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EDITORIAL

# The Pendulum Swings on Glucocorticoids in Rheumatoid Arthritis

Few pharmacologic agents have had as transformative an effect as glucocorticoids on the practice of medicine, with remarkable efficacy and wide applicability to numerous conditions and across specialties. Nowhere is this more evident than in rheumatology, where use of long-term low-dose steroid therapy is commonplace throughout the world, including in long-term management of diseases like polymyalgia rheumatica, systemic lupus erythematosus, and rheumatoid arthritis. However, these benefits come at a price, as the adverse effects of glucocorticoid therapy also manifest very reliably in proportion to the dose and duration of therapy, including hypertension, diabetes, loss of bone density, cushingoid features, infections, skin atrophy, weight gain, mood changes, and peptic ulcers (1).

Rheumatologists have grappled with these adverse effects for decades, and the practice of rheumatology has shifted to emphasizing the substitution of other immunosuppressive agents for steroid sparing, which has become increasingly possible due to the introduction of disease-modifying antirheumatic drugs and biologic therapies. Treatment guidelines for rheumatoid arthritis in the United States recommend against long-term use of glucocorticoids (2).

Still, rheumatologists are often compelled to turn to glucocorticoids for patients who are intolerant of steroid tapering, or in situations requiring rapid intervention to improve disease control. The low cost and wide availability of glucocorticoids is also an important consideration when alternative agents can be vastly more expensive. That dilemma persists to the present, as rheumatology practitioners try to balance competing goals—to obtain the rapid and substantial clinical benefit from glucocorticoids in diseases like rheumatoid arthritis, while using other medications for steroid sparing to limit the total amount of glucocorticoid therapy.

There is a sense in some quarters that the benefits of glucocorticoids are real and underemphasized and that the concerns about toxicity from these agents exists in excess of the absolute magnitude of that risk, particularly with low-dose therapy (3). The Outcome Measures in Rheumatology Group has done important work to build and validate measures to better quantify the positive and negative effects of glucocorticoids, including patient input (4, 5).

The study by Palmowski and colleagues (6) in this issue of *Annals* represents, in part, swinging back of the pendulum, emphasizing that the risks of low-dose glucocorticoid therapy may be smaller and more manageable than they may appear based on observational studies. They analyze patient-level data from several interventional randomized clinical trials using glucocorticoid therapy for rheumatoid arthritis to assess the effect of low-dose (≤7.5 mg prednisone equivalent) therapy on weight gain and blood pressure. This method allows for a more unified statistical assessment of the patient outcomes, with improved power to detect differences and assessment for differences among subgroups than would be possible with a standard meta-analysis method. Critically, the use of data from interventional trials is able to account for unmeasured confounders much better than the currently available observational data. One such concern is confounding by indication, where determining the effect of the disease and the intervention can be difficult to disentangle, since the sickest patients would be expected to receive the highest doses of glucocorticoids.

Palmowski and colleagues found that over a 2-year period, blood pressure increased in both groups by a small amount, without a clear difference among patients treated with glucocorticoids, and no statistically significant changes in antihypertensive therapy were observed. Similarly, they detected weight gain in both groups, but the patients in the steroid-treated group gained an additional 1.1 kg, on average, a statistically significant finding.

These results are very helpful in defining in more concrete terms the precise effect of glucocorticoids in rheumatoid arthritis, but they have some limitations. A 2-year span is relatively long in terms of clinical trial data, but that is a limited time scale over which to evaluate the effect of weight gain and hypertension, whose effects may manifest over decades. Further, while a 1-kg weight gain may be reassuring over a 2-year period, in a chronic disease like rheumatoid arthritis, it would be a concerning trend if it continued. This study is also not able to assess the full panoply of glucocorticoid adverse effects, and additional studies would be needed to evaluate any effects on infectious risk, diabetes, peptic ulcers, or cardiovascular disease. These effects would need to be weighed against the potential benefits of glucocorticoid therapy for preventing accumulation of disease-related damage, relieving pain, and allowing for increased physical function.

These findings provide a more quantifiable assessment of the potential adverse effects of steroid therapy than had existed previously and will be helpful to providers and patients as they decide on the relative risks and benefits of glucocorticoids as part of their therapy plan in rheumatoid arthritis.

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