Efficacy and Safety of CH-1504, a Metabolically Stable Antifolate, in Patients with Active Rheumatoid Arthritis: Results of a Phase II Multicenter Randomized Study

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ABSTRACT. ***Objective.*** To investigate the potential efficacy, safety, and tolerability of daily use of CH-1504 in patients with active rheumatoid arthritis (RA). US National Institutes of Health database no. NCT00658047.

Methods. In our phase II randomized double-blind double-dummy study, patients naive to methotrexate (MTX; n = 201) and having moderate to severe RA received either CH-1504 (0.25 mg, 0.5 mg, or 1.0 mg once-daily oral doses) or MTX (titrated to 20.0 mg once-weekly oral doses). All received weekly 10-mg folate supplementation. Efficacy and safety were assessed at 2, 4, 8, and 12 weeks, with a treatment-free followup at 16 weeks. Safety and tolerability were assessed. Primary efficacy endpoint was proportion of patients achieving ACR20 response at Week 12. Secondary endpoints included difference from baseline in the 28-joint Disease Activity Score (DAS28) and individual components of the American College of Rheumatology (ACR) composite index.

Results. Demographic characteristics were similar in all treatment groups: mean age 54.3 ± 11.4 years, female sex 87%, mean baseline DAS28 6.6 ± 0.9. At Week 12, CH-1504 demonstrated comparable efficacy compared to MTX as measured by ACR20, DAS28, and ACR composite core-set measures, including tender and swollen joints. No dose-response relationship was observed. Adverse events across treatment groups were mild. Liver enzyme levels increased from baseline to Week 16 in the MTX group, with qualitatively lesser increases in the CH-1504 groups. Two patients in the MTX group withdrew because of gastrointestinal-related adverse events. CH-1504 appeared safe and well tolerated at all dose levels.

Conclusion. CH-1504 has comparable efficacy to MTX and is safe and well tolerated. Metabolically stable antifolates are a promising therapeutic option that warrants further study. (J Rheumatol First Release July 1 2011; doi:10.3899/jrheum.101038)

Key Indexing Terms:
RHEUMATOID ARTHRITIS ANTIFOLATE METHOTREXATE
DISEASE-MODIFYING ANTIRHEUMATIC DRUG

Methotrexate (MTX) is regarded as the "gold standard" disease-modifying antirheumatic drug (DMARD) for the treatment of rheumatoid arthritis (RA)[1,2,3]. It reduces disease activity[4] and can retard disease progression[5,6,7]. MTX is structurally related to folic acid and acts as an antagonist to it by inhibiting dihydrofolate reductase (DHFR), the enzyme that converts folic acid to its active form in addition to other potential modes of action. Folic acid is required for cell growth and tissue proliferation; thus, antifolates can be used effectively in disorders mediated by the rapid division or proliferation of cells, including cancer and inflammatory diseases such as RA.

However, MTX is associated with a number of side effects, including gastrointestinal (GI) disorders, stomatitis and mucosal ulcers, hepatotoxicity, skin reactions, alopecia, bone marrow suppression, and disturbances of the central nervous

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system such as fatigue, malaise and lethargy[8,9,10]. Patients receiving MTX are more likely to discontinue treatment because of adverse events (AE) than because of lack of efficacy[4,8,10,11].

A potential contributor to the AE observed with MTX[12,13] may be its conversion to polyglutamylated metabolites that accumulate in tissues. MTX is also hydroxylated in the liver to 7-hydroxymethotrexate, which may similarly be polyglutamylated and retained within the cells, possibly causing liver and kidney toxicity[14,15]. It has been hypothesized, therefore, that an MTX analog that does not form polyglutamates may be therapeutically superior to MTX in treating RA[16].

CH-1504 is a potent antifolate that inhibits DHFR with potency similar to that of MTX, but does not undergo polyglutamylation, 7-hydroxylation, or deglutamylation, potentially eliminating some of the metabolism-based AE associated with MTX[16,17,18]. CH-1504 is taken into cells by the reduced folate carrier more efficiently than is MTX, which may contribute to higher CH-1504 activity levels[16,17,18].

Our objective was to assess as a proof of concept the efficacy, safety, and tolerability of oral CH-1504 in a small number of patients with active RA who were MTX-naive.

MATERIALS AND METHODS

This trial is registered in the US National Institutes of Health database, clinicaltrials.gov, no. NCT00658047.

Patient population. Patients aged 18 to 80 years with a diagnosis of active RA according to American College of Rheumatology (ACR) criteria, and with at least 6 swollen joints and 6 tender joints (based on joint counts of 66 and 68, respectively) were eligible. Patients also had to have ≥ 1 of the following criteria at screening: C-reactive protein (CRP) ≥ 1.0 mg/dl; erythrocyte sedimentation rate (ESR) ≥ 20 mm/h; or morning stiffness lasting 45 min or longer.

Patients were excluded if they had received previous therapy with MTX; any biologic agent for RA (biologic therapy for a different disease was permitted as long as the last dose was > 120 days before baseline); hydroxychloroquine within 120 days of baseline; sulfasalazine; or any steroid injections within 30 days of the baseline visit. Patients with current active infection(s) or any inflammatory arthritis other than RA were not eligible.

Patients were permitted to receive concomitant therapy with nonsteroidal antiinflammatory drugs at standard doses kept constant throughout treatment, analgesics (not to be used for 12 h prior to any study evaluation), and corticosteroids at stable doses for at least 30 days prior to baseline (maximum 10 mg/day prednisone or equivalent). All patients were required to take 10 mg folic acid on Day 2 of each dosing week.

