Original Article

Biological therapy in the treatment of moderate-to-severe ulcerative colitis patients: can colectomy be prevented?

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ABSTRACT: Ulcerative colitis treatment intends to induce remission, and its maintenance. Biological drugs, such as infliximab, have been indicated in moderate and severe cases of the disease, which are unresponsive to conventional medication. Randomized controlled trials proved the efficacy of biological treatment with high rates of sustained disease remission and mucosal healing. Recently, the concept of mucosal healing has been inversely associated with surgical treatment. Patients treated with infliximab have lower colectomy rates than those receiving conventional therapies. We suppose that earlier use of biological drugs in disease's course would lead to better clinical control and mucosal healing, with a consequent reduction in colectomy rates. To support this hypothesis, a literature review from January, 1996 to April, 2011 was performed.

Keywords: biological therapy; colectomy; colitis, ulcerative; treatment outcome.

INTRODUCTION

The treatment of inflammatory bowel disease (IBD) has dramatically changed since the introduction of biological medications, especially the monoclonal antibodies against tumor necrosis factor (anti-TNFα). The main anti-TNF drugs used in clinical practice are: infliximab, adalimumab, and more recently certolizumab pegol[1-13].

The pro-inflammatory cytokine TNF-α plays an important role in the inflammatory process of IBD, mainly in Crohn's disease. However, its role in the pathogenesis of non-specific ulcerative colitis (UC) is still an issue of debate[1-4].

The clinical control of UC patients is based on salicylate therapy, such as sulphasalazine and mesalazine. In refractory cases, most authors recommend im-

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munomodulators. Steroid treatment is only indicated for a few weeks in the remission induction, but it is not suggested for remission maintenance. The main objective of medical treatment is to induce and maintain disease remission, avoiding flare-ups and the need for steroids. Remission maintenance of the disease is inversely associated with indication of a surgical procedure, such as total colon removal and ileal pouch anal anastomosis (IPAA)[5-10]. Even so, despite clinical treatment, around 9% of patients with distal colitis and 35% of those with diffuse colitis (pancolitis) undergo surgery and have their colons removed during the course of the disease[5-10].

Several pilot studies have been performed using anti-TNF, especially infliximab, with the aim of treating patients with UC unresponsive to conventional medication[1-4]. The most important study in this topic was published in 2005[5]. Two recent randomized, controlled and double-blinded trials with UC patients denominate ACT 1 and ACT 2 (Active Colitis Trial 1 and 2) demonstrated the efficacy of infliximab for induction and maintenance of remission in patients with moderate to severe UC not responding to conventional treatment[5]. More than 60% of the patients included in this study who received infliximab achieved disease remission and intestinal mucosa healing[5]. Jarnerot et al.[6], reported that infliximab can be used as a rescue therapy in patients with moderate to severe persistent UC, which is associated with significant reduction colectomy rates.

We wondered whether earlier use of biological therapy during disease course, as well as being used in treating Crohn's disease – top-down approach – could lead to better clinical control and mucosa healing, with a consequent reduction in colectomy rates[12-13]. To support this hypothesis, a wide literature review was carried out to find better evidence over a period from January, 1996 to April, 2011.

INFLIXIMAB AND UC

Since the beginning of this decade, anti-TNFs, especially infliximab, have been used in the treatment of moderate to severe UC resistant to conventional treatment. Sands et al.[2] published one of the first studies regarding using infliximab in patients with UC. Those who received infliximab presented clinical and endoscopic improvement compared to the Placebo Group, but without statistical significance. Amongst the initial 60 patients planned for inclusion, only 11 were randomized: 3 received placebo and the others, different infliximab doses. All three placebo patients had colectomies at the end of the study and among the eight receiving infliximab, only four underwent surgery[2].

