Editorial



# Use of Low-Dose Glucocorticoids and the Risk of Cardiovascular Morbidity and Mortality in Rheumatoid Arthritis: What Is the True Direction of Effect?

People with rheumatoid arthritis (RA) experience an increased burden of cardiovascular disease (CVD) and reduced survival compared to the general population[1]. Myocardial infarction (MI) and heart failure appear to be more prevalent in RA compared to subjects without RA[2]. In one study, the risk of congestive heart failure was 2-fold higher among RA subjects compared to non-RA controls[3]. Much of the best evidence suggests that systemic inflammation plays an important role in the pathogenesis of CVD in RA[1].

Still, a nagging question persists in the minds of many rheumatologists today: What is the role of glucocorticoids (GC)? A common view is that GC harm the cardiovascular system. We wish to examine an alternative hypothesis: that GC might actually reduce the risk of CVD in patients with RA. Our aim is not to provide a comprehensive review of the cardiovascular effects of GC but rather to bring balance to the debate of how use of GC might affect the development of CVD in patients with RA.

A discussion of GC is highly relevant given current rheumatology practice. GC have been used to treat people with RA for the last half-century, and recently, there has been renewed interest in these medications[4]. Use of GC is highly prevalent among people with RA; for example, these are taken by 30–50% of patients enrolled in recent therapeutic trials[5]. Rheumatologists commonly use GC as "bridge therapy" awaiting efficacy of slow-acting disease modifying antirheumatic drugs (DMARD), and also for treating disease flares. Frequently, delays occur in initiating biologic agents due to time required for insurance company authorization, tuberculin skin testing, and/or patient education visits. For these reasons, GC will likely continue to be an important component of the armamentarium for patients with RA, at least for the foreseeable future.

Despite years of use, relatively little is known regarding the longterm effects of GC, particularly on the development of CVD[4]. In light of the increased burden of CVD in RA, it is critical to better understand how GC affect the development of CVD in this population, whether beneficial or harmful.

Inflammation plays a fundamental role in the pathogenesis of CVD in RA. For example, abnormalities in traditional cardiovascular risk factors alone cannot explain the increased risk of CVD in this population[6]. Also, clinical features in RA that are associated with high inflammatory disease activity such as elevated acute phase markers and extraarticular manifestations are associated with cardiovascular events and mortality[3,7-10]. Theoretically, GC could modulate the risk of CVD in RA in 2 competing ways. The risk could increase due to potentially deleterious effects of GC on lipids, glucose tolerance, hypertension, or obesity[11]. Alternatively, by alleviating systemic inflammation, GC may actually decrease the risk of atherosclerosis and CVD[1,12]. Evidence supporting both directions of effect will be reviewed. Furthermore, there is evidence that effective treatment of systemic inflammation with DMARD is associated with lower risk of cardiovascular mortality[13]. Treatment with antagonists of tumor necrosis factor-alpha (TNF-α) may lower the risk of heart failure[14]. Therefore, it is reasonable to consider the possibility that GC may also reduce the risk of cardiovascular events and mortality.

A number of novel findings in epidemiological studies suggest that "flares" of inflammation in RA may be involved in triggering cardiovascular events. First of all, the risk of cardiovascular events is independent of the duration of RA[8]. Second, the risk of sudden death and silent MI appears to be increased very early, even prior to patients ful-

*See* Steroids for RA: the honeymoon revisited (once again), *page 1863*

filling American College of Rheumatology (ACR) classification criteria[7]. Third, there is new evidence that the erythrocyte sedimentation rate (ESR) rises significantly in the 6-month period immediately prior to onset of heart failure in patients with RA[9]. Similarly, increases in systemic inflammation due to acute infections have been linked with a short term increased risk of MI and stroke in non-RA subjects[15]. These associations between episodic fluctuations in level of systemic inflammation and onset of cardiovascular events suggest the possibility that using GC to control flares of disease activity may actually lower the risk of cardiovascular events.

## PROBLEMS WITH THE "EVIDENCE" AGAINST GC IN RA

Several authors who have written on this subject over the years have concluded that GC likely cause CVD[11,16-18]. However, fair questions can be raised regarding the "evidence" that GC are associated with an increased risk of CVD, at least in the context of RA. Several of these review papers cite mechanistic studies that assess *in vitro* or animal models[19], or studies of other disease states (i.e., Cushing's disease[20], systemic lupus erythematosus[21,22], and asthma[23]), to support the hypothesis that GC have harmful cardiovascular effects. Frequently, these studies contain a heterogeneous sample of patients treated for many different rheumatic and non-rheumatic diseases[23,24] and often include otherwise healthy subjects. Therefore, it is unclear how relevant this literature is to RA. Nashel[16] described a paper by Kalbak[25] in 1972 as "the strongest evidence that longterm corticosteroid therapy is important in the development of arteriosclerosis." This study found a higher rate of radiographic arterial calcification at the ankle among patients with RA treated with steroids compared to patients not treated[25]. However, more clinically relevant events such as MI, heart failure, or death were not assessed. Additionally, no information regarding confounding variables was provided. While this sort of information is compelling and warrants further study, it is no substitute for longitudinal studies with objective clinical endpoints.