Study design. This was a phase II randomized MTX-controlled study of 3 months' duration, conducted at 27 centers globally including Canada, Poland, Russia, and Ukraine. Our study was double-blind and double-dummy. All patients provided written informed consent prior to participating. Relevant ethical committees' approval was received at each of the participating sites. The study was carried out according to the Declaration of Helsinki (as amended) and conducted in accord with the International Conference on Harmonization Good Clinical Practice guidelines.

Patients meeting the eligibility criteria were randomly assigned to one of 4 treatment arms in a 1:1:1:1 ratio to receive capsulated CH-1504 0.25 mg/day, 0.50 mg/day, or 1.0 mg/day, or capsulated MTX (10 mg/week for the first 2 weeks, then 15 mg/week for the next 2 weeks and 20 mg/week thereafter) for 12 weeks (Figure 1). Patients randomized to the MTX arm received their weekly MTX dose on Day 1 of each dosing week. On Days 2 through 7, patients taking MTX received 2 placebo capsules to maintain the blind design of the study. The first screening assessment was conducted up to 14 days prior to the baseline visit. Patients were assessed for safety and efficacy outcomes at Weeks 2, 4, 8, and 12. A followup visit was conducted at 16 weeks.

Outcome measures and assessments. The primary efficacy outcome measure was the proportion of patients achieving 20% or greater improvement in ACR criteria (ACR20) from baseline to 12 weeks. Secondary efficacy outcome measures included proportions of patients achieving 50% and 70% improvements in ACR criteria from baseline (ACR50 and ACR70); proportion of patients achieving European League Against Rheumatism (EULAR) responses of "good" or "moderate"; and change from baseline in individual components of the ACR composite index and Disease Activity Score in 28 joints (DAS28). Assessments of disease activity and laboratory analyses, including ESR and CRP, were performed at each study visit. Hepatic enzymes were evaluated as a function of their elevation above the upper limit of normal.

Safety assessments. Safety variables were assessed at each visit by physical examination, vital signs, laboratory measures, and AE reporting. Investigators recorded all AE that occurred during the study and assessed the relationship between the AE and study treatment.

Statistical analyses. The predefined primary efficacy endpoint was the proportion of patients achieving an ACR20 response at Week 12. Secondary endpoints were compared between treatment groups. The efficacy analyses were based on a modified intent-to-treat (mITT) population, which included all patients who were randomized, received ≥ 1 dose of the study medication, and who contributed ≥ 1 on-treatment efficacy assessment. The safety population included all patients who were randomized and received ≥ 1 dose of the study medication. This population was used for all safety and demographic analyses.

Our study was not designed for head-to-head statistical comparisons; rather, it was exploratory in design. Summary statistics were presented for continuous variables. Efficacy data were summarized for each treatment group using descriptive statistics. Relative risks, comparing each treatment with MTX, were estimated including 95% CI as appropriate.

RESULTS

Baseline characteristics and patient disposition. Of the 302 patients screened, 201 were randomized across the 4 treatment arms and 185 (92%) completed the study (Figure 2). Baseline characteristics were generally similar across treatment groups. No patient had received prior biologic therapy for any disease. The mean age at enrollment for the entire study population was 54.3 ± 11.4 years; 87% of patients were women; and the mean DAS28 at baseline was 6.6 ± 0.9 (Table 1).

Sixteen patients discontinued treatment during the study (Figure 2). Among the CH-1504 treatment groups, 1 patient receiving 0.5 mg/day and 1 receiving 1 mg/day withdrew because of an AE. The patient receiving 0.5 mg/day CH-1504 experienced mild anxiety, which was deemed possibly related to treatment and resolved without complications. The patient receiving 1 mg/day experienced allergic dermatitis deemed moderate and unlikely to be related to the study medication. Beyond AE, 1 patient in the 1-mg/day group withdrew from the study because of a respiratory disorder, which was assessed as mild and not related to the study medication. The illness resolved. Twelve patients withdrew for reasons including withdrawal of consent, patient decision, and noncompliance with the treatment regimen. One patient from the MTX group was excluded from the mITT population because of withdrawal of consent and no efficacy assessments. One

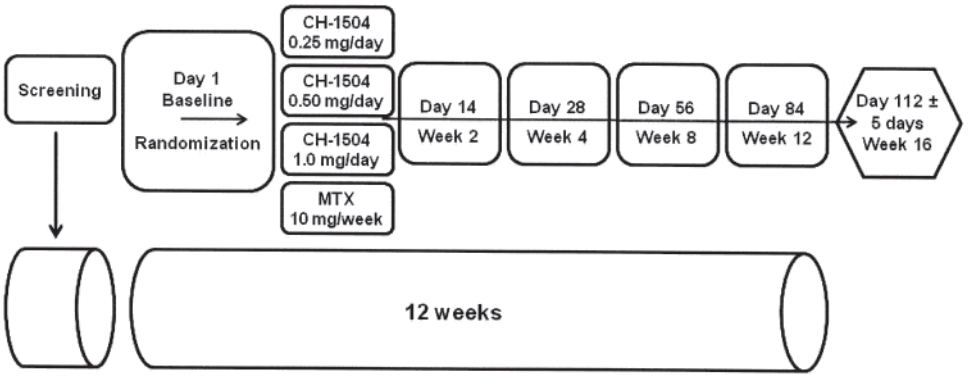

Figure 1. Study design. MTX: methotrexate.

