Immunomodulators for all patients with inflammatory bowel disease?

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***Abstract*:** Recent insight into the pathogenesis of Crohn's disease (CD) and ulcerative colitis (UC) have led to the development of new treatment options, with a progressive shift to more evidence-based strategies based on sound pathophysiological rationales. A better understanding of inflammatory bowel disease (IBD) pathophysiology has progressively resulted in a more frequent use of immunomodulators. We review the recommended or suggested use of conventional immunomodulators such as azathioprine, 6-mercaptopurine, methotrexate in the treatment of IBD. Moreover, an effort is made to explore some critical areas in which early and more diffuse use of these agents may be advocated.

***Keywords*:** azathioprine, Crohn's disease, immunomodulators, inflammatory bowel disease (IBD), treatment, ulcerative colitis

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Introduction

Inflammatory bowel disease (IBD), i.e. Crohn's disease (CD) and ulcerative colitis (UC), are chronic, inflammatory disorders of the gastrointestinal tract, with an increasing prevalence in developed countries. While the etiology has remained unknown, understanding of the molecular mediators and mechanisms of tissue injury has greatly advanced, and certain features of these diseases have suggested several areas of possible importance, such as genetic, infectious, immunologic and inflammatory factors [Ardizzone and Bianchi Porro, 2002]. However, the specific cause(s) remained to be identified, and whether or not IBD is a response to noxious factors which are either single or multiple is unclear, appearing as a kind of 'puzzle', the composition of which is difficult to understand until the different pieces are recognized and correctly assembled.

The treatment of IBD consists of sulphasalazine (SASP), 5-aminosalicylic acid (5-ASA), corticosteroids, immunomodulator drugs [azathioprine (AZA), 6-mercaptopurine (6-MP), methotrexate (MTX)], calcineurin inhibitors (cyclosporin and tacrolimus), and anti-TNF-alpha antibodies (infliximab, adalimumab, certolizumab), the choice of which depends on the clinical goal (induction or maintenance of remission), extent and severity of disease, response to current or prior medication and the presence of complications.

Recent insight into the pathogenesis of CD and UC have led to the development of new treatment options, with a progressive shift to more evidence-based strategies based on sound pathophysiological rationales [Korzenik and Podolsky, 2006]. Thus, a better understanding of IBD pathophysiology has progressively resulted in more frequent use of immunomodulators and the anti-TNF-alpha antibodies.

Aiming to answer the question in the title of this article, we review the recommended or suggested use of conventional immunomodulators such as AZA/6-MP and MTX in the treatment of IBD. Moreover, an effort is made to explore some critical areas in which early and more diffuse use of these agents may be advocated.

Who is the IBD-patient candidate for treatment with conventional immunomodulators?

In a regional inception cohort study, 1161 UC patients from the County of Copenhagen, Denmark, were followed up from diagnosis up to 25 years [Langholz *et al.* 1994]. The distribution of disease activity was remarkably constant each year, with about 50% of patients in clinical remission. After 10 years, the colectomy rate was

24%, while the cumulative probability of relapse was 90% after 25 years of follow-up. Disease course changed between remission and relapse without significant predictors, except for disease activity in foregoing years. In years 3–7 after diagnosis, 25% of patients were in remission; 18% had activity every year; and 57% had intermittent relapses. Activity in the first 2 years after diagnosis significantly correlated with having an increased probability of 5 consecutive years of disease activity ($p = 0.00001$).

In another study by the same group [Munkholm *et al.* 1995], an inception cohort of 373 CD patients from the County of Copenhagen was followed for a period of 25 years. An annual assessment was made for each year of follow-up, assessing the maximal clinical activity within the year and whether continuous or intermittent that year. Eighty percent of the patients had high activity at diagnosis, decreasing to an almost stable value of 30% in the following years. Although the individual patients with relapse and remission changed from year to year, a constant 15% had a low activity, and about 55% could expect to be in clinical remission each year. The probability of a relapse-free course decreased rapidly with time, being 22% after 5 years (95% CI, 13–33%), and 12% after 10 years (95% CI, 7–19%). The probability of a continuously active course without remission was low, being 4% after 5 years (95% CI, 1–8%) and 1% after 10 years (95% CI, 0–4%).

These data suggest that most IBD patients have a benign clinical course and only a minority have their disease continuously active.

Why should conventional immunomodulators be prescribed to IBD patients?

Several controlled trials and meta-analyses have shown that conventional immunomodulators are effective in treating IBD patients.

