Balancing the benefits and risks of low-dose glucocorticoid in rheumatoid arthritis

Santiago T[1], Jacobs JW[2], Saag KG[3], Buttgereit F[4], Pereira da Silva JA[1]

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ABSTRACT

Glucocorticoids (GCs) have potent anti-inflammatory and immunomodulatory effects and are widely use in the management of rheumatoid arthritis in combination with other synthetic and with biological disease--modifying anti-rheumatic drugs. Concerns about the risk of adverse effects of glucocorticoids, especially if they are given at higher dosages and for a longer time, hamper their use, despite the clear symptomatic and disease-modifying benefits. However, the evidence base for these concerns for low dose glucocorticoid therapy is quite limited due to the scarcity of quality literature on its safety in rheumatoid arthritis. This review discusses: 1) the current understanding about its disease-modifying effects, 2) toxicity data from recent trials and observational studies, 3) recommendations for its management and the current efforts to improve the therapeutic ratio of glucocorticoid through the development of new formulations, such as modified-release prednisone.

Keywords: Rheumatoid arthritis; Glucocorticoids; Benefits; Risks.

INTRODUCTION

With over 60 years of experience, the number of patients treated with glucocorticoids (GCs), and the range of clinical applications are more extensive than with any other treatment. GCs represent a true anchor treatment for rheumatoid arthritis (RA). This is supported by data indicating that up to 60% of all patients with RA in Germany is treated with GCs at some time during the course of their disease[1]. Similarly, 34 to 93% of all patients entering recent clinical trials of biologics, and thus with active disease, were receiving GCs at baseline[2]. Such data are in contrast with the literature predominantly addressing the risks of these agents and the caution advised by every treatment recommendations. Clinicians, and presumably patients, seem thus to value the anti-inflammatory, immunosuppressive and disease-modifying therapeutic effects of GCs. In contrast, both the literature and the medical community seem to be split between those in favour and those against the use of low-dose GCs in RA. This contention cannot be resolved without a clear understanding of the potential risks of adverse effects of these drugs. Unfortunately, currently available evidence is limited, but the need to optimize benefit-risk ratio of GCs represents a continuous challenge to the practicing clinician. This review reinforces the need for balancing risks and benefits of GCs use in RA, with a focus on chronic oral therapy. First, we address the rapid effect of GCs on disease activity and their long-term effects on radiographic damage, followed by their prolonged use in controlled disease. Next, we discuss the toxicity of low-dose GC therapy. Finally, we describe strategies and recommendations for its safe use and new therapeutic approaches, including chronotherapy, which may improve our ability to tailor treatment to the individual patients' needs.

1 Rheumatology Unit, Centro Hospitalar e Universitário de Coimbra, Portugal. Faculdade de Medicina da Universidade Coimbra, Portugal
2. Department of Rheumatology and Clinical Immunology, University Medical Center Utrecht, The Netherlands
3. Division of Clinical Immunology and Rheumatology, University of Alabama, Birmingham, USA
4. Department of Rheumatology and Clinical Immunology, Charité Universitätsmedizin, Berlin, Germany

A. BENEFITS

Symptomatic benefit

In active RA, prednisone is frequently added for a short period to the treatment regimen to rapidly minimize disease activity while awaiting a clinical response to a slower-acting disease-modifying antirheumatic drug (DMARD). A review[3] provided evidence of short-term benefit in RA: a dose below prednisolone 15 mg/day is

