# Algorithm for monitoring patients with axial spondyloarthritis depending on the activity of the disease

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*Axial spondyloarthritis (axSpA) is actively treated with biologic disease-modifying antirheumatic drugs, but their efficacy decreases over time, leading to the development of exacerbation, the onset of severe and chronic pain, progression of structural changes and deterioration of quality of life, as well as significant economic losses. The international community is increasingly concerned about the problem of identifying difficult-to-treat (D2T) patients. In this context, it is necessary to develop strategies and markers for their identification and effective treatment. The authors propose a regimen of follow-up that represents an innovative approach to monitoring patients with D2T axSpA.*

***Keywords:*** *axial spondylitis; biologic disease-modifying antirheumatic drugs; difficult-to-treat patients; follow-up regimen.*
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***For reference:*** *Datsina AV, Erdes ShF. Algorithm for monitoring patients with axial spondyloarthritis depending on the activity of the disease. Sovremennaya Revmatologiya=Modern Rheumatology Journal. 2025;19(1):72–75.* ***DOI:*** *10.14412/1996-7012-2025-1-72-75*

In recent decades, after the start of the use of biologic disease-modifying antirheumatic drugs (bDMARDs) and targeted synthetic basic anti-inflammatory drugs (NSAIDs), the treatment of inflammatory rheumatic diseases has changed dramatically [1].

Spondyloarthritis (SpA) is a heterogeneous group of immune–mediated diseases that manifest themselves in a wide range of clinical phenotypes, including peripheral arthritis, axial changes, dactylitis, enthesitis, as well as skin and nail lesions (psoriasis), diseases of the eyes (uveitis), and the intestines (Crohn's disease, ulcerative colitis, and subclinical colitis) [2]. In addition, SpA is often accompanied by such concomitant diseases as obesity, type 2 diabetes mellitus, hypertension, metabolic syndrome, fatty liver disease, cardiovascular diseases and fibromyalgia [3].

SpAs are characterized by common clinical and genetic features, as well as similar changes detected by X-ray examination and magnetic resonance imaging (MRI). SpAs are classified as axial and peripheral types. Axial spondyloarthritis (axSpA) is further subdivided into non-radiological and radiological, the latter is traditionally called ankylosing spondylitis (AS) and is the key nosology of this group. For many years, the treatment of this disease has been limited to the use of NSAIDs, but it led to 40% improvement according to the criteria of the International Society for the Assessment of Spondyloarthritis (ASAS) in only 35% of patients, and to partial remission in 16% of cases [4]. It was the introduction of bDMARDs (such as tumor necrosis factor α [iTNFα] inhibitors, and then interleukin 17 [iIL17] inhibitors and Janus kinase inhibitors [iJAK]) into clinical practice that led to a breakthrough in the treatment of patients with active axSpA due to the rapid relief of most symptoms of the disease, normalization of acute phase parameters and a decrease in the severity of other signs of inflammation of the spine and joints, as well as extra-skeletal manifestations [5–7]. Data from randomized controlled trials showed that 24 weeks after the start of treatment, on average, 30% of patients with axSpA had an inactive disease according to the ASDAS index (Ankylosing Spondylitis Disease Activity Score). However, long–term observations showed that about 80% of patients continued this treatment one year after the start of using the first iTNFα, 60-70% after 2 years, and only every second patient after 5 years [8]. Thus, despite the emergence of highly effective methods of axSpA therapy, many patients stop responding to treatment over time, which leads to the development of exacerbation, severe and chronic pain, structural progression and deterioration of quality of life, as well as significant economic losses [6, 9, 10].

Today, in axSpA, as in many other rheumatic diseases, the tactic of "Treatment to target" (T2T) therapy is recommended, the goal of which is to achieve remission or low activity of the disease. A. Molto et al. [11] tried to assess the practical effectiveness of T2T in SpA in a prospective controlled open-label study designed for 1 year, which compared the strategy of tight-control (TC)/T2T with traditional therapy (TT) of axSpA. The study included 160 patients (80 in each group), whose mean age was 37.9±11.0 years, and the duration of the disease was 3.7±6.2 years; 51.2% of the participants were men. At the moment of inclusion in the study the average ASDAS index was 3.0±0.7, and the average ASAS-HI Health Index was 8.6±3.7. Quality of life improved by ≥30% in 47.3% of patients in the TC/T2T group, and in 36.1% of patients in the TT group ($p>0.05$). Adverse events (AE) were slightly more common in the TC/T2T group, but these differences did not reach statistical significance. Safety profiles were the same in both groups, although bDMARDs were significantly more often prescribed in the TC/T2T group and caused more allergic reactions at the injection site. The authors concluded that there was no significant difference in the effectiveness between T2T and TT strategies [11]. It became obvious that active therapeutic measures do not lead to the desired results in all patients.

Currently, the term "difficult-to-treat" (D2T) is becoming increasingly widespread in many fields of medicine; it allows to identify a special group of patients who do not achieve the goal of therapy against the background of optimal management tactics [6, 12]. The D2T criteria were proposed by the EULAR (European Alliance of Associations for Rheumatology) Working Group for

