IJCNP, Volume 2, Issue 10, 2024 ISSN: 2995-536X
https://medicaljournals.eu/index.php/IJCNP

INTERNATIONAL JOURNAL OF COGNITIVE NEUROSCIENCE AND PSYCHOLOGY

Selection And Use of TNF-A Inhibitors in The Treatment of Ankylosing Spondylitis

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Abstract: A review of recommendations for the use of tumor necrosis factor α (TNF-α) inhibitors in patients with ankylosing spondylitis (AS) is presented. The data on the efficacy of TNF-α in patients with AS are presented. On the basis of international and domestic recommendations, indications for the appointment of this therapy, criteria for assessing its effectiveness and safety are formulated.

Keywords: ankylosing spondylitis; tumor necrosis factor-α inhibitors; efficiency; safety.

Ankylosing spondylitis (AS) is a chronic inflammatory disease from the group of spondyloarthritis (SpA), characterized by a mandatory lesion of the sacroiliac joints (SIJ) and / or the spine with a potential outcome in ankylosis, with frequent involvement in the pathological process of entheses and peripheral joints. The progression of the disease is primarily associated with the proliferation of bone tissue, manifested mainly by the growth of syndesmophytes (and / or enthesophytes) and the process of ankylosis, usually the SIJ [1]. The possibilities of AS therapy have now expanded significantly. A new class of drugs that has appeared over the past decade and a half - tumor necrosis factor α (TNF-α) inhibitors - provide rapid clinical improvement and a positive effect on the quality of life in SpA [2]. In addition, there is evidence that long-term use of them slows down the progression of the disease [3]. The first report on the clinical efficacy of TNF-α in SpA was published in 2000. These data were obtained in a pilot study of a small group of patients receiving infliximab (IFN) [4]. Later, the results were confirmed in prospective controlled studies [5]. In 2001, data appeared on the effectiveness of etanercept (ETC) [2], in 2004 - adalimumab (ADA), in 2008 - golimumab (GLM) [12] and in 2013 - certolizumab pegol (CP) [3].

Based on the studies carried out in 2003, the first recommendations for the use of TNF-α in AS were created [6]. Later, under the auspices of the International Expert Group for the Study of SpondyloArthritis (ASAS, Assessment of SpondyloArthritis International Society), they were systematically updated. In 2011, expanded recommendations on the use of TNF-α in patients with axial SpA (axSpA) [7] appeared, and in the summer of 2013, recommendations were published on the treatment of SpA to achieve the goal [8]. According to international and domestic recommendations, IFNO-α should be prescribed to a patient with a diagnosis of AS, established on the basis of the modified New York criteria, or to patients with axSpA, who meet the ASAS 2009 criteria [9]. In this case, a high activity of the disease should be present: BASDAI ≥4.0 (Bath Ankylosing Spondylitis Disease Activity Index) or ASDAS> 2.1 (Ankylosing Spondylitis Disease Activity Score), which persists despite standard therapy - at least two consecutively prescribed non-steroidal anti-inflammatory drugs (NSAIDs), used in a full dose for a total of at least 4 weeks in the axial variant of the disease, and in the peripheral (presence of arthritis) - NSAIDs in combination with sulfasalazine and local administration of glucocorticoids (GC). The positive opinion of the expert is separately taken into account [10]. For an objective assessment of disease activity, the ASDAS index is increasingly used as an integral indicator, which includes not only clinical, but also laboratory parameters [5].

It should be noted that, according to the opinion of Russian experts, it is possible to prescribe IFNO-α for AS not only with high disease activity, but also for patients without signs of activity from the musculoskeletal system if they have such unfavorable prognosis factors as recurrent anterior uveitis that does not respond to standard therapy, or progressive coxitis. It has been proven that in the early stages of SpA, the effectiveness of TNF-α is significantly higher [11]. At the same time, predictors of a good response to drugs in this group are: young age, short duration of the disease, low level of functional impairment, high level of C-reactive protein (CRP) and / or ESR, HLA-B27-positivity

and the presence of signs of active inflammation according to MRI data. [one]. At the same time, according to previous studies, it is the condition of patients with active inflammation (osteitis) according to MRI who are positive for HLA-B27 and have high CRP levels that are more likely to progress to the radiologically significant stage of sacroiliitis [7], i.e. e. to the AC. There is an opinion that such patients with typical clinical symptoms of SpA who do not have reliable X-ray signs of sacroiliitis, but with changes in the SIJ characteristic of SpA on MRI in the T2-FatSat / STIR mode can be regarded as patients with early AS [3]. According to another point of view, they are classified as patients with non-radiological axSpA (nr-axSpA) [11]. In the case of initiation of TNF-α therapy in patients with ax-SpA, including those with nr-axSpA, the drugs of choice according to the registered indications are CZP, ETC and GLM.

