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TOPIC HIGHLIGHT

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Are we giving azathioprine too late? The case for early immunomodulation in inflammatory bowel disease

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Abstract

Inflammatory bowel disease (IBD) includes two entities, Crohn's disease and ulcerative colitis. Both are chronic conditions with frequent complications and surgical procedures and a great impact on patient's quality of life. The thiopurine antimetabolites azathioprine and 6-mercaptopurine are widely used in IBD patients. Current indications include maintenance therapy, steroid-dependant disease, fistula closure, prevention of infliximab immunogenicity and prevention of Crohn's disease recurrence. Surprisingly, the wide use of immunosuppressants in the last decades has not decreased the need of surgery, probably because these treatments are introduced at too late stages in disease course. An earlier use of immunossupressants is now advocated by some authors. The rational includes: (1) failure to modify IBD natural history of present therapeutic approach, (2) demonstration that azathioprine can induce mucosal healing, a relevant prognostic factor for Crohn's disease and ulcerative colitis, and (3) demonstration that early immunossupression has a very positive impact on pediatric, recently diagnosed Crohn's disease patients. We are now awaiting the results of new studies, to clarify the contribution of azathioprine, as compared to infliximab (SONIC Study), and to demonstrate the usefulness of azathioprine in recently diagnosed adult Crohn's disease patients (AZTEC study).

Key words: Inflammatory bowel disease; Crohn's disease; Ulcerative colitis; Immunosuppressants; Azathioprine

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INTRODUCTION

IBD and azathioprine

Inflammatory bowel disease (IBD) includes two main entities, ulcerative colitis (UC) and Crohn's disease (CD). Both are chronic, inflammatory disorders of the gastrointestinal tract, with an increasing prevalence in developed countries. IBD affects patients early in life, resulting in an enormous personal, social and economic burden. Although the etiology of IBD remains unknown, major progress has been done in our understanding of IBD pathophysiology in recent years. We now believe that IBD develops in genetically predisposed individuals, due to an abnormal recognition of microbiota antigens by certain elements and cells of the innate immunity, leading to a deregulated immune reaction and, ultimately, resulting in bowel inflammation and injury [1].

Treatment of IBD has greatly evolved in the last two decades. A better understanding of IBD pathophysiology has progressively resulted in a more frequent use of inmunossupressants, such as azathioprine (AZA), mercaptopurine and methotrexate and the arrival of the so called "biological therapy", represented by the anti-TNF-α antibodies. Whether this "more aggressive" approach has really had any impact on IBD patient's outcome is still a matter of controversy. As an example, an interesting work by Cosnes and colleagues revealed that, in spite of the striking increase in the azathioprine use in CD patients, the natural history of CD, as judged by the percentage of CD patients requiring surgical resection, had remain unchanged over the last 40 years

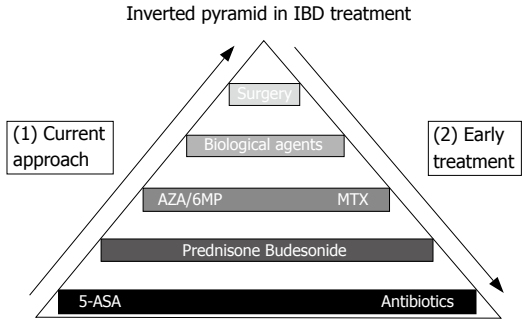

Figure 1 Inverted pyramid. Represents two different treatments approaches in IBD: (1) Current practice: Initially treatment with 5-ASA and antibiotics and then depends on the responsiveness scale to steroids, immunomodulators and biological agents. (2) Top-Down strategy: New tendencies. Initially aggressive treatment with early immunosuppresion and biological therapy.

