Doxycycline versus Doxycycline and Rifampin in Undifferentiated Spondyloarthropathy, with Special Reference to *Chlamydia*-Induced Arthritis. A Prospective, Randomized 9-Month Comparison

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ABSTRACT. ***Objective.*** *Chlamydia* is a known trigger of reactive arthritis (ReA). It may also be common cause of undifferentiated spondyloarthropathy (uSpA). Persistent, metabolically active, *Chlamydiae* have been observed in the synovial tissue of these patients years after their initial exposure. Trials with lymecycline and rifampin have shown benefit in early/acute *Chlamydia*-induced arthritis. *In vitro* data suggest that persistent *Chlamydia* become resistant to chronic monotherapy of tetracyclines or rifampin, whereas no such resistance is noted when rifampin is added to antimicrobials that are active against *Chlamydia*. Rifampin and doxycycline also show synergistic effect against *Chlamydia*. In addition, rifampin inhibits chlamydial production of heat shock proteins (HSP). HSP60 plays a key role in the chronic persistent state of *Chlamydia*. We conducted a prospective, randomized 9-month trial to evaluate the efficacy of doxycycline versus a combination of doxycycline and rifampin in the treatment of uSpA.

Methods. The study enrolled 30 patients with chronic inflammatory arthritis (average disease duration 10 yrs) who fulfilled the European Spondylarthropathy Study Group criteria, with no evidence of inflammatory bowel disease, psoriasis, ankylosing spondylitis, or preceding dysentery. Patients received doxycycline 100 mg po twice daily or a combination of doxycycline 100 mg po twice daily and rifampin 600 mg po daily. They received a 4-question self-questionnaire and a blinded joint examination at each visit. The questions include a visual analog scale (VAS) for their current amount of back pain, duration of morning stiffness, back pain at night, and peripheral joint pain. The blinded joint examination consisted of a swollen joint count (SJC) and a tender joint count (TJC). These 6 variables were assessed at baseline and at 1, 3, 6, and 9 months. Responders were defined as those who improved ≥ 20% in at least 4 of the 6 variables at 9 months of therapy.

Results. Comparing the doxycycline + rifampin arm (D/R) versus the doxycycline arm (D) at 9 months of therapy, all 6 variables improved more in D/R versus D, 4 of which were statistically significant. The mean VAS (scale of 100) decreased 24.4 points in D/R in contrast to 3 points in D ($p < 0.03$). Duration of morning stiffness decreased by 1.2 h in D/R, with a slight increase of 0.1 h in D ($p < 0.003$). The back pain at night and peripheral joint pain both improved in D/R group versus D (not statistically significant). Finally, the SJC and TJC also improved in D/R (–2.1 and –2.5) versus D (–0.4 and –0.6; $p = 0.02$, $p = 0.03$, respectively). Eleven of 15 patients in the D/R arm were responders, whereas only 2 of 15 D group patients were considered responders ($p < 0.003$).

Conclusion. The combination of doxycycline and rifampin for 9 months seemed to be effective in treatment of chronic uSpA. This is the first study to demonstrate therapeutic benefit with antimicrobials to a chronic inflammatory arthritis possibly secondary to persistent *Chlamydia*. (J Rheumatol 2004;31:1973–80)

Key Indexing Terms:
REACTIVE ARTHRITIS SPONDYLOARTHROPATHY *CHLAMYDIA*
DOXYCYCLINE RIFAMPIN HEAT SHOCK PROTEIN

Certain bacterial infections can lead to an inflammatory arthritis that may or may not be associated with a variety of extraarticular manifestations. If the original bacterial infection is known, then the subsequent inflammatory arthritis is referred to as reactive arthritis (ReA). If the original bacterial infection is occult or unproven, the inflammatory arthritis would be best classified as undifferentiated spondyloarthropathy (uSpA).

