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Review

Benefits and risks of low-dose glucocorticoid treatment in the patient with rheumatoid arthritis

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Abstract

Glucocorticosteroids (GCs) have been employed extensively for the treatment of rheumatoid arthritis (RA) and other autoimmune and systemic inflammatory disorders. Their use is supported by extensive literature and their utility is reflected in their incorporation into current treatment guidelines for RA and other conditions. Nevertheless, there is still some concern regarding the long-term use of GCs because of their potential for clinically important adverse events, particularly with an extended duration of treatment and the use of high doses. This article systematically reviews the efficacy for radiological and clinical outcomes for low-dose GCs (defined as $\leqslant$10 mg/day prednisone equivalent) in the treatment of RA. Results reviewed indicated that low-dose GCs, usually administered in combination with synthetic DMARDs, most often MTX, significantly improve structural outcomes and decrease symptom severity in patients with RA. Safety data indicate that GC-associated adverse events are dose related, but still occur in patients receiving low doses of these agents. Concerns about side effects associated with GCs have prompted the development of new strategies aimed at improving safety without compromising efficacy. These include altering the structure of existing GCs and the development of delayed-release GC formulations so that drug delivery is timed to match greatest symptom severity. Optimal use of low-dose GCs has the potential to improve long-term outcomes for patients with RA.

Key words: rheumatoid arthritis, glucocorticoids, prednisone, disease modifying, treatment strategies, benefit–risk.

REVIEW

Introduction

The role of glucocorticoids in the treatment of RA

Glucocorticosteroids (GCs) have a long history of good efficacy and safety in the treatment of RA. This has resulted in their inclusion in guidelines for the management of this disease. For example, the European League Against Rheumatism (EULAR) guidelines recommend that GCs be added at low to moderately high doses to synthetic DMARD monotherapy (or combinations of synthetic DMARDs) since they have been shown to provide benefit as an initial short-term treatment. However, it is also generally recommended that GCs should be tapered as rapidly as clinically feasible [1]. The Canadian Rheumatology Association treatment recommendations state that GCs (oral, intramuscular or intra-articular) can be added to DMARD therapy as part of the initial treatment strategy for patients with RA, and may be an option for managing flares as bridge therapy while waiting for a DMARD to take effect, or for symptom control if no other options exist [2].

While the use of GCs in patients with RA is supported by clinical trial results, there is still some concern surrounding their use because of potential associations with clinically important adverse events, particularly when they are administered at high doses and/or for long duration [3–5]. While caution is certainly warranted in the use of GCs in patients with RA, results from a large number of studies have indicated that combination of low doses of these agents with DMARDs may have significant benefit with respect to joint preservation and also acceptable safety. In addition, new GC molecules are being developed in an effort to improve their efficacy and tolerability.

The aim of this article was to systematically review the efficacy (radiological and clinical outcomes) and safety of low-dose GCs when used as part of treatment regimens for patients with RA. The analysis included studies in

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which GCs were administered at low doses ($\leqslant$10 mg/day prednisone equivalent). In some trials, GCs were delivered at higher doses for a short interval prior to tapering to a dose $\leqslant$10 mg/day.

Literature review

PubMed was searched using the following query, rheumatoid AND (hydrocortisone OR methylprednisolone OR budesonide OR betamethasone OR dexamethasone OR prednisone OR prednisolone OR corticosteroid OR glucocorticoid). The results were limited to randomized controlled trials with the appearance of the words in the title or abstract. This search resulted in retrieval of 218 studies. The abstract or, when necessary, full text of each study was then reviewed for relevance for this article using the following criteria: (i) treatment of adult patients with RA, (ii) use of oral GC doses $\leqslant$10 mg/day, (iii) treatment arms and data presentation that permitted assessment of the effects of GCs on treatment outcomes (e.g. studies in which GCs were permitted along with other treatments in multiple study arms; studies in which results were not presented separately for patients receiving and not receiving GCs were excluded). Secondary and redundant publications of results from a given study were also excluded. The reference sections of the papers included in the review were also evaluated for additional citations not recovered by the PubMed search. The search resulted in retrieval of 55 papers that met the above-listed criteria. This total included non-redundant reports at different time points for several long-term studies, all of which are included in the analysis.