more effective than either placebo or a nonsteroidal anti-inflammatory drug (NSAID), with a large effect size of 1.75 on pain. In 2000, a Cochrane meta-analysis[4] including 7 studies (253 patients in total) evaluating the symptomatic effect of GC treatment in RA, concluded that prednisone (or a comparable GC preparation) at a mean dosage of less than or equal to 15 mg/day for a period of 6 months, was significantly more effective than placebo, with an effect size for pain of 0.43. Significant improvement was also documented in other outcomes measures: standardized mean difference for tender joints = -0.37 (95%CI: -0. 59 to -0.14), swollen joints = -0.41 (-0.67 to -0.16) and functional status = -0.57 (-0.92 to -0.22). Another meta-analysis of short-term (median length of treatment was one week in the ten studies included) found that prednisolone (<15 mg/day) had a clear superior effect on pain compared to placebo (standardized effect size 1.75; 0.87 to 2.64) and compared to NSAIDs (1.25; 0.26 to 2.24)[3]. Recently, numerous clinical trials in early RA have demonstrated significant symptomatic benefit and clinical improvement, already at 3 months after the start therapy, which is maintained at all time points thereafter, until 2 years of follow-up[5-7] (Table I). In the Arthritis Research Council (ARC) trial[8], the patients in the prednisolone group had greater reductions than the patients in the placebo group in scores on an articular index and for pain and disability at 3 months; for pain at 6 months; and for disability at 6, 12, and 15 months (all $p < 0.05$). In 2002, van Everdingen et al.[5] found a greater clinical improvement in multiple measures, particularly in the first 6 months, in the 10 mg/day prednisone treated group. However, this additional benefit was sustained only for joint tenderness at 24 months. The Better Anti-Rheumatic FarmacOTherapy (BARFOT) study[6] compared the addition of 7.5mg/day prednisolone to methotrexate (MTX) or sulfasalazine (SSZ) with DMARD alone in 250 patients with a disease duration of less that one year. The patients treated with DMARD plus prednisolone had a significant reduction of DAS28 and HAQ score. These differences were already seen at 3 months, and were present at all time points thereafter, during the 2-years of follow-up. In the prednisolone group, the mean (SD) DAS28 decreased from 5.3 (1.1) to 2.7 (1.5) *versus* 5.4 (1.0) to 3.3 (1.5), ($p<0.001$) after 1 year, and to 2.7 (1.3) *versus* 3.2 (1.4), ($p<0.005$) after 2 years. After 1 year, 51% of patients in the pre-dnisolone group had achieved disease remission compared with 39% of patients in the no-prednisolone group ($P = 0.06$). After 2 years, this difference had increased to 56% in the prednisolone group compared with 33% in the placebo group ($P = 0.0005$). The Computer Assisted Management in Early Rheumatoid Arthritis trial-II (CAMERA-II)[7] evaluated the effect of prednisolone 10 mg/day from start, added to an MTX-based strategy with computer-assisted dose adjustments based on the level of disease activity *versus* the effect of the MTX-based strategy with placebo-prednisone in 236 patients with symptoms duration <1 year. Also this treat-to-target (target defined as remission) study[7] confirmed the efficacy of prednisone 10 mg/day added to DMARD in reducing disease activity and physical disability at 24 months. The patients treated with prednisone at 10 mg/day had more symptomatic benefit during the first three months - mean difference of DAS28 was -1.56 (CI, -1.88 to -1.25). This difference was sustained but was not significantly different anymore at the end of two years: -0.26 (CI, -0.68 to 0.16), because both step-up strategy arms were aimed at remission. The response rates after 1 year of treatment for the MTX-based strategy plus prednisone and the MTX-based strategy plus placebo were respectively for the ACR20 70% *versus* 66% ($P = 0.45$); for the ACR50 56% *versus* 43% ($P= 0.037$), and for the ACR70 27% *versus* 26% ($P = 0.82$). Similar differences were seen at 2 years.

Regarding efficacy seen with 5 to 7 mg/day, in the study of Capell et al.[9] a dose of 7 mg/day prednisolone was associated with a non-significant improvement ($p=0.07$) in individual clinical measures and a "modified" ACR 20% response (20% improvement in Ritchie articular index, erythrocyte sedimentation rate, pain scores, physician global, patient global, HAQ) in the prednisolone group *versus* placebo.

In intensive (tight-control, treat-to-target) treatment strategies in early RA, GCs are mainly used to achieved fast symptomatic improvement and disease-control. As an alternative to initial high oral doses such as in Combinatietherapie Bij Reumatoïde Artritis (COBRA), recently trials have shown positive effects of either one intramuscular 120 mg methylprednisolone administration[10], and even intra-articular GC injections into inflamed joints[11].

Long-term symptomatic efficacy

Several papers and textbooks state that the beneficial effects of GCs upon symptoms tend to wear off or disappear after one or two years of treatment. Such opinions are contradicted by studies demonstrating that

TABLE I. EFFECTS OF LOW- TO MEDIUM-DOSE OF GCs DURING RCTs, AND FOLLOW-UP THEREAFTER, IN RA.

Study name	Study details	Disease activity	Function	Radiographic damage	Follow-up
ARC Kirwan et al. (1995)[8] Hicking P et al. (1998)[30]	– 2 year study – n=128, RA<2yrs – GC=61, Controls=67 – PDN 7.5mg/day plus any DMARD	++	++	++	1 year after trial: joint destruction continued after stopping PDN
van Everdingen et al. (2002)[5]	– 2 year study – n=81, RA<1yr – GC=41, Controls=40 – PDN 10.0mg/day, no DMARD (SSZ rescue after 6 months)	++		++	5 years after trial: significantly less radiographic progression in the PDN group[19]
WOSERACT Capell et al. (2004)[9]	– 2 year study – n=128, RA<3yrs – GC=61, Controls=67 – PDN 7mg/day, plus SSz	+	+	-	Not reported
LDPT Wassenberg et al. (2005) (15)	– 2 year study – n=76, RA<2yrs – GC=34, Controls=42 – PDN 5mg/day plus IM gold or MTX	+	+	+	3 years afterwards: disease-modifying properties persisted after clinically guided tapering and withdrawal of PDN treatment[19]
BARFOT Svensson et al. (2005)[6]	– 2 year study – n=258 – GC=119, Controls=139 – PDN 7,5mg/day plus any DMARD (MTX/SSZ)	++	++	++	At 4 years: among patients in clinical remission at 2 years, those originally treated with PDN presented less radiographic progression than those originally treated with DMARDs alone[31]
CAMERA II Bakker et al. (2012)[7]	– 2-year study – n=236, RA<1year – GC=117, Controls=119 – PDN 10mg/day added to MTX-based strategy	++	++	++	Not reported
Montecucco et al. (2012)[32]	– 1 year study – n=220, RA<1year – GC=110, Controls=110 – PDN 12.5mg/day for 2 weeks tapered to 6.25mg/day	++	Not reported	Not reported	Not reported

In total, 1127 patients were included (GC = 543; controls = 584). In most cases, the comparator was placebo with DMARD
++, Statistically significant effect; +, non-statistically significant trend; -, no effect. PDN: prednisone or prednisolone

the withdrawal of even very low doses of GCs, in patients with stable disease under long-term therapy, is followed by disease flares in a high percentage of patients.

