# Updated: Managing RA

This is the lay version of the EULAR recommendations for the management of rheumatoid arthritis using synthetic and biologic disease-modifying antirheumatic drugs. The original publication can be downloaded from the EULAR website: www.eular.org.

Smolen JS, Landewé RBM, Bergstra SA, et alEULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 updateAnnals of the Rheumatic Diseases Published Online First: 10 November 2022. doi: 10.1136/ard-2022-223356

## Introduction

EULAR gives advice to doctors, nurses, and patients about the best way to treat and manage diseases. In 2022, EULAR updated its recommendations on the management and treatment of people with rheumatoid arthritis (sometimes shortened to RA). Since the 2019 update, no new drug class has been approved for use in people with rheumatoid arthritis, but there is important new evidence about safety.

Doctors, nurses, other health professionals and patients worked together to develop this advice. The patients in the team ensured that the patient point of view was included. The authors looked at the evidence for three specific groups of drugs for people with rheumatoid arthritis.

## What do we already know?

Rheumatoid arthritis is a condition where the joints become stiff, painful and damaged due to the immune system attacking the body's own tissues and causing inflammation. These recommendations include information on three types of disease modifying anti-rheumatic drugs (often shortened to DMARDs) that are used to treat rheumatoid arthritis. These drugs aim to change the course of the disease by reducing inflammation, and can prevent flares and disease worsening. They can also help to improve function and stop the progression of joint damage.

The three different types of DMARDs included in these recommendations are:

1. **Conventional synthetic** DMARDs (sometimes shortened to csDMARDs).
   This includes methotrexate, leflunomide, and sulfasalazine.

2. **Biologic** DMARDs (also called bDMARDs, biologics or biologicals).
   The bDMARDs used in rheumatoid arthritis include tumour necrosis factor inhibitors (TNFi), interleukin-6 inhibitors (IL-6i), rituximab and abatacept. The individual TNFi drugs are adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab. This also includes biosimilars. The individual IL-6i are tocilizumab and sarilumab.

3. **Targeted synthetic** DMARDs (shortened to tsDMARDs).
   The tsDMARDs used in rheumatoid arthritis are all Janus kinase inhibitors (JAKi).
   The individual drugs in this class are tofacitinib, baricitinib, filgotinib, and upadacitinib.

The EULAR recommendations on the management of people with rheumatoid arthritis were first written in 2010, and have been updated regularly. The 2022 update is based on new evidence that has become available since the last version in 2019. EULAR also considered two important publications from other experts. In 2021, the US Food and Drug Administration – the body that makes decisions on which drugs can be used in the United States – warned about cardiovascular and malignancy risks with tofacitinib compared to TNFi. And then, the American College of Rheumatology decided to discourage use of glucocorticoids, reasoning that the toxicity outweighs the benefits. EULAR has looked at the evidence for both of these points



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when developing the new 2022 recommendations. In addition, all new evidence regarding efficacy and dose-reduction upon achievement of the desired good outcome was assessed.

## What do the recommendations say?

In total, there are 5 overarching principles and 11 recommendations. The principles say that rheumatologists are the specialists who should primarily care for people with rheumatoid arthritis, and treatment should aim at best care and be based on a shared decision between the patient and their rheumatologist. This decision should consider each person's individual disease activity, safety issues and other factors, such as comorbidities and progression of structural damage. People with rheumatoid arthritis require access to multiple drugs with different modes of action, and they might need to try different therapies at different points in their life. Finally, the principles acknowledge that rheumatoid arthritis has high individual, medical and societal costs, all of which should be considered in its management.

Each recommendation is based on the best current knowledge from studies of scientific evidence or expert opinion. The more stars a recommendation has the stronger the evidence is. However, recommendations with limited scientific evidence may be important, because the experts can have a strong opinion even when the published evidence may be lacking.

One star (*) means it is a recommendation with limited scientific evidence.

Two stars (**) means it is a recommendation with some scientific evidence.

Three stars (***) means it is a recommendation with quite a lot of scientific evidence.

Four stars (****) means it is a recommendation supported with a lot of scientific evidence.

## Recommendations

- **People should be prescribed a DMARD as soon as they are diagnosed with RA.****
  If you have symptoms, it is important to get a specific diagnosis quickly so that treatment can be started as soon as possible. Early treatment can prevent irreversible joint damage. This recommendation is unchanged from the previous version.

- **For every person the treatment aim should be sustained remission or low disease activity.****
  Achieving remission or low disease activity are the main targets for therapy. If your disease activity is higher than this after trying a treatment for 6 months, then you do not have adequate disease control, and your doctor may change your treatment. This recommendation is unchanged from the previous version. The definition of remission should be based on ACR-EULAR criteria.

- **Your rheumatoid arthritis should be monitored every 1–3 months when you have active disease; treatment should be adjusted if there is no major improvement after 3 months, or if your target has not been reached by 6 months.*****
  Your doctor should check your disease activity and examine your joints regularly to see how well your treatment is working. This should be done using a tool that includes swollen joint count. By measuring your disease activity the doctor can see if you are in remission (or low disease activity). If there has been no improvement in at least half of your complaints within 3 months of starting a new drug, then it probably will not work for you and your therapy should be adjusted. If there are such signs of improvement, you should carry on taking that drug for at least another 3 months to see if it can put you into remission. If the target has not been met by 6 months, your therapy should be adjusted. This might mean staying on the same drug but changing the dose, or you might need to switch to a different type of drug. This recommendation is unchanged from the previous version.