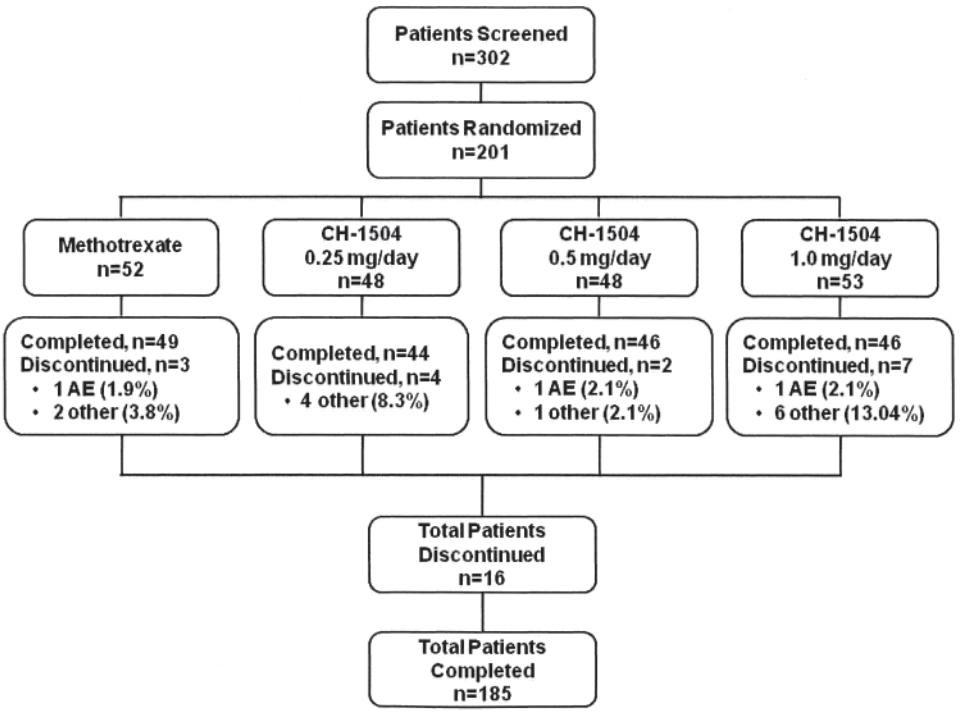

Figure 2. Study design and patient disposition. AE: adverse event.

patient receiving MTX withdrew because of GI-related AE. Thus the mITT analysis included 200 patients.

Efficacy. At the primary endpoint evaluation (Week 12), ACR20 response was achieved in 43.8% of patients (21/48) receiving 0.25 mg/day CH-1504, 39.6% (19/48) receiving 0.5 mg/day CH-1504, and 34% (17/53) receiving 1 mg/day CH-1504, compared with 39.2% of patients (20/51) receiving MTX (Table 2). Thus, ACR20 response was similar among all treatment groups ($p > 0.5$).

At Week 12, 13.7% of patients receiving MTX achieved an ACR50 and 5.9% achieved an ACR70 response. In the 3 groups receiving CH-1504, ACR50 and ACR70 response rates at 12 weeks were highest in the group receiving 0.5 mg/day CH-1504 (Table 2). No patient in the 1 mg/day treatment group achieved ACR70 at Week 12.

At the 16-week followup visit, ACR20 responses were maintained in most subjects: 37.3% of patients receiving MTX and 35.4%, 41.7%, and 32.1% of patients receiving the 3 different dosages of CH-1504 had achieved an ACR20 response (Figure 3). Also at Week 16, ACR50 and ACR70 response rates in each CH-1504 group were higher than at Week 12 (Figures 4 and 5). In contrast, ACR50 and ACR70 response rates in MTX-treated patients were identical at Weeks 12 and 16 (Table 2).

Individual components of the ACR composite index. The mean change from baseline to Weeks 12 and 16 for the individual

Table 1. Baseline patient demographics and disease characteristics (mITT population). Except where otherwise indicated, values are mean (± SD).

Characteristic	MTX, n = 51*	CH-1504 0.25 mg/day, n = 48	CH-1504 0.5 mg/day, n = 48	CH-1504 1 mg/day, n = 53
Demographics				
Women, n (%)	43 (84.3)	44 (91.7)	38 (79.2)	48 (90.6)
White, n (%)	51 (100)	48 (100)	48 (100)	53 (100)
Age, yrs	53.2 (10.1)	54.7 (10.4)	55.2 (12.0)	52.3 (12.8)
Age range, yrs	34–75	27–76	21–78	19–78
Concomitant medications				
Glucocorticoids, n (%)	17 (32.7)	16 (33.3)	16 (33.3)	23 (43.4)
Other antiinflammatory/antirheumatic agents, n (%)	18 (34.6)	8 (16.7)	10 (20.8)	17 (32.1)
Acetic acid derivatives, n (%)	10 (19.2)	11 (22.9)	12 (25.0)	17 (32.1)
COX-2 inhibitors, n (%)	0 (0)	2 (4.2)	1 (2.1)	2 (3.8)
Disease measures				
Tender joint count	27.6 (12.8)	32.5 (14.3)	28.7 (14.2)	26.7 (13.0)
Swollen joint count	16.2 (7.7)	17.9 (8.1)	16.4 (9.0)	16.9 (10.2)
Patient's assessment of pain#	57.5 (21.4)	60.2 (19.5)	61.4 (20.1)	56.6 (19.4)
Patient's global assessment of disease activity#	58.2 (19.7)	61.2 (19.2)	61.1 (21.0)	59.9 (18.6)
Physician's global assessment of disease activity#	56.0 (13.9)	56.7 (14.5)	57.3 (17.4)	56.3 (13.5)
HAQ-DI	1.54 (0.6)	1.60 (0.6)	1.61 (0.5)	1.60 (0.6)
CRP, mg/l	18.48 (23.0)	14.54 (24.2)	14.38 (17.9)	14.5 (15.2)
ESR, mm/h	42.9 (23.5)	46.1 (24.2)	45.1 (22.9)	43.0 (24.8)
DAS28	6.52 (0.9)	6.87 (0.8)	6.60 (0.9)	6.51 (0.8)

