Immune thrombocytopenia in adults: a prospective cohort study of clinical features and predictors of outcome

by Lamiae Grimaldi-Bensouda, Clementine Nordon, Marc Michel, Jean-François Viallard, Daniel Adoue, Nadine Magy-Bertrand, Jean-Marc Durand, Philippe Quittet, Olivier Fain, Bernard Bonnotte, Anne-Sophie Morin, Nathalie Morel, Nathalie Costedoat-Chalumeau, Brigitte Pan-Petesch, Mehdi Khellaf, Antoinette Perlat, Karim Sacre, François Lefrere, Lucien Abenhaim, and Bertrand Godeau

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Immune thrombocytopenia in adults: a prospective cohort study of clinical features and predictors of outcome.

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*Contributing members of the PGRx-ITP Study Group are listed at the end of the manuscript

**Statement of equal authors' contribution:** LGB contributed to the study design, conduct and data analysis; CN contributed to data analysis and wrote the manuscript; MM participated in the recruitment and follow-up of patients, and the writing of the manuscript; JFV, DA, NMB, MK, JMD, PQ, OF, BB, NM, NCC, BPP, AP, KS, and FL participated in the recruitment and follow-up of patients as well as data collection; LA contributed to the study design; BG contributed to the study design, participated in the recruitment and follow-up of patients, and in the writing of the manuscript. All authors read and approved the final version of the manuscript for publication.
Contributions Emmanuelle Smith and Rita Moreira De Silva performed the English language editing.

Conflict of interest statement LGB, CN, and LA, who is also a stockowner and chairman, are currently employed by LASER, Research and Consulting Agency, an independent research organization that owns and develops the PGRx System database and working with the pharmaceutical industry, therefore collaborating with virtually any pharmaceutical company. LASER has no commercial interests in any of the products studied. Members of the LASER network have no interest in any drug or other factors studied. Private companies or agencies using PGRx for their studies obtain data by subscription. MM, JFV, DA, NMB, MK, JMD, PQ, OF, BB, NM, NCC, BPP, AP, KS, FR declare no conflicts of interest. BG has served as a consultant for Amgen and GSK and received research support from Roche, participated on advisory boards and/or as a speaker at medical education events supported by Amgen, Roche and GSK and declares no other competing financial interests.

Ethics approval This research was approved by the consultative committee for non-interventional research (“comité consultatif sur le traitement de l'information en matière de recherche”) and the French Data Protection Authority (“commission nationale de l'informatique et des libertés”) was informed that data was being collected for this purpose. All patients included in the PRGx database provided informed consent.

Running head Outcome of immune thrombocytopenia in adults
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This prospective observational cohort study aimed to explore the clinical features of incident immune thrombocytopenia in adults and predictors of outcome, while determining if a family history of autoimmune disorder is a risk factor for immune thrombocytopenia. All adults, 18 years of age or older, recently diagnosed with immune thrombocytopenia were consecutively recruited across 21 hospital centers in France. Data were collected at diagnosis and 12 months after. Predictors of chronicity at 12 months were explored using logistic regression models. The association between family history of autoimmune disorder and the risk of developing immune thrombocytopenia was explored using a conditional logistic regression model, after matching each case to 10 controls. One hundred and forty-three patients were included: 63% were female, mean age was 48 years old (Standard Deviation=19), and 84% presented with bleeding symptoms. The median platelet count was $10 \times 10^9$/$L$. Initial treatment was required in 82% of patients. After 12 months, only 37% of patients not subject to disease-modifying interventions achieved cure. The sole possible predictor of chronicity at 12 months was a higher platelet count at baseline [Odds Ratio 1.03; 95%CI=1.00, 1.06]. No association was evidenced between the outcome and any of the following features: age, gender, presence of either bleeding symptoms or antinuclear antibodies at diagnosis. Likewise, family history of autoimmune disorder was not associated with incident immune thrombocytopenia. Immune thrombocytopenia in adults has shown to progress to a chronic form in the majority of patients. A lower platelet count could be indicative of a more favorable outcome.