A randomized double-blind placebo controlled withdrawal trial of prednisone included 31 patients with RA in remission with stable doses of 1 to 4 mg/day prednisone for at least 12 weeks. Patients were randomized to the same dose prednisone in 1 mg tablets or identical placebo tablets, for 24 weeks[12]. Patients who were switched from stable doses of prednisone to identical placebo tablets were significantly more likely to withdraw the study due to lack of efficacy over a subsequent 6–9-month period (11 out of 15) than those who were randomized to continued prednisone (3 out of 13, p=0.02). Another study by Tengstrand *et al*.[13], with a similar design, included 58 RA patients treated with 5 to 7.5 mg prednisolone/day for at least 2 years. Of the 26 patients randomized to stop prednisolone treatment (median DAS28 at baseline 3.8), 11 (42%) succeeded to stop treatment and 15 (58%) failed withdrawal of GCs because of increased joint symptoms. Finally, in a withdrawal study among patients, whose RA had been controlled for at least 3 months mean GCs treatment duration, 7.5 years; (mean daily dose, 8.6mg/d), the GCs dose was decreased each month by steps of 1 mg/day[14]. At study end, 10 patients successfully has stopped prednisolone but 23 patients had experienced a flare of the disease (1 patient stopped the study because of adrenal insufficiency and 4 were lost to follow-up). However, only one patient had been able to decrease the dose by 1 mg/month steps as planned; the mean decrease for all patients was 1 mg/3.5 months. Successful withdrawal was more common among patients who had been on GC treatment for less than 5 years[14].

Taken together, notwithstanding the relatively small number of patients included, these results suggest that GCs may retain favourable symptomatic effects for a long time, even in patients in remission. This would suggest that GC withdrawal should not be considered an obligatory path but should rather depend on the evaluation of risks and benefits in the individual patient. Interestingly, some authors tend to refer to the aggravation of disease after GC withdrawal as "rebound effect" or physical dependency. However, none of the withdrawal studies we revised suggests that the disease gets worse or more difficult to control after GC treatment is stopped. This concept of "rebound" is exclusively used in respect to GCs – when observed with other medications, it is taken as evidence of efficacy. Furthermore, aggravation of disease activity after stopping another DMARD than prednisone is never seen as physical dependency, so why then should it be physical dependency for prednisone? These, at least apparent, biases deserve reflection.

DMARD properties in early RA

The disease-modifying effects of GCs have been well established in a number of randomized controlled trials of up to 2 years duration, using 5-10 mg/day of prednisolone or equivalent, in early RA[6, 9, 15] and have been confirmed in two meta-analyses[16, 17] (Table I).

In 1995, in the ARC trial, after two-year treatment, prednisolone therapy had resulted in significantly fewer hand erosions (22 *versus* 46%)[18].

In 2002, van Everdingen *et al.*[5] found that radiographic progression was less in the prednisone-treated group, and this advantage persisted for at least three years following the completion of two years of prednisone treatment study[19].

Also in the CAMERA-II study[7], the MTX-based strategy plus prednisolone was more effective than MTX-based strategy plus placebo in reducing the progression of erosive joint damage as assessed at 104 weeks. This study additionally demonstrated the joint sparing benefit of prednisone even if added to an MTX-based tight-control strategy. After 2-year treatment, the prednisone group showed a statistically significantly lower progression of radiologic scores than the placebo group, although the absolute difference was small (difference in Sharp-van der Heijde score of 0.87 units) because of low radiologic scores in both strategy groups due to intensive therapy[7].

In the study of Capell *et al.*[9] a dose of 7 mg/day of prednisone was not better than placebo in inhibiting radiographic joint damage. Authors attributed this negative result to factors such as different therapeutic protocols, different baseline populations and a different radiographic scoring system (Larsen score), compared to studies that demonstrated a DMARD-effect of prednisone.

In 2007, a Cochrane meta-analysis included randomized controlled trials with at least one arm including GC treatment and one arm without this therapy. All studies measured radiographic change in joints of the hand and/or feet. Fifteen studies, with approximately 1400 patients mostly with **early RA**, provided clear evidence that GCs substantially reduce the rate of radiographic progression in early RA[16]. If including

studies with very low doses of GCs and patients not taking DMARDs, the average reduction in the rate of progression was almost 70%.

In 2014, another systematic review[17] assessing the efficacy of GCs in **early RA** (<2 years of duration) confirmed that initial treatment with low-dose prednisolone plus MTX results in better structural outcomes compared with MTX alone.

The joint-sparing effects persist after glucocorticoid treatment discontinuation

Finally, some studies report enduring effects of GC upon structural damage progression long after GCs have been discontinued[6, 19, 20]. In the Utrecht trial, the radiographic scores showed significantly less progression over 3 years of follow-up after study closure in the former prednisolone group than in the former placebo group[19]. However, the inhibition effect of GCs on formation of erosions, is only partial and additional DMARD therapy is required for control of radiographic joint damage[19].

