

Ulcerative colitis - treatment with biologicals

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Final version: October 07, 2018

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<http://dx.doi.org/10.1590/1806-9282.65.4.547>

The Guidelines Project, an initiative of the Brazilian Medical Association, aims to combine information from the medical field in order to standardize producers to assist the reasoning and decision-making of doctors.

The information provided through this project must be assessed and criticized by the physician responsible for the conduct that will be adopted, depending on the conditions and the clinical status of each patient.

INTRODUCTION

The pharmacological treatment of ulcerative colitis (UC) aims to reduce the inflammatory process and maintain remission of symptoms^{1,2}. Despite the therapeutic progress, treatment options for moderate to severe active UC remain limited, due to the partial control obtained with conventional therapy (sulfasalazine, aminosalicylates, glycyclorticoids and immunosuppressants) in a substantial proportion of patients, and the existence of adverse events. Currently, the drugs of choice for the therapeutic approach of these patients are anti-tumor necrosis factor alpha (anti-TNF- α) agents, infliximab, adalimumab, and golimumab, and more recently, the anti-integrin agent (vedolizumab) selective antagonist of this adhesion molecule in the intestine.

METHOD

The objective of this guideline is to provide recommendations, which may assist in decision making, in relation to patients with ulcerative colitis, regarding

the benefit or harm of biological treatment. For this, a systematic review of the literature was carried out, with the descriptors according to the peak: patients with ulcerative colitis, i of biological indicator and the outcome of benefit or damage. Without restriction of period, in the Medline database, the search strategy was: (((Inflammatory Bowel Diseases) OR (Colitis, Ulcerative)) NOT (Crohn Disease)) AND (Antibodies, Monoclonal OR Antibodies, Monoclonal, Humanized OR Tumor Necrosis Factor-alpha OR anti-TNF OR Infliximab OR Adalimumab OR Golimumab OR Vedolizumab OR Integrins) AND Random*. A total of 310 papers were found, 22 being used to answer the clinical question: Are biologicals effective and efficient in the treatment of ulcerative colitis? The recommendations will be prepared by the authors of the review, with the initial characteristic of synthesis of the evidence, being submitted to the validation by all the authors participating in the preparation of the Guideline. The degree of recommendation to be used stems directly from the

available strength of the studies included according to Oxford²⁵, and the use of the GRADE system²⁶.

RESULTS

Induction of remission

Infliximab

Monotherapy / combined therapy

Some studies compared infliximab associated with azathioprine versus infliximab associated with placebo and azathioprine associated with placebo, and others compared infliximab with placebo.

Studies such as ACT1 and ACT2 involving patients with moderate to severe ulcerative colitis (Mayo score 6-12) who were refractory to corticosteroids alone or in combination with azathioprine or 6-mercaptopurine (ACT 1) or with 5-aminosalicylates (ACT 2) were performed to assess the clinical response at week 8. Patients with prior anti-TNF use were excluded. This was more common in patients treated with infliximab (5 mg / kg IV) compared to the placebo group (69% vs 37% in ACT 1, $p < 0.001$) and (65% vs 29% in ACT 2, $p < 0.001$). Patients taking infliximab also had a higher clinical response rate at week 30 ($p \leq 0.002$ in both studies)³(A).

Patients with ulcerative colitis, corticoid refractory were randomized to infliximab (5 mg / kg) IV at weeks 0 and 2 or placebo. The remission rate (ulcerative colitis symptom score less than 2) was 39% in the infliximab group and 30% in the placebo group by the 6th week, with a 9% difference between groups that was not statistically significant (95% CI 19 to 34%, $p = 0.76$). In this period the health-related quality of life using IBDQ and EQ-5D was not significantly different between the groups ($p = 0.22$ and 0.3, respectively)⁴(A).

