Arthritis & Rheumatism (Arthritis Care & Research)
Vol. 59, No. 7, July 15, 2008, pp 905–910
DOI 10.1002/art.23824

ORIGINAL ARTICLE

A Randomized, Double-Blind, Multicenter, Controlled Clinical Trial of Chicken Type II Collagen in Patients With Rheumatoid Arthritis

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Objective. **To assess the efficacy and safety of chicken type II collagen (CCII) in rheumatoid arthritis (RA) compared with methotrexate (MTX).**

Methods. **We conducted a prospective, 24-week, followup, multicenter, double-blind, controlled study of CCII (0.1 mg/day) versus MTX (10 mg/week) in patients with active RA. Clinical assessments were performed at screening and at 12, 18, and 24 weeks of treatment.**

Results. **A total of 236 RA patients were included; 211 patients (89.4%) completed the 24-week followup. In both groups there was a decrease in pain, morning stiffness, tender joint count, swollen joint count, Health Assessment Questionnaire score, and investigator and patient assessment of function; all differences were statistically significant. In the MTX group, erythrocyte sedimentation rate and C-reactive protein level decreased. Rheumatoid factor did not change in either group. At 24 weeks, 68.57% of patients in the CCII group and 83.02% in the MTX group met the American College of Rheumatology 20% improvement criteria (ACR20), and 40.95% and 57.54%, respectively, met the ACR50 criteria. The ACR20 and ACR50 response rates in the CCII group were lower than those in the MTX group, and this difference was statistically significant ($P < 0.05$). Gastrointestinal symptoms were common in both groups. There were fewer and milder side effects in the CCII group than the MTX group. The difference in incidence of adverse events between the 2 groups was statistically significant ($P < 0.05$).**

Conclusion. **CCII is effective in the treatment of RA. CCII is well tolerated, and the incidence of adverse events of CCII is lower than that of MTX.**

INTRODUCTION

Rheumatoid arthritis (RA) is a highly disabling disease that limits mobility, hampers work, and reduces quality of life. It is also a chronic inflammatory disease characterized by pain, swelling, and stiffness of multiple joints. Chronic inflammation commonly results in progressive joint destruction, deformity, and loss of function. Complex immune mechanisms contribute to the pathology of RA (1). Currently, most drugs for RA are analgesics, immune suppression reagents, and cytotoxic drugs. These therapies suppress the immune system nonspecifically and are associated with significant side effects, including infections, anorexia, dyspepsia, and so on. Immune tolerance, a state of immunologic unresponsiveness induced by oral administration of antigens, has posed intriguing possibilities for the treatment of autoimmune diseases, including RA (2–5).

In RA, type II collagen (CII) of the articular cartilage is one of the candidate autoantigens, and some patients with RA demonstrate immunity against CII. Oral administration of CII has been shown to ameliorate arthritis in animal models of joint inflammation, and previous studies have suggested that this novel therapy is clinically beneficial and safe in patients with RA (6–9). Investigators in our group found that collagen-induced arthritis (CIA) could be established in Wistar rats and Kunming mice with chicken type II collagen (CCII) (10,11). Feeding CCII to rats by oral

ChiCTR: 2003L00641.

Supported by the Shanghai Materia Medica Bioengineering Institute.

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Submitted for publication November 19, 2007; accepted in revised form March 8, 2008.

Table 1. Study population*

	CCII group (n = 118)	MTX group (n = 118)
Withdrawal		
Adverse events	3 (2.54)	5 (4.24)
Noncompliance	1 (0.84)	2 (1.69)
Lack of response	5 (4.24)	3 (2.54)
Lost to followup	4 (3.39)	2 (1.69)
Finished followup	105 (88.98)	106 (89.83)

* Values are the number (percentage). CCII = chicken type II collagen; MTX = methotrexate.

administration decreased the arthritis index. Meanwhile, cartilage degeneration, synovium hyperplasia, and inflammatory cell infiltration in the knee joints of mice and rats with CIA were suppressed by CII (12). These experiments in rodents have provided the basis for human clinical trials. In this study, we conducted a randomized, double-blind, multicenter, controlled trial to evaluate the efficacy and safety of CCII in patients with RA.

