Review article: infliximab for Crohn’s disease treatment – shifting therapeutic strategies after 10 years of clinical experience

S. Danese*, J.-F. Colombel†, W. Reinisch‡ & P. J. Rutgeerts§

*Division of Gastroenterology, Instituto Clinico Humanitas, IRCCS in Gastroenterology, Milan, Italy.
†Department of Hepato-Gastroenterology, Hospital Huriez, Lille, France.
‡Abteilung Gastroenterologie und Hepatologie, Universitätsklinik Innere Medizin III, Vienna, Austria.
§Department of Gastroenterology, University Hospitals Leuven, Leuven, Belgium.

Correspondence to:
Dr S. Danese, IBD Unit, Division of Gastroenterology, Instituto Clinico Humanitas, IRCCS in Gastroenterology, Via Manzoni 56, Rozzano, Milan 20089, Italy.
E-mail: sdanese@hotmail.com

Publication data
Submitted 25 August 2010
First decision 22 September 2010
Resubmitted 19 January 2011
Accepted 20 January 2011
EV Pub Online 15 February 2011

This commissioned review article was subject to full peer-review.

SUMMARY

Background
Crohn’s disease is a progressive condition, with most patients developing a penetrating or stricturing complication over time. A decade ago, treatment goals consisted of immediate symptomatic control. The introduction of anti-tumour necrosis factor (anti-TNF) therapies, however, has changed the way patients with Crohn’s disease are treated. Over 10 years of clinical data and experience have demonstrated these therapies to be highly effective in Crohn’s disease.

Aim
To provide clinicians guidance on optimising treatment with anti-TNF therapies in Crohn’s disease by introducing an evidence- and personal opinion-based treatment algorithm using infliximab initial anti-TNF therapy.

Methods
Scientific literature was reviewed using MEDLINE to evaluate data on clinical trials with infliximab in luminal and fistulising Crohn’s disease.

Results
The data from several landmark infliximab trials have changed clinical practice and led to a readjustment of treatment goals in Crohn’s disease, allowing patients to achieve more than just symptomatic relief including sustained steroid-free remission. Infliximab induces complete mucosal healing and reduces the rates of hospitalisation and surgery. Based on disease-related risk factors, a treatment algorithm for infliximab is delineated in favour of a rapid step-up approach in patients at high risk for a disabling course of disease.

Conclusion
Adopting the suggested treatment algorithm for infliximab into clinical routine is aimed to optimise outcomes for patients with Crohn’s disease.

Aliment Pharmacol Ther 2011; 33: 857-869
INTRODUCTION
Crohn’s disease (CD) is a progressive disease that can be subdivided into three phenotypes: inflammatory, stricturing and penetrating. Initially, inflammatory disease is present in the majority of patients with CD. Over time, however, most patients will develop a penetrating or stricturing complication, because of uncontrolled inflammation. Within 20 years, 88% of patients will experience either stricturing (18%) or penetrating fistulising disease (70%).

The course of CD is heterogeneous and the progression of the disease varies considerably between patients. Many patients (43%) suffer a very severe initial flare and then experience few symptoms over the next 10 years. The majority of patients (51%), however, experience chronic continuous (19%) or relapsing/remitting symptoms (32%). In an inception cohort of 373 patients with CD, Munkholm et al. showed that many patients (45%) with active CD in the initial years continued to have chronically active disease over subsequent years (follow-up 8 years). Fifty percent had a chronic remitting disease course, while only 5% had inactive disease after 8 years.

The ultimate treatment goal in the management of CD should be to strive to change the underlying course of CD and restore normal bowel function. This requires the suppression of the underlying inflammation and the induction of complete mucosal healing. Mucosal healing has been associated with a reduction in serious complications (hospitalisation and surgery) and is an attainable goal with appropriate treatment.5–7

WHEN TO START ANTI-TUMOUR NECROSIS FACTOR THERAPY
There is a potential window of opportunity to influence the long-term evolution of CD early in the disease course when it is primarily inflammatory. Anti-tumour necrosis factor (anti-TNF) therapy is indicated in steroid-refractory, steroid-dependent and/or immunomodulator-refractory luminal CD and in patients intolerant to these conventional therapies. Additionally, anti-TNF therapy in conjunction with surgical drainage is indicated in complex fistulas in CD. Whether combination therapy improves efficacy is a key question, which may depend on the patient population. The risks of combined immunosuppression should be considered, especially in children, young adults or the elderly. The thiopurine immunomodulators 6-mercaptopurine (MP) and mercaptopurine (MP) are frequently prescribed for patients in whom first-line therapies fail – in particular, those who are dependent on or do not have a response to systemic corticosteroids. When starting biological therapy in patients with CD naive to thiopurines the combination of an anti-TNF agent and AZA is better for induction of remission and mucosal healing over 1 year. Whether combination therapy could improve outcomes from each of the anti-TNF agents remains unknown.