Azathioprine and 6-mercaptopurine

The first meta-analysis assessing the effectiveness of AZA and 6-MP in inducing remission of active CD and the effectiveness of AZA in maintaining remission of quiescent disease, was published by Pearson *et al.* [Pearson *et al.* 1995]. Nine randomized, placebo-controlled trials of AZA or 6-MP therapy were identified: four addressed active disease, two addressed quiescent disease, and three had multiple therapeutic arms. Compared with placebo, AZA or 6-MP therapy had an odds ratio (OR) for response of 3.09 (95% CI, 2.45–3.91) in patients with active CD. When the single trial that used 6-MP in active disease was excluded from the analysis, the OR of response was 1.45 (95% CI, 1.12–1.87). No trials of quiescent disease used 6-MP; the OR of response in these trials of quiescent disease was 2.27 (95% CI, 1.76–2.93). For active disease, continuation of therapy for at least 17 weeks improved response ($p = 0.03$). For quiescent disease, a higher dose improved response ($p = 0.008$). Increased cumulative dose improved response in both groups ($p < 0.001$ for active disease and $p = 0.01$ for quiescent disease). A steroid-sparing effect was seen in active disease [OR, 3.69 (95% CI, 2.12–6.42)] and in quiescent disease [OR, 4.64 (95% CI, 1.00–21.54)]. Fistulae improved with therapy [OR, 4.44 (95% CI, 1.50–13.20)]. Adverse events requiring withdrawal from a trial, primarily allergy, leukopenia, pancreatitis and nausea, were increased with therapy [OR, 5.26 (95% CI, 2.20–12.60)].

More recently, two other meta-analyses further focused on the effectiveness of AZA/6-MP for the induction and maintenance of remission in CD.

In active CD [Sandborn *et al.* 2000], the OR of a response to AZA/6-MP therapy compared with placebo in active CD was 2.36 (95% CI, 1.57–3.53). This corresponded to a number needed to treat (NNT) of about 5 to observe an effect of therapy in one patient. When the two trials using 6-MP in active disease were excluded from the analysis, the OR of response was 2.04 (95% CI, 1.24–3.35). Treatment >17 weeks increased the OR of a response to 2.51 (95% CI, 1.63–3.88). A steroid-sparing effect was seen with an OR of 3.86 (95% CI, 2.14–6.96), corresponding to a NNT of about 3. Adverse events requiring withdrawal from a trial (mainly allergy, leukopenia, pancreatitis, and nausea) were increased on therapy with an OR of 3.01 (95% CI, 1.30–0.96) and a NNT of 14 to observe one adverse event in one patient treated with AZA or 6-MP.

In the second meta-analysis [Prefontaine *et al.* 2009], seven trials of AZA therapy and one of 6-MP were included. AZA and 6-MP had a positive effect on maintaining remission in CD. The Peto OR for maintenance of remission with AZA was 2.32 (95% CI, 1.55–3.49) with a NNT of 6. The Peto OR for maintenance of remission with 6-MP was 3.32 (95% CI, 1.40–7.87) with a NNT of 4. Higher doses of AZA improved response.

A steroid-sparing effect with AZA was noted, with a Peto OR of 5.22 (95% CI, 1.06–25.68) and NNT of 3 for quiescent disease. Withdrawals due to adverse events were more common in patients treated with AZA (Peto OR 3.74; 95% CI, 1.48–9.45; NNT = 20) than with placebo.

Based on this strong evidence, AZA and 6-MP are effective in treating active CD and in maintaining remission. Cumulative dose was an important factor in predicting response. On the flip side of the coin, adverse effects were more common among patients receiving therapy.

As far as the efficacy of AZA/6-MP in UC is concerned, the available controlled clinical trials provide conflicting and controversial data, in contrast to several open studies showing that AZA or 6-MP can be effective in the treatment of patients with UC.

