NSAIDs, proton pump inhibitors, vasodilators	No categorisation of statin dose; related to Hippisley-Cox 2010 but different methodology to interrogate the same research database; Newcastle-Ottawa 9 stars
Vinogradova *et al*[28]	United Kingdom, population based	Case-control	3159 cancers, 13041 controls	All statins, statin use as defined by 2 prescriptions over a 5 year period at least 12 mo prior to cancer diagnosis; read codes within QResearch database	Use of statins OR = 0.88 (95%CI: 0.77-1.01); adjusted for Townsend score, smoking, circulatory disease, diabetes mellitus, rheumatoid arthritis, COX-2 inhibitors	Data for EAC and ESC combined; no individual confirmation of pathology. No categorisation of statin dose; related to Hippisley-Cox 2010 but different methodology to interrogate the same research database; Newcastle-Ottawa 9 stars

Hippisley-Cox *et al*[31]	United Kingdom, population based	Prospective cohort	1809 cancers, 2004692 overall participants	All statins, new users of statins defined by a new statin prescription in the study period; read codes within QResearch database	Men, statin HR = 0.78 (95%CI: 0.66-0.91); women, statin HR 0.68 (95%CI: 0.52-0.88); adjusted for, age, BMI, smoking, townsend score, type 2 diabetes	Data for EAC and ESC combined. No individual confirmation of pathology; no adjustment for aspirin or NSAIDs; no data on duration or long term statin exposure; Newcastle-Ottawa 9 stars
Kaye *et al*[29]	United Kingdom, population based	Case-control	100 cancers, 430 controls	All statins, current use defined as a statin prescription that started within 12 mo of cancer diagnosis; read codes within GPRD	Statin use OR = 0.80 (95%CI: 0.30-1.80); adjusted for smoking, BMI, number of GP visits	Data for EAC and ESC combined. No individual confirmation of pathology; no adjustment for aspirin or NSAIDs; no data on duration or long term statin exposure; Newcastle-Ottawa 9 stars
Friedman *et al*[30]	United States, population based	Retrospective cohort	68 cancers, 4413032 controls	All statin, any statin use prior to cancer diagnosis, Kaiser Permanente Cancer Registry and Pharmacy management systems	Overall unadjusted statin use OR = 1.0 (95%CI: 0.77-1.27); men with > 5 yr statin use OR = 1.70 (95%CI: 1.05-12.75).	Data for EAC and ESC combined; no individual confirmation of pathology; no dose-effect relationship examined; no correction for confounding variables; small number of cancers; Newcastle-Ottawa 9 stars
Lai *et al*[27]	Taiwan, population based	Case-control	549 cancers, 2196 controls.	All statins, statin prescription prior to cancer diagnosis; data from Taiwanese NHI programme	Statin use OR = 0.66 (0.45-0.95); atorvastatin = 12 mo OR = 0.14 (95%CI: 0.04-0.56); adjusted for esophageal diseases, *H. pylori* infection, alcoholism, smoking, lipid lowering drugs, proton pump inhibitors, H2RA, NSAIDs and aspirin	Data for EAC and ESC combined; no individual confirmation of pathology; no dose-effect relationship examined; Newcastle-Ottawa 9 stars
Bhutta *et al*[33]	United Kingdom, population based	Case-control	Not clearly defined	Not clearly defined; read codes within general practice research database	Statin use OR for EAC 0.61 (95%CI: 0.35-0.94), OR for ESC (95%CI: 0.21-0.80); unclear what adjustments applied	No individual confirmation of pathology; insufficient data for inclusion in meta-analysis appears to be essentially the same cohort as Bhutta 2011; no response from author when asked for further information; not quality rated or included

EAC: Esophageal adenocarcinoma; HGD: High-grade dysplasia; ESC: Esophageal squamous cell cancer; H2RA: Histamine-2 receptor antagonist; NSAIDs: Non-steroidal anti-inflammatory drug; *H. pylori*: Helicobacter pylori; NHI: National Health Insurance; BMI: Body mass index; COX-2: Cyclooxygenase-2.

0.59, 95%CI: 0.45-0.77), again without any heterogeneity (Figure 2C).

Two of the studies specifically reported the association of the combination of cyclo-oxygenase inhibitors (aspirin and/or non-steroidal anti-inflammatory drug, NSAIDs/coxibs) with a statin and esophageal adenocarcinoma in patients with Barrett's esophagus[25,26]: as shown in Figure 2D this combination was associated with a significantly lower incidence of esophageal adenocarcinoma (OR = 0.26; 95%CI: 0.1-0.68), that seen with either statins or aspirin/NSAIDs alone (Figure 2D).

Only one of the five studies reported data on statin dose: in this one study, higher doses (greater than 40 mg simvastatin or equivalent daily) were associated with a lower incidence of EAC compared to lower doses[26].

Similarly there were inconsistencies in the reporting of duration of statin use: Kastelein *et al*[25] reported no difference with either more or less than 5 years use of statin (OR both approximately 0.50), whilst Nguyen et al reported that more than one year of statin was associated with a lower incidence of EAC [corrected incidence density ratio (0.52, 95%CI: 0.30-0.91)] than use for less than 12 mo [corrected incidence density ratio (0.63, 95%CI: 0.38-1.06)][24]. Beales *et al*[26] reported that more than 5 years of statin use (OR = 0.41; 95%CI: 0.15-0.85) was associated with lower incidence of EAC than use for less than 2 years (OR = 0.77; 95%CI: 0.29-1.87).

Statin use and all esophageal cancers

A total of 6 studies reported the association of statin use and all cancers of the esophagus[27-32]. These were all population-based studies utilizing databases, without any individual confirmation of the precise pathology involved. There were no studies specifically examining the relationship between statins and squamous cell cancer. One study reported separate data for men and women and these were included separately in the meta-analysis[31]. Data from a total of 371203 esophageal cancers and 6083150 controls were included in this meta-analysis. There was considerable and significant heterogeneity in the data for unadjusted OR: overall there was no association of statin use and esophageal cancer (OR = 1.08; 95%CI: 0.91-1.29, I^2 = 83%) (Figure 2E). There was less heterogeneity in the pooled adjusted OR (pooled OR = 0.81; 95%CI: 0.75-0.88, I^2 = 0%) which showed a significant negative association between statin use and the incidence of all

esophageal cancers (Figure 2F). Sensitivity analysis of the pooled adjusted data showed that omission of any one single study did not alter the overall effects.

