

## Mucosal healing in inflammatory bowel disease: Maintain or de-escalate therapy

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### Abstract

In the past decade, thanks to the introduction of biologic therapies, a new therapeutic goal, mucosal healing (MH), has been introduced. MH is the expression of an arrest of disease progression, resulting in minor hospitalizations, surgeries, and prolonged clinical remission. MH may be achieved with several therapeutic strategies reaching success rates up to 80% for both, ulcerative colitis (UC) and Crohn's disease (CD). Various scoring systems for UC and for the transmural CD, have been proposed to standardize the definition of MH. Several attempts have been undertaken to de-escalate therapy once MH is achieved, thus, reducing the risk of adverse events. In this review, we analysed the available studies regarding the achievement of MH and the subsequent treatment de-escalation according to disease type and administered therapy, together with non-invasive markers proposed as predictors for relapse. The available data are not encouraging since de-escalation after the achievement of MH is followed by a high number of clinical relapses reaching up to 50% within one year. Unclear is also another question, in case of combination therapies, which drug is more appropriate to stop, in order to guarantee a durable remission. Predictors of unfavourable outcome such as disease extension, perianal disease, or early onset disease appear to be inadequate to foresee behaviour of disease. Further studies are warranted to investigate the role of histologic healing for the further course of disease.

**Key words:** De-escalation; Mucosal healing; Biological therapy; Deep remission; Discontinuation; Ulcerative colitis; Crohn's disease; Immunosuppressors

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**Core tip:** Mucosal healing is achieved in a discrete number of patients with immunomodulators, biologics

or combined therapies. Attempts to de-escalate therapy, thus permitting a drug holiday, are disappointing. Clinical predictors to identify patients at risk for early relapse after drug withdrawal are still insufficient. Further investigations are needed to prospectively evaluate the validity of histologic healing and to validate an appropriate scoring system for histology in ulcerative colitis and in Crohn's disease.

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## INTRODUCTION

Inflammatory bowel diseases (IBD) are a group of diseases of growing importance in the Western world, due to the steady increase in terms of incidence and prevalence<sup>[1]</sup>. IBD are characterized by gut mucosal inflammation and a chronic relapsing behaviour<sup>[2]</sup>, therefore, it is necessary to ensure a long-term therapeutic strategy for patients, avoiding surgery, and achieving a good level of quality of life<sup>[3]</sup>.

In the last few years, the goals of therapy have changed: Thanks to the introduction of anti-TNF $\alpha$  drugs, in monotherapy or in combination with immunomodulators, there are higher rates of response, also in more complicated cases of both ulcerative colitis (UC) and Crohn's disease (CD). Thus, the target of therapy has become not only clinical remission but also mucosal healing (MH), *i.e.*, "deep remission". According to available evidence, deep remission is associated with less flares, lower surgery rates and less hospitalizations<sup>[4]</sup>.

Although the role of these drugs in achieving clinical remission and MH has been recognized, their prolonged use, above all when in combination with immunomodulators, exposes the patient to a higher risk of infection and adverse events<sup>[5]</sup> especially with increasing patient's age or in the presence of comorbidities<sup>[6]</sup>. Since IBD are lifelong diseases, it becomes important to spare years of immunosuppressive therapy for patients, whenever possible, without the risk of undertreatment, thus minimizing the risk of infection or malignancies<sup>[7]</sup>. While on the one hand, the importance of reaching endoscopic remission is now generally accepted, on the other hand, there are no clear indications in current guidelines regarding how long to continue immunosuppressive therapies after reaching MH and, in the case of therapy reduction, which drugs to use as maintenance therapy<sup>[8,9]</sup>.

## ENDOSCOPIC SCORES AND DEFINITION OF MH

Several endoscopic scores are available to assess disease

activity in UC and CD. For CD, the first endoscopic score was CD Endoscopic Index of Severity (CDEIS), a score based on the evaluation of: (1) Presence and absence of ulcers (superficial or deep); (2) presence or absence of stenosis (ulcerated or non ulcerated); and (3) measurement of the surface extension of disease activity, evaluating five intestinal segments (terminal ileum, right, transverse, and left colon and rectum) with a final numerical rating between 0 and 44<sup>[10]</sup>. The newer Simple Endoscopic Score-CD (SES-CD) was created subsequently by Daperno *et al.*<sup>[11]</sup>; this score is obtained by evaluating: (1) The surface affected by ulcers; (2) the surface affected by other lesions; (3) the presence of ulcers; and (4) the presence of narrowing in five gut segments (terminal ileum, right colon, transverse, left colon and rectum). Each variable can be quantified with a score from 0 to 3, reaching a final score between 0 and 60. Finally, for the assessment of recurrence of disease after resective surgery, the Rutgeerts score is used; this score is based on a rating between 0 and 4; i0: No recurrence, i1: < 5 aphtous lesions, i2: > 5 severe aphtous lesions, i3: Diffuse inflammation with diffuse ulcers, i4: Nodules and/or narrowing<sup>[12]</sup>.

In UC, several scores have been proposed; the Truelove and Witts score evaluated just hyperemia and granularity<sup>[13]</sup>. Subsequently, the Baron score, based on bleeding and friability, with a range from 0 to 4, was developed<sup>[14]</sup>. The Sutherland score and the Powell-Tuck score are both sigmoidoscopic scores and consider only bleeding features<sup>[15,16]</sup>. The first score to assess not only bleeding and hyperaemia but also ulcers, granularity and erosions was the Rachmilewitz Endoscopic score, based on the evaluation of bleeding (by contact or spontaneous), mucosal disease (ulcers, erosions and presence of mucus), granularity and vascular pattern<sup>[17]</sup>. Severity is assessed with a range from 0 to 12.

The Mayo score is currently the most used score to evaluate clinical activity in UC, and consists of four subscores: (1) Stool frequency; (2) rectal bleeding; (3) endoscopic findings; and (4) physician's global assessment. Each one of these subscores ranges from 0 to 3, arriving at a final score between 0 and 12 ( $\leq$  2 remission, 3-5 mild disease, 6-10 moderate disease, 11-12 severe disease)<sup>[18]</sup>. The endoscopic subscore divides the endoscopic findings into four degrees of severity: 0 remission; 1 mild disease with erythema and mild friability; 2 moderate disease with presence of marked erythema, friability, erosions and absence of vascular pattern; 3 severe disease with spontaneous bleeding and diffuse ulcerations. A recent endoscopic score, is the UC Endoscopic Index of Severity (UCEIS); this score evaluates three variables: Vascular pattern, ranged with a score between 0 and 3 points, while bleeding and presence of erosions/ulcers (divided into superficial and deep) are evaluated in a range between 0 and 4 points. Compared with the Mayo score, this score better evaluates the depth of the ulcers, but it is not yet widely used<sup>[19]</sup>.

In 2013, a new score, the UC Colonoscopy Index of

Severity was validated; it is calculated on four variables: Vascular pattern, granularity, ulceration, bleeding/friability and severity of damage in each colon segment. The evaluation of damage is based on a four-points scale and on a 10 cm-visual scale<sup>[20]</sup>.

The major drawback of all UC scores is that they do not consider the extension of disease since they are all based on the worst appearing segment explored by endoscopy and only the most recent modified Mayo endoscopic score seems to overcome this issue<sup>[21]</sup>. In CD, endoscopic scores are limited to the appearance of gut mucosa in a transmural disease.

## DEFINITION OF MH

MH is now defined, in most of the more recent UC and CD trials, as the complete absence of ulcers and inflammatory lesions (Mayo score 0, SES-CD 0, CDEIS 0). Nevertheless, in many UC trials, the definition of MH includes the presence of friability and hyperaemia at endoscopic examination, without ulcers and erosions (Mayo score 1).

