Tofacitinib in the management of ulcerative colitis refractory to anti-TNF and anti-integrin therapies

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INTRODUCTION

The pathogenesis of ulcerative colitis (UC) is multifactorial and comprises genetic, environmental, microbial, and immune response components(1). The current treatment algorithm of UC includes glucocorticoids, aminosalicylates, immunosuppressants, anti-tumour necrosis factor (TNF) agents and, more recently, anti-integrins(2). The introduction of anti-TNF agents, such as infliximab (IFX) and adalimumab (ADA), has improved UC treatment with reduction of hospitalizations and surgery(3,4). However, anti-TNF therapy has significant risks of loss of response and higher infectious adverse events rates, when compared to other therapies(5,6). Vedolizumab (VEDO), an anti-α4β7 integrin, on the other hand, has shown efficacy and an adequate safety profile, due to gut-selectivity properties. Thus, as every new biologic agent in the market, price and reimbursement are still an important issue, specially in developing countries such as Brazil(7).

Janus kinase (JAK) inhibitors are small molecules that are currently under investigation for the treatment of several immune diseases including psoriasis, rheumatoid arthritis (RA) and alopecia areata. In late 2014, tofacitinib (TOFA), a JAK inhibitor, has been successfully tested in UC patients and the importance of having another treatment option with different mechanism of action, like tofacitinib.

The aim of this brief communication is to describe in detail a case of a UC patient with primary non-response to anti-TNF agents (IFX and ADA) and an anti-integrin (VEDO), who was successfully treated with TOFA.

THE DIFFICULT ULCERATIVE COLITIS PATIENT

A 44-year-old man was electively admitted to an outpatient private clinic with an 8-week history of bloody diarrhea. He had been diagnosed with UC for 3 years and was maintained in remission with oral mesalamine MMX 2.4 g/day in combination with azathioprine (AZA), until a flare with gradual onset of bloody diarrhea. His bowel frequency was 10 times per day, associated with significant abdominal pain, tenesmus and weight loss of 10 kg. Over the previous 8 weeks of admission to our unit, he started prednisone 40 mg per day with symptomatic improvement. However, symptoms recurred right after reduction of the dose of steroids. His vital signs were stable and no remarkable findings were seen during clinical and abdominal examination. Laboratory investigations revealed a hemoglobin of 10.2 g/dL, C-reactive protein (CRP) of 75.0 mg/L, white blood count of 6.1×10⁹, an albumin of 31.0 g/L, and an a fecal calprotectin of 450 μg/g.

Ileocolonoscopy demonstrated oedema, erosions, friability, spontaneous bleeding and ulcerations from the transverse colon to the rectosigmoid junction extending to the transverse colon (Mayo endoscopic subscore of 3) (FIGURE 1A). In view of these findings, a decision to start IFX 5 mg/kg at weeks 0, 2, and 6, and then every 8 weeks, in combination with azathioprine, 2 mg/kg/day, was made. After 20 weeks on IFX therapy, the patient was still symptomatic. CRP was still elevated, 25.0 mg/L, and fecal calprotectin increased to 550 μg/g. Flexible sigmoidoscopy showed no significant improvement, with similar endoscopic findings (FIGURE 1B). After discussing the options with the patient, we decided to switch to subcutaneous...
A switch to intravenous VEDO, 300 mg weeks 0, 2, and 6, and then every 8 weeks was attempted. At week 22, the patient was still symptomatic, malnourished and referred mild improvement of symptoms. In addition to that, all laboratory exams were still abnormal (hemoglobin 10.7 g/dL, CRP 94.0 mg/L, albumin 25 g/L and fecal calprotectin of 470 μg/g). Clostridium difficile toxins A and B and CMV serology were both negative. Another flexible sigmoidoscopy revealed persistence of inflammation (FIGURE 1C). Oedema, friability, multiple erosions, and ulcerations were still present (Mayo endoscopic subscore of 2). In view of the primary non-response to three biological agents, two anti-TNFs and one anti-integrin, a subtotal colectomy with a temporary ileostomy was indicated and discussed with the patient. He refused to be operated and be given an ileostomy.

As an alternative, we offered him an off-label treatment with TOFA, after a detailed discussion of the pros and cons of postponing surgery. Oral TOFA, 10 mg bid, was then initiated. Eight weeks after starting the treatment, the patient referred a remarkable symptomatic improvement, with no diarrhea and bleeding. The laboratory results also demonstrated significant improvement: hemoglobin 11.4 g/dL, CRP 14.0 mg/L, albumin 33.0 g/L and fecal calprotectin of 250 μg/g and normal cholesterol levels. No adverse events were detected during the treatment. We de-escalated the dose of TOFA to 5 mg bid for maintenance. A flexible sigmoidoscopy was performed 3 months after starting TOFA, and revealed full mucosal healing of the sigmoid and rectum (FIGURE 1D), with a Mayo endoscopic subscore of 0. The patient was followed for 6 months, with sustained clinical and laboratory remission, with ongoing maintenance therapy.


