26. Specchio N, Wirrell EC, Scheffer IE, Nabbout R, Riney K, Samia P, et al. International league against epilepsy classification and definition of epilepsy syndromes with onset in childhood: position paper by the ILAE task force on nosology and definitions. Epilepsia. 2022; 63(6): 1398–442. doi.org/10.1111/epi.17241.
27. Vlachou M, Ryvlin P, Armand Larsen S, Beniczky S. Focal electroclinical features in generalized tonic–clonic seizures: Decision flowchart for a diagnostic challenge. Epilepsia. 2024; 65(3): 725–38. doi.org/10.1111/epi.17895.
28. Walsh S, Merrick R, Brayne C. The relevance of social and commercial determinants for neurological health. Anniversary Lecture. 2022: 21(12), 1151–1160. doi.org/10.1016/S1474-4422(22)00428-8.
29. Wirrell EC, Nabbout R, Scheffer IE, Alsaadi T, Bogacz A, French JA, et al. Methodology for classification and definition of epilepsy syndromes with list of syndromes: report of the ILAE Task Force on Nosology and Definitions. Epilepsia. 2022; 63 (6): 1333–48. doi.org/10.1111/epi.17237.
30. World Health Organization. Intersectoral global action plan on epilepsy and other neurological disorders 2022–2031. Geneva: World Health Organization; 2023. Licence: CC BY-NC-SA 3.0 IGO.

Стаття надійшла 29.05.2024 р.

DOI 10.26724/2079-8334-2025-2-92-239-248
UDC 616-072.7:616.12-008.331.1:616.12-008.318.4

O.M. Kulchytska, N.V. Kuzminova, S.E. Lozinsky, I.I. Kniazkova[1], V.M. Khomenko, Yu.L. Shkarivsky, M.M. Velychkovych
National Pirogov Memorial Medical University, Vinnytsia
[1]Kharkiv National Medical University, Kharkiv

EFFICACY, SAFETY, AND FUTURE DIRECTIONS OF ADVANCED THERAPY METHODS FOR PATIENTS WITH INFLAMMATORY BOWEL DISEASES

e-mail: olenakulchytskavnmu@gmail.com

Crohn's disease and ulcerative colitis are the most common inflammatory bowel diseases. They are chronic diseases characterized by inflammation of the gastrointestinal tract that lead to poor quality of life and disability for patients around the world. The number of people with inflammatory bowel disease worldwide is approximately five million, however, the exact number is unknown, as prevalence data may vary depending on the level of health care, diagnosis, and access to treatment in different countries. The causes of these diseases are multifactorial, but one of the main ones is dysregulation of the immune system. Treatment of such patients is aimed at achieving and maintaining periods of remission. The development of newer therapies, including biologics and oral small molecules, targets different immune response mechanisms, opening up new opportunities for treatment. New therapies can significantly improve the quality of life by helping to achieve and maintain remission. However, their cost remains an important aspect that needs to be addressed in the context of treatment accessibility.

Key words: inflammatory bowel disease, Crohn's disease, ulcerative colitis, rheumatoid arthritis, advanced therapy.

О.М. Кульчицька, Н.В. Кузьмінова, С.Е. Лозинський, І.І. Князькова, В.М. Хоменко, Ю.Л. Шкарівський, М.М. Величкович

ЕФЕКТИВНІСТЬ, БЕЗПЕКА ТА ПЕРСПЕКТИВИ СУЧАСНИХ МЕТОДІВ ТЕРАПІЇ ПАЦІЄНТІВ ІЗ ЗАПАЛЬНИМИ ЗАХВОРЮВАННЯМИ КИШЕЧНИКА

Хвороба Крона та неспецифічний виразковий коліт є двома найбільш поширеними запальними захворюваннями кишечника. Це хронічні хвороби, які характеризуються запаленням шлунково-кишкового тракту і призводять до погіршення якості життя та інвалідизації пацієнтів по всьому світу. Загальна поширеність запальних захворювань кишечника становить приблизно п’ять мільйонів осіб, проте, точна цифра може варіювати, оскільки дані про поширеність можуть змінюватися в залежності від рівня медичного обслуговування, діагностики та доступу до лікування в різних країнах. Причини цих захворювань є багатофакторними, однак однією з основних є дисрегуляція імунної системи. Лікування таких пацієнтів спрямоване на досягнення та підтримку періодів ремісії. Розвиток новітніх методів лікування, зокрема біопрепаратів, а також пероральних малих молекул, які націлені на різні механізми імунної відповіді, відкриває нові можливості для пацієнтів. Нові методи лікування можуть значно покращити якість життя, допомагаючи досягти та підтримувати ремісію, хоча питання їх вартості залишається важливим аспектом, який потребує уваги в контексті доступності лікування.

Ключові слова: запальні захворювання кишечнику, хвороба Крона, неспецифічний виразковий коліт, ревматоїдний артрит, розширена терапія.

The work is a fragment of the research project “Cardiovascular remodeling, structural and functional state of the liver and kidneys and their relationship with cardiometabolic risk factors in patients with cardiac pathology and comorbidities. Possibilities of treatment optimization”, state registration No. 0124U002036.

Expanded therapy is a term applied to biologics as well as small molecules that are commonly used for moderate to severe Crohn's disease (CD) and ulcerative colitis (UC) [20]. This therapy targets several immune pathways that play a role in the immune dysregulation, and occurs in inflammatory bowel disease (IBD). Small-molecule oral medications are prescribed once or twice a day. Biologic drugs are large molecules administered intravenously (IV) and/or subcutaneously with a variable dosing

frequency. Some biological products are available as reference products and biosimilars (biological products that do not have clinically significant differences from the reference product) [4, 26]. Many of these dosage forms did not exist five years ago. Expanding therapeutic options may be beneficial for people with IBD and UC. Recommending an advanced therapy to a patient is an important step in treatment. However, the patient cannot be successfully treated if it does not have consistent access to the medication. One of the main barriers to access is the high cost of these drugs.

The purpose of the study was to review modern approaches to the treatment of inflammatory bowel diseases (advanced therapy), specifically examining the characteristics of the main drugs used in therapy, as well as exploring promising pharmaceutical agents currently under clinical trials.

We analyzed the literary sources of local and foreign authors. For this purpose, the electronic databases of medical and biological publications, Pubmed, and Web of Science were used. For data analysis, we used literary sources that had a full-text version. The depth of the search was 5 years. This review includes mostly randomized controlled trials and articles covering the latest recommendations of the European Crohn's and Colitis Organization (ECCO). After the analysis, we also searched for references to the selected publications. The articles were selected by reviewing their titles and abstracts, as well as from the bibliographies of the selected articles. The keywords used to find relevant articles included "inflammatory bowel disease", "Crohn's disease", "ulcerative colitis", "rheumatoid arthritis", "advanced therapy".

