
Rheumatoid arthritis and glucocorticoids; the contribution of a literature search to the development of a EULAR recommendation on treatment with glucocorticoids in RA

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ABSTRACT

In 2010 the EULAR recommendations on the treatment of rheumatoid arthritis (RA) was published. The search for evidence for treatment of rheumatoid arthritis with glucocorticoids and the development of a EULAR Task Force Guideline on this subject is described in this paper.

Introduction

The treatment of rheumatoid arthritis (RA) comprises several principles; drug treatment including non-steroidal anti-inflammatory drugs (NSAIDs), disease-modifying drugs (DMARDs) and glucocorticoids, but also non-pharmacological principles, such as physical, functional and psychological approaches of treatment. Since their discovery in 1948 (1), GCs have been used successfully in the treatment of rheumatoid arthritis (RA), because of its anti-inflammatory and immune modulating effects. After a successful initial phase, the use of GCs has become contra indicated in most situations because of adverse effects, but has recently revived with upcoming evidence on relative safety in moderate and low doses, which show disease-modifying properties in rheumatoid arthritis (2, 3).

In the last decades, DMARD therapy has changed dramatically. In the nineties, early and aggressive treatment with high dosages of DMARDs (methotrexate) was found to be far superior to the previous treatment strategies using modest dosages of DMARDs, only in advanced RA patients and resulting in less favourable treatment outcomes (4). More recently, the introduction of biological agents such as TNF- α blocking agents, anti-CD 20 therapy, anti interleukin-1 and anti interleukin 6 have improved disease outcome considerably (5). The QUEST-RA study showed in a multinational cohort that

a mean of 62% of RA patients use MTX, (45%–75%), 18% (1%–45%) a biological DMARD and almost 50% prednisone (15%–90%) (6). Many trials have been published, most of them concerning treatment with biological DMARDs, although most of the RA patients are successfully treated with synthetic DMARDs. Therefore it is difficult to decide on the different therapeutic treatment options available with the overwhelming but unbalanced information on treatment options.

The European league Against Rheumatism (EULAR) has therefore formulated major objectives, which specify among other aspects that “by 2012, EULAR will have provided standards of care and foster access to optimal care of people with musculoskeletal conditions in (7)”. It was the objective of this EULAR Task Force to find consensus on recommendations of RA with synthetic and biological DMARDs (8, 9). The Task Force installed subgroups on different treatment modalities and one subgroup was dedicated to the treatment of RA with glucocorticoids (GCs); specific questions were to consider the efficacy of GCs in RA and whether the addition of GCs to synthetic DMARD monotherapy and combination therapy increased efficacy (10).

The subgroups formulated research questions and extensive literature searches among clinical trials and meta-analyses were performed by the different groups. The results were presented to the entire Task Force. A process of consensus finding by the expert committee (Task Force) using the results from the literature reviews resulted in 15 recommendations regarding the treatment of rheumatoid arthritis, of which one recommendation addressed the use of glucocorticoids (8). In this paper, the main results of the literature review will be discussed and we will present the

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recommendation regarding the use of glucocorticoids in the treatment of RA as developed by the Task Force.

Results

Literature review

– Is bridging therapy effective in RA?

There is some evidence that bridging with GCs has beneficial effects on the main outcomes signs, symptoms, function and structural damage. Indirect evidence was found from a Cochrane review (11) from which they inferred that prednisolone in dosages up to 15 mg/day can be used to intermittently control disease activity. In one of the trials of this Cochrane review (12) more direct evidence was found, since GCs were used as bridging therapy after initiating MTX therapy in RA patients. One RCT (13) showed that pulse therapy with GCs after the start of MTX therapy, results in better outcomes than without GC pulse therapy at initiation of MTX therapy.

– Is there evidence for the efficacy of GC in addition to synthetic DMARD monotherapy?

Several randomised clinical trials (RCTs) have shown a beneficial effect of the addition of GCs to DMARD monotherapy, regarding signs and symptoms, function, and radiographic progression (14, 15-18). These effects were obtained with rather low dosages of prednisolone (most of them a maximum of 7.5 mg/day), and resulted in lower disease activity and for some studies overt inhibition of radiographic progression.

– Is there evidence for the efficacy of GC in addition to combinations of synthetic DMARD?

Several studies include GCs (in low doses) as part of the initial treatment strategy, in combination with 2 other DMARDs (19-21). In the COBRA study (20), combining MTX and sulfasalazine, prednisone in a dosage of 60 mg/day was started at start of the trial and was tapered first in 6 weeks to 7.5 mg, and finally tapered to 0 mg in a 20-week period. The combination arm outperformed the monotherapy arm with regard to clinical outcomes as well as radiographic outcomes. Also

in the combination treatment arm of the FIN-RACo study (sulfasalazine, MTX, hydroxychloroquine and GCs), radiographic progression was significantly inhibited in the combination arm and resulted in better clinical outcomes (19). Two important observations were made; it was clear that early benefits in clinical outcomes were associated with long-term benefits in radiographic progression, and that in combination DMARD trials, the treatment arms in which GCs were added performed better with regard to the main outcomes (signs, symptoms, function and radiological damage) than treatment arms without GCs. With regard to this last observation, one could argue whether this is the result of the combination of DMARDs and GCs, or that it is the merits of GCs alone. Since treatment with DMARD combination alone did not perform better than DMARD monotherapy, it has been suggested that the added efficacy observed in the trials assessed in the review (10) might be due to the addition of GCs, although formal evidence was lacking.

