# Double-Blind, Randomized, Controlled, Pilot Study Comparing Classic Ayurvedic Medicine, Methotrexate, and Their Combination in Rheumatoid Arthritis

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**Objective:** To compare classic Ayurveda, methotrexate (MTX), and their combination in a double-blind, randomized, double-dummy, pilot trial in rheumatoid arthritis (RA) for 36 weeks.

**Methods:** Forty-three seropositive RA patients by American College of Rheumatology (ACR) criteria with disease duration of less than 7 years were assigned to the following treatment groups: MTX plus Ayurvedic placebo (n = 14), Ayurveda plus MTX placebo (n = 12), or Ayurveda plus MTX (n = 17). Outcomes included the Disease Activity Score (DAS28-CRP), ACR20/50/70, and Health Assessment Questionnaire – Disability Index. All measures were obtained every 12 weeks for 36 weeks. Analyses included descriptive statistics, analysis of variance, $\chi^2$, or Student *t* test. The unique features of this study included the development of placebos for each Ayurvedic pharmacological dosage form and individualization of Ayurvedic therapy.

**Results:** All groups were comparable at baseline in demographics and disease characteristics. There were no statistically significant differences among the 3 groups on the efficacy measures. ACR20 results were MTX 86%, Ayurveda 100%, and combination 82%, and DAS28-CRP response were MTX −2.4, Ayurveda −1.7, and combination −2.4. Differences in adverse events among groups were also not statistically significant, although the MTX groups experienced more adverse event (MTX 174, Ayurveda 112, combination 176). No deaths occurred.

**Conclusions:** In this first-ever, double-blind, randomized, placebo-controlled pilot study comparing Ayurveda, MTX, and their combination, all 3 treatments were approximately equivalent in efficacy, within the limits of a pilot study. Adverse events were numerically fewer in the Ayurveda-only group. This study demonstrates that double-blind, placebo-controlled, randomized studies are possible when testing individualized classic Ayurvedic versus allopathic treatment in ways acceptable to western standards and to Ayurvedic physicians. It also justifies the need for larger studies.

**Key Words:** Ayurvedic, methotrexate, rheumatoid arthritis, controlled trial

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Rheumatoid arthritis (RA) is a chronic, immune-mediated, systemic disease that causes a great deal of pain and suffering.[1] Although there have been significant advances, treatment remains unsatisfactory for many patients.[2] At present, methotrexate (MTX), which is a basic DMARD therapy for RA, achieves a response in 40% to 60% of patients,[3] representing a gratifying but not satisfactory outcome. Further, MTX is associated with distressing and potentially serious adverse effects. Consequently, as surveys indicate, 68% to 94% of RA patients use complementary and alternative medicine (CAM) therapies, including Ayurveda.[4] As documented in the media, an increasing number of RA patients from the West make the journey to India to undergo complete classic Ayurvedic treatment.[5,6]

The pathogenesis and treatment of rheumatic diseases described in ancient Ayurvedic texts from 1500 BC show remarkable similarities to modern descriptions of RA features.[7] Ayurveda is a 3000-year-old medicine system, which has been recognized by the World Health Organization as a complete system of natural medicine, and is used by millions. It is a holistic, multifaceted system of treatment which includes complex herbal-mineral combinations, dietary and lifestyle modification, oil therapies, and detoxification routines. Herbal-mineral formulations, which form the core of classic Ayurvedic treatment, include thousands of formulas in a variety of dosage forms to treat more than 200 diseases.[8]

Placebo-controlled trials of classic Ayurveda are necessary to establish whether it is effective, and this trial method will provide the basis for a meaningful comparison with allopathic treatment. Although a literature search on PubMed[9] yielded 61 clinical trials of Ayurvedic medicine, there are no randomized clinical trials (RCTs) of classic Ayurvedic treatment as a system of care[10] or any that used placebos for the traditional Ayurvedic pharmacological dosage forms so as to allow individualization of therapy as required by this system of care.

There is 1 published study of complete classic Ayurveda. It is an unblinded 7-year World Health Organization–sponsored study of 240 RA patients.[11,12] Although this was not an RCT, its results were positive enough to warrant exploration of classic Ayurvedic treatment of RA.

Well-controlled double-blind studies of classic Ayurveda have been difficult to conduct because of the lack of placebos for its traditional, individually varied, pharmacological dosage forms and its therapies. For the first time, in this study, 6 placebos, appearing identical to the traditional pharmacological dosage forms for classic Ayurvedic treatment of RA, were developed and dispensed, including powders, liquids, pills, jams, and oils.

The primary objective of this pilot study was to compare the efficacy of outpatient classic Ayurvedic treatment versus

conventional allopathic treatment using MTX, or their combination, for RA in a randomized placebo-controlled 36-week study. All Ayurvedic formulations were based on classic texts of Ayurveda.