In the COBRA trial, patients with early RA treated with prednisolone (initially 60 mg/day, rapidly reduced to 7.5 mg/day during weeks 7–28 and subsequently stopped) together MTX and SSZ showed significantly less radiographic progression compared with the group treated with SSZ alone. The benefits of short-term combination therapy on disease progression were still evident at 5-year and 11-year follow-up[20, 21]. Can these differences be attributed to GCs? In fact, two randomized controlled 52-week trials, in patients with early RA[22, 23], treated with SSZ or MTX or MTX plus SSZ (with no GC use in any of the three groups) have proven that MTX plus SSZ was not more effective than either drug alone. These observations suggest that the superiority of combination therapy over monotherapy in COBRA may primarily rest upon the effects of prednisolone.

Recently, a non-inferiority trial comparing COBRA and COBRA-light therapy (initial prednisolone 30 mg/day plus MTX increased to 25 mg/week) revealed similar efficacy in suppression of clinical disease activity and improvement of function. Both groups showed major improvements in DAS44 at 52 weeks: mean (SD) –2.41 (1.2) in the COBRA and –2.02 (1.0) in the COBRA-light group (p=ns). In addition, both strategies have been shown to effectively suppress progression of joint damage at 52 weeks of treatment[24].

Although these benefits on disease progression have been shown, it is difficult to distinguish the contributions made by different individual components in a combination strategy that includes GCs and synthetic DMARD. It may also be that the COBRA trials, as other intensive treatment strategy studies[25,26], provide support for an intensive target-oriented strategy rather than for the use of specific individual disease-modifying drugs, as they are strategy trials, not drug trials[27].

Are Glucocorticoids DMARDs?

Drugs are considered DMARDs in RA if they reduce inflammation and pain, limit joint destruction and improve long-term disease outcome. Based on the evidence available, the question above can only receive a clear and solid YES, as a response, at least in **early disease** and when GCs are used in combination with other DMARDs. The evidence to support it is, actually, much more robust than that available to support the DMARD quality of agents typically included in this category, such as hydroxychloroquine or SSZ.

It must be recognized that structural effects of GCs have not been adequately investigated in patients with **longstanding disease**: they should not be presumed to be present but they cannot be excluded to exist, either. The inclusion of patients with longstanding disease may have contributed to the lack of structural effect of GCs reported by the study of Capell et al.[9], but this was not been specifically investigated. The same may have occurred in the study reported by Hansel et al.[28] where 102 patients with active RA were randomly allocated to treatment with DMARD alone or DMARD and prednisolone, and followed-up for 1 year. Prednisolone was given in a dose regimen adapted to the disease activity of the individual patient with a mean daily dose of 6mg during the trial. The authors reported that there were no benefits of prednisolone use with regard to radiological damage (Larsen score). However, the intention-to-treat analysis revealed a significantly higher rate of progression (delta Larsen score) in the group on DMARD alone (3.5 *versus* 1.8; p<0.03). Unfortunately, the disease duration at baseline was significantly higher in the DMARD alone group (8.5 *versus* 2.8 years; p<0.05) and no efforts were done to elucidate the impact of this parameter. Structural outcomes in RA seem to get less emphasis in the current literature because of the use of effective tight-control strategies, relatively low rates of radiographic damage observed in recent clinical trials and the estimation that 1 Sharp/van der Heijde unit of radiological damage corresponds to 0.01 unit in deterioration on the HAQ[29]. However, prevention of structural damage remains the hallmark of a real DMARD.

