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PLATELETS AND THROMBOPOIESIS

# Characteristics, outcome, and response to therapy of multirefractory chronic immune thrombocytopenia

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## Key Points

- The baseline characteristics of multirefractory ITP differed from "typical" ITP, outcome was severe, and was associated with high morbidity and mortality.
- Combining immunosuppressant therapy with a thrombopoietin-receptor agonist may be a relevant option for these patients.

**Refractory immune thrombocytopenia (ITP) was previously defined as lack of a minimum response to splenectomy and the requirement for long-term treatment to reduce the risk of significant bleeding events. In this multicenter study, we included 37 patients with multirefractory ITP, defined as no response to splenectomy, rituximab, romiplostim, and eltrombopag. As compared with a historical cohort of 183 ITP patients, matched on the calendar year of ITP diagnosis with a 5:1 ratio, patients with multirefractory ITP were more likely to have secondary ITP (odds ratio [OR], 4.84; 95% confidence interval [CI], 1.31-17.86; $P = .018$) and monoclonal gammopathy of undetermined significance (OR, 5.94; 95% CI, 1.08-32.48; $P = .04$). The median duration of ITP before being recognized as multirefractory was 78 months (range, 6-450). The patients showed failure of a median of 10.5 prior treatment lines for ITP (range, 6-15). At the end of follow-up (median, 84 months; range, 12-455), only 1/14 patients achieved response with immunosuppressant therapy alone. By contrast, 7/10 patients achieved response with a combination of immunosuppressant therapy and thrombopoietin-receptor agonists that lasted for a median of 15 months (range, 6-32). Throughout the course of ITP, 5/37 patients died, 3 with ITP (bleeding, n = 2; sepsis n = 1); 15 (40%) had at least 1 bacterial infection and 9 (24%) at least 1 episode of thrombosis. In conclusion, multirefractory ITP was associated with high morbidity and mortality. Combining an immunosuppressant therapy with thrombopoietin-receptor agonists may be a good strategy for management for these patients with severe disease. (*Blood.* 2016;128(12):1625-1630)**

## Introduction

Immune thrombocytopenia (ITP) is an acquired bleeding disorder characterized by antibody-mediated destruction of platelets and impaired platelet production.[1] Refractory ITP was previously defined as lack of a minimum response to splenectomy and the requirement for long-term treatment to reduce the risk of significant bleeding events.[2] More than 10 years ago, McMillan[3] characterized this subgroup of

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patients with refractory ITP as having chronic thrombocytopenia, continuous bleeding, and significant morbidity and mortality. In the past decade, the emergence of effective drugs, such as rituximab (RTX), commonly used off-label in many countries for ITP, and thrombopoietin-receptor agonists (Tpo-RAs), now licensed for chronic ITP, has deeply changed the management of ITP.[4,5] However, neither the characteristics nor outcome of the few patients with failure to respond to those different treatment lines nor the treatment options for these patients are known.

The aim of this study was to describe the characteristics and outcome of ITP without a durable response to splenectomy and with failure to respond to RTX and to romiplostim and eltrombopag, the 2 Tpo-RAs available in Europe.

## Methods

### Study design

This was a multicenter retrospective cohort study of patients with multirefractory ITP diagnosed from 1990 to 2014. All participating centers were tertiary care university hospitals belonging to the French national network for adult ITP. This study was conducted in accordance with the Helsinki Declaration.

### Study population

Multirefractory ITP was defined as severe (ie, symptomatic) chronic ITP not responding to RTX (see definition that follows), splenectomy (or if splenectomy was contraindicated), and the 2 Tpo-RAs licensed in France (ie, romiplostim and eltrombopag) administered at least at the maximal approved dose (ie, 10 μg/kg body weight per week for romiplostim, 75 mg/day for eltrombopag), except for patients in whom Tpo-RAs had to be stopped because of severe side events. Patients with the multirefractory ITP defined previously could have achieved a transient response to corticosteroids and/or IV immunoglobulin (IVIG) because these are considered first-line and/or rescue therapies. Clinical data were retrospectively collected from medical charts for each patient and completed by telephone interviews with patients and physicians by using a standardized questionnaire.