## PATIENTS AND METHODS

The Indian government and the ethical review boards of the University of Washington, the University of California in Los Angeles, and the Ayurvedic Trust approved the pilot study protocol. All patients provided voluntary, written, informed consent before enrollment in the study.

### Patients

Patients were recruited in Coimbatore, India, through advertising in the local media. They were screened for eligibility at the Ayurvedic Trust by the designated allopathic physician (P.G.S.), who documented their RA diagnosis by American College of Rheumatology (ACR) criteria and evaluated their responses.

Eligible patients were older than 18 years; had a history of RA symptoms for less than 7 years; had RA by ACR criteria; were ACR functional RA class I, II, or III; had hemoglobin level more than 8 g/dL without evidence of active bleeding; and were positive for rheumatoid factor (RF) or anti–cyclic citrullinated protein at study entry. Acetaminophen and nonsteroidal anti-inflammatory drug within the approved dosage regimens were allowed. Patients were asked to keep their dosing regimens of these drugs stable or use them as little as possible if used intermittently.

Exclusion criteria included other connective tissue diseases, previous treatment with greater than 6 weekly doses of methotrexate at any dose, joint trauma within 1 year, complete classic Ayurvedic treatment within 1 year or over-the-counter Ayurvedic medicines within 1 month, enrollment in another clinical study within 3 months, intra-articular corticosteroid injections within 2 months, oral corticosteroids, disease-modifying drugs (e.g., hydroxychloroquine, sulfasalazine, azathioprine) within 1 month, leflunomide in the past 4 months, chronic infections or infections requiring antimicrobial therapy within 1 month, or biologic agents such as adalimumab, anakinra, etanercept, or infliximab within 3 months. Also excluded were those with poorly controlled diabetes or hypertension; with active or chronic hepatitis; with active, unresolved, or previous chronic liver disease (serum alanine aminotransferase and/or total bilirubin >2 times above the laboratory upper limit of normal); with cardiac failure (New York Heart Association classification stage III or IV); with history of cancer or lymphoproliferative disease in the past 5 years (exception: history of basal or squamous cell carcinoma, free of cancer for at least 1 year after carcinoma in situ); with active tuberculosis; with congenital or acquired immunodeficiency (including human immunodeficiency virus); with serum creatinine more than 1.5 times laboratory ULN; white blood cell count less than 3000/mL; platelet count less than 100,000/mL, requiring more than 4 g of acetaminophen or daily dose of nonsteroidal anti-inflammatory drug greater than that approved for the treatment of RA; and pregnant or lactating. Other exclusion criteria included compromised ability to absorb, metabolize, or excrete study medications; history of recent drug or alcohol abuse; life expectancy of less than 2 years for any reason; noncompliance; and any condition that would prevent them from giving voluntary, fully informed consent.

### Study Design

Eligible RA patients were randomized in a 1:1:1 ratio as follows: group 1, MTX verum plus placebo Ayurveda; group 2, verum Ayurveda plus MTX placebo; and group 3, MTX verum plus verum Ayurveda. The treatment duration was set at 36 weeks because the Ayurvedic physicians felt that it might take that long for the outpatient Ayurvedic treatment's effects to become evident. Because clinical trials using disease-modifying antirheumatic drugs typically have study durations of 6 months, we report results for 24 weeks as well.

Patients were seen once every 2 weeks at the Ayurvedic Trust by both Ayurvedic and allopathic physicians. In keeping with the double-blind design of the study, neither the Ayurvedic physician nor the allopathic physician knew whether the patients were on verum MTX, or verum Ayurvedic therapies, or both.

Potential participants were screened in 2 phases. At the initial screening, all those who responded to recruitment efforts underwent preliminary screening for eligibility including RA disease and medication history, joint count, and physical examination but had no laboratory tests. Those who satisfied the initial screening criteria proceeded to the final screening, when blood and urine samples were collected and radiography was done as per the exclusion criteria.

### MTX Dosing

The oral MTX dose was adjusted for milligrams per meter square and for the albumin level (which is lower in Indian patients), so that the equivalent starting dose of 10 mg/m$^2$ for North American patients was adjusted to 8 mg/m$^2$. This was then adjusted for the 2.5-mg tablets available for prescription. Thus, patients weighing 30 to 39 kg and height up to 137 cm started at 7.5 mg/wk, patients weighing 40 to 59 kg and height 138 cm and taller started at 10 mg/wk, and for those 50 to 70 kg and 138 cm or taller or 70 to 79 kg but up to 138 cm in height, the starting dose was 12.5 mg/wk. For those taller than 137 cm and weighing 70 kg or more, the starting doses were from 15 to 17.5 mg/wk. Doses were up-titrated to tolerance in 2.5-mg/wk increments every 8 weeks. The maximum dose was 25 mg/wk. The range of doses at 24 weeks was 2.5 to 22.5 mg/wk, with a mean of 18.5 mg/wk orally. The range of doses at 36 weeks was 5 to 25 mg/wk, with a mean of 20.3 mg/wk orally. A pharmaceutical firm (Stanpro Pharmaceuticals, Coimbatore, India) manufactured the MTX placebo, which was identical in appearance to the true MTX tablets.

