Editorial

All Patients with Rheumatoid Arthritis Should Receive Corticosteroids as Part of Their Management

The dramatic clinical effects of glucocorticosteroids (GC) in humans were first described by Philip S. Hench and his colleagues in 1949. Their first patient, a 29-year-old woman who was temporarily bedridden because of severe, destructive rheumatoid arthritis (RA) of 4.5 years' duration, received daily intramuscular injections of 100 mg 17-hydroxy-11-dehydrocorticosterone (compound E). Within a week, "her articular and muscular stiffness had almost completely disappeared, and tenderness and pain on motion, and even swellings, were markedly lessened. The next day she shopped downtown for three hours, feeling tired thereafter, but not sore or stiff"[1]. Thirteen other patients with moderate to severe RA treated with compound E for 8 to 61 days experienced similar benefits. However, upon cessation of the drug, symptoms returned within 2 to 4 days in the majority of patients. Two other patients treated with 100 mg of adrenocorticotropic hormone (ACTH) intramuscularly for 12 days experienced clinical improvement similar to that from the use of compound E.

In his initial publication, Hench, *et al* had observed "interesting and important phenomena when the usual dose was employed but especially when larger doses were utilized to control flare-ups." Their initial patient received compound E for 6 months and she developed weight gain, acne, mild hirsutism, rounding of her facial contour, and amenorrhea. The authors concluded that more experience was needed to determine whether prolonged administration of compound E was effective and safe.

Hench was awarded the Nobel Prize in Medicine for his landmark discovery. Almost 60 years later, millions of patients with RA worldwide have been treated with CS. However, despite this accumulated experience, controversy still surrounds their use and is the source of interesting debates in the literature including an editorial by Boers in this issue of *The Journal*[2-4]. While no one disputes the very dramatic and dose-related efficacy of CS in relieving the symptoms of the disease, their longterm efficacy and safety as well as their capacity to prevent joint damage is still questioned.

Thanks to the recent publication of well designed studies addressing the issues of longterm efficacy, disease-modifying properties, and safety of corticosteroids, I believe that there are no longer reasons for this controversy. In this review, I present data supporting my long-held view that all patients with RA should receive corticosteroids as part of their management.

CORTICOSTEROIDS ARE CLINICALLY EFFECTIVE

The first randomized trials of cortisone acetate in RA were conducted in Great Britain in the 1950s under the banner of the Joint Committee of the Medical Research Council and the Nuffield Foundation[5-7] and by the Empire Rheumatism Council[8,9]. These trials compared cortisone acetate with acetylsalicylic acid in early[5-7] and late RA[8,9]. None of these trials showed any therapeutic advantage of cortisone over aspirin at one[5-8], 2, and 3 years of followup[9]. Following the demonstration of the superiority of prednisone over cortisone in the treatment of RA[10], a pivotal trial was conducted by the Joint Committee comparing prednisolone with aspirin[11]. In this trial, 84 patients with RA of less than 2 years' duration were randomized to receive prednisolone in an initial dosage of 20 mg/day (n = 45) versus aspirin 6 g/day (n = 32) or phenylbutazone 400 mg/day (n = 7). Seventy-seven patients (92%) were followed for 2 years. In comparison to the patients randomized to aspirin and phenylbutazone, those randomized to prednisolone reported a greater early improvement in both clinical (joint swelling and functional capacity) and laboratory (erythrocyte sedimentation rate and hemoglobin) variables, and this improvement, although less pronounced, was still significant after 2 years (mean dosage of 10 mg at the end of the

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trial). Importantly, there was a significant difference between the 2 treatment groups in the rate of progression of erosive changes. Thus, although both groups showed similar radiological changes at the beginning of the trial, 74% of the hand radiographs and 71% of the foot radiographs from the patients randomized to aspirin and phenylbutazone showed deterioration at 2 years as compared to 42% and 10%, respectively, of the radiographs from the patients receiving prednisolone ($p < 0.03$ and $p < 0.001$). This study was the first to suggest that corticosteroids could have disease-modifying properties in addition to relieving symptoms of the disease. However, because of observation of a higher rate of side effects in the prednisolone-treated patients, including major complications in 5 patients (2 cases of psychosis and 3 of peptic ulceration), the authors concluded that the optimal daily dose of prednisolone for longterm management of the average patient with RA should not exceed 10 mg.