Effects of GCs on structural outcomes in patients with RA

Fifteen of the studies retrieved provided information about radiological outcomes for patients receiving low-dose GCs (Table 1). Analysis of the results from these 15 studies supports the view that administration of GCs in combination with synthetic DMARDs, most often MTX, significantly improves structural outcomes in patients with RA. Results from all 15 clinical trials with results for this endpoint are summarized in Table 1. One of the more convincing demonstrations of the efficacy of adding GCs to conventional treatment for RA is the Combination Therapy of RA (COBRA) trial. In this study, 155 patients with early RA received SSZ monotherapy (SSZ group) or a combination of step-down prednisolone, MTX and SSZ (COBRA group). After 11 years of follow-up, less progression of joint damage was observed in the COBRA group [11]. However, it should also be noted that the incidence of treatment for hypertension, diabetes and cataracts were all significantly higher in the COBRA group *vs* the SSZ group. Conversely, hypercholesterolaemia, cancer, infection and mortality all showed trends favouring initial high-dose GC treatment in COBRA [11]. A second long-term trial, the BeSt study, compared four treatment strategies: sequential substitution DMARD monotherapy, step-up add-on DMARD combination therapy, initial combination therapy that included prednisone (60 mg/day initial dose tapered to 7.5 mg/day over 7 weeks; similar to that in COBRA) and initial combination therapy with a DMARD plus the TNF inhibitor infliximab.

Results from the BeSt study showed that combination therapy that included initial high-dose prednisone slowed joint erosion *vs* sequential monotherapy or step-up combination treatment that did not include a high-dose GC [13–15]. After 5 years, the initial benefit of combination therapy was maintained, with significantly less joint damage than in patients who did not receive a GC [16]. The Better Anti-rheumatic Farmacotherapy (BARFOT) study showed that the addition of prednisolone 7.5 mg/day to initial DMARD therapy retarded the progression of erosions after 2 years in patients with early RA and provided a higher remission rate than DMARD therapy alone. Remission achieved after 2 years was associated with less radiographic damage after 4 years, which when analysed according to initial treatment group, was statistically significant only for patients receiving early GC therapy [19, 20]. Results from the COBRA, BeSt and BARFOT studies are consistent with those from a large number of additional studies that assessed radiographic damage (e.g. joint erosion) in patients with RA who received GCs for shorter periods (Table 1).

Not all studies retrieved demonstrated a significant benefit of GC treatment on structural outcomes (Table 1). A trial that included 167 patients with RA who were followed for 2 years indicated no radiological or clinical benefit of adding 7 mg/day prednisolone to SSZ [21]. A 3-year study compared radiographic progression rates in paired hand radiographs in patients taking NSAIDs alone or NSAIDs plus $\leqslant$5 mg/day prednisolone. Study results indicated that for a subset of 252 patients with an RA duration of 12–24 months, changes from baseline radiographic scores were not different in those taking or not taking prednisone ($P = 0.994$) [23].

Effects of GCs on clinical outcomes: efficacy

The majority of the 55 studies reviewed indicated that treatment with low-dose GC alone *vs* placebo or a combination of low-dose GCs with DMARDs *vs* DMARDs only significantly improved outcomes for measures that included ACR responses [21, 24], HAQ scores [14, 25], tender and swollen joint counts [24] and DAS [26] (see supplementary Table S1, available at *Rheumatology* Online).

An example of the effects of low-dose GC monotherapy on clinical endpoints is provided by a 12-week, double-blind, randomized controlled trial in which 143 patients with active RA received budesonide 3 or 9 mg/day, prednisolone 7.5 mg/day or placebo. Treatment with either 9 mg/day budesonide or prednisolone significantly decreased tender and swollen joint counts *vs* placebo ($P < 0.05$) and ACR20 responses were achieved by 22% and 42% of patients who received budesonide 3 or 9 mg/day and 56% of those on prednisolone *vs* 25%

Table 1 Radiological outcomes for studies in which low-dose GCs were included in the treatment of RA patients