### Definitions

Primary and secondary ITP were defined according to the international working group definitions.[2] Bleeding was graded according to the bleeding score previously reported by our group with censured data for age.[6] Underlying autoimmune diseases associated with ITP were defined according to the international guidelines (American College of Rheumatology for systemic lupus erythematosus, revised Sapporo criteria for antiphospholipid syndrome).[7,8]

Treatment lines included any medication used for ITP. Corticosteroids, IVIG, and RTX were each considered as a single treatment line regardless the number of courses or cycles.

### Criteria of response

Response (R) and complete response (CR) were defined according to standardized international criteria: platelet count $>30 \times 10^9$/L with at least a doubling of the baseline value or $>100 \times 10^9$/L.[2] Nonresponse was defined as the absence of platelet count increase $>30 \times 10^9$/L with at least a doubling of the baseline count or the need for rescue therapy (IVIG and/or corticosteroids).

### Definition of clinical outcomes

Venous thromboembolism was defined by the presence of a deep vein clot seen on a Doppler ultrasonography and/or enhanced computed tomography scan. Severe infections were defined as requiring hospitalization and/or the need for IV antimicrobial drugs.

### Comparison with an historical cohort of ITP patients

The patient database of the department of internal medicine of Henri Mondor University Hospital, the French national referral center for adult immune cytopenias, includes 867 patients with definite ITP registered between 1990 and 2014. We randomly selected and matched ITP patients to multirefractory patients on the calendar year of ITP diagnosis with a 5:1 ratio. For these patients, the following data were recorded: age and sex, history of bleeding at diagnosis, nadir platelet count at the time of ITP diagnosis, primary and secondary ITP, detection of antinuclear antibodies and antiphospholipid antibodies, and direct antiglobulin test and serum electrophoresis results.

### Statistical analysis

Data are presented as number and percentage for categorical variables and median (interquartile range) for continuous variables. For the case-control study, we used conditional allogistic regression models. The variables associated with multirefractory status threshold of 20% on univariate analyses were included in the multivariate model (stepwise backward procedure, $\alpha = 5\%$). Odds ratios (ORs) with their 95% confidence intervals (95% CIs) were computed. Statistical analyses involved use of SAS 9.2 software (Cary, NC).

## Results

### Initial characteristics of patients with multirefractory ITP

We included 37 patients (25 women [67.5%]) fulfilling the study criteria for multirefractory ITP. The median age at ITP diagnosis was 47.2 ± 19.8 years (range, 12-79). Overall, 28 patients (75.7%) presented some bleeding symptoms at ITP diagnosis; for 11 (30%), the bleeding score was severe (including extensive cutaneous and mucosal bleeding).[6] Thirteen patients (35%) presented secondary ITP according to the international definition criteria (Figure 1).[2] Five patients had definite autoimmune disease (antiphospholipid syndrome, n = 1; lupus erythematosus, n = 1; Evans syndrome [warm autoimmune hemolytic anemia, wAIHA], n = 3), 7 an associated malignant hematologic disorder, and 1 a primary immunodeficiency. Of note, in 4 of 7 patients, the diagnosis of ITP preceded that of a malignant hematological disorder. Among the 24 patients with primary ITP, 12 had isolated biological features of autoimmunity including positive direct antiglobulin test and/or positive antinuclear antibodies without definite clinical autoimmune disease, and in 7 primary ITP patients, ITP was associated with monoclonal gammopathy of undetermined significance (MGUS) (immunoglobulin G n = 6, immunoglobulin M n = 1, <3 g/dL). All patients with MGUS had a normal bone marrow aspirates or biopsy with clonal plasma cell <10%.

