Withdrawal of Epoprostenol Therapy in a Patient with Pulmonary Hypertension Associated with Sjögren’s Syndrome

Tetsuo Fujita, Nobuhiro Tanabe, Yasunori Kasahara, Toshihiko Sugiura, Seiichiro Sakao and Koichiro Tatsumi

Abstract

Pulmonary arterial hypertension (PAH) is a rare complication, but a significant prognostic factor in patients with Sjögren’s syndrome (SjS). Despite its efficacy, the long-term use of intravenous epoprostenol is sometimes complicated by adverse effects, such as catheter-related infection. This case involves a 38-year-old woman with PAH associated with SjS (PAH-SjS) who was transitioned from treatment with long-term intravenous epoprostenol therapy to combination oral therapy containing bosentan and tadalafil. She has remained in stable condition for more than two years following epoprostenol discontinuation. The details of this report suggest that long-term epoprostenol therapy can be safely tapered off and replaced with combination oral therapy in carefully selected patients with PAH-SjS.

Key words: combination oral therapy, epoprostenol, pulmonary arterial hypertension, Sjögren’s syndrome, transition

(Intern Med 53: 2237-2240, 2014)
(DOI: 10.2169/internalmedicine.53.2885)

Introduction

Pulmonary arterial hypertension (PAH) is a life-threatening complication of connective tissue disease (CTD). Epoprostenol treatment plays a significant role in the management of PAH, including that associated with CTD (PAH-CTD). Despite its efficacy, the long-term use of intravenous epoprostenol is sometimes complicated by adverse effects, such as catheter-related infection. We herein present a case of PAH associated with Sjögren’s syndrome (PAH-SjS) in which the selected treatment resulted in the successful withdrawal of intravenous epoprostenol therapy.

Case Report

A 38-year-old woman complaining of dyspnea on exertion was diagnosed with pulmonary hypertension in November 2001, with a mean pulmonary arterial pressure (mPAP) of 54 mmHg. She was simultaneously diagnosed with SjS based on positive findings for antibodies to SS-A as well as positive results on Shihmer’s test, the Rose-Bengal test, a chewing gum test and sialography, which demonstrated significant atrophic sialadenitis. Taken together, the patient was diagnosed with pulmonary hypertension associated with SjS, and various treatments were initiated. The administration of several plasma exchange procedures was ineffective in decreasing the pulmonary arterial pressure. No further therapies, including an anticoagulant (warfarin), diuretic and orally administered prostacyclin analogue (beraprost), ameliorated her symptoms. Furthermore, the short-term administration of steroids (prednisolone, 40 mg/day for 4 weeks) followed by a clinical trial of oral sildenafil (100 mg/day), failed to improve the patient’s functional capacity and hemodynamics. Her dyspnea subsequently progressed (WHO functional class III), and she was referred to our hospital in October 2002.

Laboratory examinations showed that the serum brain natriuretic peptide (BNP) level was high (426 pg/L), with a PaO₂ of 67.1 Torr and a PaCO₂ of 33.8 Torr. Meanwhile, an-
tinuclear antibodies were positive, at a titer of 1:1,280 (speckled type), as were antibodies to SS-A, at a titer of 1:256. In contrast, antibodies to both SS-B and ribonucleoprotein (RNP) were negative. A chest X-ray demonstrated clear lung fields with enlarged pulmonary arteries and cardiomegaly (Figure A), while a chest CT scan revealed slight ground glass opacity in the bilateral lower lobes. The six-minute walk distance (6MWD) was 160 m. Echocardiography showed enlargement of the right ventricle, with a tricuspid regurgitation pressure gradient (TRPG) of 67 mmHg. Pulmonary perfusion scans showed no segmental defects. Right heart catheterization revealed precapillary pulmonary hypertension (Table), and the patient was subsequently diagnosed with PAH-SjS. Treatment with intravenous epoprostenol and prednisolone (45 mg/body) was introduced in December 2002, and the dose of epoprostenol was gradually increased to 8 ng/kg/min. The patient’s hemodynamic parameters, clinical data and cardiomegaly each improved significantly three months after treatment (Table) (Figure B). Her WHO functional class remained stable following the administration of intravenous epoprostenol, along with prednisolone, the dose of which was gradually decreased to 15 mg/body. However, we were unable to increase the amount of epoprostenol due to thrombocytopenia, and the patient suffered from a catheter-related infection and several other incidents; one incident required catheter replacement. In light of her stable clinical condition, we attempted to transition the treatment from intravenous epoprostenol to oral drugs in order to reduce the risk of catheter-related infections in 2011. Repeat tests of hemodynamic parameters showed almost the same results as those obtained 10 years earlier (Table). After admission, bosentan was given orally at a dose of 62.5 mg/day for nine days, followed by a dose of 125 mg/day. In addition, tadalafil (20 mg/day) was added

