Evidence-based use of anti-TNF α therapy in Crohn's disease; where are we in 2011?

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Accepted 7 March 2011
Published Online First
4 April 2011

Abstract

The efficacy of anti-tumour necrosis factor (anti-TNF α) therapy with infliximab and adalimumab in moderate to severe Crohn's disease has now been proved. This article reviews the evidence supporting best practice with these agents in the light of recent National Institute for Health and Clinical Excellence guidance. Recent studies point to greater efficacy when these drugs are used early in the disease, particularly when mucosal healing can be achieved. For infliximab, the combination with immunomodulator drugs appears to afford greater efficacy, but possibly at the expense of the risk of rare but serious side effects. Patients should be selected carefully for treatment based on prognostic factors predicting aggressive disease, on the one hand, and comorbid factors that might predict side effects, on the other. Multiple drug combinations should be avoided where possible. Finally, a minority of patients in stable remission with complete mucosal healing may be selected for anti-TNF α drug withdrawal.

Introduction

Since the initial reports of anti-tumour necrosis factor (anti-TNF α) antibody treatment for Crohn's disease in 1997 the use of both infliximab and adalimumab has become widespread, yet variable, in Europe and the Western world. Adalimumab and infliximab are both monoclonal antibodies that have a high affinity for TNF α . Infliximab is a chimeric human-murine antibody delivered intravenously according to body weight (usually 5 mg/kg), whereas adalimumab is a recombinant human antibody that is delivered subcutaneously and is not weight related (usually 40 mg every other week).

National Institute for Health and Clinical Excellence (NICE) guidance was published in 2010 and both drugs are now recommended as treatment options for severe active Crohn's disease which has not responded to conventional treatment (including immunosuppressive and/

or corticosteroid treatments). It is recommended that treatment should normally be started with the less expensive drug, though this is not as straightforward as simply a measure of body weight and should include consideration of the cost of dose escalation and drug administration, and the guidance also allows for individual preference to be considered in drug choice. Infliximab is recommended as the preferred treatment for people with active fistulising Crohn's disease and for paediatric disease. NICE also recommends that patients should have their disease reassessed 12 months after the start of treatment to determine whether ongoing treatment is still clinically appropriate.¹ Despite this clear guidance, questions of when and in whom to start treatment, whether immunomodulators (IMs) should be co-prescribed, what to do if response is lost and how to assess when treatment can be withdrawn remain uncertain. In this article we review the evidence that helps answer some of these key clinical questions.

Efficacy of treatment

Short-term induction trials of both infliximab and adalimumab show similar efficacy. Week 4 response rate after a single dose of infliximab (all combined doses) was 65% and remission rate was 33%, both being better than placebo.² Week 4 response rates for adalimumab were 59% for both 80 mg/40 mg at weeks 0/2 and 160 mg/80 mg but remission rates were significantly better for the higher dose (24% vs 36%, respectively), and only the higher dose was significantly better than placebo.³ Infliximab may have a more rapid onset of action than adalimumab—NICE guidance recommends that response should be evaluated after two doses (usually after 6 weeks) for infliximab but after 12 weeks for adalimumab.

There are five trials for maintenance of remission in Crohn's disease with anti-TNF α agents in patients who had

a clinical response to open-label induction therapy.⁴ Infliximab was better than placebo for maintenance of remission (RR=2.50), clinical response (RR=2.19), steroid-sparing effects (RR=3.13) and complete fistula healing (RR=1.87) to week 54. Although RRs were not combined in the two adalimumab trials, in the larger CHARM trial (Crohn's Trial of the Fully Human Antibody Adalimumab for Remission Maintenance) adalimumab was better than placebo for maintenance of clinical remission (RR=3.28), clinical response (RR=2.69) and steroid-sparing effect (RR=4.25) to week 54. No significant differences in clinical efficacy were noted when comparing infliximab 5 mg/kg with 10 mg/kg, or comparing adalimumab 40 mg every other week with weekly. Trials comparing infliximab with adalimumab have not been performed, but clinical remission rates appear to be similar between the two drugs. For example, in the ACCENT 1 (A Crohn's disease Clinical study Evaluating infliximab in a New long term Treatment regimen) and CHARM trials, respectively, remission rates were 41.8% at week 30 with infliximab and 42.9% at week 26 with adalimumab.