In total, 24 patients (68.6%) achieved a transient initial response to first-line steroid therapy (CR: n = 10; R: n = 12) and 22 (68.6%) to IVIG (CR: n = 7; R: n = 15).

### Comparison of initial characteristics with the historical cohort of ITP patients

The median follow-up of the 183 ITP controls was 48 months (range, 12-369). As compared with the ITP controls, matched on the calendar year of ITP diagnosis at a 5:1 ratio, patients with multirefractory ITP were more likely to have secondary ITP (OR, 4.84; 95% CI, 1.31-17.86; $P = .018$), with some underlying autoimmune disease or biological features of underlying autoimmunity without clinical symptoms (Table 1). The presence of MGUS was also independently associated with multirefractory ITP (OR, 5.94; 95% CI, 1.08-32.48; $P < .04$). In addition, risk of developing multirefractory ITP during follow-up was associated with bleeding symptoms at ITP onset (OR,

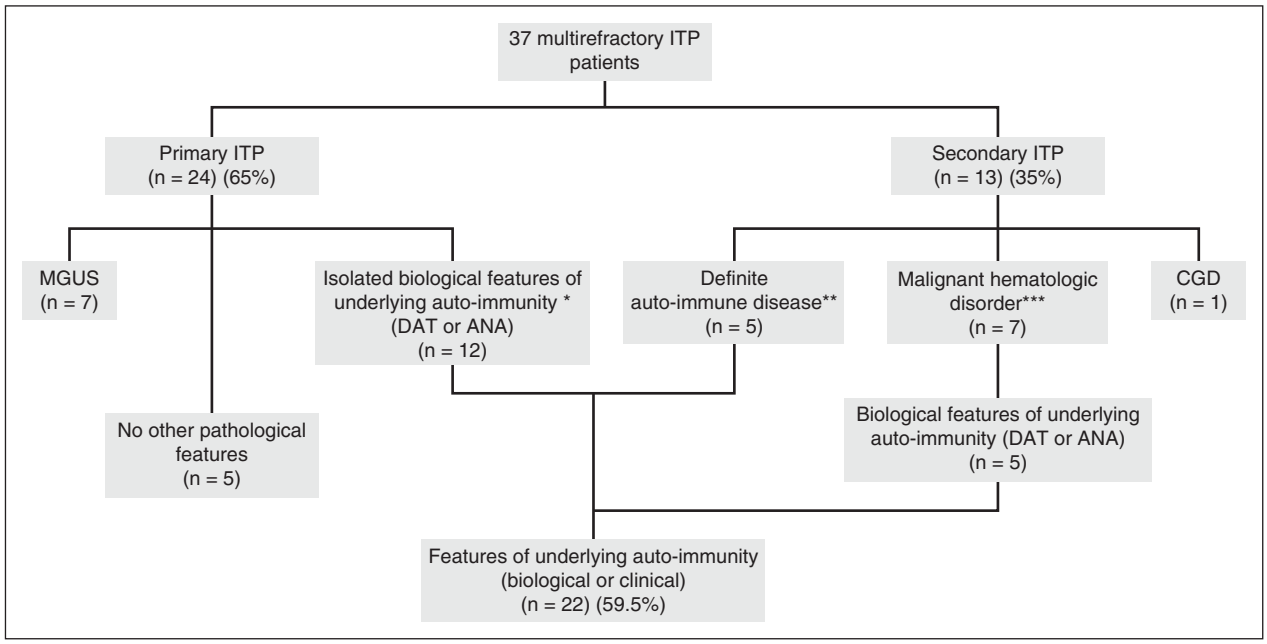


**Figure 1. Overview of the initial characteristics of patients with multirefractory ITP.** *Biological: antinuclear antibodies or direct antiglobulin test positivity. **Antiphospholipid syndrome, n = 1; lupus erythematosus, n = 1; Evans' syndrome (wAIHA), n = 3. ***Lymphoma (n = 3), chronic myelomonocytic leukemia (n = 1), cold agglutinin disease (n = 1), Waldenström macroglobulinemia (n = 1), smoldering myeloma (n = 1). ANA, antinuclear antibody; CGD, chronic granulomatous disease; DAT, direct antiglobulin test.

