SUCCESSFUL THERAPY WITH DANAZOL IN REFRACTORY AUTOIMMUNE THROMBOCYTOPENIA ASSOCIATED WITH RHEUMATIC DISEASES

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SUMMARY

The objective was to assess the efficacy of therapy with danazol in refractory immune thrombocytopenia associated with different rheumatic diseases. Patients with severe immune thrombocytopenia (platelet counts <40 \times 10^9/l) with a bone marrow biopsy showing megakaryocytes in normal or increased number and normal morphology were included if they fulfilled at least one of the following criteria: (a) thrombocytopenia refractory to prednisone (\geq 1 mg/kg/day during \geq 4 weeks); (b) patients requiring an unacceptably high dose of prednisone for >2 months (prednisone dose \geq 20 mg/day); (c) no response to at least another drug besides corticosteroids. Other causes of thrombocytopenia were excluded. They were treated with danazol (100–200 mg q.i.d.) and followed for at least 12 months. Four patients diagnosed with systemic lupus erythematosus, two with rheumatoid arthritis and one with primary antiphospholipid syndrome met the inclusion criteria. All of them achieved acceptable platelet counts within the first 4 weeks of danazol therapy that allowed the prednisone dosage to be tapered. No important side-effects related to danazol therapy were observed. Danazol therapy seems to be a useful and well-tolerated treatment for refractory immune thrombocytopenia associated with different rheumatic diseases.

KEY WORDS: Danazol, Autoimmune thrombocytopenia, Systemic lupus erythematosus, Rheumatoid arthritis, Primary antiphospholipid syndrome.

THROMBOCYTOPENIA is an important complication of several autoimmune diseases. It occurs in 7–26% of patients with systemic lupus erythematosus (SLE) and is severe in 5–10% of them [1]. On the other hand, thrombocytopenia has long been recognized as one of the cardinal manifestations of the antiphospholipid syndrome [2, 3]. In patients with rheumatoid arthritis (RA), thrombocytopenia is mainly related to side-effects of drugs; however, it has also been described as related to RA itself [4, 5].

Corticosteroids remain as the initial and principal therapy for autoimmune thrombocytopenia [6]. However, in many cases, a reduction in the dose of corticosteroids leads to relapse of thrombocytopenia. In other cases, thrombocytopenia is either refractory to corticosteroids or they must be maintained on an unacceptably high dose, leading to severe drug-related side-effects. In these cases, splenectomy, i.v. immunoglobulins, cytotoxic agents and/or danazol may be used. Splenectomy is frequently the next approach to therapy. However, this major surgical procedure may increase the risk of infections in immunosuppressed patients. Moreover, the immune thrombocytopenia of some autoimmune diseases such as SLE frequently does not respond to splenectomy [7]. Intravenous immunoglobulins often increase the platelet counts, but the response in most cases is transient. In this regard, they have been widely used in the treatment of children with ‘acute’ idiopathic thrombocytopenia purpura, but their efficacy seems to be more limited in other entities that usually present ‘chronic’ thrombocytopenia, such as adults with idiopathic thrombocytopenia purpura or autoimmune thrombocytopenia related to SLE [8, 9]. Cytotoxic therapies such as vincristine, 6-mercaptopurine and cyclophosphamide have also been used [10]. However, these agents generally yield a low remission rate and sometimes they have mutagenic risk [11].

Danazol is a synthetic attenuated androgen which has been used in several unrelated immune-mediated diseases [12, 13]. Also, it has been used successfully in different diseases associated with autoimmune thrombocytopenia. This drug has a corticosteroid-sparing effect and increases the platelet count even in patients refractory to the former therapeutic approaches. In this sense, danazol has been used successfully in autoimmune thrombocytopenia of idiopathic thrombocytopenic purpura [14], SLE [15, 16] and RA [4]. Moreover, its efficacy has recently been reported in a patient with primary antiphospholipid syndrome [17].

We report our experience on the use of danazol in patients with refractory autoimmune thrombocytopenia associated with different immune diseases followed in our divisions of rheumatology.