At the UC-SUCCESS, 239 patients with moderate to severe ulcerative colitis (Mayo score 6-12) were randomized, without previous therapy with TNF inhibitors. At week 16, there was a greater corticoid free remission rate (Mayo score ≤ 2) higher with the combination of infliximab and azathioprine (39.7%) compared to infliximab alone (22.1%; $p = 0.0170$) or azathioprine alone (23.7%; $p = 0.813$). The major changes, for the better quality of life in the IBDQ and SF-36 since the beginning of the study, were for the association of infliximab and azathioprine ($p < 0.05$ compared to use of azathioprine or infliximab alone).⁵(A)

Rescue therapy

It is agreed that patients diagnosed with severe acute and fulminant colitis should be hospitalized and treated with high doses of intravenous corticosteroids. In those who do not respond to treatment after a period of 48 to 72 hours, some type of rescue therapy should be introduced before surgical treatment is indicated. Despite intensive treatment, approximately 50 to 60% are submitted to surgical treatment surgery (colectomy). The authors concluded that infliximab would be indicated as rescue therapy in the treatment of patients with moderate and severe colitis in order to reduce the number of colectomies⁶(B). In the failure of intravenous corticosteroids to control symptoms, patients with severe colitis were randomized to receive either infliximab (N = 24) or placebo (N = 21). The authors observed a significant reduction in the number of colectomies in patients receiving a single dose of infliximab (5mg / kg body weight) compared to those receiving placebo (IFX = 29% vs. placebo = 67%), odds ratio = 4.9, 95% CI 1.4-17, $p = 0.017$), in a follow-up of 3 months⁶(B). In this study, after the randomization, it was verified that the group of patients who had previous diagnosis of UC had a greater number of patients who received infliximab when compared to the group of patients who presented with the disease for the first time (21 vs 9). We can therefore infer that the sample of patients with probable major tissue damage secondary to disease related to time their time of evolution was allocated to the infliximab group.

In spite of this, after the multivariate analysis, the sample of patients who manifested the disease for the first time and who was consequently allocated with more patients to the placebo group also benefited from the use of infliximab (OR = 3.6; 95% CI 1.0 – 13.7). The results of the same cohort of patients were evaluated 3 years after treatment⁷(B). About 50% of those treated with infliximab had no need for surgery and most of them remained in remission without the use of corticoids. However, 76% of those recruited for the placebo group were submitted to colectomy ($p = 0.012$)⁷(B). We can therefore conclude that the benefit of rescue treatment with infliximab remains in the long-term⁷(B).

Infliximab versus Cyclosporine

Authors compared the results of cyclosporine versus infliximab as rescue therapy in patients with severe non-corticosteroid responsive UC. Six retrospec-

tive studies (historical cohort) were included, with a total of 321 patients analyzed (142 in the cyclosporine group vs 179 in the infliximab group). There was no difference between the groups in the colectomy rate at 3 months (odds ratio (OR) = 0.86, 95% CI 0.31 to 2.41, $p = 0.775$) and at 12 months (OR = 0.60, 95% CI 0.19 to 1.89, $p = 0.381$). There was no difference in the number of adverse reactions (OR = 0.76, 95% CI 0.34 to 1.70, $p = 0.508$) and in postoperative complications (OR = 1.66, 95% CI 0.26 to 10.50, $p = 0.591$)^{8(B)}.

In a randomized controlled open-label trial (N = 115), the objective of which was to compare cyclosporine with infliximab, no difference in drug efficacy was observed for efficacy in severe UC without response to corticosteroids. The clinical response on day 7 was approximately 85% in both groups ($p > 0.50$). There was also no difference in the colectomy rate at 3 months (cyclosporine 18% vs infliximab 21%, $p = 0.66$) and in the number of severe adverse events ($p = 0.23$)^{9(B)}.

Another open clinical study compared efficacy between the two drugs. Patients with severe UC corticosteroids, (N = 83) received cyclosporine (n = 45) or infliximab (n = 38). Cyclosporine increased the risk of colectomy by 20% (NNH = 5, 95% CI 2 to 2116) within 3 months and by 21% (NNH = 5, 95% CI 2 to 215) within 1 year^{10(B)}.