The most important controversies about MH regard the weight of mucosal remission assessed by endoscopic examination in CD; many authors consider this an inadequate parameter to evaluate a progressive, full thickness disease of the bowel wall, characterized during its natural history by the presence of fistulas, strictures, abscesses and surgical resections. These features are well evaluated by the Lémann score, recently created to combine the characteristics already considered by previous endoscopic scores, with the new concept of "cumulative bowel damage"<sup>[22]</sup>. The Lémann score combines upper endoscopy and ileo-colonoscopy findings with the radiological findings obtained by computed tomography enterography and magnetic resonance enterography (MRE). This score, for each gastrointestinal segment (divided into upper digestive tract, small bowel, colon or rectum and anal or perianal), ranges between 0 and 3 according to severity of the disease<sup>[23]</sup>. The overall score is obtained by adding the above subscores up to 10 points. The Lémann score, however, is still rarely used, for its complexity and poor practicality.

MRE today represents the gold standard technique to study the small bowel; it assesses wall thickness, presence of edema, deep ulcers and/or strictures, together with the evaluation of surrounding tissues, with high accuracy. In 2011, the Magnetic Resonance Index of Activity (MaRia) score was proposed; this score measures all the above parameters and is calculated according to the formula  $\text{MaRia} = [1.5 \times \text{wall thickness (mm)}] + (0.02 \times \text{relative contrast enhancement}) + (5 \times \text{edema}) + (10 \times \text{ulcer})$ . In a prospective, multicentre study, Ordás *et al.*<sup>[24]</sup> demonstrated that the MaRia score well correlates with CDEIS and with endoscopic findings. MRE is a useful tool to assess disease activity in CD and may be a good alternative to endoscopy in clinical practice and trials.

## NON-INVASIVE BIOMARKERS OF INFLAMMATION

Several biomarkers have been studied in the last few years, to find an inexpensive and non-invasive way to assess the presence or absence of gut mucosal inflammation and, thus for the follow-up in IBD patients. A Norwegian group recently reported a significantly higher mucosal gene expression of TNF, IL17A and FOXP3 in CD patients who relapsed within six months after anti-TNF withdrawal<sup>[25]</sup>. The dimeric isoform of M2-pyruvate kinase (M2-PK) was elevated in IBD patients, both in active and in inactive disease<sup>[26]</sup>. This latter marker was even higher in faeces of pediatric IBD patients with a good response to corticosteroids<sup>[27]</sup>, and elevated serum and mucosal levels of the long pentraxin (PTX3) were found in patients with active UC<sup>[28]</sup>. A complete revision of every marker investigated at this moment is however beyond the scope of this editorial (for review see<sup>[29,30]</sup>). In the present review we focus on two well-known and largely used biomarkers, C-reactive protein (CRP) and fecal calprotectin (FC), and on the neutrophil gelatinase-associated lipocalin (NGAL) and matrix metalloproteinase 9 (NGAL-MMP-9) complex, a novel marker of mucosal inflammation, recently investigated in CD and UC.

### CRP

CRP is an acute-phase protein with a circular, pentameric conformation synthesized by the liver; its serum levels increase in response to inflammation and in particular to IL-6 secretion; its physiological role is to bind lysophosphatidylcholine present on the surface of dying cells or bacteria, to activate the complement system<sup>[31]</sup>. Blood CRP levels rise in several cases like infections, sepsis, inflammation, neoplastic processes, cardiovascular diseases and infarction.

The role of CRP in the diagnosis and follow-up of IBD is well known. Determination is non-invasive and cheap, yet few studies have confirmed its reliability in the assessment of mucosal inflammation, mainly because of its poor specificity and the fact that a percentage of around 25% of patients with CD, and up to 80% with distal UC, do not have a CRP-positive inflammatory response<sup>[32,33]</sup>. CRP seems to be less reliable in reflecting endoscopic inflammation, compared to stool markers, like calprotectin or lactoferrin, while the combination of stool markers, CRP and the clinical scores, can improve the diagnostic accuracy, especially in UC<sup>[34,35]</sup>.

### FC

FC is a heterodimer composed of two subunits, S100A8 and S100A9, representing almost 60% of neutrophilic cytosolic soluble proteins; it can bind calcium and *in vitro* it showed mild antifungal and bacteriostatic activity. It is released by neutrophils during their activation or death and, being highly represented in the luminal side of the enterocytes, it is easily measurable in faeces. Measurement correlates with gut inflammatory activity

with good accuracy, and several studies have shown a significantly higher level of FC in subjects with IBD compared to normal controls<sup>[36]</sup>.

To date, FC is considered a useful tool in the IBD diagnostic work-up, with a sensitivity of 95%-100% and a specificity of 35%-50%, according to different studies<sup>[35,37]</sup>. However, considering adjusted cut-offs, FC specificity increased, especially compared to other non-invasive markers, like polymorphonuclear-elastase or lactoferrin, though the latter has been proven to have slightly higher sensibility in UC<sup>[35]</sup>. In clinical practice, FC is increasingly used also in the follow-up of IBDs, to guide clinical and therapeutic choices, such as optimization or discontinuation of treatment<sup>[37]</sup>.

In former studies, FC has proven to have a good correlation with endoscopic findings and scores, both in UC<sup>[35]</sup> and CD<sup>[38]</sup>, and in a very recent paper, a cut-off level of 192 mg/kg of FC identified patients with MH assessed by the Mayo endoscopic subscore and UCEIS with negative predictive values of 0.90 and 0.93, respectively. Moreover, a cut-off level of 171 mg/kg identified patients with histological healing<sup>[39]</sup>.

### NGAL-MMP-9 complex

MMP-9 is a zinc-dependent peptidase, belonging to the bigger family of MMPs, involved in the degradation of extracellular matrix, in angiogenesis, in remodelling of tissues, and wound healing. MMP activity is regulated by tissue inhibitors of metalloproteinases that bind MMPs in order to balance the process of matrix degradation and synthesis. Another protein involved in this process is NGAL, mostly contained in secondary granules of neutrophils. This marker, measured in the urine, has been shown to promptly respond to Infliximab (IFX) infusion<sup>[40]</sup>. MMP-9 and NGAL blood levels are both increased in active IBDs. Recent studies have assessed that NGAL binds MMP-9 to avoid degradation of the latter. A dosage of NGAL-MMP-9 complex has been reported to be a sensitive marker of MH. In a recent study, serum NGAL-MMP-9 complex was measured in UC patients before and after treatment with IFX; at the endoscopic check, MH was defined as Mayo 1 or Mayo 0 endoscopic subscore. The serum NGAL-MMP-9 complex was higher in UC patients in comparison to healthy controls; a cut-off level of 97.7 ng/mL identified patients with MH at endoscopy<sup>[41]</sup>. Similar findings have now been reported also in CD<sup>[42]</sup>.

## HOW TO ACHIEVE MH

Almost every kind of therapy has been described to achieve MH and the choice of treatment depends on the severity of the disease. In the classical step-up model of therapy, the first choice is mesalazine (limited to UC) followed by low bioavailability steroids, systemic steroids, immunomodulators and, finally, biologics. We hereafter briefly review the available data on treatment success in terms of MH with the different therapies in

UC and in CD.

## UC

### Salicylates

Although most studies concerning mesalamine (5-aminosalicylic acid, 5-ASA) had been carried out before the introduction of the new paradigm of MH, there are several studies that evaluated efficacy of 5-ASA or newer formulations to induce MH. Vecchi *et al.*<sup>[43]</sup>, comparing oral 5-ASA 4 g daily vs oral 5-ASA 2 g + 2 g daily + enema in UC patients, demonstrated the achievement of MH, respectively in 58% and 71% of patients at week 6, assessed by the Rachmilewitz score (Table 1). Mansfield *et al.*<sup>[44]</sup> compared Balsalazide 6.75 g/d vs Sulfasalazine 3 g/d; at week 8, MH rate was similar in both groups of UC patients, 27% and 25%.

