What is the Effectiveness of Roxithromycin in Management of the Signs and Symptoms of Rheumatoid Arthritis?

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What is the Effectiveness of Roxithromycin in Management of the Signs and Symptoms of Rheumatoid Arthritis?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Science-Physician Assistant

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

December 14, 2012
Objective: The objective of this selective EBM review is to determine whether or not roxithromycin is effective in management of the signs and symptoms of rheumatoid arthritis.


Data Sources: Randomized, controlled and double blind clinical trials testing the effectiveness of roxithromycin in management of inflammation and signs and symptoms of rheumatoid arthritis were found using the PubMed and Ovid databases.

Outcomes Measured: Improvement in the signs and symptoms of tenderness/inflammation using the American College of Rheumatology-20 (ACR-20) scoring approach, improvement of quality of life with the sinonasal outcome test-20 (SNOT-20) method, medication safety, and overall response to treatment.

Results: The Ogrendik studies showed a significant number of patients met ACR 20 improvement criteria with roxithromycin 300mg treatment at 6 months compared with those patients who received placebo. One study showed significant reductions in pain and duration of morning stiffness, quality of life improvement, and reduction in disease activity as demonstrated by objective clinical measurements. The Cervin et al study showed statistically significant improvements in sinonasal inflammation among patients who received roxithromycin 150mg, depicted by patient response scales. Roxithromycin-treated patients in this study also showed significant improvements in SNOT-20 scoring after 12 weeks of treatment with the macrolide; however, improvements were not noted at the 6 week mark of treatment.

Conclusions: Collectively, the three RCT’s evaluated depicted the effectiveness in management of signs and symptoms of rheumatoid arthritis. Ogrendik studies indicate that this particular macrolide is effective in complaints that are most bothersome to RA patients, including morning stiffness and decreased quality of life.4,5 Also, the Cervin et al study proves the effectiveness of long-term use of roxithromycin in controlling inflammation.6 Further research is needed to assess the risk of bacterial resistance to roxithromycin with prolonged use, and whether or not there is a relationship between disease activity and antibodies to anaerobic bacteria among RA patients.

Key words: inflammation, rheumatoid arthritis, roxithromycin
Introduction:

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease, which primarily involves the synovitis of multiple joints. As an autoimmune disease, rheumatoid arthritis is considered a symmetric polyarthritis, with a tendency for the small joints of the hands and feet.\textsuperscript{1} The distress of RA on the synovitis of joints in the human body typically results in pain and morning stiffness which lasts longer than thirty minutes. In severe cases, there may be clinical presence of deformities including subcutaneous nodules and ulnar deviation of the wrist; in addition, there may be extra-articular findings on physical exam, such as: pericarditis, pleural effusion, interstitial lung disease, splenomegaly, and vasculitis. The exact cause of RA is unknown. However, there is known to be increased risk among people with HLA class II genotypes. There are also known modifiable risk factors, including: smoking, use of oral contraceptives, use of HRT, women who breastfeed, and women with irregular menses/early menses.\textsuperscript{2} It is also of significant importance to note that high levels of antibodies to oral anaerobic bacteria have been found in both serum and synovial fluid of those with RA.\textsuperscript{5}

The disease process of rheumatoid arthritis can commence at any age; however, the peak onset of disease typically presents during the fourth or fifth decade for women and the sixth to eighth decades for men. While the prevalence of RA is 1%, it is seen more often in women, with a ratio of 3:1.\textsuperscript{1}

The exact total healthcare cost for RA could not be specified; however, 2009 statistics depict total hospital charges of $545 million (mean charge of $35,000 per person) related to treatment of the disease.\textsuperscript{2} Limited information is accessible regarding the total number of health care visits within the last several years; however, in 2007, there were 2.9 million ambulatory care visits in the United States among people with RA. Most of these were physician office visits.
(2.6 million) with 1.9 million visits to medical specialty offices.\textsuperscript{2} Statistics of 2009 indicate that there were 15,600 hospitalizations related to RA.\textsuperscript{2}