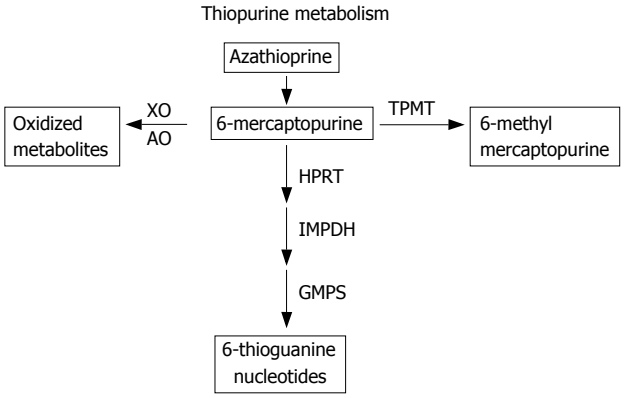

Figure 2 Metabolism of azathioprine (AZA): AZA is converted to 6-mercaptopurine (6-MP). 6-MP by thiopurine methyltransferase (TPMT) and xantino oxidase (XO) in inactive metabolites, but phosphoriboxyltransferase (HPRT), inosine monophosphate dehydrogenase (IMPDH) and guanosine monophosphate synthetase (GMPS) catalize the synthesis of active 6-thioguanine nucleotides (6-TGNs).

and until our days[2]. Although the results of this study might indicate indeed that azathioprine is unable to modify CD natural history, a closer view of this study reveals that in most CD patients azathioprine had been introduced really late in the patient's course, often after the development of a penetrating phenotype or following a surgical procedure. This fact sets the notion that an early use of immunosuppressants might result in a significant impact on IBD patient's natural course.

The aim of this article is to make a critical analysis of the current use of thiopurines, but also attempts to analyze the new tendencies in terms of optimal time to initiate immunosuppression with antimetabolites in IBD (Figure 1).

Pharmacology of azathioprine

6-Mercaptopurine (6-MP) and its prodrug azathioprine are thiopurine analogues and are immuno-modulatory agents. Of the AZA compound, 88% is converted *via* nonenzymatic process to 6-MP. Then 6-MP undergoes several enzymatic pathways and is transformed to active and inactive metabolites (Figure 2). The first step in the 6-MP metabolism is a catabolic process by xanthine-oxidase, which is present in the intestinal mucosa and liver, resulting in inactive oxidized metabolites, such as 6-thiouric acid. 6-MP also serves as a substrate for the thiopurine methyltransferase (TPMT) which, by methylation, converts 6-MP into inactive metabolites, such as 6-methyl mercaptopurine. Anabolic processes led to the synthesis of active metabolites. First hypoxanthine phosphoribosyltransferase initiates the transformation of 6-MP into active metabolites, or 6-thioguanine nucleotide[3-4]. These nucleotides act as purine antagonists interfering DNA and RNA synthesis which has been demonstrated to result in a significant inhibition of lymphocyte proliferation and a decreased immunity response.

Not all individuals methylate thiopurines equally, a series of processes that depend on the genetic variability in the TPMT activity. The TPMT gene is inherited as an autosomal co-dominant trait. Most of the Caucasian population (about 89%), have normal to high enzyme activity (known as homozygous wild-type TPMT), 11% have intermediate enzyme activity (heterozygous TPMT) and 0.3% have low or absent enzyme activity (homozygous mutated TPMT). The two last groups are associated with major elevations of 6-TGN levels and an increased risk of adverse effects[3,5]. This genetic variation can be studied at different levels. First, the genetic study will ascertain the patient's genotype. Second, it is also possible to measure the enzyme activity in a blood sample. Third, also the blood levels of active and inactive, methylated metabolites can be quantified. A widely accepted consensus on the best way to address this issue has not been achieved to date.

Safety of azathioprine

There is little doubt that patients treated with azathioprine have a higher rate of adverse events than placebo treated patients. A Cochrane meta-analysis, by Sandborn and colleagues, analyzed the usefulness and safety of AZA and 6-MP when used to induce remission in CD patients[6]. 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 also addressed the issue of azathioprine safety in another Cochrane meta-analysis, but specifically devoted to patients receiving this drug as maintenance therapy for CD. Drug withdrawal due to adverse effects were found 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[7].

