Establishing a biologics service for patients with inflammatory bowel disease

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Abstract

The use of anti-TNF therapy in the management of Crohn's disease and, to a lesser extent ulcerative colitis, is increasing. This article aims to discuss the practicalities of establishing a biologics service for patients with inflammatory bowel disease. Current guidelines on the use of these drugs are reviewed followed by a discussion on the choice of which anti-TNF agent to use based on costs and patient choice. A model for the initiation, administration, monitoring and assessment of patients receiving anti-TNF therapy is proposed. The need for a national biologics registry is highlighted in the summary.

Introduction

Establishing a safe and cost-effective environment for the treatment of patients with inflammatory bowel disease (IBD) with biological therapy is vital. A benchmarking guide for the commissioning of anti-tumour necrosis factor (anti-TNF) therapy has been published and estimates that approximately 10 500 adults per year in the UK with Crohn's disease (CD) are at the severe end of the spectrum and may be eligible for treatment with these drugs.¹ The figure for ulcerative colitis (UC) is significantly less. Based on the population prevalence of UC and those with acute severe UC, for whom the National Institute for Health and Clinical Excellence (NICE) has sanctioned use of anti-TNF therapy, the figure is in the order of 500 patients per year. This compares with approximately 35 000 patients with rheumatoid arthritis, 18 000 with psoriasis and 7000 patients with ankylosing spondylitis who are likely to be eligible for anti-TNF therapy (table 1).¹

The aim of this article is review the practicalities of establishing delivery of biological agents to patients with IBD to incorporate existing guidelines, the choice of drug, pretreatment screening,

safety, monitoring of treatment and the (often crucial) role of the IBD clinical nurse specialist.

Current guidelines: IBD service standards, European Crohn's and Colitis Organisation (ECCO), NICE and the British Society of Gastroenterology

Aspects of the delivery of biological therapy are dealt with directly by the IBD service standards (<http://www.ibdstandards.org.uk>) and can form the basis of establishing a service within any hospital trust. There should be arrangements for review of complex cases by an IBD multi-disciplinary team (standard A3), there should be defined clinical responsibility for prescribing, administering and monitoring the drugs, including audit of local practice (standards A6 and B1). Ensuring that patients have rapid access to specialist advice and are also supported and educated to make an informed choice about treatment options is essential (standards C2–C4 and D1). In addition, the proposed biological therapy national database will be vital for monitoring safety and clinical outcomes (standards E1–E3).

Existing guidelines from ECCO highlight the role of infliximab and adalimumab in the management of CD² and, in the case of infliximab, UC.³ The 2010 NICE technology appraisal guidance for anti-TNF therapy in the management of CD⁴ has finally given us some clarification in some key areas and this was addressed in a recent review in this journal.⁵

It is likely that the new British Society of Gastroenterology guidelines will endorse the NICE recommendations for biological therapy of IBD.⁶

Choice of anti-TNF therapy

Drug costs

NICE propose that 'treatment should normally be started with the less expensive

drug', but it also acknowledges that this is not purely related to the cost of the drug.

The simplistic view of the cost of the drug alone is as follows. A 100 mg phial of infliximab costs £419.62 (excluding VAT; *British National Formulary*, 58th edition). The cost will vary between individuals as the drug is prescribed according to body weight (5 mg/kg initially). The example used in the NICE guidance is of a 73 kg patient where the cost per infusion would be £1678, corresponding to four 100 mg phials needed for a dose of 365 mg. The cost of a full 12 months of treatment for this patient is estimated at £12 584.

Adalimumab costs £357.50 per 40 mg prefilled syringe (excluding VAT; *British National Formulary*, 58th edition). Induction treatment of 80 mg followed by 40 mg 2 weeks later will cost approximately £1073 and to continue 40 mg every other week for 1 year will cost £9295.

At first glance therefore adalimumab appears to be cheaper for both induction and maintenance treatment of CD. However, there may well be differences in the induction regimens of both drugs. It is well established that single-dose induction treatment with infliximab is inappropriate in view of the likely problems with antibodies to the drug and subsequent infusion reactions. The three-dose induction of 5 mg/kg at 0, 2 and 6 weeks has therefore been used in many centres. However, the response rates to this regimen in clinical trials demonstrate that those patients who will respond to treatment have usually done so at the time of their third infusion at week 6.⁷ For this reason NICE recommends a two-dose induction regimen for severe CD and then assessment of response at week 6. If the patient is deemed to have responded then a further dose at week 6 and then episodic or scheduled 8-weekly treatment is recommended. Interestingly a three-dose (0, 2 and 6 weeks) induction regimen is still recommended for fistulising disease followed by episodic or scheduled 8-weekly treatment if a patient is deemed to have responded.

