# The course of severe autoimmune thrombocytopenia in patients not undergoing splenectomy

Thomas Sailer
Klaus Lechner
Simon Panzer
Paul Alexander Kyrle
Ingrid Pabinger

**Background and Objectives.** Splenectomy is the most effective treatment for patients with severe autoimmune thrombocytopenia (AITP) who do not have a spontaneous or drug- induced remission. However, this treatment has some short and long term risks. There is no consensus on the indications and optimal timing of splenectomy, since it is unknown up to which time from onset of symptoms a remission can be expected without splenectomy.

**Design and Methods.** We studied the incidence of complete or partial remissions in a cohort of 114 adult patients (68 women, 46 men, median age 49.8 years, interquartile range 28.3-68.4) with severe AITP (platelet count < $20\times10^9$/L at diagnosis) using Kaplan Meier analysis. Patients who underwent splenectomy during the observation period were censored at the time of splenectomy.

**Results.** The probability of a complete remission was 61% and that of at least a partial remission was 86% at 5 years. The incidence of complete remission was highest within the first 6 months (30%), but increased up to 53% between 6 months and 3 years after diagnosis. The probability of a remission was not related to age, gender, or the presence or absence of platelet antibodies, but was higher in patients with an acute onset of symptoms in comparison to those with an insidious onset ($p$=0.0003). The chance of a late remission was higher in patients with an insidious onset of disease.

**Interpretation and Conclusions.** These data indicate that splenectomy may be delayed for up to 3 years, in particular in those patients whose AITP has had an insidious onset.

Key words: autoimmune thrombocytopenia, late remission, platelet antibodies, splenectomy

Haematologica 2006; 91:1041-1045



*From the Department of Internal Medicine I, Division Haematology and Haemostaseology (TS, KL, PAK, IP); Clinic for Blood Group Serology, Medical University of Vienna, Austria (SP).*

*Correspondence:*
*Ingrid Pabinger, Department of Internal Medicine I, Division Haematology and Haemostaseology, Medical University of Vienna, 1090 Vienna, Währingergürtel 18-20, Austria. E-mail: ingrid.pabinger@meduniwien.ac.at*

Adult autoimmune thrombocytopenia (AITP) is a heterogeneous disease. It affects mainly women and its severity ranges from very severe, requiring intensive treatment, to mild without need of therapy. The clinical onset may be dramatic with severe bleeds or may be insidious with a slow development of mild bleeding symptoms or no bleeding. The standard first line treatments in patients with platelet counts of less than $20\text{-}30\times10^9$/L and hemorrhage are steroids or high-dose immunoglobulins. With this treatment platelet counts often increase and the bleeding symptoms can be controlled in most patients. However, when treatment is discontinued or the dosage is reduced only 30-40% of patients remain in complete remission after 3-12 months.[1-3] Many of these patients require continuous treatment with steroids and/or relatively toxic second or third line drugs. Therefore, splenectomy, which offers a 66% chance of complete remission,[4-6] is usually recommended. However, splenectomy is associated with both, short- and long-term risks, and the success rate is difficult to predict. Thus, the question of whether a patient failing drug treatment after 3-6 months has a fair chance of a remission without splenectomy within a reasonable period of time is very important. We addressed this question by retrospectively analyzing a group of adults patients with severe AITP over the course of their disease and a long follow-up.

## Design and Methods

The clinical records of all patients, who had been given the diagnosis of severe AITP between 1991 and 2001 and were treated at the Division of Hematology and Hemostaseology, Department of Internal Medicine I of the Medical University of Vienna, were analyzed retrospectively. The diagnosis was

**Table 1. Demographic and laboratory data of the patients at diagnosis.**

| *No. of patients* | *114* |
|---|---|
| Age* (years), | 49.8 (18.7–89.9) |
| Gender (female/male) | 68/46 |
| Platelet count* at diagnosis | $6\times10^9$/L (0-$20\times10^9$/L) |
| Onset (acute, insidious, unknown) | 44/67/3 |
| Autoantibody (IIb/IIIa; Ib/IX; both; none, not known) | 13/4/18/54/25 |
| Time to splenectomy* (months) | 9.3 (1.4–105.5) |
| Observation time* (years) | 3.3 (0.12–10.7) |

