Intravenous Immunoglobulin Therapy for Refractory Recurrent Pericarditis

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**KEY WORDS**
recurrent pericarditis, intravenous immunoglobulins, child, pericardial effusion/therapy

**ABBREVIATIONS**
IL—interleukin
IVIG—intravenous immunoglobulin
RP—recurrent pericarditis
TNF—tumor necrosis factor

Drs del Fresno, Peralta, and Domínguez-Pinilla conceptualized the work, carried out the collection and interpretation of the patients’ data, performed the literature review, and drafted the initial manuscript; Drs Granados, Enríquez, and de Inocencio participated in data acquisition and revised the manuscript critically; and all authors approved the final manuscript as submitted.

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**abstract**

Recurrent pericarditis is a troublesome complication of idiopathic acute pericarditis and occurs more frequently in pediatric patients after cardiac surgery (postpericardiotomy syndrome). Conventional treatment with nonsteroidal anti-inflammatory drugs, corticosteroids, and colchicine is not always effective or may cause serious adverse effects. There is no consensus, however, on how to proceed in those patients whose disease is refractory to conventional therapy. In such cases, human intravenous immunoglobulin, immunosuppressive drugs, and biological agents have been used. In this report we describe 2 patients with refractory recurrent pericarditis after cardiac surgery who were successfully treated with 3 and 5 monthly high-dose (2 g/kg) intravenous immunoglobulin until resolution of the effusion. Our experience supports the effectiveness and safety of this therapy. *Pediatrics* 2014;134:e1441–e1446
Recurrent pericarditis (RP) is a chronic disease characterized by repeated episodes of pericardial effusion. After an episode of acute pericarditis, up to 36% of the patients develop recurrences. In children, almost 50% of the cases occur after cardiac surgery. RP is a condition that is difficult to manage and often results in the frustration of patients, families, and treating physicians. The guideline on pericardial syndrome by the European Society of Cardiology, updated in 2012, recommends non-steroidal anti-inflammatory drugs with additional colchicine as the first line of therapy, with the use of low-dose steroids for those who do not respond. It is not uncommon, however, for patients to become steroid-dependent or to continue to have pericardial effusion. In such cases, several therapies have been successfully used, including immunosuppressive agents such as azathioprine or methotrexate, interleukin (IL)-1 receptor antagonist, anti-tumor necrosis factor (anti-TNF) drugs, and intravenous immunoglobulin (IVIG).

Herein, we report on 2 children with refractory postpericardiotomy syndrome who were successfully treated with IVIG.

CASE REPORTS

Patient 1
A 4-year-old girl underwent corrective surgery for tetralogy of Fallot at our center in April 2012. The patient was diagnosed at birth, but surgery was delayed because parents refused surgical treatment. One week later, an echocardiogram revealed a moderate pericardial effusion without elevation of acute-phase reactants or hemodynamic compromise. Her electrocardiogram revealed a broad QRS of 125 ms with RSR pattern and T wave inversion in leads V1 to V4. Indomethacin was started, but 48 hours later it was discontinued due to gastrointestinal intolerance, and prednisone (2 mg/kg per day) was initiated because of increasing serum creatinine levels and worsening of the effusion. The pericardial effusion improved gradually, allowing prednisone tapering after 2 weeks. Eleven weeks after surgery, the pericardial effusion was resolved and prednisone was stopped.

Three weeks later, however, she developed a recurrence and exhibited a large pericardial effusion (Fig 1). Prednisone (1 mg/kg per day) and colchicine (0.5 mg/day) were started with no improvement after 8 weeks of therapy. At that time (September 2012), she received IVIG, 2 g/kg per month given as a single dose. After 2 doses, the effusion began to decrease, allowing steroid tapering. By the time she received her third IVIG treatment, the prednisone dose had been decreased to 0.1 mg/kg per day. In January 2013, after 5 doses of IVIG, her disease was in complete remission. IVIG and prednisone were stopped and colchicine was maintained for another 8 weeks. She has discontinued all medications for the last 13 months without recurrences.