Over the past decade, the treatment options for IBD have expanded significantly. Currently, 6 different classes of advanced therapies, including biologic agents and targeted oral small molecules with unique mechanisms of action, are approved for the treatment of IBD: Tumor necrosis factor (TNF)-α antagonists (infliximab, adalimumab, golimumab, certolizumab pegol), anti-integrin agents (vedolizumab, natalizumab), interleukin (IL)-12/23 antagonists (ustekinumab) IL23 antagonists (rituximab, miricizumab), Janus kinase inhibitors (tofacitinib, upacitinib and filgotinib (approved in Europe) and sphingosine 1-phosphate receptor (S1PR) modulators (ozanimod, etrasimod) [20] (Table 1).

Table 1

Medications for advanced therapy: mechanism of action and routes of administration

Medication	Mechanism	Route: Induction	Route: Maintenance
Infliximab	Anti-tumor necrosis factor (TNF)	intravenous	intravenous, subcutaneous
Adalimumab		subcutaneous	subcutaneous
Certolizumab		subcutaneous	subcutaneous
Golimumab		subcutaneous	subcutaneous
Vedolizumab	Anti-integrin	intravenous	intravenous, subcutaneous
Natalizumab		intravenous	intravenous
Ustekinumab	Anti-interleukin 12/23	intravenous	subcutaneous
Risankizumab	Anti-interleukin 23	intravenous	subcutaneous
Mirikizumab-mrkz		intravenous	subcutaneous
Tofacitinib	Janus kinase (JAK) inhibitor	oral	oral
Upadacitinib		oral	oral
Ozanimod	Sphingosine 1-phosphate (S1P) receptor modulator	oral	oral
Etrasimod		oral	oral

Tumor necrosis factor (TNF)-α antagonists (infliximab, adalimumab, golimumab, certolizumab pegol).

Tumor necrosis factor (TNF) plays a central role in the pathogenesis of numerous inflammatory conditions, including CD and UC. TNF is produced intracellularly, mainly by activated macrophages. The TNF precursor is converted to soluble TNF after proteolysis by TNF-converting enzyme. This soluble TNF then oligomerizes to form the biologically active TNF homotrimer. Two types of TNF are very closely related, TNF-alpha and TNF-beta. The activity of both TNFs is mediated through binding to TNF receptor I and II (TNFRI and TNFRII), which are present on almost all cell types (except erythrocytes) [24].

Binding of TNF to TNFRI and TNFRII activates several signaling pathways, including activation of transcription factor (nuclear factor-κB), proteases and protein kinases. This leads to activation of the target cell, which results in an inflammatory and immune response by releasing several cytokines and initiating the apoptotic pathway. Thus, the biological effects of TNF include activation of other cells (macrophages, T cells, B cells), production of proinflammatory cytokines (IL-1, IL-6), chemokines (IL-8), expression of adhesion molecule (E-selectin), inhibition of regulatory T cells, increased matrix expression, production of metalloproteinase, and induction of apoptosis [20].

Tumor necrosis factor-alpha inhibitors, including infliximab, adalimumab, certolizumab-pegol and golimumab, are biologic agents approved by the FDA for the treatment of ankylosing spondylitis, Crohn's disease, ulcerative colitis, juvenile idiopathic arthritis, plaque psoriasis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, rheumatoid arthritis, and uveitis. There are also several off-label indications [33].

Infliximab is administered by infusion. The infusion should be administered over at least 2 hours and should not be administered with other biologic immunosuppressants. Infusion-related reactions are possible and, if necessary, antihistamines, acetaminophen, and corticosteroids can be used as premedication to prevent these reactions [36].

Adalimumab is administered by subcutaneous injection. The injection sites should be changed and moved away from previous injection sites.

Certolizumab pegol is injected subcutaneously into the thigh or abdomen.

Golimumab may be administered intravenously or subcutaneously. The infusion should be administered over 30 minutes and should not be administered in combination with other biologic immunosuppressants. An autoinjector is used for subcutaneous injections [21].

Tumor necrosis factor antagonists are generally well tolerated, with common side effects being mild and not requiring discontinuation [9]. However, serious side effects have been reported, the most common of which were severe infections. Before starting tumor necrosis factor antagonists, appropriate screening for severe infection should be performed; this includes screening for infections such as tuberculosis, HIV, hepatitis B and hepatitis C, and treatment if infection is detected. Physicians should be cautious about recommending treatment to elderly patients, patients with a history of malignancy, or patients with a predisposition to infection [21].

Common side effects of all drugs in this group (occurring in more than 10 % of patients) include headache, injection site reaction in subcutaneous administration and infusion reaction in intravenous administration, rash, anemia, upper respiratory tract infections, sinusitis, cough, pharyngitis, diarrhea, nausea, and abdominal pain [20].

Anti-integrin agents (vedolizumab, natalizumab)

In IBD, tumor necrosis factor plays an important role in the the disease deterioration, but several other pathways are also involved in the formation of an inflammatory response. One of these pathways is the invasion of the intestinal mucosa by leukocytes. Leukocytes in the systemic circulation travel to sites of inflammation, though blocking this pathway can be an important strategy for treating IBD. Anti-integrin therapy blocks the action of integrin on the surface of circulating immune cells and endothelial cell adhesion molecules, thereby inhibiting the interaction between leukocytes and intestinal blood vessels [20].

Natalizumab, which acts on α4-integrin, was the first such drug approved for the treatment of Crohn's disease, but its use is limited due to the risk of progressive multifocal leukoencephalopathy. Natalizumab is a chimeric recombinant human IgG4 antibody that targets the α4 subunit of integrins α4β7 and α4β1 on leukocytes. Natalizumab was first approved by the U.S. Food and Drug Administration (FDA) as a treatment for multiple sclerosis, an autoimmune disease of the central nervous system (CNS).

Vedolizumab (VDZ) is a humanized IgG1 monoclonal antibody against α4β7-integrin that inhibits leukocyte adhesion to the endothelium by blocking the interaction between α4β7-integrin and MAdCAM-1, which is expressed on blood vessels and lymph nodes associated with the gastrointestinal tract. The main difference between natalizumab and VDZ is that natalizumab inhibits leukocyte trafficking in many organs, including the brain, while VDZ acts specifically only on gut-trophic α4β7 heterodimers and thus selectively inhibits lymphocyte trafficking in the intestine [11].