Figure. A: Chest X-ray obtained on admission demonstrated clear lung fields with enlarged pulmonary arteries and cardiomegaly. B: The cardiomegaly improved significantly three months after the induction of epoprostenol. C: The cardiomegaly did not worsen, although reticular shadows were apparent in the bilateral lower lung fields over two years after the discontinuation of epoprostenol.

Table. Hemodynamics and Clinical Data at Each Period of Medication Changes

<table>
<thead>
<tr>
<th>Date</th>
<th>baseline</th>
<th>after epo</th>
<th>before d/c</th>
<th>after d/c</th>
<th>f/u</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Right heart catheterization</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAPsys/dia(m)</td>
<td>mmHg</td>
<td>88/37(54)</td>
<td>60/26(38)</td>
<td>52/24(36)</td>
<td>54/24(36)</td>
</tr>
<tr>
<td>PAWP</td>
<td>mmHg</td>
<td>6</td>
<td>6</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>CO</td>
<td>L/min</td>
<td>3.27</td>
<td>4.15</td>
<td>4.57</td>
<td>5.66 N/A</td>
</tr>
<tr>
<td>CI</td>
<td>L/min/m²</td>
<td>2.41</td>
<td>2.99</td>
<td>3.07</td>
<td>3.82</td>
</tr>
<tr>
<td>PVR</td>
<td>dyne·sec·cm⁻³</td>
<td>1.174</td>
<td>597</td>
<td>507.5</td>
<td>395.6</td>
</tr>
<tr>
<td>PaO₂</td>
<td>Torr</td>
<td>67.1</td>
<td>85.3</td>
<td>64.1</td>
<td>69.0 85.6</td>
</tr>
<tr>
<td><strong>Echocardiogram</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRPG</td>
<td>mmHg</td>
<td>67</td>
<td>38</td>
<td>46</td>
<td>46   41</td>
</tr>
<tr>
<td><strong>Six minutes walk test</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distance</td>
<td>m</td>
<td>160</td>
<td>320</td>
<td>330</td>
<td>340 320</td>
</tr>
<tr>
<td><strong>Laboratory test</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BNP</td>
<td>pg/mL</td>
<td>322.9</td>
<td>36.6</td>
<td>16.6</td>
<td>7.1 6.3</td>
</tr>
</tbody>
</table>

epo: epoprostenol, d/c: discontinuation of epoprostenol, f/u: follow up two years after discontinuation of epoprostenol. Date represents the date of right heart catheterization (except f/u) or echocardiogram (f/u). PAP: pulmonary arterial pressure, sys: systolic, dia: diastolic, m: mean, PAWP: pulmonary arterial wedge pressure, CO: cardiac output, CI: cardiac index, PVR: pulmonary vascular resistance, TRPG: tricuspid regurgitation pressure gradient, BNP: brain natriuretic peptide, N/A: not available.
18 days after the induction of bosentan treatment. The dose of epoprostenol was gradually decreased simultaneously with the introduction of bosentan and ultimately discontinued 24 days after the start of tapering, which did not result in any deterioration of the patient’s functional class or other objective data (Table). After discharge, azathioprine (100 mg/day) was added for arthralgia due to SjS, and the doses of bosentan and tadalafil were increased to 250 mg/day and 40 mg/day, respectively. Although it has been over two years since the discontinuation of epoprostenol, the patient’s clinical state remains stable, despite worsening of interstitial pneumonia (Figure C) (Table).

