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SHORT REPORT

Platelets, Thrombosis and Haemostasis

Difficult-to-treat primary immune thrombocytopenia in adults: Prevalence and burden. Results from the CARMEN-France registry

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Summary

The aim of this study was to assess the prevalence and the burden of difficult-to-treat primary ITP (pITP), defined by the need for another ITP treatment after romiplostim and eltrombopag. Adult patients were selected in the prospective, real-world CARMEN-France registry up to December 2021. Out of 821 adult patients with pITP, 29 had difficult-to-treat ITP (3.5%; 95% confidence interval [CI]: 2.3%–4.8% in total; 7.6%; 95% CI: 4.9%–10.2% of patients needing \geq 2nd line treatment). The 3-year cumulative incidence of bleeding, infection and thrombosis was 100%, 24.1% and 13.8% respectively. The median cumulative duration of hospital stays was 31 days (median follow-up: 30.3 months).

KEY WORDS

difficult-to-treat, epidemiology, immune thrombocytopenia, infection, refractory, thrombosis

The members of the CARMEN-France Investigators Group are listed in [Appendix 1](#).

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INTRODUCTION

Immune thrombocytopenia (ITP) is a rare autoimmune disease with a prevalence of about 20/10⁵ individuals.¹ The first-line treatment is based on corticosteroids and/or intravenous immunoglobulin (IVIg).^{2,3} In case of relapse, second-line treatments are indicated (thrombopoietin receptor agonists—TPORAs—or immunosuppressants).^{2,3} Other drugs are currently in development.⁴ A splenectomy is an option in case of chronic disease.^{2,3} TPORAs are the preferred second-line treatment in most countries due to their high and rapid effectiveness.³ In this study, we aimed to assess the prevalence and the burden of adult patients with difficult-to-treat primary ITP, defined by the need for another treatment after the exposure to both TPORAs marketed in France (romiplostim and eltrombopag).

METHODS

Study design

We conducted an observational study in the prospective, multicentre CARMEN-France registry ([Supplementary Material](#), Data source).

Study population

The study population was selected among the patients included in the CARMEN-France registry with a diagnosis of primary ITP up to December 2021 and with a ≥3-month follow-up. The patients who needed any treatment for ITP after an exposure to romiplostim and eltrombopag corresponded to the study population defining difficult-to-treat ITP and were selected. Only the treatments prescribed after the second TPORA withdrawal were considered to meet the definition criteria (and not, for instance, short courses of steroids during the exposure to TPORA).

Outcomes

We assessed the prevalence of difficult-to-treat ITP among all adult patients with primary ITP included in the registry during the study period, as well as among the subgroup of patients who needed a treatment for ITP. The burden of ITP in these patients was assessed with the description of frequency of bleeding, infections, thromboses and hospital contacts due to ITP during the follow-up. Because a cornerstone approach of treating difficult-to-treat/refractory ITP is to reconsider the diagnosis of ITP,⁵ we described whether these patients identified with primary ITP had another diagnosis causing thrombocytopenia during the follow-up.

Statistical analyses

Descriptive analyses were performed. Cumulative incidences of bleeding, infection and thrombosis at 1, 2 and 3 years were calculated with their 95% confidence interval (CI). For prevalence calculation, sensitivity analysis was performed in patients with a ≥6-month and a ≥12-month follow-up.

Ethics approval

The Toulouse university Hospital ethics committee gave approval to the registry in 2012 (no. 27-0512). According to French law, authorization was obtained by the *Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé* (CCTIRS, no. 12.067) and by the *Commission Nationale de l'Informatique et des Libertés* (CNIL, DE-2012-438).

RESULTS

Prevalence

Out of 1035 adult patients with a new diagnosis of primary ITP included in the registry during the study period, 821 had a ≥3-month follow-up. Among them, 687 (83.7%) were treated for ITP, including 384 (46.8%) with a second-line treatment. Twenty-nine patients met the definition of difficult-to-treat ITP, accounted for 3.5% (95% CI: 2.3%–4.8%) of all patients with primary ITP, 4.2% (95% CI: 2.7%–5.7%) of patients with primary ITP who needed a treatment and 7.6% (95% CI: 4.9%–10.2%) of patients with primary ITP who needed at least one second-line treatment.

In sensitivity analyses, the prevalence of difficult-to-treat ITP was 3.9% (95% CI: 2.5%–5.3%) and 4.8% (95% CI: 3.0%–6.5%) among all adult patients with primary ITP and a ≥6-month and a ≥12-month follow-up respectively.