### Ayurvedic Treatment and Placebos

Before the start of the study, the Ayurvedic physician provided a list of all possible medicines that he might use in individualizing therapy over the course of the study. This list contained 148 separate multiherbal compounds. However, they were contained within 6 dosage forms of Ayurvedic pharmacological medicine (decoction, powder, pills, jam, herbal wine, and herb-infused oil). Each dosage form included 20+ multiherbal compounds. We therefore made and tested placebo formulations for these dosage forms. We found from blinded tests before the study began that we could use 1 placebo formulation for all the herbal compounds within a given dosage form because there was no appreciable difference in appearance, color, texture, taste or smell when the herbs were combined within that particular dosage form. Therefore, 1 placebo formulation for each of the 6 dosage forms was developed. The number of placebos was 6, with each placebo representing the 20+ herbal compounds of that particular dosage form.

Of the 148 multiherbal compounds in the original list, the Ayurvedic physician used 40 compounds during the course of the study when the treatment called for verum Ayurveda. The placebo formulations alone were used when placebo Ayurveda

was called for. These placebos were shown to effectively double-blind the trial; details of the success of blinding and related issues have been published.[13]

Because this was a study of classic Ayurvedic treatment, the Ayurvedic physician was free to prescribe any combination of medicines and therapies for all patients, based on his clinical judgment. Thus, the patients received individualized therapy as per true Ayurvedic precepts. Consequently, not all patients were expected to receive all the dosage forms (or corresponding placebos) but were dispensed verum or placebo for all their prescriptions, depending on their particular treatment group assignment. All medicines and placebos were well within US Food and Drugs Administration standards for heavy metals and microbiological contaminants and were cleared for use in the study by the University of Washington's institutional review board. Periodic quality control checks were done, and appropriate action was taken as needed to ensure the safety of the placebos and medicines.

Because this was a study of outpatient RA treatment, patients were not expected to undergo intensive Ayurvedic therapies that are part of classic Ayurvedic inpatient treatment of RA (e.g., enemas) requiring hospital stay. Nevertheless, we had prepared protocols for sham therapies in case the Ayurvedic physician wished to prescribe intensive therapies.

Blood and urine samples were obtained and tested at an accredited laboratory. Blood tests done at weeks 0, 6, 12, 18, 24, 30, and 36 included complete blood cell count, C-reactive protein (CRP), liver and renal function tests, electrolytes, and lipid profile. Our previous experience with erythrocyte sedimentation rate (ESR) in the United States showed that, when a sample was kept in the laboratory for more than 4 hours at room temperature before analysis, ESR increased (unpublished observations). Because prolonged waiting times for laboratory tests were common in India, we used CRP in the calculations of DAS28 and ACR20/50/70 instead of ESR.

## Statistical Analysis

Because this was a pilot, exploratory study, the sample size of 43 patients was based on a convenience sample; analysis was exploratory and was limited by the small sample size.

Descriptive statistics were calculated for baseline demographics and disease assessments. The primary endpoint of the study was response at week 36, based on the Disease Activity Score (DAS28-CRP), which is a composite index using tender and swollen joint counts of 28 joints, the CRP, and a visual analog scale indicating the patient's global assessment of disease activity.[14] Secondary endpoints included the following: the proportions of patients achieving a response according to the ACR20/50/70 criteria for clinical improvement[15] at weeks 24 and 36; changes in the DAS28-CRP from baseline to weeks 24 and 36; changes in the individual components of the DAS28 and ACR criteria, including the Ayurvedic and allopathic physicians' global assessment of disease activity; and changes in the Health Assessment Questionnaire – Disability Index (HAQ-DI) to weeks 24 and 36. The HAQ-DI evaluates physical function in 8 domains on a 0 to 3 scale.[16] Comparisons among groups utilized Analysis of variance with last abbreviation carried forward.

## Safety Assessments

Patients were monitored for adverse events (AEs) during each visit for the entire duration of the study. Evaluation of drug and placebo safety and tolerability was based on detailed records of AEs, focusing on the types and frequencies of common and serious AEs that occurred. A serious AE was defined as an AE that was fatal or life threatening; that required prolonged inpatient hospitalization; resulted in persistent or significant disability, congenital anomaly, birth defect, miscarriage or elective abortion; or that required medical/surgical intervention to prevent another serious outcome.

# RESULTS

## Disposition of Patients

Figure 1 summarizes the disposition of the patients in the study. Of the 249 patients who gave informed consent, 172 were eliminated at initial screening (see Fig. 1 for reasons). A further 11 patients were eliminated at the final screening (Fig. 1). Records for 3 individuals who were not recruited contained no reason for their exclusion.

