Anti-TNF-alpha treatment strategies: results and clinical perspectives

Traitement anti-TNF dans les maladies inflammatoires chroniques intestinales : résultats et perspectives

G. D’Haens*

Imelda GI Clinical Research Centre, Imelda General Hospital, Imeldalaan 9, 2820 Bonheiden, Belgium

Summary
The advent of anti-TNF therapies has led to a significant expansion of the therapeutic armamentarium for inflammatory bowel diseases. Control of inflammation has been achieved with three biologic agents infliximab, adalimumab and certolizumab pegol. All agents are effective in both induction and maintenance of remission. For fistula healing in Crohn’s disease, both infliximab and adalimumab have been shown to be effective, whereas for mucosal healing hard evidence is only available for infliximab. Anti-TNF agents appear to be more effective in patients who have a shorter disease history and who have not yet been treated with any of these agents. There is a clear tendency to use anti TNF therapy earlier in the course of inflammatory bowel disease, but predictive markers to select patients who really need these therapies are urgently needed.

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G. D’Haens*

Imelda GI Clinical Research Centre, Imelda General Hospital, Imeldalaan 9, 2820 Bonheiden, Belgium

Résumé
Les traitements anti-TNF ont considérablement modifié la prise en charge des maladies inflammatoires chroniques intestinales. Trois anticorps anti-TNF ont ainsi permis un contrôle plus efficace de l’inflammation muqueuse digestive : l’infliximab, l’adalimumab et le certolizumab pegol. Ces trois médicaments sont efficaces à la fois pour l’induction et pour le maintien de la rémission. Dans les formes fistulantes de la maladie, l’infliximab et l’adalimumab ont prouvé leur efficacité, seul l’infliximab ayant pour l’instant montré sa capacité à cicatriser la muqueuse. Ces traitements sont plus efficaces chez les malades ayant une maladie plus récente, et chez ceux n’ayant jamais été traités par ce type d’agents biologiques. Si une tendance générale à une utilisation plus précoce de ces molécules dans la prise en charge thérapeutique des maladies inflammatoires chroniques intestinales semble se dégager, il n’en reste pas moins qu’il est nécessaire de trouver des marqueurs prédictifs capables de mieux identifier les malades auxquels l’utilisation de ces traitements apporte le plus de bénéfices.

* Corresponding author:
E-mail address: geert.dhaens@imelda.be (G. D’Haens).

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Introduction

The advent of anti-TNF agents has altered the management and outcome of patients with inflammatory bowel disease (IBD) to an important extent. Infliximab (Remicade®, Centocor, Malvern PA, USA) and adalimumab (Humira®, Abbott, Chicago IL, USA) are currently the two agents that have been approved and registered for the treatment of Crohn’s disease in Europe, whereas infliximab is also approved for the treatment of ulcerative colitis. A third anti-TNF agent, Certolizumab pegol (Cimzia®, UCB, Brussels, Belgium) has so far only been approved in Switzerland and North-America.

These three drugs are potent anti-inflammatory agents that are administered parenterally and have a combined effect on induction and maintenance of remission for a duration of at least 6 months.

The striking mucosal healing that was observed with infliximab (and that is being studied for the other agents) has changed the treatment goals of IBD: healing is now considered to offer the best ‘protection’ against the development of complications, although further prospective studies will need to ascertain the genuine benefit of healing versus only symptom suppression.

Anti-TNF agents are also beginning to be used earlier in the disease course, in an attempt to limit exposure to corticosteroids and possibly to alter the course of the disease. The question how we can identify patients that benefit from early anti-TNF treatment needs further investigation. Finally, it may become feasible to treat IBD without systemic corticosteroids after all.

