

Treatment of rheumatoid arthritis: strategies for achieving optimal outcomes

Allan Gibofsky,¹ Yusuf Yazici²

In this issue of the *Annals of Rheumatic Diseases*, the EULAR task force, working together with the subgroups who conducted detailed reviews of available data on five specific topics on rheumatoid arthritis (RA) also published in this issue, present their recommendations for the management of RA with synthetic and biological disease-modifying antirheumatic drugs (DMARDs).^{1–6} This follows the similar effort by the American College of Rheumatology (ACR) in 2008⁷ and is a welcome addition to the current thinking and discussion about the management of RA. Taken together, these recommendations are both comprehensive and evidence-based and provide a framework for standardising care of patients with RA.

The task force, with the help of the subgroups, has put together 3 overarching principles and 15 recommendations. The overarching principles state correctly that RA needs to be treated by a rheumatologist, who can likely better manage disease activity and treatment guided by a target score, as very well demonstrated in studies such as TICORA, BeSt and FinRACo, to name a few.^{8–10} Although only one of these studies included a treatment arm with a biological agent,⁹ intervention in early disease was generally superior to that in trials of patients with established disease who received biological agents.

Unfortunately, the use of objective treatment targets as the rationale for defining therapy is not yet as widespread as it could be—especially in the USA where these measurement tools have yet to be routinely incorporated into care of the patient with RA. The treatment of patients with RA is better now than in past decades, an

improvement often attributed to the development of biological therapies. Although biological agents are an important advance for a significant number of patients with RA, three other major developments also seem to account for improved patient status: (1) adoption of early and intensive treatment; (2) widespread use of methotrexate (MTX); and (3) increased awareness that regular monitoring with quantitative disease measures improves outcomes compared with traditional non-quantitative ‘impressions’ (eg, the ‘gestalt’ of ‘doing well’). The EULAR guidelines also acknowledge this approach.

The emphasis on ‘best care’ is appropriate; we may even soon substitute ‘care that you would give your mother’ as the gold standard, which may help to put things in perspective. With regard to economic issues, although the acquisition cost of biological agents is said to be ‘high’, their utilisation costs are justifiable, given that our primary concern is to offer the patient optimal therapy that has the greatest likelihood of resulting in remission or, if not, low disease activity. The emphasis on the rheumatologist as the specialist who should provide primary care for patients with RA is timely, as mentioned above, especially given that in some settings other healthcare professionals with limited experience and training may be assigned to patient care.

The 15 recommendations of the task force are evidence-based and emphasise early treatment, even to the extent of advocating initiating DMARDs when the diagnosis of RA is only suspected.¹¹ Suggested frequent monitoring and targeting low disease activity or remission should become the cornerstone of our treatment plans, and we concur with the recommendations of the task force that suggest the objective measurement of disease activity should be part of every patient visit.¹² In addition, we would suggest another validated tool—the RAPID3 (a patient-only measures index) which performs similar to DAS28 and CDAI¹³—as part of the list of valid measures, also recommended by the ACR.⁷

MTX, as also stated in the recommendations, is the anchor drug¹⁴ and its use, we

believe, should not be limited to moderate or high disease activity. In the absence of a clinical contraindication, patients with low disease activity should be treated with MTX before any other agents. Part of this reasoning is the high rate of continuation of MTX, regardless of disease activity, which seems better than most biological agents.¹⁵ The task force statement in favour of using low-dose corticosteroids is welcome. Frequent patient objections to corticosteroid use may require increased efforts in patient and physician education about the true nature and benefits and risks of low-dose corticosteroids.

Recommendations regarding the use of combination synthetic DMARDs are also appropriate and should determine where and how they are used (in our opinion, in the patient who cannot take MTX and glucocorticoids).

The task force suggests the use of poor prognostic factors as a determinant of therapy. One potential problem with this approach—and especially with those factors listed (rheumatoid factor and/or anti-CCP antibodies, acute phase reactants)—is that these may be negative in as many as 40% of patients with RA.^{16–18} As also suggested by the authors, there are no head-to-head trials using these risk factors for stratification and, until there are, we would suggest using the more intensive treatment approach for any patient with a diagnosis of RA, especially given the favourable benefit/risk ratios of the drugs we use.

As for the use of biological agents, we would suggest that those that have shown similar efficacy in similar patients can potentially be used as first-line agents in an ideal world. Currently, there are published data on etanercept, adalimumab, infliximab and abataceptⁱ suggesting no real differences in efficacy in the majority of patients who use them. (In the USA, two other tumour necrosis factor inhibitors, golimumab and certolizumab pegol, also authorised by EMEA in Europe, have recently been added to the list of possible first-line agents.) Rituximab and tocilizumabⁱⁱ, when data are available and published, may be the next candidates to be added to this list. Data (which are mostly from registries) regarding switching preferences between biological agents at this time are limited and have tended to show no preference for one over another.¹⁹

ⁱ The label for abatacept differs between US and EMEA.