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Bacteria that commonly cause ReA are *Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*, and *Chlamydia trachomatis*. There is also mounting evidence that *Chlamydia pneumoniae* is another etiology of ReA[1-3]. Acute *Chlamydia trachomatis* infections are often asymptomatic or occult[4]. *Chlamydia pneumoniae* is a common cause of atypical pneumonia or bronchitis, and as many as 70% of infections are asymptomatic[5,6]. In addition, when an acute infection with *Chlamydia pneumoniae* is symptomatic, a definitive diagnosis of this organism is often never established.

In 1996, the US Centers for Disease Control estimated 3 million new cases of *Chlamydia trachomatis* infections among persons 15 to 44 years of age in the United States[7]. A study in that same year in the US revealed that 4.1% of people with a definitive or probable *Chlamydia trachomatis* infection developed ReA[8]. This would equate to an annual incidence of 123,000 cases of ReA to *Chlamydia trachomatis* in the US. As a comparison, the estimated annual incidence of rheumatoid arthritis (RA) in the US is 44.6/100,000[9]. In the 2000 US census, the population was 281 million. This would equate to about 125,000 new cases of RA in the US every year. A recent study in Sweden found the annual incidence of ReA to be higher than that of RA[10]. Thus, ReA represents a considerable burden on the US population, and around the world, that may be vastly underrecognized.

The use of antibiotics in the treatment of ReA and uSpA is controversial. However, ReA to *Chlamydia* may be uniquely susceptible to antimicrobial therapy. Lymecycline taken for 3 months showed benefit to patients with acute *Chlamydia*-induced ReA, while ReA to dysenteric organisms showed no benefit[11]. More recent trials with ciprofloxacin and azithromycin showed no benefit in 4 trials[12-15]. However, a subgroup analysis of patients with *Chlamydia*-induced ReA showed a trend toward improvement in one of the trials[14]. There was no such subgroup analysis in the other trials. A followup of one of these ciprofloxacin trials suggested that this antibiotic significantly improved the longterm prognosis[16]. In addition, a 9-month trial with rifampin did show significant improvement in patients with early ReA[17].

We conducted a prospective, randomized 9-month trial to evaluate the efficacy of doxycycline versus a combination of doxycycline and rifampin in the treatment of uSpA. While many of these patients had a clinical history consistent with an immediate preceding *Chlamydia trachomatis*, and in some cases possible *Chlamydia pneumoniae*, infection, definitive proof of the organism was not obtained. Thus, we felt that these patients were best classified as having uSpA rather than ReA. A combination of antibiotics has never been studied in the treatment of ReA or uSpA.

MATERIALS AND METHODS

Patients. The study was conducted from January 2000 to January 2003. Patients were recruited from the rheumatology division at the James A. Haley Veterans Administration and University of South Florida (USF) Medical Clinics in Tampa, Florida. Patients were required to meet the European Spondylarthropathy Study Group (ESSG) criteria[18] without evidence of ankylosing spondylitis (AS), psoriasis, inflammatory bowel disease, or preceding dysentery. The ESSG criteria require that the patient have inflammatory spinal pain or peripheral synovitis, plus at least one of the following: preceding urethritis or cervicitis, buttock pain, enthesopathy, or radiographic evidence of sacroiliitis[18].

Patients were excluded if they had previously received a longterm trial (> 2 weeks) of any antibiotic for their inflammatory arthritis, or if they were taking any medications that were known to interact with doxycycline or rifampin. They were also excluded if they had any evidence of serious liver, renal, or hematological disorders. Patients were allowed to take nonsteroidal antiinflammatory drugs (NSAID) or disease modifying antirheumatic drugs (DMARD), if they were using these drugs prior to enrollment and the dose remained unchanged throughout the trial. To distinguish patients with AS, patients were also excluded if they had bilateral symmetric sacroiliitis, marginal vertebral syndesmophytes, squaring of vertebral bodies, or spinal ankylosis.

The institutional review board at the James A. Haley VA and USF approved the study. All patients provided written informed consent.

