Glucocorticoids (GC) are a mainstay of the therapy in rheumatoid arthritis (RA). Currently, and despite their extensive use, the discussion about the benefits and adverse effects of low dose GC in the management of RA persists. In recent years, a number of clinical trials have attempted to establish the benefits of long-term GC use as a disease-modifying antirheumatic drug in RA, and to define their side effects. Results of these clinical trials provide solid evidence that low-dose GC can inhibit radiographic damage in early RA, and that side effects of GC, when used in that clinical framework, are limited to hyperglycemia, cataracts, and transient weight gain.

Key words: Rheumatoid arthritis. Glucocorticosteroids. Disease-modifying anti-rheumatic drugs.

Introduction

Use of glucocorticoids (GC) began more than 50 years ago for the treatment of rheumatoid arthritis (RA). However, up until a decade ago, its potential role as a disease modifying anti-rheumatic drug (DMARD) and its capacity to prevent radiologic damage had not been proposed. Some initial studies indicated a disease modifying drug, but in the following years, probably due to questions regarding the appearance of multiple side effects, GC use started to be more cautious and few studies on their use in RA were carried out.

In the past few years, different clinical trials have been published in which research into the role of low-dose GC as DMARDs in RA is carried out, as well as a characterization of side effects. They are mostly randomized clinical trials with different designs and variable follow-up periods; its main characteristics are summarized in Table.

Efficacy of Systemic Glucocorticoids in Rheumatoid Arthritis

The first study that indicated a possible effect of GC on structural damage in RA was published by Harris et al in 1983. It was a randomized and placebo controlled trial in which 18 patients with RA were treated with low-dose prednisone (5 mg/day) for 24 weeks, which was abruptly...
Clinical Trials That Evaluate the Effect of Glucocorticoids in Rheumatoid Arthritis

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<td>GC superior to placebo</td>
<td>GC similar to placebo</td>
<td>Weight gain. Glaucoma. Hypertension. Gastric ulcer (without reaching statistical significance)</td>
</tr>
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aNSAID indicates non-steroidal anti-inflammatory drugs; RA, rheumatoid arthritis; BMD, bone mineral density; DMARD, disease modifying anti-rheumatic drugs; GC, glucocorticoid; MTX, methotrexate; NS, not significant; SSZ, sulphasalazine.
suspended afterward in comparison to 16 patients with placebo. Although at 12 weeks there had been an improvement in the number of painful joints in the group treated with prednisone, no differences between the groups were observed at 24 weeks. After the suspension of the drug there was a clear worsening of the prednisone group, something that was interpreted as a sign of efficacy. With regard to radiologic progression, at the end of follow-up there were evident erosions in 1 of the patients of the prednisone group and in 4 patients of the placebo group. Unfortunately, the total number of patients which were included was small, something that impedes the establishment of solid conclusions.

Twelve years had to pass before Kirwan\(^4\) published the results of a double blind clinical trial in which 128 patients with active RA of less than 2 years since onset were included, who were randomized to receive 7.5 mg of prednisolone every day or placebo. Additionally they were allowed to receive any other drug for the treatment of RA based on the judgment of their usual medical team, except systemic corticosteroids. Using the Larsen radiologic assessment method, the disease progressed in the first year from a mean of 0.73 units in the prednisolone group versus 3.63 units in the placebo group (\(P=0.052\)). At 2 years, the Larsen index increased 0.72 units in the prednisolone group versus 5.37 units in the placebo group (\(P=0.004\)). At 3 months since the start of treatment there was a larger reduction in the incapacity and pain indexes, as well as in the joint counts in patients treated with prednisolone, and after 2 years of follow-up, only 22% of the patients who had received prednisolone presented radiologic erosions, versus 45% in the placebo group (\(P=0.007\)). After suspending treatment with prednisolone at 2 years, during the third\(^9\) there was an increase in radiologic damage in spite of the fact that most of the patients still received a baseline treatment with DMARD. During the third year, radiologic progression was similar to that presented in the placebo group during the first year of follow-up.

van Gestel et al\(^9\) carried out a randomized, double blind, and placebo controlled trial in which 40 patients with RA treated with parenteral gold salts after the failure of other DMARDs were included. The inclusion criteria of this study did not set a limit to the time since onset of RA; except systemic corticosteroids. Using the Larsen radiologic assessment method, the disease progressed in the first year from a mean of 0.73 units in the prednisolone group versus 3.63 units in the placebo group (\(P=0.052\)). At 2 years, the Larsen index increased 0.72 units in the prednisolone group versus 5.37 units in the placebo group (\(P=0.004\)). At 3 months since the start of treatment there was a larger reduction in the incapacity and pain indexes, as well as in the joint counts in patients treated with prednisolone, and after 2 years of follow-up, only 22% of the patients who had received prednisolone presented radiologic erosions, versus 45% in the placebo group (\(P=0.007\)). After suspending treatment with prednisolone at 2 years, during the third\(^9\) there was an increase in radiologic damage in spite of the fact that most of the patients still received a baseline treatment with DMARD. During the third year, radiologic progression was similar to that presented in the placebo group during the first year of follow-up.

