Rheumatol. Forum
2022, vol. 8, No. 4, 148–155
 ISSN: 2720-3921, e-ISSN: 2720-3913 DOI: 10.5603/RF.2022.0021
VIA MEDICA
www.journals.viamedica.pl

Brygida Kwiatkowska

Department of Early Arthritis, National Institute of Geriatrics, Rheumatology and Rehabilitation, Warszawa, Poland

Steps towards standard medical treatment of rheumatoid arthritis: A practical guide

ABSTRACT

Rheumatoid arthritis (RA) is the most common inflammatory rheumatic disease, involving the long-term use of drugs that act by different mechanisms to treat this disease in an effective way. Current eligibility criteria enable early diagnosis of RA, which should result in early treatment. An important component of therapy is good cooperation with a patient, who has an impact on modifiable factors that affect the course of RA and the efficacy of treatment, such as treatment of periodontal infections, weight reduction and smoking cessation. RA treatment should follow the treat-to-target (T2T) strategy, according to which patients should be continuously monitored for treatment efficacy and therapy should be adjusted to achieve improvement after 3 months and disease remission after 6 months. There is an increasing number of drugs available that allow a more precise choice of therapy, however, there is still little availability of drugs reimbursed under the B.33 Drug Program.
During the course of therapy, it is also necessary to monitor the safety of the treatment used.

Rheumatol. Forum 2022, vol. 8, No. 4: 148–155

KEY WORDS: rheumatoid arthritis; modifiable RA risk factors; methotrexate; T2T strategy; conventional disease-modifying drugs; disease remission

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic immune-mediated inflammatory disease (IMID) with a varied course involving the possibility of using multiple drugs with different mechanisms of action throughout the patient's life. The major symptoms of RA affect the joints; however, this disease also causes irreversible changes in many organs and body systems.

Rheumatoid arthritis is more likely to affect women, with the peak incidence occurring during the most active period of life, i.e. 30–50 years of age. In Poland, RA affects approximately 0.9% of the adult population [1].

The basic principles of successful treatment of this disease are based on:

— the earliest possible diagnosis and immediate treatment as soon as the diagnosis is made;
— changes in modifiable risk factors for a worse disease course;
— conducting treatment according to a T2T strategy;
— use of drugs in accordance with current recommendations;
— use of drugs in accordance with current recommendations;
— constant cooperation with the patient and change of modifiable factors that affect the course of the disease;
— continuous monitoring of treatment in terms of safety and efficacy;
— maintenance of disease remission or low disease activity (Fig. 1).

DIAGNOSIS OF RA

For the diagnosis of RA, it is useful to rely on current classification criteria of the American College of Rheumatology/European Alliance of Associations for Rheumatology (ACR/EULAR) [2, 3] (Fig. 2).

The ACR/EULAR criteria have high sensitivity and specificity and are mainly based

Address for correspondence:
prof. dr hab. n. med. Brygida Kwiatkowska
Department of Early Arthritis, National Institute of Geriatrics, Rheumatology and Rehabilitation
ul. Spartańska 1, 02–637 Warszawa
e-mail: brygida.kwiatkowska@spartanska.pl

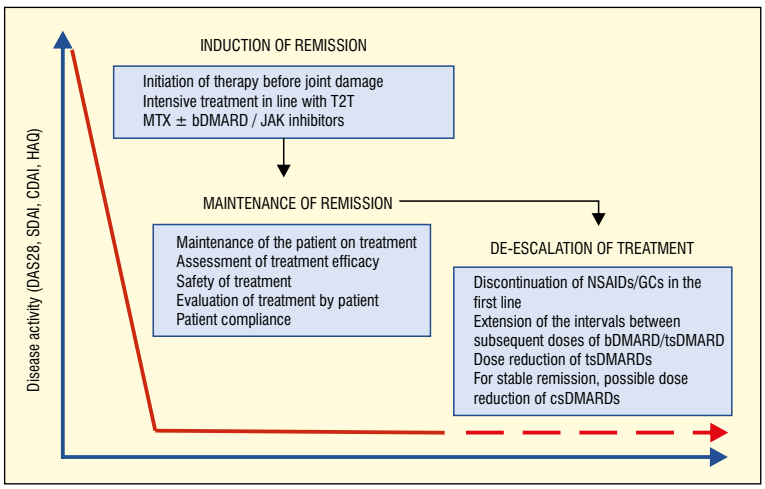

Figure 1. Basic principles of RA treatment (based on [2]). bDMARD — biologic disease-modifying anti-rheumatic drugs; csDMARD — conventional synthetic disease-modifying antirheumatic drugs; JAK — Janus kinase; MTX — methotrexate; tsDMARD — targeted-synthetic disease-modifying antirheumatic drugs

