Adult idiopathic thrombocytopaenic purpura: therapeutic approach: Analysis of 30 cases (1991-1995) with a brief review of the literature

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Abstract

Background: We analyzed epidemiological data, therapies, clinical efficacy and evolution of patients with adult idiopathic thrombocytopenic purpura (ITP).

Patients and methods: A retrospective study of patients with an established diagnosis of ITP, referred to our Internal Medical Department between 1991 and 1995, was carried out.

Definitions of therapy efficacy and evolution are as follows: complete remission > 150.000/mm^3; continuous complete remission: platelets >150.000/mm^3 for at least 2 months without therapy; partial remission: platelets > 50000<150000/mm^3; without therapy response<50000/mm^3.

Results: Between 1991 and 1995, 30 patients were admitted with IPT (23 female; 7 male; average ages: 49.5 years). Corticosteroid therapy was given to 30 patients, 9 achieved complete remission; 4 of those were in continuous complete remission; 15 patients had partial remission and 6 failed to achieve a response. 14 patients received gammaglobulin intravenously; 1 achieved complete remission; 9 had partial remission and 6 had no response.

Only 4 patients were splenectomised; 3 achieved partial remission and 1 patient had no response. Danazol was used in 2 patients with no beneficial effect.

Mean follow-up for 24 months revealed: 13 patients had multiple relapses; 4 achieved continuous complete remission and 1 died; 12 patients were lost to follow-up.

Conclusion: Corticosteroid therapy was the most effective therapy in ITP, with 30% of patients achieving complete remission in our study.

In spite of the many different treatment regimens available, 43% of patients had a chronic disease evolution, in line with the international ITP disease statistics.

Key words: adult idiopathic thrombocytopenic purpura, therapy, responses, evolution.

Key words: systemic amyloidosis, potassium permanganate test, classification, diagnosis, clinical manifestations.

Introduction

Idiopathic thrombocytopenic purpura (ITP), also known as primary immune purpura, is defined by the presence of thrombocytopenia in the peripheral blood, in the absence of other causes of thrombocytopenia and/or alterations in the myelogram. ITP in adults is typically a chronic disease, and is more common in females.[1]

Its therapeutic approach is sometimes very complicated, causing the physician to confront very severe situations, and therapeutic options that can lead to severe secondary effects of therapy, which are definitive in nature, as in the case of splenectomy, and which do not always lead to satisfactory remission.

Based on this experience, it was decided to carry out a retrospective study of patients admitted to an Internal Medicine Service in a five-year period, with a diagnosis of ITP, in order to evaluate the epidemiological characteristics, the therapeutic approach, and the responses obtained.

For this purpose, a review was carried out of the therapeutic strategies currently used in the treatment of ITP, according to the literature.

Patients and methods

The clinical processes were reviewed of 30 patients admitted to an Internal medicine Service, over a five-year period (1991-1995), with a diagnosis of ITP, based on the presence of thrombocytopenia in the peripheral blood and absence of alterations in myelogram; patients with thrombocytopenic purpura secondary to another pathology were excluded. The population was studied from the epidemiological

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point of view, therapy carried out, therapeutic responses, and evolution.

Complete remission was defined as a platelet count > 150000/mm^3; continuous complete remission as maintenance of the platelet count within the normal range without therapy for a period of more than two months; partial remission as platelet counts >50.000<150.000/mm^3; and absence of response, as a platelet count <50.000/mm^3.

Results

During the period 1991 to 1995, a total of 12,341 patients were admitted to our service, 30 of whom had a discharge diagnosis of ITP. Twenty-three patients were female, and seven were male. The mean age was 49.5 years (minimum age – 20 years; maximum age – 60 years).

Clinically, all the patients had cutaneous purpura on admission, with three also presenting genitourinary hemorrhage, and two gingival bleeding.

The mean platelet count on admission was 7.200/mm^3 (minimum value - 2000/mm^3; maximum value - 12.000/mm^3).

All the patients received corticoid therapy; nine patients had complete remission, with two patients presenting continuous complete remission after one year of evolution, one patient after six months and another two after two years; fifteen patients had partial remission; in six patients there was no response to the corticotherapy. It is emphasized that one of the patients in continuous complete remission had six cycles of dexamethasone in high dose (40 mg/day) for 4 days.