Following this pivotal study, a number of randomized trials were conducted in patients with RA comparing prednisolone with placebo or nonsteroidal antiinflammatory agents (NSAID). Gøtzsche and Johansen reported a metaanalysis in 1998 that included 10 of these trials[12]. Their metaanalysis confirmed that prednisolone at a dose of 2.5 to 15 mg daily is not only much more effective than placebo in improving joint tenderness and grip strength, but is also significantly more effective than NSAID. The differences between prednisolone and placebo were 12 (6 to 18) tender joints and 22 mm Hg (5 to 40 mm Hg) for grip strength, and 9 (5 to 12) tender joints and 12 mm Hg (–6 to 31 mm Hg) between prednisolone and NSAID. It is important to emphasize that outcomes were assessed after a median length of treatment of only one week. Another metaanalysis conducted by Criswell, *et al* looked at the medium-term effectiveness of low-dose corticosteroids (≤ 15 mg prednisolone daily)[13]. Nine trials were included in this metaanalysis, and the authors focused on the outcome at 6 months. Prednisolone was still found to be effective, but the difference with placebo was much smaller than in the previous metaanalysis, as it corresponded to only 2.4 tender joints (0.3 to 4.6).

CORTICOSTEROIDS HAVE DISEASE-MODIFYING PROPERTIES

While it is well accepted that CS provide significant symptomatic relief, until recently, it was unclear if they could also prevent joint damage. In 1995, Kirwan, on behalf of the Arthritis and Rheumatism Council Low-Dose Glucocorticoid Study Group, reported on the first large double-blind, placebo controlled trial designed specifically to answer this question[14]. One hundred twenty-eight patients with RA of less than 2 years' duration were randomized to receive prednisolone 7.5 mg daily for 2 years or placebo in addition to their usual treatment. The primary outcomes were progression of damage in the hands as measured by the Larsen index (0–140) at one and 2 years and the development of erosions in hands that were free of erosions at baseline. In the prednisolone-treated patients, the Larsen index progressed by a mean of 0.73 unit after one year and by 0.72 unit after 2 years, indicating negligible changes. In contrast, in the placebo-treated patients, the Larsen index progressed by a mean of 3.63 units after one year ($p = 0.05$) and by 5.37 units after 2 years ($p = 0.004$), indicating substantial joint destruction. In the 106 patients with radiographs from baseline and 2 years, 147 of their 212 hands (69%) had no erosions at the start of the study. Fifteen of 68 hands (22%) in the prednisolone group developed erosions in comparison to 36 of 79 hands (46%) in the placebo group, a difference of 23% ($p = 0.007$). Although these results strongly suggest that prednisolone has disease-modifying properties, the fact that the degree of joint damage at baseline differed between the 2 treatment groups prevented a firm conclusion (Larsen index of 2.65 in the prednisolone group vs 6.23 in the placebo group).

Additional support for prednisolone being a disease-modifying drug was obtained from the COBRA trial, a pivotal, multicenter, double-blind, randomized trial designed by Boers and his associates to assess the value of intense combination therapy in early RA[15]. One hundred fifty-five RA patients with mean disease duration of 4 months were randomized to combination therapy, including prednisolone, methotrexate (MTX), and sulfasalazine versus sulfasalazine alone. The daily dosage of prednisolone was 60 mg in week 1, 40 mg in week 2, 25 mg in week 3, 20 mg in week 4, 15 mg in week 5, 10 mg in week 6, and 7.5 mg thereafter until week 28, when it was slowly tapered over the following 6 weeks and discontinued. The cumulative dose of prednisolone was 1190 mg over the first 6 weeks and 2345 over the first 28 weeks. MTX dosage was 7.5 mg/week until week 40, when it was tapered and discontinued over the following 6 weeks. The dosage of sulfasalazine in both groups was 500 mg/day, which was increased to 2000 mg/day over 3 weeks. The philosophy behind the combination protocol was to rapidly control disease activity with a short period of high-dose oral corticosteroid, rapidly tapered to a low maintenance dose, and to discontinue the more toxic component of the regimen (MTX) with the hope of maintaining disease control with sulfasalazine, a drug generally considered to be very safe. At week 28, 55 (72%) and 37 (49%) patients in the combined-treatment group reached the American College of Rheumatology (ACR) response level of ACR20 and ACR50 as compared to 39 (49%) and 21 (27%) patients in the sulfasalazine group ($p = 0.006$ and $p = 0.007$, respectively). The difference in efficacy between the 2 treatment groups was no longer significant after the prednisolone was withdrawn and there was no further change when MTX was withdrawn. Joint destruction, as measured by the van der Heijde modification of the Sharp method (SHS 0–448), progressed significantly less in the combined-treated group