Jarnerot et al.[6], in a multicenter Scandinavian study, evaluated the efficacy of infliximab as a rescue therapy in patients with UC resistant to conventional drugs and indicated for colectomy. Forty-five patients were included (24 treated with infliximab and 21 with placebo). Twenty-nine per cent (7/24) of infliximab patients were submitted to surgery, while 67% of the Placebo Group (14/21) had their colons removed due to lack of response. This was the first report in literature with strong evidence supporting the use of infliximab as a rescue therapy before colectomy indication[5]. In a multicenter retrospective study performed in Italy, Kohn et al.[10] reported infliximab use in 83 patients with an acute moderate or severe episode of UC indicated for colectomy, due to resistance to intravenous corticosteroids. As a rescue therapy before colectomy, all patients received between one and three doses of infliximab (5 mg/kg) every two or four weeks, without any pre-established protocol. Those who did not respond to treatment were submitted to colectomy. Eighty-two per cent avoided colectomy at two months. Sixty-one patients (73%) reached clinical remission at one month. Seventy patients (84%), who attained the primary endpoint (no colectomy or death), were followed-up for a median period of 23.4 months. Over this period, 97% patients discontinued glucocorticoids. There was a total of 12 (29%) colectomies among the 83 patients included in the study[10].

Rutgeerts et al.[5] performed a randomized, controlled, double-blinded, clinical study – ACT-1 and ACT-2. They reported about the efficacy of infliximab in patients with moderate and severe UC resistant to conventional therapy with corticosteroids and immunomodulators[5]. In a recently published post-hoc analysis of ACT-1 and ACT-2, Sandborn et al.[9] observed 41% reduction risk of colectomy in the Infliximab Group during the treatment period of 54 weeks. The objective of this post-hoc analysis was to establish whether infliximab could reduce the number of colectomies over a one-year period. Treatment with

this biologic led to a 7% reduction in absolute risk of colectomy. This was statistically significant in patients treated with 10 mg/kg infliximab (18/242, 8%, p=0.0007), but it was not statistically significant in patients treated with 5 mg/kg (28/242, 12%, p=0.166), when compared to placebo (36/242, 17%)[5,9].

INFLIXIMAB, MUCOSAL HEALING, AND COLECTOMY

Currently, the main purpose of treating Crohn's disease is to promote intestinal mucosal healing[12]. There is no question regarding intestinal healing as the main predictive factor related to long-term clinical remission[12,14,15]. In analogy to Crohn's disease, the early use of biological drugs since disease diagnosis – top-down therapy – could also lead to improved intestinal healing rates for UC patients with the consequent long-term control of symptoms[12,13].

A Norwegian, population-based, cohort study of UC patients reported that mucosal healing after one year of treatment was associated with low risk of future colectomy[16]. A population-based cohort of 843 incident cases of IBD in Norway was collected from 1990 to 1994 and subjected to a scheduled prospective follow-up, with a one-year visit and a five-year visit. Data from a total of 513 incident UC patients were available from the inflammatory bowel disease in Southeastern Norway (IBSEN) study. After exclusion of patients undergoing colectomy during the first year after diagnosis (n=15), and some patients who did not meet follow-up criteria, 448 patients with UC were eligible for the one-year follow-up. Of the patients with mucosal healing at the one-year follow-up, three were recorded as having undergone surgery at five years, compared with 13 in the group without mucosal healing at one year (p=0.02).

Moreover, multiple logistic regression analyses were performed with mucosal healing or endoscopic inflammatory activity as the dependent variable and different subsets of variables. Only educational level and disease extension (proctitis, proctosigmoiditis, left sided, extensive colitis) were recognized as significant mucosal healing predictors (p=0.004 and p=0.02, respectively). The authors concluded that, indeed, there is a relationship between disease's extension and mucosal healing as a result of more aggressive treatment in patients with extensive colitis[16]. Furthermore, in an univariate analysis, it was found a positive relationship between mucosal healing and fever at baseline in patients with Crohn's disease and also by the significant predictive role of other symptoms, such as pain on subsequent mucosal healing[16].

Indeed, this fact supports the hypothesis and it allows us to speculate that, maybe, patients with extensive disease or severe symptoms may have been treated earlier and more aggressively. The authors suggested that we must adopt a strategy for the earliest possible treatment in both children and adults. Such strategy can reduce hospitalization and surgery costs and may prevent complications and disability at a young age[16].