– Is there a difference in efficacy of GC treatment between patients with early RA and patients with advanced RA?

In patients with early RA, treated with low-dose GCs, one Cochrane review analysed the outcome in radiological progression in this group of patients. From 15 RCTs, including 1414 patients and including many studies with combination DMARD therapy, it was clear that the addition of low-dose GCs, or a step down high-dose GCs, resulted in a substantial reduction in the progression of joint damage (22). On the other hand, in patients with longstanding RA, the addition of GCs in doses up to 15 mg/day was analysed by Criswell in a Cochrane review (23) and showed a positive effect on signs, symptoms and functional status for those patients treated with GCs.

– Is there evidence that timing of GC administration is important with regard to efficacy and safety?

Since the clinical responses and side effects of glucocorticoids are known

to be related to the circadian rhythms, the development of a modified release form of glucocorticoids seemed promising. Recently a modified released form of prednisone has been developed and has become available on the market. Indeed, the effects on morning stiffness are substantially better with this modified release tablet, than with the conventional prednisone, and with a comparable safety profile (24). Good news for prescribing doctors and patients, who still suffer from the fear of side effects and the use of GCs, despite strong suggestions from several studies that low-dose glucocorticoids treatment are only associated with modest side effects (2, 25).

– Is there evidence for a certain way of tapering GC administration with regard to efficacy and safety?

The comparison between different strategies in tapering GCs administration is lacking, and scarce indirect evidence was found in other studies. Van Gestel *et al.* (12) tapered GCs in 6 weeks from 10 mg to 0, and concluded that this happened too fast. In the COBRA trial (20) GCs were also tapered according to a strict regime and this resulted in some loss of benefit in clinical outcomes after tapering. Tengstrand tapered GCs in a study where patients were on longstanding low-dose GCs and reported increased disease activity with tapering of the GCs (26). A definite conclusion on the best tapering strategy for glucocorticoids could not be made, but GCs should be tapered as soon as possible in accordance with the clinical situation, because of its toxicity. It was suggested that tapering should preferably take place in a slow manner.

– EULAR recommendation regarding the use of GCs in RA

After collecting the evidence and discussion within “The EULAR Task Force for the management of rheumatoid arthritis with synthetic and biological disease-modifying anti-rheumatic drugs”, the following recommendation with regard to the treatment with GCs was developed based on literature evidence as well as expert opinion:

“GCs added at low to moderately high

doses to synthetic DMARD monotherapy (or combinations of synthetic DMARDs) provide benefit as initial short-term treatment, but should be tapered as rapidly as clinically feasible" (8).

Discussion

In this paper, results from our literature study as published in 2010 (10) are discussed. Evidence was especially searched for among clinical trials and meta-analyses, but additional information on the clinical use of glucocorticoids in RA might also be found among observations in clinical practice. We tried to incorporate these elements by using the expert committee's opinion on the use of glucocorticoids and combine literature evidence with this more expert based information in the development of the recommendations.

Evidence was found on the bridging capacities of GCs in the treatment of RA; its efficacy in bridging the gap until a newly started DMARD reaches its clinical effect, but also its capacity to improve disease activity in disease flares in longstanding RA. From the Kirwan Cochrane review it was found that low-dose GCs given early in the disease course have disease-modifying effects (27), a result supported by others (28-30). In 2009, after selecting the literature for the EULAR task force, Pincus *et al.* (31) published a prednisone withdrawal study in RA in which they documented the efficacy of a low dose of prednisone (1-4 mg/day) in RA patients.

In addition, GCs in low to moderate doses up to 15 mg/day in patients with longstanding RA, improve signs, symptoms and function. There was robust evidence that addition of GCs to DMARD monotherapy and DMARD combination therapy significantly improves clinical outcomes as well as prevents structural damage.

Although it is difficult to disentangle the isolated effects of GCs from the combined effects of DMARD therapy without GCs, the observation that combination DMARD therapy does not result in better outcomes than DMARD monotherapy in most trials (32), strongly supports the fact that it

is the GC component in the treatment strategies that accounts for the added benefit. Adverse effect of GCs have been abundantly reported and feared by patients and doctors. However, more evidence emerges from critical reviews and meta-analyses, showing that adverse effects associated with low-dose glucocorticoid-treatment are modest, but side effects with moderate to high doses cannot be ignored (25). Tapering of glucocorticoids in rheumatoid arthritis should therefore be considered during every visit, whenever possible, but according to the clinical scenario in patients with RA to optimise the benefit/harm ratio. High disease activity itself yields additional risks, such as more infectious complications and fewer possibilities to exercise and hence sustain muscle power. One should keep in mind while treating RA patients early in the disease, that GCs do have DMARD capacities in reducing radiographic progression and therefore should not per se be avoided because of its side effects (28-30). Clear evidence on how to taper GCs in patients with RA was not found in the literature, although some studies suggest that tapering should not go too fast (12, 20).

To conclude, it is obvious that GCs are important therapeutic drugs in the treatment of RA because of its proven effect on clinical outcomes such as signs, symptoms and function, and its DMARD properties with regard to radiographic progression. However, safety and toxicity are always important aspects when treating RA patients with GCs (or any medication). Recently, evidence has become available from RCTs and meta-analyses on the relative safety of low-dose glucocorticoid treatment, however chronic treatment with moderate to high doses remains contraindicated (2, 25). Promising results are to be expected from the development of safer drugs and alternative modes of GC administration, designed to result in a better benefit/harm risk ratio (33).

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