than in the sulfasalazine group. Thus radiographic scores increased by a median of 1 (range 0–28), 2 (0–43), and 4 (0–80) in the combined-treated group at weeks 28, 56, and 80, respectively, as compared to a median of 4 (0–44), 6 (0–54), and 12 (0–72) in the sulfasalazine group ($p < 0.0001$, $p = 0.004$, and $p = 0.01$). New erosive damage in joints previously free of erosions also developed less commonly in the combined-treated group [median of 0 (0–5) at 28 weeks, 0 (0–6) at 56 weeks, and 1 (0–7) at 80 weeks] as compared to the sulfasalazine group [median of 1 (0–6), 1 (0–7), and 2 (0–8); ($p < 0.0001$, $p < 0.0001$, and $p = 0.0004$, respectively]. Based on a previous trial demonstrating that the combination of MTX and sulfasalazine is not superior to sulfasalazine alone[16], the authors concluded that CS were responsible for the lower radiological progression observed in the combined-treated group. Over the following 4 years of followup, the patients from the combination group continued to experience a slower progression of joint damage than the patients from the sulfasalazine group, independently of the subsequent antirheumatic therapy received[17].

Stronger evidence for prednisone having disease-modifying properties was provided by van Everdingen and her colleagues[18]. In this trial, 81 patients with early (disease duration < 1 yr), previously untreated RA were randomized to prednisone 10 mg daily (n = 41) or placebo (n = 40). After 6 months, sulfasalazine (2 g/day) could be used as rescue medication. Seventy-one patients completed the 2-year study. Of these, 19 in the prednisone group and 20 in the placebo group received sulfasalazine after 6 months. Patients in the prednisone group reported more rapid clinical improvement in the first 6 months than the placebo group, but only grip strength and the 28-joint score for tenderness differed significantly after 2 years [difference in grip strength of 9 kPa (0 to 19; $p = 0.05$) and of 2 tender joints (1 to 5, $p = 0.01$)]. From month 12 onward, radiological scores as measured by the SHS method showed significantly less progression in the prednisone group than in the placebo group. At 24 months, the mean total SHS scores were 27 ± 28 and 44 ± 37 for the prednisone and placebo groups, respectively ($p = 0.02$). Followup radiographic data after 3 years showed that inhibition of joint damage persisted after cessation of prednisone therapy[19].

Three very well designed randomized trials published in 2005 should eliminate any remaining doubt that rheumatologists may have about the clinical effectiveness and disease-modifying properties of prednisolone[20-22]. The first study originated in Sweden and was a pragmatic, multicenter, open randomized trial that included 250 patients with early RA (disease duration ≤ 1 yr) naive to disease-modifying agents (DMARD)[20]. At the start of their initial treatment with a DMARD, patients were randomly assigned to receive either prednisolone 7.5 mg/day or no prednisolone for 2 years. Followup was available in 242 patients (97%). At 2 years, 55.5% of the patients in the prednisolone group had achieved disease remission as compared to 32.7% in the no-prednisolone group ($p = 0.005$). There was no difference between the 2 groups in the concomitant treatment received, except that only 44% of patients in the prednisolone group were taking NSAID at 2 years, compared with 65% in the no-prednisolone group ($p = 0.001$). The radiographic progression was significantly less after 2 years in the prednisolone group [median and interquartile range (IQR) in the total SHS scores 1.8 (0.5–6.0)] versus the no-prednisolone group [3.5 (0.5-10)]. There were also fewer newly eroded joints in the prednisolone group at 2 years (median 0.5; IQR 0–2) vs (2.0; IQR 0–3.25 in the no-prednisolone group). Twenty-six percent of the patients in the prednisolone group had radiographic progression beyond the smallest detectable difference as compared with 39% in the no-prednisolone group ($p = 0.03$).