* One patient in the MTX group was excluded from the mITT population because consent was withdrawn and the patient left the study. # 100-mm visual analog scale. mITT: modified intent to treat; MTX: methotrexate; COX: cyclooxygenase; CRP: C-reactive protein; DAS28: Disease Activity Score in 28 joints; ESR: erythrocyte sedimentation rate; HAQ-DI: Health Assessment Questionnaire-Disability Index.

Table 2. Percentage of patients with rheumatoid arthritis achieving 20%, 50%, and 70% improvement in ACR measure (mITT population).

Treatment Group	ACR20		ACR50		ACR70	
	12 wk	16 wk	12 wk	16 wk	12 wk	16 wk
MTX, n = 51	39.2 (CI 25.8, 53.9)	37.3 (CI 24.1, 51.9)	13.7 (CI 5.7, 26.3)	13.7 (CI 5.7, 26.3)	5.9 (CI 1.2, 16.2)	5.9 (CI 1.2, 16.2)
CH-1504 0.25 mg/day, n = 48	43.8 (CI 29.5, 58.8)	35.4 (CI 22.2, 50.5)	8.3 (CI 2.3, 20.0)	12.5 (CI 4.7, 25.2)	2.1 (CI 0.1, 11.1)	4.2 (CI 0.5, 14.3)
CH-1504 0.5 mg/day, n = 48	39.6 (CI 25.8, 54.7)	41.7 (CI 27.6, 56.8)	10.4 (CI 3.5, 22.7)	22.9 (CI 12, 37.3)	4.2 (CI 0.5, 14.3)	10.4 (CI 3.5, 22.7)
CH-1504 1 mg/day, n = 53	34 (CI 21.5, 48.3)	32.1 (CI 19.9, 46.3)	5.7 (CI 1.2, 15.7)	9.4 (CI 3.1, 20.7)	0	3.8 (CI 0.5, 13)

ACR: American College of Rheumatology; mITT: modified intent to treat; MTX: methotrexate.

components of the ACR composite index were comparable across groups for all components (Table 3). At Week 12, the greatest improvement from baseline in patient assessment of pain, patient global assessment of disease activity, physician global assessment of disease activity, Health Assessment Questionnaire-Disability Index (HAQ-DI), and ESR occurred in the MTX group. However, improvement in tender joint count (TJC) at Week 12 was observed in the 0.5 mg/day CH-1504 group, and in swollen joint count (SJC) in the 1 mg/day CH-1504 group.

At Week 16, changes from baseline in all of these measures were more pronounced in the CH-1504 groups compared with the MTX group (Table 3). There was a worsening in the MTX group from Weeks 12 to 16 in TJC, assessment of pain, both patient and physician assessment of disease activity, CRP, and ESR.

Although an inverse dose-response trend to 0.25 mg, 0.5 mg, and 1.0 mg doses of CH-1504 was seen for the ACR20 response criteria, a positive dose-response trend appeared for some ACR components. An escalating improvement from baseline to Week 12 was observed in the TJC (58.3%, 62.5%, and 72.5%, respectively), patient global assessment of disease activity (39.6%, 54.2%, and 79%), and HAQ (35.4%, 43.8%, and 51%).

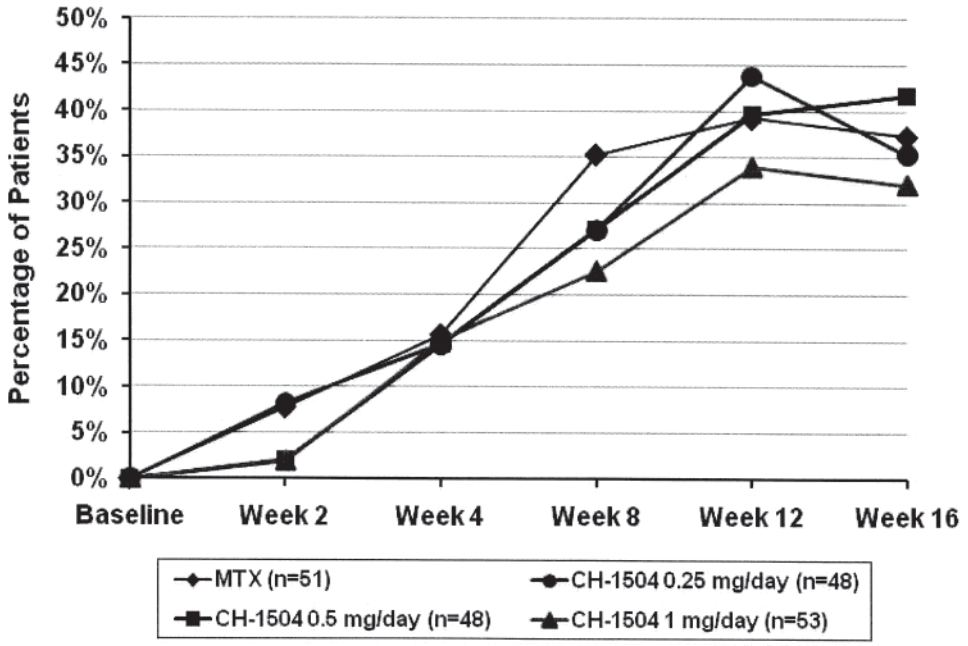

Figure 3. American College of Rheumatology (ACR) 20 response rates over time. MTX: methotrexate.

