DOI 10.26724/2079-8334-2025-1-91-238-246
UDC 616-072.7:616.12-008.331.1:616.12-008.318.4

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MODERN APPROACHES TO THE TREATMENT OF PATIENTS WITH A COMBINATION OF ANKYLOSING SPONDYLITIS AND CROHN`S DISEASE

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Ankylosing spondylitis and Crohn's disease are chronic inflammatory conditions that impact both physical and psychological health. Ankylosing spondylitis primarily affects the spine, causing pain, inflammation, and stiffness, potentially leading to disability. Crohn's disease affects the gastrointestinal tract, causing inflammation, tissue damage, and complications such as stenosis and fistulas, with symptoms like abdominal pain and diarrhea. Although these diseases affect different areas, their inflammatory processes share similar mechanisms and often coexist in the same patient. Both conditions involve immune system dysregulation, leading to chronic systemic inflammation. Treatment aims to reduce symptoms, achieve remission, and prevent complications. However, therapy for comorbid Ankylosing spondylitis and Crohn's disease must be carefully planned, as drugs used for one condition, such as non-steroidal anti-inflammatory drugs for Ankylosing spondylitis, can worsen Crohn's disease. Biological agents targeting inflammatory mechanisms, such as tumor necrosis factor α inhibitors and interleukin blockers, have significantly improved treatment, though individual approaches are necessary due to varying effectiveness and side effects.

Key words: ankylosing spondylitis, inflammatory bowel disease, Crohn's disease, ulcerative colitis.

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ЛІКУВАННЯ ПАЦІЄНТІВ З ПОЄДНАННЯМ АНКІЛОЗУЮЧОГО СПОНДИЛІТУ ТА ХВОРОБИ КРОНА

Анкілозуючий спондиліт і хвороба Крона — це хронічні запальні захворювання, які впливають як на фізичне, так і на психологічне здоров'я. Анкілозуючий спондиліт в основному вражає хребет, спричиняючи біль, запалення та скутість, що може призвести до інвалідності. Хвороба Крона вражає шлунково-кишковий тракт, викликаючи запалення кишечнику, пошкодження тканин та ускладнення, такі як стеноз і нориці, з симптомами болю в животі та діареї. Хоч ці захворювання вражають різні ділянки тіла, їх запальні процеси мають подібні механізми і часто співіснують у одного пацієнта. Обидва захворювання пов'язані з дисфункцією імунної системи, що призводить до хронічного системного запалення. Лікування спрямоване на зменшення симптомів, досягнення ремісії та запобігання ускладненням. Однак терапія для супутніх анкілозуючого спондиліту і хвороби Крона повинна бути ретельно спланована, оскільки препарати, що використовуються для одного захворювання, такі як нестероїдні протизапальні препарати для анкілозуючого спондиліту, можуть погіршити перебіг хвороби Крона. Препарати біологічної терапії, які націлені на запальні механізми, такі як інгібітори фактора некрозу пухлини α та блокатори інтерлейкінів, значно покращили лікування, однак необхідні індивідуальні підходи через різну ефективність і побічні ефекти.

Ключові слова: анкілозивний спондиліт, запальні захворювання кишечнику, хвороба Крона, наспецифічний виразковий коліт.

The work is a fragment of the research projects "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.

According to recent reports, comorbidity of inflammatory bowel disease (IBD) and ankylosing spondylitis (AS) is prevalent. This comorbidity is bidirectional. This means that having AS may increase the likelihood of being diagnosed with IBD, having IBD may increase the chances of being diagnosed with AS, and people diagnosed with IBD are more likely to develop AS in the future [9, 11].

From 5 to 10 % of AS cases are associated with IBD, in particular Crohn's disease (CD). The percentage of patients with AS and subclinical intestinal inflammation detected endoscopically or histologically is much higher [9,16].

The treatment of IBD-related AS with nonsteroidal anti-inflammatory drugs (NSAIDs) is problematic due to the danger of re-activation of IBD under the influence of NSAIDs. In recent years, significant progress has been made with the introduction of monoclonal antibody therapy to tumor necrosis factor alpha (anti-TNF alpha) in AS, other spondyloarthritis, and IBD [21]. Anti-TNF alpha drugs are of particular importance and evidence-based in the treatment of patients with AS with concomitant IBD, so further studies with other biological therapies are important and necessary concerning the course characteristics and comorbidity [24].

