

Therapies for Active Rheumatoid Arthritis after Methotrexate Failure

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Abstract

Rheumatoid arthritis (RA) is a common autoimmune inflammatory arthritis with a one percent prevalence worldwide. Left untreated, it leads to chronic progressive joint disease. Joint damage and erosions develop within two years of disease onset in a majority of patients, and early control of disease activity has been shown to improve long-term outcomes. Methotrexate has long been the staple of RA treatment and has been proven effective as a disease modifying agent in RA, as well as proven to decrease mortality in RA patients. While about twenty-five percent of patients achieve good response with methotrexate alone, the rest require additional or other therapy. This review discusses some of the sentinel trials looking at how best to treat RA patients who have failed methotrexate therapy. In particular, it focuses on the trials comparing triple therapy to biologics. It also addresses the tolerability and cost associated with some of these therapies. The next decade will bring more treatment options, and hopefully, more answers with regards to how to provide the best value therapy for each individual patient.

Keywords: Rheumatoid arthritis; Inflammatory arthritis; Methotrexate

Commentary

Rheumatoid arthritis (RA) is a common autoimmune, inflammatory arthritis with up to a 1% prevalence around the world [1] in the U.S. Untreated, RA is a chronic, progressive disease and currently there is no cure. Joint damage or erosions develop within 2 years of disease onset in a majority of patients, and early control of disease activity has been shown to improve long-term outcomes [2]. Over the past twenty-five years, there have been dramatic changes in the outcomes of patients with RA. The creation of effective disease-modifying anti-rheumatic drugs therapies (DMARDs), and subsequently biologic therapies, the use of these drugs early and when necessary in combinations and pushing therapies to achieve lower disease activity has made it possible to arrest the progression of the disease and prevent joint damage and disability in many the majority of patients. With the increased number of therapeutic choices and combinations, however, come questions about which drugs to choose first and when to add or switch therapies. to control inflammation. While there is now good data on some of these choices, unanswered questions remain., particularly in the realm who needs biologic therapies and when.

Methotrexate remains the anchor drug for treatment of RA. Methotrexate is an anti-folate agent that inhibits the enzyme dihydrofolate reductase [3]. It has been proven to be effective in both treating Rheumatoid arthritis and additionally proven to decreasing mortality in RA patients [4,5]. A review of the results of clinical trials involving methotrexate showed that about forty percent of patients with early arthritis achieved a good response with methotrexate monotherapy (defined as reduction in tender and swollen joint count by 50%, ACR 50 criteria) There have been a number of studies looking at the efficacy of methotrexate as single therapy [6-8]. These were among the trials that were included in a systematic review of methotrexate, which found that 23 out of 100 patients on methotrexate

alone experienced an ACR 50 response [9]. But what happens to the other sixty percent of patients who do not respond completely, or partially respond, to methotrexate therapy? The answer is that there is a plethora of options. This answer, however, then becomes the question of which therapy option to choose after methotrexate failure. Those who are incomplete methotrexate responders need additional medication. While combination therapy is now considered a standard practice in RA, the question of when to add biological drugs is important and should be based on individual patient factors [9].

Trials comparing treatment regimens have been undertaken to answer some therapy questions. One of the initial landmark trials was the Dutch BeST trial, published in 2005 [10]. In this randomized controlled trial, 500 RA patients were assigned to four different treatment strategies (sequential monotherapy, step-up combination therapy, initial combination with prednisone, and initial combination with infliximab.) All the treatment groups except initial combination therapy with infliximab received DMARDs, and only went onto biologics if they failed multiple DMARDs. In the first year of this trial, patients with initial combination therapy with either prednisone or infliximab had more rapid functional improvement, as well as less radiographic progression on joint imaging. In the second year of follow-up, however, physical function improved further in all four groups. By the end of two years, radiographic progression was suppressed equally in all four groups. The most important message from this trial was that regardless of what treatment regimen the patient is started on, all groups can do well if therapy is escalated to achieve low disease activity.