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- **Methotrexate should be part of your first treatment strategy.******
  Methotrexate is a csDMARD. It is a good choice to try first for people with rheumatoid arthritis, because it is a well-known, effective and inexpensive drug. Your doctor may try different doses to find the right one for you, and may prescribe folic acid to be taken alongside, because this can reduce the side effects you might get. Methotrexate can be taken in combination with other drugs for rheumatoid arthritis, but this is normally saved for later stages of the disease. This recommendation is unchanged from the previous version.

- **Leflunomide or sulfasalazine should be considered instead of methotrexate for people who cannot take it, or who have side effects.******
  If you have kidney or liver disease, you may not be able to take methotrexate. A few people also find that they cannot tolerate methotrexate – it may cause sickness or other side effects. If this is the case, you may be prescribed leflunomide or sulfasalazine instead. Both are also csDMARDs. You may receive them alone or combined with other drugs. This recommendation is unchanged from the previous version.

- **You may need to take steroids when you start or change your csDMARDs, but they should be tapered and discontinued as quickly as possible.******
  This recommendation has been amended from the 2019 version. Adding glucocorticoids, a type of steroid medicine, to csDMARDs can help them to work better. This can help to bridge the gap when starting a new treatment until the csDMARD shows its benefit. Your doctor may give you a single steroid injection, or pills to take for up to 3 months. Using steroids for longer than this is not recommended because of the risk of side effects. The dose will be gradually reduced (sometimes called tapering) to help you come off the steroids as soon as possible. The important change in the new version is to specify that tapering should aim for discontinuation, rather than just dose reduction.

- **If you do not reach your target with the first csDMARD, and there are no adverse prognostic factors, a different csDMARD should be tried.***
  Prognostic factors are aspects that can be used to predict how much your disease may damage your joints. Poor or adverse prognostic factors include having moderate or high disease activity after receiving csDMARDs, or if you have certain auto-antibodies or high levels of markers of inflammation in your blood. Antibodies are proteins produced by your immune system as part of your natural defence against infections. Some diseases cause the immune system to make auto-antibodies against the body's own tissues, and these can be detected in your blood. If none of these things apply to you, your doctor may replace your first csDMARD with another one if it is not working. This recommendation is unchanged from the previous version.

- **If you do not reach your target with the first csDMARD strategy, and you have poor prognostic factors, a bDMARD should be added; JAKi may be considered, but risk factors must be taken into account.****/*****
  If you have poor prognostic factors and your first csDMARD has not worked, a bDMARD may be added instead of trying a second csDMARD. This recommendation has been amended from the 2019 version, when JAKi were considered at a similar level as bDMARDs in terms of effectiveness and safety. This has been changed because of new safety findings. Therefore JAKi should only be used after thorough evaluation of specific risk factors for cardiovascular disease and cancer, such as history of smoking and of previous cardiovascular events, among several others.

- **bDMARDs and tsDMARDs should be combined with a csDMARD; if you cannot use csDMARDs, you may be offered IL-6 inhibitors or tsDMARDs.******
  All bDMARDs and tsDMARDs work better when combined with methotrextate than when taken on their own. If you cannot use methotrexate or other csDMARDs, you might be offered a type of biologic called



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an IL-6-receptor inhibitor (IL-6-Ri), or a group of tsDMARDs called JAK inhibitors. If these are not taken with csDMARDs they get better results than other drug types.. This recommendation is unchanged from the previous version.

- **If a bDMARD or tsDMARD* does not work for you, you may receive a different one; if one TNFi or IL-6-Ri has failed, you may receive another agent with the same or different mode of action.**
  If you try a bDMARD or tsDMARD and it does not work for you, you can swap to another drug in the same class. For example, if one TNF inhibitor therapy has failed, patients may receive an agent with another mode of action or a second TNF inhibitor. However, if more than one of the same type of drug does not work for you, then your doctor should switch you to a drug that works in a different way. This recommendation has been amended from the 2019 version to include IL-6-Ri as well as TNFi.

- **After glucocorticoids have been discontinued and you are in sustained remission, dose reduction of DMARDs may be considered.****
  This recommendation has been amended from the 2019 version. The sequence which drug should be reduced in dose (or increased in interval) first is not of relevance. Stopping all DMARDs is not recommended. If treatment has worked and you have achieved remission then it may also be possible to lower the dose of your medicine – either by taking a smaller dose, or taking it less often. It is very important that you do not change your dose yourself without talking to your doctor.

## Summary

Overall, these recommendations give guidance to health professionals and patients about what EULAR regards an optimal way for the management and treatment of people with rheumatoid arthritis. They also highlight how many different options there are, which means treatment can be tailored to people's individual needs.

Recommendations with just one or two stars are based mainly on expert opinion and not backed up by studies, but these may be as important as those with three or four stars.

If you have any questions or concerns about your disease or your medication, you should speak to a health professional involved in your care.



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