Overcoming Secondary Loss of Response to Infliximab in Patients With Ulcerative Colitis With the Use of Mesenchymal Stromal Cells

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BACKGROUND: Long-term experience with infliximab (IFX) shows that within a year, 20-30% of patients with ulcerative colitis (UC) develop acquired drug resistance (secondary inefficiency). Aim: To establish the possibility of overcoming the secondary inefficiency of IFX in UC patients using mesenchymal stromal cells (MSCs).

METHODS: In the IBD treatment department, the clinical status of 84 UC patients receiving IFX therapy was evaluated. Secondary loss of response was registered in 28 UC patients, which required optimization of IFX therapy. Twelve patients (group 1), in order to overcome the secondary loss of response, were administered MSCs three times every four weeks. 16 patients with UC (group 2) received standard optimized IFX therapy. The effectiveness of therapy was evaluated after 12 weeks of therapy (reduction of the Mayo score) and normalization of laboratory parameters (erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), hemoglobin, FCP). The comparative analysis was carried out using the method of four-field tables using nonparametric statistical criteria.

RESULTS: In 10 (83.3%) of 12 patients of group 1, a significant positive dynamic was observed after 12 weeks: a decrease in the Mayo index and normalization of laboratory parameters (ESR, CRP, hemoglobin, FCP). However, 12 patients from group 2 were transferred to therapy with other anti-TNF-α drugs and drugs with a different mechanism of action (HR-0.222, 95% CI 0.041-0.816; P = 0.0034).

CONCLUSION: The use of mesenchymal stromal cells of the bone marrow helps to overcome the secondary loss of response to infliximab in patients with ulcerative colitis.

Dependence of the Duration of Clinical Remission in Crohn’s Disease From the Frequency of Introduction of Mesenchymal Stromal Cells

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BACKGROUND: Anti-cytokine therapy with anti-TNF-α drugs results in the achievement of persistent remission of Crohn’s disease (CD). Allogeneic mesenchymal stromal cells (MSCs) of the bone marrow are also used for the treatment of CD. Objective: to evaluate the duration of remission in the context of mesenchymal stromal cells (MSC) therapy of the bone marrow, depending on the frequency of MSC administration.

METHODS: 76 patients with luminal CD (terminal ileum, colitis, and ileocolitis) were divided into two groups. The first group of patients aged 19 to 58 years (Me-29; n = 34) received culture of MSCs according to the scheme: 0-1-2-6-26-52 weeks; the second group received culture of MSCs according to the scheme: 0-1-2-6-26-52 weeks to achieve remission within one year. The effectiveness of therapy was evaluated at 12, 24, 36, 48 and 60 months after the start of therapy using the Harvey-Bradshaw index.

RESULTS: During 12 months of follow-up, 4/34 patients (11.7%) relapsed among patients in first group. In second group, relapse occurred in 5/22 (11.9%) (HR-0.839; 95% CI 0.288–3.397; P = 0.84). After 24 months, 6/34 patients (17.6%) relapsed in first group. In second group, patients of the disease relapsed in 11/22 (6.2%) (HR-0.674; 95% CI 0.278–1.654; P = 0.37). After 36 months, the disease relapsed in 19/74 patients in the first group (25.6%). In the second group, relapse was in 18/42 (42.8%) (HR-0.48; 95% CI 0.228–1.014; P = 0.38). After 48 months, 1/34, 1/22 and 1/22 patients (5.9%) relapsed in first group; the second group, respectively. Biochemical remission was achieved in 61.3% of patients (114/186). Corticosteroid-free remission at the time of diagnosis of vasculitis. Vasculitis involved the skin in all five patients: 4 presented with papular purpura, 3 had ulcerated lesions, and 1 had erythematous macules. No patient exhibited extracutaneous manifestations. Of note, all 5 skin biopsy specimens showed leukocytoclastic vasculitis (LV) on histology examination. Anti-TNF-α therapy was interrupted in all patients, and then was a remarkable response of LV with oral steroids. All patients had complete remission of skin lesions between 4 to 12 weeks after switching prednisone therapy. The duration of steroid therapy was 3 months (range, 2.5 to 5.0 months). In order to keep the IBT treatment, three patients changed the biological mechanism of actions (two patients with CD started ustekinumab and one patient with UC started vedolizumab). Two of the 5 patients were rechallenged with another anti-TNF-α agent (i.e., infliximab) after discontinuation of adalimumab. None of patients presented vasculitis recurrence after switching the biological therapy during a mean follow-up after LV diagnosis of 214 months (range, 12-28 months).

CONCLUSION: LV is an uncommon complication of anti-TNF-α therapy in IBT patients. In this setting, clinicians should have a high index of suspicion for LV in patients developing unexplained cutaneous rash.

Long-Term Effectiveness and Safety of Ustekinumab for the Treatment of Crohn’s Disease: A Brazilian Multicentre Real-world Study

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BACKGROUND: Real world data regarding long-term effectiveness and safety of ustekinumab (UST) for the treatment of Crohn’s disease (CD) is lacking in South America. We report the outcomes of a Brazilian multicentre retrospective cohort in patients with moderate to severe CD treated with UST in a real-world setting.

METHODS: Between November 2017 and December 2019, a retrospective study was performed including patients from 12 inflammatory bowel disease (IBD) academic medical centers diagnosed with moderately to severely active CD starting on UST (weight-based single IV infusion dose followed by 90 mg subcutaneous maintenance dose administered 8 weeks after the initial intravenous dose). Between 8 weeks thereafter, the primary outcome was clinical remission (Harvey-Bradshaw index ≤ 4) at 16 weeks. Secondary outcomes included clinical remission at weeks 24 and 56, clinical response at weeks 8 and 16 (HBI decrease ≥ 3), biochemical remission at week 16 (C-reactive protein [CRP] normalization in patients with elevated CRP baseline levels), corticosteroid-free remission and drug discontinuation.

RESULTS: Among 241 patients included (mean age 39.9 years old), 86% had been previously exposed to at least one biologic, 66 (31.9%) had been treated with only one biologic agent, and 141 (68.1%) with two or more biologics. Twenty-five percent (50/204) received combined therapy with immunomodulators. Corticosteroids were administered during induction in 97 patients (57.7%, 97/170). At baseline, mean HBI was 10.3 (range 5-23) and mean CRP was 20.5 (range 0-125). Clinical response at week 8 was observed in 66.7% of patients (144/216). In non-responder imputation (NRI) analysis, clinical remission was achieved in 60.2%, 51.4% and 24.1% at week 16, 24 and 56 respectively. Biochemical remission was achieved in 61.3% of patients (114/186). Corticosteroid-free remission was achieved in 59.6% of patients at their last follow up. A total of 39 patients (18.2%) interrupted their treatment and the main reasons for discontinuation were loss of response / disease progression (35.9%), primary failure (25.6%), lack of access / no reimbursement (17.9%), pregnancy (15.4%) and adverse effects (5.1%). HBI higher than 9.5 at baseline, previous exposure to anti-TNF-α and penetrating disease were associated with lower rates of clinical remission. No new safety signals were observed.

CONCLUSION: This is the first study to show the long-term safety and real-world effectiveness of UST in a cohort of moderate to severe CD patients in Brazil. This study confirms the previous reported effectiveness and long-term maintenance of response of UST in CD patients exposed to biological therapy, especially to anti-TNF agents. UST was well tolerated, and no new safety signals were identified in this study.

Autoimmune Bone Marrow Transplantation in Refractory Crohn’s Disease: A Case Report

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