Sixty-three patients were enrolled, of whom 20 were terminated or dropped out at various points during the study as noted in Figure 1. Forty-three patients completed 24 weeks. Three patients were terminated at 24 weeks because of neuropathy (MTX group), fractured femur (Ayurveda group), and pregnancy (Ayurveda group), and the remaining 40 patients completed the trial at 36 weeks. They had been randomized as follows: group 1, MTX verum plus Ayurvedic placebo (MTX group) n = 14; group 2, verum Ayurveda plus MTX placebo (Ayurveda group) n = 12; and group 3, verum Ayurveda plus MTX verum (combination group) n = 17.

## Demographic and Baseline Characteristics

Patients in all 3 groups were comparable at baseline in demographic and disease characteristics (Table 1). The groups' mean ages ranged from 45 to 47.9 years, they had mean weights from 56.06 to 63.3 kg, and 83% to 88% of all patients were women. Mean disease duration was between 1.1 and 2.7 years, and mean CRP levels ranged from 27 to 42 mg/dL. Scores in

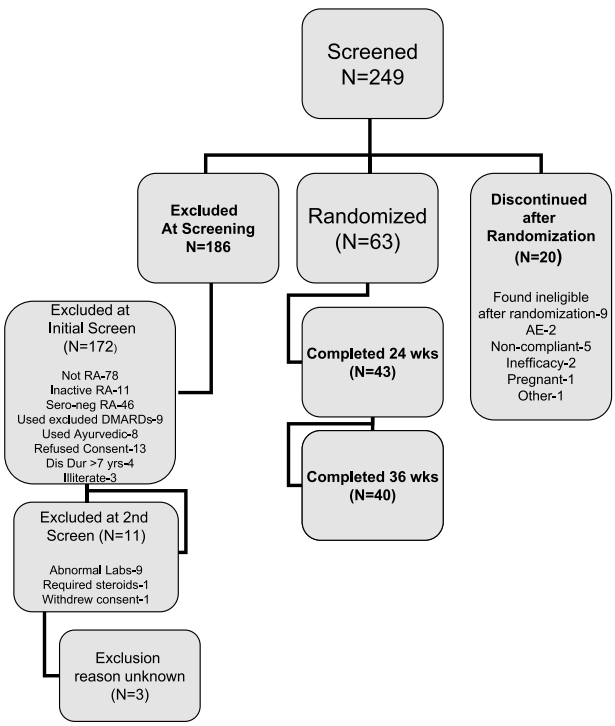


**FIGURE 1.** Disposition of patients during the study. Color online-only figure is available at http://www.jclinrheum.com.

