BRIEF COMMUNICATION

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Induction therapeutic drug monitoring regimen with infliximab: a simplified evidence-based algorithm for inflammatory bowel disease

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ABSTRACT – Therapeutic drug monitoring (TDM) of infliximab (IFX) has been recognized as an important strategy in the management of secondary loss of response to this agent, guiding clinical decision-making in the management of inflammatory bowel diseases (IBD). Although most of the data on the application of TDM for IFX refer to the maintenance phase of treatment, many studies have associated higher drug concentrations, specially in the induction phase, with achievement of important treatment targets, such as clinical remission and mucosal healing. This brief communication aims to summarize the literature on the use of TDM during induction phase of IFX and propose application of a simplified approach which can be useful into clinical practice, aiming better outcomes to IBD patients.

HEADINGS – Inflammatory bowel diseases. Drug monitoring. Biological therapy.

INTRODUCTION

Over the past 20 years, biological therapy has changed therapeutic paradigms in inflammatory bowel diseases (IBD). Infliximab (IFX), the first anti-tumor necrosis factor (anti-TNF) approved agent for the management of IBD, has proven its efficacy in inducing and maintaining clinical remission for both Crohn's disease (CD)[1,2] and ulcerative colitis (UC)[3]. It has also been associated with important therapeutic outcomes such as mucosal healing, reduction of hospitalizations and surgeries, and improvement in patient´s quality of life[4,5].

The understanding of the complex pathophysiology of IBD has lead to the development of new biological agents, targeting different mechanisms of action. However, even with the evolution and overspread use of these new agents, anti-TNFs are still considered one of the main treatment options for IBD[6] and their use as first-line agents is recommended in many situations, such as acute severe ulcerative colitis[7], fistulizing CD[8] and extra-intestinal manifestations of IBD[9].

One of the main drawbacks related to anti-TNF therapy consists on their rate of primary non-response (up to 30%)[10,11] and significant rates of secondary loss of response over time. In responders, dose intensification is needed in 23–46% of patients after 12 weeks of therapy, and drug discontinuation occurs in 5–13% yearly[12,13].

Pharmacokinetics of anti-TNF agents and immunogenicity (development of anti-drug antibodies) have been implicated in loss of response over time in a significant proportion of patients who initially respond to treatment[14,15]. Moreover, exposure-response relationship has been demonstrated for different biologicals[16] and higher drug concentrations of anti-TNF agents, specially during induction, have been associated with better long-term therapeutic outcomes as clinical remission and mucosal healing[17].

In this context, measurement of serum drug concentrations and antibody levels, known as therapeutic drug monitoring (TDM), has recently emerged as an effective approach aiming optimizing anti-TNF therapy in IBD[18].

This brief communication aims to summarize the current evidence in the field regarding TDM for IFX during the induction phase and provides practical advice through the development of a simplified algorithm with application of these concepts into clinical practice.

Proactive TDM with IFX: is it valid in the induction period?

Proactive TDM is defined by measurement of serum drug and antibody levels immediately before the next infusion (trough concentration), aiming guidance on dose escalation and prevention of loss-of-response as a consequence of low drug concentrations[19].

Although many observational retrospective studies reinforced the benefits of proactive TDM[20-22], the lack of agreement regarding specific cut-offs, the uncertain frequency whether proactive TDM should be performed and the absence of statement recommendations from different societies limit the overspread use of this approach in clinical practice.

Moreover, two randomized controlled trials failed to demonstrate the superiority of dose escalation of IFX based on drug concentrations (proactive TDM) over an empirical approach, with dose optimization based on clinical findings.

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The Trough Level Adapted Infliximab Treatment (TAXIT) trial was the first prospective study assessing the efficacy and cost-effectiveness of proactive TDM in IBD patients during maintenance treatment[23]. All included patients had IFX doses optimized or de-escalated aiming a therapeutic range between 3–7 µg/mL (optimization phase). Although better disease control was achieved among CD patients with sub therapeutic drug levels, whose dose was increased in the optimization phase, there was no long-term benefit in adjusting dosing based on TDM as compared with clinically based dosing in terms of maintenance of remission. However, the TDM group had lower chance of relapse over time and lower rate of antibody formation.

The TAILORIX trial, another prospective, double-blind, randomized study[24] evaluated the rate of corticosteroid-free clinical and endoscopic remission in three groups of CD patients (naïve to biological agents) following induction of IFX: two groups where dose escalation of IFX was based on a combination of symptoms, biomarkers and serum drug levels and a control group where dose optimization was simply based on clinical symptoms. Again, the trial failed to demonstrate better outcomes in the TDM group although many explanations were raised to justify this limitation. The main drawback was that only 16% of dose escalations in the TDM-guided groups were exclusively based on IFX serum levels. Moreover, the majority of patients that were dose escalated in the control group had normal biomarkers, whereas 53% of dose escalations based on symptoms in the TDM arm were avoided, as biomarkers were not elevated, becoming difficult to identify a difference between groups.

Even though the lack of prospective evidence demonstrating benefits of the proactive TDM approach in the maintenance phase of IFX treatment, many studies have associated higher drug levels in weeks 2, 6, 10 and 14 with favorable outcomes in the short and long-term[25-27]. This means that proactive TDM during the induction phase could play a significant role on therapeutic targets by reducing the rates of primary and secondary loss of response, avoiding inappropriate switching of the drug due to presumed loss of response and increasing patient retention of the first biologic[28]. Moreover, the achievement of early therapeutic drug concentrations has the potential to decrease immunogenicity due to sub therapeutic drug concentrations[29] with subsequently lower need for combination therapy with immunomodulators[30].

