Why Don’t We Just Measure Infliximab Drug Levels in IBD?

Infliximab (IFX) is potentially immunogenic, causing anti-infliximab antibodies that may interfere with the clinical efficacy and safety of the drug. There is an industry in measuring these antibodies, but the technicalities are legion, association with response poor and if they affect pharmacokinetics, it is by influencing drug levels. In contrast, IFX levels are associated with clinical response. So why make it complex? In this paper, we evaluate studies reporting the incidence of IFX antibodies in IBD, their impact on efficacy, safety and pharmacokinetics of IFX.

**INTRODUCTION**

Infliximab (IFX) has transformed the management of inflammatory bowel disease (IBD) [1,2]. It is a peptide and, like all proteins, is immunogenic. This means that the body recognizes the protein as foreign and generates antibodies in an endeavor to neutralize its impact. IFX is also expensive, costing £16456 ($26000) for induction and a year of maintenance therapy in the UK [3]. Drug and administration costs, of course, don’t reflect wider health benefits and economic benefits through reduced hospitalization or surgery and increased productivity at work. We won’t even go there, other than to regret that such pharmacoeconomic studies were not hard wired into the registration trials. It is hardly surprising therefore, that much effort has been spent on trying to predict response, non-response and to account for loss of response.

IFX is structurally comprised of 75% human and 25% murine protein sequences. The murine component isn’t the cause of immunogenicity (think of antibodies that develop during blood transfusion—fully human proteins are also immunogenic), but generally promotes drug immunogenicity. Adalimumab, for instance, is also immunogenic. Immunogenicity is defined as the potential for an antigen (usually a protein) to induce an immune response after it has been recognized by a pre-existing T-cell or B-cell receptor. It is worth identifying some of the other terminology
that confuses the literature at this stage. Chimeric antibodies such as IFX induce human anti-chimeric antibodies (HACA), also referred to as antibodies-to-infliximab (ATI). This biological phenomenon, only partially understood, has been associated with detrimental effects on the clinical outcomes of patients treated with IFX. There is consequently a demand for measurement of antibody and drug levels to aid clinical practice, which industry has not been slow in filling [4]. Consequently it is worth asking whether such tests stand up to scrutiny. A series of questions arise. The focus is on IFX, because that is where there are most data: the same arguments apply to adalimumab (ADA) or certolizumab pegol (CZP) and mention is made where published data are available.

**WHY SHOULD IMMUNOGENICITY TO INFLEXIMAB MATTER IN IBD?**

Antibodies to infliximab (ATI) have been reported to interfere with bioactivity, clinical efficacy and drug safety [5]. The real problem about the vexed question of whether or not drug antibodies (and their prevention) have any clinical relevance, is that there are technical differences in assays and clinical differences between patients, so there are many different ways of presenting or interpreting the data. Consequently authors (and industry!) can have it almost any way they choose. Outcomes can be (and are) reported in terms of antibodies (positive, negative, or inconclusive), concentration (higher or lower), threshold (above or below an arbitrary level), drug concentration, clinical effect (variably defined as duration or continuity of response, need for dose escalation, or switching), or impact on safety (infusion reactions).

**IS IMMUNOGENICITY A DRUG-SPECIFIC PROBLEM?**

The concept that fully human proteins are non-immunogenic is unfounded. All exogenous proteins have the potential to induce immunogenicity. There are many examples of antibody formation to human therapeutic proteins, including recombinant human insulin or fully human recombinant factor VIII [6]. This needs stressing, because the degree of ‘humaneness’ of a biological agent is not the sole determinant of immunogenicity. The very same antigen (drug) can induce a different intensity of immune response, depending upon factors such as the mode of administration, uptake by, or co-stimulation of antigen presenting cells, patient factors (such as age or concomitant immunosuppression) and drug chemistry (such as glycosylation). Data for ADA and CZP confirm that anti-drug antibodies develop, despite success at decreasing their incidence [7].

**WHAT IS THE INCIDENCE OF ANTI-DRUG ANTIBODIES?**

The true incidence of ATI in patients treated with IFX for Crohn’s disease remains unknown. The question is what would facilitates the formation of ATI. Detection of ATI has two components: patient-related and technical. Patient-related factors include the mode and frequency of IFX administration (mainly episodic vs. scheduled therapy) and concomitant medication with immunomodulators among them. Technical factors include the method of measuring ATI and timing of measurement. During episodic IFX, the incidence of ATI is high (36-61%) [8–11]. This is significantly decreased by maintenance schedules, with ATI in 5–18% [12–15]. Concomitant immunomodulator therapy is usually the main factor affecting ATI other than dose regimen. All studies agree that concomitant azathioprine, mercaptopurine, or methotrexate significantly decrease the incidence of ATI during episodic therapy [8,10,11], although whether this applies to scheduled therapy remains unclear [12–15]. Although lowers rate of anti-drug antibodies have been reported during treatment with ADA or CZP [5], attempts to compare immunogenicity between agents are compromised by differences in trial design, concomitant medication, route of administration, assay techniques (which are often proprietary), the timing of antibody determination and failure to measure or publish their prevalence.