Infliximab, adalimumab and certolizumab pegol: 3 anti-TNF antibodies for IBD

Infliximab is a chimeric anti-TNF antibody with approximately 25% murine material directed against the proinflammatory molecule tumor necrosis factor (TNF). TNF is both freely present in the mucosa and expressed on inflammatory cells. Infliximab binds TNF and induces, through complement activation, apoptosis of these inflammatory cells thus ‘washing away’ the inflammatory infiltrate that is typical for chronic mucosal inflammation [1, 2]. Infliximab is routinely administered via intravenous infusions. Adalimumab is a fully human anti-TNF antibody that is administered subcutaneously. It also induces apoptosis of mucosal inflammatory cells [3]. Certolizumab pegol is a pegylated (humanized) Fab' fragment of an anti-TNF monoclonal antibody that, unlike the other two molecules, does not activate complement and does not induce apoptosis [4]. Although it was originally believed that apoptosis was necessary for the anti-inflammatory activity of anti-TNF antibodies, this concept was abandoned because of the biologic activity of certolizumab pegol without inducing this biological effect. Further studies are needed to unravel the molecular effect of anti-TNF agents as to find out exactly which mechanism is responsible for the potent anti-inflammatory effect.

The efficacy of anti-TNF treatments for induction and maintenance of remission in active Crohn’s disease

Several large clinical trials have demonstrated the efficacy of anti-TNF agents in Crohn’s disease. The Accent-trial with infliximab studied 3 maintenance regimens (infliximab 5 mg/kg every 8 weeks, infliximab 10 mg/kg every 8 weeks or episodic infliximab retreatment ‘as clinically needed’) in patients who responded to a single induction infusion of 5 mg/kg [5]. Patients who lost response received a higher dose for the rest of the trial. At week 30, 39-45% of patients receiving eight-weekly infusion of infliximab were in remission, versus 21% of patients receiving ‘episodic treatment’. The trial was accompanied by a side study in which 99 patients underwent an ileocoloscopy before the start and at week 10 and 54 of the trial. Strikingly, absence of ulcers was observed more frequently in patients receiving ‘scheduled’ than ‘episodic’ retreatment and, more importantly, healing was associated with a lower need for surgical interventions and hospitalizations [6].

The CHARM trial with adalimumab used a similar design [7]. Patients with active Crohn’s disease refractory to aminosalicylates, corticosteroids and/or immunomodulators received an open label induction regimen with 80 mg of adalimumab (2 subcutaneous injections of 40 mg) at week 0 and 40 mg (1 injection) at week 2. Responders (drop in CDAI of ≥70 points, observed in 58% of the patients at week 4) as well as non-responders were then enrolled in the maintenance treatment arm with 40 mg adalimumab every week, 40 mg adalimumab every other week or placebo, after stratification for response or not to induction treatment. The two active treatment arms were superior to placebo: after one year of treatment, 36% of the patients receiving 40 mg adalimumab every other week and 41% of those receiving adalimumab 40 mg weekly were in remission (no significant difference). This study did not look at endoscopic healing in a sufficiently large subgroup. An earlier study, the CLASSIC-1 study, looked at dose-response relationships with adalimumab therapy in almost 300 patients naive to anti-TNF therapy and came to the conclusion that an induction regimen of 160 mg adalimumab (4 injections) at week 0 and 80 mg (2 injections) led to superior results for induction of remission [8]. With the high-dose regimen, 36% of patients were in remission at week 4 versus 24% with 80/40 and 12% with placebo. For this reason, an induction regimen with 160/80 at week 0 and 2, respectively, is considered to be superior.

The efficacy and safety of certolizumab pegol in Crohn’s disease was assessed in a series of studies named the ‘Precise program’. In the Precise 2 study, patients with active Crohn’s disease received 400 mg certolizumab pegol (2 injections of 200 mg) every 2 weeks for 6 weeks and were then randomized to receiving placebo or active maintenance therapy with 400 mg certolizumab pegol every 4 weeks, to be switched to 400 mg every 2 weeks in case of loss of response [9]. Sixty-four% of the patients responded to induction treatment and started maintenance therapy. At 26 weeks, 48% of those patients were in remission, regardless of background therapy with corticosteroids and/or immunomodulators. In the Precise 1 study, published simultaneously in 2007, patients...
were randomized to receiving active treatment with an induction regimen of certolizumab pegol 400 mg at week 0, 2 and 4 followed by maintenance therapy with 400 mg injections every 4 weeks or to placebo [10]. Remission at 6 months was achieved in 29% of patients on active treatment versus 18% of those on placebo. All the patients that reached the 26 week endpoint in both Precise studies were then invited to receive further open label treatment in the Precise 3 program, whereas those who lost response (on active maintenance therapy or on placebo) received one extra 400 mg injection at a 2-week interval and further received open label treatment in the Precise 4 program [11, 12]. Whereas 48% of the patients were in remission at the start of Precise 3 (the end of Precise 2), 42% were still in remission at week 56 and 37% at week 80. Seventy-five patients on placebo and 45 patients on active treatment received re-induction treatment in the Precise 4 program, leading to remission rates of 36 and 35%, respectively, one year down the line.

