Corticosteroids in Rheumatoid Arthritis: Resurrection, Revival or Rethinking?

R Handa

INTRODUCTION

Rheumatoid Arthritis (RA) is the commonest autoimmune inflammatory joint disease encountered in clinical practice. Non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, disease modifying anti-rheumatic drugs (DMARDs) and biologics are the frontline agents used to treat RA. Nothing evokes as strong a feeling in physicians as the mention of corticosteroids—drugs that are widely used, and equally, widely misused to treat rheumatic diseases. The discovery of cortisone was a major triumph in the fight against rheumatoid arthritis (RA) which culminated in the award of the Nobel Prize to Dr. Philip Showalter Hench and his colleagues Edward C. Kendall and Tadeus Reichstein. The recognition of several side effects associated with steroids led to a decline in their usage and the initial euphoria waned. This, coupled with the emergence of other effective drugs like gold, sulfasalazine, methotrexate, hydroxychloroquine, leflunomide etc, relegated steroids to the background in RA. A reappraisal of steroid therapy began in the 1980s, with recognition that long-term, low dose corticosteroids in doses of 10 mg/day or less, and preferably 5 mg/day or less, had minimal toxicities and considerable efficacy for many patients. There has been a growing realization that the side effects discernible with steroids are mainly due to high dosages. Despite polemics, corticosteroids are very widely used in RA with a recent paper from the National Databank for Rheumatic Diseases reporting current corticosteroid use in one-third of patients while as many as two-thirds were exposed to these agents over the period of observation (lifetime). This write up outlines the current thinking about the role of corticosteroids in RA (Figure 1).

NOMENCLATURE AND TERMINOLOGY

There is considerable confusion regarding terminology used to describe corticosteroid usage. In this context the European League against Rheumatism (EULAR) Standing Committee on International Clinical Studies including Therapeutic Trials has made recommendations regarding standardized nomenclature that are tabulated in Table 1.

![Fig.1: Re-appraisal of Corticosteroids in Rheumatoid Arthritis: Status 2011](image)

**Table I. Nomenclature of corticosteroid dosing**

- Low dose: <7.5 mg prednisone equivalent a day
- Medium dose: >7.5 mg, but <30 mg prednisone equivalent a day
- High dose: >30 mg, but <100 mg prednisone equivalent a day
- Very high dose: >100 mg prednisone equivalent a day
- Pulse therapy: >250 mg prednisone equivalent a day for one or a few days
EARLY VERSUS ESTABLISHED RA

It is critically important to differentiate established RA from early disease, especially in context of steroids. Although disease definitions may vary, most expert groups define early RA (ERA) as a disease duration less than 1 year. Very early and late early RA (VERA and LERA) refer to disease duration less than 3 months and between 3 months and 1 year respectively. Established RA is defined as a disease duration in excess of 1 year. The cut off between early and established RA is a moving target and current studies have progressively lowered this cut off from 3 years to 2 years to 1 year.

It is pertinent to point out here that the 1987 American College of Rheumatology criteria for classification of RA do not perform well in picking up early disease, a drawback which has been rectified in the new criteria proposed in late 2010.4,5

CORTICOSTEROIDS IN EARLY RA

The disease modifying role of corticosteroids in RA has been the subject matter of endless debate and ceaseless controversy. As far back as 1995 it was demonstrated that in patients with early, active RA prednisolone (7.5 mg daily) given for two years in addition to other treatments substantially reduced the rate of radiologically detected progression of disease.6 However, the fear of adverse effects was a major detractor to the use of corticosteroids as DMARDs. It is now believed that the side effect profile of ‘low dose’ corticosteroids is very different from ‘high dose’ steroids.7 A recent Cochrane review demonstrates that low doses of glucocorticoids (7.5 mg per day of prednisolone) taken for 1-2 years in addition to standard DMARDs like methotrexate have a powerful effect on reducing the progression of joint destruction in patients with early RA (disease duration <2 years).8 The Cochrane reviewers examined clinical trials published from 1966 to 2005, as well as the Cochrane Controlled Trials Register, to identify studies of corticosteroids in RA. Trials selected were required to be randomized controlled or cross-over trials that investigated adult patients with RA; the trials had to include at least one treatment arm with corticosteroids and one without steroids, in addition to an evaluation of radiographs of hands and/or feet. These rigorous criteria were met by 15 studies that included 1414 patients, most with early RA (disease duration < 2 years). In most of the regimens, steroids were added to other DMARD treatment, and the mean cumulative dose over the first year of treatment was 2300 mg of prednisone equivalent (range 270-5800 mg). The standardized mean difference (SMD) in radiographic progression was 0.40 in favor of steroids (95% CI 0.27, 0.54). In studies lasting 2 years (806 patients included), the SMD in progression in favor of steroids at 1 year was 0.45 CI (0.24, 0.66) and at 2 years was 0.42 CI (0.30, 0.55). All studies except one showed a numerical treatment effect in favor of steroids. The proportion of benefit gained by steroids in reducing the progression of erosions from an average of all the studies over 1 year was 67.2%. and over 2 years was 61.3%. This benefit was achieved in patients who were already receiving DMARD treatment and signified a gain over and above any benefits from DMARDs alone. Thus, the evidence available as of date, suggests that low dose prednisolone 7.5 mg/day should be added to DMARDs like methotrexate in patients with early RA <2 years. The authors of the Cochrane review also highlight that it is likely that patients with disease duration of 3 or 4 years would benefit too, but it would be inappropriate to extrapolate into longer disease durations without more firm evidence. It cannot but be emphasized that corticosteroids should never be used as the sole disease modifying agents in RA.