**Characteristics of patients with D2T axSpA**

| Source | Number of patients | Factors related to the development of D2T axSpA |
|---|---|---|
| S.F. Erdes et al., 2023 [6] | D2T axSpA was detected in 30 (6.6%) of 458 patients, mainly men (66.6%), with high clinical activity of the disease and inefficiency of at least 2 GEBDs. | The disease began with reactive arthritis. High laboratory activity of the disease, especially ESR (p=0.002); peripheral arthritis, coxitis (69.2%), and the condition after total joint replacement were detected more often. |
| D. Di Giuseppe et al., 2022 [16] | The study included 8,398 patients, of whom 6,056 (63% men, mean age 42 years) were prescribed the first GEBD/tsBAID; the proportion of patients who received 3, 4 or 5 drugs over the 3- year follow–up period was 8%, 3% and 1%, respectively. | The initial characteristics associated with multiple switching ( 3 GEBD/tsBAID) were female gender, shorter duration of the disease, higher overall assessment of the patient, concomitant diseases and the presence of psoriasis, but not uveitis. |
| C. Philippoteaux et al., 2024 [2] | The study involved 311 patients with axSpA, 88 (28.3%) of whom had D2T axSpA | In the D2T axSpA group, compared with controls, peripheral lesion (34.9 vs. 21.4%; p=0.015), inflammatory bowel disease (41.7 vs. 3.1%; p<0.001), fibromyalgia (17.4 vs. 4%; p<0.001) were more common; BASDAI values (63.7±16.5 vs. 58.8±14.7; p=0.015) and the level of CRP (42.0±31.3 vs 17.8±23.1 mg/dl; p=0.010) were also higher. |
| O. Fakih et al.,2023 [17] | The study included 22,932 patients, 2115 (19.59%) of whom had D2T axSpA | D2T axSpA was more common in women, in patients with peripheral lesions, psoriasis, hypertension, and depression (p<0.001 for each comparison). There were no differences in the frequency of deaths (p=0.87) |
| D. Dua et al.,2022 [18] | Of the 166 patients (71% men, mean age – 48 years), 62 (27%) showed signs of D2T axSpA | The presence of HLA-B27 (positive correlation), time from the moment of diagnosis to administration of GEBDs (sustained response to NSAIDs, negative correlation), concomitant chronic widespread pain (negative correlation), cumulative BASDAI on GEBD therapy (positive correlation) and response to GEBD (both iTNFα and iIL17). |

BASDAI – Bath Ankylosing Spondylitis Disease Activity Index.

Rheumatoid Arthritis (RA) and imply the persistence of disease activity against the background of the use of ≥2 bDMARDs [13]. However, in addition to inflammation, there are other factors that cause treatment ineffectiveness in many patients, leading to rapid radiological progression or a decrease in the quality of life. These include, for example, nociplastic pain associated with fibromyalgia, complications associated with immunotherapy (for example, hypertension and comorbid infections), lack of compliance, limited access to medical care, discrepancies between the results reported by patients and the assessments of specialists [14]. Given the difficulties described above, it is extremely important to identify specific causes that prevent remission and clearly distinguish between the subgroups of RA patients.

However, a generally accepted definition of D2T has not yet been formulated for axSpA. In a recent publication by D. Wendling et al. [15], the possibility of extrapolating the definition of D2T used for RA to patients with axSpA was discussed. Currently, more and more data on such patients is accumulating in the literature [2, 6, 16-18] and ASAS is working on agreed recommendations for D2T axSpA [19].

The preliminary results show that the duration of treatment with the first and second GEBD bDMARD is inversely proportional to the number of treatment failures [2, 16] (see the Table). Clinical and laboratory predictors of the effectiveness of the first course of iTNFα treatment in AS have already been studied [20, 21]. It has been shown that the lower the activity of the disease, the worse the response to therapy. Interestingly, patients with an unusually large number of different symptoms of the disease had a lower response rate to treatment and a shorter duration of response [22, 23]. In addition, other factors affect the likelihood of achieving remission in axSpA, including the duration of the disease, the risk of misdiagnosis, and the effectiveness and duration of therapy. In young patients with repeated drug switching, the T2T strategy does not often achieve its goal [24, 25]. At the same time, it has been established that male sex and an increase in CRP levels are predictors of the effectiveness of therapy [26, 27].

Due to the lack of an effective monitoring system for patients with axSpA when using the T2T strategy, we recommend considering a monitoring scheme for such patients depending on the activity of the disease. Disease activity is determined by the ASDAS index. Patients with high disease activity (ASDAS ≥2.1) should be examined by a rheumatologist once a month with general blood and urine tests, assessment of creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and CRP levels. Patients with moderate disease activity should be monitored every 6 months for correction of therapy with control tests performed every 3 months. In case of low disease activity or remission, a laboratory test is performed every 6 months. In patients with high disease activity MRI is performed every 3 months, and then every 12 months. Pelvic radiography is required once in 2 years in the absence of coxitis. When using a disease-modifying antirheumatic drugs, the effectiveness of treatment should be evaluated 12 weeks after its administration, and in the case of a good clinical response, a rheumatologist's consultation is indicated every 3 months or less frequently, with a control blood test (complete blood count with differentials, determination of creatinine levels, ALT, AST, CRP). In the case of poor tolerability of treatment or lack of effect, a consultation of a rheumatologist is recommended once a month. When adding a GEBD, a control examination of the chest organs and screening for tuberculosis are also necessary. Given that most patients take NSAIDs for a long time, it is recommended to perform an

esophagogastroduodenoscopy once a year in order to exclude NSAID-induced gastropathy.

Thus, the definition of intractable axSpA has not yet been developed, and further research is needed to better understand this condition. It remains to be seen whether multiple switching really indicates a difficult-to-treat disease. For such studies, it may be of interest to regularly determine the activity of the disease, record the causes of discontinuation of bDMARDs / targeted synthetic disease-modifying antirheumatic drugs, assess the dynamics of concomitant diseases and extra-articular manifestations during the follow-up, as well as identify the most significant diagnostic methods.

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Received/Reviewed/Accepted
24.10.2024/10.01.2025/13.01.2025

**Conflict of Interest Statement**

The investigation has not been sponsored. There are no conflicts of interest. The authors are solely responsible for submitting the final version of the manuscript for publication. All the authors have participated in developing the concept of the article and in writing the manuscript. The final version of the manuscript has been approved by all the authors.

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