In 2003, Kruis *et al.*<sup>[45]</sup> compared the efficacy in UC of three different doses of oral 5-ASA: 0.5 g t.i.d., 1 g t.i.d. and 1.5 g t.i.d.; MH was achieved respectively in 53%, 84% and 70% of patients, assessed at week 8 by the Rachmilewitz score and considering as MH an improvement of the Histological Activity Index (HAI; a score that assesses the degree of mucosal inflammation, ranged between 0 and 3) of at least one point. In 2009, the same author investigated the use of fractionated doses of oral 5-ASA (1 g t.i.d.), with the administration of a single dose (3 g once/day), finding no difference in terms of MH between the two groups of patients (respectively 71% vs 70%)<sup>[46]</sup>. In the ASCEND I study, Hanauer *et al.*<sup>[47]</sup> evaluated two doses of oral delayed-release 5-ASA in mild to moderate UC: 4.8 g/d vs 2.4 g/d. Efficacy was assessed by Inflammatory Bowel Disease Questionnaire and by patient's global assessment (PGA) a four-point score, based on stool frequency, rectal bleeding, endoscopic findings, patient's functional assessment and the investigator's clinical assessment. At sigmoidoscopy performed at week 3 and 6, no differences were found between the two groups in terms of MH. Nevertheless, considering only the subgroup of patients with moderate disease, PGA and sigmoidoscopy scores improved significantly in the group on 4.8 g/d compared with 2.4 g/d (84% vs 67%). In another trial with 5-ASA multi matrix system (MMX), Kamm *et al.*<sup>[48]</sup> compared 5-ASA MMX 4.8 g/d, 2.4 g/d and placebo; an endoscopic follow-up, scheduled at week 8, showed the achievement of MH, defined by a modified Sutherland score < 1, in 77%, 69% and 46% of the patients, respectively.

### Steroids

Most trials using corticosteroids have clinical outcomes; this is due to the fact that only recently greater emphasis has been put on mucosal and histological healing.

In 2011, Ardizzone *et al.*<sup>[49]</sup> published a prospective study, based on the observation of 157 patients with moderate to severe UC, needing their first systemic steroid course (40 mg to 60 mg of oral prednisone or parenteral methylprednisolone) within 12 mo from diagnosis. The endoscopic check, scheduled at month

Table 1 Studies concerning the achievement of mucosal healing

Ref.	Design	No. of patients	Drugs (dose)	Time of endoscopy	Endoscopic index	Definition of MH	Results
5-ASA							
Vecchi <i>et al</i> <sup>[43]</sup>	RCT, mc	130 UC	5-ASA 4 g p.o. vs 2 + 2 g and enema	6 wk	Rachmilewitz	< 4	58% vs 71%
Mansfield <i>et al</i> <sup>[44]</sup>	RCT, db, mc	50 UC	Balsalazide 6.75 g vs SASP 3 g	8 wk	4 point score	Score 0	27% vs 25%
Kruis <i>et al</i> <sup>[45]</sup>	RCT, db, mc	321 UC	5-ASA 0.5 g × 3 vs 1 g × 3 vs 1.5 g × 3	8 wk	Rachmilewitz	Histology improvement	53% vs 84% vs 70%
Hanauer <i>et al</i> <sup>[47]</sup>	RCT, db, mc	391 UC	Asacol 4.8 g vs 2.4 g	6 wk	No score	Normal endoscopy	84% vs 67% (in moderate UC)
Kamm <i>et al</i> <sup>[48]</sup>	RCT, db, mc	343 UC	Mesalamine MMX 4.8 g vs 2.4 g vs 1.2 g	8 wk	Mod. Sutherland index	< 1	77% vs 69% vs 46%
Kruis <i>et al</i> <sup>[46]</sup>	RCT, db, mc	380 UC	5-ASA 3 g vs 1 g × 3	8 wk	Rachmilewitz	< 4	71% vs 70%
Steroids							
Ardizzone <i>et al</i> <sup>[49]</sup>	RA, sc	157 UC	Systemic steroids 40-60 mg	3 mo	Mod. Baron score	Score 0	38%
Sandborn <i>et al</i> <sup>[50]</sup>	RTC, db, mc	672 UC	Budesonide MMX 9 mg vs 6 mg vs placebo	8 wk	UCDAI mucosal appearance	0	27% vs 16% vs 17%
Van Assche <i>et al</i> <sup>[51]</sup>	RTC, db, mc	282 UC	BDP 5 mg/d vs PD 40 mg/d (tap.)	4 wk	DAI subscore	0	23% vs 21%
Immunomodulators							
D'Haens <i>et al</i> <sup>[60]</sup>	PA, sc	15 CD	AZA 2 mg/kg	26 wk	Rutgeerts score	Ri 0	40%
Ardizzone <i>et al</i> <sup>[52]</sup>	RCT, sc	72 UC	5-ASA vs AZA	3 mo and 6 mo	Baron score	Improving mean Baron index	At 3 mo: 2.3 vs 1.1 at 6 mo: 2.2. vs 0.9
Mantzaris <i>et al</i> <sup>[61]</sup>	RCT, sc	57 CD	AZA 2-2.5 mg/kg vs budesonide 6-9 mg	52 wk	CDEIS	CDEIS < 4	83% vs 24%
Laharie <i>et al</i> <sup>[62]</sup>	RTC, sc	51 CD	MTX 15-25 mg/wk vs AZA 2-3 mg/kg vs IFX 5 mg/kg		CDEIS	CDEIS < 4	11% vs 50% vs 60%
Rispo <i>et al</i> <sup>[53]</sup>	PA, sc	104 UC	AZA or 6-MP	104 wk	Mayo	Mayo 0-1	36%
Biologics							
Colombel <i>et al</i> <sup>[63]</sup>	RCT, db, mc	508 CD	AZA 2.5 mg/kg vs IFX 5 mg/kg vs SONIC	26 wk	No score	Absence of ulcers	16% vs 30% vs 44%
Reinisch <i>et al</i> <sup>[54]</sup>	RCT, db, mc	390 UC	ADA 160/80/40 mg vs 80/40 mg vs placebo	8 wk	Mayo	Mayo 0-1	47% vs 37% vs 41%
Sandborn <i>et al</i> <sup>[55]</sup>	RCT, db, mc	518 UC	ADA 160/80/40 mg vs placebo	8 wk and 52 wk	Mayo	Mayo 0-1	18% vs 10% (Sustained MH)
Rutgeerts <i>et al</i> <sup>[64]</sup>	RCT, db, mc	135 CD	ADA only induction (plc in maintenance) vs ADA continuous	12 wk and 52 wk	CDEIS	CDEIS 0	Baseline CDEIS ≤ 9: Continuous at 12 wk 40%, at 52 wk 30%. Baseline CDEIS < 9: Continuous at 12 wks 16% at 52 wk 19%
Laharie <i>et al</i> <sup>[58]</sup>	RA, mc	63 UC	IFX 5 mg/kg	6-52 wk	Mayo	Mayo 0-1	48%
Feagan <i>et al</i> <sup>[56]</sup>	RCT, db, mc	746 UC	Vedolizumab every 8 wk vs Vedolizumab every 4 wk vs placebo	6 wk and 52 wk	Mayo	Mayo 0-1	6 wk: VDZ 41% vs placebo 24%; 52 wk: 56% vs 51% vs 20%
Sandborn <i>et al</i> <sup>[59]</sup>	RCT, db, mc	774 UC	Golimumab 400/200 mg vs 200/100 mg vs placebo	6 wk	Mayo	Mayo 0-1	17.9% vs 17.8% vs 6.4%

RCT: Randomized controlled trial; MH: Mucosal healing; 5-ASA: 5-aminosalicylic acid; mc: Multicenter; db: Double-blind; sc: Single-centre; RA: Retrospective analysis; AZA: Azathioprine; CDEIS: Crohn's Disease Endoscopic Index of Severity; UC: Ulcerative colitis; CD: Crohn's disease; MMX: Multi Matrix System; IFX: Infliximab; MTX: Methotrexate; PA: Prospective analysis; BDF: Beclomethasone dipropionate.

