Anti-TNF therapy

The classics in perspective

Julián Panés, Subrata Ghosh

With the development and introduction of anti-cytokine therapies as biological agents, our therapeutic approach to Crohn disease and inflammatory diseases in general has dramatically expanded within the past few years. Biological agents technically mean a molecule that is the product of a biological system and functionally that is an agent that targets a specific biological molecule. Gastroenterologists are facing a remarkable wave of new biological therapies for inflammatory bowel diseases (IBD), including anti-tumour necrosis factor (TNF) antibodies (infliximab, adalimumab, certolizumab pegol), an anti-CD3 antibody (visilizumab), an anti-integrin antibody (natalizumab), and an anti-IL-12p40 and anti-IL6 receptor antibody (tocilizumab). Several biological therapies have also proven to be ineffective in large clinical trials, despite good initial promise, such as antibodies against soluble TNF receptors (etanercept, onercept), interleukin-10 and granulocyte–macrophage colony-stimulating factor (sargramostim).

Infliximab, an intravenously administered chimeric monoclonal antibody to TNF, has been for some years the only biological molecule approved for the treatment of Crohn disease, and more recently ulcerative colitis. Currently, two new subcutaneously administered anti-TNF molecules are in the process of being incorporated into the therapeutic armamentarium, including a fully human antibody (adalimumab) and a humanised pegylated Fab fragment (certolizumab pegol). The efficacy of adalimumab for induction of remission in patients with active Crohn disease not previously exposed to anti-TNF therapy was assessed in the CLASSIC (CLinical assessment of Adalimumab Safety and efficacy Studied as an Induction therapy in Crohn's) I trial,[1] showing that remission rates at week 4 in patients receiving two injections of 160 mg and 80 mg of adalimumab (the highest dose tested) at weeks 0 and 2 were significantly higher than in placebo-treated patients (36 vs. 9%). The CLASSIC II study, reported in this issue of *Gut* (***see page 1232***),[2] is a continuation trial assessing the efficacy and safety of adalimumab 40 mg alternate weekly or weekly, compared with placebo, to maintain remission. The selection of remission as the primary outcome measure, rather than the maintenance of response as used in pivotal trials of infliximab and certolizumab, is one of the merits of the CLASSIC II trial design, as this should be the aspiration of any Crohn disease treatment in clinical practice. CLASSIC II includes two patient populations. The first is the subset of patients who achieved remission in CLASSIC I (at week 4) and maintained remission during 4 additional weeks of treatment with open-label adalimumab 40 mg alternate weekly; these patients were randomised to placebo, 40 mg adalimumab weekly or 40 mg adalimumab alternate weekly. The second population is the group of patients that failed to achieve remission at either of the aforementioned time points; this group of patients was enrolled in an open-label arm. It is relevant to note that the randomised part of the study includes a highly selected group of patients that had rapidly responded to the drug (remission after 4 weeks of treatment) and had also shown the ability to maintain remission with further open-label treatment during an additional period of 4 weeks before randomisation. Within this group, the proportions of patients that were in remission at week 56 after treatment with adalimumab were very high both for the alternate weekly (79%) and the weekly (83%) treatment schedules, with significant differences compared with patients receiving placebo during maintenance (44%). The CLASSIC II study is unique in recruiting patients who responded to anti-TNF therapy by remaining in remission over a 4-week period (CDAI; Crohn's Disease Activity Index <150), as all other long-term studies with anti-TNF therapy have recruited responders with variable definitions (table 1).

However, we should beware of the trial detail, in case we cease to see the wood for the trees. The 30 patients under treatment with adalimumab that achieved remission in the induction phase and were in remission at week 56, represent 16% of the cohort of all patients that received active treatment during all the study. Furthermore, these patients did not have sustained remission, because steroid withdrawal was mandatory in the randomised cohort, and 21% of patients treated with adalimumab and in remission at week 56 were on steroids. This observation is quite similar to the results observed in the recently published CHARM (Crohn's Trial of the Fully Human Antibody Adalimumab),[3] in which 22% of patients receiving active adalimumab treatment for induction (using 80 mg followed by 40 mg after 2 weeks) and maintenance of remission were responders in the induction phase and in remission at week 56, and also similar to the results obtained with infliximab in the ACCENT (A Crohn's disease Clinical trial Evaluating infliximab in a New long-term Treatment regimen) I trial,[4] in which 19% of patients receiving active drug all along the study were responders in the induction phase and were in remission at week 54. The pivotal certolizumab pegol trials PRECISE ((PEGylated antibody fRagment Evaluation in. Crohn's disease: Safety and Efficacy) 1[5] and PRECISE 2,[6] limit their follow-up to 26 weeks, but the proportion of patients in remission (26% and 18%) is very similar to that of infliximab and adalimumab trials at the same time point.