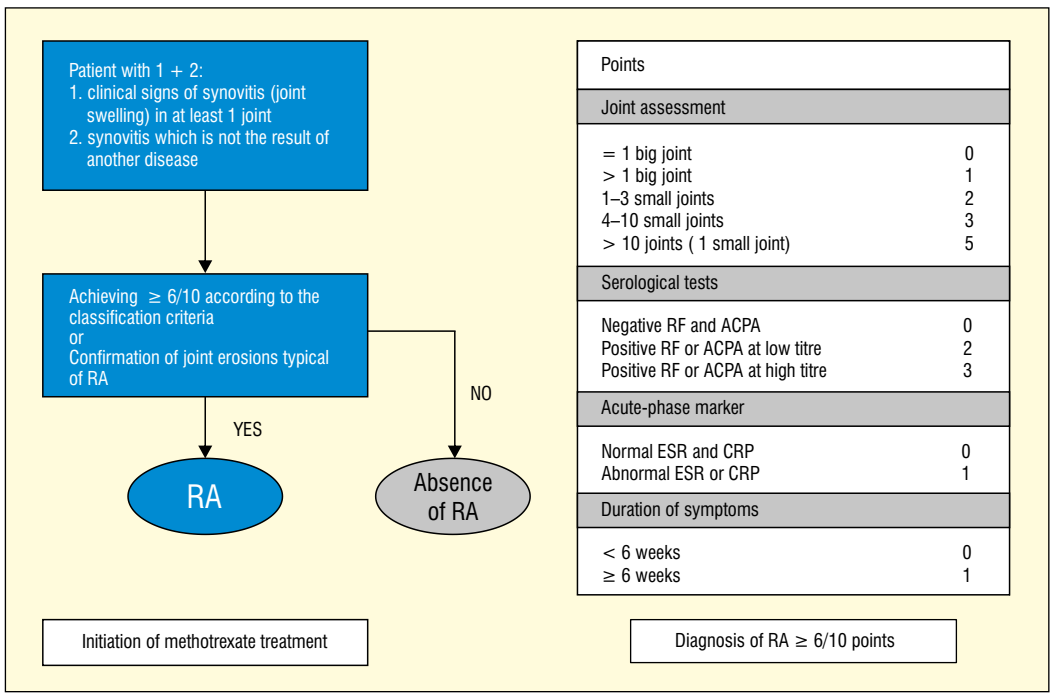

Figure 2. Diagnosis of RA (based on [2, 3]). ACPA — anti-citrullinated protein antibodies; CRP — C-reactive protein; ESR— erythrocyte sedimentation rate; RA — rheumatoid arthritis; RF — rheumatoid factor

on anamnesis, musculoskeletal examination, basic blood tests and do not include imaging studies. Recently, however, the imperfection of these criteria in terms of the high scoring of positive serological tests has been highlighted, which results in delays in diagnosis in the group of patients in whom rheumatoid factors (RF) and anti-citrullinated protein antibodies (ACPA) are not detected. Both RF and ACPA are present in approximately 50–70% of RA patients [4]. In patients with absent RF and ACPA, the diagnosis of RA is only possible with a much higher number of involved joints, high ESR (erythrocyte sedimentation rate) and/or C-reactive protein (CRP) levels. **Therefore, it should be noted that in a group of patients who present with swelling of at least one joint, have high CRP levels or accelerated ESR and it is not possible to specify diagnosis, it is not advisable to wait for the diagnosis to be established — EULAR recommendations for early arthritis should be followed. This means that in such a situation methotrexate should be initiated as soon as possible at doses recommended as in RA [5].**

CHANGES IN MODIFIABLE RISK FACTORS FOR A WORSE DISEASE COURSE

There are environmental factors that have a proven impact on the development of RA and its worse course. They include:
— smoking,
— periodontitis,
— overweight/obesity.

