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EDITORIAL

Common misconceptions about 5-aminosalicylates and thiopurines in inflammatory bowel disease

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Abstract

Misconceptions are common in the care of patients with inflammatory bowel disease (IBD). In this paper, we state the most commonly found misconceptions in clinical practice and deal with the use of 5-aminosalicylates and thiopurines, to review the related scientific evidence, and make appropriate recommendations. Prevention of errors needs knowledge to avoid making such errors through ignorance. However, the amount of knowledge is increasing so quickly that one new danger is an overabundance of information. IBD is a model of a very complex disease and our goal with this review is to summarize the key evidence for the most common daily clinical problems. With regard to the use of 5-aminosalicylates, the best practice may to be consider abandoning the use of these drugs in patients with small bowel Crohn' s disease. The combined approach with oral plus topical 5-aminosalicylates should be the first-line therapy in patients with active ulcerative colitis; once-daily treatment should be offered as a first choice regimen due to its better compliance and higher efficacy. With regard to thiopurines, they seem to be as effective in ulcerative colitis as in Crohn' s disease. Underdosing of thiopurines is a form of undertreatment. Thiopurines should probably be continued indefinitely because their withdrawal is associated with a high risk of relapse. Mercaptopurine is a safe alternative in patients with digestive intolerance or hepatotoxicity due to azathioprine. Finally, thiopurine methyltransferase (TPMT) screening cannot substitute for regular monitoring because the majority of cases of myelotoxicity are not TPMT-related.

Key words: Crohn' s disease; Ulcerative colitis; Inflammatory bowel disease; Aminosalicylates; Steroids; Azathioprine; Mercaptopurine; Misconceptions

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INTRODUCTION

Daily clinical practice requires constant decision making, and each is open to possible errors[1-6]. Misconceptions are very common in clinical practice, but can be prevented[1-5]. More than 10 years ago, the Institute of Medicine issued its groundbreaking report, "To err is human: building a safer health system", which revealed that approximately 100 000 Americans die each year from preventable errors in hospitals[7]. The publication fundamentally changed the debate about health care quality in the United States and reconfigured how we think about the quality of care; attracted great interest

among payers and employers for improvement of care and patient safety; and produced substantial increases in research support[2]. In fact, safety issues have been a key factor in many human activities during the past few decades, and it is shocking how late the general culture of safety is reaching the health-care business. As recently summarized in a must-read book[8], "to get things right" can be a complex task but an indispensable one.

It has been pointed out that variation itself is a natural consequence of medicine being as much art as science, and thus some basal level of variation is to be expected[9]. However, in many instances, the current process of care exceeds the expected levels of natural variation, and at times may be extreme to the point of possibly indicating suboptimal overall care[9]. Medical advances have generated an increase in scientific literature and have made decision making more complex. From a scientific point of view, evidence-based medicine provides various highly useful tools for patient treatment, including clinical guidelines or consensus documents. However, frequent digressions from evidence-based recommendations and published guidelines exist, despite the wide dissemination of practice guidelines, which denotes poor quality of care[9-12].

When faced with the same set of facts, healthcare providers often make different diagnoses, employ different tests, and prescribe different therapies[9,13]. Wide practice variations might have several explanations, including the need for more evidence to determine the best course of action; the possibility that multiple approaches might be equally effective for a clinical scenario; or the need for existing evidence to be more effectively consolidated into guidelines and disseminated into practice[12]. Despite the wide dissemination of practice guidelines, clinical pathways and utilization review protocols, extreme variation continues to exist throughout all fields of medicine[9-11]. Within the field of gastroenterology, inflammatory bowel disease (IBD) is likely to generate diversions from clinical guidelines and extreme variations in the process of care[12,14-16]. There are at least three factors that establish IBD as a target for variation[9]: (1) the diagnosis of IBD is often uncertain, and this diagnostic uncertainty may lead to a potentially arbitrary sequence of diagnostic testing with various modalities; (2) the presentation of IBD is heterogeneous, and the multiple presentations of IBD mandate different diagnostic and therapeutic approaches; and (3) the treatments for IBD are themselves varied, and new treatments are always being developed and disseminated. It has been emphasized that demonstration of significant variations in the process of care in IBD indicates a need to disseminate better the available information in this area. Furthermore, identifying specific factors that predict extremes in resource utilization and clinical practice may allow for improved targeting of areas where doctor knowledge or education is inadequate[9].

