Ann. Ist. Super. Sanità, vol. 34, n. 4 (1998), pp. 457-461

Treatment of acute idiopathic thrombocytopenic purpura in children. A retrospective evaluation of 120 cases

Carlo BARONCI, Angelamaria PETRONE, Crescenzo MIANO, Alessandra LOMBARDI, Maurizio CANIGLIA, Lidia Angiolina RUSSO, Matteo LUCIANI, Rita Maria PINTO, Ippolita RANA, Roberta CARUSO and Giulio DE ROSSI

Divisione di Ematologia, Ospedale Pediatrico "Bambino Gesù", Rome, Italy

Summary. - Acute idiopathic thrombocytopenic purpura (AITP) in children is generally a benign disease with a high frequency of spontaneous remission. Nevertheless the debate over treating or not is still open, because of the high risk of hemorrhage as long as the platelet count remains below 20 x 10^9/l. We have retrospectively evaluated 120 pediatric cases from our center, receiving different treatments at diagnosis: no treatment (76); IVIG: 400 mg/kg/d for 5 days (28); continuous oral PDN: 1-1.5 mg/kg/d for at least two weeks (16). No patients had been previously treated for AITP. Follow-up is up to fifty months. We found no significant differences as to the percentage of responses among the three groups. We conclude that waiting without treatment is safe and appropriate in most cases; whether the hemorrhagic risk suggests treatment, standard dose continuous oral PDN and IVIG may be equally effective, but IVIG may achieve a significantly faster rise in the platelet count. The timing of treatment and the cost/benefit ratio are discussed.

Key words: immune thrombocytopenic purpura, immunoglobulins, steroid.

Riassunto *(Trattamento della porpora trombocitopenica idiopatica acuta del bambino. Studio retrospettivo di 120 casi).* - La porpora trombocitopenica idiopatica acuta (AITP) del bambino è generalmente una malattia benigna con un'alta percentuale di remissione spontanea. L'opportunità di stabilire comunque un trattamento in casi con elevato rischio emorragico, e quale tipo di trattamento, sono tuttora oggetto di discussione. Abbiamo condotto uno studio retrospettivo su 120 bambini sottoposti a differenti trattamenti alla diagnosi: nessun trattamento (76); Ig e.v.: 400 mg/kg/die per 5 giorni (28); PDN continuo *per os*: 1-1,5 mg/kg/die per almeno 2 settimane (16). Nessun paziente era stato precedentemente trattato per AITP. Il *follow-up* è di 50 mesi. Non sono state osservate percentuali di risposta significativamente diverse nei tre gruppi. Riteniamo pertanto che la sola attesa senza trattamento sia una condotta possibile in molti casi; qualora ci sia indicazione alla terapia per l'esistenza di un alto rischio emorragico la somministrazione continua di PDN *per os* e le Ig e.v. si sono dimostrati ugualmente efficaci, ma le Ig e.v. permettono di ottenere una più rapida risalita della conta piastrinica. Vengono qui discusse le indicazioni utili per iniziare un trattamento ed il rapporto costo/beneficio dei diversi approcci terapeutici.

Parole chiave: porpora trombocitopenica idiopatica, immunoglobuline, steroidi.

Introduction

Acute idiopathic thrombocytopenic purpura (AITP) is an acquired hemorrhagic syndrome characterized by immune thrombocytopenia with a normal or increased number of megakaryocytes in the bone marrow (BM), without associated pathologies which might otherwise cause a low platelet count, such as systemic lupus eritematosus (SLE), disseminated intravascular coagulation (DIC), leukemia, lymphoma, human immunodeficiency virus (HIV) infection, cytomegalovirus (CMV) infection, splenomegaly, megaloblastic anemia, hepatic and renal failure.

AITP is quite common in the pediatric age, with an incidence of 4-8 cases per 100 000 children per year [1, 2].

The onset generally follows one or two weeks after a viral illness or a vaccination with live inactivated viruses; the use of drugs, such as trimethoprim/sulfamethoxazole, quinine/quinidine, dipyridamole etc., has also been reported as associated to the onset of AITP [3].

Many patients have a high titer of platelet associated autoantibodies IgG (PAIgG), directed against target antigens on the platelet membrane, but it is not clear whether they play a role in the pathogenesis of AITP [4]. Platelet halflife is shortened to a few days or even a few hours and platelet destruction takes place in the reticuloendothelial system, mainly in the spleen, by fixed macrophages [2, 5].

