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EXPERT'S CORNER: A PERSONAL APPROACH

Adult patients with immune thrombocytopenic purpura. New expectations

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Introduction

Immune thrombocytopenic purpura (ITP) is an acquired autoimmune disorder involving antibody and cell mediated destruction of platelets. In acute cases the majority of patients have clinical bleeding and less than 30,000 platelets. Nowadays, there is enough evidence that immune destruction of circulating platelets and suppression of platelets production in the bone marrow is also happening.

Diagnosis is usually an easy task, requiring an isolated thrombocytopenia below 100×10^9/L, no other obvious cause for the condition and no clinically evident secondary form of immune thrombocytopenia.[1,2] The incidence has geographic variation, but there are nearly 30 new cases per million annually, it is more prevalent in women and its incidence increases with age.[3] Over 70% of affected children resolve spontaneously, whereas ITP in adults is a more complicated disease, typically having an insidious onset with no preceding viral or other illness and usually following a persistent or chronic course.[4]

The stages of ITP according to the recent guidelines include the following: *a)* acute ITP— months 0-3 after presentation; *b)* persistent ITP— 4-12 months; *c)* chronic ITP— >12 months; *d)* refractory ITP— patient without response to splenectomy, and *e)* severe ITP— patient has suffered major clinical bleeding.

Diagnosis

There is no special recommendation other than the exclusion of an isolated cause of thrombocytopenia; in other words, there is not a "gold standard" test for ITP. I usually rule out HIV, hepatitis C, lupus, non-Hodgkin lymphoma, liver disease and *Helycobacter pylori* infection.

It is very important to carefully review the blood smear in order to confirm the level of thrombocytopenia and rule out pseudo-thrombocytopenia and unexpected hematological diseases. The bone marrow is rarely studied in ITP, but it sometimes can be useful in selected elderly patients.

Treatment

In patients with thrombocytopenia of 30,000 or less, treatment is usually indicated. Prednisone is the more common corticosteroid used as standard initial therapy. The dose is 1-2 mg/kg per day for 2-4 weeks, and is given until a rise in the platelet count is obtained, which happens in about 75% of cases. However, many patients have a relapse when the dose of corticosteroids is reduced; only 5-30% will obtain a sustained remission.[6-8] Splenectomy is considered the best option for patients suffering from chronic disease, but approximately 40% of splenectomized patients do not respond or relapse after surgery and are at risk of further infections.[9]

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The thrombopoietin receptor agonists are truly "the new kids on the block" in the therapeutic armamentarium against ITP. Romiplostin and eltrombopag are both effective for chronic ITP, but they are dependent on continuous administration and therefore both drugs are expensive, and its use in the patient suffering from the chronic form of the disease is not a realistic option in countries with economic problems belonging to the so called "underdeveloped" world.[10,11]

The role of high-dose dexamethasone in the treatment of acute ITP is not yet clarified, but pulses of this drug were effective as an initial therapy in 125 patients receiving 40 mg/day for 4 consecutive days. In this study, a total of 106 patients (85%) obtained a good initial response. Nevertheless, 50% relapsed within 6 months.[12] Both prednisone in "low doses" daily for 2-4 weeks, and dexamethasone in "high doses" for 4 days once or twice in the first month, are very good options. However, this lack of sustained response after stopping corticosteroids has prompted the search for a treatment able to modify both the underlying mechanism and the natural course of the disease.

The use of high doses of intravenous IgG is very effective. I rarely use this option because the response only lasts 3-4 weeks; 0.4 g/kg/day for 4 days is one way to administer the protein. Another effective way to give the drug is 1 g/kg in a single day. This drug, in combination with 40 mg of dexamethasone per day for 4 days, is indicated in patients with severe ITP.

Rituximab is a chimeric monoclonal antibody directed against CD20, an antigen expressed by mature B cells.[13] It was approved and licensed in 1997 for the treatment of follicular B cell lymphoma and has since been extensively studied in various autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, acquired hemophilia, thrombotic thrombocytopenic purpura, autoimmune hemolytic anemia and ITP.[14,15] Rituximab is generally administered at a dose approved for lymphomas (375 mg/m^2 weekly for 4 weeks). However, the tumor burden in lymphomas is often high, whereas in ITP the B cell mass is considered normal. Therefore, lower doses of rituximab (100 mg/m^2) have been used in the treatment of ITP, showing similar activity to the standard dose. It is important to note that rituximab is usually indicated in persistent or chronic cases, as a second line of therapy, and usually before splenectomy.[16-21]

New options in patients with ITP

In order to obtain a rapid and sustained response in ITP patients, we have used rituximab/dexamethasone or eltrombopag plus dexamethasone as an initial therapy.[22,23] Eligible patients for these prospective studies were ≥18 years old with newly-diagnosed ITP. Patients were excluded if they had an active bacterial or viral infection, HIV, HCV, or HBsAg positive serology, pregnancy or concomitant malignant disease.

Patients received dexamethasone at 40 mg/day for 4 consecutive days (+1, +2, +3, +4) and rituximab was administered at a fixed dose of 100 mg as an IV infusion weekly for 4 consecutive doses (days +1, +7+, +14 and +28). In the other study the patients received the same scheme of dexamethasone plus eltrombopag at 50 mg per day, from day 5, for 28 days. The results are encouraging, since 65 to 76% of patients obtained a sustained response. There is evidence that both rituximab and eltrombopag also have the capability of modifying the T cell repertoire and the levels of T regs, improving the immune regulation. These studies showed promising results, however more studies are needed in order to confirm these preliminary observations.

Conclusions

For more than 50 years, conventional therapy of ITP has included corticosteroids as a front-line treatment. However, despite the high initial therapeutic efficacy, in most cases steroid tapering withdrawal is followed by a drop in platelet count and the need for additional treatment. Splenectomy is the most effective alternative in chronic cases, but ITP sometimes resolve spontaneously even in persistent cases, therefore I recommend to wait at least 12 months before the surgery. Rituximab is a very good alternative in order to obtain a longer and sustained response in persistent or chronic cases, and I usually use this drug before splenectomy. Conventional and lower doses of rituximab are effective in the majority of patients. On the other hand, there are several drugs used as a second or third line in the treatment of ITP: danazol, vinca-alcaloids, cyclophosphamide, azathioprine, cyclosporine, etc., but eltrombopag and romiplostin are now considered the best options, if their high cost is not a problem. Finally, it is important to consider that danazol is a good alternative, it is also an inexpensive and safe oral drug, useful in chronic ITP, especially in cases where the thrombopoietin agonists are not available.

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