

Optimal treatment of rheumatoid arthritis: EULAR recommendations for clinical practice

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KEY WORDS

recommendations, rheumatoid arthritis, strategies, treatment

ABSTRACT

Three important concepts have become standard of care in treating rheumatoid arthritis (RA): 1) development of new drugs: biologic agents; 2) treatment strategies: not an individual drug, but the timely combination of different drugs, given as a specific strategy; 3) treat to target: targeting treatment to the individual patient and adapting treatment when necessary. These concepts led to the development of the European League against Rheumatism recommendations for the management of rheumatoid arthritis (RA) with synthetic and biological disease-modifying antirheumatic drugs. Three so called overarching principles have been formulated, followed by 15 concrete recommendations for the management of RA. These 15 recommendations are described and discussed in this review, with some personal comments. An enormous gain in the development of RA has been achieved, and it is now time to consolidate that gain and make optimal treatment available for every RA patient in Europe. The guidelines described in this article will help physicians to actually do so.

Introduction There has been spectacular development in the treatment of patients with rheumatoid arthritis (RA) in the last 20 years. It is based on 3 important concepts, which now have become standard of care:

1 Development of new drugs: the arrival of biologic agents to treat RA has been a major breakthrough; although this medication is very costly, its efficacy is really impressive.¹

2 Treatment strategies: it has become clear from many clinical studies and observations that not an individual drug, but the timely combination of different drugs, given as a specific strategy, is much more effective than the previously used strategy of trying one drug after the other.^{2,3}

3 Treat to target: different studies have shown that targeting treatment to an individual patient, and thus adapting treatment every time when necessary, is much more efficacious than just treatment A or treatment B.⁴

These concepts were timely reasons to formulate new European League against Rheumatism (EULAR) recommendations for the management of RA with synthetic and biological disease-modifying antirheumatic drugs (DMARDs). Under

the guidance of Josef Smolen and Robert Landewe, over 30 European rheumatologists have been discussing the many results from literature searches and their own experience from daily practice. In the end, 3 so called overarching principles have been formulated, followed by 15 concrete recommendations for the management of RA.⁵

In the present review, overarching principles are discussed, the concrete recommendations are presented in the [TABLE](#) and explained in the text; sometimes my private comments are given, as requested by the editors of this journal.

Overarching principles

A. Rheumatologists are the specialists who should primarily care for patients with RA. Different studies have shown that treatment by a rheumatologist has a much better effect, with regard to disease activity and joint damage, than treatment given by a general practitioner, an internal medicine specialist, or an orthopedic surgeon. This, of course, does not implicate that other doctors and health professionals are not important in the treatment of RA patients, but does indicate that coordination of treatment should be with a rheumatologist.

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B. Treatment of patients with RA should aim at the best care and must be based on a shared decision between the patient and the rheumatologist. Best care is the final goal in the EULAR recommendations; we should aim to deliver this care to all patients with RA in Europe. In the treatment of every chronic disease, involvement of patients in the decision making progress is important; this is also paramount in the treatment of RA.

C. RA is expensive as far as medical and productivity costs are concerned, both should be considered by the treating rheumatologist. The more the advantages of especially biological drugs become clear, the more these drugs are used. The cost of these drugs is growing rapidly. Not many countries are able to supply them unlimited to all patients that need them. Even in such countries as the Netherlands, where up to 30% of RA patients use these drugs, financial constraints are felt and unpopular government rulings are pending. It should be a mission of the European rheumatologists to make sure that those patients who really need these expensive drugs are indeed able to receive them. It is expected that clinical trials will be started to evaluate whether it is possible in certain patients to decrease the dosage of these drugs or even to stop them completely, when patients have come into remission.

Recommendations In the [TABLE](#), the 15 EULAR recommendations for the management of RA are given.

1. Treatment with synthetic DMARDs should be started as soon as the diagnosis of RA is made Different studies have shown that the earlier the therapy with DMARDs is started, the more efficacious it is.² In our own department in Utrecht, the Netherlands, DMARD-therapy (methotrexate [MTX]) is started as soon as the clinical diagnosis of RA is made. It is expected that the new EULAR/American College of Rheumatology criteria for the diagnosis of RA will help us identify these patients as soon as possible.⁶ We often speak of the “window of opportunity”, meaning that there is only a limited space of time that we are able to make a real difference in the outcome for our patients. If we wait too long, it will become very difficult to reach remission and to prevent damage. Therefore, the sooner we start, the better.