Intracranial hemorrhage is the major complication to be feared, especially during the first 4 weeks of illness; it is unfrequent and occurrs in about 1% of the patients

with a platelet count of less than 20 x 10^9/l [6, 7]. Fever, a history of recent trauma, viral eruptive infections, surgical operations, a very low platelet count (below 20 x 10^9/l), raise the hemorrhagic risk.

The incidence of chronic ITP, defined as persistence of thrombocytopenia for more than 6 months, is 10-20% [8, 9]. Features of the illness known to be associated with an increased risk of chronic thrombocytopenia include a history of purpura for more than 2 to 4 weeks before diagnosis, female sex, age over 10 years at diagnosis, and a higher platelet count at onset [10-14].

Although AITP is considered a benign disease, management of children affected by it is still controversial and the relative advantages of therapy *versus* no therapy are still debated [15, 16].

A high percentage (over 70%) of patients with AITP have a spontaneous remission [1, 2, 17], nevertheless treatment is mandatory in cases presenting a high risk of life threatening hemorrhages, so that a faster rise in the platelet count can be obtained and fatal events prevented.

Usual therapy of AITP includes steroids, given both orally and intravenously at various dosages, intravenous immunoglobulins, anti-D immunoglobulins, and immunosuppressive drugs.

Therapy may fail to achieve a response in 30-40% of cases, and 10-20% of relapses have been reported after initial response [1, 2, 18, 19]. Furthermore there is no evidence of the superiority of one type of therapy over another one; nor does it seem possible to define the time, in the natural course of the illness, at which starting treatment could modify the outcome.

In order to contribute to determine whether, when, and how to treat children with AITP, we have retrospectively reviewed our data, obtained from 120 children who had received different managements of AITP: waiting without therapy ("wait and see"); intravenous immunoglobulins (IVIG), continuous oral conventional steroid therapy.

Patients and methods

We have retrospectively evaluated data obtained from children with AITP diagnosed and treated in the Haematology Division of the "Bambino Gesù" children's hospital in Rome, between January 1990 and May 1995. At that time we had not yet adopted a standard protocol for the treatment of AITP and patients received different managements of AITP mainly according to their clinical features; they were not randomized to different treatments.

The choice of the treatment to perform, or the choice of not to treat, was based mainly upon the evaluation of the hemorrhagic risk and the feasibility of observation without treatment and without hospitalization, depending on the family's reliability.

We have excluded from evaluation patients already treated for AITP, patients relapsed after a previous recovery from AITP, and patients who were less than 3 months old at diagnosis, since these might have circulating maternal antibodies responsible for thrombocytopenia. Children with thrombocytopenia and other associated pathologies, such as SLE, leukemia, lymphoma, DIC, HIV infection, CMV infection, splenomegaly from any cause, megaloblastic anemia, hepatic or renal failure, have been excluded too.

One hundred and twenty evaluable patients were found: 52 females and 68 males. Median age at the time of diagnosis was 49 months (from 3 to 178 months). All were at the onset of their illness and no one had received any treatment for AITP before admission at the hospital.

Hospitalization was performed at diagnosis, and in case subsequently at relapse, just for patients with high hemorrhagic risk, based upon the very low platelet count, the history of recent trauma, the evidence of actual viral illness. Patients without important risk factors for hemorrhages were admitted at the day hospital.

Complete physical examination and history had been obtained for each patient on admission. BM aspirate was performed at diagnosis for all the evaluated patients. Laboratory testing at onset included: hemoglobin level, total leukocyte and differential cell count, platelet count, direct Coombs test, reticulocyte count, quantitative immunoglobulin levels, antinuclear antibody (ANA) test, serology for HIV, toxoplasma, rubella, cytomegalovirus, herpes virus, hepatitis A, B, C.

Platelet count was obtained at least once every two days during the first week of illness, and subsequently at least once a week during the first month after diagnosis, and then at least once a month.

We have divided the 120 evaluable patients into three groups, according to the different management of AITP (Table 1): 76 patients received no therapy; 28 patients received IVIG 400 mg/kg/d, in 6 hour infusion for 5 days; 16 patients received oral steroid therapy 1-1.5 mg/kg/d prednisone (PDN) for at least 2 weeks.

We considered a response to be a rise in the platelet count to at least 100 x 10^9/l for at least three weeks; we did not consider partial responses.