The purpose of the study was to review current approaches to treating ankylosing spondylitis and Crohn's disease, emphasize the importance of a multidisciplinary approach, and discuss the specifics of therapy for patients with a combination of these pathologies.

Materials and methods. 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 Assessment of SpondyloArthritis International Society (ASAS), the European Alliance of Associations for Rheumatology (EULAR), and 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 "ankylosing spondylitis", "inflammatory bowel disease", "Crohn's disease", and "ulcerative colitis".

Ankylosing spondylitis (AS) is a chronic inflammatory autoimmune disease that primarily affects the joints of the spine, causing severe chronic pain and may eventually lead to spinal fusion. As an autoimmune disease, AS develops through a complex interaction between genetic background and environmental factors [20]. Although significant progress has been made in recent decades, the etiology of AS remains somewhat unclear. To date, studies have identified some factors that may be associated with the onset of AS, including genetic background, immune response, microbial infection, and endocrine disorders [17].

Genetic factors have been recognized as crucial in the pathogenesis of AS. The correlation between AS and genetics has been an ongoing topic since hereditary factors for AS were first confirmed in families as early as 1961. One of the most important genetic factors is the HLA-B27 class I allele of the major histocompatibility complex, which was discovered in 1973. Despite the unclear pathomechanism, HLA-B27 is associated with the prevalence of AS in different populations worldwide. Studies have shown that 90–95 % of patients with AS are HLA-B27 positive. In addition to the association with the genesis of AS, HLA-B27-positive patients demonstrated a significantly lower mean age and a higher prevalence of acute uveitis than HLA-B27-negative patients [25].

HLA-B27 has a high degree of polymorphism. Currently, more than 100 subtypes have been identified with different prevalence rates among numerous ethnic groups, especially between people of East Asian and Caucasian descent. Reportedly, the most common subtypes are HLA-B2705 (Caucasian population), HLA-B2704 (Chinese population), and HLA-B2702 (Mediterranean population). In addition, genetic influence is not the only factor in the development of AS. Studies of β2-microglobulin (β2m), the non-covalent part of the MHC-I complex, in HLA-B27 transgenic rats have shown that additional β2m reduces HLA-B27 misfolding and contributes to the development of arthritis and spondylitis. This result suggests that abnormal β2m may coordinate with HLA-B27 in the development of AS, which can be explained by theories of protein misfolding [29].

AS is associated with a series of autoimmune diseases, including inflammatory bowel disease (IBD), uveitis, and psoriasis, suggesting that they may have a shared genetic basis and some common immunological processes. As a result, the same patient may have two or even three pathologies simultaneously, which greatly complicates treatment [11, 15].

IL-23/IL-17 play a leading role in the pathogenesis of the disease. Studies have shown higher serum levels of IL-23 and IL-17 in patients with AS. In addition, the course of AS was shown to be significantly alleviated by the administration of drugs that reduce the level of IL-23/IL-17, which further indicates a significant role of these interleukins in AS progression [5]. The interaction of genetic and epigenetic influences, in particular Th17 and Th22 cells, with several types of stress, such as mechanical stress, gut microbiota stress, and environmental factors, leads to the production of proinflammatory molecules, including IL-17, IL-22, TNF-α, and IL-23 [27]. In AS, differentiated T lymphocytes can generate IL-17 and then trigger osteoclast activation, thus inhibiting bone regeneration. In addition, lymphocytes can produce IL-22 under the influence of IL-23 to stimulate osteoproliferation. This contradictory process may explain the coexistence of erosion and bone formation in patients with AS [27].

TL1A also plays an important role in the development of inflammation. TL1A (Tumor Necrosis Factor-like cytokine 1A) is a cytokine that belongs to the TNF cytokine family. It plays an important role in the progression of inflammatory diseases, especially ankylosing spondylitis (AS), due to its ability to activate T- and other cells, belonging to the immune system [1, 5].

The role of TL1A in the development of AS can be summarized as follows:

– Activation of T cells: TL1A interacts with receptors on the surface of T cells such as DR3-receptor (Death Receptor 3), which contributes to the activation of these cells. This leads to increased inflammation and the development of autoimmune reactions characteristic of AS.

– Inflammation and dysfunction of the immune system: TL1A actively promotes the production of pro-inflammatory cytokines such as TNF-α, IL-17, which increases inflammation in joints and tissues, in particular in the spine, where degenerative changes can occur as a result of prolonged inflammation.

