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ORIGINAL ARTICLE

Treatment of rheumatoid arthritis with ornidazole: a randomized, double-blind, placebo-controlled study

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Abstract The aim of our study was to evaluate the clinical efficacy, safety, and tolerability of ornidazole in patients with rheumatoid arthritis (RA). This was 3 months, randomized, double-blind,placebo-controlled study. A total of 160 patients with active RA were randomly assigned to receive 1,000 mg ornidazole ($n = 53$), 500 mg ornidazole ($n = 55$), or placebo ($n = 52$). A significantly greater percentage of patients treated with 1,000 mg ornidazole met the American College of Rheumatology 20% improvement criteria (achieved an ACR20 response) at 3 months compared with patients who received placebo (62.0 vs. 32.4%; $P < 0.001$). Greater percentages of patients treated with 1,000 mg ornidazole also achieved ACR50 responses (38.3 vs. 10.9%; $P < 0.001$) and ACR70 responses (19.6 vs. 1.2%; $P < 0.001$) compared with patients who received placebo. Ornidazole treatment was also associated with significant reductions in pain and duration of morning stiffness, significant improvement in the quality of life and both the physician's and patient's global assessments, and significant reductions in disease activity as assessed by objective laboratory measures (erythrocyte sedimentation rate and C-reactive protein level). Ornidazole was well tolerated. There were no dose-limiting toxic effects. In this 3-month-trial ornidazole was safe, well tolerated, and associated with improvement in the inflammatory symptoms of RA.

Keywords Ornidazole · Rheumatoid arthritis · Treatment

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Introduction

Rheumatoid Arthritis (RA) is a polyarticular, chronic, inflammatory, and systemic disease [1]. Although many disease modifying antirheumatic drugs (DMARDs) and biological agents are used in the treatment of this disease, new pharmaceutical drugs are required to achieve better efficacy and lower costs.

In many previous studies, this rheumatic disease has been found at frequencies in individuals with periodontitis, and rheumatoid arthritis resembles periodontitis in many pathological aspects [2, 3]. High levels of oral anaerobic bacterial antibodies have been found in the serum and synovial fluid of RA patients [4, 5].

Previously, antibiotic treatment was employed in RA therapy. Sulfasalazine and tetracycline are effective against this disease [6–8]. The chronic use of sulfasalazine decreases gram-negative anaerobic bacteria numbers and *Bacteroides* in the intestines of patients with rheumatoid arthritis [9].

Ornidazole is a nitroimidazole antiprotozoal drug that also has potent antibacterial activity against anaerobes, including *Bacteroides* and *Clostridium* species [10]. Its adverse effects are very mild when compared with those of metronidazole [11]. Adverse effects include nausea, headache, dry mouth, or metallic taste in the mouth. It was demonstrated that it

has efficacy surpassing 94% especially against oral anaerobic bacteria in the alveolar canal [12].

Biologic treatment agents and specifically TNF alpha-blockers are effective in rheumatoid arthritis therapy [13, 14]. Periodontopathic bacteria are powerful simulators for TNF alpha and other pro inflammatory cytokines in humans [15–18].

In this study, the purpose was to monitor the efficacy and reliability of ornidazole, an effective antibiotic specifically against *Bacterioides* genus in rheumatoid arthritis treatment.

Materials and methods

Patients

Patients enrolled in this study met the ACR (formerly, the American Rheumatism Association) criteria for the diagnosis of RA (functional classes I, II, or III) [19]. Patients had active disease defined as ≥ 12 tender joints based on a 68 joint assessment, ≥ 10 swollen joints based on a 66 joint evaluation, and either an erythrocyte sedimentation rate (ESR) ≥ 28 mm/1 h or a serum C reactive protein (CRP) concentration ≥ 2.0 mg/dl.

Previous DMARD therapies such as hydroxychloroquine, gold, sulfasalazine, methotrexate, azathioprine, leflunomide, and cyclosporine were applied and turned out to be insufficient in the treatment of the patients. Disease modifying antirheumatic drugs were discontinued at least 4 weeks before the study began. Stable doses of nonsteroidal antiinflammatory drugs and prednisone (≤ 10 mg daily) were allowed.

The criteria for exclusion from the study were as follows: use of antibiotics in the last 30 days prior to the study, some other infection, renal or hepatic functional dysfunction, and pregnancy. Women of reproductive age were required to take appropriate contraceptive measures.

