The case for corticosteroids in the treatment of early rheumatoid arthritis

Corticosteroids are potent agents that have anti-inflammatory effects through multiple inhibitory effects along the inflammatory pathway [1]. Hench was awarded the Nobel prize for the discovery of these agents and their effect in established rheumatoid arthritis (RA). However, doubts over long-term efficacy and concerns over toxicity have made systemic corticosteroid treatment in RA controversial to date. In this editorial, I will make a case for a re-examination of and more positive look on such treatment, especially in early RA, based on new paradigms and recent data.

Initial enthusiasm with corticosteroids, drugs that induced apparent cures in patients with previously intractable disease, hindered the study and application of other useful drugs such as sulphasalazine and methotrexate for many years. This is especially significant in view of the subsequent disillusionment with corticosteroids caused by the rapid appearance of unacceptable side-effects of long-term high-dose treatment, and loss of efficacy at lower dosing.

The dogma became that treatment with systemic corticosteroids caused only temporary symptomatic relief, led to habituation with the discovery of ever-increasing doses necessary to maintain effect, and that chronic treatment universally caused unacceptable side-effects. Therefore, it was to be considered a treatment of last resort, at the top of the therapeutic pyramid [2], given mostly to patients with severe, unremitting RA or with systemic complications such as vasculitis. In accordance, corticosteroids were regarded as a category separate from the class of drugs named ‘slow acting’ or — without any substantial evidence to back the term — ‘disease modifying’.

An associated idea was that RA was in most cases a benign disease, which, although incurable, caused significant disability only in a minority of cases. The combination of these ideas caused most rheumatologists to return to traditional treatment schemes that emphasized rest, lifestyle adjustment, treatment with non-steroidal anti-inflammatory drugs, and spa treatment. In unresponsive cases, i.m. gold was advised, followed in later decades by d-penicillamine and azathioprine [2]. This treatment style (and consequent rare use of corticosteroids) was aided in Europe by the wide availability of clinical care in general and specialized hospitals as well as health spas. In America and Australia, clinical care for chronic conditions such as RA quickly became more and more of a problem. In the (unofficial) view expressed by many of my colleagues who experienced this period, this is the main reason that corticosteroid use remained much more widespread in these continents than in the old continent. (I have no data on Asia and Africa.) Although the official views (as expressed in textbooks on both sides of the Atlantic) were similar and consistent in their universal opposition to corticosteroid treatment, surveys and trials throughout the years point to chronic corticosteroid treatment in at least half of reported RA patients.

On what evidence is classical dogma on the position of corticosteroids in RA based? In line with most knowledge in rheumatology and other fields, it is astonishing to note the paucity of published data that can stand up to critical assessment by current standards. From Felson et al.’s [3] review of anti-rheumatic therapy, we learn that in the early 1990s the total number of RA patients entered in published randomized clinical trials of (slow-acting) anti-rheumatic drugs did not exceed 6000. To the credit of rheumatology, the situation has been improving since then, but is still far removed from fields such as cardiology. Also, important data on the applicability of treatment can come from other sources, such as prospective cohort series and case–control studies. Although the number of patients included in such studies is bound to be larger, it is universally recognized that bias increases as design methodology decreases. It is even more humbling to realize that the total number of controlled trials on the anti-rheumatic efficacy of corticosteroids up to 1990 (as available to me on informal review) was very low: irrespective of the criteria applied to include studies, the total remained below 10. The total number of patients in the corticosteroid arms totalled ~100. In this period, the best trial was that published by the Medical Research Council and Nuffield Foundation in 1959 [4]. Although certainly not without flaws, this trial quite convincingly showed that corticosteroid treatment at intermediate doses (10–20 mg prednisone/day) consistently suppressed disease activity and even slowed damage progression compared to non-steroidal treatment. However, in view of the side-effect profile in these patients and the design flaws, the results were disregarded in line with prevailing dogma. A later trial showed that stopping low-dose prednisone led to a symptomatic flare in most patients [5]. A few other trials showed that high-dose pulses of parenteral corticosteroids had only short-term benefits. Despite the above scant evidence pointing the other way, the view held that oral corticosteroids led only to short-term symptomatic improvement, without lasting effect on damage progression.

The almost universal appearance of side-effects of corticosteroid treatment at high or chronic dosing provided little impetus to study corticosteroid toxicity in a
systematic and rigorous way. Thus, most of our views on this subject are based on hearsay, anecdotal experience and retrospective studies, often of poor design. A case in point is corticosteroid osteoporosis: the presence of this sometimes devastating side-effect is nowhere in doubt. However, in an exhaustive attempt to review all prospective studies to quantify this effect, we were able to find only 18 studies and 329 patients in which bone mass was studied prospectively while on corticosteroid treatment for any disease [6]. Again, to the credit of rheumatology, the majority of studies were of rheumatological origin. This scant evidence pointed to only a limited effect of low-dose prednisone. Another example is gastrointestinal ulceration: oft cited as an important side-effect, but with little data to support the claim, and available data pointing the other way [7].

