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Ulcerative colitis- ustekinumab as a new biologic therapy, review 2024

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Abstract: Biologic agents have significantly transformed the therapeutic approach to ulcerative colitis. Anti-tumor necrosis factor (TNF) agents were the pioneering biologic drugs introduced to induce and maintain remission in this inflammatory bowel disease. Recently, ustekinumab, another biologic option, has been approved for the treatment of moderate-to-severe ulcerative colitis. Ustekinumab demonstrates a favorable clinical efficacy and safety profile for the treatment of moderately to severely active ulcerative colitis. As the first biologic agent to target the IL-12/IL-23 pathways, ustekinumab represents a viable therapeutic option, particularly following the failure of other biologics such as anti-tumor necrosis factor-α (TNF-α) antagonists and anti-α4ß7 integrin antagonists.
Aim of the study: The aim of this study was to summarise the current knowledge on the use of ustekinumab in the biological therapy of ulcerative colitis.
Methodology: A literature review was performed in the PubMed database, Via Medica journal database, Google Scholar and the guidelines of the British Society of Gastroenterology. Articles were searched using the keywords: ustekinumab, ulcerative colitis. The search showed 508 results, of which, after rejection of papers not meeting the criteria, 37 were used in the paper
Current state of knowledge: The treatment of ulcerative colitis, due to the alternating periods of exacerbation and remission, requires different therapeutic approaches. Therapy is selected according to the severity of the disease process and the individual characteristics of the patient. Ustekinumab therapy is recommended for moderate and severe forms.
Summary: Biologic agents have significantly transformed the therapeutic approach to ulcerative colitis. Anti-tumor necrosis factor (TNF) agents were the pioneering biologic drugs introduced to induce and maintain remission in this inflammatory bowel disease. Recently, ustekinumab, another biologic option, has been approved for the treatment of moderate-to-severe ulcerative colitis. Ustekinumab demonstrates a favorable clinical efficacy and safety profile for the treatment of moderately to severely active ulcerative colitis. As the first

biologic agent to target the IL-12/IL-23 pathways, ustekinumab represents a viable therapeutic option, particularly following the failure of other biologics such as anti-tumor necrosis factor-α (TNF-α) antagonists and anti-α4ß7 integrin antagonists. This paper presents the current state of knowledge on the treatment of ulcerative colitis with ustekinumab. The aim of this paper was to summarise the data available in the literature, as well as recent reports and studies, in order to better understand the nature of the disease and its treatment with the drug ustekinumab

Key words: ustekinumab, interleukin 12/23 inhibitor; inflammatory bowel disease; ulcerative colitis;.

Current state of knowledge

Ulcerative colitis is an idiopathic disease causing chronic inflammation of the colonic mucosa. The disease is usually located in the terminal ileum, spreading proximally with the possibility of spreading through the whole colon. The disease spreads continuously, leaving no sections of unchanged mucosa [1]. There are two peaks of incidence, the first in the 2nd and 3rd decades of life and the second in the 6th and 8th decades [2]. The pathogenesis is multifactorial, involving genetic predisposition, mucosal barrier impairment and dysfunction of the immune response [3]. The natural course of the disease includes periods of exacerbations and remissions. Exacerbations require escalation of therapy, hospitalization and, in the most severe cases, surgical treatment involving removal of the large bowel - colectomy. The disease requires prolonged and intensive treatment in order to regain control of its course and prevent from complications [4-6].

While the etiology of the disease is not entirely clear, the underlying cause is an abnormal inflammatory response mediating the production of pro-inflammatory cytokines such as interleukin 12, interleukin 23, TNF a or interferon alpha [7].

The aim of therapy is to achieve glucocorticosteroid-free remission, a reduction in intestinal discomfort, including fewer bloody stools, and thus endoscopic remission [8]. The Ameican College of Gastronterology 2019 guidelines define the goals of ulcerative colitis therapy:

Achieve and maintain remission without the need for glucocorticosteroids

Psychosocial well-being

Achieve good quality of life

Prevention of hospitalizations, complications, cancer and surgery

The choice of therapy depends on clinical symptoms and patient preference. Factors such as clinical symptoms, the location and extent of the inflammatory process and the progression of the disease should be taken into account. The aim of therapy is to achieve remission and long-term control of the disease process. Depending on the severity of the disease process, patients are distinguished based on the Truelove and Witts criteria. A distinction is made between mild, moderate and severe forms.

