CADTH

TECHNOLOGY REVIEW: FOCUSED CRITICAL APPRAISAL

Efficacy and Safety of Combination Therapy with Conventional Synthetic Disease-Modifying Antirheumatic Drugs in Adult Patients With Moderate or Severe Rheumatoid Arthritis After Failure of, or Suboptimal Response to Methotrexate

Service Line:	Technology Review
Version:	2.0 Corrected Version (see page 15 for correction)
Issue:	26
Publication Date:	February 2020
Report Length:	15 Pages

CADTH

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Cite As: *Efficacy and Safety of Combination Therapy with Conventional Synthetic Disease-Modifying Antirheumatic Drugs in Adult Patients with Moderate or Severe Rheumatoid Arthritis After Failure of or Suboptimal Response to Methotrexate*. Ottawa: CADTH; 2020 Jan. (CADTH Technology Review: Focused Critical Appraisal; no. 26).

Acknowledgments: Mike Innes, Robyn Butcher, Amanda Allard

ISSN: 2369-7385 (online)

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Background and Rationale

Rheumatoid arthritis (RA) is a chronic, systemic, autoimmune disease.[1,2] It is characterized by the infiltration of T cells, B cells, and monocytes into the synovial membranes of multiple joints that are thought to play an important role in the pathophysiology of RA.[2,3] RA is a debilitating disease that affects physical functioning, work productivity, and health-related quality of life.[3] If left untreated, or if insufficiently treated, 80% of patients will develop joint deformity and 40% will be unable to work within 10 years of disease onset.[3]

Disease-modifying antirheumatic drugs (DMARDs) are a class of medications used to treat the signs and symptoms associated with RA, to slow the progression of disease, and to improve physical function.[3] There are synthetic DMARDs and biologic DMARDs.[3] Synthetic DMARDs are small molecules and are usually taken orally.[3] This group is further classified into conventional synthetic DMARDs (csDMARDs) and targeted synthetic DMARDs (tsDMARDs). csDMARDs include methotrexate (available in oral and injectable formulations), sulfasalazine, hydroxychloroquine, and leflunomide. tsDMARDs include the Janus Kinase (JAK) inhibitors tofacitinib, baricitinib, and upadacitinib.[3] Biologic DMARDs (bDMARDs) are large proteins which target specific components of the immune response and are administered parenterally.[2,3] They include the tumour necrosis factor (TNF) inhibitors and non-TNF inhibitors.[2,3]

Treatment with a csDMARD (usually methotrexate) is recommended as first-line therapy in patients with early or established RA for any level of disease activity according to the 2015 American College of Rheumatology Guidelines;[4] similarly, the Canadian Rheumatology Association recommended that methotrexate monotherapy be the initial treatment in patients with RA unless contraindicated.[5] Synthetic DMARDs take approximately eight to twelve weeks to be effective.[6] However, an initial csDMARD course will fail to achieve treatment goals (i.e., remission or low disease activity) in approximately 50% to 60% of patients.[3,7,8] When monotherapy with a csDMARD has been ineffective or partially effective (disease activity remains moderate or high), or when treatment-related side effects are considered intolerable, patients may be treated with other csDMARDs alone or in combination, with tsDMARDs such as JAK inhibitors, or with biologics.[3] Biologic DMARDs or tsDMARDs are not recommended as first-line treatments.[3]

In Canada, there are differences in reimbursement criteria for drugs used to treat RA by government-sponsored drugs plans, particularly for patients in whom initial treatment with a csDMARD has failed. Some jurisdictional funding policies permit these patients to receive a biologic DMARD after a trial of double csDMARD therapy, while other jurisdictional policies require non-response on three different csDMARDs (monotherapy and/or combination therapy).[9] Given these differences in jurisdictional coverage policies for patients with RA, understanding the efficacy and safety of triple therapy versus double therapy with csDMARDs after initial treatment failure is critical to informing optimal treatment and efficient use of health care resources.

Objective

The objective of a CADTH Focused Critical Appraisal is to examine the methodology, scientific rigour, and clinical findings of a published clinical trial.