Taking all these trials together, it becomes clear that anti-TNF agents indeed offer significant clinical benefit to a large proportion of patients, but that the therapeutic results are still far from optimal and that continued research is needed to identify patients that have the greatest benefit and to 'optimize' the regimens in which these treatments should ideally be used. Along those lines, a few striking findings became apparent when the data of these studies was further analysed.

One observation was the finding that patients enrolled in the Charm and Precise studies who had received treatment with other anti-TNF agents (mainly infliximab) before enrollment clearly had a poorer response to the new anti-TNF agent. With adalimumab 40 mg injections every week, 48% of the patients who had never received anti-TNF therapy responded to treatment at 1 year, versus 34% of those who had received anti-TNF before [7]. With certolizumab pegol, 69% of patients had a response at week 26 when they had never received previous anti-TNF therapy versus 44% in case of previous anti-TNF therapy [9]. From these data it can be concluded that previous anti-TNF therapy has a negative impact on the response to an alternative anti-TNF treatment. The reason why this is the case remains controversial. There may be cross-reactivity between different agents at the level of immunogenicity or there may be an increased level of fibrosis possibly as a consequence of previous treatments leading to diminished response.

Another important observation is the negative relationship between the duration of the disease and the likelihood of a response to anti-TNF therapy. This phenomenon had already been observed in a limited pediatric trial with infliximab [13], and offers a strong plea in favour of treatment with anti-TNF agents earlier in the course of the disease. Clinical response to 26 weeks of cetolizumab pegol therapy in the Precise 2 program was seen in 90% of patients if Crohn’s disease had been diagnosed less than 1 year ago, in 75% if the diagnosis was made 1 to 2 years before, in 62% for a diagnosis between 2 and 5 years before and in 57% if the diagnosis was older than 5 years [14]. Similarly with adalimumab, remission rates at week 56 in the Charm trial were 51, 44 and 35% for patients with a disease duration of less than 2 years, 2 to 5 years and more than 5 years, respectively [15]. This leads to the question whether patients with a recent diagnosis of Crohn’s disease are perhaps more ‘sensitive’ to treatment with anti-TNF agents. In a recently published study Kugathasan and colleagues from Cleveland offered a possible explanation demonstrating that mucosal T cells isolated from the gut of children with early Crohn’s disease, express a strongly polarised Th1 type response with excessive production of IFN-γ [16]. This profile was lost with progression to late Crohn’s disease, suggesting a variable type of immunoregulation as the disease becomes ‘chronic’.

This concept of ‘early treatment’ was addressed prospectively in a randomized controlled trial in the Benelux [17]. Patients with newly diagnosed Crohn’s disease (never exposed to corticosteroids and/or immunomodulators) received either early combined immunosuppression with three infusions of infliximab (weeks 0, 2 and 6) in combination with azathioprine 2.5 mg/kg from day 1 onwards, or conventional treatment with corticosteroids, with association of azathioprine in case of relapse or corticodependence and infliximab only in refractory cases. Infliximab infusions were repeated as clinically needed. Azathioprine was replaced by 6-MP or Methotrexate in case of intolerance and corticosteroids were only given if all these measures failed to induce remission. The primary endpoint of this trial was clinical remission at month 6 and 12 after inclusion, and was reached in a significantly higher proportion of patients treated with early combined immunosuppression (60 versus 36% at week 26 and 62 versus 42% at week 52). Moreover, the median time to clinical relapse was significantly longer in the combined immunosuppression group (329 versus 174 days). Intriguingly, mucosal healing that was assessed endoscopically after 2 years of treatment was significantly better in patients receiving the ‘aggressive’ treatment when compared to the conventional group: absence of ulcers was observed in 73% of patients in the combined immunosuppression group versus in 30% of patient receiving conventional management. Further follow-up of the patient cohort up to 4 years after randomization showed that endoscopic remission (both treatment arms) was associated with fewer relapses and a lower need for repeated infliximab treatment [18].