Mild form includes: <4 stools per day, occasional blood in stools, body temperature <37.5°C, pulse <90/min, haemoglobin: >11.5 mg/dl, ESR <20mm/h, CRP within normal limits. Patients may report minor abdominal pain
Moderate form includes: ≥4 bloody stools per day, body temperature ≤37.8°C, haemoglobin ≥10.5 mg/dl, ESR. ≤30mm/h, CRP ≤30 mg/l
Severe form includes: ≥ 6 bloody stools, body temperature ≥ 37.8°C, heart rate >90/min, haemoglobin <10.5 mg/dl, ESR >30mm/h, CRP >30 mg/l
Clinical remission as defined by Truelove-Witts criteria includes: 1.2 stools per day with no pathological admixtures, no fever, no tachycardia, with haemoglobin levels returning towards normal [9].
Stratification of disease severity is based on assessment of the extent of colonic lesions according to the Montreal scale
E1 - proctitis, when lesions do not extend beyond the rectum. In this form, patients complain of a feeling of pressure on the stool, bleeding from the lower gastrointestinal tract
E2 - distal, left-sided form, in which the inflamed colon does not extend beyond the splenic fold
E3 - extensive form in which the lesions extend beyond the splenic fold, the entire large intestine and even sections of the ileum may be involved [10,11].

Treatment methods in ulcerative colitis

Drugs such as 5-aminoacylic acid derivatives, glucocorticosteroids, purine analogues such as azathioprine, 6-mercaptopurine, antibiotics - tacrolimus - up to biologics are used to achieve clinical and endoscopic remission. The first line of therapy is 5-ASAs and the second line is glucocorticosteroids. In some patients, clinical and endoscopic remission can be achieved with the above-mentioned drugs. 5-ASA derivates can be used for maintenance treatment, while long-term use of glucocorticosteroids is not recommended due to numerous side effects and lack of long-term efficacy. Biologic drugs are recommended for moderate to severe ulcerative colitis, especially in patients with steroid resistance or steroid dependence. Biologic drug therapy aims to induce an immunomodulatory effect, i.e. to reduce the inflammatory response induced by the overproduction of pro-inflammatory cytokines [12].
Biological therapies use drugs from TNF-a inhibitors - (infliximab, adalimumab, golimumab), humanised human IgG1 anti-integrin a4b7 antibody - vedolizumab, Janus kinase inhibitors - tofacitinib[12].
The aim of therapy is to selectively block the above-mentioned cytokines using modern biological therapies. Substances of proven efficacy used in therapy were infliximab, adalimumab or golimumab - which act antagonistically to the TNF-a factor [13,14]. Their use was associated with clinical and endoscopic remission, and reduced the frequency of colectomies [15-17].
Two randomised, double-blind, placebo-controlled clinical trials, ACT1, ACT2, tested the efficacy of infliximab in the treatment of moderate to severe ulcerative colitis patients who failed to achieve remission with glucocorticosteroids. Statistically significant responses and remissions have been obtained in patients taking infliximab compared to those receiving placebo [18,19] Despite the initial efficacy of these drugs, resurgence of the active inflammatory process may occur after time. [20]The most common side effects include increased susceptibility to infection, increased liver transaminases, increased risk of lymphoma and melanoma [21]A study of the efficacy of adalimumab (ULTRA1)-a human IgG1 antibody against TNFa-found sustained clinical remission in patients taking adalimumab compared to placebo [22-24].