Patients

Patients' characteristics are described in [Table 1](#). At ITP diagnosis, the median age was 64.0 years (min–max: 25–90). Thirteen patients (44.8%) were women. The median platelet count at ITP diagnosis was 6.0 × 10⁹/L; 26 (89.7%) had bleeding at ITP diagnosis. All 29 patients but four had a bone marrow examination at ITP diagnosis; it was in favour of ITP in all cases. Response to corticosteroids or IVIg (platelet count ≥30 × 10⁹/L) was achieved in 96.2% of patients. Of note, four patients had already received rituximab before the second TPORA.

TABLE 1 Characteristics of patients with difficult-to-treat ITP (patients exposed to an ITP treatment after eltrombopag and romiplostim).

| Variables | Difficult-to-treat ITP (n=29) |
|--|-------------------------------|
| Demographics | |
| Median age at ITP diagnosis (min–max), years | 64.0 (25.0–90.0) |
| Women, n (%) | 13 (44.8) |
| ITP at diagnosis | |
| Median platelet count at ITP diagnosis (min–max), $\times 10^9/L$ | 6.0 (1.0–53.0) |
| Bleeding at ITP diagnosis, n (%) | 26 (89.7) |
| Medical history and comorbidities^a | |
| Cardiovascular risk factors at ITP diagnosis except age and sex, n (%) | 16 (55.2) |
| Median Charlson's comorbidity index score (min–max) | 0.0 (0.0–4.0) |
| Treatments for ITP before the end of the second TPORA, n (%) | |
| Corticosteroids | 28 (96.6) |
| Intravenous immunoglobulin | 20 (69.0) |
| Rituximab | 4 (13.8) |
| Dapsone | 7 (24.1) |
| Hydroxychloroquine | 4 (13.8) |
| Vinblastin | 1 (3.4) |
| Belimumab | 1 (3.4) |
| Previous response to corticosteroids/intravenous immunoglobulin^b | |
| Response (platelet count $\geq 30 \times 10^9/L$) | 25 (96.2) |
| Complete response (platelet count $\geq 100 \times 10^9/L$) | 13 (50.0) |
| No response (platelet count $< 30 \times 10^9/L$) | 1 (3.8) |
| Median time from ITP diagnosis to first treatment after the two TPORAs (min–max), months | 10.4 (2.0–48.1) |
| Median time of exposure to TPORAs up to the definition of difficult-to-treat ITP (min–max), days | 137.0 (30.0–906.0) |
| Treatments received after the two TPORAs, n (%) | |
| Corticosteroids | 20 (69.0) |
| Intravenous immunoglobulin | 20 (69.0) |
| Rituximab | 13 (44.8) |
| Splenectomy | 4 (13.8) |
| New exposure to romiplostim | 19 (67.9) |
| New exposure to eltrombopag | 5 (17.2) |
| Mycophenolate | 7 (24.1) |
| Azathioprine | 2 (7.0) |
| Ciclosporin | 1 (3.5) |
| Daratumumab | 1 (3.5) |
| Fostamatinib | 1 (3.5) |
| Dapsone | 1 (3.5) |
| Hydroxychloroquine | 2 (7.0) |
| Combination of treatments ^c | 11 (37.9) |

Abbreviations: ITP, immune thrombocytopenia; TPORA, thrombopoietin receptor agonist.

^aComorbidities from the Charlson's index were: myocardial infarction or angina (n=5), cardiac failure (n=1), stroke (n=2), peripheral artery disease (n=1), diabetes (n=5), chronic pulmonary disease (n=2) and chronic kidney disease (n=1). Cardiovascular risk factors not included in the Charlson's index were chronic arterial hypertension (n=13) and dyslipidaemia (n=5). Additionally, autoimmune comorbidities were thyroiditis (n=1), psoriasis (n=2), psoriasis with psoriatic rheumatism (n=1) and granulomatosis with polyangiitis (n=1). Four had a history of malignancy >5 years before ITP, cured and not considered related to ITP (one colorectal cancer, one Hodgkin lymphoma, one chronic myelomonocytic leukaemia cured by allogeneic stem cell transplantation and one patient with prostate cancer + non-melanoma skin cancer).

^bResponses were not evaluable in three patients.

^cCombinations of treatments, not considering additional courses of steroids or IVIg as rescue treatment, were (some of them in the same patients, 11 patients in total): romiplostim + mycophenolate (n=6), romiplostim + rituximab (n=5), romiplostim + ciclosporin, romiplostim + azathioprine, romiplostim + azathioprine + rituximab, eltrombopag + mycophenolate, eltrombopag + rituximab (1 each).

Treatments received after the two TPORAs

After the exposure to the second TPORA, all patients received another ITP treatment than corticosteroids or IVIg, and 20 (69.0%) were still on treatment at the end of follow-up. Notably, 13 received rituximab after the exposure to the second TPORA, including seven with no further treatment; four were splenectomized, but three needed another treatment after splenectomy. Eleven patients (37.9%) were exposed to a combination of TPORA + immunosuppressant (Table 1).