A burning question has therefore arisen. How can patients that would benefit from early treatment with anti-TNF agents be identified and which (surrogate) markers could be used in this algorithm? Beaugerie and colleagues retrospectively looked at a cohort of 1,123 Crohn’s disease patients treated in France [19]. Patients were considered to have ‘aggressive Crohn’s disease’ if any of the following events occurred in the first 5 years after diagnosis: more than 2 corticosteroid courses and/or steroid dependence, hospitalization for a relapse and/or complication, continuous disabling symptoms for more than 12 months, need for immunosuppression, bowel resection and surgery for perianal disease. Based on these criteria, ‘disabling disease’ was observed in 85% of the cohort and this was associated with an age below 40 years, isolated colonic disease, perianal lesions at diagnosis and the need for corticosteroids for the first relapse. Of course, it is rather unlikely that anti-TNF treatment would be indicated in 85% of newly diagnosed Crohn’s disease patients. Further studies are now looking at serological and genetic markers in an attempt to allow a more refined patient selection. Dubinsky was able to show that in a paediatric population positivity for the serological markers ASCA, OmpC, cBir 1 and I2 was
associated with ‘progressive disease’ and tissue destruction [20]. It must be clear that these efforts are only the beginning of patient stratification and ‘individualized care’.

Long term anti-TNF treatment

Controlled clinical trials have had a limited duration of follow-up up to one year [5,7], although more prolonged follow-up data with open label treatment is being recorded. In addition, two large registries with patients receiving infliximab and a control group receiving standard treatment are ongoing (TREAT in the USA and ENCORE in Europe) [21]. The main purpose of these registries is to collect safety rather than efficacy data. The largest experience with prolonged anti-TNF treatment was recently reported by the group in Belgium [22]. At that centre, 440 patients with Crohn’s disease were treated with either episodic or scheduled maintenance infliximab therapy for luminal (82%) or fistulising disease (20%) from 1999 until 2007. With a mean follow-up of 41 months, 60% of these patients had sustained benefit from this maintenance therapy. It can be concluded that the majority of patients on long-term anti-TNF therapy continue to respond and/or remain in remission.

Loss of response: how to manage?

Although many patients on anti-TNF treatment do well, loss of response is a phenomenon that is increasingly being observed. This creates a significant challenge to patients and physicians. The most common reason for loss of response with infliximab is the development of neutralizing antibodies to the chimera. An ‘episodic’ or ‘on demand’ treatment schedule led to antibody formation in more than 70% of patients treated with infliximab at a single centre [23]. The antibody titres correlated significantly with the occurrence of infusion reactions and loss of response to therapy. Also, the duration of response after an infliximab infusion was importantly reduced if an infusion reaction had occurred and antibody levels were high (> 8 μg/ml). Suppression of antibody formation was significant with immunomodulators, without significant difference between patients cohorts treated with azathioprine/6-MP or methotrexate [24].

It is now commonly accepted that antibody formation can be prevented to a certain level by systematic administration schedules rather than episodic (‘on demand’) therapy, by pretreatment with corticosteroids and by concomitant use of immunosuppressives (Table 1). In addition, maintenance therapy following an induction regimen has been associated with better clinical outcome and fewer complications, albeit at a higher direct cost [6].

How long concomitant immunosuppression needs to be continued has recently been studied in a randomized prospective trial where continued immunosuppression was compared to discontinuation in a cohort of patients on systematic 8-weekly infliximab treatment for at least 6 months. The investigators did not find differences in the proportions of patients experiencing allergic reactions or loss of response, although the infliximab serum levels tended to decrease in patients who discontinued immunosuppression [25].

