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► **To cite this version:**

Silvio Danese, Jean-Frédéric Colombel, Walter Reinisch, Paul Rutgeerts. Review Article: Infliximab for Crohn's disease treatment: shifting therapeutic strategies after 10 years of clinical experience. *Alimentary Pharmacology and Therapeutics*, 2011, 33 (8), pp.857. 10.1111/j.1365-2036.2011.04598.x . hal-00614697

HAL Id: hal-00614697

<https://hal.science/hal-00614697>

Submitted on 15 Aug 2011

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**Review Article: Infliximab for Crohn's disease treatment:
shifting therapeutic strategies after 10 years of clinical
experience**

Journal:	<i>Alimentary Pharmacology & Therapeutics</i>
Manuscript ID:	APT-0735-2010.R2
Wiley - Manuscript type:	Review Article
Date Submitted by the Author:	19-Jan-2011
Complete List of Authors:	Danese, Silvio; Istituto Clinico Humanitas, Gastroenterology Colombel, Jean-Frédéric; Centre Hospitalier Universitaire de Lille, Service d'Hépatogastroentérologie Reinisch, Walter; Univ.-Klinik Innere Medizin IV, Gastroenterologie Rutgeerts, Paul; University of Leuven, Gastroenterology
Keywords:	Inflammatory bowel disease < Disease-based, Crohn's disease < Disease-based, Immunosuppression < Topics, Biologics (IBD) < Topics

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3 **Review Article: Infliximab for Crohn's disease treatment: shifting therapeutic**
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5 **strategies after 10 years of clinical experience**
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58 **Running title:** Infliximab in Crohn's disease
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Abstract

Background: Crohn's disease (CD) 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-TNF therapies, however, has changed the way patients with CD are treated. Over 10 years of clinical data and experience have demonstrated these therapies to be highly effective in CD.

Aim: To provide clinicians guidance on optimising treatment with anti-TNF therapies in CD 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 CD.

Results: The data from several landmark infliximab trials have changed clinical practice and led to a readjustment of treatment goals in CD, 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.

Conclusions: Adopting the suggested treatment algorithm for infliximab into clinical routine is aimed to optimise outcomes for patients with CD.

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Key words: infliximab, Crohn's disease, treatment algorithm

For Peer Review

Introduction

Crohn's disease (CD) is a progressive disease that can be subdivided into 3 phenotypes: inflammatory, stricturing and penetrating.¹ Initially, inflammatory disease is present in the majority of patients with CD. Over time, however, most patients will develop a penetrating or stricturing complication, owing to uncontrolled inflammation.² Within 20 years, 88% of patients will experience either stricturing (18%) or penetrating fistulising disease (70%).²

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.³ The majority of patients (51%), however, experience chronic continuous (19%) or relapsing/remitting symptoms (32%).³ 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).⁴ 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-TNF 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-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

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3 immunosuppression should be considered, especially in children, young adults, or the elderly.⁸ The
4
5 thiopurine immunomodulators AZA and 6-mercaptopurine (6-MP) are frequently prescribed for
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7 patients in whom first-line therapies fail—in particular, those who are dependent on or do not have
8
9 a response to systemic corticosteroids.⁹⁻¹¹ When starting biological therapy in patients with CD
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11 naïve to thiopurines the combination of an anti-TNF agent and AZA is better for induction of
12
13 remission and mucosal healing over 1 year. Whether combination therapy could improve outcomes
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15 from each of the anti-TNF agents remains unknown.⁸
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20 Two anti-TNF therapies are available for treatment of patients with CD (Table 1).^{12,13} Infliximab
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22 (intravenous infusion) was licensed for use in CD in the United States in 1998 and in Europe in
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24 1999. Current use of infliximab has evolved based on evidence from clinical trials. Furthermore,
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26 infliximab has the broadest inflammatory bowel disease (IBD) label available in Europe and is
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28 approved for adult luminal and fistulising CD, paediatric luminal CD and adult ulcerative colitis
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30 (UC).¹² Adalimumab (subcutaneous injection) was also licensed for use in CD in Europe and in the
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32 United States in 2007.
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37 Over the past decade, the efficacy of anti-TNF has been demonstrated in various patient groups,
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39 including patients with different disease durations and previous exposure to conventional
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41 therapies.^{5,14-23} The spectrum of anti-TNF trials has provided lessons on an optimised way to treat
42
43 patients with CD and raised the threshold for treatment goals. It is now clear that CD treatment
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45 must go beyond simply providing symptomatic control and aim to change the course of the
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47 disease. The anti-TNF clinical trial data have raised awareness and expectations of what treatment
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49 goals can be achieved (Table 2).^{24,25} Mucosal healing is becoming an increasingly important
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51 parameter, as in some studies it has been shown to be linked with reductions in hospitalisations
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53 and surgeries as well as long-term remission. Achieving these goals will require rapid and
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55 sustained control of inflammation and appropriate management with earlier, more intensive use of
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57 biologic therapy in most patients.
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3 Recently, SONIC (Study Of biologic and immunomodulator-Naive patients In Crohn's disease) was
4 conducted in AZA-naïve patients with moderate to severe CD (mean duration 2.3 years) and
5 demonstrated that infliximab monotherapy or infliximab plus AZA combination therapy is superior
6 to AZA alone in immunomodulator-naïve patients.¹⁶ SONIC also showed that the best results were
7 achieved in patients with a high inflammatory burden (high C-reactive protein [CRP] and/or
8 mucosal lesions) at baseline.¹⁶ This trial is a landmark paper for CD management and has
9 profound therapeutic implications for clinical practice.
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20 Practical matters, such as patient preference regarding the mode of administration, may play a role
21 in the selection of adalimumab as initial anti-TNF therapy.²⁶ The current European Crohn's &
22 Colitis Organisation (ECCO) consensus in CD management states that 'All currently available anti-
23 TNF therapies appear to have similar efficacy and adverse-event profiles, so the choice depends
24 on availability, route of delivery, patient preference, cost and national guidance'.²⁷ A qualitative
25 study of patient preferences of anti-TNF agents in rheumatoid arthritis suggests that younger
26 patients are more confident about self-administering treatment and slightly prefer the convenience
27 of subcutaneous dosing, whereas older patients prefer the perceived safety of infusion in a clinic.²⁸
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20 This paper will review the infliximab clinical trial data and introduce an evidence-based infliximab
21 treatment algorithm for the management of luminal and complex fistulising CD, based on the
22 clinical data and expert opinion, and will discuss the clinical and practical implications of the
23 SONIC trial in the daily management of CD.
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Identifying patients with progressive disease (including fistulising disease)