This assessment focused specifically on the clinical efficacy and safety of triple csDMARDs compared with double csDMARDs in adult patients with moderate or severe RA in whom treatment with methotrexate has failed or who are intolerant to methotrexate. Based on a previous systematic review of published clinical evidence conducted by CADTH[9] for this patient population and an updated search of the literature, one relevant publication was retrieved and is the object of this CADTH Technology Review: Focused Critical Appraisal.

Research Question

What is the comparative clinical efficacy and safety of triple csDMARDs compared with double csDMARDs in adult patients with moderate or severe RA in whom treatment with methotrexate has failed or who are intolerant to methotrexate?

The trial under review was: O'Dell JR, Leff R, Paulsen G, et al. *Treatment of rheumatoid arthritis with methotrexate and hydroxychloroquine, methotrexate and sulfasalazine, or a combination of the three medications: results of a two-year, randomized, double-blind, placebo-controlled trial. Arthritis Rheum.* 2002;46:1164-1170.[10]

The population of interest in this Technology Review was treatment-experienced adults with moderate or severe active RA in whom treatment with methotrexate has failed or who are intolerant to methotrexate. The study by O'Dell et al. presented results for a subgroup of patients who had previously been treated with methotrexate at study entry and in whom methotrexate had failed (termed methotrexate-suboptimum responders). Information about patients who were methotrexate-intolerant was not found in the literature and these patients were not included in the O'Dell et al. study.[10]

Detailed Description of Trial Under Review

Objective

The objective of the trial conducted by O'Dell et al.[10] was to compare the efficacy of combination therapy with methotrexate and hydroxychloroquine, methotrexate and sulfasalazine, and methotrexate in combination with hydroxychloroquine and sulfasalazine in patients with RA.

Trial Characteristics and Statistical Analysis

Study Design

O'Dell et al.[10] conducted a two-year, multi-centre (US), double-blind, randomized, placebo-controlled, parallel-group trial in patients with moderate or severe RA. Patients were randomized to one of three treatment groups including double or triple csDMARD combination therapy.

Patients were stratified according to previous treatment with methotrexate at randomization; this included patients who had not previously been treated with methotrexate; and those who had a suboptimum response to methotrexate administered orally. Suboptimum responders were the focus of this Technology Review and were defined in this trial as patients who continued to have active disease despite treatment with oral methotrexate at a dose of 17.5 mg per week.

Inclusion and Exclusion Criteria

Patients were eligible for inclusion in the trial by O'Dell et al. if they were between 19 and 80 years, were diagnosed with RA fulfilling the criteria of the American College of Rheumatology, and if they had active disease for at least six months defined by at least three of the following features: erythrocyte sedimentation rate (ESR) greater than 28 mm per hour, duration of morning stiffness greater or equal to 45 minutes, eight or more tender joints, and three or more swollen joints.

Patients were excluded from the trial if they had received previous combination therapy with any of the medications studied in the trial protocol; had stage IV disease; had an allergy to any of the study drugs; were women of childbearing age who were not using adequate contraception; or if they had significant liver, renal, hematologic, pulmonary, or cardiovascular disease.

Interventions

Patients were randomized to receive one of three treatment combinations:

- Methotrexate and hydroxychloroquine
- Methotrexate and sulfasalazine
- Methotrexate in combination with hydroxychloroquine and sulfasalazine.

Each trial patient was blinded to their allocated treatment and matching placebo was employed for patients randomized to treatment with double csDMARD therapy. Specifically, patients received three treatment bottles containing two active medications and one bottle with placebo or all three active medications. The first bottle contained methotrexate; the second bottle contained hydroxychloroquine or a matching placebo; and the third bottle contained sulfasalazine or a matching placebo.

For methotrexate-naive patients, an initial dose of 7.5 mg of oral methotrexate was administered weekly for the first two months and then increased to 12.5 mg weekly; this dose could be increased to a maximum weekly dose of 17.5 mg after four months if remission was not achieved. Patients who previously experienced a suboptimum response to methotrexate did not require titration and received 17.5 mg of oral methotrexate at the start of the trial and weekly thereafter. All trial patients received hydroxychloroquine at a dose of 200 mg twice per day and this dose remained constant throughout the study. The starting dose of sulfasalazine was 500 mg twice daily for all trial patients and this dose was increased to 1 gram twice daily in patients who did not achieve remission after six months.