Adalimumab

The ULTRA 1 study evaluated the efficacy of adalimumab (ADA) in the induction of remission up to 8 weeks in patients with moderate to severe ulcerative colitis who did not respond with corticosteroids and/or immunosuppressants. A total of 186 patients (mean age = 37 years) who were randomized to adalimumab (160 mg at week 0, 80 mg at week 2, then 40 mg every two weeks) versus placebo, subcutaneously were randomized. Another 390 patients were randomized, following a change in protocol, to adalimumab high dose (160 mg at week 0, 80 mg at week 2, then 40 mg every two weeks) versus low dose (80 mg at week 0 and followed by 40 every two weeks) versus placebo subcutaneously. No patient in this study had previously been treated with anti-TNF. The outcomes were: clinical remission (Mayo score ≤ 2 , no individual subscore score greater than 1 and reduction of ≥ 1 rectal bleeding at 8 weeks) and clinical response (reduction of Mayo score ≥ 3 , reduction $\geq 30\%$ of baseline value, and reduction of the subscore of rectal bleeding ≥ 1 or subscore of absolute rectal

bleeding 0 or 1). In this study 18.5% of the ADA 160 mg initial dose group patients ($p = 0.031$ vs. placebo, NNT = 11) and 10% ADA 80 mg initial dose (nonsignificant vs. placebo) entered remission at week 8, compared to 9.2% of the placebo group. The clinical response at week 8 was 54% with ADA 160 mg initial dose (nonsignificant vs. placebo) and 51.5% with ADA 80 mg initial dose (nonsignificant vs. placebo), compared to 44.6% with placebo placebo^{11(A)}.

A second study (ULTRA 2), in which 40% of patients had previously been treated with anti-TNF, showed a higher rate of remission in adalimumab-treated patients than in those treated with placebo at week 8 (16.5% vs. 9.3%, $p = 0.019$)^{12(A)}.

The incidence of adverse events was similar with ADA or placebo in ULTRA 1 (50.2% vs. 48.4%, respectively). The most frequent adverse event was worsening or flare-up of ulcerative colitis (ADA 3.6% vs placebo 4.0). The majority of adverse events were mild to moderate^{11(A)}.

A meta-analysis, which included ULTRA 1 and ULTRA 2, aimed to verify remission rates in the 8th week of treatment, showed a clinically relevant effect favorable to the ADA, with relative risk (RR) 1.85 (95% CI 1.26 to 2.72); $I^2 = 0\%$ and NNT = 13 (95% CI 7 to 42). While 17.2% (65/378) of Adalimumab patients were in remission, this rate for the Placebo group was 9.3% (35/376)^{13(A)}.

Another double-blind clinical trial evaluated the use of ADA in the induction and maintenance therapy of 273 patients with moderate to severe ulcerative colitis who were not responsive to corticosteroids and/or immunosuppressants without previous use of anti-TNF¹⁷. Patients were randomized to receive ADA 160 mg at week 0, 80 mg at week 2, then 40 mg every two weeks, or 80 mg at week 0 and then 40 every two weeks, or placebo, subcutaneously. By week 8, there was no significant difference in remission rate, but more patients treated with ADA 160 mg at baseline had a clinical response compared to placebo (50% vs. 35%, $p = 0.044$)^{14(A)}.

Golimumab

The PURSUIT-SC trial evaluated the efficacy of golimumab in the period of induction of remission of moderate to severe ulcerative colitis^{15(A)}.

PURSUIT-SC was an integrated clinical trial that included a dose-determination study and a double-blind dose confirmation study evaluating subcutaneous golimumab therapy in patients without pri-

or anti-TNF- α therapy, moderate to severe ulcerative colitis (Mayo score 6-12 and endoscopic subscore \geq 2 points), which did not respond to conventional therapy. In the dose confirmation study, clinical response rates at week 6 were 51% among patients treated with golimumab 200 mg, followed by golimumab 100 mg, and 30.3% in those in the placebo group, a statistically significant difference ($p < 0.0001$). Golimumab was also associated with a significantly greater rate of remission than placebo (17.8% vs. 6.4%, $p < 0.0001$)^{15(A)}.