Although experts and community providers are in general consensus about diagnostic decision making in Crohn' s disease, extreme variation exists both between and within groups for key therapeutic decisions in this disease[9]. When the standard of outpatient care provided has been evaluated, it has been demonstrated that the specialist IBD clinic provides better care than the non-specialist general gastroenterology clinics; even in the specialist clinic, however, the care of a relevant minority of patients does not fulfill certain criteria[17]. Some authors have performed a vignette survey to measure variations in decision making in areas of controversy dealing with ulcerative colitis, and have concluded that community gastroenterologists and ulcerative colitis experts vary dramatically in their approach to many areas of uncertainty, which suggests that current practice patterns are highly disparate and focus attention on specific areas of disconnect that should be further investigated[12]. Finally, a recent study has aimed to determine whether patients referred for a second opinion were receiving therapy in accordance with practice guidelines; it was concluded that patients with IBD often do not receive optimal medical therapy[18].

Our aim was to review several common misconceptions in the management of IBD. We focus on ambulatory patients who have predominantly mild or moderate disease treated with 5-aminosalicylates (5-ASAs) and thiopurines; the two most widely used drugs in IBD. Although decision making in the outpatient setting appears to be less difficult than in hospital situations, the reality of every day care makes human errors even more possible in outpatients. Thus, in the clinical setting, decisions need to be made immediately, with the pressure of limited time, and the understanding that an enormous variety of possible clinical situations exist. The approach taken in this paper is to state the most commonly found misconceptions in clinical practice, to review the related scientific evidence, and finally propose appropriate recommendations.

5-AMINOSALICYLATES

Aminosalicylates are the undisputed first-line option for treating and maintaining remission in ulcerative colitis[19-24]. Furthermore, they may have chemopreventive properties against colorectal cancer[25]. However, the role that these drugs may play in the management of Crohn' s disease has been controversial.

5-ASA drugs are as effective for the treatment of Crohn' s disease as for ulcerative colitis

Initially published trials have shown that oral aminosalicylates are effective treatment for active ileal, ileocolic, or colonic Crohn' s disease[26,27]. Sulfasalazine 3-6 g/d is effective in patients with colonic, but not in those with small bowel disease[28,29]. Asacol is effective in ileocolic or colonic disease[30] and Pentasa has been reported to be effective for ileitis, ileocolitis and colitis[31]. As a consequence, mesalazine has become a popular treatment for mild Crohn' s disease. However, more recently, a meta-analysis of the three placebo-controlled trials of Pentasa 4 g/d for active Crohn' s disease for 16 wk in a total of 615 patients, showed a mean reduction of the Crohn's disease activity index (CDAI) of 63 points, compared to 45 points for placebo (that is, a difference of only 18 points)[32].

Although this confirmed that a time-dependent de-

layed release formulation of mesalazine, Pentasa 4 g/d, is superior to placebo, the clinical significance of the reduction in CDAI is debatable because in individual trials, a 70- to 100-point decrease generally is required to establish clinical efficacy[32]. From these data, an alternative conclusion seems to be more plausible; namely, that Pentasa is ineffective for the treatment of symptomatic Crohn' s disease[33]. Thus, at this stage, mesalazine should be considered clinically no more effective than placebo for active ileal or colonic Crohn' s disease[33]. Accordingly, the European Crohn' s and Colitis Organization (ECCO) have concluded, "the benefit of mesalazine is limited"[26,27]. Therapeutic agents now exist that offer safe and highly effective alternatives to 5-ASA for the treatment of mild-to-moderate Crohn' s disease[34]. Specifically, in ileal or ileocolonic disease, budesonide provides the benefits of prednisone with less systemic side effects[35].

When faced with the same set of facts, healthcare providers often make different diagnoses, employ different tests, and prescribe disparate therapies. Esrailian *et al*[9] have constructed a survey with five vignettes to elicit provider beliefs regarding the appropriateness of therapies in Crohn' s disease. The authors measured agreement between community gastroenterologists and Crohn' s disease experts (the latter following, theoretically, more closely practice guidelines recommendations), and measured variation within each group. In the management of a patient with newly diagnosed Crohn' s disease, 75% of community providers endorsed the use of 5-ASA products, whereas less than half of experts (44%) employed 5-ASA therapies.

In summary, in the setting of modest efficacy and more potent alternatives, the best practice may be to consider abandoning the use of 5-ASA in patients with small bowel Crohn' s disease, until the appropriate patient population where these drugs may theoretically be effective is better delineated[33,34].