Two anti-TNF therapies are available for treatment of patients with CD (Table 1). Infliximab (intravenous infusion) was licensed for use in CD in the US in 1998 and in Europe in 1999. Current use of infliximab has evolved based on evidence from clinical trials. Furthermore, infliximab has the broadest inflammatory bowel disease (IBD) label available in Europe and is approved for adult luminal and fistulising CD, paediatric luminal CD and adult ulcerative colitis (UC). Adalimumab (subcutaneous injection) was also licensed for use in CD in Europe and in the US in 2007.

Over the past decade, the efficacy of anti-TNF has been demonstrated in various patient groups, including patients with different disease durations and previous Table 1 | European indications for infliximab and adalimumab in Crohn’s disease (CD) and/or ulcerative colitis (UC)

| Treatment of severe, active CD in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant, or who are intolerant to or have medical contraindications for such therapies |
| Treatment of fistulising, active CD in adult patients who have not responded despite a full and adequate course of therapy with conventional treatment (including antibiotics, drainage and immunosuppressive therapy) |
| Treatment of severe, active CD in paediatric patients aged 6-17 years who have not responded to conventional therapy, including a corticosteroid, an immunomodulator and primary nutrition therapy, or who are intolerant to or have contraindications for such therapies |
| Treatment of moderately to severely active UC in adult patients who have had an inadequate response to conventional therapy, including corticosteroids and mercaptopurine or azathioprine, or who are intolerant to or have medical contraindications for such therapies |
exposure to conventional therapies.5, 14–23 The spectrum of anti-TNF trials has provided lessons on an optimised way to treat patients with CD and raised the threshold for treatment goals. It is now clear that CD treatment must go beyond simply providing symptomatic control and aim to change the course of the disease. The anti-TNF clinical trial data have raised awareness and expectations of what treatment goals can be achieved (Table 2).24, 25 Mucosal healing is becoming an increasingly important parameter, as in some studies it has been shown to be linked with reductions in hospitalisations and surgeries as well as long-term remission. Achieving these goals will require rapid and sustained control of inflammation and appropriate management with earlier, more intensive use of biological therapy in most patients.

Recently, SONIC (Study Of biologic and immunomodulator-Naïve patients In Crohn’s disease) was conducted in AZA-naïve patients with moderate to severe CD (mean duration 2.3 years) and demonstrated that infliximab monotherapy or infliximab plus AZA combination therapy is superior to AZA alone in immunomodulator-naïve patients.16 SONIC also showed that the best results were achieved in patients with a high inflammatory burden [high C-reactive protein (CRP) and/or mucosal lesions] at baseline.16 This trial is a landmark paper for CD management and has profound therapeutic implications for clinical practice.

Practical matters, such as patient preference regarding the mode of administration, may play a role in the selection of adalimumab as initial anti-TNF therapy.26 The current European Crohn’s and Colitis Organisation (ECCO) consensus in CD management states that ‘All currently available anti-TNF therapies appear to have similar efficacy and adverse-event profiles, so the choice depends on availability, route of delivery, patient preference, cost and national guidance.’27 A qualitative study of patient preferences of anti-TNF agents in rheumatoid arthritis suggests that younger patients are more confident about self-administering treatment and slightly prefer the convenience of subcutaneous dosing, whereas older patients prefer the perceived safety of infusion in a clinic.28 Decisions should be made on an individual basis and consider the preferences of both the patient and physician.16, 27

This article will review the infliximab clinical trial data and introduce an evidence-based infliximab treatment algorithm for the management of luminal and complex fistulising CD, based on the clinical data and expert opinion, and will discuss the clinical and practical implications of the SONIC trial in the daily management of CD.

### Identifying Patients with Progressive Disease (Including Fistulising Disease)

The treatment of patients with CD should be customised according to factors that predict progressive disease. The ECCO consensus on the management of CD recognises that the course of CD may be predicted by clinical factors at diagnosis (including age and perianal disease), which should be taken into account when determining the initial therapeutic strategy.27 Several studies have confirmed that young age at diagnosis (<40 years old) and perianal disease are associated with poor outcomes/disabling disease.29–31 Perianal fistulas are the most common type of fistula.32 Perianal fistulas are a therapeutic challenge and are associated with decreased quality of life (QoL) and increased risk of total resection.32, 33 Perianal fistulas are classified as either simple or complex. Simple fistulas are superficial, with a single external opening, with no pain or fluctuation suggesting abscess, rectovaginal fistula or anorectal stricture. All other fistulas, including active rectal disease, are considered complex.34

### Treating Complex Fistulising CD

**Infliximab Clinical Data.** The ACCENT II (A Crohn’s disease Clinical trial Evaluating infliximab in a New Long-term Treatment regimen in patients with fistulising Crohn’s disease) trial demonstrated that infliximab is effective in treating fistulising CD. In this double-blind, placebo-controlled trial, 306 adult patients with CD and one or more draining abdominal or perianal fistulas of at least 3 months’ duration were randomised to receive a three-dose induction regimen of infliximab 5 mg/kg at weeks 0, 2 and 6. Sixty-nine per cent of patients (195/282) responded (50% reduction in draining fistulas) to infliximab. At week 14, these responders were randomly assigned to receive placebo maintenance (n = 99) or infliximab maintenance (n = 96). The remaining initial nonresponders (n = 87) were randomly assigned to receive maintenance therapy with infliximab (n = 43) or