The second study was a double-blind, placebo controlled trial that assessed the effect of very low-dose prednisolone on disease progression[21]. At the start of treatment with either parenteral gold or MTX, 192 patients with RA of less than 2 years' duration were assigned to receive either prednisone 5 mg/day or placebo for 2 years. One hundred sixty-six patients were available for the intent-to-treat (ITT) analysis and 76 patients completed the study per protocol. After 2 years, radiological progression as measured by Ratingen score and SHS score was significantly less in the prednisolone group than in the placebo group in both the ITT and per-protocol populations [mean difference in the total SHS scores between the 2 groups in the ITT population of 7.20 (0.93, 13.47); $p = 0.02$].

The BeSt study was designed to evaluate the optimal strategy for preventing longterm joint damage and functional decline in patients with RA[22]. Five hundred eight patients with disease of less than 2 years' duration were randomly assigned to one of 4 strategies: (1) sequential monotherapy starting with MTX 15 mg/week; (2) step-up combination therapy; (3) initial combination therapy with prednisone prescribed according to the COBRA protocol; and (4) initial combination of infliximab 3 mg/kg with MTX 25–30 mg/week. After one year, low disease activity as defined by a 44-joint Disease Activity Score of ≤ 2.4 was reached by 53%, 64%, 71%, and 74% of patients from groups 1 to 4, respectively ($p = 0.004$ for group 1 vs group 3; $p = 0.001$ for group 1 vs group 4; p not significant for other comparisons). Patients randomized to groups 3 and 4 experienced more rapid functional improvement than patients from groups 1 and 2 [mean Health Assessment Questionnaire (HAQ) score of 1.0 at 3 months in groups 1 and 2 and 0.6 in groups 3 and 4 ($p < 0.001$)] and this difference was still significant after one year [HAQ scores of 0.7 in groups 1 and 2 and 0.5 in groups 3 and 4 ($p = 0.009$)]. Patients from groups 3 and 4 also had less progression of radiographic joint damage than patients from groups 1 and 2. The median progressions in the total SHS were 2.0, 2.5, 1.0, and 0.5 in groups 1–4,

respectively ($p < 0.001$). What is important to remember from this pivotal trial is that patients from group 3 did as well functionally and radiologically as patients allocated to strategy 4, which is currently considered to be the most aggressive (and expensive) strategy. Seventy-eight percent of the patients from group 3 who had achieved persistent low disease activity after one year discontinued prednisone, while only 50% of the patients from group 4 achieving the same status stopped infliximab.

CS ARE EFFECTIVE AND THEY HAVE DISEASE-MODIFYING PROPERTIES, BUT ARE THEY SAFE?

The major limitation to the use of oral corticosteroids in the management of RA has always been concerns about their safety. Shortly after their discovery, it was recognized that the prolonged use of doses higher than 15 mg was associated with significant side effects[11]. Unfortunately, the majority of the trials performed in the 1960s and 1970s did not comment on adverse events[12,13].

The recent trials on the longterm daily use of very low (5 mg)[21] and low (7.5–10 mg)[18,20] doses of prednisolone daily are most informative, as the authors carefully documented the incidence of side effects in a controlled setting. Weight gain was the most striking side effect reported in Wassenberg's trial, with the patients taking prednisolone gaining an average of 5 kg as compared to 0.3 kg in the placebo group[21]. Weight gain was also observed in van Everdingen's trial, as the mean body weight of the patients in the prednisone group increased significantly (from 77 ± 19 kg at baseline to 80 ± 20 kg after 2 yrs; $p = 0.001$), while it did not change in patients taking placebo[18]. Two patients in Svensson's trial randomized to prednisolone withdrew from the study because of weight gain[20].

Bone mineral density was measured in the lumbar spine and femoral neck in 189 patients at baseline and after 2 years in Svensson's trial; results did not differ between the prednisolone and no-prednisolone groups[20]. In the van Everdingen trial[18], new vertebral fractures occurred in 5 patients in the prednisone group versus 2 in the placebo group. In contrast, in Wassenberg's trial[21], fractures occurred in one patient taking prednisolone and in 3 patients taking placebo.

The rate of infection was similar between the treatment groups in all 3 trials. In one of the trials, cataracts developed in 5 patients taking prednisolone and in 6 patients taking placebo. Three patients (2 prednisolone and one placebo) developed diabetes mellitus in one trial[18]. Diabetes was the cause of withdrawal of one prednisolone-treated patient in another trial[20].