Smoking has a proven effect on faster progression of radiographic changes [6], while the severity of periodontal disease correlates with greater RA activity [7]. Sarcopenic obesity is often found in RA patients. It was found that obesity in the course of RA results in higher disease activity and reduces the efficacy of RA treatment [8].

TREATMENT ACCORDING TO THE T2T STRATEGY — GOAL-DIRECTED TREATMENT (REMISSION/LOW DISEASE ACTIVITY)

GROUPS OF DRUGS USED IN THE TREATMENT OF RA (TAB. 1)

TOOLS FOR ASSESSING RA ACTIVITY

Tools such as the shortened version of the disease activity index (DAS28, DAS28OB and DAS28CRP), clinical disease activity index (CDAI) and simplified disease activity index (SDAI) are most commonly used for assessing disease activity.

The most commonly used scales include DAS28 and SDAI, and they are applicable for eligibility for the B.33 Drug Program.

DAS28 SCALE

The DAS28 scale is based on the assessment of 28 joints for pain and swelling, as well as on ESR or CRP levels and disease activity as assessed by the patient on a linear scale from 0 to 100 mm. The above-mentioned data are then recalculated according to the mathematical formula of disease activity. Ready-to-use calculators for calculating DAS28 are available online, for example at https://medycynaistatystyka.pl/skala-das28; https://www.sandoz-med.pl/reumatologia/kalkulatory/kalkulator-DAS28 (Fig. 3).

Table 1. Drug groups for the treatment of RA

Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs)	Methotrexate (MTX) Leflunomide (LEF) Sulfasalazine (SSA) Hydroxychloroquine
Biological drugs, including biologic disease-modifying anti-rheumatic drugs (bDMARDs) that are bioequivalent	**TNF-α inhibitors** Infliximab Etanercept Adalimumab Golimumab Certolizumab **IL-6 inhibitors** Tocilizumab Sarilumab **Drugs modulating T-cell costimulation, CD28 + abatacept** **Anti-CD-20 monoclonal antibodies to a subpopulation of B lymphocytes** Rituximab
Targeted-synthetic disease-modifying antirheumatic drugs (tsDMARDs)	**Janus kinase (JAK) inhibitors** Tofacitinib Baricitinib Upadacitinib Filgotinib
Glucocorticosteroids (GCs)	Methylprednisolone Prednisolone Prednisone
Nonsteroidal anti-inflammatory drugs (NSAIDs)	Selective and non-selective COX inhibitors
Analgesics	Paracetamol, weak opioids, strong opioids*

*recommended only for patients in whom the above-mentioned pharmacological treatment or surgical treatment cannot be used due to co-morbidities.
TNF-α — tumour necrosis factor α