In particular, in a large retrospective cohort [Fraser *et al.* 2002] of 346 UC patients, with a mean duration of the initial course of treatment with AZA of 634 days, the overall remission rate (without steroids) was of 58%. For the 424 patients who received more than 6 months of treatment, remission rates were 87%, with a sustained efficacy of AZA for over 5 years. Moreover, the duration of AZA treatment did not affect the relapse rate after stopping treatment. Bearing in mind this discrepancy, we performed a randomized, investigator-blind, controlled trial aimed at comparing AZA and 5-ASA in the treatment of steroid-dependent UC [Ardizzone *et al.* 2006]. Seventy-two patients with steroid-dependent UC were admitted to this investigator-blind study. Steroid-dependence was defined as a requirement for steroid therapy of over 10 mg/day during the preceding 6 months, with at least two attempts to discontinue the medication. The disease had to be clinically and endoscopically active at study entry, and all patients were taking systemic prednisolone (40 mg/day). Patients were randomized to receive AZA 2 mg/kg/day or oral 5-ASA 3.2 g/day, for a 6 month follow-up period. The outcome of the treatment was defined as (1) success, indicating induction of clinical and endoscopic remission and steroid discontinuation, or (2) failure, indicating the absence of clinical and endoscopic remission and therefore the need for at least one further cycle of systemic steroids to control symptoms, apart from the initial one, or colectomy. Significantly more patients in the AZA than in the 5-ASA group had clinical and endoscopic remission, and discontinued steroid therapy, both in the intention to treat [AZA *versus* 5-ASA: 19/36 patients (53%) *versus* 7/36 (21%); OR 4.78 (95% CI, 1.57–14.5)] and per protocol [AZA *versus* 5-ASA: 19/33 patients (58%) *versus* 7/34 (21%); OR 5.26 (95% CI, 1.59–18.1)] analysis.

The evidence for the effectiveness of AZA and 6-MP for the maintenance of remission is still controversial. A recent meta-analysis [Timmer *et al.* 2007] evaluated six studies including 286 patients with UC. The study quality was mostly poor. AZA was shown to be superior for the maintenance of remission as compared to placebo based on four trials (failure to maintain remission: OR 0.41; 95% CI, 0.24–0.70). Two trials that compared 6-MP to oral 5-ASA, or AZA to SASP showed significant heterogeneity. Both studies using active comparators were open label. Adverse events were reported for 11 out of 127 patients on AZA, and three controls (OR 3.1; 95% CI, 1.0–9.3). Pancreatitis occurred in three out of 141 cases, jaundice/hepatitis in one out of 127 cases, and bone marrow suppression was reported for 5 out of 127 patients on AZA. Deaths, opportunistic infection or neoplasia were not reported. However, no mention was made about thiopurine methyltransferase (TPMT) testing prior the administration of AZA/6-MP or their dose.

Very recently, another meta-analysis evaluating the efficacy of AZA/6-MP in UC was published [Gisbert *et al.* 2009]. Thirty noncontrolled studies (1632 patients) were included in the systematic review. Mean efficacy of AZA/6MP was 65% for induction and 76% for maintenance of the remission. Seven controlled studies were included in the meta-analysis. (i) Induction of remission: four studies (89 AZA/6-MP-treated patients) showed mean efficacy of 73% *versus* 64% in controls (OR = 1.59; 95% CI, 0.59–4.29). (ii) Maintenance of remission: six studies (124 AZA/6-MP-treated patients) showed mean efficacy of 60% *versus* 37% in controls (OR = 2.56; 95% CI, 1.51–4.34). When only studies comparing AZA/6-MP *versus* placebo were considered, OR was 2.59 (95% CI, 1.26–5.3), absolute risk reduction was 23% and the NNT to prevent one recurrence was 5.

Thus, AZA/6-MP is an effective therapy both in inducing and maintaining remission for patients who have failed or cannot tolerate 5-ASA or

SASP and for patients who require repeated courses of steroids.

Methotrexate

The success of MTX as a treatment for rheumatoid arthritis led to its evaluation in patients with refractory CD. MTX has been studied for induction of remission in refractory CD and has become the principal alternative to AZA/6MP therapy.

In a meta-analysis [Alfadhli *et al.* 2004], five randomized trials were included. These studies differed with respect to participants, intervention, and outcomes to the extent that it was considered to be inappropriate to combine the data statistically. Three small studies which employed low doses of MTX orally showed no statistically significant difference between MTX and placebo/control medication treated patients. One small study [Ardizzone *et al.* 2003] which used a higher dose of intravenous/oral MTX showed no statistically significant difference between MTX and AZA. A larger study [Feagan *et al.* 1995] which employed a higher dose of MTX intramuscularly showed substantial benefit (number needed to treat, NNT = 5). Adverse effects were more common with high dose intramuscular methotrexate therapy than with placebo. Thus, there is evidence from a single large randomized trial on which to recommend the use of MTX 25 mg intramuscularly weekly for induction of remission and complete withdrawal from steroids in patients with refractory CD.