– Formation of osteoporosis and ankylosis: TL1A may affect cells that regulate bone resorption and bone formation, an important mechanism of progression of ankylosis (joint fusion) and osteoporosis characteristic of AS.

– Interaction with other inflammatory molecules: TL1A has a synergistic effect in combination with other proinflammatory cytokines such as TNF-α, IL- 23, and IL-17, which increases the overall inflammatory process and the severity of the disease [1].

Due to these mechanisms, TL1A is considered an important cytokine for targeted therapy in patients with AS.

Treatment of patients with AS includes non-pharmacologic and pharmacologic interventions. During the last few years, the pharmacologic options for AS have expanded significantly. For a long time, if the patient did not receive nonsteroidal anti-inflammatory drugs (NSAIDs), the only alternative option was tumor necrosis factor inhibitors (anti-TNF). Currently, the availability of TNF inhibitors, as well as interleukin-17 (IL-17) inhibitors (IL-17i) and Janus kinase inhibitors (JAKi), provides more therapeutic options and hope for people living with this disease [3, 19]. Data on different treatment options are obtained mainly from placebo-controlled trials. On the other hand, in routine clinical practice, the choice between different drugs is permanent throughout the patient's treatment course. A personalized approach to management based on individual needs and supported by scientific evidence is crucial. Existing guidelines generally favor data from observational studies, including efficacy and safety data, as they better reflect real-world populations and actual clinical practice [10].

The guidelines of ASAS (Assessment of SpondyloArthritis International Society) and EULAR (European Alliance of Associations for Rheumatology) for AS management were first developed in 2006 and updated in 2010, 2016, and 2022. This article presents an update of the 2022 ASAS-EULAR guidelines for AS treatment, based on new evidence available since the 2016 update was released [24]. ASAS-EULAR guidelines for the treatment of AS, update 2022:

1. The treatment of patients with AS should be individualized according to the current signs and symptoms of the disease (axial, peripheral, EMMs) and the patient characteristics including comorbidities and psychosocial factors [24, 10].

2. Disease monitoring of patients with SA should include patient-reported outcomes (PROs), clinical findings, laboratory tests, and imaging, all with the appropriate instruments and relevant to the clinical presentation. The frequency of monitoring should be decided on an individual basis depending on symptoms, severity and treatment [24].

3. Treatment should be guided according to a predefined treatment target [24].

4. Patients should be educated about axSpA and encouraged to exercise on a regular basis and stop smoking; physiotherapy should be considered [24].

5. Patients suffering from pain and stiffness should use an NSAID as first-line drug treatment up to the maximum dose, taking risks and benefits into account. For patients who respond well to NSAIDs, continuous use is preferred if needed to control symptoms [24].

6. Analgesics, such as paracetamol and opioid-(like) drugs, might be considered for residual pain after previously recommended treatments have failed, are contraindicated, and/or poorly tolerated [24].

7. Glucocorticoid injections directed to the local site of musculoskeletal inflammation may be considered. Patients with axial disease should not receive long-term treatment with systemic glucocorticoids [18, 24].

8. Patients with purely axial disease should normally not be treated with csDMARDs; sulfasalazine may be considered in patients with peripheral arthritis [24].

9. Anti-TNF, anti-IL-17, or JAK inhibitors should be considered in patients with persistently high disease activity despite conventional treatments [24] (Fig. 1); current practice is to use anti-TNF or anti-IL-17 [24].

10. If there is a history of recurrent uveitis or active IBD, preference should be given to a monoclonal antibody against TNF. In patients with significant psoriasis, an IL-17i may be preferred [24].

11. Absence of response to treatment should prompt re-evaluation of the diagnosis and consideration of the presence of comorbidities [24].