CORTICOSTEROIDS VERSUS BIOLOGICS IN EARLY RA

The BeSt trial, a single-blind, multicenter randomized clinical trial evaluated the efficacy of four commonly used treatment strategies in over 500 patients with early RA (disease duration <2 years).9 Group 1 received sequential monotherapy, group 2 received step-up combination therapy, group 3 was assigned initial combination therapy with tapered high-dose prednisone, and group 4 was treated with initial combination therapy with infliximab. Patients were monitored every 3 months and treatments were adjusted to achieve and maintain disease activity scores (DAS) <2.4. Primary study endpoints were functional ability (measured with the Health Assessment Questionnaire) and radiographic joint damage (measured by the Sharp-van der Heijde score). The objective for all 4 strategies was to obtain a clinically significant low level of disease activity. Results at 2 years revealed more rapid clinical improvement during year 1 in both groups that got initial combination therapy, but similar clinical improvement in all four groups at the end of year 2 (p=0.257).10 Radiographic progression was lesser in the two combination-therapy groups. Severe progression of the total Sharp-van der Heijde score (increase of >20 points) was seen in 18 patients on sequential monotherapy, 7 on step-up combination therapy, one on initial combination with prednisone, one on initial combination with infliximab.
The salient messages from this pivotal trial are:

a) For patients at the time of their initial diagnosis of RA, there appears to be an opportunity to achieve a lasting benefit in their disease course.

b) Tight disease control should be the goal regardless of the strategy.

c) In early-onset disease, it would be particularly important to further define risk factors for poor outcome so that this group can be selected for aggressive intensive combination treatment containing biologics; if biologics are not available, a high dose and a short course of steroids as part of the combination might suffice.

The last statement is particularly true in resource constrained settings like India where biologic treatments are economically not feasible for the vast majority of patients.

Graudal and Jurgens have recently reported meta-analyses summarizing data from 70 randomized placebo-controlled or drug-controlled studies including 112 comparisons and 16 interventions. Trials were included that assessed the effect of drug treatment on the percentage of the annual radiographic progression rate (PARPR). This meta-analysis confirms that aggressive treatment with combination DMARDs does reduce structural joint damage as compared with less aggressive treatment with a single DMARD and that combination-DMARD treatment, especially when combined with periodic glucocorticoids, may be as effective as a biologic agent plus methotrexate. The authors recommend that a more intensive use of DMARDs and periodic glucocorticoid treatment may reduce the number of patients in whom biologic agents are needed, again relevant for our country.

CORTICOSTEROIDS IN ESTABLISHED RA

Corticosteroids in established RA are used in the following situations:

- As ‘bridge therapy’ at the time of institution of DMARDs like methotrexate. DMARDs take several weeks to show their effects. Corticosteroids bridge the gap between institution of DMARDs and onset of action. This use is for 10-12 weeks.
- Pregnancy and Lactation: Low dose prednisolone is safe during pregnancy and lactation. It does not cross the blood brain barrier. DMARDs that are safe during pregnancy and lactation include hydroxychloroquine and sulfasalazine.
- Disease flares when corticosteroids may be used for a few weeks to suppress disease activity.
- Patients with refractory disease may require low dose corticosteroids to maintain an acceptable quality of life.
- RA with extra-articular manifestation like interstitial lung disease, vasculitis, mononeuritis multiplex etc. may require corticosteroids, often in high dosages. Most of the aforementioned conditions require low-medium dose corticosteroids. Some conditions like vasculitis may require higher dosages. Eye conditions may require topical corticosteroids while the odd, recalcitrant joint that is active in face of globally quiescent disease can be injected with intra-articular steroids rather than hiking systemic treatment.

