Corticosteroids in Rheumatology: Use, Misuse or Plain Abuse?

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Introduction

The therapeutic nihilism and pharmacologic pessimism have been the bane of rheumatic diseases. The advent of corticosteroids in 1950 changed this bleak landscape and proved to be a boon for patients and doctors battling rheumatoid arthritis (RA). Heralded as a major triumph in the fight against RA, this discovery culminated in the award of the Nobel Prize to Drs. Philip Showalter Hench, Edward C. Kendall and Tadeus Reichstein. Corticosteroids soon came to be touted as a cure for RA. Unbridled use and the mega dosages employed led to the emergence of serious side effects and the boom story went bust. The initial euphoria waned, and soon corticosteroids came to be shunned by the medical community. Misuse and abuse cropped up as time went by. The drugs are undeniably effective. This coupled with the low cost and quick onset of action led to widespread misuse by quacks. Corticosteroids came to be surreptitiously used in the guise of traditional medicines in total disregard of indications or diagnosis. The ease of availability led to self use or abuse by patients to achieve symptomatic relief. Contributing to this saga was the irrational use by many physicians. The drugs, despite being good, got a bad name. Even today, corticosteroids continue to evoke and provoke strong feelings in physicians. Despite polemics, corticosteroids are 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 article summarises the current use of corticosteroids in Rheumatology with special reference to RA. Old perceptions are discussed in light of new understandings.

Corticosteroids in RA

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 in the contemporaneous treatment of RA. Corticosteroids were first used to treat RA at the Mayo Clinic, USA in 1948. Over the next few years adverse effects of high dose prednisolone became apparent and physicians became circumspect in their use of these drugs. This, along with the emergence of other effective drugs like gold, sulfasalazine, methotrexate and hydroxychloroquine, 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. The current thinking about the role of corticosteroids in RA is outlined in 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.

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.

Corticosteroids in Early RA

The disease modifying role of corticosteroids in RA has been the subject matter of endless debate and ceaseless controversy.

Table 1: Nomenclature of corticosteroid dosing [Reference 3]

- 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
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. However, the fear of adverse effects was a major detractor to the use of corticosteroids. It is now believed that the side effect profile of ‘low dose’ corticosteroids is very different from ‘high dose’ steroids. 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). 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-blinded, multicenter randomized clinical trial evaluated the efficacy of four commonly used treatment strategies in over 500 patients with early RA (disease duration <2 years). Group 1 received sequential monotherapy, group 2 received step-up combination therapy, group 3 was assigned initial combination therapy with tapered high-dose prednisone,(527,539),(551,574) 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). 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 and one on initial combination with infliximab.

One of the salient messages from this pivotal trial is that 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 21 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 hinging systemic treatment.

The European League against Rheumatism (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)

**Corticosteroids in Other Arthritides/Soft Tissue Rheumatism**

Unlike RA, the response to systemic corticosteroids is not as good in spondarthritis (SpA). Prolonged oral corticosteroid therapy is best avoided. Intraarticular corticosteroids are recommended for the persistent synovitis of the knee or ankle in peripheral SpA. Painful enthesopathy or refractory plantar fascitis may also benefit from local corticosteroid injection. Direct injection into tendons should be avoided so as to avoid tendon rupture.

Corticosteroids may be used in patients with acute gout if they have contra-indications to the use of NSAIDs. While NSAIDs remain the treatment of choice for acute attacks of gout, some patients have co-morbidities like renal failure or congestive cardiac failure that preclude the use of NSAIDs. Oral prednisolone 20-40 mg daily tapered over 2 weeks or intra-muscular methyl prednisolone 40-120 mg may be used in such patients. There is no consensus on agent, dose or route of administration. Intraarticular corticosteroids are extremely effective in acute gout.

Intraarticular corticosteroids are effective adjuncts in managing knee osteoarthritis (OA) with effusion. It is mandatory to rule out sepsis before injecting corticosteroids into the joint. Most authorities now believe that there is no real evidence that intraarticular steroids hasten joint destruction or cartilage degeneration. However, it is common practice not to inject the same joint more than 3 times a year. Strict aseptic technique is mandatory.

Local steroid injections may benefit soft tissue conditions like tennis elbow, plantar fascitis, adhesive capsulitis of shoulder etc. in selected patients.

**Corticosteroids in Connective Tissue Diseases**

Corticosteroids are beneficial in most of the lupus manifestations. Since SLE is a multisystem disorder which can affect any organ, it is clinically important to categorize patients into those with ‘major’ organ involvement and those with ‘minor’ organ involvement. Therapy is directed accordingly. Minor involvement includes serositis, mucocutaneous, musculoskeletal or constitutional symptoms. The major manifestations include lupus nephritis neuro-psychiatric SLE, significant cytoptenias and interstitial lung disease. In general, patients with minor organ involvement of lupus can be treated with NSAIDS and hydroxychloroquine. Corticosteroids, if needed, are given in relatively small doses (prednisolone 0.25-0.5 mg/kg/day). On the other hand, major organ involvement necessitates initial use of high dose corticosteroids (prednisolone 1 mg/kg/day or higher) and even cytotoxics. In emergent and life threatening situations methyl prednisolone pulses may be used (1 Gm intravenous infusion daily for 3 days). Patients with minor organ involvement may also require high dose corticosteroids during disease flare. In the same vein, once patients with major organ involvement go into quiescence, the corticosteroids can be tapered to a maintenance dose. In many patients steroids can be tapered and even discontinued once the disease is quiescent for a prolonged period of time. However, some patients of SLE have a minimum corticosteroid threshold— reduction of steroid dose below this threshold leads to a lupus flare. Such patients may need life long corticosteroids.

Corticosteroids are also used in systemic sclerosis, vasculitides, inflammatory muscle disorders etc., the details of which are beyond the scope of this article.

**Type of Corticosteroid- Does it Matter?**

Prednisolone, methylprednisolone, betamethasone, dexamethasone, triamcinolone 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 Acharjiya, well-designed clinical trials are needed, especially to clarify the appropriate ratio of doses for bioequivalence with prednisolone.

Interestingly, a PubMed search using the key words of prednisolone, methylprednisolone and deflazacort and a limit of 5 years revealed 7544, 3510 and 72 publications respectively. Of note, most of the methylprednisolone publications pertained to pulse use and not oral methylprednisolone. In summary, at present, there is no convincing data to show that more expensive preparations like deflazacort or oral methylprednisolone are significantly better than oral prednisolone.
Box 1: Key points about Corticosteroids in Rheumatology

- Corticosteroids are important agents in the treatment of autoimmune rheumatic diseases.
- Low dose steroid treatment differs from high dose treatment in terms of side effects, and possibly, mechanism of action.
- 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.
- Steroids are effective in connective tissue diseases like SLE. Exact dose and duration are governed by organ involvement. Major organ involvement like nephritis requires higher doses for long periods while minor manifestations like skin may need lower doses for shorter periods.
- Decision to use steroids in a given patient should be individualized.
- Intra-articular steroids are helpful in knee OA with effusion.
- 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 a promising new class of steroids.
- Chronotherapeutic manipulation like the use of modified release prednisolone may offer better relief from early morning stiffness.

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. 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. 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. 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. 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. 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. 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 overcomes 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 tuberculatiformis 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 rheumatic diseases (Box 1). Judiciously used, they are invaluable in the fight against inflammation. Minimum dose should be used for the shortest time. 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. The drugs are not bad, their inappropriate and injudicious use is!

References

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