Fourteen patients had intravenous gammaglobulin (400 mg/kg for five days); there was one complete remission, nine partial remissions and no response in four patients; ten of these patients had received corticoids previously with partial remission and clinical evidence of hemorrhagic diathesis; four patients did not have any previous response to the corticotherapy.

Four patients received immunosuppression therapy with azathioprine; partial remission was obtained in three of them and there was no response in one patient; one of these patients had had no response to the corticoids and gammaglobulin, and the other three had a partial response to these therapies, with persistence of hemorrhagic diathesis.

Four patients underwent splenectomy, obtaining complete remission in two. The response in the other two is unknown; it is highlighted that in two patients there was no response to the corticoids, and in another two, there was no response to the corticoids and intravenous gammaglobulin.

Two patients, without previous response to corticoids, gammaglobulin and azathioprine, received therapy with danazol, with persistence of platelets <50.000/mm^3.

Of the thirty patients studied, thirteen had a chronic evolution with periods of relapse/remission during a mean follow-up time of two years; four patients are in complete remission without therapy, and one patient died; twelve patients were in follow-up with their attending physician.

Discussion

ITP in adults is characterized by thrombocytopenia in the absence of exogenous or pathological etiological factors associated with secondary thrombocytopenia.[2] It is typically a disease with insidious onset, with a chronic evolution, and it is more common in young adults and women.[3,4]

ITP is the result of the production of class IgG auto-antibodies targeted against glycoproteins on the surface of the platelets. The epitopes present in glycoprotein IIb/IIIa are the preferential target, although glycoprotein-targeted antibodies may be present, namely, Ib/V/IX, Ia/IIa and glycoprotein IV.[4] These auto-antibodies induce not only peripheral destruction of the platelets, particularly in the spleen, but also interfere in thrombopoiesis and platelet function.[3]

Chronic TPI has a fluctuating course, with periods of remission and exacerbation. The hemorrhagic manifestations are of the purpura type, generally involving the skin and mucosa. The most severe manifestation is hemorrhage of the central nervous system, which occurs in less than 1% of these patients; it is generally associated with lower platelet counts.[3]

Patients aged over 60 years, with a previous history of hemorrhage, have a higher risk of developing more severe hemorrhagias;[5] in our case series, the one patient that died was 60 years of age.

In the laboratory evaluation of the patients, the myelogram showed a normal or high number of megakaryocytes, with interest particularly in the exclusion of other differential diagnoses.

The attempts to demonstrate the presence of antiplatelet antibodies in the serum of these patients by conventional serological methods have met with

TABLE I

Corticotherapy – 1st line therapy

Prednisolone	Methylprednisolone
40 – 60 mg/day	32 – 48 mg/day

4-6 weeks ⇒ weaning

If there is no response

⇑ doses of corticoids for 80 – 100mg/day ⇒ splenectomy

If there is partial remission

expectant attitude without corticotherapy

Maintain corticoids at low dose

splenectomy

limited success, given the proven absence of sensitivity and the presence of distinct specificities among the antibodies associated with the platelets and platelet glycoprotein IIb/IIIa-targeted antibodies.[6] Recently, a more sensitive technique was developed to detect IgG antibodies associated with platelets, designated PAIg, which is based on direct research of antibodies involved in the auto-immune destruction of the platelets; false positive results have been found in patients with septicemia and hypogammaglobulinaemia. False negative results are observed in patients with platelets <10.000 or>75.000 or sometimes due to technical error.[3] More details on the different techniques used to detect these auto-antibodies and in relation to the problems investigated in its interpretation are outside the scope of this work; however, it is emphasized that they are unimportant for the diagnosis and therapy.

In our work, all the patients had cutaneous purpura with petechiae and ecchymoses; two patients had associated gingival bleeding and three had hematuria.