The 2010 EULAR recommendations on the use of steroids in RA incorporate a systematic literature review the gist of which is:

1) There is robust evidence that GCs are effective in bridging the gap between the start of a DMARD course and the occurrence of its clinical effect (Level of evidence 1b)
2) In early RA, the addition of low-dose GCs (<7.5 mg/day) to DMARDS leads to a reduction in radiographic progression (Level of evidence 1a)
3) In longstanding RA, GCs (up to 15 mg/day) improve disease activity (Level of evidence 1a)
4) There is some evidence that appropriate timing of GC administration may result in less morning stiffness. (Level of evidence 1b)

TYPE OF CORTICOSTEROID- DOES IT MATTER?

Prednisolone, methylprednisolone, betamethasone, dexamethasone and deflazacort are the corticosteroids used in clinical practice. It is important to realize that different dosages elicit responses in different ways. Genomic effects are mediated by cytosolic receptors that alter expression of specific genes whereas non-genomic effects are mediated by steroid selective membrane receptors. Prednisolone and methylprednisolone have similar genomic potency but in high dose therapy the non-specific non-genomic effect of methylprednisolone is more than threefold stronger. This is the reason for the empirical clinical preference for methylprednisolone for pulse therapy. So far as oral use is concerned, there is no strong evidence to suggest that methylprednisolone confers any advantage over cheaper prednisolone. It is noteworthy that betamethasone has very low non-genomic potency because of which this drug is rarely used systemically although it has the same genomic potency as dexamethasone.
I would like to make a special mention of deflazacort here. Deflazacort is an old drug introduced in 1969 although it was marketed in India much later. Clinical studies have indicated that the average potency ratio of deflazacort to prednisolone is 0.69-0.89 and 6 mg of deflazacort is equivalent to 5 mg of prednisolone. Deflazacort is available in the UK but not in USA. It has been suggested that deflazacort appears to have less effect than prednisolone on parameters that may be associated with the development of corticosteroid-induced osteoporosis. Other advantages claimed have been less severe adverse effects on carbohydrate metabolism, linear growth in children and less GI side effects. However, these claims have been questioned on the basis of some doubts as to the dose equivalence of deflazacort and the glucocorticoid of reference, prednisolone. Most of the data on the bone sparing effect of the drugs are obtained from trials that are relatively small or of short duration. As pointed out by Nayak and Acharya, well-designed clinical trials are needed, especially to clarify the appropriate ratio of doses for bioequivalence with prednisone.16

Interestingly, a PubMed search using the key words of prednisolone, methyl prednisolone and deflazacort and a limit of 5 years revealed 7594, 171 and 71 publications respectively. Of note, most of the methyl prednisolone publications pertained to pulse use and not oral methyl prednisolone. In summary, at present, there is no convincing data to show that more expensive preparations like deflazacort or oral methyl prednisolone are significantly better than oral prednisolone.

SIDE EFFECTS OF CORTICOSTEROIDS
It is relevant to segregate low dose from high dose steroid use. Recent publications emphasize that lumping all steroid use in one basket may be incorrect. There is a strong possibility that the balance of risks/benefits of low-dose treatment might be different from that of medium- and high-dose treatment, for which the mechanisms of action may be different.3,7 The overall fear of steroid toxicity in RA, as quoted in textbooks and review articles, is probably overestimated, based on extrapolation from observations with higher dose treatment.7 A recent meta-analysis looked at double-blind, placebo controlled, randomized trials of medium to long-term glucocorticoid therapy (defined as 1 year or longer) in RA.17 This meta-analysis used patient withdrawal as a marker for toxicity and adverse effects. It was demonstrated by the authors that the toxicity of glucocorticoid therapy in trials lasting ≥2 years is low. This was further supported by the lack of difference in both adverse events and serious adverse events associated with glucocorticoid therapy compared with placebo in the This meta-analysis of studies using lower dose of prednisolone (mean dose 6.5 mg/day), reported NNT:NNH ratio of 0.25, implying good tolerability. [NNT=numbers needed to treat, NNH=numbers needed to harm]. I would like to emphasize that low dose steroid therapy is not absolutely safe and due diligence must be exercised while using steroids irrespective of dose, as with any other drugs. Patients with RA treated with low-dose steroids were compared to patients never treated with steroids. Steroid users showed a higher prevalence of fractures, arterial hypertension, myocardial infarction, and serious infections, especially after 5 years of treatment.18 Thus, strategies to minimize complications like bone protective agents etc. should be instituted concurrently with the steroids. The lowest dose for the shortest time should be employed.