Vedolizumab has been approved by the FDA and the European Medicines Agency for the treatment of adult patients with moderate to severe UC and CD who have not responded to one or more conventional therapies such as steroids, immunosuppressants, or TNF antagonists. The results of VDZ clinical trials have shown different treatment effects in patients with UC and CD. There are several theories explaining why the clinical effect of inhibiting leukocyte transport in CD appeared later than in UC. CD can have systemic manifestations and affect the entire gastrointestinal tract from the mouth to the anus, showing inflammation in all layers of the intestine; in contrast, UC is limited to the colon mucosa, which may explain the difference in response to treatment. Thus, further in-depth studies are needed to better understand the pharmacokinetics and pharmacodynamics of VDZ in CD.

Vedolizumab causes few systemic side effects because it targets gut-trophic integrin α4β7, so it causes relatively small systemic immunosuppression [28].

Newer drugs in this group, which act on different integrin-related targets, such as AJM300, abrilumab, and PF-00547659, have also been developed and are currently in clinical trials.

Interleukin (IL)-12/23p40 antagonists (ustekinumab).

Ustekinumab is a human monoclonal antibody commonly used to treat moderate to severe plaque psoriasis, psoriatic arthritis, moderate to severe Crohn's disease, or moderate to severe ulcerative colitis. Ustekinumab mediates the body's T-cell response by acting as an antagonist against interleukin-12 (IL12) and interleukin-23 (IL23). While the FDA has not approved ustekinumab for many other inflammatory diseases, it has been used off-label to treat purulent hydradenitis, Takayasu arteritis, giant cell arteritis, Behcet's disease, myelodysplastic syndrome, synovitis, acne, pustulosis, hyperostosis and osteitis syndrome, atopic dermatitis, and systemic lupus erythematosus, among others [33].

IL-12 and IL-23 are cytokines that modulate lymphocyte function and are involved in the pathogenesis of systemic inflammatory diseases. IL-12 is a cytokine produced by antigen-presenting cells, such as dendritic cells and macrophages, which are involved in the development of Th1 cells that secrete gamma interferon. IL-23 is a pro-inflammatory cytokine that is predominantly produced by dendritic cells, monocytes, and macrophages, which induces the differentiation and activation of Th17. Both cytokines share the p40 subunit. As a human IgG1 monoclonal antibody, ustekinumab blocks the p40 subunit, and this antagonistic effect inhibits the interaction of these cytokines with the IL-12Rβ1 receptor. The IL-12Rβ1 receptor is located on the surface of NK cells and T cells. In this case, ustekinumab can inhibit IL-12 and IL-23 signaling, activation and production of cytokines, which leads to downregulation of the immune system, which reduces inflammation and changes the body's immune response.

Ustekinumab is available for injection in prefilled syringes and vials. The drug is administered by subcutaneous injection or intravenous infusion. Dosage and administration recommendations depend on the specific indications for treatment and the patient's weight. The treatment of Crohn's disease and ulcerative colitis is based on an initial intravenous infusion based on body weight, followed by a subcutaneous maintenance schedule.

Serious side effects, such as serious infections, are rare. The side effect profile in patients with psoriasis and psoriatic arthritis is similar. However, abdominal pain, fever, and diarrhea have been reported with maintenance doses of ustekinumab for patients with UC and IBD.

As with all biologic medicines, screening for severe infection should be performed before starting a drug such as ustekinumab. Physicians should be cautious about recommending treatment to elderly patients, patients with a history of malignancy, or a predisposition to infections.

Ustekinumab may be used during pregnancy. Based on limited human data, there is no expected risk of fetal harm, and teratogenicity has not been demonstrated in animal studies. The drug can also be used during breastfeeding. No human data are available at this time, but no harm to infants can be expected based on the properties of the drug.

IL23p19 antagonists (rituximab, miricizumab, guselkumab).

Monoclonal antibodies targeting the p19 subunit of IL23 are effective treatments for CD and UC. Currently, 2 IL23 antagonists are approved by the FDA: rituximab and miricizumab. These agents are mechanistically similar but different from ustekinumab, which blocks IL12 and IL23 by inhibiting their common p40 subunit, and these seemingly minor pharmacodynamic differences may have important clinical implications [3].

Risankizumab was approved in 2022 for the treatment of CD (based on 2 phase 3 trials, the 12-week induction trials ADVANCE and MOTIVATE, and the 52-week maintenance trial FORTIFY) [16] and in 2024 for the treatment of moderate to severe UC (INSPIRE induction trial, COMMAND maintenance trial). Following the approval of rituximab, several cohort studies have confirmed its real-world efficacy. Based on the results of clinical trials, in clinical practice, rituximab has become the biologic drug of choice for most patients with moderate-to-severe UC and UC who have not previously been treated with TNF antagonists [23]. In 2023, mirikizumab was approved for the treatment of moderate to severe UC (based on the phase 3, 12-week induction trial LUCENT-1 and the 40-week maintenance trial LUCENT-2), and in January 2025, for the treatment of CD (based on the phase 3, 52-week trial VIVID-1) [6, 22].

Another representative of this group of drugs is Guselkumab. Guselkumab was first approved by the FDA for the treatment of adults with moderate to severe plaque psoriasis in 2017. In 2022, Guselkumab was approved by the FDA for the treatment of patients with moderate to severe UC (based

on the results of the clinical trial QUASAR). In the Phase 2 GALAXI-1 study involving patients with moderate-to-severe UC, the rate of clinical and endoscopic outcomes with guselkumab was significantly higher than with placebo and numerically higher than with ustekinumab as a control group at weeks 12 and 48. Full Phase 3 data on the induction and maintenance of remission in patients with CD are currently awaited. Guselkumab is not currently approved by the FDA for the treatment of Crohn's disease [2, 14].

Janus kinase inhibitors (tofacitinib, upacitinib, filgotinib).

Janus kinases (JAKs) are a family of cytosolic tyrosine kinases that regulate cytokine signal transduction, including cytokines involved in several inflammatory diseases such as rheumatoid arthritis, psoriasis, atopic dermatitis, and IBD. Several small-molecule JAK inhibitors (SMIs) are currently approved for various immune-mediated inflammatory diseases [35]. However, key differences between these agents could potentially translate into unique clinical profiles. Each JAKi has a unique chemical structure, which leads to a special way of binding in the catalytic cleft of the target JAK and creates distinctive pharmacological characteristics. In addition, the available agents have different selectivities for JAK isoforms, as well as off-target effects against non-JAKs. Other differences include effects on hematologic parameters, DNA damage repair, reproductive toxicity, and metabolism/elimination [20].