Patient 2
A 4-year-old boy diagnosed with hypertrophic obstructive cardiomyopathy was transferred to our institution in November 2011 for corrective surgery (fibromuscular ring resection and placement of an infundibular patch). After surgical repair, he developed mild to moderate asymptomatic pericardial effusion. Acute-phase reactants were not elevated. His electrocardiogram was normal, except for tall P waves in leads I, II, and V1 to V3 and an RSR pattern in V1. He was managed at his local hospital with ibuprofen for 2 weeks, followed by prednisone (2 mg/kg per day) and colchicine (0.75 mg/day). In February 2012, oral methotrexate was added because of worsening effusion and onset of fatigue, with no effect (Fig 2). After 2 months, methotrexate was stopped. Several unsuccessful attempts were made to taper prednisone, requiring doses of ≥0.6 mg/kg per day to keep the effusion under control despite concomitant colchicine therapy. In September 2012, he received his first dose of IVIG (400 mg/kg per day for 4 consecutive days). No significant change in the pericardial effusion was observed and he was transferred to our center.

In November 2012, IVIG was administered at a dose of 2 g/kg per month. After

FIGURE 1
Patient 1 before IVIG therapy. Subcostal echocardiographic view reveals a moderate to severe global pericardial effusion that is more intense behind the atria (arrow). No signs of hemodynamic compromise were noted during the examination. LA, left atrium; LV, left ventricle; PE, pericardial effusion; RA, right atrium.
the administration of a second 2-g/kg dose of IVIG, the patient developed severe headache and malaise. The effusion, however, resolved and prednisone was discontinued in February 2013. In March, a small recurrence was noted. It was managed with small doses of prednisone (<0.2 mg/kg per day), which did not require further administration of IVIG for its control. This time the effusion resolved quickly, allowing discontinuation of prednisone in July and of colchicine 3 months later.

DISCUSSION

RP is a chronic disease characterized by recurrent episodes of fever, chest pain, pericardial friction rubs, electrocardiographic changes, and pericardial effusion. Laboratory tests usually reveal leukocytosis and elevated acute-phase reactants. Relapses may present as an intermittent (symptom-free intervals longer than 6 weeks without therapy) or as an incessant type (discontinuation or attempts to taper off treatment result in early reappearance or worsening of symptoms), as happened to our 2 patients.16

Recurrences develop in up to 36% of pediatric patients after the first episode of idiopathic acute pericarditis and in 50% of children after pericardial injury.3 Age at the time of cardiac surgery is a major factor associated with the development of postpericardiotomy syndrome in pediatric patients. For undetermined reasons, younger children rarely present this complication.17 Post–cardiac injury syndrome develops after pericardial damage caused by cardiac surgery, accidental trauma, or post–myocardial infarction. Much less common causes of RP include certain rheumatic conditions (systemic juvenile idiopathic arthritis, systemic lupus erythematosus) and autoinflammatory diseases (familial Mediterranean fever, TNF receptor–associated periodic syndrome).2

The pathogenesis of the disease is unknown. The most commonly accepted theory is that RP represents an autoimmune phenomenon.18 Patients with the disease have circulating anti–heart and anti–intercalated disk autoantibodies, as well as antinuclear antibodies.19,20 In addition, the analysis of pericardial effusions reveals the presence of proinflammatory cytokines, including IL-6, IL-8, and interferon-γ.21

This theory might explain both idiopathic and post–cardiac injury pericarditis. In the first group, a virus could trigger an autoimmune process through a mechanism of molecular mimicry. In the latter, surgery, trauma, or infarction would expose or release cardiac autoantigens and stimulate an immune response. An additional hypothesis that could explain some cases is that recurrent pericarditis represents an autoimmune disease due to a genetically determined dysfunction of the innate immune system that causes a dysregulation of the inflammatory process.22,23 Serosal inflammation is a common feature of familial Mediterranean fever and TNF receptor–associated periodic syndrome, and recurrent pericarditis might be the only clinical manifestation at disease onset.24,25

The mainstay of therapy is nonsteroidal antiinflammatory drugs (aspirin, ibuprofen, or indomethacin) for 10 to 14 days with additional colchicine (0.5–1 mg/day) for 6 months.4 If there is intolerance or no response, patients could receive low-dose steroids (0.2–0.5 mg/kg per day). Paradoxically, for this indication, steroids appear to be beneficial only at low doses; in fact, corticosteroids at high doses (≥1 mg/kg per day) seem to increase the risk of recurrences.2–4,26

