Long-term efficacy and safety of clarithromycin treatment in patients with diffuse panbronchiolitis

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Summary Diffuse panbronchiolitis (DPB) can now be cured with long-term erythromycin treatment. Our group conducted a prospective open trial of long-term treatment with a macrolide antibiotic, clarithromycin. We studied ten patients who were treated for 4 years with oral clarithromycin (200mg once a day). Pulmonary function test, blood gas analysis, comprehensive improvement score, and bacterial culture of sputum were examined at 3, 6, 12 months, and at 2, 3, 4 years after the initiation of the therapy. Pulmonary function improved in most of the patients within 6 months: the forced expiratory volume in one second showed a maximal increase from a mean (SE) value of 1.74 (0.12) l at baseline to 2.31 (0.22) l at 6 months ($P < 0.01$) and the volume (l) of forced vital capacity also showed a maximal increase within 6 months. The partial pressure of arterial oxygen at rest significantly increased at 3–6 months. The comprehensive improvement score also reached maximum within 6 months in nine of the patients. The majority of patients have developed sputum culture in which bacteria were negative within 6 months after the therapy. All of the patients maintained a stable condition with continued therapy, and no side effects of clarithromycin were observed during the study. This prospective study demonstrated that 6-month treatment with clarithromycin might be necessary to improve the clinical conditions of patients with DPB and the drug could be safely used for a long term.

Introduction

Diffuse panbronchiolitis (DPB) is a chronic inflammatory airway disease that was first described in 1969 by Yamanaka et al. as a new clinicopathologic entity. Though the disease is restricted almost exclusively to Asian countries such as Japan, China, Taiwan, and Korea, several cases have been reported in non-Asian individuals. The etiology of DPB is not yet clear, and the natural history of the disease is respiratory failure leading to cor pulmonale and ultimately death. Hemophilus influenzae and Streptococcus pneumoniae are often isolated from the sputum repeatedly or continuously over a long period early in the course of the disease and these bacteria are replaced by Pseudomonas aeruginosa in most cases when the disease reaches its advanced stage. The chronic P. aeruginosa infection is caused by mucoid strains of these bacteria growing as a biofilm which is virtually impossible to eradicate by antibiotics. During this time, the respiratory bronchioles become obstructed and the nearby airway bronchioles become dilated. These changes are quite similar to those of cystic fibrosis seen primarily in Western countries.

The prognosis of this disease was poor before 1985 in spite of numerous treatment alternatives.
with several antibiotics, corticosteroids, and life-saving supportive therapy. According to the Research Project Team of the Japanese Ministry of Health and Welfare, the 10-year survival rate of DPB cases in 1987 was 12.4% for cases infected with *P. aeruginosa* and 73.1% for cases without *P. aeruginosa* infection. After 1985, treatment was modified to long-term erythromycin therapy at a daily dose of 400–600 mg, based on the first report of an open trial showing the beneficial effects of “low-dose, long-term” treatment with erythromycin (400–600 mg/day for more than 6 months) in DPB. This effect was later confirmed by a placebo-controlled, double blind clinical trial. Other studies have also shown that erythromycin is more effective than a new quinolone antibacterial agent administered for 3 months, and ampicillin administered for 3 months. Treatment using this regimen has resulted in a significant improvement in the survival rate of patients with DPB since 1985. For example, the 10-year survival rate has increased to more than 90%, marking a dramatic improvement over the rates reported between 1970 and 1984. Subsequent to the above clinical trial studies, we reported that oral administration ofroxithromycin (150 mg/day) for more than 1 month also produced good results, such as improvements in FEV₁ and FVC to levels comparable to those obtained with erythromycin. Our results also showed no significant difference in the comprehensive improvement score between patients treated withroxithromycin and those treated with erythromycin. Other macrolide antibiotics, clarithromycin and azithromycin, have also been reported to be equally effective in DPB.

However, since those studies were retrospective with short courses of therapy (approximately 1–24 months) and a variety of assessment periods, it has remained unclear when the efficacy of these drugs appears and whether the drugs can be used safely for a long term. Our group, therefore, conducted a prospective open trial of long-term treatment with the macrolide antibiotic. Clarithromycin instead of erythromycin was employed in this study because of the lower adverse effect on the gastrointestinal tract.