Burden outcomes

Burden outcomes are described in Table 2. With a median follow-up of 30.3 months (min–max: 3.2–93.1), all patients with difficult-to-treat primary ITP had experienced bleeding (including one intracranial bleeding), seven (24.1%) an infection, three (10.3%) a venous thrombosis and one (3.5%) an arterial thrombosis. Infections and thromboses are described in Tables S1 and S2 respectively. Among the seven infectious events, three were serious (WHO definition): two urinary tract infections and one *Campylobacter* septicaemia. All four thromboses occurred during an exposure to TPORA; three patients had other risk factors for thrombosis and two patients had thrombocytosis at the time of thrombosis.

The median number of hospital stays for ITP was 7 (min–max: 1–17), with a median cumulative duration of hospital stays for ITP of 31 days (min–max: 6–142). The median number of outpatient hospital contacts was 10 (min–max: 3–30).

Two patients died during the follow-up: an 82-year-old woman 41 months after the ITP diagnosis and a 70-year-old man who developed myelodysplastic syndrome (see below).

Other causes of thrombocytopenia emerging during the follow-up

A myelodysplastic syndrome was diagnosed in two patients, 3 and 4 years after the ITP diagnosis. Both had a bone marrow examination considered normal at ITP diagnosis. The first patient died from complications of the myelodysplastic syndrome.

DISCUSSION

This study demonstrated that difficult-to-treat ITP needing ITP drug after an exposure to two TPORAs account for <5% of all adult patients with primary ITP and 7.6% of those who need at least one second-line treatment. Recently, experts from an intercontinental group suggested a new definition of refractory ITP: platelet count $< 20 \times 10^9/L$ and bleeding, with no or short (<7 days) response to corticosteroids or IVIg, and with no response to two TPORAs, rituximab and

TABLE 2 Outcomes in patients with difficult-to-treat ITP.

| Outcomes | Difficult-to-treat ITP (n=29) |
|---|-------------------------------|
| Number of patients with bleeding during the disease course, n (%) | 29 (100) |
| Median number of bleeding events per patient during the follow-up (min–max) | 4.0 (1.0–13.0) |
| Cumulative incidence of bleeding during the disease course, % [95% CI] | |
| 1-year | 96.6 [82.2, 99.9] |
| 2-year | 100.0 [89.1, 100.0] |
| 3-year | 100.0 [89.1, 100.0] |
| Type of bleeding at least one time during the disease course, n (%) | 29/29 |
| Cutaneous | 28 (96.6) |
| Epistaxis | 15 (51.7) |
| Oral bullae | 25 (86.2) |
| Gross haematuria | 3 (10.3) |
| Menorrhagia or metrorrhagia | 4 (13.8) |
| Gastrointestinal | 3 (10.3) |
| Intracranial | 1 (3.4) |
| Number of patients with infection during the disease course, n (%) | 7 (24.1) |
| Cumulative incidence of infection during the disease course, % [95% CI] | |
| 1-year | 17.2 [7.2, 36.4] |
| 2-year | 20.7 [8.0, 39.7] |
| 3-year | 24.1 [12.2, 42.1] |
| Number of patients with venous thrombosis during the disease course, n (%) | 3 (9.4) |
| Number of patients with arterial thrombosis during the disease course, n (%) | 1 (3.1) |
| Cumulative incidence of any thrombosis during the disease course, % [95% CI] | |
| 1-year | 10.3 [2.2, 27.4] |
| 2-year | 10.3 [2.2, 27.4] |
| 3-year | 13.8 [3.9, 31.7] |
| Median number of hospital visits for ITP during the follow-up (min–max) | 10.0 (3.0–30.0) |
| Median number of hospital stays for ITP during the follow-up (min–max) | 7.0 (1.0–17.0) |
| Median cumulative duration of hospital stays for ITP during the follow-up (min–max), days | 31.0 (6.0–142.0) |

≥1 other immunosuppressive drug.⁵ Our pragmatic definition of ‘difficult-to-treat’ ITP was close, with the need for another treatment after two TPORAs, whatever the reason why. This definition reflects the real-world difficulties in treating patients with ITP and the need for other treatment lines, but it does not necessarily correspond to refractory patients in the meaning of ITP resistant to a drug. However, 6/13 patients who received rituximab after the two TPORAs needed another treatment, and 37.9% of difficult-to-treat

patients needed a combination of TPORA and immunosuppressants like suggested in refractory ITP.^{6,7}