3.54; 95% CI, 1.12-11.22; $P = .032$) and no response to steroid therapy (OR for response to steroids, 0.38; 95% CI, 0.20-0.72; $P = .003$).

### Response to therapy in patients with multirefractory ITP

The median duration of ITP before being considered multirefractory was 78 months (range, 6-450); patients had received a median of 10.5 treatment lines for ITP (range, 6-15, including splenectomy, RTX, and both Tpo-RAs). Among the 37 patients, 34 (91.8%) showed failure to achieve a prolonged response with RTX, splenectomy, and the 2 Tpo-RAs at the maximum tolerated dose (ie, 10 μg/kg body weight per week for romiplostim, 75-150 mg/day for eltrombopag). Of note, 9 patients received higher doses of eltrombopag than the approved one (7 patients received 100 mg/day, and 2 received 150 mg/day) without efficacy. Three patients had not undergone splenectomy because of a contraindication to surgery; 1 patient had received only 1 of the 2 Tpo-RAs because deep venous thrombosis and pulmonary embolism occurred during Tpo-RA therapy.

Among the 7 patients in whom ITP was associated with a malignant hematological disorder, 3 achieved a sustained response with chemotherapy (2 CR, 1 R); 1 patient with smoldering myeloma received lenalidomide and then Tpo-RAs, with no efficacy; and the 3 remaining patients did not receive any specific treatment of the malignant hematological disorder apart from RTX.

**Table 1. Results of the case-control study (n = 220: 37 cases and 183 controls)**

| | Values | | Univariate analyses | | Multivariate analysis | |
|---|---|---|---|---|---|---|
| **Variable** | **Cases** | **Controls** | **OR (95% CI)** | ***P*** | **OR (95% CI)** | ***P*** |
| Age at diagnosis, y, mean ± SD (range) | 47.2 ± 19.8 (12-79) | 40.9 ± 19.8 (3-91) | — | — | — | — |
| Age at diagnosis >40 y, n (%) | 25 (67.6) | 85 (46.5) | 2.51 (1.17-5.40) | .0186 | — | — |
| Female sex, n (%) | 25 (67.6) | 127 (69.4) | 0.91 (0.43-1.92) | .8074 | — | — |
| Secondary ITP, n (%) | 13 (35.1) | 16 (8.7) | 6.01 (2.44-14.81) | <.001 | 4.84 (1.31-17.86) | .0179 |
| Autoimmunity (clinical or biological), n (%) | 22 (59.5) | 52 (28.4) | 3.36 (1.67-6.82) | .0008 | — | — |
| ANA positive, n (%)* | 13 (35.1) | 43 (25.2) | 1.5 (0.72-3.28) | .2692 | — | — |
| DAT positive, n (%)† | 12 (35.3) | 43 (25.2) | 2.39 (0.86-6.69) | .0954 | — | — |
| MGUS, n (%)‡ | 7 (18.9) | 5 (2.9) | 10.00 (2.55-39.24) | .0010 | 5.94 (1.085-32.48) | .0400 |
| Malignant hematological disorder, n (%) | 7 (18.9) | 0 (0) | — | — | — | — |
| Bleeding symptoms at ITP diagnosis, n (%) | 28 (75.7) | 96 (52.8) | 2.79 (1.25-6.24) | .0124 | 3.54 (1.12-11.23) | .0320 |
| Platelet count at ITP diagnosis, g/L, median ± IQR | 8.5 ± 13.0 [0-79] | 17.0 ± 25.0 [0-137] | — | — | — | — |
| Platelet count at ITP diagnosis ≤10 g/L, n (%) | 26 (70.3) | 72 (39.1) | 3.78 (1.73-8.23) | .0008 | — | — |
| Response to corticosteroids, n (%)§ | 24 (68.6) | 142 (91.6) | 0.34 (0.20-0.58) | <.0001 | 0.384 (0.205-0.720) | .0029 |
| Response to IVIG, n (%)‖ | 24 (68.6) | 54 (83.1) | 0.54 (0.30-0.96) | .0362 | — | — |

