46 *Resurgence of Low Dose Steroids in Management of Rheumatoid Arthritis*

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Abstract: The depressing description of rheumatoid arthritis described by Sir William Osler has changed dramatically due to use of early aggressive therapy. The discovery of glucocorticoids in 1949 and its subsequent use in a patient with RA led to noble prize to the discoverers, Philip, Kendell and Reichstein. However, due to its indiscriminate use, various adverse effects became prominent. Glucocorticoids became a taboo. Its use was met with criticism and skepticism. Then came the biologic response modifiers. Rheumatologists thought it a panacea for all the connective tissue diseases. But the BRMs were able to achieve only 40-50% ACR70 response. They are very expensive and not a first line DMARDs in most countries. The medical research council and Nuffield Foundation trials in the mid 1950s and mid 1960s suggested a possible disease modifying role of glucocorticoids. *In 1995, Kirwan demonstrated a significant reduction in progression of radiologic joint damage with low dose glucocorticoids continued for 2 years. In a further follow-up of these patients in 1998, Hickling, et al, showed resumption of joint destruction after prednisolone was stopped.*

Everdingers, et al, in 2002, in a unique trial assessed the effects of steroids on joint damage independent of DMARDs. Patients were randomized to receive low dose prednisolone (10 mg/day) or placebo. There were significant improvement in the prednisolone group after 6 months. They concluded that glucocorticoids have disease modifying effects, albeit on a limited scale.

Two recent trials published in 2005 viz. LDPT study group by Wassenberg and BARFOT Study group by Svensson have clearly demonstrated that low dose prednisolone 5-7.5 mg/day added to initial DMARD retarded the progression of radiographic damage of patients with early RA, provided high remission rate and was well tolerated without significant adverse effects.

Da Silva, et al, in 2006, in a meta analysis, vindicated those above statements and suggested that adverse effects associated with low dose glucocorticoids are modest and often not statistically different from those of placebo.

Over and above these disease modifying properties, glucocorticoids also improve the low cardiovascular safety profile by suppressing the inflammatory endothelial dysfunction.

Abbreviation: *ACR*—American College of Rheumatology, *BRM*—Biological Response Modifiers, *DMARD*—Disease modifying anti-rheumatic drug, *RA*—Rheumatoid Arthritis, *GC*—Glucocorticoids.

INTRODUCTION

Father of modern medicine, William Osler, in 1909, wrote a description of rheumatoid arthritis: "Arthritis deformans, once established, the disease is rarely curable. Too often it is a slow, but progressive crippling of the joints, with a disability that makes the disease one of the most terrible of human afflictions."

This picture of the disease has changed dramatically during the last decade due to early referral, early aggressive therapy with disease modifying antirheumatic drugs, glucocorticoids and biological response modifiers.

Now actually we are thinking in terms of cure of rheumatoid arthritis by "switching off" the inflammatory process at a very early stage by multiple interventions. Klaus P Machold in a very recent article in 2006 has written that rheumatoid arthritis has become milder at presentation in recent years due to early referral.[1] In its very early stages, the cytokine profile reflects T cell activation and switches to abundant proinflammatory cytokines thereafter. Disease modifying antirheumatic drugs plus glucocorticoids are highly effective, as is early use of tumor necrosis factor blockers.

GLUCOCORTICOIDS IN RHEUMATOID ARTHRITIS

Discovery of glucocorticoids by Philips Hench, Kendall and Reichstein in 1949, followed by its use in a crippled bedridden rheumatoid arthritis patient, and subsequent Nobel prize to the above scientists, was perhaps the most dramatic and useful drug known to human beings.[2] This is perhaps the greatest contribution to modern therapeutics by the discipline of rheumatology.

During the decade 1950s and 1960s, this drug was indiscriminately used and fell into disrepute because of its severe systemic and widespread adverse effects on prolonged unsupervised use.[3]

During 90s, steroid use became limited to only as "bridge therapy awaiting efficacy of slow acting disease modifying antirheumatic drugs (DMARDs) and also for treating disease flares.[4]

Another reason for not using glucocorticoid was the ignorance about disease modifying property of glucocorticoids.