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placebo (n = 44) until week 54.35 From week 22, patients receiving placebo who experienced a loss of response were eligible to crossover to treatment with infliximab 5 mg/kg, and patients in the infliximab 5 mg/kg group could crossover to treatment with infliximab 10 mg/kg.25 The primary analysis was the time to loss of response among patients who responded at week 14 and underwent randomisation.35

Among responders, those receiving infliximab maintenance therapy had a significantly longer time to loss of response than those receiving placebo. The median time to loss of response was 14 weeks in the placebo group compared with more than 40 weeks in the infliximab group (P < 0.001). Overall, 62% of placebo patients had a loss of response compared with 42% of patients receiving infliximab.35 At week 54, significantly more responders in the infliximab maintenance group had a fistula response compared with placebo (46% vs. 23%, P = 0.001). A similar level of efficacy was observed in patients who had a complete response (absence of draining fistulas) of patients in the infliximab group (36% vs. 23%, P = 0.009).35

Reduced hospitalisation/surgery rates. ACCENT II also demonstrated that infliximab significantly reduces the rate of hospitalisation and surgery in patients with fistulising CD. Patients receiving maintenance infliximab were more than twice less likely to be hospitalised because of fistulising disease than those receiving placebo (18.6% vs. 18.9% (all randomised patients) and 7.3% vs. 18.2% (week 14 responders), P < 0.05 for both).33 Importantly, scheduled infliximab treatment resulted in a 50% reduction in the mean number of all surgeries and procedures (e.g. resection of the bowel, fistula-related surgeries, ostomy placement/revision) compared with placebo for all randomised patients (P < 0.01) and patients randomised as responders (P < 0.05).33 While the cumulative number of surgeries and procedures for patients randomised as responders during the study increased at a relatively slow rate in the infliximab group, the increase in the placebo group was markedly greater.33

Evidence-based treatment recommendation. ACCENT II provides clear evidence of the effectiveness of infliximab in treating fistulising CD. Based on those data and clinical experience, patients with complex fistulising CD should start treatment with infliximab with or without 2–2.5 mg/kg AZA/MP immediately (Figure 1). Prior surgical intervention should be considered, with potential abscess drainage and seton placement.

STRATIFYING PATIENTS WITH LUMINAL CD BASED ON RISK FACTORS

Early in the course of luminal CD, patients should be stratified according to their risk of progressive disease. Unfortunately, there are no consistent criteria across studies and more work needs to be carried out to establish clinical, serological and genetic predictors for progressive disease. Beaugerie et al. identified factors at diagnosis predictive of a subsequent 5-year disabling CD course. This study defined ‘disabling disease’ as the presence of at least one of the following clinical severity criteria: ≥2 steroid courses, steroid dependence, hospitalisation, chronic (>12 months) symptoms, need for immunosuppressants or need for surgery.29 Of the 1123 patients with 5-year follow-up data, the rate of disabling disease was 85.2%.29 In a prospective validation cohort of 302 patients, three independent risk factors for disabling disease course were identified: initial steroid requirement, age <40 years and the presence of perianal disease.29 Patients with ≥2 risk factors have been shown to have a high likelihood of a disabling course.29 Although this study defined disabling disease, no consistent definition for disabling disease has been adopted from many other studies. For example, the study by Beaugerie et al. included need for immunosuppression as disabling disease, whereas in other studies, this term was referred to as steroid dependency,30 stenosis/obstruction36 or mortality.37 Additional risk factors for progressive disease in luminal CD can be found in Table 3. From clinical experience, patients with the following characteristics should also be considered as those at risk for progressive disease: extensive small bowel disease, severe upper GI disease, severe rectal disease, younger age and perianal lesions.

Treating luminal CD

Historically, the treatment of luminal CD has taken a sequential step-up approach that involves starting therapy with the least toxic drug and adding in other drugs if there is no response. In practice, this means starting with 5-ASA and then progressing to corticosteroids,
immunosuppressants, anti-TNF therapy and finally surgery. The use of infliximab tends to be limited to patients with refractory CD, steroid-resistant patients or patients not responding to immunosuppressants. Many patients receiving conventional therapy, however, remain on drugs with low efficacy for long periods and continue to have active disease. This uncontrolled inflammation can often lead to mucosal damage.

