TITLE: Safety of Leflunomide and Methotrexate as Combination Therapy for Rheumatoid Arthritis: A Review of the Clinical Evidence

DATE: 10 May 2011

CONTEXT AND POLICY ISSUES

Rheumatoid arthritis (RA) is a long-term disease which is characterized by the inflammation of the joints and surrounding tissues, which if not treated, leads to structural damage and long term disability. Methotrexate (MTX) and leflunomide (LEF) have been commonly used as monotherapy in the treatment of RA as well as many other disease-modifying antirheumatic drugs (DMARD).

MTX is a folate antagonist and its immunosuppressive activity may be a result of inhibition of lymphocyte multiplication.¹ Its mechanism of action in the management of rheumatoid arthritis is not known, although suggested mechanisms have included immunosuppressive and/or anti-inflammatory effects.¹ LEF is an isoxazole immunomodulatory agent which inhibits de novo pyrimidine synthesis and has antiproliferative activity.² While the mechanism of action of LEF and MTX are different, their pharmacodynamic action on cell division interference is similar; therefore their combined use might potentially lead to hepatic toxicity and haematopoiesis suppression.²

Kremer et al.³ investigated the potential efficacy of this combination and found that the combination therapy with LEF and MTX provides statistically significant clinical benefit in patients with active RA who are receiving MTX therapy. The product monograph for LEF contraindicates the coadministration with other hepatotoxic drugs including MTX.²,³ In September 2010, the U.S. Food and Drug Administration (FDA) issued a boxed warning regarding the liver injury that can be induced by LEF and recommended stopping the medication, if alanine transaminase (ALT) elevation > 3 fold upper limit of normal (ULN) occurs.⁴ This report was undertaken to summarize the evidence on the safety of combination therapy with LEF and MTX.
RESEARCH QUESTION

What is the evidence regarding the safety of LEF and MTX as combination therapy in adults with rheumatoid arthritis?

KEY MESSAGE

The available evidence related to the safety of combination therapy with LEF and MTX in patients with RA is limited and inconclusive. There is some suggestion of increased risk of abnormal liver function with LEF and MTX combination therapy.

METHODS

A limited literature search was conducted on key resources including PubMed, Ovid EMBASE, The Cochrane Library (2011, Issue 3), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population and conference abstracts were excluded from the search results. The search was also limited to English language documents published between January 1, 2006 and April 11, 2011.

SUMMARY OF FINDINGS

The literature search identified two systematic reviews examining the efficacy and toxicity of combination therapy of MTX and non-biologic DMARD compared to either LEF or MTX alone. Five relevant non-randomized studies were identified, one of which was included in the above systematic review, and the remaining four are reviewed in this report.

No relevant health technology assessment reports and randomized controlled trials (RCTs) were identified. Additional articles of interest are listed in the appendix.

Systematic reviews and meta-analyses

The characteristics of the systematic reviews are summarized in table 1. The safety outcome, author’s conclusions and limitations of the systematic reviews are summarized in table 2.

The systematic review by Katchamart et al. included 19 RCTs of which only one RCT compared DMARDS relevant to the research question of this report. In this RCT, of 24 weeks duration, patients received LEF (10 mg/day after loading dose) versus placebo while continuing MTX (15 to 20 mg/week). The outcome measures were efficacy, toxicity and withdrawal rate.

The systematic review by Osiri et al. included 33 trials (RCTs and controlled clinical trials) of which six trials compared the combination of LEF and MTX versus either as a monotherapy. Exposure duration on MTX and LEF was between 24 weeks and 36 months. The major endpoints analyzed were improvement of clinical outcomes [as defined by the American College of Rheumatology (ACR) or the European League against Rheumatism (EULAR)], improvement of the patients’ Health Related Quality of Life (HRQoL) and incidence of side effects. A greater number of RA patients taking LEF and MTX met the ACR 20, ACR 50 and ACR 70 criteria compared to MTX alone; furthermore, these patients had improved swollen
and tender joints counts, improved Health Assessment Questionnaire (HAQ) scores and reduction in pain at 24 weeks.

The safety data were stratified by DMARD combination and pooled across trials for each combination. The safety results in these systematic reviews are conflicting in regards to the liver function abnormalities. This can be explained by the variety of study design and heterogeneity of the population included.