2. Treatment should be aimed at reaching a target of remission or low disease activity as soon as possible in every patient; as long as the target has not been reached, treatment should be adjusted by frequent check-ups (every 1 to 3 months) and strict monitoring. The CAMERA study has convincingly shown that tight control in patients with early RA is indeed feasible, even in very crowded outpatient clinics.⁴ In that particular study, 300 patients were randomized to 2 different treatment strategies,

both with MTX monotherapy and defined rescue medication. One group was treated very intensively: patients were evaluated every month and treatment was rapidly adapted to a maximum dose of 30 mg MTX weekly. The other group was randomized to conventional treatment: patients were seen every 3 months and treatment was adapted when physician and patient deemed it necessary. A computer program was developed to make the decisions in the intensive group, taking into account not only the actual disease activity, but also change from previous measurement. The group treated with the intensive schedule fared much better than the conventionally treated group. In the end, the total MTX dose was comparable in both groups, because patients in the intensive group were able to reduce their MTX dose when they reached remission.

Remission is, of course, the optimal target, and perhaps reachable in the majority of patients if we start treatment early enough. However, when the disease has become chronic for quite some time, remission is often no longer possible (in line with the “window of opportunity” discussion), but low disease activity should be our aim then.

3. MTX should be part of the first treatment strategy in patients with active RA. From many comparative and strategy studies, it has become clear that MTX is the most effective drug given in early RA, but also in established RA. We probably did not use the most adequate dosage in the past. Nowadays, we use the dose of 20 to 30 mg/weekly, which is quite well tolerated.⁷ Subcutaneous administration of MTX might improve tolerance, especially if there are gastrointestinal complaints. Also the addition of 2 times weekly 5 mg folic acid is helpful in reducing adverse events, especially disturbances in liver function tests. MTX has been shown to have a favorable long-term safety profile and is used as a stand-alone treatment, but also as part of most treatment strategies. For instance, the effect of different tumor necrosis factor α (TNF- α) blockers on radiological changes is clearly improved by the addition of MTX.

4. When MTX contraindications (or intolerance) are present, the following DMARDs should be considered as part of the (first) treatment strategy: leflunomide, sulfasalazine (SSZ), or injectable gold. Though clear comparator studies are missing, it is generally felt, based on long-term efficacy data of different drugs, that MTX is by far the most effective DMARD. However, when there are contraindications, such as liver problems, leflunomide, SSZ, or injectable gold can be given as a stand-alone treatment in RA. Their efficacy as monotherapy is limited; therefore, they are preferably used as part of a treatment strategy. Studies on the added value of hydroxychloroquine as part of a treatment strategy are not convincing; therefore, hydroxychloroquine did not receive a prominent place in the current EULAR recommendations.

TABLE EULAR recommendations for the management of rheumatoid arthritis

1	Treatment with synthetic DMARDs should be started as soon as the diagnosis of RA is made.
2	Treatment should be aimed at reaching a target of remission or low disease activity as soon as possible in every patient; as long as the target has not been reached, treatment should be adjusted by frequent check-ups (every 1–3 months) and strict monitoring.
3	MTX should be part of the first treatment strategy in patients with active RA.
4	When MTX contraindications (or intolerance) are present, the following DMARDs should be considered as part of the (first) treatment strategy: leflunomide, SSZ, or injectable gold.
5	In DMARD-naïve patients, irrespective of the addition of GCs, synthetic DMARD monotherapy rather than combination therapy of synthetic DMARDs may be applied.
6	GCs added at low-to-moderately high doses to synthetic DMARD monotherapy (or combinations of synthetic 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 biological DMARD should be considered when poor prognostic factors are present; in the absence of poor prognostic factors, switching to another synthetic DMARD strategy should be considered.
8	In patients responding insufficiently to MTX and/or other synthetic DMARDs with or without GCs, biological DMARDs should be started; current practice would be to start a TNF inhibitor combined with MTX.
9	Patients with RA for whom a first TNF inhibitor has failed, should receive another TNF inhibitor, abatacept, rituximab, or tocilizumab.
10	In cases of refractory severe RA or contraindications to biological agents or the previously mentioned synthetic DMARDs, the following synthetic DMARDs might be also considered as monotherapy or in combination with some of the above: azathioprine, cyclosporin 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, after having tapered GCs, one can consider tapering biological DMARDs, especially if this treatment is combined with a synthetic DMARD.
13	In cases of sustained long-term remission, cautious titration of synthetic DMARD dose could be considered, as a shared decision between the patient and the doctor.
14	DMARD-naïve patients with poor prognostic markers might be considered for combination therapy of MTX plus a biological agent.
15	When adjusting treatment, apart from disease activity, factors such as progression of structural damage, comorbidities, and safety concerns should be taken into account.

