Introduction

Chronic diffuse sclerosing osteomyelitis of the mandible (DSOM) is a relatively rare disease that is characterized by major symptoms such as repetitive mandibular pain, swelling and trismus; radiography shows diffuse sclerotic changes with partial osteolysis.1 Because DSOM does not respond to various forms of conventional antimicrobial therapy, it is usually treated surgically. However, there are many intractable cases in which postoperative acute exacerbation frequently recurs and symptoms persist for a number of years.1–3

It has been shown4,5 that long-term erythromycin therapy can be useful for treating diffuse panbronchiolitis (DPB),6 an intractable chronic respiratory infection. Since then, other reports have shown the usefulness of the non-antimicrobial action of 14- and 15-membered macrolides, for example in inhibiting the hypersecretion of mucus7, inhibiting elastase production8 or biofilm formation,9,10 inhibiting neutrophil chemotaxis11–13 and lymphocyte activity,14 stimulating macrophages and splenocytes to produce cytokines,15 or inhibiting production of various cytokines.16–19 Kobayashi9,20 has pointed out that a major factor in the intractability of DPB is biofilm and that the ability of 14- and 15-membered macrolides to inhibit the formation of biofilms and destroy them, and the anti-inflammatory action of these compounds, play an important role in their therapeutic effects. Chronic osteomyelitis is also considered to be a biofilm disease,21,22 but to our knowledge there are no published results of long-term macrolide treatment for osteomyelitis in humans, DSOM included. The purpose of this study was to assess the efficacy of roxithromycin—a 14-membered macrolide and erythromycin derivative—for long-term treatment of DSOM.

Materials and methods

The subjects were nine DSOM patients who were seen in the Oral and Maxillofacial Surgery Department between 1992 and 1997, and whose clinical course could be observed on a long-term basis. No other patients with this disorder were seen during this period. The diagnostic criteria in-
cluded histories of intermittent pain and swelling of the mandible, and occasionally trismus, and radiographic findings characterized by ill-defined osteolytic areas in sclerotic zones.\textsuperscript{1,2,3} Patients with acute or subacute suppurative osteomyelitis and osteoradionecrosis were excluded. The subjects were fully informed about the treatment in advance and their consent was obtained. The research protocol was reviewed by the Ethics Committee. The patients, four men and five women, ranged in age from 19 to 70 years (average 41.2 years) and had no underlying diseases. The causative factor for DSOM onset was tooth extraction in three cases, pericoronitis in two and apical periodontitis in four. The lesion was located in the area from the mandibular body to the ramus (B–A–R) in five cases, the mandibular body to the angle area (B–A) in one and in the mandibular body area only (B) in three. Two patients (cases 2 and 3) who had undergone surgical treatment before the start of long-term roxithromycin treatment were intractable cases with repeated postoperative acute exacerbation.

Roxithromycin was administered orally in a daily dosage of 300 mg in two divided doses. The clinical efficacy was determined mainly by the change in symptoms such as pain, trismus and degree of improvement in radiographs, in addition to the results of blood tests. The clinical symptoms and radiographic findings were divided into three grades for categorization as follows: spontaneous pain (2, complete disappearance of spontaneous pain; 1, decreased severity of pain even with recurrence; 0, no improvement in spontaneous pain); trismus (2, improvement of $\geq 40$ mm in opening of the mouth; 1, restricted opening of the mouth without problems in daily life; 0, no improvement in the opening of the mouth); and radiographic findings (2, recovery of normal bone trabeculae; 1, no improvement in osteosclerosis and no additional osteolysis; 0, additional osteolysis). The clinical course was evaluated every 2 weeks, and each time a decision was made on whether or not to continue treatment. The scores in each category were summed; overall efficacy was regarded as ‘poor’, ‘good’ or ‘excellent’ when the total score was 0–2 points, 3–5 points and 6 points, respectively. The final evaluation of efficacy was performed at the end of treatment. Blood tests such as white and red blood cell counts (WBC and RBC), haemoglobin, haematocrit, platelet count and concentrations of glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, alkaline phosphatase, blood urea nitrogen, creatinine, Na\textsuperscript{+}, K\textsuperscript{+}, Cl\textsuperscript{–}, glucose and C-reactive protein were performed every 1–2 months to determine whether or not they were affected by the use of roxithromycin.

