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# Idiopathic Thrombocytopenic Purpura in Elderly Patients: A Two-center Retrospective Study of 41 Cases

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## Abstract

**Objective:** This work aimed to report our observations on idiopathic or immune thrombocytopenic purpura (ITP) in elderly patients.

**Patients and Methods:** We retrospectively reviewed a cohort of 41 consecutive elderly ITP patients (≥65 years old) in two ITP reference centers, namely the university hospital groups of Strasbourg and Reims, France. We particularly analyzed patient clinical characteristics, along with the therapies used and side-effects, and patient response rates.

**Results:** The mean age of the 41 patients was 76.7 years (range: 65-91), 21 (51%) were older than 75 years and 27 were female. Initial presentations included the following: thrombocytopenia revealed by routine blood count or bleeding limited to the skin in 27 cases (66%); severe cutaneous bleeding or visceral bleeding in one or more other sites in 14 (34%). The mean platelet count was 34.4 x $10^9$/L (range: 1-120). Spontaneous remission and complete response under therapy were reported in eight patients (20%) and 33 (80%) still exhibited chronic ITP at time of writing. There were three deaths during long-term follow-up. After 6 months, the response rate was 35% with corticosteroids, 50% with splenectomy, and 40% with danazol. Side-effects were reported in 100% of elderly ITP patients, with 60% and 50% corresponding to corticosteroids and danazol, respectively. The response rate to biological agents, namely rituximab and thrombopoietin (TPO) receptor agonists, was 80%, with no adverse effects observed.

**Conclusions:** Our results confirm that age influences the hemorrhagic pattern of ITP expression as well as responses to and adverse effects of conventional ITP therapies.

**Keywords:** Idiopathic thrombocytopenic purpura; Immune thrombocytopenic purpura; Primary immune thrombocytopenia; Elderly; Age; Treatment

## Introduction

Idiopathic or immune thrombocytopenic purpura (ITP), also currently called primary immune thrombocytopenia (PIT), is defined as the presence of an isolated low platelet count (thrombocytopenia) with no bone marrow abnormalities, in the absence of any other causes of thrombocytopenia [1,2].

ITP is an autoimmune disease involving the peripheral and central opsonization of platelets by auto-antibodies, which are directed against different surface glycoproteins and cause their premature destruction by the reticulo-endothelial system [1]. Recent research indicates that an impaired production of the glycoprotein hormone thrombopoietin (TPO), which serves to increase platelet production, may contribute to the reduction in circulating platelets [3].

The etiology of ITP in adults is as yet unknown, with ITP diagnosis based solely on exclusion of other causes, and its clinical course is variable and unpredictable [1,4]. Although this disease is considered to be primarily observed in young adults, with females predominantly affected, ITP does occur in the elderly [5,6].

In this report, we describe our observations on ITP in elderly patients.

## Patients and Methods

### Patient selection

This study was conducted retrospectively, involving 41 elderly patients ≥65 years old who had been consecutively diagnosed with ITP in the period of 2008 to 2015 at the Department of Internal Medicine of the Strasbourg University Hospital (France) and the Department of Geriatric and Internal Medicine of the Reims University Hospital (France), both of which are ITP reference centers in France.

ITP diagnosis was primarily based on patient history, physical examination, complete blood cell count, and analysis of both peripheral venous blood smear and bone marrow aspiration [6,7]. All patients exhibited a platelet count <150 x $10^9$ /l for at least two consecutive blood counts and presented no other clinical or biological findings to account for this. We excluded cases with no idiopathic immune thrombocytopenia [6,7], such as those induced by drugs, infectious agents, or related to other diseases like systemic lupus erythematosus, antiphospholipid syndrome, lymphoma, or myelodysplasia.

### Study procedure

We performed a retrospective analysis of the 41 consecutive patients that met inclusion criteria. Partial data of these 41 patients has already featured in the French congress of Internal Medicine [8]. All the analyzed data was obtained from patient medical files, in addition to patient information gathered from relatives or personal physicians.

For each case, the following information was collected: age, gender, and clinical characteristics; complete blood count and bone marrow aspiration analysis; drugs administered, including dose, administration method, start and withdrawal date, and potential side-effects; outcome; mortality rate.