A cornerstone issue face to difficult-to-treat/refractory ITP patients is to reassess the diagnosis to exclude another cause of thrombocytopenia. For clinical practice, ITP is diagnosed by the exclusion of other diagnoses causing thrombocytopenia. A very low platelet count, normal bone marrow aspiration and response to corticosteroids/IVIg are strong arguments for ITP.⁸ In adults, the misdiagnosis of inherited thrombocytopenia is rare,⁹ and none of our patients had genetic testing. In contrast, myelodysplastic syndrome may be misdiagnosed, or a cause of secondary ITP in adults,⁹ with lower rates of response to some ITP treatments.¹⁰ Interestingly, two patients in our study were diagnosed for myelodysplastic syndrome during follow-up, enlightening the need for diagnosis reassessment in case of difficult-to-treat ITP.⁵

The bleeding burden was important in this difficult-to-treat population, with a very low platelet count at diagnosis (median: $6 \times 10^9/L$) and a frequency of bleeding >80%, in contrast with $18 \times 10^9/L$ and 58% in the whole population of adults with ITP in the registry.¹¹ This pattern has been identified in multirefractory patients.⁶ In contrast with this latter retrospective study, the burden of infection was not so important, with only three serious infections in our cohort. This may be explained by the positioning of TPORAs early in the disease course the last decade in France¹² and warning by the referral centres about infection prevention after the evidence of insufficient vaccinations of patients in the early 2010s.¹³ Four thromboses occurred, all during treatment with TPORAs. As previously described, the cumulation of thrombosis risk factors may have played a role in these patients.¹⁴

The main limitation of this study to assess the patient ITP burden is the absence of quality-of-life data. However, we assessed the frequency of hospital contacts and days of hospitalization as surrogates, which leads us to think that the subgroup of adult patients with difficult-to-treat ITP have a high burden of the disease. Another limitation is that all centres in France managing ITP are not participating in the registry. Avatrombopag is not marketed in France; therefore, we cannot assess the proportion of patients who would have needed another treatment after exposure to the three TPORAs.¹⁵ Lastly, like in every real-world cohort, the outcomes are measured at each visit, depending on the real-world follow-up. Measurement bias in this dynamic cohort has been minimized by the inclusion of patients with a minimal follow-up.

In conclusion, adult patients with difficult-to-treat primary ITP has a heavy clinical burden, particularly in terms of bleeding, infection, thrombosis and hospital contact.

AUTHOR CONTRIBUTIONS

G.M. and M.R. designed the study. M.Ma, J.F.V., T.C., S.C., S.A., M.E., L.T., J.C.L., P.Y.J., B.B., M.Mi. and B.G. are members of the registry scientific committee and therefore critically reviewed the protocol. A.D., S.B., A.D., I.H. and H.O.

contributed to protocol reviewing. G.M. and M.R. conducted the statistical analyses. G.M. wrote the paper; all other authors critically reviewed the manuscript and gave final approval for publication. The corresponding author attests that all the listed authors meet the authorship criteria and that no others meeting the criteria have been omitted. G.M. is the guarantor.

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This study was supported by Sanofi Pharma SAS. A.D., S.B., A.D., I.H. and H.O. critically reviewed the protocol. The analyses were made independently by the data managers and statisticians of Toulouse university hospital under the supervision of Dr Guillaume Moulis. Sanofi did not have access to the data contained in the registry. A.D., S.B., A.D., I.H. and H.O. have reviewed the aggregated results and the manuscript written by Dr Guillaume Moulis to give final acceptance like other authors (without any major changes).

CONFLICT OF INTEREST STATEMENT

GM: research funding from Amgen, Grifols, Novartis and Sanofi; advisory board for Amgen, Argencx, Grifols, Novartis, Sanofi and Sobi; meeting attendance grants from Amgen, Grifols and Novartis; speaker at educational sessions for Amgen, Grifols and Novartis. JFV: advisory board and speaker at educational sessions for Amgen, Grifols, Novartis. TC: advisory board and speaker at educational sessions for Abbvie, AstraZeneca, Celgene, Novartis, Takeda. SC reports advisory board for Novartis and Sobi; research funding from Bioverativ, Novartis and Protalex. SA: advisory board and speaker at educational

sessions for Amgen, Argencx, Novartis, Sobi and research grant from Novartis. ME: speaker at educational sessions for Amgen, Grifols and Novartis; advisory board for Grifols and Novartis. BB: speaker at educational sessions for Novartis. MMi: advisory board and speaker at educational sessions for Amgen, Argencx, Novartis, Sobi and UCB. BG: advisory board and speaker at educational sessions for Amgen, Grifols, Novartis and Sobi. AD, SB, AD, IH and HO are employed by Sanofi.

DATA AVAILABILITY STATEMENT

Data are not publicly available. The data management and statistical analysis code is available on reasonable request from the corresponding author.

PATIENT CONSENT STATEMENT

All patients received oral and written information about the registry and their rights. Written consent is not mandatory for this observational study.

CLINICAL TRIAL REGISTRATION (INCLUDING TRIAL NUMBER)

NCT02877706

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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APPENDIX 1

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