CURRENT ASPECTS OF THE THERAPEUTIC APPROACH FOR ANKYLOSING SPONDYLITIS

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Abstract.

The article briefly presents modern methods of treatment of ankylosing spondylitis (AS), based on clinical guidelines and clinical trials. In a concise form, the main tasks and principles of non-pharmacological and drug exposure in AS are presented. The obligatory nature of physiotherapy exercises is emphasized, since its role in maintaining the functional status in this category of patients is well proven. At the same time, it is indicated that basic anti-inflammatory drugs in this disease play a purely auxiliary role, without affecting the progression of the disease. The pronounced clinical efficacy of all tumor necrosis factor-α inhibitors and IL-17 inhibitors is emphasized, some differences in their therapeutic effect are highlighted.

Key words: ankylosing spondylitis; therapy; tumor necrosis factor-α inhibitors; Janus kinase inhibitors.

Ankylosing spondylitis is a chronic inflammatory disease from the group of spondyloarthritis (SpA), characterised by obligatory involvement of the sacroiliac joints (SIJ) and/or spine with a potential outcome in ankylosis, with frequent involvement of entheses and peripheral joints in the pathological process [1].

Traditionally, the treatment of axial spondyloarthritis (axSpA), including AS, has been divided into conservative and surgical treatment. This presentation will review both well-studied and some little-known methods of treatment of this disease that have emerged in recent years, as well as promising directions of AS therapy.

Non-medicamentous therapies play an important role in the management of patients with axSPA. First of all, it should be noted that ASAS-EULAR (Assessment of SpondyloArthritis International Society - European League Against Rheumatism) recommends informing patients about the disease and explaining to them the benefits of regular exercise and smoking cessation [2]. It has been established that therapeutic physical exercise (TPE) in auxSpA is an important part of non-medication therapy and has a good clinical effect, especially in organised groups

under the guidance of an instructor. Supervised group exercises lead to a more pronounced improvement in quality of life, spinal mobility, and the patient's global assessment of his or her condition than unsupervised individual exercise programmes or their independent performance at home [3]. In turn, incorporating aerobic training, cardiorespiratory exercises and educational programmes into traditional LFC programmes can improve clinical outcomes, as can hydrokinesotherapy (exercise in water), although the development of the most effective physical rehabilitation packages and standardisation of approaches to their evaluation remain relevant.

The combined use of cardiorespiratory and strength exercises is promising, which, according to a small pilot study, had a pronounced positive effect on emotional state, fatigue, and performance during the day in patients with ascSPA [4]. High-intensity exercise reduces the symptoms of the disease (pain, fatigue, stiffness) and inflammatory activity, improves functional capacity and quality of life in patients with ascSpA. At the same time, the authors of the DESIR cohort analysis [5] showed no improvement in function in patients with early axSpA on the background of early-started physical therapy (at least 8 sessions under the guidance of an instructor during the first 6 months of the disease). In addition, it was shown that despite subjective reduction of inflammatory activity of the disease and significant improvement of physical activity in patients with both neurogenological axSpA (nraxSpA) and AS, the quality of life practically did not change, no positive dynamics of biomarkers of bone metabolism was observed. This indicates that although LFC is important for the health of patients with axSpA, it does not seem to affect bone metabolism.

According to recent data, some effect of mud therapy (Euganean thermal zone, Padua province, Italy) [6] and acupuncture (simple needlingtherapy) has been reported. However, high-quality randomised clinical trials (RCTs) are needed to confirm the efficacy of these methods. In general, most authors positively evaluate physiotherapy, but due to the low level of evidence of its effectiveness, they are cautious about its use, especially in patients with osteoporosis, ankyloses, and high disease activity. Thus, medical rehabilitation, or regenerative medicine, is an

important method of treating rheumatic diseases (RHD), including AS. However, it has not been recognised by specialists, which is primarily due to the insufficient use of evidence-based medicine in this area. At the same time, publications summarising the accumulated experience have recently appeared [7].

Patient organisations play an important role in axSPA. In different countries, health authorities establish patient advisory groups to involve patients in decision-making processes related to different parts of health care delivery. For example, the Expert Group for the Study of SpA at the Russian Association of Rheumatologists, organised in January 2014, includes the president of the domestic patient organisation 'Society for Mutual Assistance in Bekhterev's Disease', who participates in decision-making and development of clinical recommendations for the management and monitoring of AS patients [8]. Remote monitoring of patients, which has been actively developed recently, deserves special attention. As the data of Chinese authors show, out of 1201 patients with axSPA who installed the SpAMS (Smart-phone SpondyloArthritis Management System) programme on a smartphone, 57% had inactive disease or minimal disease activity at the beginning of observation, and after 13 months. - 79% of patients [9]. At the same time, indirect medical costs decreased by 16%. Remote patient monitoring systems provide real help as an alternative method of communication between the patient and the attending physician.