Again data on dose, duration and individual statins were inconsistently presented and formal meta-analysis of these data is problematical if not impossible. Vinogradova *et al*[28] reported that the OR for less than 12 mo statin use (OR = 0.90; 95%CI: 0.67-1.20) was similar to that in those using statins for greater than 73 mo (OR = 1.03; 95%CI: 0.07-1.52). Lai *et al*[27] reported that use atorvastatin but not other statins for greater than 12 mo was associated with a significantly reduced incidence of esophageal cancers, (adjusted OR = 0.14; 95%CI: 0.04-0.56). Sub-groups analysis of the study by Hippisley-Cox and Coupland[31] showed that there seemed to be a dose-response relationship but only in men: low simvastatin dose (10/20 mg), (adjusted OR = 0.91; 95%CI: 0.73-1.12), compared to high dose (40/80 mg) (adjusted OR = 0.66; 95%CI: 0.48-0.91). Statin dose-relationships were not reported in the other studies.

DISCUSSION

Our meta-analysis has confirmed a significant negative association between the use of statins and a reduced incidence of esophageal adenocarcinoma in patients with Barrett's esophagus. This suggests that statins may have important chemopreventive effects that should now be explored further in interventional studies. The results from all 5 studies are consistent with each other, with no statistical heterogeneity.

Our data have consistency with those previously published: the pooled adjusted OR for cyclo-oxygenase inhibitor use (combined aspirin, NSAIDs and coxibs) in the 5 studies of adenocarcinoma development in Barrett's esophagus is 0.59 (95%CI: 0.45-0.77). This result is consistent with previous studies and meta-analysis[35-37], although other studies have failed to show a negative association between cyclooxygenase inhibitor use and adenocarcinoma development in Barrett's esophagus[38]. Within these current studies there were sufficient data to perform a meta-analysis on the combined effects of statin and cyclooxygenase inhibitor usage and this showed that the combination was associated with a greater reduction in adenocarcinoma incidence. These findings are consistent with the laboratory data in Barrett's cancer and non-cancer cell lines, where the anti-proliferative and pro-apoptotic effects of statins are mechanistically both separate from, and additive to, the effects of pharmacological inhibitors of the COX/prostaglandin production pathway[11,12,14]. Our data strongly support further experimental and interventional studies exploring the combination of aspirin and statin for chemoprevention. Further studies are required to define which of the various families of cyclo-oxygenase inhibitors have the greatest negative association with EAC. The available do not allow differentiation between traditional NSAIDs, coxibs and aspirin.

All the studies included in the meta-analysis were observational in nature, and despite the consistency of results the possibility of bias must still be considered. The pooled adjusted and adjusted ORs both showed that statin use is associated with a lower incidence of adenocarcinoma in Barrett's esophagus, but it is possible that a degree of confounding by uncorrected factors remains. In general the known risk factors that direct the clinical use of statins (risk of circulatory disease, obesity, smoking *etc.*) also increase the risk of adenocarcinoma development, which would tend to diminish the apparent protective effects of statins[39-41]. It is possible that other factors related to the use of statins within a cohort of Barrett' s patients (perhaps some dietary factor) may have led to residual confounding. However the consistency of the results in 5 geographically distinct cohorts suggests that this is not likely to be a significant effect. Singh *et al*[42] recently published a similar meta-analysis examining statins and esophageal cancers, although with slightly different inclusion criteria and an earlier cut-off point for the literature review. The results are very similar to ours: in that study statin use was associated with a reduced incidence of adenocarcinoma in Barrett's esophagus [pooled unadjusted OR = 0.57 (95%CI: 0.44-0.75), pooled adjusted OR = 0.59 (95%CI: 0.45-0.78)]. Whilst further suitably sized randomized studies are required to fully inform choices over statin and aspirin use as chemopreventive agents in Barrett's esophagus, the currently available data do suggest that these should certainly be prescribed to Barrett's patients with increased risk of circulatory diseases.

Despite the meta-analysis including over 300 cancers and nearly 2000 Barrett's non-cancer controls, there are insufficient data on the dose- and duration-relationships, in the negative association between statin use and adenocarcinoma development. These areas require further investigation. There are also insufficient data on either individual statins or lipophilic versus hydrophilic statins. All 5 studies grouped all statins together and only in one were individual drugs examined. These areas also require important follow up studies. Based on available data, the most plausible mechanism underlying the chemopreventive effect of statins is inhibition of the mevalonate synthetic pathway and subsequent reduction in the availability of functional signalling mediators that promote proliferation and inhibit apoptosis within the Barrett's epithelium[11,13]. The cell line studies suggest that these effects are mediated by statins at the level of the Barrett's epithelial cells, but the contribution of overall reduction in mevalonate pathway synthetic function (predominantly in the liver) to any esophageal clinical effects remain to be explored. This may have some bearing as lipophilic statins (simvastatin and atorvastatin) are thought to be able to enter all cells by passive diffusion, whereas the hydrophilic statins (pravastatin and rosuvastatin) require the presence of an active transport mechanism[43]. The latter is expressed by hepatocytes and not usually in other cells (although to our knowledge has not been specifically explored in normal and pathological esophageal epitheli-

um)[44]. In addition other mechanisms such as altered adipokine secretion or altered inflammatory responses could contribute to the possible protective effects of statins against esophageal adenocarcinoma[45] and the individual statins or their chemical properties, such as intrinsic antioxidants effects, could be important determinants of these effects[43].