**Methods**

**Patients**

DPB was diagnosed using the following clinical criteria established by the Ministry of Health and Welfare of Japan in 1995. (1) Symptoms: all of chronic cough, sputum, and dyspnea on exertion. (2) Physical signs: coarse crackles, rhonchi, or wheezes on auscultation of the chest. (3) Chest radiographic findings: chest roentgenogram reveals bilateral fine nodular shadows mainly in the lower lung fields, and all patients received chest computed tomograms in which the findings showing small rounded areas of high attenuation with a centrilobular distribution, branching linear areas of high attenuation, and hypointensification in the peripheral lung are more helpful in the diagnosis. (4) Pulmonary function tests and blood gas analysis: FEV₁% <70% and PaO₂ < 80 mmHg. (5) Elevated titers of cold hemagglutinin, ×64 or higher. (6) Past history or coexistence of chronic parasinusitis. Such clinical findings can be used in making the diagnosis of DPB. Histological studies, when possible, can confirm the diagnosis. The histological features of DPB are characteristics and include accumulation of lymphocytes and plasma cells localized predominantly in the respiratory bronchioles and adjacent centrilobular regions, and accumulation of foamy macrophages in the wall of respiratory bronchioles, adjacent alveolar ducts, and alveoli with infiltration of lymphoid cells. If patients were diagnosed only using the clinical criteria, patients with a history of exposure to organic or inorganic dust or drugs known to cause bronchiolitis and those with connective tissue disease or other chronic lung diseases causing bronchiolitis were excluded and other obstructive pulmonary diseases such as chronic bronchitis, bronchial asthma, chronic emphysema and cystic fibrosis were carefully ruled out. The study was conducted between March 1995 and April 2000 in Nagasaki University Hospital. The protocol was approved by the ethics committee of Nagasaki University Hospital, and all the patients provided written informed consent.

**Study design**

Once diagnosed, the patients were treated with 200 mg of clarithromycin per day for 4 years. If patients had signs or roentgenographic findings suggesting pneumonia or acute exacerbation of the disease before enrollment in the study, adequate antibiotics were administered. Thus, none had an acute pulmonary infection in the 1 month before enrollment in the study. The patients were instructed at each outpatients attendance to take one tablet of clarithromycin (200 mg) every 24 h, at home, and were given a 4-week supply. They were instructed to bring back any remaining tablets at each visit so that the numbers of remaining
tablets could be checked. Patients did not use any other treatment for their disease during the entire duration of the study, except for a short-term antibiotic use when patients had acute exacerbation of the disease.

Clinical and laboratory assessments, sputum culture, pulmonary function tests, arterial blood gas analysis at rest, and chest X-ray and CT scan were performed at baseline, at 3, 6, and 12 months, and at 2, 3, and 4 years after initiating the treatment. To evaluate the clinical efficacy of clarithromycin treatment at each time point, we also applied the comprehensive improvement score\textsuperscript{13,14} assessed by the total score of five items, namely chest radiographic abnormalities including CT findings, FEV\textsubscript{1}, PaO\textsubscript{2}, the Hugh-Jones score, and C-reactive protein (improvement = +1, no change = 0, and worse = −1).

Patients were monitored for the occurrence of all adverse events. Laboratory assessments were made at each time point during the entire study period and included complete blood count, chemistries, and urinalysis. Clinically significant laboratory abnormalities that could not be attributed to other medical conditions were reported as adverse events.

Statistical analysis

All values were expressed as mean (SE), and were compared using one-factor ANOVA with Tukey–Kramer post hoc analysis by the StatView 5.0 statistical package. A \( P \)-value of \(<0.05\) was considered significant.

Results

Patients

We enrolled ten patients (four men and six women, mean age 50.3 (4.4) years, all non-smokers). The clinical characteristics of the patients were summarized in Table 1. Four of the patients were pathologically diagnosed by surgical lung biopsy, and the remaining were based on the clinical criteria (all of six items were fulfilled in four of the patients and five of the six items in the other two patients). All patients completed the study.