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DISCUSSION

More than 80% of UC patients respond to aminosalicylates and less than one third of them will need biological therapy during the disease course(9). When salicylates fail, thiopurines (azathioprine and 6-MP) are a valuable option, especially in steroid dependent patients(2). Anti-TNF therapy (IFX, ADA and golimumab) have turned out to be the treatment of choice in UC patients who are refractory to conventional therapy(10). However, the treatment with anti-TNF drugs has some drawbacks. It is associated with loss of response in long term (approximately 13% per year), mainly due to neutralizing antibody formation(10). Moreover, anti-TNF therapy is associated with potential adverse events(10). The last TREAT registry reported an increased rate of severe infections (opportunistic infections, tuberculosis, histoplasmosis, etc.) in inflammatory bowel diseases (IBD) patients treated with IFX, when compared to conventional therapy(10). Recently, a gut-specific biological agent (VEDO) became available for UC patients, with a potential advantage of having no systemic immunosuppression, what can improve the safety profile during treatment(10).

We reported here an unusual case of a UC patient who was treated with three biological agents (IFX, ADA and VEDO) after being refractory to conventional therapy. The patient was a primary non-responder to three biologicals with different mechanisms of action: TNF inhibition and α4β7 blockage. After considering all the available options, we first recommended colectomy. As the patient refused the surgical option, which is not uncommon in this scenario, due to fear of permanent stomas, we proposed an off-label treatment with a JAK inhibitor (TOFA)(11). Clearly, at this point, an attempt with cyclosporine could be made. However, as the patient failed previous therapy with azathioprine, maintenance therapy after induction would remain a significant problem.

JAK inhibitors have already been incorporated in the management of immune-mediated diseases such as RA (in Brazil, since late 2014)(7). The drug is currently being investigated for the treatment of psoriasis and IBD(12-15). TOFA (CP-690,550) is an oral small-molecule drug (SMD) with a molecular weight of 312.3 Da. It inhibits JAK1, JAK3, and, to a lesser extent, JAK2(13-15). This inhibition ends up blocking signals for several inflammatory cytokines such as interleukin (IL)-2, IL-4, IL-6, IL-7, IL-9, IL-15, IL-21 and interferon-gama, among others(13-15). These cytokines are involved in the pathogenesis of IBD and play a role in many immune signaling routes including lymphocyte activation, function, and proliferation(12-15).

The initial favorable results of TOFA in a phase II multicenter randomized trial in UC, prompted a phase III program (OCTAVE) investigating the efficacy and safety of induction and maintenance therapy in patients with moderately to severely active UC(9,10). In the OCTAVE induction 1 trial (n=476 in the TOFA group; n=122 in the placebo group) remission at 8 weeks was 26.8% in the placebo group (P=0.001) and 42.7% in the TOFA group (P<0.001). In the OCTAVE induction 2 trial, with similar methodology, remission at 8 weeks was observed in 16.6% in the TOFA group versus 6.6% in the placebo group (P=0.001). An interesting observation was that in both trials the treatment effects were similar between those who had received previous treatment with a TNF antagonist and those who had not(9). In the OCTAVE sustain trial, two maintenance doses, 10 mg twice daily (n=197) and 5 mg twice daily (n=198) were compared with placebo (n=198) for 52 weeks in patients who completed the OCTAVE 1 or 2 trials and had a clinical response defined as a decrease in the total Mayo score of at least three points, with an accompanying
TOFACITINIB IN THE MANAGEMENT OF ULCERATIVE COLITIS REFRACTORY TO ANTI-TNF AND ANTI-INTEGRIN THERAPIES

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Both comparisons) (9). These findings emphasize that patients with previous exposure to biological agents, mainly anti-TNFs, can still have TOFA as an important option, as remission can be observed and mucosal healing can be observed in 30%-45% of patients. This was exactly the outcome observed in our patient.

A numerically higher rate of herpes zoster infection (usually less than 1.5%) was observed in the TOFA groups in the maintenance trial, mainly with the higher dose (10 mg twice daily). No cases of herpes zoster infection was considered serious or resulted in discontinuation of the drug (9). Across the three trials, lipid levels (i.e., cholesterol levels, LDL and HDL) increased with TOFA (usually in less than 30% of patients) and the increased plateaued after approximately 4 weeks (9). Among patients with RA or psoriasis, tofacitinib has also been associated with an increase in lipid levels without an increased risk of cardiovascular events. More cases of non-melanoma skin cancer occurred with TOFA (five cases) than with placebo (one case) across the OCTAVE trials. All cases had previous exposure to thiopurines. No cases of tuberculosis were reported in the three trials. Our patient did not develop any adverse event during TOFA therapy. However, the follow-up period with the drug was short, and monitoring is currently ongoing. Data from the ongoing open-label extension trial (OCTAVE open) of TOFA in UC may further elucidate the long-term safety profile of this drug (9).

In summary, we briefly communicated a patient with active UC with primary non-response to three biological agents, with different mechanisms of action, who refused surgical treatment and had a favorable response to TOFA, with clinical and endoscopic remission. No adverse events were observed with the use of the drug. This case illustrates the difficulties in managing refractory UC patients in an era of many biologicals as therapeutic options. It also emphasized the importance of a new mechanism of action as inhibition of JAKs, as a valid option in the therapeutic armamentarium in UC. Approval of TOFA by regulatory agencies worldwide is awaited, and growing expertise with the use of the drug is a question of time.

Authors’ contribution

Teixeira FV, Damião AOMC and Kotze PG drafted the article and all authors gave final revision and permission for publication.

REFERENCES