3, showed MH in 38% of patients assessed by the modified Baron score.

Sandborn *et al*<sup>[50]</sup> compared the use of Budesonide MMX 9 mg/d, 6 mg/d and placebo in 672 UC patients; at week 8, considering a UCDAI score of 0 for MH, 27% of patients achieved MH with Budesonide MMX 9 mg/d. No differences were found between patients on Budesonide MMX 6 mg/d and placebo<sup>[50]</sup>.

Van Assche *et al*<sup>[51]</sup> have recently realized a trial, randomizing 282 UC patients, to receive beclome-

thasone dipropionate (BDP)-prolonged release tablets 5 mg once daily for 4 wk, and then on alternate days for an additional 4 wk, or oral prednisone (PD) 40 mg once daily tapered by 10 mg every 2 wk during the 8 wk of observation. After 4 wk of treatment, the two cohorts of patients, BDP and PD, shows similar rates of endoscopic remission, respectively of 23% and 21%, while 45% and 60% showed mild mucosal activity. No statistical differences were reported between the two groups in terms of MH<sup>[51]</sup>.

**Immunomodulators**

Ardizzone *et al.*<sup>[52]</sup> compared the use of 5-ASA vs azathioprine (AZA) in 72 steroid-dependent UC patients, with a follow-up at 3 and 6 mo. They showed a highly significant superior mean Baron index in patients treated with 5-ASA compared to those on AZA, both at month 3 (2.3 vs 1.1) and at month 6 (2.2 vs 0.9)<sup>[52]</sup>.

In a recent Italian study, analyzing prospective data from 205 steroid-dependent IBD patients who received a 2-year maintenance treatment with thiopurines (AZA or 6-mercaptopurine, 6-MP), good MH rates were seen, particularly in UC compared to CD: 36% vs 16%<sup>[53]</sup>.

**Biological treatments**

At the beginning of this decade, many trials regarding the use of biological drugs, both in UC and CD, were published and most of them had MH as primary outcome in accordance with the latest knowledge on the importance of achieving this aim, in terms of maintenance of clinical remission, reduction of hospitalization and improvement of quality of life.

In 2011, a large trial, ULTRA 1, was published on the use of Adalimumab (ADA) in UC. In this study, Reinisch *et al.*<sup>[54]</sup> compared three different schedules of induction: The first group of patients received ADA 160 mg/80/40 mg at weeks 0, 2, 4 and 6. The second group of patients was randomized to a second induction protocol with subcutaneous ADA 80/40 mg at weeks 0, 2 and thereafter every 2 wk. The last group of patients was randomized to placebo. At week 8, a colonoscopy was performed: MH (defined by a Mayo score of 0-1) was achieved in almost 47% of the first group of patients, compared to 37% of the second group, and 41% of the placebo group. This unusual data was not statistically nor clinically significant. One year later, Sandborn *et al.*<sup>[55]</sup>, in the ULTRA 2 trial, randomized 518 UC patients to subcutaneous ADA 40 mg/every 2 wk (induction with 160/80/40 mg) and to placebo. Endoscopy control was performed at weeks 8, 32 and 52. The percentage of patients who maintained a sustained MH (Mayo 0-1) at all endoscopic checks was about 18% compared to 10% for the placebo group.

In 2012, Feagan *et al.*<sup>[56]</sup> published the results of the GEMINI 1 trial, a very large study involving 746 UC patients. During the induction phase, 225 patients received Vedolizumab at a dose of 300 mg, or placebo, intravenously at weeks 0 and 2; 521 patients received open-label Vedolizumab at weeks 0 and 2. In the maintenance phase, Vedolizumab was administered every 8 wk or every 4 wk. MH was achieved at week 6 in 41% of patients who received Vedolizumab compared to 24% of patients who received placebo. At week 52, MH was achieved in 56% of patients who received Vedolizumab every 4 wk, in 51% of patients who received Vedolizumab every 8 wk, and in only 20% of patients who received placebo.

The same study for CD patients (GEMINI 2) considered only clinical outcome and did not include endoscopic assessment<sup>[57]</sup>.

A small French study on UC patients reported an MH rate of 48% in subjects treated with IFX, with an endoscopic check carried out between 6 and 52 wk after treatment start<sup>[58]</sup>.

Sandborn *et al.*<sup>[59]</sup>, in the PURSUIT trial, investigated the efficacy of Golimumab with three different induction protocols in 774 patients with moderate-to-severe UC. At weeks 0 and 2, the first cohort received placebo, the second cohort received subcutaneous Golimumab at a dose of 200 mg/100 mg, and the third received subcutaneous Golimumab at a dose of 400 mg/200 mg; at the 6<sup>th</sup> week, MH, defined by the endoscopic Mayo subscore of 0-1, was achieved respectively in 6%, 17.8% and 17.9% of patients<sup>[59]</sup>.

**CD****Immunomodulators**

In 1997, D'Haens *et al.*<sup>[60]</sup> evaluated the use of AZA (at a dose of 2 mg/kg per day) in CD patients who underwent surgery and subsequently developed severe recurrences; at endoscopy, scheduled at week 26, they showed MH in 40% of cases, rated by the Rutgeerts score equal to i0.

Mantzaris *et al.*<sup>[61]</sup> compared the use of AZA 2-2.5 mg/kg per day to Budesonide 6-9 mg/d in CD patients; at endoscopic check at week 52, 83% of patients on AZA achieved MH compared with 24% of patients on Budesonide. MH was defined by a CDEIS score < 4.

In another recent trial on CD patients, Laharie *et al.*<sup>[62]</sup> evaluated methotrexate (MTX) 15-25 mg/wk, AZA 2-3 mg/kg per day, and IFX 5 mg/kg. The endoscopic control, performed according to clinical needs (median follow-up 13.2 mo), showed achievement of MH in 11%, 50% and 60% of patients respectively; MH corresponded to a CDAI score of less than 4.

**Biological treatment**

In 2010, the SONIC trial<sup>[63]</sup> compared treatment with AZA, IFX and combination therapy (IFX plus AZA) in 508 patients with CD, naive both to biologics and immunomodulators. The first group of patients was randomized to AZA 2.5 mg/kg per day, the second group to intravenous IFX 5 mg/kg per day and the third group to a combination therapy with intravenous IFX 5 mg/kg and AZA 2.5 mg/kg. The results in terms of MH were clear: The combination therapy was more effective than others in inducing MH (defined by the absence of mucosal ulceration), achieving it in 44% of patients at the 26<sup>th</sup> week, compared to 30% of patients treated with only IFX and 16% of patients treated with only immunosuppressor. In 2012, the results from the EXTEND trial<sup>[64]</sup> were published; in this study, 129 patients with CD were divided into two groups: The first group was randomized to subcutaneous ADA only during induction and placebo for maintenance, the second group to a maintenance treatment with ADA. Endoscopic checks were performed at baseline and at weeks 12 and 52. The results were stratified according to the baseline

CDEIS in two groups: Patients with baseline CDEIS  $\leq$  9 and patients with baseline CDEIS  $>$  9. Patients with ADA maintenance achieved MH (considered as CDEIS 0) at week 12 in 40% (CDEIS  $\leq$  9) and 16% (CDEIS  $>$  9); the MH rate dropped to 30% (CDEIS  $\leq$  9) and 19% (CDEIS  $>$  9) at week 52. The second group of patients (ADA induction only) achieved MH at the 12<sup>th</sup> week in 13% (CDEIS  $\leq$  9) and 14% (CDEIS  $>$  9); at the 52<sup>nd</sup> week no patient maintained MH.