ANA, antinuclear antibodies; DAT, direct antiglobulin test; IQR, interquartile range.
*12 missing values among controls.
†113 missing values among controls and 3 among cases.
‡10 missing values among controls.
§28 missing values among controls and 2 among cases.
‖118 missing values among controls and 2 among cases.

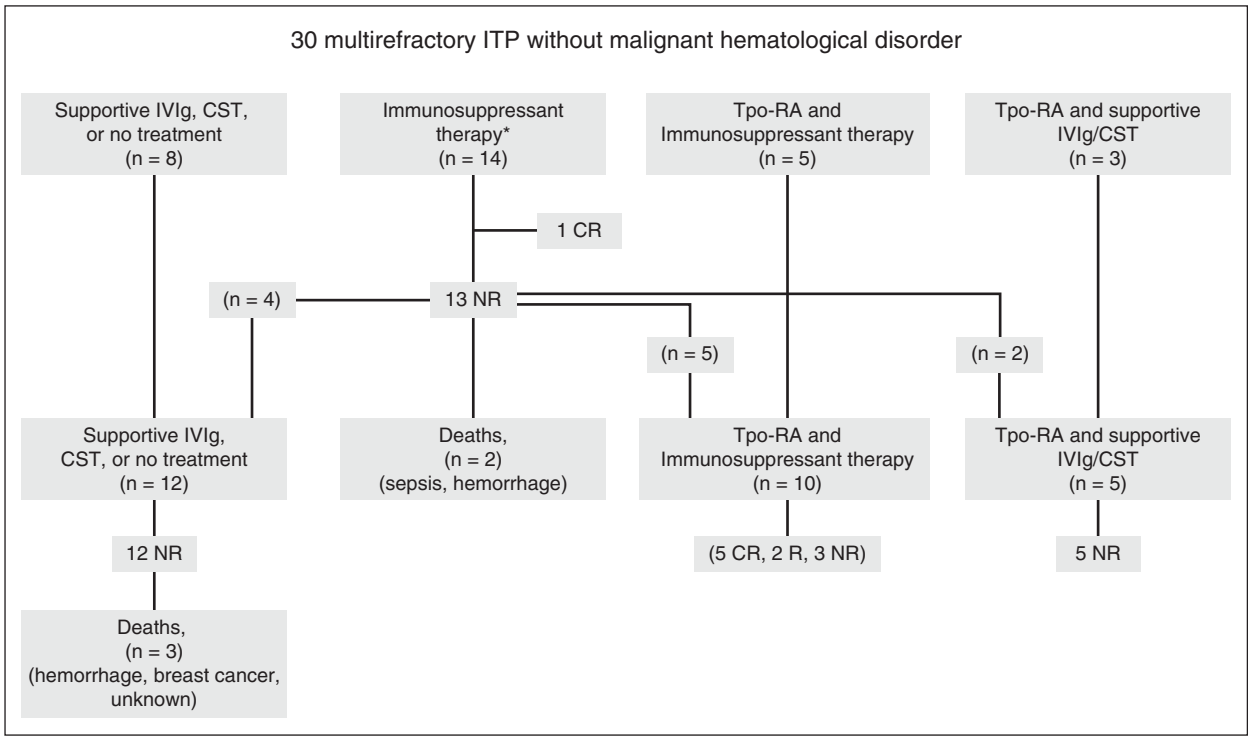


**Figure 2. Response to therapy in patients with a multirefractory ITP.** *Cyclophosphamide, n = 1; azathioprine, n = 4; cyclosporine, n = 1; mycophenolate mofetil, n = 2; alemtuzumab, n = 1; high-dose cyclophosphamide followed by autologous HSCT, n = 1. R and CR were defined according to standardized international criteria by platelet count $>30 \times 10^9$/L with at least a doubling of the baseline value or $>100 \times 10^9$/L, respectively.[2] Nonresponse (NR) was defined as the absence of platelet count increase $>30 \times 10^9$/L with at least a doubling of the baseline count or the need for rescue therapy (IVIG and/or corticosteroids [CST]).