Abbreviations: DMARD – disease-modifying antirheumatic drug, EULAR – European League against Rheumatism, GC – glucocorticoid, MTX – methotrexate, RA – rheumatoid arthritis, SSZ – sulfasalazine, TNF – tumor necrosis factor

5. In DMARD-naïve patients, irrespective of the addition of glucocorticoids (GCs), synthetic DMARD monotherapy rather than combination therapy of synthetic DMARDs may be applied.

Though many rheumatologists firmly believe that DMARDs are more effective in DMARD-naïve patients as part of a combination therapy, there is insufficient evidence in literature to really make this statement. Apart from studies in which GCs vs. placebo were added to DMARDs, no studies adding one DMARD or placebo to another DMARD have been performed. Therefore, it seems feasible to give a patient in this setting monotherapy with a DMARD, provided that tight control and monitoring is installed. For the research agenda this is an important question that needs to be solved in the future.

6. GCs added at low-to-moderately high doses to synthetic DMARD monotherapy (or combinations of synthetic DMARDs) provide benefit as initial short-term treatment, but should be tapered as rapidly as clinically feasible.

In the last years, good evidence for the beneficial effects of GCs, especially early in the disease, has been provided. Different studies, summarized in a Cochrane review, have shown that GCs, when added to other drugs, such as MTX, gold, and other DMARDs, are able to reduce the progression of erosive disease.⁸ The doses used varied between 5 and 10 mg daily; based on the effect sizes, a dose between 7.5 and 10 mg

daily seems to be effective, especially in the first 6 months of the disease. In studies where GCs were used for 26 weeks or longer, it has been shown that also after stopping the GCs, after up to 5 years, still a significant difference in erosive damage existed in favor of the groups originally treated with GCs. From different randomized controlled studies, it has been extrapolated that the symptomatic effect of GCs starts to wane after 6 months. Therefore, it seems reasonable to try to stop the added GCs after about 6 months, of course based on the individual patient. In most current combination therapies, GCs have become part of that regimen. Of course, we should be very well aware of the possible adverse events of GCs. Specific EULAR recommendations are formulated how to use GCs as safely and as effectively as possible.⁹

7. If the treatment target is not achieved with the first DMARD strategy, addition of a biological DMARD should be considered when poor prognostic factors are present; in the absence of poor prognostic factors, switching to another synthetic DMARD strategy should be considered.

Not all risk factors for a bad prognosis of RA are as yet known. Associations have been found with (high) rheumatoid factor, including anticyclic citrullinated peptide antibody, high disease activity at start, early presence of erosions, and some genetic markers. It is expected that we will learn more about these risk

factors in the coming years, when personalized treatment will also be introduced in RA. It is suggested that if an RA patient who does not have any of the well known risk factors and fails his/her first DMARD (MTX), it is worthwhile to try another DMARD first. However, if 1 or more risk factors are present, it is suggested to start a biological, namely a TNF- α inhibitor. Logical choices for a second DMARD are leflunomide, SSZ, or injectable gold. Frequent monitoring of these patients is recommended, to prevent losing too much time awaiting an improvement that is not to come. However, the percentage of patients responding to a second DMARD warrants this step in the lower risk group.