ⁱⁱ The label for tocilizumab differs between US and EMEA.

Correspondence to Allan Gibofsky, Department of Medicine, Hospital for Special Surgery, New York, NY 10021, USA; gibofskya@hss.edu

¹Department of Medicine and Public Health, Weill Medical College of Cornell University and Center for Inflammatory Arthritis and Biologic Therapy, Hospital for Special Surgery, New York, USA

²Department of Medicine, New York University School of Medicine and Seligman Center for Advanced Therapeutics, NYU Hospital for Joint Diseases, New York, USA

The intensive medication strategy recommendation may not be taking into account the fact that all the randomised controlled trials of biological agents average about 30 tender and 20 swollen joints in the cohorts studied, a presentation seen in less than 10% of patients in routine RA clinical care.^{20–21} Nevertheless, there are likely to be patients for whom combination therapy (traditional DMARD plus a biological agent) would be the appropriate initial regimen.

As stated in recommendation 12, in the best case scenario one-third of patients with RA in remission on a biological combination, with or without glucocorticoids, flare and may not be put into remission again. We would advise against tapering or stopping the combination of medications which were required to achieve remission unless there was a safety concern. Just as we would not consider stopping treatment for diabetes or hypertension, this chronic disease treatment approach²² should also be considered in patients with RA. We would also not advocate stopping glucocorticoids in daily doses of <5 mg as there is evidence to suggest that patients lose efficacy if stopped and risks are minimal.²³

While the recommendations of the task force do emphasise anatomical joint damage, studies have shown that function rather than radiographic scores are better long-term prognostic indicators.²⁴ Patients with low disease activity or in remission very rarely have any progression in radiographic scores. In addition, changes in radiographic scores reported in trials, even though usually statistically significant, show no real clinically relevant differences among any of the active treatment arms.²⁵ There may be a better role for MRI or ultrasound imaging in assessing structural damage, but the role of these modalities needs to be determined in long-term outcomes studies before they are universally accepted.

Further investigation is needed as to which drug to use and when to use it. It is not clear at this time if patients with RA who start treatment very early—even before fulfilling RA criteria—may be able to discontinue their medications yet maintain remission or low disease activity. As noted above, data from trials looking at patients with established RA who go into remission and stop their DMARDs are helpful in answering this question, and correlation with genetic and/or biomarker studies may be required.

In conclusion, the new recommendations are a welcome summary of the current thinking in the management of RA.

The need for early and intensive treatment using whatever DMARDs and combinations may be necessary to achieve these goals and setting target values for treatment using one of the validated composite outcome measures should become the standard way to treat RA today. The research agenda presented is a particularly good reminder that, as far as we have come in the last decade, there is more we have yet to accomplish for our patients.

Competing interests AG is a consultant and speaker for Abbott, Amgen, BMS, Pfizer, Roche, Wyeth, UCB and a stockholder in Amgen, Abbott, BMS, Johnson & Johnson, Pfizer; YY is a consultant, speaker and has received research support from BMS, Celgene, Centocor, Genentech, Pfizer, Roche, Schering Plough, UCB.

Provenance and peer review Commissioned; externally peer reviewed.