Classically, AZA-related adverse events have been categorized in two types: allergic, idiosyncratic or none dose dependent, and dose-dependent. Allergic reactions include, among others, malaise, rush, fever, pancreatitis and hepatitis. All of them are infrequent, occurring in a 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 dependant adverse effects are much more frequent than the previous.

Table 1 Vienna classification of Crohn's disease[12]

Parameter	
Age at diagnosis	A1 < 40 yr A2 ⩾ 40 yr
Maximal location of disease prior to first surgery	L1 Terminal ileal L2 Colonic L3 Ileocolonic L4 Any upper GI, regardless of disease elsewhere in bowel
Disease behavior	B1 Nonstricturing, nonpenetrating (inflammatory) B2 Stricturing B3 Penetrating disease Behavior could be defined at any time after diagnosis

Table 2 Montreal classification of Crohn's disease[13]

Parameter	
Age at diagnosis	A1 ⩽ 16 yr A2 17-40 yr A3 ⩾ 40 yr
Maximal location of disease prior to first surgery	L1 Terminal ileal L2 Colonic L3 Ileocolonic L4 Upper GI only +L4 Additional designation to be added if patient has upper GI and distal disease
Disease behavior	B1 Nonstricturing, nonpenetrating (inflammatory) B2 Stricturing B3 Penetrating disease *P* = Perianal penetrating disease Recommended behavior assessed > 5 yr after diagnosis

Bone marrow suppression is the most common dose-dependent adverse effect. Leukopenia appears in 2% to 15% of AZA-treated patients, depending on the cut-off used for its definition, is influenced by the degree of TPMT activity and can 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 steam 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%[8]. The most common are viral infections, such as cytomegalovirus, Epstein-Barr virus, varicella zoster virus and herpes simplex virus. Noteworthy, infections can occur in the absence of leukopenia. Thiopurine-induced liver toxicity is also a relevant issue. It's 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)[9]. The majority of these syndromes respond to drug withdrawal.

Finally the relationship between thiopurines and development of cancer, and specially hematologic malignancies such as lymphomas, remains a controversial topic. A meta-analysis of risk of malignancy associated to the use of immunosuppressive drugs in inflammatory bowel disease identified 9 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}/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[10]. The issue of relationship between lymphoma and IBD is complex, because the effect caused by the disease "*per se*", by disease activity, and by different IBD therapies clearly overlap. In a Meta-analysis of Kandiel and colleagues[11] they identify 6 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. 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's outcome would clearly overweight the risk caused by the drug itself.

PRESENT USE OF AZATHIOPRINE IN IBD

Use in Crohn's disease

Crohn's disease is a heterogeneous entity that requires an individual approach. Several attempts have been done to homogenize CD evaluation. The classification obtained as result of the consensus effort held in Vienna, in 1998[12], categorize CD in subgroups according age at diagnosis, disease location and disease behavior (inflammatory, fistulating or stenosing) (Table 1).

In spite of its initial usefulness, significant advances have been made in recent years. It has become clear that children have different presentation, disease location can be simultaneous in different segments of the bowel and disease behavior is dynamic. Because of these in 2005 the Montreal classification[13] added a separate category for children with onset at ⩽ 16 years, acknowledged the coexistence of CD in the upper GI tract with distal disease and differentiated between internal and perianal penetrating disease (Table 2).

AZA to induce CD remission

Because of the delayed onset of action of thiopurines analogues, even with intravenous administration[14], this drugs have been most frequently used, with concomitant use of steroids or more recently with infliximab[15], in patients with active disease in the context of corticosteroid-dependent CD. A Cochrane database meta-analysis[6] found eight randomized,

placebo-controlled trials in adults that evaluated the use of azathioprine or 6-mercaptopurine in active Crohn's disease. The outcome measure was the proportion of patients with clinical improvement or remission (as defined by the CDAI score, the Harvey-Bradshaw Index, subjective evaluation or steroid sparing effect). The pooled response rate was 54% for the group with thiopurine analogues *versus* 34% for the placebo treated patients, with a peak response odds ratio reached at 17 wk of therapy. The number needed to treat is 5 in order to benefit 1 patient.