In patients with CD who enter remission after treatment with MTX, a low dose of the drug can maintain remission. In a double-blind, placebo-controlled, multicenter study [Feagan *et al.* 2000] of patients with chronically active CD who had entered remission after 16 to 24 weeks of treatment with 25 mg of MTX given intramuscularly once weekly, patients were randomly assigned to receive either MTX at a dose of 15 mg intramuscularly once weekly or placebo for 40 weeks. Remission was defined as a score of 150 or less on the CD Activity Index (CDAI). Forty patients received MTX, and 36 received placebo. At week 40, 26 patients (65%) were in remission in the MTX group, as compared with 14 (39%) in the placebo group ($p = 0.04$; absolute reduction in the risk of relapse, 26.1%; 95% CI, 4.4–47.8%). Fewer patients in the MTX group than in the placebo group required prednisone for relapse [11 of 40 (28%) *versus* 21 of 36 (58%), $p = 0.01$].

To review the effectiveness of MTX in inducing remission in patients with UC, all randomized controlled trials comparing MTX with placebo or an active comparator in patients with active UC were considered in a recent meta-analysis [Chande *et al.* 2007]. However, only one trial fulfilled the inclusion criteria [Oren *et al.* 1996]. This study randomized 30 patients to MTX 12.5 mg orally weekly and 37 patients to placebo for 9 months. During the study period, 14/30 patients (47%) assigned to MTX, and 18/37 patients (49%) assigned to placebo achieved remission and complete withdrawal from steroids (OR 0.92, 95% CI, 0.35–2.42; $p = 0.87$). The mean time to remission was 4.1 months in the MTX group and 3.4 months in the placebo group. In contrast to this controlled study, several open trials suggest that MTX could be effective in treating active UC. A new trial using higher doses of MTX and/or parenteral route in a population of adequate size should be considered.

What is the safety profile of immunomodulators?

Azathioprine and 6-mercaptopurine

There is little doubt that patients treated with AZA have a higher rate of adverse events than placebo-treated patients. In the Cochrane meta-analysis by Sandborn and colleagues [Sandborn *et al.* 2000], the usefulness and safety of AZA and 6-MP when used to induce remission in CD patients was analyzed. In this meta-analysis, adverse events occurred in 9.3% of patients taking AZA or 6-MP *versus* 2.3% of those taking placebo. The number needed to harm (number of patients that should be treated to develop a single adverse event) was 14. Pearson and colleagues [Pearson *et al.* 1995] also addressed the issue of AZA safety, but specifically for patients receiving this drug as maintenance therapy for CD. Drug withdrawal due to adverse effects occurred in 5.8% of patients receiving thiopurines, as compared to 1.3% of patients without treatment. In this case, the number needed to harm was 19.

Classically, AZA-related adverse events have been categorized into two types: allergic, idiosyncratic or non-dose-dependent, and dose-dependent [Etchevers *et al.* 2008; Dubinsky, 2004]. Allergic reactions include, among others,

malaise, rash, fever, pancreatitis and hepatitis. All of them are infrequent, occurring in 5–10% of AZA-treated patients. These adverse events are not related to the dose of AZA used or the variations in drug metabolism. In general, dose-dependent adverse effects are much more frequent than non-dose-dependent ones.

Bone marrow suppression is the most common dose-dependent adverse effect. Leukopenia appears in 2–15% of AZA-treated patients, depending on the cut-off used for its definition, is influenced by the degree of TPMT activity and can be modified by other concomitant drugs if they impact the enzyme activity. Such myelosuppression is reversible upon AZA dose reduction or transient suspension of the drug.

Another potential source of AZA-related adverse reactions stems from the immune suppression caused by the drug. AZA and 6-MP therapy is associated with an increased risk of infections ranging from 0.3% to 7.4%. The most common are viral infections, such as cytomegalovirus, Epstein–Barr virus, varicella zoster virus and herpes simplex virus. Infections can occur even in the absence of leukopenia. Thiopurine-induced liver toxicity is also a relevant issue. Its incidence varies between 3% and 10% of AZA-exposed patients and it can be classified into different entities: hypersensitivity, idiosyncratic cholestatic reaction, and endothelial cell injury (the later resulting in raised portal pressures, veno-occlusive disease or peliosis hepatis). The majority of these syndromes respond to drug withdrawal. Finally, the relationship between thiopurines and development of cancer, and especially hematologic malignancies such as lymphomas, remains a controversial topic. A meta-analysis [Masunaga *et al.* 2007] of risk of malignancy associated to the use of immunosuppressive drugs in IBD identified nine studies reporting colorectal cancer, malignant melanoma, leukemia and lymphoma cases. The weighted mean difference of malignancy incidence in IBD patients who received immunosuppressive agents, as compared to IBD patients not exposed to immunosuppressants, was -0.3×10^{-3} per person per year. There was no significant difference when the authors analyzed the length of exposure to immunosuppressants or whether the patients had CD or UC.

