Effect of Azithromycin on Patients with Diffuse Panbronchiolitis: Retrospective Study of 51 Cases

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Abstract

**Background**  Patients with diffuse panbronchiolitis (DPB) are routinely treated with erythromycin, clarithromycin, and roxithromycin. The clinical effect of azithromycin on DPB has not been confirmed in a large cohort.

**Objective**  The present study was undertaken to investigate the clinical effects of azithromycin on patients with DPB.

**Methods**  Fifty-one patients with DPB treated with azithromycin in Shanghai Pulmonary Hospital, China, from July 2001 to April 2007 were analyzed retrospectively. Azithromycin (500 mg a day) was administrated intravenously in the first 1-2 weeks, taken orally (500 mg, once a day) for 3 months, and tapered to 3 times a week for 6-12 months. The patients were followed up until September 1, 2009. The therapeutic effect, according to their clinical and radiological findings, arterial gas analysis, lung function, and sputum bacterium before and after the therapy, was categorized into the following five grades: 1) cured; 2) improved; 3) no response; 4) aggravation, and 5) relapse.

**Results**  With azithromycin therapy, 14 (27.5%) patients with DPB were completely cured. The symptoms were eliminated to certain degrees for the other 36 cases (70.6%) of DPB. Five-year survival in this cohort was 94.1%.

**Conclusion**  Azithromycin is effective and well tolerated for patients with diffuse panbronchiolitis.

Key words: zithromycin, macrolides, diffuse panbronchiolitis (DPB)


Introduction

Diffuse panbronchiolitis (DPB), a chronic inflammation disease of airway, involves respiratory bronchioles of the bilateral lung (1). It was originally reported in Japan (2). However, an increasing number of cases have been reported in Europe (3, 4) and America (5-9), as well as in Asia (10), including Thailand (11), India (12), and China (13-20).

With macrolide therapy, the prognosis of DPB has greatly improved (21-27). Erythromycin has been used as the first choice according to clinical guidelines in Japan (2, 28). Several studies verified the efficiency of 14-membered and 15-membered ring macrolides for DPB (21-23, 29, 30). However, the adverse effects of erythromycin, such as gastrointestinal (31, 32) or hepatic dysfunction (33), and its administration frequency (usually 3 times a day) (26), have limited its clinical application.

Azithromycin, a 15-membered ring macrolide, is characterized by fewer adverse effects (34), longer post antibiotic effect (PAE) and less frequent administration (35, 36), which may present a better option for DPB. However, azithromycin has not been used in a large cohort of DPB patients to prove its efficacy. In this study, we analyzed 51
Chinese patients with DPB treated with azithromycin and evaluated the clinical effect.

### Materials and Methods

**Patient characteristics**

This study was performed in Shanghai Pulmonary Hospital, an 825-bed university teaching hospital in China. Fifty-one (30 males and 21 females) of the patients who fulfilled the definite diagnostic criteria proposed in 1998 by a working group of the Ministry of Health and Welfare of Japan (2) were enrolled into the study. They were admitted to the hospital from July 1, 2001 to April 31, 2007 and were followed up until September 1, 2009. Their clinical characteristics are shown in Table 1. The patients were all of the Han ethnic group. Informed consent was obtained from all of the patients. The study received institutional review board approval at Tongji University. All of the patients’ confidential information was maintained.

All 51 patients received chest X-rays and CT scans. Five of them had pathological data, 4 by video-assisted thoracoscopic lung biopsy (VATS) and one by open lung biopsy. Other tests included arterial blood gas, spirometry, cold hemagglutinin (CHA), HLA-BWS4, erythrocyte sedimentation rate (ESR), sputum cultures, serum antigen and antibody tests for different microorganisms including tuberculosis, atypical Mycobacterial infection, fungal infection, Mycoplasma pneumoniae, Chlamydia pneumoniae, and others to exclude different infectious diseases and other sicknesses, including chronic obstructive pulmonary disease (COPD), bronchiectasis, bronchial asthma, pulmonary tuberculosis, interstitial lung diseases (ILD), sarcoidosis, alveolar cell carcinoma, occupational lung diseases and fungal infection.

**Azithromycin therapy**

All patients were treated by azithromycin once diagnosed with DPB. Azithromycin (500 mg, once a day) was administered intravenously in the first 1-2 weeks and was then taken orally (500 mg, once a day) while their symptoms, physical signs and radiographic findings improved. Three months later, administration tapered to 3 times a week (500 mg, once a day in first three days of a week). This program usually ran for 6 to 12 months, but for some patients, it had to be prolonged until they recovered completely.