Within these limitations, data for CZP report an incidence of 8–12% [16,17 and 3–17% for ADA in Crohn’s disease while reports for ADA describe an incidence of antibodies to adalimumab (ATA) of
3–17% during maintenance therapy [18–21]. Since there are no data on episodic therapy for ADA or CZP, the similar prevalence of antibody formation to scheduled IFX is striking. Concomitant immunomodulators do not seem to affect the development of antibodies to ADA [20]. As might be expected, antibodies are drug-specific, rather than a class-effect, so antibodies to one agent does not preclude switching drugs.

**DO ANTI-DRUG ANTIBODIES AFFECT THE EFFICACY OF ANTI-TNF AGENTS?**

About 10% of patients are primary non-responders to IFX and many more lose response. The dose often needs to be increased, either by shortening the interval between, or increasing the dose [21]. It remains unclear if ATI per se are associated with this secondary loss of response, or if a lower incidence of ATI (either through scheduled therapy or concomitant immunomodulators) has complementary effects on efficacy and safety [5]. Most trials of episodic IFX for Crohn’s disease report that ATI are associated with secondary loss of response [8–10], but this is not confirmed during studies of scheduled re-treatment. Whether this is because circulating IFX interferes with the assays of ATI during scheduled re-treatment is unclear, but the message is that ATI are not necessarily associated with loss of response [5]. While no studies have addressed the clinical impact of anti-CZP antibodies on efficacy or safety, preliminary studies suggest that antibodies to ADA do reduce efficacy [19,21]. This has been confirmed in a study of 168 patients with Crohn’s disease treated with ADA after failure to IFX [20]. The presence of antibodies to ADA was associated with lower trough drug concentrations throughout the follow-up period in patients who subsequently had to discontinue ADA, but no predictive factors (including antibody formation) were independently associated with response. Induction with ADA 160/80 mg was superior to 80/40 mg in terms of rate and time to discontinuation of ADA, which correlated with higher trough concentrations, but was unrelated to antibody development. Concomitant immunomodulator therapy at baseline did not affect treatment outcome, did not influence ADA trough concentration and did not decrease antibodies to ADA [20].

**DO ANTI-DRUG ANTIBODIES AFFECT THE SAFETY OF ANTI-TNF AGENTS?**

ATI have been associated with acute infusion reactions (4–40% of ATI-positive patients) and, to a lesser extent, delayed hypersensitivity to IFX. This applies to episodic IFX therapy, but the presence of ATI appears unrelated to infusion reactions during scheduled IFX. This further questions the value of measuring ATI. Moreover, the fact that infusion reactions also occur in ATI-negative patients, illustrates that the mechanisms are more complex than antibody formation alone. It is true that more patients who are ATI-positive have at least one infusion reaction, but the studies are in danger of over-analysing their data. They conclude that although ATI are associated with a 12% absolute increase in infusion reactions, they are unrelated to serious reactions leading to discontinuation of therapy. The truth is that they are underpowered to substantiate any effect [5]. It is perhaps notable that no relation has been found between antibodies to ADA and adverse events [20]: were anti-drug antibodies so pivotal to drug reactions (including those at the injection-site) then this would not be drug-specific.

**WHAT IS THE RELATIONSHIP BETWEEN ANTI-DRUG ANTIBODIES AND TROUGH LEVELS OF DRUG?**

A relationship between anti-drug antibodies and trough levels of drug is implied by the definition of antibody detection: patients classified as being without detectable antibodies include both those with a double negative test (neither detectable antibody nor detectable drug) and single negative tests (no antibody, but detectable drug). In spite of this, ATI have received considerable attention as a critical factor associated with undetectable serum IFX and loss of clinical benefit [8,9,11,12]. In the Leuven study using episodic IFX [11], it was notable that patients who developed ATIs during follow-up already had lower IFX trough levels 4 weeks after the first infusion, compared with patients who never developed (continued on page 18)
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ATIs. The low trough IFX levels had a high positive predictive value (PPV) for detecting high titers of ATI during treatment. This means that IFX levels measured after the first infusion (at 4 weeks) are likely to be a good prognostic parameter for development of immunogenicity. Unfortunately, this study did not describe the impact of IFX levels on efficacy or safety, since it focused on ATI. It is nevertheless worth noting that 16–39% of patients receiving scheduled IFX have undetectable drug prior to the next infusion, without antibody formation [13,14,22]. This probably reflects more rapid drug clearance in these patients. Why should we accept measurement of ATI as a surrogate marker of the readily measured serum level of IFX. After all, unless IFX is even more remarkable than marketed, no detectable drug implies no detectable action.