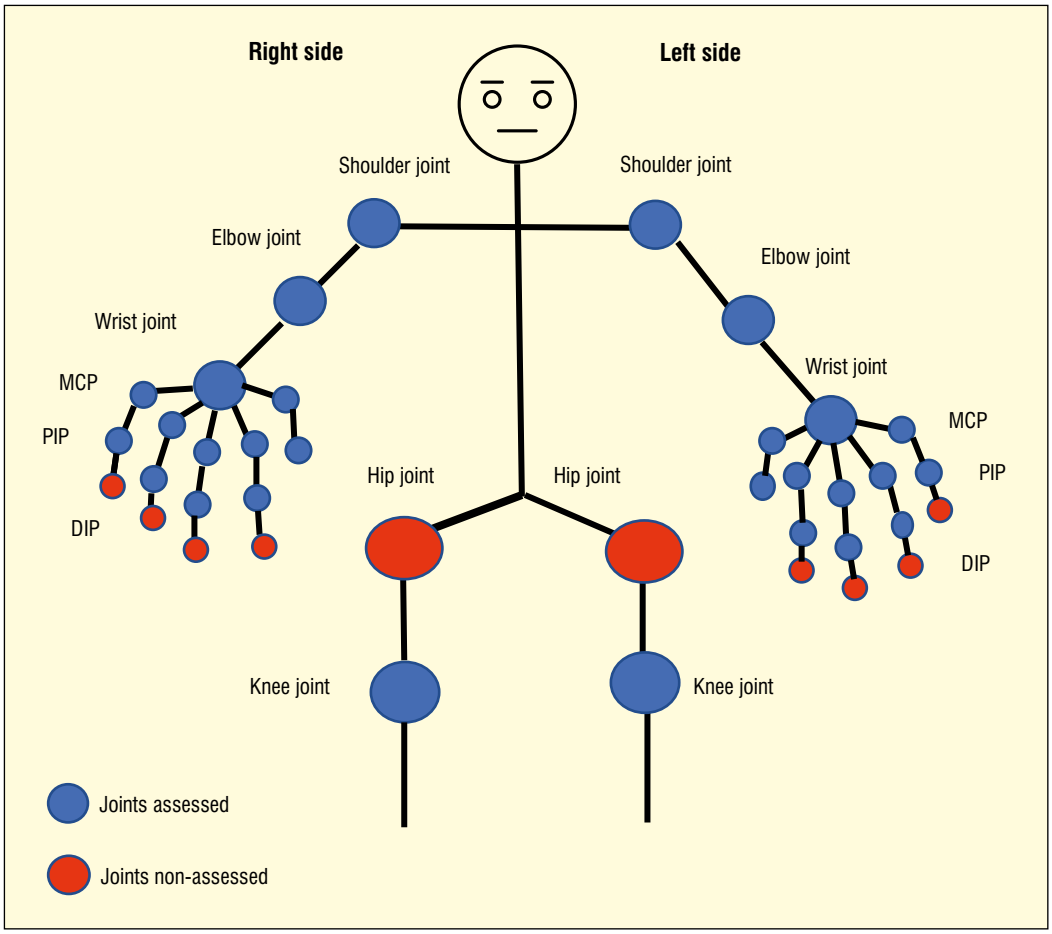

Figure 3. Joints assessed by the DAS28 calculator. DIP — distal interphalangeal joints; MCP — metacarpophalangeal joints; PIP — proximal interphalangeal joints

Range of possible DAS28 scores: 0–9.4.

Disease activity score by DAS28:

— < 2.6 pts — remission;
— ≤ 3.2 — low disease activity;
— > 3.2 and ≤ 5.1 — moderate disease activity;
— >5.1 — high disease activity.

Treatment response assessment:

— good response — reduction in activity by ≥ 1.2 and low activity;
— moderate response — reduction in activity by > 0.6 and < 1.2, and low or moderate activity or a change by ≥ 1.2, and high or moderate activity;
— no response — change by < 0.6 or < 1.2 and high activity.

The DAS28 scale does not assess joints of the feet. For patients whose arthritis predominantly affects joints of the feet, other scales should be used for the assessment of disease activity and such patients should be selected for the Drug Program according to non-standard therapy.

SDAI SCALE

The SDAI scale, like DAS28, is based on the assessment of 28 joints. The number of swollen and painful joints, disease activity as assessed by patient and physician on a visual analogue scale (VAS) (1–10) are assessed, as well as CRP levels (mg/dL).

The SDAI calculator is also available online, for example at https://bml.pl/narzedzia/kalkulatory/reumatologia/sdai-simplified-disease-activity-index; https://www.sandoz-med.pl/reumatologia/kalkulatory/kalkulator-sdai.

SDAI = number of painful joints + number of swollen joints + VAS of disease activity by patient (0–10 cm) + VAS of disease activity by physician (0–10 cm) + CRP levels (0.1–10 mg/dL)

Range of possible SDAI scores: 0.1–86.

Disease activity score by SDAI:

— ≤ 3,3 — remission;
— ≤ 11 — low disease activity;
— > 11 and ≤ 26 — moderate disease activity;
— > 26 — high disease activity.

Treatment response assessment:
— Major improvement — reduction by > 21;
— Moderate improvement — reduction by 10-21;
— No improvement — reduction by ≤ 9.

CDAI CALCULATOR

The CDAI calculator is a simplified form of the SDAI calculator. It is also based on an assessment of 28 joints and does not involve laboratory tests or calculators.

CDAI = number of painful joints + number of swollen joints + VAS of disease activity as assessed by patient (0–10) + VAS of disease activity as assessed by physician (0–10)

Range of possible CDAI scores: 0.1–76.
Disease activity score by CDAI:
— ≤ 2.8 — remission;
— > 2.8 and ≤ 10 — low disease activity;
— > 10 and ≤ 22 — moderate disease activity;
— > 22 — high disease activity.