The issue of the relationship between lymphoma and IBD is complex, because the effects caused by the disease *per se*, by disease activity, and by different IBD therapies clearly overlap. A meta-analysis of Kandiel and colleagues [Kandiel *et al.* 2005] identified six cohort studies with AZA or 6-MP exposure that have been specifically designed to evaluate cancer as adverse outcome. The total number of observed cases was 11 with a pooled relative risk of 4.18. Recently, results from the very large French population-based CESAME study [Beaugerie *et al.* 2008] suggest a doubling of the risk of lymphoma in patients with IBD, with the majority of cases occurring in association with immunosuppressive therapy. Because these data were obtained from observational studies it is not possible to fully exclude the possibility of severity of the disease as confounding factor. As a global conclusion, the consensus about the relationship between immunosuppressants and lymphoma is that, if any association exists, it would be of small magnitude and, in any case, the beneficial effects exerted by these drugs on IBD patient outcomes would clearly outweigh the risk caused by the drug itself.

With the advent and success of anti-tumor necrosis factor (TNF) and other biological therapies, investigators have sought to define the place of concomitant immunomodulator therapy, and its effect on the risk–benefit equation. Although anti-TNF therapy can effectively treat CD, there is concern that it may increase the risk of non-Hodgkin's lymphoma (NHL). A meta-analysis was performed to determine the rate of NHL in adult CD patients who have received anti-TNF therapy and to compare this rate with that of a population-based registry and a population of CD patients treated with immunomodulators [Siegel *et al.* 2009]. Twenty-six studies involving 8905 patients and 21,178 patient-years of follow-up were included. Among anti-TNF treated subjects, 13 cases of NHL were reported (6.1 per 10,000 patient-years). The majority of these patients had previous immunomodulator exposure. Compared with the expected rate of NHL in the SEER database (1.9 per 10,000 patient-years), anti-TNF treated subjects had a significantly increased risk (SIR, 3.23; 95% CI, 1.5–6.9). When compared with the NHL rate in CD patients treated with immunomodulators alone (4 per 10,000 patient-years), the SIR was 1.7 (95% confidence interval, 0.5–7.1). Thus, the use of anti-TNF agents with immunomodulators is associated with an increased risk of NHL in adult CD patients, but the absolute rate of

these events remains low and should be weighed against the substantial benefits associated with treatment [Lewis *et al.* 2000].

Methotrexate

As far as the safety of MTX in IBD is concerned, very little data is available, especially for long-term use. However, reassuring data are coming from rheumatological experience. A systematic literature review of the long-term safety of MTX monotherapy in rheumatoid arthritis (RA) was recently published [Salliott and van der hei; de 2009]. Adults with RA who had received MTX monotherapy for more than 2 years were studied and 88 published studies were included. Over 12 years of treatment, the termination rate of MTX due to toxicity was less than for sulfasalazine, gold and d-penicillamine, and higher than for hydroxychloroquine (level of evidence 2a–2b). Long-term use of MTX does not appear to be a risk factor for serious infections, including herpes zoster (2b–4), and could provide a survival benefit by reducing cardiovascular mortality (2b). The prevalence of raised liver enzymes (more than twice the upper limit of normal) is close to 13% of patients; 3.7% of patients stopped MTX permanently owing to liver toxicity (2b). Data on the risk for liver fibrosis/cirrhosis are conflicting: a meta-analysis showed an incidence of fibrosis of 2.7% after 4 years of MTX (2a). However, two other studies on sequential liver biopsies did not show evidence for developing severe damage (2b). Insufficient data are available to fully assess the risk of lymphoma and malignancies, although there is no strong evidence of increased risk (2b–4). Thus, this systematic literature search on MTX monotherapy with relatively low-dose use during at least 2 years shows favorable long-term safety.

Anti-TNF therapy with or without antimetabolites?