The natural history of inflammatory intestinal diseases can be changed if we adopt an effective treatment, which heals intestinal mucosa[12,16]. Recently, a Swedish/Danish group published the long-term efficacy of infliximab as a rescue therapy in severe UC patient[7]. The ones who participated in the first study published in 2005 were followed-up for a median of 55 months (range 36 to 79 months)[6-7]. In the original study, patients with severe UC were randomized to receive a single infusion of infliximab or placebo, and colectomy rates were measured after 90 days[6]. Patients of the same cohort were followed-up for three years. Additional anti-TNF therapy was allowed for clinical relapse. Clinical remission was defined as total Mayo score ≤1 and endoscopic remission as Mayo endoscopic subscore=0[5,7]. Eleven of 15 patients that did not undergo surgery at follow-up were in clinical remission and 12 of 15 patients not operated were in endoscopic remission. Fifty percent (7/14) of the patients who had their colon removed were not in endoscopic remission in the moment of operation. On the other hand, none (0/8) of the patients in endoscopic remission was operated. After three years, the authors reported a significant reduction in colectomy rates observed in the first study[6]. Fifty percent (12/24) of the patients treated with infliximab were operated compared to 76% (16/21) treated with placebo (p=0.012)[7].

The anti-TNF drugs used in Crohn's disease and UC therapy intend to the macroscopic healing of the intestinal mucosa (absence of erosion and ulcers)[12,14,15,17]. Also, infliximab is associated with an improvement of inflamed tissue ultra-structure[17]. Fra-

tila and Craciun[17] reported intracellular improvement in the mucosa of UC patients treated with infliximab. Four weeks after receiving two infusions of infliximab (5 mg/kg) – weeks 0 and 2 –, patients were submitted to colonoscopy and inflamed colon mucosa biopsy. An important intracellular improvement was seen after infliximab treatment. The authors reported improvement in the morphology and function of the epithelial organelles, rich mucus secretion, and recovery of the chorionic components. At the end of treatment, the new ultra-structural assessment clearly showed signs of epithelial barrier recovery, with appearance of the goblet cells, microvillus border, Golgi complex, and mitochondria, resulting in a general aspect of tissue healing. The metabolic activity and the energetic function were re-engaged due to numerous vesicles synthesized in the cytoplasm and electron-dense normal mitochondria[17].

Therefore, it is evident that treatment with biological drugs promotes an improvement in clinical symptoms, and macroscopic (endoscopy) and microscopic mucosa healing, including the cellular level[17]. Such findings may indicate a change in the disease's natural history.

At present, unfortunately, there is no scientific evidence that support the theory that top-down approach in UC patients would be better than conventional treatment. However, in patients with moderate to severe UC, it has shown higher rates of mucosal healing when comparing infliximab to conventional therapy[5]. Therefore, it is pertinent to speculate whether patients treated early with infliximab and who received a regular maintenance dose every two months, would have healed colon, and in the long-term, reduced number of complications and lower probability of colectomies.

CONCLUSIONS

Anti-TNF biological drugs are a landmark in the treatment of inflammatory bowel disease, especially infliximab and adalimumab[5-11,13-22]. The anti-TNFs promote healing of the inflamed intestinal mucosa with reduction in the local inflammatory process, erosions, and ulcerations[5,16]. Also, the use of infliximab in UC can lead to the ultra-structural improvement in inflamed cells[17]. Such macroscopic and ultra-structural changes observed in intestinal mucosa after treatment with anti-TNFs were defined in literature as mucosal healing. Healing of the mucosa is directly associated with the reduction in number of colectomies in UC patients who received anti-TNF therapy[7-10,16,20-22]. Finally, just as we see a modification in the natural history of Crohn's disease, patients who receive early biological – top down therapy –have sustained disease remission, fewer relapses, fewer hospitalizations, and consequent reduction in intestinal surgery, we believe that the UC patients could also have the same favorable clinical evolution if treated early with biological therapy[12,16].

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RESUMO: O tratamento da colite ulcerativa tem como objetivo induzir a remissão, além da manutenção da remissão da doença. Agentes biológicos como o infliximabe têm sido indicados em casos moderados e graves da doença, os quais não respondem à medicação convencional. Ensaios clínicos randomizados comprovaram a eficácia do tratamento biológico com altas taxas de remissão da doença e cicatrização sustentada da mucosa. Recentemente, o conceito de cicatrização da mucosa tem sido inversamente associado com o tratamento cirúrgico. Pacientes tratados com infliximabe têm taxas mais baixas de colectomia se comparados com aqueles que receberam terapias convencionais. Supõe-se que quanto mais cedo for introduzida a terapia biológica no curso da doença, melhor seriam o controle clínico e a cicatrização da mucosa, com consequente redução nas taxas de colectomia. Para apoiar esta hipótese, foi realizada uma revisão da literatura entre janeiro de 1996 e abril de 2011.

Palavras-chave: terapia biológica; colectomia; colite ulcerativa; resultado do tratamento.

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