Table 1: Characteristics of systematic reviews comparing the efficacy and safety of DMARDs including concomitant LEF and MTX versus either as a monotherapy.

<table>
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<tr>
<th>Systematic reviews</th>
<th>Objectives</th>
<th>Search strategy</th>
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<td>Katchamart et al 2010&lt;sup&gt;6&lt;/sup&gt;</td>
<td>To compare the efficacy and toxicity of MTX monotherapy with MTX and DMARDs combination in adults with RA.</td>
<td>Searched MEDLINE (1950 to 2009), EMBASE (1980 to 2009), the Cochrane Controlled trials Registry (CENTRAL) (up to 2009), the American and European scientific meeting abstracts 2005-9. Search methods well described, all languages were included</td>
<td>Randomized controlled trials comparing MTX monotherapy versus MTX combined with other non-biologic DMARDs of at least 12 weeks of trial duration in adult RA patients.</td>
<td>19 RCTs were selected representing 10 combinations; 1RCT compared the combination MTX and LEF vs MTX alone</td>
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<td>Osiri et al. 2010&lt;sup&gt;5&lt;/sup&gt;</td>
<td>To assess the efficacy and toxicity of LEF monotherapy or combined with another DMARD compared to placebo or DMARDs in adults with RA</td>
<td>Searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library), MEDLINE, EMBASE, Current Contents for trials (to June 2008), handsearched reference lists and consulted content experts</td>
<td>All randomized controlled trials (RCTs) or controlled clinical trials (CCTs) comparing LEF as monotherapy or in combination with another DMARD to placebo or other DMARDs. Studies comparing LEF at a dose of 20</td>
<td>Of the included 33 trials, 4 trials compared combined LEF and MTX with MTX alone; 2 trials compared the combination to LEF alone</td>
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**Systematic reviews** | **Objectives** | **Search strategy** | **Selection criteria** | **Included studies**
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| | to 25 mg/day with placebo or other DMARDs. | Duration of treatment in the trials must have been at least three months |

DMARDs: disease modifying antirheumatic drugs; LEF: leflunomide; MTX: methotrexate

**Table 2: Outcome, conclusion and limitations**

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<th>Systematic Reviews</th>
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<th>Author’s Conclusions</th>
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<td>Katchamart et al 2010&lt;sup&gt;6&lt;/sup&gt;</td>
<td>The incidence of adverse events was similar in MTX and LEF combination and MTX monotherapy groups. (RR [95% CI] = 1 [0.94 to 1.08]) Compared with MTX monotherapy, MTX and LEF combination significantly increased the risk of gastrointestinal adverse events (RR [95%CI] = 1.67 [1.17 to 2.4]) Compared to MTX monotherapy, MTX and LEF combination significantly increased the risk of abnormal liver function (RR [95%CI] = 4.3 [2.58 to 7.15]) Compared with MTX monotherapy, there was no significant difference in the risk of infection with MTX and LEF combination (RR [95% CI] = 0.79 [0.6 to 1.02])</td>
<td>LEF combined with MTX for MTX non-responders improved efficacy but increased the risk of gastrointestinal adverse events and liver toxicity</td>
<td>Quality assessment performed but not reported in details The validity of trials included was not reported There were different regimens of combination therapies selected and only one clinical trial studied the combination LEF and MTX; data could not be compared to other studies because they had different combinations</td>
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<td>Osiri et al. 2010&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Compared with MTX monotherapy, there was no significant difference in withdrawal rates with MTX and LEF combination at both 24</td>
<td>Overall, MTX and LEF combination is more effective than MTX alone. Adverse events were reported more</td>
<td>Patient characteristics and baseline disease severity differed in the trials included. There is a potential of...</td>
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<td>Systematic Reviews</td>
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<td>months (RR [95%CI] = 1.25 [0.52 to 3.01] and 36 months (RR [95%CI] = 0.75 [0.39 to 1.43]).</td>
<td>frequently for combined therapy than for MTX alone but withdrawal rates were not significantly different.</td>
<td>bias as some trials are open-label extension studies. Different doses of MTX were used in the studies selected. Quality of the trials appears to be assessed by the Jadad scale although not all were RCTs. It is unclear why this method was used</td>
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<td>Compared with MTX monotherapy, there was no significant difference in withdrawal rates due to adverse event with MTX and LEF combination at both 24 months (RR [95% CI] = 1.40 [ 0.46 to 4.23 ]) and 36 months (RR [95%CI] = 0.86 [0.41 to1.81]).</td>
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<td>Subgroup analysis for treatment during 24 to 48 weeks. Group 1: patients who were on (placebo+MTX) up to 24 weeks then switched to (MTX+ LEF) and continued with (MTX+LEF) up to 48 weeks. ([placebo+MTX] →[MTX+LEF])</td>
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<td>Group 2: patients who were on (LEF+ MTX) up to 24 weeks then continued on the same treatment up to 48 weeks. ([MTX+LEF] → [MTX+LEF])</td>
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<td>- Adverse events were more frequently observed in patients in Group 1 than in Group 2. These include diarrhea (RR [95%CI] = 5.33 [1.61 to 17.71]) and alopecia (RR [95%CI] = 8.0 [1.02 to 62.74])</td>
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<td>- The risk of nausea, skin rash infection as well as elevated liver enzymes was not significantly different in the two treatment groups</td>
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<td>- Serious adverse events were not significantly different between the two treatment groups (RR [95%CI] = 0.87 [0.44, 1.72])</td>
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CI: confidence interval; LEF: leflunomide; MTX: methotrexate; RR: relative risk.
Non-randomized studies