Concurrent therapy with systemic corticosteroids was permitted if the dose remained stable throughout the study period and if patients did not exceed 10 mg of prednisone daily or its equivalent. The use of nonsteroidal anti-inflammatory medication and up to two joint injections with corticosteroids during the two-year trial period was also permitted.

Outcome Assessment

The primary end point of the trial was the percentage of patients who had achieved a 20% response to therapy according to the American College of Rheumatology (ACR) improvement criteria (ACR 20) at two years. Treatment was considered successful if patients achieved ACR 20 at the one-year evaluation and maintained this response until two years (end of trial). Patients were considered as having experienced treatment failure if they did not achieve ACR 20 at one year or if they withdrew from the study early due to medication side effects or inefficacy.

Additional end points reported included the individual components of the ACR core set of disease activity measures, the duration of morning stiffness, as well as the percentage of patients who achieved a 50% response and a 70% response to therapy according to ACR criteria (ACR 50 and ACR 70, respectively).

All outcome assessments were performed by physicians who were unaware of patients' study medication assignment. Patients were evaluated every two months for the first six months, and then every three months until the end of the two-year study period.

Treatment toxicity was monitored through monthly laboratory tests, including complete blood counts, measurement of serum levels of aspartate aminotransferase and albumin; ophthalmic examination at every six months; and, measurement of ESR at the beginning and at the end of the trial.

Statistical Analysis

O'Dell et al. used chi-square analysis to compare the distribution of treatment failures (or percentage of responders) among the treatment groups for the primary end point (ACR 20) and additional end points that measured response to therapy according to ACR improvement criteria (ACR 50, ACR 70). Pairwise comparisons were made using a chi-square test when there were significant differences in the distribution of failures across the three treatment groups. A Bonferroni correction was used to adjust for multiple comparisons, resulting in an adjusted significance level of 0.0167.

Several additional analyses were conducted for the primary ACR 20 end point: logistic regression analysis was used to adjust the treatment comparison for possible confounding factors; time to treatment failure for patients in each of the three treatment groups was depicted using a Kaplan-Meier plot, and the log-rank test was used to compare treatment groups; and, analysis of variance was used to compare the average change in outcome over the treatment period among the three treatment groups for the individual components of the ACR core set of disease activity measures and for the duration of morning stiffness.

The subgroup analysis relating to treatment response in patients who had been previously treated with methotrexate and experienced suboptimum response to methotrexate before enrolment was of specific interest for this report. However, details regarding the statistical analysis for this subgroup were not overtly reported by O'Dell et al.

Results

The population of interest in this Technology Review was treatment-experienced adults with moderate or severely active RA in whom treatment with methotrexate has failed or who are intolerant to methotrexate. Therefore, findings relating to treatment response after combination therapy with csDMARDs in patients who had previously been treated with methotrexate at study entry and in whom methotrexate had failed (termed methotrexate-suboptimum responders in O'Dell et al.) were summarized.[10] Information pertaining to methotrexate-intolerant patients was not found in the literature and these patients were not included in the O'Dell et al. study.

Results regarding the full intent-to-treat trial population and results relating to the methotrexate-naive patients are described in the original O'Dell et al. publication.[10] These results did not address the research question of interest for this assessment and were therefore not summarized.

Baseline Characteristics of Trial Patients – Suboptimum Responders to Methotrexate

Of the 171 patients who entered the trial conducted by O'Dell et al., 92 patients (53%) were considered suboptimum responders to methotrexate at enrolment, defined as patients who continued to have active disease despite treatment with oral methotrexate at a dosage of 17.5 mg per week; 79 patients who enrolled in the trial were methotrexate-naive. Among suboptimum responders to methotrexate, 33 patients received treatment with methotrexate and hydroxychloroquine, 28 patients received methotrexate and sulfasalazine, and 31 patients received all three csDMARDs (methotrexate in combination with hydroxychloroquine and sulfasalazine).