**Data are shown as median (range).*

**Table 2. Characteristics of untreated patients with severe AITP at onset of disease.**

| *Patient* | *Gender* | *Age (years)* | *Onset* | *Bleeding* | *Outcome* |
|---|---|---|---|---|---|
| 1 | Female | 78.6 | Insidious | Hematoma after trauma | PR |
| 2 | Female | 23.4 | Insidious | Petechia | CR |
| 3 | Female | 28.6 | Insidious | Hematoma | PR |
| 4 | Male | 61.9 | Insidious | No bleeding | PR |
| 5 | Male | 47.8 | Insidious | Hematoma, one petechia | PR |

based on standard criteria:[7] isolated thrombocytopenia, no other disease known to be associated with thrombocytopenia, such as human immunodeficiency virus infection, lymphoproliferative disease, liver disease or systemic lupus erythematosus and no evidence of drug induced thrombocytopenia. Only adult patients (age > 18 years) with a platelet count of <$20\times10^9$/L at diagnosis were included. Patients who were only seen once, mostly for diagnostic purposes, were not included. Cases with clinical records that were not complete enough to determine the time-point of remission were not eligible for evaluation. A total of 114 patients fulfilled the eligibility criteria and were included in this study. The demographic and laboratory data of the study population are presented in Table 1. The survival data of these patients have already been published by our group.[8]

### Treatment

Five patients received no treatment because they had only minor bleeding or refused treatment (Table 2). A total of 109 patients received the following first line treatments: 72 patients received only steroids (usually prednisolone at a dose of 1 mg/kg/day), nine received only high-dose intravenous immunoglobulin (0.5–2g/kg) and 28 a combination of both. The steroid dosage was tapered as soon as the bleeding ceased and the platelet count rose to a safe level. Steroids were continued at the lowest possible dose to keep the patient free of bleeds or until at least a partial remission was achieved. Only four patients received other immunosuppressive agents as second-line treatment (cyclosporine in three patients and azathioprine in one patient). Some non-responders with platelet counts between 10-$30\times10^9$/L who had no or only minor bleeding remained untreated. Splenectomy was performed in 27 patients who failed to achieve a sustained remission after medical therapy. The median time to splenectomy was 9.3 months (range 1.4-105.5 months).

### Methods

EDTA-anticoagulated blood was used for the determination of platelet counts (Sysmex 2000, Tao, Kobe, Japan), and isolation of platelets for their investigation by direct monoclonal antibody-specific immobilization of platelet antigens (MAIPA)[9] for *in vivo* bound antibodies using the following monoclonal antibodies for immunoprecipitation: anti-CD41a (GPIIb/IIIa, clone P2, Immunotech, Marseille, France) and anti-CD42a (GPIb/IX, clone FMC-25, Serotec, Oxford, England), Platelets were considered to be coated by antibodies if the changes in optical density (ΔOD: optical density after subtraction of blank) was >0.070, which is the mean+3SD from the values in negative controls.

### Definitions

Acute onset of AITP was defined as the sudden appearance of any of the following bleeding symptoms: petechial rash, large hematomas, nose bleeds, hematuria, gastrointestinal and/or cerebral bleeding lasting for less than one week. An insidious onset was defined by the absence of these symptoms and a slow onset, although the presence of single petechiae and small hematomas was compatible with an insidious onset. A complete and partial remission were defined as a platelet count of >$100\times10^9$/L and between 30 and $100\times10^9$/L, respectively, sustained for at least 1 month after the cessation of treatment. A durable remission up to the end of the observation period was described as continuous complete or continuous partial remission. Patients, who achieved no remission after splenectomy were classified as having chronic refractory AITP. Relapse was defined as a fall of the platelet count to less than $30\times10^9$/L. The probabilities of a first complete remission and complete and partial remission were estimated by Kaplan Meier analysis. Data were censored at the time of the last visit or at the time of splenectomy. The log-rank test was applied to compare the probabili-

