Sustainability of Biologic DMARDs in the Treatment of Rheumatoid Arthritis

In the treatment of rheumatoid arthritis, the cumulative evidence with biologic disease-modifying antirheumatic drugs (DMARDs) is quite compelling. Clinical trials have consistently demonstrated clear and radiographic efficacy with these agents in rheumatoid arthritis and have led to their inclusion in clinical practice guidelines. Broadly speaking, efficacy data with TNF inhibitors (adalimumab, certolizumab, etanercept, golimumb or infliximab) or biologics with other mechanisms of action (abatacept, rituximab or tocilizumab) appear to be similar among biologic-naïve patients. However, our experience with these agents grows, one of the areas in which there appears to be some differences emerging is in relative sustainability over the long term.

This brief summary will review data on discontinuation rates, sustainability of the biologic therapies, both among patients who are biologic naïve and among patients switched to other biologics following failure of another.

Sustainability of Biologies in Biologic-Naïve Patients

Most of the data for sustainability with biologics in biologic-naïve patients comes from the TNF inhibitor class. Despite the fact that current clinical practice guidelines do not favor one type of biologic over another for initial treatment, the TNF-blocking agents have been in use for RA for the longest period and the evidence base is, consequently, much larger than for the newer agents with different mechanisms of action. Similarly, within the TNF-inhibitor class, there are far more data for adalimumab, etanercept and infliximab—the three more established agents—than for certolizumab and golimumb. Most data seem to indicate that retention rates are lower with infliximab than with either of the other two. A recent analysis of the Swedish RA database showed that discontinuation rates over eight years were significantly different for adalimumab, etanercept and infliximab, with discontinuation rates being lowest for etanercept and highest with infliximab. Dutch, French and Greek researchers have found that etanercept retention rates with adalimumab and etanercept compared to infliximab, with no difference between the former two agents. However, there have been other researchers who have reported no difference in retention between infliximab and the other TNF antagonists.

Importantly, however, in contrast to these data with TNF inhibitors, tocilizumab retention does not appear to be influenced by whether or not patients also take MTX. The tocilizumab retention rates in the AMBITION LTE discussed above were significantly lower than the likelihood of a good response to the first.

Switching to a second TNF inhibitor has been shown to be effective for some patients who have failed TNF-inhibitor therapy. Most of the data for sustainability with biologics in biologic-naïve patients come from the TNF inhibitor monotherapy compared to those who take the combination of a biologic and methotrexate (MTX). An analysis of the Rheumatoid Arthritis: A National Registry database, for example, showed that retention rates for the TNF inhibitors adalimumab and etanercept were markedly lower for those individuals who were not simultaneously taking MTX compared to those who were (Figure 1). Authors using data from other registries, including those from Sweden, Norway and Greece, have also demonstrated superior retention rates when TNF inhibitors are combined with MTX compared to TNF inhibitors alone.

Registries data have shown less desirable outcomes for those patients who are on TNF inhibitors who are monotherapy compared to those who are on a TNF biologic and methotrexate (MTX). An analysis of the RA registry, for example, showed that discontinuation rates for the TNF inhibitors adalimumab and etanercept were markedly lower for those individuals who were not simultaneously taking MTX compared to those who were (Figure 1). Authors using data from other registries, including those from Sweden, Norway and Greece, have also demonstrated superior retention rates when TNF inhibitors are combined with MTX compared to TNF inhibitors alone.

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Sustainability of Biologics in Biologic-experienced Patients

Research has indicated that there may be differences among the biologic DMARDs with respect to sustainability, both among biologic-naïve patients and among those who have already been treated with TNF inhibitors. These differences should be considered when recommending a course of therapy. The importance of continuation of MTX should also be stressed, as research consistently shows that this improves outcomes and enhances biologic sustainability. The relative exception to this is with tocilizumab therapy, which does not appear to require MTX co-administration to enhance efficacy or to prolong treatment retention.

Case Studies

Madeleine is a 35-year-old woman with a ten-year history of rheumatoid arthritis. Her past treatment history includes oral methotrexate in monotherapy, and the combination of oral methotrexate (MTX) and sulfasalazine, both of which led to incomplete responses and continued disease activity. Madeleine also experienced several undesirable side effects while on these treatments.

Two years ago, Madeleine began therapy with infliximab + methotrexate, which quickly led to a dramatic improvement in her symptoms and quality of life. Her DAS28 score, which was 5.2 at the time of infliximab initiation and 2.4 (DAS28 remission), was maintained up until her last visit, six months ago.

Presentation: Madeleine presents with a substantial worsening of symptoms. Examination reveals 12 left and 8 swollen joints. Asked to rate her current state on a scale of 0 to 100, with 0 being the best and 100 the worst, she scores herself at 70. Laboratory work shows that her current CRP is 13.0 mg/L. Her DAS28-ESR is 5.4 (high disease activity).

What is the next best step for Madeleine’s treatment?

References

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Sustainability of Biologics in Biologic-experienced Patients

For patients who do not take their initial biologic regimen, current clinical practice guidelines recommend switching to another biologic. For those who were initially on a TNF inhibitor, the choices include switching to a second TNF inhibitor or to a biologic with another mechanism of action (abatacept, rituximab or tocilizumab).

Each of the agents with different mechanisms of action were evaluated in a large randomized trial in TNF-experienced patients in their clinical trial programs, with the efficacy demonstrated in these trials leading to their approval for use in patients who have failed TNF-inhibitor therapy. Switching to a second TNF inhibitor has been shown to be effective for some patients as well, with better results having been shown among patients who switch due to intolerance rather than inefficacy with the previous TNF inhibitor.

However, the likelihood of having a good response to a second TNF inhibitor is significantly lower than the likelihood of a good response to the first.

Conclusions

Given that RA is a chronic, life-long disease that often manifests at a young age, the sustainability of the regimens that we use to treat these patients is an important variable to consider in RA management.

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