Protocol. Patients were randomly assigned to receive either doxycycline 100 mg by mouth twice daily or a combination of doxycycline 100 mg by mouth twice daily and rifampin 600 mg by mouth daily for 9 months. This was an open-label trial with a blinded joint assessment. All patients were screened with a physical examination, complete blood count (CBC), comprehensive metabolic panel, urinalysis, and a plain radiograph of the sacroiliac joints and lumbar spine. Patients were also tested for HLA-B27. A repeat CBC, metabolic panel, and urinalysis was performed at 3 months of therapy. These same investigations were repeated at any time if the patient developed any symptom including nausea, vomiting, or abdominal pain.

Clinical assessments were performed at baseline and then after 1, 3, 6, and 9 months of therapy. A self-assessment questionnaire and a blinded physical examination were employed at each visit to evaluate disease activity. Questionnaires were used to determine the patient's degree of back pain, duration of morning stiffness (minutes), amount of back pain at night, and peripheral joint pain. Their degree of back pain was determined on a 100 mm visual analog scale (VAS), 0 indicating no pain and 100 mm the most severe pain. The amount of back pain at night was graded on a 4-point scale, with 1 being no pain at all and 4 representing terrible pain that is constant and causes marked interference with sleep. Their peripheral joint pain was rated on a 5-point scale, 1 being none and 5 representing very severe pain. These 4 questions were taken directly from the large Veterans Administration clinical trial assessing sulfasalazine in the treatment of reactive arthritis[19].

A single physician (FBV) conducted the physical examination in a blinded manner at each visit. It consisted of a 64-joint swollen joint count (SJC) and 66 joint tender joint count (TJC). Both were judged on a 4-point scale with 0 indicating none; 1, mild; 2, moderate; and 3, severe.

Adverse events. Patients were questioned about any potential side effects from their medications at each visit. These questions included, but were not limited to, nausea, vomiting, diarrhea, flu-like symptoms, dysphagia, odynophagia, epigastric/chest pain, or photosensitivity. Patients were also provided a telephone number to report any potential side effects at any point during the study. Laboratory values were rechecked at 3 months.

Outcome measures. The primary endpoint was the VAS of their current amount of back pain. Secondary outcome measures included the patient's duration of morning stiffness on the day of the interview, the questions describing their current nocturnal back pain and peripheral joint pain, the SJC and TJC, and the number of patients considered to be responders. Responders were defined prior to the study as those that improved 20% or more in at least 4 of the 6 aforementioned variables compared to their baseline.

Statistical analysis. The study was designed with 80% power to detect a 70% response rate in the group receiving both doxycycline and rifampin compared to a 30% response rate in those receiving only doxycycline. The target sample was 30 patients to allow for withdrawal of one patient in each group.

Analysis was performed on an intention-to-treat principle. Data were compared in both groups from their last visit to their baseline visit. The change from baseline was calculated in each patient. The mean changes were then compared in the 2 groups using the Mann-Whitney test. A 2-tailed Fisher exact test was used for categorical or ordinal data. All patients were included in the analysis. If they stopped their study drugs or were lost to followup, then the last observation carried forward was employed. All statistical tests were 2-sided, with a p value ≤ 0.05 considered statistically significant.

RESULTS

Patients. Patient's baseline demographics are shown in Table 1. Twenty-seven men and 3 women were enrolled in the study. The mean age was 47 years, and patients had chronic disease with an average disease duration of roughly 10 years. Fourteen of the 30 patients (47%) were HLA-B27 positive. Thirteen of the 15 patients in the doxycycline group (D) were taking stable doses of NSAID, and 14 of 15 in the group receiving both doxycycline and rifampin (D/R) were as well (data not shown). None of these differences were statistically significant. Only one patient in the study was receiving a DMARD at baseline; he was in the D/R group and he was taking a stable dose of methotrexate (MTX) and sulfasalazine. He was advised to continue these medications, at the same dose, throughout the study, but he discontinued his MTX at one month into the trial because of clinical improvement.

