Controlled Trial of Methotrexate Versus CH-1504 in the Treatment of Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To investigate the clinical efficacy, safety, tolerability, and toxicity profile of a metabolically stable antifolate, CH-1504, compared to methotrexate (MTX) in the treatment of rheumatoid arthritis (RA).

Methods. A 24-week open-label trial of MTX and CH-1504 was performed in 20 patients with RA.

Results. Improvements in clinical and laboratory indicators were observed in both study groups. Improvement in the CH-1504 group was greater than in the MTX group. Both treatments were generally well tolerated; however, the liver function test abnormalities and gastrointestinal related adverse events expected with this class of medication were not seen with CH-1504.

Conclusion. CH-1504 appears to be clinically efficacious and may possess a superior safety and tolerance profile compared to MTX. (J Rheumatol 2006;33:862–4)

Key Indexing Terms:
EFFICACY ANTIFOLATE CH-1504 RHEUMATOID ARTHRITIS

Side effects of methotrexate (MTX), the disease modifying antirheumatic drug most commonly prescribed for the treatment of rheumatoid arthritis (RA), include skin reactions, pulmonary pneumonitis, gastrointestinal disturbances, ulcerative stomatitis and hemorrhagic enteritis, hepatotoxicity, and renal toxicity[1-4]. It is estimated that roughly 30% of patients discontinue MTX therapy due to side effects[5].

MTX undergoes a number of metabolic processes, specifically, polyglutamylation, 7-hydroxylation, cleavage of the glutamate moiety, and cleavage of the 9-10 bridge bond. It has been postulated that a significant part of MTX toxicity is the result of its conversion to more toxic and less efficacious byproducts[6]. Thus, a molecule possessing the efficacy of MTX but metabolically stable would be desirable. CH-1504 (4′-methylene-5,8,10-trideazaaminopterin) has been designed to be metabolically inert[7]; it was synthesized and encapsulated at the University of South Alabama[6]. It has been shown *in vitro* to be nonpolyglutamylatable, nonhydroxylatable, and stable to cleavage of the 4′-methyleneglutamate moiety[6]. CH-1504 has the efficacy-associated activity of antifolates that inhibit dihydrofolate reductase[8], and is more efficiently taken up into cells by the reduced folate carrier than is MTX[6]. It is our hypothesis that CH-1504 would demonstrate clinical efficacy and be safer and better tolerated due to the lack of toxicity secondary to the formation of metabolites.

MATERIALS AND METHODS

This was an open-label, nonrandomized trial. Following a baseline evaluation (history, physical examination, determination of eligibility), patients were assigned to receive either weekly 10 mg dose of MTX or daily 6.7 mg dose of CH-1504. Patient visits occurred every 4 weeks over a 24-week treatment period.

Efficacy was assessed using American College of Rheumatology response criteria as follows: swollen and tender joint counts; patient and physician assessment of disease activity, pain, Health Assessment Questionnaire results, erythrocyte sedimentation rate, and C-reactive protein. Clinical improvement was defined as attainment of an ACR 20% response.

Safety and tolerability were assessed through frequency and severity of adverse reactions as well as standard hematology and clinical chemistry results.

RESULTS

Twenty of 26 patients screened met entry criteria and 10 were assigned to each group; all patients completed the trial. Demographics were similar for the 2 groups, except for average duration of disease: 7.3 years in the MTX treatment group versus 16.7 years in the CH-1504 group; 4 patients who started MTX and experienced failure of efficacy were assigned to the CH-1504 group (Table 1). Patients continued taking stable

Table 1. Patient demographics.

Variable	Methotrexate	CH-1504
Female, %	90	90
Age, yrs	53.7	54.8
Range, yrs	36 to 78	45 to 78
Disease duration, yrs	7.2	16.7
Rheumatoid factor, %	100	100
Average prior DMARD		
Failures, no.	6	7
Previous MTX failure, no.	0	4

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doses of nonsteroidal antiinflammatory drug and/or oral corticosteroid at a weekly dose not greater than 10 mg prednisone (or equivalent).

The response to therapy for both groups trended toward improvement (Table 2). Six CH-1504 patients, compared to one MTX patient, achieved an ACR20 response by Week 4. The overall response rate improved over time for both groups, appearing to plateau starting at Week 12 (Figure 1). Nine CH-1504 patients were assessed as responders at the end of the study, in contrast to 4 patients treated with MTX. The single CH-1504 nonresponder patient had previously failed MTX. Four CH-1504 patients and one MTX patient attained an ACR50 response by Week 24.

No severe or serious adverse events were reported in either treatment group. Compared to MTX, only mild somnolence (with no effect on activities of daily living) was associated more frequently with CH-1504 treatment (Table 3). Gastrointestinal-related adverse events were seen with MTX but not with CH-1504.

No clinically significant alterations were observed in the clinical chemistry data from patients treated with CH-1504. Three patients taking MTX had elevations of ALT above the

Table 2. Clinical responses in pilot study. Data are means (standard error of the mean).