**Evaluation of the therapeutic effect**

The clinical therapeutic effect was assessed based on the improvement of clinical symptoms/signs, radiographic findings, pulmonary function, arterial blood gas and sputum cultures. The deadline of follow-up was September 1, 2009. Responses of 51 cases were evaluated as follows: 1) Cured; all the clinical symptoms and signs were eliminated. Radiological image, arterial blood gas and pulmonary function were completely recovered. 2) Improved; remarkable improvement was observed in clinical symptoms and signs; radiological image on chest CT scans were absorbed; Partial improvement meant that more than one of the following were improved: symptoms, signs or radiographic changes. 3) No response; symptoms and signs remained and no improvement on radiographic changes was observed. 4) Aggravation; at least one of the following was aggravated: clinical symptoms, signs or radiographic changes. 5) Relapse; symptoms, signs or radiographic changes recurred during the follow-up period.

**Statistical analysis**

All patient data were analyzed by SPSS 13.0. Continuous data were expressed as mean ± standard deviation (SD). The means of all continuous variables before and after treatment were analyzed by t tests. Statistical significance was established at a p value < 0.05. Actuarial survival curves were constructed using the Kaplan Meier method.

### Results

**Patients**

Fifty-one patients with DPB were included in this study. Diagnosis of DPB was based on the definite diagnostic cri-
Table 2. Clinical Findings in 51 Diffuse Panbronchiolitis Patients before and after Treatment

<table>
<thead>
<tr>
<th>Clinical situation</th>
<th>Total cases</th>
<th>≤3days</th>
<th>Percentage (%)</th>
<th>4~7days</th>
<th>Percentage (%)</th>
<th>&gt;7days</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>51</td>
<td>45</td>
<td>88.2</td>
<td>4</td>
<td>7.8</td>
<td>2</td>
<td>3.9</td>
</tr>
<tr>
<td>Expectoration</td>
<td>50</td>
<td>44</td>
<td>88.0</td>
<td>4</td>
<td>8.0</td>
<td>2</td>
<td>4.0</td>
</tr>
<tr>
<td>Dyspnea on exertion</td>
<td>49</td>
<td>43</td>
<td>87.8</td>
<td>5</td>
<td>10.2</td>
<td>1</td>
<td>2.0</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>14</td>
<td>7</td>
<td>50.0</td>
<td>3</td>
<td>35.7</td>
<td>2</td>
<td>14.3</td>
</tr>
<tr>
<td>Wheezing sound</td>
<td>33</td>
<td>27</td>
<td>81.8</td>
<td>3</td>
<td>9.1</td>
<td>3</td>
<td>9.1</td>
</tr>
<tr>
<td>Crackles</td>
<td>49</td>
<td>27</td>
<td>55.1</td>
<td>20</td>
<td>40.8</td>
<td>2</td>
<td>4.1</td>
</tr>
</tbody>
</table>

Figure 1. Images of a computed tomography scan of a DPB patient in this cohort. A. Nodular shadows were distributed in a centrilobular fashion. B. Centrilobular nodular shadows were obviously attenuated after 14 days of azithromycin therapy. C. Centrilobular nodular shadows disappeared entirely after three months of azithromycin therapy.
cated with hypertension, cor pulmonale, bronchial asthma, rheumatoid arthritis, and thymic hyperplasia.

The course and adverse effect of azithromycin therapy

The course of azithromycin treatment for 51 patients was 4 to 54 months, the mean course 20.7 ± 8.3 months. All patients were treated with azithromycin intravenously for the first 1-2 weeks, oral administration daily for three more months. Azithromycin was then reduced to 3 times a week for 6 to 12 months. Thirty patients (58.8%) took the drug 3 times per week after 3 months’ daily oral administration. Five patients (9.8%) had gastrointestinal side effects (nausea, diarrhea, vomiting, and abdominal pain) in the course of treatment and symptoms were improved after ranitidine interference. None of them stopped azithromycin treatment because of adverse effects. No other side effects were found. Only one out of 51 patients decided on his own to discontinue azithromycin after six months of treatment.