Efficacy

Serial analysis of pulmonary function tests after clarithromycin treatment is shown in Fig. 1. The forced expiratory volume in 1 s started to rise from
a mean of 1.74 (0.12) l at baseline to 2.21 (0.19) l at 3 months ($P<0.01$), and reached to a maximal value with 2.31 (0.22) l ($P<0.01$, compared to that at baseline) at 6 months and thereafter sustained the same value until 4 years (Fig. 1a). The significant increase in FEV$_1\%$ also started after 6 months of treatment ($P<0.05$), and kept the same value over the next follow-up periods (Fig. 1b). The V$_{25}$/Height (HT) also increased to a peak value of 0.45 (0.07) l/s/m from 0.28 (0.06) l/s/m at baseline after 6 months of treatment, although not statistically significant. The volume (l) of forced vital capacity also rose to a maximal value within 6 months [3.16 (0.26) vs 2.57 (0.15) at baseline; $P<0.005$], comparable with the value at each time point (Fig. 1c). Although the forced vital capacity was not deteriorated at baseline, it also increased significantly from a mean of 88.2 (5.3)% of the predicted value at baseline to 103.6 (3.9)% after 3 months of treatment ($P<0.001$), and no differences were observed between each time point (Fig. 1d). The partial pressure of arterial oxygen at rest significantly increased to 85.0 (2.6) mmHg at 3 years compared with that at baseline, and this
value were significantly higher than that at 3 or 6 months ($P<0.05$). However there were no significant differences in the values between 3 or 6 months and 4 years (Fig. 1e). The comprehensive improvement score reached maximum at 3 months in seven, 6 months in two and 2 years in one of the patients with an excellent improvement in eight, a moderate improvement in one and a mild improvement in one, and thereafter kept their stable condition (Table 2). The latter patient (patients No. 10) showed only minimal response to therapy because she had normal lung function and low CHA titer at baseline which could not be markers of significance.

The organisms identified on sputum culture throughout the 4-year period of clarithromycin therapy are shown in Table 3. Sputum cultures were performed at least 3 times during each treatment period in the following 2, 3, 4 years. Sputum sample isolated from the patients at each time point was from their stable condition except for case 6 in which acute exacerbation occurred at 6 months after the therapy. Five of the patients demonstrated no bacterial growth in their sputum and sputum in two of the patients disappeared within 6 months. Sputum in another three of the patients also disappeared throughout the study period (two and one of the patients at 12 months and 2 years, respectively). The remaining patients (patient No. 2, 6, 8, 9, 10) still had sputum but decreased even with positive bacterial culture ($Klebsiella pneumoniae$: $4 \times 10^4$ cfu/ml).

### Table 2 Comprehensive improvement score after clarithromycin treatment.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>3 months</th>
<th>6 months</th>
<th>12 months</th>
<th>2 years</th>
<th>3 years</th>
<th>4 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>+5</td>
<td>+5</td>
<td>+5</td>
<td>+5</td>
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<td>+4</td>
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<td>+5</td>
<td>+5</td>
<td>+4</td>
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<tr>
<td>9</td>
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<td>+4</td>
<td>+4</td>
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<td>+4</td>
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</tr>
<tr>
<td>10</td>
<td>+1</td>
<td>+1</td>
<td>+1</td>
<td>+1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

+4 to +5: excellent improvement, +2 to +3: moderate improvement, +1: mild improvement, 0: no change.

### Table 3 Bacteria isolated from sputum of the patients after clarithromycin treatment.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>before</th>
<th>3 months</th>
<th>6 months</th>
<th>12 months</th>
<th>2 years</th>
<th>3 years</th>
<th>4 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HPh (0.02$^a$)</td>
<td>SP (1)</td>
<td>SM (0.01)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>HI (0.4)</td>
<td>HI (0.2)</td>
<td>NF</td>
<td>NF</td>
<td>NF</td>
<td>NF</td>
<td>NF</td>
</tr>
<tr>
<td>3</td>
<td>HI (0.005)</td>
<td>NF</td>
<td>NF</td>
<td>PA (6)</td>
<td>PA (10)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>SP (10)</td>
<td>NF</td>
<td>PA (6)</td>
<td>HPh (0.04)</td>
<td>PRSP (4)</td>
<td>HI (10)</td>
<td>HI (4)</td>
</tr>
<tr>
<td>5</td>
<td>NF</td>
<td>NF</td>
<td>(—)$^b$</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>NF</td>
<td>MC (20)</td>
<td>HI (20)</td>
<td>PRSP (4), HPh (0.04)</td>
<td>HI (8)</td>
<td>HI (10)</td>
<td>HI (4)</td>
</tr>
<tr>
<td>7</td>
<td>PA (10)</td>
<td>SA (0.2)</td>
<td>BB (6)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>8</td>
<td>NF</td>
<td>NF</td>
<td>NF</td>
<td>HPh (0.2)</td>
<td>KP (3)</td>
<td>NF</td>
<td>KP (0.004)</td>
</tr>
<tr>
<td>9</td>
<td>SP (6)</td>
<td>PA (10)</td>
<td>NF</td>
<td>NF</td>
<td>PA (5)</td>
<td>NF</td>
<td>NF</td>
</tr>
<tr>
<td>10</td>
<td>NF</td>
<td>NF</td>
<td>NF</td>
<td>NF</td>
<td>NF</td>
<td>NF</td>
<td>AF (0.05)</td>
</tr>
</tbody>
</table>


$^a$Number of isolated bacteria; $\times 10^7$ cfu/ml.