Treatment of rheumatoid arthritis typically involves both non-pharmacologic and pharmacologic regimens with efforts toward reduction of pain, inflammation, and deformities, as well as preservation of function. Non-pharmacologic treatment includes OT/PT programs, systemic and articular rest, exercises which preserve joint motion and improve muscular strength, assistive devices and splints, as well as weight loss for patients over ideal body weight. Pharmacologic treatment typically begins with a synthetic disease-modifying antirheumatic drug (DMARD), with methotrexate being the initial treatment of choice. The initial dose is typically 7.5mg taken by mouth orally one time per week. Improvement is typically not clinically apparent for 2-6 weeks. Non-steroidal anti-inflammatory drugs (NSAIDS) are not effective when used as monotherapy, but may be used in conjunction with DMARDS. Corticosteroid treatment, involving low dose prednisone, provides a rapid improvement in inflammation in patients suffering from RA. They may be used temporarily as “bridge therapy” until DMARDS become effective; however, their side effects limit their role in long-term use. Biologic DMARDS, including rituximab, TNF inhibitors, and abatacept, are effective in management of RA, however, are typically reserved for patients who do not respond to initial synthetic DMARD treatment.\textsuperscript{1}

One study (Cervin et al) mentions that substantial evidence has developed within the recent years suggesting that macrolide antibiotics may have an anti-inflammatory effect in addition to its antibiotic effect; however, their role in rheumatoid arthritis management has never been established. For forthcoming discussion, roxithromycin is linked to the macrolide class. Macrolides are known to be both inhibitory and bactericidal. Roxithromycin is available in
Turkey and Australia (which accounted for the setting of the 3 RCTs utilized in this review) with a clinician’s prescription in the form of 150 and 300mg tablets; however availability and pricing of roxithromycin is unavailable to date in the United States. 7

Objective:

The objective of this selective EBM review is to determine whether or not roxithromycin is effective in management of the signs and symptoms of rheumatoid arthritis.

Methods:

All studies utilize three, randomized, double-blind and controlled clinical trials. Participants consist of patients greater than 18 years of age with active signs and symptoms of inflammation. Before entering the trials, all patients gave written informed consent. All studies concentrated on the intervention roxithromycin, an oral antibiotic of the macrolide class, comparing its effects at varying doses to visually matched placebo. No medications incorporated within the rheumatoid arthritis treatment regimen were to be given during the period of time in which the participants were studied.

There were two studies carried out by Ogrendik. One involved the administration of roxithromycin 300 mg by mouth daily for 3 months or a visually matched placebo for comparison among 31 patients with active RA.4 The other also evaluated the comparison of roxithromycin 300mg by mouth daily versus a visually matched placebo to 100 patients; however, these interventions were provided for 6 months.5 Cervin et al involved patients with inflammation due to active rhinosinusitis and compared effects of roxithromycin 150mg by mouth daily for 3 months to visually matched placebo.

Data sources included studies found through PubMed and Ovid research databases throughout. In order to encompass randomized controlled clinical trials on roxithromycin
effectiveness, key words during searches included: “roxithromycin”, “rheumatoid arthritis” and “inflammation”. All articles were published in peer-reviewed journals in the English language. Articles were selected based on relevance to clinical topic of interest, dates in which they were published, and whether they represented patient-oriented evidence that matters. To be considered as adequate studies to be reviewed, experimentation was required to involve randomized, controlled and double blind clinical trials published no earlier than 1996, as well as involve participants over the age of 18 years old.\textsuperscript{4,5,6} Exclusion criteria included: pregnant women, impaired hepatic/renal function, chronic/recurrent infections, history of adverse reactions to macrolides, recent dosages of steroids that were unstable or>7.5mg per day, recent intra-articular injections, diagnoses of RA for longer than 1 year previously, and immune deficiency.\textsuperscript{4,5,6} The summary of statistics reported include: p-value/confidence interval (CI), relative benefit increase (RBI), absolute benefit increase (ABI), absolute risk increase (ARI), relative risk reduction (RRR), numbers needed to treat (NNT), and numbers needed to harm (NNH).

Table I: Demographics and characteristics of included studies for analysis of effectiveness of roxithromycin in management of inflammation and improvement of quality of life.

