First-Line Methotrexate Upheld by Euro Panel

BY MITCHEL L. ZOLER

COPENHAGEN — Methotrexate is the "anchor drug" for treating rheumatoid arthritis, and treatment should start at the time of diagnosis, according to the first European League Against Rheumatism recommendations for managing the disease.

"Methotrexate should be part of the first treatment strategy in patients with active rheumatoid arthritis," said Dr. Robert B.M. Landewé at the annual meeting of the European Congress of Rheumatology.

Methotrexate can be either monotherapy or used as part of combination therapy, but "methotrexate should be considered a sort of anchor drug," said Dr. Landewé, professor of rheumatology at Maastricht (the Netherlands) University.

"This is where treatment has been for 5-10 years. There is nothing new with methotrexate as the anchor drug, except now an expert panel explicitly says it," he said in an interview.

Dr. Landewé, epidemiologist for the task force, and several colleagues presented the current draft of the new EULAR recommendations for RA treatment to an overflow crowd in a 90-minute session at the meeting. Although it is likely in close-to-final form, the draft still needs sign-offs by the full task force of about 40 people, said the task force convener, Dr. Josef S. Smolen, professor of medicine and chairman of rheumatology at the Medical University of Vienna.

The final version of the guidelines will be published soon, Dr. Smolen said.

Although methotrexate is at the top of the treatment hierarchy, it's on a short leash, Dr. Smolen noted. The second of the task force's 15 major recommendations says that treatment aims to produce "remission or low disease activity as soon as possible in every patient."

As long as this goal is not achieved, the adjustment of treatment "should be done by frequent and strict monitoring."

Although methotrexate is at the top of the treatment hierarchy, it's on a short leash.

DR. SMOLEN

What this means is that if methotrexate alone doesn't produce a good outcome by about 3 months, then the recommendations endorse adding something to methotrexate, he said in an interview.

The recommendations also relegated biologic disease-modifying antirheumatic drugs (DMARDs), such as tumor necrosis factor inhibitors, to the niche category of patients with poor-prognosis factors, such as positivity for rheumatoid factor and anti–cyclic citrullinated peptide antibody, early erosive disease, rapidly progressing disease, or high disease activity. Cost is the major factor limiting biologic DMARDs to just these patients.

"There is a strong opinion" among the task force members that only poor-prognosis patients should receive biologic DMARDs, "because patients without a poor prognosis will do well on synthetic DMARDs," Dr. Landewé said in the interview.

"The cost-effectiveness analysis clearly shows that [biologic DMARDs] are not cost effective. Nonetheless, there is a subgroup of patients who benefit from the combination" of methotrexate and a biologic, he said.

If circumstances warrant a biologic DMARD, current practice would start with a tumor necrosis factor inhibitor (such as etanercept, infliximab, or adalimumab) along with methotrexate, he added.

"It's a value decision. You need to balance improvements in outcomes against cost," commented Dr. Paul Emery, professor of rheumatology at the University of Leeds (England), EULAR president, and chairman of the recommendations session at the meeting. (Dr. Emery is not a member of the recommendations task force.)

"The recommendations allow biologics, especially in poor-prognosis patients, where the benefit is greatest. Recommendations always err on being conservative," Dr. Emery said in an interview.

On this point, the EULAR recommendations are consistent with the most recent, major RA treatment recommendations that were issued by the American College of Rheumatology (Arthritis Rheum. 2008;59:762-84).

The ACR recommendations call for using biologic DMARDs in patients with highly active disease and poor prognosis who have no cost or insurance limitations.

A major point on which the ACR and EULAR recommendations diverge is the role for the synthetic DMARD leflunomide. The EULAR recommendations make methotrexate the lone top agent, placing leflunomide along with sulfasalazine and injectable gold as the top DMARD options for patients who are intolerant of or have contraindications for methotrexate.

'This is where treatment has been for 5-10 years. There is nothing new with methotrexate as the anchor drug, except now an expert panel explicitly says it.'

In contrast, the ACR recommendations made leflunomide completely comparable with methotrexate for initial monotherapy.

The EULAR task force "made a strong point for methotrexate, which reflected the preference of our committee," Dr. Landewé explained. "We think that methotrexate is more effective than leflunomide."

The recommendations also deal with other issues, such as tapering, using glucocorticoids, and determining how to follow failed treatment with tumor necrosis factor inhibitor therapy. (See box.)

The task force rated each recommendation and the level of evidence for each recommendation for both scientific content and cost-effectiveness. ■

RA Treatment Recommendations From European League Against Rheumatism

Dr. Landewé summarized the following 15 items at the core of the new EULAR rheumatoid arthritis treatment recommendations:

1. Therapy with synthetic disease-modifying antirheumatic drugs (DMARDs) should start as soon as RA is diagnosed.
2. Treatment should aim at achieving remission or low disease activity as soon as possible in every patient. As long as these goals are not met, adjustment of treatment should be done with frequent and strict monitoring every 1-3 months.
3. Methotrexate should be part of the first treatment strategy in patients with active RA, either as monotherapy or in combination therapy.
4. If patients have contraindications to or are intolerant of methotrexate, then sulfasalazine, leflunomide, and injectable gold should be part of the first treatment strategy.
5. In DMARD-naive patients, monotherapy with a synthetic DMARD is an alternative to combination therapy with two or more synthetic DMARDs.
6. Glucocorticoids can be useful, short-term initial therapy in combination with synthetic DMARDs. ("Glucocorticoids are very effective" but present toxicity concerns, Dr. Landewé said.)
7. If the treatment target isn't achieved with the first DMARD strategy, adding a biologic DMARD should be considered in patients with a poor-prognosis factor. Patients without a poor-prognosis factor are candidates for switching to another synthetic DMARD. Poor-prognosis factors are positivity for rheumatoid factor and anti–cyclic citrullinated peptide antibody, or early erosive disease, rapidly progressing disease, or high disease activity.
8. Patients who respond inadequately to methotrexate alone or in combination with other synthetic DMARDs should start treatment with a biologic DMARD. Current practice starts with a tumor necrosis factor (TNF) inhibitor, used with methotrexate.
9. Patients who fail on an initial TNF inhibitor should receive a different TNF inhibitor or receive abatacept, rituximab, or tocilizumab.
10. Azathioprine, cyclosporin A, and cyclophosphamide, which are considered to be "second-line" DMARDs, can be used as monotherapy or in combination with one of the agents above in patients with severe and refractory RA or contraindications to either biologic DMARDs or the previously mentioned synthetic DMARDs.
11. An intensive medication strategy should be considered for every patient. Patients with a poor-prognosis factor have more to gain from an intensive strategy.
12. Glucocorticoids should be tapered in patients who are in persistent remission. Tapering biologic DMARDs can be considered, especially when they are used with a synthetic DMARD.
13. In patients with a sustained, long-term remission, cautious down-titration of a synthetic DMARD can be considered as a shared decision between a patient and physician.
14. DMARD-naive patients with poor-prognosis markers can be considered for combination therapy with methotrexate and a biologic DMARD. ("This strategy is clearly not cost effective, but there is a subgroup for whom early treatment with methotrexate and a biologic could be advantageous," Dr. Landewé said.)
15. When adjusting therapy, take into account factors beyond disease activity such as safety, comorbidities, and progression of structural damage.