

## Editorial

# Steroids for Rheumatoid Arthritis: The Honeymoon Revisited (Once Again)



Glucocorticoids constitute one of the most common treatments for rheumatoid arthritis (RA). Registries and large databases have estimated the prevalence of steroid use at 20%–40% of new enrollees, with up to 75% of patients exposed at any time in their course<sup>1-3</sup>. These statistics belie an uncomfortable truth: despite their pervasiveness, limited data support longterm steroid use, and evidence of their deleterious effects continues to mount. Physician practice patterns thus may reflect an amalgam of (1) personal opinions about longterm efficacy, extrapolated from short-term exposure data; (2) a failure to be familiar with or convinced by the toxicity literature; or (3) patient preferences, characteristics, or outcomes heretofore not captured in the existing longterm data.

## EFFICACY

That steroids — even at low doses — provide short-term relief from the symptoms of RA is not disputed. Data from randomized controlled trials (RCT) of less than 2 weeks' duration consistently show improvement in measures of pain and tenderness compared to placebo and nonsteroidal antiinflammatory controls<sup>4</sup>. For intermediate and longer-term use (3 months or greater), the data are sparse but also generally support the use of steroids to abate the signs and symptoms of active disease. A metaanalysis found the effect size to be modest and similar to that of treatment with aspirin or chloroquine<sup>5</sup>.

Some recent studies suggest that prednisone at 5 mg<sup>6</sup>, 7.5 mg<sup>7</sup>, and 10 mg<sup>8</sup> may initially slow the rate of radiographic progression of RA, although these findings are by no means universal<sup>9</sup>. In the British Arthritis and Rheumatism Council Low Dose Glucocorticoid (ARC LDG) and the German Low Dose Prednisone Therapy studies, radiographic improvement was evident at early timepoints, with loss of statistical significance once steroids were discontinued in the ARC LDG study<sup>10</sup>. It is interesting to note that even in

the studies that do show radiographic protection, a small minority of patients (typically 10%) account for the disparity in radiographic scores, and the overall effect is modest. For longer-term studies, functional measures and patient assessments may show minor benefits for steroid use at 2 years<sup>6,7,9,11</sup>. After 24 months of followup in the study by Van Everdingen, *et al*, only radiographic scores and grip strength differed between placebo and steroid-exposed patients (and these may be potentially explained by subtle baseline differences between treatment cohorts). Finally, the varying study design of RCT [i.e., presence of concurrent disease modifying antirheumatic drugs (DMARD), duration of RA, randomization protocol, choice of endpoints, etc.] clearly precludes a simple reconciliation of their findings.

A number of trials have employed elevated initial doses of glucocorticoids, with a subsequent taper<sup>12-14</sup>. Results from these trials point to broad potential benefits for the use of steroids. Unfortunately, it is unclear whether the benefits derive from steroid use with specific DMARD combinations, from the fact that short-term higher-dose steroids invoke molecular mechanisms that differ from those at lower doses, or from an alternative explanation<sup>15</sup>. A 4-fold variance in the dose of steroids and heterogeneous baseline patient characteristics further obscures the conclusions one may draw from among these “burst-then-taper” investigations.

## SHORT-TERM/INTERMEDIATE TOXICITY

Unfortunately, the literature provides very limited insight into the adverse effects of short-term and medium-term steroids. Such studies would likely require large numbers of subjects, making a prospective trial impractical. Retrospective observational studies, however, suggest that excess adverse events (e.g., fractures) are present after as few as 3 months<sup>16</sup>. This corroborates the finding of a

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*See Use of low-dose glucocorticoids and the risk of cardiovascular morbidity and mortality in RA, page 1856 and New glucocorticoids on the horizon: repress, don't activate!, volume 32: July, page 1199*

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prospective placebo-controlled trial, which detected a diminished bone mineral density in subjects 5 months after initiating a tapering course of prednisone 10 mg.