When a clinical effect is achieved (low activity or clinical remission), it is not recommended to immediately reduce the dose, increase the interval between drug injections or cancel it. The patient should receive the same dose of TNF-α for at least 3 months according to the standard administration regimen, and only then, depending on the clinical situation, it may be possible to gradually increase the intervals. A successful experience of increasing the intervals of administration of ETC, INF, ADA without loss of effectiveness in most patients has been described [5]. At the same time, the probability of maintaining the achieved result is higher in the presence of a short duration of the disease, high activity before the start of therapy with a rapid decrease in it in the first 3 months, and the absence of extra-skeletal manifestations [6].

It should be emphasized that when clinical remission is achieved during treatment with TNF-α, it is not recommended to completely cancel NSAIDs, since their effect on the progression of AS is manifested only with continuous administration and does not depend on the activity of the disease [12].

It has been shown that TNF-α has virtually no effect on X-ray progression (new bone formation) of the disease during the first 2–4 years of therapy. However, the results of later studies demonstrate that with their long-term use (over 4 years), the formation of syndesmophytes slows down significantly. Thus, the inhibition of the progression of the disease is observed only after prolonged and continuous use of TNF-α [8]. A number of studies suggest that the appointment of TNF-α in the early stages, when chronic foci of inflammation have not yet formed, probably prevents the development of structural changes and the growth of syndesmophytes. Currently, there are data on the maintenance of drug-free remission in patients with early SpA after a long course of this therapy [5].

There are some differences in the effectiveness between different TNF-α in terms of the effect on the extraskeletal manifestations of AS, which must be taken into account when choosing them. In inflammatory bowel diseases, it is necessary to use only monoclonal antibodies (INF, ADA, GLM, CZP), and in uveitis, their effectiveness is slightly higher than that of soluble receptors (ETC). However, if it is impossible to use monoclonal antibodies to TNFα in AS patients with uveitis, ETC can be an adequate substitute [13]. At the same time, with a high risk of activation of tuberculosis infection, the appointment of soluble receptors is more expedient.

Before and during treatment with TNF-α, patients should undergo regular examinations, during which the development of active tuberculosis should be excluded and the dynamics of the state of latent tuberculosis infection should be assessed. For this, screening for tuberculosis (chest X-ray, tuberculin diagnostics (Mantoux test with 2 TE), and / or a test for the release of interferon γ in vitro (QuantiFERON © -TBGold), and / or / or a skin test with a recombinant tuberculosis allergen (Diaskintest®). Patients should be monitored by a phthisiatrician for another 6 months after the completion of TNF-α therapy.

TNF-α therapy in carriers of hepatitis C virus (HCV) and especially hepatitis B virus (HBV) should be carried out with extreme caution and under close laboratory supervision. The risk of reactivation of the infection can be reduced if the viral load and the level of hepatic enzymes are monitored before the appointment of therapy and throughout its duration (at least once every 3 months). If necessary, treatment with TNF-α is carried out after preliminary antiviral therapy, which is prescribed by a hepatologist or infectious disease specialist, or against the background of such treatment. Treatment of TNF-α in patients with congestive heart failure can lead to its decompensation, therefore the use of TNF-α in such patients should be carried out with extreme caution and in accordance with the following principles: patients with compensated heart failure (NYHA class I and II) need conduct an echocardiographic study; patients with normal

ejection fraction (> 50%) can receive therapy with close monitoring of clinical manifestations; in patients with advanced heart failure, therapy should be interrupted; it is impossible to prescribe TNF-α to patients with decompensated heart failure.

Treatment with TNF-α is considered effective if, 12 weeks after its initiation, BASDAI decreases by 50% or at least 2 points, ASDAS decreases by more than 1.1. If during this period the patient does not achieve 20% improvement on the BASDAI, he should be transferred to another TNF-α. In this case, the effectiveness of the second TNF-α will be higher if the first is canceled due to loss of effectiveness, and not due to primary inefficiency [14, 15].

One of the reasons for the ineffectiveness of TNF-α may be the immunogenicity of these drugs. Chimeric drugs are more likely to induce an immune response than fully human TNF-α. By itself, the presence of antibodies to the drug does not correlate with a decrease in the effectiveness of treatment. Thus, the frequency of detecting antibodies to INF ranges from 12 to 44%, to ADA - from 1 to 87%, to ETC - from 0 to 18%, with no apparent effect on their effectiveness or the incidence of adverse reactions. At the same time, it has been demonstrated that a high level of antibodies to INF and ADA is associated with their lower efficiency [11]. Currently, there are works in which the use of methotrexate and, to a lesser extent, sulfasalazine for SpA allowed to reduce the level of antibodies and immunogenicity of drugs [10], to increase the duration of effective therapy. In general, with the development of secondary ineffectiveness of TNF-α, it is preferable to transfer the patient to a drug from this group, but with a different mechanism of action.

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