These current clinical data are important when discussing the mechanistic cell-line studies: some of the latter are open to, (perhaps valid) criticism that the statin concentrations employed *in vitro* (often significantly greater than 1 mmol/L)[46] are rather higher than those generally seen with *in vivo* therapeutic use (in the nmol/L range)[47,48]. The correlation of positive clinical and laboratory studies is supportive of a chemopreventive effect of statins against EAC.

The data from the population-based studies examining the incidence of all esophageal cancers in relation to statin use are rather less robust than the more specific Barrett's-adenocarcinoma data. There was considerable heterogeneity in the crude pooled data but the pooled adjusted ORs did show a significantly lower incidence of all esophageal cancers in statin users. In contrast to the Barrett's group studies, all of these population-based studies relied on interrogation of databases and were not specifically designed to examine esophageal cancer incidence (this was one of many outcomes assessed). Data on drug exposure is probably not as complete in this set of studies as aspirin, NSAIDs and statins are all available over the counter in many of the relevant areas and non-prescription use would not have been detected in these prescribing database studies. We feel that this is unlikely to greatly affect the results but does increase the level of uncertainty. The previously mentioned meta-analysis by Singh *et al*[42] did not separately examine population-based (but non-Barrett's) esophageal cancers, and included overall less subjects (9285 cases and 1132969 total patients) than our current study. However the pooled results for all studies examining statin use and esophageal cancer incidence was similar to ours [pooled unadjusted OR = 0.74 (95%CI: 0.62-0.90), pooled adjusted OR = 0.72 (95%CI: 0.60-0.86)], considering the that the Singh *et al*[42] results are affected by the inclusion of the Barrett's adenocarcinoma studies, where statins seem to be associated with greater protection against cancer compared to the true population-based studies.

The major difficulty in interpreting the population-based studies is that the cancer diagnoses would have included a mixture of esophageal adenocarcinoma, gastroesophageal junction adenocarcinoma and esophageal squamous cell cancer. These have different risk factors and pathology and it is not clear whether the negative association with statin use reported reflects a similar effect against all possible esophageal cancer types or whether there is a more obvious negative association with adenocarcinoma, as suggested by the Barrett's-cancer data and a less obvious, or indeed no, association with a reduced incidence of squamous cell cancer. This area needs further clarification. Again there were insufficient data, and what were available were too inconsistently reported to draw any conclusions regarding the dose and duration relationships between statin use and esophageal cancer incidence or whether individual statins or statin classes had different effects.

In addition to the single study showing some modest effects with lovastatin in esophageal squamous cell lines[16], anti-cancer effects of statins have been also demonstrated *in vitro* against non-esophageal squamous cancer cell lines, such as lung, skin or head and neck cancers[49-52]. However although some clinical studies have suggested a non-statistically significant trend to improved outcomes in statin-treated squamous cell cancer patients[50], other large studies have failed to show any benefit. Further studies are clearly required to examine the associations (if any) between statin use and esophageal squamous cell cancer[28,53]. Similarly, further studies are required to examine whether statin use has any association with the incidence of Barrett's metaplasia, all the studies in our meta-analysis examined adenocarcinoma (or high-grade dysplasia) development in Barrett's mucosa.

The potential cancer chemopreventive effects of statins continue to attract widespread attention: statins have been reported to be associated with reduced overall cancer-related mortality[54] but data on the clinical effects of statins on the incidence or prognosis of cancers various different sites have often been inconclusive and require that different cancers are addressed separately (reviewed by Boudreau *et al*[55].

Our meta-analysis has shown that statin use is consistently associated with a reduced incidence of adenocarcinoma in populations of patients with Barrett's esophagus. The combination of a cyclo-oxygenase inhibitor and statin is associated with a greater reduction in the incidence of adenocarcinoma. In population based studies of all esophageal cancers statin use was also associated with a reduced cancer incidence. The chemopreventive actions of statins, especially in combination with aspirin/NSAIDs deserves further exploration in interventional trials.

COMMENTS

Background

Cancers of the esophagus are common causes of mortality and morbidity worldwide. The incidence of esophageal adenocarcinoma is increasing in the Western world and although it is accepted that most cases of esophageal adenocarcinoma arise from metaplastic Barrett's esophagus, there are, as yet, no proven chemopreventive interventions. Laboratory-based experimental cell-line studies have shown that statins have potentially useful anti-cancer effects against esophageal cancer and that in some model systems, at least, these effects can be enhanced by combining with a cyclo-oxygenase inhibitor. At present there are only limited data on the clinical correlations of these observations.

Research frontiers

It is not clear if the clinical use of statins is associated with a reduced incidence of esophageal cancers and equally the effects of combined use of statins and cyclo-oxygenase on the development of esophageal cancer are unclear. Several of the laboratory cell-line studies have used relatively high concentrations of statins to show anti-cancer effects, probably higher than seen in usual clinical therapeutic use, and hence it is important to determine the relationship between

statin use and esophageal cancer incidence with usual clinical use of the drugs.

Innovations and breakthroughs

This is the largest systematic review and meta-analysis in this area and has included over 300 cases of Barrett's-related adenocarcinoma, 1999 non-cancer Barrett's controls. In addition the population-based studies included over 370000 total cases of esophageal cancer and almost 6 million controls. The results show that statin use in patients Barrett's esophagus was associated with a 43% reducon in the incidence of adenocarcinoma. Inhibition of cyclo-oxygenase (COX) with aspirin, non-aspirin non-steroidal anti-inflammatory agents or selective COX-2 inhibitors was independently associated with a reduced adenocarcinoma incidence in Barrett's esophagus (41% decrease). The combination of a statin plus a cyclo-oxygenase inhibitor was associated with a greater reduction in adenocarcinoma incidence than either alone (74% reduction). The data from the population-based studies are more heterogeneous, containing a mixture of esophageal cancer types but again statin use was associated with a reduced incidence of cancer development (19% reduction).