In the RA setting and in GC users overall, epidemiological studies conflict regarding the risk of CVD associated with GC exposure. Several studies have found potentially harmful effects of GC[26-29] whereas others have found either no effect or beneficial effects[8,12,30-32]. Table 1 shows selected studies that have assessed the association of GC exposure and CVD in RA. It is apparent from these study findings that the magnitude and even the direction of the effect of GC on cardiovascular morbidity and mortality are unclear.

The most significant limitation of observational study designs for this question is the potential for confounding by indication (also called channeling bias)[17,33]. For patients with RA, this implies that the association between GC exposure and CVD is not causal but rather operates through a third factor: disease activity/severity. In other words, people with more active and/or severe RA receive more GC and are also more likely to develop CVD. To understand this, consider an example. A patient with longstanding RA with no cardiovascular history develops a flare of polyarthritis with a high ESR. If the patient has a MI a week after starting GC, then it might seem as though GC were the cause. However, in light of current evidence, it is also possible that the "flare" triggered the MI. A second example: a patient with seropositive, erosive RA has received a large cumulative dose of GC over many years. The patient has congestive heart failure. Could the large dose of GC be to blame, or the many disease flares over the years for which the GC were prescribed?

Although confounding by indication is widely acknowledged as a limitation of observational study designs for RA treatment effects, few studies have attempted to measure the extent of this bias. Wolfe and others showed that patients with RA or osteoarthritis who were switched to cyclooxygenase-2 inhibitors when they became available in 1999 had clinically important increases on several measures of disease severity compared to those who remained on conventional nonsteroidal antiinflammatory drugs (NSAID)[34]. Erkan and colleagues surveyed US rheumatologists and found a strong preference to prescribe GC as first-line therapy to RA patients with higher disease activity/severity, irrespective of whether medication cost was considered a factor[35]. These data provide support that confounding by indication is a clinically important phenomenon in observational studies of GC effects in RA.

Investigators have attempted to account for this confounding by statistically modeling the association between GC exposure and cardiovascular events, adjusting for a broad range of variables that are markers of RA severity: for example, rheumatoid factor (RF), tender/swollen joint counts, erosive disease, Health Assessment Questionnaire scores, and ESR. Despite this technique, studies have reported divergent effects of GC on cardiovascular risk albeit with varying degrees of adjustment (see Table 1 for model descriptions). Wolfe and Michaud recently reported that GC exposure predicted MI in the following 6 months in a large cohort of patients with RA[29]. Wallberg-Jonsson and colleagues showed complex effects of GC exposure[12,32]. Early use in the first 3 years was associated with a higher risk of cardiovascular events; in contrast, cumulative GC use more than one year before cardiovascular events was associated with a lower risk in a subset of patients who experienced cardiovascular events during followup.

Wei and others[26] recently examined GC exposure (defined by prescription records) and the risk of subsequent cardiovascular events. Their large sample was heterogeneous, including many different disease processes; a subset with inflammatory arthritis (n = 1165) was defined by taking subjects who had prescriptions for NSAID and DMARD

*Table 1*. Epidemiologic studies examining the association of GC exposure and cardiovascular outcomes in RA. Confidence intervals (95%) are shown in brackets.