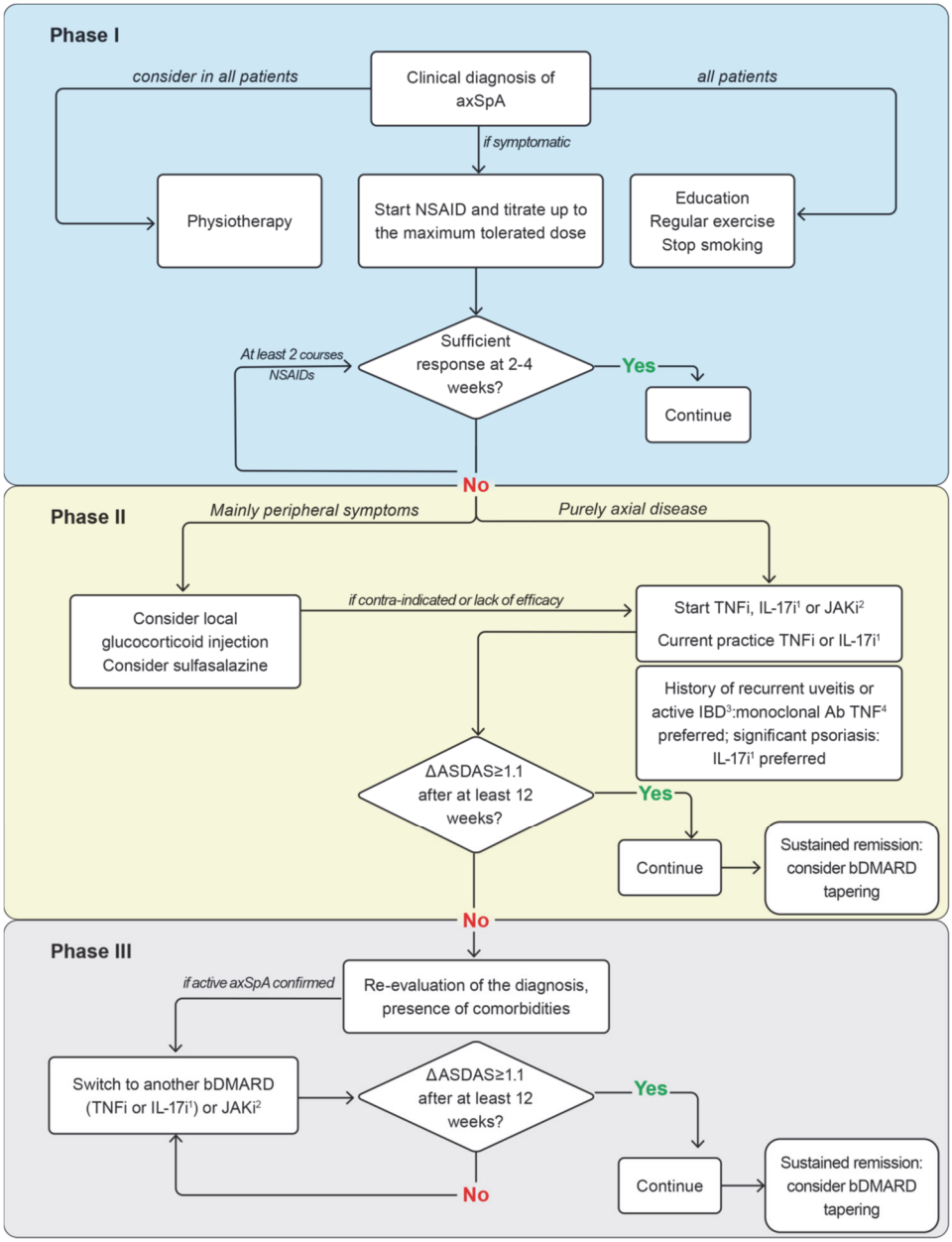

Fig. 1. An algorithm based on the ASAS-EULAR recommendations for the management of axial spondyloarthritis (axSpA). Ab, antibody; ASAS, Assessment of SpondyloArthritis international Society; ASDAS, Ankylosing Spondylitis Disease Activity Score; bDMARD, biological disease-modifying antirheumatic drug; IBD, inflammatory bowel disease; IL-17i, interleukin-17 inhibitors; JAKi, Janus kinase inhibitors; NSAID, non-steroidal anti-inflammatory drug; TNFi, tumour necrosis factor inhibitors [24].

12. Following a first b/tsDMARD failure, switching to another bDMARD (TNFi or IL-17i) or a JAKi should be considered [24].

13. If a patient is in sustained remission, tapering of a bDMARD can be considered [24].

14. Total hip arthroplasty should be considered in patients with refractory pain or disability and radiographic evidence of structural damage, independent of age; spinal corrective osteotomy in specialised centres may be considered in patients with severe disabling deformity [24].