## WHAT TO DO AFTER ACHIEVING CLINICAL REMISSION OR MH?

No clear indications are available regarding the correct timing of drug withdrawal in IBD. Excluding studies on clinical remission achieved by 5-ASA monotherapy and subsequent dose reduction or withdrawal, the following studies investigated the relapse rate starting from patients in clinical remission, with or without endoscopic assessment.

## THIOPURINE DISCONTINUATION

In 2002, a large retrospective study, (Fraser *et al.*<sup>[65]</sup>), analyzed 346 UC patients and 272 CD patients in treatment with AZA; during the observation period, 517 of these patients needed to stop AZA for several reasons (clinical remission or side effects) (Table 2). Authors compared the cumulative remission rate over the years in those who continued and in those who discontinued: At the first year, 95% who continued remained in clinical remission (defined as Harvey Bradshaw Index, HBI  $<$  4) vs 63% of patients who stopped AZA; at the second year, the remission rate was respectively 90% vs 44%, at the third 69% vs 34% and 62% vs 25%, at the fifth year. Predictors for a lower risk of relapse, while the patients were still on treatment, were a minimum leucocyte count less than 5000 el/mmc, an age of more than 36 years at start of treatment and male gender, the latter only for CD. There was no difference in terms of maintenance of remission, according to the duration of previous treatment with AZA. Similar results have been reported examining 61 UC patients taking 6-MP; among these patients, 22 persons discontinued 6-MP. The median time to relapse was 58 wk in patients that continued therapy, and 24 wk in those who discontinued. On multivariate analysis, the authors did not find any significant differences between the two groups in terms of age, gender, extent/duration of disease and duration of treatment with 6-MP before achieving remission<sup>[66]</sup>.

In a French study, the cumulative recurrence rate after an 18 mo follow-up was higher in CD patients in clinical remission who had stopped AZA (21%), compared to patients who had continued (8%), although according to their results it did not reach statistical significance<sup>[67]</sup>. CRP levels  $>$  20 mg/L, time steroid-free  $<$  50 mo and a hemoglobin level  $<$  12 g/dL, on

multivariate analysis, were all risk factors for relapse.

In 2009, Cassinotti *et al.*<sup>[68]</sup>, retrospectively analyzed data from 127 UC patients in therapy with AZA for at least 3 mo and in steroid-free remission. Patients who continued therapy with AZA were included in the first group, while in the second group, patients who discontinued it electively, mainly for adverse events, were included. In the withdrawal group, the cumulative relapse-free survival was 65% in the first year, 51% in the second, 41% in the third, 39% and 35%, respectively in the fourth and fifth year. Stratifying patients for the duration of AZA treatment, authors observed a higher relapse-free survival in patients with longer treatment duration before discontinuation<sup>[68]</sup>.

A similar study has been published by Treton *et al.*<sup>[69]</sup> on 66 CD patients with long standing remission while on AZA. Cumulative relapse rates after AZA withdrawal were 14% in the first year, 52% in the third and 62% in the fifth. According to their data, a CRP level  $\geq$  20 mg/L, neutrophil count  $\geq$  4000/mmc, hemoglobin level  $<$  12 g/dL were risk factors associated with a higher probability of relapse<sup>[69]</sup>.

More recently, Kennedy *et al.*<sup>[70]</sup> have studied a large cohort of IBD patients (129 CD, 108 UC) in deep remission with thiopurines after drug withdrawal. In the first 12 mo, 22% of CD patients had a moderate to severe relapse, vs 12% in UC patients (only moderate, none severe). At 2 years, the relapse rate grew to 39% in CD and 25% in UC. Elevated CRP levels at thiopurine withdrawal were associated with higher relapse rates at 12 mo in CD, while elevated WBC counts were predictive for relapse in UC<sup>[70]</sup>. A Spanish group studied the withdrawal of thiopurines after a treatment duration of at least 6 mo and a sustained steroid-free remission of at least 6 mo. After a median follow-up of 27 mo (IQR, 9-75), the cumulative percentages of clinical relapse were 18.8% after one year, 36.5% at year 3, and 43% at the fifth year. Predictive factors for relapse were biological remission, thiopurine treatment duration, pancolitis, time from diagnosis until start of thiopurines, number of relapses before the withdrawal<sup>[71]</sup>. Very recently, Qiu *et al.*<sup>[72]</sup> have reported on 109 CD patients after discontinuation of thiopurines with a median follow-up of 46 mo. Endoscopic flares occurred in 45% of patients during follow-up, clinical flares in 37%, surgery was necessary in 16%, and hospitalizations in 23%. Independent risk factors for flare were prior bowel complication (HR 1.74), perianal disease at diagnosis (HR 2.24) and CRP  $>$  3 mg/L (HR 4.05)<sup>[72]</sup>.

## ANTI-TNF DISCONTINUATION

Van Assche *et al.*<sup>[73]</sup> randomized 80 CD patients to receive a combined treatment, for more than 6 mo, with IFX and an immunosuppressant (AZA, 6-MP or MTX) (Con), or to stop immunosuppressants receiving only *i.v.* IFX maintenance (Dis) (Table 3). They considered several clinical and endoscopic outcomes during a scheduled follow-up of 104 wk; the need to change or to stop

**Table 2** Studies concerning withdrawal of immunomodulators

Ref.	Design	Disease n. patients	Intervention	Surveillance	Evaluation	Main outcome	Results	Predictive factors
Fraser <i>et al</i> <sup>[65]</sup>	RA, sc	272 CD 346 UC	Continue AZA <i>vs</i> discontinue AZA	-	Clinical assessment	Cumulative remission rate	At 1 yr 95% <i>vs</i> 63%, at 2 yr 90% <i>vs</i> 44%, at 3 yr 69% <i>vs</i> 34%, at 4 yr 63% <i>vs</i> 28%, at 5 yr 62% <i>vs</i> 25%	Risk factors for relapse: Female sex (only CD) and higher WBC; no differences for treatment duration of AZA
Lobel <i>et al</i> <sup>[66]</sup>	RA, sc	61 UC	Continue 6-MP <i>vs</i> discontinue 6-MP	Median f-u: 40 mo (range 4-344)	Clinical and endoscopic assessment	Median time to relapse (wk)	58 wk <i>vs</i> 24 wk Relapse at 1 yr: 43% <i>vs</i> 77%	No significant risk factors for relapse were found
Lémann <i>et al</i> <sup>[67]</sup>	RCT, db, mc	83 CD	Continue AZA <i>vs</i> placebo	18 mo	Clinical assessment	Relapse rate	8% <i>vs</i> 21%	Risk factors for relapse: CRP > 20 mg/L, time steroid-free < 50 mo, Hb < 12 g/dL
Van Assche <i>et al</i> <sup>[73]</sup>	RCT, db, mc	80 CD	Continue IFX + IS <i>vs</i> IFX + stop IS	104 wk	Clinical and endoscopic assessment	Median CRP; Median TL; Median SES-CD; AE rate; 12-mo relapse	1.6 mg/L <i>vs</i> 2.8 mg/L; 2.8 µg/mL <i>vs</i> 1.6 µg/mL; 1 <i>vs</i> 2.5 7.5% <i>vs</i> 7.5%; 58% <i>vs</i> 72.7%	Not significant P-value for endoscopic features in either groups
Cassinotti <i>et al</i> <sup>[68]</sup>	RA, mc	127 UC	AZA discontinuation	Median f-u: 55 mo (range 1-182)	Clinical assessment	Cumulative relapse rate	At 1 yr 35%, at 2 yr 49%, at 3 yr 59%, at 4 yr 61%, at 5 yr 65%	Risk factors for relapse: Short treatment duration of AZA
Treton <i>et al</i> <sup>[69]</sup>	PA, mc	66 CD	AZA discontinuation	Median f-u: 54 mo (IQR 20-69)	Clinical assessment	Cumulative relapse rate	At 1 yr 14%, at 3 yr 53%, at 5 yr 62%	Risk factors for relapse: Higher WBC count
Kennedy <i>et al</i> <sup>[70]</sup>	RA, mc	129 CD  108 UC	Thiopurine discontinuation	12 mo and 24 mo	Clinical assessment	Cumulative relapse rate	CD at 12 mo: Severe 8.5%, moderate 14%; at 24 mo: Severe 12%, moderate 27%. UC at 12 mo: Severe 0%, moderate 12%; at 24 mo: Severe 3%, moderate 22%	Risk factors for relapse: Elevated CRP (only in CD), higher WBC count (only in UC)
Moreno-Rincón <i>et al</i> <sup>[71]</sup>	RA, mc	102 UC	Thiopurine discontinuation	Median f-u: 27 mo (IRQ 9-75)	Clinical assessment	Cumulative relapse rate	At 1 yr: 18.8%, at 3 yr: 36.5%, at 5 yr: 43%	Risk factors for relapse: Biological remission, thiopurine treatment duration, pancolitis, time from diagnosis until the starting of thiopurines, number of relapse before the withdrawal
Qiu <i>et al</i> <sup>[72]</sup>	PA, sc	109 CD	Thiopurine discontinuation	Median f-u: 46 mo (IQR 27-67)	Clinical and endoscopic assessment	Cumulative relapse rate	45% endoscopic flare, 37% clinical flare, 16% surgery, 23% hospitalization	Risk factors for relapse: Prior bowel complication, perianal disease at diagnosis, CRP > 3 mg/L