20 The treatment of patients with CD should be customised according to factors that predict
21 progressive disease. The European Crohn's and Colitis Organization (ECCO) consensus on the
22 management of CD recognises that the course of CD may be predicted by clinical factors at
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3 diagnosis (including age and perianal disease), which should be taken into account when
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5 determining the initial therapeutic strategy.²⁷ Several studies have confirmed that young age at
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7 diagnosis (<40 years old) and perianal disease are associated with poor outcomes/disabling
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9 disease.²⁹⁻³¹ Perianal fistulas are the most common type of fistula.³² Perianal fistulas are a
10
11 therapeutic challenge and are associated with decreased QoL and increased risk of total
12
13 colectomy.^{32,33} Perianal fistulas are classified as either simple or complex. Simple fistulas are
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15 superficial, with a single external opening, with no pain or fluctuation suggesting abscess,
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17 rectovaginal fistula or anorectal stricture. All other fistulas, including active rectal disease, are
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19 considered complex.³⁴
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25 **Treating complex fistulising CD**

26 Infliximab clinical data

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29 The ACCENT II (A Crohn's disease Clinical trial Evaluating infliximab in a New Long term
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31 Treatment regimen in patients with fistulising Crohn's disease) trial demonstrated that infliximab is
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33 effective in treating fistulising CD. In this double-blind, placebo-controlled trial, 306 adult patients
34
35 with CD and one or more draining abdominal or perianal fistulas of at least 3 months' duration were
36
37 randomised to receive a 3-dose induction regimen of infliximab 5 mg/kg at weeks 0, 2 and 6. Sixty-
38
39 nine percent of patients (195/282) responded (50% reduction in draining fistulas) to infliximab. At
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41 week 14, these responders were randomly assigned to receive placebo maintenance (n=99) or
42
43 infliximab maintenance (n=96). The remaining initial nonresponders (n=87) were randomly
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45 assigned to receive maintenance therapy with infliximab (n=43) or placebo (n=44) until week 54.³⁵
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47 From week 22, patients receiving placebo who experienced a loss of response were eligible to
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49 cross over to treatment with infliximab 5 mg/kg, and patients in the infliximab 5 mg/kg group could
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51 cross over to treatment with infliximab 10 mg/kg.³⁵ The primary analysis was the time to loss of
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53 response among patients who responded at week 14 and underwent randomisation.³⁵
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59 Among responders, those receiving infliximab maintenance therapy had a significantly longer time
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to loss of response than those receiving placebo. The median time to loss of response was 14

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3 weeks in the placebo group compared with more than 40 weeks in the infliximab group ($P<0.001$).
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5 Overall, 62% of placebo patients had a loss of response compared with 42% of patients receiving
6
7 infliximab.³⁵ At week 54, significantly more responders in the infliximab maintenance group had a
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9 fistula response compared with placebo (46% vs 23%, $P=0.001$). A similar level of efficacy was
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11 observed in patients who had a complete response (absence of draining fistulas) of patients in the
12
13 infliximab group (36% vs 23%, $P=0.009$).³⁵
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18 *Reduced hospitalisation/surgery rates*

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20 ACCENT II also demonstrated that infliximab significantly reduces the rate of hospitalisation and
21
22 surgery in patients with fistulising CD. Patients receiving maintenance infliximab were more than
23
24 twice less likely to be hospitalised due to fistulising disease than those receiving placebo (8.6% vs
25
26 18.9% [all randomised patients] and 7.3% vs 18.2% [week 14 responders], $P<0.05$ for both).³³
27
28 Importantly, scheduled infliximab treatment resulted in a 50% reduction in the mean number of all
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30 surgeries and procedures (eg, resection of the bowel, fistula-related surgeries, ostomy
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32 placement/revision) compared with placebo for all randomised patients ($P<0.01$) and patients
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34 randomised as responders ($P<0.05$).³³ While the cumulative number of surgeries and procedures
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36 for patients randomised as responders during the study increased at a relatively slow rate in the
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38 infliximab group, the increase in the placebo group was markedly greater.³³
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45 Evidence-based treatment recommendation

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47 ACCENT II provides clear evidence of the effectiveness of infliximab in treating fistulising CD.
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49 Based on those data and clinical experience, patients with complex fistulising CD should start
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51 treatment with infliximab with or without 2-2.5 mg/kg AZA/6MP immediately (Figure 1). Prior
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53 surgical intervention should be considered, with potential abscess drainage and seton placement.
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58 **Stratifying patients with luminal CD based on risk factors**

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3 Early in the course of luminal CD, patients should be stratified according to their risk of progressive
4 disease. Unfortunately, there are no consistent criteria across studies and more work needs to be
5 done to establish clinical, serological and genetic predictors for progressive disease. Beaugerie et
6 al identified factors at diagnosis predictive of a subsequent 5-year disabling CD course. This study
7 defined 'disabling disease' as the presence of at least one of the following clinical severity criteria:
8 ≥ 2 steroid courses, steroid dependence, hospitalisation, chronic (>12 months) symptoms, need for
9 immunosuppressants or need for surgery.²⁹ Of the 1123 patients with 5-year follow-up data, the
10 rate of disabling disease was 85.2%.²⁹ In a prospective validation cohort of 302 patients, 3
11 independent risk factors for disabling disease course were identified: initial steroid requirement,
12 age <40 years and the presence of perianal disease.²⁹ Patients with ≥ 2 risk factors have been
13 shown to have a high likelihood of a disabling course.²⁹ Although this study defined disabling
14 disease, no consistent definition for disabling disease has been adopted from many other studies.
15 For example, the study by Beaugerie et al. included need for immunosuppression as disabling
16 disease, whereas in other studies, this term was referred to was steroid dependency,³⁰
17 stenosis/obstruction³⁶ or mortality.³⁷ Additional risk factors for progressive disease in luminal CD
18 can be found in Table 3. From clinical experience, patients with the following characteristics should
19 also be considered as those at risk for progressive disease: extensive small bowel disease, severe
20 upper GI disease, severe rectal disease, younger age and perianal lesions.
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44 **Treating luminal CD**