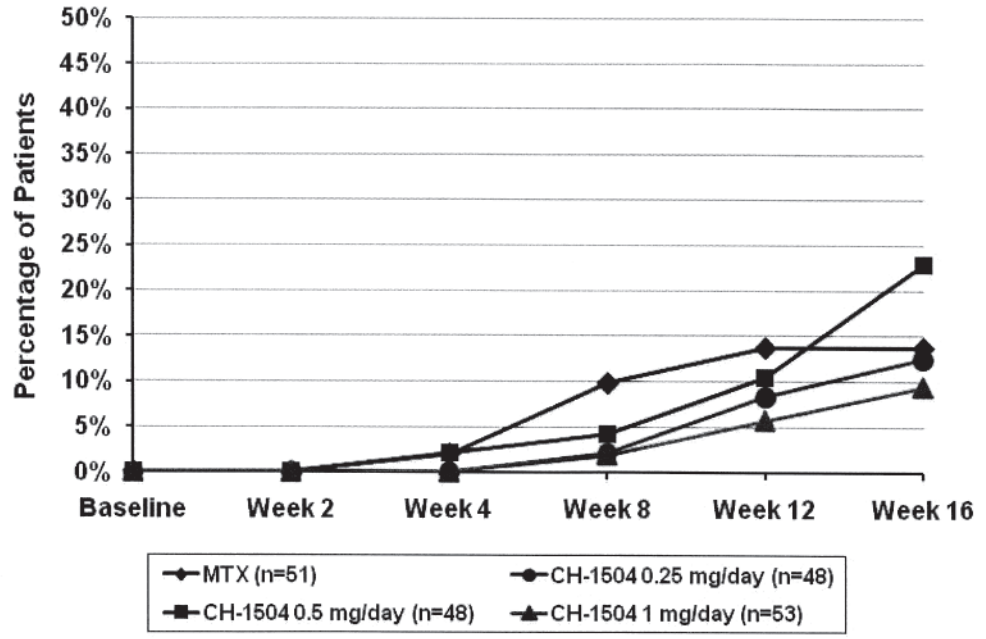

Figure 4. American College of Rheumatology (ACR) 50 response rates over time. MTX: methotrexate.

DAS28 and EULAR response. Overall, mean disease activity improved from baseline to Weeks 12 and 16 in all treatment groups, although the majority of patients still had moderate (DAS ≥ 3.2 to ≤ 5.1) or high (DAS > 5.1 to ≤ 10) disease activity at the end of the study. The greatest mean change in the DAS28 from baseline was –1.51, observed in the 0.5 mg/day CH-1504 group at Week 16 (SD 1.54).

At Week 12, a "good" or "moderate" EULAR response had been achieved by 47% (n = 24) of patients receiving MTX (95% CI 32.9, 61.5); 39.6% (n = 19) of patients receiving 0.25

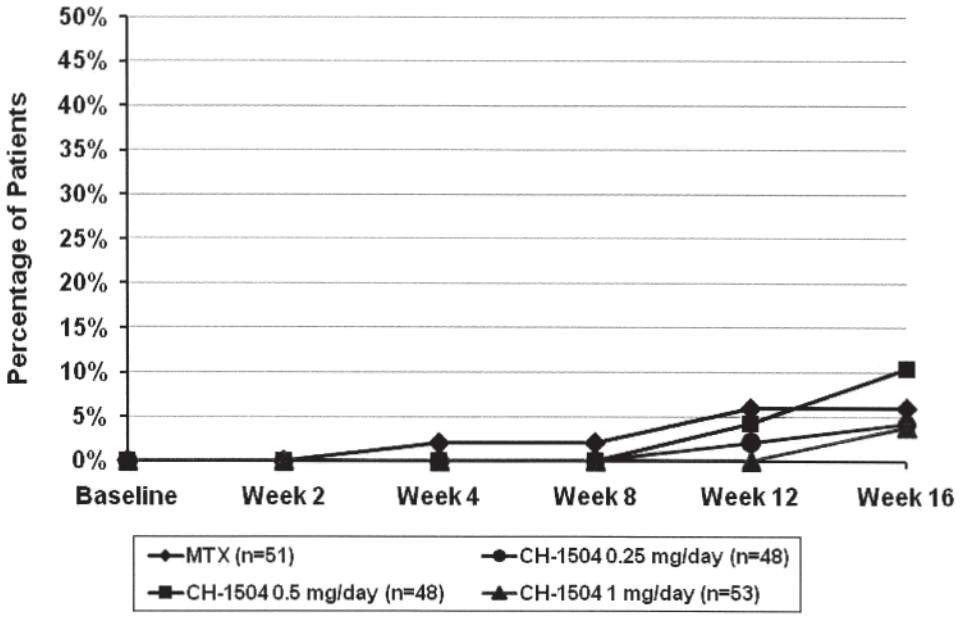

Figure 5. American College of Rheumatology (ACR) 70 response rates over time. MTX: methotrexate.