Vedolizumab

In 4 randomized controlled trials (RCTs), vedolizumab has been shown to be effective in inducing remission in adults with UC¹⁹. The rate of induction of clinical remission with vedolizumab in 4 to 6 weeks (77%), observed in 606 adults with UC, presented a lower failure than the placebo group (92%); RR = 0.86 (95% CI 0.8 to 0.91); NNT = 6 to 12; $I^2 = 0\%$. Vedolizumab also showed a lower failure rate in clinical response (48%) at 6 weeks in the analysis of 3 RCTs (N = 601 adults), compared to the placebo group (72%) RR = 0.68 (95% CI 0.59 to 0.78); NNT = 4 to 7; $I^2 = 0\%$. The clinical recurrence at 52 weeks was 56.7% in the vedolizumab group compared to 84.1% in the placebo group ($p < 0.0001$, NNT = 4), in 1 RCT (N = 373 adults). There was no difference with statistical significance for adverse events (any or severe) between groups^{16(A)}.

Vedolizumab remission induction therapy (300 mg dose) was compared with placebo intravenously in 6 of 374 patients with active ulcerative colitis in cohort 1 of the GEMINI 1²⁰ study. The response rate was 47.1% in the placebo group. Vedolizumab versus 25.5% in the placebo group ($p < 0.001$). Clinical remission occurred in 16.9% of the vedolizumab group and 5.4% in the placebo group ($p = 0.001$). In this cohort, 42.2% of the patients were tested for anti-TNF^{17(A)}.

RECOMMENDATIONS

In the induction of remission, all biological agents (adalimumab, golimumab, infliximab and vedolizumab) present clinical response, clinical remission and mucosal healing superior to placebo. (A) HIGH QUALITY EVIDENCE.

Infliximab combination therapy associated with azathioprine in patients with moderate to severe UC without previous use of anti-TNF is more effective than infliximab monotherapy in the rate of induction

of remission (B) MODERATE QUALITY EVIDENCE.

As rescue therapy, Cyclosporine and infliximab can be used in patients with severe non-corticosteroid UC. (B) MODERATE QUALITY EVIDENCE.

Infliximab used as rescue therapy in patients with severe acute or fulminant colitis is effective in short (3 months) and long term (3 years) in reducing the need for colectomy. (B) MODERATE QUALITY EVIDENCE.

Infliximab and golimumab were comparable in terms of efficacy in inducing remission. (B) MODERATE QUALITY EVIDENCE.

MAINTENANCE OF REMISSION

Infliximab

In patients responding to remission induction therapy, infliximab should be used to maintain remission. In ACT 1, clinical response to week 54 occurred in 46% of patients receiving infliximab 5 mg / kg IV compared to 20% in the placebo group ($p < 0.001$). There was improvement in the significant quality of life with the use of infliximab when compared with placebo. There was no difference in the proportion of patients with adverse events between the infliximab and placebo groups, however, more adverse events occurred among patients with infliximab in the ACT 1 study than in those in ACT 2 (87.6% compared to 81.8%). The most common adverse event in ACT 1 was worsening of ulcerative colitis (infliximab 19.0% vs placebo 33.1%), whereas in ACT 2 it was headache (infliximab 15.7% vs placebo 14.6%). There were more serious adverse events in the placebo group of both RCTs (ACT 1 infliximab 21.5% vs placebo 25.6%, ACT 2 infliximab 10.7% vs placebo 19.5%). More patients discontinued treatment by adverse event in the placebo group in both RCTs^{3(A)}. In the long term, the ACT-1 and ACT-2 Extension studies included 229 of the 489 patients treated in the ACT-1 and ACT-2 studies, and these patients were followed for up to three years with an average follow-up time of 113 weeks. Sixteen patients (7%) had the infliximab dose optimized for 10 mg/kg every 8 weeks. Of the 229 patients, 70 (30.6%) patients discontinued use of infliximab: 24 (10.5%) due to adverse effects, 11 (4.8%) due to loss of efficacy, 1 (0.4%) required colectomy and 34 (14.8%) other reasons that included withdrawal of informed consent, loss of follow-up, non-adherence of the patient. At week 104, 67.9% (108 out of 159) of the patients who were still being followed had no signs of disease activity^{18(B)}.

