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**Are Antibiotics, Other Than Roxithromycin, An Effective Way to  
Manage Joint Pain in Rheumatoid Arthritis?**

Kelly A. Hoffman, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies  
Philadelphia College of Osteopathic Medicine  
Philadelphia, Pennsylvania

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## ABSTRACT

**OBJECTIVE:** The objective of this selective EBM review is to determine “Are antibiotics, other than roxithromycin, an effective way to manage joint pain in rheumatoid arthritis?”

**STUDY DESIGN:** Review of three double-blind, randomized-controlled studies published in English between 2001-2007.

**DATA SOURCES:** Three randomized controlled trials published between 2001 and 2007 were found using PubMed/MEDLINE and Cochrane databases.

**OUTCOMES MEASURED:** Clinical outcome for all three studies used American College of Rheumatology (ACR) criteria, which assesses joints for swelling and tenderness.

**RESULTS:** In the Odell et al.<sup>1</sup> study, at 24 months 28 participants did meet the ACR50 criteria. In treatment group 1, 18 of 30 (60%) participants and 10 of 30 (33%) participants in treatment group 2 met the ACR50 criteria, ( $P=0.04$ ). Ogrendik et al.<sup>2</sup> 34% of participants in the antibiotic treatment group had an ACR50 response at 6 months versus 10% in treatment group 2. Ogrendik et al.<sup>3</sup> found that 34.2% of participants in the antibiotic treatment group had an ACR50 response at 6 months compared to 7.9% in treatment group 2.

**CONCLUSIONS:** The statistical results from all three studies found that antibiotics had greater efficacy in treating pain in rheumatoid arthritis compared to other interventions or placebo. It would be beneficial to study the effects of antibiotic use in patients who had chronic RA.

**KEYWORDS:** antibiotics, rheumatoid arthritis

## INTRODUCTION

Rheumatoid arthritis is a chronic autoimmune disease that can potentially lead to permanent disability.<sup>3</sup> The disease process begins when immune cells begin to release chemicals that target the synovium and destroy cartilage and bone. The destruction of cartilage leads to joint stiffness, tenderness, swelling, and limited mobility. While RA particularly affects the smaller joints of the hands and wrist, it can also affect other joints and organs in more advanced stages of the disease process.<sup>7</sup> This paper evaluates three double-blind, randomized controlled studies that look at the effectiveness of antibiotics, other than roxithromycin, in the management of joint pain in RA.

RA is a serious autoimmune disease that can progress to permanent destruction and limited mobility of certain joints, especially in the hands and wrists.<sup>6</sup> RA affects approximately one million Americans, 75% of those being women.<sup>7</sup> The incidence of RA in the United States has significantly decreased since the 1960s, but it continues to be the most common type of autoimmune arthritis.<sup>8</sup> Women are affected in the 4<sup>th</sup> and 5<sup>th</sup> decades, whereas men are affected later in the 5<sup>th</sup> and 6<sup>th</sup> decades. In 2013, approximately \$19 billion was spent on RA treatment (medications, hospitalizations, office visits, and physical therapy), which amounts to about \$30,000 a year per patient. The costs for RA treatment is expected to increase over the next 4 years due to the development of new medications; newer medications mean increased costs.<sup>6</sup> Per 2007 data, 2.6 million annual doctor's visits were attributed to RA, and 2012 data showed approximately 9,100 RA related hospitalizations.<sup>9</sup>

The exact etiology of RA is unknown. However, there are many risk factors and comorbidities that are associated with RA. It is thought that a combination of environmental and genetic factors contributes to the incidence of RA. Modifiable risk factors include: smoking, oral

contraceptives, hormone replacement therapy, breastfeeding, and irregular menses. Non-modifiable risk factors include: genotypes HLA-DR4 and DRB1, age (40-60s), and sex (female).<sup>9</sup> There are also several comorbidities associated with RA. Though the exact correlation between cardiovascular disease and RA is not fully understood, research has shown that with further progression of RA the higher the prevalence of CVD. Also, infections, such as tuberculosis, are also closely associated with RA.<sup>9</sup> Data has shown up to ¼ of deaths in RA patients are related to infections. Researchers are unsure if the infections associated with RA are due to immune system failure or immunosuppressant used for treatment.<sup>9</sup>

Synthetic disease modifying antirheumatic drugs (DMARD) are the initial drug of choice for RA, specifically methotrexate. Other synthetic DMARDs include sulfasalazine, leflunomide, tofacitinib, and hydroxychloroquine.<sup>4</sup> There are also biological DMARDs used in the treatment of RA, which include: TNF inhibitors, abatacept, rituximab, and tocilizumab. Typically, DMARDs are most effective when used in combination with each other. The most common combination is methotrexate and a TNF inhibitor.<sup>4</sup> Low dose corticosteroids are also used for 2-6 weeks until the biologic DMARD reaches its full efficacy.<sup>4</sup> Combination DMARDs are currently the standard of care. Antibiotic treatment, alone or in combination with a DMARD, has been researched to determine their effectiveness at managing painful joints when used in early RA.

