

An Open-Label, Non-Randomized, Pilot Clinical Trial of a Novel, Metabolically Stable Antifolate, CH-1504 in the Treatment of Advanced Rheumatoid Arthritis

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Abstract

Purpose: Several studies suggest that a significant proportion of the toxicity profile of Methotrexate can be attributed to its polyglutamylated and/or hydroxylated metabolites. We tested the clinical safety, tolerance and efficacy of a novel antifolate which is neither hydroxylated nor polyglutamylated in patients with advanced rheumatoid arthritis.

Methods: Groups of 10 patients fulfilling the ACR criteria for RA and on stable doses of NSAIDs and low dose steroids were assigned to receive either 6.67mg daily oral dosing of CH-1504 or 10mg once weekly oral dosing of methotrexate (MTX) for a period of 24 weeks. Patients were evaluated monthly for safety and tolerance as demonstrated by clinical biochemistry and hematology evaluations as well as adverse event reporting. Patients were evaluated for efficacy using standard parameters to determine the ACR response rate.

Results: Baseline characteristics for the two treatment groups were similar with two exceptions. Firstly, the average duration of disease was 7.2 years for the MTX treatment group and 16.7 years for the CH-1504 group. Secondly the CH-1504 group included 4 previous MTX failures. Three patients on MTX had elevations in ALT levels above the limit of normal commencing at 8 weeks of therapy and persisting through the end of study. There were no serious adverse events reported and all patients completed the study. The incidence of treatment related adverse events was 70% in the methotrexate group and 20% in the CH-1504 group. Neither treatment group demonstrated any clinically significant changes in hematology over the course of the trial. In comparison to methotrexate, only somnolence appeared to be more frequently associated with CH-1504 treatment. It was considered mild in nature as it was reported to have had no effect on activities of daily living. The majority of AEs reported for MTX were GI related (nausea, vomiting, dyspepsia, abdominal pain) it was of note that treatment with CH-1504 was not associated with any GI disturbances. Regarding efficacy, under the conditions of this study the 24 week ACR20 was determined to be 40% for MTX and 90% for CH-1504. An ACR50 was achieved in 40% of patients treated with CH-1504 by the 24 week time point. Efficacy with CH-1504 was also seen to develop rapidly achieving an ACR20 of 60% at 1 month of treatment.

Conclusions: The results of this open-label, non-randomized pilot clinical trial suggests that the novel, non-metabolized antifolate, CH-1504 may possess an improved safety and tolerance profile when compared to the current standard of care MTX. In addition significant efficacy was reported although with small numbers. Larger dose-ranging trials are needed to see if similar findings can duplicate the positive results reported in this small pilot study.

Introduction

CH-1504 is metabolically stable, specifically it is:

- Nonpolyglutamylatable
- Nonhydroxylatable
- Stable to hydrolytic cleavage by carboxypeptidase secreted by intestinal flora
- More efficiently taken up into cells by the reduced folate carrier (RFC) system than is MTX
- An antifolate with significant inhibitory activity on both DHFR and TS enzymes

It is our hypothesis that:

- CH-1504 will demonstrate an improved safety profile because it is devoid of the toxicity secondary to the formation of the polyglutamylated and hydroxylated metabolites
- CH-1504 will demonstrate improved efficacy relative to antifolates such as methotrexate because the improved safety profile will allow greater systemic exposure to the active agent without the accumulation of toxic metabolites
- The lack of polyglutamylated metabolites, which are retained intracellularly, will result in a more relevant pharmacokinetic profile

Patients & Methods

Study Design:

- Open-label, non-randomized clinical trial
- 24 weeks duration
- Patients received either 10 mg methotrexate once per week as a tablet or 6.7 mg CH-1504 daily

Inclusion Criteria:

- Active Rheumatoid Arthritis per ACR criteria
- Disease onset after age 18 and duration greater than 6 months
- Stable dose NSAID and/or low dose steroids

Exclusion Criteria:

- Patients receiving more than 10mg daily of steroids
- Patients receiving DMARD therapy within two months prior to baseline
- Patients with clinically significant laboratory abnormalities

Statistical Analysis:

- For each efficacy variable the area under the time-response curve was calculated for both the MTX treated group as well as the CH-1504 group. Statistical comparison was made using a Student t test with P < 0.05 set as the level of significance

Study Procedures:

- Baseline (visit 0) evaluation included a complete history, physical examination, and determination of eligibility criteria
- Patient visits occurred every 4 weeks for a total of 24 weeks (visits one through six)
- The following clinical variables were assessed for efficacy: tender and swollen joint counts, patient and doctor assessment of disease activity, degree of pain on a Visual Analogue Scale, Health Assessment Questionnaire (HAQ), ESR and CRP
- Safety and tolerability were assessed by adverse reactions and laboratory parameters including complete blood cell count with differential and platelet count, creatinine, alkaline phosphatase, ALT, AST