RCT: Randomized controlled trial; UC: Ulcerative colitis; CD: Crohn's disease; mc: Multicenter; db: Double-blind; sc: Single-centre; AZA: Azathioprine; RA: Retrospective analysis; PA: Prospective analysis; IRQ: Interquartile range; CRP: C-reactive protein.

IFX dosing (primary endpoint) was seen in 60% in the continuation group and in 55% of the discontinuation group ( $P = 0.65$ ). As secondary endpoints, median CRP levels were lower in the first group (Con), whereas the median IFX trough levels (TL) were higher compared with the discontinuation group. Median SES-CD was 1 (range 0-14) in patients who continued combination therapy and 2.5 (range 0-13) in patients who discontinued immunosuppressants. Endoscopic healing was reached in 64% in the first cohort *vs* 61% in the second one; there was no difference in terms of adverse events

(7.5% *vs* 7.5%). Authors concluded affirming that combined therapy (IFX plus immunosuppressants) was not superior to IFX monotherapy, despite the increased median levels of CRP and lower TL of patients treated with only IFX. The higher CRP level and the decrease of TL, after immunosuppressant withdrawal, could be useful as early predictors of loss of response.

In 2010, Waugh *et al*<sup>[74]</sup> observed 48 CD patients in clinical remission in maintenance therapy with IFX every 8 wk. These patients discontinued therapy for reasons other than loss of response or an inadequate follow-up.



**Table 3** Studies concerning withdrawal of biologic therapies

Ref.	Design	Disease n. patients	Drugs and intervention	Surveillance	Evaluation	Main outcome	Main findings	Predictive factors
Waugh <i>et al</i> <sup>[74]</sup>	PA, mc	48 CD	IFX discontinuation	Median f-u: 4.1 yr (IQR 0.5-6.7)	Clinical assessment	Cumulative relapse rate	50% relapse rate at a median of 477 d; 35% remain in remission without treatment	Probably 35% in deep remission are different genetic-kind of CD
Louis <i>et al</i> <sup>[75]</sup>	PA, mc	115 CD	IFX + IMM (IFX discontinuation)	30 mo after withdrawal	Clinical and endoscopic assessment	Cumulative relapse rate	At 1 yr: 44%, at 2 yr: 52%	Risk factors for relapse: Male sex, absence of surgical resections, CDEIS > 0, IFX TL > 2 mg/L, CS use between 6 and 12 mo before baseline, WBC count > 6000/mm <sup>3</sup> , Hb ≤ 14.5 g/dL, CRP ≥ 5 mg/L and fecal calprotectin ≥ 300 µg/g
Steenholdt <i>et al</i> <sup>[76]</sup>	RA, sc	53 CD 28 UC	IFX discontinuation	1 yr and 2 yr	Clinical assessment	Cumulative remission rate (no need to restart IFX, no need of CS, no surgery)	at 1 yr: 61% CD, 75% UC at 2 yr: 20% CD, 40% UC	Risk factors for relapse: Long disease duration (only in CD)  (univariate)
Molnár <i>et al</i> <sup>[77]</sup>	PA, mc	121 CD	Anti-TNF discontinuation	1 yr	Clinical assessment	Cumulative relapse rate	45%	Risk factors for relapse: Smoking, using CS at the start of anti-TNF, previous biological therapy, elevated CRP level at the start of anti-TNF and a dose intensification in the first yr of anti-TNF (univariate)
Farkas <i>et al</i> <sup>[78]</sup>	PA, mc	51 UC	IFX discontinuation	1 yr	Clinical assessment	Cumulative relapse rate (need to restart IFX)	35%	Risk factors for relapse: Previous biological therapy
Rismo <i>et al</i> <sup>[25]</sup>	PA, sc	37 CD	Anti-TNF discontinuation	1-44 mo (range)	Clinical assessment	Cumulative relapse rate	74%	Risk factors for relapse: Elevated mucosal TNF and IL17 expression
Molander <i>et al</i> <sup>[79]</sup>	PA, sc	17 CD 30 UC 5 IBDU	Anti-TNF discontinuation	12 mo	Clinical and endoscopic assessment	Cumulative remission rate	67% clinical remission, 85% endoscopic remission	No significant risk factors for relapse were found
Brooks <i>et al</i> <sup>[80]</sup>	PA, mc	86 CD	Anti-TNF discontinuation	Median f-u: 495 d (365-2160)	Clinical, endoscopic and radiologic assessment	Whole cohort relapse rate; Endoscopic cohort	At 90 d: 4.7%, at 180 d: 18.6%, at 365 d: 36%, 6.3%, 12.5%, 31.3%	Risk factors for relapse: Montreal location and previous anti-TNF therapy
Chauvin <i>et al</i> <sup>[81]</sup>	RA, sc	92 CD	IFX + IMM (IFX discontinuation)	Median f-u: 47.1 mo (4.4-110.2)	Clinical assessment	Cumulative relapse rate	Cumulative: 72%, at 1 yr: 30%, at 2 yr: 48%	Risk factors for relapse: Smoking, previous antimetabolite failure, perianal disease (multivariate)
Dai <i>et al</i> <sup>[82]</sup>	PA, sc	109 CD 107 UC	IFX discontinuation	12 mo	Clinical and endoscopic assessment	Cumulative relapse rate (need to restart IFX)	Pt achieved clinical remission: 13.9% Pt achieved full remission: 6.5% Pt achieved MH: 10%	No significant risk factors for relapse were found. MH doesn't not predict sustained clinical remission
Ben-Horin <i>et al</i> <sup>[83]</sup>	RA, mc	30 CD 18 UC	Anti-TNF discontinuation	Median f-u: 12 mo	Clinical and endoscopic assessment	Cumulative relapse rate	Detectable drug: 80%, undetectable drug: 30%	Risk factors for relapse: Detectable drug levels