EUROPEAN RECOMMENDATIONS IN LINE WITH CURRENT EUROPEAN RECOMMENDATIONS AND T2T

The European Alliance of Associations for Rheumatology (EULAR) has defined poor prognostic factors that should be taken into account when selecting therapy in RA (Tab. 2)

INITIAL THERAPY

Immediately after the diagnosis of RA, therapy with MTX should be initiated. MTX is still considered the most important first-line drug due to its good safety profile and high efficacy. A therapeutic dose of MTX 20–25 mg per week should be achieved within 6 weeks. However, if a patient does not tolerate the target dose, the highest well-tolerated dose by the patient should be maintained. In addition to its therapeutic effect on RA, MTX was found to reduce the risk of pulmonary fibrosis, cardiovascular complications and the risk of death from heart failure. Even recent studies have also shown a reduced risk of developing type 2 diabetes (T2D) in RA patients [10–12]. Increased efficacy can be achieved by initiating subcutaneous MTX therapy that which improves efficacy by achieving higher therapeutic levels with lower MTX doses (as observed with doses ≥ 15 mg per week) and by faster therapeutic effects that are achieved after only 4–6 weeks. Moreover, combination therapy with MTX and low-dose GCs (prednisone < 7.5 mg or equivalent according to EULAR) is recommended for a short period of time (maximum 3 months). The most beneficial approach for the patient is to initiate glucocorticoid withdrawal by reducing the dose as early as the 6–8th week of treatment with MTX or other csDMARDs. **The need for short-term administration of GCs is due to an increase in complications during prolonged use of GCs, including an almost threefold increase in the risk of death and cardiovascular complications [14].** In the case of contraindications to MTX therapy or early clinically significant intolerance to MTX, another csDMARD should be used, such as LEF at standard doses (usually 10–15 mg once daily) [15] or SSA at a target dose of 2–3 g/day. For LEF, the 10 mg dose is a therapeutic dose in most patients and adverse effects are more frequently observed with the 20 mg dose. However, recent studies have revealed quite different levels of the active metabolite of LEF (A77 1726) in patients receiving the same dose, which indicates the benefit of measuring its serum levels to select the optimal and effective therapeutic dose [16]. Hydroxychloroquine is not recommended as a csDMARD which can be used in monotherapy (especially in patients with extremely low disease activity) (Fig. 4).

TREATMENT IN CASE OF NO IMPROVEMENT AFTER 3 MONTHS OF THERAPY WITH MTX OR ANOTHER CSDMARD AND/OR FAILURE TO ACHIEVE REMISSION AFTER 6 MONTHS

In the absence of improvement after 3 months of therapy with MTX or another

Table 2. Factors for poor prognosis in RA patients according to EULAR [9]

— Persistent moderate or high disease activity despite treatment with csDMARDs as assessed by current tools
— High levels of acute phase reactants (ESR and/or CRP)
— Large number of swollen joints
— Presence of RF and/or ACPA, particularly at high levels
— Presence of early erosions
— Ineffective two or more csDMARDs

ACPA — anti-citrullinated protein antibodies; CRP — C-reactive protein; csDMARDs — conventional synthetic disease-modifying antirheumatic drugs; ESR — erythrocyte sedimentation rate; RF — rheumatoid factor