| Study | Year | Study Design and Population | Definition of GC Exposure | Outcome | Results |
|---|---|---|---|---|---|
| Jacobsson, *et al*[54] | 1993 | Population-based cohort of Pima Indians with RA | Ever exposure (yes/no) | Mortality | HR 1.03 (0.32, 2.70)[a] |
| Wolfe, *et al*[55] | 1994 | RA cohorts from 4 U. S. centers (ARAMIS system) | Prednisone use at first physician visit | Mortality | RR 1.42 (1.17, 1.73) – Saskatoon[b]<br>RR 1.61 (1.22, 2.12) – Wichita<br>RR 1.29 (0.95, 1.55) – Stanford |
| Wallberg-Jonsson, *et al*[32] | 1997 | Retrospective population-based RA inception cohort in Sweden | Oral GC exposure ≥ 1 yr | Mortality<br>1st CV event | Not significant (data not given)<br>Not significant (data not given) |
| Wallberg-Jonsson, *et al*[12] | 1999 | Retrospective population-based RA inception cohort in Sweden | Cumulative ≥ 1 yr before event (in a subset of patients who suffered CV events during followup) | Combined[c] | RR 0.51 (0.30, 0.89)[d] |
| | | | Early GC use (first 3 yrs after onset) | Combined[c] | RR 1.82 (1.09, 3.05)[e] |
| | | | Extensive GC use (≥ 1 yr) | Combined[c] | Not significant (data not given) |
| | | | Early GC use (first 3 yrs after onset) | Mortality | RR 1.88, p < 0.001 (univariate) |
| | | | Extensive GC use (≥ 1 yr) | Mortality | Not significant (data not given) |
| Wolfe and Michaud[29] | 2004 | Clinic-based RA cohort in US | GC use in 6 month periods | MI incidence in next 6 mo | HR 1.7 (1.1, 2.6); p = 0.045 – 0.085 after adjusting for HAQ values[f] |
| Suissa, *et al*[29] | 2004 | Nested case-control study in RA cohort | GC use | MI incidence | RR 1.0 (0.7, 1.5) |
| Souverein, *et al*[27] | 2004 | Population-based nested case-control study within the GPRD (data here from subset with inflammatory arthritis) | Current GC use (RA subset only here) | CHF<br>IHD | OR 1.55 (1.16, 2.07)[g]<br>OR 1.36 (1.02, 1.81)[g] |
| Wei, *et al*[26] | 2004 | Population-based cohort study in Tayside, Scotland (data here from subset with inflammatory arthritis) | Lose dose GC (< 2.5 mg/day) | Combined[h] | 0.98 (0.62, 1.57)[i] |
| | | | Medium dose GC (5–2.5 mg/day) | Combined[h] | 1.50 (0.98, 2.30)[i] |
| | | | High dose GC (> 7.5 mg/day) | Combined[h] | 5.17 (1.56, 17.18)[i] |
| Maradit-Kremers, *et al*[8] | 2005 | Population-based RA inception cohort in Olmsted County, MN | Ever GC use | CV mortality | HR 1.54 (1.12, 2.11)[j] |
| | | | Ever prednisone compared to never use in subset with coronary heart disease | CV mortality | HR 0.79 (0.43, 1.46)[k] |
| Bernatsky, *et al*[31] | 2005 | Nested case-control study in RA cohort | Current GC use (within 45 days prior to index event) | Hospitalized CHF | OR 0.9 (0.7, 1.2)[l] |

GC: glucocorticoid; HR: hazard ratio; RR: relative risk; OR: odds ratio; CV: cardiovascular; MI: myocardial infarction; HAQ: health assessment questionnaire; CHF: congestive heart failure; GPRD: general practice research database; IHD: ischemic heart disease. [a] Age- and sex- adjusted. [b] From Stepwise multivariable Cox regression models, stratified by center. [c] Includes MI, deep venous thrombosis/pulmonary embolism, and transient ischemic attack/stroke. [d] From a multivariable Cox regression model including age at disease onset, hypertension, male sex, and haptoglobin. [e] From multivariable Cox regression model including ESR last value, duration × last value ("interaction between last ESR value registered before cardiovascular event and duration from disease onset to that sampling"), and corticosteroids before event. [f] From multivariate model including Health Assessment Questionnaire scores (remainder not available in abstract). [g] Adjusted for smoking, BMI, and medication use including anti-hypertensives, nonsteroidal antiinflammatory drugs, and disease-modifying antirheumatic drugs. [h] Includes hospitalizations with primary diagnoses of myocardial infarction, angina, angioplasty or coronary revascularization, stroke, transient ischemic attack, congestive cardiac failure, or cardiovascular death during follow-up. [i] Adjusted for age, sex, social deprivation, use of angiotensin-converting enzyme inhibitors, anticoagulants, antiplatelets, α-blockers, ß-blockers, calcium-channel blockers, cardiac glycosides, diuretics, nitrates, lipid-lowering drugs, hormone replacement therapy and oral contraceptives, nonsteroidal anti-inflammatory drugs, disease-modifying antirheumatic drugs, and bronchodilators during the follow-up; non-cardiovascular hospitalization in the past 6 months, diabetes mellitus, cancer, and renal disease. [j] From a multivariable Cox regression model including personal history of CHD, smoking, hypertension, diabetes mellitus, body mass index, peripheral vascular disease, chronic pulmonary disease, ulcers, malignancies, dementia, renal disease, and history of alcoholism. [k] From a multivariable Cox regression model including smoking, hypertension, diabetes mellitus, body mass index, peripheral vascular disease, chronic pulmonary disease, ulcers, malignancies, dementia, renal disease, history of alcoholism, sedimentation rate, vasculitis, and lung disease. [l] From a conditional logistic regression model adjusted for age, sex, cohort, co-morbidity, and current DMARD use.

or by hospitalization before study entry. High dose (> 7.5 mg/day) GC use was associated with increased risk of heart failure, MI, stroke, and overall mortality. This was also true for the subset of patients with inflammatory arthritis. These results were adjusted for a broad range of medications, including antirheumatic drugs.