The combination of oral and topical 5-ASA treatment is not necessary, as each treatment on its own is similarly effective

Pharmacokinetic studies have demonstrated that, when given *per os*, the active moiety of mesalazine is delivered mainly to the distal ileum and proximal large bowel, thus ensuring a higher mucosal drug concentration in the right than in the left colon, with only negligible amounts of the drug reaching the rectal mucosa[36,37]. The increase in the oral dosage further increases the mucosal concentration in the proximal colonic segments, but does not significantly modify distal drug distribution[38]. Conversely, topical mesalazine administration assures considerable drug availability in the recto-sigmoid sites and, to a lower extent in the descending colon[39-41]. Therefore, it appears that, to increase mucosal mesalazine concentration in ulcerative colitis patients, along the entire length of their large bowel, besides oral dosage, topical treatment should be given[42].

As David Sachar has accurately emphasized, a form of undertreatment is overlooking the benefits of topical formulations[16]. The advantages of the combination of oral and topical aminosalicylates have been demonstrated for both inducing ulcerative colitis remission and for maintaining it. For treatment of an acute flare of the disease, on one hand, an already considered classic trial on patients with distal colitis has shown that combined therapy works more rapidly and effectively compared to oral or topical therapy alone[43]. Accordingly, the ECCO states that "left-sided active ulcerative colitis of mild-moderate severity should initially be treated with topical aminosalicylates combined with oral mesalazine. Mesalazine alone is also effective, but less effective than combination therapy"[44]. The beneficial effect of the combined regimen has also been confirmed in extensive colitis by Marteau *et al*[45]. Furthermore, patient-reported health-related quality of life in data collected from this study was investigated, and it was concluded that combined oral plus topical mesalazine treatment significantly improved this important parameter in patients with active ulcerative colitis[46].

On the other hand, there have been several randomized controlled trials comparing combination treatment, including oral mesalazine plus intermittent mesalazine enema, to oral mesalazine alone for maintaining remission[42,47-49], and success rates have been higher in patients receiving the combination regimen. Furthermore, combined oral and topical 5-ASA therapy also appear to have a favorable cost-effectiveness ratio in pharmacoeconomic analyses[47,48].

Although most authors have claimed that patients find long-term rectal treatment acceptable, a postal survey of British patients has shown that 80% preferred oral treatment alone[50]. Therefore, this form of combination treatment (with the aim of maintaining remission) could be appropriate and may be reserved for patients with a high probability of suffering relapse, because it has been demonstrated that the continuous use of topical mesalazine, associated with a high oral dosage, significantly improves the clinical course of ulcerative colitis in patients at high risk of relapse[42]. Thus, adding rectal therapy is a treatment option for patients who have relapsed on oral 5-ASA alone[44].

In summary, owing to the superiority of the combined approach - oral plus topical 5-ASA - it should be used as first-line treatment in patients with ulcerative colitis; mainly in those with predominant rectal syndrome[51].

Total 5-ASA dose should be divided at least twice daily, because a single daily dose is less effective

Oral 5-ASA is an established treatment for ulcerative colitis and the current standard of care for most patients requiring long-term maintenance treatment throughout their lives[52]. However, adherence rates - particularly in patients in remission - may be as low as 40% outside of the clinical trial setting[53]. It is now becoming relevant to find tools that improve patient adherence to treatment[54], as it has been found that multiple dosing is a predictor of non-compliance in IBD[55] and is related to a significantly increased risk of ulcerative colitis flare-ups[56].

Formulations to deliver 5-ASA to the disease activity

site, both orally and topically, have been often inconvenient and have classically required multiple daily dosing[57]. Such regimens can interfere with normal life and reduce the overall quality of life, with a negative impact on treatment adherence and poorer long-term outcomes[52]. Thus, ulcerative colitis patients cite treatment regimen complexity, tablet quantity and dose frequency as key negative influencers of adherence[52,57].

Pharmacokinetic studies in healthy volunteers have suggested that once-daily dosing may be an effective option in patients with ulcerative colitis. Hussain *et al*[58] have shown that serum, urinary, fecal, and rectal tissue concentrations are similar for once and three times daily mesalamine dosing regimens. Also, in a recent study, 4 g oral ethylcellulose-coated mesalamine given once daily was bioequivalent to a twice-daily regimen after single or repeated administration[59].

A new oral delayed-release formulation of mesalazine utilizing Multi Matrix System (MMX) technology was recently approved[60,61]. It is a high-dose (1.2 g/tablet), delayed-release form. Several studies with MMX have shown that mesalamine can be administered once-daily[62-64]. What is most important is that not only the new once-daily mesalazine formulations, but also older forms of 5-ASA may be administered in a single daily dose; apparently with adequate effects.