The COBRA\(^5\) study compared, in patients with RA of less than 2 years since onset (median of 4 months) with poor prognosis criteria, a combination of SSZ, MTX, and prednisolone (in a descending schedule from 60 mg/day to 7.5 mg/day and suspension at week 28) with SSZ monotherapy. The Sharp modified index was significantly larger in the SSZ monotherapy group at 28 (\(P<0.0001\)), 56 (\(P=0.004\)), and 80 weeks (\(P=0.01\)). A reduced radiologic deterioration was maintained in the group with prednisolone treatment after 5 years of follow-up.\(^1\) If we assume that both SSZ as the combination of MTX and SSZ have a similar effect in the progression of the disease, as seems to be demonstrated by several studies,\(^10-13\) the difference in the improvement between the 2 groups could be attributed to the prednisolone schedule. What’s more, in the BeSt study,\(^13\) in which the combined schedule of the COBRA study (COBRA schedule) was compared with other treatment modalities (sequential monotherapy with different DMARDs, step-up addition of MTX, SSZ, and HCQ, and first treatment with MTX plus infliximab) in 508 patients with RA of at least 2 years since onset, the patients who had undergone the COBRA schedule presented a faster functional improvement and a reduced radiologic progression after a year of treatment when compared to patients in the sequential or DMARD step-up monotherapy groups. Also, the results of the COBRA schedule were clinically and radiologically similar to those with combined MTX plus infliximab therapy.

However, Hansen et al,\(^14\) in a randomized, unblinded, and uncontrolled trial published in 1999, were not able to demonstrate the superiority of prednisolone at a mean dose of 6 mg/day versus not adding GC to DMARD for the prevention of radiologic damage after a year of treatment. It is possible that this difference in results with respect to the study by Kirwan\(^4\) owes itself in part to the fact that it did not include patients with early RA and that the patients in the group that received GC presented a significantly lower time since the onset of RA (2.8 years vs 8.5 years in the group without GC), something that could have led to a higher speed of the radiologic progression in the group that was treated with GC. Another study, published by Paulus et al,\(^15\) with a post hoc analysis, did not show any action of prednisone on the radiologic progression either, though such a trial was not specifically designed to study the effects of prednisone.
and included RA patients with a time since onset of disease between 1 and 7 years.

In 2000 Rau et al. published a randomized, double blind study in which the daily administration of 5 mg of prednisone was compared with placebo in patients with RA of less than 2 years since onset and who were allowed to receive concomitant treatment with MTX or parenteral gold salts. Significant differences were found in the radiologic damage indexes at 6, 12, and 24 months between both groups, due mainly to the rapid progression during the first 6 months in the placebo group, something that quadrupled the progression in the group treated with prednisolone. During the second year there was only a small progression in both groups, although only 76 of the 196 patients included completed the 2 years of follow-up. The authors recommended the treatment with low dose prednisolone during the first 12 months after the diagnosis of RA as a bridge therapy, waiting for the effect of DMARD on the radiologic progression. In a previous study of the same group, in which baseline therapy with cyclosporine A and parenteral gold salts were compared, a possible protective effect of GC on radiologic progression could already be seen.