This stepwise approach controls the disease in most patients. There is a small group of patients, however, who are refractory to conventional therapy, such as the 2 presented in this report. In such cases, different immunosuppressive or immunomodulatory drugs have been used on the basis of the suspected autoimmune pathogenesis of the disease, including azathioprine,24 methotrexate,5 and, more recently, anti–IL-1
<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Patient Number</th>
<th>Gender</th>
<th>Diagnosis</th>
<th>Age at Onset, years</th>
<th>Number of Relapses Before IVIG</th>
<th>Treatments Before IVIG</th>
<th>Dose/Cycle</th>
<th>Number of Cycles</th>
<th>Monitored Time Free From Relapses, months</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tona (2003)</td>
<td>1</td>
<td>Male</td>
<td>Idiopathic recurrent pericarditis</td>
<td>30</td>
<td>?</td>
<td>ASA 4–6 g/d, COL 1 mg/d, PDN 75 mg/d, AZA 150 mg/d, CSA 300 mg/d, CYC 100 mg/d</td>
<td>0.5 g/kg per day × 5 d</td>
<td>1</td>
<td>42</td>
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<td></td>
<td>2</td>
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<td>19</td>
<td>?</td>
<td>COL 1 mg/d, PDN 50 mg/d, MPIV 180 mg/d × 3 d, CSA, CYC, MTX</td>
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<td>5</td>
<td>COL 1 mg/d, PDN 50 mg/d</td>
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<td>28</td>
<td>5</td>
<td>COL 1 mg/d, PDN 50 mg/d</td>
<td>0.4 g/kg per day × 5 d</td>
<td>7</td>
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<tr>
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<td>3</td>
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<td>21</td>
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<td>COL 1 mg/d, PDN 50 mg/d</td>
<td>0.4 g/kg per day × 5 d</td>
<td>7</td>
<td>12</td>
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<td></td>
<td>4</td>
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<td>Idiopathic recurrent pericarditis</td>
<td>11</td>
<td>15</td>
<td>COL 1 mg/d, PDN 50 mg/d, MTX 15 mg/s, CSA 4 mg/kg per day, AZA 150 mg/d</td>
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<td>9</td>
<td>?</td>
<td>Mild headache</td>
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<td>Wendelin (2008)</td>
<td>1</td>
<td>Female</td>
<td>Postpericardiotomy syndrome</td>
<td>12</td>
<td>8</td>
<td>ASA 75 mg/kg per day, PDN 2 mg/kg per day</td>
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<td>1</td>
<td>54</td>
<td>None</td>
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<td>Moretti (2013)</td>
<td>1</td>
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<td>Idiopathic recurrent pericarditis</td>
<td>27</td>
<td>6</td>
<td>ASA 1.8 g/d, COL, PDN 35 mg/d, AZA</td>
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<td>3</td>
<td>156</td>
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<td>3</td>
<td>IND 50–100 mg/d, PDN 25 mg/d, MTX, CSA</td>
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<td>1</td>
<td>84</td>
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<td>30</td>
<td>6</td>
<td>COL 1.5 g/d, IND 150 mg/d, COL, PDN 25 mg/d, MTX</td>
<td>0.5 g/kg per day × 5 d</td>
<td>1</td>
<td>96</td>
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<td>4</td>
<td>IND 150 mg/d, IBU 1.8 g/d, COL, PDN 50 mg/d</td>
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<td>69</td>
<td>5</td>
<td>IND 150 mg/d, COL, PDN, AZA</td>
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<td>1</td>
<td>12</td>
<td>None</td>
</tr>
<tr>
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<td>Idiopathic recurrent pericarditis</td>
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<td>6</td>
<td>IBU 2 g/d, COL, PDN 25 mg/d</td>
<td>0.5 g/kg per day × 5 d</td>
<td>1</td>
<td>24</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>Male</td>
<td>Idiopathic recurrent pericarditis</td>
<td>37</td>
<td>3</td>
<td>COL 1.5 g/d, IBU 1.2 g/d, COL, PDN 50 mg/d</td>
<td>0.5 g/kg per day × 5 d</td>
<td>1</td>
<td>12</td>
<td>None</td>
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<tr>
<td></td>
<td>8</td>
<td>Male</td>
<td>Postpericardiotomy syndrome</td>
<td>47</td>
<td>7</td>
<td>IND 150 mg/d, ASA 3 g/d, COL</td>
<td>0.5 g/kg per day × 5 d</td>
<td>1</td>
<td>24</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>Male</td>
<td>Idiopathic recurrent pericarditis</td>
<td>35</td>
<td>6</td>
<td>IBU 1.8 g/d, IND 150 mg/d, COL, PDN 5 mg/d</td>
<td>0.5 g/kg per day × 5 d</td>
<td>2</td>
<td>24</td>
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<td>1</td>
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<td>Postpericardiotomy syndrome</td>
<td>4</td>
<td>1</td>
<td>COL 0.5 mg/d, PDN 2 mg/kg per day</td>
<td>2 g/kg per day × 1 d</td>
<td>5</td>
<td>13</td>
<td>None</td>
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<tr>
<td></td>
<td>2</td>
<td>Male</td>
<td>Postpericardiotomy syndrome</td>
<td>4</td>
<td>5</td>
<td>IBU 30 mg/kg per day, COL 0.75 mg/d, PDN 2 mg/kg per day, MTX</td>
<td>0.4 g/kg per day × 4 d (1 cycle), 2 g/kg per day × 1 d (2 cycles)</td>
<td>3</td>
<td>11</td>
<td>Malaise, headache</td>
</tr>
</tbody>
</table>