Keywords

Immune thrombocytopenia; Platelet Count; Prospective Studies; Adult
INTRODUCTION

Immune thrombocytopenia (ITP) is an autoimmune disorder mediated by platelet antibodies thought to accelerate platelet destruction while inhibiting also their production,\(^1\) resulting in low platelet counts with potentially spontaneous bruising, petechial rash, mucosal bleeding or even life-threatening hemorrhage. ITP affects children and adults, with an incidence rate for the latter estimated between 2.8 and 3.9 per 100,000 person-years in Europe,\(^2,6\) and namely 2.9/100,000 in France.\(^6\) The onset of ITP is frequently insidious and low platelet counts often last beyond six months.\(^7\) A recent retrospective study based on administrative registers reported that about two thirds of adult ITP patients are likely to develop a chronic form of the disease.\(^6\) The risk factors for chronicity were mainly explored in children\(^8-10\) and rarely in adults.\(^11\) Regarding the genetic risk, a few studies reported clusters of ITP incidence within families,\(^12,13\) but it is unknown whether a family history of autoimmune disorder can be a risk factor for developing ITP.

In France, a nationwide prospective cohort of adult patients presenting with a newly diagnosed episode of ITP was constituted primarily to explore the association between exposure to common vaccines and risk of developing ITP.\(^14\) In this context, the present study aimed at describing the clinical features of adult ITP and its evolution over a 12-month period and exploring the baseline predictors of chronicity. We also explored whether a history of autoimmune disorder in first-degree relatives could constitute a risk factor for developing ITP.

METHODS

Source of data

This was a prospective observational cohort study using data from the Pharmacoepidemiologic General Research eXtension (PGRx) information system which is a set of population-based registries including case-patients (cases) with specific diseases.
recruited by their specialist physician and referent-patients (controls) routinely recruited by
their general practitioner (GP).\textsuperscript{14,15} Inclusion and exclusion criteria are similar for cases and
controls, except for the disease of interest. Medical information is collected by specialists –
for cases – and GPs – for controls. All patients undergo the same standardized telephone
interview collecting information on family medical history, lifestyle and medication use.

\textit{Study population}

Participating physicians in the “PGRx-ITP” registry were requested to consecutively include
cases of ITP, \textit{i.e.}, all the patients meeting the following criteria: (1) age between 18 and 79
years; (2) diagnosis of primary ITP according to international consensus;\textsuperscript{16} (3) delay between
the first symptoms of ITP and inclusion <365 days; (4) normal physical examination, except
for bleeding symptoms; (5) living in continental France; (6) able to understand and read
French; and (7) agreeing to participate. The process used for diagnosis ascertainment was
strict (see Appendix and Table 1). In order to determine whether a history of autoimmune
disorder in first-degree relatives constituted a risk factor for developing ITP or not, up to 10
controls with no lifetime history of ITP were identified from the “PGRx-General Practice”
registry and matched to each case on gender, age (± 1 year), and inclusion date (± 5 years).

\textit{Measures}

All patient data were collected through dedicated case report forms (CRFs), similar in cases
and controls regarding socio-demographics, personal medical history and family history of
autoimmune disorder (in first-degree relatives): multiple sclerosis, lupus, rheumatoid arthritis,
Crohn’s disease, chronic ulcerative colitis, Hashimoto’s thyroiditis or Graves-Basedow
disease. In cases, data were also collected on the ITP at baseline and after 12 months of
follow-up (see Appendix). The time elapsing between diagnosis and outcome measure at 12
months was preferred, given that first symptoms are often more difficult to specify. Recovery
and chronicity were defined as in Table 1.
Statistical Analyses

Analyses were performed with SAS software version 9.3\textsuperscript{19} and all comparative tests were two-sided with a type-1 error set at $\alpha=0.05$. Bleeding symptoms were categorized into: (a) no bleeding; (b) cutaneous bleeding alone; and (c) severe bleeding defined as mucocutaneous and/or visceral bleeding (epistaxis, or bleeding of the mucous membrane, or visceral bleeding). The titration of antinuclear antibodies (ANA) was considered positive if the titer was $>1/80$. The detailed statistical plan is provided in Annex.

