DOI: 10.1590/S0004-28032016000100002 ARQGA/1818

THE APPROVAL OF VEDOLIZUMAB FOR THE MANAGEMENT OF INFLAMMATORY BOWEL DISEASES IN BRAZIL: the beginning of a new biological era

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Received 8/10/2015
Accepted 9/10/2015

Dear sir,

The management of inflammatory bowel diseases (IBD), has evolved significantly over the last decades. From an era when only corticosteroids and aminosalycilates were used in the eighties, passing through the administration of immunomodulators in the nineties and culminating in the use of biological agents such as infliximab (IFX) and adalimumab (ADA) in the late nineties and the beginning of this century, it is clear that even with the development of new drugs, remission rates still need to be improved in the IBD management[4].

The experience with medical therapy for both Crohn's disease (CD) and ulcerative colitis (UC) also increased, and to date, the spread of the use of biological agents with no doubt improved outcomes and made patients' quality of life better over the last years[6]. In Brazil, IFX was approved in the year 2000 and ADA in 2007, and several publications demonstrated the implementation of the biological therapy in our country[5]. Still, anti-TNF agents do not represent the holy grail in the management of these inflammatory conditions. Several patients even do not respond or do have an initial response and loose efficacy over time. It is clear that anti-TNF agents changed paradigms in the management of these patients. However, several cases still need to switch treatment due to secondary loss of response, development of anti-drug antibodies and low serum levels[1].

In the first semester of 2015, vedoluzimab (VEDO), an humanized antibody that blocks integrin α4-β7, was approved for the management of CD and UC simultaneously in Brazil. The mechanism of action of this agent is the blockage of CD4 T lymphocites trafficking from the endothelium to the gut by blocking the addressin cell adhesion molecule 1 (MAdCAM-1), consequently reducing the inflammation in the tissue. VEDO has the property to be gut-selective, without significant action in other regions of the body such as the central nervous system. This property differentiates VEDO from other anti-integrins such as natalizumab (an anti-integrin α4-β1), a molecular property that avoids important systemic adverse events, such as progressive multifocal leukoencephalopathy (PML), and can improve the safety profile of the drug. Systemic adverse events tend to be reduced with a gut-selective agent. Therefore, infections such as tuberculosis, a significant problem in some regions of the world as Latin America, may also be reduced with this kind of therapy[10].

The efficacy of VEDO in inducing and maintaining clinical remission was proved in two big randomized clinical trials. GEMINI 1 tested the efficacy of VEDO in UC. In this study, at week 6, clinical remission was observed in 16.9% of the patients on the VEDO group versus 5.4% in placebo patients (P=0.001)[3]. At week 52, these numbers increased significantly, and remission was described in 41.8% of the patients using VEDO every 8 weeks versus 15.9% in placebo patients (P<0.001). The efficacy of VEDO in the long term was more significant in patients naive to previous anti-TNF therapy. This study also demonstrated, as secondary objectives, greater rates of mucosal healing and clinical response in the VEDO patients, as compared to placebo.

This article did not have any funding source

Disclosure: Kotze PG, Damião AOMC and Moraes AC are speakers and consultants for Abbvie, Janssen and Takeda. Damião AOMC is an employee for Nestlé.

Studied carried out at Serviço de Coloproctologia do Hospital Universitário Cajuru, PUCPR (Curitiba, PR, Brasil), Serviço de Gastroenterologia da Faculdade de Medicina da Universidade de São Paulo, FMUSP (São Paulo, SP, Brasil) and Serviço de Gastroenterologia do Hospital Clementino Fraga Filho, UFRJ (Rio de Janeiro, RJ, Brasil).
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The GEMINI 2 trial studied the efficacy of VEDO in CD patients[7]. After induction with 300 mg intravenously at weeks 0 and 2, outcomes were measured at week 6, and clinical remission was described in 14.5% in patients in the VEDO group versus 6.8% in patients under placebo (P=0.02). At week 52, remission rates were also more significant in the VEDO group as compared to placebo (39% vs 21.6% respectively, with P<0.001). Additional secondary outcomes also demonstrated higher rates of steroid-free remission in the VEDO patients, and higher remission and response rates in patients without previous exposure to anti-TNF agents. A subanalysis also demonstrated higher fistula closure rates in the VEDO patients.

An additional study, GEMINI 3, tested the efficacy of VEDO only in CD patients with previous exposure to anti-TNF agents[8]. In this study, an extra infusion of 300 mg of VEDO intravenously was performed at week 6. Remission rates were not more significant than placebo at week 6 (15.2% vs 12.1%; P=0.433). However, at week 10, the remission rates were higher in the VEDO group as compared to the placebo (26.6% vs 12.1%; P=0.001). These findings suggest a slower action of VEDO in CD, and the possible benefits of an extra infusion at week 6. However, these findings still need to be better explored in real life cohorts.

In terms of safety, the gut selectivity of the inhibition of the α4-β7 and consequent blockage of the MAd-CAM1 did not demonstrate new or different adverse events. Differently from the studies with natalizumab, no cases of PML were observed in the three studies, with more than 2000 patients followed in the safety analysis[3,7,8]. Common infectious adverse events were observed in these trials in VEDO patients, such as sinusitis and faringitis with similar rates as compared to patients with placebo infusions. Infusion reactions occurred in 5%-10% of the patients. Gastrointestinal infections can occur due to the gut-selectivity properties of VEDO, but in general, serious adverse events were similar in the VEDO and placebo groups. CD patients can also develop perianal abscesses, and this was observed in both groups in the GEMINI 2 and 3 studies[7,8].

VEDO is the first biological agent approved worldwide simultaneously for the management of both UC and CD, with a mechanism of action different from the inhibition of TNF alpha. It seems that the drug requires more time to act, and can be really useful in maintenance of the reponders, mainly in UC patients. The experience with anti-TNF agents is solid over the last 15 years, and for sure the knowledge of different strategies with VEDO will come over time. Several questions still need solid answers with this new agent: is VEDO's efficacy better with concomitant immunomodulators or as monotherapy? Can VEDO be indicated before anti-TNF agents as first line therapy? Can patients' disease control be improved with early use of VEDO, as top-down therapy?[2]

Surely, the introduction of VEDO in Brazil will initially help several patients that are refractory to anti-TNF agents, and are waiting for new therapies for the management of their diseases. This is now occurring in several countries, and the initial case series of patients apart from pivotal trials are currently being published[9]. However, the role of VEDO as a new effective therapy for IBD, even in patients naive to anti-TNF agents, will be clearly stated after some years of experience in clinical practice. For sure a new era of biological therapy is just beggining with this new gut-selective agent. More drugs are prompt to come to our armamentarium over the next years, in a full pipeline devoted to CD and UC. Brazilan physicians and patients will definitely explore the potential of this new agent in the best way as possible.

Authors' contributions

Kotze PG, Damião AOMC and Moraes AC drafted the article and gave final revision.

Kotze PG, Damião AOMC, Moraes AC. Aprovação do vedolizumabe no manejo das doenças inflamatórias intestinais no Brasil: o início de uma nova era biológica. Arq Gastroenterol. 2016,53(1):3-4.

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