IBD REVIEWS REVIEW ARTICLE

Measuring drug levels and drug antibodies in inflammatory bowel disease patients

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Abstract

The applications of biologic therapy have revolutionized the treatment of inflammatory bowel disease (IBD), evolving from palliative and symptomatic treatment, to healing and structural and physiologic harm prevention. We have carried out a literature review on the application of biological serum level measures (infliximab, adalimumab, certolizumab pegol, golimumab, vedolizumab, and ustekinumab) in patients with IBD can reduce the disease burden, reduce costs, and have better clinical outcomes. In this article, we discuss the use, advantages, and disadvantages of therapeutic monitoring and treatment with biological agents for this group of conditions. There is not yet enough evidence to support the implementation of therapeutic drug monitoring as routine in the clinical practice. The studies done to date are not conclusive about the results and benefits of this treatment, which, in addition, has the disadvantage of its high cost, which makes it inaccessible for the vast majority of the population. We believe that in future can be standard of treatment in some special population as, for example, Crohn an severe activity of IBD. (IBD Rev. 2018;4:92-8)

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Introduction

During the past decade, the treatment of inflammatory bowel diseases (IBD) has evolved from symptomatic management to remission and prevention of intestinal damage and dysfunction with the optimal use of biological or immunomodulatory agents. Despite the current therapies, not all IBD patients achieve mucosal healing and may also persist with varying degrees of inflammation and/or lose effect over time and in the absence of other factors such as infection or neoplastic, the presence of failure to therapy should be classified as follows: (1) lack of primary response as a mechanism of action of the drug or (2) secondary failure due to inadequate levels of the drug and/or the formation of antibodies against it. One reality

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is that there is no certainty that by applying biologics, the disease will remit or even maintain remission at all times.

Background

The therapeutic drug monitoring (TDM) is the clinical practice that observes, records, detects, and analyses the therapeutic effects of a drug administered to a patient. It is based on the concentration of the drug, usually in blood, to adjust the treatment according to the own patient's pharmacokinetic characteristics[1-3]. It is unnecessary to employ TDM for the majority of medications, and it is used mainly for monitoring drugs with narrow therapeutic ranges, high toxicity, and medications with remarkable pharmacokinetic variability, for which target concentrations are difficult to verify, and drugs known to cause adverse effects of importance, such as anticonvulsants, immunosuppressant, β-lactams, antifungals, aminoglycosides, vancomycin, and more recently, to measure the levels of biological treatments[2,4-9]. TDM can be implemented to achieve therapeutic doses more rapidly minimum or without toxicity, improving the control of the disease, decreasing the need for other treatments and restraining the use of unnecessary high doses, and, therefore, lowering the costs of treatment[3]. As an example, due to its narrow therapeutic index and large interpatient pharmacokinetic variability, tacrolimus TDM has been implemented for individualization of dose to maintain drug efficacy and minimize the consequences of overexposure after renal transplantation[4,5].

TDM is an emerging strategy for optimizing the biological treatment of IBD, which includes determining serum levels of drugs and antibodies against them. Its objective in this scenario is to establish a systematic investigation of the levels of these drugs and their antibodies that allow the evaluation of the efficacy or potential failure of the treatment to improve the treatment and clinical outcomes of patients as well as minimize toxicity, with the further objective of individualizing treatments[2,3,8,10,11].

Available test to measure biological drug levels and antidrug antibodies

There are different methods to measure infliximab (IFX) concentration and antibody status: enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), and a fluid phase mobility shift assay[10,12,13]. The most widespread used test is the bridging ELISA. This test can also be used to detect anti-infliximab antibodies (ATI); however, ATI can only be measured when serum IFX levels are undetectable. RIA is similar to ELISA but has the downside of using a radioactive agent, thus making it harder to be implemented in the clinical practice, even though it is a sensitive, specific, and inexpensive test. Like the ELISA, RIA cannot detect ATI in the presence of IFX. The mobility shift assay was developed as an alternative to the before mentioned tests, neither of which can measure ATI when IFX is detectable in the serum. This test can measure both the concentration of IFX and ATI using high-performance liquid chromatography, giving it an advantage over others, but limiting its extended use due to its high cost[12,13]. The electrochemiluminescence immunoassay (ECLIA) can also detect ATI in the presence of serum IFX. Nevertheless, its implementation in the clinical practice cannot be recommended due to the lack of validation data available[13].

Adalimumab (ADA) concentrations can be tested by ELISA, ECLIA (to measure the concentrations of ADA and antibody to ADA), and by a fluid phase mobility shift assay that detects both concentrations of ADA and antibodies to ADA. As with IFX, its use is not recommended due to the lacking clinical validation data[13].