Biological agents, more specifically anti-TNF antibodies, have been usually initiated as second- or third-line immunosuppressives in patients failing steroids and/or AZA. In recent years and with the data from early intervention trials, anti-TNF agents have been used earlier in the disease course including patients naïve to AZA. For these different patient profiles the added value of combined biological and antimetabolite therapy *versus* anti-TNF monotherapy has been highly debated in the last year. Combined therapy may have synergistic immunosuppressive effects adding to efficacy, but this synergism also may increase long-term toxicity. Contrary to what has been shown in rheumatoid arthritis patients on MTX, a therapeutic synergism of combined therapy with traditional immunosuppressives (AZA/6-MP or MTX) and anti-TNF antibodies has never been clearly demonstrated in IBD. On the contrary, biological agents approved for IBD treatment, such as anti-TNF antibodies, are proteins and have an intrinsic potential for inducing antidrug antibodies when used (immunogenicity) [Cassinotti and Travis, *et al.* 2009]. Immunosuppressives were shown to downsize the development of neutralizing anti-infliximab antibodies when this drug was used in an episodic, on-flare strategy [Baert *et al.* 2003]. Infliximab serum levels were also significantly higher in patients with concomitant immunosuppressive therapy [Vermeire *et al.*. 2007]. More recently, it became clear that this protective effect is much less if present at all when patients are treated with infliximab in a scheduled maintenance regimen [Rutgeerts *et al.* 2004]. With the more humanized anti-TNF adalimumab and certolizumab-pegol, the added clinical benefit for efficacy of combined therapy with immunosuppressives has not been established, although antidrug antibody development is decreased when patients are taking AZA/6-MP or MTX concomitantly. Moreover, adalimumab was effective both in inducing and maintaining remission in CD, without any difference between patients in monotherapy or treated in combination with antimetabolites [Colombel *et al.* 2007; Sandborn *et al.* 2007; Hanauer *et al.* 2006].

In patients naïve to purine analogues and MTX the question is very different. Preliminary data from the large ($n = 508$) blinded double-dummy controlled SONIC trial comparing AZA monotherapy, infliximab monotherapy (2.5 mg/kg/day) and combined infliximab and AZA therapy have been released [Sandborn *et al.* 2008]. At 26 weeks the steroid-free remission rates in patients receiving combined immunosuppressive therapy with infliximab and AZA were higher than with infliximab monotherapy (57 *versus* 45%, $p < 0.05$) and these were also higher than remission rates in patients with AZA monotherapy (45 *versus* 30%, $p < 0.01$). A course of steroids was allowed in all patients until week 12 to compensate for the slow onset of the therapeutic effect of AZA. The total disappearance of mucosal ulcers was also higher in the combined infliximab and AZA group [44% infliximab + AZA *versus* 19% AZA ($p < 0.001$)]. In contrast, preliminary data

from a recent Canadian collaborative trial showed no additional clinical benefit of MTX (25 mg/week) in combination with infliximab maintenance every 8 weeks over infliximab therapy alone [Feagan *et al.* 2008]. Infliximab serum levels from both trials have not yet been publicly released. Since all patients in the SONIC were naive to azathioprine and in the absence of pharmacokinetic data, it is logical to assume that at least AZA may act synergistically with infliximab to induce clinical remission and to maintain that over 6 months. The downside of immunosuppressive synergism is toxicity. Whether combined AZA/6-MP and anti-TNF therapy increases toxicity long term is still debated, but the recent studies of 17 hepatosplenic T-cell lymphomas in young patients with combined therapy have raised considerable concern [Mackey *et al.* 2007].

It is less clear whether it is beneficial to use the infliximab–AZA combination in patients who previously failed therapy with AZA. In this setting, a prospective open-label trial demonstrated that withdrawing immunosuppressives in patients with CD on combined infliximab and immunosuppressives therapy for at least 6 months did not affect efficacy over 2 years of follow-up, but tended to decrease infliximab trough levels [Van Assche *et al.* 2008]. This trial indicated that the impact of withdrawing antimetabolites in patients treated with scheduled infliximab maintenance therapy has limited or no risk of loss of efficacy, although the impact on infliximab trough levels warrants further long-term follow-up. All patients in this trial had received combination therapy for at least 6 months and most had been failing AZA therapy before entering the trial. More data are needed but, in selected patients, particularly those previously exposed to purine analogues or AZA, scheduled maintenance monotherapy with anti-TNF antibodies long term is certainly a valid option.

When are conventional immunomodulators indicated?

Based on the aforementioned evidence, both European and American guidelines advise on how to correctly use conventional immunomodulators in treating patients with IBD [Travis *et al.* 2008; Lichtenstein *et al.* 2006; Travis *et al.* 2006].

The main role for AZA/6-MP is their steroid-sparing effect. There is general agreement that immunomodulators should be started in CD and UC patients with steroid-dependent or steroid-refractory disease.

For arbitrary but practical purposes, AZA/6-MP and MTX are considered appropriate for:

- patients who have a severe relapse;
- those who require two or more corticosteroid courses within a calendar year;
- those whose disease relapses as the dose of steroid is reduced below 15 mg;
- relapse within 3 months of stopping steroids.

