EULAR Updates Recommendations for the Management of RA

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The first European League Against Rheumatism (EULAR) recommendations for the management of rheumatoid arthritis (RA) with synthetic and biologic disease-modifying antirheumatic drugs (DMARDs) were published in 2010 [Smolen JS et al. *Ann Rheum Dis* 2010]. A task force led by Josef S. Smolen, MD, Medical University of Vienna and Hietzing Hospital, Vienna, Austria, proposed updated recommendations in April 2013. The task force included rheumatologists, patient representatives, an infectious disease specialist, and a health economist. The updated recommendations are intended for a large target audience of healthcare professionals, patients, rheumatology societies, hospital managers, health insurance representatives, and politicians.

The 2013 preliminary recommendations are based on three systemic literature reviews on the following topics: 1) DMARDs, including tofacitinib and glucocorticoids; 2) biologic DMARDs, including biosimilars; and 3) safety issues. At the final task force meeting on April 9, 2013, four breakout groups evaluated each of these topics.

PRELIMINARY RECOMMENDATIONS

The 2013 recommendations include three overarching principles and 14 recommendations. The overarching principles are similar to those included in the 2010 recommendations (Table 1). Essentially, the task force recommended switching the order of principles A and B and slightly rewording principle C.

Table 1. EULAR 2010 Overarching Principles for Treatment of Rheumatoid Arthritis

Overarching Principles 2010	
A.	Rheumatologists are the specialists who should primarily care for RA patients.
B.	Treatment of RA patients should aim at the best care and must be based on a shared decision between the patient and the rheumatologist.
C.	RA is expensive in regards to medical costs and costs related to loss of productivity, both of which should be considered by the treating rheumatologist.

RA=rheumatoid arthritis.

The 2010 recommendations are shown in Table 2 for reference.

Among the key preliminary changes, the task force proposed dividing the second 2010 guideline into two recommendations, with recommendation 2 reiterating that treatment should be aimed at reaching a target of remission or low disease activity in every patient. Prof. Smolen noted that remission should be defined according to the American College of Rheumatology Boolean-based definition or index-based definition using the simplified disease activity index and clinical disease activity index. If remission is not likely to be achieved, low disease activity may be used as the treatment target. Preliminary recommendation 3 clarifies when therapy should be adjusted, proposing that if the patient does not improve by 3 months after the start of treatment, or if the target has not been reached by 6 months, therapy should be adjusted. Injectable gold has been eliminated from the proposed recommendations due to limited use and lack of availability in some countries.

Another key recommendation clarifies that in DMARD-naïve patients, either conventional synthetic DMARD monotherapy or a combination of conventional synthetic DMARDs should be used, irrespective of the addition of glucocorticoids. The 2010 recommendation 5 stating that "synthetic DMARD monotherapy rather than combination synthetic DMARD therapy may be used" was not meant to imply that use of combination synthetic DMARDs was incorrect, but only that it was not needed, according to Prof. Smolen. The 2013 recommendation reiterates the evidence-based view that synthetic DMARD monotherapy is effective, while more explicitly endorsing combination synthetic DMARD therapy. A preference to use combination DMARDs is not stated because of possible limitations in trial designs and conflicting trial data. Prof. Smolen pointed out that the level of evidence for the first six preliminary recommendations is very high, with 87% to 100% agreement among task force members and strength of recommendation of 9.0 to 9.8.

The updated recommendations give preference to low-dose glucocorticoids (≤10 mg/day) added to synthetic DMARDs over the "low to moderately high doses" recommended in 2010. The 2010 guidelines recommend biologic therapy with a tumor necrosis factor inhibitor combined with methotrexate (MTX) after insufficient response to MTX or other synthetic DMARDs; the 2013 preliminary recommendations add abatacept and tocilizumab (and under certain circumstances, rituximab) to the biologic therapy options. This addition was based on registry data and 5 years of experience with abatacept, tocilizumab, and rituximab showing no advantage for any agent as the first biologic therapy. The updated recommendations also state a preference for combining all biologics with MTX or other synthetic DMARDs. If monotherapy

must be used, tocilizumab is recommended as the preferred agent. The level of evidence for the proposed recommendations 7 and 8 was high, with 73% to 100% agreement among task force members and strength of recommendation of 8.9 to 9.4.

