Corticosteroids as Disease Modifying Drugs in Rheumatoid Arthritis Treatment

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Abstract

The current approach to treatment of RA includes early and aggressive treatment with routine monitoring of outcomes to give patients the best chance of decreasing disease activity as much as possible, with low disease activity and remission being a realistic goal for many patients. In this quest, DMARDs, especially MTX, are the anchor treatment, and low dose prednisone should also be considered in combination with MTX as the best initial choice for RA treatment. Current data suggest that corticosteroids are disease modifying agents that enhance the effects of DMARDs with no real impact on adverse events. We are much better positioned now then in earlier times to provide a good outcome for our patients, and every available tool needs to be considered and utilized for this purpose.

The treatment of patients with rheumatoid arthritis (RA) is better now than in past decades, an improvement often attributed to the development of biological therapies. Biological agents are an important advance for 30% to 40% of patients with rheumatoid arthritis, but three major developments also seem to account for improved patients’ status: adoption of early and aggressive treatment, widespread use of methotrexate, and increased awareness that regular monitoring with quantitative disease measures improves outcomes compared with traditional non-quantitative impressions. Several studies, such as TICORA, BeSt, and Fin-RACo, have shown that regular quantitative review with a target level of disease activity led to better outcomes.

The main target for RA treatment has become, with the concept of “treating to target”, achieving the lowest possible disease activity with the least toxic combination of medications. Frequently used but not often included, as also left out of the latest ACR RA treatment guidelines, is the use of low dose corticosteroids (CS) in the treatment of RA. EULAR recommendations suggest CS as a bridging therapy; yet in most registry data, close to 50% to 60% of RA patients are on chronic CS treatment, making this one of the most commonly used agents for RA management. One of the reasons given for not including CS in RA treatment guidelines is that there seems to be inconstancy about whether CS are DMARDs—defined as controlling both signs and symptoms of RA, in addition to slowing or halting radiographic progression.

This paper will review some of the data that shows CS to be DMARDs and make the argument that they should be part of our treatment paradigm not as an afterthought but one of the mainstays.

Current treatment for new patients usually starts with methotrexate, the anchor drug for RA, at the start of treatment or within the first 3 months. It is the investigator’s practice to also start 5 mg of prednisone orally in all RA patients in addition to MTX. The MTX dose is increased from 7.5–10 mg to 20–25 mg a week to achieve maximum response within 3 to 6 months. Prednisone dose is usually maintained at 5 mg daily and sometimes decreased to 2.5 mg a day, but rarely discontinued. Disease progress should be monitored with one of the many composite indices. The Routine Assessment of Patient Index Data (RAPID3) is preferred by this investigator because this score is the simplest to use in routine care, requiring 5 to 10 seconds rather than 100 to 120 seconds without need for a formal joint count and is strongly correlated.
with disease activity score and clinical disease activity index.\(^\text{11}\)

**Corticosteroids as DMARDs**

When CS are considered as DMARDs, several factors need to be taken into account. The dose and duration and what exactly the aim of starting CS are the most important. Low dose CS are generally accepted to be 5 mg or less. However, even as recently as 2012, there are still reports calling 10 mg a day “low dose” even though an important factor, side effect profile, is very different for 5 and 10 mg a day of CS, as discussed elsewhere in this issue.

Kirwan and colleagues published in 1995 the first major randomized clinical trial (RCT) of low dose prednisone as a disease modifying agent, described by effect on slowing radiographic progression in the treatment of RA.\(^\text{12}\) Patients, who had less than 2 years of active RA, were randomized to two groups: 7.5 mg of prednisolone daily for 2 years vs. placebo. They were allowed to use other medication during the trial. The primary outcome was the progression of damage over 2 years on radiographs of the hands as measured by Larsen index and development of new erosions in those who did not have them at baseline. One hundred and six patients had radiographs at study end, and these showed an increase of 0.72 units on Larsen scores in the prednisolone arm and 5.37 units in the placebo arm, a significant difference (\(p < 0.004\)). Of the patients who had no erosion at baseline, significantly more on placebo developed new erosions compared to the prednisolone using arm (36/79 vs. 15/68 hands, \(p < 0.007\)). There were no differences among the groups in the other DMARDs used during the trial, and the adverse events were also similar between the groups. The prednisolone group also saw significantly more improvement in pain and disability; however, these were more pronounced only in the first year of the trial.

In this trial, prednisolone had all the characteristics of a safe DMARD: slowing down radiographic progression, controlling signs and symptoms of RA, and not leading to increased adverse events.