Ustekinumab – mechanism of action

Ustekinumab has proven efficacy in the treatment of moderate to severe UC. It is indicated for the treatment of adults in whom previous treatment has not been fully effective, there has been a loss of response to therapy or intolerance to other classical therapies or TNFa antagonist therapy, or there are contraindications to these therapies.
Ustekinumab is a fully human IgG1 monoclonal antibody showing high specificity with the p40 protein subunit of the cytokines Il-12, Il-23. It inhibits the activity of cytokines by blocking their binding to receptors on the surface of immune cells. By binding the p40 subunit, it prevents receptor binding on the surface of NK cells, T lymphocytes, APC cells resulting in blocking the signalling pathway for the production of pro-inflammatory cytokines. Ustekinumab inhibits the bioactivity of interleukin 12 and 23 by blocking the p40 protein subunit and its binding to the Il12RB1 receptor, which is found on the surface of immune cells. Ustekinumab does not bind to interleukins that are already bound to the Il-12RB1 receptor and thus does not affect complement activity or the phenomenon of cytotoxicity. [25,26]
Underlying the inflammatory process in inflammatory bowel diseases is the pro-inflammatory activity of cytokines from the interleukin-12 family, which includes cytokines such as IL-12, IL12, IL-27, IL-35 [27]. They play key roles in the pathogenesis of inflammation in inflammatory bowel disease. They are secreted mainly by tissue macrophages located in the gut. Interleukin 12 promotes the differentiation of Th1 lymphocytes to produce inflammatory cytokines such as TNFa, or INFs, while interleukin 23 promotes the inflammatory response by activating Th17 lymphocytes for their differentiation and proliferation. Activated Th17 lymphocytes stimulate a further inflammatory response with pro-inflammatory cytokines, activation of neutrophils, NK cells, intraepithelial lymphocytes, in addition to blocking the anti-inflammatory functions of Treg lymphocytes. [28,29] Abnormal regulation of IL-12, IL-23 function leads to autoimmune diseases such as ulcerative colitis, Crohn's disease, psoriasis. Ustekinumab is thought to be able to interrupt the signalling cascade and the Th1 and Th17 cytokine cascade, which are responsible for the development of the inflammatory response.

Efficacy and safety

In the UNIFI study conducted for phase 3 treatment involving patients with moderate to severe forms of ulcerative colitis, a satisfactory clinical response was achieved compared to placebo. The study included adults with failure of standard treatment or failure of TNF-a inhibitor therapy, and/or vedolizumab. Treatment efficacy compared to placebo was reported in both groups. The study was a fully randomised, double-blind, placebo-controlled trial and included an eight-week induction treatment cycle followed by a 44-week fully randomised maintenance dose cycle. Exclusion criteria were previous administration of IL-12 or IL-23 inhibitors and administration of TNF-a inhibitors in less than the last 8 weeks prior to the start of the study and vedolizumab within the last 4 months. Patients were randomized into three groups, one receiving ustekinumab at a dose of 130 mg, the second group at a weight-dependent dose of 6 mg per kilogram of body weight and the third receiving placebo. Patients who achieved remission during the induction treatment phase (decrease according to the Mayo scale of ≥30%) progressed to the maintenance phase.
The maintenance phase consisted of patients in group 1 receiving 90mg ustekinumab subcutaneously every 12 weeks, group 2 receiving 90 mg ustekinumab every 8 weeks and group 3 receiving placebo. The endpoint was clinical remission after the induction phase and after the maintenance phase. The clinical remission rate was higher than placebo (15.6% for the fixed dose, 15.5% for the maintenance dose, 5.3% placebo). In addition, after the maintenance dose, the percentage of clinical remission was higher in patients taking ustekinumab in both the group receiving the drug every 12 weeks (38.4%) and the group taking it every 8 weeks (43.8%) compared with placebo (24.0%) [30,31]. Patients were