The task force proposed eliminating the 2010 recommendations 10, 11, and 14. The updated recommendation 11 is new, stating that therapy with tofacitinib may be considered after biologic treatment has failed. Although tofacitinib is not approved in the European Union, the task force decided to include it because the EULAR recommendations are not only for EU countries, and available evidence demonstrates its clinical, functional, and structural efficacy. Because some risks, such as herpes zoster infection, may be higher with tofacitinib than with biologics, the task force proposed that it should be used after at least one biologic therapy has failed, and, preferably, after two have failed. The level of evidence for recommendations 11 through 14 was high, with 90% to 100% agreement among task force members and strength of recommendation of 7.6 to 9.7.

SUMMARY OF PRELIMINARY 2013 RECOMMENDATIONS

Synthetic DMARDs, including combination therapy, are still considered effective for first-line treatment of RA. All biologic agents are considered equally safe and effective for initial biologic therapy. A combination of biologic therapy and MTX is preferable to monotherapy when MTX monotherapy does not control disease activity. However, biologic agents should not be used for initial DMARD therapy, as a treat-to-target approach leads to similar outcomes. The treat-to-target strategy is based on tight control of disease activity by routine assessment and adjustment of treatment aimed at a predefined target [Vermeer M et al. *Arthritis Res Ther* 2012].

The updated recommendations reflect evidence gathered on RA therapies since the publication of the 2010 recommendations. They clarify issues such as the use of combination conventional synthetic DMARDs in DMARD-naïve patients and address the use of tofacitinib—even though it is not approved for use in the European Union. These recommendations will allow clinicians and patients to make shared, evidence-based treatment decisions.

Table 2. EULAR 2010 Rheumatoid Arthritis Recommendations

2010 Guidelines
1. Treatment with DMARDs should be started as soon as the diagnosis of RA is confirmed.
2. Treatment should be aimed at reaching a target of remission or low disease activity as soon as possible in every patient; if the target has not been reached, treatment should be adjusted by frequent (every 1-3 months) and strict monitoring.
3. MTX should be part of the first treatment strategy in patients with active RA.
4. If MTX is contraindicated (or not tolerated), the following DMARDs should be considered as part of the (first) treatment strategy: leflunomide, sulfasalazine, or injectable gold.
5. In DMARD-naïve patients, synthetic DMARD monotherapy rather than combination therapy of synthetic DMARDs may be used, irrespective of the addition of glucocorticoids.
6. Glucocorticoids added to DMARD monotherapy at low to moderately high doses (or combinations of DMARDs) provide benefit as initial short-term treatment, but should be tapered as rapidly as clinically feasible.
7. If the treatment target is not achieved with the first DMARD strategy, addition of a biologic DMARD should be considered when poor prognostic factors are present; in the absence of poor prognostic factors, switching to another DMARD strategy should be considered.
8. In patients responding insufficiently to MTX or other DMARDs— with or without glucocorticoids—biologic DMARDs should be started; current practice would be to start a TNF inhibitor combined with MTX.
9. If treatment with a TNF inhibitor has failed, RA patients should receive another TNF inhibitor, abatacept, rituximab, or tocilizumab.
10. In cases of refractory severe RA, or when there are contraindications to biologic agents or the previously mentioned synthetic DMARDs, the following might be considered as monotherapy or combination therapy: azathioprine, cyclosporine A (or exceptionally, cyclophosphamide).
11. Intensive medication strategies should be considered in every patient, although patients with poor prognostic factors have more to gain.
12. If a patient is in persistent remission, glucocorticoids should be tapered, and one can consider tapering biologic DMARDs, especially if this treatment is combined with a DMARD.
13. In cases of sustained long-term remission, cautious titration of DMARD dose could be considered, as a shared decision between patient and physician.
14. DMARD-naïve patients with poor prognostic markers might be considered for combination therapy of MTX plus a biologic agent.
15. When adjusting treatment, factors apart from disease activity—such as progression of structural damage, comorbidities, and safety issues—should be taken into account.

DMARDs=disease-modifying antirheumatic drugs; MTX=methotrexate; RA=rheumatoid arthritis; TNF=tumor necrosis factor.