15. If a significant change in the course of the disease occurs, causes other than inflammation, such as a spinal fracture, should be considered and appropriate evaluation, including imaging, should be performed [24].

The 2022 update of the ASAS-EULAR guidelines allows physicians to improve and optimize the treatment of patients with AS. However, as noted above, quite often AS is not the only pathology in a patient and in 10 % of cases it is combined with Crohn's disease, which significantly complicates the selection of the optimal treatment regimen since not all treatment regimens proposed by the ASAS-EULAR 2022 guidelines can be used to treat patients who have Crohn's disease in addition to AS.

Crohn's disease is a chronic, relapsing, and remitting IBD characterized by transmural inflammation and involvement of various sites along the entire gastrointestinal tract. The incidence and

prevalence vary in different geographical regions and are highest in Europe, Oceania, and North America. In addition, in recent years, there has been an increase in the incidence in Asia, Africa, and South America, which emphasizes the global problem posed by CD [7].

The pathogenesis of CD continues to be elucidated and is believed to involve a complex interplay between environmental factors, immune factors, the gut microbiome, and genetic susceptibility. Current research shows that environmental exposure in a genetically susceptible person can lead to dysbiosis of the intestinal microbiota and intestinal barrier dysfunction, subsequently leading to impaired immune regulation [6].

The pathogenesis of Crohn's disease is based on tissue inflammation caused by an immune response against luminal bacterial antigens. Immune cells, such as CD4 T cells, CD8 T cells, B cells, CD14 monocytes, and natural killer cells, are involved in this process when they enter the intestines of patients with CD. Partially the immune-mediated susceptibility to CD is contained in some innate defense mechanisms against infectious diseases, and intestinal mucus secretion is a part of them [22]. Experiments have shown that variants of the Muc2 gene that reduce mucus production are associated with CD in a mouse model. In addition, molecules that mediate bacterial adhesion correlate with the disease. This is the case with FUT2 encoding the fucosyltransferase enzyme, responsible for the secretion of soluble forms of ABO antigens. People who have FUT2 variants reducing antigen secretion have altered interactions with bacteria and are more prone to developing CD [6]. The pathogenesis is also supported by the interaction of these cells with integrins, adhesion molecules, and several chemokines responsible for the production of elevated levels of inflammatory cytokines, which are targeted by immune and non-immune cells and contribute to mucosal inflammation. Thus, among the many adhesion molecules, some evidence for the involvement of leukocyte MAcCAM-1, the α4β4 integrin receptor, seems to play a crucial role [2]. Along with leukocyte adhesion, the role of the extracellular matrix in leukocyte activation has been investigated. Proteins such as CD44 and CD26, as well as metalloproteins (MMPs), have been shown to play a role, as MMP1 and MMP3 are found in large quantities in granular tissue near areas of inflammation in CD, and are therefore responsible for leukocyte activation. The mucous membrane of patients with CD invariably reveals dysregulation of various components of the immune system. The most pronounced change is the hyperactivity of T cells with excessive production of cytokines, namely IL-12 and IFN-γ, which promote the TH1 lymphocyte phenotype, as opposed to TH2, which correlates with ulcerative colitis. In addition, TNF-α production has been demonstrated to increase the number of CD4+ FoxP3 + Treg cells, especially in the mucosa of children with CD. Inhibition of effector cytokines such as TNF-α attenuates the harmful effects in subgroups of patients with CD [2]. In addition, the expression of interleukins, a subset of cytokines associated with the enhancement or suppression of other cytokines in many different regulatory pathways, such as immune cell maturation, growth, and response, should be considered abnormal in patients with CD [23].

Further analysis of T-cell subsets revealed the presence of TH1 and TH17 cells in CD, while the cytokines that are considered to be more involved are TNFα, IL12, and IL23. In addition to these cytokines, IL-34 is also associated with IBD and CD in particular. IL34 expression is more pronounced in areas of active inflammation, especially in CD, and seems to induce TNF-α and IL6 expression through an ERK-mediated mechanism. In addition, IL-34 has been described as an inducer of CCL20 through interaction with its receptor M-CSFR1, which is abundantly expressed in inflamed colon epithelium but not in healthy controls. On the contrary, IL-25 inversely correlates with the inflammatory state of IBD patients, decreasing in patients with CD as opposed to healthy subjects, and is reduced in the affected areas of the colon compared to the surrounding normal tissue [23]. Among all the possible interleukins associated with the pathogenesis of CD, IL-12 and IL-23 are targeted for therapy, but side effects such as increased risk of infection and blocking of specific immunological targets that can induce alternative signaling or homing pathways are possible. The latter mechanism may also partially explain the frequent lack of response to biologic therapies, such as infliximab, a monoclonal antibody used to treat autoimmune diseases that acts by binding to TNF-α, which causes a decrease in the expression of IL-34, which is involved in the differentiation, survival, and function of monocytes and macrophages [21].