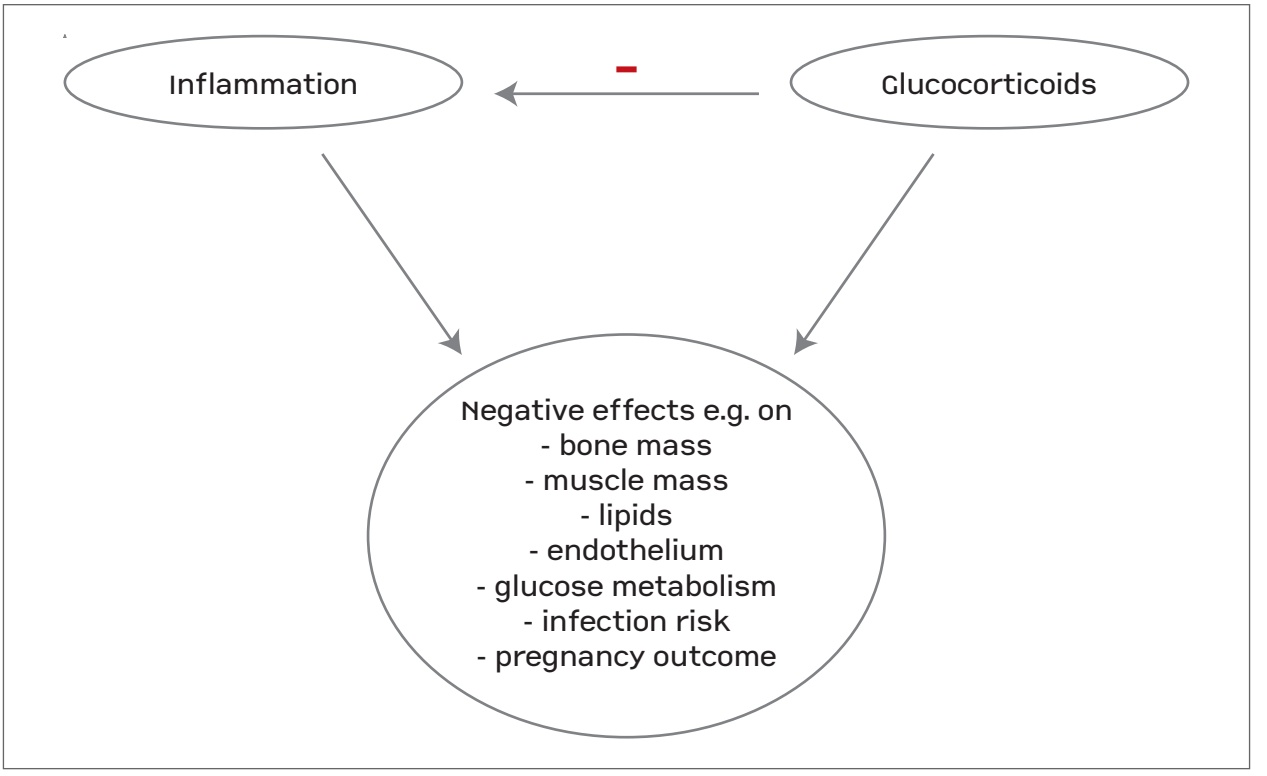

FIGURE 1. Association between the inflammatory disease, glucocorticoid treatment, and specific negative effects. Adapted from Jacobs JW 2012 [73]

B. RISKS

In 2006, a comprehensive review on the safety of low-dose GC treatment in RA[30] combining data from available long-term RCTs[5,8,9,15,31] concluded that adverse effects associated with this treatment in clinical trials *are modest, and often not statistically different from those of placebo*. In a recently published update of this review[32], with three additional RCTs[6,7,33] scarce evidence was added to the previous conclusions. The authors concluded that the safety profile of low-dose GC, as demonstrated by RCTs, seems mild and hardly different from that described for placebo, except for weight gain and glaucoma[34].

The risks for adverse effects of low-dose GCs seem, therefore, to be often overestimated and this may be due to several reasons. It may be that the tolerability profile of high-dose GCs excessively influences perceptions regarding low-dose GCs, possibly exacerbated by a lack of literature on the risks at low-doses as well as bias by indication. Patients with severe disease are more likely to be prescribed GCs and also more likely to experience adverse events associated with the disease itself. Negative effects arising as a consequence of both RA and GC treatment may be attributed only to GC therapy. Examples include negative effects upon bone mineral density, lipids, endothelium, glucose metabolism and infection risk. It is conceivable that low-doses of GCs may actually inhibit or balance these negative effects of the disease process by reducing disease activity. Discriminating the negative effects of disease and adverse-effects of its treatment is impossible in the absence of randomization. This is well illustrated in **Figure 1**, the so-called "**magic triangle**". This dynamic process was well recognized in the CAMERA-II, in the analysis of changes in bone mineral density (BMD) between the treatment groups[35]. BMD increased significantly over time in both treatment groups at the lumbar spine with a mean of 2.6 % during the first year ($p<0.001$), but not at the hip; at none of the time points did BMD differ significantly between the prednisone and placebo group. Higher age and lower weight at baseline and higher disease activity scores during the trial, but not GC therapy, were associated with lower BMD at both the lumbar spine and the hip

in mixed-model analyses. This was attributed to the effective dampening of the inflammatory process by GCs in early RA, especially of pro-inflammatory cytokines such as IL-1 and TNF. Of note, all patient received calcium, vitamin D and a bisphosphonate.

Regarding the impact of GCs upon glucose metabolism, similar perspectives can be drawn from the study by Hoes *et al*[36]. The authors measured glucose tolerance, insulin sensitivity and β-cell function in two RA populations (58 chronic GC-users and 82 GC-naive) and in 50 healthy controls, with no known type 2 diabetes mellitus. Chronic GC-users and GC-naive RA patients presented similar metabolic parameters, with decreased insulin sensitivity and β-cell function in comparison to controls. Cumulative doses of GCs had a negative impact on glucose tolerance state and insulin sensitivity. The results highlight a complex interplay of three factors. First, the pro-inflammatory state in RA has a negative impact on glucose metabolism. Second, GCs down regulate disease activity, which may reduce this effect, but, third, GCs themselves, especially at higher dosages, impair glucose metabolism. These could be the reasons that data arising from observational studies and RCTs are quite different and contradictory.

This was clearly demonstrated by a recent systematic-review by Dixon *et al.*[37]. The authors collected data from 21 RCTs (including 1026 GC-treated patients with RA) and 42 observational studies. The estimated relative risk (RR) of infection associated with GC therapy was not significantly different from placebo in the RCTs (RR 0.97 (95%CI, 0.69-1.36). In contrast, the observational studies suggested an excess risk of infection of 67% in association with GCs (RR: 1.67, 95%CI: 1.49-1.87). There was significant heterogeneity of results between the observational studies, which the authors attributed to GC dose, cumulative exposure, time-varying exposure, co-therapy, comorbidity, recruitment methods, outcome and bias (in particular publication bias)[37].

