Review: Clinical Trial Outcomes

CLINICAL INVESTIGATION

New strategies for the treatment of inflammatory bowel diseases

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Anti-TNF therapy is the most important treatment for inflammatory bowel disease patients. However, primary nonresponders are frequent and clinical recurrence under maintenance therapy is reported in 40% of the treated patients. The aim of this article is to explain the most important targets for the future of treatments in inflammatory bowel disease and to report the results of these news drugs in clinical practice. Two Phase III studies clearly indicate the interest of golimumab and vedolizumab in induction and maintenance treatment for ulcerative colitis patients. Soon it will be possible to analyze the principal regulation defect in each patient to design a more personalized treatment. Before this step, it is important first to try to optimize treatment and then to consider a switch to another drug.

Keywords: Crohn's disease • treatment • ulcerative colitis

Xavier Roblin*[1], William Dronne[1], Stéphane Paul[2] & Emilie Del Tedesco[1]

[1]Department of Gastroenterology, University Hospital of Saint-Étienne, Saint-Étienne, France
[2]Immunology Laboratory, University Hospital of Saint-Étienne, Saint-Étienne, France
*Author for correspondence:
E-mail: xavier.roblin@chu-st-etienne.fr

Crohn's disease (CD) and ulcerative colitis (UC) are inflammatory chronic diseases that affect the intestinal tracts and patient quality of life [1]. CD is characterized by a transmural inflammation of any portion of the GI tract from the mouth to the anus. In total, 25% of CD patients will develop perianal involvement as anal fissures, fistulas or abscesses [2–4]. For UC, the rate of colectomy is approximately 20% at 20 years [5]. Although new molecules, such as anti-TNFα antibodies, demonstrate high efficacy in severe inflammatory bowel disease (IBD), the natural history of the patients remains unchanged. New therapeutic strategies are needed to modify this situation, particularly in patients who are at risk of disease progression.

Evaluation of the step-care versus top-down strategies for CD patients

The natural history of CD is marked by early, severe and active forms that may lead to worsening clinical complications, such as abscesses or fistulas [2–4] and a non-negligible early surgery rate. In addition, it is important to remember that despite the effectiveness of current treatments, such as anti-TNF, the natural history of IBD remains unchanged, with a 50% rate of surgery at 10 years [6]. It is essential to identify patients who are suitable for early treatment because they are at high risk of disease progression as well as those who are at low-risk for whom overtreatment will result in a poor therapeutic index. In each patient, benefits must always be weighed against risks. It is therefore necessary, especially in CD, to determine the severity of the impairment (mild to severe) and to predict the impact and the evolution on the digestive tract. For this purpose, the new Lemann clinical score takes into account anatomical, extension and severity of the disease [7].

Currently two types of treatment strategies in CD are proposed: accelerated step-care and top-down.

Sequential increase and additive therapy is recommended for the management of CD focusing on acute exacerbations and maintaining remission thereafter [8–10].

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The first line of treatment includes corticosteroids and immunosuppressants for steroid-refractory illness. Anti-TNF therapies are only used for refractory patients or those intolerant to conventional therapies.

Although this strategy is well recognized, it has never resulted in a change in the natural history of IBD and has never been compared with other existing strategies.

■ Accelerated step-care strategy

There are currently two contradictory studies based on this strategy. In the first study by Candi *et al.*, 63 patients with active CD were randomized in a double-blind trial [11]. The patients were treated by azathioprine (AZA; 2.5 mg/kg) or placebo. After 15 months, there was a highly significant difference in the proportion of patients in remission (42% receiving AZA vs 7% receiving placebo; p = 0.001), demonstrating the great interest of AZA for the maintenance of remission induced by corticosteroids.

By contrast, the second study, a randomized placebo-controlled trial of AZA in combination with corticosteroids, has recently reported a different set of findings [12]. Sans and coworkers evaluated the efficacy of early introduction of AZA in patients with recently diagnosed CD (diagnosed within 8 weeks). Patients (n = 131) were randomized to receive either AZA (2.5 mg/kg/day; n = 68) or placebo (n = 63). CD activity index (CDAI) score was measured as a reflection of disease activity at the date of randomization. The CDAI score was 120 points in the AZA group and 90 points in the placebo group. There was no significant difference in corticosteroid-free remission rates between patients with quick introduction of AZA and those with conventional strategy therapy (44.1 vs 38.1%; p = 0.52).

Recently, Cosnes *et al.* reported a randomized trial that compared two strategies for CD patients with predictive factors of disability: a classic treatment with steroids and AZA when patients present failure to steroids and AZA in the first months (above 6 months) with steroids that will be tapered [13]. The primary end point was the number of trimesters in remission. The results were comparable for each group whether there was early or no prescription of AZA. The inclusion criteria were not good enough to isolate subgroups of patients in which this step care strategy would be useful.

■ Early top-down

Four randomized trials have evaluated the use of combined TNF antagonist and immunosuppressive therapy for the induction of remission in patients with active CD.

In the first trial, 113 CD corticosteroid-dependent patients were randomized to receive infliximab (IFX) induction therapy at week 0, 2 and 6 [14].

All patients received concomitant AZA treatment. This study demonstrated that combination therapy was superior to AZA monotherapy (Table 1). Those results may understate the efficacy of combined immunosuppressants as IFX was only used during the induction phase [14].

The second trial was performed in patients with no prior treatment [15]. In total, 130 patients were randomly assigned to receive either early combined immunosuppression (three 5 mg/kg IFX infusions at weeks 0, 2, and 6, with AZA) or conventional treatment. The primary outcome was corticosteroid-free remission at 6 months and 1 year.

These results suggest that the introduction of combined immunosuppression early in the course of CD is superior to the traditional step-care approach (Table 2). However, the percentage of patients with steroid-free remission at 2 years was comparable in the two groups.

In the SONIC trial, Colombel *et al.* evaluated, in a double-blind trial, the efficacy of IFX monotherapy, AZA monotherapy, and the combination of the two drugs in 508 adults with moderate-to-severe CD [16]. Patients had no prior history of TNF antagonist use or immunosuppressive therapy. The primary end point was corticosteroid-free remission at week 26 (Figure 1).

Similar results were also obtained at 1 year of treatment. These results demonstrate the superiority of combination therapy over AZA or IFX monotherapy in naive patients treated relatively early in the course of the disease.

Feagan and coworkers conducted a 500-week, double-blind, multicenter, controlled trial that compared combination therapy of methotrexate (MTX) and IFX to IFX alone in active CD [17]. Patients were randomly assigned to receive 25 mg of MTX subcutaneously weekly or placebo. Both groups received intravenous (iv.) IFX (5 mg/kg) in induction and then every 8 weeks. Prednisone was also tapered, beginning at week 1, to discontinuation by no later than week 14. By week 50, 30.6% of patients in the MTX group had failed treatment compared with 29.8% of those assigned to placebo (p = 0.63).

In contrast to the strong efficacy signal for combination therapy identified in the SONIC trial, no benefit for combined therapy was observed in this patient population with relatively long-established disease [17].

Which strategy before an inactive CD?

In the authors' practice, the primary goal is to obtain a clinical remission, but is that enough? In fact, should we monitor those patients through the use of imaging, endoscoping or biomarkers? Agreement is unanimous to obtain mucosal healing under treatment in IBD for symptomatic patients, though for asymptomatic patients, this aim is still controversial.

In a recent study, Schoepfer questioned 270 gastroenterologists [18]. From a total of 153 respondants, 70% took their therapeutics decisions on clinical data only, 24% on endoscopic data and 6% on biomarkers. Even if this study had methodological weaknesses, it shows that the impact of mucosal healing in therapeutic decision making remains limited.

From the importance of mucosal healing to lasting & deep remission

In the age of anti-TNFα therapy, mucosal healing is a very common end point in trials. Each study demonstrates a favorable evolution in both the short- and long-term in patients with active CD who display mucosal healing.