The cytokine TL1A also plays an important role in the development of Crohn's disease due to its effect on the immune response and inflammatory processes, which are key to the pathogenesis of this disease. TL1A interacts with the DR3 receptor on the surface of T cells, which promotes their activation and production of pro-inflammatory cytokines such as TNF-α and IL-17, which increase inflammation in the intestine and contribute to the development of chronic inflammatory processes. TL1A also interacts with other molecules, such as IL-23, to increase inflammation and worsen the course of the disease. Blocking TL1A may be a promising approach to controlling the symptoms and progression of CD [6, 23].

The gut microbiota also plays a recognized role in the development of the inflammatory response in IBD and especially in CD. There is growing evidence that products of some microbial genes can influence gene expression in the host [6, 25]. The complex network that emerges from this assumption is called the microbe-associated molecular pattern (MAMP), which is perceived by toll-like receptors on immune cells, promoting their activation in the context of chronic inflammation [30].

The inflammation that develops in CD is usually transmural, and on pathological examination, granulomas can be identified on biopsy with an intermittent distribution along the longitudinal axis. This inflammatory process often leads to irreversible tissue damage in the form of intestinal stenosis or fistulas, inflammatory masses, or intra-abdominal abscesses. Patients may develop one or more of these findings, and they often tend to progress from inflammatory to penetrating or stricture disease [22].

The European Crohn's and Colitis Organization (ECCO) is the leading international organization that brings together experts and researchers in the field of inflammatory bowel disease, including Crohn's disease and ulcerative colitis. ECCO develops and publishes guidelines to help clinicians and researchers improve the diagnosis, treatment, and support of patients. The latest ECCO guidelines were published in 2024 and provide important recommendations on current approaches to the treatment of Crohn's disease, based on the latest scientific advances and clinical evidence.

The general results of the ECCO Guidelines 2024 in the treatment of Crohn's disease are as follows:

– 5-aminosalicylic acid (5-ASA) is not recommended for induction of remission in CD, as its effectiveness has not been proven. Also, 5-ASA derivatives should not be used for maintenance therapy in CD [8].

– Budesonide is recommended for induction of clinical remission in patients with mild to moderate CD limited to the ileum and/or ileum. At the same time, systemic corticosteroids are suggested as induction therapy for patients with active, moderate, and severe CD [8].

– Thiopurines (azathioprine, mercaptopurine) are not recommended as monotherapy for induction of remission in CD, as the effectiveness of this approach is limited. However, thiopurines can be used as maintenance therapy, but this is a weak recommendation due to the lack of high-quality evidence [8].

– Methotrexate can be used as a parenteral induction therapy for moderate to severe CD. It has also shown efficacy as a maintenance therapy in such cases, but its use requires caution due to potential side effects [8, 12].

– Infliximab is a recommended drug for induction and maintenance of remission in moderate to severe active hepatitis C. Combination therapy with infliximab and thiopurines is effective in the initial stages of treatment, which allows achieving rapid remission. However, in patients who have achieved prolonged remission, a gradual dose reduction or withdrawal of thiopurines is possible [8, 21].

– Adalimumab and ustekinumab have strong recommendations for induction and maintenance of remission in moderate to severe CD. They are effective biologic drugs, especially in patients who have not previously received biologic therapy. However, although these drugs have shown similar efficacy, the choice between them may depend on individual patient characteristics [8, 28].

– Certolizumab can also be used to induce and maintain remission in moderate to severe CD, but recommendations for this drug are less strong, and the evidence for its effectiveness in this role is not as convincing as for other biologic agents [8].

– Rizankizumab and vedolizumab are recommended as first-line drugs for induction and maintenance of remission in moderate to severe CD, with high quality evidence supporting their efficacy. They are important alternatives in the treatment of CD, especially in cases where traditional drugs do not bring the desired effect [8, 2].