Study protocol

This study was conducted from August 2001 to August 2005 in Salihli and Nazilli State Hospital in Turkey. This was 3 months, randomized, double-blind, placebo-controlled study. The study was conducted in accordance with the principles of Good Clinical Practice, according to the Declaration of Helsinki. Before entering this study, all patients gave written informed consent. Basic clinical measures included the below parameters: complete count of swollen and tender joints (68 joints evaluated; cervical spine and hips evaluated only for tenderness), duration of morning stiffness, disability [disability index of the health-assessment questionnaire (HAQ)] [20], physician's and patient's global assessment on scale from 0 (asymptomatic) to 10 (severe symptoms), patient's assessment of pain on a visual–analogue scale from 0 (no pain) to 10 (severe pain) [21], Westergren erythrocyte sedimentation rate, and CRP [22]. The disease activity measures taken after the first day were repeated once every week in the first month and biweekly in the following period.

The patients were taken in for control first on a biweekly basis following the 3-month study. These controls continued until the number of patient inflamed joints reached pre-study levels or the patient required a previously administered therapy or a new one.

During the study as well as post-study evaluation period, hematological tests, serum biochemistry, and urinary analysis test assays were performed. All patients were evaluated for side effects and laboratory anomalies.

Treatment

Patients were randomly assigned to one of the three treatment groups: placebo orally, 500 mg ornidazole (250 mg twice a day) orally, or 1,000 mg ornidazole (500 mg twice a day) orally.

Concomitant medications

The use of analgesics such as acetaminophen, codeine, or propoxyphene for pain relief was permitted.

Statistical analysis

The percent change from base line to 3 months in the swollen-joint count, tender-joint count, and total count of swollen or tender joints was the primary measure of efficacy. Secondary end points included pain, quality of life, duration of morning stiffness, erythrocyte sedimentation rate, C-reactive protein level, and physician's and patient's global assessments. If a subject withdrew from the study, the last available value was used as the 3 month value. The data were also analyzed to determine the number of patients meeting American College of Rheumatology criteria for 20, 50, and 70% improvement.

An ACR 20 response is defined as a reduction of at least 20% in the number of tender joints and swollen joints plus an improvement of at least 20% in at least three of the following five criteria: patient's assessment

of pain, patient's assessment of disease activity, physician's assessment of disease activity, patient's assessment of physical function, and serum C-reactive protein concentration [23, 24]. ACR50 and ACR70 were defined in the same manner as ACR20 but with ≥ 50 or ≥ 70% degree of improvement, respectively.

The values were compared with the use of analysis of variance. The percentages of patients with ACR 20, ACR 50, and ACR 70 responses were compared with the use of chi-square tests.

Results

The pre-treatment baseline characteristics of patients are given in Table 1. A total of 160 patients between the ages 19 and 69 were included in the study, 35 of them males and the remaining 125 females. There were no significant differences between the groups in neither baseline disease activity nor pre-treatment characteristics. A total of 53 patients completed 1,000 mg ornidazole daily, 55 patients completed 500 mg ornidazole daily, and 52 patients completed placebo therapy. The primary response for withdrawal from the study was the noncontrol of arthritis symptoms. About 5% of the patients in 1,000 mg daily ornidazole group withdrew from the study. The ratios of withdrawals for 500 mg ornidazole and placebo groups were 19 and 42%, respectively.

Efficacy

Ornidazole had an effect of pronounced improvement in the assays of disease activities (Table 2). These improvements were observed to be most prominent in the group that was administered 1,000 mg ornidazole. While the total joint numbers showed a decrease of 60%, in placebo this ratio was 20% ($P < 0.001$). A positive correlation can be observed between the increased dosage of ornidazole and decrease in swollen joint count and tender joint count. The decreases in the number of swollen and tender joints commenced in the first week and continued until the end of treatment.

Ornidazole treatment was also associated with significant reductions in pain and duration of morning stiffness, significant improvement in the quality of life and physician's and patient's global assessments, and significant reductions in disease activity as assessed by objective laboratory measures (erythrocyte sedimentation rate and C-reactive protein level) (Table 2).

While patients complying with ACR20 criteria in the 1,000 mg ornidazole treatment group at the end of the 3-month period were 62.0%, this ratio was 32.4% in the placebo group ($P < 0.001$). While patients complying with ACR50 criteria in the 1,000 mg ornidazole treatment group at the end of the 3-month period were 38.3%, this ratio was 10.9% in the placebo group ($P < 0.001$). While patients complying with ACR70 criteria in the 1,000 mg ornidazole treatment