Thus, current evidence suggests a beneficial effect of some medical rehabilitation methods on patients with AS. However, their use in nraxSpA is poorly studied. The inclusion of aerobic and cardiorespiratory exercise and educational programmes into the treatment package may improve clinical outcomes, although there is a need to identify the most effective protocols [10].

Nonsteroidal anti-inflammatory drugs (NSAIDs). Traditionally, NSAIDs are the first-line therapy for AS, which is reflected in the clinical guidelines of all rheumatological associations [11]. NSAIDs allow good control of pain and stiffness in axSpA, improve functional capabilities of patients, and also reduce the severity of active sacroiliitis according to magnetic resonance imaging (MRI) [12]. At the

same time, no differences in efficacy between selective and non-selective cyclooxygenase 2 inhibitors are observed.

The most controversial issue is the effect of NSAIDs on the radiological progression of AS. For the first time, A. Wanders et al. [13] proved that the constant intake of celecoxib for 2 years slows down the progression of AS. Later, in a posteriori (post hoc) analysis, it was found that this effect was more pronounced in patients with an increased level of acute-phase inflammatory indices or high and very high activity according to the ASDAS (Ankylosing Spondylitis Disease Activity Score) index [14]. However, in a 2-year study of diclofenac, a reduction in the rate of AS progression could not be confirmed. Later, it was proved that the progression of structural changes of the spine in AS patients with a high index of NSAID intake was slowed down. This effect was observed almost exclusively in patients with baseline syndesmophytes and elevated CRP levels. The results of our study suggested that in early axSpA, continuous use of NSAIDs may reduce radiological progression of sacroiliitis.

Glucocorticoids (GCs). The use of GCs in patients with axSpA is discussed only when NSAIDs are ineffective or insufficiently effective [15]. Their administration in CPS is considered as one of the ways to treat spA. The efficacy of GC administration in CPS compared to placebo was proved in two RCTs (n=30) conducted at the end of the last century. Subsequently, in open trials, a good response to topical GC therapy for sacroiliitis was registered in more than 80% of cases, the average duration of improvement was more than 8 months, there was a decrease in osteitis signs according to MRI [16].

Not only in European, but also in the latest recommendations of American rheumatologists strictly do not show systemic use of HA. However, back in 2014, the results of a double-blind randomised placebo-controlled trial of 2 weeks' duration were published, showing that daily oral administration of prednisolone at a dose of 50 mg rapidly leads to marked clinical improvement in patients with active AS. Although the duration of the achieved effect was not specified, this method can apparently be used in clinical practice as a bridge therapy.

Synthetic baseline anti-inflammatory drugs (SBAD). Methotrexate and leflunomide, which are actively used in rheumatoid arthritis (RA), are not practically recommended for the treatment of AS, especially in the presence of axial manifestations only. They may, however, be prescribed for patients with peripheral arthritis or chronic uveitis. According to ASAS guidelines, sulfasalazine is the drug of choice for peripheral symptomatology [17]. However, all experts agree that SSRIs in AS have little efficacy and do not significantly affect the course of the disease.

This is a new class of drugs for the treatment of RA, which are used in RA, are being actively introduced in psoriatic arthritis (PsA) and are being studied in axSpA. To date, already three Janus kinase inhibitors - tofacitinib (TOFA, targeting JAK 1, 2 and 3), filgotinib and upadacitinib (both targeting predominantly JAK 1) - have shown clinical superiority over placebo in AS. The results of a 16-week placebo-controlled phase II RCT demonstrated significant efficacy of TOFA in active AS resistant to NSAIDs [18]. The highest frequency of achieving ASAS20 was observed at a dose of 10 mg/day, especially in patients with both elevated CRP levels and signs of active sacroiliitis according to MRI. No association between the dose of the drug and the frequency of achieving clinical response was observed. Differences in efficacy between TOFA and placebo were evident 4-8 weeks after initiation, indicating a slower development of response to therapy than with tumour necrosis factor-α (TNF-α) inhibitors.