8. In patients responding insufficiently to MTX and/or other synthetic DMARDs with or without GCs, biological DMARDs should be started; current practice would be to start a TNF inhibitor which should be combined with MTX. TNF- α blockers have been shown to be very effective in patients with active RA. The introduction of these drugs at the end of the last century has completely changed clinical rheumatology. As could be expected, most impressive gains were observed in those patients with most severe disease. Roughly, it can be stated that $\frac{1}{3}$ of RA patients respond extremely well; $\frac{1}{3}$ respond well, and the last $\frac{1}{3}$ do not respond at all. Therefore, it is very important to make an adequate use of these drugs: determine which patients will respond best, but also decide in which patients it is better to stop because the drug is ineffective. Apart from the clear clinical effects, improvement has been noted in less erosive damage and in the possibility of patients to participate more in their work and social activities. During the years of development of the TNF- α blockers, these drugs have become more and more humanized, and the frequency in which the drugs need to be given subcutaneously has decreased, from twice a week to only once a month.

Different products have their own characteristics. There is insufficient data to predict which patient will respond best to a specific drug. Research is now ongoing in targeting specific patient groups for specific drugs. This would have clear advantages, namely not losing "window of opportunity" time by giving a patient an inadequate drug, but also not spending money on a drug that is not working in that specific patient. As mentioned before, the efficacy of TNF- α blockers is increased by adding MTX, not only with regard to radiological damage but also with regard to the occurrence of antibodies against TNF- α blockers.

9. Patients with RA in whom the first TNF inhibitor has failed should receive another TNF inhibitor, abatacept, rituximab, or tocilizumab. Present data suggest that it is worthwhile to try another TNF blocker when the first one has failed. However, there are good reasons to choose one of the other biologicals. At present, we do not have adequate

scientific data to make evidence-based choices in this regard, though it has been suggested that B-cell depletion is a more logical choice in patients that are rheumatoid-factor positive.

10. In cases of refractory severe RA or contraindications to biological agents or the previously mentioned synthetic DMARDs, the following synthetic DMARDs might be also considered as monotherapy or in combination with some of the above: azathioprine, cyclosporin A (or exceptionally cyclophosphamide). Despite all treatment modalities discussed above, there are still patients with refractory RA in whom these treatment strategies fail. In these patients, it is worthwhile to try azathioprine, cyclosporin A, or, in exceptional cases, cyclophosphamide. Also in cases of financial constraints, the use of azathioprine or cyclosporin A in individual cases could be considered before biologicals are given. In these exceptional cases, arguments for this choice would not be evidence in literature, but costs.

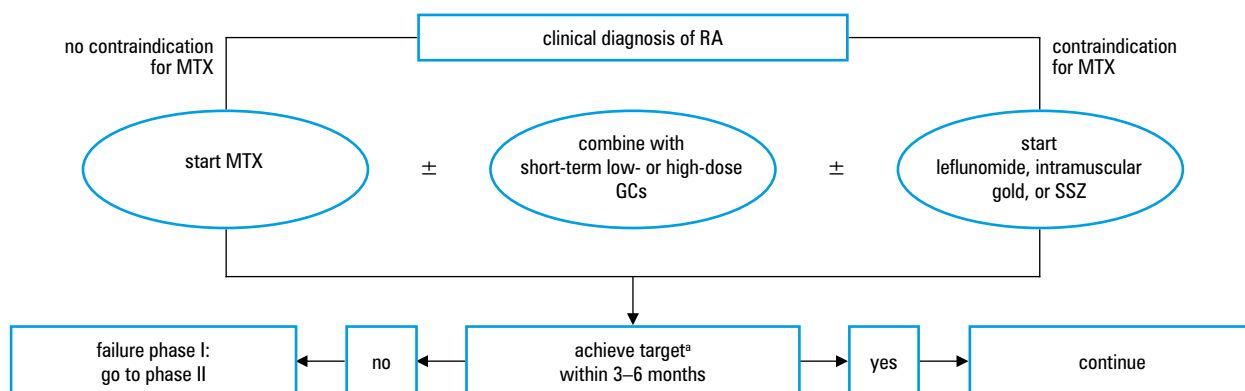
11. Intensive medication strategies should be considered in every patient, although patients with poor prognostic factors have more to gain. This recommendation was already mentioned above. Combinations of MTX with GCs and/or biologicals have been used extensively; also combination therapies with different DMARDs, such as MTX with cyclosporin A have been shown to be effective. Important elements of intensive strategy are: frequent monitoring and adapting treatment as soon as deemed necessary.