Tight control of disease is an important treatment concept in RA. The TICORA trial published in 2004 introduced this concept [11]. Patients were randomized to one of two groups, either intensive management or routine care. Patients assigned to the intensive group were seen every month by the same rheumatologist, versus those in the routine care group that were seen every three months with no formal disease activity measure. Those in the intensive group received either intra-articular steroid injection and/or escalation of their oral therapy

if their disease activity DAS score (DAS) was more than 2.4. Those in the routine group received drug escalation based on the discretion of the treating rheumatologists. Primary outcome measures were mean fall is disease activity score and proportion of patients in remission. Patients also received radiographs at baselines and 18 months. At the end of 18 months, patients in the intensive group had a higher rate of good response and had reduced progression of erosion scores. Not surprisingly, those in the intensive group were more likely to be treated with more medications. It is important to note, however, that the tight control was achieved with standard oral disease-modifying therapies without the use of biologicals.

The next group of studies looked at how best to achieve tight control in RA. In the TICORA trial, the most common combination of drugs needed to achieve tight control and disease remission was methotrexate, sulfasalazine, and hydroxychloroquine, a combination known as triple therapy. Triple therapy was proven effective in a landmark trial by O'Dell et al., in which methotrexate therapy alone was compared to the combination of the methotrexate, sulfasalazine, and Plaquenil [12]. As the anti-TNF drugs were developed, questions arose as to the efficacy of combination DMARD therapy versus the newer, and costlier, biologics. The first blinded trial to address this was the TEAR trial, a two-year double-blind randomized trial in which triple therapy was compared to etanercept plus methotrexate in early RA patients [13].

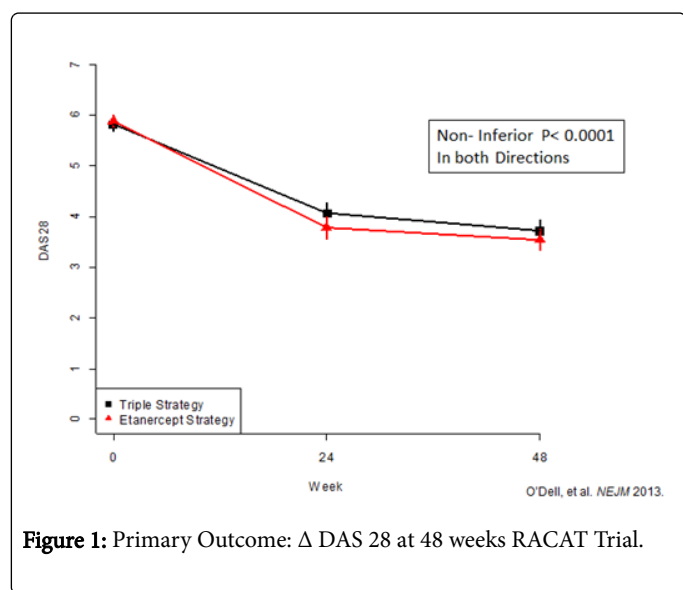


Figure 1: Primary Outcome: Δ DAS 28 at 48 weeks RACAT Trial.

There were no differences found in the primary outcome measure of mean DAS28-ESR scores proportion achieved between 48 weeks during the second and 102 weeks, and year of the trial or in radiological progressing remission between the groups. In addition, after 102 weeks there were no differences in radiographic outcomes. Another trial the RACAT trial [14] was a double blind randomized trial that proved the non-inferiority of triple therapy to etanercept plus methotrexate, in patients who had active disease despite methotrexate (mean dose 19.6mg/week) (Figure 1). Importantly, the RACAT trial has published for the first-time data that showed that patients who have failed triple therapy do benefit from switching to etanercept and patients who fail etanercept benefit when switched to triple therapy. Further, the SWEFOT trial compared triple therapy to methotrexate and infliximab with no difference found at two years for disease

activity or for work loss days [15]. These trials taken together have solidified the place of triple therapy in the approach to treating RA.