Is the 1-year remission rate of 16–22% all we can get from anti-TNF antibody treatment? The clinical arena of Crohn disease treatment is probably not so equivocal. In randomised controlled trials of both infliximab[4] and adalimumab[2], patients who lost response were considered treatment failures for primary efficacy assessments, and there are data for infliximab showing that dose escalation regains response in a considerable proportion of patients.[7] In the open-label part of CLASSIC II, patients with continued lack of response or who experienced a flare could have the dose of adalimumab raised to weekly administration, and 42% of patients receiving adalimumab weekly were in remission at week 56. Nevertheless, this estimation should be interpreted with extreme caution, as these patients received the open-label active drug, which may increase the placebo effect, and there was no comparator group.

Is the considerable proportion of patients in remission at week 56 among the group of patients receiving open-label adalimumab in the CLASSIC II study, an indication that treatment should be maintained independently of the initial response? Long-term response to adalimumab seems to be strongly influenced by the initial response to it. Thus, from the CHARM and CLASSIC II studies, we

Table 1 Comparing the characteristics of pivotal long-term trials with anti-TNF agents in Crohn disease

TRIAL	Proportion of patients previously exposed to anti-TNF (%)	Proportion of patients on immunomodulator therapies (%)	Week at which randomisation of responders	Criteria of randomisation
ACCENT I (infliximab)	0	29.1	2 (following on open-label induction)	Response (CDAI drop of at least 70 points and 25% reduction of CDAI
CLASSIC II (adalimumab)	0	29.4	8 (following on randomised induction study CLASSIC I)	Clinical remission at week 0 and 4 of CLASSIC II
CHARM (adalimumab)	49.6	46.7	4 (following on open-label induction)	Response (CDAI drop of at least 70 points)
PRECISE I (certolizumab pegol)	28.1	37.5	Randomised at induction)	Not applicable
PRECISE II (certolizumab pegol)	24.2	40.7	6 (following on open-label induction)	Response (CDAI drop of at least 100 Points)

CDAI, Crohn Disease Activity Index.

may infer that if patients achieve remission in the induction phase, the expected proportion that will be in remission 1 year later is 81%, whereas if treatment is continued in patients that achieve either remission or response during the induction phase, the proportion of those that will be in remission at week 56 is reduced to 38%. Although both CHARM and CLASSIC II maintained treatment in initial non-responders, separate results for this subpopulation have never been reported. Given the considerable drop in long-term efficacy when comparing patients achieving remission after the induction phase versus those with remission or response in the induction phase, and the lack of evidence on efficacy among those without response in the induction phase, it seems prudent to withhold further treatment in initial non-responders.

CLASSIC II, like other recent trials of anti-TNF therapy in Crohn disease[8] and ulcerative colitis,[9] reported similar response rates in patients with and without concomitant immunosuppressants, and a lack of effect of immunosuppressants on drug efficacy has been claimed, based on these observations. However, it is conceivable that patients that were taking immunosuppressants at the time of inclusion in the trial represent a subpopulation that had more severe and/or more prolonged disease duration. These are factors that may affect response to anti-TNF therapy,[4 10] and the response of this subgroup of patients might have been worse without concomitant treatment. In the CLASSIC study programme, there was no difference in the baseline patient characteristics between the randomised and open-label cohort, reinforcing our lack of robust predictive factors in determining anti-TNF response. There is also a clear need to compare the relative efficacy of treatment strategies: monotherapy versus combined therapy. For this, the results of the SONIC (Study Of biologic and Immunomodulator Naive patients in Crohn's disease) trial prospectively comparing monotherapy with infliximab or thiopurines and with combined therapy are eagerly awaited.

The CLASSIC II trial provides information on adalimumab immunogenicity in Crohn disease, which is lacking in the CHARM trial. In CLASSIC II, 2.6% of patients, all without concomitant immunosuppressant treatment, developed anti-adalimumab antibodies. Contributing factors to this low immunogenicity probably include the fact that adalimumab is a fully human antibody, and also that the drug was administered on a pre-established schedule of weekly or alternate weekly injections, avoiding long periods off the drug. The importance of the latter is best exemplified in the infliximab ACCENT I trial, in which episodic and scheduled treatment arms were compared. Development of antibodies to infliximab was detected in 28% of patients in the episodic treatment arm, but only in 7.5% of patients in the scheduled treatment arms.[8] In this study, a significant effect of immunosuppressants reducing antibody formation could only be demonstrated in the episodic treatment arm. Comparison of immunogenicity between different anti-TNF antibodies is difficult, however, as the sensitivity of ELISA assays may not be comparable, interference from serum anti-TNF may be problematic, and the highly variable effect of immunogenicity on serum anti-TNF antibody concentration has to be taken into account. A difference in efficacy between anti-TNF monotherapy and combination with immunomodulator therapy has not been demonstrated with any of the anti-TNF agents when administered as scheduled maintenance therapy in inflammatory bowel disease. However, treatment strategy based on subgroup analysis (immunomodulator + anti-TNF versus anti-TNF alone) may be underpowered and is unwise. These subgroups are also not ''clean'', as a significant proportion received concurrent corticosteroid therapy. Given the similarity in remission and response rates among all three anti-TNF antibodies currently, or soon to be, available for treatment of Crohn disease, drug choice will probably rely on patient preference of route, convenience, cost and frequency of drug administration. More data is required regarding patient preference. However, the differences between these trials of long-term efficacy of anti-TNF agents in terms of patient population and selection of responders needs to be kept in mind, and direct comparison is unwise (table 1).