Papamichael <i>et al</i> <sup>[84]</sup>	PA, sc	100 CD	IFX discontinuation	Median f-u: 9.7 yr	Clinical assessment	Cumulative remission rate	Cumulative: 52%, at 1 yr 96%, at 2 yr 93%, at 3 yr 88%, at 4 yr 80%, at 5 yr 73%	At the univariate analysis were associated with a SCR: Age at diagnosis $\geq$ 25 yr, disease duration from diagnosis to start of IFX < 1 years, MH at the IFX dis., IFX TC < 6 mg/mL at the IFX dis., positive serum VCAM-1 at the IFX dis.
Bortlik <i>et al</i> <sup>[85]</sup>	PA, sc	61 CD	IFX discontinuation	Median f-u: 28 mo (7-47)	Clinical assessment	Cumulative relapse rate	At 6 mo 18%, at 12 mo 41%, at 24 mo 49%. With MH: 18%, 36%, 60%	Risk factors for relapse: Ileal disease
Monterubbiansi <i>et al</i> <sup>[86]</sup>	RA, sc	58 CD	Anti-TNF discontinuation	5 yr	Clinical and endoscopic assessment	Cumulative relapse rate	At 1 yr 31%, at 2 yr 48% at 5 yr 65%	MH doesn't not predict sustained clinical remission
Bodini <i>et al</i> <sup>[87]</sup>	RCT, sc	9 CD 6 UC	Anti-TNF discontinuation; maintenance with AZA vs 5-ASA	Median f-u: 48 wk (20-78)	Clinical assessment	Cumulative relapse rate	AZA 0% vs 5-ASA 30%	Patients in therapy with 5-ASA have an earlier recurrence
Ampuero <i>et al</i> <sup>[88]</sup>	RA, sc	75 CD	IFX + IMM (IFX dis vs IMM dis.)	12 mo	Clinical and endoscopic assessment	Cumulative relapse rate	30.9% vs 20%	Risk factors for relapse: CRP > 5 mg/L, younger age at diagnosis

RCT: Randomized controlled trial; UC: Ulcerative colitis; CD: Crohn's disease; mc: Multicenter; db: Double-blind; sc: Single-centre; AZA: Azathioprine; RA: Retrospective analysis; PA: Prospective analysis; IRQ: Interquartile range; CRP: C-reactive protein; IFX: Infliximab; 5-ASA: 5-aminosalicylic acid; MH: Mucosal healing; TL: Trough level; CS: Corticosteroid; TNF: Tumor necrosis factor; IL: Interleukin; IMM: Immunomodulator.

Fifty percent of relapse was reached at a median interval of 477 d from discontinuation; interestingly, 35% of patients remained in long-term remission beyond follow-up (median follow-up 4.1 years, IQR 0.5-6.7)<sup>[74]</sup>; authors concluded that patients still in remission 5 years later might have a genetically different type of CD.

In 2012, an observational study on 115 CD patients in combined therapy with IFX and an antimetabolite (AZA, 6-MP or MTX), reported cumulative relapse rates after IFX discontinuation as high as 44% in the first year and 52% in the second year, with a median follow-up of  $28 \pm 2$  mo. At multivariate analysis, relapse increased with an increasing number of unfavorable factors, such as male sex, absence of surgical resections, CDEIS > 0, IFX trough level > 2 mg/L, corticosteroid use between 6 and 12 mo before baseline, WBC count > 6000/mm<sup>3</sup>, Hb  $\leq$  14.5 g/dL, CRP  $\geq$  5 mg/L and FC  $\geq$  300  $\mu$ g/g<sup>[75]</sup>.

A retrospective study evaluated the cumulative remission rate in 81 IBD patients, with a primary response to IFX and in steroid-free remission, following IFX discontinuation; in the first year, 61% and 75%, respectively in CD and UC, were still in remission; at the second year, the percentage dropped to 20% and 40%. Long disease duration was the unique risk factor for relapse only in CD patients<sup>[76]</sup>.

In a prospective study, 121 CD patients who had achieved clinical remission after one year of anti-TNF therapy were followed after withdrawal of biologics. In 45% of patients, a restart of biological therapy was necessary within one year because of clinical relapse. On univariate analysis, smoking, the use of corticosteroids at the start of anti-TNF therapy, previous biological therapies, elevated serum CRP levels at start of anti-TNF therapy and a dose intensification in the first year of

biological treatment were all significantly associated with the need to restart anti-TNF. At multivariate analysis, only male gender and a previous biological treatment were independently associated with relapse<sup>[77]</sup>.

In another prospective trial that involved several IBD centers in Hungary, 51 UC patients who stopped IFX while in clinical remission were analyzed. At follow-up, 35% of patients needed to restart biologic therapy within the first year. Only previous biological therapy was associated to the need to restart biologics<sup>[78]</sup>.

Rismo *et al*<sup>[25]</sup> observed 37 CD patients who stopped the anti-TNF drugs after achieving MH; before discontinuation, biopsies from the healed mucosa were taken in order to evaluate mucosal gene expression of inflammatory cytokines. According to data, at the end of follow-up (range 1-44 mo), 74% of patients experienced a relapse. Gene expression of TNF, IL17A and FOXP3 were significantly higher in patients who relapsed before six months. Normalization of the latter was associated with long-term remission<sup>[25]</sup>.

In the same year, Molander *et al*<sup>[79]</sup> included 52 IBD patients who had achieved clinical and endoscopic remission and suspended the anti-TNF treatment in a retrospective study; in the first year after withdrawal, 65% of the patients maintained clinical remission and 85% of these were still in endoscopic remission. No significant risk factors predictive for relapse were found<sup>[79]</sup>.

In 2014, Brooks *et al*<sup>[80]</sup> published a well-designed, prospective trial on 86 CD patients in clinical and/or endoscopic remission with anti-TNF drugs. They evaluated clinical, endoscopic and radiologic relapse after anti-TNF discontinuation. The follow-up was scheduled at 90, 180 and 365 d: In the whole cohort, relapse rates

were respectively 4% (at 90 d), 18% (at 180 d) and 36% (at 365 d); in patients assessed endoscopically, the rates were 6%, 12%, and 31%, respectively. Ileocolonic localization at diagnosis (OR 3.1) and previous anti-TNF therapy (OR 8.9) were found to predict relapse at any point of follow-up<sup>[80]</sup>.

In a retrospective analysis, 92 CD patients were investigated after stopping IFX coming from a combined therapy with an immunomodulator (thiopurines or MTX) and IFX. After a median follow-up of 47 mo, the cumulative relapse rate was 72%. In the first year, 30% of the patients relapsed, while 48% of patients had a relapse in the second year. Based on multivariate analysis, the risk factors for relapse were active smoking, previous antimetabolite failure and perianal disease<sup>[81]</sup>.

In a large trial, Dai *et al.*<sup>[82]</sup> investigated relapse rates, defined as the need to restart IFX, in 109 CD patients and in 107 UC patients after discontinuation of IFX, after 1 year of continuous therapy. Need to restart IFX was observed in 13.9% of patients in clinical remission and in 6.5% of patients in deep remission. The Kaplan-Maier analysis did not show differences between clinical remission and MH concerning time to restart IFX (flare), in neither CD nor in UC<sup>[82]</sup>. A good response rate to retreatments with IFX was reported (78% in CD and 66% in UC). An interesting result came from a study conducted by Ben-Horin *et al.*<sup>[83]</sup> on 48 IBD patients (30 CD and 18 UC) in remission who discontinued anti-TNF: During 12 mo median follow-up a higher incidence of relapse (80%) was observed in patients with measurable TL compared with patients (30%) who had undetectable levels ( $P = 0.002$ ). Probably, the patients with undetectable TL were in remission independently of anti-TNF therapy<sup>[83]</sup>.