Adalimumab induction therapy of 80 mg followed by 40 mg at week was no better than placebo for remission rates at week 4.⁸ For this reason it is frequently given as 160 mg (ie, 4×40 mg prefilled syringes), followed by 80 mg, in an effort to achieve a more rapid response to treatment but also in an attempt to avoid subsequent dose escalation to 40 mg weekly (which obviously doubles the annual cost of the drug) rather than every other week. This strategy does, however, significantly increase the cost of adalimumab induction therapy.

In addition to the cost of the drug itself, numerous factors must be considered when calculating the relative costs of treatment. When infliximab is being reconstituted within the controlled environment of the pharmacy unit, with sterile production facilities, there is an opportunity for phial sharing. In day-case or specific infusion centres where several patients are attending on the same day the possibility of phial sharing can result in significant cost-savings. Within our own department this has led to cost-savings of £120 000/year for gastroenterology patients alone, which is approximately 12% of our total annual spend on anti-TNF therapy.

The newly published NICE biologics commissioning guide¹ and links to the costings templates and audit tools via the NICE technology appraisal⁴ can assist units in benchmarking their annual drug costs.

Associated costs

The fundamental difference between infliximab and adalimumab is the mode of administration—that is, intravenous versus subcutaneous injection. The need for intravenous treatment with infliximab therefore requires a day-case visit for a 2 h infusion. Local facilities, in addition to local agreements with commissioners, will govern how much this will affect the unit cost of the drug. Clearly it is not ideal for patients who should be receiving scheduled drug treatments to be competing with medical and surgical admissions within the acute

Table 1 Assumptions used in estimating the population benchmark for adults requiring biologic drugs for the treatment of inflammatory disease (reprinted with permission from the National Institute for Health and Clinical Excellence Commissioning Guide¹)

Condition	Estimated number of people with the condition	Estimated number of people with the condition eligible and receiving treatment with biologic drugs	Estimated percentage of people with the condition eligible and receiving treatment with biologic drugs
Rheumatoid arthritis	350,000	35,000	10.0%
Ankylosing spondylitis	71,000	6,900	9.7%
Psoriatic arthritis	263,000	6,300	2.4%
Psoriasis	607,000	18,000	3.0%
Crohn's disease (adults)	81,000	10,500	13.0%
Ulcerative colitis	77,000	750	1.0%
Juvenile idiopathic arthritis	8,500	1,300	15.0%
Crohn's disease (children)	1,800	240	13.0%

bed base. However a short-stay ward or dedicated infusion unit can ensure that infusions are delivered in a timely manner and confer several other advantages, including increased experience with the drug, specialist nurse input, phial sharing and clinical review and an opportunity to adopt the accelerated infusion protocol to minimise lengths of stay⁹ (table 2).

The advantage of adalimumab in this setting is that after a brief period (usually after two to four treatments) the patients can self-administer the drug at home. This incurs some additional costs of drug delivery and storage, which are easily offset by the savings on hospital attendance and nursing time.

Choice of anti-TNF therapy

Patient factors

Once drug costs have been assessed in line with local factors, there are a number of additional issues to consider when choosing which anti-TNF drug to prescribe. These are best dealt with by careful discussion with the patient and their relatives or carers. NICE describes some situations where infliximab is specifically recommended. These include for active fistulising disease and in children or adolescents (aged 6–17 years) with severe active CD.⁴

Safety is clearly paramount and has been considered in the associated paper¹⁰ but there appear to be no new safety signals with adalimumab other than the problem of injection site reaction. For some people there may be concerns about adherence to self-administration. This may include their judgement as to when an injection should be delayed or postponed (eg, with a perianal abscess or chest infection). These patients may be best served by attending hospital either for the injection or for an infliximab infusion. Other patients may not like the idea of self-injection but often this can be overcome with careful guidance and reassurance from the IBD nursing team.

