Do the treatment with glucocorticoids and/or the disease itself drive the impairment in glucose metabolism in patients with rheumatoid arthritis?

Frank Buttgereit

Opinions on the value of glucocorticoids (GCs) have fluctuated between euphoric acceptance and outright rejection. This ambivalence in opinions arose because of their important clinical effects, on one hand, and their potential risks, on the other hand. It seems, however, that these important drugs have now found their correct place in rheumatology (and other special areas in medicine). The current view on these drugs is that they are indispensable; however, they should be administered as much as necessary but as little as possible.

THE CURRENT ROLE OF GCs IN RHEUMATIC DISEASES

Without any doubt, GCs at higher dosages are needed to terminate flares and/or to reduce the activity of rheumatic diseases. However, this ‘emergency’ usage represents only one option for successfully administering these drugs since many patients are more or less continuously treated with ‘maintenance treatment’. For example, when looking at rheumatoid arthritis (RA), it is obvious that, very often, lower dosages of GCs are given in combination with conventional or biological disease-modifying anti-rheumatic drugs (DMARDs) (and, of course, other drugs such as non-steroidal anti-inflammatory drugs or analgesics). This therapeutic approach has the following rationale: a sensible combination of drugs with different modes of action ideally results in additive or even synergistic effects, while potential adverse effects remain at a level associated with the dose of each component. For GC treatment, this means that the more effective the treatment is with DMARDs, the lower can be the GC dosages. Consequently, less pronounced adverse effects are induced by these drugs (figure 1).

Given the widespread and successful usage of biological DMARDs, what does this mean in terms of actual GC dosages administered concomitantly? We have recently presented a report of a detailed time course of GC intake under tumour necrosis factor α inhibitor (TNFαi) treatment with a long duration of follow-up. In this work, we have shown that in a cohort of 110 patients with RA, disease activity significantly decreased after TNFαi initiation. As a consequence, GC doses could be significantly reduced from 7.5 (5–12.5) mg/day to 2.5 (0–5) mg/day. In more detail, GC doses were reduced in 81 patients and even stopped in 28 patients. These results highlight the effectiveness of TNFαi in allowing a reduction of GCs to low doses in the majority of patients based on a significant reduction of disease activity. Of note, this effect was observed as early as within the first 3 months and persisted up to the end of the observation after 5 years. At the same time, however, these results illustrate that GCs still are obviously will be indispensable drugs but, fortunately, to a lesser extent and at lower dosages necessary than in the past.

There are two other lines of evidence that support the statement that low-dose GC treatment is still a cornerstone of RA treatment. First, a random search for five RA trials published in recent months in both The Annals of Rheumatic Diseases and Arthritis and Rheumatism demonstrated that more than 50% of patients with RA who are included in phase II to phase IV trials investigating biological drugs are concomitantly treated with GCs: atacicept (55–67%), rituximab (39–48%), tocilizumab (62–70%) and golimumab (50–55%). In the June issue of Nature Reviews Rheumatology, it has been stated very similarly, ‘... the percentage of patients who received concomitant prednisone treatment ranged from 34% to 93% across the studies, and varied across biologic drugs (abatacept, 74.4%; golimumab, 67.9%; infliximab, 60.6%; certolizumab, 57.5%; rituximab, 57.5%; etanercept, 54.4%; tocilizumab, 52.8%; adalimumab, 50.4%)’.

Second, also when looking at ‘normal daily clinical practice’ outside the ‘study and EBM world’, similar numbers apply. Very recently, Neovius et al reported on the nationwide prevalence of RA and the penetration of disease-modifying drugs in Sweden. They found that 28,698 out of 58,102 patients (ie, patients with RA who were still alive in 2008) received GC treatment, corresponding to a 49% GC exposure.

For Germany, actual data on GC treatment in patients with RA are shown in figure 2. These data were obtained from the national database of the German Collaborative Arthritis Centres (internal report data for 2009). In 2009, 17 rheumatological units (university departments, departments of rheumatology at general hospitals) and presumably 67% of all rheumatic departments in Germany (figure 1).

**Figure 1** Drug combination in rheumatoid arthritis treatment. A sensible combination of drugs with different modes of action ideally results in additive or even synergistic effects, while potential adverse effects remain at a level associated with the dose of each component.

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hospitals and rheumatologists in private practice) recorded a total of 7337 patients with RA, according to the American College of Rheumatology criteria. The key message is that the percentage of GC-treated patients with RA is fairly constant over the years at about 56%, but with an increase in the use of GC dosages of \(\leq 7.5\) mg/day (doses refer to prednisone equivalent per day). Data were adapted from the national database of the German Collaborative Arthritis Centres (internal report data for 2009).

