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CURRENT KEY DEVELOPMENTS

Revitalising glucocorticoids for (rheumatoid) arthritis

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Glucocorticoids (also called corticosteroids or steroids) have been used to treat rheumatoid arthritis (RA) ever since they were discovered in 1948.[1] They have a potent anti-inflammatory effect, and even in low doses (7.5 mg daily prednisolone or equivalent) they can control the symptoms of inflammation more effectively than non-steroidal anti-inflammatory drugs for a few weeks or a few months.[2,3] This makes them a useful treatment in the short to medium term, but it is likely that the benefit wears off after a year or so.[4] Concerns about potential adverse effects (which are widespread when high doses are used) meant that for many years in the 1970s and 1980s they were advocated only for short courses to treat severe exacerbations or 'flares' of inflammation. The position was unsatisfactory – publicly rheumatologists declared their intention to avoid glucocorticoids, but in practice many patients were being treated with them.[5]

In the last 15 years strong evidence has emerged for an additional, fundamental effect of glucocorticoids on the disease process in RA, while in the last five years novel formulations of glucocorticoids have revitalised interest in their wider potential:

- there is now incontrovertible evidence that they are disease modifying agents with the power to halt the destructive changes of RA
- short exposure to high dose glucocorticoid (followed by low dose) can control the overall clinical picture just as effectively as modern (and very expensive) anti-tumour necrosis factor (TNF) 'biologic' drugs
- this positive effect on arthritis may persist even several years after the treatment has been stopped, leading to the exciting possibility that there is an opportunity to have a long-lasting effect on the disease process following an early intervention
- new formulations of glucocorticoids are being tested for their ability to enhance therapeutic effects while avoiding adverse effects
- the potential for selective glucocorticoid agonists is emerging from a greater understanding of cellular mechanisms of action.

Although a number of early trials in the 1950s and 1960s had hinted at the ability of glucocorticoids to control joint destruction, this was not established with confidence until 1995 by the ARC Low Dose Glucocorticoid study and the 1997 COBRA study.[5,6] In the first, adding 7.5 mg prednisolone daily to standard treatment with disease modifying drugs substantially

reduced the rate of radiological progression over two years in patients with early RA. In the second, combining methotrexate, sulphasalazine and short-term high dose glucocorticoids (prednisolone 60 mg daily, reduced over six weeks to 7.5 mg daily then stopped after 28 weeks) not only strongly suppressed erosion progression, but also controlled symptoms in a manner similar to anti-TNF therapy, against which it was compared a few years later.[7] A recent meta-analysis of all 14 appropriate randomised controlled trials now in the literature confirms this protective effect on joints, which clearly has implications for the long-term development of disability and the need for surgical intervention in late disease.[8] Combination therapy including glucocorticoids may offer the most cost-effective way of controlling RA when it is first diagnosed. At the moment, there is insufficient evidence to decide if this is also true for patients who have had their disease for many years.

Recent reports suggest that glucocorticoids in early disease may also have an additional, and perhaps surprising, effect. Two reports of the longer-term follow-up of patients who took part in the original trials have found a continuing protective benefit on the suppression of joint destruction many years after the trial treatment was discontinued.[9,10] These results of glucocorticoid therapy are the first hard evidence that it might be possible, by an appropriate intervention early in the disease, to modulate the continuing pathology and future course of RA.

What about the side effects of glucocorticoids? The evidence suggests it all depends on the dose used and the disease which is being treated. In RA, low doses of glucocorticoids may have very few adverse effects, as attested by an extensive review of the published literature.[11] Adverse events known to occur in other diseases treated with higher doses of glucocorticoids (such as severe asthma) may not occur when low dose glucocorticoids are used to treat RA. These include abnormalities in lipid profiles, cardiovascular risk in general and osteoporosis.[12–14] In fact, recent studies challenge the classic assumption that glucocorticoids are responsible for a pro-atherogenic effect in patients with rheumatic diseases and early immuno-intervention to control disease activity may reduce the risk of the atherosclerotic process and cardiovascular events in early RA patients.

New efforts are being made to develop glucocorticoids, glucocorticoid combined with other agents, and glucocorticoid analogues that are targeted to inflammatory tissues or specific gene activations, so that potent effects might be obtained with little or no increased risk of adverse reactions.[15] In addition, some patients with glucocorticoid resistance might benefit as the mechanisms of such resistance are elucidated and circumvented. The recognition that circadian symptoms in RA may relate to an overnight surge in serum interleukin-6 (IL-6) concentrations has led to the developing and testing of a timed release preparation.[16] This is taken before bed but the glucocorticoid is delivered in the early hours of the morning and can thus suppress the IL-6 surge and produce additional clinical benefits.[17,18] Thus, not only is glucocorticoid therapy still relevant in RA, but it may soon undergo a renaissance whereby its true beneficial effects in the specific circumstances of the disease will lead to a new confidence in appropriately managed dose regimens.

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