It is becoming clear that conventional therapy may not be the optimal approach as there are important limitations to consider. Corticosteroids may also control symptoms on the short term; long-term outcomes are less favourable and discouraged. Significantly, corticosteroids are not effective in maintaining remission; only 25% of patients taking corticosteroids will be in remission after a year, even if given with immunomodulators. Corticosteroids are also not effective for inducing mucosal healing. In addition, long-term corticosteroid use is associated with serious side effects, such as weight gain, cataracts, hyperglycaemia, osteoporosis and increased risk of infection. Consequently, it is important to limit the use of corticosteroids and avoid repeated cycles of these drugs. AZA may be used as adjunctive or steroid-sparing therapy in some patients; however, its slow onset of action prevents it from being used as monotherapy in active CD. Additionally, its effect on the mucosa is limited.

There is now a body of evidence demonstrating that earlier use of immunosuppressants and anti-TNF therapy improves clinical outcomes. This has been clearly demonstrated with infliximab trials. It is becoming accepted that an accelerated step-up approach is needed in patients with moderately or severely active luminal CD. The earlier use of immunosuppressants and anti TNF therapy will induce and maintain remission, reduce steroid use and promote mucosal healing. Achieving this will provide the opportunity to impact the natural history of CD and thus reduce the risk of serious complications, such as hospitalisation and surgery.

An alternative to drugs could be surgery in patients with limited ileo-caecal CD. Understanding the best strategy will be clarified by the randomised-controlled study now undergoing in The Netherlands; the Laparoscopic Ileocolic Resection Versus Infliximab Treatment of Distal Ileitis in Crohn’s Disease (LIRIC) trial. Once this study is completed, it will provide information if surgery will lead to avoiding the use of medication and longer symptom-free efficacy than anti-TNF therapies. The results of this trial can be expected in 2012 or 2013.

However, patients with luminal disease should first be assessed for risk factors of disease progression. These at-risk patients may require a more intensive treatment than those without risk factors.

**Infliximab clinical data in luminal CD.** The ACCENT I trial demonstrated the efficacy of infliximab in luminal CD. In this study, 573 patients with active CD [Crohn’s Disease Activity Index (CDAI) 220–400] received a single infusion of infliximab 5 mg/kg. After the initial infusion, 58% of patients responded to infliximab. At week 2, patients responding to infliximab were randomised to receive either episodic (infliximab 5 mg/kg infusion followed by placebo infusions at weeks 0, 2 and 6 and then every 8 weeks) or scheduled treatment (infliximab 5 mg or 10 mg/kg at weeks 0, 2 and 6 and then every 8 weeks). At 1 year, over three times as many patients receiving scheduled infliximab (29%) were in steroid-free remission compared with those receiving episodic infliximab (9%) \( (P = 0.004) \). A sustained clinical response was more likely with scheduled rather than episodic treatment. ACCENT I showed that scheduled infliximab treatment every 8 weeks is more effective than episodic treatment and formed the basis for infliximab dosing. In addition, scheduled infliximab was associated with fewer hospitalisations and higher rates of mucosal healing. Furthermore, ACCENT I demonstrated the efficacy of infliximab dose escalation. Among patients receiving infliximab 5 mg/kg scheduled treatment who lost response, approximately 90% re-established response after receiving 10 mg/kg. Approximately 80% of patients who lost response while in the 10 mg/kg scheduled strategy group achieved response after receiving 15 mg/kg.

The GETAID (Groupe d’Etude Therapeutique des Affections Inflammatoires Digestives) study also demonstrated the benefits of initiating infliximab treatment.
earlier by showing that infliximab plus AZA combination therapy is more effective than AZA monotherapy in AZA-naïve patients. In the Getaid trial, 113 steroid dependent patients with active CD were stratified into two groups: AZA/MP failures and AZA/MP-naïve patients. Patients were randomised to infliximab 5 mg/kg or placebo at weeks 0, 2 and 6, with no maintenance treatment. All patients were treated with stable doses of AZA/MP throughout the 52-week trial. The primary endpoint was clinical remission (CDAI < 150) off steroids. Significantly more patients receiving infliximab plus AZA/MP compared with patients receiving AZA/MP alone were in steroid-free clinical remission at week 12 (75% vs. 38%; \( P < 0.001 \)) and week 24 (57% vs. 29%; \( P = 0.003 \)). The effect of infliximab on clinical remission was greater in AZA-naïve patients than AZA-failures, suggesting that earlier infliximab use may be beneficial in CD patients.

Importantly, the Getaid study also indicated that the proportion of patients receiving AZA who achieved steroid-free remission at week 12 declined over the course of the study, demonstrating that there was no ‘bridging effect’ and confirming that infliximab should not be used as a bridge to immunomodulator therapy in this patient population. This clearly shows that AZA cannot sustain the efficacy induced by infliximab, and these patients are more likely to benefit from scheduled infliximab maintenance therapy. Additionally, Treton et al. assessed the impact of AZA withdrawal after long-term remission with AZA treatment (median duration of 68.4 months) in a cohort of 66 patients. The primary endpoint was clinical relapse, and the study found that AZA withdrawal was associated with a high rate of relapse regardless of remission duration under treatment.

