Editorial

Innovative combination strategy to enhance effect and diminish adverse effects of glucocorticoids: another promise?

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Published: 27 February 2009
This article is online at http://arthritis-research.com/content/11/1/105

Arthritis Research & Therapy 2009, **11:**105 (doi:10.1186/ar2615)

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Abstract

In a paper by Zimmermann and colleagues in this issue of *Arthritis Research & Therapy*, results of extended laboratory research with the drug combination of prednisolone and dipyridamole are reported. There seems to be a boost and extension of the glucocorticoid effect by the combination, without a clear increase of adverse effects, potentially allowing the application of lower dosages. However, laboratory models are not patients and the glucocorticoid mechanisms leading to effects and adverse effects are manifold. The next required step will be to demonstrate the improved therapeutic window in patients in adequate comparative clinical trials, assessing predefined beneficial effects and adverse effects in a standardized way.

In this issue of *Arthritis Research & Therapy*, Zimmermann and colleagues, employees of CombinatoRx [1], a company that specializes in finding and developing synergistic combinations of (existing) drugs, report on extended *in vivo* (rats and mice) and *in vitro* research with the combination of the drugs prednisolone and dipyridamole [2]. The results suggest that this combination has a synergistic immunosuppressive effect.

Dipyridamole is a phosphodiesterase inhibitor that increases intracellular levels of cyclic adenosine and guanine monophosphate by inhibiting their conversion. In platelets, this leads to reversible inhibition of platelet aggregation, for which the drug is used, often in combination with low-dose aspirin. In addition, dipyridamole has several other effects. The synergistic effect of prednisolone with dipyridamole is described as being based on the inhibition of additional inflammatory mediators, such as chemokine (C-C motif) ligand 5 (CCL5), also known as RANTES, a proinflammatory chemokine and matrix metallopeptidase 9 (MMP9), also known as gelatinase B, an enzyme involved in the breakdown of extracellular matrix; these additional effects seem limited to inflammatory cell mechanisms. In collagen- and adjuvant-induced arthritis, the combination had an equipotent anti-inflammatory action compared with a considerably higher dose of prednisolone alone. Furthermore, in models assessing glucocorticoid-induced adverse effects, the combination induced fewer adverse effects than prednisolone alone at the required higher dose for equipotent anti-inflammatory activity. So there seems to be a boost and extension of the glucocorticoid effect, without a clear increase of adverse effects, potentially allowing the application of lower dosages than would be necessary for glucocorticoid therapy alone and thus avoiding systemic adverse effects.

Glucocorticoids are the most effective and generally used immunosuppressive drugs worldwide in immune-mediated diseases. The demonstration of disease-modifying capacity of low-dose glucocorticoid therapy in rheumatoid arthritis has boosted the interest of rheumatologists in this medication [3]. In early rheumatoid arthritis, the application of combination therapy of disease-modifying agents, including glucocorticoids, has already become a generally accepted strategy. The advantages of low doses of glucocorticoids outweigh the disadvantages [4]. The European League Against Rheumatism evidence-based recommendations on the use of glucocorticoids are tools for avoiding adverse effects of glucocorticoids [5] and aim at using as low a dose as possible (reconsidering at each clinical visit the need for glucocorticoids and the dose level) and at preventive measures such as calcium and bisphosphonates. Another strategy enabling lower dosing of glucocorticoids and thus avoiding adverse effects is combination therapy with other immunosuppressive or so-called steroid-sparing drugs, like azathioprine and methotrexate.

For many years, research has also aimed at developing new preparations with beneficial glucocorticoid effects but fewer adverse effects. The first step, about five decades ago, was the development of synthetic glucocorticoids such as

prednisone and dexamethasone with more potent effects and fewer mineralocorticoid effects compared with the natural cortisol. The synthetic glucocorticoid deflazacort (an oxazoline derivative of prednisolone) was claimed to have the same anti-inflammatory and immunosuppressive activity as prednisone with fewer adverse effects but did not fully live up to expectations [6]. More recently, a modified release tablet of prednisone was developed, releasing prednisone about 4 hours after ingestion. When this tablet was taken in the evening (thus synchronising its prednisone release to the circadian rhythm of cortisol), the duration of early morning stiffness in rheumatoid arthritis was less compared with that associated with the same dose of prednisone taken early in the morning [7]. Further research will have to shed light on issues such as long-term efficacy regarding all rheumatoid arthritis symptoms and signs, the effect on radiological joint destruction, and long-term adverse events of this preparation [8]. Glucocorticoid analogues that would have dissociated effects on transrepression and transactivation, like selective glucocorticoid receptor agonists, and that could have a more favorable balance of clinical effects and adverse effects than conventional glucocorticoids are being developed [9]. However, glucocorticoids also have non-genomic actions (especially at higher doses) and the genomic actions transrepression and transactivation are not fully synonymous with inflammatory and immunosuppressive activity and with adverse effects, respectively. For instance, hypopituitary-pituitary-adrenal axis suppression and increased risk of infection are linked to transrepression, not to transactivation.

Another promising development is the targeting of glucocorticoids to inflammatory sites using polyethylene glycol liposomes as a vector, increasing local levels and reducing systemic concentrations of glucocorticoids and thus limiting the adverse effects [10]. Glucocorticoid-nitric oxide compounds releasing nitric oxide might exhibit enhanced anti-inflammatory properties at lower systemic concentrations of glucocorticoid [11], but these drugs are also still in an early test phase.

The new development of the CombinatoRx drug is important, and the results reported by Zimmermann and colleagues [2] are promising indeed. However, laboratory models, rats, and mice are not patients and the glucocorticoid mechanisms leading to effects and adverse effects are manifold. Ultimately, the proof of the pudding is in the eating. Comparative clinical trials of long duration with adequate numbers of patients and regular assessments of predefined beneficial effects and adverse effects in a standardized way are warranted. This is the next challenge.

Competing interests

The authors declare that they have no competing interests.

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