12. If a patient is in persistent remission, after having tapered GCs, one can consider tapering biological DMARDs, especially if this treatment is combined with a synthetic DMARD. It is not clear whether in case of persistent remission, tapering synthetic DMARD or tapering biological DMARD is the best choice. Cost factors stimulate trying to taper the biological DMARD first.

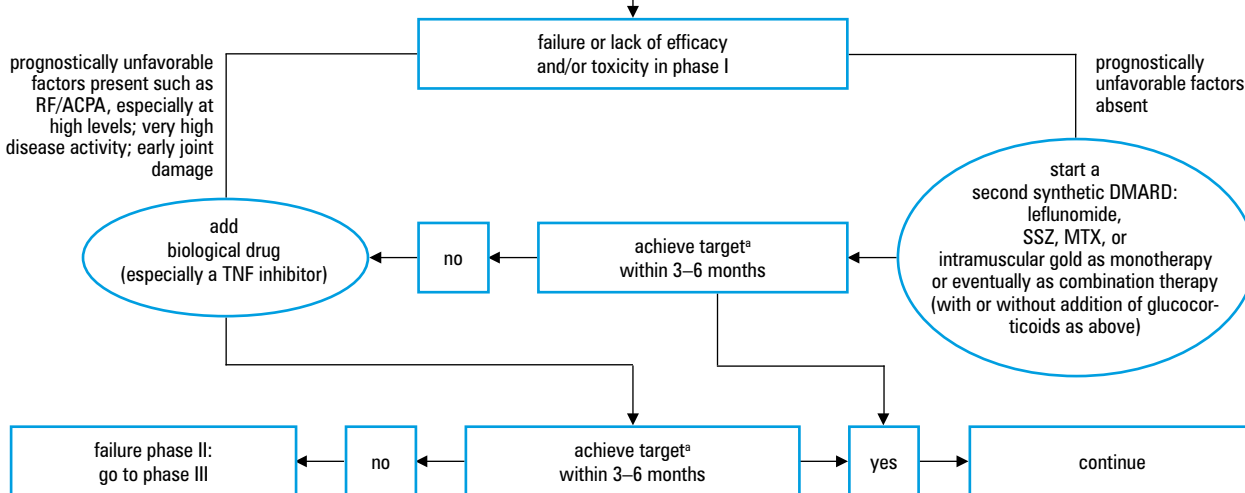
13. In cases of sustained long-term remission, cautious titration of synthetic DMARD dose could be considered, as a shared decision between the patient and the doctor. When remission is sustained, after stopping the biological DMARD it might be worthwhile to taper the other DMARDs. A general advice would be to do this very slowly. There have been studies on tapering DMARDs when patients were in remission; however, at that time remission was not as well defined as it is now.¹⁰ We now have more sophisticated measures to decide whether or not a patient is in remission. As soon as consensus on the definition of remission, and how to measure it, is reached, studies will be undertaken to decrease treatment in those patients who are truly in remission.

Personally, when a patient with longstanding RA is in "clinical remission" with for instance 15 mg MTX weekly, I am not in a hurry to taper this medication, especially when the patient has no complaints about this treatment.