Adalimumab

The ULTRA 2 study, in which 40% of patients had previously been treated with anti-TNF, showed a higher rate of remission in adalimumab-treated patients than in those treated with placebo at week 52 (17.3% vs. 8.5%, $p = 0.004$). This difference was also favorable for ADA up to one year among patients without previous anti-TNF therapy (22% vs. 12.4%, $p = 0.029$, NNT = 11) and previous anti-TNF therapy (10.2% vs. 3%, $p = 0.039$, NNT = 14). Of the patients in remission at week 8, 8.5% of the ADA group and 4.1% of placebo remained in remission at week 52 ($p = 0.047$)^{12(A)}.

The incidence of adverse events was similar with ADA or placebo in ULTRA 2 (82.9% vs. 83.8). The most frequent adverse event was worsening or flare-up of ulcerative colitis (ADA 22.6% vs placebo 29.2%). The majority of adverse events were mild to moderate in severity. A higher number of patients in the placebo group discontinued treatment due to an adverse event (13.1%) than patients randomized to the ADA group (8.9%)^{11,12(A)}.

In the study by Suzuki et al., which evaluated the use of ADA in the induction and maintenance therapy of 273 patients with moderate to severe ulcerative colitis who were not responsive to corticosteroids and/or immunosuppressants, without previous use of anti-TNF, at week 52 more patients in maintenance therapy with ADA, compared with placebo, had clinical response (31% versus 18%, $p = 0.021$) and remission (23% versus 7%, $p = 0.001$). There was no difference in the number of serious adverse events between groups^{14(A)}.

In the long term, an extension of the ULTRA 1 and 2 study evaluated the efficacy of adalimumab use by the fourth year of follow-up. From week 52, 600 of the 1094 patients enrolled in ULTRA 1 or 2 received adalimumab 40 mg every 2 weeks or required a dose adjustment to 40 mg weekly (141 patients). An intention to treat analysis was performed. Of this total, 199 were still under follow-up at the end of 4 years. The remission rate based on the partial Mayo score (without the endoscope criterion), remission for the Inflammatory Bowel Disease Questionnaire (IBDQ), mucosal healing and discontinuation of the corticosteroid at week 208 was 24.7%, 26.3%, 27.7% and 59.2%, respectively. Considering only the patient population that came to be followed in the period known as ULTRA 3 (from week 52), remission by the Mayo partial score was 63.6% and mucosal healing was 59.9% (not responder imputation)^{19(B)}.

Golimumab

In the PURSUIT-M clinical trial, which aimed to assess the efficacy of golimumab in maintaining remission, patients whose disease had responded to induction therapy in two previous trials (including PURSUIT-SC) were randomized to golimumab sc 50 mg, golimumab sc 100 mg or placebo. The clinical response was maintained for 54 weeks in 47.0% in the golimumab 50 mg group, 49.7% in the 100 mg group and 31.2% in the placebo group ($p = 0.010$ and $p < 0.001$, respectively)^{20(A)}. The proportion of patients who were in remission at both weeks 30 and 54 was higher in the golimumab 100 mg (27.8%) and golimumab 50 mg (23.2%) than in the placebo group (15.6%; $p = 0.004$ and $p = 0.122$, respectively), although the difference between golimumab 50 mg and placebo was not statistically significant. The number of adverse events was similar in the 50 mg and 100 mg groups. However, among patients with golimumab 50 mg, 8.4% had a severe adverse event and 5.2% discontinued treatment due to an adverse event, compared with 14.3% and 9.1% respectively, in group of patients who used the 100 mg dose. The main cause of treatment discontinuation, however, was clinical worsening of the disease^{20(A)}.