### INTERMEDIATE/LONGTERM TOXICITY

There is considerable controversy surrounding the safety of longer-term glucocorticoids. In this issue of *The Journal*, for example, Davis and colleagues review the apparent association of low-dose glucocorticoid use and the risk of cardiovascular morbidity/mortality<sup>17</sup>. Their discussion highlights the complexities that obscure the relationship of predictor and outcome, emphasizing the difficulties in establishing causation. Many such criticisms are not unique to this subject matter; rather, they appear to impugn the very fundamentals of observational analyses. In point of fact, investigators have largely found concordance when correlating the findings of randomized trials and well-designed observational studies<sup>18</sup>. It is also important to distinguish retrospective studies, which mine preexisting incomplete data sources, with observational studies based on prospectively-collected information ("trohoc" studies)<sup>19</sup>. Provided the appropriate covariates are assembled, trohoc studies may avert certain forms of bias that hinder retrospective investigations.

Further, as the size and power of such observational studies have increased, they have gradually decreased the "threshold" steroid dosage at which adverse events are recognized. Recent reports of longterm prednisone use suggest that even exposures of less than 5 mg a day may be associated with potentially severe outcomes<sup>20</sup>. Conversely, adverse events have not been identified with any precision in longterm prospective RCT of oral corticosteroid use. This should be understood as an indication of the limits of RCT in establishing safety data, i.e., the absence of sufficiently powered analyses, rather than an endorsement of steroids' benign nature. Indeed, the largest of these trials has enrolled fewer than 130 patients, which is insufficient to examine toxicity in a reliable manner.

### ADDITIONAL CONSIDERATIONS

Physicians face numerous uncertainties in the use of corticosteroids for RA: should these agents be restricted to only the most severely afflicted (and should this severity reflect an unacceptable level of pain or degree of functional loss?). Are the recognized predictors of poor prognosis (elevated Health Assessment Questionnaire score, high rheumatoid factor titer, presence of nodules, etc.) also useful indicators of patients that are likely to benefit from steroids? Similarly, should the occurrence of certain comorbidities counsel against the use of corticosteroids (such as preexisting lung disease associated with increased rates of pneumonia<sup>20</sup>)? In any case, the meager amount of presently published data implies that characteristics of the prescribing rheumatologist are more predictive of glucocorticoid use than patient characteristics<sup>21</sup>.

Does the prescribing of steroids bias further decision-making by the patient and physician? The immediate clinical benefit of oral glucocorticoids, regrettably, could represent a double-edged sword: patients and their physicians may now believe that their improved status no longer warrants remittive therapy. A recent study supports this phenomenon, reporting that among patients followed consistently by rheumatologists but who were not taking DMARD, 37% received oral steroids<sup>22</sup>. Similarly, it has been stated<sup>23</sup> (without clear published evidence) that the immediate gratification afforded by steroids may make it difficult to discontinue them.

Some physicians rely upon parenteral corticosteroids, in an attempt to avert adverse effects. It seems unlikely, however, that an alternative route of administration (intramuscular or intraarticular steroids, for example) would arrest the untoward effects of steroids if chronically prescribed; systemic side effects have been repeatedly demonstrated even with inhaled glucocorticoids used to treat asthma<sup>24</sup>. Such findings admittedly provide only circumstantial evidence, as compelling safety data for intraarticular and intramuscular steroids are virtually nonexistent. This deficiency likely stems from the fact that parenteral glucocorticoids are typically not administered on a longterm or intensive basis.

Undoubtedly, the decision to institute steroid therapy emanates in part from the simple desire to rapidly alleviate patients' symptoms irrespective of their role in the progression of disease. Until the introduction of biologics, physicians had no immediate remedy other than glucocorticoids. Fortunately, there appear to be a number of novel alternatives in development, which are reviewed by Song and colleagues in a recent issue of *The Journal*<sup>25</sup>. These therapies will require comparison with traditional steroids as they progress through the various stages of drug development. Perhaps these new studies might improve our understanding of traditional steroids, in terms of magnitude of response, durability of response, and adverse events.

The most recent American College of Rheumatology Guidelines for the management of RA now acknowledge the need to balance the benefits and potential risks associated with glucocorticoid use<sup>26</sup>. The fundamental question is whether we need more data in order for physicians to weigh this decision more competently.

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