Applications

These data from observational studies suggests that statins may have useful chemopreventive effects against esophageal cancer; particularly against the development of adenocarcinoma in Barrett's esophagus when used in combination with a cyclo-oxygenase inhibitor. Further interventional studies are warranted. As patients with Barrett's esophagus are at increased risk of circulatory diseases, statins should not be withheld from such patients where otherwise indicated.

Terminology

Statins are inhibitors of the enzyme hydroxymethylglutaryl-CoA reductase. This is the rate limiting step on cholesterol biosynthesis. These drugs are widely used to treat and prevent circulatory diseases. Intermediates of the cholesterol synthetic pathway are also essential in other cell signalling pathways which are important in controlling many functions including cell proliferation and survival.

Peer review

Chemoprevention for esophageal cancers, especially in the context of Barrett's esophagus, is an area of active interest around the world. This systematic review and meta-analysis examined the association with statin use and the incidence of esophageal cancers. The study results show a consistent and significant negative between statin use and the development of esophageal adenocarcinoma. It also showed that the combined use of statins with aspirin or other cyclooxygenase inhibitors was associated with even lower incidence of adenocarcinoma development in patients with Barrett's esophagus. The results would further stimulate research and interest in combined chemoprevention. The findings are topical and relevant to clinical practice.

REFERENCES

1 **Spechler SJ**, Sharma P, Souza RF, Inadomi JM, Shaheen NJ. American Gastroenterological Association technical review on the management of Barrett's esophagus. *Gastroenterology* 2011; **140**: e18-e52; quiz e13 [PMID: 21376939 DOI: 10.1053/j.gastro.2011.01.031]

2 **Ferlay J**, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010; **127**: 2893-2917 [PMID: 21351269 DOI: 10.1002/ijc.25516]

3 **Pohl H**, Welch HG. The role of overdiagnosis and reclassification in the marked increase of esophageal adenocarcinoma incidence. *J Natl Cancer Inst* 2005; **97**: 142-146 [PMID: 15657344 DOI: 10.1093/jnci/dji024]

4 **Brown LM**, Devesa SS, Chow WH. Incidence of adenocarcinoma of the esophagus among white Americans by sex, stage, and age. *J Natl Cancer Inst* 2008; **100**: 1184-1187 [PMID: 18695138 DOI: 10.1093/jnci/djn211]

5 **Wu X**, Chen VW, Andrews PA, Ruiz B, Correa P. Incidence of esophageal and gastric cancers among Hispanics, non-Hispanic whites and non-Hispanic blacks in the United States: subsite and histology differences. *Cancer Causes Control* 2007; **18**: 585-593 [PMID: 17406989 DOI: 10.1007/s10552-007-9000-1]

6 **Bollschweiler E**, Wolfgarten E, Gutschow C, Hölscher AH. Demographic variations in the rising incidence of esophageal adenocarcinoma in white males. *Cancer* 2001; **92**: 549-555 [PMID: 11505399]

7 **Bosetti C**, Levi F, Ferlay J, Garavello W, Lucchini F, Bertuccio P, Negri E, La Vecchia C. Trends in oesophageal cancer incidence and mortality in Europe. *Int J Cancer* 2008; **122**: 1118-1129 [PMID: 17990321 DOI: 10.1002/ijc.23232]

8 **Sikkema M**, de Jonge PJ, Steyerberg EW, Kuipers EJ. Risk of esophageal adenocarcinoma and mortality in patients with Barrett's esophagus: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2010; **8**: 235-244; quiz e32 [PMID: 19850156 DOI: 10.1016/j.cgh.2009.10.010]

9 **Yousef F**, Cardwell C, Cantwell MM, Galway K, Johnston BT, Murray L. The incidence of esophageal cancer and high-grade dysplasia in Barrett's esophagus: a systematic review and meta-analysis. *Am J Epidemiol* 2008; **168**: 237-249 [PMID: 18550563 DOI: 10.1093/aje/kwn121]

10 **Das D**, Chilton AP, Jankowski JA. Chemoprevention of oesophageal cancer and the AspECT trial. *Recent Results Cancer Res* 2009; **181**: 161-169 [PMID: 19213566]

11 **Ogunwobi OO**, Beales IL. Statins inhibit proliferation and induce apoptosis in Barrett's esophageal adenocarcinoma cells. *Am J Gastroenterol* 2008; **103**: 825-837 [PMID: 18371146 DOI: 10.1111/j.1572-0241.2007.01773.x]

12 **Fang D,** Das KM, Cao W, Malhotra U, Triadafilopoulos G, Najarian RM, Hardie LJ, Lightdale CJ, Beales IL, Felix VN, Schneider PM, Bellizzi AM. Barrett's esophagus: progression to adenocarcinoma and markers. *Ann N Y Acad Sci* 2011; **1232**: 210-229 [PMID: 21950815 DOI: 10.1111/j.1749-6632.2011.06053.x]

13 **Holstein SA**, Wohlford-Lenane CL, Wiemer DF, Hohl RJ. Isoprenoid pyrophosphate analogues regulate expression of Ras-related proteins. *Biochemistry* 2003; **42**: 4384-4391 [PMID: 12693933 DOI: 10.1021/bi027227m]

14 **Konturek PC**, Burnat G, Hahn EG. Inhibition of Barret's adenocarcinoma cell growth by simvastatin: involvement of COX-2 and apoptosis-related proteins. *J Physiol Pharmacol* 2007; **58** Suppl 3: 141-148 [PMID: 17901590]

15 **Sadaria MR**, Reppert AE, Yu JA, Meng X, Fullerton DA, Reece TB, Weyant MJ. Statin therapy attenuates growth and malignant potential of human esophageal adenocarcinoma cells. *J Thorac Cardiovasc Surg* 2011; **142**: 1152-1160 [PMID: 22014341 DOI: 10.1016/j.jtcvs.2011.08.004]

16 **Ye F**, Zhang GH, Guan BX, Xu XC. Suppression of esophageal cancer cell growth using curcumin, (-)-epigallocatechin-3-gallate and lovastatin. *World J Gastroenterol* 2012; **18**: 126-135 [PMID: 22253518 DOI: 10.3748/wjg.v18.i2.126]

