Low-dose corticosteroids and disease-modifying drugs in patients with rheumatoid arthritis

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ABSTRACT

Low-dose glucocorticoids (GCs) exhibit a differential effect on continuation of disease-modifying anti-rheumatic drugs (DMARDs), and the degree of adverse effects (AE) associated with DMARDs. Therefore, GCs address important problems in DMARD use in rheumatoid arthritis (RA), i.e. cumulative toxicity and frequent AE. Low-dose GCs often are recommended to achieve a better symptomatic control or as 'bridge therapy' before the onset of action of DMARDs. RA patients with GC co-medication had better radiographic outcomes but experienced more GC-related AE. Further long-term studies are needed to focus on timing of administration, duration and identification of risk factors for developing AE to establish the optimal use of GCs in the treatment of RA.

Introduction

Rheumatoid arthritis (RA) is a chronic, debilitating disease that affects an estimated 1% of the population, and induces considerable healthcare costs. A limited number of anti-rheumatic drugs are available to modify disease activity and progression of joint destruction with subsequent disability (1). There are four general classes of drugs commonly used in the treatment of RA: non-steroidal anti-inflammatory agents, corticosteroids, disease-modifying anti-rheumatic drugs (DMARDs), and biological agents (2). In most cases the pharmacological therapy of RA is based on DMARDs with or without accompanied administration of glucocorticoids (GCs). In one study of German centres, GC therapy was administered more often in combination with tumour necrosis factor inhibitors (81%), cyclosporine A (80%), or leflunomide (77%) than with more traditional DMARDs such as MTX (63%) or SSZ (55%) (3).

The main problem of GC drug schedules in RA is cumulative toxicity and frequent adverse effects (AE) (4-5). In addition, drug toxicity is a common cause for discontinuation of any type of therapy in RA (6). It was shown that except for MTX (median survival time 4.62 years), half of the patients with RA have discontinued a second-line drug approximately 1.5 years (median survival time 1.41 years) after it was begun, either because of lack of efficacy or AE, and rarely for other causes (7). In this respect, several studies could demonstrate a significant difference in retention rates of various DMARDs (8-10). Since the introduction of GC in the therapy of RA a possible influence of GC on DMARD survival was of interest. This article will focus on the interaction of GC on survival time and AE of DMARDs in RA therapy.

Survival time of DMARDs and efficacy of a combination therapy of low-dose GCs and DMARDS

Recent evidence suggests that low-dose GCs slow radiographic progression of articular disease in early RA (8, 10), although joint damage increased following the withdrawal of GC therapy (11-12). For example, a highly significant reduction was observed in the frequency of erosive RA in patients with low-dose GC co-medication (49%) compared to patients without low-dose GCs (80.4%; OR 4.05, CI 1.91-8.66, $p<0.0001$) (13). Overall, longitudinal analyses indicated that patients who took prednisolone had a higher probability of being in remission over the entire course of the disease (14). Furthermore, there exists some evidence that the effect of DMARDs in early RA is magnified by concomitant GCs (4, 15-16). Concurrent treatment with stable low-dose prednisolone was associated with an increased likelihood of response to MTX therapy (adjusted OR 2.84, 95% CI 1.43 to 5.63) (17). One study demonstrated a decreased renal clearance of MTX under GC

with higher doses of prednisolone (18). Furthermore, co-medication with low-dose GCs prolonged the survival time for SSZ and MTX (SSZ from 10.4±2.3 to 22.5±1.9 months as well as for MTX from 21.8±2.9 to 43.3±2.7 months) due to a delay until loss of efficacy pointing in this direction (13).

One clinical trial revealed fewer withdrawals of SSZ under combination therapy with GCs (19). In another study, addition of prednisone at 7 mg/day to SSZ monotherapy led to a significant difference in the erythrocyte sedimentation rate at year 1 in favour of the prednisone-treated group (20). Interestingly, it was shown that mandatory GCs (median dose used: 5 mg prednisone) combined with SSZ, MTX, or HCQ was significantly more effective compared to the respective monotherapy with optional GC therapy. The difference for clinical outcome parameters was significant at year 1, but these benefits had disappeared thereafter (11). Therefore, the modulated DMARD survival might be due to a better disease control which would be in contrast to a negative analysis of GC in RA (21).