There also appear to be similar rates of complete fistula closure: 36% for infliximab in the ACCENT 2 trial and 33% for adalimumab in a subgroup analysis of the CHARM trial, both at week 54. In a large cohort study of 614 patients treated with infliximab over 55 months from Leuven 89.1% of patients had a clinical improvement in symptoms after initial treatment, with 48.1% demonstrating a partial response and 41.0% a complete clinical response.⁵

Both infliximab and adalimumab maintenance therapy have been shown to reduce the number of hospitalisations and operations.^{6,7} Furthermore, complete healing of mucosal ulcers at colonoscopy is an important determinant of longer-term outcomes. This has been demonstrated in a group of patients treated very early in the course of their disease with infliximab (the step-up top-down study), in which mucosal healing at 2 years predicted sustained clinical remission at 4 years.⁸ In the Leuven cohort and in the ACCENT 1 trial, mucosal healing was more likely with scheduled maintenance therapy and was associated with fewer hospitalisations and operations.⁹

Predictors of poor prognosis

Crohn's disease will progress to fibrotic or penetrating behaviour phenotypes in up to 88% of patients¹⁰ and this can occur as early as 1 year into the course of disease.¹¹ These patients are more likely to require surgery and follow a more disabling course.¹² Factors that predict a poorer outcome have been evaluated in a number of studies. In the large study by Beaugerie *et al*,¹³ poor prognostic factors at diagnosis were the initial requirement for steroid use (OR=3.10), age <40 years (OR=2.1) and the presence of perianal disease (OR=1.8). The presence of two or three of these factors had a positive predictive value for a disabling

course of 0.91 and 0.93, respectively. In another study looking at more severe disease outcomes (complex perianal disease, two ileal operations, a single colonic operation or formation of stoma), predictors included stricturing behaviour (HR=2.11) and weight loss of >5 kg at presentation (HR=1.67).¹⁴

Evaluation of inception cohorts demonstrates that the presence of ileal disease at diagnosis predicts stricturing behaviour whereas colonic disease predicts penetrating behaviour.¹¹ The presence of upper gastrointestinal and, particularly, pan enteric disease, predicts a poorer outcome, as do young age at presentation and smoking.¹⁵⁻¹⁸ Finally, deep colonic ulcers have been shown to be highly predictive of subsequent need for colectomy.¹⁹ Taking these factors into consideration at presentation allow counselling of the patient and individual tailoring of treatment.

The case for earlier treatment?

Owing to the expense and perceived risk of anti-TNF α therapy, standard practice has been to step-up treatment through repeated courses of corticosteroids and IMs such as azathioprine (AZA)/6-mercaptopurine or methotrexate, resulting in significant delays before the patient receives effective treatment. Steroid therapy rarely heals the mucosa, often results in dependence and is associated with higher infection and mortality than anti-TNF α therapy.²⁰ Thus, recent studies have examined whether there is a role for earlier introduction of treatment in an attempt to prevent disease progression and minimise steroid exposure.

The possibility of using anti-TNF α therapy as a 'bridge' to longer-term immunosuppression has been examined by the GETAID group (Groupe d'Etude Therapeutique des Affections Inflammatoires du Tube Digestif). In steroid-dependent patients with long-term disease, short-term induction therapy with infliximab was compared with placebo in patients either started or maintained on AZA. Although steroid-free remission rates were better at 12 months (52% vs 32% for AZA naive patients), all benefit was lost by year 4, suggesting short-term induction is not beneficial in this group.^{21,22} However, induction therapy has been studied at disease onset in the 'step-up top-down' study. Patients received either conventional step-up treatment with corticosteroids then AZA and infliximab when a flare occurred or with 'top-down' treatment received three-dose infliximab induction therapy with maintenance AZA and further infliximab as necessary.²³ At week 52, the steroid-free remission rate in patients receiving early combined immunosuppression was 61.5% compared with 42.2% in the conventional management group ($p=0.03$) but by 2 years, the remission rates between the two groups were similar. However, at 2 years, no ulcers were seen in 73.1% patients of the early combined immunosuppression group compared with 30.4% of the conventional management group ($p=0.003$) and absence of ulcers strongly predicted steroid-free remission at years

3 and 4.⁸ This was a provocative study but is difficult to interpret. The early symptomatic response from aggressive treatment is lost later on as conventional treatment is increased and the absence of mucosal ulcers at 2 years may be as much to do with earlier immunosuppressive therapy as the three doses of infliximab at the start. However, these data do imply that early aggressive treatment aimed at healing the mucosa can have long-lasting benefits for disease progression.