Response to 5-ASA is better correlated with tissue concentrations and best predicted by concentrations of the drug within the lumen of the colon. Some authors have used computer simulation to predict colonic 5-ASA levels after Asacol administration[65]. An Asacol dosage of 800 mg, three times daily, was compared to 2400 mg given once daily. The predicted maximum and average 5-ASA concentrations in the total colon and individual colonic segments differed by < 10% between dosing regimens. This model supports once-daily administration of 5-ASA as standard treatment for ulcerative colitis.

In a initial pilot clinical study, patients were randomized to receive either once daily or conventional (twice or three times daily) mesalazine for maintenance of remission in ulcerative colitis[66]. After 6 mo, patients in the once-daily arm appeared more satisfied with their regimen and consumed more medication than those in the conventional arm (90% *vs* 76%). More recently, preliminary results from a randomized trial have confirmed these encouraging results[67].

Data for the administration of a single daily dose of 5-ASA are available for both the induction and maintenance of remission of ulcerative colitis. On one hand, some authors have determined the therapeutic equivalence and safety of once-daily *vs* three times daily dosing of a total daily dose of 3 g Salofalk granules in patients with active ulcerative colitis[68]. On the other hand, other authors have confirmed this equivalence for patients with quiescent ulcerative colitis[69]. The results of the first long-term efficacy trial of maintenance therapy (with Pentasa as the 5-ASA) showed that 71% of patients receiving a single daily dose of 2 g mesalazine remained in remission, as compared to 59% of those taking 1 g twice daily; the differences being statistically significant[69]. Patients with ulcerative colitis given 5-ASA once daily had better remission rates, acceptability, and self-reported adherence to therapy compared with patients given 5-ASA twice daily. Another study was conducted to determine the efficacy and safety of once-daily dosing of delayed release mesalamine (Asacol) compared with twice-daily dosing for maintaining remission in ulcerative colitis patients, and demonstrated equivalent results with both regimens[70].

The totality of these data suggests that the success of once-daily dosing for all of these compounds may be due to the pharmacodynamic properties of 5-ASA, and may not depend on the specific characteristics of the formulation determining drug delivery[70]. In other words, given comparable efficacy between once-daily and divided dosing regimes for the treatment of ulcerative colitis with mesalazine MMX, and also with other 5-ASA formulations, the effect is likely to be generic rather than compound specific[44].

In summary, once-daily treatment should be offered as a first-choice regimen to ulcerative colitis patients. Indeed, the availability of treatments that can be taken once daily allows increased flexibility to tailor therapy according to patient preference and lifestyle, and may also have the potential to enhance compliance[69]. In fact, improved efficacy with once-daily dosing seems to be at least partly related to improved compliance[69]. These results and subsequent recommendations reinforce the principle that continued medication consumption, rather than actual drug regimen, is important in preventing disease relapse[67]. Also, that adherence, rather than medication regimen, appear to be important in disease outcome, mainly in the long term[67].

AZATHIOPRINE AND MERCAPTOPURINE

Thiopurine drugs azathioprine and mercaptopurine have been shown to be effective at inducing and maintaining remission in IBD[71,72]. These drugs are becoming increasingly popular, and their use is, at present, being considered at earlier phases of the disease than before.

Correct dose of azathioprine for Crohn's disease is 1-2 mg/kg, because higher doses are not more effective and are associated with increased adverse effects

The choice of azathioprine and mercaptopurine dose is generally based on the patient's weight, with the intention to achieve the highest therapeutic efficacy and, at the same time, to reduce the incidence of adverse effects[73-75]. Based on reported clinical trials, the most effective doses appear to be azathioprine 2.0-3.0 mg/kg and mercaptopurine 1.0-1.5 mg/kg, although there has not yet been a head-to-head comparison at various dose levels or a comparative trial evaluating the efficacy of mercaptopurine versus azathioprine in patients with IBD[76].

A meta-analysis has been performed to evaluate the

efficacy of these agents for the maintenance of remission of quiescent Crohn' s disease[77]. The pooled analysis for maintaining remission was stratified by the dose of azathioprine. When the maintenance therapy data were analyzed for the effect of azathioprine dose (1.0-2.5 mg/kg per day), the odds ratio (OR) for response increased from 1.20 (95% CI: 0.60-2.41) at 1.0 mg/kg per day to 3.01 (95% CI: 1.66-5.45) at 2.0 mg/kg per day, and to 4.13 (95% CI: 1.59-10.71) at 2.5 mg/kg per day. Thus, a common error is to step up the treatment strategy, giving up on thiopurine drugs (for example changing from these drugs to anti-tumor necrosis factor (TNF)α, before being absolutely sure that they have been administered at correct, maximal doses[16].