Janus kinase inhibitors are oral, small-molecule drugs that inhibit the transcription of proinflammatory cytokines. This inhibition is selective in different ways: tofacitinib, which was approved by the Food and Drug Administration (FDA) for the treatment of UC in 2018, predominantly inhibits JAK1 and JAK3 [38], and upacitinib, which was approved by the FDA for the treatment of UC in 2022 and CD in 2023, predominantly inhibits JAK1 (Fig. 1).

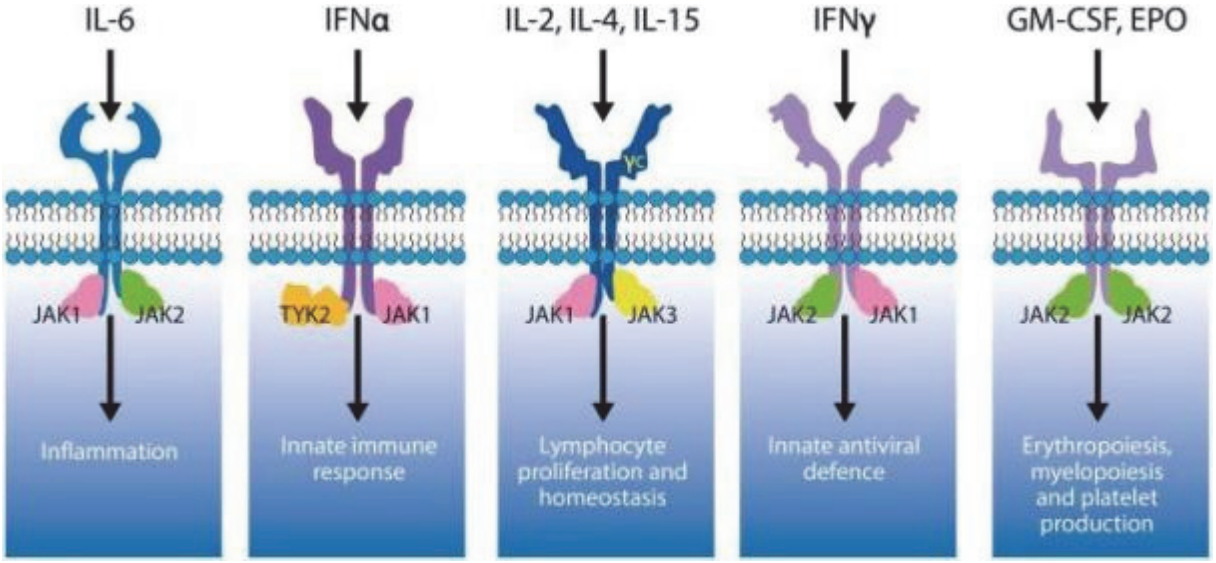

Fig. 1. Cytokine receptors are associated with different pairs of JAKs. γc: common γ-chain; EPO: erythropoietin; JAK: Janus kinase; TYK: tyrosine kinase [34].

The FDA labels indicate that these drugs are indicated for patients with ineffectiveness or contraindications to TNF antagonists [35].

The efficacy and safety of Janus kinase inhibitors are dose-dependent. Therefore, the optimal dose is the lowest dose that achieves and maintains remission [38]. Both tofacitinib and upacitinib have a rapid onset of action, with a significant proportion of patients with UC experiencing clinical improvement within 1-3 days of starting therapy [12]. Similarly, in patients with CD, upadacitinib can reduce abdominal pain and stool frequency within 1 week of treatment initiation in clinical trials [19]. The initial dose of tofacitinib for outpatients with moderate-to-severe UC is 10 mg twice daily for 8 weeks. After induction therapy, patients can maintain the dose of 10 mg twice daily or reduce it to 5 mg twice daily. The induction dose of upadacitinib for outpatients with moderately severe UC and CD is 45 mg daily for 8 and 12 weeks, respectively. After induction, both upadacitinib 15 mg daily and 30 mg daily are approved doses for the maintenance of UC and CD [34].

Another representative of this group of drugs is filgotinib. Filgotinib is currently approved by the European Medicines Agency (EMA) for the treatment of rheumatoid arthritis, and its use in the treatment of UC and CD is under clinical trial [12].

Sphingosine-1-phosphate receptor (S1PR) modulators (ozanimod, etrasimod).

Etrasimod and ozanimod are two oral S1P receptor modulators that are currently approved for the treatment of moderate to severe UC. There are 5 subtypes of S1P receptors (S1P1-S1P5) that have different expression in lymphoid, hematopoietic and specific organ systems, including the brain, heart and gastrointestinal tract. It is assumed that S1PR modulators work by binding the S1P receptor on the surface of immune cells [15]. Subsequent internalization of the receptor prevents the cell from sensing S1P, a signaling sphingolipid important for immune cell trafficking, thus affecting the migration of immune cells from lymphoid organs such as lymph nodes to the circulatory system. By isolating activated immune cells in the lymph nodes, S1PR modulators result in fewer immune cells being transported to the peripheral circulation, and subsequently fewer immune cells available to travel to target sites of active inflammation, such as the colon in UC patients [29].

In 2021, ozanimod, an S1PR modulator targeting S1P1 and S1P5, was approved for the treatment of moderate to severe UC based on a phase 3, 10- week induction study and a 52-week maintenance trial in the TRUE NORTH program [5]. Ozanimod is administered with a "ramp-up" dose titration during the first week of treatment, starting with an oral dose of 0.23 mg daily for the first 4 days, followed by 0.46 mg daily for the next 3 days, then 0.92 mg starting on day 8, and continuing at 0.92 mg as a maintenance dose [31]. This titration strategy reduces the risk of bradycardia, which is an effect of the S1PR class of modulators [5, 25]. Before starting ozanimod, a baseline electrocardiogram (to screen for existing conduction disorders and QTc prolongation), complete blood count, and liver function tests should be performed; in addition, fundus examination is required in patients with a history of diabetes, uveitis, or macular edema of the optic nerve. With a slow dose titration and due to the mechanism of action aimed at lymphocyte sequestration, ozanimod acts relatively slower [17, 25].

Etrasimod was approved for the treatment of moderate to severe UC in 2023. In the ELEVATE 12 and ELEVATE 52 trials, patients treated with etrasimod, an S1PR modulator targeting S1P1, S1P4, and S1P5, experienced higher clinical remission rates compared to placebo [32]. Etrasimod is administered orally at a daily dose of 2 mg during induction and maintenance therapy without dose titration. Similar to ozanimod, a baseline electrocardiogram, complete blood count, and liver function tests are warranted [25]. In addition, the FDA suggests that all patients undergo fundus examinations and skin cancer screening before or shortly after starting treatment.