In ACCENT 1, induction or maintenance treatment with IFX is efficient to obtain mucosal healing in patients with CD [19]. At week 10, mucosal healing rates were 29% after three iv. infusions compared with 3% for only one infusion (p = 0.006). These findings were also confirmed with a long-term follow up, with 44 versus 18% (p = 0.041) at week 54 for three and one infusions, respectively. In the same trial, patients with mucosal healing at week 54 remained asymptomatic for a mean of 20 weeks compared with just 4 weeks in the absence of mucosal healing [19].

In a substudy of ACCENT 1's endoscopic results, Rutgeerts *et al.* found a corrilation between CD-related hospitalization rates and the absence of mucosal healing [20].

The EXTEND study was the first to analyze mucosal healing as a primary end point in CD [21]. In total, 135 patients with active ileocolonic CD were treated by adalimumab (ADA) in an induction regimen (160 then 80 mg at week 2). At week 4, patients were double-blindedly randomized into two groups (ADA 40 mg/14 days or placebo). Every patient underwent an endoscopy at weeks 12 and 54. Mucosal healing was defined by an absence of endoscopic ulcerations. Mucosal healing rates under ADA were 27.4 and 24.2%, respectively, at weeks 12 and 54 compared with 13.1 (p = 0.056) and 0% (p < 0.01) with the placebo, respectively.

In a *post hoc* study, Colombel *et al.* investigated the impact of deep remission in monitoring of patients [22]. This new concept was defined by a clinical CDAI score of <150 and the pressence of mucosal healing. In the group of 11 patients with a deep remission at week 12, hospitalization rates and hospitalizations for CD were both 0% over a 52-week period, in contrast with patients without deep remission, whose rates were 17 and 9%, respectively.

In a cohort study on 214 patients with CD treated by IFX and followed for 5 years, 64.8% of patients who demonstrated mucosal healing remained in clinical remission until the end of the following period, compared with 39.5% of patients without mucosal healing (p = 0.0004) [23]. Hospitalization rates were also lower in the mucosal healing group (42 vs 59%; p = 0.01). In fact, the use of abdominal surgery was significantly lower (14 vs 38.4%; p < 0.0001) with patients who exhibited mucosal healing.

From the Ibsen cohort, Frøslie *et al.* have studied the impact of long-term mucosal healing in IBD [24]. Approximately 458 patients with IBD were enrolled and followed for clinical and endoscopical results at 1 and 5 years. Mucosal healing rates decrease the colectomy rate in UC and the use of intestinal resection in CD (p = 0.1).

If the concept of deep remission seems to be strongly correlated to a favorable evolution, it is difficult to know which endoscopic criteria have to be obtained. Mucosal healing could be defined as the absence of

Table 1. Superiority of combination therapy over monotherapy on corticosteroids-free remission in Crohn's disease patients between infliximab plus azathioprine versus placebo plus azathioprine groups at weeks 12, 24 and 52.

Week	Corticosteroid-free remission		p value
	Infliximab (%)	Placebo (%)	
12	75	38	<0.001
24	57	29	0.03
52	40	22	0.04

Table 2. Corticosteroid-free remission at 6 and 12 months in combined therapy versus conventional therapy group.

Months	Corticosteroid-free remission		p value
	Combined therapy (%)	Conventional therapy (%)	
6	60	35.9	0.006
12	61.5	42.2	0.03

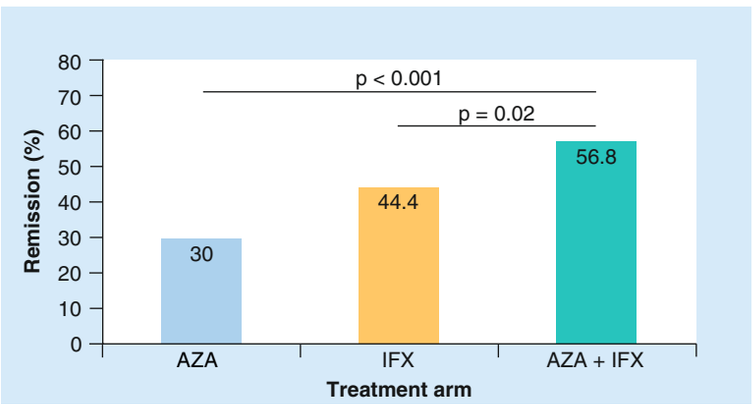

Figure 1. Corticosteroid-free remission at week 26 in azathioprine, infliximab and azathioprine-plus-infliximab groups in Crohn's disease. AZA: Azathioprine; IFX: Infliximab.

mucosal ulcerations, complete endoscopic remission (CD endoscopic index of severity score [CDEIS] < 3) or endoscopic remission (CDEIS < 6). In a Belgian cohort, a significant (but not complete) endoscopic improvement was also associated with a significantly decreased recourse to surgery compared with patients with complete mucosal healing (14.1 vs 14.0%) [23]. Conversely, in the STORI study, which analyzed the associated factors for clinical relapse after interruption of IFX plus AZA combination therapy in patients with clinical remission for at least 6 months, CDEIS scores of approximately 0 were associated with a clinical relapse under AZA [25].

Inflammatory biomarkers & news therapeutic concepts

Many biomarkers have been studied to provide uninvasive measures of mucosal healing. Two such factors seem to offer a potential benefit in the monitoring of IBD – the use of CRP and fecal calprotectin levels, which correlate closely with endoscopic activity during maintenance care.

Fecal calprotectin

Numerous studies have clearly demonstrated the correlation between endoscopic activity and fecal calprotectin assay in CD. In a prospective study, Schoepfer *et al.* included 140 patients with CD, as well as ilecolonoscopy and reported endoscopic activity (Simple Endoscopic Score for Crohn's Disease [SES-CD]), clinical scores (CDAI), fecal calprotectin and CRP levels [26]. The correlation between CDAI and SES-CD was relatively low (p = 0.38) with a diagnostic accuracy for detecting high CDAI endoscopic activity of only 40%. Conversely, fecal calprotectin was highly correlated with a SES-CD score (p = 0.75) with an accuracy to detect endoscopic activity of 87% for a threshold of 70 µg/g of stool. In a similar work in 77 CD patients, Sipponen *et al.* have reported a fecal calprotectin threshold of 200 µg/g of stool, which demonstrates a positive predictive value of endoscopic activity (CDEIS ≥ 3) of 94% and negative predictive value of 61% [27].

Fecal calprotectin also predicts clinical recurrence during the maintenance care. A Spanish study has reported data on 163 patients with IBD (74 CD) and clinical remission for at least 6 months [28]. The average fecal calprotectin levels were significantly higher in patients with a relapse in the aftermath of the disease than those remaining in the follow up in clinical remission (239 vs 136 µg/g of stool). A fecal calprotectin level of >150 µg/g of stool increased by four-times the subsequent risk of recurrence (28 vs 7%).

With fecal calprotectin levels of >150 µg/g of stool, most studies report similar findings, with a hazard ratio for response of 4.1–5.53 [29]. In a *post hoc* STORI study, De Suray *et al.* monitored the CRP and fecal calprotectin levels every 2 months [30]. In total, 113 patients were included and 51 demonstrated a clinical recurrence for a median follow up of 10 months. Calprotectin levels (median) were significantly higher in the relapse group of patients (151 vs 51 µg/g of stool; p = 0.001). Increase of calprotectin above 250 µg/g of stool was associated with a risk of relapse in the short term (<6 months) with a hazard ratio of 6.5 (95% CI: 2.7–15.6; p < 0.01).

Finally, an early normalization of fecal calprotectin predicts a favorable outcome with anti-TNF therapy. A total of 60 patients with IBD (34 with CD) treated with anti-TNF (IFX or ADA), were monitored for their calprotectin level after induction regimen [31]. In total, 52% of patients had normalized this biomarker after induction regimen of anti-TNF (<100 µg/g of stool). At 12 months, 84% of patients, having normalized their calprotectin early, remained in clinical remission compared with 38% of the group with a rate of >100 µg/g of stool after induction. In this study, a threshold of fecal calprotectin after induction by TNF blockers of 139 µg/g of stool had a sensitivity of 72% and a specificity of 80% for predicting unfavorable clinical outcomes [31].