In CD, AZA/6-MP is usually used before MTX, because of longer clinical experience, more controlled data and safety during conception or pregnancy. Some patients who are intolerant of AZA may tolerate 6-MP. Some consider AZA/6-MP specifically appropriate for patients with perianal CD, but this may reflect the persistent activity of perianal disease. MTX is generally reserved for treatment of active or relapsing CD in those refractory to or intolerant of AZA or 6-MP.

Future potential use – critical areas

There are some critical areas where early and more diffuse use of conventional immunomodulators is advocated (Table 1). In particular, what is their role in preventing postsurgical recurrence? Can their early use modify the subsequent clinical course? Can we stratify the patients for risk factor of disabling clinical course? Moreover, since some data suggest a correlation between lack of mucosal healing and higher surgery rate, dysplasia and cancer risk, could these agents, if early used, alone or in combination with biologics, help us to accelerate the healing of mucosal lesions?

Preventing postsurgical recurrence in Crohn's disease

Up to 80% of patients with CD require intestinal resection during the course of their disease. Moreover, since operative resection of the

Table 1. Future potential use of immunomodulators – critical areas.

- Postsurgical recurrence in Crohn's disease
- Early therapeutic approach
- Definition of high risk patients
- Correlation between persistence of mucosal lesions and
  - High relapse rate
  - High hospitalization rate
  - High surgery rate
  - High dysplasia and colorectal cancer risk

diseased bowel is not curative, postoperative recurrence remains a problem in patients with CD.

A meta-analysis evaluating the efficacy and safety of AZA/6-MP in the prevention of postoperative recurrence in CD was performed [Peyrin-Biroulet *et al.* 2009]. Four controlled trials enrolled 433 patients and compared AZA ($n = 3$) or 6-MP ($n = 1$) with control arms (placebo with or without antibiotic induction therapy, or mesalamine) [D'Haens *et al.* 2008; Herfarth *et al.* 2006; Ardizzone *et al.* 2004; Hanauer *et al.* 2004]. In overall analysis, purine analogs were more effective than control arms to prevent clinical recurrence at 1 year (mean difference, CI 95%: 8%, 1–15%, $p = 0.021$, NNT = 13) and 2 years (mean difference, CI 95%: 13%, 2–24%, $p = 0.018$, NNT = 8). In sensitivity analyses, the efficacy of purine analogs was superior to placebo for prevention of clinical and endoscopic recurrence at 1 year (mean differences, CIs 95%: 13%, 1.8–25%, $p = 0.025$, NNT = 7, and 23%, 9–37%, $p = 0.0016$, NNT = 4, respectively). At 1 year, in overall analysis, purine analogs were more effective than control arms in preventing severe (i2–4 Rutgeerts score) endoscopic recurrence (mean difference, CI 95%: 15%, 1.8–29%, $p = 0.026$, NNT = 7), but were not effective for prevention of very severe (i3–4 Rutgeerts score) recurrence. The rate of adverse events leading to drug withdrawal was higher in thiopurine-treated patients than in control arms (17.2% *versus* 9.8%, respectively, $p = 0.021$). Thus, purine analogs are more effective than placebo in preventing both clinical and endoscopic postoperative recurrence in CD, but are associated with a higher rate of adverse events leading to drug withdrawal.

Healing of mucosal lesions

Mucosal healing (MH) is defined as a normal or mildly altered endoscopic appearance of the mucosa. The clinical relevance of MH has been recently underlined by different authors. A Norwegian population cohort prospectively analyzed 740 patients diagnosed with UC and CD and evaluated MH at 1 and 5 years [Froslie *et al.* 2007]. At 5 years UC patients with MH had significantly low risk of future colectomy ($p = 0.02$) and for patients with CD, MH was significantly associated with less inflammation ($p = 0.02$) and decreased future steroid treatment. Not all IBD therapies impact MH equally. Glucocorticosteroids are not very effective in achieving MH in CD patients and a poor correlation between clinical and endoscopical parameters has been described. Moreover, endoscopic remission in colonic CD is of 29% and in ileal disease almost null [Modigliani *et al.* 1990; Olaison *et al.* 1990]. In contrast to steroids, immunosuppressants and biological agents are associated with a high rate of MH. In a study by D'Haens *et al.* of 19 patients with recurrent Crohn's ileitis treated with AZA, 15 could be re-evaluated at 6 months, of them 6 patients had complete MH and 5 near complete healing [D'Haens *et al.* 1997]. Another study from the same group analyzed 20 patients with Crohn's colitis or ileocolitis who achieved symptoms relief with corticosteroids and in were clinical remission with at least 9 months of treatment with AZA [D'Haens *et al.* 1999]. The ileocolonoscopy at 24.4 months showed 70% with complete healing and 10% with near-complete healing. If we believe that MH is indeed a relevant clinical outcome, as a growing body of evidence seems to suggest, then we have a strong reason to recommend an earlier and wider use of both immunosuppressants and biological agents, which have clearly demonstrated their ability to induce MH. Although not formally proven yet, it seems very reasonable to admit that maintaining an endoscopically normal mucosa over time should result in higher proportions of patients maintaining disease remission and also in a lower risk of developing CD related complications, such as fistulas and strictures.