17 **Nguyen DM**, El-Serag HB, Henderson L, Stein D, Bhattacharyya A, Sampliner RE. Medication usage and the risk of neoplasia in patients with Barrett's esophagus. *Clin Gastroenterol Hepatol* 2009; **7**: 1299-1304 [PMID: 19523538 DOI: 10.1016/j.cgh.2009.06.001]

18 **Kantor ED**, Onstad L, Blount PL, Reid BJ, Vaughan TL. Use of statin medications and risk of esophageal adenocarcinoma in persons with Barrett's esophagus. *Cancer Epidemiol Biomarkers Prev* 2012; **21**: 456-461 [PMID: 22241250 DOI: 10.1158/1055-9965.EPI-11-1014]

19 **Hvid-Jensen F**, Pedersen L, Drewes AM, Sørensen HT, Funch-Jensen P. Incidence of adenocarcinoma among patients with Barrett's esophagus. *N Engl J Med* 2011; **365**: 1375-1383 [PMID: 21995385 DOI: 10.1056/NEJMoa1103042]

20 **Desai TK**, Krishnan K, Samala N, Singh J, Cluley J, Perla S, Howden CW. The incidence of oesophageal adenocarcinoma in non-dysplastic Barrett's oesophagus: a meta-analysis. *Gut* 2012; **61**: 970-976 [PMID: 21997553 DOI: 10.1136/gutjnl-2011-300730]

