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Vedolizumab for Inflammatory Bowel Disease: for now only rescue therapy in the Republic of Srpska

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Abstract

Introduction: Vedolizumab (VDZ) is a humanized monoclonal antibody ?4?7 integrin-receptor antagonist indicated for the treatment of patients with moderately to severely active ulcerative colitis or Crohn's disease. We want to show our modest experience with the use of vedolizumab as a rescue therapy when other medical therapies have failed. Methods: An observational study was carried out on patients with inflammatory bowel disease treated with VDZ for at one year. An evaluation was performed on the activity indices, fecal calprotectin, and C-reactive protein levels. Results: Our study included 7 patients (5 CD, 2 UC, mean age 40 years). Previous treatment failures with ??? 2 anti-TNFs. At one year, in all patient maintained the clinical response and remission. The C-reactive protein and fecal calprotectin decreased significantly in both CD and UC patients. Discussion: Our experience indicates that a long-term effect can be achieved, even beyond 1 year of treatment. Vedolizumab is generally well tolerated. Vedolizumab may be used as a rescue therapy in patients with medically refractory ulcerative colitis or Crohn's disease..

Inflammatory bowel diseases (IBD)—a term including both ulcerative colitis (UC) and Crohn's disease (CD)— are two chronic, disabling conditions causing an uncontrolled inflammatory process in the gastrointestinal tract, with a relapsing and remitting course. It is considered that IBD appears in genetically predisposed subjects after the interaction with diverse environmental factors, therefore it is described as a complex disease where there is an interaction between multiple factors that has not been fully elucidated so far. The interaction between luminal antigens and the mucosal immune system seems to be crucial and mediated through an increased intestinal permeability, at least during the early stages of the disease. This interaction may trigger an abnormal and uncontrolled inflammatory response in susceptible individuals, leading to progressive bowel damage and symptomatic disease . Due to our increased knowledge of the immunological disturbances observed in these patients, new treatment options have been developed in recent years. Over the past 20 years, tumor necrosis factor (TNF)-antagonists have transformed the medical management of IBD due to their ability to induce a complete control of symptoms, induce mucosal healing in a significant proportion of patients, and reduce the long-term requirements of surgery and hospitalization. Despite their impact in the paradigm of disease control, many challenges remain: around two-thirds of IBD patients demonstrate short-term clinical response to anti-TNF therapy and ~40% of patients who initially improve subsequently lose response . These data about the efficacy should be added to the potential adverse events associated to anti-TNF therapy, that underlines the urgent need of alternative therapeutic options targeting new disease pathways for refractory patients. In recent years, the experience with new biologics blocking leukocyte migration mediated through integrins—vedolizumab—or the immune pathways regulated by interleukin (IL)-12/23—ustekinumab (UST)—have increased the chance to obtain better disease control and improve quality of life. Hence, these new therapeutic options imply a greater probability of inducing disease remission in difficult-to-treat patients. Despite this important progress, the selection of first-line biologic therapy seems to be crucial, as it has consistently been shown that there is a stepwise reduced response rate with each subsequent biologic therapy . Contrary to the aforementioned steps toward disease control, many regulatory authorities have approved UST only after anti-TNF failure, which significantly reduces the overall efficacy of the drug.

UST is a fully human immunoglobulin G1 monoclonal antibody that blocks the p40 subunit of IL-12 and IL-23, precluding cytokine-mediated cellular activation. IL-23 promotes the differentiation of naïve T cells into Th17 phenotype, whereas IL-12 regulates the Th1 polarization. The downstream effect of the IL-12/23 blockade is the neutralization of human IL-12 and IL-23-mediated cell signaling, cell activation, and cytokine production involved in the pathogenesis of CD (19). UST has demonstrated its efficacy inducing response and remission in CD patients in randomized clinical trials and also in real-life studies. The UNITI study, a phase III multicenter, double-blind, placebo-controlled randomized clinical trial included an induction (UNITI-1 and 2) and a maintenance phase (IM-UNITI) (20). Patients started UST after primary non-response, loss of response or intolerance to anti-TNF agents (UNITI-1), but also failure or severe adverse events during conventional therapy with immunosuppressants or steroids (UNITI-2). The primary aim—defined as a reduction in the Crohn's Disease Activity Index [CDAI] ≤100 or CDAI <150 at

week 6—was achieved by 22, 34, and 34% in the placebo, UST 130 mg and UST 6 mg/kg groups, respectively, in the UNITI-1 trial (714 patients) and 29, 52, and 56% in the UNITI-2 (628 patients). In the IM-UNITI study, including 397 responders during the induction, the primary endpoint—clinical remission (CDAI <150) at week 44—was achieved by 36, 49, and 53% in the placebo, UST 90 mg q12w and 90 mg q8w arms, respectively. Long-term data from the IM-UNITI study show that 62 and 70% of patients in the q12w and q8w arms were in clinical remission at week 152, respectively.

A treat-to-target approach based on endoscopic findings at week 16 has been evaluated with UST in the STARDUST trial (NCT03107793). This is the first randomized trial evaluating the efficacy of UST under a dose adjustment strategy based on biomarkers (fecal calprotectin and C-reactive protein) and symptoms (CDAI), compared with a standard, clinically-driven approach. Pre results have been presented at United European Gastroenterology Week 2020, were the treat-to-target strategy showed a numerically higher endoscopic response, but there were no clear differences between both treatment arms.

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