The data of the phase II 12-week placebo-controlled RCT evaluating the efficacy of filgotinib 200 mg/day in patients with active AS refractory to NSAIDs [19] showed its statistically significant positive effect on disease activity, which was observed already at the 1st week. Improvement in ASDAS (Ankylosing Spondylitis Disease Activity Score) was recorded in 33% of patients in the study group and 2% of patients in the placebo group. As with TOFA, the clinical effect developed after 4-8 weeks of treatment. Other Janus kinase inhibitors (abrocitinib, itacitinib, peficitinib, ruxolitinib, GSK2586184) are currently being studied in various immunoinflammatory diseases. Active and rapid introduction of drugs of this group into clinical practice has contributed to the development of the first recommendations for their use and monitoring.

Genetically engineered biological drugs (GIBPs). Currently, there is a large number of different GIBPs, of which IFNα and interleukin 17 inhibitors are recommended by European, American, and domestic rheumatologists for axSpA [20]. Numerous data support their efficacy and safety in this disease.

IFNα in axSpA. Numerous studies conducted at the beginning of the 21st century proved the high efficacy of IFNα: infliximab (INF), etanercept (ETC), adalimumab (ADA), golimumab (GLM) and certolizumab pegol (CZP) in axxspA, both in nraxspA and AS. In the work of X. Baraliakos et al. confirmed the clinical efficacy and safety of 12-month IFNα therapy in real-world clinical practice, which is consistent with data obtained previously in RCTs.Initial short-term data from RCTs using IFNα were compared with data obtained from studies of historical cohorts of AS patients who did not receive IFNα. These studies were not long enough to establish a protective effect of such therapy on radiological progression of AS [21]. However, more recent studies using modern methods of assessing axSpA demonstrated a significant reduction in the rate of radiological progression with early and continuous IFNα therapy, especially if its duration exceeded 4 years. In a subsequent analysis, it was shown that radiological progression was significantly slowed in AS patients treated with IFNα for 4-8 years. The claim that long-term IFNα administration inhibits pathological bone proliferation in axSPA was further substantiated in other studies. In addition, when studying the effect of INF on bone tissue, it was found that it can significantly improve its metabolism, thus confirming the data on the increase in bone mineral density on the background of INF administration [22].

Given that GIBP molecules are very large and have a complex structure, and their production requires the use of labour-intensive biotechnologies, it is practically impossible to synthesise a bioanalogue identical to the original drug. Therefore, since the emergence of bioanalogues, their efficacy and tolerability have been actively compared with those of the original drugs. Thus, according to the data of Scandinavian authors, in bionaive patients with axSpA the duration of retention on therapy with INF and ETC biosimilars was the same as in original GIBPs. At the same time, switching from the original ETC to its biosimilar (SB4) was associated

with lower retention on therapy and reduced disease activity in the study group compared to the historical cohort receiving the original drug. In the group of patients with inflammatory arthritis, in 12.6% of cases after switching from the original ETC to its biosimilar, treatment was discontinued either due to the development of adverse events or for other subjective reasons [23]. At the same time, another biosimilar of ETC (GP2015) showed complete similarity to the original in terms of clinical efficacy and immunogenicity in psoriasis patients. In patients with early axSPA at least 12 weeks in remission on ETC biosimilar (Yisaipu®), continued treatment at full or half dose was superior in clinical effect to its complete discontinuation. When comparing the original INF with its biosimilar, a high concordance in terms of efficacy and safety parameters was also found.

IL17 inhibitors in axSPA. The role of IL17 in the pathogenesis of spA is being actively studied. Thus, by the end of 2019 alone, more than 3000 papers have been published on this topic. New drugs directed against this cytokine, such as secukinumab (SEC), ixekizumab (ICS), brodalumab, bimekizumab and netakizumab (NTC), are currently available or will soon become available.

The efficacy and tolerability of the first IL17 (SEC and ICS) were described in detail several years ago [20]. It was subsequently shown that in AS at the 3rd and 4th year of follow-up, SEC demonstrates sustained efficacy, independent of baseline CRP levels, and safety. By the 4th year of follow-up, almost 80% of patients showed no disease progression.

Interesting data were obtained when analysing the efficacy of IL17 inhibitors ICS in AS patients [22]. It was shown that patients who did not receive IFNα were more likely to achieve a good clinical effect (ASAS40) than those in whom they were cancelled due to primary or secondary ineffectiveness. In addition, in the COAST-V study, switching from effective ADA therapy to ICS did not lead to a loss of positive response to treatment, moreover, it was found to increase further. Also on the background of ICS therapy patients showed improvement of labour productivity and reduction of disease activity, which were achieved by the 16th week and were maintained at the 52nd week of follow-up.

Thus, at present, therapy of axSpA is not only symptomatic, but also pathogenetic treatment, which allows to modify the course of the disease. There are new developments that can significantly increase its effectiveness.

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