21 **Stroup DF**, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal

for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000; **283**: 2008-2012 [PMID: 10789670 DOI: 10.1001/jama.283.15.2008]
22 **Kimball BP**, LiPreti V, Bui S, Wigle ED. Comparison of proximal left anterior descending and circumflex coronary artery dimensions in aortic valve stenosis and hypertrophic cardiomyopathy. *Am J Cardiol* 1990; **65**: 767-771 [PMID: 2316458 DOI: 10.1111/apt.12177]
23 **Alexandre L**, Broughton T, Loke Y, Beales IL. Meta-analysis: risk of esophageal adenocarcinoma with medications which relax the lower esophageal sphincter. *Dis Esophagus* 2012; **25**: 535-544 [PMID: 22129441 DOI: 10.1111/j.1442-2050.2011.01285.x]
24 **Nguyen DM,** Richardson P, El-Serag HB. Medications (NSAIDs, statins, proton pump inhibitors) and the risk of esophageal adenocarcinoma in patients with Barrett's esophagus. *Gastroenterology* 2010; **138**: 2260-2266 [PMID: 20188100 DOI: 10.1053/j.gastro.2010.02.045]
25 **Kastelein F**, Spaander MC, Biermann K, Steyerberg EW, Kuipers EJ, Bruno MJ. Nonsteroidal anti-inflammatory drugs and statins have chemopreventative effects in patients with Barrett's esophagus. *Gastroenterology* 2011; **141**: 2000-2008; quiz 2000-2008 [PMID: 21878200 DOI: 10.1053/j.gastro.2011.08.036]
26 **Beales IL**, Vardi I, Dearman L. Regular statin and aspirin use in patients with Barrett's oesophagus is associated with a reduced incidence of oesophageal adenocarcinoma. *Eur J Gastroenterol Hepatol* 2012; **24**: 917-923 [PMID: 22569083 DOI: 10.1097/MEG.0b013e3283543f01]
27 **Lai SW**, Liao KF, Lai HC, Muo CH, Sung FC. Atorvastatin correlates with decreased risk of esophageal cancer: a population-based case-control study from Taiwan. *Libyan J Med* 2012; **7** [PMID: 22891079 DOI: 10.3402/ljm.v7i0.18830]
28 **Vinogradova Y**, Coupland C, Hippisley-Cox J. Exposure to statins and risk of common cancers: a series of nested case-control studies. *BMC Cancer* 2011; **11**: 409 [PMID: 21943022 DOI: 10.1186/1471-2407-11-409]
29 **Kaye JA**, Jick H. Statin use and cancer risk in the General Practice Research Database. *Br J Cancer* 2004; **90**: 635-637 [PMID: 14760377 DOI: 10.1038/sj.bjc.6601566]
30 **Friedman GD**, Flick ED, Udaltsova N, Chan J, Quesenberry CP, Habel LA. Screening statins for possible carcinogenic risk: up to 9 years of follow-up of 361,859 recipients. *Pharmacoepidemiol Drug Saf* 2008; **17**: 27-36 [PMID: 17944002 DOI: 10.1002/pds.1507]
31 **Hippisley-Cox J**, Coupland C. Unintended effects of statins in men and women in England and Wales: population based cohort study using the QResearch database. *BMJ* 2010; **340**: c2197 [PMID: 20488911 DOI: 10.1136/bmj.c2197]
32 **Bhutta HY,** Clark A, Holt S, Lewis MPN, Hart AR. Oesophageal cancer - an aetiological investigation into the potential protective effect of statins in the UK general practice research database (GPRD). *Gut* 2011; **60**: A36-A37 [DOI: 10.1136/gut.2011.239301.72]
33 **Bhutta HY,** Alexandre L, Clark A. Do statins prevent the histological subtypes of oesophageal cancer? Prospective data from the UK General Practice Database (GPRD). *Gut* 2012; **61**: A299-A300 [DOI: 10.1136/gutjnl-2012-302514d.8]
34 **Beales IL,** Vardi I, Dearman L, Broughton T. Statin use is associated with a reduction in the incidence of esophageal adenocarcinoma: a case control study. *Dis Esophagus* 2012 Sep 18; Epub ahead of print [PMID: 22989236 DOI: 10.1111/j.1442-2050.2012.01412.x]
35 **Vaughan TL,** Dong LM, Blount PL, Ayub K, Odze RD, Sanchez CA, Rabinovitch PS, Reid BJ. Non-steroidal anti-inflammatory drugs and risk of neoplastic progression in Barrett's oesophagus: a prospective study. *Lancet Oncol* 2005; **6**: 945-952 [DOI: 10.1016/S1470-2045(05)70431-9]
36 **Corley DA**, Kerlikowske K, Verma R, Buffler P. Protective association of aspirin/NSAIDs and esophageal cancer: a systematic review and meta-analysis. *Gastroenterology* 2003; **124**: 47-56 [PMID: 12512029]
37 **Abnet CC**, Freedman ND, Kamangar F, Leitzmann MF, Hollenbeck AR, Schatzkin A. Non-steroidal anti-inflammatory drugs and risk of gastric and oesophageal adenocarcinomas: results from a cohort study and a meta-analysis. *Br J Cancer* 2009; **100**: 551-557 [PMID: 19156150 DOI: 10.1038/sj.bjc.6604880]
38 **Gatenby PA**, Ramus JR, Caygill CP, Winslet MC, Watson A. Aspirin is not chemoprotective for Barrett's adenocarcinoma of the oesophagus in multicentre cohort. *Eur J Cancer Prev* 2009; **18**: 381-384 [PMID: 19620873 DOI: 10.1097/CEJ.0b013e32832e0955]
39 **van der Burgh A**, Dees J, Hop WC, van Blankenstein M. Oesophageal cancer is an uncommon cause of death in patients with Barrett's oesophagus. *Gut* 1996; **39**: 5-8 [PMID: 8881798]
40 **Solaymani-Dodaran M**, Logan RF, West J, Card T. Mortality associated with Barrett's esophagus and gastroesophageal reflux disease diagnoses-a population-based cohort study. *Am J Gastroenterol* 2005; **100**: 2616-2621 [PMID: 16393209 DOI: 10.1111/j.1572-0241.2005.00340.x]
41 **Moayyedi P**, Burch N, Akhtar-Danesh N, Enaganti SK, Harrison R, Talley NJ, Jankowski J. Mortality rates in patients with Barrett's oesophagus. *Aliment Pharmacol Ther* 2008; **27**: 316-320 [PMID: 18062791 DOI: 10.1111/j.1365-2036.2007.03582.x]
42 **Singh S**, Singh AG, Singh PP, Murad MH, Iyer PG. Statins Are Associated With Reduced Risk of Esophageal Cancer, Particularly in Patients With Barrett's Esophagus: A Systematic Review and Meta-analysis. *Clin Gastroenterol Hepatol* 2013; **11**: 620-629 [PMID: 23357487 DOI: 10.1016/j.cgh.2012.12.036]
43 **Mason RP**. Molecular basis of differences among statins and a comparison with antioxidant vitamins. *Am J Cardiol* 2006; **98**: 34P-41P [PMID: 17126678]
44 **Nezasa K**, Higaki K, Takeuchi M, Nakano M, Koike M. Uptake of rosuvastatin by isolated rat hepatocytes: comparison with pravastatin. *Xenobiotica* 2003; **33**: 379-388 [PMID: 12745873 DOI: 10.1080/0049825031000066259]
45 **Jalving M**, Koornstra JJ, De Jong S, De Vries EG, Kleibeuker JH. Review article: the potential of combinational regimen with non-steroidal anti-inflammatory drugs in the chemoprevention of colorectal cancer. *Aliment Pharmacol Ther* 2005; **21**: 321-339 [PMID: 15709983 DOI: 10.1111/j.1365-2036.2005.02335.x]
46 **Beales IL**. Letter: Potential chemopreventive effects of statins in oesophageal adenocarcinoma. *Aliment Pharmacol Ther* 2012; **36**: 1105; author reply 1105-1106 [PMID: 23130778 DOI: 10.1111/apt.12083]
47 **Corsini A**, Bellosta S, Baetta R, Fumagalli R, Paoletti R, Bernini F. New insights into the pharmacodynamic and pharmacokinetic properties of statins. *Pharmacol Ther* 1999; **84**: 413-428 [PMID: 10665838]
48 **Jacobson TA**. Comparative pharmacokinetic interaction profiles of pravastatin, simvastatin, and atorvastatin when coadministered with cytochrome P450 inhibitors. *Am J Cardiol* 2004; **94**: 1140-1146 [PMID: 15518608]
49 **Takeda I**, Maruya S, Shirasaki T, Mizukami H, Takahata T, Myers JN, Kakehata S, Yagihashi S, Shinkawa H. Simvastatin inactivates beta1-integrin and extracellular signal-related kinase signaling and inhibits cell proliferation in head and neck squamous cell carcinoma cells. *Cancer Sci* 2007; **98**: 890-899 [PMID: 17428261 DOI: 10.1111/j.1349-7006.2007.00471.x]
50 **Zhao TT**, Le Francois BG, Goss G, Ding K, Bradbury PA, Dimitroulakos J. Lovastatin inhibits EGFR dimerization and AKT activation in squamous cell carcinoma cells: potential regulation by targeting rho proteins. *Oncogene* 2010; **29**: 4682-4692 [PMID: 20562912 DOI: 10.1038/onc.2010.219]
51 **Pelaia G**, Gallelli L, Renda T, Fratto D, Falcone D, Caraglia M, Busceti MT, Terracciano R, Vatrella A, Maselli R, Savino

R. Effects of statins and farnesyl transferase inhibitors on ERK phosphorylation, apoptosis and cell viability in non-small lung cancer cells. *Cell Prolif* 2012; **45**: 557-565 [PMID: 23045963 DOI: 10.1111/j.1365-2184.2012.00846.x]

52 **Chen J**, Hou J, Zhang J, An Y, Zhang X, Yue L, Liu J, Li X. Atorvastatin synergizes with IFN-γ in treating human non-small cell lung carcinomas via potent inhibition of RhoA activity. *Eur J Pharmacol* 2012; **682**: 161-170 [PMID: 22510296 DOI: 10.1016/j.ejphar.2012.02.015]

53 **Dore DD**, Lapane KL, Trivedi AN, Mor V, Weinstock MA. Association between statin use and risk for keratinocyte carcinoma in the veterans affairs topical tretinoin chemoprevention trial. *Ann Intern Med* 2009; **150**: 9-18 [PMID: 19124815 DOI: 10.7326/0003-4819-150-1-200901060-00004]

