Effect of oral erythromycin therapy in patients with aseptic loosening

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Introduction: Aseptic loosening (AL) is a major complication of total joint replacement (TJR). There is currently no cure for AL except surgical revision. A recent approach to limiting osteolysis has focused on understanding and manipulating osteolysis at a molecular level through pharmacological intervention. However, no studies exist to address whether the inflammatory changes of periprosthetic tissues could be improved by drug treatment. Erythromycin (EM) demonstrates a unique phagocyte targeted property, with a tropism for monocytes and macrophages in bone marrow and inflammatory tissues. EM treatment reduces the 10-year survival rate of diffuse panbronchiolitis (a chronic non-infectious lung inflammation). Using a mouse osteolysis model, we have demonstrated that EM significantly inhibits wear debris-induced inflammation, osteoclastogenesis, and bone degradation [Ren WP, et al. J. Ortho. Res. 24:280-290, 2006]. The purpose of the current clinical study was to determine whether oral EM treatment could generate a similar effect in a group of AL patients who are candidates for surgical revision. Our outcome measurements included periprosthetic tissue profiles and cytokine levels in serum and joint fluids.

Materials and Methods: We evaluated 32 AL patients who were candidates for revision surgery. AL patients were treated with either EM (600 mg/day orally, n=18) or placebo (n=14) daily, started one month before surgical revision and ending on the day of surgery. Two blood samples were obtained, prior to drug treatment and on the day of revision surgery. During revision surgery, the joint fluid and the periprosthetic tissue were collected. Histological analyses of periprosthetic tissue included hematoxylin and eosin (H&E) staining for cell density, total infiltrating cell numbers, vascular density, fibrous tissues, and particle deposit, TRAP staining for osteoclasts, and immunostaining of CD68, RANKL, and OPG proteins. Gene activity of RANKL, OPG, IL-1β, and TNFα in periprosthetic tissues were determined by real-time RT-PCR techniques. ELISA was used to measure cytokine levels from sera, joint fluids, and culture media of wear debris-stimulated peripheral mononuclear cells in AL patients. These findings open up new possibilities for the treatment of AL, especially during the early stages of AL progression. We propose that oral EM treatment is a promising strategy to prevent or reduce the formation of chronic inflammation provoked by wear debris in the periprosthetic tissue, hence representing a biological cure for those patients who might need repeated revision and/or show the early signs of progressive osteolysis after joint replacement. Through there are already a number of approved anti-osteolysis drugs available, the advantage of using EM for the treatment of AL includes its clinical safety, efficacy, simplicity, and projected good compliance.

Results: Patient characteristics The demographic data demonstrated a good match of age and gender between patients treated with and without EM (Table 1). Patients tolerated oral EM treatment well and had no apparent toxic effects associated with EM treatment.

Effects of EM treatment on pathological profiles of periprosthetic tissue. Patients treated with EM exhibited improved pathological profiles in their periprosthetic tissues when compared with patients treated with placebo, based upon the reduction of infiltrating cell numbers (p = 0.061), the number of CD68+ cells (p = 0.127), the number of RANKL+ cells (p = 0.116), and the number of TRAP+ cells (p = 0.129). Using real time RT-PCR technology, a remarkable decrease of TNFα (96-fold), IL-1β (21.2-fold), and RANKL (76-fold) gene transcripts were observed in periprosthetic tissues of patients treated with EM, as compared with that of patients treated with placebo (p < 0.05, Figure 1).

The effect of EM treatment on UHMWPE particle-induced cytokine release of peripheral mononuclear cells There were no statistical differences in the release of either TNFα or IL-1β in all patients prior to drug treatment. The level of TNFα release from patients treated with EM was significantly reduced (6.7± 2.5 pg/ml) when compared to levels prior to treatment (12.5± 5.2 pg/ml, p < 0.05). The level of IL-1β release from patients treated with placebo was similar before (20.2± 6.4 pg/ml) and after drug treatment (18.3± 7.7 pg/ml). The level of IL-1β release was significantly reduced (8.4± 3.6 pg/ml, p < 0.05) following EM treatment.

Changes in various cytokine levels in the serum and joint fluid after EM treatment There were no statistical differences in serum cytokine levels between the groups at the time of randomization. Serum levels of both TNFα and IL-1β were significantly reduced following EM treatment (p < 0.05). No significant differences serum OPG concentrations were found between patients treated with and without EM. Serum RANKL concentrations were significantly reduced after EM treatment (p<0.05), but no such a change was found in patients treated with placebo. Joint fluid IL-1β levels in the group of patients treated with EM was significantly lower than that of patients treated with placebo (4.8 ± 2.51 pg/ml vs. 7.64 ± 1.48/ml, p < 0.05). There were no statistical differences in other cytokine levels (TNFα, OPG and RANKL) in the joint fluid between patients treated with EM and patients treated with placebo.

Discussion: The results of this clinical study demonstrate that oral EM treatment reduces the inflammation of periprosthetic tissues, lowers the concentration of serum cytokines, and inhibits the cytokine release of UHMWPE particle-challenged peripheral mononuclear cells in AL patients. These findings open up new possibilities for the treatment of AL, especially during the early stages of AL progression. We propose that oral EM treatment is a promising strategy to prevent or reduce the formation of chronic inflammation provoked by wear debris in the periprosthetic tissue, hence representing a biological cure for those patients who might need repeated revision and/or show the early signs of progressive osteolysis after joint replacement. Through there are already a number of approved anti-osteolysis drugs available, the advantage of using EM for the treatment of AL includes its clinical safety, efficacy, simplicity, and projected good compliance.

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Table 1: Baseline values for the Placebo vs. Erythromycin (EM) group

<table>
<thead>
<tr>
<th>Age</th>
<th>Placebo (n=16)</th>
<th>EM (n=18)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>64.8 (14.4)</td>
<td>70.7 (11.2)</td>
<td>0.79</td>
<td></td>
</tr>
<tr>
<td>Male/Female</td>
<td>2/6</td>
<td>8/10</td>
<td>0.68</td>
</tr>
<tr>
<td>Years post OP</td>
<td>7.5 (6.0)</td>
<td>9.3 (6.7)</td>
<td>0.39</td>
</tr>
<tr>
<td>Hip (Knee)</td>
<td>9.5 (3)</td>
<td>8.1 (10)</td>
<td>0.80</td>
</tr>
</tbody>
</table>

* Average (SD)

* p value for Student’s t test for groups