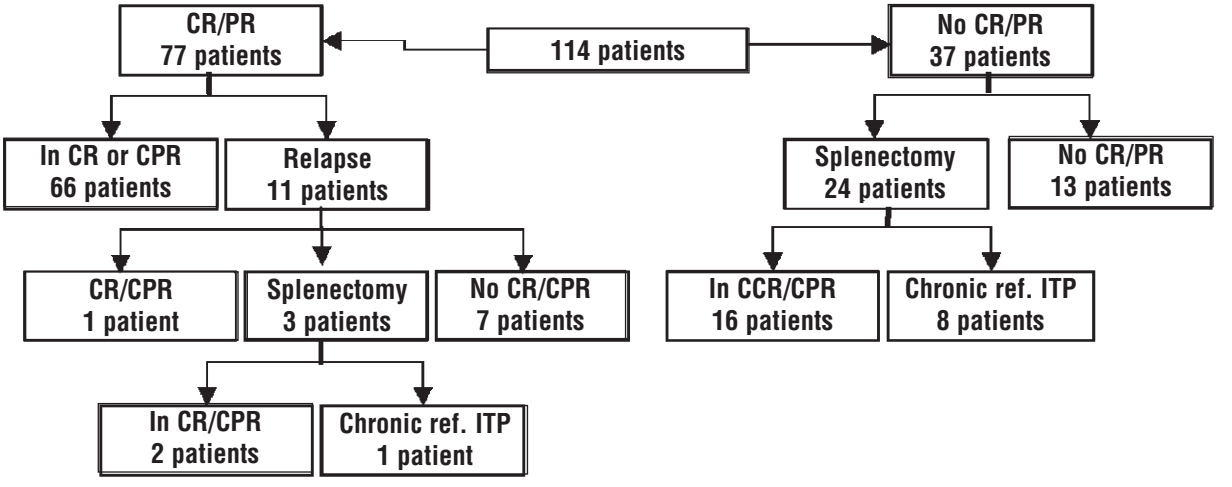


**Figure 1.** Overall outcome of the 114 adult patients with ITP. CR: complete remission; PR: partial remission; CCR: continuous complete remission; CPR: continuous partial remission; ref. refractory.

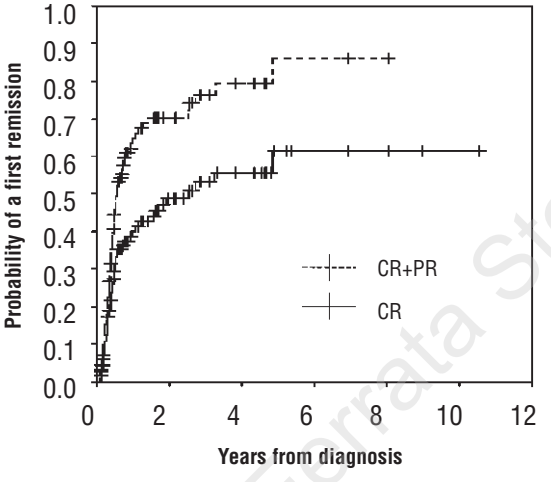


**Figure 2.** Probability of a first remission in 114 adult patients with severe AITP. Splenectomized patients were censored at the time of splenectomy. CR: complete remission; PR: partial remission.

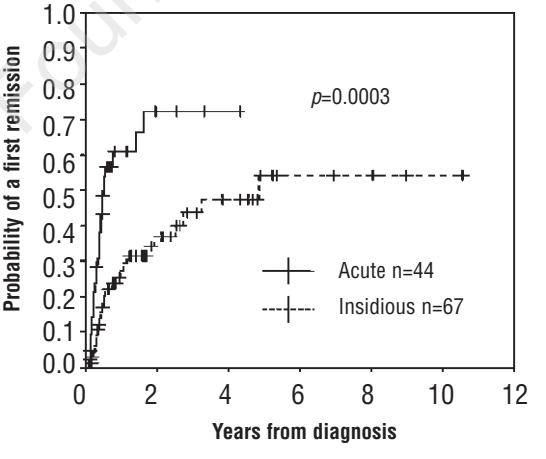


**Figure 3.** Probability of a first complete remission according to the type of onset (insidious versus acute). Splenectomized patients were censored at the time of splenectomy.

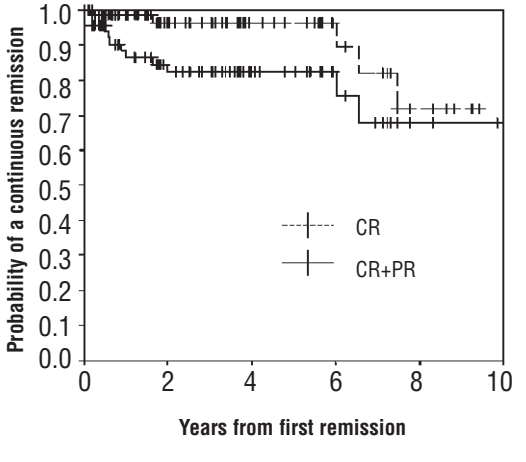


**Figure 4.** The probability of a continuous complete and continuous complete and partial remission in patients who had achieved a CR or PR without splenectomy. : CR: complete remission; PR partial remission.

ties of remission between groups. A $p$-value of <0.05 was regarded as statistically significant. All calculations were performed using the Statistical Package of Social Science (SPSS 11.5).