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PATIENTS AND METHODS

Inclusion criteria

Patients with severe immune thrombocytopenia (platelet counts < 40 × 10^9/l) with a bone marrow biopsy showing megakaryocytes in normal or increased number and normal morphology, and with a follow-up of at least 12 months, were included if they fulfilled at least one of the following criteria: (a) thrombocytopenia refractory to prednisone (>1 mg/kg/day during >4 weeks); (b) patients requiring an unacceptably high dose of prednisone for >2 months (prednisone dose ≥20 mg/day); (c) no response to at least another drug besides corticosteroids (methotrexate, azathioprine, i.v. immunoglobulin).

RA and SLE were diagnosed according to the criteria proposed by the American College of Rheumatology (formerly the American Rheumatism Association) [18, 19]. Antiphospholipid antibody syndrome was diagnosed according to the criteria proposed by both Alarcón-Segovia et al. [2] and Harris [3].

Laboratory tests

Standard blood and bone marrow examinations were carried out in all the patients meeting the inclusion criteria. Immunological tests were performed as follows: rheumatoid factor (RF) (determined by nephelometry), antinuclear antibodies (ANA) (determined by indirect immunofluorescence using as substrate Hep2 cells), anti-native DNA (by indirect immunofluorescence using as substrate Crithidia lucilae). Serum levels of C3 and C4 were determined by nephelometry. Finally, anticardiolipin antibodies (aCL) (IgG and IgM isotypes) were measured by ELISA and the lupus anticoagulant by using the Russell’s viper venom clotting time.

Therapeutic schedule

In all the cases, therapy with danazol was added to the prednisone therapy at an initial dose of 100 mg q.i.d. and then was progressively increased up to a maximum of 200 mg q.i.d. The dose of prednisone was maintained constant for at least 1 month and then it was progressively tapered according to platelet counts. Platelet counts were initially performed every 2 weeks until acceptable levels (>90 × 10^9/l) were reached. Then, platelet counts were performed monthly.

RESULTS

Four patients diagnosed with SLE, two with RA and one with primary antiphospholipid syndrome met the inclusion criteria. The main features of the seven patients are summarized in Tables I and II. In all the patients, other causes of thrombocytopenia were excluded and a confirmatory bone marrow examination showed increased or normal megakaryocytes. All of them achieved acceptable platelet counts (>90 × 10^9/l) within the first 4 weeks of danazol therapy.

### TABLE I

Main features of seven patients with secondary and refractory autoimmune thrombocytopenia that responded successfully to danazol

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/sex*</th>
<th>Disease†</th>
<th>Duration of disease (yr)</th>
<th>Duration of thrombocytopenia (yr)</th>
<th>Previous treatment‡</th>
<th>At danazol onset</th>
<th>After 4 weeks of danazol</th>
<th>Follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>21/F</td>
<td>SLE</td>
<td>2</td>
<td>1</td>
<td>P/MTX</td>
<td>33</td>
<td>90</td>
<td>42</td>
</tr>
<tr>
<td>2</td>
<td>46/F</td>
<td>SLE</td>
<td>3</td>
<td>2.5</td>
<td>P/AZA/S</td>
<td>39</td>
<td>103</td>
<td>36</td>
</tr>
<tr>
<td>3</td>
<td>52/F</td>
<td>SLE</td>
<td>5</td>
<td>1</td>
<td>P/Ig</td>
<td>28</td>
<td>130</td>
<td>23</td>
</tr>
<tr>
<td>4</td>
<td>39/F</td>
<td>SLE</td>
<td>2</td>
<td>1.5</td>
<td>P/AZA</td>
<td>32</td>
<td>154</td>
<td>29</td>
</tr>
<tr>
<td>5</td>
<td>62/F</td>
<td>RA</td>
<td>12</td>
<td>3</td>
<td>P/MTX</td>
<td>33</td>
<td>154</td>
<td>19</td>
</tr>
<tr>
<td>6</td>
<td>51/M</td>
<td>RA</td>
<td>7</td>
<td>1</td>
<td>P/MTX</td>
<td>21</td>
<td>213</td>
<td>21</td>
</tr>
<tr>
<td>7</td>
<td>78/M</td>
<td>APS</td>
<td>0.5</td>
<td>0.5</td>
<td>P/Ig</td>
<td>7</td>
<td>122</td>
<td>12</td>
</tr>
</tbody>
</table>

*F, female; M, male.
†SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; APS, primary antiphospholipid syndrome.
‡P, prednisone; MTX, methotrexate; AZA, azathioprine; Ig, i.v. immunoglobulin; S, splenectomy.
§Platelet counts (>10^9/l).

