Management of loss of response to anti-TNF drugs: Change the dose or change the drug?

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1. Introduction

The advent of biological therapy has dramatically changed our concept of treating refractory inflammatory bowel disease (IBD). Chimeric and more humanized anti-TNF Abs have shown to be highly efficacious in these illnesses, but all issues have not been resolved. Indeed, still 20–30% of patients with refractory Crohn’s disease1, 6 and 30–40%7 of those with refractory ulcerative colitis do not respond to anti-TNF treatment. Moreover, the long-term use of anti-TNF monoclonal antibodies is associated with immunogenicity, which interferes with efficacy, and with the risk of infectious complications. Secondary loss of response to monoclonal antibodies is a reality and clinicians should be prepared to optimize therapy.

A rapidly declining response to a given drug in patients responding to the first doses is usually called tachyphylaxis. Underlying reasons for a rapid loss of response can be very diverse. First, the human body usually reacts to external activators of endogenous proteins by decreasing the expression of the target protein or by internalizing membrane bound receptors. Second, alternative pathways can be recruited to restore the bioactivity targeted by a given drug. Third, the bioavailability and/or pharmacokinetics of therapeutic compounds are highly variable among individuals and liable to dramatic changes over time. The last mechanism can also induce a gradual loss of response, which is more commonly observed with anti-TNF agents. We will focus on loss of response with the use of anti-TNF antibodies in IBD and suggest strategies to optimize therapy in these patients.

2. Anti-TNF agents: different degree of humanization

Several strategies have been followed in drug development to improve the efficacy and tolerability of biological agents. Progress in protein engineering has resulted in the elimination of immunogenic non-human peptide sequences from anti-human antibodies, a technique called humanization.8 Third generation, humanized antibodies (±95% human) and fourth generation, fully (100%) human antibodies, are usually associated with less immunogenicity as compared to chimeric (75% human) monoclonals such as infliximab. Anti-TNF agents currently available differ in their degree of humanization.

The chimeric monoclonal anti-TNF IgG1 antibody infliximab (Remicade®, Centocor/Schering-Plough) has proven to be an efficacious induction and maintenance agent in...
patients with refractory CD and UC. Infliximab also induces rapid and profound endoscopic healing in IBD and appears to reduce hospitalizations and surgery. The fully human IgG1 antibody, adalimumab (Humira®, Abbott) is commercially available in Europe for the treatment of rheumatoid arthritis and Crohn’s disease. In luminal Crohn’s disease adalimumab has been shown to induce and maintain clinical remission and preliminary evidence points towards a decrease in hospitalizations. Also, certolizumab pegol or CDP-870 (Cimzia®, Celltech/UCB), a humanized Fab antibody fragment binding tumor necrosis factor and linked to polyethylene glycol (PEG) for subcutaneous administration, showed efficacy in refractory CD patients in two large placebo-controlled trials. The compound is marketed in the US and in Switzerland.

3. Loss of response to anti-TNF agents: how much of a problem?

As discussed above rapidly occurring ‘tachyphylaxis’ and more gradual loss of response can have different reasons. For loss of response to anti-TNF agents several possible mechanisms come to mind. First, patients may no longer have active inflammation and as a consequence little benefit can be expected from inhibiting a pro-inflammatory cytokine. Disease specific complications such as strictures or post-inflammatory bowel often provoke symptoms including abdominal pain and diarrhea. Biological disease markers like CRP, faecal markers and endoscopy may assist clinicians in decision making when structural disease is suspected. Second, due to its high degree of redundancy the immune system can activate alternative immune pathways bypassing TNF as the mediator of the cross talk between immunocytes. Although this mechanism of tachyphylaxis should be further explored, at present data are insufficient to understand how much alternative immune pathways contribute to the loss of response with anti-TNF agents. Third, the development of anti-drug antibodies is intrinsically linked with the use of therapeutic proteins. However, in clinical practice only antibodies, which interfere with drug efficacy (neutralizing antibodies) or instigate adverse events, really matter.