In 1998, the first biologic drug etanercept was approved by the FDA for use in RA. This was followed a year later by infliximab [16]. Since then, multiple new biologics have been approved, widening the once narrow landscape of RA treatment. These include, but are not limited to, rituximab, abatacept, and tocilizumab, as well as the newer targeted synthetic DMARD and tofacitinib. Each of these latter drugs has a unique mechanism of action, and targets a different aspect of disease pathogenesis. While we know that all of them are effective proven by their individual trials (Figure 2), there have been a paucity of head-to-head comparisons of these medications. Furthermore, there are and no trials that have compared most of these agents to triple therapy.

The continual introduction of novel biologic treatments have resulted in a large number of published multiple treatment comparison meta-analyses. Unfortunately, many of these arrive at different conclusions about the comparative effectiveness. This may be due to the inconsistencies between methodologies and statistical differences between all of these studies. Such discrepancies make it difficult for clinicians to determine true effectiveness [17].

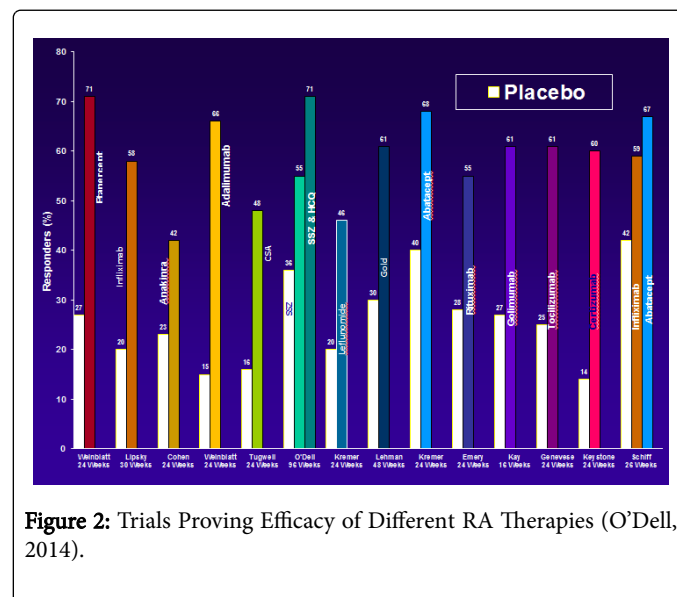


Figure 2: Trials Proving Efficacy of Different RA Therapies (O'Dell, 2014).

One important factor in choosing a drug is side effects. One of the most significant side effects of any biologic drug compared to any DMARD is the increased risk of infection. While some many of these infections are not life-threatening, others some can be as in the case of reactivation of tuberculosis or infection with other atypical typical organisms [18]. Another side effect that is seen with biologics as opposed to oral DMARDs is the risk of injection site or infusion reactions. The exception to this is the class of janus kinus inhibitors, such as tofacitinib, which are the only oral biologic drugs available to date. Finally, each individual drug has its own safety and tolerability profile. Those drugs that are more tolerable may lead to better compliance in individuals, and hence better outcomes. A recent study double-blinded randomized trial by Peper et al. looked at the durability of triple therapy versus methotrexate-etanercept after completion of the RACAT trial [19]. In this study, RA patients with suboptimal response to methotrexate had been were randomized to either triple therapy or methotrexate-etanercept and followed for 48 weeks, and some additionally for another 72 weeks open label. The primary

outcome of the Peper study was treatment durability, as well as clinical response. The group that received triple therapy were significantly more likely to stay on the therapy compared to the group on etanercept-methotrexate. This occurred despite the fact that there were no significant differences in disease activity scores between the two groups, suggesting that side effects of the biologic drug, or as discussed below, cost may have contributed to durability the switch.