A study based on the German biologics register - Rheumatoid Arthritis Observation of Biologic Therapy (RABBIT) - enrolled 5044 RA patients, in whom 392 serious infections occurred, to evaluate the risk of serious infection associated with TNF inhibitors[38]. A clear dose–response relationship was seen for treatment with GCs: the adjusted incidence rate ratios (IRR) of serious infections increased from 2.1 to 4.7 as prednisone-equivalent GC dose increased from 7.5-14 to ≥15 mg/day. No significant increase in risk was observed for treatment with <7.5 mg/day (IRR=1.1 (95%CI 0.8; 1.7). These rates may reflect that GCs enhance infection risk in a dose-dependent way, but the importance of the underlying disease cannot be fully excluded in this study design.

Another adverse effect often overestimated is the weight gain. In a sub-analysis of the CAMERA-II study, Jurgens *et al.* showed that at least part of the difference in weight gain between groups was due to an earlier and better control of disease activity with prednisolone[39]. Weight gain has also been reported as a result of TNF-inhibitors in RA[40, 41].

Thus, weight gain under GCs and anti-TNF-inhibitors may, at least in part, be explained by normalization of body composition through control of inflammation - the recovery of weight lost due to the catabolic state associated with high disease activity. Conversely, decreasing disease activity might be expected to result in increased physical mobility, which could promote weight loss.

Additionally, data arising from observational studies and RCTs deserve serious reflection.

RCTs are considered to be the gold standard to evaluate the effectiveness of treatment, and are often designed to ensure a good internal validity of results, i.e., the potential of confounding by indication is removed by randomization. However, they also have their limitations, with emphasis on the strict inclusion/exclusion criteria, which preclude generalizability of the results and their direct extrapolation to daily clinical practice. The typical patient in daily clinical practice will commonly be older, have less severe disease and more comorbidities than patients included in trials[42]. None of the RCTs included in Table I was designed to assess the toxicity of GCs and the assessment of adverse-effects was frequently poorly structured or described. Reporting of adverse effects is also highly variable and potential confounders, such as concomitant therapies, are not systematically reported or accounted for. Furthermore, the available studies on GCs are relatively small and of short duration, thus limiting their ability to exclude all potentially significant adverse effects.

Observational studies, on the other hand, are inextricably exposed to the risk of bias by indication. Huscher *et al.*[43], provided some real-life data on the adverse effects of GCs in RA. The authors describe self-reported health problems related to dose and duration of GC intake in unselected patients from routine practice. Two distinct patterns were identified: A "linear

pattern" - approximately linear rising in the frequency of adverse events with increasing dose – was seen in relation with Cushingoid phenotype, ecchymosis, leg edema, mycosis, parchment-like skin, shortness of breath and sleep disturbance. And a "threshold pattern" - an elevation in the frequency of health problems beyond a certain threshold value. From the study data, glaucoma, depression/listlessness and an increase in blood pressure only became issues at dosages above 7.5 mg/day. Dosages of 5 mg/day or above turned out to be relevant for epistaxis and weight gain; and <5 mg/day for eye cataract. These data may guide the clinician in adapting therapy with GCs accordingly and improve the benefit–risk ratio. Again, correction for the characteristics of the underlying disease and its inherent risk of negative effects was limited by the observational nature of the data.

In summary, given the limitations of currently available RCTs and the inherent problems of observational data, all we can state is that there is no evidence that low-dose GCs are associated with significant toxicity in early RA for over two years. Definite conclusions about the safety of GCs require randomized clinical trials with sufficient dimension and duration and with appropriate standardization in the definition and monitoring of adverse effects.

Clearly, the conclusion would be totally different if we considered medium and high doses of GCs, but these are not typically used chronically in the treatment of RA.

C. THE BALANCE

How can the physician achieve the best possible benefit over risk in GC therapy? Which adverse-effects should be monitored in clinical practice and how?

The EULAR recommendations on monitoring adverse events of low-dose glucocorticoid therapy provide the best available guidance. Evidence on monitoring proved to be scarce and most recommendations were based on consensus[44]. Monitoring for an adverse effect was considered especially useful if it is common or severe, the cost of screening is low, the monitoring is feasible in daily practice, and the adverse event is preventable and/or treatable and/or reversible after dose reduction or stopping the GC, if possible.

For clinical practice, the EULAR Task Force recommended that, for most potential adverse-effects, physicians may adhere to "*standard care*" ie, the same practice advised as good clinical care in all patients with an inflammatory rheumatic disease. This standard care applies to hypertension, cardiovascular disease, peptic ulcer disease, diabetes and body weight. Adherence to national guidelines is recommended regarding GC-induced osteoporosis. Baseline assessments of ankle edema, fasting blood glucose and risk factors for glaucoma (family history, high myopia and diabetes) are also recommended. Patients at risk for glaucoma should undergo an ophthalmologic observation. The EULAR Task Force made no recommendations for monitoring in clinical practice in the context of low-dose GC-therapy regarding lipids, electrolyte disturbances, infections, mood disturbances, psychosis, sex or adrenal hormone changes, skin changes, osteonecrosis or myopathy, because these did not satisfy one or more of the criteria for monitoring describe above.

Monitoring should be expanded and/or intensified in patients with GC-related adverse effects[45].