**TABLE 1.** Patient Mean (SD) Demographics and Disease Characteristics at Baseline (N = 43)

| | Group 1: MTX + Ayurvedic Placebo (n = 14) | Group 2: Ayurveda + MTX Placebo (n = 12) | Group 3: MTX + Ayurveda (n = 17) | *P* for Comparisons |
|---|---|---|---|---|
| Age, yr | 47.3 (15.5) | 47.2 (10.6) | 47.1 (12.7) | 0.999[a] |
| Women, n (%) | 12 (85.7) | 10 (83.3) | 15 (88.2) | 0.931[b] |
| Primary language, n (%) | | | | |
| Malayalam | 4 (28.6) | 0 (0) | 4 (23.5) | 0.370[b] |
| Tamil | 10 (71.4) | 11 (91.7) | 11 (64.7) | |
| Kannada | 0 (N/A) | 0 (N/A) | 1 (5.9) | |
| Telugu | 0 (N/A) | 1 (8.3) | 1 (5.9) | |
| Weight | 123.6 (33.4) lb | 139.6 (33.6) lb | 132.0 (28.8) lb | 0.443[a] |
| | 56.06 (15.1) kg | 63.3 (15.2) kg | 59.8 (13.06) kg | |
| Disease duration (<1 yr = 0) | 2.3 (2.2) | 1.1 (0.7) | 2.7 (2.4) | 0.094[a] |
| RF+, n (%) | 11 (78.6) | 11 (91.7) | 12 (71) | 0.388[b] |
| Anti-CCP+ in RF− patients, n (%)[c,d,e] | 3 (21.4) | 1 (8.3) | 5 (29.4) | 0.388[b] |
| Erosions, % | 61.5 | 69.2 | 64.7 | 0.918[b] |
| No. tender/painful joints (28-count) | 18.3 (6.5) | 16.4 (6.2) | 18.3 (3.6) | 0.593[a] |
| No. swollen joints (28-count) | 19.7 (5.8) | 18.8 (5.4) | 19.5 (4.5) | 0.903[a] |
| No. swollen joints (66-count) | 31.3 (9.2) | 31.5 (7.4) | 31.7 (6.3) | 0.984[a] |
| No. tender/painful joints (66-count) | 31.0 (10.1) | 28.5 (10.0) | 29.5 (8.2) | 0.789[a] |
| Patient's assessment of joint pain[f] | 68.1 (16.1) | 69.7 (15.5) | 57.7 (21.36) | 0.159[a] |
| Patient's global assessment of disease activity[f] | 72.3 (15.5) | 68.5 (20.5) | 60.0 (20.1) | 0.214[a] |
| Ayurvedic physician's global assessment of disease activity[f] | 62.0 (6.4) | 60.5 (7.5) | 59.6 (10.7) | 0.752[a] |
| Allopathic physician's global assessment of disease activity[f] | 71.9 (7.5) | 74.2 (4.5) | 72.3 (6.3) | 0.633[a] |
| CRP, mg/dL[c,d,g] | 2.73 (3.79) | 3.35 (3.26) | 4.20 (5.86) | 0.672[a] |
| DAS28-CRP | 6.5 (0.93) | 6.5 (0.84) | 6.5 (0.80) | 0.997[a] |
| HAQ-DI score | 1.7 (0.60) | 1.6 (0.49) | 1.5 (5.9) | 0.515[a] |
| Creatinine, mg/dL (0.6–1.3)[g] | 0.78 (0.13) | 0.81 (0.12) | 0.78 (0.15) | 0.805[a] |
| AST, U/L (15–37)[g] | 18.9 (2.8) | 21.1 (9.1) | 18.6 (8.2) | 0.638[a] |
| ALT, U/L (30–65)[g] | 28.3 (6.3) | 35.4 (20.5) | 30.3 (9.1) | 0.355[g] |
| Albumin, g/dL (3.4–5)[g] | 3.6 (5.4) | 3.4 (0.33) | 3.5 (0.57) | 0.472[a] |
| Alkaline phosphatase, U/L (50–136)[g] | 86.5 (42.2) | 93.9 (34.8) | 118.2 (99) | 0.421[a] |
| Platelet count, $\times 10^3$/mL (150–400)[g] | 311.1 (72.1) | 391.0 (123.2) | 354.1 (86.3) | 0.108[a] |
| WBC, $\times 10^3$/mL (4–11)[g] | 7.5 (2.1) | 8.7 (3.3) | 7.3 (1.7) | 0.257[a] |
| Hemoglobin, g/dL (11.5–15)[g] | 11.8 (1.8) | 11.1 (1.3) | 11.2 (1.7) | 0.474[a] |

This table represents the mean (SD), unless otherwise noted, of patient demographics and disease characteristics by treatment group at baseline.
[a]On the basis of one-way ANOVA.
[b]On the basis of Pearson $\chi^2$.
[c]Max upper limit of normal = 1.0 mg/dL.
[d]Results are imputed from a titer.
[e]Patients who were RF-negative, but had 7 of 66 swollen joints, were tested for anti-CCP positivity.
[f]Using a 100-mm visual analog scale.
[g]Laboratory reference range.
NA, not applicable.

DAS-CRP at baseline indicated high disease activity for all 3 groups (mean, 6.5). Sixty-one and one-half percent to 69.2% had erosions on radiographs of the hands and feet (determined by D.F.). Patients had active, seropositive disease. No statistically significant differences between groups were found among the baseline variables.

## Efficacy Outcomes

Table 2 shows efficacy outcomes at weeks 24 and 36. A decrease of 1.2 or more in the DAS28-CRP score is indicative of a good response to treatment. Patients in all 3 groups met this criterion at 24 and 36 weeks; there was no statistically significant difference between groups.

The MTX and the Ayurveda groups showed greater improvement (*P* = NS) in HAQ-DI scores than those receiving the MTX and Ayurveda combination. Patients in all 3 groups achieved a clinically meaningful reduction (>0.22) at weeks 24 and 36.

Figure 2 shows ACR20/50/70 responses. None of the tested differences between groups was statistically significant except