Corticoids constitute the first line therapy in the initial approach to ITP, obtaining partial remissions in 79-90% of patients, and complete remissions in 15-60%, according to the authors and the works.[3]

The initial target of action of the corticosteroids is the microvascular endothelium, which is affected in patients with severe thrombocytopenia. This action is seen after four days of corticotherapy, even before an increase in platelet counts is seen[7]. Corticoids act subsequently, by inhibiting the synthesis of immunoglobulin and their binding to the surface of the

TABLE II

Indications for Splenectomy

No response to corticotherapy

Recurrence after weaning or suspension of the corticotherapy.

Need for high doses of corticoids

Difficulty guaranteeing follow-up

Contraindications for corticoids

platelets, by a decrease in phagocytosis, particularly in the spleen,[3] and through an increase in platelet production through the binding of the antibodies to the bone marrow megakaryocytes.[8]

Various regimens have been proposed. One of the most recommended is that shown in *Table 1*.[1,3]

In our study, corticotherapy was the first therapeutic approach used in all the patients, obtaining complete remission in 30% of patients and partial remission in 50%.

Corticoids should not be maintained for periods longer than six months, given the associated side effects.[3]

Splenectomy is the treatment of choice in patients who do not enter complete remission with corticoids.[2] The response to splenectomy is immediate, in the first 24-48h, with maintained remissions in 50-90% of patients.[3,8]

The action of the splenectomy in patients with chronic ITP results in removal of the most important organ in the synthesis of antibodies, and in the main site of destruction of the platelets.[9] The indications for performing splenectomy are those reported in *Table 2*.[3] Splenectomy has proven ineffective in 5-20% of patients; 10% of these patients have accessory spleens.[1] In patients with ITP, splenectomy can be performed by laparoscopy.[10] All the patients submitted to splenectomy should be vaccinated in advance against pneumococci, haemophilus influenzae and meningococos.[11] Curiously, in our study, only four patients were submitted to splenectomy.

The treatment of chronic refractory ITP constitutes a major challenge for the physician, since 20-30% of patients with ITP have this evolution.[11] The criteria for refractory chronic ITP are as follows:[1]

1) previous therapy with corticoids and/or splenectomy;

2) age > 10 years;

3) platelet count < 50.000/mm^3;
4) duration of the disease > 3 months;
5) absence of another disease associated with the thrombocytopenia.

The approach in this situation has to be individualized, bearing in mind the chronicity and the age group of the patients.[4] The response to therapy is poor, and there is major morbidity resulting from the disease or the iatrogenic, and mortality of 10%.[11]

In the initial phase, corticoids are the drug of choice, when it is possible to maintain safe platelet counts with low doses of corticoids.[11] In cases where it is not possible, pulses of dexamethasone can be administered, 40 mg a day, during four successive days, every 28 days, with a total of six cycles.[11] In a pioneering study of this approach involving ten patients, an increase in platelet count was observed in all the patients with minimum side effects.[12]

Other studies have demonstrated that dexamethasone in high doses has a relatively limited effect, and major side effects.[13]

In our case series, there was one patient who received 6 cycles of dexamethasone; the patient is now in complete remission after two years of follow up.

The value of the vinca alkaloids in the treatment of ITP are well established.[12] They may be administered in a weekly intravenous intermittent bolus (vincristine 0.025mg/kg to a maximum of 2 mg; vinblastine 0.125 mg/kg),[1] in intravenous infusion for 6-8 hours weekly[12] or allogenic platelet clusters.[1] The start of action is rapid (7-19 days).[14] The main collateral effect of vincristine is peripheral neuropathy and that of vinblastine is myelosuppression.[1]

Danazol is a semi-synthetic androgen with few virilizing effects. It was initially used in the treatment of endometriosis, and subsequently used in other pathologies, particularly ITP. It has slow start of action (3-6 weeks), and the mechanism of action on ITP is unknown. The optimum dose has not yet been established, but it should be started at around 400-800 mg/day, for at least 6 months. If there is a response, the dose should be decreased and maintained for at least one year.[11,15,16] In our case series, Danazol was used in two patients without response.