PHASE I



PHASE II



PHASE III

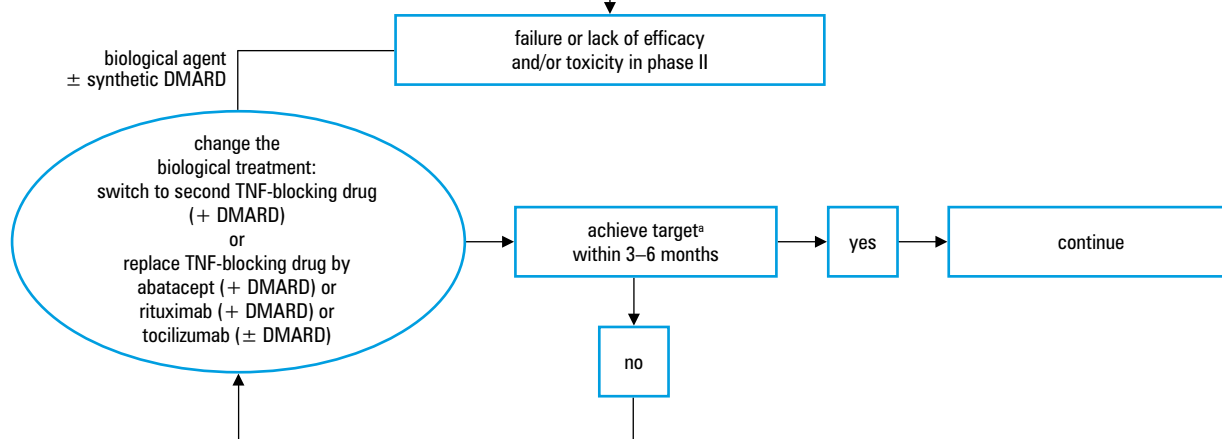


FIGURE Algorithm based on the European League Against Rheumatism recommendations on rheumatoid arthritis management (reproduced from Smolen JS, et al. Ann Rheum Dis. 2010; 69: 964-975)

a the treatment target is clinical remission or, if remission is unlikely to be achieved, at least low disease activity

Abbreviations: RF/ACPA – rheumatoid factor/anticitrullinated peptide antibodies, others – see [TABLE](#)

14. DMARD-naïve patients with poor prognostic markers might be considered for combination therapy of MTX plus a biological agent.

We all know patients with a very aggressive early RA. These patients have a poor prognosis, and there is good reason to start treatment as intensive and as soon as possible, despite limited data from literature. Indirect data from the BEST study show that patients treated with a high dose of GCs have comparable results to patients starting with a biological straight away.¹¹ Obviously, in this group of patients, GCs will have a place as well.

15. When adjusting treatment, factors apart from disease activity, such as progression of structural damage, comorbidities, and safety concerns should be considered. This recommendation advertises good clinical practice. Of course comorbidities and safety concerns should be part of every choice made in the treatment of patients with RA. However, we should realize that RA can be a very aggressive disabling disease; thus, a careful balance between the disease and its treatment should be made, with all relevant factors considered.

In order to help physicians and patients in individual decisions, the [FIGURE](#) provides an algorithm based on the EULAR recommendations.⁵

Conclusion Present times are very interesting for RA patients and for those who care for them. We have gained a lot; we can probably gain even more. However, we have to be aware of the financial constraints brought about by this progress. It has been proved in different studies that adequate use of anchor drugs, such as MTX and GCs, may be beneficial for many patients. It will be a challenge for the coming years to find the optimal balance in the treatment of our patients. The new area of personalized medicine, in which we will be able to diagnose RA very early, to make a reliable prognosis early in the disease, and to predict response to different treatment regimens, will help us reach these goals.

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Optymalne leczenie reumatoidalnego zapalenia stawów – zalecenia EULAR dla praktyki klinicznej

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SŁOWA KLUCZOWE

leczenie,
reumatoidalne
zapalenie stawów,
strategie, zalecenia

STRESZCZENIE

Trzy ważne koncepcje wyznaczają standardy opieki nad chorymi z reumatoidalnym zapaleniem stawów (RZS): 1) opracowanie nowych leków – leki biologiczne; 2) strategie leczenia – nie pojedyncze leki, ale stosowanie w odpowiednim czasie kombinacji różnych leków w ramach określonej strategii; 3) dążenie do osiągnięcia celów terapeutycznych – dopasowywanie leczenia do konkretnego pacjenta i w razie konieczności zmiana terapii.

Koncepcje te doprowadziły do sformułowania zaleceń European League against Rheumatism dotyczących leczenia RZS syntetycznymi i biologicznymi lekami przeciwreumatycznymi modyfikującymi przebieg choroby. Sformułowano 3 zasady ogólne oraz 15 konkretnych zaleceń dotyczących leczenia RZS. W niniejszym przeglądzie przytoczono i omówiono te 15 zaleceń, dodając własny komentarz. Osiągnięto ogromne postępy w leczeniu RZS; nadszedł czas, aby je skonsolidować i udostępnić optymalne leczenie wszystkim chorym z RZS w Europie. Omówione w tym artykule wytyczne będą w tym zakresie pomocą dla lekarzy.

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