The secondary loss of response to infliximab has been best characterized since this compound has been used in clinical practice for more than a decade. With episodic on-flare use of infliximab patients run a clear risk of developing antibodies to infliximab (ATIs). The remaining mouse peptide regions in the chimeric protein are at least partially responsible for the formation of antibodies to infliximab (ATI). These antibodies are neutralizing and are associated with decreased drug serum levels and shorter duration of response. Using one specific assay to measure ATIs our group demonstrated that ATI levels above 8 µg/mL were associated with shorter duration of response. With episodic use, ATIs have been reported to occur in up to 75% of patients. For the more humanized anti-TNF agents introduced recently in the care of patients with IBD, long-term data are more limited. The humanized and pegylated anti-TNF Fab fragment, certolizumab, induces anti-drug antibodies in up to 12% of patients, but it is not clear how many of these antibodies are neutralizing the drug. Data on induction of anti-adalimumab antibodies (AAA) in Crohn’s disease are available from one trial only with long-term administration of this compound and maximally 3.8% of patients in this trial developed antibodies. From data in rheumatoid arthritis we now know that AAA are neutralizing. Antibodies to therapeutic proteins may not always reflect the full extent of immunogenicity since the classic solid phase ELISAs can only reliably measure anti-drug antibodies when drug serum levels are very low. Also differences between the assays impair comparison between individual cohorts. Drug trough levels, therefore, also reflect the degree of drug degradation and may be a more clinically relevant surrogate marker of tachyphylaxis. IFX drug levels correlate with the presence of ATIs and with duration of response, but this correlation is not absolute. Also, a decrease in drug levels may be driven by mechanisms other than the induction of anti-drug antibodies.

For patients with IBD more relevant than the underlying mechanism of tachyphylaxis is their chance of needing accelerated dosing due to secondary loss of response. From clinical trials we can infer some of this information. However, it is important to note up front that in the long-term trials with infliximab patients increased the dose and that with adalimumab a decrease in dosing interval was used to enhance drug exposure. In the first maintenance trial for luminal Crohn’s disease with infliximab, ACCENT 1, after one year 30% of patients treated with 5 mg/kg IFX IV stepped up to the higher dose group of 10 mg/kg because they experienced a disease flare. In the maintenance trials with adalimumab, CHARM and CLASSIC II, the percentage of patients stepping down their dosing interval to once weekly after one year was 27% and 46% respectively. In the long-term maintenance trial with infliximab for fistulizing disease, ACCENT 2, 25% of patients increased the dose to 10 mg/kg because their fistulas started draining again.

4. Optimizing treatment strategies to avoid loss of response

Several treatment strategies such as systematic maintenance therapy, concomitant immunosuppression and prophylactic systemic steroids, decrease the incidence of anti-drug antibody formation. The first reports on the high incidence of ATIs with the use of infliximab were all generated in patient cohorts with episodic, on-flare use of this antibody. In these cohorts patients with concomitant immunosuppressives (azathioprine/6-mercaptopuine or methotrexate) the induction of ATIs was clearly decreased and this coincided with a longer duration of response. Similarly, pre-treatment with corticosteroids before every infliximab infusion, decreases the induction of ATIs. More recent data from clinical trials and referral center cohorts indicate that episodic use of infliximab increases immunogenicity. In the ACCENT 1 trial 38% of patients in the episodic arm and 11% in the scheduled maintenance arm developed ATIs. Of interest, concomitant immunosuppressives only reduced the induction of ATIs in patients treated episodically, but not in those on scheduled maintenance therapy. The findings from ACCENT 1 were confirmed in a retrospective cohort at the Mount Sinai Hospital in Toronto. In this cohort ATIs correlated with low trough levels, with CRP and with the absence of long-term...
remission. Immunosuppressives were again only protective in patients treated episodically. Immunosuppressives also appear to protect against the induction of anti-adalimumab and anti-certolizumab pegol antibodies, but as for infliximab they don’t increase efficacy in patients treated with scheduled maintenance. Recently, in a cohort of 121 consecutive RA patients treated in Amsterdam AAA were shown to be present using a soluble phase radioimmunoassay in 17% of patients treated for 28 weeks with adalimumab and concomitant methotrexate use was lower in the group with AAA (52% vs. 84%, P=0.003). At 28 weeks patients with EULAR clinical response were less likely to have AAA than those not responding (5% vs. 34%).