In summary, a form of undertreatment with thiopurines is underdosing[16]. The habit of automatically administering mercaptopurine or azathioprine at fixed doses of 50 mg/d should have been long abandoned, as higher doses of azathioprine (2.5 mg/kg per day) are more effective than lower doses (1.0 or 2.0 mg/kg per day) for treating Crohn' s disease.

Azathioprine and mercaptopurine are ineffective in ulcerative colitis (or, at best, much less effective than in Crohn' s disease)

Thiopurine drugs are the gold-standard treatment for steroid-dependent Crohn' s disease, because these drugs have been shown to be effective both at inducing and mainly, maintaining remission of the disease[71,72]. In addition, a clear steroid-sparing effect in active or quiescent Crohn' s disease has been observed with azathioprine/mercaptopurine therapy[71,72]. However, debate exists regarding whether thiopurine therapy is as effective in ulcerative colitis as it is in Crohn' s disease[78]. There have been surprisingly few randomized controlled trials, most of which were performed several decades ago and suffered from small sample sizes, used inadequate dosing of azathioprine, had ambiguous endpoints, and other methodological limitations[79].

Some meta-analyses have evaluated the efficacy of azathioprine/mercaptopurine in patients with ulcerative colitis[80-82]. The first one[80], which included studies up to the year 2003, identified only four clinical trials, and the pooled OR of the response to azathioprine therapy compared with placebo for the maintenance of remission was 2.26 (95% CI: 1.27-4.01). In the second meta-analysis[81], the literature search was performed up to the year 2006, and azathioprine was also shown to be superior for the maintenance of remission compared to placebo. Finally, the results of the most recent meta-analysis comparing azathioprine/mercaptopurine *vs* placebo or 5-ASA for the maintenance of remission in ulcerative colitis[82] has been published in 2009, and included six studies[83-88]. A therapeutic benefit of azathioprine, both overall (OR: 2.56; 95% CI: 1.51-4.34) and, particularly, when azathioprine was compared with placebo (OR: 2.59; 95% CI: 1.26-5.3), was demonstrated[82]. The number needed to treat (NNT) to prevent one recurrence with azathioprine/mercaptopurine, when compared with placebo, was only five (which compares favorably with the NNT of seven reported with azathioprine in Crohn' s disease[71]). These favorable results were confirmed when the experience from the non-controlled studies were reviewed: when these drugs were evaluated for the maintenance of remission of ulcerative colitis, the efficacy rate was as high as 76%[82].

A clinically meaningful steroid-sparing effect is achieved by thiopurine treatment, not only in Crohn' s disease patients but also in ulcerative colitis[89-92]. The number of cumulative hospitalizations significantly decreases during azathioprine treatment, both in Crohn' s disease and in ulcerative colitis patients[92,93]. Furthermore, the cumulative number of surgical interventions in patients treated with azathioprine/mercaptopurine has been reported to also be significantly lower after starting thiopurine treatment than before[92]. Finally, some authors have evaluated mortality by IBD medication, and have found that use of immunomodulators (mainly azathioprine and mercaptopurine) were associated with 50% decreased mortality in ulcerative colitis[94].

Few studies have directly compared thiopurine therapy efficacy between ulcerative colitis and Crohn' s disease. Kull *et al*[95] have compared the 6-mo efficacy of azathioprine in patients with both diseases, and found that clinical remission rates were slightly higher for ulcerative colitis than for Crohn' s disease (77% *vs* 70%); furthermore, complete corticosteroid weaning was obtained significantly more often in ulcerative colitis than in Crohn' s disease patients (59% *vs* 30%). Verhave *et al*[96] have concluded that patients with ulcerative colitis treated with azathioprine respond similarly to their Crohn' s disease counterparts. Moreover, they have determined that the beneficial effect occurs 1 mo sooner in ulcerative colitis patients than in Crohn' s disease patients. Fraser *et al*[97] have shown that azathioprine was more likely to achieve remission in patients with ulcerative colitis than Crohn' s disease (58% *vs* 45%), but was equally effective for the maintenance of remission. This study is also worth mentioning because of the long mean follow-up of patients, which provides valuable information to the clinician. In the study by Bastida *et al*[98], the beneficial effect of azathioprine was independent of the type of IBD. Finally, Gisbert *et al*[92] have found in a recent prospective study that azathioprine was similarly effective for Crohn' s disease and ulcerative colitis patients (49% *vs* 42%). Furthermore, azathioprine treatment resulted in a similar reduction in the number of hospitalizations and surgical procedures in both diseases[92].