Reference	Patients	Duration, design and treatment	Evaluations/endpoint	Outcome
van Everdingen *et al.* [6]	81 patients with early active RA who had not been treated with DMARDs	2-year randomized, double-blind, placebo-controlled clinical trial Patients received 10 mg prednisone or placebo NSAIDs were allowed in both groups and SSZ could be prescribed for rescue	Radiological studies were performed every 6 months	After month 6, radiological scores showed significantly less progression in the prednisone group than in the placebo group
Hickling *et al.* [7]	128 patients with early active RA	2-year, randomized, double-blind, placebo-controlled trial 7.5 mg prednisolone daily in addition to routine medication over 2 years in 128 patients with early RA	Annual radiological evaluation of the hand with Larsen scoring	Prednisolone treatment resulted in significantly fewer erosive changes *vs* placebo Withdrawal of prednisone during the third year of the study resulted in disease progression similar to that observed in the control group
Rau *et al.* [8]	196 patients with active RA	2 year, double-blind, randomized, multicentre study Patients receive 5 mg prednisolone or placebo Patients also received DMARD treatment with either gold sodium thiomalate or MTX	Radiographs were taken at 6, 12 and 24 months and evaluated using the Ratingen score and van der Heijde's modification of Sharp's method	After 24 months the total score had increased by 2.6% of the maximum score in the placebo group and by 1.1% in the prednisolone group
Boers *et al.* [9], Landewé *et al.* [10], van Tuyl *et al.* [11]	155 patients with early RA	1-year, multicentre, double-blind, randomized trial Patients received a combination of SSZ (2 g/day), MTX (7.5 mg/week) and prednisolone (initially 60 mg/day, tapered in 6 weekly steps to 7.5 mg/day) or SSZ alone Prednisolone and MTX were tapered and stopped after 28 and 40 weeks, respectively.	Sharp–van der Heijde radiographic damage score in hands and feet	After 26 weeks the median radiographic damage scores increased by 1 in the combination treatment groups *vs* 4 for SSZ. The respective values at week 80 were 4 *vs* 12 During the 4- to 5-year follow-up period, the Sharp progression rate was 8.6 points/year in the SSZ group and 5.6 in the combination treatment group The 11-year follow-up also indicated less joint damage in the combination treatment group
Malysheva *et al.* [12]	154 patients with RA	Retrospective analysis of patients followed for 2–62 months Various treatments, including GCs (7.5 mg prednisone equivalent), MTX, SSZ, HCQ, and AZA	Routine radiological evaluation	A significant reduction was observed in the frequency of erosive RA in patients with GC co-medication *vs* those without low-dose GCs

(continued)

Table 1 Continued

Reference	Patients	Duration, design and treatment	Evaluations/endpoint	Outcome
Goekoop-Ruiterman *et al.* [13–15], Klarenbeek *et al.* [16], van der Kooij *et al.* [17]	508 patients with early RA	Multicentre randomized trial with four treatment groups: (i) sequential monotherapy, (ii) step-up combination therapy, (iii) initial combination therapy with tapered high-dose prednisone and (iv) initial combination therapy with infliximab	Radiographic joint damage according to the modified Sharp–van der Heijde score	At 1 year, median increases in the total Sharp–van der Heijde radiographic joint score were 2.0, 2.5, 1.0 and 0.5 in groups 1–4, respectively After 5 years, initial combination therapy resulted in significantly less joint damage progression
Svensson *et al.* [18], Svensson *et al.* [19], Hafstrom *et al.* [20]	187 patients with early RA	Long-term multicentre observational study of patients with early RA in southern Sweden Within this study, 187 patients were randomized to open label: (i) initial treatment for 1 month with 7.5 mg prednisolone (for 28 patients, MTX was added) or (ii) SSZ or AUR	Radiographic evaluation at 2 years with Larsen scoring	Addition of prednisolone to initial DMARD therapy retarded the progression of erosions after 2 years in patients with early RA and provided a higher remission rate than DMARD therapy alone Remission achieved after 2 years was associated with less radiographic damage still present after 4 years, which when analysed according to initial treatment group was statistically significant only for patients receiving early prednisolone therapy
Capell *et al.* [21]	167 patients with RA for <3 years	2-year, randomized, double-blind, placebo-controlled trial Patients were started on SSZ and randomized to prednisolone 7 mg/day or placebo	Radiological damage as assessed by the modified Sharp method	There were no significant between-group differences in radiological scores or clinical and laboratory measures at 2 years
Kirwan *et al.* [22]	128 patients with active RA for <2 years	2-year, randomized, double-blind, placebo-controlled trial Patients were randomized to 7.5 mg of prednisolone or placebo plus any other prescribed medication	Progression of damage as seen on radiographs of the hand after 1 and 2 years, as measured by the Larsen index,and the appearance of erosions in hands that had no erosions at baseline	After 2 years, Larsen scores increased by a mean of 0.72 U in the prednisolone group and by 5.37 U in the placebo group ($P = 0.004$). Of the 212 hands of these patients, 69.3% had no erosions at the start of the study. At 2 years, 22.1% of those in the prednisolone group and 45.6% of those in the placebo group had erosions ($P = 0.007$)
Paulus *et al.* [23]	824 patients with RA	3-year prospective, randomized clinical trial comparing the NSAIDs etodolac and ibuprofen DMARDs were not permitted Prednisone $\leqslant 5$ mg/day was continued by 197 patients (mean dose = 4.37 mg/day) who had started prednisone therapy $\geqslant 6$ months before study entry, but new prednisone starts were not allowed	Rate of increase in erosion scores	For the subgroup of 252 patients with RA duration of 12–24 months, changes from baseline in radiographic scores (mean monthly erosion) were not different in those taking or not taking prednisone ($P = 0.994$)