Results

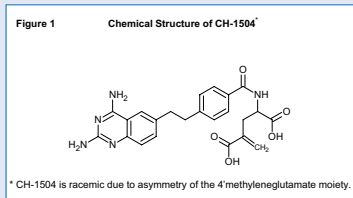
- Twenty patients met entry criteria and 10 were assigned to each group
- All 20 patients completed the trial
- Table 1 details patient demographic information

Efficacy:

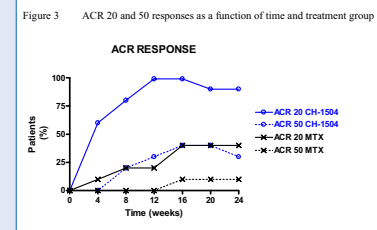
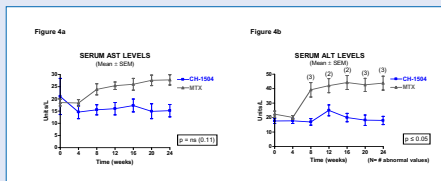
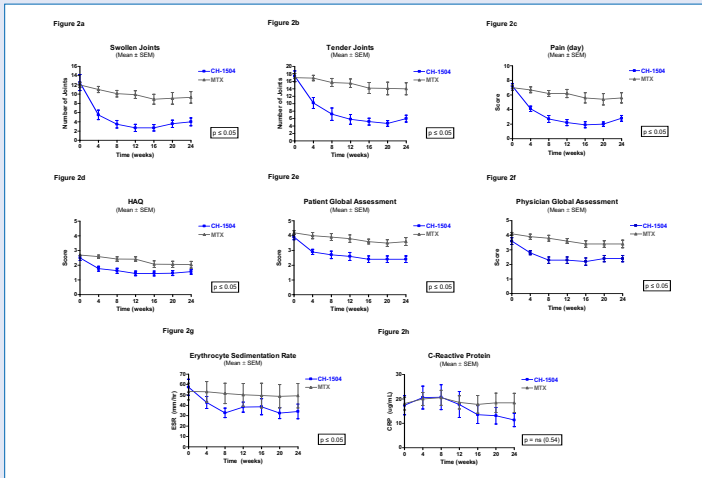
- The response observed in each individual efficacy parameters for both groups can be found in Figures 2a - 2h
- Each individual response criteria was statistically superior for the CH-1504 group compared to the MTX group with the exception of CRP
- Individual response variables were summarized into a single categorical response variable (Figure 3) as per the American College of Rheumatology (ACR) guideline for ACR response rates standard definition
- For the CH-1504 group there was a rapid onset of clinical efficacy with the attainment of an ACR20 in 6 patients seen at the first visit
- The overall response rate continued to improve up to week 16 (visit 4) at which time the extent of clinical benefit appeared to plateau for both CH-1504 and MTX
- Only one patient treated with CH-1504 was a non-responder contrasted with 6 of the patients that received MTX therapy
- The one non-responder to CH-1504 was one of the 4 MTX failures that were enrolled in the CH-1504 treatment arm
- Of the 9 patients treated with CH-1504 who responded, 4 reached the ACR50 definition of response contrasted with 1 of the MTX treated patients

Safety and Tolerance:

- No severe or serious adverse events were reported in either group during this study
- The incidence of treatment related adverse events were 40% in the methotrexate group and 20 % in the CH-1504 group
- Only somnolence appeared to be more frequently associated with CH-1504 treatment (Table 2)
- It was noted that gastrointestinal adverse events (tolerance) were associated with MTX treatment they were not associated with CH-1504 treatment
- No clinically significant alterations were observed in the clinical chemistry laboratory data from patients treated with CH-1504
- Three patients on MTX had elevations of ALT above the upper limit of normal that persisted from visit 2 through the end of the study, as a consequence the average ALT reported for the MTX treatment group trends higher over the course of the study (Figure 4b)
- No abnormal findings were reported with regards to hematology in either group. Data from the CH-1504 group are shown in Table 3



Parameter	Methotrexate	CH-1504
Female (%)	90	90
Age (years)	53.7	54.8
Disease Duration (years)	7.2	16.7
RF (%)	100	100
Previous MTX Failure (N)	0	4
Swollen Joints (N ± SEM)	12.0 ± 2.4	12.5 ± 5.7
Tender Joints (N ± SEM)	18.2 ± 1.8	17.4 ± 4.4
Pain (N ± SEM)	6.4 ± 2.4	6.5 ± 2.4
HAQ (N ± SEM)	2.5 ± 0.2	2.3 ± 0.5
ESR (mm/hr ± SEM)	53.2 ± 25.5	57.4 ± 24.2
CRP (ug/ml ± SEM)	18.1 ± 8.3	17.4 ± 12.4



