No increased risk of acute myeloid leukemia in adults with primary immune thrombocytopenia treated with thrombopoietin receptor agonists: a French nationwide population-based study

Immune thrombocytopenia (ITP) is a rare autoimmune disease due to platelet destruction and impaired megacaryopoiesis.[1] Thrombopoietin receptor agonists (TPO-RA) are widely used as second-line treatment in ITP.[2-4] Due to the presence of the thrombopoietin receptor on hematopoietic stem cells, the possibility of leukemogenic risk with TPO-RA is a concern.[5] In 2013, a pharmacovigilance study in the Food and Drug Administration Adverse Event Reporting System database identified 62 spontaneous reports of acute myeloid leukemia (AML) among a total of 4,821 adverse drug reactions reported in patients with ITP between 2002 and 2011.[6] An association between AML reports and the exposure to TPO-RA was found with an adjusted reporting odds ratio of 10.5 (95% confidence interval [CI]: 3.3-34.2) for romiplostim and 5.9 (95% CI: 1.9-18.3) for eltrombopag.

Because many factors influence the spontaneous reporting of adverse events, association between TPO-RA and AML must be assessed in a large cohort of ITP patients.[7-9] This was the aim of the present study.

The data source was the FAITH (French Adult Immune Thrombocytopenia) cohort,[10] built in the French National Health Insurance System Database. This database links socio-demographic, outpatient and hospitalization data for the entire French population (67 million individuals).[11,12] We identified adult patients with ITP diagnosed between January 1, 2011, and December 31, 2018, using a validated algorithm based on the International Classification of Diseases, tenth version (ICD-10) D69.3 code recorded as hospital discharge diagnosis or long-term disease diagnosis (the latter is coded by general practitioners). This algorithm had a positive predictive value of 95.8% (95% CI: 92.8-98.8) in a previous validation study.[13] Secondary ITP (*Online Supplementary Table S1*) and prevalent cases were excluded using a prior observation period of ≥1 year. The occurrence of AML after the diagnosis of ITP was identified using ICD-10 diagnosis codes (C92.0, C92.4-C92.9) recorded as hospital discharge diagnosis or long-term disease diagnosis up to December 31, 2018. The exposure to TPO-RA was identified using pharmacy dispensing data in the whole country. Only romiplostim and eltrombopag are available in France.

Due to the rarity of the event, we designed a nested case-control study to assess the association between AML onset and a previous exposure to TPO-RA. Cases and controls were matched (1:6) for age at ITP diagnosis (± 1 year), sex, region of residency, year of ITP diagnosis (± 2 years) and duration of ITP. Potential association was investigated through a conditional regression model adjusted for immunosuppressant exposure. In a sensitivity analysis, the patients with a diagnosis of myelodysplastic syndrome before ITP were also excluded because this condition may mimic ITP and increases the risk of AML.

This study was approved by the Institut des Données de Santé (Health Data Institute) in March 2012 (number 40) and the Commission Nationale de l'Informatique et des Libertés (French Data Protection Agency) in July 2012 (DE-2012-076). The study also received the European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP) study seal approval in October 2013.

Between 2011 and 2018, 8,172 adult patients with primary ITP were selected. Patient characteristics are described in Table 1. The median age was 63.2 years and 54.3% were women. The total follow-up time was 31,410 person-years. In total, 1,636 (20.0%) patients were exposed at least once to a TPO-RA: 1,238 (15.2%) to eltrombopag with a median cumulative exposure time of 5.7 months (up to 87.5 months), and 786 (9.6%) to romiplostim with a median cumulative exposure time of 6.6 months (up to 90.9 months). The follow-up time was similar between the 1,637 patients ever exposed to TPO-RA and the 6,535 patients never exposed to a TPO-RA (median: 3.7 and 3.8 years, respectively). In total, 265 (3.2%) patients were exposed at least once to an immunosuppressant (azathioprine: N=143, 1.8%; mycophenolate mofetil: N=90, 1.1%; ciclosporin: N=66, 0.8%) with a median cumulative exposure time of 6.9 months (up to 57.3 months).