RECENT ADVANCES
Chronotherapeutics and Corticosteroid treatment
Traditionally, corticosteroids are recommended as a single morning dose to reduce adverse effects. This does not eliminate the morning stiffness in all patients. Recent trials have utilized a novel modified-release (MR) prednisone formulation given at bed time.19 This releases the drug at about 2:00 AM to coincide with the rising phase of the circadian cycle prior to the rise of early morning pro-inflammatory cytokines. It has been suggested that such use overcome an inadequate cortisol release in RA, presumably leading to better clinical effects. The physiological circadian rhythm of endogenous cortisol is mimicked with less disturbance of the hypothalamic pituitary axis. The clinical benefit of the new MR formulation was shown in the Circadian Administration of Prednisone in Rheumatoid Arthritis trial (CAPRA-1), an active-controlled clinical trial in which MR prednisone demonstrated a clinically relevant reduction of morning stiffness of the joints.

Corticosteroids with Dissociated Action
Better elucidation of the cellular mechanistic pathways of steroid action has stimulated a lot of research in the area of dissociated steroids or selective glucocorticoid receptor agonists (SEGRAs) that dissociate transrepression from transactivation. Briefly, glucocorticoids (GCs) enter cell by diffusion through the cell membrane, bind to the glucocorticoid receptor (GR) and induce conformational change. It is thought that the anti-inflammatory effects of steroids are mainly caused by the interaction of GR, in the form of a monomer, with transcription factors that
drive proinflammatory gene expression, including NF-κB. The dimerisation of GR and direct binding to GC response elements (GREs) in the nucleus contributes to the endocrine side effects of GCs. Drugs that show a selective antagonistic effect on pro-inflammatory transcription factors but are devoid of its agonistic effects on GRE-driven genes hold promise. Compound A (CpdA), a stable analogue of the hydroxyphenyl aziridine precursor found in the Namibian shrub Salsola tuberculiformis Botschantzev, is a selective GR modifier that dissociates GR-mediated transrepression from its transactivation function in vitro. The initial results in collagen induced arthritis are promising.

**CONCLUSIONS**

Corticosteroids play an important role in the treatment of RA (Box 1). Judiciously used, they are invaluable in the fight against inflammation. The current standard of care for early RA envisages the use of low dose prednisolone added to methotrexate for the first two years of disease. Corticosteroids reduce disease activity in established RA where minimum dose should be used for the shortest time. Other situations in RA where steroids help include disease flares, pregnancy/lactation and extra-articular disease like rheumatoid vasculitis. SEGRAs represent an important new class of steroids whereas chronobiology permits the use of modified release prednisolone to combat early morning stiffness. The need of the hour is to strike a balance between efficacy and side effects while individualizing treatment.

**Box 1. Key points**

- Corticosteroids are important agents in the treatment of RA
- Low dose steroid treatment differs from high dose treatment in terms of side effects, and possibly, mechanism of action
- Decision to use steroids in a given patient of RA should be individualized
- Rationale for use in early RA differs from that in established RA
- The current standard of care for early RA (disease duration <2 years) is a combination of methotrexate+low dose prednisolone because low dose prednisolone used for 1-2 years in early RA reduces radiographic progression. This benefit is over and above that conferred by DMARDs.
- Steroids should always be used in combination with other DMARDs like methotrexate and never as the sole disease modifying drugs in RA
- Steroids lower disease activity in established RA and can be used to treat disease flares. The lowest dose for the shortest possible time should be used
- Despite the favorable risk benefit ratio of low dose steroids, no dose is absolutely safe
- All patients on steroids should be monitored for adverse effects and appropriate steps taken to minimize their occurrence e.g. bone protection strategies etc.
- SEGRAs represent an promising new class of steroids
- Chronotherapeutic manipulation like the use of modified release prednisolone may offer better relief from early morning stiffness

**REFERENCES**