AUR: auranofin; GCs: glucocorticosteroids.

for placebo. Results for both 9 mg/day budesonide ($P < 0.001$) and prednisolone ($P = 0.02$) were significantly different from placebo [24]. The benefit of adding low-dose GC to MTX-based treatment was demonstrated by results from the Computer-Assisted Management in Early Rheumatoid Arthritis (CAMERA) II trial. This study included 236 patients with early RA (<1 year) who received either MTX or MTX plus 10 mg prednisone and were followed for 2 years. Results for the 28-joint DAS (DAS28), pain and HAQ scores decreased more rapidly in patients who received MTX plus prednisone *vs* those on MTX alone, but differences between treatment groups declined over the course of follow-up. Longitudinal regression analysis indicated lower significantly better improvement for all disease activity variables with MTX plus prednisone *vs* MTX alone ($P < 0.001$). At the end of the 2-year follow-up period, 65% of patients receiving MTX plus prednisone and 61% on MTX only achieved a 20% improvement in ACR criteria (ACR20; $P = 0.56$); the respective values for ACR50 were 53% and 42% ($P = 0.091$) and those for ACR70 were 38% and 19% ($P = 0.002$) [27].

There is considerable ongoing debate about the optimal means of defining remission in RA, and various measures have been suggested [28]. Nevertheless, remission has come to be considered the primary therapeutic goal of RA treatment [1, 2]. Results from several studies, using varying definitions, have shown that the addition of GC to the treatment regimen for a patient with RA may increase the probability of achieving disease remission [19, 27, 29–32] (see supplementary Table S1, available at *Rheumatology* Online). Results from a study of 105 patients with early active RA indicated that the addition of low-dose prednisone to treatment significantly increased the probability of achieving and sustaining remission over 2 years of follow-up [31]. A randomized trial of 220 patients with active RA <2 years from symptom onset indicated that addition of 6.25 mg/day prednisone to MTX resulted in significant increases in both clinical (DAS28 <2.6) and ultrasonographic remission rates *vs* MTX plus placebo over 12 months of follow-up [30]. Results from the CAMERA II trial, a 2-year prospective study that included 236 patients with early RA (<1 year), indicated that the combination of prednisone and MTX was superior to MTX alone in slowing erosive joint damage, reducing disease activity and physical disability and achieving sustained remission [27]. Results from the Finnish RA combination therapy trial showed that inclusion of prednisone with other conventional DMARDs in 199 patients with RA significantly increased the probability of achieving the modified minimum disease activity (MDA) and strict ACR criteria for remission over 11 years of follow-up [32].

It is important to note that not all of the studies reviewed indicated sustained clinical benefit of low-dose GC in patients with RA. A study of 81 patients with early RA (<1 year duration) indicated that 10 mg/day prednisone was significantly superior to placebo for decreasing pain at 3 months ($P = 0.003$) and improving general well-being at 3 and 6 months ($P = 0.003$ and $P = 0.04$, respectively), but not thereafter over a 2-year follow-up period [33].

