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

Running head: AML in ITP Adults Treated With TPO-RA

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Main Text

Immune thrombocytopenia (ITP) is a rare autoimmune disease due to platelet destruction and impaired megacaryopoiesis.[1] Thrombopoietin receptor agonists (TPO-RAs) 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-RAs 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-RAs 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-RAs 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 (Supplemental Table 1) 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-RAs 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-RAs. Cases and controls were matched (1:6) for age at ITP diagnosis (± 1 year), sex, department 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 (No. 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-RAs 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 an AML (median age of 74.8 years, 60.9% of men). The 8-year cumulative incidence of AML was 1.0% (95% CI 0.6-1.4, Supplemental Figure 1). The median time between ITP diagnosis and AML was 1.3 years (Q1-Q3: 0.5-2.8). Thirty-six AML occurred in patients never exposed to TPO-RAs (0.6%; 95% CI: 0.4-0.8) and 10 among the patients ever exposed to TPO-RAs (0.6%; 95% CI: 0.3-1.1): all 10 patients had been exposed to eltrombopag, and 3 to eltrombopag and romiplostim sequentially. Among these 10 patients, the median age was 72.3 years (Q1-Q3: 67.8-80.0) and 7 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-RAs 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, Supplemental Figure 2).

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 in 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-RAs. 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 during more than one 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 with 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 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, because few patients developed AML, we could not compare the risk between eltrombopag versus romiplostim. Finaly, 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 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-RAs in adult patients with primary ITP.

References

1. Cooper N, Ghanima W. Immune Thrombocytopenia. N Engl J Med. 2019;381(10):945-955.
2. Provan D, Arnold DM, Bussel JB, et al. Updated international consensus report on the investigation and management of primary immune thrombocytopenia. Blood Adv. 2019;3(22):3780-3817.
3. Neunert C, Terrell DR, Arnold DM, et al. American Society of Hematology 2019 guidelines for immune thrombocytopenia. Blood Adv. 2019;3:3(23):829-3866.
4. Moulis G, Chen F, Carli G, et al. Use of second-line and beyond maintenance therapies in adult patients with primary immune thrombocytopenia in Europe: a parallel study of six prospective multicenter national registries. Haematologica. 2025;110(12):3094-3098.
5. Liebman HA, Pullarkat V. Diagnosis and management of immune thrombocytopenia in the era of thrombopoietin mimetics. Hematology Am Soc Hematol Educ Program. 2011;2011:384-390.
6. Oshima Y, Yuji K, Tanimoto T, Hinomura Y, Tojo A. Association between acute myelogenous leukemia and thrombopoietin receptor agonists in patients with immune thrombocytopenia. Intern Med. 2013;52(19):2193-2201.
7. Weber J, Rainsford K, Velo G. Epidemiology of adverse reactions to nonsteroidal anti-inflammatory drugs. Adv Inflammation Res. 1984;6:1-7.
8. Pariente A, Gregoire F, Fourrier-Reglat A, Haramburu F, Moore N. Impact of safety alerts on measures of disproportionality in spontaneous reporting databases: the notoriety bias. Drug Saf. 2007;30(10):891-898.
9. Moulis G, Sommet A, Durrieu G, et al. Trends of reporting of 'serious'vs. 'non-serious' adverse drug reactions over time: a study in the French PharmacoVigilance Database. Br J Clin Pharmacol. 2012;74(1):201-204.
10. Moulis G, Sailler L, Adoue D, Lapeyre-Mestre M. Pharmacoepidemiology of Immune Thrombocytopenia: protocols of FAITH and CARMEN studies. Therapie. 2014;69(5):437-448.
11. Bezin J, Duong M, Lassalle R, et al. The national healthcare system claims databases in France, SNIIRAM and EGB: Powerful tools for pharmacoepidemiology. Pharmacoepidemiol Drug Saf. 2017;26(8):954-962.
12. Moulis G, Lapeyre-Mestre M, Palmaro A, Pugnet G, Montastruc JL, Sailler L. French health insurance databases: What interest for medical research? Rev Med Interne. 2015;36(6):411-417.
13. Mezaache S, Derumeaux H, Ferraro P, et al. Validation of an algorithm identifying incident primary immune thrombocytopenia in the French national health insurance database. Eur J Haematol. 2017;99(4):344-349.
14. Mannering N, Zadro Y, Hansen DL, et al. Risk of cancer in adults with primary immune thrombocytopenia: a binational population-based real-world cohort study from Denmark and France. Haematologica. 2025;110(11):2764-2773.
15. Haute Autorité de Santé. Protocole national de diagnostic et de soins (PNDS) - Purpura thrombopénique immunologique de l'enfant et de l'adulte. Published online May 2017. https://www.has-sante.fr/upload/docs/application/pdf/2017-06/dir36/pnds-_purpura_thrombopenique_immunologique.pdf Accessed 2024, January 1.
16. Ertz-Archambault N, Kosiorek H, Taylor GE, et al. Association of Therapy for Autoimmune Disease With Myelodysplastic Syndromes and Acute Myeloid Leukemia. JAMA Oncol. 2017;3(7):936-943.