**Results**

The duration of roxithromycin therapy was between 68 days and 66 months. Pain was reduced in all of the patients and ceased completely in seven of the nine patients. Trismus was eliminated in three of the six patients suffering from it. Radiographic findings at the end of treatment showed no improvement in osteosclerosis in any of the patients but revealed the disappearance of osteolysis (‘moth-eaten’ bone) in six of nine patients. Overall, the clinical efficacy at the end of treatment was judged as good in seven of nine patients (77.8\%). In two patients (cases 2 and 4), treatment was continued because of the lessening of pain during acute exacerbation, but these cases were ultimately judged as ‘poor’ since pain did not disappear completely and radiographic findings showed no improvement in ‘moth-eaten’ bone (Table I). In most of the patients, WBC count and C-reactive protein concentration did not increase even when an exacerbation occurred. As for adverse reactions, gastrointestinal symptoms such as diarrhoea and stomach discomfort appeared temporarily in case 3 but improved when treatment was stopped for a few days, allowing continued long-term treatment. Treatment was discontinued in case 8 because of a slight increase in GOT (56 IU/L) but

**Table I. Clinical efficacy of long-term roxithromycin treatment**

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Location of lesion</th>
<th>Duration of roxithromycin therapy</th>
<th>Scores for symptoms and X-ray findings</th>
<th>Clinical efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>pain</td>
<td>trismus</td>
</tr>
<tr>
<td>1</td>
<td>50</td>
<td>F</td>
<td>B–A–R</td>
<td>34 months</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>66</td>
<td>F</td>
<td>B–A–R</td>
<td>66 months</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>26</td>
<td>F</td>
<td>B–A–R</td>
<td>15 months</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>49</td>
<td>F</td>
<td>B–A–R</td>
<td>39 months</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>19</td>
<td>F</td>
<td>B–A–R</td>
<td>9 months</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>70</td>
<td>M</td>
<td>B–A</td>
<td>68 days</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>26</td>
<td>M</td>
<td>B</td>
<td>6 months</td>
<td>2</td>
<td>–</td>
</tr>
<tr>
<td>8</td>
<td>35</td>
<td>M</td>
<td>B</td>
<td>73 days</td>
<td>2</td>
<td>–</td>
</tr>
<tr>
<td>9</td>
<td>30</td>
<td>M</td>
<td>B</td>
<td>76 days</td>
<td>2</td>
<td>–</td>
</tr>
</tbody>
</table>

Abbreviations: F, female; M, male; B, mandibular body; A, mandibular angle; R, ramus.
Long-term roxithromycin therapy for osteomyelitis

Table II. Relationship between location of lesion, clinical course and time taken for symptoms to disappear

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Location of disease</th>
<th>Time from onset of illness until start of roxithromycin therapy</th>
<th>Time (months) taken for all symptoms to disappear</th>
<th>Duration of follow up after roxithromycin therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>B–A–R</td>
<td>13 years</td>
<td>12</td>
<td>3 years</td>
</tr>
<tr>
<td>2</td>
<td>B–A–R</td>
<td>11 years</td>
<td>did not disappear completely</td>
<td>1 year, 9 months</td>
</tr>
<tr>
<td>3</td>
<td>B–A–R</td>
<td>2 years, 8 months</td>
<td>10</td>
<td>4 years, 5 months</td>
</tr>
<tr>
<td>4</td>
<td>B–A–R</td>
<td>2 years</td>
<td>did not disappear completely</td>
<td>1 year, 5 months</td>
</tr>
<tr>
<td>5</td>
<td>B–A–R</td>
<td>2 months</td>
<td>2</td>
<td>2 years, 5 months</td>
</tr>
<tr>
<td>6</td>
<td>B–A–R</td>
<td>2 months</td>
<td>2</td>
<td>1 year, 10 months</td>
</tr>
<tr>
<td>7</td>
<td>B</td>
<td>1.5 months</td>
<td>1</td>
<td>1 year, 2 months</td>
</tr>
<tr>
<td>8</td>
<td>B</td>
<td>2 months</td>
<td>1</td>
<td>2 years, 2 months</td>
</tr>
<tr>
<td>9</td>
<td>B</td>
<td>1 months</td>
<td>1.5</td>
<td>1 year, 3 months</td>
</tr>
</tbody>
</table>

B, mandibular body; A, mandibular angle; R, ramus.

the level had returned to normal on re-examination. No other abnormal blood test results were observed and no adverse reactions were noted in any of the other cases.