Effects of GCs on clinical outcomes: safety

The adverse events associated with GC treatment in patients with RA have been enumerated in many publications over the years. Commonly reported adverse events include weight gain, elevated blood pressure (BP), glucose intolerance and increased risk for diabetes and its complications, development of cataracts and increased incidence of glaucoma, increased susceptibility to infections, hyperlipidaemia, gastrointestinal adverse events (e.g. ulcers, lower gastrointestinal bleeding, perforations), development of osteoporosis and insufficiency fractures, osteonecrosis and changes in physical appearance (e.g. Cushingoid appearance, hirsutism, abdominal striae) [34–37]. GC-associated adverse events are significantly associated with the daily dose and treatment duration [38]. An important question related to long-term use of low-dose GCs in patients with RA is the extent to which risks for GC-associated adverse events might be attenuated at lower doses of these agents.

The results from the clinical trials included in this systematic review indicate that at least some of the adverse events observed with high-dose GCs also occur with lower doses of these drugs. The studies reviewed indicated that treatment with low-dose GCs were associated with weight gain [21, 39], hyperglycaemia [30] and diabetes [11, 19], increased blood pressure [21, 40, 41] and hypertension [11, 42], decreased BMD [42–45], increased risk for fractures [46], cognitive dysfunction [47], increased risk of infection [48] and cataracts [11].

Discussion

The results summarized in the preceding sections, Table 1 and supplementary Table S1 (available at *Rheumatology* Online) support the conclusion that the addition of low-dose GC to treatment with conventional DMARDs significantly improves both clinical and radiological outcomes in patients with RA, but that there are still safety concerns associated with the long-term use of these agents. The results of this review concerning radiological outcomes with GCs are consistent with those from two previously published meta-analyses. Results from an analysis of 15 trials that included 1414 patients (mean cumulative GC dose of 2300 mg prednisone equivalent/year) indicated that GCs given in addition to standard therapy can substantially reduce the rate of erosions in RA. For all the studies, the standardized mean difference in progression was 0.40 in favour of GCs (95% CI 0.27, 0.54). In studies lasting at least 2 years, the standardized mean difference in progression in favour of GCs at the end of the study period was 0.42 (95% CI 0.30, 0.55). All studies except one showed a numerical treatment effect in favour of GCs [49]. A more recent meta-analysis carried out to inform EULAR recommendations for the treatment of RA indicated that the addition of GCs to either standard synthetic DMARD monotherapy or combinations of synthetic DMARDs yielded clinical benefits and inhibition of

TABLE 2 Adverse events with low-dose GCs

	No GCs in past 12 months, %	Patients with GC intake for >6 months		
		<5 mg/day, %	5–7.5 mg/day, %	>7.5 mg/day, %
Cushingoid phenotype	2.7	4.3	15.8	24.6
Ecchymosis	6.8	17.4	23.5	24.6
Leg oedema	9.5	11.6	20.2	26.2
Mycosis	4.5	5.8	6.6	8.2
Parchment-like skin	3.2	10.1	15.8	21.3
Shortness of breath	9.5	10.1	12.6	16.4
Sleep disturbance	20.7	33.3	37.2	44.3
Eye cataract	2.7	10.1	7.7	8.2
Epistaxis	1.4	1.4	6.6	4.9
Weight gain	9.5	8.7	22.4	21.3
Depression, listlessness	12.6	10.1	13.7	19.7
Glaucoma	2.7	2.9	2.7	6.6
Increase in blood pressure	18.9	18.8	16.4	23.0

GCs: glucocorticosteroids. Modified from Huscher *et al.* [36] with permission from the copyright holder, BMJ Publishing Group Ltd.

radiographic progression that may extend over many years [50].

The benefits of low-dose GCs in patients with RA have led to multiple statements that these agents should be employed as part of the initial therapeutic regimen for patients with RA [51–54].