However, the obvious key advantage of subcutaneous self-administration of anti-TNF therapy is the freedom of not having to attend hospital. Maintaining quality of life, including the ability to work and attend school or college, are key treatment goals of CD treatment. In addition, frequent hospital trips can incur considerable financial costs for public transport or

hospital parking. Some of the homecare companies are keen to extend their services to include intravenous drug administration in the home and there is some precedence for this approach.¹¹ This strategy may also reduce the cost of the drug to commissioning groups. Clearly there are significant safety concerns that would have to be overcome here, such as the management of infusion reactions and the ultimate responsibility for drug monitoring.

Initiating anti-TNF therapy

Patient information

Once a decision has been made about the appropriateness of anti-TNF therapy and which drug is to be given it is important to check that there are no obvious contraindications to treatment, that patients are well informed about the potential risks and benefits of treatment and that some simple pretreatment checks have been made (figure 1).

Our policy in Leeds is that all patients spend time with the IBD nurse specialist discussing the treatment and its implications. They receive a patient information leaflet about the drug. These leaflets may be hospital-specific but are also available at <http://www.nacc.org.uk>. Additional information for patients is available linked to the NICE technology appraisal website⁴ (NICE guidance written for patients and carers) and via the electronics medicines compendium (<http://www.medicines.org.uk/EMC>).

A proposed checklist before initiating anti-TNF therapy is given in table 2.

Screening and vaccination before anti-TNF treatment

Screening and vaccination before anti-TNF treatment has been extensively reviewed and detailed guidance given by ECCO, including the management of opportunistic infections in immunocompromised patients.¹² One of the most important aspects of safety for the use of anti-TNF drugs is patient education (table 2). This includes counselling about the need for immunisation against flu (annually) and pneumococcus. Additional recommendations from ECCO include varicella (for those with no clinical history of chicken pox or shingles and for whom varicella zoster serology is negative), human papilloma virus and hepatitis B vaccinations. If

Table 2 Proposed checklist before the initiation of anti-tumour necrosis factor (anti-TNF) therapy

Disease assessment and confirmation of activity
Discussion of risks and benefits and patient information leaflets
Exclude contraindications—for example, NYHA III/IV heart failure, demyelination, recent history of cancer, etc
Screening for TB: BTS guidelines
Baseline bloods FBC, U&E, LFT, CRP, Hep B/C, VZV IgG
Vaccination history confirmed and updated
Completion of booking form and prescription
Initiation of treatment and planned review date in clinic to assess response

BTS, British Thoracic Society; CRP, C-reactive protein; FBC, full blood count; LFT, liver function test; NYHA, New York Heart Association; TB, tuberculosis; U&E, urea and electrolytes; VZV, varicella zoster virus.

Figure 1 Algorithm for initiating and monitoring anti-TNF therapy in Crohn's disease. *Monitoring response is by IBD CNS at times of IFX infusions and should be 3 monthly in clinic for patients receiving home care. BTS, British Thoracic Society; CRP, C-reactive protein; eow, every other week; FBC, full blood count; CNS, clinical nurse specialist; HBI, Harvey Bradshaw Index; IBD, inflammatory bowel disease; IFX, infliximab; LFT, liver function test; PGA, physician's global assessment; PIL, patient information leaflet; TB, tuberculosis; TNF, tumour necrosis factor; U&E, urea and electrolytes; VZV, varicella zoster virus.

they have plans for travel then relevant vaccinations should be administered, although patients need to be aware that they should not receive live vaccines while immunosuppressed. The vaccinations could be coordinated via the general practitioner with advice from the IBD team.

With regards to screening for latent tuberculosis (TB) there are guidelines from the British Thoracic Society¹³ in addition to those of ECCO. One of the key difficulties in detecting latent TB is the sensitivity of the tuberculin skin test in patients receiving high doses of steroids or who are taking immunomodulators, which is likely to include the majority of patients starting biological therapy. Thus BTS guidelines suggest that if patients are taking these drugs and have a normal chest x-ray a calculation of the annual risk of TB (which is dependent on age, ethnicity and place of birth) and the risks of isoniazid prophylaxis should be performed. Essentially this will mean that black Africans over the age of 15 and South Asians born outside the UK should be considered for chemoprophylaxis. The role of the interferon γ release assays (such as ELISPOT or

QuantiFERON-TB) is not yet clear but they may be more sensitive in immunocompromised individuals.¹⁴

Facilities for administering anti-TNF therapy

An ideal model of drug delivery should include a choice of drug and place of delivery (where possible). In addition, the surroundings should be comfortable and safe and able to deliver treatment in a timely manner which least disrupts the patient's quality of life. Concerns over bed availability and cancellations of treatments can only add to the worries of patients who attend hospital for their treatment. In addition, many units will have a system where a patient has to be 'clerked in' by a junior doctor, which means they may have to reiterate their IBD history each time. A nurse specialist-led clinic greatly improves patient continuity as these patients are well known to the IBD team.