During follow-up, 46 (0.6%) patients developed AML (median age of 74.8 years, 60.9% men). The 8-year cumulative incidence of AML was 1.0% (95% CI: 0.6-1.4; *Online Supplementary Figure S1*). The median time between ITP diagnosis and AML was 1.3 years (quartile [Q]1-Q3: 0.5-2.8). Thirty-six AML occurred in patients never exposed to TPO-RA (0.6%; 95% CI: 0.4-0.8) and ten among the patients exposed to TPO-RA (0.6%; 95% CI: 0.3-1.1): all ten patients had been exposed to eltrombopag, and three patients had been exposed to eltrombopag and romiplostim sequentially. Among these ten patients, the median age was 72.3 years (Q1-Q3: 67.8-80.0) and seven were men. The median time between ITP diagnosis and AML was 1.1 years (Q1-Q3: 0.4-2.3; min-max: 0.4-5.4). The median time between the first dispensing of TPO-RA and AML diagnosis was 8.9 months

(Q1-Q3: 4.2-16.0; min-max: 1.7-62.8). The median cumulative duration of exposure to TPO-RA before AML was 3.9 months (Q1-Q3: 2.1-5.7; min-max: 1.7-12.7). After excluding the patients with a diagnosis of myelodysplastic syndrome before ITP, the 8-year cumulative incidence of AML was 0.8% (95% CI: 0.5-1.3; *Online Supplementary Figure S2*).

In the nested case-control analysis, the adjusted odds ratio was 1.0 (95% CI: 0.5-2.4; Table 2). The analysis excluding the patients with a history of myelodysplastic syndrome yielded similar results (Table 2).

The incidence of AML in adult patients with ITP has been demonstrated to be higher than in the general population in a recent epidemiological study in France and Denmark.[14] However, this real-world nationwide pharmacoepidemiological study on 8,172 adult patients with primary ITP did not confirm the signal of increased risk of AML with TPO-RA. The short duration of TPO-RA exposure time among AML patients suggests that a causal relationship is unlikely. Conversely, more than one quarter of the patients treated with TPO-RA in the whole cohort were exposed for more than 1 year (up to 7 years), with no occurrence of delayed case of AML, which is reassuring

Our study has some limitations. First, we cannot exclude residual misclassification of AML patients identified wrongly as ITP. However, at the time of this study, a systematic bone marrow aspiration (results not available in the database) was recommended by French ITP management guidelines in all patients aged >60 years, making these misdiagnoses unlikely.[15] Moreover, the analysis excluding the patients with a previous diagnosis of myelodysplastic syndromes, a condition with a higher risk of AML and that can mimic or be associated with ITP, led to similar results. Second, due to a clear clinical and biological phenotype when AML occurs, an underestimation of AML during follow-up is unlikely, even if repeated bone marrow examinations are not recommended in patients treated with TPO-RA in France. Eventually, as few patients developed AML, we could not compare the risk between eltrombopag *versus* romiplostim. Finally, the AML frequency appears to be higher among patients exposed to immunosuppressants. However, it should be taken with caution because of the limited number of cases (4 AML patients previously exposed to ciclosporin and 1 to azathioprine). Conversely, 265 patients in the cohort were exposed to immunosuppressants (including 90 patients treated

Table 1. Characteristics of the overall cohort of primary immune thromocytopenia patients.