## Results

The overall outcome of the disease in the 114 patients over the whole observation period is shown in Figure 1. At 6 months 28 and 15 patients were in a complete and partial remission, respectively. In six patients the observation time was less than 6 months and another six underwent splenectomy within the first 6 months from diagnosis. The remaining 59 patients were non-responders at 6 months. Out of the 28 patients with complete remission at 6 months, 19 had continuous complete remissions and one experienced a relapse to a partial remission in the period between 6 months and 3 years after diagnosis. The observation time for the remaining eight patients was less than 3 years. Of the 15 patients in partial remission at 6 months, five had a continuous partial remission and four experienced a relapse. For six patients the observation time was less than 3 years. The probability of a complete remission was 30% in patients receiving first line therapy and that of a complete and partial remission 44% at 6 months from diagnosis. Within the time from 6 months to 3 years, 17 additional patients (without splenectomy) achieved a complete remission and eight additional patients had a partial remission. The Kaplan Meier curve (Figure 2) shows two parts with different slopes. In the first part (0–6 months) the incidence of complete remission was 5%/month and in the second part (6 months to 3 years) it was 0.5%/month. Beyond 3 years new remissions were rare. Altogether, patients who did not undergo splenectomy had a cumulative probability of a complete remission of 61% and of complete and partial remission of 86% at 5 years (Figure 2).

There was no difference in the complete and partial remission rate and the slope of the remission curves between females and males ($p$=0.988 for complete remission rate and $p$=0.24 for complete + partial remission rate) or between older (> 60 years) and younger patients ($p$=0.415 for complete remission rate and $p$=0.931 for complete + partial remission rate). However, the complete remission rate and the slope of the remission curve was different between patients with acute or insidious onset of disease (Figure 3). In patients with insidious onset the overall complete remission rate was lower and the remissions occurred later. The incidence of complete remission was 3 %/month during the first 6 months and 0.8 %/month from 6 months to 3 years after diagnosis. In patients with acute onset almost all remissions occurred within 1 year.

There was no difference in the probability or the time to remission between patients with or without detectable plateled antibodies ($p$=0.468 for complete remission rate and $p$=0.988 for complete + partial remission rate). Almost all patients who achieved a complete remission sustained this status for 5 years; however, there were some late relapses after 5 years. In patients with at least a partial remission the remissions were less stable (Figure 4).

## Discussion

Severe adult AITP may be associated with dramatic clinical symptoms at onset, but several studies have shown that - if treated properly - it is a relatively benign disease.[10] Death from bleeding is rare, but complications or death from (over-) treatment may be less rare.[8,11] The efficacy and side effects of first-line therapies (steroids or high dose immunoglobulin) have been extensively studied in randomized trials.[2,3] About 50% to 75% of patients do not achieve a complete or partial remission and most of these require further treatment. Our short term (6 months) results after first-line therapy were similar to those reported by others.

Splenectomy is the most effective second-line treatment and has a success rate of 66%.[4,5] The mortality of this procedure is very low, but postoperative morbidity may be considerable, even with laparoscopic surgery. Moreover, despite prophylactic vaccination, overwhelming septicemia, although rare, is a highly feared complication. In addition, the chance of success is difficult to predict.[5] Therefore, a decision to perform a splenectomy is not easy and there are no evidence-based recommendations available on the optimal timing of splenectomy. In many institutions splenectomy is recommended if the patient still has severe steroid-dependent thrombocytopenia after a trial with steroid or high-dose immunoglobulins after 6 weeks to 6 months from diagnosis.[1] These time points may have been chosen because a spontaneous or steroid-induced complete or partial remission is regarded as unlikely thereafter. However, this assumption is not based on good evidence. Cooper *et al*. showed that treatment with anti-D antibody and delaying splenectomy resulted in sustained remissions in 12 out of 28 patients (42%) in a small group of steroid-refractory patients.[12] Our data confirm and extend this observation in a larger number of patients. We show that between 6 months and 3 years after diagnosis patients with AITP have a chance of obtaining remissions during treatment with or without low-dose steroids. This was particularly the case for patients whose disease had had an insidious onset. Thus, splenectomy may be delayed in patients with insidious onset of thrombocytopenia whereas the chance of a late remission is much lower those with acute onset of thrombocytopenia. Other factors, such as

sex, age and the presence of a plateled antibody did not predict for late responses in our patients.