**TABLE 2.** Mean (SD) Treatment Outcomes at Weeks 24 and 36, by Group (N = 43)[a]

| | Group 1: MTX + Ayurvedic Placebo (n = 14) | | Group 2: Ayurveda + MTX Placebo (n = 12) | | Group 3: MTX Plus Ayurveda (n = 17) | | *P* Value by ANOVA | | *P* Value for Paired Differences | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Outcome Measure** | **0–24 wk** | **0–36 wk** | **0–24 wk** | **0–36 wk** | **0–24 wk** | **0–36 wk** | **0–24 wk** | **0–36 wk** | **0–24 wk** | **0–36 wk** |
| DAS28-CRP (0–10 units) | −1.9 (1.5) | −2.4 (1.5) | −1.2 (1.1) | −1.7 (1.4) | −2.1 (1.4) | −2.4 (1.5) | 0.222 | 0.379 | 0.000 | 0.000 |
| Tender joint count (max = 28) | −10.5 (7.5) | −13.7 (7.0) | −9.1 (7.5) | −11.3 (8.2) | −11.8 (6.5) | −13.8 (5.2) | 0.596 | 0.581 | 0.000 | 0.000 |
| Swollen joint count (max = 28) | −9.1 (7.4) | −11.3 (7.7) | −5.3 (7.4) | −8.2 (8.8) | −10.9 (7.9) | −11.6 (7.4) | 0.162 | 0.492 | 0.000 | 0.000 |
| Patient pain assessment[b] | −31.6 (32.1) | −44.0 (25.4) | −27.5 (16.9) | −44.9 (14.4) | −13.7 (27.2) | −23.2 (27.9) | 0.157 | 0.026 | 0.000 | 0.000 |
| Patient's global assessment of disease activity[b] | −35.7 (29.5) | −43.8 (23.8) | −28.3 (18.6) | −45.2 (18.7) | −16.2 (28.8) | −25.4 (31.1) | 0.133 | 0.073 | 0.000 | 0.000 |
| Ayurvedic physician's global assessment of disease activity[b] | −16.6 (3.6) | −22.8 (8.6) | −15.7 (5.4) | −15.7 (7.4) | −13.1 (11.6) | −17.8 (13.9) | 0.466 | 0.223 | 0.000 | 0.000 |
| Allopathic physician's global assessment of disease activity[b] | −31.8 (20.7) | −45.1 (13.0) | −25.2 (16.9) | −44.6 (19.4) | −31.4 (17.7) | −46.3 (18.1) | 0.596 | 0.959 | 0.000 | 0.000 |
| CRP, mg/dL | −10.3 (34.1) | −12.9 (37.4) | −9.33 (37.8) | −2.8 (41.0) | −30.1 (58.8) | −26.2 (44.8) | 0.383 | 0.327 | 0.015 | 0.020 |
| HAQ-DI score | −0.64 (0.71) | −0.87 (0.72) | −0.67 (0.63) | −0.86 (0.58) | −0.60 (0.65) | −0.64 (0.55) | 0.966 | 0.508 | 0.000 | 0.000 |

This table illustrates the mean and standard deviation of patient disease characteristics and quality of life outcomes at weeks 24 and 36 by treatment group. Statistical tests compare the changes between groups and the differences that occurred within patient groups over time.

[a]Intent-to-treat population with last observation carried forward.

[b]On the basis of 100-mm visual analog scale.

for the ACR70 response at week 24 (MTX, 29%; Ayurveda, 0%; combination, 6%; $P = 0.049$). Because this represents one result among many comparisons, this result can be by chance alone.

All treatments were generally well tolerated in this study, with a similar incidence of AEs (Table 3). Nearly all AEs were mild or moderate in intensity. The most commonly occurring AEs in all 3 treatment groups were in the ear, nose, and throat category. There was a greater frequency of AEs in the MTX-containing than the Ayurveda regimens (MTX, 174; Ayurveda, 112; combination, 176; $P$ = NS). Although numerical differences in specific AEs were frequently noted, they were not statistically significant. The largest differences were in stomatitis (MTX, 8; Ayurveda, 2; combination, 7), dyspepsia (MTX, 5; Ayurveda, 3; combination, 17), abdominal pain (MTX, 4; Ayurveda, 0; combination, 5), headache (MTX, 18; Ayurveda, 8; combination, 8), and nausea (MTX, 8; Ayurveda, 1; combination, 11).

Only 2 serious AEs occurred, requiring hospitalization: peripheral neuropathy (MTX group) and fractured femur due to a fall (Ayurveda group). Neither of these was considered to be related to the study treatments (Table 4). Each group developed 6 infections requiring oral antibiotics, and 1 pregnancy occurred (in the Ayurveda group). No deaths occurred.

## DISCUSSION

Thus far, Ayurveda has not been studied as a system of care or in the context of a double-dummy, double-blind, randomized, placebo-controlled trial. This pilot study of allopathic treatment (using MTX) and classic Ayurvedic outpatient treatment of RA represents the first trial of its kind. Its unique features include the development of placebos for each of the several pharmacological dosage forms used in the Ayurvedic treatment of RA and the Ayurvedic physician having the freedom to individualize Ayurvedic therapy, as per true Ayurvedic precepts. The double-blind was successful.[13]

A systematic review of the literature on Ayurvedic medicine for RA identified only 7 studies that fit the criteria of RCTs.[17] Only 3 of these studies were placebo-controlled RCTs.[18–20] None studied classic Ayurvedic treatment of RA or allowed individualization of therapy. In the only methodologically high-quality trial[18] (based on a Jadad score[21] of 5) from this group, except for a significant increase in hemoglobin and a decrease in RF ($P < 0.01$) in the experimental group, the active treatment was not significantly superior to placebo. The second study,[19] which indicated potentially beneficial effects of an Ayurvedic preparation compared with placebo, was not reported completely. The third trial's incompletely reported results showed no difference between the active treatment and placebo.[20] In general, because there were methodological flaws, none of these RCTs was credible enough to allow any opinion.