Ethics approval

This research was approved by the consultative committee for non-interventional research (“comité consultatif sur le traitement de l'information en matière de recherche”) and the French Data Protection Authority (“commission nationale de l'informatique et des libertés”) was informed that data was being collected for this purpose. All patients included in the PRGx database provided informed consent.

RESULTS

Over a 28-month period, 188 patients diagnosed with ITP were consecutively included in the “PGRx-ITP” registry by hematologists and internists from 21 hospitals across France. Of these, 18 patients were excluded once completing the diagnostic ascertainment process and another 27 patients were excluded as a result of failure to confirm diagnosis of ITP at 3 months, thus leaving 143 patients for analysis.

Characteristics of ITP at onset

A median of 35 days elapsed between the first symptoms and inclusion in the study, and 35 (24.5\%) patients were recruited at 90 days or later following the onset of ITP symptoms. Figure 1 and Table 2 resume the characteristics of the 143 patients and incident ITPs upon diagnosis. The median age was 50 years and on average there were more female than male,
with a female/male ratio of 1.6 overall but which dropped to 1 in patients older than 50 years. Information on family history of autoimmune disorder was available in 109 (76.2%) patients. In 23 (16.1%) patients, bleeding symptoms were absent and the diagnosis was made fortuitously after a routine blood test. Visceral bleeding was present in 7 (4.9%) patients and none of the patients presented with intracerebral hemorrhage. The median platelet count was 10×10⁹/L, and 99 (69.2%) patients showed values <20×10⁹/L at presentation. A bone marrow aspiration was performed in 111 (77.6%) patients, namely in 93.5% of patients over 60 years old (n=43). ANA was tested in 136 (95.1%) patients. A “watch and wait” strategy was decided for 18 (12.6%) patients. Among patients initiating treatment, 61 (48.8%) were administered corticosteroids and intravenous immunoglobulins (IVIg), 50 (40.0%) corticosteroids alone, and 14 (11.2%) IVIg alone. In 7 patients, additional therapy was necessary (vinblastine, vincristine or platelet transfusion).

Table 3 provides comparisons among 35 patients testing positive for ANA (titer>1/80) and 101 patients with a negative ANA test. The two groups differed, albeit non-significantly, in terms of bleeding symptoms at diagnosis – the absence of such symptoms being more frequent in patients testing positive for ANA. The presence of a family history of autoimmune disorder was twice as frequent in patients with a positive ANA test, yet not statistically significant. Other characteristics (age, gender, and platelet count) did not differ between groups.

Twelve-month outcome

A total of 28 (19.6%) patients were lost to follow-up at twelve months after ITP was first diagnosed. Among the 115 patients with data available at one year, 58 (50.4%) showed progression to chronic ITP whereas 57 recovered: 43 (37.4%) did it spontaneously (i.e., with no disease-modifying treatment) and 14 (12.2%) achieved cure with a disease-modifying treatment: either rituximab alone (n=12) or rituximab plus splenectomy (n=2).
Table 4 provides the results from univariate logistic regression models exploring the baseline factors associated with 12-month outcome in patients showing progression to chronic ITP (n=58) and patients with spontaneous recovery (n=43). The presence of a higher platelet count or the absence of severe bleeding at baseline was found to be associated with increased odds of chronicity at 12 months. No difference was found among patients in terms of gender, age and testing positive for ANA. A bivariate model was fitted to explore the independent predictive effect of platelet counts (continuous variable) and severe bleeding (severe vs. no bleeding or cutaneous bleeding alone) at baseline. The model revealed that severe bleeding was not associated with chronicity (OR=0.47; 95%CI=0.19, 1.19; p=0.11), whereas a higher platelet count remained associated with increased odds of chronicity, despite not reaching the 0.05 significance level (OR=1.03; 95%CI=1.00, 1.06; p=0.08). The interpretation of this result needs to take into account that "platelet counts" have been used as a continuous variable: for every 10x10⁹/L increase in the platelet counts (e.g., from 10x10⁹/L to 20x10⁹/L, or from 20x10⁹/L to 30x10⁹/L), the equivalent increase in terms of odds of chronicity is about 34%. All results were similar when exploring the odds of chronicity vs. recovery, which included also patients who recovered after disease-modifying treatment (data not shown).