The patients' baseline clinical characteristics are also shown in Table 1. All patients had inflammatory spinal pain, and the majority had peripheral synovitis. Most patients (83%) had evidence of sacroiliitis (either grade II or grade III) on plain radiographs. Of the 13 patients in group D who had sacroiliitis, 12 had unilateral sacroiliitis (10 right-sided and 2 left-sided). One patient in group D had asymmetric bilateral sacroiliitis that was worse on the right. In group D/R, 12 patients had sacroiliitis. Nine of these patients had unilateral sacroiliitis (6 right-sided and 3 left-sided), and 3 patients had asymmetric bilateral sacroiliitis (2 worse on the right and one worse on the left). Regarding the patients who had peripheral synovitis (12/15 in each group), 5 patients had a monoarthritis (3 in group D: 1 knee and 2 wrists; and 2 in group D/R: 1 knee and 1 ankle). No patient in the study had more than 8 swollen joints. There were no statistically significant differences in the clinical characteristics in each group.

Seven of the 30 patients had a history of preceding urethritis or cervicitis. Four of these 7 stated that their preceding urethritis or cervicitis was caused by *Chlamydia trachomatis*, but definitive proof was not obtained. Of these 4 patients, 2 were in the D group and 2 in the D/R group. There were also 2 other patients who recalled an episode of atypical pneumonia (possibly *Chlamydia pneumoniae*) immediately prior to their inflammatory arthritis (both in the D/R group). Thus, 9 of the 30 patients (30%) had either a possible or probable preceding symptomatic *Chlamydia* infection.

Efficacy. All 6 variables that were followed as markers of disease activity improved more in group D/R compared to group D. Four of these 6 variables improved to a significant degree. Regarding the primary endpoint, patients in group

Table 1. Patients' demographics and clinical characteristics.

	Doxycycline (D), n = 15	Doxycycline + Rifampin (D/R), n = 15
Sex	13 M; 2 F	14 M; 1 F
Mean age, yrs (range)	47.13 (22–71)	47.13 (27–70)
Disease duration, yrs (range)	9.4 (0.5–25)	10.4 (1.17–34)
HLA-B27 + *, n (%)	6/15 (40)	8/15 (53)
Ethnicity		
Caucasian	10	11
African American	3	1
Hispanic	2	3
Clinical characteristics**, n (%)		
Inflammatory spinal pain	15/15 (100)	15/15 (100)
Synovitis	12/15 (80)	12/15 (80)
Preceding urethritis/cervicitis	3/15 (20)	4/15 (27)
Buttock pain	14/15 (93)	13/15 (87)
Enthesopathy	5/15 (33)	8/15 (53)
Sacroiliitis	13/15 (87)	12/15 (80)

No statistically significant differences between patient groups. * HLA-B27 incidence depends on the population studied. The incidence in previous ReA trials varies from < 50% to 80%[11–15, 17]. ** ESSG criteria[18] (without evidence of AS, psoriasis, inflammatory bowel disease, or preceding dysentry).

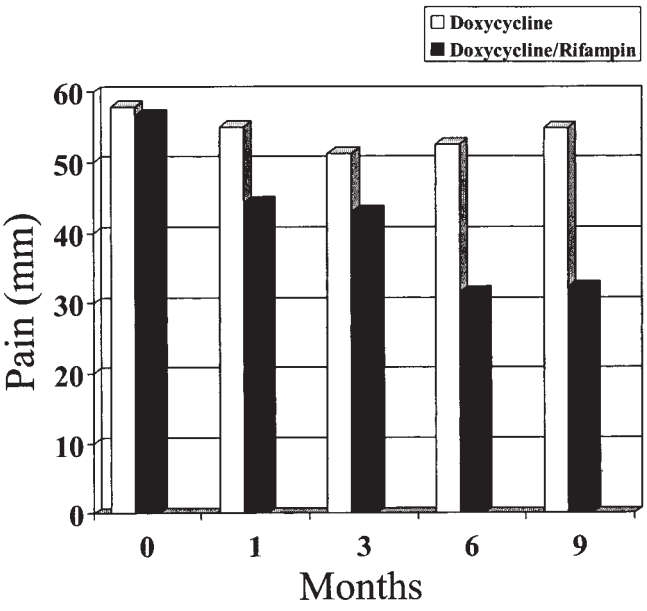

Figure 1. VAS for back pain at 9 months improved 24.4 points in D/R group compared to 3 points in D group ($p < 0.03$).