Table 3. Mean change from baseline in individual components of the American College of Rheumatology index (mITT population). Values are mean (± SD).

Disease Measures	MTX, n = 51*		CH-1504 0.25 mg/day, n = 48		CH-1504 0.5 mg/day, n = 48		CH-1504 1 mg/day, n = 53	
	Wk 12	Wk 16	Wk 12	Wk 16	Wk 12	Wk 16	Wk 12	Wk 16
Tender joint count	–9.6 (14.72)	–8.5 (12.70)	–8.6 (11.97)	–11.5 (13.0)	–9.7 (12.89)	–12.3 (13.92)	–9.4 (11.12)	–12.0 (13.08)
Swollen joint count	–7.8 (8.15)	–8.9 (7.80)	–6.9 (8.48)	–8.6 (8.58)	–8.4 (9.02)	–9.8 (10.32)	–8.9 (9.03)	–9.8 (10.77)
Patient's assessment of pain**	–16.6 (23.57)	–12.3 (25.93)	–9.3 (18.92)	–9.3 (25.01)	–15.1 (23.92)	–17.2 (27.34)	–9.1 (22.49)	–11.0 (27.10)
Patient's global assessment of disease activity**	–15.7 (22.69)	–13.2 (24.66)	–9.5 (17.09)	–9.5 (24.21)	–14.5 (24.49)	–17.9 (27.93)	–11.0 (23.11)	–12.6 (25.16)
Physician's global assessment of disease activity**	–20.0 (18.92)	–16.7 (19.44)	–12.6 (17.45)	–12.2 (17.89)	–16.0 (20.88)	–17.7 (20.99)	–12.0 (20.33)	–14.8 (20.70)
HAQ-DI	–0.39 (0.59)	–0.39 (0.59)	–0.27 (0.66)	–0.27 (0.66)	–0.30 (0.54)	–0.48 (0.63)	–0.28 (0.43)	–0.35 (0.50)
CRP, μg/ml	–6.02 (27.65)	–4.38 (18.9)	3.84 (18.68)	–1.48 (17.26)	2.11 (15.09)	–3.82 (15.31)	3.49 (18.53)	0.93 (18.12)
ESR, mm/h	–11.4 (9.37)	–9.9 (30.80)	–4.9 (20.69)	–7.4 (16.81)	–5.3 (15.97)	–11.9 (23.43)	–2.9 (18.01)	–3.5 (20.30)

* One patient in the MTX group was excluded from the mITT population because consent was withdrawn and the patient left the study. ** 100-mm visual analog scale. mITT: modified intent to treat; MTX: methotrexate; HAQ-DI: Health Assessment Questionnaire-Disability Index; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

mg/day CH-1504 (95% CI 25.8, 54.7); 43.8% (n = 21) of patients receiving 0.5 mg/day CH-1504 (95% CI 29.5, 58.8); and 32.1% (n = 17) of patients receiving 1 mg/day CH-1504 (95% CI 19.9, 46.3). By Week 16 followup, these numbers had increased to 49.1% (95% CI 34.8, 63.4), 41.7% (95% CI 27.6, 56.8), 43.8% (95% CI 29.5, 58.8), and 43.4% (95% CI 29.8, 57.7), respectively.

Safety results. Through Week 12 across all treatment groups, 64 patients (31.8%) experienced AE (Table 4). The majority of AE were mild and resolved. Two patients in the MTX group withdrew from the study because of GI-related events.

Three serious AE were reported: 2 in the MTX group (cholecystitis acute and exacerbation of RA) and 1 in the 0.25 mg/day CH-1504 group (exacerbation of RA). None of the reported serious AE was considered related to the study drug, and all resolved without sequelae. There were no deaths during the study.

In general, there were no differences in hematology or chemistry values between treatment groups. An increase from baseline in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) was observed in a small number of patients across all groups. The investigator did not consider these changes to be clinically relevant.

However, when hepatic enzymes were evaluated as a func-

Table 4. Safety findings through Week 12 (safety population*). Values are number of patients (%).

Adverse Events (AE)	MTX, n = 52	CH-1504 0.25 mg/day, n = 48	CH-1504 0.5 mg/day, n = 48	CH-1504 1 mg/day, n = 53
Total AE	16 (30.8)	12 (25.0)	19 (39.6)	17 (32.1)
Common AE				
Upper respiratory tract infection	0	0	0	1 (1.9)
Diarrhea	0	0	1 (2.1)	1 (1.9)
Nausea	1 (1.9)	0	0	1 (1.9)
Constipation	0	0	1 (2.1)	0
Dyspepsia	0	1 (2.1)	0	0
Vomiting	1 (1.9)	0	0	0
Headache	0	1 (2.1)	1 (2.1)	0
Dizziness	1 (1.9)	0	0	0
Pruritus	1 (1.9)	0	0	0
Urticaria	0	0	0	1 (1.9)
Hyperuricemia	0	0	1 (2.1)	0
Hypertension	0	0	0	1 (1.9)
Increased ALT**	3 (5.8)	1 (2.1)	3 (6.3)	1 (1.9)
Increased AST**	1 (1.9)	2 (4.2)	3 (6.3)	2 (3.8)
Increased blood creatinine	1 (1.9)	0	0	0
Serious AE	2 (3.8)	1 (2.1)	0	0