– Upadacitinib has shown good results as an induction and maintenance therapy for patients with moderate to severe CD and is recommended as a means to achieve disease control [8].

– Regarding combination therapy, there is currently insufficient evidence to recommend combining the recommended agents in the early stages, especially in patients who have not received prior treatment [8].

These guidelines help clinicians choose the most effective therapy for patients with CD based on the latest scientific findings and taking into account the individual needs of each patient. However, some approaches still require additional research to draw clearer conclusions.

Thus, treating AS or Crohn's disease is a complex and multistage process, and the treatment of patients with both pathologies is extremely difficult. Regarding the latest ASAS-EULAR and ECCO

guidelines and the results of numerous studies, several promising approaches to treating patients with comorbid AS and CD can be identified and the drugs that can be used in such patients can be considered.

Non-selective anti-inflammatory drugs are the first line of therapy in patients with AS [24]. While non-selective cyclooxygenase (COX) inhibitors are generally contraindicated in patients with IBD due to the risk of disease exacerbation, two clinical trials have shown that selective COX-2 inhibitors are safe and effective when used for short-term treatment in inactive IBD [22]. While routine NSAID therapy is generally avoided in patients with IBD due to concerns about potentially harmful effects on the intestinal mucosa, there is growing evidence that selective COX-2 inhibitors, and celecoxib in particular, are safe and effective.

Sulfasalazine (SAS) is one of the disease-modifying drugs that is effective in treating peripheral arthritis symptoms in IBD, but ineffective in axial CA [13]. Even though SAS is one of the oldest medications used to treat UC, its mechanism of action is not fully understood. SAS are prodrugs that are broken down by nitrogen reductase produced by the colon microbiota into sulfapyridine and 5-aminosalicylate (5-ASA), which are released into the distal intestine. It remains unclear whether one or more intestinal microorganisms play a role in this process of SAS activation [9].

More modern drugs for the treatment of IBD are 5-aminosalicylic acid (mesalazine). 5-ASA may provide mechanical benefits for mucosal healing by acting through PPARγ (peroxisome proliferator-activated receptor gamma) [7]. However, according to the latest ESCC 2024 guidelines, 5-AHAs are not recommended for treating CD, as their efficacy has not been proven [8].

The use of TNFα antagonists is the mainstay of therapy for both AS and CD. The efficacy of TNFα blockade underlies the putative pleiotropic effect of TNFα on many common pathways. Indeed, the effectiveness of anti-TNFα therapy in AS correlates with a decrease in the number of Th17 cells in the peripheral blood after treatment [12]. Despite this peripheral blood response, it is unclear whether it reflects the tissue activity of TNFα antagonists in IBD-related AS. Systematic reviews of TNFα antagonist therapy confirm the overall efficacy of TNFα blockade in IBD-related AS [23], including axial and peripheral spondyloarthritis. However, interventional studies reporting infliximab, adalimumab, and certolizumab pegol efficacy in the treatment of arthritis associated with IBD did not use objective criteria for diagnosis or for determining response/remission ofjoint disease [2]. Although limited research data are available to characterize the impact of joint disease activity [12], these biologics are considered first-line therapy in patients with AS and IBD.

The strong genetic association of both AS and IBD with genetic variants of IL23R and overlapping mechanisms involving the IL23/IL17 axis has emphasized the potential role of specific blockade of this pathway in drug development. In addition, increased levels of IL-17, but not TNFα, have been reported in the combination of AS with CD compared with active CD alone [28, 30]. It is very important to translate these findings into therapeutic strategies using drugs such as ustekinumab, guselkumab, secukinumab, and ixekizumab, which require evidence from clinical trials.

Vedolizumab is approved for induction and maintenance of remission in IBD [2]. Although vedolizumab (anti-α4β7) was originally developed as a selective drug, it may also affect systemic immunity. One theory is that blocking α4β7 homing in tissue increases the amount of these effectors in the peripheral blood, thereby enhancing systemic immune activation. A thorough analysis of studies revealed a reduction in the incidence of arthritis in CD and no increase in the incidence of arthritis in patients with UC treated with vedolizumab compared to placebo [14]. More recently, a systematic review of 11 trials in which vedolizumab was used in patients with extraintestinal manifestations of IBD demonstrated no effect on pre-existing arthralgia and arthritis, but a lower incidence of new rheumatic symptoms among vedolizumab users compared to placebo [9]. Although there are indications of benefit of vedolizumab in patients with a combination of CD and spondyloarthritis, a significant limitation of these analyses is the lack of a unified clinical phenotyping of inflammatory arthritis and prospective assignment of disease activity indices, which will need to be addressed in future analyses.