Table 3. Mis-diagnosed Diseases in 51 Diffuse Panbronchiolitis Patients

<table>
<thead>
<tr>
<th>Mis-diagnosis</th>
<th>Cases</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchiectasis</td>
<td>30</td>
<td>58.8</td>
</tr>
<tr>
<td>Chronic bronchitis</td>
<td>23</td>
<td>45.1</td>
</tr>
<tr>
<td>Pulmonary tuberculosis</td>
<td>13</td>
<td>25.5</td>
</tr>
<tr>
<td>IPF*</td>
<td>10</td>
<td>19.6</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>3</td>
<td>5.9</td>
</tr>
<tr>
<td>Asthma</td>
<td>2</td>
<td>3.9</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>2</td>
<td>3.9</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

*IPF: idiopathic pulmonary fibrosis

Therapeutic effect

The actuarial survival curve was constructed and the 5-year survival rate with azithromycin treatment was 94.1% in this cohort by Kaplan-Meyer method, suggesting that azithromycin was effective. This result is similar to that of a Japanese cohort of DPB patients treated with erythromycin (2). During the course of azithromycin treatment, 14 patients were completely cured, while 36 cases were significantly improved regarding clinical symptoms and signs (Table 4). Among the 36 cases, three patients died from extrapulmonary diseases, one from diabetes mellitus ketoacidosis, one from renal cancer, and the last from myocardial infarction. But DPB relapsed easily if the therapy was terminated early. In our study, 2 patients relapsed when the therapy was stopped (one in the 6th month and the other in the 4th month). They were given the same treatment again and recovered fully. The follow-up duration for the patients ranged from 19 to 96 months with a mean term of 52.7 ± 16.8 months. One case had a poor prognosis due to the patient’s lack of compliance to medicine after six months of treatment.

Most of our patients responded well to azithromycin. Clinical features including cough, expectoration, dyspnea and wheezing sounds were greatly improved in over 80% of the cases within 3 days after treatment. Hemoptysis and crackles were ameliorated in 50% to 55% of the patients in 3 days as well (Table 2), and more than 90% of cases had improved in chest X-rays and CT scans, among them, there was almost 50% with significant improvement between day 5 and day 40 after the start of therapy (Fig. 1B and C). The symptoms of paranasal sinusitis were also improved during the course of therapy.

Pulmonary functions in those who took tests twice showed significant improvement in their FEV1% after therapy (p = 0.001). Arterial blood gas suggested that PaO2 and SaO2 increased significantly (p< 0.001), while there was no significant reduction in PaCO2 and pH value before and after the treatment (Table 5).

Microbiological analysis of 49 cases demonstrated that the positive presence of Pseudomonas aeruginosa in sputum was present in 34.7%. Among P. aeruginosa positive cases,
Table 4. Therapeutic Effect of Azithromycin for 51 Diffuse Panbronchiolitis Patients

<table>
<thead>
<tr>
<th>Grade</th>
<th>Cases</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cured</td>
<td>14</td>
<td>27.5%</td>
</tr>
<tr>
<td>Improved*,$</td>
<td>36</td>
<td>70.5%</td>
</tr>
<tr>
<td>No response</td>
<td>1</td>
<td>2%</td>
</tr>
<tr>
<td>Aggravation</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Relapse*</td>
<td>2</td>
<td>4%</td>
</tr>
</tbody>
</table>

*Included three cases died, $Three patients died from extrapulmonary diseases, °These 2 cases were from Improved group.

Table 5. Pulmonary Function and Arterial Blood Gas before and after Treatment

<table>
<thead>
<tr>
<th>Observed items</th>
<th>Pre-therapy</th>
<th>Post-therapy</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Examination number</td>
<td>X±S*</td>
<td>Re-examination number</td>
</tr>
<tr>
<td>FEV1.0%#</td>
<td>20</td>
<td>49.74±18.95</td>
<td>20</td>
</tr>
<tr>
<td>PaO2 (mmHg)◊</td>
<td>50</td>
<td>68.06±13.15</td>
<td>37</td>
</tr>
<tr>
<td>PaCO2 (mmHg)</td>
<td>50</td>
<td>38.28±6.97</td>
<td>37</td>
</tr>
<tr>
<td>SaO2%◊</td>
<td>50</td>
<td>92.33±3.98</td>
<td>37</td>
</tr>
<tr>
<td>pH◊</td>
<td>50</td>
<td>7.41±0.04</td>
<td>37</td>
</tr>
</tbody>
</table>

*X±S: average value ± standard deviation.
#Cases who had pulmonary function before and after therapy were re-examined at least 3 months after therapy.
◊The days when arterial blood gases were re-examined ranged from day 3 to day 22 after therapy.

