Monotherapy in Rheumatoid Arthritis

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Abstract
Therapeutic strategies for rheumatoid arthritis (RA) have evolved over time. Novel therapies have morphed in parallel to the ever-increasing understanding of RA pathogenesis, diagnosis and outcomes tools. For a century, the principal armamentarium was mainly composed by steroidal and non-steroidal anti-inflammatories. Over the last 25 years, however, the concept of disease-modifying anti-rheumatic drugs (DMARDs) has made possible the notion that the natural history of RA could actually be altered. Since then, synthetic DMARDs—particularly methotrexate (MTX)—have been used as monotherapy with significant success. This was followed by a revolutionary paradigm shift with the advent of anti-TNFα inhibitors and other “biologics” in the 1990s. Contemporary guidelines advocate for the use of a combination therapy (i.e., MTX and a biological) in aggressive RA cases given their proven additive effect. However, some patients are either intolerant to synthetic DMARDs or develop side effects that preclude their use. New data has recently emerged pointing towards the potential for biological DMARD monotherapy regimens in certain RA cases. This review will therefore, describe the available evidence supporting the use of biological DMARDs and the circumstances in which they are indicated.

Since the term rheumatoid arthritis (RA) was first coined by Sir Alfred Garrod in 1851, treatment options have slowly emerged. What was initially an attempt to control symptoms and inflammation (i.e., utilizing non-steroidal anti-inflammatory agents [NSAIDs] and corticosteroids) was gradually transformed into a strategy to prevent damage and disease progression. The 1970s and 1980s underwent the first radical change in this regard. Specifically, methotrexate (MTX) was FDA-approved for RA in 1988, given its demonstrated efficacy in limiting both symptomatic manifestations and the overall progression of natural history of disease. This, paired with a very good tolerability and safety profile, has since made MTX the anchor drug for the treatment of RA. Subsequently, the term disease-modifying anti-rheumatic drug (DMARD) emerged as a novel label for those drugs capable of preventing or delaying erosive changes that typically lead to deformity and disability. DMARD monotherapy has initially been the rule. In the 1990s, a step-up approach, usually beginning with methotrexate along with small dose steroids, became the dominant treatment paradigm for the rest of the century. The last two decades, however, have witnessed a second revolutionary shift in the therapeutic approaches to RA. A novel class of medications, popularized by the term “biologics” (Table 1), proved not only similar efficacy to oral DMARDs, but more significantly, improved outcomes when prescribed in combined fashion. Multiple studies have confirmed these findings and along the way altered, once again, the treatment model for RA. Initial aggressive therapy, often in conjunction with close follow-up and medication adjustments, are now the standard strategy. The so-called “treat-to-target” (T2T) approach is meant to reduce RA symptoms and radiographic progression, increase quality of life, attempt low disease activity, and when possible, complete remission.

Despite these noble goals, substantiated by the latest ACR guidelines, MTX (and other DMARDs such as sulfasalazine or leflunomide) is occasionally not well-tolerated or associated with side effects that prevents its use.

This review will focus on the available monotherapy approaches to RA and include data from TNF inhibitors (TNFi)
and recently approved biologics such as interleukin (IL)-6 receptor blockers and the small molecules (JAK inhibitors).

**TNF Inhibitors as Monotherapy**

As discussed, there are currently five FDA-approved TNF-inhibitors for the treatment of RA, including etanercept, adalimumab, certolizumab, infliximab, and golimumab (Table 1). Only the first three, however, have an indication for use as monotherapy. Despite this, convincing and validated randomized clinical trial (RCT) data demonstrated that the combination of TNFi plus a DMARD (usually MTX) is typically superior to either alone, and that there is no statistical difference when comparing TNFi to MTX when used in monotherapy. Since the year 2000, very few studies have addressed the efficacy of TNFi in DMARD-naïve (or partially exposed) RA patients.