O'Dell et al. further reported that the distributions of age, disease duration, rheumatoid factor positivity, sex, and steroid usage were roughly balanced across treatment groups in the intention-to-treat trial population; however, it was not reported whether baseline characteristics of suboptimum responders to methotrexate were balanced at baseline.

Efficacy – Suboptimum Responders to Methotrexate

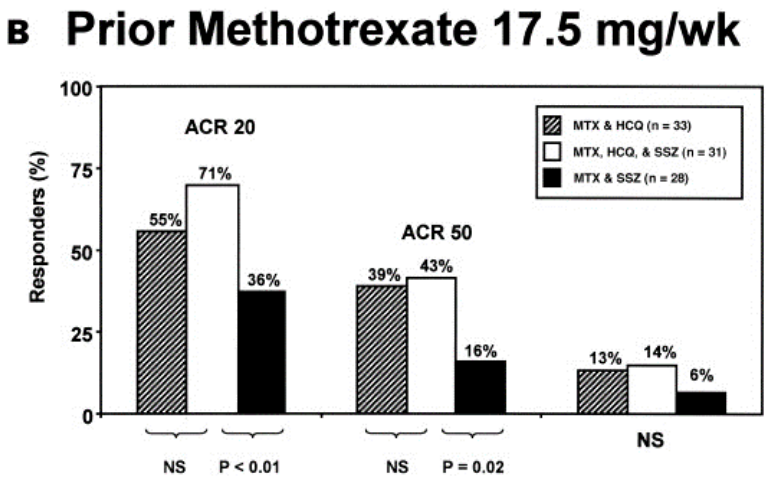
For the primary end point (i.e., percentage of patients who achieved a 20% response to therapy according to ACR improvement criteria), 71% of suboptimum responders to methotrexate treated with triple csDMARDs (methotrexate in combination with hydroxychloroquine and sulfasalazine) achieved an ACR 20 response at two years, compared with 55% of patients treated with methotrexate and hydroxychloroquine, and 36% of patients treated with methotrexate and sulfasalazine.

For the secondary ACR response end points, there were a total of 43% and 14% of patients treated with triple csDMARDs who achieved ACR 50 and ACR 70 response, respectively. Of those treated with methotrexate plus hydroxychloroquine, 39% achieved ACR 50 and 13% achieved ACR 70. This trend was similar but less pronounced for patients treated with methotrexate plus sulfasalazine, with 16% of patients having achieved ACR 50 response and 6% who achieved ACR 70.

Overall, findings revealed that more patients responded to the triple csDMARD therapy than to either of the double csDMARD combinations. This difference reached statistical significance in favour of triple therapy compared with methotrexate with sulfasalazine for ACR 20 and ACR 50 responses in patients who entered the trial as suboptimum responders to methotrexate. No statistically significant difference was found between triple csDMARD therapy and combination therapy with methotrexate and hydroxychloroquine for any of the three ACR outcomes.

Figure 1 provides a graphical representation of results regarding ACR response at two years for suboptimum responders to methotrexate, as reported by O'Dell et al.[10]

Figure 1: ACR 20, ACR 50, and ACR 70 responses at two years for suboptimum responders to methotrexate therapy



HCQ = hydroxychloroquine; MTX = methotrexate; NS = not significant; SSZ = sulfasalazine.

Reprinted from Arthritis & Rheumatology, Vol 46 (5), 1164-70. O'Dell J, Leff R, Paulsen G et al. Treatment of rheumatoid arthritis with methotrexate and hydroxychloroquine, methotrexate and sulfasalazine, or a combination of the three medications: results of a two-year, randomized, double-blind, placebo-controlled trial. Copyright (2002), with permission from Wiley.

Safety – Suboptimum Responders to Methotrexate

O'Dell et al. reported that a total of 14 patients withdrew from this trial due to adverse events, and that these patients were evenly distributed among the three treatment groups (five patients from the methotrexate and sulfasalazine group, five patients from the methotrexate and hydroxychloroquine group, and four patients from the group that received triple therapy). However, these data were not reported for the subset of patients who were considered suboptimum responders to methotrexate.