Over the past few years, the development of biologic agents targeting cytokines and receptors involved in IBD pathogenesis has led to better outcomes and improved disease progression. Despite their efficacy, drugs such as tumor necrosis factor (TNF) inhibitors, anti-interleukin-12/23, and anti-integrins fail to respond in about one-third of patients, and 40% of patients lose response over time [1]. Therefore, more effective treatments are needed. Recent studies have shown that TL1A (tumor necrosis factor-like cytokine 1A) acts as a regulator of mucosal immunity and is involved in immunological pathways involved in the pathogenesis of IBD. Inhibition of TL1A is a promising therapeutic strategy, as evidenced by encouraging clinical trial results for moderate and severe IBD. Future studies may elucidate the broader impact of TL1A on immunity, epithelial integrity, and fibrosis, suggesting new avenues for therapeutic intervention and biomarker discovery. Ongoing Phase 3 trials are key to evaluating TL1A inhibitors as effective and safe treatments for IBD. In addition, investigating the role of TL1A in fibrosis-related complications and its potential as a biomarker of treatment response holds promise for personalized medicine approaches. Consideration of TL1A inhibition in concomitant immune-mediated inflammatory diseases suggests broader therapeutic implications beyond the gastrointestinal manifestations of IBD [20].

Phase 2 clinical trials of anti-TL1A drugs have shown promising results, demonstrating improved endoscopic and histologic outcomes for both UC and IBD. Phase 2 and 3 clinical trials are ongoing and are expected to provide further clarity on the efficacy and safety of TL1A-targeted drugs in the treatment of IBD [20].

The current approach to positioning therapy for moderate to severe IBD is based on a careful combination of comparative efficacy and safety in the context of individual disease risk and treatment-related complications, as well as patient preferences (regimen and frequency of administration), speed of onset, comorbidities, and, importantly, access to therapy. Effective disease control with corticosteroid avoidance is the main goal of treatment to maintain sustained remission and avoid disease complications. Although the general approach to the treatment of patients with IBD is similar, there are clear differences in the treatment of UC and IBD [8].

Crohn's disease.

Integrating data from direct clinical trials with network meta-analysis and real-world comparative efficacy and safety studies, infliximab (usually with an immunomodulator) and adalimumab are probably

the most effective methods of inducing remission in patients with CD who have not previously received biologic agents, especially in patients with more complex disease (e.g., perianal disease, fistulizing and constricting disease) and high inflammatory activity [33]. In patients with CD with moderate inflammation, ustekinumab and rituximab are reasonable alternatives with a better safety profile and are often the drugs of choice [10].

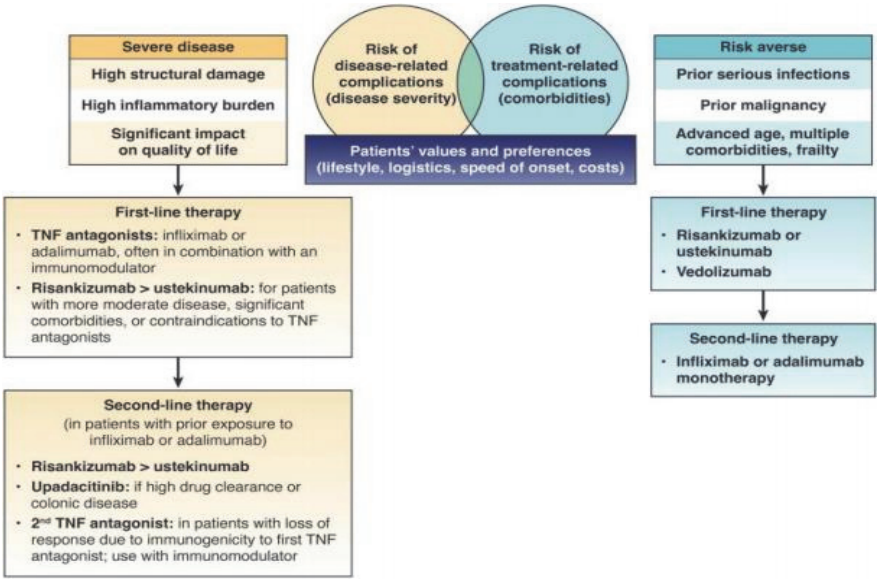

Fig. 2. Proposed algorithm for the treatment of patients with moderate to severe Crohn's disease, combining data on the comparative efficacy and safety of therapy in the context of individual risk of disease and treatment- related complications [20].

In patients with previous TNF-α antagonist failure, rituximab and upacitinib are likely to be the most effective treatments. According to the SEQUENCE study, rituximab is more effective than ustekinumab in these patients; in addition, real-world data suggest that a significant proportion of patients treated with ustekinumab may respond after switching to rituximab [18]. Based on numerous observational studies and indirect treatment comparisons, all of these drugs seem to be more effective than vedolizumab as second-line therapy. Second-line therapy with a TNF antagonist may be appropriate for patients who have discontinued the first TNF antagonist due to intolerance or immunogenicity (in this case, the second TNF antagonist is better used in combination with an immunomodulator). The overall safety profile of rituximab compared to upacitinib with comparable efficacy often leads us to prefer rituximab as a second-line drug [18]. However, in patients with high drug clearance, low albumin levels, CD with colon involvement, severe inflammatory arthritis (especially axial), or perianal disease, we may prefer to use upacitinib as second-line therapy after TNF antagonists have failed [7]. Fig. 2 summarizes the proposed algorithm for the treatment of patients with moderate and severe CD.