It is crucial that patients with, or at risk of, GC-induced osteoporosis receive appropriate preventive and/or therapeutic interventions[46]. According to Van Staa *et al*., fracture risk increases even with small doses of GCs between 2.5 and 7.5 mg prednisone equivalent daily[47].The relative fracture risks during the first year of therapy were 1.77 (95%CI: 1.55–2.02) and 2.27 (95%CI: 1.94–2.66) for patients taking prednisolone in doses of 2.5–7.5 mg and > 7.5 mg daily, respectively[47]. Several meta-analyses showed efficacy of therapy with calcium, vitamin D and bisphosphonates in preventing and treating GC-induced osteoporosis[48,49]. Bisphosphonates have proven efficacy in increasing bone mineral density and in reducing frequency of vertebral fractures[50-52].

Furthermore, appropriate timing of GC administration might influence its efficacy, as signs and symptoms, as well as serum levels of pro-inflammatory cytokines show a circadian rhythm[53, 54]. Thus, administration of GC in the early morning[53], or the use of modified-release prednisone (MR-pred) at bedtime (see below) may result in improved efficacy and, thus, lower doses and less risk of adverse effects. Patients should be adequately informed about the risks and benefits of GC therapy and be advised about the danger of abrupt cessation of the medication after long-term use[55].

It is generally recommended that GCs should be used in the lowest dose for the shortest period of time to achieve the treatment goals. This statement is based on the current evaluation of the risks of GC and on the fact that DMARD-properties have only been demons-

TABLE II. OVERVIEW OF CAPRA-1, CAPRA-1 EXTENSION AND CAPRA-2 CLINICAL STUDIES IN RHEUMATOID ARTHRITIS. ADAPTED FROM (57)

	CAPRA-1 Buttgereit et al. (2008) (54)	CAPRA-1 extension Buttgereit et al. (2010) (58)	CAPRA-2 Buttgereit et al. (2013) (56)
Design	Randomized Double-blind Double-dummy Active control	Open label	Randomized Double-blind Placebo-controlled
Patients	N= 288, on stable low-dose GC (2.5-10mg/day) Stable DMARD allowed	N= 249, from CAPRA-1	N= 350, not on glucocorticoid Stable DMARD allowed
Study treatments	Continue same conventional prednisone (morning dose) (n= 144) OR same dose MR-pred (evening dose) (n= 144)	All patients (n= 249) continue on stable dose, taken as MR-pred (evening dose)	Placebo OR (n= 119) MR-pred 5mg/day (n= 119) (both evening doses)
Primary endpoint	Change in duration of morning joint stiffness	Change in duration of morning stiffness Change in IL-6, DAS28, pain, ACR20	ACR20 response
Duration	12 weeks	9 months	12 weeks

DMARD: Disease-modifying anti-rheumatic drug; MR-pred: Modified-release prednisone.

trated in early disease and for up to 2 years of treatment. As knowledge on these aspects expands and improves, this recommendation may need revision in the future.

Of course it is generally true that a drug should be used in the lowest dose for the shortest period of time to achieve the treatment goals, but this statement is predominantly made and repeated regarding GCs. This may be seen as a reflection of the (over-?) evaluation of the risks of GC and (under-?) evaluation of their DMARD-properties, and deserves contemplation if we want to base our decisions on evidence and not on "common wisdom".

Deflazacort

Deflazacort, an oxazoline derivative of prednisolone, has been proposed to have similar anti-inflammatory and immunosuppressive effects but fewer adverse events than prednisolone, especially with regards to glucose and bone metabolism[56-58]. However, the data to support this concept are inconsistent and come from small and relatively short duration trials[59, 60]. A double-blind controlled randomized one-year study with 76 RA patients suggested that deflazacort has equivalent efficacy to prednisolone only in a dose ratio of 1.2:1[57]. However, other studies indicated that deflazacort may be actually less potent, its equivalent dose to prednisolone being more in the range of 1.5 to 1.6:1[61,62]. This completely abrogates the presumed advantage of deflazacort in terms of safety. Taken together, there is no scientific evidence to support that deflazacort in equipotent doses is safer than other GCs.

NEW GLUCOCORTICOID DEVELOPMENTS

Timing therapy

As describe above, the EULAR recommendations noted the importance of timing of GC administration with respect to the circadian rhythms of both the natural cortisol secretion and the disease processes[45]. A recent approach, already licensed for clinical use, is modified-release prednisone (MR-pred), and has shown a clinically relevant reduction in early morning stiffness compared with conventional prednisone[54, 63].

The **efficacy and safety** of MR-pred were examined in the CAPRA (Circadian Administration of Prednisone in Rheumatoid Arthritis) studies (Table II). In CAPRA-1, the MR-pred tablet was taken at bedtime, to be released with a delay of 4 hour after ingestion. This new formulation was shown to be clinically superior to the conventional prednisone with respect to reducing morning stiffness (primary endpoint of this study)[54]. MR-pred reduced the duration of morning stiffness

(when patients used prednisone) by 22.7% compared with 0.4% reduction with continuation of conventional prednisone (p = 0.045) from baseline to 12-week of treatment. The **safety profile** showed no differences between the two preparations.

The CAPRA-1 trial was followed by an open-label 9-month extension study, with 249 participants[64]. Patients on conventional prednisone switched to MR-pred (pred/MR-pred), while patients on MR-pred maintained their treatment (MR-pred/MR-pred). Thus, during this extension trial a reduction in morning stiffness was reported after 3-months (33.1% *versus* no change), after 6 months (56% *versus* 54%); and after 12 months (55% *versus* 45%), respectively in the MR-pred/MR-pred and in the pred/MR-pred group.