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

Parameter	Time (weeks)							
	0	4	8	12	16	20	24	
Hemoglobin	12.0	11.8	12.4	12.2	12.3	12.6	12.5	
g/dl	(1.4)	(1.7)	(2.1)	(1.6)	(1.4)	(1.4)	(1.5)	
Hematocrit	36.2	36.0	36.9	37.8	37.9	39.0	38.4	
%	(4.3)	(4.9)	(5.2)	(4.4)	(4.9)	(4.3)	(4.1)	
WBC	7.5	7.8	7.5	8.0	7.4	6.6	7.1	
X10 ³ /mm ³	(1.6)	(2.0)	(2.6)	(1.3)	(2.1)	(2.0)	(1.7)	
Platelets	343.7	416.0	395.3	391.6	339.7	303.1	268.6	
X10 ³ /mm ³	(88.7)	(135.7)	(76.4)	(74.4)	(86.9)	(87.1)	(103.1)	
PMN A	1.3	1.5	2.3	1.7	1.9	1.7	1.7	
X10 ³ /mm ³	(1.3)	(2.1)	(1.4)	(2.6)	(1.2)	(1.4)	(1.3)	
PMN S	61.8	64.5	65.2	66.3	64.6	63.6	64.5	
X10 ³ /mm ³	(10.0)	(9.5)	(9.5)	(9.5)	(3.9)	(5.0)	(7.8)	
LMN	25.1	25.8	19.6	22.3	25.3	22.5	22.5	
X10 ³ /mm ³	(10.5)	(8.0)	(7.0)	(5.9)	(9.1)	(5.4)	(6.6)	
Monocytes	10.4	6.7	11.8	9.6	7.8	10.8	10.7	
X10 ³ /mm ³	(6.3)	(3.4)	(6.9)	(8.5)	(6.0)	(5.5)	(5.6)	

Data are means (Standard Deviation)

Discussion

The mechanism of action of methotrexate in RA is currently unknown and there is no definitive relation between its antifolate activity and its antirheumatic effects. In fact the toxicity of methotrexate can be reduced with folate supplementation in patients with RA without affecting efficacy. This observation clearly suggests that the mechanism(s) resulting in clinical efficacy and toxicity can be distinguished. It is our contention that a significant proportion of the low dose methotrexate side-effect profile is due to the hydroxylated and polyglutamylated metabolites of the parent compound^(1,2). Therefore it is in theory possible to reduce the toxicity and enhance efficacy. The present trial tests this hypothesis: CH-1504 is a potent inhibitor of dihydrofolate reductase that is metabolically inert and therefore it may show significantly improved safety and tolerability in patients with rheumatoid arthritis

In this study CH-1504 demonstrated a capacity to induce a significant improvement in all clinical efficacy parameters at the completion of the trial. Specifically, 90% of patients had a clinically significant improvement as defined by attainment of an ACR20. The methotrexate group had a substantially inferior response rate of 40% however it should be noted that the dose of methotrexate was held to 10mg per week. Consequently, there can be no definitive conclusion drawn as to the relative efficacy of the two treatments. However the fact that 3 of 4 previous methotrexate failures did respond positively to treatment with CH-1504 is intriguing.

With respect to the safety profile, the results are supportive of the theoretically envisioned benefits of CH-1504. Specifically, there was no evidence of any impact on liver function as indicated by plasma level of ALT and AST liver enzymes (Figure 4a and 4b). This compared favorably to the experience of the methotrexate group where elevations were noted in some patients. It was also noted that the gastro-intestinal disturbances which are characteristic of methotrexate were absent in the CH-1504 treated group. The only side effect noted to occur more frequently with CH-1504 treatment was mild somnolence. This was seen in two patients and was persistent in only one patient.

In summary, our experience with CH-1504 has been favorable in this limited trial. It is encouraging that the anticipated benefits of a metabolically stable anti-folate in the treatment of RA have been observed. However the efficacy and safety of this drug requires further evaluation in larger blinded and randomized trials.

Conclusions

- CH-1504 appears to be an efficacious therapy for the treatment of Rheumatoid Arthritis characterized by a rapid onset of action with potential superiority to MTX
- CH-1504 appears to have a favorable safety and tolerability profile with potential to be superior to MTX
- The results of this pilot study warrant further evaluation in larger, randomized, blinded trials

References

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