Discussion

Epoprostenol, a systemic prostacyclin, is an effective vasodilator that also inhibits platelet activation and smooth muscle cell growth. It has been used to treat patients with moderate to severe idiopathic PAH as a first-line treatment in Japan since 1999 and has been shown to improve exercise capacity, hemodynamics and survival rates in patients with PAH-CTD (1, 2). Since the endothelin receptor antagonist bosentan was made available in Japan in 2005, followed by the introduction of other oral vasodilators, the treatment protocol for PAH has been modified (3-6). Currently, patients with a functional class III status are frequently started on therapy with oral vasodilators, as the long-term use of intravenous epoprostenol may be complicated by various adverse effects, including recurrent catheter-related infection, thrombosis and limitations in the quality of life imposed by parenteral drug administration (7, 8). Moreover, abrupt discontinuation may lead to rebound pulmonary hypertension and acute right ventricular failure. In CTD patients in particular, the risk of catheter-related infection may be increased because these patients often receive corticosteroids or immunosuppressive medications. Recent reports have also shown that these medications exhibit potential efficacy for PAH-CTD (9). In addition, continuous intravenous administration is often limited by concerns regarding CTD-related skin complications or fragility due to the use of corticosteroids.

Previous reports have demonstrated the successful transition from epoprostenol to oral drugs in patients with PAH (10, 11). However, we were unable to find a single case report of successful transition in the setting of PAH-SjS, due to the rarity of the disease (12). However, various predictors for successful transition have been reported, such as the application of a lower dose of epoprostenol and the importance of a low pulmonary arterial pressure prior to transition (10) and a longer duration of epoprostenol therapy (11). In the present case, the dose of epoprostenol was low (8 ng/kg/min), while the mPAP (36 mmHg) was similar to that observed in previous cases of long-term success (38±7, 38±11 mmHg) (10, 11) and the duration of epoprostenol treatment was longer than that noted in prior reports (41±22, 26±17 months) (10, 11), all of which may have been keys to a successful transition in the present case of PAH-SjS. Previous reports include six cases of PAH associated with systemic lupus erythematosus (SLE) in which the patients successfully transitioned from epoprostenol to bosentan or sildenafil (11, 13). In these cases, the mean dose of epoprostenol was 14±2 ng/kg/min, the mPAP was 30±5 mmHg and the mean duration of epoprostenol therapy was 24±18 months, which also supported our attempt at a transition in our case of PAH-SjS.

The best treatment strategy for PAH-SjS remains to be defined, although it should include combination therapy with PAH-specific drugs (14). A recent meta-analysis suggested that epoprostenol is nearly as effective for increasing exercise capacity (6MWD) in patients with PAH-CTD as in those with all forms of PAH. In contrast, endothelin receptor antagonists have been found to be less effective in the setting of PAH-CTD than in all forms of PAH (15). However, we found five PAH-SLE patients whose therapy was switched from epoprostenol to bosentan monotherapy among previous reports (11, 13). For this reason, we first chose bosentan as an alternative oral drug in the present case. It has also been reported that immunosuppressive therapy combined with cyclophosphamide and glucocorticosteroids results in clinical improvements in patients with PAH associated with SLE and mixed CTD (16, 17). In the present case, the dose of steroids was not changed before or after the cessation of epoprostenol, although the addition of azathioprine after discharge may have contributed to the patient’s stable condition of PAH following cessation. A cohort study (18) demonstrated that PAH-CTD patients, with the exception of those with systemic sclerosis (SSc), tend to display better survival rates than those with PAH-SSc. Therefore, predictors of successful transition in patients with PAH-SSc and other forms of PAH-CTD, including PAH-SjS, should be examined in further studies.

The present case report suggests that long-term epoprostenol therapy can be safely discontinued and replaced with combination oral vasodilative therapy in carefully selected patients with PAH-SjS. However, it is important to accurately assess the patient’s pulmonary hemodynamics using right heart catheterization on admission when preparing for transition. If the patient shows signs of deterioration, it is necessary to either suspend weaning or reintroduce epoprostenol prior to weaning, as several patients have failed to achieve a successful transition, with a worsening clinical status or even mortality, in previous reports (10, 13). Furthermore, long-term monitoring for disease progression several years after epoprostenol cessation is required (19, 20).

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

References


© 2014 The Japanese Society of Internal Medicine
http://www.naika.or.jp/imonline/index.html