Some studies revealed that there might be a DMARD-specific effect of GC co-medication on DMARD survival time (13, 22). GCs exhibited a beneficial effect on adherence to MTX and hydroxychloroquine (HCQ) due to a delayed onset of AE. Previous studies suggest that concomitant or prior GC use is associated with an increased likelihood of DMARD discontinuation, although it is not clear whether effects of GCs on DMARD efficacy are synergistic or additive (7, 10). For example, expressed in terms of "5-year survival", an average of 55.7% of RA patients continued MTX 5 years after it was started, especially in the subgroup of patients receiving GCs. However, steroids did not prolong drug survival in those receiving IM gold, HCQ, penicillamine or AZA (7). For example, in patients taking AZA, the duration of therapy was 44.4±2.6 months in patients taking AZA only, compared to 22.3±1.6 months in patients taking AZA with concomitant GCs, associated with both time-until-AE and loss of efficacy (13). In one study, only a weak effect of early GC medication on discontinuation was observed, while prior or concomitant GC use had no effect on DMARD discontinuation (23).

A more recent study examined the outcome of MTX, cyclosporine and GCs in RA patients (24). Based on the estimated ORs from a stratified factorial analysis (from the MTX arm), the number needed to treat (NNT) to stop erosive progression was 11 (95% CI 6, 120) with added GCs and 10 (95% CI 6, 39) with added cyclosporine. The estimated NNT for the triple therapy of MTX+cyclosporine+GC was 6 (95% CI 4, 14). In addition, HAQ scores as well as disease activity decreased with all treatments from 6 months until 24 months of treatment. Stratified factorial analysis indicated a significant synergistic interaction between the therapies studied (p=0.01).

Most of above-mentioned studies were conducted before the introduction of biologic agents. Currently there are no studies concerning the co-medication of GCs and biologics. Hence, we cannot draw any conclusions on the possible synergistic effects of GCs and biologics.

Modulation of DMARD adverse effects by GCs

So far there exist only few randomised clinical trials (RCT) studying a combination therapy of GCs and various DMARDs (20, 25-27). Capell *et al*. described AE in the GC group at year 1, *i.e*. anti-resorptive osteoporosis treatment was more often used and a trend towards higher diastolic blood pressure as well as a significant weight gain was observed. However, AE necessitated withdrawal of SSZ monotherapy (22%) in a significantly higher proportion of patients compared to a combination therapy of SSZ and prednisolone (11%) (20).

In the CARDERA study, the number needed to harm (NNH) for any adverse event leading to withdrawal was 20 (95% CI 8, 1280) with added cyclosporine and 14 (95% CI 6, 65) with added prednisolone. The estimated NNH for the triple therapy, based only on data from patients receiving this therapy, was 6 (95% CI 3, 23).

Otherwise, data stratifying the withdrawal of DMARDs for occurrence of AE and loss of efficacy revealed that GC co-medication increased significantly the time-until-AE for MTX (3.0±0.6 *vs*. 18.8±1.3 months), HCQ (34.5±4.6 *vs*. 54.4±5.1 months) and gold (6.6±0.9 *vs*. 10.5±0.9 months) (13). Of interest, only low-dose GC therapy longer than 48 weeks in combination with DMARDs conferred the increased risk for serious AE as osteoporosis and diabetes mellitus (13).

Taken together, the DMARD specific effect of GCs is the integrative result of multiple possible interactions between the compounds. GCs may interact via genomic and non-genomic mechanisms with the pharmacodynamic and pharmacogenetic characteristics of various DMARDs (28-29). Furthermore, interaction of active as well as inactive metabolites may interfere with the kinetics, efficacy and toxicity of DMARDs (5, 30-31).

In conclusion, available data indicate that co-medication of low-dose GCs with DMARDs, both in usual care and in RCT, has an important effect on DMARD continuation and reduction of AE associated with the DMARD utilised. Furthermore, RA patients with GC co-medication had a better outcome regarding radiological progression but did experience more GC-related AE. Further long-term studies dealing with low-dose GC and DMARD co-medication are warranted to focus on timing of administration, duration of treatment, and identification of risk factors for developing AE, in order to develop optimal recommendations for use of GCs in the treatment of RA.

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