The Leeds immune mediated inflammatory disease centre is a day-case centre for rheumatology and gastroenterology patients who are receiving biological therapy for their disease. This is a 24-bed unit, of which gastroenterology has access to 10 beds for

three sessions a week. Some patients well established on infusion treatment can equally well sit in a chair to receive the drug. Non-specialist nurses monitor observations, cannulate and administer infusions to patients with IBD or rheumatological conditions. This allows the specialist nurses time to complete the clerking proforma (appendix 1), which records such information as disease activity scores and any problems since the previous treatment, in addition to updating the biological therapy database. The IBD nurse can also answer queries about a patient's treatment or disease generally and also educate and train patients in the self-administration of adalimumab. These clinics are completely nurse-led. Where there are concerns about whether a treatment should go ahead or that a patient may be losing response to treatment or other such enquiries the specialist nurse will contact the referring consultant for advice. Where patients receive their anti-TNF therapy as an infusion our local protocol allows infliximab to be infused over 1 h from the fifth infusion and over just half an hour from the tenth infusion, greatly improving the convenience for patients and increasing the capacity of the unit (table 3).

While smaller units may not have such a volume of patients this type of cross-specialty nurse specialist-led unit can confer considerable advantages on patients and on the trust. Patients report increased satisfaction compared with the previous system of admission to non-specialist short-stay wards or the acute bed base and benefit from the continuity of care provided by the nurse specialist. The trust saves considerably from drug phial sharing and also, because there is a specialist nurse review at each infusion, there are fewer clinic outpatient visits and more rapid detection of problems such as loss of response to treatment. This system requires administrative support for the coding and booking of clinics. An additional benefit of this administrative support is that patients can be contacted 48 h before an infusion to confirm their attendance as infusions are prepared 24 h before. This minimises the small but expensive chance of a patient forgetting to attend or having a problem which means that a treatment should be postponed.

For those patients receiving adalimumab the specialist nurse documents the training and decides when a patient is confident and safe to self-administer before their home deliveries of the drug are initiated. These patients will have follow-up within the usual IBD clinic thereafter.

Assessing and recording response to treatment

Assuming that there are no problems with initial infusions or injections of the drugs, timing of the clinical assessment of the initial response to treatment should comply with the new NICE guidance⁴ (figure 1). Our measure of disease response is based on clinical symptoms, inflammatory markers and the Harvey Bradshaw Index (HBI) Score which is recorded before each treatment. While this index has limitations, it is more practical in a clinical setting than the Crohn's disease activity index and is useful to confirm clinical impressions, provide internal audit data and data to satisfy drug and therapeutics committees and external commissioning bodies.

Once a decision has been made about response to initial treatment the next step is to decide on the duration of maintenance treatment. The new NICE recommendations now suggest a 'planned course of treatment' for a 12-month period assuming continued response and no significant adverse events. As discussed a future challenge to clinicians will be what will constitute this reassessment at 12 months. In reality there will need to be a detailed discussion with the patients about the relative merits of continued treatment. In our experience those patients who have responded well to anti-TNF therapy where other interventions have failed are frequently reluctant to discontinue treatment. However, the concept of 'deep remission', where mucosal healing reduces the subsequent risks of relapse after treatment withdrawal,¹⁵ will aid discussions with patients about the nature of their disease assessment and subsequent treatment options. While treatment could be restarted in the event of relapse, this may carry the risk of secondary loss of response or an infusion reaction where antibodies to infliximab have formed.

Continuing immunomodulator therapy when patients are maintained on anti-TNF therapy is still open to debate. ECCO recommends that "the long-term combination of thiopurines and anti-TNF therapy is best avoided in young people because of the risk of hepatosplenic T-cell lymphoma".² Further evidence is required before final recommendations covering all patient groups can be made.