In clinical practice the use of azathioprine as monotherapy to induce remission in active CD is very rarely indicated, due to its delayed action. In mild-to-moderate, chronically active CD, AZA can be an option in selected patients.

AZA to obtain a steroid–sparing effect in CD

The efficacy of AZA and 6-MP, as compared with placebo, in the subgroup of corticosteroid-dependent CD is well established. This effect is observed in patients with active CD and in patients with quiescent but corticosteroid-dependent disease. Both scenarios were analyzed in two Cochrane Database Meta-analyses.

In active disease, five studies showed that the use of antimetabolites results in a pooled reduction from 65% to 36% in the percentage of patients receiving steroids, as compared to the placebo group. In this case, the number needed to treat to obtain a steroid-sparing effect was 3 patients[6].

In patients with clinical remission but corticosteroid-dependent behavior, only two small studies (overall 30 patients) were randomized, double-blind, placebo-controlled. The global effect in reduce steroid consumption was 87% (13/15) for the AZA group *versus* 53% (8/15) for the placebo group with a number needed to treat for one reduction in steroid consumption of 3[7].

AZA to maintain remission in CD

Once CD is quiescent, the thiopurine analogues are a very effective therapeutic option to maintain disease remission. This situation was analyzed by Pearson and colleagues in a Cochrane Meta-analysis. They found five trials that satisfied the inclusion criteria as randomized, double-blind, and placebo-controlled. In spite the variability in terms of doses and duration of therapy, the overall remission maintenance was 67% with AZA compared with 52% of the placebo group. It's worth to mention that the effect is dose-dependent with optimal benefit at dose of 2.5 mg/kg per day[7]. All these data support the use of antimetabolites as maintenance therapy.

In the pediatric study by Markowitz and colleagues[16], only 4% of patients (1 children) of the 6-MP group required another course of steroids within 540 d, after being weaned off of prednisone, clearly in contrast to the 57% of pediatric CD patients receiving placebo which need to restart prednisone within 360 d ($P < 0.0001$).

AZA to prevent disease recurrence after surgery in CD

The incidence of surgery in the course of CD is very high, reaching a cumulative risk of 78%-91% in some classic studies[17-18]. Postoperative recurrence approaches the 100% of patients, at 3 years, when assessed endoscopically[19]. Fortunately, clinical recurrence and the need for repeated surgery are lower (15%-45% after 3 years). AZA and 6-MP are effective as a therapy to prevent disease recurrence. AZA or 6-MP are probably more efficacious than 5-ASA compounds, but the design of the studies aimed at clarifying this issue does not allow a strong statement in that respect[20-21].

AZA to induce remission in fistulizing CD

The risk of developing internal or perianal fistulas is really high in CD patients and close to 50% of them will develop any form of penetrating behavior in a lifetime. The rate of complete healing with the available medical treatments is 50% and multiple relapses are frequents. In the Cochrane Database Meta-analyses perfomed by Sanborn and colleagues, 55% of the patients with AZA compared with 29% of the placebo treated patients achieved a response. The number needed to treat to observe one patient with fistula healing was 4, which confirms that AZA is a potent therapeutic strategy for this type of CD-related complications[6].