Critical Appraisal of Trial Under Review

Validity of Outcomes

American College of Rheumatology Response Criteria

The ACR criteria for assessing joint status was initially developed for patients with RA.[11] ACR criteria provide a composite measure of improvement in swollen and tender joint counts and at least three of five additional disease criteria:

- patient global assessment of disease activity
- physician global assessment of disease activity
- patient assessment of pain
- health assessment questionnaire (HAQ)
- levels of either C-reactive protein (CRP) or ESR.

The ACR joint count for RA assesses 68 joints for tenderness and 66 joints for swelling. Patient and physician assessments are conducted using visual analogue scale or Likert scale measurements. ACR 20, 50, or 70 responses represent at least a 20%, 50%, or 70% improvement, respectively, in tender and swollen joint counts as well as in three of the five additional core measures listed above. This core set of measures included in the ACR response criteria was established through a consensus process of clinical experts. Individual criteria were selected based on their construct validity, face validity, content validity, criterion validity, and discriminant validity.[12] In the assessment of criterion validity, standards for comparison included death, physical disability, and radiologic evidence of joint damage. It was considered that physical functioning capacity was a strong predictor of mortality as measured by the HAQ and that many other risk factors for premature mortality were insignificant after adjusting for functional capacity. Predictors of radiographic progression included swollen joint counts and levels of acute phase reactants such as ESR and CRP.[12] When considering the ability of an outcome measure to detect change, pain assessments, global assessments, tender joint counts, and HAQ scores all had strong discriminant validity.

While the ACR response criteria are seldom used in clinical practice, the ACR 20 is most commonly used as the primary end point in randomized controlled trials evaluating treatments for RA. The US FDA considers ACR 20 a well-validated composite end point for assessing the signs and symptoms of rheumatoid arthritis, as noted in guidance provided to industry on the conduct of trials in patients with RA.[13] ACR 50 and ACR 70 are often reported in clinical trials and are considered more stringent outcome measures.

Chung et al.[14] conducted a meta-analysis of 21 randomized controlled trials of RA therapies published between 1997 and 2004 to compare the discriminant capabilities of the ACR 50 and ACR 20 responses and to determine whether ACR 50 is as informative as ACR 20 in distinguishing between active therapies and control groups. While both measures could distinguish an active therapy compared with a control therapy, the levels of improvement captured by ACR 20 response did not generally represent an optimal clinical improvement. Furthermore, since the development of the ACR 20 response criteria, much more aggressive therapies have become available for RA treatment and larger clinical responses can be expected. This meta-analysis concluded that ACR 20 and ACR 50 are similar in distinguishing between active and control therapies but that ACR 50 represents a more robust clinical response and may be a preferred end point in clinical trials.[14]

ACR 70 is considered even more rigorous than ACR 50. It is a component of the definitions established by the FDA in order to satisfy labelling requirements for RA drugs. Specifically, a "major clinical response" as defined by the FDA refers to a statistically significant increase in the proportion of patients achieving an ACR 70 response, maintained over six months, with active therapy compared with the control group.[13]

With widespread use of the ACR criteria in clinical trials over the past 20 years, some limitations have been identified. For example, while ACR response indicates the change from baseline, it does not indicate the final level of disease severity that the patient attains. This limitation also means that patients who are classified as ACR responders could have very different levels of disease activity.[15] Other criticisms of the ACR criteria include the subjective nature of most of its component measures, that dichotomous measures such as ACR lack sensitivity to change compared with continuous measures of response, and that the ACR 20 response threshold is too low relative to treatment goals applied in clinical practice (e.g., remission or low disease activity).[16] The relevance of this measure to clinical practice is therefore limited. In response to these criticisms, attempts have been made to develop improved outcome measures for RA, although none have achieved widespread acceptance nor have been used consistently in clinical trials.[16,17]