Monitoring during treatment

Patients also need to be aware of any new symptoms which may suggest problems such as an infection or worsening heart failure, for example. These patients should have appropriate assessment and investigation before treatment is restarted. It is very important,

Table 3 The Leeds accelerated infliximab infusion protocol: infusions 1–4 are given over 2 h, infusions 5–9 over 1 h and subsequent infusions are given over 30 min

Dose number	Infusion time	Mid-infusion observations	Postinfusion observations
1–4	2 h	Pulse and BP every 30 min	Pulse and BP every 30 min for 2 h
5–9	1 h	Pulse and BP every 30 min	Pulse and BP every 30 min for 1 h
10+	30 min	Pulse and BP every 30 min	Pulse and BP every 30 min for 30 min

therefore, that they have rapid access to advice via a drop-in clinic or IBD phone helpline to avoid delays in diagnosis of potentially serious adverse events.

Regular (3-monthly) monitoring of full blood count and liver function are required. These can be coordinated with primary care through shared care guidance, although in practice, patients will often have their blood checked when they attend the day-case unit for treatment.

All patients receiving anti-TNF therapy require regular clinic review by experienced clinicians. For patients self-administering adalimumab this should be 3 monthly. However, one advantage of having clinical nurse specialist input at the time patients are receiving their treatments is that they can perform a full clinic review at the same time. Where there is an ongoing treatment plan agreed between the IBD team and the patient and no problems with the treatment, then routine outpatient clinic visits can be reduced to 6 or 12 monthly (figure 1).

The use of a biological therapy database/registry has greatly increased our understanding of the longer-term outcomes of anti-TNF therapy.¹⁶ Our own simple database allows monitoring of efficacy and safety of these drugs and has aided internal audits. The efforts of the IBD national audits and the subsequent publication of the IBD service standards are leading towards the establishment of a national biologics registry.

Summary

An ideal biological therapy service should include some key characteristics. An individual case should be discussed by a multidisciplinary team to reflect on treatment options. The risks and benefits of these treatment options should then be discussed with the patient. If anti-TNF therapy is to be used then the choice of drug should be tailored to an individual and based on preference with unit cost, route of administration, local facilities and ability to safely deliver and monitor treatment taken in to account. The role of the IBD nurse specialist can be crucial in counselling and educating patients, coordinating treatments, monitoring treatment and collecting data about treatment outcomes. A specialist treatment unit can facilitate a more cost-effective and efficient service and could be cross-specialty. Careful review of response and remission and clear treatment plans, including duration of treatment, what to do about concomitant treatments or loss of response to treatment, are also important. The use of a national biologics register will enhance our experience and improve the quality of a service within any individual unit.

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Appendix 1 Infliximab clerking proforma

Name:
Unit number:
DOB:
Consultant:

DATE:
PATIENT TEL No.

Current history:

Examination: BP pulse Temp Weight:

Presence of fistulae? ☐ Number fistulae ☐ Current discharge? ☐

Type: peri-anal ☐ entero-vaginal ☐ entero-vesical ☐

entero-cutaneous ☐

Evidence of current infection? ☐ Details:
If evidence of current sepsis postpone the infusion

Current Harvey Bradshaw Index (HBI)

1) Number stools/day (total) ☐

2) General well being (0=well; 1=below par; 2=poor; 3= v.poor; 4=terrible) ☐

3) Extra-intestinal manifestations: ☐
(1 each for: arthralgia/iritis/uveitis/pyoderma/erythema nodosum/fissure/fistula/abscess/fever)

4) Abdominal mass: (0=none; 1=dubious; 2=definite; 3=definite+tender) ☐

5) Abdominal pain: (0=none; 1= mild; 2=moderate; 3=severe) ☐

Total (add scores in boxes 1-5): ☐

Previously recorded HBI: ☐

Patient assessment Better ☐ Worse ☐ The Same ☐

Clinical assessment Better ☐ Worse ☐ The Same ☐

Previous infliximab ☐

Number doses ☐

Past infusion reaction? ☐

Infections since previous
Infusion ☐

Other comments:

TB excluded?

CXR: ☐

Previous BCG: ☐

Heaf test/PPD: ☐

Recent contacts: ☐

Recent travel: ☐

UK born ☐

Country of origin ☐

Immunosuppression:

	Current	previous	dose
azathioprine	☐	☐	☐
methotrexate	☐	☐	☐
mycophenolate	☐	☐	☐
prednisolone	☐	☐	☐
If none give 200mg IV hydrocortisone prior to infusion			☐