assessed for achieving clinical remission, endoscopic improvement, achieving clinical response and histo-endoscopic mucosal healing (histo-endoscopic healing). A significant response to the treatment was achieved in all endpoints, compared to placebo.
The study took into account the safety of the drug. During the induction phase, the rate of at least one adverse effect was: 41.4% for the 130mg dose, 50.6% for the 6mg/kg dose and 48.0% for placebo. Common side effects of the drug included: rhinosinusitis, headache, arthralgia, upper respiratory tract inflammation, anaemia, influenza and fever. Serious adverse events included three cardiovascular episodes, including one sudden cardiac death, myocardial infarction complicated by ARDS and stroke.
The GETAID study on the efficacy and safety of ustekinumab used intravenous injections at a dose of 6mg/kg followed by three doses of 90 mg subcutaneously at weeks one, eight and 10. In addition, unlike the UNIFI trial, this trial included patients previously treated with immunomodulatory therapy with both TNF-alpha inhibitors and vedolizumab. Steroid-free clinical remission was achieved in 35% of patients. The endpoint assessing clinical remission according to the Mayo scale was a Mayo score of <2 along with a reduction in number stools and rectal bleeding, which was achieved in 41% of patients [32] The results of the study indicate significant efficacy in inducing glucocorticosteroid-free remission, and the drug has a good safety profile. Prior biological therapy with TNF-a inhibitor drugs and vedolizumab may reduce clinical response and achievement of glucocorticosteroid-free remission. In terms of drug safety, the rate of all adverse events was 7.8%, severe adverse events 3.9%. The authors mentioned the following adverse events: arthralgia, exacerbation of colitis, pneumonia, perianal abscesses, skin rash, and symptomatic cholelithiasis. A serious adverse event was defined as one leading to discontinuation of therapy, requiring hospitalization, or one leading to functional impairment or permanent organ damage or requiring colectomy or leading to death.
The ENEIDA study assessed the durability of ustekinumab therapy. Two steroid-free remission checkpoints were defined, one to assess short-term efficacy at week 16 of therapy and the other to assess long-term effects - follow-up at weeks 24 and 52, respectively. A dose of 6mg/kg was adopted. Remission was achieved in one-third of patients, despite resistance to previous anti-TNFa and/or vedolizumab biologic treatment In addition, approximately one-third of patients achieved steroid-free remission at follow-up at weeks 24 and 52. A correlation was found between elevated CRP levels and a lower chance of achieving clinical remission. In terms of long-term efficacy, more than 60% of patients continued treatment with ustekinumab after 12 months, suggesting that the drug is also beneficial in the long term. The safety profile is similar to that previously reported for ustekinumab. and the main reason for treatment discontinuation was primary treatment failure[33].
A meta-analysis including 19 clinical trials on 3786 patients assessed the efficacy of ustekinumab. More than 92% of patients had been previously treated with a biologic drug, 61.1% with both anti-TNF and vedolizumab, and 16.4% with any biologic drug and tofacitinib. Clinical remission was achieved in 45.4% of patients at week 8 (95% CI: 30.1%-60.6%), 43.8% (38.4%-49.2%) at weeks 12-16, 44.6% (35.9%-53.3%) at 6 months and 50.6% (36.3%-64.8%) at 12 months. Clinical response was achieved in 61.2%, 59.4%, 65.2% and 76.8% at week 8, weeks 12-16, after 6 months and after 12 months, respectively. Corticosteroid free remission (CS) was achieved in 18.7%, 36.8%, 34.5% and 39% at week 8, weeks 12-16, after 6 months and after 12 months, respectively. Overall, 58.2% of patients had endoscopic improvement at 12 months. Almost 30% of patients required a dose increase[34-37].
In summary, the safety of ustekinumab in the treatment of ulcerative colitis has been well studied in clinical and observational studies. These studies found that the most common

adverse effects occurring during ustekinumab therapy tended to be infections, skin reactions at the site of drug administration, inflammation of the nasopharyngeal cavity and headache. Most of these were mild and it was not necessary to discontinue treatment during the clinical trial. However, overall, ustekinumab appears to be well tolerated by patients with colitis ulcerosa. Ustekinumab has the advantage of being highly effective in achieving clinical response, clinical and endoscopic remission. The drug induces a response quickly, within 6-8 weeks, making it comparable to other biologic drugs with fewer doses needed to achieve a similar effect. Flexibility in dose selection is also an advantage. [24]

Results

The efficacy of ustekinumab in the treatment of ulcerative colitis (colitis ulcerosa) has been confirmed in several large clinical trials. The results of these studies suggest that ustekinumab may be an effective drug for inducing and maintaining remission in patients with moderate to severe disease. Ustekinumab is the first biologic drug and blocks the action of IL-12/IL-23, which is important given the role of these cytokines in the pathogenesis of ulcerative colitis. Patients who have not responded to treatment with other biologic drugs, such as tumor necrosis factor-α (TNF-α) antagonists, may also achieve therapeutic benefit with ustekinumab. The conclusion of this study suggests that ustekinumab may be an effective and safe drug for the treatment of colitis ulcerosa, increasing therapeutic options for patients with the disease. However, as always, the decision to initiate ustekinumab therapy should be made on a case-by-case basis by the physician, taking into account the specific characteristics and needs of the patient.

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