With the method of prednisolone administration used in the COBRA trial, weight gain and bone loss were not different at 56 weeks between the 2 treatment groups [1.7 kg (0.8–2.6) in the prednisolone-treated group vs 1.2 kg (0.2–2.2); $p = 0.49$] and [–1.3% bone loss (–2.3, –0.4) in the lumbar spine in the prednisolone group vs –0.3% (–1.4, 0.8); $p = 0.15$][15]. In the BeST trial, which used a similar protocol for prednisolone administration, a total of 41% of all patients experienced ≥ 1 adverse event, with no difference between the 4 treatment groups [1. sequential monotherapy (43%); 2. step-up combination therapy (47%); 3. combination therapy with prednisone (37%); and 4. combination infliximab/MTX (39%); $p = 0.36$][22]. Bone mineral density was not measured systematically in that trial.

CONCLUSION

When the editors approached me to write this review, they suggested the title, "The Rational Use of Steroids in Rheumatoid Arthritis — Pros and Cons." I have to admit that I have never been concerned about the "cons" of using steroids, as for the past 15 years, I have used low-dose prednisone in essentially all my patients as "bridge therapy" for 2 months while waiting for DMARD to work. The dosage that I typically use is 10 mg daily, decreased by 2.5 mg every other week until cessation. I repeat the same protocol at the end of 2 months in patients not achieving a significant clinical response with the other DMARD prescribed.

I believe that this literature review confirms what rheumatologists have always known: prednisone, even in low dose, is very effective in rapidly relieving the symptoms and improving function in patients with rheumatoid arthritis. However, it also clearly demonstrates, supported by at least 5 well designed clinical trials, that very low[21] or low-dose[18,20] prednisone administered daily for up to 2 years, or temporarily in higher doses as per the COBRA protocol[15,22], can also prevent longterm joint damage. It is time for prednisone to be reclassified as a true DMARD. Indeed, I would suggest that there is now more evidence supporting prednisone as a DMARD than there is for antimalarials, gold, sulfasalazine, or D-penicillamine!

The remaining question is whether the side effects associated with the use of corticosteroids are acceptable. Even at low dose, weight gain is clearly a problem when prednisone is used daily for more than a few months. Some patients will also develop Cushingoid features, including skin fragility and easy bruising. On the other hand, based on the trials cited above, osteoporosis does not seem to be a significant problem, although bisphosphonates were not used systematically as per the current recommendations of the American College of Rheumatology[23]. The rate of infection was not higher than in patients not receiving CS. There is also a growing body of evidence suggesting that the use of low-dose CS may decrease the risk of cardiovascular morbidity and mortality in patients with RA, perhaps through amelioration of systemic inflammation and improvement of lipid abnormalities[24].

As suggested by a recent review of the literature, common fears of CS toxicity seem to originate from excessive weight on anecdotal data and observations with high doses,

such as used in systemic lupus erythematosus, polymyositis, systemic vasculitis, or organ transplantation[25]. I agree with the authors of that review that this fear is associated with a high risk of "throwing out the baby with the bath water." It is time to review our treatment strategies for RA. Low-dose prednisone is effective and safe and prevents joint destruction. It is also a lot cheaper and as effective as anti-tumor necrosis factor-α agents when used temporarily in combination with other DMARD[22]. What more evidence do we need before revising our treatment algorithms?