Curtis et al 2010\(^8\) conducted a cohort study using the Consortium of Rheumatology Researchers of North America (CORRONA) data base to determine the relationship between the use of DMARD medication and the incidence of ALT and aspartate transaminase (AST) elevations. The funding sources were the Doris Duke Charitable Foundation and the National Institutes of Health. The study included 9,755 adult patients with RA and 1,108 adult patients with psoriatic arthritis (PsA) receiving care in community and academic settings across the US. The observation period was extended through April 1\(^{st}\), 2007. The primary outcome was elevation of ALT\(\times 2\)/or AST > upper limits of normal (ULN) and the secondary outcome was elevation of AST and/or ALT > 2x ULN. Patients were receiving MTX, LEF (10 or 20 mg/day), both in combination or other non biologic DMARD combinations. The observation time began after initiation of any new DMARD. This study included patients with confirmed diagnosis of RA and PsA, currently on treatment with non biologic DMARD or anti-TNF and with normal ALT and AST levels at baseline. Patients with concomitant diagnoses of RA and PsA were excluded.

The authors found that in RA patients, the incidence of ALT or AST abnormalities were greater in patients receiving MTX and LEF combination; 31% for AST or ALT > 1x ULN and 5% for ALT or AST > 2x ULN versus respectively 17% and 2% for patients on LEF alone and 22% and 1% for patients on MTX alone. The data showed an increased incidence of abnormal liver function test for treatment with combined MTX and LEF compared with MTX alone; the increase being two to five-fold depending on the MTX dose.

Sensitivity analysis revealed that a synergistic effect of combination MTX and LEF is a factor that could be associated with AST or ALT elevations; other factors could be a past history of liver disorder and daily alcohol use. Depending on the dose of MTX, combination MTX and LEF was associated with greater risk of abnormal liver function, compared with MTX monotherapy as indicated by the odds ratio (OR) and confidence interval (CI): OR (95% CI) = 2.91 (1.23 to 6.90) with MTX = 10-17 mg/week and OR (95%CI) = 3.98 (1.72 to 9.24) with MTX ≥ 20 mg/week.

This study suggested an increased risk of toxicity with combination therapy. The study included a large number of patients treated with DMARDS but the numbers of patients specifically receiving LEF, MTX or (LEF+MTX) were not reported. The duration of the observation period was not clearly mentioned however, the authors provided information on the mean number of follow-up visits at which liver enzyme tests were performed: mean ± standard deviation for combination LEF and MTX was (2.3 ± 1.1), MTX alone was (2.1 ± 1.0) and LEF alone was, (2.2 ± 1.0). The mean time between two visits at which liver function tests were performed was approximately 5 months. Data regarding the incidence of elevated enzyme were collected for patients with at least one follow up visit and data used in the sensitivity analysis were collected for patients with at least 2 to 3 follow up visits.