**Family history of autoimmune disorder**

A familial history of auto-immune disorder was found in 9 (8.3%) out of the 109 case-patients explored. Table 5 provides the results from conditional logistic regression models comparing 109 case-patients to 913 controls matched on gender, age, and inclusion date. Overall, having a first-degree relative with a history of autoimmune disorder was not associated with increased odds of developing ITP. No association was found in either the subgroup of ITP patients with a positive ANA test at baseline or the subgroup of ITP patients progressing to a chronic form of the disease.
**DISCUSSION**

**Main results**

Epidemiology data on ITP has been thus far based on retrospective studies and/or administrative registers.\(^6,22\) We hereby report for the first time results based on a prospective nationwide cohort of adults with incident ITP consecutively studied, using stringent diagnostic criteria and followed up for at least one year. This one-year follow-up study releases interesting insights into characteristics of ITP as well as the risk factors predicting which patients will evolve to chronic forms of the disease.

First, our results reiterate earlier findings that ITP in adults is more frequently found in females, with a female/male ratio of 1.7 overall and a female/male ratio of 2.8 for patients between the ages 18 and 49 years. Both ratios are concordant with previous results.\(^23,24\) Regarding the clinical symptoms of ITP, only 16% of patients with ITP showed no signs of bleeding, a figure that is twice as low as the one reported in the observational study “PARC-ITP Registry”.\(^24\) This discrepancy in results may be explained by the diagnostic ascertainment process used in our study. In the present study, patients with no bleeding symptoms and no record of a normal platelet count in the preceding year were excluded, thus overestimating the frequency of bleeding symptoms at diagnosis. It is interesting to note that only 4.9% of patients presented with visceral bleeding at baseline and that no patient had a fatal hemorrhage, thus confirming that ITP is rarely associated with life-threatening bleeding events at diagnosis.\(^25\)

Second, our results evidence that a large majority of adults with newly diagnosed ITP are likely to develop a chronic form of the disease after one year. In our sample, only 37% of patients “spontaneously” recovered, that is, without the need for disease-modifying treatment such as rituximab or splenectomy. That confirms previous data suggesting that ITP is more
likely to follow a chronic course in affected adults, as opposed to children in whom cure is achieved within several weeks in most patients.\textsuperscript{10}

In this context, the ability to predict the course of newly diagnosed ITP in adults is crucial for both patients and physicians, allowing for a potential decrease in healthcare costs, patients’ anxiety, and less need for aggressive initial treatment, such as splenectomy or immunosuppressant drugs. Our results confirm that gender and age are not risk factors for chronicity.\textsuperscript{26} Likewise, no association was evidenced between bleeding symptoms at baseline and chronicity. Interestingly, a higher platelet count at baseline was found to be associated with increased odds of chronicity at 12 months, independent of confounders. However, it did not reach the 5\% level of significance and further studies would be necessary to confirm, or deny, this association, which was also found when considering all patients recovering from ITP, regardless of disease-modifying treatment. Although interesting, this predictive association is insufficiently robust to be considered for clinical practice and to be taken into account by physicians when tailoring treatment decisions to individual patients. In our opinion, clinicians would be able to reliably predict progression to chronic status only through the use of clinical and biological factors combined. We previously reported that the presence of platelet antibodies detected by a MAIPA assay could help in predicting chronicity in ITP.\textsuperscript{11} However, the poor sensitivity of this test and its limited availability in many countries restricts its potential use. In the present study, the detection of platelet antibodies using a MAIPA assay was not systematically performed across all the participant hospitals, and therefore this measure was not taken into account. Other clinical and biological predictive factors should therefore be identified.

