Future strategies for corticosteroid therapy

Sir, A veritable feast of editorial articles on the glucocorticosteroids has accompanied the 50th anniversary of Dr Philip Hench’s first use of these agents in rheumatoid arthritis (RA) [1–4]. The most recent contributions offer two conflicting views of the future of these drugs which are a fair reflection of the division of opinion which exists between rheumatologists. The optimistic view suggests that the unparalleled potency of corticosteroids as anti-inflammatory agents, coupled with tantalizing data suggesting disease-modifying activity, indicates that we are on the verge of a new era of steroid therapeutics provided that the safety profiles of these drugs can be improved by future research effort [1, 2]. The opposing opinion stresses the toxicity of these drugs, the lack of hard evidence for anything more than short-term, symptomatic relief, and the reluctance of clinician and patient alike to embark on long-term therapy [3]. Yocum [4], in an earlier editorial, highlights the fundamental problem at the heart of this debate—that there is a basic lack of good scientific evidence to support the clinical use of these drugs. Controversy abounds over the merits of low-dose corticosteroids as disease-modifying or ‘bridging’ agents in RA [5], whilst the rheumatologist is still shouldered with the responsibility of trying to tailor the use of these drugs on an empirical basis, both in acute and chronic circumstances. There is no doubt that combination therapy [6], better monitoring of side-effects and reluctance to use chronic ‘high’ (>20 mg/day) doses of corticosteroid have improved their safety profile in recent years, but many issues, such as the development of steroid dependence, still remain. If the lack of effective alternatives indicates their continued usefulness in the clinic for the foreseeable future, then an effective strategy is required to provide a more rational basis for their deployment. I would therefore propose that the development of routine laboratory assays for assessing corticosteroid sensitivity could be an important first step in this direction. Current therapeutic strategies assume equal responsiveness to steroids until the development of side-effects or lack of response indicates otherwise. The ‘holy grail’ of corticosteroid therapeutics must surely be to be able to titrate the exact amount of corticosteroid required to control inflammation and exert whatever disease-modifying effects it may possess without exhibiting adverse effects in the longer term. Until now, attempts to determine corticosteroid responsiveness in RA patients have been few and far between [7], and have not been prospective. Given the ready availability of assays for a range of corticosteroid-regulated pro- and anti-inflammatory mediators, markers of bone turnover and proteolytic enzymes in serum or synovial fluid, it would not be too difficult to decide upon a representative panel of corticosteroid-responsive factors in order to create a workable index of biological responsiveness. With commercial backing, these could be developed for the routine laboratory environment.

Further in the future, we may well gain a greater understanding of the mechanisms of the anti-inflammatory actions of corticosteroids at the molecular level. Knowledge of the interactions of intracellular glucocorticoid receptors with the plethora of transcriptional regulators, and their subsequent effect on the transcription of inflammatory mediators, will be critical to the development of novel corticosteroid derivatives which target inflammatory mechanisms preferentially over other metabolic pathways [8]. Until then, having a rapid, quantitative measure of the extent of a patient’s response to administered corticosteroid would be of great practical clinical value and, additionally, would augment future clinical studies of corticosteroid efficacy in RA.

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