CRP

Measuring CRP is also important before applying anti-TNF treatment. In the SONIC study, three distinct regimens were compared in IBD patients (AZA, IFX or combotherapy) [32]. The use of IFX alone or in combination with AZA was associated with a significantly more favorable clinical course compared with the AZA-alone arm in patients with a baseline CRP level of >0.8 mg/l. In the CHARM study (comparing ADA with placebo in CD maintenance), clinical remission rates at week 26 and 56 were significantly higher with ADA but without any impact on CRP at baseline [33].

Could elevation of CRP also be associated with an increased risk of clinical recurrence in a patient with CD who are asymptomatic? Numerous studies demonstrate a elevated CRP to be strongly predictive of clinical relapse (OR: 3.08–58.6%) [29]. In a subanalysis of STORI, the median concentration of CRP was higher in patients who are going to relapse (3.9 vs 2.8 mg/l; p = 0.07) [30]. An increase of CRP beyond 5 mg/l was associated with early relapse (within 4 months) with a hazard ratio of 4.2 (1.9–9.2; p = 0.01).

In a study of 201 patients with CD treated with ADA, a normalization of CRP within 12 weeks after the start of treatment was predictive of mucosal healing [34]. In an extensive work that included 718 patients with CD treated with IFX, Jurgens *et al.* studied the impact of CRP on immediate and long-term response [35]. IFX-naive patients with high CRP levels respond more to

subsequent IFX treatment (90.8 vs 82.6%; p = 0.014). An early normalization of CRP was also correlated with a sustained response with IFX (p < 0.001). The threshold of CRP remains significantly higher in cases of loss of response to IFX. During the exhaust to IFX therapy, CRP levels were significantly higher (median = 11.2 mg/l). Finally, CRP was correlated with mucosal healing with a predictive value of up to 90% (p = 0.033) [35].

However, some points limit the use of these biomarkers. For CRP, genetic polymorphisms may explain normal CRP levels in active CD. Denis *et al.* reported on 28 CD patients with CDAIs > 150, who had normal CRP levels [36]. In almost a third of cases, the CDEIS was ≥6. Regarding fecal calprotectin, even if its use is simple, its reproducibility over time is not perfect. De Suray *et al.* found significant intra-individual variability with this assay [29]. Moum *et al.* have reported similar results comparing 63 pairs of stools at 24-h intervals [37]. Currently, this assay is not commonly used in clinical practice in France. In the future, it may be carried out by the patient on their own stool, as the technique has given reliable results in preliminary studies. This 'bedside' assay may help to increase patient complience.

Optimizing the treatment of CD using biomarkers

In view of the data, this appears to be a very interesting concept. In practices, we could discuss a decrease of therapy in patients in deep remission. The STORI study [25] included 113 patients in clinical remission treated with a IFX–AZA combination for at least 6 months. Patients stopped IFX at inclusion. The aim of this work was to isolate predictive factors of relapse under AZA monitoring alone. Deleterious factors were found in the absence of surgery, steroid use between 6 and 12 months before stopping IFX, male gender, hemoglobin Phase II 14.5 g/dl, leukocytes > 6 × 10^9/l, high-senstitivity CRP ≥ 5 mg/l, fecal calprotectin ≥ 300 µg/g of stool, CDEIS > 0 and IFX concentration ≥ 2 mg/l. Patients who stopped IFX with at least four of these criteria rarely relapse by the 1-year follow up. This is in contrast to those with more than six criteria, for whom the systematic relapse was within less than 1 year (Figure 2). It is important to note that patients with recurrence were in remission with new IFX therapy for up to 90% of included patients. The study also demonstrates that mucosal healing is necessary but not sufficient before decreasing therapy. Only 30% of patients with healing mucosa (CDEIS = 0) did not present recurrence in the follow up. Moreover, CRP, calprotectin and healing mucosa on endoscopy are independent factors.

Regarding the feasibility to interrupt AZA treatment in patients treated for more than 4 years, Treton *et al.* have reported a significant relapse rate dependent on the duration of the pre-AZA period (14% at 1 year, 52% at 3 years and 62% at 5 years) [38]. CRP over 20 mg/l had a hazard ratio of 58 for risk of relapse and seems to be a factor associated with relapse after AZA interruption.

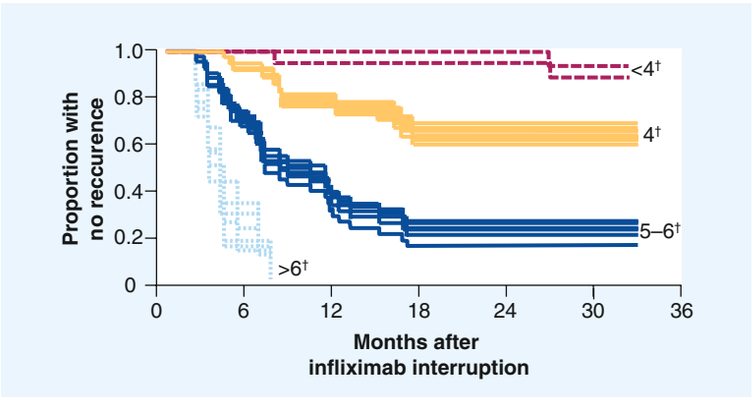

Figure 2. Predictive model for time to recurrence in the STORI cohort.
Kaplan-Meier curves of time to recurrence following models and multivariate scores generated by a Cox model using a multiple imputation method. Independent factors associated with relapse: no previous surgery, corticosteroid use in 6–12 months before stopping infliximab, male, hemoglobin ≤ 14.5 g/dl, leukocytes > 6 × 109/l, high-sensitivity CRP ≥ 5 mg/l, fecal calprotectin ≥ 300 µg/g, Crohn's disease endoscopic index of severity score >0, infliximab ≥ 2 mg/l.
†Number of deleterious factors.
Reprinted with permission from [24].

Optimizing therapy in asymptomatic patients with elevated biomarkers

To date, no study can support this concept. Recently, a working group at the European Crohn's and Colitis Organisation has reported these findings on mucosal healing and therapeutic impact [39]. The current findings are clear: intensified therapy for mucosal healing in patients with CD in clinical remission without mucosal healing, is not recommended. Nonetheless, some experts have embrased the concept. In a recent development, Louis *et al.* have finally proposed an empirical monitoring to validate the support of CD (Figure 3) [40].

To confirm this concept of therapeutic optimization based on the use of biomarkers, two multicenter studies are ongoing. The ADACAL study has been opened under the direction of three societies as GETAID in France. Patients with CD who have been treated with AZA alone and have a CDAI clinical score of <220 but with an increase fecal calprotectin beyond 250 µg/g stool and/or elevated CRP > 5 mg/l, will be included. Endoscopy is performed for each patient. Included patients have CDEIS >3 or more than 10% in one segment. These patients will be randomized into two groups: placebo or ADA add patterns with

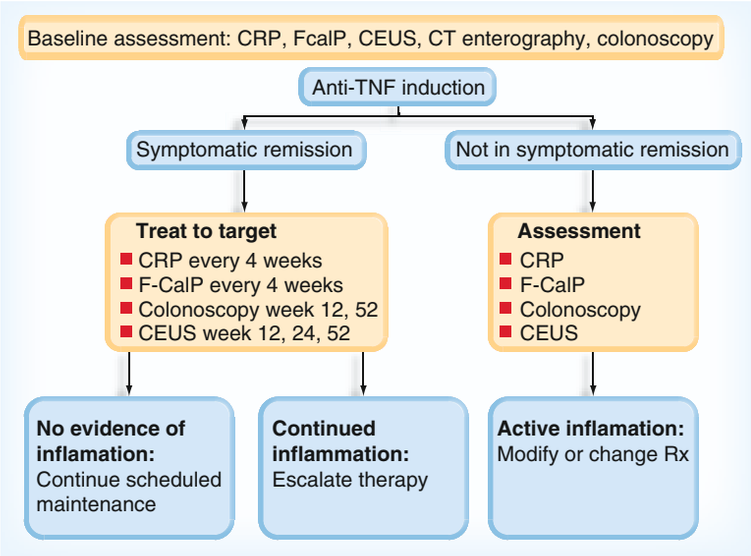

Figure 3. Assessment and monitoring for Crohn's disease patients.
CEUS: Contrast-enhanced ultrasound; CT: Computed tomography; F-CalP: Fecal calprotectin; Rx: Treatment.
Reprinted with permission from [39].

conventional induction and maintenance. The primary end point is the rate of treatment failure at week 48. Determination of clinical score, quality of life and biomarkers will be performed every 12 weeks. In each arm, increase of these biomarkers over 50% will be followed by endoscopy and treatment will be intensified in case of non-mucosal healing. The results are strongly expected to confirm whether or not CD patient treatment can be optimized based only on biomarkers.