Long-term roxithromycin treatment started from between 1 month and 13 years after onset. Of the four patients (cases 1–4) whose duration of illness after onset was as long as 2–13 years, two (cases 2 and 4) did not show complete cessation of symptoms, while the remaining two patients (cases 1 and 3) took a long period of time, 12 and 10 months, respectively, to improve. In the other five patients (cases 5–9), the period from onset to the start of roxithromycin therapy was short, from 1 to 2 months, and the duration after treatment until the symptoms disappeared was similarly short, only 1–2 months.

We also analysed whether the extent of the lesion affected therapeutic efficacy; 12, 10 and 2 months were required before the symptoms disappeared in three (cases 1, 3 and 5, respectively) of the five patients whose lesions extended from the mandibular body to the ramus area, while the symptoms disappeared within 2 months and no further recurrence was noted in four patients (cases 6–9) whose lesions were limited to the mandibular body or angle area (Table II).

In seven patients whose response to therapy was assessed as 'good', the clinical course was observed for between 1 year and 2 months to 4 years and 5 months after the end of roxithromycin treatment. During this period, no recurrence was noted in any of the cases. However, in radiographs taken at the last follow-up, osteosclerosis was still evident in most of the patients, and only two patients (cases 7 and 8) had radiographs that showed an improvement in osteosclerosis and normal bone trabeculae.

Case presentations

Case 1. Case 1 was a 50 year-old woman with DSOM resulting from infection after extraction of the left mandibular third molar. The lesion extended from the left mandibular body to the ramus area. Because she had refused surgical treatment, various antimicrobial agents had been given on each recurrence over a period of 12 years, during which time the left mandibular bone had become markedly deformed by osteolysis. After starting long-term roxithromycin treatment, acute exacerbation was observed twice every 3–4 months but the number of days when analgesics were used gradually decreased and the severity of trismus lessened (Figure 1). The patient’s WBC count was 5.5–6.5 × 10^9/L and her C-reactive protein concentration was <0.24 mg/dL when exacerbations occurred. Inflammation no longer reappeared after 12 months and the treatment was terminated 2 years and 9 months later. The response in this case was assessed as good, although osteosclerosis could still be observed in radiographs 2 years and 5 months after the end of treatment (Figure 2).

Case 5. Case 5 was a 19 year-old woman with DSOM due to pericoronitis of the right mandibular third molar. The lesion extended from the right mandibular body to the ramus area. After the start of roxithromycin therapy, acute exacerbation occurred once but WBC count (5.9 × 10^9/L) and C-reactive protein concentration (<0.24 mg/dL) were not increased. The symptoms halted after 2 months of treatment, and treatment continued for an additional 7 months. The outcome was judged as good. Radiographs taken at the end of treatment displayed no ‘moth-eaten’ osteolytic changes but there were more osteosclerotic changes than before the start of treatment. No recurrence was noted during the 2 year follow-up, although according to radiographs osteosclerosis had not improved (Figure 3).

Discussion

Therapy for DSOM is often unsuccessful. Many patients experience recurrences despite systemic or local antibiotic therapy, administration of anti-inflammatory drugs, treatment with hyperbaric oxygen and removal of infectious foci. Therefore decortication of the affected areas has
been widely used in the treatment of DSOM. However, even after decortication, recurrence rates have been reported to be as high as 50–75%. Chronic osteomyelitis is considered to be a biofilm disease. In biofilms, bacteria adhere to natural and synthetic, medically important surfaces within an extracellular polymer generically termed the glycocalyx. The formation of biofilms can cause difficulties in antimicrobial chemotherapy, since biofilm bacteria have increased resistance to antibiotics. The suggested mechanisms underlying this resistance are a low growth rate, the barrier effect of the glycocalyx and nutrient deprivation. The enhanced antibiotic resistance of bacteria, relative to ‘floating’ (‘planktonic’) bacteria, encourages the establishment of chronic bacterial infections such as osteomyelitis.