54 **Nielsen SF**, Nordestgaard BG, Bojesen SE. Statin use and reduced cancer-related mortality. *N Engl J Med* 2013; **368**: 576-577 [PMID: 23388012 DOI: 10.1056/NEJMoa1201735]

55 **Boudreau DM,** Yu O, Johnson J. Statin use and cancer risk: a comprehensive review. *Expert Opin Drug Saf* 2010; **9**: 603-621 [PMID: 20377474 DOI: 10.1517/14740331003662620]

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CASE REPORT

Diarrhoea in a patient with metastatic melanoma: Ipilimumab ileocolitis treated with infliximab

Rob ME Slangen, Alfonsus JM van den Eertwegh, Adriaan A van Bodegraven, Nanne KH de Boer

Rob ME Slangen, Department of Gastroenterology and Hepatology, HagaZiekenhuis, 2545 CH Den Haag, The Netherlands
Alfonsus JM van den Eertwegh, Department of Medical Oncology, VU University Medical Centre, 1007 MB Amsterdam, The Netherlands
Adriaan A van Bodegraven, Nanne KH de Boer, Department of Gastroenterology and Hepatology, VU University Medical Centre, 1007 MB Amsterdam, The Netherlands
Author contributions: Slangen RME wrote the manuscript and was involved in the medical treatment of the ipilimumab ileocolitis as a consulting doctor of the Gastroenterology and Hepatology department; van den Eertwegh AJM was the treating Medical Oncologist and critically reviewed the manuscript; van Bodegraven AA and de Boer NKH performed the colonoscopy and critically reviewed the manuscript; all authors approved the final version of the manuscript.
Correspondence to: Nanne KH de Boer, MD, PhD, Department of Gastroenterology and Hepatology, VU University Medical Center, PO Box 7057, 1007 MB Amsterdam, The Netherlands. khn.deboer@vumc.nl
Telephone: +31-20-4440613 Fax: +31-20-4440554
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Abstract

Administration of ipilimumab, a cytotoxic T-lymphocyte associated antigen-4-blocking monoclonal antibody, leads to enhancement of the anti-tumor T-cell respons and as a result shows a significant survival benefit in metastatic melanoma patients. Therefore patients are currently receiving this promising therapy as a second-line strategy. Unfortunately, by activation of the T-cell immune reponse, ipilimumab therapy may lead to an unwanted induction of different autoimmune phenomena. Diarrhoea and colitis occur in up to one third of patients. Here we present a case of ipilimumab induced ileocolitis which was successfully treated with infliximab, an anti-tumor necrosis factor monoclonal antibody, after corticosteroid therapy failure. Although formal trials are lacking, recently publicated series suggest that infusional therapy of infliximab is effective in ipilimumab induced ileocolitis.

Key words: Melanoma; Ipilimumab; Colitis; Infliximab; Cytotoxic T-lymphocyte associated antigen-4

Core tip: This paper presents a case of ipilimumab induced ileocolitis which was successfully treated with infliximab, an anti-tumor necrosis factor monoclonal antibody, after corticosteroid therapy failure. Although formal trials are lacking, recently publicated series suggest that infusional therapy of infliximab is effective in ipilimumab induced ileocolitis.

Slangen RME, van den Eertwegh AJM, van Bodegraven AA, de Boer NKH. Diarrhoea in a patient with metastatic melanoma: Ipilimumab ileocolitis treated with infliximab. *World J Gastrointest Pharmacol Ther* 2013; 4(3): 80-82 Available from: URL: http://www.wjgnet.com/2150-5349/full/v4/i3/80.htm DOI: http://dx.doi.org/10.4292/wjgpt.v4.i3.80

INTRODUCTION

Ipilimumab administration has shown a survival benefit in metastatic melanoma patients, therefore more patients are likely to receive this therapy as a second-line treatment. Unfortunately, ipilimumab therapy may lead to an unwanted induction of autoimmune phenomena. Here we present a case of ipilimumab induced ileocolitis successfully treated with infliximab after corticosteroid therapy failure.

CASE REPORT

A 53-year-old man with a medical history of metastatic melanoma (metastasized to lungs, lymph nodes and peri-

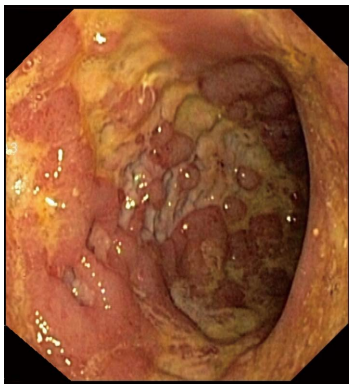

Figure 1 Deep ulcerations in the colon (endoscopic image).

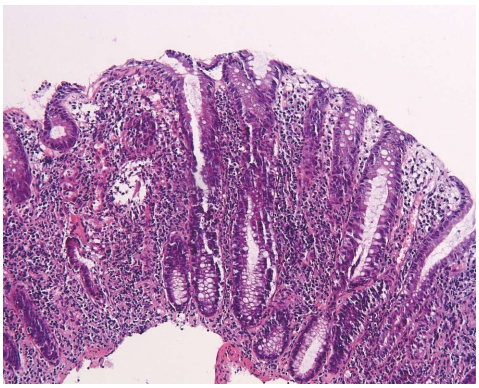

Figure 2 Histopathology of colon biopsies (hematoxylin and eosin staining, × 10).

cardium), was presented at our endoscopy ward because of highly frequent, non-bloody diarrhoea without fever. His medication consisted of morphinomimetics and haloperidol. Four weeks earlier, he started with ipilimumab (3 mg/kg body weight), a fully humanized IgG antibody against the Cytotoxic T-lymphocyte associated Antigen-4 (CTLA-4), of which he had received two administrations. His diarrhoeal complaints had started one week after the second infusion. Routine stool cultures, including *Clostridium difficile*, were negative. A colonoscopy was performed, which showed a patchy colitis with deep, confluent Crohn-like ulcerations (Figure 1). Histopathological examination demonstrated a severe cryptitis with a few abscesses. No granulomas or architectural changes were seen (Figure 2). Furthermore, cytomegalovirus infection was excluded. A computed tomography-scan was performed, showing diffuse thickening of the wall of the entire colon and terminal ileum. A diagnosis of ileocolitis associated with anti-CTLA-4 treatment was made. Our patient was treated with prednisolon (1 mg/kg) for 10 d without beneficial clinical effect. For that reason, intravenous infliximab therapy was initiated (a chimeric IgG antibody against tumour necrosis factor-α) in a dosage of 5 mg/kg body weight (at week 0 and 2)[1,2], after two administrations his diarrhoeal complaints resolved completely.