Characteristics	Total N=8,172	Patients who developed AML during follow-up N=46	Patients who did not develop AML during follow-up N=8,126
Age at ITP onset, years, median (Q1-Q3)	63.2 (42.0-77.3)	74.8 (66.3-82.8)	63.1 (42.0-77.3)
Female sex, N (%)	4,436 (54.3)	18 (39.1)	4,418 (54.4)
Serious bleeding at ITP onset, N (%) Gastrointestinal Intracranial	225 (3.1) 186 (2.3) 73 (0.9)	2 (4.4) 1 (2.2) 1 (2.2)	253 (3.1) 185 (2.3) 72 (0.9)
TPO-RA During follow-up, N (%) Cumulative exposure, median (Q1-Q3) Eltrombopag During follow-up, N (%) Cumulative exposure, median (Q1-Q3) Romiplostim During follow-up, N (%) Cumulative exposure, median (Q1-Q3)	 1,636 (20.0) 8.3 (3.2-22.4) 1,238 (15.2) 5.7 (2.3-15.1) 786 (9.6) 6.6 (2.8-18.4)	 10 (21.7) 3.9 (2.1-5.7) 10 (21.7) 3.4 (2.1-4.3) 3 (6.5) 1.3 (1.1-2.5)	 1,626 (20.0) 8.5 (3.2-22.6) 1,228 (15.1) 5.8 (2.3-15.4) 783 (9.6) 6.7 (2.8-18.6)
Immunosuppressants During follow-up, N (%) Cumulative exposure, median (Q1-Q3) Azathioprine During follow-up, N (%) Cumulative exposure, median (Q1-Q3) Ciclosporin During follow-up, N (%) Cumulative exposure, median (Q1-Q3) Mycophenolate mofetil During follow up, N (%) Cumulative exposure, median (Q1-Q3)	 265 (3.2) 6.9 (2.3-18.6) 143 (1.8) 4.9 (1.9-12.1) 66 (0.8) 8.9 (2.8-21.2) 90 (1.1) 6.5 (2.7-19.2)	 5 (10.9) 3.4 (2.0-7.7) 1 (2.2) 9.2 (9.2-9.2) 4 (8.7) 2.7 (1.5-5.5) 0 (0.0) -	 260 (3.2) 6.9 (2.3-19.0) 142 (1.7) 4.6 (1.9-12.1) 62 (0.8) 9.8 (3.3-23.5) 90 (1.1) 6.5 (2.7-19.2)

AML: acute myeloid leukemia; ITP: immune thrombocytopenia; Q1: first quartile; Q3: third quartile; TPO-RA: thrombopoietin receptor agonist.

Table 2. Association of development of acute myeloid leukemia with previous exposure to thrombopoietin receptor agonists in adult patients with primary immune thrombocytopenia.

Variables	Patients, N (%)		Median cumulative exposure time, months (Q1-Q3)		Crude OR (95% CI)	Adjusted OR[b] (95% CI)
	Cases	Controls	Cases	Controls		
Primary analysis TPO-RA[a]	N=46 10 (21.7)	N=276 47 (17.0)	3.9 (2.1-5.7)	3.9 (2.0-11.8)	1.3 (0.6-2.8)	1.0 (0.5-2.4)
Sensitivity analysis (excluding prior MDS) TPO-RA[c]	N=34 8 (23.5)	N=204 35 (17.2)	4.0 (1.9-5.8)	5.7 (2.1-14.6)	1.5 (0.6-3.5)	1.0 (0.4-2.6)

[a]Exposure at least once during follow-up to thrombopoietin receptor agonists (TPO-RA) including eltrombopag (N=10 cases; N=33 controls), and romiplostim (N=3 cases; N=22 controls). [b]Adjusted for the exposure to immunosuppressants (azathioprine, ciclosporin and mycophenolate mofetil). [c]Exposure at least once during follow-up to TPO-RA including eltrombopag (N=8 cases; N=25 controls), and romiplostim (N=3 cases; N=16 controls). CI: confidence interval; MDS: myelodysplastic syndrome; OR: odds ratio; Q1: first quartile; Q3: third quartile.

with mycophenolate). The durations of exposure up to 57,3 months are reassuring. Of note, an association between the exposure to immunosuppressants and the occurrence of AML or myelodysplastic syndrome has been demonstrated in primary autoimmune diseases with azathioprine, but not with mycophenolate.[16] In our cohort study, no case of AML occurred following an exposure to mycophenolate, while this drug is used widely in some countries.[4]

In conclusion, this study is reassuring regarding the possible risk of AML with TPO-RA in adult patients with primary ITP.

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Disclosures

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Contributions

YZ, ML and GM designed the study. YZ conducted the data management and the statistical analyses. YZ, ML, AS, M-LM and GM interpreted the results. YZ and GM wrote the paper. All authors reviewed the manuscript and gave final approval for publication.

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Data-sharing statement

The SNDS data may be obtained from a third party and are not publicly available. Importantly, data are fully anonymized. Data may be accessed by submitting a request to the Health-Data-Hub at https://www.health-data-hub.fr/depot. The data management and statistical analysis code is available on reasonable request from the corresponding author.

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