**Etanercept**

The three-arm Early Rheumatoid Arthritis (ERA) trial was a 12-month, double-blinded RCT. Patients with early, active RA were randomized to receive either twice-weekly subcutaneous etanercept (10 mg or 25 mg) or weekly oral MTX (mean dosage 19 mg/week). RA subjects enrolled for this study had disease duration of less than 3 years and were considered to have bad prognosis (i.e., seropositive, erosive disease with elevation in both tender or swollen joint-count and acute phase reactants). About 40% of patients were previously treated with DMARDS. Etanercept 25 mg was shown to be significantly more effective than MTX in improving signs and symptoms of disease and in inhibiting radiographic progression.\(^2\) Although by month 12 clinical responses were no longer different, a follow-up open label phase revealed that more patients in the etanercept group met ACR20 criteria at the 24-month time-point.\(^3\)

The Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes (TEMPO)\(^4\) was also conducted in a double-blinded, three-arm, RCT fashion. In this case, however, the comparison was between MTX (up to 20 mg/week), etanercept monotherapy (25 mg twice/week), and the combination of both. Inclusion criteria deferred from the ERA study in that: 1. enrolled patients had disease duration of 6 months to 20 years, 2. patients were required to be considered DMARD inadequate responders (IR) other than MTX, and 3. patients could be enrolled while on MTX if they did not experience side effects or IR. Although this time there were no demonstrable differences in outcomes when comparing MTX to etanercept monotherapy groups, the combination of etanercept and MTX was significantly superior in terms of reduction of disease activity (both by ACR 20/50/70 and DAS measurement), improvement of functional disability, and retardation of radiographic progression compared to either medication alone. Interestingly, this was one of the first trials to show encouraging remission rates (of up to 35% at 1 year for the combination group). Once again, a 2-year follow-up study showed sustained benefit in overall clinical response, function, and radiographic progression.\(^5\)

**Adalimumab**

The PREMIER study, published in 2006,\(^6\) described the results of a 2-year, multicenter, RCT comparing combination
therapy (adalimumab and methotrexate) versus MTX (20 mg/week) or adalimumab (40 mg every other week) alone in patients with early (< 3 years of disease), aggressive RA who had not been previously exposed to MTX. As in TEMPO, results here showed that adalimumab plus MTX combination therapy was superior—clinically, functionally, and radiographically—to either monotherapy regime alone, and this was true at 1- and 2-year time-points. Intriguingly, although ACR20/50/70/90 were similar between monotherapy groups, ACR20 response at 12 months was significantly better in patients receiving MTX. Further, the PREMIER study confirmed the initial observation that a robust remission rate (as defined by DAS28 < 2.6) at 12 and 24 months was achievable in a large proportion of patients.

**Golimumab**

The third TNFi to be tested as monotherapy for RA treatment was golimumab. The phase III, RCT was named GO-BEFORE (Golimumab Before Employing MTX as the First-line Option in the Treatment of Rheumatoid Arthritis of Early Onset). MTX-naïve patients with RA were randomized to receive placebo plus MTX (group 1), golimumab 100 mg plus placebo (group 2), golimumab 50 mg plus MTX (group 3), or golimumab 100 mg plus MTX (group 4). At week 24, the primary endpoint (ACR50) was not met, and an intent to treat (ITT) analysis did not show a significant difference between the combined group and group 1. A post hoc, modified ITT-analysis (after excluding three participants) did demonstrate that the efficacy of golimumab plus MTX was superior to MTX alone, including remission rates. The efficacy of golimumab alone, however, was still similar to that of MTX monotherapy. In a 2-year imaging follow-up study, golimumab in combination with MTX inhibited radiographic progression significantly better than did MTX alone. Although approved as monotherapy for PsA, golimumab requires MTX in RA.

**The Efficacy of Inhibiting IL-6 receptor (IL-6R) Without DMARDs**

Three recently conducted studies have shown that tocilizumab, the only approved IL-6R inhibitor to date, does not appear to require combination with MTX or any DMARD in order to improve its overall efficacy.

The Actemra versus Methotrexate double-Blind Investigative Trial In mONotherapy (AMBITION) trial studied the efficacy and safety of tocilizumab monotherapy versus MTX in patients with active RA for whom previous treatment with either MTX or biological agents had actually not failed. This was a 24-week, double-blind, double-dummy, parallel-group study, randomized to either tocilizumab (8 mg/kg every 4 weeks), MTX (titrated up to 20 mg/week within 8 weeks), or placebo for 8 weeks followed by tocilizumab 8 mg/kg. Patients were included if they had moderate to severe RA for at least 3 months and were excluded if they had been unsuccessfully treated with a TNFi agent, had received MTX in the 6 months preceding randomization, or discontinued previous MTX treatment because of adverse effects or lack of efficacy. Mean disease duration was about 6 years, and in total, two thirds of patients were MTX naïve. The primary end point was the proportion of patients achieving ACR20 response at week 24. The ITT analysis demonstrated that tocilizumab was significantly better than MTX with a higher ACR20/50/70 response and larger proportion of patients achieving remission (by DAS28). This was also true for those patients who were MTX- naïve at the time of enrollment, making it the first trial to show that a biologic was superior to MTX in active RA patients who had limited or no exposure to MTX.