Third, the present findings provide further insight on the frequency and prognostic value of autoimmune markers, particularly ANA at ITP onset, which were so far controversial.\textsuperscript{27,28} ANA has been found to be a possible predictor of chronicity in childhood ITP.\textsuperscript{28} In adults,
this is most likely not the case. We previously reported, in a retrospective study focused on adults, that the presence of autoimmune markers did not correlate with presenting features, response to treatments, or long-term outcome of ITP. These conflicting results explain why assays for ANA are not routinely recommended by an international panel of experts. In our sample, assays for ANA were performed at baseline in nearly all of the participants and the test was found positive (titer>1/80) in more than 25% of patients, a finding that is in line with previous reports. In patients with a positive ANA titer, the absence of bleeding symptoms was significantly more frequent, and unsurprisingly, the proportion of females was higher than that of males, and the presence of autoimmune disorder history in first-degree relatives was twice as frequent, although not significantly, probably because of low sample size and insufficient statistical power. Unexpectedly, a positive ANA titer was not associated with ITP evolution. These results suggest that routine ANA assays appear non-mandatory in newly diagnosed ITP in adults. However, taking into account that the follow-up period for our study was limited to one year, we cannot exclude that the presence of ANA at the time of diagnosis may be a risk factor for late development of systemic lupus erythematosus.

Finally, using a case-control design, we explored whether a family history of autoimmune disorder was a risk factor of developing ITP in adulthood. Our results suggest that such is not the case.

**Study limitations**

The study setting used the entire network of French reference centers, which are highly specialized centers for ITP. Thus, more severe patients could have been included. However, there is no reason to believe that this selection bias confounded the predictive value of patient characteristics or modified the results regarding family history of autoimmune disorder. Due to strict eligibility criteria for the analyses, the population used for the analyses consisted of 143 out of 188 adult patients initially identified and recruited. The choice to select patients
with confirmed diagnosis of primary and incident ITP has consequently lowered the statistical power for some analyses, in particular regarding any association between ANA positivity and patients’ characteristics.

Conclusion

The study confirms that ITP is more common in women than men, and is frequently associated with cutaneous bleeding, even if life-threatening bleeding is rare. Initial treatment is required in more than 80% of patients and only 37% of patients achieve cure at one year of follow up with no need for disease-modifying treatment, indicating that ITP is a chronic disease in adults with a less favorable outcome compared to children. The predictors of chronicity were explored prospectively for the first time in adults, suggesting that higher platelet counts at diagnosis are negatively correlated with the risk of chronicity. However, further research is needed to confirm this finding and potentially to identify other predictive factors for chronicity at the time of diagnosis.
REFERENCES


<table>
<thead>
<tr>
<th>Condition</th>
<th>Definition</th>
<th>Exclusion/inclusion criteria</th>
</tr>
</thead>
</table>
| Isolated thrombocytopenia | • platelet count <100x10^9/L at baseline  
• in the absence of abnormality at physical examination, aside from bleeding                                                                                                                                  | Patients with platelet count ≥100x10^9/L at baseline were excluded.                                                                                                                                                         |
| Secondary ITP              | • titration of human immunodeficiency virus (HIV) or hepatitis C virus (HCV) either not performed or returning a positive result  
• and/or any of the following comorbidities: lymphoproliferative disorder, definite antiphospholipid syndrome, common variable immunodeficiency, thyroid disease, and overt systemic lupus erythematosus | All patients diagnosed with secondary ITP were excluded.                                                                                                                                                                  |
| Incident ITP               | • presence of thrombocytopenia (<100x10^9/L) upon diagnosis  
• with a reference platelet count >150x10^9/L in the 12 months preceding diagnosis, even in the absence of bleeding symptoms upon diagnosis                                                                 | In the absence of a reference platelet count >150x10^9/L in the 12 months preceding diagnosis, only patients with both acute bleeding symptoms and a platelet count ≤50x10^9/L were not excluded.  
Also, patients showing a delay between the first symptoms and inclusion of more than 365 days were excluded.                                                                 |
| Recovery at 12 months      | • platelet count ≥100x10^9/L  
• in the absence of ongoing treatment for ITP in the previous 8 weeks                                                                                                                                 | Patients showing a platelet count ≥100x10^9/L at 12 months but who had been treated for ITP in the previous 8 weeks, were subject to a new evaluation at 14 months and considered cured only if showing a sustained response without treatment between 12 and 14 months. |
| Chronic ITP               | Platelet count <100x10^9/L at 12 months, regardless of treatment.                                                                                                                                                                                                   |                                                                                                                                                                                                                           |
Table 2. Characteristics and initial medical management of 143 adult patients diagnosed with a first lifetime episode of immune thrombocytopenia