Results

Forty-one (53.9%) of 76 patients in group A (no treatment) showed a spontaneous response within a median time from diagnosis of 10 days (range 2-55 days). In this group just one (2.4%) of the 41 responders subsequently relapsed (45 months after diagnosis). The median follow up for children in group A is 50 months (Table 2).

All patients in group A initially had clinical features which allowed waiting without treatment; i.e. absence of severe cutaneous and/or mucosal hemorrhages and/or a platelet count higher than 10 x 10^9/l; 35/76 patients (26.1%) in group A had to be subsequently withdrawn

Table 1. - Treatment groups

Group A - No treatment ("wait and see")

76/120 patients
median age at diagnosis: 47 months (range 5-178 months)
median platelet count at diagnosis: 19 x 10^9/l
(range 4-70 x 10^9/ l)

Group B - IVIG 400 mg/kg/d for 5 days

28/120 patients
median age at diagnosis: 43 months (range 3-161 months)
median platelet count at diagnosis: 9 x 10^9/l
(range 3- 36 x 10^9/l)

Group C - Oral PDN 1-1.5 mg/kg/d for at least two weeks

16/120 patients
median age at diagnosis: 50 months (range 16-149 months)
median platelet count at diagnosis: 9 x 10^9/l
(range 1-47 x 10^9/l)

IVIG = intravenous immunoglobulins; PDN = prednisone.

from "wait and see" management, because of the occurrence of important hemorrhagic symptoms and/or because of a drop in platelet count to below 10 x 10^9/l, or because no signs of spontaneous remission could be noticed despite a quite long wait (at least 10 days). Twenty-six of these 35 patients received IVIG 400 mg/kg/d for 5 days (19/26 responded), and 9 received oral steroid therapy (5/9 responded).

Seventeen (60.7%) of the 28 patients of group B, who had been treated with IVIG, responded within a median time of 6 days (range) from the start of treatment and just one (5.8%) relapsed 20 months after initial response. The median follow up in group B is 39 months (Table 2).

The 11 patients who did not responde to IVIG received steroid therapy and all but one responded.

Twelve (75%) of the 16 patients of group C, treated with oral PDN, showed a response within a median time of 15 days from the start of treatment (range 5-58 days). Of the 12 responders only one (8.3%) relapsed 15 months after initial response. The median follow up from diagnosis for group C patients is 50 months (Table 2).

Four of the 16 patients, who did not respond to conventional oral steroid therapy, were subsequently treated: 2 patients with high dose methylprednisolone, successfully, and 2 patients with IVIG without response.

No serious adverse effect could be observed with any of the treatments. Most children treated with oral prednisone showed slight weight gain. No reactions, such as fever, nausea, vomiting, headache, nor anaphylactic reactions, could be observed with IVIG. None of the non treated patients (group A) had life-threatening hemorrhages.

Discussion

AITP in children is generally a benign and self-limiting disease with spontaneous recovery in over 70% of the cases [1, 2, 10, 11, 17]. Treatment for children with ITP is essentially aimed at preventing important hemorrhages, such as CNS bleeding, although this is a rare event (less than 1% of patients with a platelet count lower than 20 x 10^9/l) [6, 7].

The debate over treatment *versus* no treatment is still unresolved, because of the high frequency of spontaneous remissions without therapy, the low morbidity and mortality of AITP, the ineffectiveness of treatment in about 30-40% of the cases, and the possibility of relapse after initial response in 10-20% of the cases [1, 2, 17, 20].

Furthermore the questions whether early treatment is better and which course of therapy for AITP would be optimal are still debated, since there is no evidence of the superiority of one type of therapy over another, nor does it seem possible to define the time in the natural course of the illness at which starting treatment will modify the outcome.

Treatment for AITP is based on the assumption of an immune pathogenesis, and generally calls for the use of steroids, IVIG, anti-D Ig, and other immunosuppressive drugs.

Anti-D Ig are less effective than IVIG in raising the platelet count, and the possible occurrence of hemolytic anemia, as a side-effect, restricts its role in AITP therapy [2, 17, 21].