Internal Validity

O'Dell et al. conducted a well-designed trial which addressed an appropriate and clearly focused question. The assignment of patients was randomized; although randomization was handled at a single off-site location and designed to be blocked for every six patients (to ensure balance in sample size across treatment groups over time), the randomization method was not specified. Allocation concealment was adequately performed using sequentially numbered envelopes that were opened as patients were enrolled, and the design of the trial kept study patients, investigators, and outcome assessors blinded to treatment allocation. The only difference between treatment groups appeared to be the csDMARD combination regimens under investigation, and all relevant outcomes were measured in a standard, valid, and reliable way. Although enrolment occurred at seven member centres of the Rheumatoid Arthritis Investigational Network in the US, it is unclear whether results were comparable for all sites as no site-specific data were reported. All study patients were analyzed in the groups to which they were randomly allocated, and the last observation carried forward method was used to impute any missing data.

Despite numerous strengths in the overall design of this trial, several factors may limit the internal validity of findings concerning the subgroup of patients who were suboptimum responders to methotrexate. First, it was unclear if subgroup analyses were pre-specified or undertaken after the study results were obtained. Second, O'Dell et al. did not report a sample size calculation or any other scientific parameter to justify the number of patients recruited in the trial; therefore, it is uncertain whether this study had sufficient power to detect a statistically significant or clinically relevant difference between treatments among suboptimum responders to methotrexate. The risk of type II error therefore cannot be ruled out among this subgroup. It was also unclear if there were any clinically relevant differences in factors that may have influenced the outcomes measured in suboptimum responders to methotrexate. Although the characteristics of the study patients were balanced across treatment groups in the full trial population, the study authors did not report whether treatment groups among suboptimum responders to methotrexate were similar at the start of the trial. Additionally, the rate of dose escalation of methotrexate and sulfasalazine used in the trial may be lower than that used in current clinical practice; however, it is unlikely that

this would bias the results since all patients were managed in exactly the same way. Finally, it is not known whether randomization was preserved among suboptimum responders to methotrexate due to the high rate of attrition in this study. Specifically, O'Dell et al. reported that a total of 74 (43.4%) patients were lost to follow-up before the end of the two-year study; of these 74 patients, 49 (66.2%) discontinued the study due to lack of efficacy. The investigators did not, however, report the proportion of patients lost to follow-up who were suboptimum responders to methotrexate. The distribution of study withdrawal and reasons for withdrawal across treatment groups in methotrexate-suboptimum responders was also not reported. Although missing data were accounted for in the analysis by carrying forward the last observation for each missing data point, any differences between suboptimum responders who were lost to follow-up and those who continued the study may have influenced the treatment response observed in this subgroup. The magnitude of effect of attrition bias on the outcomes of this subgroup remains unknown in the absence of an analysis of the per-protocol population or other sensitivity analyses.

External Validity

The generalizability of findings from this trial to Canadian clinical practice may be limited by several important factors. Most notably, patients who were enrolled in this trial as suboptimum responders to methotrexate may not reflect patients who do not respond adequately to methotrexate administered in Canadian clinical practice. This is because suboptimum responders were specifically defined in this trial as persons who had active disease despite treatment with a maximum dosage of 17.5 mg oral methotrexate per week; yet, the maximum dosage of oral methotrexate administered in Canadian clinical practice may be up to 25 mg per week. It is therefore unclear whether suboptimum responders to methotrexate observed in Canadian practice would experience a similar response to combination treatment with csDMARDs as those who were enrolled in this trial. While the rate of dose escalation for methotrexate and sulfasalazine does not pose any threat to the study's internal validity (since all patients were identically managed), dose escalation for these medications occurs more rapidly in current clinical practice. Additionally, since O'Dell et al. did not report the baseline demographics and disease characteristics of suboptimum responders to methotrexate, it is difficult to determine whether this subgroup is generally representative of patients in Canadian clinical practice in whom methotrexate has previously failed, despite the possible demographic, geographical, and socioeconomic similarities between the full trial population and the target population. The applicability of study findings to routine practice in Canada may also be limited owing to the trial's strict eligibility criteria (e.g., no stage IV disease, no comorbidities, no current pregnancies, strict treatment doses) and the highly controlled nature of the study which may not reflect typical patient behaviour (e.g., above-average adherence to therapy).