van Everdingen et al. published in 2002 the results of a placebo controlled clinical trial with a novel design. In this clinical trial were included 81 RA patients with less than a year since the onset of disease and who had not received any DMARD previously. The patients were randomly assigned to 2 groups of treatment in such a way that 41 patients received 10 mg of prednisone a day and 40 received placebo for 2 years. The use of non-steroidal anti-inflammatory drugs (NSAID) was allowed in both groups as was the introduction of SSZ at a 2 g/day dose as rescue medication after the first 6 months of treatment. At 6 months, 39 of the 71 patients who completed the study were receiving SSZ (20 of 35 patients in the placebo group and 19 of 36 in the prednisone group). The prednisone group had a higher clinical improvement in almost all of the measured variables, but this difference was not maintained after 6 months, except when it came to the tender joint count and grip strength. After analyzing variables related to well being, statistically significant differences were found regarding mood and visual analog scales (VAS) for pain and the global disease evaluation on behalf of the patient after 3 months of the trial. Radiologic progression was significantly lower in the prednisone group, and this difference was maintained if at 2 years (Sharp index score of 16 [23] in the prednisone group vs 29 [26] in the placebo group at 2 years; P=0.007). The authors opinion was that the discrepancy between the clinical and radiologic results probably could be attributed to a higher use of complementary treatments, such as analgesia, NSAID, physiotherapy, or joint infiltration, in the placebo group, which could improve the clinical variables without avoiding radiologic damage. In the 5 year follow-up study (between 2 and 3 years after suspending treatment), yearly radiologic progression was evaluated as well as the number of patients with non-erosive disease at the end of treatment. No differences were found regarding the use and duration of DMARD therapy, the disease activity score (DAS)-28 or the clinical variables, except the concentration of C-reactive protein (CRP), which was lower in the group that received prednisone. Less radiologic progression was found in the prednisone group when compared to the placebo group, both in the total score of the Sharp/van der Heijde radiologic index (P=-0.01) as in the joint pinch test (P=-0.02), with a tendency similar to that seen in erosive disease. These latter results indicated that low-dose prednisone in recent onset RA had a disease modifying capacity.

In contrast, the study by Capell et al. did not show evidence of any effect by the GC on the prevention of radiologic damage. This randomized, double blind, placebo controlled clinical trial included 167 RA patients with less that 3 years since onset treated with SSZ who were randomized to receive 7 mg a day of prednisolone (84 patients) or placebo (83 patients) for 2 years. Fifty-nine per cent of the patients with erosions in the placebo group had radiologic progression, without differences in the 2 groups and 61% of the prednisolone group presented radiologic progression, without differences between 2 groups in any of the radiologic variables. There were no significant differences regarding clinical efficiency either. These results are an enormous contrast with those obtained by other authors. Differences between the populations studied (genetical and the percentage of patients with erosive disease), the systematic use of SSZ as a DMARD and different methods for evaluating radiologic damage could explain this discrepancy.

Svensson et al. selected 250 patients with active RA of less than 1 year since onset of disease, randomizing 119 to receive 7.5 mg/day of prednisolone and compared them to 131 patients who did not receive systemic GC. Placebo was not employed and therefore there was no blinding. All of the patients also received a DMARD chosen by their physician (fundamentally MTX or SSZ), and the use of NSAID and joint infiltrations with hexacetonide of triamcinolone was allowed. The change in the total radiologic score according to the modified Sharp/van der Heijde score was less marked in the group receiving prednisolone both at 1 year as at 2 years, with significant differences between the 2 groups. The erosion index was also significantly reduced in the prednisolone group and registered a similar tendency, without statistical significance, regarding the joint pinch index. With regard to clinical efficacy, quantified through DAS-28, significant differences were found between both groups in favor of prednisolone from 3 months of treatment; these differences were maintained all throughout the follow-up (6, 12, 18, and 24 months).

Recently, Wassenberg et al. have published new data on the previu study by Rau et al., in which 192 patients
were included (94 in the prednisolone 5 mg/day and 98 in the placebo group) with RA of less than 2 years since onset, treated with MTX or parenteral gold salts. Differences in the radiologic progression, according to the Ratingen index, between both groups were significant in favor of the prednisolone group during all of the 24 month follow up, though much more evident during the first 6 months. However, the largest clinical efficacy of the GC was not maintained beyond 6 months.

In a Cochrane Library\textsuperscript{24} 2006 review, in which only studies with low dose corticosteroids were taken into account compared with placebo or low dose NSAIDs and followed up for a brief period, the conclusion was that doses equivalent or inferior to 15 mg of prednisolone were very effective in the treatment of RA. This analysis excluded most of the previously cited studies because of the long-term follow-ups.

### Security of Systemic Glucocorticoids in Rheumatoid Arthritis

On of the main causes of the polemic surrounding chronic GC use in the treatment of RA is the fear of it numerous and sometimes serious side effects. It is a frequent tendency to mix the prevalence of adverse events of GC without taking into account the baseline disease, the dose or the duration of treatment. But if the long list of the well-known side effects secondary to GC use is limited to those related with low doses, and concretely in patients with RA, it will be easy to understand that, in spite of these suspicions, GC are still a first line drug in the chronic treatment of RA.