The ADACTA study was conducted to compare tocilizumab (8 mg/kg every 4 weeks) to adalimumab (40 mg every other week), each in monotherapy, among patients intolerant to MTX. Subjects enrolled had severe RA for 6 months or more (with a mean disease duration of approximately 7 years) and were either intolerant to MTX or were inappropriate for continued MTX treatment. Patients previously treated with a biologic agent were excluded, and all patients underwent a washout period for synthetic DMARDs. The primary endpoint was change in DAS28 from baseline to week 24. The mean change in DAS28 for the tocilizumab group (-3.3) was significantly greater than in the adalimumab group (-1.8). There were also significant differences favoring tocilizumab in the proportion of patients achieving DAS28 remission rates and low disease activity.

In ACT-RAY, a double-blinded, 2-year study, adults with active RA despite MTX use were randomly assigned either to continue MTX with the addition of tocilizumab (8 mg/kg every 4 weeks) or switch to tocilizumab and placebo. The investigators found no difference between groups in achieving the primary endpoint (DAS28 remission rate at week 24), although the combination was more commonly associated with transaminase increases.

**Small Molecules**

Tofacitinib is a novel oral Janus kinase (JAK) inhibitor that was recently FDA-approved for the treatment of moderate to severe RA in patients that failed or were intolerant to MTX. Tofacitinib inhibits signaling through JAK1/JAK3, blocking downstream signaling for several cytokines integral to lymphocyte function. The ORAL Solo study was a phase 3, double-blind, placebo-controlled, parallel-group, 6-month trial. Patients had moderate to severe, active RA and had had an inadequate response to at least one synthetic DMARD or a biologic (due to lack of efficacy or toxicity). The primary endpoints were ACR20, HAQ-DI scores and achievement of remission (DAS28 < 2.6) at month 3. Although a higher percentage of patients in the tofacitinib groups than in the placebo group met the criteria for ACR20 response and reduction in HAQ-DI scores, the remission rates were similar between groups.

ORAL Standard was a 12-month, phase 3 trial, in which active RA patients (mean disease duration: 7 to 8 years)
who were receiving stable doses of MTX (but deemed incomplete responders) were randomly assigned to 5 mg of tofacitinib twice daily, 10 mg of tofacitinib twice daily, 40 mg of adalimumab once every 2 weeks, or placebo. The primary outcomes were the same as in ORAL Solo. At month 6, a significantly greater percentage of patients receiving active treatment than those receiving placebo met the criteria for an ACR20 response (51.5% in the 5-mg tofacitinib group, 52.6% in the 10-mg tofacitinib group, and 47.2% in the 40-mg adalimumab group, as compared with 28.3% in the placebo group (p < 0.001). There were also greater reductions in the HAQ-DI score at month 3 and higher percentages of patients achieving remission at month 6 in the active-treatment groups than in the placebo group. Suggesting that in patients with RA receiving background MTX, tofacitinib is significantly superior to placebo and similar to adalimumab in efficacy.

Conclusions and Future Directions

The field of RA has adopted many different treatment paradigms over time. Currently, guidelines from the major rheumatology societies advocate for the use of concomitant oral DMARD therapy for most patients when a biologic is prescribed. However, in clinical practice, many patients will either be intolerant to conventional DMARDs or will self-discontinue the drugs. Under these not uncommon scenarios, the understanding and applicability of biologic monotherapy becomes highly relevant. TNF-inhibitors, for instance, appear to double their efficacy when combined with MTX but have not been proven superior to synthetic DMARDs when used in monotherapy. Interestingly, however, the use of the IL6-R blocker tocilizumab and possibly the JAK1/3 inhibitor tofacitinib do not appear to require MTX to improve their performance. In the best of possible worlds, RA management would include a sole medication with the following characteristics: very easy administration route, steady bioavailability, no required dose adjustment under any circumstances, 100% efficacy within a short period of time, and no side effects whatsoever. Although far from that scenario, we have made significant advances in RA, and we now aim for rapid remission. The current challenge, while we aspire to the Spinozan world, is to strike the right balance between early, aggressive treatment and avoidance of side effects. The rational use of monotherapies may certainly help achieve that goal in a subset of patients.

Disclosure Statement

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