Very recently, Fardet et al\textsuperscript{1} reported that, over the past 20 years, long-term oral GC prescriptions in the UK have increased by 34%. Remarkably, the long-term use of GCs for RA did not decrease between 1991 and 2008, although several new DMARDs have entered the market.\textsuperscript{11} 12 In theory, the introduction of these new drugs should have resulted in a lesser need for GCs, which was obviously not the case. In an accompanying editorial to this publication, a possible explanation has been suggested: systemic low-dose GCs are now more frequently added to combinations of other DMARDs for better clinical and radiological outcomes.\textsuperscript{12}

On the basis of this information and being aware of the potential of GCs to induce adverse events, the crucial current question is: how long should we aim at using concomitant GC treatment in RA? There are virtually three scenarios. (1) GCs could/should be used as bridging therapy only, i.e. as an initial short term treatment followed by tapering off as rapidly as clinically feasible. This procedure represents the current recommendation.\textsuperscript{13} (2) GCs at low dosages could or should be used for at least 2 years (‘long-bridge’ treatment) because of their beneficial effects.\textsuperscript{14} (3) GCs at very low dosages could be administered in many patients with RA concomitantly as a maintenance treatment, assuming that this approach improves the overall benefit RR (as illustrated in figure 1). The answer to this question is open since we do not have enough scientifically sound data for the time being. Therefore, further effort is needed to understand these drugs in more detail. The current goals in this regard are:

1. to understand in more detail how the molecular mechanisms of genomic and non-genomic GC actions (and their dose dependency) mediate the clinically wanted benefits and the known adverse effects;
2. to improve treatment with conventional GCs;
3. to develop innovative GCs or novel GC receptor ligands.

**GC EFFECTS ON GLUCOSE METABOLISM**

In this issue of The Annals of Rheumatic Diseases, Hoes et al\textsuperscript{15} provide very interesting data addressing the first two goals mentioned above. The authors have investigated GC effects on glucose metabolism. It should be noted that GCs were named such because these hormones became known very early on as having a strong impact on glucose metabolism—for example, the stimulation of gluconeogenesis, that is, the facilitated synthesis of glucose from substrates such as amino acids and glycerol from triglyceride breakdown. In order to provide these substrates, GCs also stimulate protein catabolism and fat breakdown. GCs are also known to inhibit the use of glucose by muscles and adipose tissues. Altogether, these effects ultimately result in an increase in glucose concentrations in the blood, which is the positive aspect of our response to stress (i.e., a ‘quick burst of energy’). However, when GCs are given for longer periods, these effects may lead to adverse effects such as hyperglycaemia and/or GC-induced diabetes mellitus.

Although these facts are beyond any doubt, we sometimes forget that the disease under GC treatment may per se impair glucose metabolism. This important question has been addressed thoroughly by Hoes et al.\textsuperscript{15} They measured glucose tolerance, insulin sensitivity and \(\beta\) cell function in patients with RA who were treated with or without low to medium doses of GCs. One of their take-home messages is that GC-using and GC-naive patients with RA had comparable metabolic parameters and decreased insulin sensitivity and \(\beta\) cell function in comparison with healthy controls. In other words, the disease itself (i.e., the pro-inflammatory state induced by the disease) does impair the metabolic state in patients with RA, but as expected, the GC treatment also does negatively interfere with glucose metabolism. The authors report cumulative GC doses as having a negative impact on glucose tolerance state and insulin sensitivity.

The latter observation is, however, not easy to interpret. First, as discussed by the authors, confounding by indication has to be taken into account. Second, there is a complicated interplay of three mechanisms that influence glucose metabolism: (1) the RA-induced pro-inflammatory state negatively impacts on glucose metabolism; (2) GC downregulates disease activity, which in turn weakens the negative impact of the disease on glucose metabolism and (3) GC itself impairs glucose metabolism, as outlined above.

**GC EFFECTS ON THE BONE AND ON THE CARDIOVASCULAR SYSTEM**

Similar considerations apply to GC effects on the bone and on the cardiovascular system, where we also see this ‘magical triangle’ or the ‘Janus-head-like behaviour of GCs’.\textsuperscript{16} For example, accelerated bone loss in RA includes radiological periarticular osteoporosis and joint erosions. GCs at low dosages have been shown to reduce the rate of the radiographic progression of the disease and the extent of disease-related periarticular osteoporosis. However,
prolonged GC treatment per se does result in rapid and profound reductions in bone mineral density (especially within the first months of treatment).

The second example refers to GC effects on the cardiovascular system. Chronic inflammatory diseases increase the risk of cardiovascular diseases. The use of TNF antagonists has been recently shown to be associated with a reduced risk of cardiovascular events in patients with RA. GCs may also lower this inflammation-mediated risk since they reduce disease activity. However, here, too, GCs per se are also assumed to represent an independent determinant of greater cardiovascular risk in patients with chronic inflammatory diseases. Therefore, from the current point of view, it seems to be clear that GCs convey a considerable cardiovascular risk, but disentangling this from the cardiovascular risk mediated by the underlying disease, in a quantitative manner, is currently not possible.

CONCLUSION

In conclusion, how to disentangle the unwanted consequences of the RA disease itself from the consequences of its treatment with GCs is still a matter of debate. This is true for glucose metabolism and also for the bone and the cardiovascular system. The work by Hoes et al represents an important contribution in this regard since their results considerably enhance our knowledge of glucose metabolism in patients with chronic RA who are treated with or without GCs. Nevertheless, the question on how harmful long-term GCs are with regard to their capability to exert diabetogenic effects on patients with RA needs further assessment in well-designed, longitudinal, randomised trials.

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