Table 6. Changes of Sputum Bacterium before and after Treatment

<table>
<thead>
<tr>
<th>Category of sputum bacterium</th>
<th>Pre-therapy</th>
<th>Post-therapy*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test cases</td>
<td>Positive cases (%)</td>
<td>The cases from positive to negative (%)</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>49</td>
<td>17/(34.7)</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>49</td>
<td>3/(6.1)</td>
</tr>
<tr>
<td>Haemophilus parainfluenzae</td>
<td>49</td>
<td>5/(10.2)</td>
</tr>
<tr>
<td>Fluorescence pseudomonas</td>
<td>49</td>
<td>1/(2.0%)</td>
</tr>
</tbody>
</table>

*The day of re-examination ranged from day 5 to day 50 after therapy. All above profiles were from the last examination before discharged from hospital.

3 (17.6%) of them were re-tested negative, and most of them remained positive after treatment. The positive percentages of Hemophilus parainfluenzae, Klebsiella pneumoniae and Fluorescence Pseudomonas were much lower than that of Pseudomonas aeruginosa, and most of them were negative after therapy (Table 6).

The CHA test (cut-off line was ≥1 : 64 and the highest was 1 : 256) showed 9 positive out of 51 cases before treatment and the titer changed to normal after therapy. Thirty-one patients experienced an increased ESR (21-126 mm/h), and 4 of them reduced to normal after a 15-day treatment. HLA-BW54 determination was detected in 12 cases and 3 of them were positive (25.0%).

Discussion

DPB was initially recognized in Japan and rarely known in other countries and ethnic populations. Nevertheless, the number of DPB reported has increased gradually outside of Japan in recent years. After the first case was diagnosed in 2001 in Shanghai Pulmonary Hospital (41), there were 51 DPB patients treated up until April 2007, which is the largest cohort of DPB patients reported in China. DPB is probably not rare in China (42); it was often misdiagnosed as other diseases such as bronchiectasia, COPD, IPF, phthisis miliaris, sarcoidosis or alveolar cell carcinoma. In the present study, the average period of misdiagnosis exceeded 12 years with a median of 10 years and up to 40 years. Therefore, it is important to recognize DPB correctly in the early stage. We analyzed the clinical data of these 51 cases with DPB and evaluated the effect of azithromycin for DPB.

The clinical diagnosis criteria published by the Ministry of Health and Welfare of Japan in 1998 (2) is quite suitable to diagnose our Chinese patients with DPB. However, the cold hemagglutinin (CHA) titer was only 17.6% of positive in our DPB patients, suggesting that the CHA titer might
not be as important for the diagnosis of Chinese DPB patients as it for Japanese (27, 43). Additionally, positive HLA-BW54 was only detected in 3 of 12 (25.0%) patients in this group, suggesting that the relationship between HLA-BW54 and Chinese DPB patients might not correlate as well as with Japanese DPB patients (44). Among diagnostic tests, a chest CT scan provides the most valuable diagnostic means for such patients.

In the present study, azithromycin treatment showed efficacy and minimal adverse effects. Most of our patients responded well to azithromycin. Their clinical symptoms were relieved within the first 3 days of treatment. Imageological cacy and minimal adverse effects. Most of our patients re-

mented for such patients.

In this study because it could show both antibiotic and antiin-

flammatory action. The antibiotic spectrum of azithromycin was so limited that some patients might improve only by anti-inflammatory effect. Antibiotics in the usual dosage for several months may lead to adverse effects, in particular drug resistance. In a future study, it will be necessary to ex-

plore if low dose of azithromycin is as effective for DPB as erythromycin.

A slightly higher cost may be the disadvantage of azithro-

mycin. However, in the later period of treatment, azithromy-

cin can be tapered to 3 times a week and thus the cost can then be greatly decreased. Erythromycin is effective with a low price, but it could result in much more gastrointestinal discomfort (31, 32) and vein-stimulation adverse ef-

fects (33), and it may result in poor patient compliance be-

cause of the need for frequent administration. Therefore, we suggest that azithromycin has more advantages than erythromycin and that azithromycin represents a better choice for DPB therapy.

In summary, we conclude that: 1) DPB may be not rare among Chinese. There might be some DPB patients misdi-

agnosed as COPD, bronchiectasis and others. 2) Usually a very good prognosis can be reached for DPB. However, early diagnosis and timely and persistent treatment are im-

portant for a better prognosis. 3) Azithromycin is effective for diffuse panbronchiolitis patients because of its favorable efficacy, minimal adverse effects, and better patient compliance.

The authors state that they have no Conflict of Interest (COI).

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