In summary, it may be concluded that azathioprine and mercaptopurine seem to be at least as effective in ulcerative colitis as in Crohn' s disease patients.

Withdrawal of azathioprine should be recommended after several years if the patient is in remission

A form of undertreating with antimetabolites is suspending or discontinuing them too soon. Although azathioprine and mercaptopurine are effective for maintain-

ing remission in Crohn' s disease[99], no safe number of years has been determined after which these medications can be withdrawn without risk of relapse[16].

With the acceptance that Crohn' s disease is a chronic illness that needs long-term chronic therapy and the adoption of more aggressive goals of therapy (steroid-free remission, avoidance of surgery, and even mucosal healing), continuing an effective maintenance therapy is increasingly advised[100]. However, given the small but finite risk of significant adverse effects, coupled with the need for long-term therapy in patients who are often young and otherwise healthy, stopping immunomodulators in a patient in remission remains appealing[100,101].

The ECCO states that "for patients in remission on azathioprine as maintenance treatment, cessation may be considered after four years of "remission"[26,27]. It is also stated that "benefit and risks of continuing azathioprine should be discussed with individual patients"[27]. However, there has been no consensus about the duration of the treatment once remission has been obtained.

A retrospective study published in 1996 has suggested that withdrawal of azathioprine might be possible in patients who have been in complete remission without steroids for longer than 3.5 years, because the 2-year relapse rate seems similar whether the treatment is continued or stopped after this time[102]. This uncontrolled observation on a small subset of patients required confirmation by a prospective controlled trial. Therefore, Lemann *et al*[101] subsequently performed a multicenter, randomized, double-blind, noninferiority withdrawal trial. Patients who were in clinical remission on azathioprine for > 42 mo were randomized to continue azathioprine or to receive an equivalent placebo for 18 mo. Kaplan-Meier estimates of the relapse rate at 18 mo were 8% and 21%, respectively. Therefore, this study shows that azathioprine withdrawal is not equivalent to continued therapy with azathioprine for maintenance of remission in patients with Crohn' s disease who have been in remission on azathioprine for > 3.5 years. Consequently, the authors have concluded that azathioprine maintenance therapy should be continued beyond 3.5 years[101].

More recently, a cohort study of 66 patients in prolonged remission while being treated with azathioprine who stopped azathioprine, during or at the end of the aforementioned randomized controlled trial, underwent long-term follow-up evaluation[103]. The cumulative probabilities of relapse at 1, 3 and 5 years were 14%, 53%, and as high as 63%, respectively. In other words, two thirds of subjects still relapsed by 5 years when taken off azathioprine. This suggests that in many patients with Crohn' s disease, azathioprine withdrawal is not a feasible alternative, even after years of control, because it is associated with a high risk of relapse, whatever the duration of remission under this treatment[100].

In addition, two retrospective surveys have reported relapse rates after azathioprine or mercaptopurine withdrawal of 66%[97] and 85%[104], respectively, at 3 years. Another study[105] has reported the outcome of 29 patients in remission under continuous treatment with azathioprine for 2 years or more, randomized for continuation or withdrawal of azathioprine. At 1 year after randomization, the remission rate in each group was 85% and 47%, respectively ($P < 0.05$).

Discussion regarding the duration of an effective azathioprine treatment mainly concerns two points: (1) the magnitude of the relapse risk after stopping the drug; and (2) the toxicity of prolonged treatment[101]. As with all other agents, there will be some cost in relation to potential adverse events, including rare cases of infections and neoplasia that are probably related to the level of immunosuppression[106]. When the overall risks and benefits of prolonged maintenance therapy with azathioprine are balanced, it is likely that most clinicians and patients will accept the small, as yet unquantified, risk of a lymphoid malignancy, and the small risk of opportunistic infections, to prevent the ongoing morbidity and impact on quality of life that are related to the chronic symptomatic activity of Crohn' s disease[106].

In conclusion, even after a long duration of clinical remission under azathioprine, withdrawal of this drug is associated with a high risk of relapse. Therefore, as in transplanted patients, azathioprine maintenance therapy should probably be continued indefinitely in patients with Crohn' s disease once remission has been achieved[103,107].