PATIENTS AND METHODS

Patients. A total of 236 patients with RA (ages 18–65 years) who met the revised American College of Rheumatology (ACR; formerly the American Rheumatism Association) criteria for the diagnosis of RA (13) were entered into the study after giving their written informed consent (14). The study population is defined in Table 1. Admission criteria also included both male and female patients with RA of at least 6 months' duration with a maximum 24-month duration. Active RA was defined as the presence of at least 3 of the following: ≥6 painful or tender joints, ≥3 swollen joints, morning stiffness lasting at least 45 minutes (average during the previous week prior to entry), and an erythrocyte sedimentation rate (ESR) ≥28 mm/hour. Second-line agents were discontinued at least 4 weeks prior to entry. Continued use of nonsteroidal antiinflammatory drugs (NSAIDs) was permitted. All investigative centers had signed informed consent forms approved by their respective investigational and ethics committees.

Exclusion criteria were as follows: liver dysfunction; severe cardiovascular, urinary, hematopoietic, or endocrine system disease; immunodeficiency; uncontrolled infection or active gastrointestinal tract disease; recent vaccination; gravida; currently lactating or intending to become pregnant (women); hypersensitivity to CII; treatment with any other disease-modifying antirheumatic drugs within 30 days before enrollment; history of frequent alcohol abuse; history of hyperglycemia or motor coordination disorder; and participation in other clinical trials within 3 months before enrollment.

Study protocol. The study was a 4-center, 24-week, followup, double-blind, double-dummy, randomized, methotrexate (MTX)-controlled trial comparing efficacy and safety of CCII and MTX in RA. Patients were randomly assigned to receive either CCII (0.1 mg/day) or MTX (10 mg/week). Patients and investigators were blinded to the treatment regimens throughout the study. Patients were assessed at 0, 12, 18, and 24 weeks.

Patients were allowed to remain on diclofenac sodium (50 mg/day), an NSAID. The diclofenac sodium dose was not changed during the study.

CCII capsules (Shanghai Materia Medica Bioengineering Institute, Shanghai, China), CCII dummy capsules, MTX tablets (Shanghai Xin Yi Pharmaceutical, Shanghai, China), and MTX dummy tablets were provided by the Shanghai Materia Medica Bioengineering Institute. Patients were instructed to take oral CCII capsules or dummy capsules with 200 ml of cold water 30 minutes prior to eating breakfast every morning.

Clinical assessments. Clinical assessments of efficacy were made at baseline and repeated 12, 18, and 24 weeks later. Efficacy variables included pain (pain intensity was assessed by a visual analog scale [VAS] from 0 [no pain] to 10 [severe pain]), morning stiffness (patients were questioned about the duration of morning stiffness experienced on the day before each study visit), swollen and tender joint counts (joint counts for tenderness and swelling were the sum of the number of affected joints), physician and patient global assessments (rated according to a VAS from 0 [very good] to 10 [very poor]), functional status (assessed at baseline and at 12, 18, and 24 weeks using the Health Assessment Questionnaire [HAQ]), ESR and C-reactive protein (CRP) level (obtained at baseline and 12, 18, and 24 weeks), and rheumatoid factor positivity (determined at the screening visit and at 24 weeks) (15,16).

The primary efficacy variable was the ACR preliminary definition of improvement in RA (17). To achieve improvement according to the ACR definition, a patient with RA must improve by at least 20% in tender and swollen joint counts and by at least 20% in 3 of the other 5 measures, including patient global assessment of function, physician global assessment of function, HAQ, acute-phase reactant, and patient pain assessment. In addition to evaluating 20% improvement according to ACR criteria (ACR20), we also determined RA improvement based on more substantial changes in RA core set measures, such as requiring at least 50% improvement (ACR50) reported as secondary efficacy measures (18). Clinical parameters also included body weight, blood pressure, and heart rate. To standardize evaluation of clinical variables, prior to study entry all investigators performed a clinical evaluation of 1 patient with active RA.