45 Historically, the treatment of luminal CD has taken a sequential step-up approach that involves
46 starting therapy with the least toxic drug and adding in other drugs if there is no response. In
47 practice, this means starting with 5-ASA and then progressing to corticosteroids,
48 immunosuppressants, anti-TNF therapy and finally surgery. The use of infliximab tends to be
49 limited to patients with refractory CD, steroid-resistant patients or patients not responding to
50 immunosuppressants.²⁴ Many patients receiving conventional therapy, however, remain on drugs
51 with low efficacy for long periods and continue to have active disease. This uncontrolled
52 inflammation can often lead to mucosal damage.²⁴
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6 It is becoming clear that conventional therapy may not be the optimal approach as there are
7 important limitations to consider. Corticosteroids may also control symptoms on the short term;
8 long-term outcomes are less favourable and discouraged.²⁴ Significantly, corticosteroids are not
9 effective in maintaining remission; only 25% of patients taking corticosteroids will be in remission
10 after a year, even if given with immunomodulators.²⁷ Corticosteroids are also not effective for
11 inducing mucosal healing. In addition, long-term corticosteroid use is associated with serious side
12 effects, such as weight gain, cataracts, hyperglycaemia, osteoporosis and increased risk of
13 infection. Consequently, it is important to limit the use of corticosteroids²⁷ and avoid repeated
14 cycles of these drugs. Azathioprine (AZA) may be used as adjunctive or steroid-sparing therapy in
15 some patients; however, its slow onset of action prevents it from being used as monotherapy in
16 active CD.²⁷ Additionally, its effect on the mucosa is limited.

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

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51 An alternative to drugs could be surgery in patients with limited ileo-cecal CD. Understanding the
52 best strategy will be clarified by the randomized-controlled study now undergoing in The
53 Netherlands; the Laparoscopic Ileocolic Resection Versus Infliximab Treatment of Distal Ileitis in
54 Crohn's Disease (LIR!C) trial. Once this study is completed, it will provide information if surgery will
55 lead to avoiding the use of medication and longer symptom-free efficacy than anti-TNF therapies.
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60 The results of this trial can be expected in 2012 or 2013.⁴⁵

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3 However, patients with luminal disease should first be assessed for risk factors of disease
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5 progression. These at-risk patients may require a more intensive treatment than those without risk
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7 factors.
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10 11 *Infliximab clinical data in luminal CD*

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13 The ACCENT I trial demonstrated the efficacy of infliximab in luminal CD. In this study, 573
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15 patients with active CD (CDAI 220–400) received a single infusion of infliximab 5 mg/kg. After the
16
17 initial infusion, 58% of patients responded to infliximab.⁴⁶ At week 2, patients responding to
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19 infliximab were randomised to receive either episodic (infliximab 5 mg/kg infusion followed by
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21 placebo infusions at weeks 0, 2 and 6 and then every 8 weeks) or scheduled treatment (infliximab
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23 5 mg or 10 mg/kg at weeks 0, 2 and 6 and then every 8 weeks).⁴⁶ At 1 year, over 3 times as many
24
25 patients receiving scheduled infliximab (29%) were in steroid-free remission compared with those
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27 receiving episodic infliximab (9%) ($P=0.004$).⁴⁶ A sustained clinical response was more likely with
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29 scheduled rather than episodic treatment.⁴⁶ ACCENT I showed that scheduled infliximab treatment
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31 every 8 weeks is more effective than episodic treatment and formed the basis for infliximab dosing.
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33 In addition, scheduled infliximab was associated with fewer hospitalisations and higher rates of
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35 mucosal healing. Furthermore, ACCENT I demonstrated the efficacy of infliximab dose escalation.
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37 Among patients receiving infliximab 5 mg/kg scheduled treatment who lost response,
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39 approximately 90% re-established response after receiving 10 mg/kg. Approximately 80% of
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41 patients who lost response while in the 10 mg/kg scheduled strategy group achieved response
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43 after receiving 15 mg/kg.⁵
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51 The GETAID (Groupe d'Etude Therapeutique des Affections Inflammatoires Digestives) study also
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53 demonstrated the benefits of initiating infliximab treatment earlier by showing that infliximab plus
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55 AZA combination therapy is more effective than AZA monotherapy in AZA-naïve patients. In the
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57 GETAID trial, 113 steroid dependent patients with active CD were stratified into 2 groups: AZA/6-
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59 MP failures and AZA/6-MP-naïve patients.¹⁵ Patients were randomised to infliximab 5 mg/kg or
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61 placebo at weeks 0, 2 and 6, with no maintenance treatment. All patients were treated with stable

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3 doses of AZA/6-MP throughout the 52-week trial. The primary end point was clinical remission
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5 (Crohn's Disease Activity Index [CDAI] <150) off steroids. Significantly more patients receiving
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7 infliximab plus AZA/6-MP compared with patients receiving AZA/6-MP alone were in steroid-free
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9 clinical remission at week 12 (75% vs 38%; $P<0.001$) and week 24 (57% vs 29%; $P=0.003$).¹⁵ The
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11 effect of infliximab on clinical remission was greater in AZA-naïve patients than AZA-failures,
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13 suggesting that earlier infliximab use may be beneficial in CD patients.
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19 Importantly, the GETAID study also indicated that the proportion of patients receiving AZA who
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21 achieved steroid-free remission at week 12 declined over the course of the study, demonstrating
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23 that there was no 'bridging effect' and confirming that infliximab should not be used as a bridge to
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25 immunomodulator therapy in this patient population. This clearly shows that AZA cannot sustain
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27 the efficacy induced by infliximab, and these patients are more likely to benefit from scheduled
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29 infliximab maintenance therapy.¹⁵ Additionally, Treton et al assessed the impact of AZA withdrawal
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31 after long-term remission with AZA treatment (median duration of 68.4 months) in a cohort of 66
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33 patients. The primary end point was clinical relapse, and the study found that AZA withdrawal was
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35 associated with a high rate of relapse regardless of remission duration under treatment.⁴⁷
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41 An important question is whether it is necessary to continue with infliximab plus AZA combination
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43 therapy or can AZA be withdrawn? The influence of immunosuppressive withdrawal in patients in
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45 remission with combination therapy has been assessed in an open-label, randomised, controlled
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47 study. Patients with controlled disease (>6 months) on infliximab (5 mg/kg) plus
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49 immunosuppressives were randomised to continue or discontinue immunosuppressives. All
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51 patients received scheduled infliximab maintenance therapy for 104 weeks.⁴⁸ The study found that
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53 the continuation of immunosuppressives beyond 6 months provided no clear benefit over
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55 scheduled infliximab monotherapy.⁴⁸ This is supported by Lichtenstein et al. in a study that
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57 reviewed the effect of concomitant immunomodulator and infliximab maintenance therapy using
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59 data from the ACCENT I and ACCENT II trials. Similarly, this study also found that use of
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concomitant immunomodulators did not improve efficacy in patients receiving maintenance