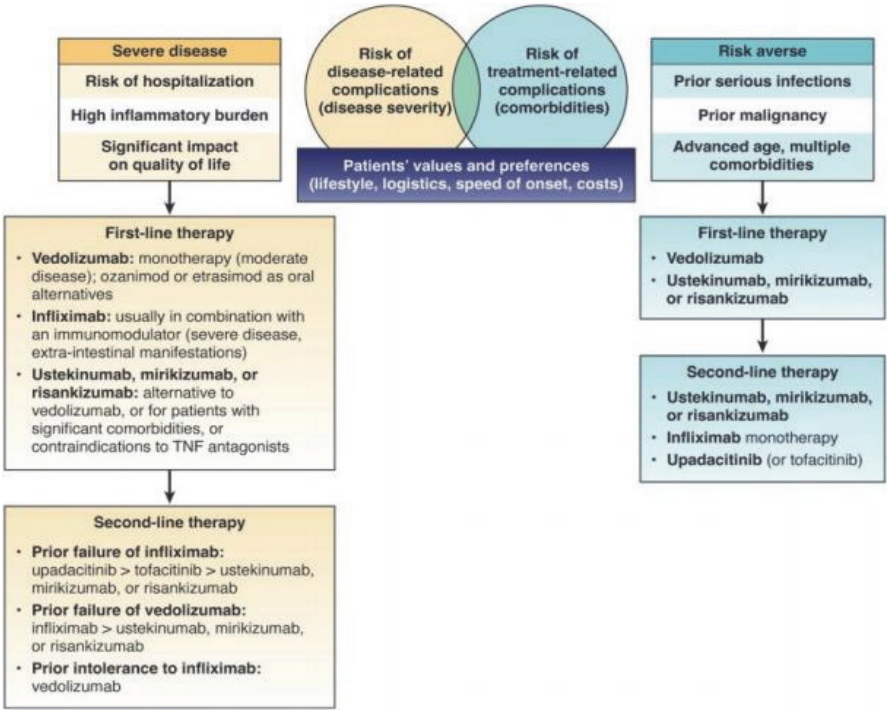

Fig. 3. Proposed algorithm for the treatment of patients with moderate and severe ulcerative colitis, integrating data on the comparative efficacy and safety of therapy in the context of individual risk of disease and treatment- related complications [20].

Ulcerative colitis. Similar to CD, there are few direct clinical trials of advanced therapies in patients with moderate-to-severe UC. Integration of data from the VARSITY trial comparing vedolizumab with adalimumab, regulatory trials of approved treatments, and recent network meta-analyses suggests that upacitinib is by far the most effective treatment for most patients with moderate-to-severe UC [19]. However, FDA black box warnings mostly limit its use to patients with prior failure or intolerance to TNF antagonists. With the

exception of upacitinib, infliximab and vedolizumab are probably the most effective methods of inducing remission in previously untreated patients with moderate-to-severe UC [20]. For most patients with moderate UC who are steroid-dependent or steroid- sensitive and do not have a short-term risk of hospitalization, vedolizumab is generally preferred, although ustekinumab or miricizumab are also considered [10]. Preference is given to infliximab (usually in combination with thiopurines, at least initially) in patients with more severe disease, high inflammatory activity, and where rapid onset of action is desired. The S1PR modulators, ozanimod and etrasimod, are also effective and attractive first-line oral small molecule drugs for patients who are not responding to 5-AHA, although they are more potent immunosuppressive agents with a potentially higher risk of infections and, especially in the case of ozanimod, drug-drug interactions [9]. However, when used after the ineffectiveness of other advanced therapies, the effectiveness of the S1PR modulator is significantly reduced [20].

For patients who do not respond to vedolizumab as first-line therapy, switching to infliximab is preferred, although ustekinumab and miricizumab are also reasonable options [20]. For patients with severe disease in whom first-line infliximab therapy has failed, upacitinib is preferred, given its high efficacy and rapid onset of action. Upadacitinib has largely replaced tofacitinib in clinical practice, except in cases related to cost or availability, or in patients already in stable remission on tofacitinib [12]. In patients who discontinue infliximab due to intolerance or concerns about side effects, most alternative agents are likely to be effective. Future direct trials and precision medicine initiatives will help to more accurately select and systematize therapies for patients with IBD. Fig. 3 summarizes the proposed treatment algorithm for patients with moderate to severe UC.

In summary, treatment options for IBD have rapidly expanded, giving hope to millions of IBD patients to avoid disability caused by disease activity and related complications [27]. An integrated synthesis of risk and benefit from multiple sources, including direct trials and real-world evidence, that incorporates patient values and preferences can inform optimal therapy positioning to improve patient outcomes. In the future, prognostic and predictive biomarkers combined with clinical factors may help facilitate accurate therapy selection [30].

Conclusions

1. Advanced therapy includes both biologic drugs and small-molecule oral agents used in moderate to severe forms of CD and UC.

2. The current treatment arsenal includes 6 main classes of drugs with different mechanisms of action (TNF-α antagonists, anti-integrins, IL-12/23 antagonists, IL-23 antagonists, JAK inhibitors, S1PR modulators).

3. TL1A is recognized as a promising new therapeutic target. TL1A inhibitors have shown encouraging results in Phase 2 clinical trials and continue to be investigated in Phase 3.

4. The effectiveness of the drugs remains limited: about 30 % of patients do not respond to therapy, and 40 % lose their response over time.

5. The selection of therapy is based on an assessment of efficacy, safety profile, comorbidities, patient preferences, availability of drugs, and expected speed of action.

6. Different treatment algorithms are used for UC and IBD, respecting the characteristics of the disease and previous treatment experience.

7. Financial barriers remain one of the main problems in access to innovative medicines.

8. Personalized medicine and the introduction of biomarkers will play a key role in the future to optimize the choice of therapy.

References

1. Ahuja D, Murad M, Ma C. Comparative speed of early symptomatic remission with advanced therapies for moderate-to-severe ulcerative colitis: a systematic review and network meta-analysis. Am J Gastroenterol. 2023 Sep 1; 118(9): 1618-1625. doi: 10. 14309/ajg.0000000000002263.

2. Allegretti J, Peyrin-Biroulet L, Feagan B. 913b The efficacy and safety of guselkumab induction therapy in patients with moderately to severely active ulcerative colitis: results from the phase 3 QUASAR induction study. Gastroenterology 2023; 164: S-S1572.

3. Alsoud D, Sabino J, Franchimont D. Real-world efficacy and safety of risankizumab in patients with moderate to severe multirefractory Crohn's disease: a Belgian multicentric cohort study. Inflamm Bowel Dis Published online January 12, 2024. https://doi.org/10. 1093/ibd/izad315.

4. Angyal A, Bhat S. Biosimilars in IBD: what every clinician needs to know. Curr Gastroenterol Rep. 2024; 26(3): 77-85. doi:10. 1007/ s11894-023- 00913-5.

5. Armuzzi A, Cross RK, Lichtenstein GR, Hou J, Deepak P, Regueiro M, et al. Cardiovascular safety of ozanimod in patients with ulcerative colitis: True North and Open-Label extension analyses. Clin Gastroenterol Hepatol 2024; 22: 1067-1076.e3. doi: 10. 1016/j.cgh.2023.11.018.