Colchicine may be useful in the treatment of chronic refractory ITP. The mechanism of action is similar to that of vinca alkaloids, and it is thought that it acts at the level of phagocytosis mechanisms dependant of the microtubules.[17] The therapy should be started at a dose of 0.6 mg three times a day for at least 2 months.[11]

Dapsone has an unknown mechanism of action in ITP; the start of action is slow, and the dose considered is 75-100 mg/day. In all the patients, glucose-6-phosphate dehydrogenase deficit should be ruled out, bearing in mind that hemolytic anemia is its principal collateral effect.[18]

Other approaches with more toxic effects are reserved for symptomatic patients with platelet counts of between 10.000-15.000/mm^3.[11]

Cyclophosphamide and azathioprine have been recommended for more than twenty years in the treatment of chronic ITP.[19] Cyclophosphamide should be preferred over azathioprine because it has a faster start of action, despite having more side effects.[3] The initial dose is 150 mg/day for at least 3 months, if there is normalization of platelet counts.[20] Azathioprine has a slow start of action (3-6 months). The usual dose is 150 mg/day, which should be maintained for eighteen months if there is a response.[11,19]

In our case series, four patients received therapy with azathioprine, obtaining partial remission in three of them; no response was obtained in the other patient.

Also in this group of patients, immunoadsorption has been used in columns with A-staphylococcal protein. It should be carried out three times a day for two weeks. The responses generally occur after three cycles.[21] In one study involving 72 patients with chronic ITP in whom this therapy was applied, a complete response was seen in 16 patients.[1]

In patients with chronic ITP that is refractory to the previous therapies, with platelet counts <10.000/mm^3 or severe hemorrhagic diathesis, cyclophosphamide pulses can be used[22] (1-1.5 g/m^2 of the body surface iv every 4 weeks), or combined chemotherapy, using regimens generally used in patients with lymphomas.[23]

In relation to other therapies, experience is limited and the responses are weak. Among this is interferon 2b, used in a study in 13 patients with chronic refractory ITP, at a dose of 3MU sc in a total of 12 doses. An increase in platelets was seen in ten patients after the final dose.[24]

Another drug used in cases of chronic ITP that is refractory to other therapies was cyclosporin at a dose of 2.5 mg/kg, twice a day.[25]

The anti-D(Rh) serum was used in a study with 43 patients with ITP Rh+ , based on its mechanism

of action in a blocking of the Fc receptors of the macrophages,[26] with an average increase in platelets of 95.000/mm^3.

Intravenous gammaglobulin has induced remissions in patients with chronic refractory ITP. It acts by blocking the Fc receptors of the macrophages of the reticuloendothelial system. The increase in platelet count is seen after 72 hours from the start of therapy. The costs and its transitory effect make its long-term use impractical for the treatment of chronic, non-complicated ITP. It has proven to be useful, particularly in the control of acute hemorrhage, in the preparation of splenectomy in patients with cortico-resistance or before surgical interventions.[27-30] It can be used at a dose of 400 mg/kg for five consecutive days, or 1 g/kg for two days.[3]

It is emphasized that in our case series, gammaglobulin was used in fourteen patients (45%), which may be a debatable therapeutic decision, given its generally transitory effect, and the high costs in a country like ours.

However, it continues to be reported as a valid alternative in the treatment of ITP, whether associated or not with corticoids, particularly when rapid corrections of thrombocytopenia are needed, and even in cases of chronic ITP in prolonged and intermittent administration to postpone the splenectomy.[27-29] One of the factors that may have also led to its use in 45% of the patients analyzed is the aforementioned significant argument of the number of platelets in a relatively short period of time, with the consequent shortening of hospitalization times, and thus, the possibility of the patient being able to be followed up as outpatients, a crucial aspect nowadays, which places a high burden on the awards. Another probable factor responsible for its use relates to the low level of side effects associated with the use of gammaglobulin, compared with other therapies.

However, as stated earlier, its effect is transitory, and in the majority of cases, it is associated with recurrences in the short term, a factor that should be carefully weighed when opting for its use. However, of the patients studied that received this therapy, ten obtained immediate effective benefit, as one had complete remission and nine partial remission.

Conclusions

Around 43% of patients in our case series had chronic evolution, which is in accordance with the literature.

Corticoids are the most effective approach in the treatment of ITP in adults, with 30% complete remissions in our study.

Gammaglobulin was used in 14 patients, with an increase in platelet count higher than 50.000/mm^3 in ten of these. ■

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