* The safety population comprised all patients who were randomized and received 1 or more doses of the study medication (n = 201). ** No specific guidance was given to investigators about when to report elevated hepatic enzymes as AE. Data represent only events reported by investigators as AE. MTX: methotrexate; ALT: alanine aminotransferase; AST: aspartate aminotransferase.

tion of their elevation above the upper limit of normal (ULN), 13.5% (7/52) of patients treated with MTX had ALT above the ULN at Week 12. The same result was observed in patients treated with CH-1504 0.25 mg [4.2% (2/48)], in patients treated with CH-1504 0.5 mg [6.3% (3/48)], and in patients treated with CH-1504 1.0 mg [7.5% (4/53)]. AST elevations, in contrast, were low across all groups at Week 12. Although a trend of increasing ALT with larger doses of the study drug was observed, no ALT result matched that of MTX at its peak dose, and all doses of the study drug had similar responsiveness. This suggests that the differential rate of ALT rise was not due to "underdosing" of the study drug.

DISCUSSION

A daily dose of CH-1504, a metabolically stable antifolate, was demonstrated to have comparable efficacy to an escalating dose of weekly MTX and was generally well tolerated in our proof-of-concept study. Improvements in ACR response and ACR composite index were observed from baseline through Weeks 12 and 16 in all CH-1504 treatment groups. The majority of AE experienced during our study were mild, and all doses of the study drug were associated with only slightly elevated serum ALT levels. Overall, there was an inverse qualitative trend for efficacy with an escalating dose of the study drug, and a statistically insignificant escalating dose-response trend for increasing ALT serum levels.

Interestingly, some of the individual components of the ACR composite index did show an escalating dose response to 0.25 mg, 0.5 mg, and 1.0 mg of CH-1504. An improvement from baseline to Week 12 was observed in the TJC, patient global assessment of disease activity, and HAQ. CRP and ESR responses also did not behave as expected. There was variable but no clear progressive response in either of the acute-phase reactant measures with CH-1504, a finding different from the observed progressive response with MTX. A disparity in such measured response tests from clinical responsiveness has been noted before in treatment with anti-tumor necrosis factor-α therapies[19].

In some of the outcome measures there appeared to be ongoing and increasing benefit with various doses of the metabolically stable drug, while with MTX there appeared to be no accrued benefits from Weeks 12 to 16. At Week 16, changes from baseline were greater in the CH-1504 groups for TJC, SJC, patient assessment of pain, patient and physician global assessment of disease activity, HAQ-DI, and ESR, despite lack of a dose response, compared with the MTX group. In fact, there was a worsening in the MTX group in TJC, assessment of pain, both patient and doctor assessment of disease activity, CRP, and ESR from Weeks 12 to 16.

Although MTX is commonly used in the treatment of RA[20], about 10% to 37% of patients discontinue because of toxicity[4,10]. However, many of the studies in the reviews that produced this discontinuation rate were conducted when folic acid supplementation, now known to decrease MTX-induced toxicity, was not standard[12,21,22]. The effect on the discontinuation rate of requiring use of concomitant folic acid is not yet clear[11].

Our study is not a true "head-to-head" comparison of opti-

mal treatment regimens for both CH-1504 and MTX. The 3-month timeframe of our study and the shortened stable dosing of MTX of 2 months because of the forced dose escalation contributed to this. However, our study does offer some evidence that CH-1504 provides significant improvement in a relatively short time that is comparable to a substantial exposure to MTX (20 mg/wk). While the study does not recreate the initial findings from a previous open-label study[23], where 9 out of 10 patients receiving CH-1504 achieved an ACR20 response by Week 12 that persisted through Week 24, compared with only 4 of 10 MTX patients who were considered responders at study end, it does confirm the hypothesis that a metabolically stable antifolate dosed daily can be an effective treatment for RA.

Safety data on hepatic enzyme elevations were observed both as AE and as a function of their elevation above the ULN. No specific guidance was given to the investigators about when to report elevated hepatic enzymes as AE. While Table 4 suggests that there are similar elevations in serum levels of AST and ALT across all treatment arms, these data represent only events that were reported by investigators as AE. These liver function test AE were reported based on the investigator's own judgment and consequently are inconsistent across our study. Therefore it is difficult to make comparisons between groups with regard to elevated hepatic enzymes reported as AE.

However, when hepatic enzymes were evaluated as a function of their elevation above the ULN, ALT was seen to rise with increasing doses of CH-1504. Nevertheless, the highest elevation seen with CH-1504 was only about half that seen with MTX. While hepatic enzyme elevations were not reported uniformly as AE, the laboratory data proved to be more reliable measures of hepatotoxicity.

Of note, the observed liver function test elevations with MTX were less than expected, which might reflect the concomitant use of a single dose of 10 mg/week of folate [as compared with the typical cumulative dose of 7 mg/week (1 mg per day) in the United States]. This folate dose regimen was chosen because of the varying dose strengths available in the regions where our study was conducted. Other factors that may have contributed to lower than expected MTX-induced liver abnormalities include the rather small sample size, the use of an escalating exposure to MTX with a stable dose of 20 mg/week for only 8 weeks, and pure chance. Thus, perhaps in another locale with a different dose of concomitant folate, the MTX-dosed patients might have had more serum elevations of AST or ALT, or both.