### Bleeding severity

Bleeding severity was classified into four categories as follows: 0=no bleeding; 1=petechiae; 2=ecchymosis or dripping with moderate blood loss; 3=bleeding of mucous membranes with copious blood loss without sequellae; 4=bleeding of mucous membranes or the parenchyma with debilitating blood loss and sequellae [9].

### Response criteria

We analyzed patient responses to the following different therapies: corticosteroids, intravenous immunoglobulin, splenectomy, dapsone, danazol, rituximab, and platelet hematopoietic growth factors (TPO agonists).

The criteria for response to treatment were categorized as follows: (1) complete response (CR) corresponding to when the platelet count reached the normal level (>150 x $10^9$/L) following treatment; (2) partial response (PR) corresponding to platelet counts of between 50 and 150 x $10^9$ /L following treatment; (3) no response (NR) corresponding to platelet counts <50 x $10^9$ /L following treatment [9,10]. Patients with an initial platelet count <50 x $10^9$/L were also categorized as PR if the platelet number doubled following treatment.

## Results

### Patient characteristics

A total of 41 patients aged ≥65 years old were analyzed. The mean age was 76.7 years (range: 65-91) and 21 (51%) were over 75 years of age. The female-male ratio in this population was 27/24.

The initial presentations included: thrombocytopenia revealed by routine blood count or bleeding limited to the skin (bleeding score between 0 to 2) in 27 cases (66%) and severe cutaneous bleeding or visceral bleeding (potentially life-threatening) in one or more other sites (bleeding score ≥3) in 14 (34%) (Table 1). On diagnosis, 14 patients (30%) were found to have a bleeding severity score of 3 or 4. The mean platelet count was 34.4 x $10^9$ /L (range: 1-120).

Twelve patients (29%) were receiving anticoagulant or antiplatelet agents due to cardiac disease.

| Clinical manifestations | Number of patients |
|---|---|
| Asymptomatic | 17 (41%) |
| Cutaneous purpura | 17 (41%) |
| Epistaxis, gingivorrhagia or conjunctival hemorrhage | 7 (17%) |
| Gastrointestinal hemorrhage | 5 (12%) |
| Macroscopic hematuria | 5 (12%) |
| Hemorrhagic bullae in the oral cavity | 3 (7%) |
| Brain hemorrhage | 1 (2%) |
| Metrorrhagia | 1 (2%) |
| Bleeding score <3<br>Bleeding score >3 | 27 (66%)<br>14 (34%) |

**Table 1:** Characteristics of the 41 elderly ITP patients.

### Response to treatment and adverse effects

Four patients (10%), referred to the hospital for either isolated thrombocytopenia detected on routine laboratory examination or mild purpura, were treatment-free during a follow-up period of 24 months. These patients exhibited spontaneous remission.

A total of 37 patients (90%) required at least first-line therapy or between two and five lines of therapy during follow-up.

Corticosteroid therapy with prednisone or prednisolone was the initial treatment administered to 23 patients (56%). Oral corticosteroids were administered to 17 patients at a daily dose ranging from 0.25 to 1 mg/kg/j, with the dose then being gradually decreased. Six patients were treated with a methylprednisolone bolus of 0.25 to 0.5 g/day for 3 consecutive days, then switched to oral corticosteroids. Some response (CR+PR) was initially obtained in 21 patients (91%), with the remaining two exhibiting no response at all. Only eight patients (35%) were responders (CR+PR) after 6 months of follow-up (Table 2).

Adverse effects were reported relating to corticosteroid therapy in 20 patients (87%). These consisted primarily of: fluid retention and hypertension (n=11 [55%]); psychiatric complications (n=6 [30%]), bacterial infections (n=6 [30%]), and diabetes mellitus (n=3 [15%]).

Six patients (16%) received intravenous immunoglobulins as initial treatment, administered at 2 g/kg/course. No response was noted at 6 months (Table 2) and no adverse effects were reported.

One patient, who presented with ITP and a mean platelet count of 78 x $10^9$ /L, was initially treated with dapsone due to his receiving anticoagulation therapy related to atrial fibrillation. He exhibited PR at 6 months, with no adverse effects observed.