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REFERENCES

1. Hench PS, Kendall EC, Slocumb CH, Polley HF. The effect of a hormone of the adrenal cortex (17-hydroxy-11-dehydrocorticosterone: Compound E) and of pituitary adrenocorticotropic hormone on rheumatoid arthritis. Proc Staff Meet Mayo Clin 1949;24:181-97.
2. Conn DL. Resolved: Low-dose prednisone is indicated as a standard treatment in patients with rheumatoid arthritis. Arthritis Rheum 2001;45:462-67.
3. Saag KG. Resolved: Low-dose glucocorticoids are neither safe nor effective for the long-term treatment of rheumatoid arthritis. Arthritis Rheum 2001;45:468-71.
4. Boers M. Studying the benefit/risk ratio of glucocorticoids in rheumatoid arthritis. J Rheumatol 2007;34:661-3.
5. Comparison of cortisone and codeine medication as an adjuvant to manipulation in rheumatoid arthritis; a report to the Joint Committee on cortisone and A.C.T.H. in chronic rheumatic diseases of the Medical Research Council and the Nuffield Foundation. Br Med J 1954;1:233-5.
6. Comparison of cortisone and aspirin in the treatment of early cases of rheumatoid arthritis; a report by the Joint Committee of the Medical Research Council and Nuffield Foundation on clinical trials of cortisone, A.C.T.H., and other therapeutic measures in chronic rheumatic diseases. Br Med J 1954;1:1223-7.
7. A comparison of cortisone and aspirin in the treatment of early cases of rheumatoid arthritis; a second report by the Joint Committee of the Medical Research Council and Nuffield Foundation on clinical trials of cortisone, A.C.T.H., and other therapeutic measures in chronic rheumatic diseases. Br Med J 1955;2:695-700.
8. Empire Rheumatism Council; multi-centre controlled trial comparing cortisone acetate and acetyl salicylic acid in the long-term treatment of rheumatoid arthritis; results up to one year. Ann Rheum Dis 1955;14:353-70.
9. Empire Rheumatism Council: multi-centre controlled trial comparing cortisone acetate and acetylsalicylic acid in the long-term treatment of rheumatoid arthritis; results of three years' treatment. Ann Rheum Dis 1957;16:277-89.
10. A comparison of cortisone and prednisone in treatment of rheumatoid arthritis; a report by the Joint Committee of the Medical Research Council and Nuffield Foundation on clinical trials of cortisone, ACTH and other therapeutic measures in chronic rheumatic diseases. Br Med J 1957;2:199-202.
11. Report by the Joint Committee of the Medical Research Council and Nuffield Foundation on clinical trials of cortisone, ACTH, and other therapeutic measures in chronic rheumatic diseases. A comparison of prednisolone with aspirin or other analgesics in the treatment of rheumatoid arthritis. Ann Rheum Dis 1959;18:173-88.
12. Gotzsche PC, Johansen HK. Meta-analysis of short-term low dose prednisolone versus placebo and non-steroidal anti-inflammatory drugs in rheumatoid arthritis. BMJ 1998;316:811-8.
13. Criswell LA, Saag KG, Sems KM, et al. Low-dose corticosteroids in rheumatoid arthritis. A meta-analysis of their moderate-term effectiveness. Arthritis Rheum 1996;39:1818-25.
14. Kirwan JR and the Arthritis and Rheumatism Council Low-Dose Glucocorticoid Study Group. 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.
15. Boers M, Verhoeven AC, Markusse HM, et al. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. Lancet 1997;350:309-18.
16. Dougados M, Combe B, Cantagrel A, et al. Combination therapy in early rheumatoid arthritis: a randomised, controlled, double blind 52 week clinical trial of sulphasalazine and methotrexate compared with the single components. Ann Rheum Dis 1999;58:220-5.
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. van Everdingen AA, Jacobs JWG, van Reesema DRS, Bijlsma JWJ. 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.
19. Jacobs JW, van Everdingen AA, Verstappen SM, Bijlsma JW. Followup radiographic data on patients with rheumatoid arthritis who participated in a two-year trial of prednisone therapy or placebo. Arthritis Rheum 2006;54:1422-8.
20. Svensson B, Boonen A, Albertsson K, van der Heijde D, Keller C, Hafström I, for the BARFOT Study Group. Low-dose prednisolone in addition to the initial disease-modifying antirheumatic drug in patients with early active rheumatoid arthritis reduces joint destruction and increases the remission rate. A two-year randomized trial. Arthritis Rheum 2005;52:3360-70.
21. Wassenberg S, Rau R, Steinfeld P, Zeidler H, for the Low-Dose Prednisolone Therapy Study Group. Very low-dose prednisolone in early rheumatoid arthritis retards radiographic progression over two years. Arthritis Rheum 2005;52:3371-80.
22. Goekoop-Ruiterman YPM, 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). Arthritis Rheum 2005;52:3381-90.
23. Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis: 2001 update. American College of Rheumatology Ad Hoc Committee on Glucocorticoid-Induced Osteoporosis. Arthritis Rheum 2001;44:496-503.
24. Davis JM, Maradit-Kremers H, Gabriel SE. Use of low-dose glucocorticoids and the risk of cardiovascular morbidity and mortality in rheumatoid arthritis: What is the true direction of effect? J Rheumatol 2005;32:1856-62.
25. Da Silva JAP, Jacobs JWG, Bijlsma JWJ. Revisiting the toxicity of low-dose glucocorticoids. Ann NY Acad Sci 2006;1069:275-88.