Virtually all monoclonal antibodies, even the so-called ‘humanized’ or ‘fully human’ molecules are immunogenic. Antibody formation was not only reported with infliximab, but also with the ‘fully human’ anti-TNF antibody adalimumab (2 patients in the Classic-1 trial at 4 weeks, 2.6% in the Classic-2 trial and 5.5% in the rheumatoid arthritis trials). With certolizumab-pegol, 8% of patients developed antibodies in the Precise-2 trial [23]. The presence of these antibodies does not seem to have a significant effect on the clinical efficacy of these agents.

For all three anti-TNF antibodies, rescue strategies were designed for patients who lose response. For infliximab, both a dose increase and a shortening of the infusion interval have been effective. Patients on adalimumab treatment can be switched from every other week to weekly injection and patients losing response to certolizumab pegol 400 mg every 4 weeks can often be ‘rescued’ by the administration of a single additional injection [12]. Of course, alternative explanations for loss of response have to be considered including the development of strictures, abscesses, cancer or intercurrent infections with viruses or other infectious agents.

Patients with luminal Crohn’s disease who had lost their response to infliximab were the specific target population for two clinical trials with adalimumab and certolizumab pegol. In the GAIN trial, patients who had become intolerant (60%) or resistant (48%) to infliximab received treatment with adalimumab 160 mg at week 0 and 80 mg at week 2 followed by maintenance therapy with 40 mg every two weeks or placebo induction and maintenance [26]. At week 4, 21% of patients receiving active treatment were in remission and 52% had a response, compared to 7 and 34%, respectively, of patients receiving placebo. The results were equally good in the population that was intolerant to infliximab as in the group that had lost response; the concomitant use of immunosuppressives and the presence of circulating antibodies to infliximab did not affect the results. A comparable trial is ongoing with certolizumab pegol. After 6 weeks of open label therapy with certolizumab pegol, 62% of patients who were intolerant or refractory to infliximab had a clinical response [27]. The second part of the trial with blinded therapy (active or placebo) beyond 6 weeks is being analyzed. It can be concluded that certain patients who fail infliximab will still respond to another anti-TNF agents, but unfortunately the results in this selected patients group are clearly less favourable than in the overall population. Recently, the clinical benefit of treatment with certolizumab pegol as the third anti-TNF agent in a cohort of 16 patients that had failed infliximab and adalimumab consecutively, was reported [28]. Of the 10 patients that received at least 3 infusions, 8 were responders, while 6 patients failed or did not tolerate the treatment.

Table 1 Measures to prevent immunogenicity with anti-TNF antibodies.

| Association of immunomodulatory drugs (azathioprine, 6-mercaptopurine, MTX) |
| Hydrocortisone prior to infusions |
| Systematic rather than episodic treatment |
| 3-infusion induction regimen for infliximab (?) |
Anti-TNF treatments for fistulizing Crohn’s disease

Infliximab is still the only biological agent that was studied in a separate trial looking at fistulizing Crohn’s disease. One year of maintenance infliximab therapy in patients with draining fistulas responding to a classic induction schedule of 3 5 mg/kg infusions at week 0, 2 and 6 (69%) led to complete fistula closure in 36% of the patients, versus in only 19% of placebo-treated patients [29]. The median duration of fistula closure in these responders was 40 weeks versus 23 weeks in the placebo group. In the CHARM study with adalimumab, drainage of fistulae was studied as a secondary endpoint but the study was not designed for fistula assessment and objective assessment of draining fistulae was lacking [30]. Despite these limitations, it was shown that patients with draining fistulae receiving adalimumab had closure of their fistulas at week 26 in 21/70 patients versus in 6/47 receiving placebo. Fistula healing with adalimumab was durable, since all fistulas that had healed at week 26 were still healed at week 52. Further trials with adalimumab and certolizumab specifically looking at draining fistulae are urgently needed. The current ECCO guidelines state that for patients with draining fistulas, infliximab therapy should be considered after failure of antibiotics (quinolones and/or metronidazole) and immunomodulators provided all perianal sepsis and abscesses have been surgically drained [31]. Imaging with magnetic resonance scanning has been of great value in guiding therapy in these difficult and often frustrating situations [32].