### Corticosteroid Osteoporosis

GC induced osteoporosis is one of the biggest concerns when speaking about side effects. Different studies related to the appearance of fractures in corticoid osteoporosis have evidenced that the risk is determined by several factors such as bone mineral density (BMD) before and after treatment, the underlying disease for which GC are prescribed, the risk of falling and, finally, bone resistance, because it has been seen that patients who receive GC have fractures with higher values of BMD.\textsuperscript{25-28} Of all these factors, the ones that have been compared the most are dose and duration of treatment, though there has not been a consensus on the dose that could be considered as safe in order not to increase the risk of osteoporotic fracture. What does seem more evident is that the risk is more firmly related to the daily dose of GC than to the cumulative dose.\textsuperscript{29} In a study\textsuperscript{30} in which 205 patients with RA who were receiving oral GC versus 205 controls who were not, a 25% of spinal deformity was seen in the group with GC treatment versus 13% in the control group (odds ratio [OR], 2.34; 95% confidence interval [CI], 1.39-3.93), and these were dose-dependent. In the case-control study by Saag et al\textsuperscript{31} a larger incidence of fractures in any localization was seen, with an OR of 3.9 (95% CI, 0.8-18.1) for the variable use/no use of prednisone. In addition, van Everdingen et al\textsuperscript{32} registered double the incidence of vertebral fractures in the prednisone group. Other studies such as those by Capell et al,\textsuperscript{33} Svensson et al,\textsuperscript{34} or Wassenberg et al,\textsuperscript{35} who evaluated BMD instead of the incidence of fractures, did not find significant differences between groups. In a subgroup of 24 patients included in the study by Kirwan,\textsuperscript{4} a spinal and hip BMD determination was carried out every year. Although the prednisolone group lost more bone mass in the lumbar spine area during the first year of treatment, this difference with the placebo group was compensated during the second year, at the end of which there were no significant differences.\textsuperscript{32} In this same way, in a review by Verhoeven et al\textsuperscript{36} the conclusion was that bone mass loss occurs prematurely in the course of treatment with low dose GC, but is stabilized with time in patients who receive prolonged treatment, and is even reversed upon the suspension of treatment.

In the COBRA\textsuperscript{8} study, in which far superior GC doses were employed, the differences in BMD also failed to achieve statistical significance. However, Hansen et al\textsuperscript{41} found a significant reduction in the BMD of the lumbar spine only in the group treated with prednisolone. Curiously, in this study, the BMD of the wrist and hand remained stable in the prednisone group and was significantly reduced in the group that only received 1 DMARD. On the other hand, some authors have pointed out that, in the treatment of RA, the initial detrimental effect of GC in bone remodeling is compensated by an important reduction in the inflammatory burden, which can even protect the bone.\textsuperscript{32,34} It is necessary to consider that RA activity leads to a reduction in physical activity and a great elevation of inflammatory cytokines that stimulate the differentiation of osteoclasts. Therefore, the reduction in the inflammatory burden would reduce the bone loss.\textsuperscript{34,35} Fortunately, osteoporosis induced by low doses of GC can be prevented by the use of calcium and vitamin D supplements in combination with a biphosphonate.\textsuperscript{36,37}

### Susceptibility to Infection

Another great worry with respect to the chronic use of GC is the increase in the susceptibility to viral, bacterial, fungal, and parasitic infections. The exact mechanism that causes this susceptibility is unknown, but it seems that the risk of infection increase with the dose and duration of treatment, and is reduced in patients who use lower doses and treatment durations, even if the accumulated dose is elevated.\textsuperscript{34} In this sense, Saag et al\textsuperscript{31} manifested a larger incidence of serious infections...
(pneumonia, septic arthritis, bursitis, and complicated urinary infections) in the prednisone group than in controls, but the mean dose and the cumulative prednisone dose were associated to a very small relative risk. In a metaanalysis of 71 studies, which included 2111 patients with different diseases and different GC doses, the relative risk seen for infection was 2. However, in the 5 studies that included patients treated with GC indicated for rheumatic disease, no greater risk for infection was found, as was also the case in the subgroup of patients treated with doses inferior to 20 mg/day of prednisone, independently of the underlying process.

Gastrointestinal Security

As for the gastro erosive potential of GC, it currently seems clear that they do not increase the risk of peptic disease by themselves, though they can multiply the effect of NSAIDs. In a study with 2105 patients and 11 500 controls the relative risk of peptic disease after the use of GC was 1.8 (95% CI, 1.3–2.4) with respect to controls, without finding significant dose-dependent differences. However, in patients who concomitantly employed GC and NSAID, the risk was 8.5 (95% CI, 3.9–18.9) times that of controls. Moreover, the risk after the use of NSAIDs did relate to the dose. Another study has found a relative risk of 14.6 (95% CI, 6.7–32) for peptic ulcer in patients that used both drugs versus those who do not use any. Therefore, in patients that use GC without NSAID, the use of proton pump inhibitors would not be indicated.