Table 2. - Results of different treatments

Type of therapy	Patients no.	Responders no. (%)	Median time for response	Relapses no. (%)	Median follow up
Group A (no therapy)	76	41 (53.9)	10 days (range: 2-55 d)	1/41 (2.4) (*)	50 months
Group B (IVIG 400 mg/kg/d x 5 d)	28	17 (60.7)	6 days (range: 3-13 d)	1/17 (5.8) (**)	39 months
Group C (oral PDN 1-1.5 mg/kg/d)	16	12 (75)	15 days (range: 5-58 d)	1/12 (8.3) (***)	50 months

IVIG = intravenous immunoglobulins; PDN = prednisone; (*) 1 relapse 45 months after initial response; (**) 1 relapse 20 months after initial response; (***) 1 relapse 15 months after initial response.

The results reported have been obtained from a retrospective evaluation of a rather large unicentric collection of 120 pediatric cases, with a long follow up (up to fifty months); patients were not randomized to different treatments; they received different management of AITP at diagnosis, according to the clinical features of their illness; no patients had previously been treated for AITP.

We have defined a response using quite severe criteria, both as to the platelet count (not less than 100 x 10^9/l) and to the duration (at least three weeks), thus excluding short-term and not significant responses.

We did not find a significant difference in response with or without treatment ($p = 0.32$). Nor did we find significant differences between patients treated with continuous oral prednisone at standard dosage (1-1.5 mg/kg/d) and patients treated with IVIG ($p = 0.47$). We observed, however, that the rise in platelet count is faster with IVIG than with oral PDN (median day of response 6 *vs* 15), as already reported in the literature [17, 20, 21].

Neither with IVIG nor with oral PDN did we observe significant side effects. Moreover we did not observe life-threatening hemorrhages among the 76 patients who did not receive any treatment.

The differences in the percentages of relapses observed within each of the three groups of patients examined, are not significant, because of the small number of patients in each group.

In our experience we also observed that patients who do not respond to one type of treatment may subsequently respond to another, i.e. non-responders to oral conventional dose PDN may subsequently respond to IVIG or to high-dose steroid therapy; analogously patients who have not responded to IVIG may still respond to high dose steroids.

In the literature similar percentages of responses are reported both with steroid therapy and with IVIG, but the time for response is evidently shorter with IVIG than with oral steroids [16, 17, 20, 21].

In 1993 Blanchette *et al.* [17] reported the results of 53 patients randomized to no therapy, IVIG, and oral prednisone; the mean time necessary to reach a platelet count of at least 50 x 10^9/l was significatively different between treated and non treated patients.

No major hemorrhages were reported in any group of patients; however the number of patients would be too low to evaluate the incidence of major bleeding events in the different groups.

Our results fit the data in the literature about the effectiveness of standard steroid therapy and IVIG [16-18, 20-25]. Comparison with the results of other studies is otherwise difficult, because the definition of response criteria is not univocal.

The decision to treat AITP at diagnosis also has to take into account the discomfort and drawbacks for the patients and their families, resulting from possible hospitalization, possible side-effects of the treatment, and cost of the therapy.

One might argue that it is impossible to compare the outcome in differently treated groups of patients if the allocation to groups was on the basis of clinical evaluation of the hemorrhagic risk. But this is what in fact happens most of the times in the practice. The choice of not to treat a little patient with AITP can be made, provided the hemorrhagic risk is low.

The "wait and see" approach is possible and appropriate when no conditions exist which make the hemorrhagic risk too high, such as the presence of many and/or large increasing cutaneous and/or mucosal hemorrhages, high fever, infections in progress, surgical operations, anamnesis of recent traumas (above all head injury), onset of neurological symptoms, arteriovenous malformations, rise in blood pressure, and platelet count below 10 x 10^9/l.

In our case histories the mean platelet count at diagnosis is somewhat higher in group A than in the other two groups: 19 x 10^9/l *vs* 9 x 10^9/l, and other authors also report a higher mean platelet count at diagnosis among not treated patients [10, 11].

There is general agreement that treatment should be started with a platelet count below 10 x 10^9/l, since such a low platelet count is generally associated with a high hemorrhagic risk and the presence of important bleeding; otherwise, if the platelet count is over 10 x 10^9/l, it is the occurrence of serious hemorrhages that mainly affects the decision to start treatment [1].

In the literature up to 87% of spontaneous remissions are reported within a time of 2 to 8 weeks from onset, most of them within the first 4 weeks. It is, in any case, unadvisable to wait without treatment for a long period of time, since the longer the time the patient remains with a low platelet count, the higher the likelihood of events which may cause serious hemorrhages (such as trauma, infections, sudden rise in blood pressure, etc.).