In addition to biological therapies, small molecule inhibitors of the immune pathway can also be used to treat both AS and CC. In particular, the non-selective Janus kinase (JAK) inhibitor tofacitinib is approved for the treatment of CD, RA, and PSA [13, 19], and a phase 3 trial in patients with AS is ongoing. Although tofacitinib did not meet efficacy endpoints in phase 2 trials in Crohn's disease [3], a significant biochemical response was observed, and retrospective analyses suggest its benefit in CD [6]. In initial studies, selective inhibitors of JAK-1 (filgotinib and upacitinib) and tyrosine kinase (TYK) have shown efficacy in Crohn's disease [4]. In addition, both filgotinib and upacitinib were found to be safe and effective in AS and PCa in their respective Phase 2 studies, while upacitinib met efficacy endpoints in a Phase 3 study in PCa [3,4]. These very encouraging results support the enthusiasm for the specific evaluation of their efficacy in patients with AS and CC.

Despite their similarities in pathogenesis, CD and AS retain unique aspects of the disease that may require an independent therapeutic approach. Although both pathologies can coexist in a patient, it is possible that they do not respond to common therapies, and therefore strategies for combining therapies should be evaluated. Treatments targeting novel mechanistic targets are being studied and also have great potential. Modulation of sphingosine-1-phosphate (S1P) is one such strategy to block the release of T cells from the lymph nodes into the bloodstream. In contrast to α4β7 blockade, this strategy can block both tissue and systemic inflammatory symptoms that depend on circulating lymphocytes [6].

In addition, anti-TL1A therapy is being developed for the treatment of IBD. Given the potential role of TL1A in joint inflammation, it remains to be seen whether this mechanism will also be effective in SA [6].

Fecal microbiota transplantation is being actively investigated for the treatment of IBD, but there is no convincing evidence for its use in routine clinical practice. The impact of fecal microbiota on inflammatory arthritis is unknown. Given the new knowledge about the potential role of strain-specific pathobionts in IBD-related AS, microbial therapy may play an important role in changing clinical outcomes [26].

Patients with AS who also have CD are a unique cohort of patients with distinct clinical, cellular, and microbial characteristics. Additional data using clinical diagnostic criteria and validated indices of joint disease activity are needed to define therapeutic responses in this unique group. Preclinical and clinical data defining the link between the gut microbiome and the inflammatory immune response in these pathologies have highlighted key pathways that can be targeted by therapeutic treatment. Combined with a multidisciplinary team approach to the such patients, future research will help guide the rational choice of targeted therapy based on the disease phenotype and develop a precise therapeutic approach to treating such comorbid patients.

Conclusions

1. The pathogenesis of AS and CD involves immune system disorders with common pathogenetic mechanisms leading to chronic inflammation. This is the basis for similar approaches to the treatment of both diseases.

2. Due to the presence of two complex diseases, each patient with AS and CD requires an individualized approach to the choice of treatment strategy. Doctors must carefully balance therapy for both diseases, regarding drug interactions, possible side effects, and the patient's specific needs. This approach will maximize the effectiveness of treatment and minimize the risk of developing new problems.

3. Biologics, such as TNF-α inhibitors, anti-integrin antibodies, Janus kinase inhibitors, and other newer drugs, are proving effective in treating both AS and Crohn's disease. Given the complexity of the combination of these diseases, the use of biologics can have a dual therapeutic effect by reducing inflammation in the joints and intestines, which is key to achieving stable remission

Further clinical trials and observations, the emergence of new developments in the treatment of patients with ankylosing spondylitis and Crohn's disease, including biologics and targeted therapies, are important breakthroughs in understanding the pathogenesis of these diseases and the ability to influence the underlying mechanisms of inflammation. The development and study of new drugs allows us to more accurately target specific molecular mechanisms of disease, significantly increasing the effectiveness of treatment, reducing inflammation and improving the quality of life of patients, while reducing the risk of side effects associated with traditional therapies.

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Стаття надійшла 12.02.2024 р.