The recently published SONIC study (study of biologic and immunomodulator naive patients in Crohn's disease) compared AZA alone with infliximab alone or combined infliximab and AZA in patients who were AZA and anti-TNF α naive and had a relatively short median disease duration of 2.3 years.²⁴ The primary end point of steroid-free remission at 26 weeks was reached by 30.0% of patients receiving AZA monotherapy, 44.4% infliximab monotherapy and 56.8% combined therapy. All differences were statistically significant and were sustained through the blinded extension to week 50. Similar differences were seen for mucosal healing (16.5%, 30.1% and 43.9%, respectively). Even higher steroid-free remission rates of 68.8% at 26 weeks were seen in the combined therapy group in patients who had both an elevated C-reactive protein (CRP) and mucosal ulcers at randomisation. There was no difference in safety outcomes between the three groups. These data confirm that in AZA naive patients, combination therapy is more effective than each agent alone and also shows that high steroid-free remission rates can be achieved in carefully selected patients treated early in the course of the disease.

IM co-prescription

Early studies of episodic treatment suggested that IM co-prescription with infliximab resulted in reduced formation of antibodies to infliximab, higher trough infliximab levels, less frequent infusion reactions and a longer duration of response.^{25–28}

However, concerns have subsequently arisen about the safety of co-prescribing AZA with infliximab, particularly in relation to opportunistic infections and the rare but usually fatal hepatosplenic T-cell lymphoma, leading many specialists to advocate withdrawal of AZA in patients with maintenance anti-TNF α therapy.^{29–31} Evidence in favour of this approach is mixed. Subanalysis of the major randomised controlled trials has suggested that AZA co-prescription offers little advantage over anti-TNF α monotherapy over 12 months. A randomised study of patients in remission receiving infliximab maintenance treatment showed no clinical effect of AZA withdrawal over 2 years.^{32–34} However, these studies do still show that AZA reduces antibodies to infliximab, increases infliximab trough levels and reduces infusion reactions. Furthermore, the SONIC study showed that in treatment naive patients, infliximab and AZA combined is better than either agent alone.²⁴ Finally, a careful retrospective study from Paris

reported significantly reduced flare rates, perianal complications and lower CRP levels in patients receiving long-term treatment with maintenance infliximab and AZA compared with infliximab alone, even in patients for whom AZA had previously failed, and AZA was better than methotrexate in this regard.³⁵

These data suggest that combination therapy using AZA and infliximab is more effective than monotherapy, and should be considered if anti-TNF α therapy is being used early in the course of the disease in treatment naive patients and in patients with poor prognostic markers or an extensive surgical history. There are limited data for adalimumab and while immunogenicity may be less of a problem, the possibility of an additive effect of two drugs cannot be fully discounted. However, caution should still be used with combined treatment, particularly in young men at risk of HSTL and those at risk of opportunistic infections.

Loss of response

Even with scheduled maintenance treatment, response to anti-TNF α therapy will diminish over time in some patients. In both the CHARM and ACCENT 1 studies >50% of initial responders had lost response by 12 months.^{33–36} In a review of 16 studies, including 2236 patients, mean loss of infliximab response was 37%, or 13% per patient-year of treatment.³⁷

If response is lost, the first step is to optimise the initial drug treatment (table 1). Options include increasing the dose or reducing the interval between treatments. In the ACCENT 1 trial, increasing the dose of infliximab from 5 to 10 mg/kg restored response in 90% of patients.⁶ In the Leuven cohort of 547 initial responders to infliximab, 50% required at least one intervention to maintain response.⁹ Interventions included reduction in dose interval to 6 weekly, increased dose to 10 mg/kg and re-induction with infusions at 0, 2 and 6 weeks, and in a small number (3.8%) combinations were used. This approach maintained infliximab response in 78.4% over 4.6 years. There are no comparative data to suggest which approach is preferable, though pharmacokinetic data from patients with rheumatoid arthritis suggest that reducing the interval to 6 weekly is more effective than increasing the dose.³⁸

Table 1 Key points: approach to loss of response to anti-tumour necrosis factor α agent (TNF α)

Optimise first agent
Infliximab
Reduce interval from 8 to 6 (occasionally 4) weekly
Increase dose to 10 mg/kg (usually for time-limited period)
Adalimumab
Reduce interval from every other week to weekly
Consider increasing dose to 80 mg
Switch to second anti-TNF α agent
Higher doses likely to be necessary

For adalimumab, dose intensification is achieved by reducing the interval from 40 mg every other week to weekly or in small numbers increasing to 80 mg weekly.³⁹ In the CHARM and CLASSIC II studies 28% and 44% of patients required dose escalation to 40 mg weekly, though this approach was successful in approaching half of the patients.^{33,40}