BIOLOGIC RESPONSE MODIFIERS

During late nineties and early part of the millennium saw the advent of anti TNFα and anti IL agents, the so called targeted therapies.[5] There is no doubt about their efficacy but debate continues regarding their use in early RA. Cost is prohibitive and there are definite chances of infection, autoimmunity and other toxic adverse effects. Moreover, biologics like TNFα blockers never achieve more than 50% ACR70 response or sustained benefit after termination. This is due to the fact that joint destruction in RA is affected by two distinct pathways. One is cytokine dependent and the other is still ill- defined.[6]

Recent studies in early RA show up to 40% remission with the combination of methotrexate and infliximab given up to 6 months. The same result was found with a short-high dose of prednisolone, weaned off in 7 weeks.[7]

As per recent consensus TNFα blockers and for that matter other biologicals should only be used when other DMARDS (especially methotrexate) have failed.[8]

So the search continues for cheaper alternative. Glucocorticoids being the strongest anti-inflammatory drug is a good alternative if used cautiously and rationally.

GLUCOCORTICOIDS AS DISEASE MODIFYING DRUG

Glucocorticoids suppress a wide variety of nonspecific inflammatory responses like cell trafficking and prostaglandin production. They also act on the immune process by cytokine modulation. At the cellular level GCs inhibit the access of leukocytes to inflammatory sites, modulate the functions of leukocytes, endothelial cells and fibroblasts, inhibit the production and functioning of a variety of proinflammatory cytokines while enhancing the production of anti-inflammatory mediators.

They also suppress the synthesis of cartilage degrading metolloproteases by fibroblasts and articular chondrocytes. All these effects as a whole, lead to marked clinical and radiological improvement in patients with RA.[4]

Now there is ample evidences regarding these by various RCTs.

The medical research council and Nuffield Foundation trials in the mid-1950s and mid-1960s suggested a possible disease modifying role of glucocorticoids. The results were difficult to interpret due to heterogeneity of the patients, long durations of disease and multiple concomitant therapies.

Kirwan JR, et al in 1995, first demonstrated conclusive evidence. In a double blind placebo-controlled RCTs of 128 patients of early RA received prednisolone 7.5 mg/day or placebo for 2 years in addition to NSAIDs (95% of patients) and DMARDs (71% of patients). After 2 years both the total number of new erosions and the number of patients with erosions were significantly lower in the glucocorticoid group.[9]

A follow-up study of the same patient cohorts by Hickling P, et al in 1998, it was observed that joint destruction resumed after 2 years post-discontinuation of prednisolone.[10]

In 1996, Saag KG, et al[11] in a meta-analysis of effectiveness of low dose corticosteroids in RA on a moderate term (7 months) found that corticosteroid is as effective as other therapies in improving disease course. Several landmark trials followed during the period from 1997 till date. Most of the trials have used prednisolone in the doses range of either 10 mg, 7.5 mg, 5 mg/day. All were double blind randomized, placebo controlled studies and almost all have shown beneficial effects of low dose prednisolone on clinical and radiographic outcome. Some of the results of important trials are presented in the subsequent paras.

Boers M, et al in 1997-155 patients with 2 DMARDs and step down prednisolone 60 mg/day tapered in 6 weekly steps to 7.5 mg/day and withdrawn at 28 weeks. In the combined group statistically significant and clinically relevant effect was seen regarding joint damage.[12]

Cobra trial—long-term (4-5 years) beneficial effects were shown regarding radiological damage following combined DMARDs with prednisolone. This study hypothesized that the superior effect of the combination therapy can be ascribed to prednisolone.[13]

Rau R, et al in 2000, in a double-blind randomized, multicenter trial studied the effect of low dose prednisolone therapy (LDPT) given for 2 years with conventional DMRDs and observed decrease in radiographic progression in early RA (< 2 years duration).[14]

In another randomized placebo controlled study on the effect of low dose prednisolone (10 mg/day) in DMARD naïve patients of early RA (< 1 year duration), Van Everdingen, et al in 2002, showed both clinical benefit as well as inhibition of progression of joint damage in first 6 months. Sulphasalazine (2 gm/day) was added as rescue DMARD in some patients when needed. The trial continued for 2 years. This study was unique because it did not include concomitant DMARD therapy at study entry. The effect of steroids on joint damage independent of DMARDs were thus assessed.[15]

More recently, in 2005, two landmark trial reports have been published: First one, by Wassenberg, et al of low-dose prednisolone (LDPT) study group, reported the effect of very low dose prednisolone in early RA. This was a multicentric, double-blind placebo-controlled trial. Patients were double-blinded to receive prednisolone or placebo while on concomitant DMARDs. Hand and front radiographs were taken at baseline and at 6, 12 and 24 months, and were evaluated according to the ratingens score and the total modified sharp/Vander Heijde score. Clinical and functional outcome tended to be better and radiographic progression was significantly less with prednisolone than with placebo group.[16] Side effect profile of the prednisolone group, viz weight gain hypertension, glucoma, Cushing's syndrome and gastric distress, were insignificant.