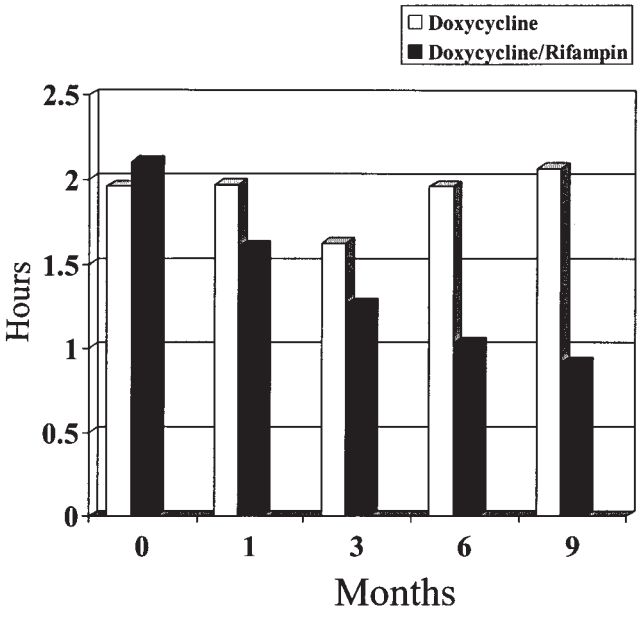

Figure 2. Duration of morning stiffness at 9 months improved by a mean of 71 minutes in D/R group compared to a slight worsening of 7 minutes in D group ($p < 0.003$). P value at 6 months = 0.008.

D/R achieved significantly greater improvement in their VAS compared to those in group D after 9 months of therapy. The VAS improved 24.4 points in D/R versus 3 points in D ($p < 0.03$) (Figure 1). There was also significantly greater improvement in the duration of morning stiffness in D/R compared to D at 9 months. The duration of morning stiffness improved by a mean of 71 minutes in D/R compared to a slight worsening of 7 minutes in D group ($p < 0.003$) (Figure 2). The patients' nocturnal back pain did not show significant improvement and their peripheral joint pain revealed a trend toward improvement favoring the D/R group ($p = 0.45$ and $p = 0.10$, respectively). The patients' blinded SJC and TJC both significantly improved in D/R compared to D ($p = 0.02$ and $p = 0.03$, respectively) (Figures 3 and 4). Both of these achieved statistical significance at 6 months of therapy.

The duration of morning stiffness and VAS scores continued to improve throughout the 9 months in D/R group. Significant improvement in morning stiffness in D/R compared to D group was initially noted at 6 months ($p = 0.008$) and continued to improve at 9 months. Significant improvement in the VAS scores of D/R compared to D was not noted until 9 months of therapy.

Compared to their baseline, the results were similar, yet more impressive. Again, all 6 variables improved in group D/R, 4 of which were statistically significant. The VAS, duration of morning stiffness, and TJC all achieved statistical significance at 3 months ($p = 0.048$, 0.04, 0.026, respectively) and continued to improve throughout the study. The SJC was significantly improved at 6 months ($p = 0.002$). The p values at 9 months compared to baseline were 0.002, 0.004, 0.003, and 0.005, respectively. At no time during the study did any of the variables in group D improve to a significant degree.

Eleven of the 15 patients in the D/R group were considered responders, whereas only 2 of the 15 in D group responded ($p < 0.003$). Of the 7 patients who had a preceding episode of urethritis or cervicitis (4 in group D/R and 3 in group D), 3 were considered responders; all 3 were in group D/R. The one patient in group D/R with preceding urethritis who was considered a nonresponder was lost to followup. Four of these 7 patients gave a history of preceding *Chlamydia trachomatis* specifically. Two were in group D/R and 2 were in group D. Both in group D/R were responders and neither in group D responded. Regarding the 2 patients who had possible *Chlamydia pneumoniae* as the etiology, both were in group D/R and both were considered responders. If we exclude the 2 patients in group D/R who were lost to followup, 11 out of 13 (85%) were responders.