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3 infliximab treatment.⁴⁹ In contrast to these studies, a recent study assessed the effect of
4
5 concomitant use of immunosuppressives (AZA or methotrexate [MTX]) with scheduled infliximab
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7 treatment in patients with IBD over semester time periods. A semester was defined as a 6-month
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9 period of infliximab treatment. The study found that patients with IBD who received combination
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11 therapy with an immunosuppressive had reduced IBD activity, reduced infliximab dose escalation
12
13 and less need to switch to another biologic.⁵⁰ Currently, the mechanism of superiority of
14
15 combination therapy is unclear. Possible explanations may include a pharmacokinetic or additive
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17 effect. Further studies are still needed to help clarify this as well as questions on how long to treat
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19 patients with combined immunosuppressive therapy and when to discontinue AZA.
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25 *Evidence-based treatment recommendation*

26 Patients with luminal CD and risk factors for progressive disease should be monitored closely.
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28 These patients require aggressive intervention and may benefit from accelerated treatment with
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30 early use of anti-TNF therapy +/- 2-2.5 mg/kg AZA.
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35 The recommended treatment pathway for patients with luminal CD with risk factors is shown in the
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37 second arm of the algorithm in Figure 2. All patients should initially receive steroids plus AZA/6-
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39 MP. Although there is no evidence in adults to support this initial treatment regimen, this approach
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41 has been very successful in paediatric CD.⁵¹ If remission is achieved, steroids should be tapered
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43 and AZA monotherapy continued. If the patient then experiences a delayed relapse (after 6
44
45 months), steroids should be reintroduced and the response assessed after 4 weeks. If the patient
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47 experiences an early relapse (within 6 months) after initial remission with steroids plus AZA/ 6-MP,
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49 then infliximab plus AZA/6-MP therapy should be initiated.
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55 If remission is not achieved using steroids plus AZA/6-MP (within 4 weeks), then treatment with
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57 infliximab +/- AZA/6-MP should be initiated. After 6 to 12 months of stable remission (normal CRP,
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59 steroid-free clinical remission with mucosal healing), stepping down to infliximab monotherapy may
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be an option for some patients.

Impact of the SONIC trial on the treatment algorithm

The recently published SONIC (Study of Biologic and Immunomodulator Naïve Patients in Crohn's Disease) trial is a landmark trial for the management of luminal CD, demonstrating the benefits of an infliximab-based treatment strategy.¹⁶ 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.¹⁶ The primary end point 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 monotherapy (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, $P<0.001$).¹⁶ 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 50.¹⁶ 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%).¹⁶ Although SONIC did not assess impact on outcomes

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(ie, hospitalisations/surgeries), mucosal healing has become a recognised clinical end point with infliximab since 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%).¹⁶ 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.¹⁶ 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.¹⁶ 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) study¹⁷ 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 3 infusions of infliximab 5 mg/kg) or conventional management (sequential treatment with corticosteroids, immunosuppressant and infliximab) in newly diagnosed, treatment-naïve patients with CD.

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3 The group treated with early combined immunosuppressive therapy at the end of the study period
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5 had superior mucosal healing, thus confirming the capacity of infliximab to significantly heal the
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7 intestinal mucosa in CD.
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10 11 *Evidence-based treatment recommendation*

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13 SONIC has shown that anti-TNF therapy should be initiated much earlier in patients with luminal
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15 CD. The recommended treatment pathway for patients with luminal CD (no risk factors) is shown in
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17 the third arm of the algorithm in Figure 3. Initial treatment should be with steroids and if remission
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19 is achieved (top arm), then steroids should be tapered down until they are discontinued. If there is
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21 a delayed relapse (after 6 months) after discontinuing steroids, then the patient should be re-
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23 treated with steroids and the response assessed at 4 weeks. If the patient experiences an early
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25 relapse (within 6 months) after discontinuing steroids, there are 2 options to consider: 1) initiate
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27 infliximab +/- 2-2.5 mg/kg AZA/6-MP if the patient has lesions and/or elevated CRP or 2) initiate
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29 steroids plus 2-2.5 mg/kg AZA/6-MP combination therapy and then if the patient relapses move on
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31 to infliximab +/- 2-2.5 mg/kg AZA/6-MP (moving down to lower arm).
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38 If remission is not achieved within 4 weeks of initial steroid therapy (lower arm), infliximab +/-
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40 AZA/6-MP should be initiated. In either arm, after 6 to 12 months of stable remission (normal CRP,
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42 steroid-free clinical remission with mucosal healing), stepping down to infliximab monotherapy may
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44 be an option for some patients. Infliximab should be considered as monotherapy in elderly patients.
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46 Infliximab monotherapy rather than combination therapy, however, should be given to young males
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48 with CD owing to the risk of hepatosplenic T-cell lymphoma. Although this condition is extremely
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50 rare, it is very serious, with most cases proving fatal. Thirty-six cases have been reported in which
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52 20 were treated with infliximab plus a thiopurine and 16 were on thiopurine monotherapy. Four
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54 cases that included infliximab and thiopurine also took adalimumab. One case was exposed to
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56 infliximab, adalimumab and natalizumab. Of the 31 patients whose gender was known, only 2 were
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58 female.⁵² It is prudent, therefore, not to administer infliximab plus AZA combination in young male
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3 patients. The benefit:risk ratio of infliximab or any other biologic needs to be considered before
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5 treating patients.
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8 9 **Loss of response and treatment failure**