<table>
<thead>
<tr>
<th>Clinical and biological features</th>
<th>Patients with an incident ITP (N=143)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median delay (in days) between 1st symptoms and inclusion [min, max]</td>
<td>35 [2 – 343]</td>
</tr>
<tr>
<td><strong>Clinical and biological features</strong></td>
<td>n (%)</td>
</tr>
<tr>
<td>Mean age (years) [SD]¹</td>
<td>47.8 [18.6]</td>
</tr>
<tr>
<td>Female (overall)</td>
<td>90 (62.9%)</td>
</tr>
<tr>
<td>18-49 years (n=71)</td>
<td>53 (74.6%)</td>
</tr>
<tr>
<td>50-79 years (n=72)</td>
<td>37 (51.4%)</td>
</tr>
<tr>
<td>Family history of autoimmune disorder² (n=109)</td>
<td>9 (8.3%)</td>
</tr>
<tr>
<td>Rapid onset of symptoms</td>
<td>117 (81.8%)</td>
</tr>
<tr>
<td>Bleeding symptoms</td>
<td></td>
</tr>
<tr>
<td>No bleeding symptoms</td>
<td>23 (16.1%)</td>
</tr>
<tr>
<td>Cutaneous bleeding only</td>
<td>40 (28.0%)</td>
</tr>
<tr>
<td>Severe bleeding³</td>
<td>80 (55.9%)</td>
</tr>
<tr>
<td>Mean platelet count (x10⁹/L) [SD]¹</td>
<td>16.0 [17.2]</td>
</tr>
<tr>
<td>Positive ANA test (&gt;1/80) (n=136)</td>
<td>35 (25.7%)</td>
</tr>
<tr>
<td><strong>Medical management</strong></td>
<td>n (%)</td>
</tr>
<tr>
<td>“Watch and wait” strategy</td>
<td>18 (12.6%)</td>
</tr>
<tr>
<td>Initiation of a treatment</td>
<td>125 (87.4%)</td>
</tr>
<tr>
<td>Including corticosteroids</td>
<td>111 (77.6%)</td>
</tr>
<tr>
<td>Including intravenous immunoglobulin</td>
<td>75 (52.5%)</td>
</tr>
<tr>
<td>Including other treatment⁴</td>
<td>7 (4.9%)</td>
</tr>
</tbody>
</table>

¹Mean and Standard Deviation (SD) are described for parameters assumed to be normally-distributed; ²Family history of autoimmune disorder included the following in first-degree relatives: lupus, rheumatoid arthritis, multiple sclerosis, Crohn’s disease, chronic ulcerative colitis, autoimmune thyroiditis; ³Severe bleeding included epistaxis and/or mucous membranes and visceral bleeding (gastrointestinal, cerebral, gynaecological, etc.); ⁴Other treatment included platelet transfusion, dapsone, vincristine, or vinblastine.
Table 3. Comparison of patients testing positive (>1/80) or negative for antinuclear antibodies (ANA) at baseline, in 136 patients with a newly diagnosed episode of immune thrombocytopenia