An important feature of Ayurvedic pharmacological treatment is that it requires multiple and individually changing medications, dispensed in various dosage forms over time. The studies reviewed above used fixed combinations of the same formulations throughout and did not allow for the individualization of therapies. They are thus not tests of true classic Ayurveda. For example, in the trial by Chopra et al.,[18] the individual herbs they used are part of the Ayurvedic pharmacopoeia, but the particular combination was used in an unvarying dose, and none were based on classic Ayurvedic texts nor was there any rationale provided for using this particular herbal combination and dosing for the treatment of RA. Further, the capsular form in which the active treatment and placebo were administered is not a traditional Ayurvedic dosage form. Findings from such studies may support the notion of herbs as

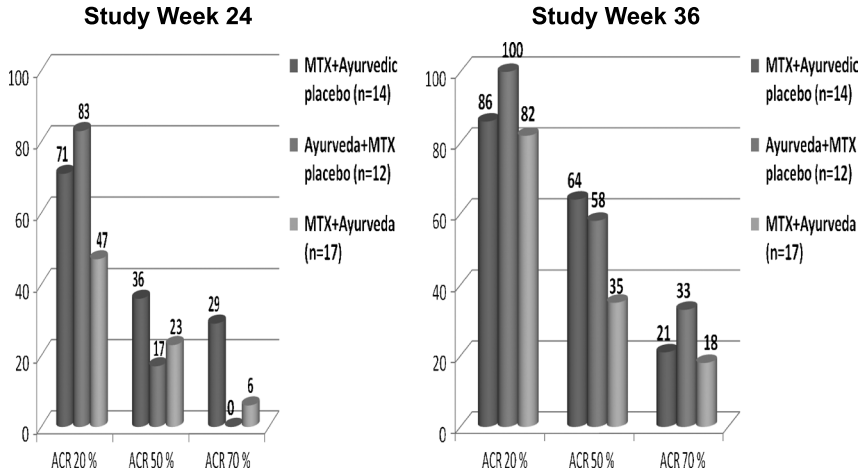


**FIGURE 2.** Percentage of ACR20/50/70 responses at weeks 24 and 36. Color online-only figure is available at http://www.jclinrheum.com.

medicines[21] but are not to be considered as studies of classic Ayurveda. Therefore, the outcomes from such studies cannot be taken as proving, or disproving, the usefulness of Ayurveda per se.

Although our study was a pilot study, the findings indicate the possibility that there was no difference in efficacy among classic Ayurvedic treatment, MTX, and their combination in this 36-week trial. Except for ACR70 response at week 24, there were no statistically significant differences among the 3 groups in the disease activity measures such as DAS28-CRP, the ACR 20, ACR 50, and HAQ-DI. Even this result, among so many comparisons, could have occurred by chance alone. The combination group (verum MTX plus verum Ayurveda) patients did no better than either Ayurveda or MTX alone.

It is important to note that there were no statistically significant differences among the 3 groups. However, patients in the Ayurveda group showed the most improvement overall at 36 weeks (Table 2). This supports the general view that Ayurveda takes longer than allopathic medicine to show its effects.

Numerous AEs were reported during the course of the study, in keeping with the finding that 70% to 92% of patients in clinical trials report AEs.[22–24] All patients received more attention than is usually available in clinical trials because they were queried about their symptoms once every 2 weeks by the 2 physicians and a study coordinator. Adverse events were distributed approximately equally among the 3 groups. Although statistically not significant, the 3 groups did show some differences, numerically. The Ayurveda group had the fewest number of AEs relative to the other 2 groups, and the combination group had the most. The small sample size limits the interpretation of these findings. One may speculate that the AEs associated with each of the single therapies (MTX and Ayurveda) may have been additive and therefore served to increase the number of such events in the combination group.

The principal limitation of this study was the small sample size, which, although adequate for a preliminary study of this kind, requires a larger trial to achieve adequate statistical power to definitively compare classic Ayurveda and allopathic

**TABLE 3.** Incidence of Clinically Important AEs by Group (N = 43)

| AEs | Group 1: MTX + Ayurvedic Placebo (n = 14) | Group 2: Ayurveda + MTX Placebo (n = 12) | Group 3: MTX Plus Ayurveda (n = 17) |
|---|---|---|---|
| Pregnancy | 0 | 1 | 0 |
| Hospitalization | 1[a] | 1[b] | 0 |
| Infections not requiring hospitalization; treated with intravenous antibiotics | 1 | 0 | 0 |
| Infections not requiring hospitalization; treated with oral antibiotics | 6 | 6 | 6 |
| Tuberculosis or opportunistic infection | 0 | 0 | 0 |
| Died | 0 | 0 | 0 |
| Life-threatening event | 0 | 0 | 0 |
| Congenital anomaly or birth defect | 0 | 0 | 0 |
| Cancer | 0 | 0 | 0 |

This table provides the count of clinically important AEs that occurred during the study by treatment group.