Papamichael *et al.*<sup>[84]</sup> performed a long-term retrospective observation of 100 CD patients from the moment of IFX discontinuation due to clinical remission. After a median follow-up of 9.7 years, the cumulative relapse rate was 48%; at univariate analysis, age at diagnosis  $\geq 25$  years, disease duration from diagnosis to start of IFX  $< 1$  years, complete MH at the time of IFX cessation, IFX TL  $< 6$  mg/mL at the time of IFX cessation and positive serum VCAM-1 at the time of IFX cessation were significantly associated with a sustained clinical remission (SCR). At multivariate analysis, only age at diagnosis  $\geq 25$  years remained associated with SCR<sup>[84]</sup>.

Very recently, Bortlik *et al.*<sup>[85]</sup> have analyzed the cumulative relapse rate after IFX discontinuation in 61 CD patients in clinical remission (median time of follow-up 28 mo) in a prospective analysis. At 6 mo of follow-up, 18% of patients relapsed, at one year 41%, and after two years of follow-up almost half of the patients. Surprisingly, among those patients who achieved MH, the cumulative relapse rates were similar: 18% at 6 mo, 36% at one year and even 60% after two years. Ileal localization of disease was the only risk factor for relapse<sup>[85]</sup>.

Monterubbianesi *et al.*<sup>[86]</sup> studied 58 CD patients in therapy for  $\geq 12$  mo with IFX or ADA who had stopped treatment because of deep remission. They observed a cumulative recurrence rate after discontinuation of anti-TNF drugs equal to 31% at one year, 48% at the second year and 65% at the third. They concluded saying that achieving MH before discontinuation did not predict a prolonged clinical remission<sup>[86]</sup>.

In a controlled trial, Bodini *et al.*<sup>[87]</sup>, randomized 15 IBD patients (6 UC and 9 CD) to AZA 2 mg/kg per day or 5-ASA 2.4 g/die in UC and 3 g/d in CD, after stopping an anti-TNF drug. During the entire follow-up (median f-u time 48 wk), 100% of patients on AZA remained in remission, unlike patients on 5-ASA who relapsed in 30% of cases. Patients on maintenance therapy with 5-ASA showed, moreover, an earlier relapse compared to the other group<sup>[87]</sup>. Finally, in a retrospective analysis, CD patients in combined treatment continued with either IFX or immunomodulator. The 1-year relapse rate was not significantly different between the two groups, being 20% for those who continued IFX, and 30.9% for those on immunomodulators<sup>[88]</sup>.

## CONCLUSION

Thanks to the advent of biological drugs, MH has become an important aim to achieve, in order to stop progress of IBD and avoid related complications. New kinds of drugs will be introduced over the coming years and will be available for physicians in the hope to get better long-term remission rates. Nevertheless, the issue of saving treatment years, introducing drug holidays<sup>[89]</sup>, will always be of central importance to ensure the least possible exposure to biologics and immunosuppressants, in an attempt to limit, as much as possible, adverse events and opportunistic infections. Another important aim is to reduce costs and ensure a sustainable future for National Health Services, in the management of a growing problem<sup>[90]</sup>. The use of immunosuppressive drugs in general (immunomodulators and biologics) has certainly changed over time, assuming greater importance, also in light of growing evidence from literature, and they have earned several indications: Early treatment in patients with more aggressive disease, use in first instance of combination therapy (the top-down strategy) in patients with steroid-resistant or steroid-dependent disease, and in the prevention of recurrences in patients who have undergone surgical resection. Important progress was also made regarding perianal disease and the importance of using the correct timing of biological therapies and surgery. Finally, the use of rescue-therapy with anti-TNF drugs or cyclosporine in severe UC has been well established.

Although the importance of achieving MH has been well documented, several recent studies have shown that maintaining or de-escalating therapy did not change the outcome significantly (Table 4), in terms of clinical and endoscopic relapse. Conversely, in a

**Table 4** Synopsis on relapse rates with or without withdrawal of immunomodulator or biologics

Drugs	Overall patients number	Relapse at 1 yr	Relapse at 2 yr	Relapse at 5 yr
Immunomodulator	659 CD, 744 UC			
Maintenance	Mixed	6%	10% <sup>[65]</sup>	48% <sup>[65]</sup>
Median (range)		(range 5-43) <sup>[65-67]</sup>		
	Only CD	6% <sup>[67]</sup>		
	Only UC	43% <sup>[66]</sup>		
De-escalation	Mixed	20.50%	44%	63.50%
Median (range)		(range 12-37) <sup>[65,68-71]</sup>	(range 25-56) <sup>[65,68,70]</sup>	(range 43-75) <sup>[65,68-71]</sup>
	Only CD	18%	39% <sup>[70]</sup>	62% <sup>[69]</sup>
	Only UC	19%	37%	54%
		(range 12-35) <sup>[68,70,71]</sup>	(range 25-49) <sup>[68,70]</sup>	(range 43-65) <sup>[68,71]</sup>
Anti-TNF	605 CD, 216 UC			
Maintenance	Mixed	49%	72%	
Median (range)		(range 23-75) <sup>[58,95]</sup>	(range 36-83) <sup>[58,73,95]</sup>	
	Only CD	75% <sup>[95]</sup>	77.5% <sup>[73,95]</sup>	
			(range 72-83)	
	Only UC	23% <sup>[58]</sup>	36% <sup>[58]</sup>	
De-escalation	Mixed	35%	48.5%	46%
Median (range)		(range 4-45) <sup>[76-80,82,84-86]</sup>	(range 7-80) <sup>[76,84-86]</sup>	(range 27-65) <sup>[84,86]</sup>
	Only CD	37.5%	48.50%	46%
		(range 4-45) <sup>[76,77,80,84-86]</sup>	(range 7-80) <sup>[76,84-86]</sup>	(range 27-65) <sup>[84,86]</sup>
	Only UC	30% (range 25-35) <sup>[76,78]</sup>	60% <sup>[76]</sup>	
Combination therapy	362 CD			
Anti-TNF de-escalation	262 CD	31%	50%	
		(range 30-44) <sup>[75,81,88]</sup>	(range 48-52) <sup>[75,81]</sup>	
Immunomodulator de-escalation	100 CD	20% <sup>[88]</sup>	58% <sup>[73]</sup>	

UC: Ulcerative colitis; CD: Crohn's disease.

recent report, a lower rate of colectomy in a 10-year follow-up period was reported in patients that reached Mayo score 0 compared to score 1<sup>[91]</sup>. These conflicting data makes the physician's choice in this moment even more difficult. Looking at the evidence related to discontinuation in patients treated with thiopurines, a higher WBC count, elevated CRP serum levels and short duration of treatment, seem to be adverse factors, capable to predict an unfavorable disease course after drug discontinuation.

For patients on treatment with anti-TNF therapy, risk factors for relapse, such as elevated WBC count or serum CRP, seem to have a weaker influence; neither does the achievement of MH seem to predict a better course of disease.

FC could be a useful tool to assess inflammatory activity of colonic disease and it correlates well with MH<sup>[80]</sup>, thus it should be dosed before withdrawal, to assess the degree of inflammation. Another important issue to be developed is histological healing, but at this moment no standardized score is available for either UC or CD<sup>[92,93]</sup>. At present, there is only one report concerning the superiority of histological over endoscopic healing in UC in terms of hospitalizations and steroid use<sup>[94]</sup>. It seems that histological healing will become an essential therapeutic target to ensure optimal disease control and less progression of organ damage, but new randomized controlled trials are needed to better define the real weight of histology in decision making, especially in transmural CD, on

withdrawal of an immunomodulator or biologic drug. This lack of knowledge and evidence could probably explain the poor correlation between achievement of MH and maintenance of remission.

At this moment, drug withdrawal in the presence of mild mucosal lesions and of concomitant unfavorable features of disease, or positive markers of inflammation (like serum CRP or FC) seems to be unreasonable.

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