TREAT TO TARGET – CASE SERIES OF PATIENTS WITH RHEUMATOID ARTHRITIS AND NO RADIOGRAPHIC PROGRESSION AT LONG-TERM FOLLOW UP

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Abstract. *Rheumatoid arthritis is a chronic autoimmune inflammatory joint disease characterized by pain, morning stiffness and symmetrical polyarthritis, leading to destruction of the affected joints in long term. The goal of the treat-to-target strategy in treating the disease is to achieve remission or low disease activity. Today, there are various conventional, biological and targeted synthetic disease-modifying antirheumatic drugs (DMARDs), which are widely used in rheumatological practice in order to personalize the therapeutic strategy for each patient. One of the main goals of treatment is to suppress and slow the radiographic progression of the disease, which leads to disability, impaired quality of life and reduced work capacity of patients. There are different scales for assessing joint destruction, based on radiographic examination of small and large joints of the hands and feet, due to which we can assess structural changes in dynamics. We present three clinical cases of patients with long-standing seropositive rheumatoid arthritis, treated with conventional and/or biologic DMARDs, who achieved long-term remission and minimal radiographic progression of the disease.*

Key words: *rheumatoid arthritis, remission, radiographic progression, treat to target*

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory joint disease characterized by pain, prolonged morning stiffness, and symmetrical erosive polyarthritis of the joints of the upper and lower extremities. According to the World Health Organization (WHO), as of 2019, the number of people suffering from rheumatoid arthritis worldwide amounted to 18 million people [1].

According to data from the European Federation of Pharmaceutical Industries and Associations (EFPIA) from 2008, there were 29,711 patients with RA in Bulgaria [2, 3]. Characteristic manifestations of the disease are inflammation and subsequent bone and cartilage destruction in the affected joints [4]. Despite the higher sensitivity of magnetic resonance tomography (MRT) and joint ultrasonography [5], the most commonly used method, which has established itself as the "gold standard" over the years for assessing structural changes and assessing disease progression, remains conventional radiography [6, 7]. Typical radiographic features of RA are: juxtaarticular osteoporosis, subchondral cysts, marginal erosions, joint space narrowing, subluxations and, in the end-stages, ankylosis [8]. In order to determine the degree of structural damage and monitor the effect of therapy, the first scales for assessing radiographic features in patients with rheumatoid arthritis were created many decades ago. In 1949, Steinbrocker et al. created the first qualitative scoring system that classified joint changes into four stages [9]. The disadvantage of this method is that it is too general and does not provide a quantitative assessment of the structural changes. In the following years, other scales were developed that are quantitative and semi-quantitative and are much more precise, such as those of Larsen, Sharp, Genant and others, which have undergone modifications over time [10, 11, 12, 13]. These tools assess the characteristic features of RA on a different number of joints from radiographs of the hands and feet. In recent years, the Sharp/van der Heijde score has become the standard in routine clinical practice and clinical trials due to its accuracy. [14]. The disadvantage of this method is that it requires experience and more time for assessment. A simpler system has been developed by van der Heijde et al. – Simplified erosion narrowing score (SENS), which uses a dichotomous method to assess erosions in 32 joints of the hands and 12 of the feet, as well as joint space narrowing in 30 joints of the hands and 12 of the feet. It is convenient for routine clinical practice and has equivalent accuracy compared to the more complex and time-consuming Sharp/van der Heijde score system [15].

Literature data show that the first structural damage is most often visualized in the second and third metacarpophalangeal joints, as well as the third

proximal interphalangeal joint of the hands [16], while erosive changes in the small joints of the feet, mainly metatarsophalangeal and proximal interphalangeal joints, may precede those in the hands [17].

We present three clinical cases of patients with long-standing seropositive rheumatoid arthritis, who are treated with conventional and/or biological DMARDs, in whom long-term remission was achieved and minimal radiographic progression of the disease was observed.

Clinical Case Descriptions

The first case is a 56-year-old Caucasian woman diagnosed with seropositive RA in 2004. The patient had bilateral polyarticular involvement of the metacarpophalangeal (MCP) joints, ankle joint pain, and elevated acute phase reactants. She was treated with Chloroquine and Nonsteroidal anti-inflammatory drugs (NSAIDs) until 2009, when she started treatment with Methotrexate 20 mg weekly. The dose was reduced to 15 mg/week after achieving clinical and laboratory remission and the therapy continues to this day. In 2020, due to high disease activity (DAS-28 > 5.1), Adalimumab was added to the therapy. In a comparative assessment of the radiographic images of the palms and fingers over the years (2009, 2011, 2013 and 2022) no significant changes were detected (SENS 7 -> SENS 9).

The second clinical case that we present is of a 67-year-old Caucasian woman, diagnosed with seropositive RA in 2007. She has had arthritis in MCP and metatarsophanalgeal (MTPS) joints II, III, IV bilaterally. Musculoskeletal ultrasound confirmed the synovitis in the listed joints. The patient had elevated values of acute phase reactants and positive rheumatoid factor. The patient was treated for 12 months with NSAIDs, Sulfasalazine 2 g/daily, Methylprednisolone 8 mg/daily per oral. Due to unsatisfactory effect, treatment with Methotrexate was started in 2009, which was discontinued in 2011 due to adverse drug reaction(ADR) from the gastrointestinal tract (nausea and vomiting). Due to persistent high disease activity, treatment with Tocilizumab 8 mg/kg monthly intravenously was started. One year later, the patient achieved complete clinical and laboratory remission. Treatment with anti-interleukin-6 continues to the present. Comparative radiography of the hands and palms from 2013 and 2022 shows lack of radiographic progression of the disease (SENS 10).