10 Some patients with CD may experience loss of response over time and/or develop intolerance to
11 infliximab. It is estimated that this might occur in about 10% of treated patients per year.⁵³ Patients
12 with diminished or loss of response to infliximab therapy may respond to optimized dosing
13 regimens of the same agent or switching to another agent.⁸ Before switching to another agent, one
14 should consider optimizing their first agent if possible. Infliximab allows some dosing flexibility
15 which has been demonstrated from experience in the Leuven cohort.⁵⁴ Schnitzler et al assessed
16 the long-term clinical benefits of infliximab in 614 consecutive patients with CD from a single centre
17 in an observational study over a median of 4.6 years. Of 547 initial responders, approximately 50%
18 needed an intervention. A reduction in the interval between infusions was needed in 108 patients
19 (19.7%); an increase in the dose to 10 mg/kg and/or a re-induction with infliximab infusions at
20 weeks 0, 2 and 6 was needed in 144 patients (26.3%); 63 patients with a re-induction and 89
21 patients with an increase in the dose of infliximab); and an increase in the dose plus a reduction in
22 the interval was needed in only 21 patients (3.8%). Overall, 103 of the 144 patients (71.5%) with an
23 increase in dose and/or a re-induction with infliximab could go back to the standard dose of 5
24 mg/kg and 61.9% of patients (13/21) with an increase in dose and a shortening of the interval could
25 go back to 5 mg/kg and dosing at 8 week intervals. A total of 28.7% of patients with a shortened
26 interval between infusions (31/108) could again extend the interval to 8 weeks. In the total cohort of
27 initial responders, only 21.6% (n=118) had to stop infliximab because of loss of response despite
28 interventions.⁵⁴ When optimizing the first agent is not successful, then switching may be an option.
29
30 In a randomized, placebo-controlled trial (GAIN [Gauging Adalimumab Efficacy in Infliximab
31 Nonresponders]), switching to adalimumab was effective in patients with previous loss of response
32 to their first anti-TNF therapy. At baseline, 48% (n=77) of patients in the adalimumab group had
33 previous loss of response to infliximab. After 4 weeks of treatment, 52% (82 of 159) of patients in
34 this group achieved a 70-point response (decrease in baseline in CDAI score of 70 points or more)
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3 versus 34% (56 of 166) of patients in the placebo group ($P=0.001$).⁵⁵ Some patients with CD will
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5 not respond to their first anti-TNF treatment. Reports on this patient population are very limited. In
6
7 a retrospective survey, Allez et al. observed that 12 out of 18 patients responded to a 3rd anti-TNF
8
9 after primary failure to one or 2 prior anti-TNF treatment(s).⁵⁶ This treatment option requires
10
11 thorough case-by-case discussion and should only be considered in patients with no other
12
13 therapeutic options.⁵⁶
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18 **When to stop treatment**

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20 To date, recommendations on when to stop anti-TNF therapy cannot be made due to insufficient
21
22 data.⁸ Patients in stable remission may have no medical reason to stop anti-TNF therapy unless
23
24 there are circumstances when cessation may be necessary—for example, if a patient is unwilling
25
26 to continue treatment with the drug, in situations such as pregnancy or if changes in
27
28 reimbursement affect coverage of treatment. Preliminary evidence suggests that some patients will
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30 remain in clinical remission for >1 year despite cessation of infliximab treatment.⁸ A retrospective
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32 study by Domenech et al, evaluated clinical outcome after a successful course of infliximab
33
34 treatment for maintenance of response in both luminal and perianal CD.⁵⁷ Infliximab
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36 discontinuation was successful for patients in patients with luminal CD treated for one year (69%
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38 cumulative probability of being free of relapse at 12 months). Conversely, patients with perianal
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40 disease demonstrated early relapse with only 34% (versus 83% in patients with luminal disease)
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42 maintaining remission at 1 year. Consequently, due to a high rate of early relapse, infliximab
43
44 discontinuation is not recommended in perianal CD.⁵⁷ The STORI (influximab diSconTInuation in
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46 CrOhn's disease patients in stable Remission on combined therapy with Immunosuppressors) trial
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48 assessed the risk of relapse after discontinuation of infliximab in patients on combined
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50 maintenance therapy with immunosuppressors.⁵⁸ Patients who received scheduled infliximab plus
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52 immunosuppressive combination therapy for at least 1 year and who were also in steroid-free
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54 remission for ≥ 6 months were included.⁵⁸ More than 50% of patients had relapsed after 18 months
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56 of treatment discontinuation; however, patients who did relapse were successfully re-treated with
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3 infliximab.⁵⁹ These results show that routine discontinuation of infliximab therapy may lead to a
4
5 very high disease relapse and could not be a sound treatment decision.
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8 9 **Managing fistulas**

10 Patients with fistulising CD with acute suppurative fistulas must not initiate infliximab therapy until a
11
12 source for possible infection, specifically abscess, has been excluded. Patients with fistulising CD
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14 who have responded to an induction regimen with anti-TNF therapy, should receive scheduled re-
15
16 treatment with infliximab or adalimumab, since this is effective for maintaining fistula closure or
17
18 response.⁸ Combined medical and surgical strategies have evolved, with drainage of sepsis and
19
20 insertion of a seton, followed by two doses of anti-TNF therapy, fistula curettage, and then further
21
22 anti-TNF therapy.^{8,60,61} Insertion of drainage seton sutures at the time of preinfliximab examination
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24 under anesthesia and removal after the second infusion are considered routine practice in this
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26 patient population.⁶⁰
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33 **Pregnancy**

34 Post-marketing reports from approximately 300 pregnancies exposed to infliximab, do not indicate
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36 unexpected effects on pregnancy outcome. Due to its inhibition of TNF α , infliximab administered
37
38 during pregnancy could affect normal immune responses in the newborn. The available clinical
39
40 experience is too limited to exclude a risk, and administration of infliximab is therefore not
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42 recommended during pregnancy.¹²
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49 **Patient screening and vaccination**

50 Patients taking TNF-blockers are more susceptible to serious infections. Tuberculosis, bacterial
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52 infections, including sepsis and pneumonia, invasive fungal infections, and other opportunistic
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54 infections have been observed in patients treated with infliximab.¹² Before starting treatment with
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56 infliximab, all patients must be evaluated for both active and latent tuberculosis.^{8,12} If active
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58 tuberculosis is diagnosed, infliximab therapy must not be initiated. No data are available on the
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60 response to vaccination with live vaccines or on the secondary transmission of infection by live

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3 vaccines in patients receiving anti-TNF therapy. It is recommended that live vaccines not be given
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5 concurrently while receiving infliximab.
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9 10 **Safety Considerations**

11 The safety findings observed in the SONIC trial demonstrate that the incidence of adverse events
12 (including serious adverse events) and serious infections was similar among the infliximab
13 monotherapy, infliximab plus AZA combination therapy and AZA monotherapy groups. However,
14 infusion reactions occurred less frequently among patients receiving combination therapy than
15 among those receiving infliximab monotherapy.¹⁶ Increased risks of rare but serious toxic effects
16 associated with combination therapy must be considered.¹⁶ Additionally, increased relative risk of
17 serious and opportunistic infections associated with concomitant use of corticosteroids as a third
18 immunosuppressive agent must be taken into account.⁶² The choice of infliximab monotherapy or
19 combination therapy in patients who have not received such therapy previously is an individualized
20 benefit–risk decision.¹⁶ Additionally, the benefit to risk profile must be considered when choosing
21 an anti-TNF agent.
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38 **Conclusions**