### TABLE II

Danazol dose and steroid-sparing effect in seven patients with refractory autoimmune thrombocytopenia that responded to danazol

<table>
<thead>
<tr>
<th>Case</th>
<th>Danazol dose (mg/day)</th>
<th>Prednisone dose (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Maximum</td>
<td>At 12 months</td>
</tr>
<tr>
<td>1</td>
<td>700</td>
<td>400</td>
</tr>
<tr>
<td>2</td>
<td>800</td>
<td>300</td>
</tr>
<tr>
<td>3</td>
<td>600</td>
<td>300</td>
</tr>
<tr>
<td>4</td>
<td>400</td>
<td>200</td>
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<td>6</td>
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<td>400</td>
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<tr>
<td>7</td>
<td>700</td>
<td>300</td>
</tr>
</tbody>
</table>
therapy that allowed the prednisone dosage to be tapered.

In the four patients with SLE, anticardiolipin antibodies and the lupus anticoagulant were normal or negative. Therefore, a secondary antiphospholipid syndrome was excluded. Thrombocytopenia was the only important clinical manifestation of SLE in these four patients. In addition to thrombocytopenia, minor manifestations of SLE such as joint involvement or constitutional symptoms were present, but neither nephritis nor central nervous system involvement occurred in these four cases.

The two patients with RA had long-standing seropositive and erosive RA, and at the time that severe thrombocytopenia was observed they were only receiving prednisone at a dose of 10 and 15 mg/day, respectively. In addition to thrombocytopenia, both rheumatoid patients presented an important disease activity. In both cases, Felty’s syndrome was excluded because neither splenomegaly (by ultrasonography) nor other haematological abnormalities were found. Initially they were treated with prednisone at high dose (1 mg/kg/day) and methotrexate (MTX) (at 7.5 mg/week) as both a disease-modifying agent and steroid-sparing drug. In spite of treatment with MTX (progressively increased up to 15 mg/week) for 3 months, thrombocytopenia relapsed in both cases as soon as the steroid dose was reduced below 30–35 mg/day. Thus, MTX was stopped and danazol was added to prednisone at the previous dose (30 and 35 mg/day, respectively). In addition to the improvement of thrombocytopenia, both patients also had an improvement in the underlying RA that persisted even when the prednisone dose was reduced. No further relapses of thrombocytopenia occurred and prednisone was gradually tapered.

The patient with primary antiphospholipid syndrome was a 78-yr-old man admitted to our hospital because of left hemiplegia, livedo reticularis and diffuse petechiae in his lower extremities. A CT scan demonstrated the presence of an ischaemic infarction in his right cerebral hemisphere. IgG ELISA anticardiolipin antibodies were positive (81.4 GPL units; normal values <18 GPL units). Antinuclear antibodies and lupus anticoagulant were negative. Intravenous immunoglobulins (1 g/kg/day for 2 days) were given. Thrombocytopenia showed an important although transient improvement. Therefore, prednisone at high dose (1 mg/kg/day) was started. However, thrombocytopenia relapsed as soon as the prednisone dose was reduced below 45 mg/day. Thus, danazol was added to prednisone at a dose of 45 mg/day. Following danazol therapy, a rapid increase in the platelet count was observed. Such an improvement in the platelet counts allowed a progressive reduction in the prednisone dose to be carried out. Moreover, an important decrease in antiphospholipid antibody levels was observed (Fig. 1).

During danazol therapy, the platelet counts were maintained within normal levels in all the seven patients (Fig. 2).

Important side-effects of danazol were not found in any of the seven patients. Only the patient with antiphospholipid syndrome had a mild and transitory
increase in transaminases that resolved without any change in the dose of this drug. Another patient with SLE had mild weight gain.

DISCUSSION

We present seven patients with refractory and severe immune thrombocytopenia secondary to several rheumatic diseases in whom danazol seemed to be a useful and well-tolerated therapy.

Effective treatment for immune thrombocytopenia should be based on a definitive understanding of how a given therapy improves the platelet counts. This implies a better knowledge of the mechanism(s) of immune thrombocytopenia. Classically, the major mechanism of thrombocytopenia in immune diseases has been an increase in platelet destruction by platelet-bound antibodies and/or altered function of the splenic macrophage Fc (IgG) receptors. These two factors could imply a reduction of the survival of circulating platelets. However, it is possible that in some cases the predominant cause could be ineffective marrow platelet production rather than an accelerated platelet removal. In this regard, Gernsheimer et al. [6] have established that in idiopathic thrombocytopenia purpura it appears that steroids may increase the effective production of platelets and splenectomy seems to increase platelet survival by removing the major organ of peripheral destruction.