Danazol was administered at a mean daily dose of 400mg to five patients (12%), as first-line therapy for three of them. Although this therapy initially proved ineffective in all five, three of the patients (40%) exhibited PR after 6 months of treatment (Table 2).

The most common adverse effects of danazol in all patients were moderate to severe elevation of serum aspartate or alanine aminotransferase levels, defined as between 2- and 10-fold higher than normal values.

Splenectomy was performed in eight patients (20%) using coelioscopy. Initially, seven patients (87%) exhibited CR and one (13%) PR. After 6 months of follow-up, response (CR+PR) was observed in four patients (50%) (Table 2). No immediate adverse effects were reported, although there was one death due to sepsis.

Rituximab was administered as third-line therapy in four patients (10%) with refractory ITP. Response (CR+PR) was reported in three (75%), with no adverse effects observed.

One patient was treated with Eltrombopag at 50 mg/day and exhibited PR with no adverse effects.

### Long-term follow-up

Spontaneous remission and complete response following therapy were reported in eight patients (20%). In 33 (80%), ITP was still chronic at the time of writing.

During long-term follow-up (mean duration: 3.5 ± 1.2 years), which involved 30 patients, three death cases (10%) were noted, two related to massive bleeding and one to fatal sepsis following splenectomy.

## Discussion

ITP is often diagnosed in elderly individuals, typically presenting as a chronic disease (60-80%) with insidious onset or different hemorrhagic expression patterns, and has proven resistant to various therapies (≥80%) [10-14], as we have described in this study. Moreover, elderly patients (>75 years) have been reported to display a higher incidence of severe hemorrhagic manifestations on diagnosis or during follow-up, as well as a higher ITP-related mortality rate (≥10%) [9-14].

To date, only few studies have been conducted evaluating ITP specifically in the elderly population [1], with the exception of the Bizzoni et al. retrospective study, which involved 178 patients (mean age: 72 years) [10], and the Michel et al. case-controlled study [11], evaluating 55 elderly patients (mean age: 77.8 years). Based on the existing literature, our study therefore included one of the largest series of elderly ITP patients, with a mean age of 76.7 years and >50% being over 75 years of age, all monitored in two dedicated ITP reference centers.

The patients reviewed in our study displayed exactly the same characteristics as those generally recognized in or attributed to elderly ITP patients, particularly in that the majority exhibited more severe hemorrhagic manifestations than those observed in younger patients [9-11,14]. In this study, over half of patients exhibited severe cutaneous or visceral hemorrhagic complications, several of which were potentially life-threatening (Table 1). It should be noted that 12 patients (29%) were receiving anticoagulant or antiplatelet agents due to cardiac disease. This was also well-documented in the case-controlled study of Michel et al. [11]. In that study, the median platelet count on diagnosis did not significantly differ between the younger and elderly patients, yet bleeding symptoms were more frequently observed in the older patients than in the controls (82% versus 68%, p=0.007), and the median bleeding score was significantly higher in the elderly (4 versus 2 without anticoagulation [p=0.034] and 7 *versus* 2 with anticoagulation [p=0.013]) [11]. In the aforementioned study by Bizzoni et al. [10], age did not appear to influence the hemorrhagic symptoms.

The management of our ITP elderly patients was based on recently published guidelines, which did not specifically focus on elderly patients [4,6,7]. Corticosteroids were the cornerstone of initial therapy in only 56% of the patients. Nevertheless, only one-third of the patients exhibited response to treatment at the 6-month follow-up (Table 2), in line with figures reported in the literature [10-15]. This confirms reports of the relatively "low" effectiveness of corticosteroids in inducing stable remission in elderly patients, defined as ≥65 years old [9-15]. Crucially, this therapy seemed to generate more serious adverse effects in elderly patients [9]. Nevertheless, as Bizzoni et al. [10] reported, long-term partial response can be observed in elderly ITP patients receiving corticosteroid therapy at low doses, with a mean daily dose of prednisone at 2.5-12.5 mg.

| | Corticosteroids (n = 23) | IVIg (n = 6) | Splenectomy (n = 8) | Danazol (n = 5) |
|---|---|---|---|---|
| Complete response | 2 (9%) | 0 | 2 (65%) | 0 |
| Partial response | 6 (26%) | 0 | 2 (25%) | 3 (60%) |
| Failure | 15 (65%) | 6 (100%) | 4 (50%) | 2 (40%) |
| IVIg: intravenous immunoglobulins | | | | |

**Table 2:** Response at 6 months to corticosteroids, intravenous immunoglobulins (IVIg), splenectomy, and Danazol in the 41 treated elderly ITP patients.