The second trial (CALM) has been designed to measure the impact of those biomarkers in therapeutic strategies and the interest of tight control of the disease (Figure 4).

This work aims to determine whether tight control of the disease (clinical and biomarker) increases the rate of mucosal healing in CD at 1 year in immunosuppressants-naive patients or those on anti-TNF therapy.

The concept of optimization therapy in asymptomatic patients with elevated biomarkers seems to be logical and promising. However, recent evidence is mainly indirect, and currently, this strategy cannot be validated in practice. It may, in each case, be discussed only in consultation meetings regarding therapy. Only the results of the major studies underway will remove any ambiguity or doubt on this type of strategy.

Trough residual IFX

In patients treated with IFX in a maintenance strategy, treatment is usually tailored to symptoms, biology and even endoscopy. The advantage of this optimization guide with trough serum IFX is highly debated and prospective trials are awaited.

Several studies on the relationship between serum IFX and efficacy in CD and UC have been reported. However, most often, the presence of very low IFX concentrations, even undetectable, is correlated with a poor response.

The study by Van Moerkercke *et al.* has the advantage in demonstrating an outline of the concentration–effect relationship with a significant difference between total endoscopic mucosal-healing rate when serum IFX is higher than 5.77 µg/ml versus absence of healing when this rate is approximately 0.95 µg/ml ($p = 0.004$) [41]. These results are consistent with those from Maser *et al.* [42], thus indicating a relationship for the concentration–effect on clinical, biological and endoscopy response. Similarly, in UC, Seow *et al.* have reported that patients with detectable trough residual IFX (TRI) present significantly more healing mucosa than patients without detectable TRI.

A retrospective study assessed the value of TRI when immunosuppressive treatment is stopped in patients

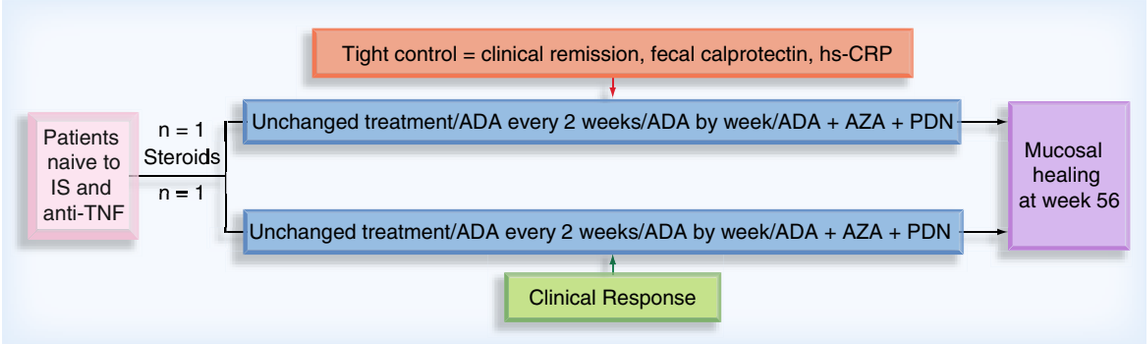

Figure 4. Tight control of the disease (clinical and biomarker) on mucosal healing in Crohn's disease at 1 year.
ADA: Adalimumab; AZA: Azathioprine; hs-CRP: high-sensitivity CRP; IS: Immunosuppressants; PDN: Prednisone.

receiving combination therapy with IFX and immunosuppressant in CD [43]. In this series of 223 patients with IFX, 158 received combination therapy and 65 monotherapy with anti-TNF. Of the 158 patients, 117 had discontinued the immunosuppressant after a median of 13 months of combination therapy. Median follow up was 40 months, 29 months after cessation of immunosuppressant. During follow up, 49% of patients had a flare of their disease requiring optimization of IFX. Of the 117 patients who discontinued the immunosuppressant, 21 had to stop IFX (7 and 14, respectively, for adverse loss of response). The authors have evaluated the impact of residual trough serum IFX rate and CRP at the time of immunosuppressant interruption to predict loss of response to IFX. The determination of serum IFX was measured with a specific home-made ELISA assay with a detection limit of 0.3 µg/ml. Two prognostic factors of loss of response to IFX after interruption of immunosuppressant were identified as undetectable serum IFX rate and CRP greater than 5 mg/l [43].

The interest to use serum IFX seems clearly established in this situation. However, variations in the results of these assays are, to date, limiting to their routine use.

Arias *et al.* have also conducted a randomized controlled trial (TAXIT) in IFX responding IBD patients treated in maintenance [44]. The aim of the study was to compare the efficacy of 1-year treatment with IFX maintenance strategy based on trough serum IFX levels versus an approach based only on the symptoms. This study is ongoing and only preliminary results were presented at the congress. The prerequisite before randomization was that all patients have the same trough serum IFX. Levels between 3 and 7 µg/ml were found to be optimal and preset for the patient population. In patients with low trough serum IFX, the optimization of IFX cannot only restore a trough serum IFX therapeutic but also to decrease CRP levels.

There are few data on the use of trough serum IFX in UC. The Louvain team has investigated whether trough serum IFX measured at week 14 were predictive of optimization and failure of IFX in their cohort of patients treated for UC refractory maintenance. Among the 135 patients, 50% were optimized with a 61% efficacy. Overall, a low trough serum IFX at week 14 was associated with optimization and failure of IFX. A threshold of 7.19 µg/ml was the most discriminating for predicting relapse of UC treated by IFX, with AUC of 0.67. These results are consistent with those from Bortlik *et al.* who have demonstrated that CD patients with TRI up to 3 µg/ml present a significantly more sustained clinical remission than patients with TRI above 3 µg/ml.

The impact of antibodies to IFX on clinical response are, however, confounding. In a recent meta-analysis, the authors have concluded that the presence of antibodies to IFX was significantly associated with relapse under IFX. However, there was a strong heterogeneity in this analysis.

For ADA, data regarding the impact of ADA trough levels and antidrug antibodies (ADAb) are very scarce. In an observational study, Karmiris *et al.* report the absence of correlation between trough levels of ADA and short-term evolution of CD. Conversely, when the authors analyzed the interruption of ADA at 24 weeks, this group of patients present significantly low levels of ADA at week 4, 8 and 12 than in patients under ADA treatment up to 24 weeks. Moreover, West *et al.* have also reported the impact of ADAb in a small cohort of 30 CD patients under ADA. Patients with detectable ADAb present a very higher failure to ADA.

These data could help to propose a new algorithm for treating patients using TNF blockers (Figure 5).

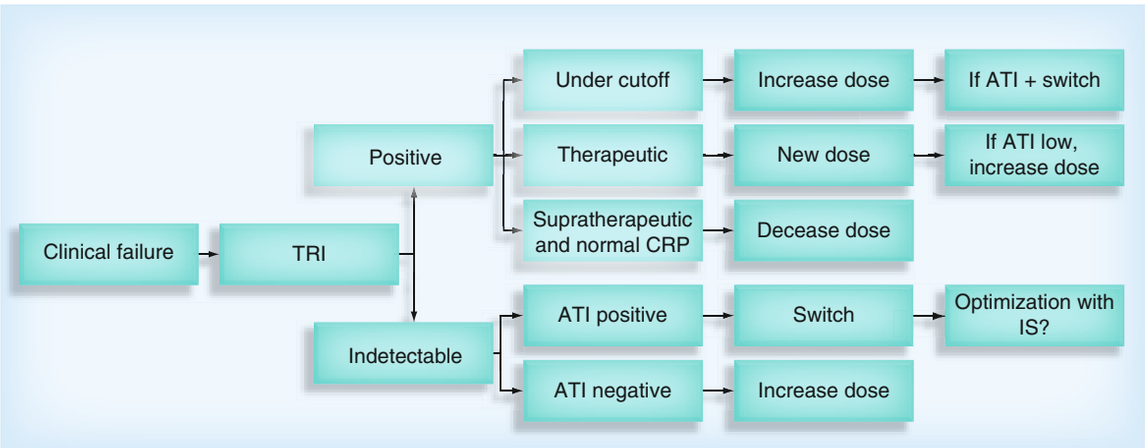

Figure 5. Therapeutic algorithm for inflammatory bowel disease patients in function of trough residual level of infliximab or antibodies to anti-TNF.