Certolizumab pegol concentration can be measured through ELISA for research purposes, but data on the comparison of assays are lacking[10,13].

The two main mechanisms predisposing different drug concentrations and higher drug clearance are immune mediated and non-immune mediated, the first is exemplified by the development of neutralizing antibodies to

anti-tumor necrosis factor (TNF) drugs and the later by the inflammatory burden[10]. The development of ATI is associated with lower serum drug concentrations and poor disease outcome, and new evidence suggests that the development of ATI might be a consequence of insufficient IFX exposure[3,13,14]. Rapid clearance of anti-TNF antagonist drugs cannot entirely explain why there is a lack of response to these medications, but it might be explained by differences in the underlying pathophysiology of the disease, and the interindividual pharmacokinetics and pharmacodynamics characteristics[14].

Inflammatory burden can increase drug clearance and trough levels (TL) of a drug[10,14]. Studies have demonstrated that low IFX concentrations correlate with low serum albumin and elevated serum C-reactive protein (CRP) levels[14,15]. Thus, adjusting an optimal trough concentration (TC) in the management of an IBD patient could prevent the formation of antidrug antibodies and induce clinical remission with mucosal healing as well as avoiding the risk of high drug clearance by an inflammatory process[14].

The best threshold value for each drug should be well defined, considering whether in the induction or maintenance phase. In the ACCENT I trail, a *post hoc* analysis, the optimal TC threshold at week 14 for a durable sustained response was > 3.5 µg/ml (and associated with a > 60% CRP decrease in patients with raised CRP at baseline)[14]. The relation of ADA TC at induction phase and clinical outcome has been analyzed in similar studies. In a cohort of 536 patients, Baert et al. observed that a TC < 5 µg/ml at week 4 was significantly associated with a risk of anti-ADA antibody formation a forthcoming elevated CRP, and ADA discontinuation related to loss of response[14,16]. Indirect evidence for proactive TDM also derives from the TAXIT (TL Adapted IFX Treatment) trail. In this study, among the patients with Crohn's disease (CD) with low TC (< 3 µg/ml) at inclusion who achieved TC of 3-7 µg/ml after dose escalation (91%), the rate of clinical remission rose from 65% to 88% after optimization. In addition, a significant decrease in median CRP concentration was observed at the same time[14,16-19].

In IBD patients with supratherapeutic drug concentrations, proactive TDM could be an option for treatment de-escalation. Drug de-escalation in CD patients with clinical remission and high TC (> 7 mg /ml) has been implemented previously by N. Vande Casteele, et al.[17] by any of these means: (1) reducing the dose to 5 mg/kg if the patient was on a 10 mg/kg formerly and (2) extending the time between infusions, by 2 weeks each time (to a maximum interval of 12 weeks)[14].

About 93% of the 72 patients in the TAXIT trail achieved a normal range, without any effect on neither the biologic IBD activity nor the clinical outcome, after receiving a dose reduction[14,17]. Paul et al. proposed a progressive dose reduction in 20 patients, who under IFX were on endoscopic and clinical remission, and were given 10 mg/kg of IFX every 8 weeks and who had elevated TC. Dose was stepped down by 1 mg/kg at each infusion until a TC between 3 and 7 µg/ml was reached. In 90% of patients, it was possible to reduce the dose, of which the majority could de-escalate to 7 mg/kg every 8 weeks without worsening of the disease[14,20].

Dose optimization of biologics

Depending on the disease activity, TDM has been studied in two scenarios for IBD patients receiving anti-TNF as maintenance therapy: (1) in patients with active disease to guide treatment adaptation (reactive testing) or (2) in patients in remission (proactive testing)[3,8,10,14,21,22].

IFX dose optimization

Once the different mechanisms of therapeutic failure are excluded and it is assumed that it is for lack of drug and without evidence of resistance to medication, it is possible to adjust the dosage, which can be done according to

different schemes empirically. Adequate serum levels of IFX have been found to correlate with better results in CD and ulcerative colitis (UC). A study of 105 patients with CD treated with 5 mg/kg IFX induction followed by scheduled interval treatment (6-8 weeks) or episodic maintenance retreatment found a correlation between IFX concentration, clinical remission, and change in endoscopic score from baseline. In addition, there was an inverse relationship between the serum concentration of IFX and the CRP. In a study of 115 patients with UC treated with three induction doses of IFX followed by scheduled maintenance doses, patients with detectable levels of serum IFX had higher remission rates (69 vs. 15%) and endoscopic improvement (76 vs. 28%) than patients with undetectable levels of IFX. An undetectable level of IFX predicted an increased risk of colectomy (55 vs. 7%) compared to patients with detectable levels of IFX. Therapeutic concentrations of IFX have been defined as > 12 mcg/ml at 4 weeks after infusion or at detectable IFX (> 1.4 mcg/ml) in the dosing channel. A retrospective analysis of the ACCENT (Clinical trial of CD evaluating IFX in a new long-term treatment regimen) patients with moderate to severe CD receiving IFX 5 mg/kg or 10 mg/kg every 8 weeks. It was found that in week 14 those with levels of 3.5 µg/ml had a sustained durable response[17,23-25].