Use in ulcerative colitis

There are less robust data of the use of thipurine analogues in UC compared to CD. In active disease most of the studies evaluated the remission of the disease in the context of corticosteroid-dependant or resistant disease with co-medication with aminosalicylates, steroids or biological agents, not as monotherapy treatment. In a prospective trial of Ardizzone *et al*[22], 72 patients with steroid dependant UC were randomized to receive azathioprine 2 mg/kg per day or oral 5-aminosalicylic acid (5-ASA) 3.2 g/day for a 6 months follow up. The AZA group achieved a clinical and endoscopic remission of 53% compared with 19% of the 5-ASA group ($P = 0.006$). There is no doubt of the efficacy of AZA and 6-MP as steroid-sparing agents in subjects with corticoid- dependence and for maintenance in patients with remission induced by cyclosporine or in whom have failed or cannot tolerate standard maintenance therapy with aminosalicylates. A recent Cochrane Database Meta-analyses by Timmer *et al*[23], found 6 studies which examined the efficacy of purine antimetabolites compared to placebo or standard maintenance therapy in ulcerative colitis. In the pooled analysis, azathioprine was superior to placebo for maintenance of remission. 56% of patients treated with AZA were on disease free after one year of treatment compared to 35% of patients who received placebo. The number needed to treat is 5 in order to benefit 1 patient. In summary, azathioprine is effective in maintenance therapy for patients who have failed or cannot tolerate aminosalicylates and patients who require repeated courses of steroids.

Length of AZA treatment

The question how long thiopurines should be continued and until how long there is a really benefit of this therapy in patients that achieved remission is not

complete resolved. The study's results are contradictory. The first who evaluated this issue was O'Donoghue in 1978 in 51 CD patients who were receiving AZA for at least 6 mo. The cumulative probability of relapse at 1 year was 5% for the AZA treated group *versus* 41% in the placebo group ($P < 0.01$)[24]. After this first report, several studies tried to further clarify this issue. A multicenter, randomized, double-blind, noninferiority withdrawal trial in CD patients who were in remission on AZA treatment for $\geqslant$ 3.5 years showed that the mean relapse rate at 18 mo in patients who stopped the drug was nearly 3 times that observed in those who were maintained on treatment (21.3% *vs* 7.9%). Therefore the authors recommended continuing with AZA maintenance therapy beyond 3.5 years[25]. Another retrospectively study in 1176 patients with IBD (CD and UC) from 16 European centers showed that within the first 4 years of treatment, AZA diminished the incidence of flares and steroid consumption in both diseases and continuation beyond 4 years improved clinical activity and steroid requirements[26]. Conversely to the mentioned study, Bouhnik Y and colleagues found that in CD patients who were in clinical remission taking AZA or 6-MP after 4 years of remission on these drugs, the risk of relapse is similar whether the therapy was maintained or stopped[27]. Recently, Mantzaris *et al* published a prospective, investigator-blind study in patients with steroid-dependant Crohn's disease in remission on AZA. They stratified patients in two groups: Group A, consisted of patients receiving continuously azathioprine for between 2 and 4 years and Group B; which consisted of patients receiving azathioprine for between 4 and 8 years. The annual relapse rate in Group A was 19.6% *versus* 11.9% in the Group B without significant difference ($P = 0.67$)[28]. For the clinician's point of view, and taking into account the published evidences, an individual decision is often required.

THE FUTURE: TOWARDS AN EARLIER USE OF AZATHIOPRINE IN IBD

Why early azathioprine? Natural history of CD

CD is a progressive condition, characterized by a frequent development of CD-related complications, such as internal fistulas and abscesses, perianal fistulas and bowel strictures. This results is a high surgical requirement, with a significant proportion of CD patients receiving bowel resection at some point. One of the key factors determining the natural history of CD is the disease duration, since an increasing number of complications have been described over time. Louis *et al* assessed retrospectively the evolution of the disease after 1 to 25 years since diagnosis. At diagnosis, 73.7% of patients had an inflammatory phenotype while at 20 years only 12% had this phenotype and 32% and 48.8% had structuring and penetrating behavior respectively. The proportion of patients who had surgery over a 10 year period was 30.4% being higher in the subgroups B2 and B3[29].