We are aware of the limitations of this study. The study was retrospective and the decision whether or not to perform splenectomy was not predetermined, not prospective and not randomized. The classification according to the mode of onset (acute, insidious) is prone to error, in particular in a retrospective analysis. Furthermore, we did not determine platelet antibodies in all patients, since this was not a requirement for the diagnosis. It is unlikely that a randomized study comparing splenectomy with drug therapy will be performed as long as no novel and effective drugs are available. Thus, in the absence of data from randomized studies, our results, combined with the data of Cooper[12] seem to indicate that postponing splenectomy in patients without early remission may be justified in some patients and may help to avoid splenectomy. A patient who achieves a complete or partial remission without splenectomy is certainly in a better situation than a splenectomized patient.

Despite the limitations of our study we believe that our data provide some evidence that delaying splenectomy until 3 years after diagnosis may be justified in selected patients.

*KL, TS and IP contributed to the study design, conduction, analysis, interpretation of results and writing; TS also contributed to statistical analysis and data entry, IP and PAK contributed in patient managment, SP performed investigation of platelet antibodies and contributed in writing. The manuscript was approved by all authors, who also declare that they have no potential conflicts of interest. Data on survival on the same group of patients were published in 2003: Sailer T, Weltermann A, Zoghlami C, Kyrle PA, Lechner K, Pabinger I. Mortality in severe, non aggressively treated adult autoimmune thrombocytopenia. Hematol J 2003;4:366-9. Manuscript received March 14, 2006. Accepted June 14, 2006.*



## References


1. Stasi R, Stipa E, Masi M, Cecconi M, Scimo MT, Oliva F, et al. Long-term observation of 208 adults with chronic idiopathic thrombocytopenic purpura. Am J Med 1995;98:436-42.
2. Bellucci S, Charpak Y, Chastang C, Tobelem G. Low doses v conventional doses of corticoids in immune thrombocytopenic purpura (ITP): results of a randomized clinical trial in 160 children, 223 adults. Blood 1988;71:1165-9.
3. Godeau B, Chevret S, Varet B, Lefrere F, Zini JM, Bassompierre F, et al. Intravenous immunoglobulin or high-dose methylprednisolone, with or without oral prednisone, for adults with untreated severe autoimmune thrombocytopenic purupura: a randomised, multicentre trial. Lancet 2002; 359:23-9.
4. Vianelli N, Galli M, de Vivo A, Intermesoli T, Giannini B, Mazzucconi MG, et al. Efficacy and safety of splenectomy in immune thrombocytopenic purpura: long-term results of 402 cases. Gruppo Italiano per lo Studio delle Malattie Ematologiche dell'Adulto. Haematologica 2005; 90:72-7.
5. Kojouri K, Vesely SK, Terrell DR, George JN. Splenectomy for adult patients with idiopathic thrombocytopenic purpura: a systematic review to assess long-term platelet count responses, prediction of response, and surgical complications. Blood 2004; 104:2623-34.
6. Rintelen-Zoghlami C, Weltermann A, Bittermann C, Kyrle PA, Pabinger I, Lechner K, et al. Efficacy and safety of splenectomy in adult chronic immune thrombocytopenia. Ann Hematol 2003; 82:290-4.
7. George JN, Woolf SH, Raskob GE, Wasser JS, Aledort LM, Ballem PJ, et al. Idiopathic thrombocytopenic purpura: a practice guideline developed by explicit methods for the American Society of Hematology. Blood 1996; 88: 3-40.
8. Sailer T, Weltermann A, Zoghlami C, Kyrle PA, Lechner K, Pabinger I. Mortality in severe, non aggressively treated adult autoimmune thrombocytopenia. Hematol J 2003;4:366-9.
9. Kiefel V, Santoso S, Weisheit M, Mueller-Eckhardt C. Monoclonal antibody-specific immobilization of platelet antigens (MAIPA): a new tool for the identification of platelet-reactive antibodies. Blood 1987;70:1722-6.
10. Vianelli N, Valdre L, Fiacchini M, Vivo M, Gugliotta L, Catani L, et al. Long-term follow-up of idiopathic thrombocytopenic purpura in 310 patients. Haematologica 2001;86:504-9.
11. Portielje JE, Westendorp RG, Kluin-Nelemans HC, Brand A. Morbidity and mortality in adults with idiopathic thrombocytopenic purpura. Blood 2001;97:2549-54.
12. Cooper N, Woloski BM, Fodero EM, Novoa M, Leber M, Beer JH, et al. Does treatment with intermittent infusions of intravenous anti-D allow a proportion of adults with recently diagnosed immune thrombocytopenic purpura to avoid splenectomy? Blood 2002; 99: 1922-7.