Variable	Time, weeks*					
	0		12		24	
	CH-1504	MTX	CH-1504	MTX	CH-1504	MTX
Pain	6.5 (2.4)	6.4 (2.4)	2.0 (1.4)	5.6 (2.5)	2.5 (1.4)	5.1 (2.7)
HAQ	2.3 (0.5)	2.5 (0.2)	1.3 (0.5)	2.2 (0.5)	1.4 (0.5)	1.9 (0.7)
Tender joints	17.4 (4.4)	18.2 (1.8)	5.8 (4.1)	15.5 (3.6)	6.0 (2.9)	14.2 (5.3)
Swollen joints	12.5 (5.7)	12.0 (2.4)	2.7 (2.7)	9.9 (2.7)	4.0 (2.8)	9.3 (4.5)
Patient global assessment	3.9 (0.6)	1.8 (0.4)	2.6 (0.8)	2.2 (0.8)	2.4 (0.7)	2.4 (0.8)
Physician global assessment	3.6 (0.7)	1.9 (0.3)	2.3 (0.7)	2.4 (0.5)	2.4 (0.7)	2.6 (0.8)
ESR, mm/h	57.4 (24.2)	53.2 (25.5)	38.3 (15.3)	50.1 (34.4)	34.1 (22.5)	49.2 (37.2)
CRP, μg/ml	17.4 (12.4)	18.1 (8.3)	17.7 (16.9)	18.6 (8.5)	11.4 (8.6)	18.4 (12.5)

* Weeks 4, 8, 16, and 20 assessments omitted for brevity. HAQ: Health Assessment Questionnaire, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein.

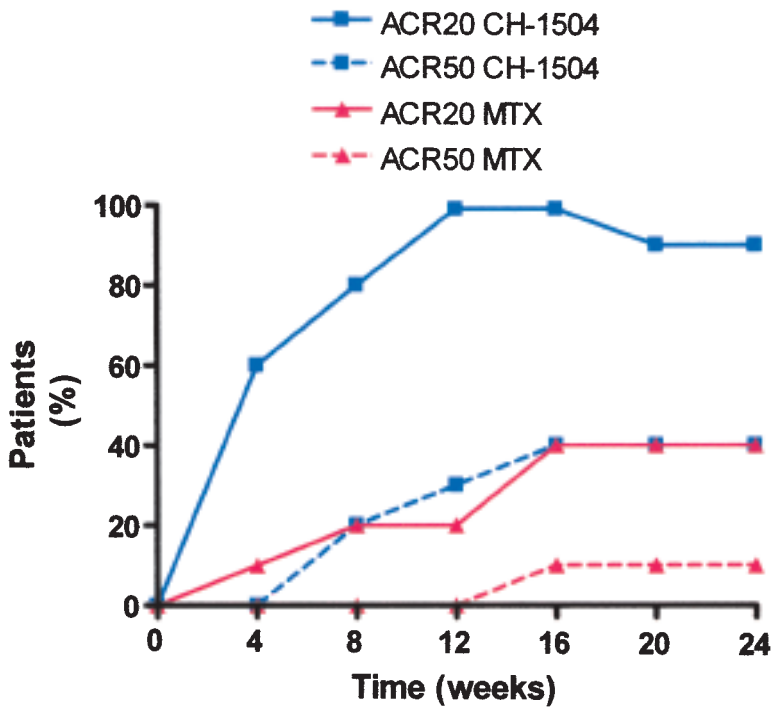

Figure 1. ACR response rates in the 2 study groups.

Table 3. Adverse events in pilot clinical study.

Adverse Event	Incidence (%) by Treatment MTX	CH-1504
Severe adverse events	0	0
Withdrawals	0	0
Dizziness	10	10
Somnolence	0	20
Nausea/vomiting	30	0
Dyspepsia	20	0
Abdominal pain	10	0
Diarrhea	10	0
Allergy	0	0
Acne	0	10
Alopecia	10	10
Infections	20	10
ALT > upper limit of normal	30	0

upper limit of normal that persisted from the second visit through the end of the study (Table 3). No abnormal hematological findings were reported in either group.

DISCUSSION

CH-1504 is a novel, metabolically inert antifolate. We tested the hypothesis that metabolic stability of the compound would not preclude clinical efficacy and could confer safety and tolerance benefits.

CH-1504 demonstrated a significant degree of efficacy in patients with RA. Specifically, there was a rapid onset of action, indicated by a 60% ACR20 response rate at Week 4 that improved to 90% by Week 12 and persisted through the end of the study. The MTX group had an inferior response rate; however, the study was not designed to allow a definitive conclusion on the relative efficacy of the 2 treatments. Nevertheless, the fact that 3 of 4 patients who experienced previous MTX treatment failures responded to treatment with CH-1504 is significant.

The safety results supported the theoretical benefits of CH-1504. Specifically, there was no elevation in liver function enzymes for the CH-1504 group. This contrasted with the experience of the MTX group, where some elevations were observed. It was also notable that gastrointestinal disturbances, which are characteristic of MTX and often contribute to intolerance, were not seen in the patients treated with CH-1504.

Our experience with CH-1504 has been favorable in this limited trial. It is encouraging that the anticipated benefits of a metabolically stable antifolate were observed. The efficacy and safety of CH-1504 warrant further evaluation in larger blinded and randomized trials.

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