Table 1 Demographic and base-line characteristics of the patients

Characteristics	Placebo ($n = 52$)	500 mg ornidazole ($n = 55$)	1,000 mg ornidazole ($n = 53$)
Mean age (year)	51 ± 12	53 ± 13	54 ± 10
Female sex (%)	80	75	71
Disease duration (year)	10 ± 8	9 ± 7	11 ± 8
RF positivity (%)	76	82	74
Swollen-joint count (No)	19 ± 7	20 ± 9	21 ± 11
Tender-joint count (No)	32 ± 12	30 ± 15	31 ± 10
Total count (No)	51 ± 21	50 ± 23	52 ± 19
Morning stiffness (h)	4.9 ± 1.2	4.7 ± 1.3	4.3 ± 1.2
Physician's assessment[a]	7.1 ± 2.3	7.4 ± 2.1	6.5 ± 2.0
Patient's assessment[a]	6.4 ± 1.8	7.0 ± 1.9	6.2 ± 1.7
Pain (visual–analogue scale)[a]	6.6 ± 1.7	6.9 ± 1.6	6.4 ± 1.8
Disability index of HAQ[b]	1.68 ± 0.6	1.81 ± 0.7	1.76 ± 0.6
Erythrocyte sedimentation rate (mm/h)	50 ± 24	48 ± 23	44 ± 21
C-reactive protein (mg/dl)	3.8 ± 3.2	3.4 ± 3.1	3.6 ± 3.2
Previous treatment (%)			
Corticosteroids	74	76	81
DMARD	100	100	100
Methotrexate	40	38	36
NSAIDs	70	72	78

HAQ Health assessment questionnaire, *DMARDs* disease-modifying antirheumatic drugs, *RF* rheumatoid factor, *NSAIDs* nonsteroidal antiinflammatory drugs. Plus–minus values are means ± SD

[a]On this scale 0 is best and 10 worst

[b]On this scale 0 is no difficulty and 3 is unable to perform activity

Table 2 Effect of treatment on measures of disease activity at 3 months

Measure of activity value	Placebo (n = 52)	500 mg ornidazole (n = 55)	1,000 mg ornidazole (n = 53)	P*
Swollen-joint count (No)	16 ± 5	13 ± 6	9 ± 3	< 0.001
Tender-joint count (No)	25 ± 8	15 ± 6	12 ± 5	< 0.001
Total count (No)	41 ± 12	28 ± 10	21 ± 9	< 0.001
Morning stiffness (h)	4.2 ± 1.2	2.4 ± 1.4	1.2 ± 1.0	< 0.005
Physician's assessment[a]	5.7 ± 1.4	4.2 ± 1.5	2.3 ± 0.9	< 0.001
Patient's assessment[a]	6.1 ± 2.3	4.7 ± 2.1	3.1 ± 1.2	< 0.001
Pain (VAS)[a]	6.2 ± 1.8	4.3 ± 1.9	2.4 ± 0.8	< 0.001
Disability index of HAQ[b]	1.62 ± 0.6	1.43 ± 0.4	1.27 ± 0.2	< 0.001
ESR(mm/h)	48 ± 21	36 ± 2.3	22 ± 13	< 0.001
CRP (mg/dl)	2.5 ± 2.3	1.9 ± 1.7	0.6 ± 0.2	< 0.001
Improvement from base-line (%)				
Swollen-joint count	16	35	57	< 0.001
Tender-joint count	22	50	61	< 0.001
Total count	20	44	60	< 0.001

VAS visual–analogue scale, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *HAQ* health-assessment questionnaire. Plus–minus values are means ± SD

*The P values obtained from an analysis of variance

[a]On this scale 0 is best and 10 worst

[b]On this scale 0 is no difficulty and 3 is unable to perform activity

group at the end of the 3-month period were 19.6%, this ratio was 1.2% in the placebo group ($P < 0.001$) (Table 3).

Safety and tolerability

Ornidazole was well tolerated and no deaths were reported by ornidazole-treated patients after 6 months of treatment. In general, adverse events were reported at a similar or lower rate in the ornidazole groups than in the placebo group. The most frequently reported adverse events were headache, dry mouth, and nausea (seen in at least 5% of patients, and excluding worsening of RA).

Only one patient withdrew because of an adverse event related to ornidazole (vertigo). Fewer adverse events were reported in the group given 500 mg ornidazole than in the group given 1,000 mg ornidazole.

Table 3 Efficacy at 3 months according to the ACR response rate criteria

Variable	Placebo (%)	500 mg ornidazole (%)	1,000 mg ornidazole (%)
ACR response rate			
ACR 20	32.4	40.1	62.0**
ACR 50	10.9	21.4*	38.3**
ACR 70	1.2	11.5*	19.6**

The P values were obtained by chi-square test comparing all three treatment groups

*$P < 0.05$, **$P < 0.001$

No major abnormalities in hematologic findings or serum chemical profiles were noted during or after the study; in fact, improvements in anemia and decreases in platelet counts were seen, which reflect a reduction in disease activity.