WHAT DOES INFLUENCE SERUM DRUG LEVELS?
The dose of drug matters. There is a linear relationship between the dose administered and maximum serum drug concentrations in adults receiving an intravenous infusion of 3–20 mg/Kg. Infusions at weeks 0, 2 and 6 afford predictable and dose-proportional drug concentrations. There is, however, a high inter-individual variability in serum IFX concentrations during treatment. Even though the initial bioavailability of IFX approaches 100% (because of the intravenous administration), differences in pharmacokinetics between patients may result in inadequate drug levels between infusions. In the ACT1 and ACT2 trials of IFX for treatment of active UC, body weight, albumin, immune response status, and gender independently affect drug clearance [23]. Immunomodulators influence drug levels, since a gradual decrease of serum IFX trough levels occurs after stopping immunomodulators during scheduled IFX therapy [8,14]. Patients taking immunomodulators were more likely to have higher IFX concentrations and, after logistic-regression analysis, only immunomodulator therapy predicted high IFX concentrations [8]. Pharmacokinetic models indicate that higher trough concentrations of IFX might be achieved by shortening the infusion interval or increasing the dose. Results from clinical practice show that dose adjustment can restore the treatment effect in the majority of patients, although there has been no systematic study. Were ATI so important, one might expect that a dose increase would be more successful in patients with low, rather than high titers of ATI, but this has not been clearly demonstrated. In the ACCENT I study in Crohn’s disease [24], dose escalation from 5 to 10 mg/Kg, or from 10 to 15 mg/Kg was successful in 80–90% of patients who lost response to IFX. Increasing the dose can be compared with shortening the infusion interval. Decreasing the dose interval by 2 weeks (in rheumatoid arthritis) resulted in a larger increase in the trough level of IFX, than raising the dose by 100 mg, and cost less [25].

WHAT IMPACT DO SERUM DRUG LEVELS HAVE ON CLINICAL OUTCOME?
Serum IFX concentrations are related to response in luminal [14,26] or fistulizing [27] Crohn’s disease, as well as in ulcerative colitis [28]. Those patients receiving maintenance IFX who had detectable trough concentrations of IFX had a higher rate of clinical remission, a lower serum C-reactive protein, and a higher rate of endoscopic improvement, irrespective of ATI status or concomitant immunesuppression [14]. Similar conclusions were drawn from 115 patients treated with IFX for moderate-severe steroid-refractory ulcerative colitis [28]. Trough drug levels relate to response and this is of no surprise for an effective drug: response cannot be expected when there is no detectable drug.

WHAT ARE THE CAVEATS OF MEASURING DRUG LEVELS AND ADJUSTING THE DOSE?
Potential adverse consequences from increasing the dose of anti-TNF agents must be kept in mind, even though we cannot predict which patients might benefit from dose escalation based on any known clinical, laboratory, or endoscopic factors. The relationship between trough levels of drug and clinical improvement is imprecise and needs more prospective data. A higher proportion of serious adverse events might occur in patients receiving more frequent dosing, although evidence is lacking. Some subjects have a
clinical response despite low trough drug levels, suggesting that trough serum levels are not, by themselves, reliable predictors of response [25]. Lack of treatment response cannot always be due to an insufficient dose of IFX. A particular disease characteristic or other host factors may preclude response to therapy.

SO WHY NOT JUST MEASURE DRUG LEVELS?

This paper outlines why antibodies to infliximab (ATI) cannot be used as a surrogate marker for immunogenicity, or to predict clinical outcome or safety. This is because up to half of patients still need dose adjustment for recurrent symptoms and 20% of patients lose response, even when treatment is optimised to avoid ATI through scheduled maintenance therapy or concomitant immunomodulators [24,29,30]. The presence or absence of ATI are neither sufficient to explain this, nor necessary for response to be lost. Measuring trough IFX levels provides more relevant information and may usefully guide treatment [31]. For instance, if there is no detectable IFX and there is still objective evidence of active Crohn’s disease (such as endoscopic ulceration), then the dose of IFX had best be increased. On the other hand, if there is detectable drug and active disease, then the drug isn’t working and a switch to another agent likely to be a more effective strategy. However, if there is detectable IFX with inactive disease (e.g. mucosal healing), then the drug is doing its job and had best be continued. But if there is no detectable IFX and complete mucosal healing has been achieved, then the job has been done and consideration given to stopping therapy. This strategy has yet to be put to the test, but appears rational. It is supported by demonstrable relationships between drug concentration, mucosal healing [32] and likely risk of relapse after stopping therapy [33]. Unfortunately it is not known what the optimal trough level is for IFX (there might be important interindividual differences), but the drug should at least be detectable before an infusion. Despite a recent retrospective study supporting the clinical utility of testing trough drug levels and ATI in specific circumstances [33] it is debatable how much value was gained by the additional measurement of ATI. Prospective studies are needed to determine if measuring drug levels are the best way of optimising therapy with IFX to improve the long-term outcome of inflammatory bowel disease. ■

References