$^b$No sputum.
**Alcaligenes faecalis**: $5 \times 10^5$ cfu/ml, *Staphylococcus aureus*: $4 \times 10^5$ cfu/ml, and normal flora) at the last time point. *S. pneumoniae* strains resistant to penicillin G (MIC: 1.0 $\mu$g/ml) and resistant to both penicillin G (MIC: 4.0 $\mu$g/ml) and erythromycin (MIC: 4.0 $\mu$g/ml) were isolated in sputum obtained from one of the remaining patients (patient No. 6) at 12 months and 2 years after the therapy, respectively. However, the bacteria were replaced by *S. aureus* during the next follow-up periods. None of the patients had been hospitalized with serious pulmonary infection including acute exacerbation caused by the bacteria isolated from sputum during the course of the study.

### Adverse events

There were no adverse effects in the physical and laboratory findings except for one patient who had transient mild diarrhea for a few days after initiating the treatment (case 7).

### Discussion

During this decade, DPB became a curable disease with low-dose and long-term erythromycin treatment. Other 14-membered macrolides such as clarithromycin and roxithromycin or 15-membered macrolide, azithromycin also have a good efficacy. However, since those studies were retrospective with a short course of the therapy for approximately 1–24 months and a variety of assessment period, it was unclear when the efficacy of the drugs appears and whether the drugs can be used safely for a long term. In a prospective study, a significant improvement was initially found in FEV$_1$, VC, %VC and PaO$_2$ at 3 months but in FEV$_1$% at 6 months after the therapy, and most of the patients had a significant maximal improvement in pulmonary ventilation at 6 months although the value between 3 and 6 months was not statistically different. Gas exchange had a maximal improvement at 3 years with a significantly higher value than that at 3 or 6 months, and no significant differences were observed in the values between 3 or 6 months and 4 years after the therapy. In addition, the comprehensive improvement score reached maximum within 6 months, and the bacteriologic data demonstrated that the majority of patients have certainly developed sputum culture in which bacteria became negative by 6 months of therapy. This study also showed that the improvement observed at 6 months was stable over the next follow-up period until 4 years with continued therapy. These results indicate that 6-month treatment with clarithromycin might be necessary to improve the clinical condition of patients with DPB. This effect of the drug was also observed in the presence of bacteria (irrespective of bacterial eradication), and it is emphasized that the two patients with *P. aeruginosa* in the sputum and marked impairment of lung function responded well to therapy since such patients have been reported to be the worse prognosis if untreated. This confirmed the previous findings that macrolides act as anti-inflammatory rather than bactericidal agents. However, the present study cannot answer the question of whether the stability would continue if the antibiotic was stopped after 6 months, or in other words, of whether orally administrated clarithromycin can last 4 years in order to keep patients’ stable condition.

Long-term administration of the drug was well tolerated by all study participants with no physical problems, laboratory abnormalities, or other serious adverse events. Additionally, it has been reported that clarithromycin-related side-effects on the gastrointestinal tract may be significantly less than those of erythromycin. These results may indicate the advantages of clarithromycin administration as compared with erythromycin. However, there has been concern about the development of *S. pneumoniae* resistant to macrolide, as multidrug-resistant *S. pneumoniae*, including penicillin- and macrolide-resistant strains, have become a serious public health problem in Japan and many other countries as the rates of infection from these bacteria continue to grow.

In this study, *S. pneumoniae* unsusceptible to macrolide was only isolated in sputum from one of the ten patients. Later in the course of the study it was replaced by other bacteria, and there was no pulmonary infection caused by resistant bacteria.

In conclusion, this study showed that 6-month treatment with clarithromycin might be necessary to improve the clinical condition of patients with DPB and the drug could be used safely with no prominent adverse effect during 4-year administration. The present result gives an important information to physicians in East Asia and even western countries coping with DPB.

### Acknowledgements

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References