ASA, acetylsalicylic acid; AZA, azathioprine; COL, colchicine; CSA, cyclosporine A; CYC, cyclophosphamide; IBU, ibuprofen; IND, indomethacin; PDN, prednisone; MPIV, intravenous methotrexate; MTX, methotrexate; sc, subcutaneous; ? data not available.

* Treatments before IVIG: It is shown highest doses for each treatment.
receptor antagonist, \textsuperscript{6-10} anti-TNF agents\textsuperscript{11} and human IVIG.\textsuperscript{12-15}

With regard to classic immunosuppressive agents, several pediatric case reports, including our patient number 2, suggest that methotrexate is not effective in the treatment of RP.\textsuperscript{3,11-13,15} Azathioprine has a similar lack of effect in children,\textsuperscript{11-13,15} although in adults it has proven to be useful.\textsuperscript{27} Therefore, although both immunosuppressant agents are recommended in most reviews, there are no robust clinical data on their precise role in the management of pediatric disease.

More recently, biological therapy has been used to treat this condition. Several reports support the effectiveness of anti--IL-1 (IL-1 receptor antagonist) therapy. In all cases, the concentration of acute-phase reactants was very high when reported and the response to therapy was often dramatic, within the first few days after the initiation of the drug.\textsuperscript{5-10} There is only 1 case series reporting on 3 patients with RP who received anti-TNF therapy.\textsuperscript{11} It revealed that anti-TNF drugs might be efficacious but require months to show clinical effect and years of continuous therapy.

A literature review revealed that in the last 10 years only 4 series have reported the efficacy of IVIG in the therapy for RP. The numbers in those series were small, except from 1 report on a series of 9 patients (Table 1).

All the studies showed that IVIG had rapid beneficial effects in patients, independently of their gender, age, diagnosis, dose, and protocol of administration. In most cases, a clinical response was obvious after 1 to 3 doses. Adverse effects were unusual and not serious (Table 1). The major limitations of IVIG include its cost and its route of administration. The use of single monthly doses and its administration in pediatric day hospitals, however, facilitate its use. A recent review\textsuperscript{28} suggested different mechanisms to explain the efficacy of IVIG in autoimmune diseases, including inhibition of phagocytosis; blockade of immune-complex access to FcyR; increased expression of FcyRIIB on effector macrophages; Fab binding to anti-idiotypes, specific cytokines, and autoantibodies; and reduction in complement deposition. These actions result in decreases in the production of proinflammatory cytokines; the down-regulation of adhesion molecule, chemokine, and chemokine receptor expression; and the neutralization of circulating autoantibodies.

In conclusion, although the use of IVIG at high doses currently represents an off-label indication, an increasing number of reports indicate that it is an effective and safe alternative for those patients whose pericarditis is refractory to conventional therapy or who become steroid-dependent. Our small series supports that this treatment represents another option in these cases. Prospective randomized studies will be required to fully determine its role in the management of this difficult and often frustrating disease.

References


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