From all these data taken together it is obvious that with episodic therapy immunosuppressive agents or steroid prophylaxis should be considered to decrease immunogenicity and secondary loss of response, but that for patients who receive scheduled maintenance with any anti-TNF antibody the benefit of having concomitant immunosuppressives is not clear.

5. Changing the dose, the interval or the drug

If despite optimizing the treatment strategy the efficacy of an anti-TNF agent fades in a patient with initial response, treatment flexibility is needed to counteract this loss of response. The two main strategies available are: (1) increasing drug exposure by decreasing the dosing interval or increasing the dose or (2) changing to another drug. To some extent the therapeutic intervention needs to be tailored to the individual patient.

To justify the first option of dose escalation, we need evidence that low trough levels are associated with loss of response and that increasing drug exposure restores efficacy. In the maintenance trial with infliximab, ACCENT 1, increasing the dose from 5 to 10 mg/kg and from 10 to 15 mg/kg restored response in 62% and in 69% of patients respectively. Conversely, in a single center patient cohort in Leuven of 547 patients with CD, 66% (75/108) patients who shortened their dose interval regained clinical response until the end of follow up. Data in patients with IBD and with rheumatoid arthritis suggest that IFX trough levels below 1 µg/mL indeed correlate with loss of response. Also in a recent trial, patients with CD and with low IFX trough levels (below median) had higher CRP levels and higher CDAI scores than those with above median drug levels. Hence, even if there is no absolute correlation between trough levels and clinical response to anti-TNF agents, increasing drug exposure with the intent to restore trough levels to therapeutic values is a valuable strategy.

Between infliximab, adalimumab and certolizumab pegol the strategies of dose escalation have been very different in clinical trials. Therefore, it is impossible to choose between a decrease in dosing interval and a decrease of the dose based on clinical trial experience. For adalimumab the European label only mentions decreasing the interval between injections, but for infliximab both options are being employed in clinical practice. A post-hoc analysis of the pharmacokinetic data collected in the ATTRACT maintenance trial with infliximab in patients with RA, suggests that decreasing the interval will lead to higher trough levels than increasing the dose per infusion. Also the response to the last infusion of infliximab can guide clinicians and patients in their decision. If patients report no response whatsoever to the previous dose of an anti-TNF agent, increasing the dose at the next administration appears more logical. Whereas in patients with a gradual shortening of the duration of response, decreasing the interval is a valid option.

Changing to the next anti-TNF agent is now an option in the treatment of patients with Crohn’s disease and should be considered in patients losing response or becoming intolerant to the first anti-TNF agent. However, in the GAIN trial with adalimumab specifically designed to include patients with loss of response to or intolerant to infliximab, remission rates 4 weeks after high dose adalimumab induction were lower as compared to an earlier dose finding trial, CLASSIC 1. This observation needs to be confirmed, but recent clinical trial data with both adalimumab and certolizumab indicate that prior exposure to infliximab attenuates the response to a second anti-TNF agent. Therefore, exhausting treatment options with the first anti-TNF compound by interval and/or dose optimization, should always be considered.

6. Conclusion and future perspectives

Secondary loss of response or tachyphylaxis to therapeutic antibodies in general and anti-TNF agents in particular is a clinical reality and we should all be ready to deal with it. Until now, we have been maneuvering in the dark as far as our interventions to optimize therapy are concerned. With the advent of more therapeutic options and with increasing knowledge about anti-drug antibodies and drug levels, it is time to go one step further. In patients losing response to an anti-TNF drug trough levels can aid in decision making. Patients with undetectable drug levels will most likely have high anti-drug antibody titers. For those patients, changing the drug is probably the best option. In patients with low to intermediate drug readouts, an attempt to restore trough levels should be considered. In patients with symptoms suggestive of active disease despite high trough levels, disease reassessment based on endoscopy, CRP, fecal calprotectin, and CT or MRI enteroclysis should be performed to exclude structural disease. If these patients have signs of active inflammation, a compound with another mechanism of action should be considered.

Conflicts of interest

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References