Adverse events. At each visit, patients were asked whether they noticed side effects during the interim. Side effects such as gastrointestinal symptoms, vomiting, anorexia, headache, dizziness, insomnia, tetter, and mouth ulcers have been known to occur frequently during treatment with CCII or MTX. Moreover, at entry, 12 weeks, and 24 weeks, the following laboratory variables were assessed to monitor safety: complete blood cell count, serum levels of liver enzymes, creatinine, uric acid, and urinalysis.

Table 2. Comparison of baseline clinical characteristics between the CCII group and MTX group*

Variables	CCII (n = 105)	MTX (n = 106)	*P*
Sex, male/female	20/85	17/89	0.565
Age, years	47.85 ± 10.15	47.37 ± 10.75	0.739
Disease duration, years	1.73 ± 0.42	1.82 ± 0.65	0.925
Body temperature, °C	36.73 ± 0.33	36.72 ± 0.31	0.738
Pain (VAS)	5.39 ± 1.48	5.51 ± 1.42	0.518
Morning stiffness, minutes	88.67 ± 28.14	79.91 ± 26.81	0.277
Tender joint count	16.22 ± 6.86	16.95 ± 6.25	0.477
Swollen joint count	11.22 ± 7.12	11.88 ± 6.93	0.313
HAQ	0.78 ± 0.39	0.81 ± 0.52	0.662
Physician's assessment (VAS)	5.86 ± 1.64	5.88 ± 1.46	0.899
Patient's assessment (VAS)	5.55 ± 1.27	5.66 ± 1.48	0.556
ESR, mm/hour	37.69 ± 21.30	40.58 ± 24.66	0.364
CRP level, mg/liter	16.29 ± 8.55	16.32 ± 9.85	0.990
Rheumatoid factor, units/ml	104.07 ± 16.90	142.61 ± 18.10	0.055

* Values are the mean ± SD unless otherwise indicated. The same variables were compared between the CCII group and MTX group. Fisher's exact test was used for categorical variables and *t*-test analysis of variance was used for continuous variables. CCII = chicken type II collagen; MTX = methotrexate; VAS = visual analog scale; HAQ = Health Assessment Questionnaire; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein.

Statistical analysis. Safety assessments were performed on all patients who consumed any masked study medication. Efficacy analyses were performed on the intent-to-treat population as well as on the population of patients who completed the 24-week study. Efficacy analysis of outcome variables was based on mean changes from baseline to end point in the intent-to-treat population. The statistical software used for these analyses was SAS, version 8.1 (SAS Institute, Cary, NC). All laboratory variables were subjected to descriptive statistics and compared by means of Wilcoxon's signed rank test. The randomization code was exposed only after the database was locked. Categorical variables were analyzed by chi-square test with Fisher's exact test and continuous variables were analyzed by *t*-test and analysis of variance. The significance level was established at 0.05.

RESULTS

Baseline characteristics. Of 236 randomized patients (118 in the CCII group and 118 in the MTX group), 25 patients withdrew early, 13 (11.02%) in the CCII group and 12 (10.17%) in the MTX group. There were various reasons for early withdrawal, such as adverse events, noncompliance, lack of response, and being lost to followup. Eight patients reported side effects. Eight patients withdrew due to lack of efficacy and 3 patients withdrew due to lack of compliance. Six patients were lost to followup (Table 1). A total of 211 patients completed 24 weeks of therapy. At study entry, the groups were well balanced with regard to demographic characteristics and disease parameters (Table 2), with no important differences among the 4 centers. All patients had active RA as defined by the inclusion criteria.

Efficacy. In both groups there was a decrease in pain, morning stiffness, tender joint count, swollen joint count, HAQ score, and efficacy as assessed by both investigators and patients. Within-group differences (study entry versus 12, 18, and 24 weeks) were statistically significant for the above clinical disease parameters (Table 3). In the MTX group, ESR and CRP level decreased. However, changes of these 2 variables in the CCII group were not significant. Rheumatoid factor was not significantly affected by either drug.