39 Ten years ago, the options available for patients with CD were limited. It was possible to achieve
40 symptomatic remission with some improvements in QoL; however, therapy was restricted to
41 episodic induction and the treatment of each individual disease flare. Today, with timely drug
42 intervention, it is possible to induce clinical remission that can be sustained over the long term with
43 scheduled maintenance therapy. Over 10 years of clinical data and experience demonstrate the
44 excellent efficacy and safety profile of infliximab.
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55 Based on the infliximab clinical trial data, it may now be possible to change the underlying course
56 of CD and restore normal bowel function, thereby improving the patient's QoL. The evidence
57 shows that there is a window of opportunity early in the course of CD when patients benefit most
58 from infliximab therapy. The landmark SONIC trial has significantly impacted the way CD is treated
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3 by showing that an infliximab-based treatment strategy, especially in AZA-naïve patients with high
4
5 inflammatory burden at baseline, provides the most benefit in improving therapeutic outcomes.
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7 Furthermore, there is clear evidence for infliximab as an option for treating fistulising CD, and
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9 patients with luminal CD with risk factors should be considered for accelerated step-up therapy.
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11 A controlled clinical trial demonstrating how the treatment approach of early intervention from the
12
13 SONIC trial can be applied to all of the anti-TNF therapies is warranted. The early use of an
14
15 evidence-based infliximab treatment algorithm, such as the one proposed in this paper, will
16
17 significantly improve outcomes for patients with CD (Figure 4).
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3 **Statement of interests:**
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5

6 **Authors' declaration of personal interest**

7 Silvio Danese has served as a speaker, a consultant and an advisory board member for Schering-
8 Plough, Abbott Laboratories, UCB, Ferring, Cellerix, Millenium Takeda, Nycomed, Actelion, Astra
9 Zeneca, Novo Nordisk, and Cosmo Pharmaceuticals.
10

11 Walter Reinisch has served as a speaker or consultant for Centocor, MSD, AESCA, Abbott, UCB,
12 Ferring, Cellerix, Millenium, Novartis, Otsuka and Biogen.
13
14

15 Jean-Frédéric Colombel has served as a consultant and an advisory board member for Abbott
16 Laboratories, ActoGeniX NV, AlbireoPharma, AstraZeneca, BayerScheringPharma, AG, Biogen
17 Idec Inc, Boehringer-Ingelheim, Inc., Bristol-Myers Squibb, Cellerix SL, Chemocentryx, Inc.,
18 Centocor, Cosmo Technologies, Ltd, Danone France, Elan Pharmaceuticals, Inc., Genentech,
19 Giuliani SPA, Given Imaging, GlaxoSmithKline, Merck & Co., Inc., Millenium Pharmaceuticals Inc.,
20 Neovacs SA, Ocerra Therapeutics, Inc. (previously named Renovia, Inc.), Otsuka American
21 Pharmaceuticals Inc., PDL Biopharma (previously named Protein Design Labs), Pfizer Inc.,
22 RiboVacs Biotech, Schering-Plough Corporation, Shire Pharmaceuticals, Synta Pharmaceutical
23 Corporation, Teva Pharmaceuticals, Therakos, UCB Pharma (previously named Celltech
24 Therapeutics, Ltd.), Wyeth Pharmaceuticals; has participated in continuing medical education
25 events indirectly sponsored by Abbott Laboratories, AstraZeneca, Centocor, Elan Pharmaceuticals,
26 Falk Pharma, Ferring, Given Imaging, Otsuka American Pharmaceuticals, PDL Biopharma,
27 Schering-Plough Corporation, Shire Pharmaceuticals, UCB Pharma; has received Grant support
28 from AstraZeneca, Ferring, Schering-Plough Corporation, UCB Pharma, Lesaffre, Giuliani SPA,
29 Danisco, Ocerra Therapeutics, Inc. (previously named Renovia, Inc.), Danone, Roquette, Mapi
30 Naxis and Dysphar and owns sotck in Intestinal Biotech Development, Lille, France.
31
32

33 Paul Rutgeerts has served as a speaker for Centocor, Schering-Plough, UCB, Abbott, Elan-
34 Biogen, a consultant for Centocor, Schering-Plough, UCB, Abbott, Elan-Biogen, NovImmune,
35 Italfarmako, Bristol-Myers Squibb, Millennium Pharmaceuticals, Tillots, GSK and ChemoCentryx
36 and has received research funding from Centocor, Schering-Plough, UCB and Abbott.
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40 **Declaration of funding interests:**

41 SD is the guarantor of this article. He wrote the first draft that was shared with and edited by WR.
42 JFC and PR. Schering-Plough Corporation, now Merck & Company, Inc, Whitehouse Station, NJ,
43 USA supported the development of this article. Synergy Medical Education, Conshohocken,
44 Pennsylvania, USA provided editorial assistance.
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For Peer Review

Tables and figures

Table 1. European indications for infliximab and adalimumab in CD and/or UC

Adult CD (infliximab and adalimumab)

- 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^{12,13}

Fistulising CD (infliximab)¹²

- 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)¹²

Paediatric CD (infliximab)¹²

- Treatment of severe, active CD in paediatric patients aged 6 to 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

Adult UC(infliximab)¹²

- Treatment of moderately to severely active UC in adult patients who have had an inadequate response to conventional therapy, including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies

Table 2. Therapeutic goals in CD^{24,25}

- Induce rapid response and maintain steroid-free remission²⁴
- Achieve and maintain complete mucosal healing²⁴
- Improve quality of life (QoL)²⁴
- Avoid complications (ie, hospitalisation and surgery)²⁴
- Prevent disease-related mortality²⁴
- Avoid treatment-related mortality²⁴/morbidity²⁵

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Table 3. Other risk factors for progressive disease in luminal CD

- Terminal ileal location³
- Strictureing, penetrating behavior³
- Smoking^{38,39}
- Serologic markers⁴⁰
 - ASCA/pANCA
- Genetic markers^{41,42}
 - *NOD2*/IBD5
- Elevated CRP⁴³
- Severe endoscopic lesions (deep ulcerations)⁴⁴