Adalimumab optimization dose

It has been found that dose escalation is very effective with ADA. A retrospective cohort study of patients with CD who required an increase in dose due to loss of response found that 24 weeks after the dose escalation, 80.4% of patients (74/92) had symptomatic clinical response. Among the 74 patients who responded to treatment, the average duration of a sustained response was 69.2 weeks. However, 56.8% of those who responded later experienced a loss of tertiary response. A retrospective cohort study at the University of Chicago attempted to identify the factors that predicted the escalating dose of ADA; the study found that 31 of 75 patients (41%) treated with ADA between 2003 and 2008 required dose intensification. Male sex, smoking, and the colonic location of the disease predicted a shorter time to increase the dose. The family history of IBD predicted the need to intensify the dose[16,26-28].

Dose optimization of certolizumab pegol

Although the trials are not commercially available to evaluate drug or antibody levels for certolizumab pegol or golimumab, clinical trial data for both agents suggest that antibodies can be formed for both drugs, and the incidence of antibody formation decreases with the use of immunomodulators[10,29,30]. The intensification of the dose was also allowed in the MUSIC trial (endoscopic improvement of the mucosa in patients with active CD treated with certolizumab pegol) and may be an option in patients who do not respond to the standard dose of certolizumab pegol. 89 patients with CD were enrolled in the MUSIC trial, which evaluated endoscopic mucosal improvement in patients with active CD who were treated with certolizumab pegol. After 10 weeks of treatment, 46 patients were adjusted from doses of 400 mg every 28 days to 400 mg every 14 days, according to the investigator's criteria. A *post hoc* analysis of the trial revealed that the highest concentrations of certolizumab pegol at week 8 were associated with the endoscopic response and remission at week 10. Therefore, in patients with CD who do not respond to certolizumab pegol, the dose increases to 400 mg every 14 days may be useful to achieve higher levels of drugs and recover the response[31]. In the PRECISE trial (evaluation of pegylated antibody fragment in CD: safety and efficacy), 8% of patients treated with certolizumab pegol developed antidrug antibodies; 4% of patients with concomitant immunomodulators formed antibodies against 10% of patients on monotherapy[32]. Similarly, in the PRECISE 2 trial, antidrug antibodies were found in 8% of patients treated with certolizumab pegol. The rate was only 2% in patients with

concomitant immunomodulators compared to 12% in patients on monotherapy[29,32,33].

Antibodies formation for integrin inhibitors

The formation of antibodies to integrin inhibitors (i.e., natalizumab and vedolizumab) has also been described[34]. However, dose adjustment of natalizumab has not been allowed due to safety concerns, and the post-marketing experience of vedolizumab is limited so far. The ENCORE trial (Efficacy of Natalizumab in CD Response and Remission) evaluated natalizumab for the induction of CD remission and described the formation of antibodies in 8% of patients (53/650) at week 12 of the study. Of the patients who formed antibodies, 14% (39/286) received monotherapy with natalizumab, 6% (8/141) received concomitant oral corticosteroids, and 3% (6/223) with other immunosuppressants[35]. Similarly, in the ENACT-2 trial that examined maintenance therapy with natalizumab, 9% of patients (36/390) developed antibodies against the drug. In general, it was found that 6% of patients (23/390) had persistently positive antibodies, while 3% of patients (13/390) had transient antibodies. Although the presence of antibodies against natalizumab can be evaluated in a commercially available assay, dose adjustment and the use of concomitant immunosuppression are not allowed due to the risk of progressive multifocal leukoencephalopathy, a severely debilitating, and possibly fatal brain infection[34]. Practically, the only option with loss of response to natalizumab is the interruption of the medication. If a patient responded to natalizumab and then had a secondary loss of response due to antibody formation, changing medications within the same class (from natalizumab to vedolizumab) would be a reasonable option[24,34,36].

Specific trails for optimization

The TAXIT trial was the first randomized controlled study to evaluate concentration-based dosing to maintain remission in IBD patients treated within IFX. The 7 μg/ml upper margin for defining an optimal in IFX TC has never been validated[14,17]. Observational studies have suggested a correlation between in IFX TC and rates of clinical remission or mucosal healing. Ungar et al. observed that IFX TCs > 5 μg/ml and ADA concentrations > 7.2 μg/ml could identify patients in mucosal healing with 85% specificity. When cutoffs increased > 8 μg/ml for in IFX or 12 μg/ml for ADA, there was a minimal further increase in the mucosal healing rate[37-39].