Lee et al. (2009)\(^9\) conducted an open-label, non-comparative, multicenter trial to evaluate the efficacy and safety of the combination of LEF and MTX for the treatment of patients with active RA. A total of 74 adult patients (60 women and 14 men) were included in the study to receive concomitantly LEF at the dosage of 10 mg/day without loading dose and MTX starting at 7.5 mg/week and titrating up to 15 mg/week. The study was conducted in five centres in republic of Korea. Safety assessment included haematology and liver function tests.
In this study, the withdrawal rate was 12.1%; reasons for withdrawal were adverse events, consent withdrawal, lack of efficacy, lost to follow-up and poor compliance. Overall, 40.5% of patients experienced one or more adverse events; the most common were liver function abnormalities gastritis, headache and nasopharyngitis. The authors found that infections were relatively uncommon in this study. The incidence of elevated transaminases (AST and/or ALT > 1.2x ULN) was 21.6%; 13.5% of patients showed an increased AST level and 20.3% of patients showed an increased ALT level.

The authors concluded that based on their data, the combination therapy of LEF and MTX is effective and can be used with careful monitoring. They recommend to start patients on LEF at a dose of 10 mg/day without loading dose and to avoid the combination therapy in patients with known hepatic disease.

The study is limited by the small sample size. There may be potential of bias as it is an open-label study. This study was funded by Aventis Pharma Korea, the manufacturer of Arava®.

Kaul et al. (2008)\textsuperscript{10} conducted a case note review in four centres in the UK with 108 adult patients with a diagnosis of inflammatory arthritis, taking the combination therapy MTX and LEF for at least six months and no other DMARD; among these patients 86 had a diagnosis of RA. The objective of this study was to evaluate the tolerability of the combination therapy (MTX and LEF) in routine clinical practice. In this study, the withdrawal rate was 49% with a mean time to discontinuation of 10.9 months (median 7.3 months, range 1-45 months) and based on statistical analysis, the authors expected that 50% of the patients would remain on therapy after 36 months. Causes for discontinuation were nausea, vomiting and diarrhea (28.8%); abnormal liver function test (11.5%); lack of efficacy (11.5%); haematological problems (1.9%); rash (9.6%); mouth ulcers (1.9%); alopecia, hypertension, facilitating conception and undefined malaise (11.5%).

The authors found that the combination therapy MTX and LEF is well tolerated by a majority of patients. Most withdrawals were due to reversible adverse events with no evidence of serious hepatotoxicity. This study is limited by the small sample size. There may be potential of bias as it is an open-label study. The source of funding of the study was not reported.

Dendooven et al. 2006\textsuperscript{11} examined the rate of continuation with treatment of LEF with or without concomitant MTX treatment in a cohort study conducted in Belgium. A total of 60 adult patients with RA were included in this study of whom 20 were given LEF monotherapy (20 mg/day) with a loading dose of 100 mg/day for three days; 40 patients received concomitant MTX from the start and, at different doses. The duration of the follow-up period was 30 months. At the end of the follow-up period, 65% of the patients on combination therapy were still on their treatment versus 55% of patients on LEF monotherapy. During this study, the majority of patients remained at a stable dosage of LEF whereas the dosage of MTX was reduced in 35% of patients and MTX was stopped in 27.5% of patients. The overall discontinuation rate because of adverse event was 15% and the number and nature of adverse events were comparable in both groups. The authors concluded that the combination therapy was useful in the treatment of RA in daily practice. The study is limited by small sample size. There may be potential of bias as it is an open-label study. The source of funding for the study was not reported.
Limitations

The literature search did not identify any relevant health technology assessment reports or any randomized controlled trials. The systematic reviews identified, compared different regimens of combination therapies with the DMARDs available. The findings of these analyses were affected by the limitations of the included studies, which were often non-randomized studies with various study designs and it was difficult to adequately assess safety concerns. Most of the non-randomized studies had small sample sizes. There may be potential of bias as they were open-label studies.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

The evidence is limited and definitive conclusions are not possible. From one RCT in a systematic review on DMARDs and one non-randomized study on DMARDs there is a suggestion of increased risk of abnormal liver function for treatment with combination of LEF and MTX. Good quality, long-term trials are needed to determine the safety of LEF and MTX combination therapy.

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References


APPENDIX

Additional information