In the follow up study,\(^\text{13}\) prednisolone was discontinued in the patients from the previous study, and they were followed for another year. Seventy five patients had radiographs at each time point. When each year’s radiographs were compared, it was noted that after the discontinuation of prednisolone, joint destruction had resumed despite the fact that most of these patients were on DMARDs. The patients who had no erosions when they first started the trial had much less progression even in the year off the prednisolone, suggesting that prednisolone may have a longer lasting effect in preventing the development of new erosions. Investigators suggest that this shows that prednisolone has the capacity to slow radiographic progression but only if taken on a continuous basis.

Wassenberg and associates studied the effects of 5 mg of prednisolone, which they referred to as “very low dose,” on radiographic progression in early RA patients over 2 years.\(^\text{14}\) Patients with active RA, less than 2 years of symptoms, were blindly assigned to prednisolone 5 mg or placebo while at the same time starting a DMARD, MTX, or gold. Hand and foot radiographs were done at baseline 6, 12, and 24 months and scored according to the modified Sharp/van der Heijde scoring system. Of 192 patients enrolled 166 were available for intent to treat analysis, and the radiographic progression was significantly less in the prednisolone group. Of note, the difference in progression was greatest between the groups in the first 6 months of therapy. In addition, clinical and functional outcomes tended to be better, and the remission rates were higher for the prednisolone group, with nearly twice the number of patients in the prednisolone group fulfilling remission criteria (13/80 in prednisolone groups vs. 8/86 in placebo). Side effects were observed more in the prednisolone group but were small in number. In conclusions, low dose prednisolone was effective in decreasing radiographic progression when added to DMARD therapy.

The BARFOT study group from Sweden also studied the effects of low dose prednisolone; this time defined as 7.5 mg a day in RA patients with early disease.\(^\text{15}\) Patients at the start of their DMARD therapy were randomized to either 7.5 mg of prednisolone daily or placebo for 2 years, and radiographs of the hands and feet were done at baseline and after 1 and 2 years of treatment. Of the 250 patients included in the study, 242 completed it, and 225 had radiographs at each time point. At 2 years, the median radiographic progressions core, as measured by the modified Sharp/van der Heijde score, was significantly lower in the prednisolone arm compared to the placebo using patients. There were also fewer newly eroded joints in the prednisolone group, in addition to 55.5% achieving remission compared to 32.8% in the placebo group (\(p < 0.0005\)), few adverse events leading to withdrawal were reported, and the bone loss during the study was similar among the two groups. Again investigators conclude that prednisolone at a dose of 7.5 mg a day added to initial DMARD therapy retarded radiographic progression and also helped with better remission rates in these patients, making a strong case for adding low dose prednisolone to DMARDs when treating RA patients, as part of routine approach to controlling disease activity.

Finally, a recent study by Bakker and coworkers\(^\text{16}\) used 10 mg of prednisolone, as low dose, which may not be accepted by some rheumatologists as low dose,\(^\text{17}\) in a 2 year randomized double blind trial. The first 6 months patients were only on prednisolone 10 mg a day or placebo, and sulfasalazine could be used as a rescue medication after 6 months. As with the previous trials the prednisolone groups showed far less radiographic progression compared to placebo, and clinical benefits were also greater. Interestingly, there were no differences in adverse event profiles. As discussed before, the trial design can be debated, but the beneficial effects of prednisolone as a DMARD were again demonstrated in this trial.
Conclusion
The current approach to treatment of RA includes early and aggressive treatment with routine monitoring of outcomes to give patients the best chance of decreasing disease activity as much as possible, with low disease activity and remission being a realistic goal for many patients. In this quest, DMARDs, especially MTX, is the anchor treatment, and as the data reviewed in this paper suggests, low dose prednisone should also be considered in combination with MTX as the best initial choice for RA treatment. In addition, the current approach to corticosteroid use, which can be summarized as mostly a bridging therapy, needs to be reconsidered, and low dose corticosteroids should be used as part of the accepted treatment plan for RA. Possibly the starting point for this consideration may be ACR and EULAR RA treatment guidelines, which are usually quiet or limited in their recommendations for low dose corticosteroid use in RA management.

We are much better positioned now then earlier times to provide a good outcome for our patients and every available tool needs to be considered and utilized for this purpose.

Disclosure Statement
Yusuf Yazici, M.D., is a consultant for Bristol-Myers Squibb, Celgene, Centocor, Genentech, Roche, and UCB.

References