The second one was by Svensson, et al of the BARFOT study group. They assessed the efficacy of low dose prednisolone (7.5 mg/day) on joint damage and disease activity in patients with early rheumatoid arthritis (RA). This was also a double-blind placebo-controlled rando-

mized study where active early RA patients (< 1 year duration) were randomly assigned to receive either 7.5 mg/day prednisolone or no prednisolone for 2 years. All patients received DMARDs. At 2 years 55.5% of patients in the prednisolone group had achieved disease remission compared with 32.8% of patients in the no-prednisolone group (P = 0.005). Total radiographic sharp score was lower in the prednisolone group (P = 0.019). In prednisolone group there were fewer newly eroded joints per patient (P = 0.007).[17]

There were few adverse events that led to withdrawal. Bone loss measured by BMD was similar in 2 treatment groups.[17]

SAFETY OF GLUCOCORTICOIDS

Although glucocorticoids are very effective drug but they have some adverse effects like weight gain, hypertension glucose in tolerance, infections, easy bruising of skin and loss of bone mass with vertebral fracture, gastric distress and gastric ulcers.

In various RCTs notably by Evendingen, et al Kirwan, et al LDPT study group and BARFOT study group did not find significant difference from placebo groups. With the use of bisphosphonates, calcium supplementation and proton pump inhibitors, most of these adverse effects have been taken care of.[15]

In 2006, Da Silva, et al published a report on published evidence and prospective trial data on safety of low dose glucocorticoids treatment in RA. They concluded that, "safety data from recent randomized-controlled trials of low dose glucocorticoids treatment in RA suggest that adverse effects associated with this drug are modest and often not statistically different from those of placebo".[18]

Moreover due to its inhibitory effects on inflammatory cytokines and its ability to suppress the synthesis of cartilage degrading metalloproteases by fibroblasts and chondrocytes, glucocorticoids have a protective effect on bone and cartilage against inflammation-induced degradation. This may explain the drug's disease modifying properties.[15]

GLUCOCORTICOIDS AND CARDIOVASCULAR RISK BENEFIT

There is now increasing awareness of cardiovascular disease burden in patients with RA.[19] There is increased risk of myocardial infarction and heart failure in RA patients.[20] These are due to traditional and some novel risk factors in RA.[21]

It is now almost conclusively proved that systemic inflammation plays an important part in endothelial dysfunction leading to atherosclerosis. There is also a particular "atherogenic lipid profile" in RA with lower than normal cholesterol and a high ratio of total cholesterol to HDL.[22] There is also increased levels of lipoproteins (a) and homocysteine. Glucocorticoids having anti-inflammatory property has been shown to correct the lipid abnormalities and lower homocysteine levels when used is low doses.[23]

Nitric oxide, another novel mediator of endothelial function has been shown to have reduced responsiveness in patients with RA.

Patients of RA have decreased responsiveness of nitric oxide (NO) which correlates with other inflammatory markers. Therapy with antirheumatic drugs that included low dose prednisolone improved the NO responsiveness.[24]

Davis, et al in a recently published (2005) meta-analysis of various RCTS on the use of gluco-corticoids in RA, concluded that eradicating inflammation in RA appears important not only for the joints, but also for longevity of the cardiovascular system.[25]

CONCLUSION

Understanding of early rheumatoid arthritis is increasing due to greater awareness and early referral. This has put a great challenge to the rheumatologists in terms of stratifying the risk

burdens and formulating drug therapies. There is a distinct possibility of thinking about cure of RA if diagnosed and treated early.

Disease modifying drugs plus glucocorticoids are highly effective. Glucocorticoids in very low doses (5-7.5 mg/day) having anti-inflammatory properties markedly ameliorate clinical features of RA. They also retard or even help radiological healing of erosions.

The adverse effects of glucocorticoids are mostly ill-founded if used in very low doses and for a limited period of 2-3 years.

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