DISCUSSION

Two recent studies demonstrated that ipilimumab therapy improves survival of patients with metastatic melanoma[1,2]. Unfortunately, blocking of CTLA-4 by ipilimumab[3], may lead to an induction of a variety of autoimmune phenomena. This may comprise inflammation of the gastrointestinal tract, leading to diarrhoea and colitis being reported in up to 31% of patients[1].

As ipilimumab administration has shown a survival benefit in metastatic melanoma patients[1,2], more patients are likely to receive this therapy as a second-line treatment. Moreover, trials of ipilimumab are ongoing in metastatic non-small cell lung cancer[4] and in castration-resistant metastatic prostate cancer patients[5]. Therefore, it is to be expected that ipilimumab induced colitis will be encountered more often.

So far, by clinical judgement, corticosteroids are most often prescribed as a first-line treatment for ipilimumab induced colitis. In prednison-refractory cases, infliximab has shown to be an effective second line treatment[6-9]. The beneficial administration of infliximab in these patients is underlined by our case.

REFERENCES

1 **Hodi FS**, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, Gonzalez R, Robert C, Schadendorf D, Hassel JC, Akerley W, van den Eertwegh AJ, Lutzky J, Lorigan P, Vaubel JM, Linette GP, Hogg D, Ottensmeier CH, Lebbé C, Peschel C, Quirt I, Clark JI, Wolchok JD, Weber JS, Tian J, Yellin MJ, Nichol GM, Hoos A, Urba WJ. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med* 2010; **363**: 711-723 [PMID: 20525992 DOI: 10.1056/NEJMoa1003466]

2 **Robert C**, Thomas L, Bondarenko I, O'Day S, M D JW, Garbe C, Lebbe C, Baurain JF, Testori A, Grob JJ, Davidson N, Richards J, Maio M, Hauschild A, Miller WH, Gascon P, Lotem M, Harmankaya K, Ibrahim R, Francis S, Chen TT, Humphrey R, Hoos A, Wolchok JD. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. *N Engl J Med* 2011; **364**: 2517-2526 [PMID: 21639810 DOI: 10.1056/NEJMoa1104621]

3 **Peggs KS**, Quezada SA, Korman AJ, Allison JP. Principles and use of anti-CTLA4 antibody in human cancer immunotherapy. *Curr Opin Immunol* 2006; **18**: 206-213 [PMID: 16464564]

4 **Reck M**, Bondarenko I, Luft A, Serwatowski P, Barlesi F, Chacko R, Sebastian M, Lu H, Cuillerot JM, Lynch TJ. Ipilimumab in combination with paclitaxel and carboplatin as first-line therapy in extensive-disease-small-cell lung cancer: results from a randomized, double-blind, multicenter phase 2 trial. *Ann Oncol* 2013; **24**: 75-83 [PMID: 22858559 DOI: 10.1093/annonc/mds213]

5 **van den Eertwegh AJ**, Versluis J, van den Berg HP, Santegoets SJ, van Moorselaar RJ, van der Sluis TM, Gall HE, Harding TC, Jooss K, Lowy I, Pinedo HM, Scheper RJ, Stam AG, von Blomberg BM, de Gruijl TD, Hege K, Sacks N, Gerritsen WR. Combined immunotherapy with granulocyte-macrophage colony-stimulating factor-transduced allogeneic prostate cancer cells and ipilimumab in patients with metastatic castration-resistant prostate cancer: a phase 1 dose-escalation trial. *Lancet Oncol* 2012; **13**: 509-517 [PMID: 22326922 DOI: 10.1016/S1470-2045(12)70007-4]

6 **Beck KE**, Blansfield JA, Tran KQ, Feldman AL, Hughes MS, Royal RE, Kammula US, Topalian SL, Sherry RM, Kleiner

D, Quezado M, Lowy I, Yellin M, Rosenberg SA, Yang JC. Enterocolitis in patients with cancer after antibody blockade of cytotoxic T-lymphocyte-associated antigen 4. *J Clin Oncol* 2006; **24**: 2283-2289 [PMID: 16710025]

7 **Johnston RL**, Lutzky J, Chodhry A, Barkin JS. Cytotoxic T-lymphocyte-associated antigen 4 antibody-induced colitis and its management with infliximab. *Dig Dis Sci* 2009; **54**: 2538-2540 [PMID: 19104936 DOI: 10.1007/s10620-008-0641-z]

8 **Lord JD**, Hackman RC, Moklebust A, Thompson JA, Higano CS, Chielens D, Steinbach G, McDonald GB. Refractory colitis following anti-CTLA4 antibody therapy: analysis of mucosal FOXP3+ T cells. *Dig Dis Sci* 2010; **55**: 1396-1405 [PMID: 19507029 DOI: 10.1007/s10620-009-0839-8]

9 **Minor DR**, Chin K, Kashani-Sabet M. Infliximab in the treatment of anti-CTLA4 antibody (ipilimumab) induced immune-related colitis. *Cancer Biother Radiopharm* 2009; **24**: 321-325 [PMID: 19538054]

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

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Telephone: +852-31779906
E-mail: bpgoffice@wjgnet.com
http://www.wjgnet.com