*Adverse event*s. There were no serious adverse events. Three patients discontinued their medicines secondary to side effects (2 in group D/R and one in group D). Of the 2 patients in group D/R, one discontinued the antibiotics because of nausea and recurrent yeast infections, and the other because of dysuria. The one patient who stopped taking antibiotic in group D did so because of recurrent yeast infections and epigastric discomfort. Another patient in group D/R experienced intermittent nausea from the antibiotics, but he chose to continue them because of clinical improvement. A final patient in group D/R decreased his doxycycline dose to 100 mg daily and rifampin to 300 mg

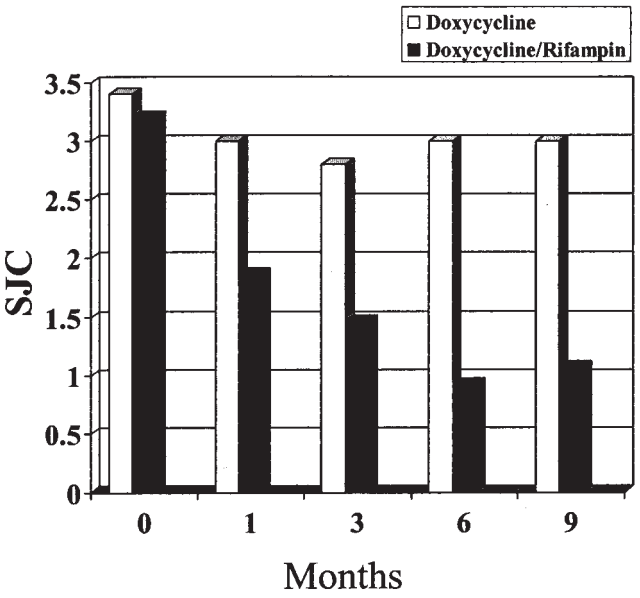

Figure 3. Patients' blinded swollen joint count (SJC) at 9 months improved significantly in D/R group compared to D group (p = 0.02). P value at 6 months < 0.05.

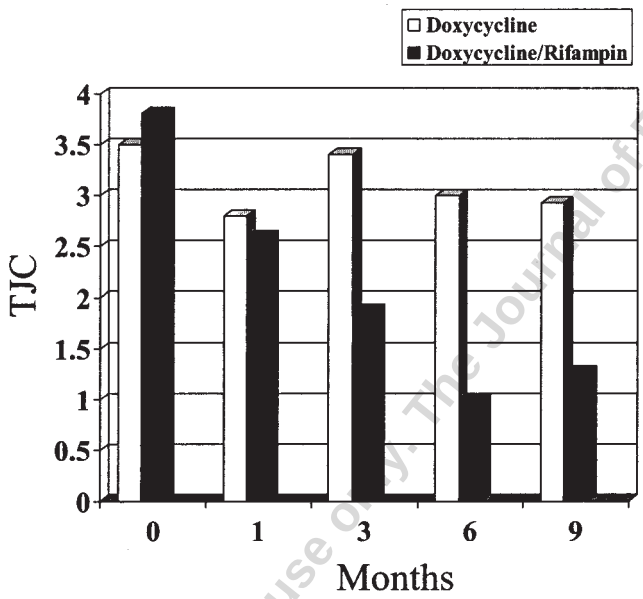

Figure 4. Patients' blinded tender joint count (TJC) at 9 months improved significantly in D/R group compared to D group (p = 0.03). P value at 6 months = 0.01.

daily because of insomnia. A total of 5 patients were lost to followup (3 in group D and 2 in group D/R), and none of these were considered responders.