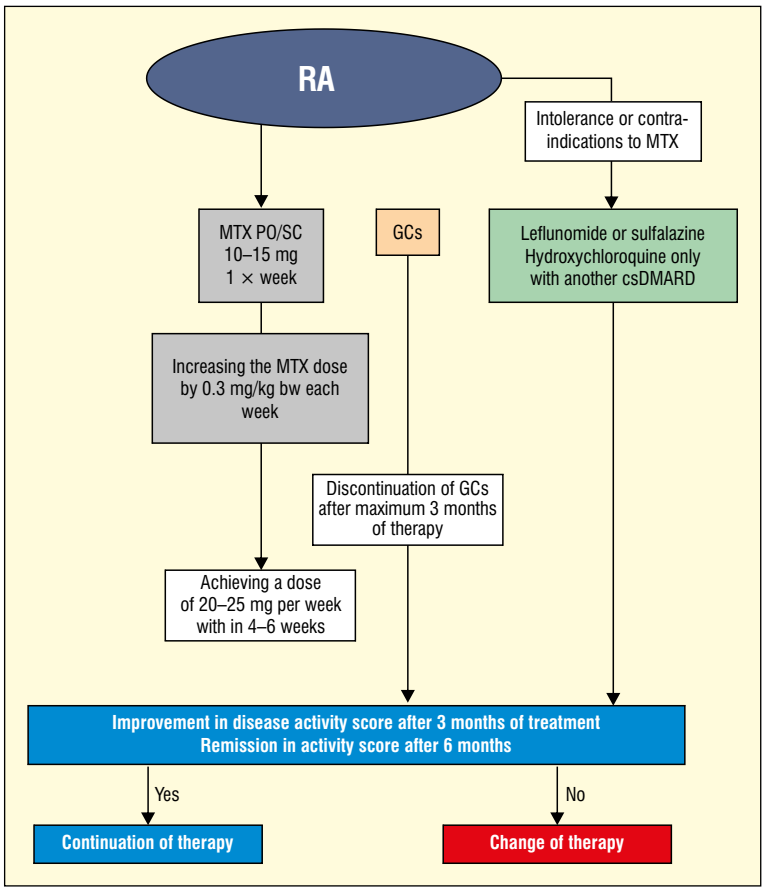

Figure 4. Initial treatment of RA as soon as the diagnosis is made. csDMARD — conventional synthetic disease-modifying antirheumatic drugs; GCs —glucocorticosteroids; MTX — methotrexate; PO — per os; RA — rheumatoid arthritis; SC — subcutaneous

csDMARD in patients with poor prognosis factors, the addition of bDMARDs or tsDMARDs should be considered. **In current drug programs for the active form of RA (B.33 Program), it is possible to use bDMARDs or JAK inhibitors already after 3 months of ineffective therapy with a csDMARD when factors of poor prognosis are identified, which is in line with recommendations.** In patients in whom no poor prognosis factors are identified, csDMARDs should be replaced with another csDMARD or combination therapy with two csDMARDs should be used. **It should be noted that in all patients who were previously treated with MTX and such a therapy was ineffective, the next step in treatment is combination therapy with MTX + an originator/biosimilar biologic drug or a JAK inhibitor. Patients receiving combination therapy with MTX achieve better treatment outcomes (Fig. 5).**

If sustained remission* is achieved in an RA patient, the next step can be:

— discontinuation of GCs and NSAIDs, provided that they were still being administered;

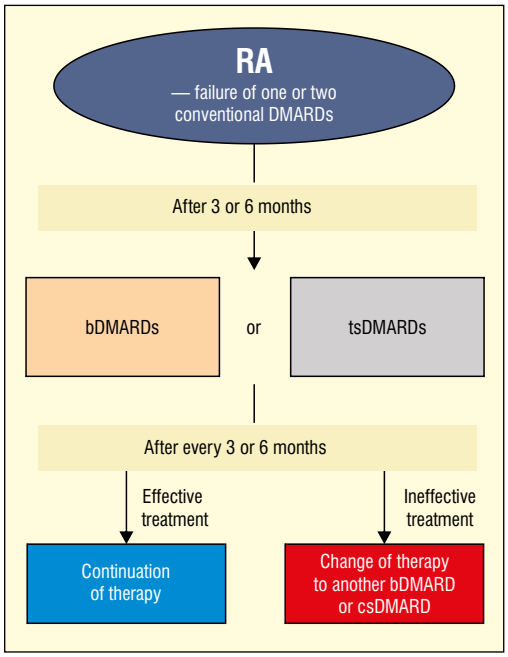

Figure 5. Further treatment steps in case of failure of one or two csDMARDs. bDMARD — biologic disease-modifying anti-rheumatic drugs; csDMARD — conventional synthetic disease--modifying antirheumatic drugs; DMARD —disease-modifying antirheumatic drugs; RA — rheumatoid arthritis; tsDMARD — targeted-synthetic disease-modifying antirheumatic drugs

— prolonging the intervals in the administration of biologics or reducing the dosage of JAK inhibitors, individually adjusting the dose for each patient so as to maintain the remission achieved.

If sustained remission is still maintained, the dose of csDMARDs should be reduced. For MTX, the dose should not be less than 10 mg per week.