An important question is whether it is necessary to continue with infliximab plus AZA combination therapy or can AZA be withdrawn? The influence of immunosuppressive withdrawal in patients in remission with combination therapy has been assessed in an open-label, randomised, controlled study. Patients with controlled disease (>6 months) on infliximab (5 mg/kg) plus immunosuppressives were randomised to continue or discontinue immunosuppressives. All patients received scheduled infliximab maintenance therapy for 104 weeks. The study found that the continuation of immunosuppressives beyond 6 months provided no clear benefit over scheduled infliximab monotherapy. This is supported by Lichtenstein et al. in a study that reviewed the effect of concomitant immunomodulator and infliximab maintenance therapy using data from the ACCENT I and ACCENT II trials. Similarly, this study also found that use of concomitant immunomodulators did not improve efficacy in patients receiving maintenance infliximab treatment. In contrast to these studies, a recent study assessed the effect of concomitant use of immunosuppressives (AZA or methotrexate) with scheduled infliximab treatment in patients with IBD over semester time periods. A semester was defined as a 6-month period of infliximab treatment. The study found that patients with IBD who received combination therapy with an immunosuppressive had reduced IBD activity, reduced infliximab dose escalation and less need to switch to another biologic. Currently, the mechanism of superiority of combination therapy is unclear. Possible explanations may include a pharmacokinetic or additive effect. Further studies are still needed to help clarify this as well as questions on how long to treat patients with combined immunosuppressive therapy and when to discontinue AZA.

Evidence-based treatment recommendation. Patients with luminal CD and risk factors for progressive disease should be monitored closely. These patients require aggressive intervention and may benefit from accelerated treatment with early use of anti-TNF therapy ±2-2.5 mg/kg AZA.

The recommended treatment pathway for patients with luminal CD with risk factors is shown in the second arm of the algorithm in Figure 2. All patients should initially receive steroids plus AZA/MP. Although there is no evidence in adults to support this initial treatment regimen, this approach has been very successful in paediatric CD. If remission is achieved, steroids should be tapered and AZA monotherapy continued. If the patient then experiences a delayed relapse (after 6 months), steroids should be reintroduced and the response assessed after 4 weeks. If the patient experiences an early relapse (within 6 months) after initial remission with steroids plus AZA/MP, then infliximab ± AZA/MP therapy should be initiated.

If remission is not achieved using steroids plus AZA/MP (within 4 weeks), then treatment with infliximab ± AZA/MP should be initiated. After 6–12 months of stable remission (normal CRP, steroid-free clinical remission with mucosal healing), stepping down to infliximab monotherapy may be an option for some patients.

Impact of the SONIC trial on the treatment algorithm

The recently published SONIC trial is a landmark trial for the management of luminal CD, demonstrating the
benefits of an infliximab-based treatment strategy. The findings from SONIC are changing the way luminal CD is treated in clinical practice and have also impacted treatment guidelines such as ECCO and European Panel on the Appropriateness of Crohn’s Disease Treatment (EPACT). Patients (n = 508) with early, moderate to severe CD and naïve to immunomodulators and biologics were randomised to receive AZA 2.5-mg/kg capsules plus placebo infusions, infliximab 5-mg/kg infusions (week 0, 2 and 6 and then every 8 weeks) plus placebo capsules or infliximab 5-mg/kg infusions plus AZA 2.5 mg/kg capsules for 54 weeks. The primary endpoint was steroid-free remission at week 26. Endoscopy was performed at weeks 0 and 26.

An important finding of the SONIC trial was that infliximab was superior to AZA monotherapy in inducing steroid-free remission. Significantly more patients receiving infliximab mono-therapy (44.4%) or infliximab plus AZA combination therapy (56.8%) were in steroid-free clinical remission compared with patients receiving AZA monotherapy (30.6%) at week 26 (IFX monotherapy vs. AZA monotherapy, P = 0.009; IFX + AZA vs. AZA monotherapy, P < 0.001). Interestingly, in this study, infliximab combination therapy was more effective in inducing steroid-free clinical remission than infliximab monotherapy (P = 0.022). These effects were sustained through to week 50. SONIC demonstrated that an infliximab-based treatment strategy is more effective than AZA monotherapy in AZA-naïve patients.

Another important finding from SONIC was the superiority of infliximab over AZA monotherapy in inducing mucosal healing. More patients experienced complete mucosal healing while receiving infliximab monotherapy (30%; P = 0.023) or infliximab-plus-AZA combination therapy (44%; P < 0.001) than AZA monotherapy (17%). Although SONIC did not assess impact on outcomes (i.e. hospitalisations/surgeries), mucosal healing has become a recognised clinical endpoint with infliximab as it is linked to improved outcomes.

SONIC also revealed that patients with high inflammatory burden (high CRP and/or endoscopic lesions) at baseline derived the greatest benefit from an infliximab-based treatment strategy. In patients with high baseline CRP levels (≥0.8 mg/dL), significantly more were in steroid-free clinical remission with infliximab plus AZA combination therapy (63.5%, P < 0.001) or infliximab monotherapy (47.5%, P = 0.004) than AZA monotherapy (27.6%). Superiority of infliximab over AZA monotherapy was also observed in patients with mucosal lesions at baseline but not in patients with no lesions at baseline. This effect was even greater in patients with both high CRP and mucosal lesions at baseline, with 68.8% of patients receiving infliximab plus AZA combination therapy and 56.9% receiving infliximab monotherapy in clinical remission at week 26 compared with 28% (P < 0.001) of AZA monotherapy-treated patients. CRP levels or mucosal lesions should, therefore, be used to identify patients who are particularly likely to benefit from an infliximab-based treatment strategy.

Data from SONIC change the traditional CD treatment algorithm. It demonstrates that early infliximab-based treatment leads to improved outcomes that include rapid symptomatic improvement, sustained steroid-free remission and complete mucosal healing compared with AZA monotherapy in AZA-naïve patients. In addition, patients with evidence of active disease (high CRP/mucosal lesions) derive the most benefit from an infliximab-based treatment strategy. It should be noted that although the present discussion focuses on the impact of SONIC on the CD treatment algorithm, results
from the Step-Up Top-Down (SUTD) study may be considered for further early intervention as a next step. Briefly, the SUTD study assessed the efficacy of combined immunosuppressive therapy (AZA 2.5 mg/kg plus three infusions of infliximab 5 mg/kg) or conventional management (sequential treatment with corticosteroids, immunosuppressant and infliximab) in newly diagnosed, treatment-naïve patients with CD.

The group treated with early combined immunosuppressive therapy at the end of the study period had superior mucosal healing, thus confirming the capacity of infliximab to significantly heal the intestinal mucosa in CD.

Evidence-based treatment recommendation. SONIC has shown that anti-TNF therapy should be initiated much earlier in patients with luminal CD. The recommended treatment pathway for patients with luminal CD (no risk factors) is shown in the third arm of the algorithm in Figure 3. Initial treatment should be with steroids and if remission is achieved (top arm), then steroids should be tapered down until they are discontinued. If there is a delayed relapse (after 6 months) after discontinuing steroids, then the patient should be re-treated with steroids and the response assessed at 4 weeks. If the patient experiences an early relapse (within 6 months) after discontinuing steroids, there are two options to consider: (i) initiate infliximab ±2–2.5 mg/kg AZA/MP if the patient has lesions and/or elevated CRP or (ii) initiate steroids plus 2–2.5 mg/kg AZA/MP combination therapy and then if the patient relapses move on to infliximab ±2–2.5 mg/kg AZA/MP (moving down to lower arm).

If remission is not achieved within 4 weeks of initial steroid therapy (lower arm), infliximab ± AZA/MP should be initiated. In either arm, after 6–12 months of stable remission (normal CRP, steroid-free clinical remission with mucosal healing), stepping down to infliximab monotherapy may be an option for some patients. Infliximab should be considered as monotherapy in elderly patients. Infliximab monotherapy rather than combination therapy, however, should be given to young males with CD because of the risk of hepatosplenic T-cell lymphoma. Although this condition is extremely rare, it is very serious, with most cases proving fatal. Thirty-six cases have been reported in which 20 were treated with infliximab plus a thiopurine and 16 were on thiopurine monotherapy. Four cases that included infliximab and thiopurine also took adalimumab. One case was exposed to infliximab, adalimumab and natalizumab. Of the 31 patients whose gender was known, only two were female. It is prudent, therefore, not to administer infliximab plus AZA combination in young male patients.

The benefit:risk ratio of infliximab or any other biologic needs to be considered before treating patients.

LOSS OF RESPONSE AND TREATMENT FAILURE
Some patients with CD may experience loss of response over time and/or develop intolerance to infliximab. It is estimated that this might occur in about 10% of treated patients per year.46 Patients with diminished or loss of response to infliximab therapy may respond to optimised dosing regimens of the same agent or switching to another agent.8 Before switching to another agent, one should consider optimising their first agent if possible.