ATI: Antibodies to infliximab; IS: Immunosuppressants; TRI: Trough residual infliximab.

Table 3. Clinical response, clinical remission, mucosal healing and change in Inflammatory Bowel Disease Questionnaire score for golimumab versus placebo at week 6.

Treatment group	Randomized patients (n)	Clinical response (%)	Clinical remission (%)	Mucosal healing (%)	Change in IBDQ score (range)
Placebo	256	29.7	6.3	28.5	14.6
GLM 200 mg/100 mg	257	51.8*	18.7*	43.2**	27.4*
GLM 400 mg/200 mg	258	55.9*	17.8***	45.3*	27*

*p < 0.0001; **p = 0.0005; ***p < 0.001.
GLM: Golimumab; IBDQ: Inflammatory Bowel Disease Questionnaire.

What is the future for patients with failure of anti-TNF?

Finally, anti-TNFα therapy is the most important treatment for IBD patients. However, primary non-responders are frequent and clinical recurrence under maintenance therapy is reported in 40% of cases. This part of the article will explain the most important targets of future treatments in IBD and to report the results of these news drugs in clinical practice.

New anti-TNFα

Golimumab (GLM) was evaluated in Phase II and III trials in induction therapy in patients with moderate-to-severe active UC despite current adequate treatment or who had previously failed and were naive to anti-TNF therapy [45].

Patients with Mayo scores between 6 and 12, inclusive, including endoscopic subscore ≥2, were randomized to receive placebo/placebo; GLM 200 mg/100 mg; GLM 400 mg/200 mg at week 0 and 2, respectively. The primary end point was clinical response at week 6. Secondary end points at week 6 are clinical remission, mucosal healing and change from the baseline in the Inflammatory Bowel Disease Questionnaire (Table 3) [45].

The impact of GLM in maintenance was reported in a multicenter, randomized trial. All included patients have presented a clinical response after the induction study. In these UC patients, two doses of GLM were compared with placebo:

- Placebo (n = 156);
- GLM 50 mg/4 weeks subcutaneously (n = 153);
- GLM 100 mg/4 weeks subcutaneously (n = 154).

The rates of clinical remission at week 54 were, respectively, for GLM 50 and 100 mg and placebo, 23.5, 26.6 and 15.4% with $p < 0.05$ when GLM 100 mg was compared with placebo.

Patients who had previously failed in anti-TNF therapy were not included in this study, this finally not allowing to know the impact of GLM in second line of anti-TNF therapy.

Similarly, the development of a vaccine against TNFα (TNF kinoid) has demonstrated promising results in animal models of chronic inflammation and rheumatoid arthritis. The TNF-kinoid was moved into Phase I/II clinical trials in patients with moderately to severely active CD [46]. Three intramuscular injections were carried out on day 0, 7 and 28. The results indicated that TNF-kinoid was well tolerated with no serious side effects (Table 4).

This trial has also demonstrated a decrease of fecal calprotectin and an endoscopic improvement. However, such approaches remain highly discuss in term of safety and long-term efficacy.

Therapies targeting mucosal intestinal immunity

New molecules are actively researched based on new knowledge of the disease and physiopathological mechanisms. One of the supposed mechanism for the pathogenesis of IBD could be a high leukocytic infiltration of the intestinal mucosa. Extravasation of leukocytes from the blood into stromal tissues is carried out in several steps. Initially, leukocytes tether to the vascular endothelium through interactions between integrins on leukocytes and their ligands on the endothelial surface. Integrins are heterodimer proteins composed of an α and a β chain. These integrins, when activated by chemokines, allow leukocytes to adhere to the endothelium and then to cross it and enter the mucosa by a paracellular pathway [47]. An important integrin involved in the pathogenesis of IBD is the α4β7 integrin, which is expressed on T cells and facilitates their binding to MAdCAM-1 [48].

An anti-MAdCAM-1 trial (PF-547659) has recently been launched [49]. In total, 80 UC patients were included, receiving anti-MAdCAM versus placebo. Response rates at week 12 were 42 versus 21%, respectively. Remission was achieved for 22% of patients receiving the drug versus 0% in the placebo group [49]. A similar study is ongoing in CD [101].

Vedolizumab is an antibody that specifically targets α4β7 integrin. Its specificity has been studied

by immunohistochemistry and demonstrates its high capacity to bind to the GI tract [50]. A Phase II trial has demonstrated the efficacy of vedolizumab for the induction of clinical and endoscopic remission in 181 patients with active UC [51]. Patients have received 0.5 or 2 mg/kg of vedolizumab versus placebo iv. The results are summarized on Table 5. The rate of side effects was similar in all treatment groups.

A similar trial was conducted in 185 patients with active CD [52]. At day 57, 37 and 30% of patients treated with vedolizumab at 2.0 and 0.5 mg/kg, respectively, had achieved clinical remission compared with 21% in the placebo group (p = 0.04 for 2.0 mg/kg vs placebo).

A first randomized Phase III, placebo-controlled, double-blind, multicenter trial (GEMINI I) studying the efficacy and safety of vedolizumab as induction therapy in patients with moderate to severe active UC in whom at least one prior therapy had failed has reported promising results (Tables 6 & 7) [53].

Similarly, the maintenance study confirms the superiority of vedolizumab in UC. It was a multicenter, randomized study that compared two doses of vedolizumab (iv. 300 mg/4 week or iv. 400 mg/8 week) and placebo. At week 52, clinical remission was, respectively, for vedolizumab/4 weeks, vedolizumab/8 weeks and placebo, 44.8, 41.8 and 15.9% (p < 0.001). Healing mucosa at week 52 was, respectively 56, 51.6 and 19.8% for each arm. Moreover, in patients who respond to induction treatment, vedolizumab is clearly effective for maintenance therapy in UC patients. Vedolizumab every 4 weeks seems to be no more effective than every 8 weeks.

Vedolizumab has been also studied in CD. GEMINI II is a randomized, placebo-controlled, double-blind, multicenter Phase III trial studying induction and maintenance in patients with moderately to severe activity. The induction phase was evaluated in 368 patients. Patients were randomized 3:2 to receive iv. vedolizumab 300 mg or placebo on day 1 and 15. The primary end points were clinical remission (CDAI Phase II 150) and clinical response (decrease of more than 100 points of CDAI from baseline) at week 6 (Table 8).

In this trial, it is important to note that 48% of the patients had prior anti-TNFα failure, with 55% of primary failure and 27% of second failure.

The maintenance phase has been studied in patients who have responded to the induction phase (decrease at week 6 of more than 70 CDAI points from baseline). Patients were randomized to receive either vedolizumab 300 mg iv. every 4 or 8 weeks, or placebo. Of the 1115 patients enrolled and who received the induction phase, 461 were included in the maintenance phase. The primary end point was clinical remission (CDAI Phase II 150) at week 52. The secondary end point was

Table 4. Efficacy of TNF-kinoid on clinical response and remission.

Week	Clinical response (%)	Clinical remission (%)
4	66	36
8	70	78
12	78	45

Table 5. Clinical and endoscopic remission at week 6: vedolizumab 0.5 or 2.0 mg/kg versus placebo in active ulcerative colitis.

