Rheumatoid Arthritis Initial Therapy: Unanswered Questions

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ABSTRACT. Recent changes in the treatment of patients with rheumatoid arthritis (RA) are high lighted in this article,with emphasis on initial therapy in RA. Critical new concepts and developments are discussed: the importance of early treatment, increased use of combination disease modifying antirheumatic therapy as initial treatment and after failure of monotherapy, the role of the newer biological therapies, and the influence of comorbidity on morbidity and mortality. (J Rheumatol 2005;32 Suppl:14-16)

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The last decade has seen sweeping changes in how we think about and treat rheumatoid arthritis (RA). With regard to treatment for patients with this disease, I would highlight 4 critical paradigm shifts: proof that early therapy is indeed critical; the use of disease modifying drug (DMARD) combinations both initially and for people who fail monotherapy; the advent of biological therapies, particularly tumor necrosis factor (TNF) inhibitors; and proof that comorbidities play a central role in the overall morbidity and mortality of RA. Arguably, the most critical of these is the realization that all patients with RA should be taking DMARD early in their course of disease. Many studies could be cited to support this contention, perhaps the most striking of which was recently published by a group of investigators from The Netherlands[1]. In their trial, patients were observed to do substantially better in terms of radiographic progression if they were treated with DMARD within 15 days of diagnosis, as compared with another group who got therapy within 4 months of diagnosis. This would be considered a triumph of very early therapy over what most would still consider early therapy. Clearly, a current goal for all patients with RA would be for their physicians to have them take DMARD by a maximum of 3 months after diagnosis.

While essentially all rheumatologists accept that patients with RA should be treated with DMARD early and are building consensus that methotrexate (MTX) is the best conventional DMARD[2,3], there is little agreement on whether initial therapy should be a single DMARD or multiple DMARD. The critical questions that remain are highlighted in Table 1. Perhaps the most important one is, how can we individualize therapy to individual patients? In other words, are there parameters that allow us to predict up front which patients are going to respond to which therapy? Unfortunately, we have very limited information that allows us to do this at this time[4], but this clearly needs to be the focus as future trials are designed.

Table 1. Initial therapy in RA: critical questions.

Mono or combination DMARD therapy? (step-up or step down)
If mono, which DMARD?
If combination, which DMARD?
Bridge corticosteroids or not?
Initial biologics?
How to select the best treatment for each individual patient?

MONOTHERAPY

MTX is overwhelmingly the choice for most rheumatologists for initial therapy when monotherapy is selected[2]. This is true because of the excellent durability of MTX responses[5,6], because of its low cost, and because of the longterm record of safety. Importantly, MTX has recently been shown to significantly prolong survival of patients with RA[7]. It is worth mentioning that if oral MTX is not providing optimal response, subcutaneous MTX has significantly increased bioavailability for some patients and is worth a trial[8].

COMBINATION DMARD THERAPY

Despite an excellent record, MTX should no longer be considered the gold standard of treatment for RA. Multiple trials have shown that combinations of DMARD are more effective than treatment with MTX or sulfasalazine alone[9-13]. Three of these trials have specifically addressed patients with early disease[11-13]. From these trials, one might conclude that all patients

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Table 2. Combination versus monotherapy in early RA.

	I Mono	II Double	II Triple	p Values I vs II	p Values I vs III	p Values II vs III
Paulus 50, %	49.1	73.2	87.9	< 0.001	< 0.001	< 0.001
Remission, %	31.5	44.6	60.3	0.007	0.007	0.007
No x-ray progression, %	24.5	64.2	68.9	0.001	0.001	0.210

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with early disease should initially be treated with combinations of DMARD. However, the critically important trial, a trial that compares combinations of DMARD as initial therapy versus step-up therapy in only those patients who need step-up therapy, has not been reported. Calguneri, *et al* (Table 2) have clearly shown when treating patients with early RA that 3 drugs are better than 2, and 2 drugs are better than one[11].