*__Sustained remission__ — defined as remission if sustained for a minimum of 6 months, as in line with Boolean ACR/EULAR remission criteria

THE ROLE OF TNF-α INHIBITORS IN THE TREATMENT OF RA

TNF-α inhibitors are drugs that have been used in the treatment of RA for many years, and rheumatologists have the most experience in their use. At the same time, there are numerous biosimilars (biologics that are bioequivalent) of reference drugs such as infliximab, etanercept and adalimumab, resulting in a very significant reduction in their price and cost of therapy. This should lead to a wider use of these drugs and greater availability of biological treatment for RA patients. Unfortunately, that is not the case. The reason for this is still unchanged eligibility criteria under the current drug program, where patients must have very high disease activity (DAS28 > 5.1) and the possibility to reimburse treatment only under drug programs operating mainly in hospital centres.

The efficacy of new drugs — JAK inhibitors — was mainly compared with adalimumab, which proves the continued strong position of this drug and its documented efficacy.

Contraindications to the receipt of adalimumab (and other TNF-α inhibitors) include [15]:

— hypersensitivity to an active ingredient or to any of the excipients;
— active tuberculosis or other severe infections such as sepsis and opportunistic infections; — moderate to severe heart failure — class III/IV according to New York Association Heart (NYHA) Classification.

Adalimumab does not need dosage adjustment in elderly patients.

Adalimumab, like other TNF-α inhibitors (excluding certolizumab), should be used during pregnancy only if absolutely necessary. This drug can be used during breastfeeding [16].

THERAPY SAFETY MONITORING

All RA patients need to be monitored not only for the efficacy of the treatment used, but also for its safety.

All therapies used for the treatment of RA increase the risk of infections.

The use of GCs, especially in high doses, exacerbates the risk of infections.

Monitoring the safety of individual therapies, in addition to the possibility of infection, should be based on the risk of adverse effects that are related to the mechanism of action of a given drug.

VACCINATION OF RA PATIENTS

Rheumatoid arthritis patients are recommended a range of vaccinations in line with the current 2019 European recommendations [17].

— Necessary vaccinations should preferably be administered before starting therapy with an immunosuppressive drug that particularly causes B-lymphocyte depletion (rituximab).
— Non-live vaccines can be administered during the use of GCs and DMARDs.
— Live vaccines can be used with caution in RA patients.

The following vaccinations are recommended: influenza vaccination, pneumococcal vaccination, SARS-CoV-2 vaccination, hepatitis A and B vaccination (at risk), and herpes zoster vaccination (dependent on a type of therapy used).

SURGICAL PROCEDURES

Due to the increased risk of infections, it is recommended that major surgical procedures be performed prior to the inclusion of biologics and, if this is not possible, it is also recommended that therapy be discontinued for 3–5 half-lives of a given drug (6–10 weeks in the case of adalimumab). In the case of JAK inhibitors, a 2–3-week discontinuation of therapy before the planned treatment is sufficient.

Both MTX and SSA should not be discontinued. Due to the long duration of the active metabolite of LEF in the body of patients at high risk of infectious complications, its washout is recommended.

Previously used GCs should not be discontinued prior to surgery.

SUMMARY

Rheumatoid arthritis is a disease that can currently be successfully treated in most patients.

The efficacy of therapy and the possibility of achieving remission is remarkably dependent on:

— treatment initiation in the early stages of the disease;
— continuous monitoring of treatment efficacy and change of therapy to achieve remission after 6 months of disease duration;
— the possibility of using a large number of drugs acting by different mechanisms so that the therapy that is safest and most effective for a given patient can be selected;
— approximately 20–30% of patients do not improve with csDMARDs and need to be treated with biologics or JAK inhibitors;
— long-term use of GCs (> 6 months) in RA patients increases the risk of cardiovascular complications and death.

CONFLICT OF INTEREST

This article was written in collaboration with Sandoz.