Tretment	Clinical remission	Endoscopic remission
Placebo	14	8
Vedolizumab 0.5 mg/kg	33*	28**
Vedolizumab 2.0 mg/kg	32*	12**

*p < 0.02; **p < 0.007.

Table 6. Clinical response, clinical remission and mucosal healing at week 6.

	Clinical response (%)	Clinical remission (%)	Mucosal healing (%)
Placebo (n = 149)	25.5	5.4	24.8
Vedolizumab (n = 225)	47.1	16.9	40.9
Differences	21.6*	11.5**	16.1***

*p<0.001; **p = 0.001; ***p = 0.0013.

Table 7. Clinical response and remission at week 6 in patients with prior anti-TNF failure and without anti-TNF exposure.

	Clinical response (%)	Clinical remission (%)
Patients with prior anti-TNF failure		
Placebo (n = 63)	20.6	3.2
Vedolizumab (n = 82)	39	9.8
Difference	18.4	6.6
95% CI	3.9–32.9	9.8–22.8
Patients without prior anti-TNF exposure		
Placebo (n = 76)	26.3	6.6
Vedolizumab (n = 118)	53.1	23.1
Difference	26.8	16.5
95% CI	13.7–39.9	2.4–30.2

Table 8. Clinical remission and clinical response in the GEMINI II trial at week 6.

Treatment	Clinical remission, week 6 (%)*	Clinical response, week 6 (%)**
Placebo (n = 148)	6.8	25.7
Vedolizumab (n = 220)	14.5	31.4

*p = 0.206; **p = 0.2322.

Table 9. Study of vedolizumab on the maintenance phase.

Treatment	Clinical remission at week 52 (%; p value)	Clinical response at week 52 (%; p value)	Corticosteroid-free remission at week 52 (%; p value)
Placebo (n = 153)	21.6	30.1	15.9†
Vedolizumab every 4 weeks (n = 154)	36.4 (0.0042)	45.5 (0.053)	28.8‡ (0.045)
Vedolizumab every 8 weeks (n = 154)	39 (0.007)	43.5 (0.0132)	31.7§ (0.0154)

†n = 82. ‡n = 80. §n = 82.

clinical response (decrease of more than 100 points of CDAI from baseline) and corticosteroid-free remission at week 52 (Table 9).

In addition to develop alternative ways to target TNFα, many approaches actually target other pro-inflammatory cytokines such as IL-12/-23 or -6.

IL-12/-23 pro-inflammatory cytokines are composed of p40 subunit and are implied in induction and maintenance of inflammatory response. Ustekizumab targets the p40 subunit of those cytokines. Ustekizumab has been tested in a Phase II trial in patients with moderate to severe active CD with promising results [54–56]. After 6 weeks of treatment, clinical response rates were significantly higher in patients receiving ustekizumab (58%) compared to the placebo (30%). However, at 8 weeks, rates were not significantly different between ustekizumab (49%) and placebo (40%). The long-term response is still unknown, but it is interesting that a subgroup who had first responded to anti-TNFα therapy had a higher response rate than the placebo group. This effect was also studied in another trial in which 59% of patients who were previously treated with IFX, also responded to ustekizumab, compared to 26% of patients treated with placebo only. A recent multicenter Phase IIb trial in patients with moderate-to-severe active CD who were unresponsive to IFX was also realized. Those patients who have responded to ustekizumab have received maintenance therapy (Table 10).

However, there was no difference between the two groups for clinical remission (Table 8). The results of those three trials demonstrate that ustekizumab may be useful in patients who had failed to respond to previous treatment with anti-TNFα therapy.

Table 10. Clinical response at week 6 and 22, and clinical remission at week 22 in Crohn's disease patients treated with ustekizumab versus placebo group.

Treatment	Clinical response week 6 (%)	Clinical response week 22 (%)	Clinical remission week 22 (%)
Ustekizumab	39.7	69.4	41.7
Placebo	23.5*	42.5**	27.4

*p = 0.005; **p < 0.001.

Already approved as a second-line treatment for patients with rheumatic polyarthritis who have failed to respond to other therapies, tocilizumab is a monoclonal antibody to the IL-6 receptor. Tocilizumab has only been studied in one controlled Phase I trial with 36 active CD patients. The results indicate that 80% of patients who were treated biweekly with an iv. perfusion of tocilizumab for 12 weeks experienced a clinical response, compared to 31% in the placebo group. However, only 20% of the tocilizumab-treated patients were in clinical remission [57].

Another target to prevent the infiltration of leukocytes is to block the chemokines axis, which allows, in combination with integrins, a paracellular pathway into the intestinal mucosa. CCR9 seems to be the key chemokine receptor in the inflammation of intestinal mucosa. CCX282-B (Traficet-EN), an inhibitor molecule of CCR9, was studied in a double-blinded, placebo-controlled, Phase II/III trial (PROTECT-1). In induction, 436 patients were included with moderate-to-severe CD and received placebo or CCX282-B at a dose of 250 or 500 mg once a day or 250 mg twice a day. The primary end point, which was a decrease in the CDAI score of 100 points at week 12, occurred in 48, 55, 42 and 40 patients receiving CCX282-B at doses of 250 or 500 mg once a day (p = 0.029) or 250 mg twice a day, respectively, compared with 40% of patients receiving placebo. After induction by CCX282-B, remission was maintained for 36 weeks in 50% of the treated patients. It also indicated that 19% of the CCX282-B group had normal levels of CRP compared to 9% in the placebo group [58]. A Phase III trial is ongoing with this molecule.

Some cytokines are also useful for lymphocytes activation, function and proliferation. Those cytokines enter in the JAK pathway. Tofacitinib (Tf) is an inhibitor of JAK 1, 2 and 3 kinases. Tf was studied in UC in a doubled-bind, placebo-controlled, Phase II trial [59]. This trial has evaluated its efficacy in 194 patients with moderate-to-severe active UC. Those patients were randomized to receive Tf at doses of 0.5, 3, 10 or 15 mg, or placebo twice daily for 8 weeks (Table 11). The primary end point was the clinical response at

Table 11. Efficacy of tofacitinib in Phase II trial.

Treatment	End point at week 8			
	Clinical response (%; p value)	Clinical remission (%; p value)	Endoscopic response (%; p value)	Endoscopic remission (%; p value)
Placebo (n = 48)	42 (NA)	10 (NA)	46 (NA)	2 (NA)
Tf 0.5 mg (n = 31)	32 (0.59)	13 (0.76)	52 (0.64)	10 (0.14)
Tf 3 mg (n = 33)	48 (0.55)	33 (0.01)	58 (0.30)	18 (0.01)
Tf 10 mg (n = 33)	61 (0.10)	48 (<0.001)	67 (0.07)	30 (<0.001)
Tf 15 mg (n = 49)	78 (<0.001)	41 (<0.001)	78 (<0.001)	27 (<0.001)

Tf: Tofacitinib.

8 weeks. The secondary end points were clinical remission, endoscopic response and endoscopic remission at 8 weeks.

Future perspective

New drugs will certainly be available for treatment of UC and CD in the near future. However, for now, we have to optimize our strategies (Table 12). If the concept of combotherapies is clear and could change the story of these diseases, an essential axiom of any early treatment paradigm is recognition that overtreatment of low-risk patients will result in a poor therapeutic index. Consequently, it is essential to identify patients who are suitable for early treatment because they are at high risk of disease progression. Moreover, benefits must always be carefully weighed against risks. The cellular and molecular pathways of IBD are increasingly better understood. We hope in the future that it will be possible to observe for each patient the role of each abnormality. So, it is difficult to envisage new strategies without those data and to treat in a personalized manner, depending on the individual mechanistic analysis.

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Table 12. Summary of the drugs tested or under evaluation for the treatment of inflammatory bowel diseases patients.