Figure 2 shows the response to therapy of the 30 patients with no malignant hematological disorder. Fourteen patients have received at least 1 immunosuppressant or cytotoxic agents (4 patients have received sequentially 2 agents), and only 1 achieved a response (mycophenolate mofetil [MMF]). One patient who received high-dose cyclophosphamide followed by autologous hematopoietic stem cell transplantation (HSCT) achieved CR but eventually died of sepsis within 3 months after the procedure. Ten patients received immunosuppressant combined with Tpo-RA, 5 had previously failed to immunosuppressant therapy given alone; all patients had received RTX at least 6 months before initiation of the combination therapy (median, 36 months; range, 6-72). Among them, 7 achieved a sustained response (MMF: n = 3; cyclophosphamide: n = 1; azathioprine: n = 1; HSCT: n = 1; cyclosporine: n = 1) with a median follow-up of 15 months (range, 6–32). The detailed characteristics of these 10 patients are in Table 2.

At the end of follow-up (median, 84 months; range, 12-455), only 11/37 patients (30%) achieved a sustained response, including the 3 with a malignant hematological disorder treated with chemotherapy. Among the 21 alive nonresponder patients, all received a supportive course of IVIG and corticosteroids associated or not with Tpo-RAs.

### Mortality and morbidity

Five patients (14%) died. The cause of death was intracranial hemorrhage (n = 2), sepsis (n = 1), breast cancer (n = 1), and unknown (n = 1). Throughout the course of ITP, all patients required several hospitalizations (median number of hospitalizations, n = 15; range, 6-100). A total of 22 patients (60%) received platelet transfusions; 6 received at least 1 red blood cell transfusion. Nine patients (24%) were admitted to intensive care units. Overall, 15 patients (40%) presented at least 1 bacterial infection and 9 (24%) experienced an episode of thrombosis; 6 events were venous and 3 were arterial thrombosis (1 stroke, 1 ischemia of the toes, 1 myocardial infarction). Six of 9 thrombotic events (arterial, n = 2; venous, n = 4) occurred in patients exposed to Tpo-RAs (approved dose). One thrombotic event occurred in a patient with antiphospholipid syndrome not exposed to Tpo-RA.

## Discussion

We describe here, for the first time, the characteristics and outcome of ITP patients who showed failure to achieve response to splenectomy, RTX, and Tpo-RAs, defined as multirefractory ITP. The baseline characteristics of multirefractory ITP clearly differed from those of controls with "typical" ITP, with the overrepresentation of secondary ITP and MGUS. This overrepresentation and the poor response to steroid therapy suggest that the immunological mechanism resulting in platelet destruction in these cases differs from the common form of ITP.[1,9] Multirefractory ITP may be subdivided into 3 distinct groups: primary ITP, ITP associated with other malignant hematological disorders, and ITP associated with other autoimmune disorders. Interestingly, ITP can precede the diagnosis of a malignant hematological disorder, which suggests that with multirefractory ITP, the diagnosis of primary ITP should be reconsidered to carefully exclude hematological disorders. Apart from B-cell malignancy, which can result in an autoreactive B-cell clone, the presence of monoclonal gammopathy without evidence of multiple myeloma in 20% of patients is more surprising. Determining whether the monoclonal immunoglobulin targets platelets or not could provide a better understanding of the disease. As mentioned previously, associated autoimmunity is common (60%), the occurrence of wAIHA was previously found associated with refractory ITP, and the poor