A trial where therapy was stepped up with a particular treatment target goal (Disease Activity Score < 2.4) has recently been compared with usual therapy[14]. These investigators found that when an aggressive target for therapy is defined and conventional DMARD are added to sulfasalazine, patients have significantly improved results (compared with routine care) with less radiographic progression at one year.

THE ROLE OF INDUCTION THERAPY

A critically important, but unanswered, question is how rapidly is it necessary to shut off active disease[15]? In this regard, 2 therapies currently available that seem to shut disease off in days or weeks rather than months are tumor necrosis factor inhibitors and corticosteroids. The Early Rheumatoid Arthritis Trial[16] has shown us that although clinical and radiographic outcomes are similar at one year for the group treated with etanercept compared with the group treated with MTX, C-reactive proteins (CRP) are dramatically suppressed (about 75%) within 2 weeks in those treated with etanercept; approximately 6 months was required to obtain this result in those treated with MTX. Some have attributed the small benefits in radiographic outcome that are seen in patients on the etanercept arm of this study at 2 years to the rapid suppression of CRP. Very similar data have been shown from the COBRA Trial[17]. In this trial, erythrocyte sedimentation rates (ESR) were suppressed by 75% within 2 weeks of onset of treatment by the corticosteroid arm of the study, whereas sulfasalazine alone took 6 months to cause similar suppression in ESR. Again, some have attributed the rapid shutting off of the inflammatory response to the radiographic benefits that have been shown for the corticosteroid arm after 5 years[17]. Therefore, one of the most important questions currently is whether all patients should have induction therapies: brief bursts of either corticosteroids or TNF inhibitors along with other DMARD early in the course of disease. This is a critical question that needs to be addressed in trials that are designed over the next decade.

MINOCYCLINE AS A TREATMENT FOR EARLY RA

Minocycline has been shown to be an effective therapy for patients with established RA[18,19]. More importantly, minocycline has been shown to be dramatically effective compared with placebo in the treatment of early RA[20] and more effective than treatment with hydroxychloroquine[21], in terms of percentage of patients who have achieved American College of Rheumatology criteria for response of 50% (ACR 50; 60% vs 33%) but also in terms of reduction of steroid dose in those patients receiving minocycline versus hydroxychloroquine ($p < 0.01$). The mechanism by which minocycline is causing this effect is not understood but is almost certainly multifactorial. It is not treating the infectious cause of RA, but its antibacterial effects may be important by treating concurrent infections (sinusitis, gingivitis, bronchitis, gastritis, etc) in a nonspecific way. These infections activate the immune system and of course will upregulate the production of proinflammatory cytokines. Minocycline has well defined mechanisms of action with regard to immunomodulation with the upregulation of interleukin 10 (IL-10) production[22] and its ability to induce lupus. Finally, its role as a metalloproteinase inhibitor[23] may very well be important in treating RA, particularly when used early in the course of disease.

SUMMARY

Critical questions remain to be answered before optimal early treatment of each individual patient with RA can be achieved (Table 1). Future trials need to address these questions, in particular, study the role of induction therapy, and, most importantly, define parameters that allow us to select individual patients that will benefit from individual therapies.