ACR response criteria. According to an intent-to-treat analysis (Figure 1), at 12 weeks, 30.47% of patients in the CCII group and 44.33% in the MTX group met the ACR20 criteria for improvement, and 19.05% and 31.13%, respectively, met the ACR50 criteria. At 24 weeks, 68.57% in the CCII group and 83.02% in the MTX group met the ACR20 criteria for improvement, and 40.95% and 57.54%, respectively, met the ACR50 criteria. The ACR20 and ACR50 response rates in the CCII group were lower than those in the MTX group. These changes were statistically different between the 2 treatment groups ($P < 0.05$).

Safety. The analysis of adverse events was carried out for all 236 randomized patients, and both treatments were generally well tolerated in all patients. Adverse events were common in both groups. At 12 weeks, the CCII group reported 16 (13.55%) adverse events while the MTX group reported 40 (38.13%). There were 25 (21.19%) adverse events in the CCII group and 50 (42.37%) adverse events in the MTX group at 24 weeks. There were fewer and milder side effects in the CCII group than in the MTX group (Table 4). The incidence of adverse events between the CCII group and the MTX group was statistically significant ($P < 0.05$).

Gastrointestinal symptoms were the most common adverse events, occurring in 7 and 14 patients in the CCII and MTX groups, respectively (Table 5). Other adverse events included vomiting, anorexia, headache, dizziness, insom-

Table 3. Results in outcome variables at entry, 12, 18, and 24 weeks*

Outcome variables	CCII	P†	MTX	P†	P‡
Pain (VAS)					
Entry	5.39 ± 1.48		5.51 ± 1.42		> 0.05
12 weeks	4.01 ± 2.01	< 0.01	3.46 ± 1.83	< 0.01	< 0.05
18 weeks	3.51 ± 2.02	< 0.01	2.87 ± 1.88	< 0.01	< 0.05
24 weeks	3.39 ± 2.19	< 0.01	2.61 ± 1.96	< 0.01	< 0.05
Morning stiffness, minutes					
Entry	88.67 ± 28.14		79.91 ± 26.81		> 0.05
12 weeks	44.91 ± 15.07	< 0.01	32.52 ± 12.21	< 0.01	> 0.05
18 weeks	32.98 ± 16.03	< 0.01	22.66 ± 13.12	< 0.01	> 0.05
24 weeks	29.02 ± 17.32	< 0.01	20.01 ± 12.78	< 0.01	> 0.05
Tender joint count					
Entry	16.22 ± 6.86		16.95 ± 6.25		> 0.05
12 weeks	10.13 ± 7.02	< 0.01	8.51 ± 6.42	< 0.01	< 0.05
18 weeks	8.31 ± 4.37	< 0.01	7.31 ± 4.23	< 0.01	> 0.05
24 weeks	8.25 ± 4.12	< 0.01	6.94 ± 4.15	< 0.01	> 0.05
Swollen joint count					
Entry	11.22 ± 7.12		11.88 ± 6.93		> 0.05
12 weeks	5.12 ± 3.21	< 0.01	4.66 ± 2.56	< 0.01	> 0.05
18 weeks	3.62 ± 2.56	< 0.01	3.75 ± 2.01	< 0.01	> 0.05
24 weeks	3.47 ± 2.34	< 0.01	3.51 ± 2.23	< 0.01	> 0.05
HAQ					
Entry	0.78 ± 0.39		0.81 ± 0.52		> 0.05
12 weeks	0.47 ± 0.21	< 0.01	0.37 ± 0.18	< 0.01	< 0.05
18 weeks	0.41 ± 0.16	< 0.01	0.28 ± 0.14	< 0.01	< 0.05
24 weeks	0.37 ± 0.24	< 0.01	0.24 ± 0.12	< 0.01	< 0.05
Global efficacy, investigator (VAS)					
Entry	5.86 ± 1.64		5.88 ± 1.46		> 0.05
12 weeks	4.72 ± 1.32	< 0.05	4.15 ± 1.28	< 0.01	< 0.05
18 weeks	4.22 ± 1.21	< 0.05	3.66 ± 1.43	< 0.01	> 0.05
24 weeks	3.81 ± 1.52	< 0.01	3.53 ± 1.64	< 0.01	> 0.05
Global efficacy, patient (VAS)					
Entry	5.55 ± 1.27		5.66 ± 1.48		> 0.05
12 weeks	4.26 ± 2.04	< 0.05	3.74 ± 1.66	< 0.01	< 0.05
18 weeks	3.73 ± 2.25	< 0.01	3.19 ± 1.74	< 0.01	< 0.05
24 weeks	3.57 ± 2.32	< 0.01	2.93 ± 2.01	< 0.01	< 0.05
ESR, mm/hour					
Entry	37.69 ± 21.30		40.58 ± 24.66		> 0.05
12 weeks	33.78 ± 20.82	> 0.05	28.53 ± 14.62	< 0.01	< 0.05
18 weeks	34.37 ± 14.28	> 0.05	25.73 ± 13.25	< 0.01	< 0.05
24 weeks	31.74 ± 13.20	> 0.05	25.38 ± 5.95	< 0.01	< 0.05
CRP level, mg/liter					
Entry	16.29 ± 8.55		16.32 ± 9.85		> 0.05
12 weeks	14.04 ± 5.21	> 0.05	11.53 ± 3.92	< 0.05	< 0.05
18 weeks	13.78 ± 4.79	> 0.05	11.04 ± 2.68	< 0.05	< 0.05
24 weeks	13.69 ± 5.38	> 0.05	7.94 ± 2.25	< 0.01	< 0.05
Rheumatoid factor, units/ml					
Entry	104.07 ± 16.90		142.61 ± 18.10		> 0.05
24 weeks	100.22 ± 16.11	> 0.05	133.51 ± 21.33	> 0.05	> 0.05