Additionally, IL-6 levels showed a 50% reduction in patients who switched from conventional to MR-pred: from baseline 1110 IU/l (of the double-blind study) to 515 IU/l, median value (end of the open-label extension phase). DAS28 and pain intensity showed important improvements, however with no differences between the treatment groups over the 12 months.

To evaluate the impact of MR-pred on the hypothalamic–pituitary–adrenal axis (HPA), cortisol response to corticotropin-release hormone (CRH test) was determined in a subgroup of 28 patients from the CAPRA-1 at 3 time-points: baseline, 3 months and 9 months. This study found no evidence for increased suppression of the HPA by MR-pred as compared with standard prednisone[64]; rather, there was some indication that GC administration in accordance with physiological circadian rhythms reduced the hypothalamic–pituitary–adrenal suppression when compared to conventional prednisone[65].

To further confirm efficacy and safety of the MR-pred, a second trial, the CAPRA-2 study, was designed including 350 patients with active RA and morning stiffness of more than 45 minutes. The group receiving MR-pred 5 mg/day plus traditional DMARDs (e.g., MTX) presented a significantly greater clinical improvement in composite measures of disease activity compared with placebo + DMARDs (ACR20 of 48 *versus* 29% and ACR50 of 22 *versus* 10%) and in reduction of morning stiffness from baseline (55 *versus* 35%). Significantly greater reductions in severity of RA and fatigue, as well as a greater improvement in evening pain and physical function were seen at week 12 with MR-pred compared with placebo. The incidence of adverse effects was similar for MR-pred and placebo.

In conclusion, the data from CAPRA-1 suggests that MR-pred may have a superior effect to conventional prednisone in reducing early morning stiffness, and this is a relevant development for many patients, given the impact of early morning dysfunction in the lives of patients with RA[66].

Certainly, a head to head comparison trial with conventional formulation of GCs is needed to determine if these agents add enough benefit over standard GCs and are ultimately cost effective. In addition, these findings need to be extended to include large numbers of patients, ideally from real-world, in different clinical stages of their inflammatory disease, to demonstrate use of MR-pred in routine clinical practice[67]. Further studies are needed to establish its use over longer periods of time and especially to explore the potential benefits of this strategy upon structural damage and disease progression, based on changes in cytokine levels.

NEW SELECTIVE AGENTS

Development research efforts into glucocorticoid-receptor ligands are based on the hypothesis that selective glucocorticoid receptor agonists (SEGRAs) may retain the anti-inflammatory properties of GCs – mechanism of transrepression – with fewer or no metabolic adverse effects - mechanism of transactivation. The results are, overall, promising and support further research[68]. However, in mouse studies some SEGRAs have failed to exert a full inflammatory response and unexpectedly retained some classic adverse effects of GCs[69]. Further studies are underway.

TARGETING THERAPY

Targeting therapy to the site of inflammation is possible through encapsulating GCs in liposomes[70]. Recently, nano-liposomes administered intravenously and subcutaneously have demonstrated a powerful suppression of the secretion of pro-inflammatory cytokines in rat models of arthritis[71]. Preclinical human studies are awaited to see whether liposomal GCs will be effective in clinical practice.

ALTERNATIVE REGIMES

The promising results of recent trials using either a single intramuscular injection of 120mg of methylprednisolone (Treatment in the Rotterdam Early Arthritis Cohort – tREACH trial)[10] or intra-articular injection of triamcinolone in active joints (Optimized Treatment

Algorithm for Patients With Early Rheumatoid Arthritis - OPERA trial)[11], both from the efficacy and the safety perspectives, indicate that there is room to improve our current strategies, seeking for the best possible use of classical GCs.

OVERALL SUMMARY

GCs have been a cornerstone in the treatment of RA for many decades. GCs can, beyond any doubt, successfully suppress disease activity and, at least in early disease, significantly reduce structural damage accrual. Although these effects have been demonstrated even in the absence of other DMARDs[5], there is general agreement that GCs should not be used as monotherapy in RA. Safety concerns, often without firm evidence, limit their widespread and long-term use.

Over the last decade, more attention has been given to monitoring and reporting adverse effects in clinical trials, although only scarce evidence could be added to that described in the comprehensive review of Da Silva *et al.* published in 2006[30].

Given their low cost, the accumulated experience and the flexibility of their use, GCs will surely continue to play an important role in the treatment of RA for the foreseeable future, despite the development of biological and targeted small molecules.

New GC formulations may offer significant advantages over conventional GC drugs, and thus more studies are warranted in this field to investigate the benefit of low-dose MR-pred chronotherapy and other alternatives. New regimes of therapy deserve consideration.

In the meantime, evidence-based recommendations for patient education, monitoring and prevention of GC-related adverse effects in RA have been published[44-46,72]. Adherence to the standardized interventions and assessments described in these documents might significantly contribute to our ability to reduce the GC-related adverse effects in RA and optimize GC use to the benefit of patients.

CORRESPONDENCE TO
Tânia Santiago
Rheumatology Unit, Centro Hospitalar e Universitário de Coimbra
Coimbra, Portugal
E-mail: tlousasantiago@hotmail.com

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