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th># Pts</th>
<th>Age (yrs)</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>W/d</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ogrendik (2009)\textsuperscript{4}</td>
<td>Double blind RCT</td>
<td>100</td>
<td>18-70</td>
<td>Active RA: ≥10 swollen joints, ≥12 tender joints, and ≥1 of the following: ESR ≥28mm/h, CRP &gt;2mg/dL, or morning stiffness for ≥45 min; inactive response to 1-4 DMARDS or patients currently taking DMARDS with a washout period of ≥1 month</td>
<td>Pregnant women, impaired hepatic/renal function, chronic/recurrent infections, history of adverse reactions to macrolides</td>
<td>9</td>
<td>Roxithromycin 300mg for 6 months</td>
</tr>
</tbody>
</table>
Two studies carried out by Ogrendik were utilized in the review of roxithromycin effectiveness among patients with RA.\textsuperscript{4,5} These studies focused on the percentage of patients who experienced a 20% improvement receiving roxithromycin 300mg or placebo. The 20% improvement was measured by assessing ACR criteria (ACR 20 response) at 3 months in one of the studies. This scoring system depicts a decrease of more than 20% in the number of tender joints and a 20% improvement in at least 3 of the following: global assessment of disease status, assessment of pain, assessment of physical function, physician’s global assessment of disease status, and CRP levels.\textsuperscript{4} The other study performed by Ogrendik assessed the same patient responses, however patients were given roxithromycin 300mg for 6 months.\textsuperscript{5} Both studies included follow-up assessments for 3 months following treatment or placebo administration.\textsuperscript{4,5}
roxithromycin 150mg or placebo daily for 3 months. In order to assess quality of life, these patients completed subjective measurement of sinonasal outcome test-20 (SNOT-20) at the initiation of study, after 6 weeks of intervention, and then again after 12 weeks of treatment. This assessed patients’ quality of life following treatment with roxithromycin among patients with inflammation related to bacterial infections.6

Results

Two of the studies (Ogrendik) which directly involved management of RA with roxithromycin 300mg among patients with active disease involved dichotomous data for interpretative results.4,5 Cervin et al, which involved assessment of roxithromycin in controlling inflammation and improving quality of life among patients with bacteria-induced rhinosinusitis involved continuous data which could not be converted to dichotomous values.6 All of the studies excluded patients under the age of eighteen and those with previous reactions to macrolide antibiotics. Remarks on compliance behavior were not included in any of the three studies.4,5,6

The RCT conducted by Cervin et al assessed the subjective questionnaire called: Sinonasal Outcome Test-20 (SNOT-20), which is a validated, specific quality of life instrument in which patients with active nasal inflammation were asked 20 questions regarding improvement in quality of life. The SNOT-20 depicted a significant improvement in quality of life for those treated with daily 150mg roxithromycin at 12 weeks (Table 2).

Table 2: Mean change in baseline of SNOT-20 among patients receiving 300mg roxithromycin versus placebo.

<table>
<thead>
<tr>
<th></th>
<th>Roxithromycin Group</th>
<th>Placebo Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-treatment</td>
<td>2.75±0.13</td>
<td>2.83±0.12</td>
</tr>
<tr>
<td>At 6 weeks</td>
<td>2.61±0.14</td>
<td>2.87±0.15</td>
</tr>
<tr>
<td>At 12 weeks</td>
<td>2.34±0.19</td>
<td>2.88±0.12</td>
</tr>
<tr>
<td>At 24 weeks</td>
<td>2.49±0.18</td>
<td>2.84±0.15</td>
</tr>
</tbody>
</table>
The results show a statistically significant decrease in SNOT-20 value at 12 weeks (p-value<0.05) among patients receiving 300mg roxithromycin in comparison to placebo, indicating improvement in inflammation and quality of life. There were no significant improvements noted in SNOT-20 scoring after 6 weeks of treatment or 3 months after the termination of treatment (p-value>0.05).6

Table 3 includes the confidence intervals calculated based on SNOT-20 scores of both treatment and placebo groups at 12 weeks post treatment.6

Table 3: 95% CI calculated for SNOT-20 12 weeks post-treatment for experimental and placebo groups.