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**Figure 3** | Treatment arm for luminal disease with no risk factors. * Normal CRP, steroid-free clinical remission with mucosal healing. † Presence of risk factors may determine mono vs. combination therapy.
Infliximab allows some dosing flexibility which has been demonstrated from experience in the Leuven cohort.47 Schnitzler et al. assessed the long-term clinical benefits of infliximab in 614 consecutive patients with CD from a single centre in an observational study over a median of 4.6 years. Of 547 initial responders, approximately 50% needed an intervention. A reduction in the interval between infusions was needed in 108 patients (19.7%); an increase in the dose to 10 mg/kg and/or a re-induction with infliximab infusions at weeks 0, 2 and 6 was needed in 144 patients (26.3%); 63 patients with a re-induction and 89 patients with an increase in the dose of infliximab; and an increase in the dose plus a reduction in the interval was needed in only 21 patients (3.8%). Overall, 103 of the 144 patients (71.5%) with an increase in dose and/or a re-induction with infliximab could go back to the standard dose of 5 mg/kg and 61.9% of patients (13/21) with an increase in dose and a shortening of the interval could go back to 5 mg/kg and dosing at 8 week intervals; 28.7% of patients with a shortened interval between infusions (31/108) could again extend the interval to 8 weeks. In the total cohort of initial responders, only 21.6% (n = 118) had to stop infliximab because of loss of response despite interventions.47 When optimising the first agent is not successful, then switching may be an option. In a randomised, placebo-controlled trial (GAIN, Gauging Adalimumab Efficacy in Infliximab Nonresponders), switching to adalimumab was effective in patients with previous loss of response to their first anti-TNF therapy. At baseline, 48% (n = 77) of patients in the adalimumab group had previous loss of response to infliximab. After 4 weeks of treatment, 52% (82 of 159) of patients in this group achieved a 70-point response (decrease in baseline in CDAI score of 70 points or more) vs. 34% (56 of 166) of patients in the placebo group (P = 0.001).48 Some patients with CD will not respond to their first anti-TNF treatment. Reports on this patient population are very limited. In a retrospective survey, Allez et al.49 observed that 12 of 18 patients responded to a 3rd anti-TNF after primary failure to one or two prior anti-TNF treatment(s). This treatment option requires thorough case-by-case discussion and should only be considered in patients with no other therapeutic options.49

WHEN TO STOP TREATMENT

To date, recommendations on when to stop anti-TNF therapy cannot be made because of insufficient data.8 Patients in stable remission may have no medical reason to stop anti-TNF therapy, unless there are circumstances when cessation may be necessary – for example, if a patient is unwilling to continue treatment with the drug, in situations such as pregnancy or if changes in reimbursement affect coverage of treatment. Preliminary evidence suggests that some patients will remain in clinical remission for >1 year despite cessation of infliximab treatment.8 A retrospective study by Domenech et al.,50 evaluated clinical outcome after a successful course of infliximab treatment for maintenance of response in both luminal and perianal CD. Infliximab discontinuation was successful for patients in patients with luminal CD treated for one year (69% cumulative probability of being free of relapse at 12 months). Conversely, patients with perianal disease demonstrated early relapse with only 34% (vs. 83% in patients with luminal disease) maintaining remission at 1 year. Consequently, because of a high rate of early relapse, infliximab discontinuation is not recommended in perianal CD.50 The STORI (infliximab diSconTinuation in CrOhn’s disease patients in stable Remission on combined therapy with Immunosuppressors) trial assessed the risk of relapse after discontinuation of infliximab in patients on combined maintenance therapy with immunosuppressors.51 Patients who received scheduled infliximab plus immunosuppressive combination therapy for at least 1 year and who were also in steroid-free remission for ≥6 months were included.51 More than 50% of patients had relapsed after 18 months of treatment discontinuation; however, patients who did relapse were successfully re-treated with infliximab.52 These results show that routine discontinuation of infliximab therapy may lead to a very high disease relapse and could not be a sound treatment decision.

MANAGING FISTULAS

Patients with fistulising CD with acute suppurative fistulas must not initiate infliximab therapy until a source for possible infection, specifically abscess, has been excluded. Patients with fistulising CD who have responded to an induction regimen with anti-TNF therapy should receive scheduled re-treatment with infliximab or adalimumab, as this is effective for maintaining fistula closure or response.8 Combined medical and surgical strategies have evolved, with drainage of sepsis and insertion of a seton, followed by two doses of anti-TNF therapy, fistula curettage and then further anti-TNF therapy.8, 53, 54 Insertion of drainage seton sutures at the time of preinfliximab examination under anaesthesia and removal after the second infusion are considered routine practice in this patient population.53
PREGNANCY
Postmarketing reports of approximately 300 pregnancies exposed to infliximab do not indicate unexpected effects on pregnancy outcome. As a result of its inhibition of TNFα, infliximab administered during pregnancy could affect normal immune responses in the newborn. The available clinical experience is too limited to exclude a risk, and administration of infliximab is therefore not recommended during pregnancy.12

PATIENT SCREENING AND VACCINATION
Patients taking TNF-blockers are more susceptible to serious infections. Tuberculosis, bacterial infections, including sepsis and pneumonia, invasive fungal infections, and other opportunistic infections have been observed in patients treated with infliximab.12 Before starting treatment with infliximab, all patients must be evaluated for both active and latent tuberculosis.8, 12 If active tuberculosis is diagnosed, infliximab therapy must not be initiated. No data are available on the response to vaccination with live vaccines or on the secondary transmission of infection by live vaccines in patients receiving anti-TNF therapy. It is recommended that live vaccines not be given concurrently while receiving infliximab.