The safety of low-dose GCs was addressed in a combined analysis of results from four placebo-controlled trials in which RA patients received GC doses $\leqslant$10 mg/day and were followed for 2 years. The results from this analysis indicated no excess cardiovascular events with low-dose GCs; no effect on BMD; a small rise in plasma glucose (from 5.1 to 5.9 mmol/l) in only one of the four studies; no increase in risk for cataracts, but increased risk for glaucoma; no increased risk for upper gastrointestinal ulcers and bleeds; no increased risk for infections and no increased risk for dermatological adverse events [35]. Analysis of 1066 patients included in the German Collaborative Centres database who received GCs for >6 months at doses of <5, 5–7.5 and >7.5 mg/day indicated that different adverse events with these drugs may have different thresholds (Table 2). The risk for some adverse events (e.g. ecchymosis, parchment-like skin, sleep disturbance and cataracts) appears to be increased with any GC dose, while others only increase with doses $\geqslant$5 mg (e.g. Cushingoid symptoms, leg oedema, weight gain) or >7.5 mg/day (e.g. shortness of breath, epistaxis, depression/listlessness, glaucoma) [36].

The concerns about side effects associated with GCs have prompted substantial efforts to improve safety profiles without compromising efficacy. Several alternative strategies have been tested in an effort to achieve this highly desirable goal.

GCs with altered structural characteristics aimed at decreasing the risk for adverse events have been evaluated in patients with RA. Deflazacort, an oxazoline derivative of prednisolone with anti-inflammatory and immunosuppressive activity, first became available in 1969. The severity of steroid-induced osteoporosis and growth retardation due to deflazacort is less than that associated with other steroids [55]. Multiple randomized clinical trials appeared to indicate that deflazacort had less severe side effects than conventional GCs, but the dose to achieve and maintain equivalent anti-inflammatory efficacy was usually higher than predicted [56]. At these higher doses, the safety advantages of deflazacort were minimized [57]. It is also important to note that the bone-sparing effects of agents used to treat RA have generally been evaluated in small-scale, short-term studies. Well-designed long-term, large-scale trials are needed to address this issue.

Selective GC receptor agonists (SEGRAs) represent another approach to modification of the steroid molecule with the aim of improving safety. The classical genomic mechanism of GC action involves transrepression, which has been suggested to be primarily responsible for a large number of the desirable anti-inflammatory and immunomodulating effects of these drugs, and transactivation, which is suggested to be more closely associated with side effects as well as with some immunosuppressive activities [58]. This understanding has prompted the development of SEGRAs aimed at retaining the benefits of conventional GCs while decreasing their adverse effects [59]. To our knowledge, SEGRAs have not yet been evaluated in patients with RA.

So-called soft drug approaches have been used to design new drugs by attempting to alter molecules in order to impact their activity, as well as the most desired way for deactivation and detoxification. This approach has been used for GCs with the molecule loteprednol etabonate [60]. Loteprednol has been shown to be as effective as dexamethasone when injected directly into the

joint of rabbits with experimentally induced arthritis [61]. Agents in this class have not yet been evaluated in patients with RA.

A macromolecular pro-drug of dexamethasone, *N*-(2-hydroxypropyl) methacrylamide (HPMA) copolymer–dexamethasone conjugate, has been developed with the aim of selectively targeting inflamed tissues. Results from studies of animal models of inflammatory diseases, including LN, have indicated that this dexamethasone formulation provides sustained resolution of inflammation [62, 63]. Studies have not yet been reported in patients with RA.

New GC formulations have also been developed. Encapsulation of conventional GCs in liposomes has the potential to improve efficacy and decrease adverse effects by targeting delivery more directly to inflammatory sites and decreasing drug exposure to normal tissue. This approach has shown promise in animal models of arthritis, and a liposomal prednisolone preparation has been tested in a small number of patients with RA [64–66].

Efforts have also been directed towards optimizing the timing of low-dose GC delivery. RA symptoms have a circadian rhythm with the greatest severity in the early morning. A number of hypotheses have been put forward to explain this, including redistribution of interstitial fluids, circadian changes in synovial fluid composition and resultant oedema of the synovium and the peri-articular structures that interfere with joint biomechanics and nocturnal elevation in inflammatory mediators such as IL-6 that are not counterbalanced by a concomitant increase in cortisol [67, 68]. Increased production of melatonin at night may also contribute to the circadian pattern of clinical symptoms of RA [69]. Until recently, only two small-scale studies had evaluated the benefits of delivering GCs with regimens other than once-daily dosing at an unspecified time during the day. One small-scale trial compared once- and twice-daily GC administration (dose range 5–10 mg/day) in a small group of 20 RA patients. Qualitative evaluation indicated no efficacy differences between the two regimens [70]. A second 2-week randomized trial compared administration of indomethacin (100 mg) and prednisolone (5 mg) at night in 24 patients with RA. Both treatments significantly decreased morning stiffness and increased grip strength [71].