According to us one should wait at least ten days, since there are reports of about 50% spontaneous remissions within this time [19].

Large clinical trials randomized to treatment *versus* no treatment are difficult to perform, because of the large number of cases required to define the effectiveness of therapy in preventing intracranial hemorrhages, which has a very low incidence, and because of ethical problems.

In any case most American haematologists now recommend the use of IVIG 1 g/kg as first-line therapy for patients with life-threatening hemorrhages, regardless of the platelet count [1].

As to cost/benefit ratio we suggest that since steroids or waiting without treatment (and without hospitalization, when feasible, depending upon family's reliability) are much less expensive than IVIG, the use of IVIG should be restricted to cases where the need of raising the platelet count as soon as possible exists.

More recently high dose prednisone or methylprednisolone have been employed as first line-therapy of AITP [27, 28] and have proved to be able to

raise the platelet count as fast as IVIG and significatively faster than oral prednisone at conventional doses [17, 18, 21, 22, 25, 29]. Higher doses of methylprednisolone, and above all dexamethasone, may achieve prompt and good responses even in patients who have not responded to different previous treatments, and in patients with resistant chronic ITP. The cost of high dose steroids is much lower than IVIG.

Furthermore, side effects of steroid therapy can mostly be observed with prolonged treatments, regardless of the dosage.

High dose steroid therapy is therefore a good first therapeutic approach, since it may give results similar to IVIG as to percentages and rapidity of responses, and with significantly lower costs and no side-effects.

Finally, considering that AITP is generally a benign disease with a high percentage of spontaneous recovery, and also with a view to the quality of life of the little patients, we suggest that treatment of AITP, when necessary, should be individualised depending on the possibility of relying on the family's collaboration and effecting a careful clinical and hematological survey, without a great discomfort for the patient.

Received on 25 February 1997.
Accepted on 15 June 1998.

REFERENCES

1. GEORGE, J.N., WOOLF, S.H., RASKOB, G.E., WASSER, J.S., ALEDORT, L.M., BALLEM, P.J., BLANCHETTE, V.S. *et al.* 1996. Idiopathic thrombocytopenic purpura: a practice guideline developed by explicit methods for the American Society of Hematology. *Blood* **88**: 3-40.

2. SCHULTZ BEARDSLEY, D. 1993. Platelet abnormalities in infancy and childhood. In: *Hematology of infancy and childhood.* D.G. Nathan & F.A. Oski (Eds). W.B. Saunders Company, Philadelphia. p. 1561-1604.

3. KAUFMAN, D.W., KELLY, J.P., JOHANNES, C.B., SANDLER, A., HARMON, D., STOLLEY, P.D. & SHAPIRO, S. 1993. Acute thrombocytopenic purpura in relation to the use of drugs. *Blood* **82**: 2714-2718.

4. KELTON, J.G. & POWERS, P.J. 1982. A prospective study of the usefullness of the measurement of platelet associated IgG for the diagnosis of aITP. *Blood* **60**: 1050-1053.

5. GUGLIOTTA, L., ISACCHI, G. & GUARINI, A. 1981. Chronic idiopathic thrombocytopenic purpura sequestration and results of splenectomy. *Scand. J. Haematol.* **26**: 407-412.

6. WOERNER, S.J., ABILDGAARD, C.F. & FRENCH, B.N. 1981. Intracranial hemorrhage in children with idiopatic thrombocytopenic purpura. *J. Pediatr.* **67**: 453-460.

7. REID, M.M. 1995. Chronic idiopathic thrombocytopenic purpura: incidence, treatment and outcome. *Arch. Dis. Child.* **72**: 125-128.

8. TAMARY, H., KAPLINSKY, C., LEVY, I., COHEN, I.J., YANIV, I., STARK B., GOSHEN, Y. & ZAIVOV, R. 1994. Chronic childhood idiopathic thrombocytopenic purpura: long term follow up. *Acta Paediatr.* **83**: 931-934.

9. LAMMI, A.T. & LOVRIC, V.A. 1973. Idiopathic thrombocytopenic purpura: an epidemiologic study. *J. Pediatr.* **83**: 31-36.