**Table 2. Patients with multirefractory ITP receiving a combination of IS and TPO-RA**

| Patients | Treatments received before multirefractory ITP | Treatment status of multirefractory ITP before IS/TPO-RA association | IS/TPO-RA association/other ITP treatments | Response to current treatment | Follow-up after IS/TPO-RA association |
|---|---|---|---|---|---|
| 1 | CST, IVIG, splenectomy, RTX 375 mg/m$^2$ ×4, romiplostim 10 μg/kg bw, eltrombopag 75 mg | AZA (NR), anti-Rh D (NR), vincristine (NR) | CST 15 mg, AZA 150 mg, romiplostim 10 μg/kg bw | CR | 12 |
| 2 | CST, vinblastine, eltrombopag 75 mg, RTX 1 g ×2, splenectomy, romiplostim 10 μg/kg bw | TPO-Ra association (NR), romiplostim 10 μg/kg bw + CST 10 mg/d (NR) | CYC 1 g ×3, eltrombopag 75 mg | CR | 17 |
| 3 | CST, IVIG, AZA, splenectomy, RTX 375 mg/m$^2$ ×4, romiplostim 10 μg/kg bw, eltrombopag 75 mg | vinblastine (NR), cyclosporine (NR), dapsone (NR), tacrolimus (NR), IVIG (NR) | MMF 1 g ×2 + eltrombopag 50 mg | CR | 29 |
| 4 | CST, IVIG, vinblastine, splenectomy, RTX 375 mg/m$^2$ ×4, eltrombopag 100 mg, romiplostim 10 μg/kg bw | IVIG (NR), danazol (NR) | MMF 1 g ×2 + eltrombopag 75 mg | CR | 13 |
| 5 | CST, IVIG, AZA, splenectomy, romiplostim 10 μg/kg bw, RTX 375 mg/m$^2$ ×4, eltrombopag 75 mg | CYC (NR), vincristine (NR), AZA (NR), cyclosporine (NR) | Autologous HSCT + eltrombopag 75 mg | CR | 32 |
| 6 | Splenectomy, romiplostim 10 μg/kg bw, eltrombopag 75 mg, RTX 1 g ×2 | _ | MMF 1 g ×2 + CST 10 mg + romiplostim 10 μg/kg bw | R | 17 |
| 7 | CST, IVIG, RTX 1 g ×2,dapsone, eltrombopag 75 mg, romiplostim 10 μg/kg bw, splenectomy, | AZA (NR) | Romiplostim 10 μg/kg bw + cyclosporine | R | 12 |
| 8 | CST, IVIG, HCQ, vinblastine, RTX 375 mg/m$^2$ ×4, romiplostim 10 μg/kg bw, eltrombopag 150 mg, splenectomy | Dexamethasone (NR) | MMF 1 g ×2 + romiplostim 10 μg/kg bw (NR), tacrolimus (NR), CYC (transient response), HCQ (NR), cyclosporine + IVIG (NR) | NR | 26 |
| 9 | CST, IVIG, vinblastine, splenectomy, RTX 1 g ×2, eltrombopag 75 mg, CYC, romiplostim 10 μg/kg bw | MMF (NR) | Eltrombopag 100 mg; MMF 1 g ×2 | NR | 6 |
| 10 | CST, IVIG, HCQ, RTX 1 g ×2, romiplostim 10 μg/kg bw, splenectomy, eltrombopag 75 mg | Vinblastine (NR) | CYC 1 g ×4 + CST + romiplostim 10 μg/kg bw (NR) | NR | 6 |

AZA, azathioprine; bw, body weight; CST, corticosteroids; CYC, cyclophosphamide; HCQ, hydroxychloroquine; IS, immunosuppressant therapy; IVIG, IV immunoglobulin; MMF, mycophenolate mofetil; NR, nonresponse.

prognosis of Evan's syndrome has been described.[10,11] In these patients, the breakdown of self-tolerance is not restricted to platelet antigens and could result from central tolerance checkpoint defects, which may be less responsive to immune-directed therapy.[1]