* Values are the mean ± SD unless otherwise indicated. See Table 2 for definitions.
† Comparison within groups.
‡ Comparison between the CCII group and the MTX group.

nia, tetter, and mouth ulcers. These adverse events were mild and did not interfere with the continuation of treatment drugs.

Laboratory variables. In the MTX group, there was a significant increase from baseline in transaminase and a decrease in white blood cell count. There were decreases in hemoglobin, platelet count, and neutrophil count in both groups, although the differences were not significant. Other laboratory variables were not significantly affected in either group.

DISCUSSION

Oral tolerance has been applied to prevent and treat autoimmune disease in several animal models, including arthritis. CII is the most abundant structural protein of hu-

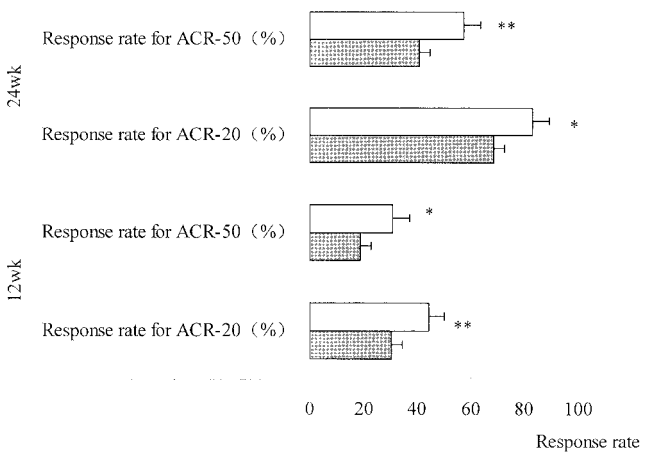

Figure 1. Comparison of the effect of the American College of Rheumatology 20% response (ACR-20) and ACR-50 between the chicken type II collagen (CCII) and methotrexate (MTX) groups at 12 and 24 weeks. According to an intent-to-treat analysis, at 12 weeks 30.47% of patients in the CCII group and 44.33% in the MTX group met the ACR-20 criteria for improvement, and 19.05% and 31.13%, respectively, met the ACR-50 criteria. At 24 weeks, 68.57% in the CCII group and 83.02% in the MTX group met the ACR-20 criteria, and 40.95% and 57.54%, respectively, met the ACR-50 criteria. ACR-20 and ACR-50 response rates in the CCII group were lower than those in the MTX group. These changes were statistically different between the 2 treatment groups. * $P < 0.05$ versus CCII group. ** $P < 0.01$ versus CCII group. Open bars represent the MTX group; shaded bars represent the CCII group.