The limitations of our study were the small size, the exploratory aspect of the dosing, the requirement to use a dose of folate that previously had not been extensively tested for its effects, and the locality (our study did not include a broad demographic). In addition, the dose of MTX 20 mg orally for 8 weeks was not optimal. Statistical comparison among the groups is limited because of the exploratory design. What role these limitations may play in the overall results is unknown.

Despite these limitations, the data suggest that CH-1504 does have potential as a promising therapeutic option in RA. Additional studies are needed to confirm these results and expand our understanding of this drug's effects. Certainly the efficacy, safety, and tolerability compared to MTX in our early proof-of-concept study warrant further investigation of this molecule.

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APPENDIX

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REFERENCES

1. Combe B, Landewe R, Lukas C, Bolosiu HD, Breedveld F, Dougados M, et al. EULAR recommendations for the management of early arthritis: report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis 2007;66:34-45.
2. American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. Guidelines for the management of rheumatoid arthritis. 2002 update. Arthritis Rheum 2002;46:328-46.
3. Saag KG, Teng GG, Patkar NM, Anuntiyo J, Finney C, Curtis JR, et al. American College of Rheumatology 2008 recommendations

for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. Arthritis Rheum 2008;59:762-84.
4. Suarez-Almazor ME, Belseck E, Shea B, Wells G, Tugwell P. Methotrexate for treating rheumatoid arthritis. Cochrane Database Syst Rev 1998;2:CD000957.
5. Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, Keystone EC, et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. N Engl J Med 2000;343:1586-93.
6. Weinblatt ME, Polisson R, Blotner SD, Sosman JL, Aliabadi P, Baker N, et al. The effects of drug therapy on radiographic progression of rheumatoid arthritis. Results of a 36-week randomized trial comparing methotrexate and auranofin. Arthritis Rheum 1993;36:613-9.
7. Lopez-Mendez A, Daniel WW, Reading JC, Ward JR, Alarcon GS. Radiographic assessment of disease progression in rheumatoid arthritis patients enrolled in the cooperative systematic studies of the rheumatic diseases program randomized clinical trial of methotrexate, auranofin, or a combination of the two. Arthritis Rheum 1993;36:1364-9.
8. Cronstein BN. Low-dose methotrexate: a mainstay in the treatment of rheumatoid arthritis. Pharmacol Rev 2005;57:163-72.
9. Aletaha D, Kapral T, Smolen JS. Toxicity profiles of traditional disease modifying antirheumatic drugs for rheumatoid arthritis. Ann Rheum Dis 2003;62:482-6.
10. Salliot C, van der Heijde D. Long-term safety of methotrexate monotherapy in patients with rheumatoid arthritis: a systematic literature research. Ann Rheum Dis 2009;68:1100-4.
11. Borchers AT, Keen CL, Cheems GS, Gershwin ME. The use of methotrexate in rheumatoid arthritis. Semin Arthritis Rheum 2004;34:465-83.
12. Kim Y-J, Song M, Ryu J-C. Mechanisms underlying methotrexate-induced pulmonary toxicity. Expert Opin Drug Saf 2009;8:451-8.
13. Schmiegelow K. Advances in individual prediction of methotrexate toxicity: a review. Br J Haematol 2009;146:489-503.
14. Jolivet J, Schilsky RL, Bailey BD, Chabner BA. The synthesis and retention of methotrexate polyglutamates in cultured human breast cancer cells. Ann NY Acad Sci 1982;397:184-92.
15. Rau R, Karger T, Herborn G, Frenzel H. Liver biopsy findings in patients with rheumatoid arthritis undergoing long-term treatment with methotrexate. J Rheumatol 1989;16:489-93.
16. McGuire JJ, Haile WH. Metabolism-blocked antifolates as potential anti-rheumatoid arthritis agents: 4-amino-4-deoxy-5, 8, 10-trideazapteroyl-d,I-4' -methyleneglutamic acid (CH-1504) and its analogs. Biochem Pharmacol 2009;77:1161-72.
17. Nair MG, Fayard M, Lariccia J, Amato AE, McGuire JJ, Galivan JH, et al. Metabolism-blocked folate analog inhibitors of dihydrofolate reductase-1. Synthesis and biological evaluation of mobiletrex. Med Chem Res 1999;9:176-85.
18. Mant T, Jurcevic S, Szakacs C, Adams L, Boland J, Hewitt LA. Two single-center, double-blind, randomized, placebo-controlled, phase I studies to investigate the tolerability and pharmacokinetics of CH-1504, an antifolate, in healthy male subjects. Clin Ther 2008;30:131-42.
19. Lipsky PL, van der Heijde D, St. Clair EW, Furst DE, Breedveld FC, Kalden JR, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. N Engl J Med 2000;343:1594-602.
20. Visser K, Katchamart W, Loza E, Martinez-Lopez JA, Salliot C, Trudeau J, et al. Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E initiative. Ann Rheum Dis 2009;68:1086-93.
21. Prey S, Paul C. Effect of folic or folinic acid supplementation on methotrexate-associated safety and efficacy in inflammatory disease: a systematic review. Br J Dermatol 2009;160:622-8.
22. Ortiz Z, Shea B, Suarez Almazor M, Moher D, Wells G, Tugwell P. Folic acid and folinic acid for reducing side effects in patients receiving methotrexate for rheumatoid arthritis. Cochrane Database Syst Rev 2000;2:CD000951.
23. Castaneda O, Nair MG. Controlled trial of methotrexate versus CH-1504 in the treatment of rheumatoid arthritis. J Rheumatol 2006;33:862-4.