<table>
<thead>
<tr>
<th></th>
<th>Positive ANA (N=35)</th>
<th>Negative ANA (N=101)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Female gender</td>
<td>25 (71.4%)</td>
<td>61 (60.4%)</td>
<td>0.2460</td>
</tr>
<tr>
<td>Mean age at diagnosis [SD]**</td>
<td>48.9 [22.3]</td>
<td>46.8 [17.3]</td>
<td>0.5686</td>
</tr>
<tr>
<td>Presence of bleeding symptoms</td>
<td>26 (74.3%)</td>
<td>88 (87.1%)</td>
<td>0.0808</td>
</tr>
<tr>
<td>Mean platelet count³ [SD]</td>
<td>18.1 [16.9]</td>
<td>15.2 [16.9]</td>
<td>0.3752</td>
</tr>
<tr>
<td>Family history of AID⁴</td>
<td>n=30</td>
<td>n=73</td>
<td>0.1895</td>
</tr>
<tr>
<td></td>
<td>4 (13.3%)</td>
<td>4 (5.5%)</td>
<td></td>
</tr>
</tbody>
</table>

*p-values from Pearson’s chi-square test or Fisher’s exact test (categorical variables) and Mann-Whitney test (age, platelet count), as appropriate; ²Mean and Standard Deviation (SD) are described for parameters assumed to be normally-distributed; ³expressed in 10⁹/L; ⁴AID=autoimmune disorder, including multiple sclerosis, lupus, rheumatoid arthritis, Crohn’s disease, chronic ulcerative colitis, and autoimmune thyroiditis.
Table 4. Baseline factors associated with the 12-month outcome, in adults recently diagnosed with an immune thrombocytopenia (ITP); patients who recovered without any disease-modifying drug are compared to patients with chronic ITP; results of univariate logistic regression models providing Odds Ratio (OR) and 95% Confidence Intervals (95%CI)

<table>
<thead>
<tr>
<th></th>
<th>Recovery without disease-modifying drug</th>
<th>Chronic ITP</th>
<th>OR [95% CI]</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=43</td>
<td>N=58</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female gender (vs. male)</td>
<td>27 (62.8%)</td>
<td>39 (67.2%)</td>
<td>1.22 [0.53 - 2.78]</td>
<td>0.64</td>
</tr>
<tr>
<td>Mean age [SD]¹</td>
<td>47.0 [19.7]</td>
<td>45.4 [16.6]</td>
<td>1.00 [0.97 – 1.02]</td>
<td>0.66</td>
</tr>
<tr>
<td>Bleeding symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No bleeding symptoms (=ref)</td>
<td>5 (11.6%)</td>
<td>14 (24.1%)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Cutaneous bleeding only</td>
<td>10 (23.3%)</td>
<td>22 (37.9%)</td>
<td>0.79 [0.22 - 2.79]</td>
<td>0.71</td>
</tr>
<tr>
<td>Severe bleeding²</td>
<td>28 (65.1%)</td>
<td>22 (37.9%)</td>
<td>0.28 [0.09 - 0.90]</td>
<td>0.032</td>
</tr>
<tr>
<td>Mean platelet count [SD]³</td>
<td>10.7 [11.4]</td>
<td>20.2 [19.7]</td>
<td>1.04 [1.01 - 1.07]</td>
<td>0.010</td>
</tr>
<tr>
<td>ANA³ dosage negative (=ref)</td>
<td>27 (62.8%)</td>
<td>38 (65.5%)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>13 (30.2%)</td>
<td>19 (32.8%)</td>
<td>1.04 [0.44 - 2.46]</td>
<td>0.93</td>
</tr>
</tbody>
</table>

¹Mean and Standard Deviation (SD) are described for parameters assumed to be normally-distributed; ²Severe bleeding included epistaxis and/or mucous membranes and visceral bleeding (gastrointestinal, cerebral, gynaecological…); ³expressed in 10⁹/L; ⁴Antinuclear antibodies
Table 5. Association between family history of autoimmune disorder and risk of developing an immune thrombocytopenia (ITP) in the adult age; results of univariate conditional logistic regression models providing Odds Ratio (OR) and 95% Confidence Intervals (95%CI)