The case for early intervention

The most solid, evidence-based proof to recommend earlier use of immunosuppressants comes from a pediatric study by Markowitz and colleagues [Markowitz *et al.* 2000]. They performed a prospective, double-blind, placebo-controlled, 18 month clinical trial in 55 children with newly diagnosed CD, randomized to receive 6-MP 1.5 mg/kg body weight daily in the treatment group, or placebo. Both groups received corticosteroids to achieve the control of the first flare of their CD. In the 6-MP group, the duration of steroid use was shorter (observed-to-expected ratio of days with prednisone of 0.73 *versus* 1.34 in the control group, $p < 0.001$).

In another prospective, multicenter observational study [Punati *et al.* 2008], 199 children with moderate to severe CD were treated with immunomodulators within 1 year of diagnosis: 150 between 0–3 months (early), 49 between 3–12 months

(late). Both groups showed a decrease in corticosteroid use by 12 months, with early group patients receiving less corticosteroids than late group patients (22% *versus* 41%, $p = 0.03$). The number of hospitalizations per patient was also noted to be significantly lower in the early group over the 2-year follow-up ($p = 0.03$).

These results support the concept that early use of AZA/6-MP could significantly affect the clinical course of CD.

Patient stratification for risk factor of disabling clinical course

Table 2 shows the number of predictors of clinical course in IBD. Although there are no validated predictive factors of a complicated disease course, more and more clinicians have started applying a more aggressive therapeutic approach and will introduce immunomodulators earlier in particular patients according to particular risk factors. For example, in a French study by Beaugerie *et al.* [Beaugerie *et al.* 2006], CD patients diagnosed below 40 years of age, perianal disease, and initial requirement for steroids had a disabling clinical course in the subsequent 5-years follow-up. Therefore in this subset of patients an early intervention with immunomodulators, with or without biologics, could be useful. However, further research is clearly needed, aiming to establish the exact role of these predictor factors alone or in combination in stratifying patients and in defining the disease behavior.

Preventing dysplasia and colorectal cancer (CRC)

The risk of CRC is increased in patients with UC, with reported incidence ranging between 3 and 20 times that of the general population. Rutter *et al.* [Rutter *et al.* 2004] showed that in long-standing extensive UC, the severity of colonic inflammation (both endoscopic and especially histological) is an important determinant of the risk of CRC. Thus, controlling the inflammation could be useful to prevent CRC development. In this context, the possible chemopreventive effect of 5-ASA is supported by a recent meta-analysis [Velayos *et al.* 2005]. However, very recently, a large study from France reported a similar effect with thiopurines in patients suffering from long-standing and extensive UC [Beaugerie *et al.* 2009]. In particular, patients receiving thiopurines had a 3.5-fold decreased risk of CRC and advanced neoplasia. Therefore, more studies are needed to establish whether these are effective therapies due to their own chemopreventive properties or, on the contrary, if the general control of chronic inflammation is the real mechanism of the observed effect on the CRC risk.

Table 2. Possible predictors of poor outcome in Crohn's disease.

1. CLINICAL PREDICTORS
— *Disease course*
— *Smoking habits*
— *Need for steroids*
— *Onset in childhood?*
2. SEROLOGIC PREDICTORS
3. GENETIC PREDICTORS
— *Disease phenotype*
— *Disease aggressiveness*
— *Therapeutic responsiveness*

Conclusions

Although there are evidence-based data to support the use of conventional immunomodulators in the treatment of patients with IBD, there are many aspects of therapy with these agents for which data are lacking or inadequate. We can expect that further, well designed, studies will provide evidence on the efficacy and safety of wider use of immunosuppressors in many clinical areas of IBD treatment, such as prevention of postoperative relapse, chemoprophylaxis and early modulation of disease course. Additional prospective data are needed to resolve these areas of controversy.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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