Use of Biologic Monotherapy for Rheumatoid Arthritis

Biologic therapy has become an integral component of the management of rheumatoid arthritis (RA). The current Canadian guidelines for the management of RA recognize the potential role of these agents by including them as an option following the failure of conventional DMARD (e.g., methotrexate [MTX]) therapy. 1 While the guidelines state that the outcomes are generally better when a biologic is combined with a traditional DMARD, this is not always the case. Certain patients may, for example, have difficulty tolerating or have previously not responded to conventional DMARDs.

An additional consideration is that although physicians may prescribe a biologic as add-on therapy to MTX, research has shown that many patients unilaterally discontinue the MTX component of their regimen. 2,3 Findings from a Canadian database showed that among patients on their first biologic for more than six months, approximately 45% did not fill a prescription for a DMARD. This illustrates the possibility that although we may prescribe a biologic in combination with MTX, the patient may wind up on biologic monotherapy anyway.

Furthermore, there is now evidence that one biologic agent, tocilizumab (an IL-6 inhibitor), is as efficacious in monotherapy as it is in combination with MTX. 4 This has not been the case with other biologics that have been used in clinical trials both as monotherapy and in combination with MTX.

The following brief review discusses the evidence for the use of biologics as monotherapy for the treatment of RA.

Biologics As Monotherapy for RA: Review of the Evidence

TNF inhibitors. There are currently five TNF inhibitors approved for the treatment of RA in Canada (adalimumab, certolizumab pegol, etanercept, golimumab and infliximab). Three of these agents have an indication for use as monotherapy: adalimumab, certolizumab and etanercept. Prescription data indicate that etanercept is the TNF inhibitor most often used in monotherapy for RA. Although TNF inhibitor have been found to be effective in monotherapy, well-designed clinical studies have also consistently shown that the combination of a TNF inhibitor and MTX is superior to the TNF alone. 5,6,7 For example, in a study evaluating adalimumab monotherapy vs. adalimumab + MTX, the co-primary endpoints were American College of Rheumatology 50% improvement (ACR50) and mean change from baseline in the modified total Sharp score (mTSS). 5 At year 1, the ACR50 response was 62% for the adalimumab + MTX arm and 41% for adalimumab monotherapy (p<0.001). For the change in mTSS from baseline, the combination arm had a mean of 1.3 points at year one and 1.9 points at year two, which were both significantly lower than the 3.0- and 5.5-point changes in the adalimumab monotherapy arm. 5

Abatacept. In its major clinical trial program, there has not been a trial evaluating abatacept monotherapy against the combination of abatacept and MTX. Monotherapy data in general on this agent are lacking.

Case Study

Presentation: Rita is a 34-year-old woman who was diagnosed with RA one year ago. At that time of diagnosis, she had 18 tender and 12 swollen joints. Her initial disease-modifying therapy was the combination of methotrexate (MTX) 20 mg per week and hydroxychloroquine (HCQ) 400 mg daily.

There was some initial response to therapy: four months after the initiation of MTX + HCQ, her tender and swollen joint counts were 12 and nine, respectively. However, she was also experiencing some significant treatment-emergent adverse effects, notably mild hair loss and persistent nausea.

Question: What is a reasonable next step for Rita’s treatment?

- Replace MTX with another traditional DMARD (e.g., leflunomide, sulfasalazine)
- Reduce the dose of MTX
- Replace the MTX with a biologic
- Switch to biologic monotherapy
- Any of the above

Presentation: After three months on...
**Rituximab.** In an early, open-label study, rituximab monotherapy was compared to the combination of rituximab + MTX, as well as the combination of rituximab and cyclophosphamide and MTX alone. The investigators reported that the ACR50 response (primary endpoint) was significantly higher with the rituximab + MTX group (35%) compared to the rituximab monotherapy group (15%) at week 48.

**Tocilizumab.** Clinical trial research suggests that this agent appears to be the exception to the rule that combination therapy with MTX enhances the efficacy of biologic therapy. In the ACT-RAY study, investigators compared the strategy of adding tocilizumab to the regimen of those who had an inadequate response to MTX to the strategy of switching to tocilizumab monotherapy. The investigators reported that there was no significant difference between the groups in terms of the primary endpoint (DAS28-ESR remission). Among all the secondary endpoints studied (% achieving low disease activity, ACR responses, tender and swollen joint counts, pain, HAQ, ESR, CRP, EULAR good and moderate response, RAQoL, CDAI, SDAI and ACR-EULAR remission) only the proportion of patients in low disease activity was significantly better for the tocilizumab-MTX combination versus the tocilizumab monotherapy arm.

There are also other well designed clinical trials that lend support to the use of tocilizumab in monotherapy. The AMBITION trial, which compared tocilizumab monotherapy to MTX monotherapy, showed that tocilizumab was superior to MTX for the primary efficacy endpoint of ACR20 response at week 24 (69.9% vs. 52.5%, p<0.001), as well as a number of secondary efficacy endpoints.

The most recent addition to the growing database supporting tocilizumab as monotherapy came from a trial comparing tocilizumab to the TNF inhibitor adalimumab, each in monotherapy, among patients intolerant of MTX therapy (the ADACTA study). The 326 patients in this study were randomized to receive either tocilizumab 8 mg every four weeks or adalimumab 40 mg every two weeks. Patients could be rescued to adalimumab 40 mg every week if they did not have a 20% improvement in SJC and TJC by week 16. The primary endpoint was change in DAS28 from baseline to week 24. As shown in Figure 1, the mean change in the tocilizumab group was -3.3, which was significantly greater that the 1.8-point mean improvement in the adalimumab group (p<0.0001). There were also substantial and significant differences in favor of tocilizumab in the proportion of patients achieving DAS28 remission (39.9% vs. 10.5%, p<0.0001) and the proportion achieving low disease activity (51.5% vs. 19.8%, p<0.0001). Similarly, differences in ACR responses, HAQ, tender and swollen joint count and the clinical disease activity index (CDAI) were all in favor of tocilizumab therapy.

**Question:** What would be your course of action now with respect to Rita’s disease-modifying regimen?

- Try another conventional-DMARD-based regimen
- Add a biologic
- Switch to a biologic in monotherapy
- Add systemic corticosteroids
- b or c

**Discussion Forum**

- **What factors might lead you to consider choosing a biologic therapy rather than another different regimen based on conventional DMARD(s)?**
- **For patients requiring biologic monotherapy, which agent(s) would you consider using and why?**
Conclusions

Although the current guidelines recommend the use of concomitant synthetic DMARD therapy for most patients when a biologic is prescribed, there are many patients who will not tolerate the conventional DMARDs and many others who will discontinue their use unilaterally.

For patients like these, it is therefore important to consider the efficacy profiles of the biologic agents in monotherapy. While most of the biologics, including the TNF inhibitors, are associated with better efficacy when combined with MTX, use of the novel biologic agent tocilizumab in monotherapy has been associated with an efficacy profile similar to that of tocilizumab-MTX combination therapy. Furthermore, tocilizumab has been shown to be superior to MTX and to the TNF inhibitor adalimumab when each is used as monotherapy.

For RA patients who require biologic monotherapy, or for those in whom compliance to MTX may be a concern, tocilizumab monotherapy should be considered to be a reasonable choice for disease-modifying treatment.

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