Following splenectomy, 50% of our elderly ITP patients achieved stable response with no immediate adverse effects (Table 2). This is consistent with the literature, which supports the theory that splenectomy provokes long durable response in elderly ITP patients [10-18]. In a previous study, our team demonstrated that age negatively influences the response to splenectomy while correlating to more frequent postoperative complications [9]. We are, as yet, unable to provide a clear explanation for this discrepancy, perhaps on account of the small number of patients evaluated. More significantly, one of our patients died due to fatal sepsis following splenectomy. It is therefore our opinion that indications for splenectomy in older patients must be carefully and thoroughly discussed, with the pros and cons fully weighed, due to its relative inefficiency (50%) and potential risks. This is especially true considering that the effectiveness of

vaccination against meningococcal and *Streptococcal pneumoniae* is lower in the elderly [19].

In accordance with the literature [20,21], danazol resulted in a good stable response rate in 50% of our patients (Table 2). Ahn et al. [22] and Maloisel et al. [23] have previously demonstrated that age significantly influences the response to danazol therapy. Danazol tolerance in our elderly ITP patients was moderate, with moderate to severe liver cytolysis (53%). We are thus of the opinion that danazol could be an effective therapeutic alternative to splenectomy in the elderly or in refractory ITP cases [9].

There is currently no data on the effects of biological agents such as rituximab or platelet hematopoietic growth factors, like the TPO receptor agonists eltrompobag or romiplostim, in elderly ITP patients [3,24,25]. Studies to further assess their effectiveness and long-term safety, as well as their mechanisms of action, are still ongoing. Our results suggest that these agents are potentially effective, with response observed in four of the five patients treated with biological agents. In order to fully confirm this assumption, controlled clinical trials with larger sample sizes are nonetheless necessary [1].

We conducted this retrospective study in two academic centers, focused on patients aged over 65 years, with well-documented and unquestionable ITP. This study represents one of the most relevant of its kind in this medical field. Yet we must cite the following weaknesses of our work: the perhaps "young" old age of our patients, while a population aged over 75 or even 80 years old could potentially yield different results; the relatively small sample size of our study; the ITP diagnostic criteria that currently require a platelet count <100 x $10^9$ /L [6].

## Conclusions

This study involved one of the largest series of elderly ITP patients (≥65 years old) ever evaluated. Our results confirm that age influences the hemorrhagic pattern of ITP expression, as well as response to and adverse effects of various conventional therapies. It is therefore our opinion that the clinical practice guidelines published for ITP are probably not fully adapted to older patients. This is why we strongly believe that further studies with larger sample sizes and controlled clinical designs are now warranted to improve treatment efficiency for elderly ITP patients.

## Author Contributions

Conception and design: E. Andrès and A.A. Zulfiqar. Collection and assembly of data: E. Andrès, A.A. Zulfiqar, and F. Maloisel. Data analysis and interpretation: E. Andrès, A.A. Zulfiqar, K. Serraj, T. Vogel, and F. Maloisel. Drafting of the article: E. Andrès and A.A. Zulfiqar; these two authors contributed equally to the creation and drafting of this manuscript. Final approval of the manuscript: E. Andrès, A.A. Zulfiqar, K. Serraj, T. Vogel, and F. Maloisel. Provision of study materials or patients: E. Andrès, A.A. Zulfiqar, T. Vogel, and F. Maloisel, j Zimmer contribute to this paper: follow up of patients; readresse and correction of the préliminaire manuscript.

## Conflicts of Interest

E. Andrès and F. Maloisel have received grants for lectures, seminars, and congresses from the following pharmaceutical laboratories: ROCHE, GSK, and AMGEN.

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