## **OBJECTIVE**

The objective of this selective EBM review is to determine “Are antibiotics, other than roxithromycin, an effective way to manage joint pain in rheumatoid arthritis?”

## **METHODS**

Participants in the 3 double-blinded randomized controlled studies reviewed for this paper included male/female adults who fulfilled American College of Rheumatology criteria. All

3 studies evaluated participants based on ACR criteria. Participants in the O'Dell et al.<sup>1</sup> study met the following criteria: 19-70 years old, positive rheumatoid factor, duration of disease > 6 weeks to <1 year, and active RA (ESR 28 mm/hr, morning stiffness >45 minutes, >8 tender joints, >3 swollen joints). Ogrendik et al.<sup>2</sup> conducted a study with participants meeting the following criteria: 18-70 years old, disease duration less than 3 years, failed DMARD therapy (azathioprine, methotrexate, sulfasalazine, penicillamine, hydroxychloroquine, or injectable gold), active disease at enrollment (12+ tender joints, 10+ swollen joints) and one of the following ESR 28mm/hr, CRP > 2.0 mg/dl, or morning stiffness > 45 minutes. Ogrendik et al.<sup>3</sup> conducted a study with participants meeting the following criteria: currently taking methotrexate for at least 6 months, active disease (12+ tender joints, 10+ swollen joints), and at least one of the following: ESR >28 mm/hr or CRP 2.0 mg/dl.

Interventions used in the above studies were: combination Minocycline 100 mg PO BID x 2 years and low dose prednisone (7.5mg or 5 mg per day) versus combination hydroxychloroquine 200 mg PO BID and low dose prednisone (O'dell et al.<sup>1</sup>), clarithromycin 500 mg PO QD x 6 months versus placebo (Ogrendik et al.<sup>2</sup>), and levofloxacin 500 mg PO QD x 6 months in combination with a stable dose of methotrexate either oral or subcutaneous versus placebo plus stable dose of methotrexate (Ogrendik et al.<sup>3</sup>). The primary outcome measured for all three studies was the reduction in the number of painful/tender joints after the appropriate intervention was administered.

The clinical studies reviewed for this paper were found using Pubmed and Cochrane Database. All sources were peer-reviewed articles printed in English between 2001-2007, and keyword searches included: rheumatoid arthritis, minocycline, and antibiotics. Inclusion criteria for this paper were randomized controlled trials, double blinded trials, all of which focused on

POEMs. The following were exclusion criteria for this paper: articles reviewing roxithromycin in the treatment of RA, peer-reviewed articles published prior to 2000, Cochrane systematic reviews, as well as previously published systematic reviews by former students. Statistics used in all three studies include: control event rate (CER), experimental event rate (EER), relative benefit increase (RBI), absolute benefit increase (ABI), number needed to treat (NNT) and p-value. **Table 1** (below) reports the demographics of each study used in this paper.

**Table 1. Demographics & Characteristics of Included Studies**

Study	Type	#pts	Age	Inclusion Criteria	Exclusion Criteria	W/D	Intervention
O'dell, 2001 (1)	RCT	60	19-70	Pts who have had RA for at least 6 weeks and fulfill ACR criteria.	Pts who received previous disease modifying drugs, who received steroids in the last 2 months, and women of childbearing age who were not on contraception.	5	Minocycline 100 mg BID vs. Hydroxychloroquine 200 mg BID  *both groups were on low dose prednisone 7.5mg or 5mg/day
Ogrendik 2007 (2)	RCT	81	18-70	Pts who have active disease, defined as 12 or more tender joints, ten or more swollen joints, and at least 1 of the following: SED rate >28mm/h, morning stiffness >45mins, and disease longer than 3 years.	Pregnant women, elevated LFT and RFT, chronic infection, and allergic to ABX used in the study.	9	500 mg of clarithromycin vs placebo
Ogrendik 2007 (3)	RCT	76	>18	Pts who had been taking methotrexate for at least 6 months, active disease, 12+ tender joints.	Pregnancy, serious infection, inadequate control of arthritis symptoms, impaired LFT and RFT, untreated HTN.	6	500 mg levofloxacin vs placebo  *both groups were given methotrexate 15-25mg/week