These analyses were certainly interesting, but although Wei and colleagues argued otherwise, confounding by indi-

cation could have affected the results. Sensitivity analyses suggested that the prevalence of such a confounder would not be sufficiently different between GC exposed and unexposed groups. Additionally, it was suggested that the risk associated with an unmeasured confounder would not be sufficiently high to explain the results. However, this argument is precarious, particularly for those with inflammatory arthritides. For example, the presence of RF in RA has been associated with a 2-fold increased risk of congestive heart failure[3]. Significant differences in the prevalence of RF could exist between users of high dose GC and non-users of GC within a heterogeneous sample of patients with inflammatory arthritis. Moreover, the possibility of other unknown inflammatory mediators associated with the disease activity requiring GC treatment as well as cardiovascular outcomes was overlooked. Therefore, the potential for confounding by unmeasured factors remains a significant concern in this study.

In another study, del Rincon and colleagues recently used high-resolution ultrasonography to examine the effects of GC on arteries of patients with RA[36]. These subjects were examined annually for a median of 39 months before the sonographic examination; joint counts were measured and averaged for these visits. They attempted to control for disease severity by adjusting for joint counts, rheumatoid nodules, RF positivity, and ESR. Among the group of patients in the highest tertile of cumulative GC exposure (> 16 g prednisone), the prevalence of both arterial plaque and incompressible arteries was higher than the unexposed group. Duration of GC exposure was not associated with arterial plaque, intima-media thickness, or incompressible vessels. However, markers of RA severity were measured during a few visits during the study, yet these large GC doses were accumulated over many years of followup (mean 7.5 years, range 4 months to 52 years). It is certainly possible that unmeasured factors of disease severity confounded the results of this study. Also, it is notable that another study reported no association between prednisolone use and carotid intima-media thickness[37]. Ultimately, each of these studies mentioned herein does not adequately answer the question of whether the association between GC use and arterial atherosclerosis is causal or mediated through the association with disease activity/severity.

From these studies, several conclusions are evident. First, therapeutic factors such as the timing of GC exposure and/or patient factors such as personal history of CVD may significantly modulate the effect of GC on the cardiovascular system. Second, these studies exemplify the difficulties in disentangling the complex effects of GC from RA disease activity/severity in pharmacoepidemiological studies. Randomization to GC versus placebo in a longterm clinical trial powered to detect cardiovascular outcomes would be the most valid study design for this question. However, such a trial would be difficult to conduct and might be unfeasible. Therefore, creative study designs and/or statistical methodologies to address the issue of confounding by indication are necessary in order to better understand the true effect of GC on cardiovascular risk in RA.

## BIOCHEMICAL EFFECTS OF GC: POTENTIALLY BENEFICIAL IN RA?

Much has been written of the potentially harmful effects of GC at the biochemical/molecular level. For example, in a comprehensive review by Girod, *et al*[18] numerous deleterious effects of GC were presented, including exacerbations in blood pressure, body composition (i.e., decreased muscle mass, increased visceral adiposity), insulin resistance, plasma lipoproteins (i.e., increased low density lipoprotein, increased triglycerides), and hemostatic factors (i.e., increased plasminogen activator inhibitor 1). The authors concluded that the net effect of GC on the cardiovascular system is likely to be harmful.

However, the GC effects in the setting of RA are possibly much different. This is because inflammatory mediators and their downstream consequences are likely to be more important in the etiology of CVD in patients with RA compared to the general population. For example, Sattar, *et al*[38] noted the striking difference in high-sensitivity C-reactive protein elevations between patients with RA and members of the general population. These authors raised the theory, which is supported well by current evidence (discussed above), that the systemic inflammatory response in RA drives the development of CVD. Inflammatory mediators that have "pleiotropic effects" were suggested to act distantly from joints on the liver, skeletal muscle, adipose, and endothelium, leading to abnormalities in many important cardiovascular factors and ultimately to cardiovascular events. If inflammatory mediators mitigate part of the cardiovascular risk associated with RA, then antagonism of such mediators by GC might lead to reduced risk of CVD. The following are examples of how GC effects might be beneficial among patients with RA.