Investigation of DPB, as it is manifest in chronic persistent biofilm disease, indicates that the most important factors are excess antigen–antibody reaction where alginate (glycocalyx) acts as the antigen, and the resultant formation of immune complex. Fourteen- and 15-membered macrolides inhibit the immune reaction induced by alginate and the macrolides’ inhibitory effect on alginate production. In DSOM the chronicity of the disease is explained by an endogenous type of infection and a triggered immunological reaction, although many factors are still in need of further investigation. Thus, we have attempted long-term roxithromycin treatment for DSOM. We obtained favourable results, with seven of nine cases deemed to have improved. Since biofilm bacteria are usually resistant to antimicrobial agents and host phagocytosis, intra-arterial infusion and antibiotic-impregnated polymethylmethacrylate beads have been used in chemotherapy for DSOM.

The duration of roxithromycin therapy for DSOM and the amount of time needed to judge efficacy could not be predetermined for this clinical trial because of the extremely small number of DSOM patients and because this was the first study of this nature. We therefore carefully observed clinical efficacy, evaluating the presence or absence of adverse reactions every 2 weeks and determining whether or not to continue the treatment. It was difficult to determine when treatment should be terminated,
Long-term roxithromycin therapy for osteomyelitis

since DSOM is more likely to recur after a few months even though the clinical symptoms may temporarily disappear. Consequently, the duration of administration varied greatly between patients. Although DPB is the first condition to be treated by the long-term administration of a 14-membered macrolide, the decision of when to stop administration seems to depend on each patient’s individual degree of improvement of clinical symptoms. Thus, it is difficult to give clear guidelines on the optimal length of treatment. Sawaki et al.\textsuperscript{43} recently studied this subject in detail, and found that there was a wide variance between patients who had been administered 14-membered macrolides for between 12 and 41 months.

Of all the patients in the current study, those who experienced recurring symptoms during roxithromycin therapy had a long clinical course after onset or a history of surgery,
and their lesions were wide, extending from the mandibular body to the ramus area. Among these subjects, those in whom long-term roxithromycin treatment was effective required 10–12 months to confirm a lack of recurrence and for all of the symptoms to completely disappear. Thus, it was considered that patients with a long clinical course after onset or those whose lesion involves a wide region up to the ramus area should be evaluated after treatment has continued for ≥10 months. In patients whose lesion was narrower, in the region from the mandibular body to the angle, the symptoms disappeared about 1–2 months after treatment and further recurrence was not noted. Accordingly, if the lesion does not involve the portion up to the ramus area, treatment may be terminated when the symptoms disappear. Termination of treatment based on radiographic findings may require an absence of osteolytic change even if osteosclerosis has not been improved, since osteolytic changes disappeared along with the disappearance of symptoms and no additional osteolysis was observed in improved cases. In blood tests, few cases showed any abnormality in WBC count or C-reactive protein concentration during the study. Even in incidences of exacerbation, there were no remarkable changes in these test results. This is a characteristic of DSOM, so WBC counts and C-reactive protein concentrations may not be adequate criteria for judging the effects of long-term roxithromycin therapy for DSOM.

Regarding the safety of this therapy, in the present study one case showed mild impairment of liver function, but no abnormalities were observed in blood tests in any of the other cases. There was one case of diarrhoea, but this was mild and disappeared when treatment was stopped. Significant adverse reactions associated with long-term treatment with 14- and 15-membered macrolides have not been reported, but some uncertainties still remain concerning the safety of roxithromycin during continuous long-term administration. Therefore adequate caution and careful observation must be exercised in future applications.

The current study does have a flaw in that the time required for judging the efficacy and duration of administration could not be predetermined, but our results suggest that long-term roxithromycin treatment may well be effective therapy for DSOM. However, since the present therapeutic method is by no means universally effective, elucidation of its pharmacological mechanism and further studies of the criteria for its clinical applicability are important requirements for future research. Larger and more comprehensively designed studies on optimum duration, dosages and drug selection clearly need to be carried out.

References

Long-term roxithromycin therapy for osteomyelitis


Received 22 August 2000; returned 24 November 2000; revised 9 January 2001; accepted 24 January 2001