Anti-TNF treatments for ulcerative colitis

Another indication for which infliximab has been approved is ulcerative colitis. The Act-trials were designed to study the effects of infliximab in active ulcerative colitis despite background therapy with aminosalicylates, corticosteroids and/or immunomodulators [33]. Strikingly, the response and remission rates in these trials were very comparable to those observed in the trials in Crohn’s disease. Patients with active ulcerative colitis despite aminosalicylate therapy (Act 2) or corticosteroids and/or immunomodulators (Act 1) received 3 induction infusions of 5 or 10 mg/kg infliximab or placebo at week 0, 2 and 6 followed by 8-weekly maintenance infusions at the same dose. Remission at week 8, the primary endpoint, was reached in 30 (10 mg/kg) to 36% (5 mg/kg) of patients versus in only 10% of the placebo patients. Patients who had endoscopic remission at week 8 had a 4-fold higher likelihood of being in remission at week 30. At week 54, sustained remission was attained in 20.2% of the infliximab-treated subjects compared with 6.6% of placebo-treated. Since the publication of these trials, infliximab has become a recommended treatment for moderate to severe refractory ulcerative colitis, although the possibility of a ‘cure’ of the disease with surgical proctocolectomy always needs to be considered.

Shortly before the end of the Act trials, another placebo-controlled trial in which infliximab was given as ‘rescue’ therapy to patients with severe refractory ulcerative colitis admitted to the hospital was published by a Swedish-Danish study group [34]. The group demonstrated that a single infusion of infliximab 5 mg/kg reduced the need for colectomy significantly. Since then, it has been questioned whether steroid refractory ulcerative colitis should be first treated with infliximab or intravenous cyclosporine. Most experts would now recommend that in patients refractory to both steroids and azathioprine, infliximab should be the treatment of choice. Cyclosporine can still be of benefit in azathioprine naïve patients as a so called ‘bridge therapy’.

Safety of anti-TNF treatments

Anti-TNF agents are still being used with a certain degree of reluctance. The most frequently cited reasons for this are the high cost and the uncertainty about long-term safety. Many toxicity problems have indeed occurred and been recognized as related to anti-TNF therapies. A few examples include deterioration of heart failure and reactivation of mycobacterial infections [35]. Fortunately, stringent post-marketing surveillance programs and registries have allowed early recognition of the majority of these problems and appropriate measures and guidelines have been developed to prevent and treat them.

Infections and septicaemia have been the most common cause of mortality associated with anti-TNF therapy. The increased incidence of infections has long been recognized to be a potential complication of corticosteroids and immunomodulators, and biologic therapy appears to add to this elevated risk. Whereas common immunomodulatory therapy has predominantly been associated with viral infections, biologic therapy is more frequently associated with mycobacterial infections and other ‘opportunistic infections’ such as Listeriosis, Nocardiosis, invasive Aspergillosis and others [35]. The incidence of ‘opportunistic’ infections in different groups of infliximab-treated patients was reported to vary between 0.3 and 0.9% [36]. On the other hand, the TREAT registry for infliximab-treated Crohn’s patients revealed an increased risk of infections which was associated with the use of corticosteroids, not with infliximab [21].

The commonest infections in IBD patients treated with anti-TNF therapies are upper respiratory tract and urinary tract infections. It is now generally accepted that if a patient is having an ongoing moderate to severe infection, it is advisable to postpone anti-TNF therapy and to treat the infection properly first.