<table>
<thead>
<tr>
<th>Roxithromycin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.97-2.71</td>
<td>2.84-2.92</td>
</tr>
</tbody>
</table>

Because there is no overlap among the calculated CIs, it can be inferred that there is a 95% probability that the results of the two groups are truly different, and not different by chance. No significant differences were noted among SNOT-20 scores in terms of age, sex, and baseline values. Nasal swabs were taken for microbiologic examination both before and after completion of treatment. In the 29 patients treated with roxithromycin, there were 12 positive cultures at the beginning of treatment; S. aureus n=4, H. Flu n=1, P. aeruginosa n=3, S. pneumonia n=4. Following treatment of these patients, there were 9 positive cultures; S. aureus n=5, H. Flu n=2, P. aeruginosa n=2, S. pneumonia n=2.6

The two RCTs conducted by Ogrendik compared oral roxithromycin 300mg with placebo among adult patients of 18 years or older in a primary outpatient clinic who are managing rheumatoid arthritis.4,5 One of the studies treated patients for 3 months and the other for 6 months.4,5 The study that assessed participants for 3 months depicted more patients who received roxithromycin 300mg experienced ACR-20 responses at 3 months compared to patients who received placebo (Table 4).4
Table 4: Analysis of RBI, ABI, and NNT of RCTs conducted by Ogrendik.4,5

<table>
<thead>
<tr>
<th></th>
<th>Relative benefit increase (RBI)</th>
<th>Absolute benefit increase (ABI)</th>
<th>Numbers needed to treat (NNT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ogrendik 3mo. RCT4</td>
<td>275%</td>
<td>55%</td>
<td>2</td>
</tr>
<tr>
<td>Ogrendik 6mo. RCT5</td>
<td>76%</td>
<td>26%</td>
<td>4</td>
</tr>
</tbody>
</table>

The NNT for the 3-month RCT indicates that 2 patients would need to be treated with roxithromycin 300mg in order to increase the likelihood of reduction of joint tenderness and inflammation among one patient.4 Likewise, the NNT that represents the 6-month RCT specifies that 4 patients would need to be treated in order to increase the likelihood of ACR-20 among one patient with rheumatoid arthritis.5

Safety

Few participants among the three RCTs experienced adverse events throughout the conveyance of the studies. Roxithromycin was well tolerated among patients and no deaths were reported. Of those that did experience adverse effects throughout the trials, gastrointestinal complaints (including nausea, vomiting, and abdominal pain) were most frequent between all studies.4,5,6 Tables 4 and 5 are indicative of the analyses of numbers needed to harm among both placebo and groups receiving 300mg roxithromycin in the RCTs conducted by Ogrendik.4,5,6

Table 5: Analysis of adverse events among placebo and experimental groups of Ogrendik’s 3-month RCT.4

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Relative Risk Increase (RRI)</th>
<th>Absolute Risk Increase (ARI)</th>
<th>Number Needed to Harm (NNH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI pain</td>
<td>86.6%</td>
<td>5.8%</td>
<td>17</td>
</tr>
<tr>
<td>Nausea</td>
<td>86.6%</td>
<td>5.8%</td>
<td>17</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 6: Analysis of adverse events among placebo and experimental groups of Ogrendik’s 6-month RCT.5

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Relative Risk Increase (RRI)</th>
<th>Absolute Risk Increase (ARI)</th>
<th>Number Needed to Harm (NNH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI pain</td>
<td>250%</td>
<td>10%</td>
<td>10</td>
</tr>
<tr>
<td>Nausea</td>
<td>50%</td>
<td>10%</td>
<td>2.5</td>
</tr>
<tr>
<td>Vomiting</td>
<td>50%</td>
<td>20%</td>
<td>50</td>
</tr>
</tbody>
</table>

As seen above in Tables 4 and 5, number needed to harm (NNH) was calculated based on most frequent adverse events. Of this subset, for example, the NNH for GI pain in Ogrendik’s 3-
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month RCT was 17, meaning that for every 17 patients taking roxithromycin, 1 additional would be experiencing GI pain in comparison to those not taking the drug.\textsuperscript{4} The remaining NNH from Ogrendik’s studies are depicted above. There were a total of five patients who withdrew from the Cervin et al study. Two of the three that withdrew from the placebo group did so due to a rash and abdominal pain. From the two subjects that withdrew from the roxithromycin group, one revoked due nausea and vomiting.\textsuperscript{6}

Discussion:

The two RCTs conducted by Ogrendik demonstrated the effectiveness of roxithromycin, of the macrolide class, among adults patients with signs and symptoms of inflammation related to active rheumatoid arthritis.\textsuperscript{4,5} However, also relating to the recent question as to whether or not roxithromycin has both anti-inflammatory and antibiotic effects, Cervin et al involved the treatment of patients with roxithromycin who suffered signs and symptoms of chronic rhinosinusitis due to bacterial infections.\textsuperscript{6}

When available, roxithromycin may be used for: pharyngitis, impetigo, bronchitis, tonsillitis, pneumonia, non-gonococcal urethritis, and skin and soft tissue infections. There has been no evidence supporting addiction to roxithromycin antibiotic. Roxithromycin is contraindicated for any patient who has an allergic reaction to any of the other drugs included within the macrolide class, such as: clarithromycin, erythromycin, or azithromycin.\textsuperscript{7} Bacteria that have depicted full clinical susceptibility to roxithromycin include: \textit{Strep. agalactiae}, \textit{Strep. Pneumonia}, \textit{N. meningitides}, \textit{L. monocytogenes}, anaerobic \textit{Mycob. pneumoniae}, \textit{C. trachomatis}, \textit{Ureaplasma urealyticum}, \textit{Legionella pneumophila}, \textit{Helicobacter}, \textit{Gardnerella vaginalis}, \textit{Bordetella pertussis}, \textit{Moraxella catarrhalis (Branhamella Catarrhalis)}, and \textit{Haemophilus ducreyi}.\textsuperscript{9}
One of the older members of macrolide class, erythromycin, has advanced in terms of treatment coverage over the last few years; however, studies have also shown limitations to its use. Barriers known to treatment with this particular intervention include several daily drug administrations and the gastrointestinal-related side effects, which abate compliance with these medications. Studies reviewed in 1992 looked at the “newer” macrolides, including azithromycin, clarithromycin, dirithromycin, and roxithromycin and their advantages over their precedent erythromycin. Specifically speaking, roxithromycin is widely distributed throughout various tissues and regions of the body, with a half-life of approximately 12 hours. These studies indicated the benefits of the newer macrolides in their superior activity against certain bacterial organisms, increased bioavailability due to acid resistance, and improvement in the incidence of adverse gastrointestinal effects. However, these adverse reactions do still exist, even among the most recent additions of this class. Gastrointestinal side effects are thought to be related to motilin, a naturally occurring bodily hormone that promotes gastric motility.8

Limitations of the studies were noted among the 3 RCTs. Small patient population sizes were found in the 3-month Ogrendik and Cervin et al studies. Because the Ogrendik RCTs were carried out in a similar fashion, some limitations overlapped among the two studies and include: the risk of bacterial resistance to roxithromycin with prolonged use not being evaluated, adverse events based solely on patient self-report, and no measurement of bacterial antibody concentrations. In addition, the 3-month trial exclusion criteria involved patients who did not previously receive DMARD therapy, which may have led to selection of patients with less severe RA.4,5,6 More specific limitations were also found with Cervin et al. The longevity of the treatment effect and optimal duration of treatment still remain unknown, and benefits of treatment should be weighed in comparison to risks of noted side effects. Although improvement
of rhinosinusitis was noted, no patients admitted to “complete improvement” at the end of the study. In addition, despite evidence of reduction of inflammation among anaerobes *P. aeruginosa* & falcutative anaerobe *H. influenzae* induced infections, reduction in anaerobic bacteria that more specifically match those found in joints of RA patients would have provided more significant and direct evidence.

**Conclusions:**

In conclusion, studies that look directly at the effectiveness of management of active RA with roxithromycin do show significant improvement in signs and symptoms. However, the evidence of whether or not macrolides are effective in managing the signs and symptoms of rheumatoid arthritis are conflicting due to limitations of studies. It is unknown if and when future studies will take place in the United States due to unavailability of roxithromycin. However, for further studies that do take place, several recommendations would be made to eliminate flaws and limitations. For one, larger studies are warranted. In addition, investigation of the relationship between disease activity and serum/joint antibodies to bacteria may be more interpretive of results. Measurement of specific oral or nasal flora may help in identification of subgroups that would be best targeted for treatment. Studies may also be more significant if inclusion criteria consisted of only patients with RA who have previously failed with DMARD therapy.
References:


