Adolescents and young adults with newly diagnosed primary immune thrombocytopenia

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Supplement: Methods

Data source

Data extraction from PARC-ITP and CARMEN registries was approved by the local review boards and national or regional ethics committees. Informed consent was obtained from all participants registered in PARC-ITP. All of the patients in the CARMEN-France registry were informed; no one opposed data collection.

PARC-ITP is an international multicenter registry that collects prospective data from children and adults with newly diagnosed ITP. Operational since May 2004, it studies the natural history of ITP in all age groups. Demographic, diagnostic, and clinical data and therapeutic choices at diagnosis, 6 and 12 months after diagnosis, and yearly thereafter are collected. The registry is sustained by the voluntary participation of pediatric and adult hematologists worldwide (Europe, Asia, North- and South America, and Africa). The participants' geographical distribution has been published elsewhere.[9]

The CARMEN registry is a prospective clinical registry for all adult patients (≥18 years) with incident ITP. Operational since 2013, it initially served the *Midi-Pyrénées* region (South of France), but has since expanded to other centers in France, including the national reference center for autoimmune cytopenias. It was renamed the CARMEN-France registry and describes the clinical features and evolution of ITP; evaluates real-world use, efficacy, and safety of drugs for ITP treatment; and monitors adherence to ITP management guidelines in adults. The participating institutions collect data during each medical checkup of ITP patients.[15]

Outcomes and definitions

Age, sex, initial platelet count, bleeding, comorbidities, and the presence of antiphospholipid and antinuclear antibodies (ANAs) were analyzed at diagnosis. Thrombocytopenia was

categorized as severe, moderate, and mild for platelet counts of $<20 \times 10^9$/L, $20–49 \times 10^9$/L, and $50–99 \times 10^9$/L, respectively. Bleeding was defined as any hemorrhagic event, regardless of intensity and frequency. Oral bleeding included spontaneous bleeding or after dental care. Epistaxis included some rare cases of hemoptysis. Gynecological bleeding was defined as menorrhagia or metrorrhagia. Mucosal bleeding (oral, epistaxis, hematuria, menorrhea, or gastrointestinal) was defined as wet bleeding. Both registries recorded infectious, autoimmune (rheumatoid arthritis and psoriasis), cardiovascular, pulmonary, gastrointestinal, and endocrinological (diseases related to the thyroid) diseases as well as cancer and splenomegaly as comorbid conditions. Patients with comorbidities raising suspicion of secondary ITP (e.g., systemic autoimmune diseases, splenomegaly, and lymphoproliferative disease) were excluded from the analysis according to Rodeghiero et al.[4]

Antiphospholipid antibody status was considered positive if lupus anticoagulant, anticardiolipin, and/or anti-ß2-GPI antibodies were positive. The two registries defined ANA differently. The CARMEN registry considered ANA positive with a titer of ≥1:160, whereas the PARC registry had no threshold. Thus, different sites varied in their thresholds and interpretations.

Any follow-up (FU) visit at 3–9 months and 11–18 months was designated as 6- and 12-month FU visits, respectively. Platelet counts were recorded as a single value at the nearest FU. Bleeding included all hemorrhagic events during the last observation period, and treatment information was recorded between two consecutive FU visits**.** Initial therapy was defined as ITP treatment within 1 week of diagnosis and not lasting more than four weeks. All FU treatments between 1 and 6 months and 6 and 12 months were recorded. In order to harmonize the data in both registries, the following drugs had to be listed in the category "other drugs:" dapsone, hydroxychloroquine, belimumab, fostamatinib, and study drugs.

Supplementary Tables and Figure

Table S1. Description of four cases of intracranial bleeding.

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4
ICH time point	Initial	Initial	At Follow-up	At Follow-up
Age (years)	**16**	**15**	**15**	**23**
Gender	male	male	female	female
Country	Canada	Egypt	United States	Brazil
Comorbidities	Infection, splenomegaly	Obesity	-	-
Comedication	-	-	-	-
Initial platelet count ($\times 10^9$/l)	7	10	2	10
Bleeding type at diagnosis	ICH + cu	ICH + cu + ep + ob	cu + ob	cu + ob + gy
Initial treatment	co	co + IVIG	IVIG	co
Remission status at 12 months	NR	NR	Unclear	Unclear

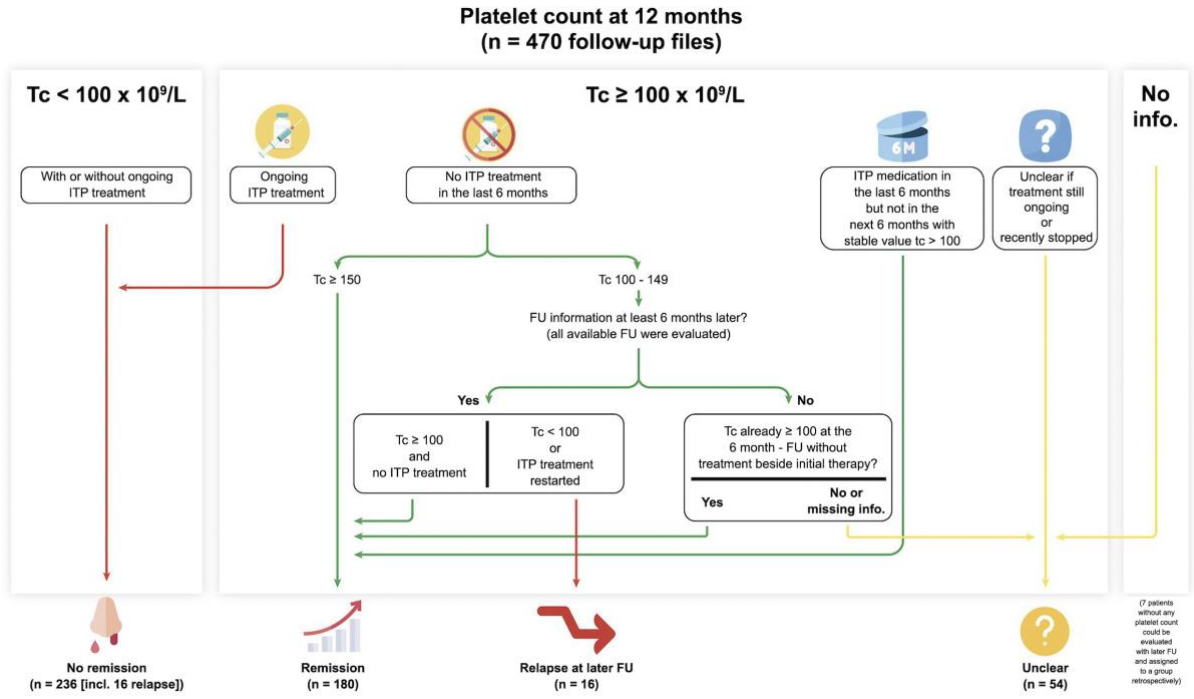
ICH: intracranial bleeding, cu: cutaneous bleeding, ep: epistaxis, ob: oral bleeding, gy: gynecological bleeding
co: corticosteroids, IVIG: intravenou immunoglobulins, Anti-D: Anti-D immunoglobulins, NR: no remission.

Table S2: Comparison of adolescents and young adults with previous publications on children and adults from the PARC registry[9]

Characteristics	AYAS (12–25 years)	Adults (≥16 years) [9]	Children (<16 years) [9]
Total patients	656	420	3360
Female (%)	402 (61)	272 (65)	1609 (48)
Mean age (SD)	15·3 (2·5)	38 (19)	5·2 (4·1)
Comorbidities (%)	100 (15)	129 (31)	360 (11)
Initial median platelet count $\times 10^9$/l (IQR)	12 (5;28)	14 (5;36)	11 (5;21)
No bleeding at disease onset (%)	118 (18)	122 (29)	449 (13)
Initial platelet-enhancing treatment (%)	431 (66)	280 (67)	2331 (69)
Chronic disease (%)*	236/416 (57)	138/271 (51)	479/1639 (29)

AYAS: Adolescent and young adults; PARC: Pediatric and Adult Registry; IQR: interquartile range
% refers to the total number of patients in the age subgroup
* Probably underestimated in PARC (2018): Patients with Tc > 100 × 10e9/L receiving platelet-enhancing drugs at the time of measurement or shortly before were included in the remission group.

Figure S1. Evaluation and definition of remission status in the combined PARC and CARMEN registries.



Legend: Decision tree for classifying the status of patients as either in remission or not in remission at 12 months. To accurately classify the patients in remission and the patients with chronic disease, the observation period for some of the patients was extended to >12 months of follow-up:

1. Patients followed up on until 12 months of follow-up (FU) only:
- Patients with platelet count (Tc) ≥ 150× 10^9/L at the 12-month FU and reporting no drugs since 6 months
- Patients with Tc < 100 × 10^9/L at 12 months
- Patients on ITP treatment at 12 months

2. Patients with an observation period longer than the 12-month FU:
- Patients with Tc >100 × 10^9/L who have taken some ITP drugs in the last 6 months (differential diagnosis "response")
- Patients with Tc between 100 and 149 × 10^9/L at 12 months and reporting no drugs in the last 6 months were carefully evaluated at all available FU. If a relapse was documented, then we corrected the remission status.

The list of participating physicians is as follows:

Intercontinental Cooperative ITP Study Group (ICIS) investigators:

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