As already mentioned, an increased incidence of tuberculosis has been associated with anti-TNF therapies. With infliximab, 75% of documented cases presented within the first 3 infusions, 97% within the first 6 infusions; the vast majority of patients had a history of prior exposure to tuberculosis. Since general awareness about this problem has penetrated into the medical community and predominantly due to screening with chest X-rays and PPD skin tests in countries where BCG vaccination is not standard, the incidence of tuberculosis reactivation during anti-TNF therapy has decreased dramatically [37]. Patients with signs of prior exposure to tuberculosis need to receive tuberculostatic therapy (isoniazide + rifampicine) several weeks prior to and during the first 3 to 6 months of anti-TNF therapy. Patients with overt tuberculosis need triple anti-tuberculosis treatment before anti-TNF therapy can be started. The PPD skin test is prone to reader variability and its outcome is
influenced by cross-reactivity with environmental mycobacteria, previous bacillus Calmette-Guerin (BCG) vaccination, and anergy in immunosuppressed individuals. There is a recent trend to replace the skin test by the more reliable measurement of T-cell-based interferon-gamma responses to *Mycobacterium tuberculosis*, which displays a stronger association with exposure, and is less biased. Further studies with this interferon-gamma assay are ongoing and will address the utility of the test in IBD patients [38].

Central nervous system infections are often difficult to diagnose. Cerebral toxoplasmosis was observed in 7/64,000 inflammatory bowel disease patients receiving infliximab therapy, and isolated reports of Listeria meningitis/meningoencephalitis have been published [39]. Unfortunately this diagnosis is often delayed and this has led to considerable mortality.

Infusion reactions frequently occur in patients receiving infliximab [23]. Patients who develop an infusion reaction should be managed rapidly with antihistamines, acetaminophen, IV corticosteroids and even epinephrin. When the infusion resumed, it should be given at a very slow infusion rate which can gradually be fastened later on. Patients who have experienced an infusion reaction often benefit from a prophylactic dose of hydrocortisone (100-500 mg) intravenously 1 hour prior to further infusions. The same approach is often advocated in patients who are scheduled to receive anti-TNF after a prolonged ‘drug holiday’ (>4-6 months), since these patients are likely to have antibodies and, hence, are at risk for infusion and delayed hypersensitivity reactions [40]. The latter occur typically more than 3 days after drug administration. Typical symptoms of delayed hypersensitivity reactions include joint pain and muscle stiffness (with even dysphagia and inability to swallow). Patients with severe delayed hypersensitivity reactions also require treatment with corticosteroids, paracetamol and antihistamines, most often leading to complete resolution of symptoms after 1 to 2 weeks.

Injection site reactions typically appear with subcutaneous preparations such as adalimumab 25-35% [8] and certolizumab pegol (5%) [9,10]. With adalimumab, the occurrence of injection site reactions increased with higher doses and included burning, pain, erythema, bruising and pruritus [8].

Biologics that cause apoptosis may induce autoimmunity with formation of antibodies against nuclear factors and DNA. In a cohort of 125 consecutive Crohn’s disease patients treated with infliximab, almost half of the patients developed antinuclear antibodies after the first infusion, and more than 75% became antinuclear antibody positive after fewer than 3 infusions [41]. Only two patients (0.2%, double-stranded DNA positive), however, developed drug-induced lupus (rash, pleuritis) without major organ damage, and 1 developed autoimmune haemolytic anaemia. In most cases with overt infliximab-induced lupus, treatment with systemic corticosteroids is indicated and infliximab is to be discontinued. It is unclear whether symptoms recur when infliximab treatment is resumed. For the time being, the presence of ANA without clinical symptoms should not affect therapeutic strategies.

The most important concerns with prolonged use of anti-TNF agents are related to cancer development. Suspicion was first raised by the occurrence of two lymphomas in the early infliximab trials, and by several uncontrolled reports of intestinal adenocarcinomas in infliximab-treated patients. However, it should be realized that the genuine cancer risk cannot be ascertained within the frame of controlled clinical trials, given the relatively small size of the patient cohorts under study. Therefore, registries and post marketing surveillance programs are particularly useful to study cancer incidence. In the TREAT registry all types of cancer taken together were observed at an incidence of 0.58 per hundred patient-years, versus 0.53 per hundred patient-years in the control population [21]. This brought the relative risk of cancer during infliximab treatment to 1.1, which was not statistically significant. Looking at lymphoma in particular, the incidence was 0.06 per hundred patient years in infliximab-treated patients versus 0.05 in control patients, also not statistically significant [33]. In spite of these data, the development of lymphoma has been a nightmare to patients and physicians using anti-TNF therapy, particularly since 6 Crohn’s disease patients were reported to have developed a hepatosplenic lymphoma (HSTL) during combined treatment with infliximab and azathioprine [42]. These young patients (age 12-31 years) had received 2-21 doses of infliximab. Hepatosplenic T-cell lymphoma is a subtype of non Hodgkin lymphoma which most frequently develops in young male adults, both immunocompromised and with normal immunity. With only 120 cases reported in the literature, the true incidence of the condition is unknown. In most cases, however, the disease is very aggressive and often fatal. Several new cases have now been reported with both infliximab and adalimumab, which led to a change in the label of both drugs.