Evolving treatment goals for IBD patients have changed from induction and maintenance of clinical remission to endoscopic healing aiming change in the natural history of the disease[31]. Emerging data support that the achievement of higher drug levels during induction correlates with endoscopic remission for both CD and UC. In a post hoc analysis from the ACT 1 and 2 trials including 484 UC patients, IFX levels ≥18.6 µg/mL at week 2 and ≥10.6 µg/mL at week 6 were associated with endoscopic remission at week 8[32].

In a post hoc analysis of TAILORIX[33], a clear relationship between IFX trough concentrations during induction therapy and endoscopic outcomes at week 12 was identified. The authors proposed that an IFX trough concentration threshold of 23.1 mg/L at week 2 and of 10.0 mg/L at week 6, are associated with a 70% rate of mucosal healing. Thus, subtherapeutic concentrations could strongly compromise mucosal healing rates, thereby supporting a potential role for early dose optimization towards these thresholds.

An important clinical trial involving luminal CD patients who were naïve to biological therapy and started treatment with IFX or adalimumab (ADA) (PANTS study), identified that trough levels at week 14 <7 mg/L for IFX and <12 mg/L for ADA were associated with the absence of primary response. It was also observed that low levels at week 14 were independently associated with non-clinical remission at week 54, and were associated with increased formation of anti-drug antibodies[34]. These data highlights the importance of achievement of therapeutic levels early during induction allowing timely optimization. Despite most of the literature data emphasizes serum levels at week 14, early measurement (at week 6, for example) could lead to earlier optimization and consequently better outcomes.

Early induction IFX levels were also associated with perianal fistula response. A retrospective observational study evaluating 36 patients with perianal fistulas demonstrated that IFX drug levels of 9.25 µg/mL at week 2 and 7.25 µg/mL at week 6 were the best predictors of cessation or significant improvement of fistula drainage[35]. Moreover, a cross-sectional study that included 117 CD patients with perianal fistulae found that levels of IFX ≥10 µg/mL were also associated with higher fistula healing rates[36]. This additional benefit is of ultimate importance, considering the morbidity and decreased quality of life observed in these patients.

Evidence-based algorithm

As TDM strategies are being more used in clinical practice, it seems clear that proactive TDM in the induction period with IFX can be associated to some advantages for IBD patients. As logistics to have serum level measurements in every single infusion are difficult, it is important to emphasize that a simplified strategy, which could be more applicable in clinical practice, can be suggested and proposed.

FIGURE 1 demonstrates a simplified algorithm of proactive TDM in the induction phase with IFX for IBD patients. A single measurement at week 6 could stratify patients who may benefit for dose optimization as compared to those who could be followed in the regular 5 mg/kg dose. The evidence over the topic demonstrates that the level of ≥10 µg/mL can be considered as adequate for keeping the same dose over the next infusion at week 14[32,33,35,36]. However, patients with serum levels ≤10 µg/mL could benefit from therapeutic strategies aiming avoidance of future loss of response and development of antibodies (addition of immunomodulators on those in monotherapy, added to dose optimization of 10 mg/kg every 8 weeks, according to the label, which is started at the

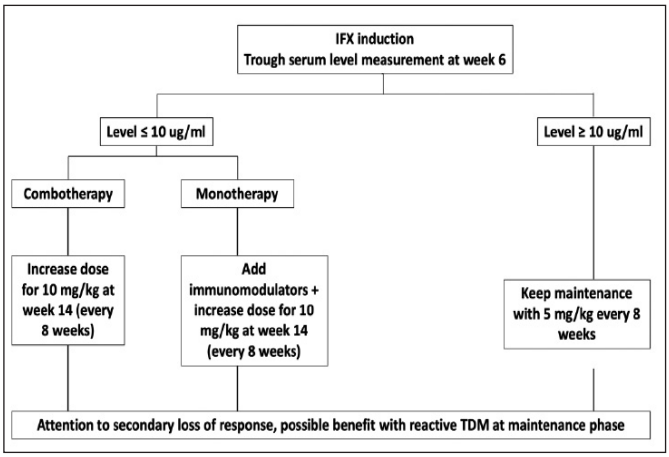

FIGURE 1. Suggested simplified TDM approach with IFX at induction phase.

week 14 infusion). The simple measurement of one single IFX level at week 6 could proactively improve patients' outcomes over the maintenance phase, if early dose optimization is undertaken.

CONCLUSION

Despite controversy on prospective data in the maintenance phase with proactive TDM, there is sufficient evidence to recommend a simplified TDM-based approach in the induction period with IFX for the management of IBD. Considering that tests and assays are becoming cheaper and more available throughout the globe, implementing serum level dosage proactively in the induction phase can benefit IBD patients, by reducing secondary loss of response and antibody rates over the long-term.

Authors' contribution

All authors were equally involved in study design, manuscript writing and review. All authors contributed to revision of the manuscript for important intellectual content, granted final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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RESUMO – A monitorização terapêutica dos níveis séricos (*Therapeutic drug monitoring* - TDM) de infliximabe (IFX) é uma estratégia reconhecida na tomada de decisão clínica frente a perda de resposta secundária a esta droga no manejo das doenças inflamatórias intestinais (DII). Embora a maioria dos dados sobre a aplicação dessa estratégia para IFX se refira à fase de manutenção do tratamento, muitos estudos associaram concentrações mais altas de IFX, especialmente na fase de indução, com o alcance de importantes alvos de tratamento, como remissão clínica e cicatrização da mucosa. Este artigo visa resumir as evidências da literatura sobre o uso de níveis séricos durante a fase de indução do IFX e propor a aplicação de uma abordagem simplificada que pode ser extremamente útil na prática clínica, visando melhores resultados para os pacientes.

DESCRITORES – Doenças inflamatórias intestinais. Monitoramento de medicamentos. Terapia biológica.

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