<table>
<thead>
<tr>
<th></th>
<th>Case-patients(^1) with a newly diagnosed ITP n (%)</th>
<th>Controls(^2) with no lifetime ITP n (%)</th>
<th>OR [95% CI]</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>In all patients</td>
<td>N=109</td>
<td>N=913</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family history of AID(^3)</td>
<td>9 (8.3%)</td>
<td>103 (11.3%)</td>
<td>0.83 [0.40 - 1.71]</td>
<td>0.614</td>
</tr>
<tr>
<td>In patients with positive ANA(^4) (titre&gt;1/80)</td>
<td>n=30</td>
<td>n=241</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family history of AID</td>
<td>4 (13.3%)</td>
<td>24 (10.0%)</td>
<td>1.43 [0.46 - 4.43]</td>
<td>0.535</td>
</tr>
<tr>
<td>In patients with chronic ITP at 12-month</td>
<td>n=50</td>
<td>n=372</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family history of AID</td>
<td>4 (8.0%)</td>
<td>40 (10.8%)</td>
<td>0.87 [0.29 - 2.59]</td>
<td>0.798</td>
</tr>
</tbody>
</table>

\(^1\)Cases were adult patients with a first lifetime episode of ITP recruited in specialized centres;  \(^2\)Controls were adults with no lifetime history of ITP and recruited in a population-based cohort; cases and controls are matched for age, gender and index date;  \(^3\)Auto-Immune Disorders (AID) included lupus, rheumatoid arthritis, multiple sclerosis, Crohn’s disease, chronic ulcerative colitis, autoimmune thyroiditis;  \(^4\)Antinuclear antibodies
Figure 1. Distribution of age and gender, in 143 adults diagnosed with a first lifetime episode of immune thrombocytopenia.
Appendix

METHODS

ITP diagnosis ascertainment

The primary objective of the PGRx-ITP registry was to establish if vaccination (several types) could be a risk factor for the development of ITP,\(^1\) enabling a strict diagnostic ascertainment process.

First, the diagnosis of incident and non-secondary ITP was systematically ascertained by the research team for all of the patients included, using criteria established by international guidelines:\(^2\) (1) isolated thrombocytopenia, (2) absence of secondary ITP, and (3) incident (i.e., newly diagnosed) ITP. The definitions used for isolated thrombocytopenia, secondary ITP and incident ITP are detailed in Table 1.

Second, the recruiting physicians were systematically requested by email to confirm the diagnosis 3 months after first recruiting a patient. All patients with a non-confirmed diagnosis were excluded.

Case report forms for ITP patients

Upon inclusion, the recruiting physician was responsible for filling in the following information:

- date of first ITP symptoms
- date of diagnosis and inclusion
- mode of onset
- clinical presentation at diagnosis
- blood test results (namely platelet count) at diagnosis
- titration of antinuclear antibodies (ANA), if tested
• results of a bone-marrow examination, if done (recommended in France for patients over 60 years old)³
• initial therapeutic management of ITP

Twelve months after diagnosis, all recruiting physicians completed data on the outcome of ITP:
• treatments administered to patients over this period
• current platelet count
• recovery or progression to chronic ITP

Statistical analyses
Parametric tests were used to compare patients testing positive for ANA (titer>1/80) and patients testing negative at baseline, regarding age, gender, history of autoimmune disorder in first-degree relatives, bleeding symptoms and platelet count at baseline.

Univariate logistic regression models were used to identify baseline variables associated to the 12-month outcome (chronicity vs. recovery), providing Odds Ratios (OR) and 95% Confidence Intervals (95%CI). The potential baseline predictors were determined a priori: gender, age, bleeding symptoms, platelet count and positive ANA test. These analyses were performed in all patients and then restricted to patients not managed with any disease-modifying intervention (defined as the use of rituximab and/or splenectomy) during the 12 months as these treatments are thought to modify the natural course of ITP.⁴,⁵

Univariate conditional logistic regression models were used to determine whether a history of autoimmune disorder in first-degree relatives was a risk factor for developing ITP or not, cases and their matched controls were compared using. These analyses were performed in the entire set of patients and in the sub-group of cases showing positive ANA test at baseline and the sub-group of cases showing progression to chronic ITP at 12 months.
Literature citations