Many different approaches for achieving an adequate platelet count have been tried in chronic ITP, but since the emergence of new therapeutic drugs, disease management has greatly improved. Nevertheless, treatment of the subgroup of patients with failure to respond to these treatments remains a critical and challenging issue. Our study provides 1 therapeutic approach for severe multirefractory ITP. It has been suggested that increasing the dose of eltrombopag beyond 75 mg/day may result in a dose-dependent platelet response, but this strategy was not efficient in our cohort of patients.[12] Chemotherapy may be needed for the few patients with lymphoma-associated secondary ITP. For primary ITP or other secondary ITP cases, immunosuppressant drugs were not effective in most cases when given alone. Our findings contrast with several reports or clinical studies showing prolonged response with such therapies, but patients showed less refractory disease than our patients.[13-19] Despite the efficacy of HSCT, the high risk of mortality associated with this procedure (1 death in our cohort) argues for its proposal for patients with no alternative therapeutic option only. However, the combination of Tpo-RAs with immunosuppressant drugs was effective with an overall response rate (R + CR) of 70% in the 10 patients who received this treatment. This promising strategy was impressive in terms of the failure with other therapies. A study by Barsam et al showed that nonresponders to Tpo-RAs had increased megakaryocytes production but no increased platelet release from the bone marrow, so the platelet release could be blocked by antibodies.[20] One interpretation of these results is that, in some patients, pro-platelet formation is completely inhibited by platelet antibodies and partially inhibited in others.[21] In some patients, immunosuppressant therapy may restore the efficacy of Tpo-RAs by dampening the pathogenic autoimmune process.[21] Further studies are needed to determine the most appropriate and tolerated immunosuppressant drug to combine with Tpo-RAs.

Multirefractory ITP is a serious and potentially life-threatening condition. We observed 2 deaths from hemorrhage and 1 from sepsis. Surprisingly, this mortality was relatively low compared with the 17.5% reported by McMillan in refractory ITP before the era of Tpo-RAs.[3] This finding might be explained by the regular use of IVIG as rescue therapy in our cohort, which was not the case for every patient from the McMillan cohort. Indeed, one-third of our patients received

supportive IVIG at the end of follow-up. The morbidity was high. Uncontrolled bleeding and therapy-related complications were the 2 most challenging problems: 60% of patients needed platelet transfusion during follow-up and 40% had at least 1 severe infection. The number of thrombotic events with Tpo-RA therapy, both venous and arterial, was high in this cohort of patients. The risk of thrombosis in this population could have been increase by comorbidities, splenectomy, hospitalization, and long-term steroid therapy.[22-24]

This study has some limitations because of its retrospective design, including some potential selection bias. However, most of the multirefractory ITP cases were managed at tertiary care centers belonging to the French reference center network, so the cohort is representative of the clinical spectrum of multirefractory ITP in France. The wide variety of previous therapies may have affected the interpretation drawn from the outcomes of the combination of Tpo-RAs with immunosuppressant drugs. However, because all patients previously showed failure to respond to both RTX and splenectomy and taking into account the time elapsed, the response finally observed with Tpo-RAs combined with immunosuppressant therapy was not likely from a delayed response of previous treatments.

In summary, in the era of new ITP therapies, a minority of ITP patients still does not show response after several treatment lines and likely has severe disease, with high morbidity and risk of death. In the absence of guidelines, an individual approach with a combination of agents taking into account the risk/benefit balance of these treatments appears the best way to improve the outcome of patients with multirefractory ITP. Combining immunosuppressant therapy with a Tpo-RA may be a promising and relevant option.

## Authorship

Contribution: M. Mahévas and B.G. designed the study. All authors recruited the patients. M.G.-V., S.G., and M. Mahévas recorded the data. M. Mahévas, G.M., M.G.-V., and B.G. analyzed the results. M. Mahévas, M. Michel, and B.G. wrote the manuscript.

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