10. LUSHER, J.M. & ZUELZER, W.W. 1966. Idiopathic thrombocytopenic purpura in childhood. *J. Pediatr.* **68**: 971-979.

11. RAMOS, M.E.G., NEWMAN, A.J. & GROSS, S. 1978. Chronic thrombocytopenia in childhood. *J. Pediatr.* **92**: 584-586.

12. ROBB, L.G. & TIEDEMAN, K. 1990. Idiopathic thrombocytopenic purpura: predictors of chronic disease. *Arch. Dis. Child.* **65**: 502-506.

13. SIMONS, S.M., MAIN, C.A., YAISH, H.M. & RUTZKY, J. 1975. Idiopathic thrombocytopenic purpura in children. *J. Pediatr.* **87**: 16-22.

14. LILLEYMAN, J.S. 1983. Management of childhood idiopathic thrombocytopenic purpura. *Br. J. Haematol.* **54**: 11-14.

15. LICHTIN, A. 1996. The ITP practice guideline: what, why, and for whom? *Blood* **88**: 1-2.

16. MEDEIROS, D. & BUCHANAN, G.R 1996. Current controversies in the management of idiopathic thrombocytopenic purpura during childhood. *Pediatr. Hematol.* **43**: 757-772.

17. BLANCHETTE, V.S., LUKE, B., ANDREW, M., SOMMERVILLE-NIELSEN, S., BARNARD, D., DE VEBER, B. & GENT, M. 1993. A prospective randomized trial of high dose intravenous immune globulin G therapy, oral prednisone therapy, and no therapy in childhood acute immune thrombocytopenic purpura. *J. Pediatr.* **123**: 989-995.

18. MORI, P.G., LANZA, T., MANCUSO, G., DE MATTIA, D., CATERA, P., MIANO, C., DEL PRINCIPE, D., FAVARETO, F., MICALIZZI, C., BOERI, E. & ROSATI, D. 1988. Treatment of acute idiopathic thrombocytopenic purpura (aITP): a Cooperative Italian Study Group Results. *Pediatr. Haematol. Oncol.* **5**: 55-64.

19. BUCHANAN, G.R. 1987. The nontreatment of childhood idiopathic thrombocytopenic purpura. *Eur. J. Pediatr.* **146**: 107-112.

20. BLANCHETTE, V., IMBACH, P. & ANDREW, M. 1994. Randomised trial of intravenous immunoglobulin G, intravenous anti-D, and oral Prednisone in childhood acute immune thrombocytopenic purpura". *Lancet* **i**: 703-707.

21. IMBACH, P., BERCHTOLD, W. & HIRT, A. 1985. Intravenous immunoglobulin versus oral corticosteroids in acute immune thrombocytopenic purpura in childhood. *Lancet* **i**: 464-468.

22. BUCHANAN, G.R. & HOLTKAMP, C.A. 1984. Prednisone therapy for children with newly diagnosed idiopathic thrompocytopenic purpura. A randomized clinical trial. *Am. J. Pediatr. Hematol. Oncol.* **6**: 355-361.

23. MC WILLIAMS, N.B. & MAURER, H.M. 1979 Acute idiopathic thrombocytopenic purpura in children. *Am. J. Hematol.* **7**: 87-96.

24. OZSOYLU, S., SAYLI, T.R. & ERTURK, G. 1993. Oral megadose methylprednisolone versus intravenous immunoglobulin for acute childhood idiopathic thrombocytopenic purpura. *Pediatr. Hematol. Oncol.* **10**: 317- 321.

25. SARTORIUS, J.A. 1984. Steroid treatment of idiopathic thrombocytopenic purpura in children. Preliminay results of a randomized cooperative study. *Am. J. Pediatr. Hematol. Oncol.* **6**: 165-169.

26. OZSOYLU, S., IRKEN, G. & KARABENT, A. 1989. High dose intravenous methylprednisolone for acute childhood thrombocytopenic purpura. *Eur. J. Haematol.* **42**: 431-435.

27. OZSOYLU, S. & ERTURK, G. 1991. Oral megadose methylprednisolone for childhood acute thrombocytopenic purpura. *Blood* **77**: 1856-1857.

28. ALBAYRAK, D., ISLEK, I., KALAYEI, A.G. & GURSES, N. 1994. Acute immune thrombocytopenic purpura: a comparative study of very high oral doses of methylprednisolone and intravenously administered immune globulin. *J. Pediatr.* **125**: 1004-1007.

29. ANDERSEN, J.C. 1994. Response of resistant idiopathic thrombocytopenic purpura to pulsed high dose dexamethasone therapy. *N. Engl. J. Med.* **330**: 1560-1564.