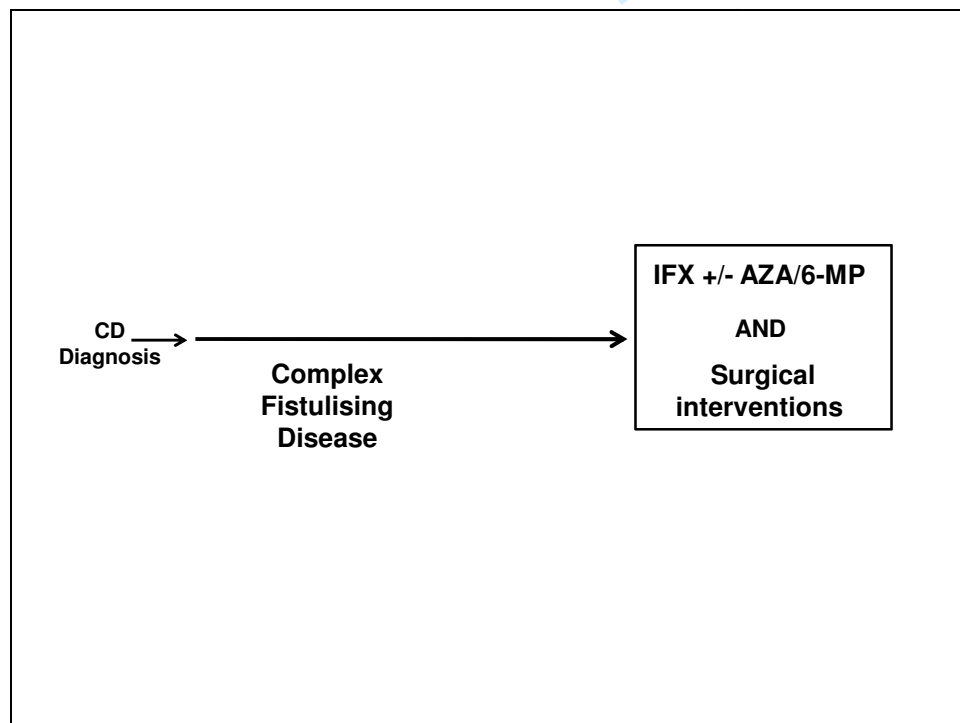


Figure 1. Treatment algorithm for complex fistulising disease with infliximab.

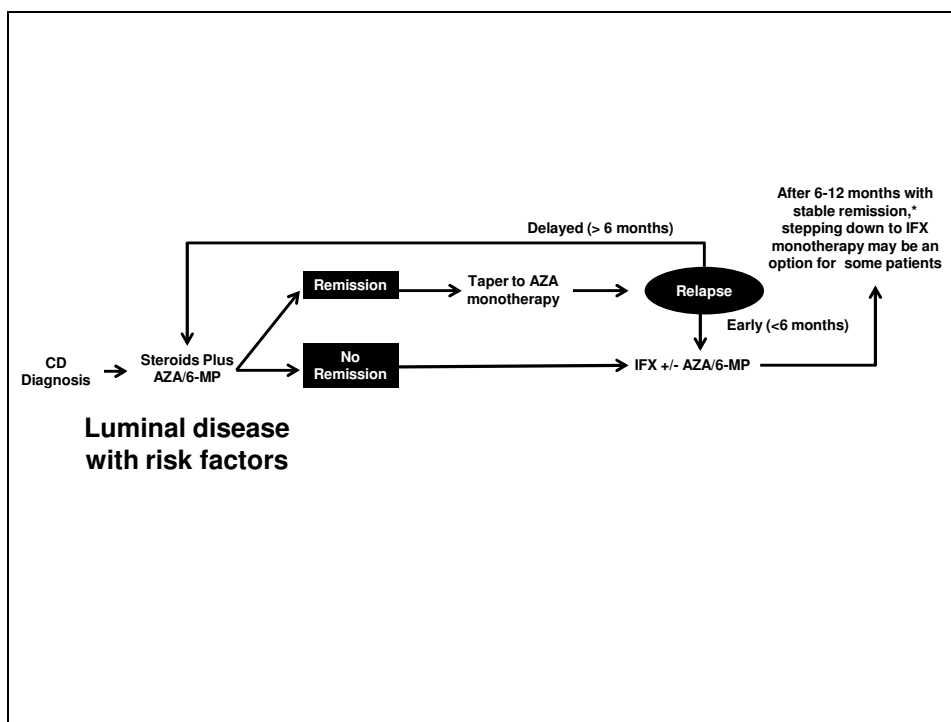


Figure 2. Treatment algorithm for luminal disease with risk factors.

* Normal CRP, steroid-free clinical remission with mucosal healing.

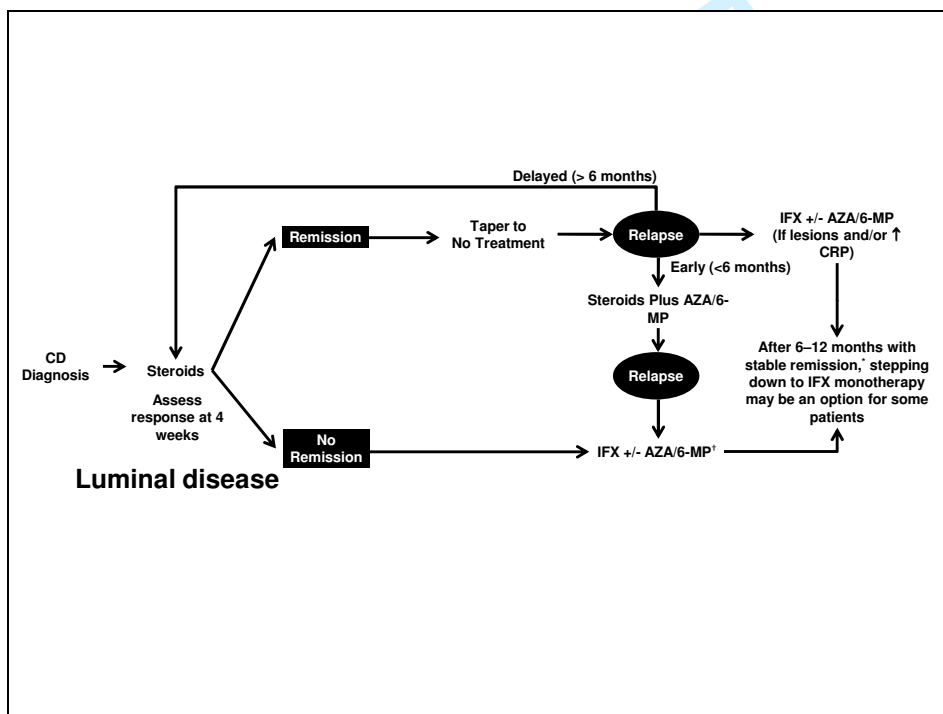


Figure 3. Treatment algorithm for luminal disease with no risk factors.

* Normal CRP, steroid-free clinical remission with mucosal healing.

† Presence of risk factors may determine mono versus combination therapy.