References

1. Batko B, Stajszczyk M, Świerkot J, et al. Prevalence and clinical characteristics of rheumatoid arthritis in Poland: a nationwide study. Arch Med Sci. 2019; 15(1): 134–140, doi: 10.5114/aoms.2017.71371, indexed in Pubmed: 30697263.
2. Tanaka Y. Rheumatoid arthritis. Inflammation and Regeneration. 2020; 40(1), doi: 10.1186/s41232-020-00133-8.
3. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative . Arthritis Rheum. 2010; 62(9): 2569–2581, doi: 10.1002/art.27584, indexed in Pubmed: 20872595.
4. Delft Mv, Huizinga T. An overview of autoantibodies in rheumatoid arthritis. Journal of Autoimmunity. 2020; 110: 102392, doi: 10.1016/j.jaut.2019.102392.
5. Combe B, Landewe R, Daien C, et al. 2016 update of the EULAR recommendations for the management of early arthritis. Annals of the Rheumatic Diseases. 2016; 76(6): 948–959, doi: 10.1136/annrheumdis-2016-210602.
6. Saevarsdottir S, Rezaei H, Geborek P, et al. SWEFOT study group. Current smoking status is a strong predictor of radiographic progression in early rheumatoid arthritis: results from the SWEFOT trial. Ann Rheum Dis. 2015; 74(8): 1509–1514, doi: 10.1136/annrheumdis-2013-204601, indexed in Pubmed: 24706006.
7. Cosgarea R, Tristiu R, Dumitru RB, et al. Effects of non-surgical periodontal therapy on periodontal laboratory and clinical data as well as on disease activity in patients with rheumatoid arthritis. Clin Oral Investig. 2019; 23(1): 141–151, doi: 10.1007/s00784-018-2420-3, indexed in Pubmed: 29589156.
8. George MD, Giles JT, Katz PP, et al. Impact of Obesity and Adiposity on Inflammatory Markers in Patients With Rheumatoid Arthritis. Arthritis Care Res (Hoboken). 2017; 69(12): 1789–1798, doi: 10.1002/acr.23229, indexed in Pubmed: 28393498.
9. Smolen JS, Landewé R, Bijlsma J, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update . Ann Rheum Dis. 2020; 79(6): 685–699, doi: 10.1136/annrheumdis-2019-216655 , indexed in Pubmed: 31969328.
10. Sun KJ, Liu LL, Hu JH, et al. Methotrexate can prevent cardiovascular events in patients with rheumatoid arthritis: An updated meta-analysis. Medicine (Baltimore). 2021; 100(7): e24579, doi: 10.1097/MD.0000000000024579, indexed in Pubmed: 33607787.
11. Baghdadi LR. Correction: Effect of methotrexate use on the development of type 2 diabetes in rheumatoid arthritis patients: A systematic review and meta-analysis. PLOS ONE. 2020; 15(12): e0243960, doi: 10.1371/journal.pone.0243960, indexed in Pubmed: 33296441.
12. Juge PA, Lee J, Lau J, et al. Methotrexate and rheumatoid arthritis associated interstitial lung disease. European Respiratory Journal. 2020; 57(2): 2000337, doi: 10.1183/13993003.00337-2020.
13. Wasko MC, Dasgupta A, Sears GI, et al. Prednisone Use and Risk of Mortality in Patients With Rheumatoid Arthritis: Moderation by Use of Disease-Modifying Antirheumatic Drugs. Arthritis Care & Research. 2016; 68(5): 706–710, doi: 10.1002/acr.22722.
14. Poór G, Strand V. Leflunomide Multinational Study Group. Efficacy and safety of leflunomide 10 mg versus 20 mg once daily in patients with active rheumatoid arthritis: multinational double-blind, randomized trial. Rheumatology (Oxford). 2004; 43(6): 744–749, doi: 10.1093/rheumatology/keh168, indexed in Pubmed: 15026583.
15. Fajardo-Robledo NS, Jacobo-Cuevas H, Perez-Guerrero EE, et al. Research Group for Factors Related to Therapeutic Outcomes in Autoimmune Diseases. Therapeutic response to leflunomide in combo therapy and monotherapy is associated to serum teriflunomide (A77 1726) levels. Sci Rep. 2022; 12(1): 1877, doi: 10.1038/s41598-022-05644-7, indexed in Pubmed: 35115601.
16. CHPL Adalimumab (Hyrimoz). https://www.ema.europa.eu/en/documents/product-information/hyrimoz-epar-product-information_pl.pdf.
17. Furer V, Rondaan C, Heijstek M, et al. 2019 update of EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. Ann Rheum Dis. 2020; 79(1): 39–52, doi: 10.1136/annrheumdis-2019-215882, indexed in Pubmed: 31413005.