Patients were first dose optimized to have an IFX TC within the interval of 3-7 mg/ml (optimization phase) according to the TAXIT algorithm[17]. Individual IFX TCs were evaluated at each infusion and the dosing regimen was changed for the next infusion according to the algorithm, until patients had a TC within the interval of 3-7 mg/ml. Briefly, in patients with supraoptimal concentrations, the dose was first reduced to 5 mg/kg (if on 10 mg/kg), after which the interval between infusions was prolonged each time by 2 weeks (to a maximum interval of 12 weeks). In patients with suboptimal concentrations, the interval between infusions was reduced each time by 2 weeks (to a minimum interval of 4 weeks), after which the dose was increased to a maximum of 10 mg/kg. Patients who successfully achieved an IFX TC within the optimal interval were then assigned to IFX dosing based on clinical symptoms and CRP or to continue dosing based on IFX TC (maintenance phase). In the clinically based dosing group, dosing of IFX was guided based on symptoms and CRP (recorded at each infusion) according to standard clinical practice criteria. In the concentration-based dosing group, individual IFX TC was evaluated at each infusion, and the dosing regimen was changed for the next infusion according to the TAXIT algorithm to keep patients within the optimal IFX TC interval. Formation of ATI inversely correlates with functional drug levels and clinical outcome[17,37,40]. Comparison of drug levels and antidrug antibody monitoring is hampered by lack of standardisation[10,41].

Nowadays, different assays are being used to measure drug and antidrug antibody levels[12,42].

Reactive versus proactive drug monitoring

Reactive TDM has emerged as the new standard of care for optimizing anti-TNF therapy in IBD as it can efficiently treat secondary loss of response and is more cost-effective when compared to empiric symptoms-based dose escalation. Recent studies suggest that proactive TDM, used to mark minimal therapeutic drug concentrations for patients in remission, is also associated with more favorable therapeutic outcomes, even compared to reactive TDM[14]. Papamichael et al. demonstrated that this therapeutic strategy of continued optimization was associated with greater drug persistence and fewer IBD-related hospitalizations compared to reactive testing alone that is currently the standard of care[14,21,22,43].

Recent investigations suggest that the measurement of biological drugs TL predicts ongoing patient response and can be used to titrate the medication to be more effective and efficient and also that antibodies against the medications predict loss of response and adverse events. Using both parameters can predict response to subsequent biological. Newer biological shows similar characteristics to those more commonly used[10,15,26,44].

Barriers to implement TDM

Biologic agents have been shown to be steroid sparing, reduce IBD-related surgeries and hospitalizations, induce mucosal healing, and improve patients' quality of life; nevertheless, up to one-third of patients show no clinical benefit after induction therapy (primary non-responders), and another 30-40% lose response during the 1st year of treatment, requiring dose escalation or a switch to another biologic[36,40]. Initial observational studies suggesting the benefit of proactive TDM have not been confirmed by controlled trials[10,14,27,31]. As stated recently by the American Gastroenterological Association, proactive TDM for anti-TNF cannot be recommended for daily practice and its impact on IBD outcome remains limited[10,14,44]. However, the growing evidence suggests that monitoring is related to longer remission and possibly prevention of complications. Within the barriers to carry out the monitoring are the following applicable for Latin America: (1) cost of the tests, (2) lack of consensus, (3) coverage for health services (private and public media), and (4) payment of the pocket of the patients. Validation of low-cost assays point of care testing, and studies that standardize the use of TDM are needed to make TDM more commonplace[45,46].

Recent data from control management on Crohn's disease[47] show that timely escalation with an anti-TNF therapy on the basis of clinical symptoms combined with biomarkers in patients with early CD results in better clinical and endoscopic outcomes than symptom-driven decisions alone without levels or antibodies. Future studies should assess the effects of such a strategy on long-term outcomes and maybe include anti-TNF levels on the basis of some patients that could have supratherapeutic levels.

Conclusions

The management of intestinal inflammatory diseases with biological treatments means a great step toward healing and preventing structural damage of the intestine secondary to these clinical entities. Disadvantages of this biological treatment, in addition to its high cost, are that it can cause the formation of antibodies which diminish its curative effect or that its therapeutic levels are not well defined yet. For this reason, therapeutic monitoring is very useful for the management of these clinical entities and should be done whenever this type of medication is used. However, the current studies are not conclusive or there is not enough information about it, so research on this subject should be abundant.

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