DISCUSSION

There is no evidence that antibiotics have a role in the treatment of the post-dysentery form of ReA. If there is a potential benefit, it is with *Chlamydia*-induced ReA. Polymerase chain reaction (PCR) technology has confirmed the presence of bacterial fragments in the synovial fluid and tissue of patients with the post-dysentery form of ReA[20-22]. These bacterial fragments are from the same bacteria that are known to trigger the dysentery form of ReA. PCR technology has proven the presence of both *Chlamydia trachomatis* and *Chlamydia pneumoniae* in the synovial tissue of patients with the post-chlamydial form[23-25]. These *Chlamydiae* exist in a persistent metabolically active state, suggesting they could be susceptible to antimicrobial agents, whereas bacterial fragments are not.

ReA frequently becomes a chronic condition[26]. The average disease duration in our patient population was about 10 years (Table 1). Synovial-based, metabolically active *Chlamydia trachomatis* and *pneumoniae* have been documented in ReA patients with chronic disease as long as 15 years[24,25]. Persistent *Chlamydia* infections, however, are very different from acute infections, for they demonstrate aberrant gene expression, and the infected cells resist apoptotic stimuli[24,27,28]. Paramount in this process is the down-regulation of chlamydial proteins, except heat shock protein 60 (HSP60)[24,25,27,29,30]. HSP60 remains elevated in persistent *Chlamydia* infections.

Heat shock proteins are conserved molecules synthesized by both prokaryotic and eukaryotic cells that play an essential role in protein-folding, assembly, and translocation between different intracellular compartments. In stressful conditions, HSP allow cells to survive lethal assaults by preventing protein denaturation[31]. HSP60 has also been shown to be pivotal in the inability of *Chlamydia*-infected cells to undergo apoptosis[27,28]. It also has a potential role in conferring antibiotic resistance[32,33].

HSP60 is essential to the pathogenic-related sequelae of persistent *Chlamydia* infections, but exactly how is unclear. Chlamydial HSP60 is either immunogenic itself, or, by providing the infected cells apoptotic resistance, it allows the persistently infected cells to chronically produce inflammatory mediators[30-32,34-36]. In either case, successful elimination of the infected cells would abrogate this process.

Rifampin binds to the beta-subunit of prokaryotic RNA polymerases and prevents initiation of transcription of heat shock proteins[37,38]. Rifampin has also been shown to specifically block HSP production in *Chlamydia trachomatis*[39]. In this study, *Chlamydia trachomatis* utilized at least 2 different pathways to induce the transcription of mRNA encoding heat shock proteins. Rifampin blocked both pathways[39].

Previous trials assessing the efficacy of antimicrobial therapy in ReA have had both positive and negative results, and have focused primarily on acute ReA. A 1991 trial suggested that lymecycline was an effective treatment for patients with acute post-chlamydial ReA, but not the post-dysentery form[11]. That the post-dysentery patients did not

respond suggests that the antiinflammatory property of lymecycline was not the therapeutic mechanism. Another study revealed that 9 months of therapy with rifampin was beneficial in 63% of patients (12/19) with early ReA (≤ 4 months' duration)[17]. This suggests that tetracyclines and rifampin are efficacious in the treatment of early *Chlamydia*-induced ReA. Therapy of chronic ReA is less well established.

Rifampin demonstrates powerful *in vitro* activity against *Chlamydia*[40-42]. It also has excellent tissue penetration, which is mandatory when treating intracellular pathogens. However, *in vitro* data show that persistent *Chlamydia* can become resistant to chronic monotherapy with several antibiotics, including rifampin, doxycycline, azithromycin, and ciprofloxacin[43-46]. This resistance is overcome when rifampin is combined with other antimicrobials that possess anti-chlamydial activity[43,47]. Also, *in vitro* susceptibilities of *Chlamydia* reveal a synergistic effect of rifampin and doxycycline[48]. Thus, antimicrobials that are effective in treating acute *Chlamydia* infections as monotherapy do not appear to be as efficacious treating chronic *Chlamydia* infections. This is supported by both *in vitro* data and clinical trials[12-15,49]. However, *in vitro* data also suggest that persistent *Chlamydia* infections may be successfully treated with combination therapy[43,47,48].