Adverse effects associated with anti-TNF therapy are now well documented from trials and registries, and the CLASSIC programme of trials confirm that serious adverse effects with anti-TNF agents are infrequent, leading to doctors feeling increasingly comfortable using these therapies. In particular, no tuberculosis or lymphomas were reported in the CLASSIC II study. However, experience from rheumatology and from the CHARM study[3] suggests that the risk of adverse effects with anti-TNF agents are common to this class of agents and that vigilance in patient selection and monitoring requires to be maintained, both for individual patients and via large registries. This is especially relevant for opportunistic infections including tuberculosis, demyelinating diseases and rare lymphomas. Injection-site reaction was reported in 38% of patients receiving the 160 mg/80 mg induction dose in CLASSIC I trial,[1] but was much lower in the CLASSIC II phase, and encouragingly, none had to be withdrawn because of injection-site reaction. The rare acute infusion reactions seen with infliximab do not appear to be a feature of adalimumab administration.

Will availability of new anti-TNF drugs affect the patient profile that is treated with these drugs? Data from PRECISE 2 show that the efficacy of anti-TNF therapy is affected by disease duration, with considerably better results in early disease, and the infliximab step-up versus top-down trial shows that early introduction of infliximab and thiopurines act as potent disease modifiers.[10 11] Furthermore, if we wish to modify disease course, we need to do so before disease complications appear. The GETAID (Groupe d'Etudes Therapeutiques des Affections Inflammatoires

Digestives) trial in steroid-dependent patients[12] and the step-up versus top-down trial[11] also demonstrate that much higher rates of steroid-free remission may be obtained with infliximab, at least in the short term, in studies that do not include patients with Crohn disease who have had multiple treatment failures.

Against this evidence, favouring early introduction of anti-TNF treatment, is the observation that the durability of response to biological therapy is limited to a proportion of patients, and some advocate ''saving'' the drug for situations in which conventional therapies fail, sometimes ignoring that in this situation anti-TNF therapy is also more likely to fail. Proper pharmacoeconomic evaluation of therapeutic strategies is also urgently required. For years, we have had only the infliximab bullet, and when the effects of the shot waned, many patients faced complications or surgery. Now our gun is loaded with two more bullets that have been shown to regain the benefits of anti-TNF therapy in a proportion of patients after response to the first one has faded. In the GAIN (Gauging Adalimumab efficacy in Infliximab Nonresponders) induction study, 21% of patients who had lost previous response to or were intolerant of infliximab went into remission at week 4 after (2 weeks induction dose of adalimumab, then 160 mg followed by 80 mg).[13] Admittedly, none of these bullets is quite magic, but these will be of great help in modifying the disease course in a proportion of our patients, especially if introduced early in the disease course.

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Fatty liver in chronic hepatitis C infection

Fatty liver in chronic hepatitis C infection: unravelling the mechanisms

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A step closer to understanding fatty liver due to HCV

Chronic hepatitis C virus (HCV) infection afflicts about 200 million people worldwide and is presently the most common cause of cirrhosis and hepatocellular carcinoma in Western countries. Over the last decade, an association between HCV infection, hepatic steatosis, insulin resistance (IR) and type II diabetes has been highlighted, although the cause–effect relationship underlying the co-existence of these phenomena has yet to be completely clarified.[1] These observations are important because the presence of steatosis and/or IR in chronic HCV infection appears to modulate the progression of fibrosis and the response to antiviral therapy in chronic HCV infection.[2–4]

Mechanisms underling steatosis development in chronic HCV infection have been demonstrated to be genotype specific, with an apparent direct steatogenic effect of genotype 3, and an IR-associated steatosis effect exerted by genotype 1.[5 6] The direct steatogenic effect of HCV genotype 3 is confirmed by findings such as those showing a correlation between HCV genotype 3 RNA level and steatosis in chronically infected patients and the resolution of steatosis in genotype 3-infected patients after response to antiviral treatment.[5–7]

Several mechanisms whereby HCV infection can directly cause steatosis have been described. HCV can affect de novo fatty acid biosynthesis, triglyceride (TG) assembly and secretion, and lipid peroxidation. HCV core protein has also been shown to localise in the periphery of TG-rich lipid droplets and on the cytosolic surface of the endoplasmic reticulum (ER) membrane, and it might physically interfere with lipids and other proteins involved in very low-density lipoprotein (VLDL) assembly.[8] Lipid secretion can be altered by the effect of HCV on microsomal triglyceride transfer protein (MTP) and apolipoproteins. MTP is an enzyme that regulates VLDL assembly and its activity is impaired by HCV core protein in core-transgenic mice.[9]

In fact, in chronic HCV infection, hypo-betalipoproteinaemia is described, especially in patients infected with genotype 3.[10 11] De novo fatty acid biosynthesis