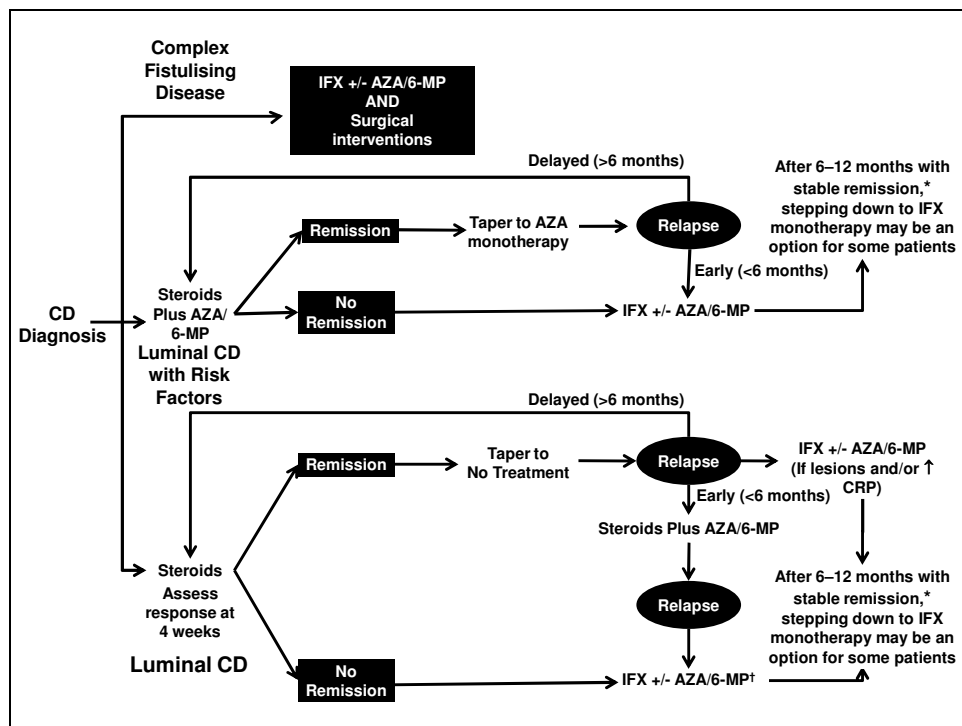


Figure 4. Full Infliximab-based treatment algorithm.

* Normal CRP, steroid-free clinical remission with mucosal healing.

† Presence of risk factors may determine mono versus combination therapy.

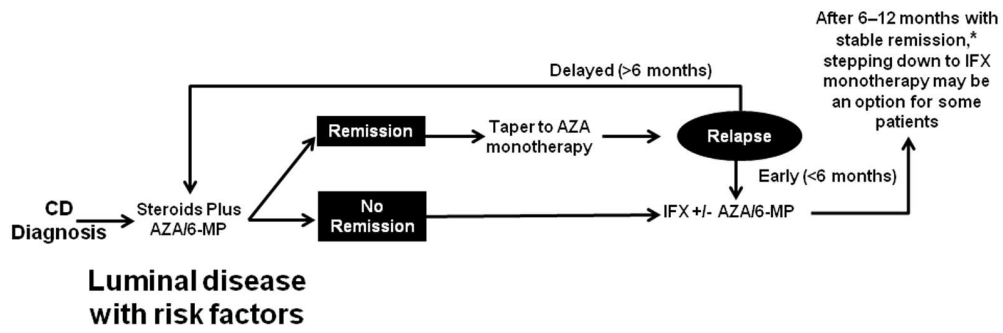
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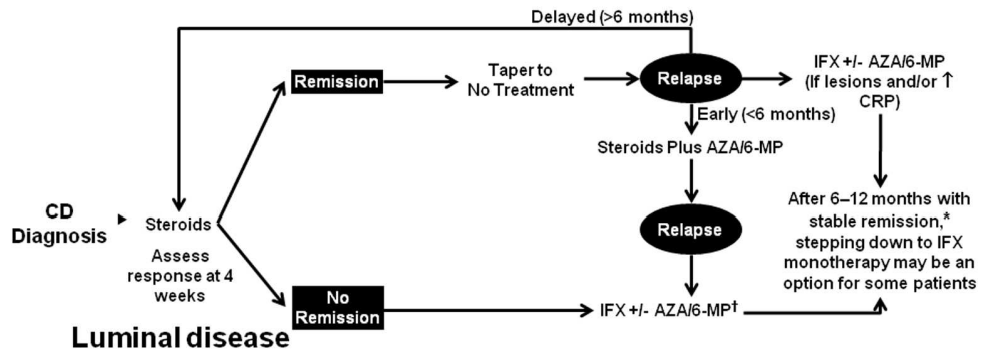
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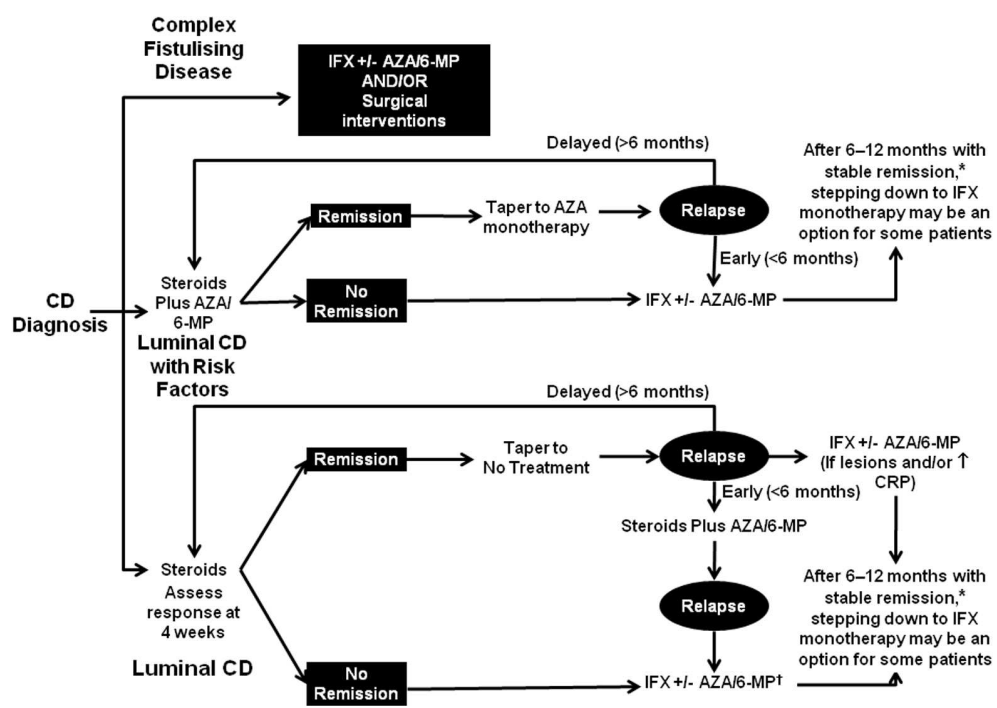


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