Diabetes Mellitus

Hyperglycemia can appear with relative speed after the start of steroid treatment. With doses lower than 8 mg of prednisone per day (equivalent to 39 mg of hydrocortisone), the risk of hyperglycemia was 1.77 (95% CI, 1.54–2.02), and increases parallel to the dose of GC employed, reaching 10.34 (95% CI, 3.16–33.90) for doses over 25 mg of prednisone per day. It can also appear after joint infiltration of GC. Patients with prior risk factors for the development of diabetes mellitus, such as obesity or a family history, also have a larger risk of presenting hyperglycemia during GC treatment. But the appearance of frank diabetes mellitus with low-dose GC is very infrequent. A slight weight gain is usual, even with low GC dose, but can be reversed after treatment suspension.

Cataracts

Posterior subcapsular cataracts are the most typically associated to GC, though cortical cataracts can also appear. In a case-control study, 29% of patients treated with prednisone developed cataracts versus 18% in the control group, after 10 years of treatment, a statistically significant difference. In addition, in the metaanalysis by Saag et al a larger incidence of cataracts in patients receiving GC was also seen.

Vascular Complications

The incidence of vascular complications, such as acute myocardial infarction, heart failure, or stroke, is not increased in patients who receive chronic treatment with doses beneath 7.5 mg a day of prednisolone. However, in patients who receive high doses of GC, it has been calculated that the relative risk of cardiovascular events (CVE) is 2.56 (95% CI, 2.18–2.99). With respect to dyslipidemia, the situation is similar to that of the action of corticoids and RA on bone metabolism. The inflammatory activity of RA alters the lipid profile, increasing the risk for CVE. Treatment of the disease, including GC, by reducing inflammatory activity, can revert these changes and therefore act as a cardioprotector. In a retrospective study with 211 patients, it was evident that hypertension, late–onset disease, and male gender increased the risk for CVE. As for GC, cardiovascular risk increased if they had been used at the beginning of the disease, but their prolonged administration (more than 1 year) did not increase the risk. In the case of observational studies, without random allocation of GC treatment, there is the possibility that the use of GC at the beginning of RA could be a marker of serious disease, something that by itself would suppose a larger cardiovascular risk. Therefore it can be concluded that, more than GC, it seems that the disease itself elevates the risk of cardiovascular complications in patients with RA.

Other Complications

As a general rule it has been seen that all of the secondary effects cannot be avoided with alternate day administration. Other complications, such as osteonecrosis, steroid myopathy, hypertension, or steroid psychosis are more infrequent and have only been related to large doses of GC. The side effects of GC at low doses, documented in different studies, are much less frequent than those observed with elevated doses of GC. If we also take into account an indication bias, it is very probable that the complications directly linked to the use of low-dose GC are even less frequent. It is necessary to emphasize that the patients with a more severe disease and with more comorbidity have a larger probability of receiving treatment with GC when compared to patients with adequately controlled RA, making the attribution of certain event to GC use something that is not exempt of criticism.
Conclusions and Practical Recommendations

There is solid evidence, generated through high methodological quality clinical trials, that low-dose GC have a modifying effect on structural damage in short term RA. The dose, and especially the ideal duration to obtain an optimal disease modifying effect, is unknown. It is also unknown if this disease modifying effect is also produced when associating low-dose GC not to a conventional DMARD, but to one of the new anti-tumor necrosis factor antagonist drugs.

From a practical standpoint, in recent onset RA and with an important inflammatory burden, the glucocorticoid scheduling of the COBRA study allows for a rapid and effective control of inflammatory activity, while DMARDs, typically methotrexate in a rapidly ascending dose, carries out it controlling effect on the disease. Keeping prednisone under 10 mg/day for the first 2 years of treatment also seems recommendable, because it adds a beneficial effect to conventional DMARDs in the progression of radiologic damage. The isolated use of GC is not justified and they should always be used with a conventional DMARD or a biologic.

Treatment with GC in these conditions presents few secondary effects, such as the development of cataracts, hyperglycemia, and a transitory weight gain. The effect on bone metabolism, as well as on cardiovascular risk factors, is still controversial because GC reduce the inflammatory burden of the disease and could even have a beneficial effect. The use of calcium, vitamin D, and bisphosphonate to prevent GC induced osteoporosis is recommended.

References