In the study of Cosnes *et al*, they evaluated retrospectively 2002 patients with CD. The rate of complication was 80% at 20 years. At 5 and 20 years after diagnosis, the actuarial risks for stricturing disease alone were 12% and 18% respectively, whereas they were 40% and 70% respectively for penetrating disease[30].

Two main conclusions can be obtained from these results, both supporting an early use of AZA/Immunossupressants in CD. First, overall, CD patients have a poor outcome, regardless of the present medical therapy offered to them, and development of complications occur in three out of four patients in their lifetime. Second, CD offers a great opportunity for aggressive, earlier treatment, because almost all patients are complication-free at diagnosis. The mentioned penetrating and stenosing complications will slowly develop in the years following diagnosis which offers physicians a wide timeframe to introduce more efficacious drugs, early in CD course.

Mucosal healing

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. In a Norweigan population cohort they prospective analyzed 740 incident patients diagnosed with UC and CD and evaluated MH at 1 and 5 years. At 5 years UC patients with MH had significant 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[31].

Not all IBD therapies impact equally MH. 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[32-33]. Conversely to steroids, immunosuppressants and biological agents are associated with a high rate of MH. In a study of D'Haens *et al* of 19 patients with recurrent Crohn's ileitis treated with azathioprine, 15 could be re-evaluated at 6 mo, of them 6 patients had complete MH and 5 near complete healing[34]. Another study from the same group analyzed 20 patients with Crhon's colitis or ileocolitis who achieved symptoms relief with corticosteroids and in clinical remission with at least 9 mo of treatment with AZA. The ileocolonoscopy at 24.4 mo show 70% of complete healing and 10% of near-complete healing[35]. In respect to infliximab therapy, several studies have demonstrated efficacy for these drug in MH[36-38]. Two other studies demonstrated recently that combined immunosuppression with azathioprine and infliximab are more effective in terms of bowel MH respect to each one separately[15,39], but both were done at relative short term (1 and 2 years respectively).

If we believe that MH is indeed a relevant clinical outcome, as a growing body of evidence seem 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 a higher proportion of patients maintaining disease remission and also in a lower risk of developing CD-related complications, such as fistulas and strictures.

First results as proof of concept

The most solid, evidence-based prove to recommend an earlier use of immunosuppressants come from the pediatric study by Markowitz and colleagues[16]. They conducted a prospective, double-blind, placebo-controlled, 18 mo clinical trial in children newly diagnosed of CD. 55 subjects were included and were randomized to receive 6-mercaptopurine 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, $P < 0.001$). This results supports the use of 6-MP as induction therapy in combination with corticosteroids in active Crohn's disease.

The "step-up *vs* top-down" study, by D'Haens and colleagues[39] is also very relevant to support the notion that introducing the most efficacious IBD drugs early in disease course has a significant impact on CD patients outcome. This randomized study compared the conventional therapeutic approach ("step-up") with a newer, more aggressive strategy ("top-down"). In the "step-up group" patients were treated first with steroids and, in case of steroid dependency or resistance, immunosuppressants and infliximab were used. In the "top-down group" patients received upfront a combined treatment of immunossupressants and infliximab. This study clearly demonstrate the superiority of the "top-down" over the "step-up" approach, as demonstrated by a significantly higher proportion of patients in remission and showing MH in the "top-down", as compared to the "step-up" group. Interestingly, this higher efficacy did not carry a higher proportion of side effects in the "more aggressively", "top-down" treated patients. One of the drawbacks of this study is the lack of long-term follow up, especially in respect to the potential impact of prolonged, intense immune suppression on the risk of developing severe infections or cancer.

Several studies, ongoing at present, will help to clarify this issue and, maybe, will provide further evidence to support an early use of azatioprine in IBD. One is the SONIC study, aimed at comparing the use of AZA alone *versus* infliximab alone *versus* combined therapy. The other, the AZTEC study, a Spanish multicenter randomized study aimed at reproducing the efficacy of AZA in recently diagnosed CD, but in adults.

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