Vedolizumab

A meta-analysis that included 4 randomized controlled trials (RCTs), and evaluated the efficacy of vedolizumab in inducing remission at weeks 4 and 6, also assessed its effectiveness at the end of the first year. The clinical recurrence at 52 weeks was 56.7% in the vedolizumab group compared to 84.1% in the placebo group ($p < 0.0001$, NNT = 4), in 1 RCT (N = 373 adults). There was no difference with statistical significance for adverse events (any or severe) between groups^{16(A)}.

The GEMINI 1 study, mentioned previously, also included a cohort 2, in which 521 patients participated and evaluated vedolizumab open-label. Patients in cohort 1 and cohort 2 who presented clinical response to vedolizumab at week 6 (n = 373) were randomized to receive vedolizumab 300 mg (once every 8 weeks versus 4 weeks) EV or placebo for up to 52 weeks. Only 56% completed the treatment and all were included in the intention-to-treat analysis (ITT). There was clinical remission at week 52 in 41.8% with vedolizumab 8/8 weeks ($p < 0.001$ vs. placebo, NNT = 4); 44.8% with vedolizumab 4/4 weeks ($p < 0.001$ vs placebo, NNT = 4) and 15.9% with placebo. Clinical

response continued through week 52 in 56% with vedolizumab 8/8 weeks ($p < 0.001$ vs. placebo, NNT = 3); 52% with vedolizumab 4/4 weeks ($p < 0.001$ vs. placebo, NNT = 4) and 23.8% with placebo. 8/8 or 4/4 weeks vedolizumab was associated with increased mucosal healing ($p < 0.001$ for both comparisons with placebo). There was no significant difference comparing the two grouped vedolizumab therapies with the placebo group^{17(A)}.

GOLIMUMAB VERSUS INFLIXIMAB VERSUS ADALIMUMAB VERSUS VEDOLIZUMAB

Because of lack of direct comparative studies between the various biological agents in the treatment of ulcerative colitis with moderate to severe activity, a meta-analysis indirectly compared these agents (network meta-analysis). Five RCTs were included to assess the efficacy of golimumab (1 RCT), infliximab (2 RCTs), and adalimumab (2 RCTs) in the treatment of moderate to severe active UC in adult patients without prior anti-TNF therapy. The outcomes evaluated included clinical response, clinical remission, mucosal healing after induction therapy (6-8 weeks), maintenance therapy (1 year), as well as clinical response and sustained remission (induction with maintenance)^{21(B)}.

For induction therapy, no statistically significant differences were found between golimumab and adalimumab or between golimumab and infliximab. The use of infliximab was statistically superior to the use of adalimumab at induction for all the considered outcomes. In the maintenance of remission, golimumab and infliximab showed similar efficacy to achieve both clinical remission and sustained clinical remission, whereas adalimumab was not significant-

ly superior to placebo in sustained clinical remission^{21(B)}.

Golimumab and infliximab also had similar efficacy to achieve maintenance, clinical response, sustained clinical response, and mucosal healing. Golimumab at a dose of 50 mg and 100 mg was statistically superior to adalimumab for clinical response and sustained clinical response and golimumab 100 mg was also superior to adalimumab for mucosal healing. Therefore, this network meta-analysis (indirect evidence) suggests that infliximab was statistically superior to adalimumab at induction, and that golimumab was statistically superior to adalimumab for sustained outcomes. Infliximab and golimumab were comparable in terms of efficacy^{21(B)}.

Another meta-analysis with 7 RCTs, with patients presenting the same characteristics of the previous meta-analysis and including a RCT comparing vedolizumab with placebo, showed that all biological agents (adalimumab, golimumab, infliximab and vedolizumab) presented more clinical response, clinical remission and mucosal healing than placebo in induction therapy. It was also suggested that infliximab was more effective than adalimumab in inducing clinical response (OR = 2.36, 95% CI 1.22 to 4.63) and mucosal healing (OR = 2.02, 95% CI, 1.133 to 3.59). There were no other indirect comparisons with statistical significance^{22(B)}.

RECOMMENDATIONS

In the maintenance of remission, golimumab and infliximab showed similar efficacy in the rate of clinical remission and sustained clinical remission, and mucosal healing. (B) MODERATE QUALITY EVIDENCE

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