Early Rheumatoid Arthritis: Is There a Best Treatment?

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.

Study Overview

Objective. To determine whether the initial clinical and radiographic improvement demonstrated by combination therapies in patients with early rheumatoid arthritis (RA) [1] persists during year 2 of follow-up.

Design. Randomized controlled trial with blinded assessors.

Setting and participants. Patients enrolled in the BeSt study [1] who completed 2 years of treatment. Between April 2000 and August 2002, 508 patients from 18 peripheral and 2 university medical centers in the Netherlands who were aged ≥ 18 years and fulfilled the American College of Rheumatology (ACR) 1987 criteria for early active RA were randomly assigned to treatment with 1 of following: sequential monotherapy (group 1), step-up combination therapy (group 2), initial combination therapy with tapered high-dose prednisone (group 3), or initial combination therapy with infliximab (group 4). Treatment adjustments were made every 3 months to achieve a low disease activity score (≤ 2.4), a continuous measure consisting of the Ritchie articular index and number of swollen joints in a 44-joint count, erythrocyte sedimentation rate, and global health as measured on a visual analogue scale.

Main outcome measures. The primary clinical efficacy endpoint was functional ability, as measured by the Dutch Health Assessment Questionnaire (HAQ), and the primary radiographic endpoint was the change in Sharp–van der Heijde score for joint damage (range, 0–448) over 2 years. Secondary clinical efficacy endpoints were 20% and 70% improvement according to ACR response criteria and clinical remission (disease activity score < 1.6).

Main results. By 2-year follow-up, all groups showed improvement in functional ability (mean overall change in HAQ score, 0.6; $P = 0.257$), and 42% of patients were in remission (overall, $P = 0.690$), an increase from 31% in year 1. Groups 3 and 4 had more rapid improvement in HAQ score during the first year and less progression of joint damage (2.0 median increase in Sharp–van der Heijde score vs. 1.0 for groups 1 and 2; $P = 0.004$). More patients in groups 1 and 2 required treatment adjustments than patients in groups 3 and 4 (67%, 69%, 42%, and 28%, respectively). After 2 years, 33%, 31%, 36%, and 53% of patients in groups 1 through 4, respectively, were receiving single-drug therapies. Overall, 41% and 38% of all patients had at least 1 adverse event in the first and second years, respectively. Most adverse events were mild to moderate and led to therapy change in less than 11% of patients; however, there were 40 and 56 serious adverse events (defined as death, disability, malignancy, hospitalization, or birth defect) during years 1 and 2, respectively. There were no significant differences in toxicity among groups.

Conclusion. Combination therapies for RA provided earlier clinical improvement and less progression of joint damage; however, at 2-year follow-up, similar improvements were seen with all treatment strategies.

Commentary

RA is a systemic, chronic autoimmune disease that affects 0.8% of adults worldwide in a 3 to 1 female to male ratio [2]. Recent evidence suggests that 30% of patients already have irreversible bony erosions on radiography at the time of diagnosis [3]. Treatment with disease-modifying antirheumatic drugs (DMARDs) within 3 months after diagnosis is crucial because even a 3-month delay in treatment has been shown to result in substantially more radiographic damage at 5 years [4]. Recent treatment guidelines published by the ACR suggest that the rheumatologist and the primary care physician are both central in diagnosis of RA and initiation of DMARDs [5]. However, with the wide array of synthetic and new biologic therapies to choose from, what is the best initial therapy?

Goekoop-Ruiterman and colleagues initiated this randomized trial to evaluate 4 different approaches to early treatment of RA, mimicking clinical practice by allowing physicians to choose the initial therapy and then step-up or step-down medications based on disease activity score [1]. The findings of this 2-year follow-up study suggest that as long as clinicians change or escalate therapy at each 3-month visit if the disease activity score is not at goal, most patients with RA will have low disease activity and some will be in remission within 2 years. The results of this study were achieved using a wide array of DMARDs and combinations that were individually tailored to the patient's tolerance. This strategy is similar to that used in treating hypertension, in which the types of medication do not necessarily matter provided that medication is appropriately changed, intensified, or added based on the patient's achieved degree of blood pressure control [6].

Unfortunately, this study's "real world" design does not permit patient or physician blinding to the treatments received; hence, measurement of functional ability on the HAQ is influenced by subjective bias. Further, the treatment goal was low disease activity rather than remission, which is a more desirable outcome. Lastly, the 3-month interval between physician visits may be a bit long, as some physicians will adjust therapies after a shorter treatment interval. Nonetheless, this study shows that aggressive management of RA with any of the current DMARDs or biologic agents can result in excellent disease control. A longer follow-up is needed to assess if early combination therapy would result in less joint damage and eventual disability. More research is needed to identify which patients would benefit from combination therapy and which would do just as well on single-agent therapy.

Applications for Clinical Practice

For patients diagnosed with RA, providers should initiate DMARDs as soon as possible and adjust therapy in a timely manner until remission or low disease activity is achieved.

—Review by Mark S. Horng, MD, MPH

References

1. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. Arthritis Rheum 2005;52:3381–90.
2. Symmons DP, Barrett EM, Bankhead CR, et al. The incidence of rheumatoid arthritis in the United Kingdom: results from the Norfolk Arthritis Register. Br J Rheumatol 1994;33:735–9.
3. O'Dell JR. Therapeutic strategies for rheumatoid arthritis. N Engl J Med 2004;350:2591–602.
4. Lard LR, Visser H, Speyer I, et al. 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.
5. American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. Guidelines for the management of rheumatoid arthritis: 2002 update. Arthritis Rheum 2002;46:328–46. Available at www.rheumatology.org/publications/guidelines/index.asp?aud=mem. Accessed 6 Apr 2007.
6. Berlowitz DR, Ash AS, Hickey EC, et al. Inadequate management of blood pressure in a hypertensive population. N Engl J Med 1998;339:1957–63.