In those patients in whom dosage adjustments have not worked the main option is to switch to another anti-TNF α agent. These patients should be reassessed to ensure the problem remains active disease and that a complication such as abscess or malignancy has not led to failure of treatment. In patients switching from infliximab to adalimumab 6-month remission rates have ranged from 31% to 82%.⁴¹ Most of these studies used an induction dose of adalimumab of 160/80 mg and large numbers of patients required dose escalation to 40 or 80 mg weekly, suggesting that this group of patients will require higher dosing schedules. There are fewer data on primary non-responders to infliximab, though the large CHOICE open-label study reported

improved quality of life and work productivity with adalimumab in this group of patients with particularly resistant disease.⁴²

Safety

Placebo-controlled safety data of anti-TNF α therapy are relatively sparse. However, in both the short-term randomised induction trials and in the longer-term maintenance trials the safety profile of both adalimumab and infliximab appear similar to each other and placebo.^{2,3,33,36} Longer-term follow-up data from large retrospective series of infliximab-treated patients are summarised in table 2.^{43–47} Overall adverse events are reported in 28–32% and serious adverse events in 9–19% of this population. For infliximab, the risk of acute infusion reactions is between 3.8% and 16.9% of patients, and delayed reactions is 0.7% and 7.3%, the risk being higher after a long drug holiday.

Infections occur in 9.6–20.8% of patients and serious infections in 3–9.9%, though infection rates do not differ significantly from control populations

Table 2 Safety profile of infliximab: results from large retrospective series

	Lees <i>et al</i> ⁵	Fidler <i>et al</i> ⁴	Zabana <i>et al</i> ⁷	Ljung <i>et al</i> ⁶	Colombel <i>et al</i> ³
Period	1999–2007	1994–2008	1999–2008	1999–2001	1998–2002
location	Edinburgh (Scotland)	Leuven (Belgium)	Badelana (Spain)	Stockholm (Sweden)	Rochester (USA)
Patients with CD (N (%))	202 (77.7)	743 (80)	152 (79.6)	217 (88)	500 (100)
Age (years (median))	31	24	37	37.6	37
Follow-up (months (median))	29	58 (3775 patient-years)			17
Maintenance IFX therapy (%)	19.8		55		19
Immunomodulator therapy (AZA/6MP or MTX) (%)	65	90 (ever used)	76	71	86
Infusions					
Total	718	7276			2211
Median per patient	3	6	5	2.6 (mean)	3
Adverse events					
Patients (total number (%))	58/202 (95 (28.7))		49/152 (64 (32.2))		
Serious adverse events					
Patients (total number (%))	30/202 (36 (14.9))	94/743 (112 (12.7))		41/217 (42 (18.9))	43/500 (43 (8.6))
Infusion reactions					
Acute reactions	19/202 (9.4%)	115/682 (16.9%)	20/152 (13.2q%)		19/500 (3.8%)
Delayed reactions (serum sickness-like)	8/202 (4.0%)	50/682 (7.3%)	1/152 (0.7%)		19/500 (3.8%)
Infections (per patient)					
All	42/202 (20.8%)		20/152 (13.2%)		48/500 (9.6%)
Serious	20/202 (9.9%)	48/743 (6.5%)			15/500 (3%)
Opportunistic	Nil	<i>Aspergillus</i> , TB, mycobacterium CMV (5), HSV (10)			Histoplasmosis, Varicella zoster (3)
Lupus	1/202	2/743	2/152		3/500
Neurological (demyelination)	1/202	2/743	1/152		1/500
Skin/hair	Alopecia 1/202	150/743 (39 psoriasiform)	3/152 psoriasis		
Malignancy	6/202 (3.0%)	21/743 (2.8%)	2/152 (1.3%)	3/217 (1.4%)	9/500 (1.8%)
Death	7 (3.5%)	12/743 (1.6%)	4/152 (2.6%)	6/217 (2.8%)	10/500 (2.0%)
Unrelated to IFX	6/7	7/12	3		5/10

AZA, azathioprine; CD, Crohn's disease; CMV, cytomegalovirus; HSV, Herpes simplex virus; IFX, infliximab; 6MP, 6-mercaptopurine; MTX, methotrexate; TB, tuberculosis.

Table 3 An evidence-based approach to using anti-tumour necrosis factor (anti-TNF α) therapy: guiding principles

Both anti-TNF α drugs currently available in the UK have similar efficacy, though there is greater experience with, and more data for, infliximab.

Assess prognosis at an early stage of the disease.

When considering anti-TNF α therapy be aware of, and counsel patients about, the potential side effects. Avoid anti-TNF α therapy, where possible, in older patients with comorbidity.