Discussion

The results of this randomized, double-blind trial show the clinical efficacy of ornidazole in patients with active rheumatoid arthritis. Treatment with ornidazole for 3 months was associated with a reduction in disease activity as assessed by a number of clinical end points, biochemical markers of disease, and quality of life.

Ornidazole produced significant, rapid, and sustained reductions in disease activity. A strong, consistent dose–response relation was seen in most of the variables measured. The few adverse events noted—headache, dry mouth, and nausea—were mild and easily managed.

Cessation of therapy was associated with an increase in disease activity, suggesting that continued administration of ornidazole is necessary for sustained effect.

Ornidazole, a synthetic nitroimidazole derivative, is used in the treatment of infections caused by periodontopathic bacteria [9]. *Porphyromonas gingivalis, Prevotella intermedia, Prevotella melaninogenica*, and *Bacteroides forsythus* are Gram-negative anaerobic bacteria and are considered to be directly responsible for the periodontitis (Periodontopathic bacteria) [25]. These bacteria are members of the normal human

mouth flora, where they cause endodontitis, odontogenic inflammation, gingivitis, and mainly periodontitis [26].

High levels of IgG antibodies against this bacteria were found in synovial fluid and blood samples from patients with RA [4, 5]. *P. gingivalis* has arginine and lysine specific proteinase [27]. Citrullination or deamination of arginine residues in autoantigenic proteins (profilaggrin/filaggrin, fibrinogen/fibrin, keratin, and vimentin) creates epitopes that are targeted by rheumatoid autoantibodies [28]. Arginine is the most important of the amino acids associated with autoantigenicity in proteins.

RA patients have significantly fewer galactose residues on their IgG Fc compared with age-matched healthy control subjects. A lack of terminal galactose residues early in disease is associated with a worse prognosis [29]. *P. melaninogenica*, as a saccharolytic bacteria, disintegrates galactose. Consequently, *P. melaninogenica* this causes this condition by binding to the Fc region of the IgG molecule and metabolizing galactose with its enzymes.

RFs have been identified as autoantibodies that react to the IgG molecule in the Fc region, and these antibodies may be of IgM, A, G, or E epitopes. *P. gingivalis* proteinase is responsible for the epitope development in the RF Fc region. Bonagura et al. identified lysine, histidine, arginine amino acid sequences for the Fc region of the IgG molecule [30]. Because *P. gingivalis* specifically decomposes lysine and arginine, the IgG3 CH2 and CH3 domains processed by *P. gingivalis* proteinase become powerful targets for the RF produced by rheumatoid cells [31]. The chronic inflammation associated with periodontitis appears to significantly increase the formation of IgM-RF. The RF detected in the serum of some periodontitis patients may be elicited by certain micro-organisms in the subgingival plaque [32, 33].

High levels of periodontopathic bacteria heat shock proteins were found in the serum of RA patients [34]. *P. gingivalis* has a 60-kDa heat shock protein (hsp.GroEL). Due to the similarity of the *P. gingivalis* hsp 60 molecule to the human hsp 60 molecule, it is a key molecule for GroEL homolog autoimmune reactions [35]. *P. melaninogenica* and *P. intermedia* heat-shock proteins of approximately 70-kDa have been found in periodontal disease processes [36]. Ueki et al. determined that *P gingivalis* GroEL and human hsp60 antibodies are found increasingly more often in periodontal patients compared to those without disease [37]. Hsp 70 antibodies have been detected in the synovial tissue of RA patients and when the hsp 70 expression is induced with certain stress stimulating factors, proinflammatory cytokines (tumor necrosis factor-alpha, IL-1, IL-6) develop in the RA synovium [38].

P. gingivalis, *P. intermedia*, *P. melaninogenica*, and *B. forsythus* produce gingival tissue destruction and autoimmune responses in periodontitis patients. T-cell and antibody responses in periodontitis confirm the infiltration of reactive T-cell clones into periodontitis lesions. These lesions demonstrate higher proliferative responses of peripheral blood mononuclear cells, cytokines (gamma-interferon, IL-4), and T-cell clonality. These findings indicate the presence of an active antibody response in synovial tissue and illustrate a potential connection between periodontal and inflammatory joint diseases.

Ornidazole treatment in RA is very economical compared with other treatments. It can be concluded from this study that ornidazole is an effective treatment for RA. The above evidence indicates that antibodies formed against oral anaerobic bacteria could be important in the aetiopathogenesis of RA. However, further studies are needed to confirm this.

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