## **OUTCOMES MEASURED**

The American College of Rheumatology (ACR) response is used in all three studies to assess the efficacy of the intervention. ACR response include the following criteria: tender/swollen joint count, acute phase reactant (such as sedimentation rate), patient assessment, physician assessment, VAS pain score, and disability/functional questionnaire. ACR 20, 50, and 70 response were assessed in all three studies. This means that a person must have improved by 20, 50, or 70% for the designated intervention to have been clinically effective. In the O'Dell et al.<sup>1</sup> study, the intervention was minocycline 100 mg PO BID x 2 years plus low dose prednisone. Ogrendik et al.<sup>2,3</sup> studies also measure ACR20, ACR50, and ACR70; interventions used in these two studies were Clarithromycin 500 mg PO QD x 6 months and Levofloxacin 500 mg PO QD x 6 months plus methotrexate 15-25 mg daily, respectively. The ACR criteria were assessed using: Ritchie Articular Index, patient's global assessment of disease activity with visual analog scale, pain assessed with visual analog scale, physician's global assessment of disease activity, and Health Assessment Questionnaire (HAQ). The statistics reported or used in the articles were relative benefit increase (RBI), absolute benefit increase (ABI), numbers needed to treat (NNT), and P values.

## **RESULTS**

All three studies looked at the efficacy of antibiotic treatment for pain management in rheumatoid arthritis. Two studies compared the use of antibiotic treatment versus placebo, and the third study compared antibiotic treatment to hydroxychloroquine.

The double-blinded RCT by O'Dell et al.<sup>1</sup> further detailed in **Table 1**, enrolled 60 participants. Patients who had previously taken DMARDs, steroid therapy in the last 2 months, or women of childbearing age were excluded from this study.<sup>1</sup> 60 participants were randomly



assigned to treatment group 1 or 2. Treatment group 1 refers to the minocycline intervention (100 mg BID), and treatment group 2 refers to the hydroxychloroquine intervention (200 mg BID). Both treatment groups were started on prednisone 7.5mg/day or 5mg/day if they weighed <60kg and tapered down if they met ACR50 criteria at 12 months. ACR50 criteria was assessed using patient's assessment of disease activity, physician's global assessment of disease activity, tender joint and swollen joint count, HAQ, erythrocyte sedimentation rate, and patient's assessment of pain on 100-mm visual analog scale. Using the Ritchie Articular Index, 38 joints were assessed for tenderness and swelling. At 24 months, 28 participants did meet the ACR50 criteria. In treatment group 1, 18 of 30 (60%) participants and 10 of 30 (33%) participants in treatment group 2 met the ACR50 criteria, ( $P=0.04$ ). At the beginning of the study, participants in treatment group 1 had an average of 18.9 tender joints and an average VAS pain score of 5.13. At the completion of the study, those participants had an average of 6.8 tender joints and an average VAS pain score of 2.5. Patient's initial global assessment in treatment group 1 was 4.7 compared to 2.0 at 24 months. At 12 months, those who met ACR50 criteria began to taper off prednisone. At the end of the 2-year study, prednisone dosages were also assessed and doses were lower in treatment group 1 (0.81 mg/day) than treatment group 2 (3.21 mg/day), ( $P<0.01$ ). Also, participants in treatment group 1 were more likely to be completely tapered off prednisone at 24 months, ( $P=0.03$ )<sup>1</sup>. 3 participants in treatment group 1 and 2 from treatment group 2 withdrew due to adverse reactions. Adverse reactions from treatment group 1 included: fingernail discoloration, dizziness, and an erythematous rash, and in treatment group 2: reasons for withdrawal were rash and gastrointestinal distress.