In IBD patients who develop azathioprine digestive intolerance, thiopurine drugs should be definitively withdrawn

Azathioprine intolerance remains an important clinical problem in patients with IBD, which leads to withdrawal of therapy in up to 30% of patients[73]. In particular, its use is limited due to digestive intolerance in 10%-15% of patients[73]. This often mandates treatment with methotrexate, an alternative second-line immunosuppressive therapy in patients with Crohn's disease, or more recently, anti-TNF therapy. For patients with ulcerative colitis, colectomy may be precipitated in some individuals by azathioprine intolerance.

However, it has been suggested that the thiopurine drugs azathioprine and mercaptopurine could be interchangeable. Thus, an alternative strategy for azathioprine intolerance (mainly due to nausea or vomiting) is treatment with mercaptopurine (or *vice versa*). Several case series have addressed this question and have shown that mercaptopurine is tolerated in > 50% of azathioprine-intolerant patients (range: 47%-73%)[108-113].

In summary, treatment with mercaptopurine is a safe alternative in patients with IBD and previous digestive intolerance of azathioprine. Given the mild character of these symptoms, these patients may be cautiously switched to mercaptopurine (or *vice versa*) before being considered for other therapy or surgery[76].

Systematic blood controls may be avoided if thiopurine methyltransferase phenotype/genotype is normal

Azathioprine and mercaptopurine are inactive compounds that must be metabolized to 6-thioguanine nucleotides

(6-TGNs) to exert their cytotoxic and immunosuppressive properties. Thiopurine methyltransferase (TPMT) metabolizes mercaptopurine into inactive 6-methylmercaptopurine[114]. Therefore, reduction in TPMT activity predisposes to bone marrow suppression because of preferential metabolism of mercaptopurine to 6-TGN[115]. Quantification of TPMT activity has been considered a promising area, because it may identify unique metabolic profiles in patients at high risk of adverse reactions prior to drug exposure[115]. Thus, high concentrations of 6-TGN are detected in patients with low activity of TPMT, while low concentrations of these metabolites are found in patients with high TPMT activity, although not all studies have demonstrated this inverse correlation[116-120].

Several studies have reported a correlation between TPMT phenotype/genotype and the risk of myelotoxicity[115]. Homozygous patients for the low TPMT activity allele have an increased risk of suffering severe myelotoxicity due to excessive accumulation of 6-TGN[115]. It has been reported that the probability of having a complete TPMT deficiency or being homozygous for this enzyme is > 6 times higher among patients who have had a myelosuppression episode, when compared with those patients with good tolerance to thiopurine drugs[121]. Furthermore, other authors have even found an incidence of myelotoxicity of up to 100% in patients who are homozygous for the low activity allele[122]. However, some authors have reported that TPMT genotype/phenotype does not predict myelotoxicity in IBD patients treated with thiopurine drugs[123-132]. In this respect, a recent study has prospectively evaluated whether the choice of azathioprine or mercaptopurine dose based on TPMT activity prevents myelotoxicity in IBD patients. Among the four patients with myelotoxicity, one had intermediate basal TPMT levels, and three even had high levels, but no patient had low levels[133]. Finally, several studies have demonstrated that TPMT deficiency phenotype or genotype explains a variable proportion of myelotoxicity cases, but in no way explains all episodes of bone marrow suppression[116-122,125,128,129,134-142].

In summary, the majority of cases of leukopenia are not TPMT-related and therefore TPMT screening can never be viewed as a substitute for the current practice of regular monitoring of white blood cell counts. For this reason, it may be concluded that several factors (e.g., environmental and pharmacological) not related to TPMT activity may be responsible for azathioprine myelotoxicity, and systematic blood controls (complete blood count; mainly leukocyte count) should be done in these patients despite the function of this enzyme being normal.

Azathioprine should always be stopped and non-thiopurine therapy used instead if liver abnormalities are detected

Acute hepatocellular and cholestatic hepatitis have both been described during thiopurine therapy[143,144]. A small percentage of patients present with slight elevation of liver tests that do not have clinical implications, and abnormalities in liver tests return to normal during follow-up, which indicates that it is not always necessary to adjust immunomodulator dose. For example, abnormal liver tests resolved spontaneously while continuing on mercaptopurine in four out of five patients in the study by George *et al*[145], and in three out of four patients in the study by Markowitz *et al*[146].