SAFETY CONSIDERATIONS
The safety findings observed in the SONIC trial demonstrate that the incidence of adverse events (including serious adverse events) and serious infections was similar among the infliximab monotherapy, infliximab plus AZA combination therapy and AZA monotherapy groups. However, infusion reactions occurred less frequently among patients receiving combination therapy than among those receiving infliximab monotherapy.16 Increased risks of rare but serious toxic effects associated with combination therapy must be considered.16 Additionally, increased relative risk of serious and opportunistic infections associated with concomitant use of corticosteroids as a third immunosuppressive agent must be taken into account.55 The choice of infliximab mono-
therapy or combination therapy in patients who have not received such therapy previously is an individualised benefit–risk decision. Additionally, the benefit-to-risk profile must be considered when choosing an anti-TNF agent.

**CONCLUSIONS**

Ten years ago, the options available for patients with CD were limited. It was possible to achieve symptomatic remission with some improvements in QoL; however, therapy was restricted to episodic induction and the treatment of each individual disease flare. Today, with timely drug intervention, it is possible to induce clinical remission that can be sustained over the long term with scheduled maintenance therapy. Over 10 years of clinical data and experience demonstrate the excellent efficacy and safety profile of infliximab.

Based on the infliximab clinical trial data, it may now be possible to change the underlying course of CD and restore normal bowel function, thereby improving the patient’s QoL. The evidence shows that there is a window of opportunity early in the course of CD when patients benefit most from infliximab therapy. The landmark SONIC trial has significantly impacted the way CD is treated by showing that an infliximab-based treatment strategy, especially in AZA-naive patients with high inflammatory burden at baseline, provides the most benefit in improving therapeutic outcomes. Furthermore, there is clear evidence for infliximab as an option for treating fistulising CD, and patients with luminal CD with risk factors should be considered for accelerated step-up therapy.

A controlled clinical trial demonstrating how the treatment approach of early intervention from the SONIC trial can be applied to all of the anti-TNF therapies is warranted. The early use of an evidence-based infliximab treatment algorithm, such as the one proposed in this article, will significantly improve outcomes for patients with CD (Figure 4).

**ACKNOWLEDGEMENTS**

_Declaration of personal interests:_ Silvio Danese has served as a speaker, a consultant and an advisory board member for Schering-Plough, Abbott Laboratories, UCB, Ferring, Cellerix, Millenium Takeda, Nycomed, Actelion, AstraZeneca, Novo Nordisk and Cosmo Pharmaceuticals. Walter Reinisch has served as a speaker or consultant for Centocor, MSD, AESCA, Abbott, Ferring, Cellerix, Millenium, Novartis, Otsuka and Biogen. Jean-Frédéric Colombel has served as a consultant and an advisory board member for Abbott Laboratories, ActoGeniX NV, AlbireoPharma, AstraZeneca, BayerScheringPharma, AG, Biogen Idec Inc, Boehringer-Ingelheim, Inc., Bristol-Myers Squibb, Cellerix SL, Chemocentryx, Inc., Centocor, Cosmo Technologies, Ltd, Danone France, Elan Pharmaceuticals, Inc., Genentech, Giuliani SPA, Given Imaging, GlaxoSmithKline, Merck & Co., Inc., Millenium Pharmaceuticals Inc., Neovacs SA, Ocerra Therapeutics, Inc. (previously named Renovia, Inc.), Otsuka American Pharmaceuticals Inc., PDL Biopharma (previously named Protein Design Labs), Pfizer Inc., RiboVacs Biotech, Schering-Plough Corporation, Shire Pharmaceuticals, Synta Pharmaceutical Corporation, Teva Pharmaceuticals, Therakos, UCB Pharma (previously named Celltech Therapeutics, Ltd.), Wyeth Pharmaceuticals; has participated in continuing medical education events indirectly sponsored by Abbott Laboratories, AstraZeneca, Centocor, Elan Pharmaceuticals, Falk Pharma, Ferring, Given Imaging, Otsuka American Pharmaceuticals, PDL Biopharma, Schering-Plough Corporation, Shire Pharmaceuticals, UCB Pharma; has received Grant support from AstraZeneca, Ferring, Schering-Plough Corporation, UCB Pharma, Lesaffre, Giuliani SPA, Danisco, Ocerra Therapeutics, Inc. (previously named Renovia, Inc.), Danone, Roquette, Mapi Naxis and Dysphar and owns stock in Intestinal Biotech Development, Lille, France. Paul Rutgeerts has served as a speaker for Centocor, Schering-Plough, UCB, Abbott, Elan-Biogen, a consultant for Centocor, Schering-Plough, UCB, Abbott, Elan-Biogen, NovImmune, Italfarmaco, Bristol-Myers Squibb, Millenium Pharmaceuticals, Tillots, GSK and ChemoCentryx and has received research funding from Centocor, Schering-Plough, UCB and Abbott. _Declaration of funding interests:_ SD is the guarantor of this article. He wrote the first draft that was shared with and edited by WR, JFC and PR. Schering-Plough Corporation, now Merck & Company, Inc, Whitehouse Station, NJ, USA, supported the development of this article. Synergy Medical Education, Conshohocken, Pennsylvania, USA, provided editorial assistance.
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