Traditional cardiovascular risk factors may respond to GC contrary to their predicted effects. For example, exacerbation of insulin resistance has been suggested as a mechanism by which GC harm the cardiovascular system. Actually, RA itself has been associated with peripheral insulin resistance, which seems to be linked to systemic inflammation[39,40]. This may be cytokine-mediated; for example, TNF-α, an important proinflammatory cytokine in RA, has the ability to induce insulin resistance by inhibiting signal transduction through the insulin receptor[41]. In small short term studies, successful treatment with GC led to amelioration of systemic inflammation and normalization of glucose handling[39,40].

Another example is dyslipidemia in RA, which is similar to that observed in insulin resistance states. This has been described as an "atherogenic lipid profile," with lower than

normal cholesterol in all lipoprotein categories, and a high ratio of total cholesterol to high density lipoprotein cholesterol[42,43]. This profile has been associated with active systemic inflammation in RA[43]. Therapy with regimens that included GC was shown to reduce systemic inflammation in RA and ameliorate the lipid abnormalities[42,43]. Similarly, lipoprotein(a) was shown to be higher among patients with RA compared to controls, and lipoprotein(a) levels were lower in patients with RA receiving GC compared to those not, although this observation was not statistically significant[44].

Inflammatory mediators are included among the novel cardiovascular risk factors currently being investigated[18]. Serum levels of cytokines (i.e., interleukin-6 and TNF[45]), C-reactive protein[46], adhesion molecules (i.e., vascular cell adhesion molecule-1[46]), and matrix metalloproteinases[47] are much higher in patients with RA compared to controls in small studies. GC treatment is predicted to cause inhibition of most of these mediators; however, data for the effect of GC on some specific mediators are lacking. GC treatment has been shown to inhibit expression of adhesion molecules in the synovium[48] as well as serum cytokine levels such as TNF-$\alpha$[49]. Homocysteine is a novel cardiovascular risk factor and prothrombotic factor found to be elevated in patients with RA, and treatment with high-dose pulse GC rapidly decreases their homocysteine levels[50].

Nitric oxide is another novel mediator that is important in endothelial function. Nitric oxide activity has been found to be reduced in RA; for example, arterial vasodilatation in response to nitric oxide stimulation was inhibited in patients with RA, suggesting that they have impaired responsiveness to nitric oxide in the vessel wall[51]. This correlated with inflammatory markers, again suggesting the role of inflammation in RA. Therapy with an antirheumatic regimen that included low dose prednisone improved the nitric oxide responsiveness[52].

These data emphasize the difficulty in understanding the complex interactions between GC, novel and traditional cardiovascular risk factors, and biochemical and molecular mediators of atherosclerosis. Indeed, from biochemical data, it appears very difficult to predict the overall impact of GC on CVD in RA. Therefore, the need for valid clinical outcome data for CVD in patients with RA cannot be over-stated.

## SUMMARY AND FUTURE DIRECTIONS

The true effect of GC on cardiovascular morbidity and mortality in the RA population remains unclear. In fact, even the direction of the GC effect is controversial: these may either increase or decrease risk. It is likely that the relationship between GC and CVD in RA is complex and multifactorial, as is the case with sepsis where there is evidence for either favorable or unfavorable effects depending on the context[53]. As shown by previous examples, the effect may depend on characteristics of GC treatment such as daily dosage, timing of therapy, and cumulative steroid dose. It is important to consider confounding by RA disease activity/severity when considering the effects of GC on CVD. Patient factors such as personal history of coronary heart disease or RA characteristics may influence the magnitude and direction of the effect. Moreover, there may be different effects depending on what cardiovascular outcome is considered, for example, MI versus heart failure.

Disentangling these complex relationships is of paramount importance given the high prevalence of GC exposure in RA and the excess burden of CVD in this patient group. Such information will also help us to more appropriately address the concerns of our patients regarding side effects of GC. Better understanding of the clinical, biochemical, and molecular effects of GC on the pathogenesis of cardiovascular disease in RA will lead to more appropriate use of GC. Additional data from population-based studies are needed to extend our knowledge of the epidemiology and pathogenesis of heart disease in RA.

In the meantime, eradicating inflammation in RA appears important not only for the joints, but also for the longevity of the cardiovascular system. Use of GC in early RA and targeted use to treat flares continues to be reasonable and possibly beneficial. However, limiting chronic exposure and employing careful measures to prevent osteoporosis, infection, and other steroid-induced sequelae are critical.

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