Drugs	Phase of trial	Type of IBD	Treatment	Duration (weeks)	Results
Ustekinumab	IIa	CD	I	6	Positive
Ustekinumab	IIb	CD	I and M	6–22	Positive
TNF kinoid	I/II	CD	I	12	Positive
Anti-MadCam	II	CD	I	12	Positive
Anti-MadCam	II	UC	I	12	Positive
Anti CCR9	II/III	CD	I and M	12–36	Positive
Tofacitinib	IIb	UC	I	8	Positive
Golimumab	III	UC	I and M	6/54	Positive
Vedolizumab	III	UC	I and M	6/52	Positive
Vedolizumab	III	CD	I and M	6/52	Positive
Anti-MadCam	III	UC	I and M	–	In progress
Anti-MadCam	III	CD	I and M	–	In progress
Ustekinuab	III	CD	I and M	–	In progress
Anti IL6	III	CD	I and M	–	In progress
Anti CCR9	III	CD	I and M	–	In progress

CD: Crohn's disease; I: Induction; IBD: Inflammatory bowel disease; M: Maintenance; UC: Ulcerative colitis.

Executive summary

- Utilization of pharmacological biomarkers (ADA, ADAb) is important for optimization of treatment. New algorithms are proposed for treatment under biotherapies.
- New drugs, such as vedolizumab and golimumab, have recently confirmed their efficacy in large Phase III trials in ulcerative coltis. The results of Phase III trials with tofacitinib in these patients are yet to be released.
- For Crohn's disease, the results of Phase III trials with ustekinumab are awaited. Recently, Phase IIb trials with this drug reported efficacy compared with placebo.
- Several Phase II and III trials are currently investigating new drugs for the treatment of inflammatory bowel disease patients, such as anti-CCR9, anti-MAdCAM and anti-IL6.
- In the future, a mechanistic approach and personalized treatment will be possible. For Crohn's disease, analyses of innate immunity and pattern recognition receptors (NOD2/CARD15, TLRs), and autophagy (IRGM, ATG16L1, MTMR3); for ulcerative coltis, analyses of barrier integrity (GNA12, HNF4A, Laminin B1, ECM1 CDH1) will be performed.

References

Papers of special note have been highlighted as:

- ▪ of interest
- ▪▪ of considerable interest

1 Blondel-Kucharski F, Chircop C, Marquis P *et al.* Health-related quality of life in Crohn's disease: a prospective longitudinal study in 231 patients. *Am. J. Gastroenterol.* 96, 2915–2920 (2001).

2 Louis E, Collard A, Oger AF *et al.* Behaviour of Crohn's disease according to the Vienna classification: changing pattern over the course of the disease. *Gut* 49, 777–782 (2001).

3 Cosnes J, Cattan S, Blain A *et al.* Long-term evolution of disease behavior of Crohn's disease. *Inflamm. Bowel Dis.* 8, 244e50 (2002).

4 Thia KT, Sandborn WJ, Harmsen WS *et al.* Risk factors associated with progression to intestinal complications of Crohn's disease in a population-based cohort. *Gastroenterology* 139, 1147e55 (2010).

5 Jess T, Riis L, Vind I *et al.* Changes in clinical characteristics, course, and prognosis of inflammatory bowel disease during the last 5 decades: a population-based study from Copenhagen, Denmark. *Inflamm. Bowel Dis.* 13, 481–489 (2007).

6 Bernell O, Lapidus A and Hellers G, Risk factor for surgery and recurrence in 907 patients with primary ileocaecal Crohn's disease. *Br. J. Surg.* 87, 1697–1701 (2000).

7 Pariente B, Cosnes J, Danese S *et al.* Development of the Crohn's disease digestive damage score, the Lemann score. *Inflamm. Bowel Dis.* 17, 1415–1422 (2011).

▪ **This score will most likely be incorporated in future trials. It represents the past and present of inflammatory bowel disease research.**

8 Lichtenstein GR, Hanauer SB, Sandborn WJ. Management of Crohn's disease in adults. *Am. J. Gastroenterol.* 104, 465–483 (2009).

9 Travis SP, Stange EF, Lemann M *et al.* European evidence based consensus on the diagnosis and management of Crohn's disease: current management. *Gut* 55(Suppl. 1), i16e35 (2006).

10 Carter MJ, Lobo AJ, Travis SP. Guidelines for the management of inflammatory bowel disease in adults. *Gut* 53(Suppl. 5), V1–16 (2004).

11 Candy S, Wright J, Gerber M *et al.* A controlled double blind study of azathioprine in the management of Crohn's disease. *Gut* 37, 674–678 (1995).

12 Sans M, Lopez-San Roman A, Esteve M *et al.* Early use of azathioprine has a steroid sparing effect on recently diagnosed Crohn's disease patients. Presented at: *Digestive Disease Week*. Chicago, IL, USA 7–10 May 2011.

13 Cosnes J, Bourrier A, Bouhnik Y *et al.* Accelerated step-care therapy with early azathioprine (AZA) vs. conventional step-care therapy in Crohn's disease. A randomized study. *Gastroenterology* 142(5), S-161 (2012).

14 Lemann M, Mary JY, Duclos B *et al.* Infliximab plus azathioprine for steroid-dependent Crohn's disease patients: a randomized placebo-controlled trial. *Gastroenterology* 130, 1054–1061 (2006).

15 D'Haens G, Baert F, van Assche G *et al.* Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. *Lancet* 371, 660–667 (2008).

▪▪ **The concept of top-down strategy for early Crohn's disease (CD). For the first time, the authors analyzed a top-down strategy in comparison with a top-up treatment.**

16 Colombel JF, Sandborn WJ, Reinisch W *et al.* Infliximab, azathioprine, or combination therapy for Crohn's disease. *N. Engl. J. Med.* 362, 1383–1395 (2010).

▪ **Combotherapy was more effective in CD than azathioprine or infliximab alone in patients naive to immmunomudulators.**

17 Feagan BG, MacDonald V, Panaccione R *et al.* A randomized trial of methotrexate in combination with infliximab for the treatment of Crohn's disease. *Gastroenterology* 135, 294–295 (2008).

18 Schoepfer AM, Vavricka S, Zahnd-Straumann N *et al.* Monitoring inflammatory bowel disease activity: clinical activity is judged to be more relevant than endoscopic severity or biomarkers. *J. Crohns Colitis* 6, 412–418 (2012).

19 Hanauer SB, Feagan BG, Lichtenstein GR *et al.* Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 359(9317), 1541–1549 (2002).

20 Rutgeerts P, Diamond RH, Bala M *et al.* Scheduled maintenance treatment with infliximab is superior to episodic treatment for the healing of mucosal ulceration associated with Crohn's disease. *Gastrointest. Endosc.* 63, 433–442 (2006).

21 Rutgeerts P, Van Assche G, Sandborn WJ *et al.* Adalimumab induces and maintains mucosal healing in patients with Crohn's disease: data from the EXTEND trial. *Gastroenterology* 142, 1102–1111 (2012).

22 Colombel JF, Rutgeerts P, Sandborn WJ *et al.* Deep remission for adalimumab-treated patients with moderate to severe ileocoloc Crohn's disease. *J. Crohns Colitis* 4, S10 (2010).

23 Schnitzler F, Fidder H, Ferrante M *et al.* Mucosal healing predicts long-term outcome of maintenance therapy with infliximab in Crohn's disease. *Inflamm. Bowel Dis.* 15, 1295–1301 (2009).

24 Frøslie KF, Jahnsen J, Moum BA *et al.* Mucosal healing in inflammatory bowel disease: results from a Norwegian population-based cohort. *Gastroenterology* 133, 412–422 (2007).

25 Louis E, Mary JY, Vernier-Massouille G *et al.* Maintenance of remission among patients with Crohn's disease on antimetabolite therapy after infliximab therapy is stopped. *Gastroenterology* 142, 63–70 (2012).

26 Schoepfer AM, Beglinger C, Straumann A *et al.* Fecal calprotectin correlates more closely with the Simple Endoscopic Score for Crohn's disease (SES-CD) than CRP, blood leukocytes, and the CDAI. *Am. J. Gastroenterol.* 105, 162–169 (2010).

■ **Reports that calprotectin could be a marker of substitution of endoscopy in CD patients.**

27 Sipponen T, Savilahti E, Kolho KL *et al.* Crohn's disease activity assessed by fecal calprotectin and lactoferrin: correlation with Crohn's disease activity index and endoscopic findings. *Inflamm. Bowel Dis.* 14, 40–46 (2008).

