**Methotrexate Should be First in Rheumatoid Arthritis, EULAR Guidelines Say**


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EULAR’s new rheumatoid arthritis treatment guidelines are comprehensive including recommendations for the use of everything from methotrexate to biosimilars.

The European League Against Rheumatism has updated its recommendations for the treatment of rheumatoid arthritis with the inclusion of synthetic, biologic and biosimilar disease-modifying anti-rheumatic drugs (DMARDs).

Led by Josef Smolen, M.D., and a 50-member international team of physicians, they offer four overarching principles and 12 recommendations based on three systematic literature reviews. The recommendations were published online March 6 in the *Annals of the Rheumatic Diseases*.

“The management of rheumatoid arthritis has changed dramatically over the past 30 years. The recommendations synthesize the current thinking on approaching rheumatoid arthritis treatment,” the authors wrote.

In rheumatoid arthritis, there are two targets for treatment — sustained remission or low disease activity. Anything other than those two responses should prompt a change in treatment. The best results for patients with rheumatoid arthritis typically comes through combinations of therapeutic agents and when one treatment fails there are options for rescue therapy which are spelled out in the recommendations.

Among some key points from the guidelines, methotrexate remains a “pivotal drug once the rheumatoid arthritis diagnosis has been made” and here, escalation of its dose is recommended as is combining it with newer disease modifying anti-rheumatic drugs (DMARDs). And, as compared to the 2013 update, conventional synthetic DMARDs combination therapy, with or without glucocorticoids, is no longer explicit.

The guidelines address glucocorticoid use and conventional synthetic DMARDs — specifically, methotrexate, leflunomide, sulfasalazine; and, biologic DMARDs — specifically, TNF inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab and infliximab); abatacept, rituximab, tocilizumab, clazakizumab, sarilumab and sirukumab. They also include biosimilar DMARDs and targeted synthetic DMARDs (Janus kinase inhibitors tofacitinib and baricitinib).

As a first course of therapy, the task force recommends methotrexate (rapid escalation to 25 mg per week) plus short-term glucocorticoid with the goal of achieving 50 percent improvement within three months and achieving the target treatment goal within six months. But if these targets are not met, they suggest switching to or adding a conventional synthetic DMARD with short-term glucocorticoid.

Thirdly, if after trying two conventional synthetic DMARDs, autoantibodies are present with high disease activity and early erosion, it is recommended that a biologic DMARD or Jak-inhibitor be added to the conventional synthetic DMARD. If this fails, any other biologic DMARD or targeted synthetic DMARD is recommended. For patients in sustained remission, biologic DMARDs can be tapered.

### Four Overarching Principles

- Best care possible should be the goal of treatment and should be based on decisions arrived at between the rheumatologist and the patient.
- Treatment decisions should be based on patient factors and disease activity such as progression of structural damage, comorbidities and safety issues.
- Rheumatologists should be the primary caregivers for patients with rheumatoid arthritis.
- Rheumatoid arthritis incurs high individual, medical and societal costs, all of which should be considered in its management by the treating rheumatologist.

### Twelve Recommendations

1. Disease modifying rheumatic drugs should be started as soon as the diagnosis of rheumatoid arthritis is made. (Unchanged from 2013)
2. Treatment should be aimed at reaching a target of sustained remission or low disease activity in every patient. (Highlights two targets for therapy)
3. Monitoring should be frequent in active disease (every 1-3 months); if there is no improvement by three months or the target has not been reached by six months, therapy should be adjusted. (Unchanged from 2013)
4. Methotrexate should be first line therapy. (“For active disease” was removed as it is implied)
5. When methotrexate is contraindicated or not tolerated, leflunomide or sulfasalazine should b considered as part of the first treatment strategy. (Unchanged in content from 2013)
6. Short-term glucocorticoid therapy should be considered when starting or changing conventional synthetic disease modifying anti-rheumatic drugs utilizing different dose regimens and routes, but should be tapered as rapidly as clinically possible. (Phrase “low dose” removed to account for alternative dosing regimens.)
7. If the patient’s treatment target is not reached with the first conventional synthetic disease-modifying drug, in the absence of poor prognostic factors, another drug in that class should be considered. (Previously the first part of recommendation 8)
8. If the patient’s treatment target is not reached with the first conventional synthetic disease-modifying drug and poor prognostic factors are present, consider adding a biologic disease-modifying anti-rheumatic drug (recommended first) or a targeted synthetic disease-modifying anti-rheumatic drug. (Previously the second part of recommendation 8, accentuating prognostic factors in the decision process.)
9. Biologic disease modifying anti-rheumatic drugs and targeted synthetic disease-modifying anti-rheumatic drugs should be combined with conventional synthetic disease modifying anti-rheumatic drugs. In patients who cannot use the conventional synthetics as co-medication, interleukin-6 pathway inhibitors and targeted synthetics may have advantages over other biologic disease modifying anti-rheumatic drugs. (Replaces prior recommendation of the same number highlighting the superior efficacy of these drugs when combined with methotrexate.)

10. If a biologic disease modifying anti-rheumatic drug or a targeted synthetic has failed, treatment with a different drug in those classes should be considered. If the first tumor necrosis factor inhibitor has failed, patients may receive another agent in the same class or a drug with another mechanism of action. (Content unchanged from 2013)

11. Rheumatologists may consider tapering biologic disease modifying anti-rheumatic drugs, especially when combined with conventional synthetic disease modifying anti-rheumatic drugs if the patient has been in persistent remission after a glucocorticoid taper. (Unchanged from 2013 guidelines)

12. Tapering the conventional synthetic disease modifying anti-rheumatic drug during periods of persistent remission can be considered. (Update clarifies that the drug should not be stopped all together)

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