Editorial

We Still Don’t Know How to Taper Glucocorticoids in Rheumatoid Arthritis, and We Can Do Better

Rheumatologists, internists, residents, and fellows frequently ask, “How do you taper glucocorticoids in rheumatoid arthritis?” Despite controlling symptoms of rheumatoid arthritis (RA) and slowing progression of radiological joint damage in early RA, low-dose glucocorticoids (GC) are associated with a plethora of chronic adverse effects, including diabetes mellitus, hypertension, atherosclerosis, weight gain, osteoporosis, skin fragility, Cushingoid appearance, and myopathy, and are also associated with increased risk of infection, cardiovascular events, depression, cataracts, and skin atrophy. To prevent or minimize these effects, GC tapering to the lowest dose necessary to maintain control of disease activity is recommended.

However, strategies to taper GC vary, and are mostly described based on expert opinion. No clinical trials have directly examined, much less compared, different GC tapering regimens in RA. Withdrawal of GC may also precipitate adverse events, including flare, adrenal insufficiency, and GC withdrawal syndrome. To attempt to answer this frequent question, we performed a systematic literature review to assess the influence of tapering regimens on successful GC withdrawal, as well as clinical outcomes. We searched PubMed and Cochrane Central to identify publications from January 1972 to February 2011 (detailed search strategy available on request). Search terms comprised 4 blocks that were combined with Cochrane hedge, “methodological filter for clinical trials.” The first block addressed disease (RA in adults); the second and third, intervention (GC/related terms AND tapering); and the fourth, outcome (withdrawal/dose reduction, effect on disease activity). We double-extracted all titles and abstracts according to the following: inclusion criteria: (a) adult patients with RA; (b) studies in which GC and related terms (e.g., corticosteroids, prednisone, prednisolone, etc.) were used; and exclusion criteria: (a) case report or case series with < 20 patients; (b) editorials, review articles, letters, opinions, etc.

Two of our 4 reviewers (ERV, SR, DEF, TGW) independently reviewed and extracted data from the remaining articles and excluded an article if: (1) it did not include an oral GC; (2) it did not include and describe the GC tapering method; and/or (3) it was an extension of a study in which GC were not tapered during the extension period. Because we were interested only in studies that described a GC tapering method, we did not include studies in which GC were stopped abruptly without any dose reduction strategy. We extracted data regarding patient characteristics, study design, interventions, and GC tapering, together with data for the influence of tapering in terms of continued disease control and any changes in adverse effects. Discordant assessments between 2 reviewers were resolved by discussion to achieve consensus.

Quality assessment was performed using the risk of bias tool from the Cochrane Collaboration. We also examined heterogeneity in terms of study design and patient characteristics, as well as availability of data on adverse events and disease control during and after tapering, to determine whether a metaanalysis could be performed.

Of the initial 1265 articles (1091 identified in PubMed, 174 in Cochrane Central), 76 met criteria for detailed review, and after reading each article in depth, only 6 randomized controlled trials (RCT) met our selection criteria. Four long-term extension (LTE) trials also provided data on tapering and withdrawal of GC as a secondary efficacy endpoint. Based on whether a study design included a specific tapering regimen, and whether efficacy and safety of GC were examined systematically during and after tapering, the quality of the RCT reports was limited for the objectives of our systematic literature review. In addition, while all the RCT reported sequence generation and allocation concealment, none randomized patients to different GC tapering regimens, and only 3 fully reported the outcomes (defined as description of effect on efficacy and at least 1 adverse event). Given the variability in tapering regimens and the inconsistency in reporting outcomes, a metaanalysis could not be performed.

Baseline demographic and disease activity characteristics of the patients with RA in each RCT were similar (Table 1). However, disease duration varied, because some studies included only patients with early RA (mean ≤ 2 years from the time of diagnosis), while other studies included patients who had established RA.

Each RCT described a different tapering approach (Table 2). The majority of studies tapered the GC to 0 mg daily, while 2 studies tapered the GC to 7.5 mg daily. Only 1 study used a quantitative disease activity measure to stop the GC taper (Disease Activity Score > 44 > 2.4). In an era when treatment targets have been defined to improve outcomes in patients with RA, failure to use existing validated measures to guide GC tapering in RCT is disconcerting.
After all the effort, we discovered a great deal of variability and no satisfactory answer. Successful tapering was lowest in the 2 RCT in patients with longer disease duration; success rates were only 31% and 42% in patients with 6.3 and 9.3 years of disease, respectively. All patients in these 2 studies had used oral GC prior to study entry. On the other hand, 2 studies evaluating GC-naive patients with a mean disease duration of < 2 years reported...
success rates of 78% and 92%.\textsuperscript{8,10} One study of early
disease allowed prior GC and still the success rate in that
study was 86%.\textsuperscript{13}

In the LTE trials, successful tapering varied from 15% to
89%, and control of RA with the biologic appeared to enable
GC tapering and withdrawal. While successful tapering was
a secondary efficacy outcome, none of the LTE trials
reported data to examine changes in adverse effects.

No studies directly compared clinical outcomes in
patients who tapered successfully versus those who tapered
unsuccessfully. Only 1 study compared baseline disease
characteristics of patients who tapered successfully versus
those who tapered unsuccessfully, and reported that patients
who tapered successfully were younger and a greater
proportion were premenopausal\textsuperscript{9}.

Despite a thorough and careful systematic literature
review, we were disappointed to find that the data for
tapering GC in RA were heterogeneous and incomplete. At
this time, there is no credible way to provide an
evidence-based answer to the question, “How do you taper
GC in RA?”

It is possible, however, to suggest a way forward. It is
clear that studies comparing GC tapering regimens are
needed, and this systematic literature review uncovered
important design features essential for such studies. First, it
is probable that disease duration will influence success, and
therefore tapering strategies for patients with early RA may
differ compared with those for patients with established RA,
who are likely to have been receiving GC chronically in
varying doses. Second, the duration of tapering may not be
as critical as the duration of disease and duration of prior GC
use. Tengstrand, \textit{et al}\textsuperscript{9} allowed up to 52 weeks to withdraw
GC and yet the failure rate was 58%. Third, it is clear that a
robust outcome measure describing success would be appro-
priate, such as maintaining a Disease Activity Score-28 <
3.2, Clinical Disease Activity Index < 11, or any definition
of remission. Fourth, it would be appropriate to consider a
uniform definition of failure, such as RA flare of sufficient
intensity and duration to result in a change in treatment.
While not yet validated, such a definition is being developed
using Outcome Measures in Rheumatology Clinical Trials
RA flare criteria\textsuperscript{19}. Fifth, studies should be designed to have
enough power to create statistical models to detect
important predictors of successful withdrawal, such as age,
sex, and type of background RA therapy. Finally, and most
importantly, improvements in safety, with regard to serious
infection and cardiovascular events as well as bone effects,
should also be considered as outcomes, acknowledging that
such a study would require large numbers and longer
followup.

Although we cannot answer the question of how to taper
GC in RA, our review provides some background information
and directions to design an appropriate clinical study to
answer this important clinical question.

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