28 Gisbert JP, Bermejo F, Pérez-Calle JL *et al.* Fecal calprotectin and lactoferrin for the prediction of inflammatory bowel disease relapse. *Inflamm. Bowel Dis.* 15, 1190–1198 (2009).

29 Lewis JD. The utility of biomarkers in the diagnosis and therapy of inflammatory bowel disease. *Gastroenterology* 140, 1817–1826 (2011).

30 De Suray N, Salleron J, Vernier Massouille G *et al.* Close monitoring of CRP and calprotectin levels to predict relapse in Crohn's disease patients. A sub analysis of the STORI study. *J. Crohns Colitis* 1, S118 (2012).

31 Molander P, Af Björkesten CG, Mustonen H *et al.* Fecal calprotectin concentration predicts outcome in inflammatory bowel disease after induction therapy with TNFα blocking agents. *Inflamm. Bowel Dis.* 4. 18(11), 2011–2017 (2012).

32 Colombel JF, Sandborn WJ, Reinisch W *et al.* Infliximab, azathioprine, or combination therapy for Crohn's disease. *N. Engl. J. Med.* 362, 1383–1395 (2010).

33 Colombel JF, Sandborn WJ, Rutgeerts P *et al.* Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology* 132, 52–65 (2007).

34 Kiss LS, Szamosi T, Molnar T *et al.* Early clinical remission and normalisation of CRP are the strongest predictors of efficacy, mucosal healing and dose escalation during the first year of adalimumab therapy in Crohn's disease. *Aliment. Pharmacol. Ther.* 34, 911–922 (2011).

35 Jürgens M, Mahachie John JM, Cleynen I *et al.* Levels of C-reactive protein are associated with response to infliximab therapy in patients with Crohn's disease. *Clin. Gastroenterol. Hepatol.* 9, 421–427 (2011).

36 Denis MA, Reenaers C, Fontaine F *et al.* Assessment of endoscopic activity index and biological inflammatory markers in clinically active Crohn's disease with normal C-reactive protein serum level. *Inflamm. Bowel Dis.* 13, 1100–1105 (2007).

37 Moum B, Jahnsen J, Bernklev T. Fecal calprotectin variability in Crohn's disease. *Inflamm. Bowel Dis.* 16, 1091–1092 (2010).

38 Treton X, Bouhnik Y, Mary JY *et al.* Azathioprine withdrawal in patients with Crohn's disease maintained on prolonged remission: a high risk of relapse. *Clin. Gastroenterol. Hepatol.* 7, 80–85 (2009).

39 Armuzzi A, Van Assche G, Reinisch W *et al.* Results of the 2nd scientific workshop of the ECCO (IV): therapeutic strategies to enhance intestinal healing in inflammatory bowel disease. *J. Crohns Colitis* 6, 492–502 (2012).

40 Louis E, Baumgart DC, Ghosh S *et al.* What changes in inflammatory bowel disease management can be implemented today? *Crohns Colitis.* 6 (Suppl. 2), S260–S267 (2012).

41 Van Moerkercke W. Patients with mucosal healing had the highest trough levels followed by those with partial healing. Patients without healing had the lowest median trough levels. Presented at: *Digestive Disease Week 2010.* New Orleans, Louisiana, USA, May 1–5, 2010.

42 Maser EA *et al.* Association of trough serum infliximab to clinical outcome after scheduled maintenance treatment for Crohn's disease. *Clin. Gastroenterol. Hepatol.* 4(10), 1248–1254 (2006).

■■ **First observational study that reported the impact of trough residual level of infliximab on inflammatory bowel disease treatment and healing mucosa.**

43 Drobne D, Bossuyt PJ, Breynaer C *et al.* Crohn's disease: infliximab trough levels and CRP during infliximab-immunomodulator combination treatment are associated with clinical outcome after immunomodulator withdrawal. *J. Crohns Colitis* 5, P17 (2011).

44 Arias MT, Van de Casteele N, Drobne D *et al.* Importance of trough levels and antibodies on the long-term efficacy of infliximab therapy in ulcerative colitis. *J. Crohns Colitis* 6(Suppl. 1) S5 (2012).

45 Sandborn W, Feagan B. A Phase 2/3 randomized, placebo-controlled, double-blind study to evaluate She safety and efficacy of subcutaneous Golimumab Induction Therapy in patients with moderately to severely ulcerative colitis. Presented at: *Digestive Disease Week 2012.* San Diego, CA, May 19–22, 2012.

46 Vandepapeliere P *et al.* Efficacy of vaccination antagonist TNF in Crohn's disease. Presented at: *Digestive Disease Week 2011.* Chicago, IL, USA, May 7–10, 2011.

47 Barreiro O, Sanchez-Madrid F. Molecular basis of leukocyte-endothelium interactions during the inflammatory response. *Rev. Esp. Cardiol.* 62, 552–562 (2009).

48 Agace W. Tissue-tropic effector T-cells: generation and targeting opportunities. *Nat. Rev. Immunol.* 6, 682–692 (2006).

49 Vermeire S, Ghosh S, Panes J *et al.* The mucosal addressin cell adhesion molecule antibody PF-547659 in ulcerative colitis: a randomized study. *Gut* 60, 1068–1075 (2010).

■ **First Phase II trial to report the interest of anti-MAdCAM drug induction in ulcerative colitis.**

50 Soler D, Chapman T, Yang L *et al.* The binding specificity and selective antagonism of Vedolizumab, an α4β7 integrin therapeutic antibody in development for inflammatory bowel diseases. *J. Pharmacol. Exp. Ther.* 330, 864–875 (2009).

51 Feagan B, Greenberg G, Wild G *et al.* Treatment of ulcerative colitis with a humanized antibody to the α 4β 7 integrin. *N. Engl. J. Med.* 352, 2499–2507 (2005).

52 Feagan B, Greenberg G, Wild G *et al.* Treatment of active Crohn's disease with MLN0002, a humanized antibody to the α 4β 7 integrin. *Clin. Gastroenterol. Hepatol.* 6, 1370–1377 (2008).

53 Feagan B, Rutgeerts P *et al.* Vedolizumab induction therapy for ulcerative colitis: results of GEMINI I, a randomized, placebo-controlled, double-blind, multicenter Phase III trial. Presented at: *Digestive Disease Week 2012.* San Diego, CA, USA, May 19–22, 2012.

54 Sandborn W, Feagan B, Fedorak R *et al.* A randomized trial of Ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with moderate to severe Crohn's disease. *Gastroenterology* 35, 1130–1141 (2008).

55 Toedter G, Blank M, Lang Y *et al.* Relashionship of C-reactive protein with clinical response after therapy with ustekinumab in Crohn's disease. *Am. J. Gastroenterol.* 104, 2768–2773 (2009).

56 Sandborn W, Gasink C, Gao L *et al.* Ustekinumab induction and maintenance therapy in refractory crohn's disease. *N. Eng. J. Med.* 367, 1519–1528 (2012).

■■ **Reports the efficacy of ustekinumab in CD patients who had failed on anti-TNF therapies.**

57 Ito H, Takazoe M, Fukuda Y *et al.* A pilot randomized trial of a human anti-interleukin-6 receptor monoclonal antibody in active Crohn's disease. *Gastroenterology* 126, 989–996 (2004).

58 Keshav S, Johnson D, Schall T *et al.* Chemokine receptor antagonist CCX282-B (Traficet En) maintained remission of Crohn's disease in PROTECT-1 study. Presented at: *Digestive Disease Week 2010*. New Orleans, LA, USA, 1–5 May 2010.

59 Sandborn WJ, Ghosh S, Panes J *et al.* Tofacitinib, an oral janus kinase inhibitor, in active ulcerative colitis. *N. Eng. J. Med.* 367, 612–624 (2012).

■■ **Reports the interest of tofacitinib in ulcerative colitis patients at induction.**

■ Website

101 ClinicalTrial Database: NCT01276509. www.clinicaltrials.gov/ct2/show/NCT01276509