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REFERENCES

1. Lard LR. Early versus delayed treatment in patients with recent-onset rheumatoid arthritis: comparison of two cohorts who received different treatment strategies. Am J Med 2001;111:446-51.
2. Mikuls TR, O'Dell J. The changing face of rheumatoid arthritis therapy: results of serial surveys. Arthritis Rheum 2000;43:464-5.
3. O'Dell JR. Methotrexate use in rheumatoid arthritis. Rheum Dis Clin North Am 1997;23:779-96.
4. O'Dell JR, Nepom BS, Haire C, et al. HLA-DRB1 typing in rheumatoid arthritis: predicting response to specific treatments. Ann Rheum Dis 1998;57:209-13.
5. Pincus T, Marcum SB, Callahan LF. Long-term drug therapy for rheumatoid arthritis in seven rheumatology private practices: II. Second line drugs and prednisone. J Rheumatol 1992;19:1885-94.
6. Wolfe F, Hawley DJ, Cathey MA. Termination of a slow acting antirheumatic therapy in rheumatoid arthritis: a 14-year ` prospective evaluation of 1017 consecutive starts. J Rheumatol 1990;17:994-1002.
7. Choi HK, Hernán MA, Seeger JD, Robins JM, Wolfe F. Methotrexate and mortality in patients with rheumatoid arthritis: a prospective study. Lancet 2002;359:1173-7.
8. Herman RA, Veng-Pedersen P, Hoffman J, Koehnke R, Furst DE. Pharmacokinetics of low-dose methotrexate in rheumatoid arthritis patients. J Pharm Sci 1989;78:165-71.
9. O'Dell JR, Haire CE, Erikson N, et al. Treatment of rheumatoid arthritis with methotrexate alone, sulfasalazine, and hydroxychloroquine, or a combination of all three medications. N Engl J Med 996;334:1287-91.
10. O'Dell JR, Leff R, Paulsen G, et al. Treatment of rheumatoid arthritis with methotrexate and hydroxychloroquine, methotrexate and sulfasalazine, or a combination of three medications. Arthritis Rheum 2002;46:1164-70.
11. Calguneri M, Pay S, Caliskaner Z, et al. Combination therapy versus monotherapy for the treatment of patients with rheumatoid arthritis. Clin Exp Rheumatol 1999;17:699-704.
12. Boers M, Verhoeven AC, Markusse HM, et al. Randomized comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. Lancet 1997;350:309-18.
13. Mottonen T, Hannonen P, Leirisalo-Repo M, et al. Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. Lancet 1999;353:1568-73.
14. Porter DR, Grigor C, Stirling A, Capell HA. A randomized controlled trial of a strategy of tight control of disease activity in rheumatoid arthritis C outcome over 18 months [abstract]. Arthritis Rheum 2003;48 Suppl:S232.
15. O'Dell, JR. Treating rheumatoid arthritis early: a window of opportunity: Arthritis Rheum 2002;46:283-5.
16. Bathon JM, Martin RW, Fleischmann RM, et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. N Engl J Med 2000;343:1586-93.
17. Landewe RB, Boers M, Verhoeven AC, et al. COBRA combination therapy in patients with early rheumatoid arthritis: long-term structural benefits of a brief intervention. Arthritis Rheum 2002;46:347-56.
18. Kloppenburg M, Breedveld FC, Terwiel JP, Mallee C, Dijkmans AC. Minocycline in active rheumatoid arthritis. Arthritis Rheum 1994;37:629-36.
19. Tilley BC, Alarcon GS, Heyse SP, et al. Minocycline in rheumatoid arthritis: a 48-week, double-blind, placebo-controlled trial. Ann Intern Med 1995;122:81-9.
20. O'Dell JR, Haire CE, Palmer W, et al. Treatment of early rheumatoid arthritis with minocycline or placebo. Arthritis Rheum 1997;40:842-8.
21. O'Dell JR, Blakely KW, Mallek JA, et al. Treatment of early sero-positive rheumatoid arthritis: a two-year, double-blind comparison of minocycline and hydroxychloroquine. Arthritis Rheum 2001;44:2235-41.
22. Ritchlin CT, Haas-Smith SA, Schwartz EM, Greenwald RA. Minocycline but not doxycycline upregulates IL-10 production in human synoviocytes, mononuclear cells and synovial explants [abstract]. Arthritis Rheum 2000;43 Suppl 9:S345.
23. Golub LM, Evans RT, McNamara TF, Lee HM, Ramamurthy NS. A non-antimicrobial tetracycline inhibits gingival matrix metalloproteinases and bone loss in Porphyromonas gingivalis induced periodontitis in rats. Ann NY Acad Sci 1994;732:96-111.

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