Delivery of a delayed-release prednisone formulation aimed at combatting the effects of the night-time increases in proinflammatory cytokines has been shown to be effective in RA. A delayed-release prednisone formulation has been developed that begins to release the drug ~4 h after ingestion. Taking this preparation at bedtime (approximately 10 P.M.) would result in the initiation of drug release at approximately 2 A.M., thereby theoretically more closely matching the increases in proinflammatory cytokines [3]. This preparation has been evaluated in two studies of patients with RA. In a 12-week, multicentre, randomized, double-blind trial, 288 patients with active RA were randomly assigned to either delayed-release prednisone or to immediate-release prednisone. The mean relative change in duration of morning stiffness of the joints from baseline to the end of treatment was significantly higher with delayed-release prednisone than with immediate-release prednisone (−22.7% *vs* −0.4%, $P = 0.045$). In this study, delayed-release prednisone also decreased IL-6 concentrations by ~50% *vs* no change for immediate-release prednisone [72]. Another similar 12-week study included 350 patients with active RA who were randomized to receive delayed-release prednisone 5 mg or placebo. The primary endpoint was the percentage of patients achieving an ACR20. Delayed-release prednisone plus DMARD treatment produced higher ACR20 (48% *vs* 29%, $P < 0.001$) and ACR50 (22% *vs* 10%, $P < 0.006$) responses and a greater median relative reduction from baseline in morning stiffness compared with placebo (55% *vs* 35%, $P < 0.002$) [73]. A 9-month extension of these studies has been reported [67].

Safety results obtained to date with this delayed-release GC indicate that it did not appear to significantly suppress the hypothalamic-pituitary-adrenal axis [74]. Patients treated for ~9 months in extensions of the phase 3 trials reported a total of 51 serious adverse events. Bone fractures occurred in three patients and tendon rupture in one. The other serious adverse events included gynaecological problems, cardiovascular disease, respiratory disease, joint replacement surgery and synovectomy. Much more information about the side effects associated with long-term administration of this new GC formulation is needed to fully understand its safety profile.

An important issue that has not been addressed in the development of new GCs and formulations is resistance to these drugs, which has been suggested to occur in as many as 30% of patients with RA [75]. Mechanisms underlying GC resistance have been studied most extensively in the setting of chronic obstructive pulmonary disease and several possibilities have been supported. These include cytokine activation of mitogen-activated protein (MAP) kinase pathways, excessive activation of transcription factor activator protein 1, reduced histone deacetylase-2 (HDAC2) expression, increased levels of macrophage migration inhibitory factor and increased P-glycoprotein-mediated drug efflux [76]. Some these resistance mechanisms may be at least partially reversible. For example, it has been suggested that elevated HDAC2 expression can be reduced by administration of theophylline. In addition, several p38 MAP kinase inhibitors are currently in development that might impact steroid resistance [76].

Conclusions

With increases in the number and mechanisms of action of potent traditional and biologic DMARDs available for the treatment of RA, the goals of treatment have been raised. Thus there is still an unmet need to allow ever more patients to achieve the highest levels of disease control [77]. There is substantial evidence that low-dose GC treatment, when combined with conventional DMARDs, can significantly slow disease progression and increase the number of patients who achieve disease

remission. Therefore GCs remain a useful adjunctive treatment for RA and for other systemic inflammatory and autoimmune disorders. Physicians and other health care providers have had concerns about long-term GC treatment because of the well-known adverse events associated with high doses of these drugs. However, adverse events with GCs are dose related and longer-term use of low-dose GCs may still be a viable therapeutic option for some patients.

Multiple approaches have been undertaken to improve the benefit–risk profile for GC treatment in patients with RA, including the development of a delayed-release low-dose prednisone formulation that has shown some clinical benefit. Additional approaches are in earlier stages of development. Optimal use of low-dose GCs has the potential to improve long-term outcomes for patients with RA.

Rheumatology key messages

- Addition of low-dose glucocorticosteroids to synthetic DMARDs improves structural outcomes, decreases inflammatory markers and reduces symptom severity in RA patients.
- New approaches to glucocorticoid delivery may further improve RA outcomes.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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