[a]Peripheral neuropathy.

[b]Fractured femur due to accidental fall.

**TABLE 4.** Adverse Events by Body System and Treatment Group (n [%])

| Body System – AE | Group 1: MTX + Ayurvedic Placebo (n = 14) | Group 2: Ayurveda + MTX Placebo (n = 12) | Group 3: MTX + Ayurveda (n = 17) | Total[a] |
|---|---|---|---|---|
| 1. General | | | | |
| Fatigue | 5 | 5 | 8 | 18 |
| 2. Constitutional | | | | |
| Fever[b] | 7 | 2 | 7 | 16 |
| 3. ENT | | | | |
| Stomatitis | 8 | 2 | 7 | 17 |
| Teeth | 1 | 0 | 2 | 3 |
| Cough | 12 | 12 | 11 | 35 |
| Cold | 2 | 2 | 3 | 7 |
| Eye | 7 | 8 | 5 | 20 |
| Other | 6 | 10 | 8 | 24 |
| Dysgeusia | 2 | 5 | 6 | 13 |
| 4. Pulmonary | | | | |
| Other | 0 | 0 | 2 | 2 |
| 5. Cardiovascular | | | | |
| Chest pain | 1 | 3 | 5 | 9 |
| Other | 1 | 0 | 0 | 1 |
| 6. Gastrointestinal | | | | |
| Abdominal pain | 5 | 0 | 5 | 10 |
| Gastrointestinal bleeding | 1 | 0 | 0 | 1 |
| Hemorrhoids | 1 | 0 | 0 | 1 |
| Dyspepsia | 5 | 3 | 17 | 25 |
| Nausea | 8 | 1 | 11 | 20 |
| Vomiting | 6 | 3 | 6 | 15 |
| Diarrhea | 6 | 9 | 5 | 20 |
| Constipation | 6 | 1 | 4 | 11 |
| Other | 5 | 3 | 8 | 16 |
| 7. Genitourinary | | | | |
| UTI | 1 | 0 | 2 | 3 |
| Menstrual abnormalities | 8 | 5 | 3 | 16 |
| Other | 2 | 1 | 0 | 3 |
| 8. MSK | | | | |
| Pain | 11 | 10 | 12 | 33 |
| Other | 6 | 0 | 2 | 8 |
| 9. Neurological | | | | |
| Headache | 18 | 8 | 8 | 34 |
| Vertigo | 4 | 2 | 8 | 14 |
| Other | 9 | 5 | 4 | 18 |
| 10. Integument | | | | |
| Rash | 4 | 1 | 1 | 6 |
| Hair loss | 5 | 2 | 5 | 12 |
| Pruritus | 5 | 3 | 4 | 12 |
| Other | 1 | 6 | 1 | 8 |
| 11. Psychological | | | | |
| Feeling hyperactive | | | | |
| Other | 2 | 0 | 2 | 4 |
| 12. Hematologic | | | | |
| Anemia | 1 | 0 | 4 | 5 |
| Other | 2 | 0 | 0 | 2 |
| Total[a] | 174 | 112 | 176 | 462 |

This table presents the number of AEs experienced by patients in each treatment group. This represents the number of instances of an AE, not the number of patients with AE. The AEs are presented by body system and are totaled by specific type and treatment group.

[a]*P* values by statistical test; Pearson $\chi^2 = 0.022$ (66% of cells had expected counts <5).

[b]By patient report except as noted otherwise.

MSK, musculoskeletal; UTI, urinary tract infection.

treatment of RA. The relatively equal degree of response among the 3 groups, however, is encouraging for further testing of Ayurveda. Another factor that may limit the generalizability of this study is that it was done in India, where people are familiar with and accept classic Ayurveda.

This study demonstrated that CAM can be compared with allopathic medicine in the context of a placebo-controlled, double-blind, randomized trial. Ayurvedic treatment was also recorded systematically and concurrently, allowing for possible future analyses. This study not only compared classic Ayurveda with allopathic medicine, but also a combination of the two, which has not been done before. This is significant because it addresses the concerns about possible interaction effects when combining herbal medicines with allopathic medicines.

The development of a method to allow placebo controls for changing and individualizing therapies is an important step in providing the basis for a meaningful comparison of not only classic Ayurveda but also other traditional medicine systems with allopathic treatment in ways acceptable to western standards. This approach also shows that double-blind, placebo-included, randomized controlled studies are possible when testing classic Ayurvedic versus allopathic medications. Larger trials are needed and are clearly possible.

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