Chlamydia is an obligate intracellular organism. The majority of the trials that evaluated antimicrobial therapy in ReA or uSpA were of 3 months' duration. Other obligate intracellular organisms, such as *Mycobacterium tuberculosis*, require combination therapy longer than 3 months to ensure therapeutic response. In this trial, the efficacy of the combination of doxycycline and rifampin continued to improve throughout the study. This too suggests that longer than 3 months of antimicrobial therapy may be warranted with chronic disease.

This is the first trial that assessed a combination of antibiotics in this setting. Both doxycycline and rifampin are potent anti-chlamydial agents. Both were also administered daily for 9 months to enhance therapeutic response. One of these antibiotics inhibits chlamydial production of HSP60, which has been shown to be pivotal in the pathogenic sequelae of persistent *Chlamydia* infections. HSP60 is also known to protect cells from lethal assaults, such as with antimicrobials. Thus the elimination of this protein is likely essential to ensure eradication of the persistent form of the organism. The patients who received a combination of antibiotics improved statistically significantly more in 4 of the 6 criteria that were followed as markers of their disease activity. Significantly more patients were considered responders in the group that received a combination of antibiotics versus those treated with monotherapy.

This study also suggests that doxycycline monotherapy does not seem to be effective in the treatment of chronic ReA. This is in agreement with another study that assessed the efficacy of a 3-month trial of doxycycline monotherapy in chronic ReA[49].

A criticism of this study is that it was an open-label trial. However, perhaps the most impressive response was noted in the swollen and tender joint counts. These were blinded. The lack of bacterial confirmation of a preceding *Chlamydia* infection in our patients could also be cited. However, we feel this actually strengthens our data. Patients with other types of inflammatory arthritis (i.e., non *Chlamydia*-induced) would not be expected to respond to this therapy, thus making it more difficult to achieve statistically significant improvement. Doxycycline is also known to possess antiinflammatory properties[50,51]. If the beneficial effects in this trial were secondary to this, we would expect to see no difference between the treatment groups. There is no evidence that rifampin has antiinflammatory properties. Further, rifampin is a potent inducer of human liver CYP2C9, which is important in the metabolism of most NSAID[52]. In this trial, 93% of the patients in group D/R were taking stable doses of an NSAID. If the mechanism of action were antiinflammatory, we would have expected group D/R to do worse.

These results are encouraging, but we feel they are preliminary and should be confirmed in another trial that is double-blinded and placebo-controlled. A future trial should also employ PCR technology to document the presence or absence of *Chlamydia* (and its gene expressions), both before and after combination antimicrobial therapy, in order to establish definitive proof. Patients should also be followed after completion of their antibiotics to check for duration of response.

Regardless of the mechanism of action of the combination of antibiotics studied in this trial or the true etiologic trigger for the patients' SpA, the therapeutic efficacy of the combination of doxycycline and rifampin cannot be denied. Although 30% of patients in the trial had a history of a *Chlamydia* infection, and patients with post-dysentery SpA were excluded (increasing the possibility of *Chlamydia* as the trigger), the goal of the study centered on treatment of uSpA. All patients met the ESSG criteria without clearly being diagnosed with a specific SpA. The 85% response rate in the patients who received both antibiotics is very similar to the response rate noted in the trials of RA patients receiving tumor necrosis factor-α-inhibiting drugs[53]. These medications are considered revolutionary in the treatment of RA. Further, these are suppressive medications, for once the drug is discontinued, the symptoms return. The combination of doxycycline and rifampin in this setting is at least suppressive, and possibly curative. However, the latter issue was not addressed with this trial.

If this combination of antibiotics, or similar regimens, proves effective, then the clinical implications could be widespread. Persistent *Chlamydia* infections have also been linked to atherosclerosis, pelvic inflammatory disease and

tubal infertility, asthma, and trachoma (the leading cause of preventable blindness)[54-60]. The chronic inflammatory state caused by cells infected with persistent *Chlamydia* is very different from the acute inflammatory response seen in acute *Chlamydia* infections. It needs to be treated as such. We believe our data show that prolonged combined antimicrobial therapy, which also inhibits *Chlamydial* HSP60 production, can be beneficial to patients with *Chlamydia*-induced chronic reactive arthritis.

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