Happily, this situation is changing rapidly. A paradigm shift has taken place in the way we look at the disease RA and its treatment. This has provided a new chance to assess the real place of corticosteroids. Several long-term studies of the last two decades show that RA as seen by rheumatologists is not benign, and leads to major disability and early death in the majority of patients [8]. As anti-rheumatic treatment obviously had had limited or no effect on these long-term consequences, increasingly rheumatologists started to call for early and more aggressive treatment of RA [9]. This provided the impetus for a series of high-quality trials of corticosteroids in early RA that have recently been completed. In this journal we have summarized the results of these trials [10–18] as part of a recent review on combination therapy [19]. Table 1 provides a brief summary. The composite message that emerges is:

1. Both the magnitude and the longevity of corticosteroid effect on disease activity depend on daily dose, total dose and dosing schedule. The optimum dosing schedule has yet to be found, but the symptomatic effect can be just as large as it was in the 1950s, i.e. as large or larger than that of any other anti-rheumatic drug, including new biological agents such as anti-tumour necrosis factor [20].

2. There is a beneficial effect on damage progression that is already apparent at low doses: it may be independent of the symptomatic effect, and additive to the effects of other disease-controlling [21] drugs. Effects may continue to be apparent well after treatment is stopped [10].

3. Side-effects are limited, manageable, reversible and in one study much less than in the non-steroid control group [10].

Apart from these results, large strides are being made especially in the field of osteoporosis. Several agents (e.g. oestrogens, bisphosphonates and vitamin D) have shown high efficacy in preventing bone loss and fractures in primary osteoporosis, and studies are now beginning to appear that show the same effect for corticosteroid osteoporosis. Although osteoporosis is but one of the many side-effects caused by corticosteroids, it has by far the most impact both in terms of the morbidity and mortality of affected patients. The other side-effects, such as hypertension, diabetes and infections, seem manageable with current levels of care, and put corticosteroids at least in the same league of toxicity as other anti-rheumatic drugs, including non-steroidal anti-inflammatory agents.

In conclusion, the points I have tried to make regarding corticosteroid treatment in (especially early) RA are that:

- the ‘classical’ view that corticosteroid therapy provides only short symptomatic benefit at the price of unacceptable harm is not based on scientific evidence; in fact, the scant available evidence has pointed the other way for almost 40 yr;
- new evidence in early RA suggests that corticosteroids are among the most potent anti-rheumatic and disease-controlling drugs available today;
- the side-effect profile of judiciously dosed cortico-

<table>
<thead>
<tr>
<th>First author</th>
<th>Patients</th>
<th>Treatment comparison</th>
<th>Beneficial effects in experimental group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boers, 1997 [10]</td>
<td>155</td>
<td>SSZ + MTX + step-down pred (60–7.5 mg/day) vs SSZ</td>
<td>High symptomatic benefit during pred therapy; progression retarded up to 1 yr after stopping pred</td>
</tr>
<tr>
<td>Ciconelli, 1996 [11]</td>
<td>38</td>
<td>3 × monthly i.v. MP (5 mg/kg) + SSZ vs SSZ</td>
<td>No effect (most patients also on oral maintenance corticosteroids)</td>
</tr>
<tr>
<td>Corkill, 1990 [12]</td>
<td>59</td>
<td>3 × monthly i.m. MP (120 mg) + i.m. gold vs i.m. gold</td>
<td>Symptomatic benefit at 3 months</td>
</tr>
<tr>
<td>FIN-RACo, 1997 [13–15]</td>
<td>195</td>
<td>MTX + SSZ + HCQ + pred (10 mg) vs single drugs ± pred</td>
<td>More remissions, less progression, equal toxicity</td>
</tr>
<tr>
<td>van Gestel, 1995 [16]</td>
<td>40</td>
<td>step-down pred (10–0 mg) + i.m. gold vs i.m. gold</td>
<td>Symptomatic benefit during pred therapy. Low toxicity</td>
</tr>
<tr>
<td>Kirwan, 1995 [17]</td>
<td>128</td>
<td>pred (7.5 mg) or placebo added to conventional treatment</td>
<td>Short symptomatic benefit. Long-lasting suppression of progression. No toxicity</td>
</tr>
<tr>
<td>Proudman, 1997 [18]</td>
<td>82</td>
<td>intra-articular pred in multiple joints + MTX + CyA + SSZ vs SSZ and ‘regular’ intra-articular pred injections</td>
<td>More improvements and remissions</td>
</tr>
</tbody>
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SSZ, sulphasalazine; MTX, methotrexate; pred, prednisolone; MP, methylprednisolone; HCQ, hydroxychloroquine; CyA, cyclosporin A.
steroids is acceptable, especially if newer anti-osteoporosis treatments are taken into account.

Nevertheless, further research is urgently needed, i.e. to define dosing regimens and combination therapy at various stages of the disease, and to study prospectively long-term efficacy, toxicity, and the place of prophylactic treatment directed against toxicity. Given the likely costs of newer treatment modalities, studies on cost-effectiveness should also be a high priority. Although the future of RA treatment may lie in early ablative therapy by ‘designer’ biological agents, it would be foolish to wait for that future and not to collect systematically and rigorously all the data we need to apply our current armamentarium optimally.

M. BOERS

Department of Clinical Epidemiology, Vrije Universiteit Amsterdam, PO Box 7057, 1007 MB Amsterdam, The Netherlands

References