6. Barnes E. A practical guide to the use of mirikizumab. Am J Gastroenterol 2024; 119: 400-403. doi: 10. 14309/ajg.0000000000002531.
7. Berinstein J, Karl T, Patel A. Effectiveness of upadacitinib for patients with acute severe ulcerative colitis: a multi-center experience. Am J Gastroenterol Published online March 27, 2024. https://doi.org/10.14309/ajg.0000000000002674.
8. Bruner L, White A, Proksell S. Inflammatory bowel disease. Prim Care. 2023; 50: 411-427. doi: 10. 1016/j.pop.2023.03.009.
9. Burr N, Gracie D, Black C, Ford A. Efficacy of biologic therapies and small molecules in moderate to severe ulcerative colitis: systematic review and network meta-analysis. Gut 2021: gutjnl-2021-326390. doi: 10. 1136/gutjnl-2021- 326390.
10. Chang S, Murphy M, Malter L. A review of available medical therapies to treat moderate-to-severe inflammatory bowel disease. The American Journal of Gastroenterology. 119 (1): p 55-80, January 2024. DOI: 10. 14309/ajg.0000000000002485.
11. Chugh R, Long M, Jiang Y, Weaver K, Beaulieu D, Scherl E, et al. Maternal and neonatal outcomes in vedolizumab and ustekinumab exposed pregnancies: results from the PIANO registry. Am J Gastroenterol 2024; 119: 468-476. Am J Gastroenterol. 2024 Mar 1; 119(3): 468-476.
12. Dalal R, Kallumkal G, Cabral H. One-year comparative effectiveness of upadacitinib vs tofacitinib for ulcerative colitis: a multicenter cohort study. Am J Gastroenterol Published online April 1, 2024. https://doi.org/10.14309/ajg.0000000000002746.
13. Danese S, Dignass A, Matsuoka K, Ferrante M, Long M, Redondo I, et al. Early and Sustained Symptom Control with Mirikizumab in Patients with Ulcerative Colitis in the Phase 3 LUCENT Program. J Crohns Colitis. 2024 Nov 4; 18(11): 1845-1856. doi: 10. 1093/ecco-jcc/jjae088.
14. Danese S, Panaccione R, Feagan BG, Afzali A, Rubin D, Sands B, et al. Efficacy and safety of 48 weeks of guselkumab for patients with Crohn's disease: maintenance results from the phase 2, randomized, double-blind GALAXI-1 trial. Lancet Gastroenterol Hepatol 2024; 9: 133-146. doi: 10. 1016/S2468-1253(23)00318-7.
15. Din S, Selinger CP, Black CJ, Ford A. Systematic review with network meta-analysis: risk of herpes zoster with biologic therapies and small molecules in inflammatory bowel disease. Aliment Pharmacol Ther. 2023 Mar; 57(6): 666-675. doi: 10. 1111/apt.17379.
16. D'Haens G, Panaccione R, Baert F, Bossuyt P, Colombel J, Danese S, et al. Risankizumab as induction therapy for Crohn's disease: results from the phase 3 ADVANCE and MOTIVATE induction trials. Lancet 2022; 399: 2015-2030. doi: 10. 1016/S0140-6736(22)00467-6.
17. Dubinsky M, Charles L, Selmaj K. Pregnancy outcomes in the ozanimod clinical development program in patients with ulcerative colitis, Crohn's disease, and relapsing multiple sclerosis. Inflamm Bowel Dis Published online January 24, 2024. https://doi.org/10. 1093/ibd/izae011.
18. Ferrante M, Panaccione R, Baert F, Bossuyt P, Colombel J, Danese S, et al. Risankizumab as maintenance therapy for moderately to severely active Crohn's disease: results from the multicenter, randomized, double-blind, placebo-controlled, withdrawal phase 3 FORTIFY maintenance trial. Lancet 2022; 399: 2031-2046. doi: 10. 1016/S0140-6736(22)00466-4.
19. Friedberg S, Choi D, Hunold T. Upadacitinib is effective and safe in both ulcerative colitis and Crohn's disease: prospective real-world experience. Clin Gastroenterol Hepatol. 2023 Jul; 21(7):1913-1923.e2. doi: 10. 1016/j.cgh.2023.03.001.
20. Fudman D, McConnell R, Ha C, Singh S. Modern Advanced Therapies for Inflammatory Bowel Diseases: Practical Considerations and Positioning. Clin Gastroenterol Hepatol. 2025 Feb; 23(3): 454-468. DOI: 10.1016/j.cgh.2024.06.050.
21. Greywoode R, Petralia F, Ullman T, Frederic Colombel J, Ungaro R. Racial difference in efficacy of golimumab in ulcerative colitis. Infamm Bowel Dis. 2023; 29(6): 843-849. doi:10. 1093/ibd/ izac161.
22. Jairath V, Sands BE, Bossuyt. OP35 efficacy of mirikizumab compared to ustekinumab in patients with moderate to severe Crohn's disease: results from the phase 3 VIVID 1 study. J Crohns Colitis 2024;18:i62-i64. https://doi.org/10.1093/ecco-jcc/jjad212.0035.
23. Horst S. A practical guide to the use of risankizumab. Am J Gastroenterol 2023; 118: 921-924. doi: 10. 14309/ajg.0000000000002139.
24. Loeb L, Nasir A, Picco M, Hashash J, Kinnucan J, Farraye F. Prior authorization of biologics in the management of infammatory bowel disease. Infamm Bowel Dis. 2023; 29(9): e37. doi:10. 1093/ibd/izad088.
25. Mattay S, Zamani M, Saturno D, Loftus E, Ciorba M, Yarur F, et al. Risk of major adverse cardiovascular events in immune-mediated inflammatory disorders on biologics and small molecules: network meta- analysis. Clin Gastroenterol Hepatol. 2024 May; 22(5): 961-970.e12. doi: 10. 1016/j.cgh.2023.09.033.
26. Najeeb H, Yasmin F, Surani S. Emerging role of biosimilars in the clinical care of infammatory bowel disease patients. World J Clin Cases. 2022; 10(14): 4327-4333. doi:10. 12998/wjcc.v10.i14.4327.
27. Odufalu F, Aboubakr A, Anyane-Yeboa A. Infammatory bowel disease in underserved populations: lessons for practice. Curr Opin Gastroenterol. 2022; 38(4): 321-327. doi:10. 1097/ MOG.0000000000000855.
28. Ouranos K, Saleem H, Vassilopoulos S. Risk of infection in patients with inflammatory bowel disease treated with interleukin-targeting agents: a systematic review and meta-analysis. Inflamm Bowel Dis Published online. March 1, 2024. https://doi.org/10. 1093/ibd/izae031.
29. Paik J. Ozanimod: A Review in Ulcerative Colitis. Drugs. 2022 Aug; 82(12): 1303-1313. doi: 10. 1007/s40265-022-01762-8.
30. Plevris N, Lees C. Disease monitoring in inflammatory bowel disease: Evolving principles and possibilities.Gastroenterology. 2022; 162: 1456-1475. doi: 10. 1053/j.gastro.2022.01.024.
31. Sandborn W, Feagan B, D'Haens G, Wolf D, Jovanovic I, Hanauer S, et al. Ozanimod as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2021 Sep 30; 385(14): 1280-1291. doi: 10. 1056/NEJMoa2033617.
32. Sandborn W, Vermeire S, Peyrin-Biroulet L, Dubinsky M, Panes J, Yarur A, et al. Etrasimod as induction and maintenance therapy for ulcerative colitis (ELEVATE): two randomized, double-blind, placebo-controlled, phase 3 studies. Lancet. 2023 Apr 8; 401(10383): 1159-1171. doi: 10. 1016/S0140- 6736(23)00061-2.
33. Sands B, Irving P, Hoops T, Izanec J, Gao L, Gasink C et al. Ustekinumab versus adalimumab for induction and maintenance therapy in biologicnaive patients with moderately to severely active Crohn's disease: a multicenter, randomized, double-blind, parallel-group, phase 3b trial. Lancet. 2022 Jun 11; 399(10342): 2200-2211. doi: 10. 1016/S0140-6736(22)00688-2.
34. Taylor P, Choy, Baraliakos X, Szekanecz Z, Xavier R, Isaacs D, et al. Differential properties of Janus kinase inhibitors in the treatment of immune-mediated inflammatory diseases. Rheumatology (Oxford). 2024 Feb 1; 63(2): 298-308. doi: 10.1093/rheumatology/kead448.