Accepted 30 March 2010

Ann Rheum Dis 2010;**69**:941–942.
doi:10.1136/ard.2010.131730

REFERENCES

1. **Smolen JS**, Landewe R, Breedveld F, *et al*. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. *Ann Rheum Dis* 2010;**69**:964–975.
2. **Nam JL**, Winthrop KL, van Vollenhoven RF, *et al*. Current evidence for the management of rheumatoid arthritis with biological disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of RA. *Ann Rheum Dis* 2010;**69**:976–986.
3. **Knevel R**, Schoels M, Huizinga TWJ, *et al*. Current evidence for a strategic approach to the management of rheumatoid arthritis with disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. *Ann Rheum Dis* 2010;**69**:987–994.
4. **Schoels M**, Wong J, Scott DL, *et al*. Economic aspects of treatment options in rheumatoid arthritis: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. *Ann Rheum Dis* 2010;**69**:995–1003.
5. **Gaujoux-Viala C**, Smolen JS, Landewé R, *et al*. Current evidence for the management of rheumatoid arthritis with synthetic disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. *Ann Rheum Dis* 2010;**69**:1001–09.
6. **Gorter S**, Bijlsma H, Cutolo M, *et al*. Current evidence for the management of rheumatoid arthritis with glucocorticoids: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. *Ann Rheum Dis* 2010;**69**:1010–14.
7. **Saag KG**, Teng GG, Patkar NM, *et al*; American College of Rheumatology. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. *Arthritis Rheum* 2008;**59**:762–84.
8. **Grigor C**, Capell H, Stirling A, *et al*. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. *Lancet* 2004;**364**:263–9.
9. **Goekoop-Ruiterman YP**, de Vries-Bouwstra JK, Allaart CF, *et al*. Comparison of treatment strategies in early rheumatoid arthritis: a randomized trial. *Ann Intern Med* 2007;**146**:406–15.
10. **Möttönen T**, Hannonen P, Leirisalo-Repo M, *et al*. Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. FIN-RACo trial group. *Lancet* 1999;**353**:1568–73.
11. **Pincus T**, Huizinga TW, Yazici Y. N-of-1 trial of low-dose methotrexate and/or prednisolone in lieu of anti-CCP, MRI, or ultrasound, as first option in suspected rheumatoid arthritis? *J Rheumatol* 2007;**34**:250–2.
12. **Pincus T**, Yazici Y, Bergman M. Saving time and improving care with a multidimensional health assessment questionnaire: 10 practical considerations. *J Rheumatol* 2006;**33**:448–54.
13. **Pincus T**, Swearingen CJ, Bergman MJ, *et al*. RAPID3 (Routine Assessment of Patient Index Data) on an MDHAQ (Multidimensional Health Assessment Questionnaire): agreement with DAS28 (Disease Activity Score) and CDAI (Clinical Disease Activity Index) activity categories, scored in five versus more than ninety seconds. *Arthritis Care Res (Hoboken)* 2010;**62**:181–9.
14. **Pincus T**, Yazici Y, Sokka T, *et al*. Methotrexate as the “anchor drug” for the treatment of early rheumatoid arthritis. *Clin Exp Rheumatol* 2003;**21**(5 Suppl 31):S179–85.
15. **Yazici Y**, Sokka T, Kautiainen H, *et al*. Long term safety of methotrexate in routine clinical care: discontinuation is unusual and rarely the result of laboratory abnormalities. *Ann Rheum Dis* 2005;**64**:207–11.
16. **Keenan RT**, Swearingen CJ, Yazici Y. Erythrocyte sedimentation rate and C-reactive protein levels are poorly correlated with clinical measures of disease activity in rheumatoid arthritis, systemic lupus erythematosus and osteoarthritis patients. *Clin Exp Rheumatol* 2008;**26**:814–19.
17. **Wolfe F**, Michaud K. The clinical and research significance of the erythrocyte sedimentation rate. *J Rheumatol* 1994;**21**:1227–37.
18. **Nishimura K**, Sugiyama D, Kogata Y, *et al*. Meta-analysis: diagnostic accuracy of anti-cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis. *Ann Intern Med* 2007;**146**:797–808.
19. **Hyrich KL**, Lunt M, Watson KD, *et al*; British Society for Rheumatology Biologics Register. Outcomes after switching from one anti-tumor necrosis factor alpha agent to a second anti-tumor necrosis factor alpha agent in patients with rheumatoid arthritis: results from a large UK national cohort study. *Arthritis Rheum* 2007;**56**:13–20.
20. **Sokka T**, Pincus T. Eligibility of patients in routine care for major clinical trials of anti-tumor necrosis factor alpha agents in rheumatoid arthritis. *Arthritis Rheum* 2003;**48**:313–18.
21. **Gogus F**, Yazici Y, Yazici H. Inclusion criteria as widely used for rheumatoid arthritis clinical trials: patient eligibility in a Turkish cohort. *Clin Exp Rheumatol* 2005;**23**:681–4.
22. **Pincus T**, Gibofsky A, Weinblatt ME. Urgent care and tight control of rheumatoid arthritis as in diabetes and hypertension: better treatments but a shortage of rheumatologists. *Arthritis Rheum* 2002;**46**:851–4.
23. **Pincus T**, Swearingen CJ, Luta G, *et al*. Efficacy of prednisone 1–4 mg/day in patients with rheumatoid arthritis: a randomised, double-blind, placebo controlled withdrawal clinical trial. *Ann Rheum Dis* 2009;**68**:1715–20.
24. **Pincus T**, Sokka T. Quantitative measures and indices to assess rheumatoid arthritis in clinical trials and clinical care. *Rheum Dis Clin North Am* 2004;**30**:725–51, vi.
25. **Yazici Y**, Yazici H. Tumor necrosis factor alpha inhibitors, methotrexate or both? An inquiry into the formal evidence for when they are to be used in rheumatoid arthritis. *Clin Exp Rheumatol* 2008;**26**:449–52.