When abnormalities in liver tests are more marked, but without associated jaundice, the dose of azathioprine/mercaptopurine may be reduced by 50%. It is probably not necessary to withdraw azathioprine or mercaptopurine completely, but frequent clinical and analytical controls should be strictly performed after reducing its dose. With this strategy, liver tests frequently normalize, and the initial azathioprine/mercaptopurine dose may be cautiously prescribed again[147,148].

A recent long-term follow-up study aimed to assess the incidence of azathioprine/mercaptopurine-induced liver injury in 786 patients with IBD (138 of whom received azathioprine/mercaptopurine)[149]. Among azathioprine/mercaptopurine-treated patients, the incidence of abnormal liver tests [liver tests between N (upper limit of the normal range) and 2 N] and hepatotoxicity (liver tests > 2 N) was, respectively, 7.1% and 2.6% per patient-year. In most patients, liver tests spontaneously normalized despite maintaining thiopurine treatment. These drugs were withdrawn due to hepatotoxicity (liver tests > 5 N, and lack of decrease despite 50% dose reduction) in only 3.6% of the patients, and all of them showed normalized liver tests.

If liver tests do not return to normal values with tapering of thiopurines, it has been recommended that therapy should be withdrawn. However, if azathioprine was initially prescribed, another possibility is to use mercaptopurine instead. Lopez-Sanroman *et al*[150] did so in 4/5 patients, and achieved complete resolution of liver test alterations in all patients. This finding is consistent with another smaller study in which seven out of eight patients with hepatotoxicity during azathioprine treatment tolerated mercaptopurine, and only one patient had hepatotoxicity again with mercaptopurine[151]. In this same way, in the study by Hindorf *et al*[111] 71% of patients with hepatotoxicity during azathioprine treatment subsequently tolerated mercaptopurine and only two of the patients had a recurrence of hepatotoxicity with mercaptopurine. Finally, Bermejo *et al*[152] have assessed tolerance to mercaptopurine in 31 patients with previous azathioprine-related liver injury; in 87% of patients, mercaptopurine was tolerated without further liver injury; and among these, 77% tolerated full mercaptopurine doses.

Nevertheless, it should be noted that in unusual cases, thiopurines may induce severe cholestatic jaundice that, in contrast to acute hepatocellular hepatitis that is generally associated with azathioprine/mercaptopurine, may not regress but even progress despite thiopurine withdrawal[153]. Therefore, these drugs should be completely withdrawn, and not only tapered, in patients who present with clinically significant jaundice during thiopu-

rine treatment[144].

In summary, most of the cases of thiopurine-induced hepatotoxicity in IBD patients are mild, and liver test abnormalities spontaneously returned to normal values despite maintenance of azathioprine/mercaptopurine; therapy withdrawal is necessary in < 5% of patients. However, when liver test abnormalities are more marked, the dose of azathioprine/mercaptopurine may be reduced by 50%. Finally, administration of mercaptopurine is a good alternative in patients with azathioprine-related liver injury before thiopurines are definitely withdrawn.

CONCLUSION

Misconceptions are common in medical practice in general and, in particular, in the health care of IBD patients. Many of these misconceptions are related to the use of 5-ASAs and thiopurines, the two most widely used drugs in IBD. A proportion of medical errors directly affects patient safety and causes accidental deaths, but the vast majority of them are effectiveness errors. However, we must not focus all our attention on prevention of safety errors while forgetting effectiveness ones. Prevention of errors needs knowledge to avoid errors being caused by ignorance. In fact, throughout history the main reason for medical errors has simply been ignorance[8]. However, at present, the amount of knowledge has increased so quickly that one new danger is overabundance of information. IBD is a model of a very complex problem, and our goal with this review is to summarize the key evidence for the most common daily clinical problems faced by physicians and patients.

With regard to the use of 5-ASAs, the best practice may to be consider abandoning the use of these drugs in patients with small bowel Crohn' s disease. The combined approach with oral plus topical 5-ASAs should be the first-line therapy in patients with active ulcerative colitis, because this is more effective than monotherapy; once-daily treatment should be offered as a first-choice regimen due to its better compliance and higher efficacy. With regard to thiopurine therapy, it seems to be as effective in ulcerative colitis as in Crohn' s disease. Underdosing with thiopurines is a form of undertreatment with these drugs. Thiopurine treatment should probably be continued indefinitely because its withdrawal is associated with a high risk of relapse. Mercaptopurine is a safe alternative in patients with digestive intolerance or hepatotoxicity due to azathioprine. Finally, TPMT screening cannot substitute for regular monitoring because the majority of cases of myelotoxicity are not TPMT-related.

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