The third case is a 32-year-old man, Caucasian, diagnosed with Juvenile idiopathic arthritis in 2007 due to recurrent arthritis of the left knee joint, who was treated with NSAIDs, Sulfasalazine, Leflunomide, Methylprednisolone 8 mg daily. In 2010 the patient's had complaints of pain and swelling in the left knee joint, both ankle and wrist joints, morning stiffness for about 1 hour. He had positive Rheumatoid factor. The patient was diagnosed with seropositive RA and treatment with Methotrexate 15 mg/week and Adalimumab 40 mg/subcutaneously every 14 days was started and remission was achieved. In April 2014 the therapy with Adalimumab was discontinued at patient's own request. Six months later, an exacerbation of the disease was observed, where the knee and the ankle joints were inflamed, and then biological treatment with Adalimumab was resumed again. In comparative radiography from 2010 and 2022 of the hand, no significant radiographic structural damage were observed in the radiographic images (SENS 4 -> SENS 6).

Radiography

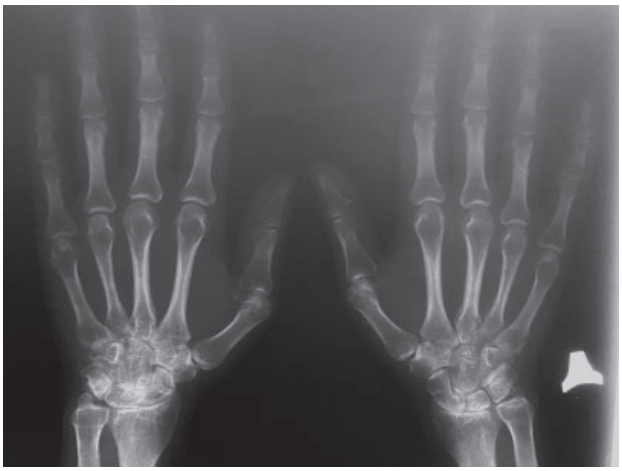


Fig. 1. Radiography – anterior-posterior of the hands – July 2011 (Case 1)



Fig. 2. Radiography – anterior-posterior of the hands – December 2022 (Case 1)



Fig. 3. Radiography – anterior-posterior of the hands – January 2013 (Case 2)



Fig. 4. Radiography – anterior-posterior of the hands – August 2022 (Case 2)



Fig. 5. Radiography – anterior-posterior of the hands – July 2010 (Case 3)



Fig. 6. Radiography anterior-posterior of the hands – August 2023 (Case 3)

Discussion

Treat-to-target strategy has been used for decades in medicine, but it was introduced in the field of endocrinology in the treatment of type 2 diabetes [18]. It is a treatment strategy that sets clear therapeutic goals that will lead to better long-term outcomes for patients. In 2010, the treat-to-target approach was introduced in rheumatology by defining ten recommendations for the treatment of Rheumatoid arthritis. The main principle of treatment is setting a therapeutic goal. In rheumatology, this measure is remission or low disease activity, close monitoring of the patient, and adaptation of the therapy if the goal cannot be achieved [19]. Many tools for measuring disease activity have been introduced in rheumatology practice. The most commonly used are the Disease activity score – 28 (DAS-28), Clinical disease activity index (CDAI), and Simplified disease activity score (SDAI) [20, 21, 22]. Despite their widespread use and the attempt to refine the objective assessment of disease activity, they cannot reflect the disability of patients in term of radiographic changes. This is one of the reasons why multifactorial assessment has become the leading one in disease staging.

In the presented patients, who have had the disease for many years and are on different therapies – with conventional and/or biological DMARDs, the radiographic progression of the hands was assessed using the SENS method. It is noteworthy that against the background of treatment, the characteristic destructive changes of rheumatoid arthritis do not oc-

cur during the period of follow-up of the patients. In essence, no significant radiographic progression compared to the baseline images is observed.

Over the years, especially after the introduction of biological DMARDs, a great deal of experience has been gained and a large number of clinical trials have been conducted regarding their effectiveness and safety [23, 24, 25, 26]. Undoubtedly, their use in patients with RA improves the quality of life, functional capacity and reduces the development of structural damage [23, 24, 25, 26].

According to a clinical study in 1997 by Drosos et al., in which radiographic changes of 30 patients with rheumatoid arthritis treated with Methotrexate and 30 patients treated with D-penicillamine were studied, it turns out that in the Methotrexate group there is a significantly slower radiographic progression of the disease. Even in 15 of the patients no progression was registered [27]. Our clinical observations confirm the data published in the international literature. In recent years, data from an increasing number of clinical trials also confirm the lack of significant radiographic progression in patients treated with biological therapy [23, 24, 25]. Numerous clinical trials have been conducted regarding the benefits of combination therapy over monotherapy in the treatment of RA. The PREMIER study included 799 patients with RA. The results confirmed that the combination therapy of Methotrexate with Adalimumab was superior to monotherapy with either drug, both in terms of rapidity of effect, low disease activity and remission, and in terms of radiographic progression [28].

Although Tocilizumab is indicated for use as monotherapy, there is evidence in the literature that the combination therapy of Tocilizumab with Methotrexate is more effective in suppressing radiographic progression[29].

Conclusion

Early diagnosis, compliance to the therapy , strict patient monitoring, and switching from one drug strategy to another on time are key factors in achieving sustained remission, preserving functional and work capacity, and preventing disability in patients with RA.

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Постъпил за печат: 29.01.2025 г.

Submitted: 29.01.2025

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