The 6-month randomized double-blind controlled study by Ogrendik et al.<sup>2</sup> randomly assigned 81 participants to either treatment group 1 (500 mg clarithromycin per day) or treatment

group 2 (placebo). Exclusion criteria for this study was the following: pregnant women, impaired hepatic enzyme tests, impaired renal function, chronic/recurrent infection, or history of allergic reactions to macrolides. Participants' outcomes were assessed using the same criteria as Odell et al.<sup>1</sup> to determine if they met ACR 20 and 50 response, but for the purposes of this paper ACR50 response will be the focus. At the beginning of the study, treatment group 1 had an average of 30 tender joints and a VAS pain score of 6.9. After 6-months, the average tender joint count for treatment group 1 was 11 and a VAS pain score of 3.2, ( $P<0.001$ ). **Table 2** shows more participants in treatment group 1 (34%) had met ACR50 criteria after 6 months compared to those in the placebo group (10%), ( $P<0.001$ ). 9 participants withdrew from the study due to unsatisfactory treatment/worsening of disease; 3 participants were from treatment group 1 and 6 were from treatment group 2. In treatment group 1, the major complaint was a metallic taste or dry mouth (46%), ( $P <0.001$ ). Also, 10% of participants in treatment group 1 and 8% in treatment group 2 complained of GI pain, ( $P<0.001$ ). 17% of treatment group 1 and 15% of treatment group 2 complained of headaches, ( $P<0.001$ ).

In the 6-month randomized double-blind controlled study, Ogrendik et al.<sup>3</sup> looked at the efficacy of levofloxacin versus placebo. Exclusion criteria for this study was the following: pregnancy, serious infection, inadequate control of arthritis, impaired renal function, untreated HTN, other inflammatory diseases, and any other relevant systemic disease. 76 participants were randomly assigned to treatment group 1 (500mg levofloxacin daily) or treatment group 2 (placebo). At baseline, treatment group 1 had an average tender joint count of 32 and a VAS pain score of 6.5. At 6 months, treatment group 1 average tender joint count was 10 and VAS pain score of 2.2, ( $P<0.001$ ). Participants were assessed utilizing the same criteria as Ogrendik et al.<sup>2</sup> ACR 50 response was assessed after 6 months to determine the efficacy of levofloxacin versus

placebo. At 6 months, treatment group 1 showed greater response per the ACR criteria. 5% of participants in treatment group 1 and 11% from treatment group 2 withdrew due to unsatisfactory response to their intervention. There were no serious adverse events reported in this study. The more frequent complaint from treatment group 1 was gastrointestinal pain (15.6%) compared to treatment group 2 (5.3%), ( $P=0.05$ ). Other adverse events included: nausea, vomiting, diarrhea, headache, and dry mouth. Overall, levofloxacin was well tolerated among participants.<sup>3</sup>

**Table 2. Comparison of ACR50 Criteria Between Treatment Group 1 and 2**

Study	ACR 50 Treatment Group 1 % Antibiotic	P-value Treatment Group 1	ACR 50 Treatment Group 2 %	P- value Treatment Group 2
O'dell et al. <sup>1</sup>	60	$p=0.04$	33	$p=0.04$
Ogrendik et al. <sup>2</sup>	34	$P<0.001$	10	$P<0.001$
Ogrendik et al. <sup>3</sup>	34.2	$P<0.001$	7.9	$P<0.001$

**Table 3** details relative benefit increase (RBI), absolute benefit increase (ABI), numbers needed to treat (NNT), and P values for each of the three studies used in this paper. P value signifies the probability that the outcome was due to chance. If the p value was less than 0.5, then it is unlikely the outcome was due to chance. All three studies had P values <0.5 ( $P=0.04$ , <0.001, 0.001, respectively). Also, NNT ranged between 3 and 5, signifying the number of patients that would need to be treated to prevent 1 adverse event.

**Table 3. O'Dell study: v. Hydroxychloroquine**

Study	CER HCQ	EER minocycline	RBI	ABI	NNT	P value
O'dell et al. <sup>1</sup>	0.33	0.60	0.82	0.27	4	$P=0.04$
Ogrendik et al. <sup>2</sup>	0.10	0.34	2.4	0.24	5	$P<0.001$
Ogrendik et al. <sup>3</sup>	0.79	0.34	2.14	0.40	3	$P<0.001$

## DISCUSSION

In Odell et al.,<sup>1</sup> combination minocycline and prednisone had more success in controlling pain compared to combination hydroxychloroquine and prednisone. Minocycline is often used in treatment of acne, cellulitis, as well as the treatment of RA. Contraindications to minocycline include a previous allergic reaction or sensitivity to it. Adrenal suppression can be a possible side effect of prednisone with long term use.<sup>4</sup>