man cartilage. The cartilage within joints mainly causes autoimmunity damage in patients with RA. Oral administration of CII is a well-established procedure for inducing peripheral immune tolerance, which suppresses autoimmune responses in patients with RA (19–21). However, the precise mechanisms of oral tolerance are not fully known. Studies have shown that oral tolerance is associated with down-regulation of proinflammatory cytokines such as interleukin-1 (IL-1) and tumor necrosis factor α expression and up-regulation of suppressive cytokines such as transforming growth factor β (TGFβ) and IL-4 expression (22). It is generally agreed that the regulation of mucosa-inducing tolerance involves several mechanisms, including active suppression induced by low doses of antigens and clonal anergy or deletion induced by high doses of antigens (23). Cells from Peyer's patches in gut-associated lymphoid tissue and TGFβ are reported to mediate the induction of active suppression (24). Based on the above, CCII was developed as a novel drug of immunologic tolerance. Compared with traditional therapies, CCII is well tolerated and has little toxic effect in patients with RA (14).

Table 4. Comparison of adverse events between the CCII and MTX groups at 12 weeks and 24 weeks*

	Adverse events, no.	Rate of adverse events, %	χ^2	P†
12 weeks			3.961	0.047
CCII group (n = 118)	16	13.55		
MTX group (n = 118)	40	38.13		
24 weeks			4.194	0.041
CCII group (n = 118)	25	21.19		
MTX group (n = 118)	50	42.37		

* See Table 2 for definitions.
† Chi-square test.

Table 5. Adverse events by treatment*

Adverse events	CCII	MTX
Gastrointestinal symptoms	7	14
Headache	1	1
Dizziness	5	11
Insomnia	2	5
Tetter	1	3
Mouth ulcers	1	2
Vomiting	0	1
Anorexia	5	11
Heart throb	0	14
Liver function abnormalities	2	5
Urinary tract infection	2	4

* CCII = chicken type II collagen; MTX = methotrexate.

The present study was undertaken to further evaluate whether oral administration of CCII is safe and effective in patients with RA. In this phase II trial, CCII at 0.1 mg/day and MTX at 10 mg/week effectively alleviated signs and symptoms of active RA. However, the efficacy of CCII did not exceed that of MTX. There was a significant difference in the incidence of treatment-related adverse events between the CCII group and MTX group. According to a previous study, CCII causes few adverse events in patients with RA (19). In the present study, treatment was administered in combination with diclofenac sodium, a type of NSAID, which can cause frequent gastrointestinal symptoms. The use of diclofenac sodium can relieve pain. Nevertheless, it can overlap with the mechanisms of action and toxicity of the trial drugs. The effect of CCII will be affected, as diclofenac sodium can damage the alimentary system (25). Long-term observations in large numbers of patients are needed to confirm the efficacy of CCII. If the efficacy were to be established, oral collagen would be a preferable treatment due to its minor toxicity.

Overall, treatment of autoimmune diseases by induction of oral tolerance is appealing because of the few side effects and easy clinical implementation of this approach. This MTX-controlled, multicenter, 24-week trial in patients with RA confirms that CCII is a safe and generally well-tolerated therapy. The results of the study partly support the mechanism of oral tolerance. These data will provide a basis for more effective application of oral tolerance induction in patients with RA.

ACKNOWLEDGMENTS

The following rheumatologists are also members of the trial group: Gui-Jun Fei, Sheng-Qian Xu, Shuang Liu, Fen Wang, Wei Zhang, Sheng Chen, Hua-Xiang Liu, Feng Ding, and Jie Shen.

AUTHOR CONTRIBUTIONS

Dr. Wei had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study design. Wei, Xu.
Acquisition of data. Xu, Bao, Ni, Li.
Analysis and interpretation of data. Zhang, Xiao.
Manuscript preparation. Zhang, Wei.
Statistical analysis. Xiao.
Coordination and organization. Wei.

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