Low-Dose Prednisone for Early Active Rheumatoid Arthritis: Should You Use It?

van Everdingen AA, Jacobs JWG, Siewertsz van Reesema DR, et al. Low-dose prednisone therapy for patients with early active rheumatoid arthritis: clinical efficacy, disease-modifying properties, and side effects. A randomized, double-blind, placebo-controlled clinical trial. Ann Intern Med 2002;136:1–12.

Study Overview

Objective. To investigate the clinical efficacy, disease-modifying properties, and side effects of low-dose glucocorticoids as monotherapy for patients with previously untreated early active rheumatoid arthritis (RA).

Design. Randomized double-blind, placebo-controlled trial.

Setting and participants. This study was performed in 2 rheumatology clinics in the Netherlands from 1992 to 1995. Patients with early active RA who were not previously treated with disease-modifying anti-rheumatic drugs (DMARDs) were invited to participate. Out of 118 eligible patients, 81 agreed to participate. Participants were followed for 2 years.

Intervention. 41 patients were assigned to receive 10 mg of oral prednisone once daily and 40 were assigned to receive placebo. Nonsteroidal anti-inflammatory drugs (NSAIDs) were allowed for both groups. Sulfasalazine (2 g per day) was allowed as rescue therapy after 6 months.

Main outcome measures. Morning pain, general well-being, joint swelling, joint tenderness, and grip strength were assessed at baseline and every 3 months. Radiographs of hands and feet were taken at baseline and every 6 months to assess progression of erosions and joint space narrowing. Use of NSAIDs, acetaminophen, and intra-articular corticosteroid injections were also recorded. Adverse events were assessed every 3 months.

Main results. Baseline characteristics between the 2 groups were not statistically different, although severity of disease tended to be lower for patients assigned to the prednisone group. 71/81 of patients completed the study, with similar dropout rates for both groups. Use of sulfasalazine rescue therapy was similar in both groups.

Radiographs showed significantly less progression in the prednisone group than the control group at 12, 18, and 24 months. Use of acetaminophen and NSAIDs was significantly lower in the prednisone group. Of the 5 clinical variables, only the scores for joint tenderness and grip strength were significantly better in the prednisone group. There was also a higher incidence of osteoporotic fractures in the prednisone group.

Conclusion. Low-dose prednisone (10 mg once daily) as monotherapy for early active RA provides some clinical benefit and retards radiologic joint damage.

Commentary

The long-term use of low-dose glucocorticoids as monotherapy for active RA previously has not been tested. Given that, rheumatologists have long avoided using them in the management of active RA, especially when considering the increased mortality and bone loss associated with their use [1]. More recently, the DMARDs, which include methotrexate, sulfasalazine, hydroxychloroquine, infliximab, and etanercept, have been shown in randomized controlled trials to improve clinical outcomes and retard joint damage when used in isolation [2,3] or in combination [4]. In light of these recent trials, ethical concerns now preclude the conduction of controlled trials to study the efficacy of glucocorticoids as monotherapy. Fortunately for us, van Everdingen et al's elegantly conducted study was done before data demonstrating DMARDs' efficacy became available, thus giving us the unique opportunity to evaluate the independent efficacy of this old therapy.

Data from van Everdingen's study is convincing. After only 12 months of monotherapy with low-dose prednisone and with sulfasalazine rescue allowed after 6 months, there was significant radiographic evidence demonstrating retardation in joint damage. Improvement in clinical variables, however, was less impressive, with only 2 out of 5 showing statistically significant improvement. When these results are compared to data from previous DMARD trials [2–4], the efficacy of a DMARD surpasses that of low-dose prednisone as a monotherapy. As the authors readily point out, a glucocorticoid should not be used in isolation in the treatment of RA.

In regards to the role of glucocorticoids as an adjuvant to a DMARD, previous research has demonstrated retardation of joint damage when low-dose glucocorticoid therapy

(7.5 mg once daily) is added to a DMARD [5]. However, how low-dose glucocorticoids compare with a second DMARD as an adjuvant remains to be studied. Furthermore, low-dose glucocorticoids at even 10 mg daily can lead to significant bone loss, and van Everdingen's study found a higher incidence of osteoporotic fracture in patients assigned to the prednisone group. Therefore, physicians need to carefully weigh the costs and benefits of long-term, low-dose prednisone and its alternatives before embarking on this therapy for managing RA.

Applications for Clinical Practice

Low-dose prednisone has disease-modifying properties in early active RA, and it can retard progression of joint destruction. However, as monotherapy, low-dose prednisone is likely to be less effective than a traditional DMARD, such as methotrexate, in controlling active RA. Further studies are also needed to determine whether low-dose prednisone as a long-term adjuvant therapy might be more efficacious and safer to use than a second DMARD. For now, its long-term role in the treatment of RA remains undefined.

–Review by Eric Poon, MD

References

1. Pincus T, Sokka T, Stein CM. Are long-term very low doses of prednisone for patients with rheumatoid arthritis as helpful as high doses are harmful [editorial]? Ann Intern Med 2002;136:76–8.
2. van der Heide, Jacobs JW, Bijlsma JW, et al. The effectiveness of early treatment with "second-line" antirheumatic drugs. A randomized, controlled trial. Ann Intern Med 1996;124: 699–707.
3. van Jaarsveld CH, Jacobs JW, van der Veen MJ, et al. Aggressive treatment in early rheumatoid arthritis: a randomized controlled trial. The Rheumatic Research Foundation, Utrecht, The Netherlands. Ann Rheum Dis 2000;59:468–77.
4. Pincus T, O'Dell JR, Kremer JM. Combination therapy with multiple disease-modifying antirheumatic drugs in rheumatoid arthritis: a preventive strategy. Ann Intern Med 1999;131: 768–74.
5. Kirwan JR. The effect of glucocorticoids on joint destruction in rheumatoid arthritis. The Arthritis and Rheumatism Council Low-Dose Glucocorticoid Study Group. N Engl J Med 1995; 333:142–6.

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