Cost is another critical factor in making therapy decisions. It is well known that biologics are much more expensive than traditional oral DMARDs. The TEAR, RACAT, and SWEFOT trials have established that triple therapy (the combination of methotrexate, sulfasalazine, and plaquenil) is non-inferior to the combination of methotrexate and an anti-TNF drug in achieving both clinical remission and radiographic outcomes. Yet triple therapy is seldom initiated before biologics in the setting of methotrexate failure in the US. One study through the Veterans Hospital showed that this occurred in only 2.5% of patients. Bansback et al. recently published a study comparing the cost-effectiveness of proceeding directly to etanercept when RA fails to respond to methotrexate [20]. Using data from 324 RACAT study participants, they calculated the costs and quality-adjusted life-years (QALY) for both treatment strategies. Switching from methotrexate directly to etanercept-methotrexate combination provided only a marginal advantage over triple therapy in QALY at both the 24 and 48-week endpoints. The cost, however, of switching to etanercept-methotrexate as opposed to triple therapy was significantly higher. At 24 weeks, the associated costs of etanercept-methotrexate were \$11,295 versus \$343 for triple therapy. This resulted in a QALY costing. Similar data have been published for TEAR and Swefot. The resultant incremental cost-effectiveness ratio (ICER) for first-line etanercept-methotrexate versus triple therapy was \$2.7 million per QALY gained over 24 weeks. When this data was extrapolated to determine the cost effectiveness of the two treatment strategies over the average patient's lifespan, the model predicted an ICER of \$521,520 per QALY gained for etanercept-methotrexate instead of triple therapy.

Similar cost effectiveness data have been published using the TEAR and Swefot trial data. Jalal et al. published a model to assess the cost-effectiveness of all four interventions in the TEAR trial [21]. Immediate triple therapy was the least expensive and most effective strategy when the endpoint was one and two years. When the endpoint was extended out to five years, immediate etanercept was marginally more effective than immediate triple therapy, but etanercept was significantly more expensive than triple therapy. The five-year associated cost of etanercept was \$148,800 versus \$52,600 for 5 years of triple therapy. This resulted in an ICER of \$12.5 million per QALY. The Swefot trial produced similar data over twenty-one-month follow-up, with the infliximab group costing 27,487 euros versus the triple therapy group costing 10,364 euros. There was no between group difference in productivity loss or QALYs. The resultant ICER was close to two million euros for use of infliximab versus triple therapy [22].

One of the most value based therapies available in rheumatoid arthritis remains methotrexate. While other therapies are added after a patient has failed methotrexate, the definition of methotrexate failure is variable and at times inadequate [23]. Many trials do not use an adequate dose of methotrexate prior to labeling the patient as a "failure." In addition, in clinical practice, there is underutilization of subcutaneous methotrexate. Rohr et al. looked at the use of subcutaneous methotrexate through national pharmacy registries [24]. It was shown that subcutaneous methotrexate is underutilized, and that physicians tend to add or switch to biologics rather than

switching the route of administration on a patient's methotrexate. Further, the mean dose of methotrexate used before a biological was only 15 mg/week. Subcutaneous methotrexate not only has a higher bioavailability but also may be better tolerated. It has been shown to have less frequency and intensity of some gastrointestinal adverse reactions, therefore leading to better compliance and efficacy. Importantly, use of subcutaneous methotrexate could provide significant cost savings because it may avoid the switch to more costly biologics. Finally, if a patient with rheumatoid arthritis is switched to biologic, it is important to continue the methotrexate along with the biologic to improve efficacy of the treatment regimen.

The clinical picture of treated RA has changed dramatically over the past several decades. Thirty years ago, it was often difficult to control inflammation with available agents. Today, inflammation in RA can be controlled effectively with many different agents. With this plethora of choices come therapy questions with regards to efficacy, tolerability, adverse events, and cost. There is significant data to support the approach of reserving biologic therapy for those patients who have failed combination DMARD therapy. Importantly, the RACAT trial has published for the first-time data that shows that patients who have failed triple therapy benefit from switching to etanercept. The next decade will certainly bring more options in the treatment of RA and hopefully, more answers with regards to how to provide the best value therapy for each best to use them in individual patients.

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