35. Taxonera C, Olivares D, Alba C. Real-world efficacy and safety of tofacitinib in patients with ulcerative colitis: systematic review with meta- analysis. Inflammatory Bowel Diseases, Volume 28, Issue 1, January 2022, Pages 32-40, https: //doi.org/10.1093/ibd/izab011.
36. Turner D, Ricciuto A, Lewis A. International Organization for the Study of IBD. STRIDE-II: an update on the Selecting Therapeutic Targets in Infammatory Bowel Disease (STRIDE) Initiative of the International Organization for the Study of IBD (IOIBD): determining therapeutic goals for treat-to-target strategies in IBD. Gastroenterology. 2021; 160(5): 1570-1583. doi:10. 1053/j. gastro.2020.12.031.
37. Whitmire N, Schlueter M, Kirkpatrick M. Advanced Therapies for Inflammatory Bowel Disease: Navigating Payer and Financial Challenges. Curr Gastroenterol Rep. 2024 Jan 20; 26(3): 68-76. doi: 10.1007/s11894-024-00916-w.
38. Yu A, Ha N, Shi B, Chang U, Mahadevan U, Beck R. Real-world experience with tofacitinib dose de-escalation in patients with moderate and severe ulcerative colitis. Clin Gastroenterol Hepatol. 2023 Nov;21(12):3115- 3124.e3. doi: 10. 1016/j.cgh.2023.05.001.

Стаття надійшла 14.06.2024 р.

DOI 10.26724/2079-8334-2025-2-92-248-253
UDC 57:54:612.08

Ya.V. Rybalka, G.A. Yeroshenko, K.V. Shevchenko, S.V. Kononenko, Yu.V. Tymoshenko, N.M. Sharlai, N.M. Pyvovar
Poltava State Medical University, Poltava
Poltava National Pedagogical University named after V.G. Korolenko, Poltava

BIOLOGICAL EFFECTS OF MONOSODIUM GLUTAMATE ON THE ORGANS OF THE NERVOUS SYSTEM

e-mail: gala_umsa@ukr.net

In the body, monosodium glutamate is a mediator of the peripheral and central nervous systems. In both parts, it is related to metabolic and excitatory functions. Monosodium glutamate is widely used in the food industry as a flavor enhancer. Although food safety regulators generally recognize its safety for health, a number of studies have questioned its long-term safety. Taking into account all of the above, it can be assumed that monosodium glutamate, added to the diet in excessive amounts or with prolonged consumption, can cause behavioral, biochemical and morphological changes in structures such as the brain, hippocampus and cerebellum of adult mammals and lead to dysfunction in the central nervous system.

Key words: monosodium glutamate, food additives, central nervous system, brain.

Я.В. Рибалка, Г.А. Єрошенко, К.В. Шевченко, С.В. Кононенко, Ю.В. Тимошенко, Н.М. Шарлай, Н.М. Пивовар

БІОЛОГІЧНІ ЕФЕКТИ ГЛУТАМАТУ НАТРІЮ НА ОРГАНИ НЕРВОВОЇ СИСТЕМИ

В організмі глутамат натрію є медіатором периферичної і центральної нервової системи. В обох частинах він має відношення до метаболічної та збудливої функції. Глутамат натрію широко використовується в харчовій промисловості в якості підсилювач смаку. Незважаючи на те, що регулюючі органи з безпеки харчових продуктів в цілому визнають його безпеку для здоров'я, низкою досліджень вона ставиться під сумнів з огляду на довгострокову перспективу. Беручи до уваги все вищесказане, можна припустити, що глутамат натрію, доданий до дієти в надмірній кількості або за тривалого споживання, може викликати поведінкові, біохімічні та морфологічні зміни в таких структурах, як головний мозок, гіпокамп і мозочок дорослих ссавців та призвести до дисфукції в центральної нервової системи.

Ключові слова: глутамат натрію, харчові добавки, центральна нервова система, головний мозок.

The study is a fragment of the research project "Structural reorganization of the organs of the immune, respiratory, nervous and excretory systems under the influence of various exogenous factors (monosodium glutamate, sodium nitrite, ethanol, methacrylate)", state registration No. 0121U108234.

In the body, glutamate can be considered as being present in two parts of the nervous system: the peripheral and the central; both are related to the metabolic and excitatory functions of the brain [5].

Despite their similar roles, it is generally accepted that the central and peripheral glutamate pools do not mix freely. Otherwise, this would pose a problem for regulating the levels of glutamate in the brain. The blood-brain barrier plays a crucial role in maintaining this separation, as it is capable of excluding most peripheral (plasma) glutamate, indicating that brain glutamate level is largely maintained by glutamate produced within the brain itself [18].

Under physiological conditions, this division of activity between the central and peripheral parts of the nervous system remains generally intact. However, in pathological states such as inflammation or hyperammonemia (which can result from various conditions, including liver failure), studies have shown activation of cerebral enzymes such as glutamate dehydrogenase, leading to an increase in extracellular glutamate concentration.