The issue was also addressed in a recently published study by Siegel and colleagues, in which a decision analytic model was constructed to determine the risk of infliximab when compared with standard therapy. In a hypothetical cohort of 100,000 Crohn’s patients receiving infliximab versus standard therapy, 201 more lymphomas would develop in the former group after 1 year [43].

Taken the available data together, it is fair to state that the risk of lymphoma in patients treated with anti-TNF agents is indeed slightly elevated. Therefore, anti-TNF therapy ought to be reserved for patients who really need it. Since most malignancies occur under combined therapy with biologics and immunosuppression, single drug strategies need to be revisited. At this point, however, it remains unclear whether it is the best strategy to discontinue immunosuppression after a certain period of combined treatment (e.g. 6 months), or rather to stop the biologic therapy and try to treat the patient with immunosuppression alone (the ‘bridging’ concept).

Neurological disorders caused by demyelination have been reported several times in anti-TNF treated patients [17, 33, 44]. It is recommended that neurological signs and symptoms, including disturbed or diminished vision, be immediately further investigated in patients receiving anti-TNF agents. Magnetic resonance scanning can reveal signs of demyelination of the central nervous system in case of doubt. Discontinuation of anti-TNF therapy is mandatory in case of persistent or progressive neurological symptoms.

Skin lesions are also a common phenomenon during anti-TNF therapy. The problem has been relatively underreported...
since the majority of lesions are limited and a causal relationship with the treatment is often unclear. Many different types of eruptions can develop: leukocytoclastic vasculitis, lichenoid drug reaction, perniosis-like eruption, superficial granuloma annulare and acute folliculitis [45]. Although anti-TNF therapies are usually effective to treat psoriasis [46] all TNF-alpha blocking agents have been reported to lead to an exacerbate psoriasis [47]. In some cases skin changes were severe enough to discontinue the medication.

A final uncommon complication with anti-TNF therapies is deterioration of cardiac failure in patients who already have a diminished myocardial function at the start [48]. It is now recommended that patients with heart failure New York Heart Association class 3 or 4 do not receive anti-TNF therapy.

**Pregnancy and anti-TNF therapy**

Several reports have now been published documenting the relative safety of infliximab during pregnancy. In a cohort of 96 pregnancies where infliximab was given around the time of conception, 67% live births, 15% miscarriages and 19% therapeutic terminations were observed. These numbers are comparable to historical controls without infliximab therapy [49]. In current practice, however, it is still recommended to avoid infliximab treatment based on the limited toxicity data, but in patients who really need the treatment it is probably safe to use it. The safety of other biological treatments during pregnancy is unknown.

**Conclusions**

Anti-TNF therapies have improved the quality of life of a significant proportion of IBD patients to an important extent. Nonetheless, these agents are associated with certain toxicities and should only be used in patients who really need the treatment. Physicians administering these drugs should be aware of the toxicity profile and of the appropriate guidelines to start and stop anti-TNF treatment and of the precautions that need to be followed. Undoubtedly, anti-TNF agents are going to be used more frequently in a larger proportion of IBD patients in the years ahead. The challenge for researchers and clinicians will be to identify the patients that benefit most form anti-TNF therapies and probably to introduce the therapy earlier in patients with a poor IBD prognosis.

**Conflict of interest:**

Geert D’Haens carried out clinical trials as main investigator and as co-investigator for Centocor, Schering Plough, Abbott and UCB. He did expert reports and gave advisory services for Centocor, Schering-Plough, Abbott and UCB. He attended conferences organized by Centocor, Schering-Plough, Abbott and UCB as contributor and audience member.

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