In patients with poor prognosis or unresponsive disease consider early combined immunosuppressive treatment. SONIC data suggest this should be continued for 12 months at least.

In patients for whom immunosuppressive therapy has failed, start anti-TNF α therapy early to avoid excessive steroid use ('accelerated step-up').

Patients should be evaluated at 12 months and if in complete mucosal and symptomatic remission, consider withdrawal of anti-TNF α therapy with close follow-up.

Immunomodulator therapy may be withdrawn during treatment with anti-TNF α therapy, but present data suggest an additive benefit for azathioprine (AZA) and infliximab, even with previous AZA failure.

Avoid triple immunosuppressive drug combinations, particularly those that include steroids.

In patients for whom the efficacy of one anti-TNF α is lost, that drug should be optimised by increasing the dose and reducing the interval before switching treatment.

with inflammatory bowel disease. In the US TREAT registry (the Crohn's Therapy, Resource, Evaluation and Assessment Tool Registry) of 6290 patients with Crohn's disease, prednisolone use and narcotic analgesia predicted serious infections whereas infliximab was not an independent factor.^{20 44} The risk of opportunistic infections increases significantly with older age and with combination drug therapies, particularly triple therapy with infliximab, AZA/6-mercaptopurine and steroids, which should be used with caution.^{29 48} Drug-induced lupus and neurological side effects, though serious, are infrequent and often improve if the drug is withdrawn. Likewise skin side effects usually respond to topical treatment.

Although malignancy is reported in 1.3–3.0% of cases, most cases are not temporally associated with the drug treatment. Two case-control studies and the TREAT registry have shown that the risk of malignancy is not increased in patients treated with infliximab compared with controls.^{44 49 50} However, concerns about hepatosplenic T-cell lymphoma in young men and case reports of lung cancer in older patients with a smoking history mandate caution in these patients.^{43 45} Finally, mortality has been reported at between 1.6% and 3.5%, though again many of these deaths were unrelated to infliximab treatment and mortalities have not differed from control groups or in the TREAT registry.^{20 44 51}

Thus, although serious adverse events can occur as a result of anti-TNF α therapy, the risk of these should not deter clinicians from treating patients with these drugs to avoid the complications of the disease or steroid use, so long as patients are selected, counselled and monitored carefully.

Withdrawal of therapy

Although data suggest that anti-TNF α therapy is safe in long-term use, discontinuation of treatment would be preferable if long-term remission could be anticipated. In the Leuven cohort, 20.1% of all patients who initially responded to infliximab were able to discontinue the treatment while the patients were in remission.⁵ NICE guidance states that treatment with infliximab

or adalimumab should only be continued if there is clear evidence of ongoing active disease as determined by clinical symptoms, biological markers and investigation at 12 months, though it is not entirely clear which investigations should be used.

In an Italian series, mucosal healing predicted sustained clinical benefit after discontinuation.⁵² This has been evaluated prospectively by the GETAID group: in the STORI trial (infliximab diSconTinuation in CrOhn's disease patients in stable Remission on combined therapy with Immunosuppressors) 115 patients taking both infliximab and an IM in stable steroid-free remission for at least 6 months discontinued infliximab therapy.⁵³ After a median follow-up time of 12 months 45 (39%) relapses were seen. After multivariate analysis, endoscopic activity, CRP level, haemoglobin and infliximab trough levels predicted increasing risk of relapse. Of those re-treated with infliximab 36/37 were in remission after 4 weeks and none experienced infusion reactions, indicating that re-infusion is safe and effective in this cohort of patients. These data suggest that if discontinuation of treatment is desired, an evaluation of mucosal healing should take place and treatment should be continued if there is active disease, though the optimal means of doing this have yet to be clearly established.

Conclusions

A considerable amount of new data exist to advise our use of anti-TNF α therapy. These data suggest that a modern approach to Crohn's disease should include assessment of the patient's underlying prognosis, with consideration of earlier introduction of anti-TNF α therapy either with, or soon after, introduction of IM therapy (often termed accelerated step-up therapy) (table 3). While safety concerns exist, these should not excessively divert clinicians from appropriate treatment of a disease with an aggressive phenotype. Although the goal remains symptomatic remission, mucosal healing predicts a good long-term outcome and may be used as a marker for treatment withdrawal in a fortunate few (the 'exit strategy').

Competing interests SME and PJH have both performed consultancy work and lecturing for Abbott and MSD (formerly Schering Plough).

Provenance and peer review Not commissioned; externally peer reviewed.

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