Also, in Ogrendik et al.,<sup>2</sup> clarithromycin had great efficacy in treating pain compared to placebo. Clarithromycin is a broad spectrum antibiotic that is often used for the treatment of upper respiratory infections, peptic ulcer disease, pneumonia, as well as skin infections.<sup>4</sup> Contraindications to this antibiotic include: concomitant use with HMG-CoA reductase inhibitors (statins) or colchicine or in patients who are renally impaired.<sup>4</sup>

Statistical results from Ogrendik et al.<sup>3</sup> study favored the use of levofloxacin. Black box warnings for this antibiotic include; tendon rupture, CNS effects, and peripheral neuropathy. It can also accentuate symptoms of myasthenia gravis. This fluoroquinolone is often used for pneumonia, UTI, and pyelonephritis.<sup>5</sup>

Firstly, the sample size for each study was considerably small. The largest study included 81 participants and the smallest was 60. Also, in the study that investigated clarithromycin, participants had an initial side effect of a metallic taste in their mouth. Researchers in this study presumed that the blinding in the studied was compromised at this point, because they believed that the taste was due to the antibiotic killing bacteria in the mouth.<sup>2</sup> Also, GI side effects are common in the use of antibiotics.<sup>5</sup> Blinding may have been compromised for this reason after researchers assessed for side effects throughout the study. Another limitation in 2 of the studies

was the use of combination treatment; for this reason it was difficult to determine the exact efficacy of levofloxacin and minocycline.

## **CONCLUSION**

This paper reviewed three double-blind randomized controlled studies that investigated the significance of antibiotic use in the management of pain in rheumatoid arthritis. The statistical results from all three studies found that antibiotics had greater efficacy in treating pain in rheumatoid arthritis compared to other interventions or placebo. Other than increasing the population size to increase the validity and reliability of antibiotic use in the management of pain in RA, future studies should consider using a higher range for ESR and CRP cutoff. Using low values would be associated with earlier stages of RA. However, it would be beneficial to study the effects of antibiotic use in patients who had chronic RA. The treatment of RA with antibiotics will hopefully be explored in the future alone or in combination with DMARDs.

## References

1. O'Dell J, Blakely K, Mallek J et al. Treatment of early seropositive rheumatoid arthritis: A two-year, double-blind comparison of minocycline and hydroxychloroquine. *Arthritis & Rheumatism*. 2001;44(10):2235-2241. doi:10.1002/1529-0131(200110)44:10<2235::aid-art385>3.0.co;2-a. Accessed October 07, 2016.
2. Ogrendik M. Effects of clarithromycin in patients with active rheumatoid arthritis. *Current Medical Research and Opinion*. 2007;23(3):515-522. doi:10.1185/030079906x167642. Accessed October 07, 2016.
3. Ogrendik M. Levofloxacin Treatment in Patients with Rheumatoid Arthritis Receiving Methotrexate. *Southern Medical Journal*. 2007;100(2):135-139. doi:10.1097/01.smj.0000254190.54327.3b. Accessed October 07, 2016.
4. Papadakis MA, McPhee SJ, Rabow MW. *Current Medical Diagnosis and Treatment: 2016*. New York, NY, United States: McGraw-Hill Professional; October 1, 2015.
5. Kasper D, Fauci A, Hauser S, Longo D, Jameson J, Loscalzo J. eds. *Harrison's Principles of Internal Medicine, 19e*. New York, NY: McGraw-Hill; 2015. <http://accessmedicine.mhmedical.com/content.aspx?bookid=1130&Sectionid=79727150>. Accessed October 07, 2016.
6. Rheumatoid Arthritis Treatment Costs - RheumatoidArthritis.org. RheumatoidArthritisorg. <https://www.rheumatoidarthritis.org/treatment/costs/>. Published August 2016. Accessed October 9, 2016.
7. Ruderman E, Tambar S. Rheumatoid Arthritis. *Diseases and Conditions*. <http://www.rheumatology.org/i-am-a/patient-caregiver/diseases-conditions/rheumatoid-arthritis>. Published August 2013. Accessed October 7, 2016.
8. RA Statistics 2013. *Rheumatoidarthritisnet*. 2016. Available at: <https://rheumatoidarthritis.net/what-is-ra/ra-statistics/>. Accessed September 16, 2016.
9. 2. Rheumatoid Arthritis (RA) | Arthritis | CDC. *Cdcgov*. 2016. Available at: <https://www.cdc.gov/arthritis/basics/rheumatoid.htm>. Accessed October 16, 2016.