The choice of outcome measures used in this trial may also limit its external validity. Namely, ACR criteria are commonly used to measure disease response in clinical trials, yet, ACR response is seldom measured in Canadian clinical practice. While it may be argued that the ACR 50 response usually mimics low disease activity and that ACR 70 mimics clinical remission, the association between these criteria and achievement of treatment goals is uncertain. Accordingly, ACR response criteria may not reflect the main goal of treatment in patients with RA (i.e., remission or low disease activity) and may not adequately address what is most important to patients (e.g., patient-reported outcomes such as pain, fatigue, health-related quality of life).

Interpretation of Results

O'Dell et al. conducted a double-blind RCT which assessed the comparative efficacy of three csDMARD combination therapies: methotrexate and hydroxychloroquine; methotrexate and sulfasalazine; and methotrexate in combination with hydroxychloroquine and sulfasalazine. Study patients were stratified according to prior methotrexate therapy at randomization; 92 (53.8%) patients (out of 171 in the intention-to-treat population) were classified as suboptimum responders to methotrexate and entered the study at a dose of 17.5 mg of oral methotrexate. Efficacy outcomes were reported based on the ACR 20, ACR 50, and ACR 70 response rates, and findings among suboptimum responders to methotrexate revealed that more of these patients responded to triple csDMARD therapy than to either of the double csDMARD study drug combinations. This difference reached statistical significance in favour of triple therapy compared with methotrexate with sulfasalazine for ACR 20 and ACR 50 responses, while no statistically significant difference was found between the triple csDMARD therapy and methotrexate with hydroxychloroquine for any of the three ACR outcomes. However, these results should be carefully interpreted given the uncertainty regarding whether subgroup analysis was prespecified, the lack of a sample size calculation for the studied population and the subgroup of interest, the potential imbalance in baseline characteristics among patients who were suboptimum responders to methotrexate, and the high proportion of patients who withdrew from the study before the end of the two-year follow-up period. Information regarding the comparative safety of triple csDMARDs versus double csDMARDs among suboptimum responders to methotrexate was not provided by O'Dell et al.

The applicability of study findings to patients with RA in Canadian clinical practice may also be limited as a result of the way O'Dell et al. defined suboptimum response to methotrexate (i.e., persons with active disease despite treatment with maximum weekly dose of 17.5 mg oral methotrexate), uncertainty regarding the subgroup's demographics and disease characteristics at study entry, the highly controlled nature of the study, and the choice of outcome measures which may not reflect treatment goals or patient preferences regarding treatment. Furthermore, response to csDMARD combination therapy in patients with moderate to severe RA who are intolerant to methotrexate is not known since these patients were not enrolled in this study.

Summary and Conclusion

One randomized controlled trial was identified that assessed the comparative clinical efficacy of triple therapy versus double therapy with csDMARDs in patients with moderate or severe RA.[10] However, in this trial, treatment response in patients for whom methotrexate had previously failed was evaluated in a subgroup analysis, and patients who were intolerant to methotrexate were not enrolled. The comparative safety of csDMARD combination regimens was not assessed in this trial and remains unknown in this patient population. Combination therapy which includes leflunomide was also not included in this trial; therefore, the efficacy and safety of leflunomide-containing combination therapy compared with other csDMARD combination regimens is unknown.

The results of this trial suggest that in patients considered suboptimal responders to methotrexate, triple csDMARD therapy may be more efficacious than double csDMARD therapy based on ACR response. However, these results are associated with several limitations, and the paucity of similar studies preclude the ability to draw any well-founded conclusions for patients with RA who have failed or are intolerant to methotrexate. Well-designed, prospective, randomized studies with an adequate sample size, follow-up period, and adapted for the Canadian setting are needed to address this evidence gap.

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Correction

In the original report published in January 2020, an author's name was omitted.

The third author's name has been added on page 2 of this version of the report.