The mechanism of danazol in autoimmune thrombocytopenia is unknown. Studies on danazol’s effect on the level of antiplatelet antibodies have yielded conflicting results. Some investigators found a reduction in the level of antiplatelet antibodies; however, others did not find such a decrease and they think that part of danazol’s mechanism of action is due to inhibition of the mononuclear phagocyte system [14, 16]. Because danazol is similar in structure to cholesterol, it might be incorporated into and affect the functions of cellular membranes. It might be hypothesized that, by such a mechanism, danazol might modify the interaction of anticardiolipin antibodies with their antigens in platelet membranes [17]. Since we do not have data on antiplatelet antibodies or on the survival of circulating platelets, we cannot draw conclusions about the pathophysiology of immune thrombocytopenia nor the mechanism of action of danazol in our seven patients. The only remarkable pathophysiological fact was that our patient with antiphospholipid syndrome had an important reduction in antiphospholipid antibodies. Moreover, in this patient there was a clear correlation between the titre of antiphospholipid antibodies and thrombocytopenia (Fig. 1). In any case, danazol was very useful in our series of patients with immune thrombocytopenia and very different underlying diseases.

We present seven patients with immune thrombocytopenia in three different underlying diseases. Danazol has proved to be efficacious in the treatment of immune thrombocytopenia of idiopathic thrombocytopenic purpura [14] and SLE [15, 16]. However, it has been exceptionally used in RA [4], and to the best of our knowledge, this efficacy has only been described in another patient with antiphospholipid syndrome [17]. It was of special interest that the two patients with RA presented a clear improvement of the underlying disease when danazol was started. Moreover, when the prednisone dose was reduced, neither thrombocytopenia nor clinical and laboratory parameters of disease showed a relapse. In this regard, an important clinical benefit following danazol therapy has been reported in other immune-mediated diseases such as Henoch–Schönlein purpura or IgA nephropathy [12, 13]. Therefore, it is possible that danazol has immunomodulatory properties [20, 21]. On the other hand, none of our four SLE patients presented major organ involvement. However, in patients with thrombocytopenia and major organ manifestations of SLE, we advocate the use of i.v. cyclophosphamide because it offers the advantage of treating the underlying disease [10].

In our series of seven patients, only mild side-effects related to danazol were found: one patient had mild weight gain, and another patient had a mild and transitory increase in transaminases. Nevertheless, peliosis hepatitis has been described with danazol and, therefore, a careful monitoring with adjustment of dosage is recommended [22]. Other described side-effects are generalized skin rash, lethargy, myalgia, itching, hair loss, mild virilizing side-effects (voice change, hair growth) and vertigo [14].

Taking into account the efficacy and side-effects of the several therapies (splenectomy, i.v. immunoglobulins, cytotoxic agents) in immune thrombocytopenia associated with rheumatic diseases, we propose the following therapeutic approach. Patients may be initially treated with corticosteroids (1 mg/kg/day or greater) for at least 1 month. If no response to this dose is observed or patients require to continue with high-dose steroid (prednisone dose > 20 mg/day) to maintain normal platelet counts, danazol may be added. We suggest starting danazol at 100 mg q.i.d. for 1 month and then, according to response, danazol should progressively be increased up to a maximum of 200 mg q.i.d., so we may set an optimal dose without overtreatment. When the optimal response is reached, this dose should be maintained for another month and then steroids should be progressively reduced to the lowest required dose. Thereafter, as soon as the steroids have been tapered to a low dose (prednisone 10 mg/day), and if the platelet counts remain in an acceptable range > 100 x 10^9/L for at least another month, an attempt to reduce danazol by 100 mg/day every month should be made.

In summary, danazol seems to be a useful and well-tolerated therapy for refractory autoimmune thrombocytopenia associated with rheumatic diseases. In patients without other further complications, danazol may probably be the second step (after corticosteroids) in the management of autoimmune
thrombocytopenia. However, a larger prospective multicentre study is needed to support these promising results.

REFERENCES