Tables

Table 1. Characteristics of the overall cohort of primary ITP 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 in 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 (%)	225 (3.1)	2 (4.4)	253 (3.1)
Gastrointestinal	186 (2.3)	1 (2.2)	185 (2.3)
Intracranial	73 (0.9)	1 (2.2)	72 (0.9)
TPO-RA			
During follow-up, n (%)	1,636 (20.0)	10 (21.7)	1,626 (20.0)
Cumulative exposure, median (Q1-Q3)	8.3 (3.2-22.4)	3.9 (2.1-5.7)	8.5 (3.2-22.6)
Eltrombopag			
During follow up, n (%)	1,238 (15.2)	10 (21.7)	1,228 (15.1)
Cumulative exposure, median (Q1-Q3)	5.7 (2.3-15.1)	3.4 (2.1-4.3)	5.8 (2.3-15.4)
Romiplostim			
During follow up, n (%)	786 (9.6)	3 (6.5)	783 (9.6)
Cumulative exposure, median (Q1-Q3)	6.6 (2.8-18.4)	1.3 (1.1-2.5)	6.7 (2.8-18.6)
Immunosuppressants			
During follow-up, n (%)	265 (3.2)	5 (10.9)	260 (3.2)
Cumulative exposure, median (Q1-Q3)	6.9 (2.3-18.6)	3.4 (2.0-7.7)	6.9 (2.3-19.0)
Azathioprine			
During follow up, n (%)	143 (1.8)	1 (2.2)	142 (1.7)
Cumulative exposure, median (Q1-Q3)	4.9 (1.9-12.1)	9.2 (9.2-9.2)	4.6 (1.9-12.1)
Ciclosporin			
During follow up, n (%)	66 (0.8)	4 (8.7)	62 (0.8)
Cumulative exposure, median (Q1-Q3)	8.9 (2.8-21.2)	2.7 (1.5-5.5)	9.8 (3.3-23.5)
Mycophenolate mofetil			
During follow up, n (%)	90 (1.1)	0 (0.0)	90 (1.1)
Cumulative exposure, median (Q1-Q3)	6.5 (2.7-19.2)	-	6.5 (2.7-19.2)

Abbreviations: 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 in months (Q1-Q3)	
	Cases	Controls	Cases	Controls
Primary analysis	n=46	n=276		
TPO-RA[a]	10 (21.7)	47 (17.0)	3.9 (2.1-5.7)	3.9 (2.0-11.8)
Sensitivity analysis (excluding prior MDS)	n=34	n=204		
TPO-RA[c]	8 (23.5)	35 (17.2)	4.0 (1.9-5.8)	5.7 (2.1-14.6)

Abbreviations: CI: confidence interval; MDS: myelodysplastic syndrome; OR: odds ratio; TPO-RA: thrombopoietin receptor agonists.

[a]Exposure at least once during follow-up to thrombopoietin receptor agonists 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 thrombopoietin receptor agonists including eltrombopag (n=8 cases; n=25 controls), and romiplostim (n=3 cases; n=16 controls).

SUPPLEMENTARY MATERIAL

No Increased Risk of Acute Myeloid Leukemia in Adults With Primary Immune Thrombocytopenia Treated With Thrombopoietin Receptor Agonists: A French Nationwide Population-Based Study.

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Table S1. Codes of the International Classification of Diseases, 10th version used for the identification of causes of secondary immune thrombocytopenia.

Figure S1. Eight-year cumulative incidence of acute myeloid leukemia in adults with primary immune thrombocytopenia with thrombopoietin receptor agonists.

Figure S2. Eight-year cumulative incidence of acute myeloid leukemia in adults with primary immune thrombocytopenia with thrombopoietin receptor agonists after excluding previous diagnosis of myelodysplastic syndrome.

Table S1. Codes of the International Classification of Diseases, 10th version used for the identification of causes of secondary immune thrombocytopenia.

Label	Codes
Hematological malignancies	
Lymphoma	C81-C85, C88
Malignant plasma cell neoplasms	C90
Leukemia	C91-C95
Infections	
Viral hepatitis C	B17.1, B18.2
Human immunodeficient virus	B20-B25
Viral infections	G05.1, J17.1, K77.0, K87.1
Helicobacter pylori	B98.0
Immune deficiency	D80.0-D80.2, D83.8, D83.9
Autoimmune diseases	
Sarcoidosis	D86.0-D86.2, D86.9
Thyroid	E06.3
Inflammatory bowel diseases	K50, K51
Rheumatoid arthritis	M05, M06, M08
Vasculitis	M30, M31
Systemic lupus erythematosus	M32
Autoimmune myositis	M33
Systemic sclerosis	M34
Sicca syndrome	M35.0
Overlap syndrome	M35.1
Polymyalgia rheumatica	M35.3
Immunological anomalies	R76.8

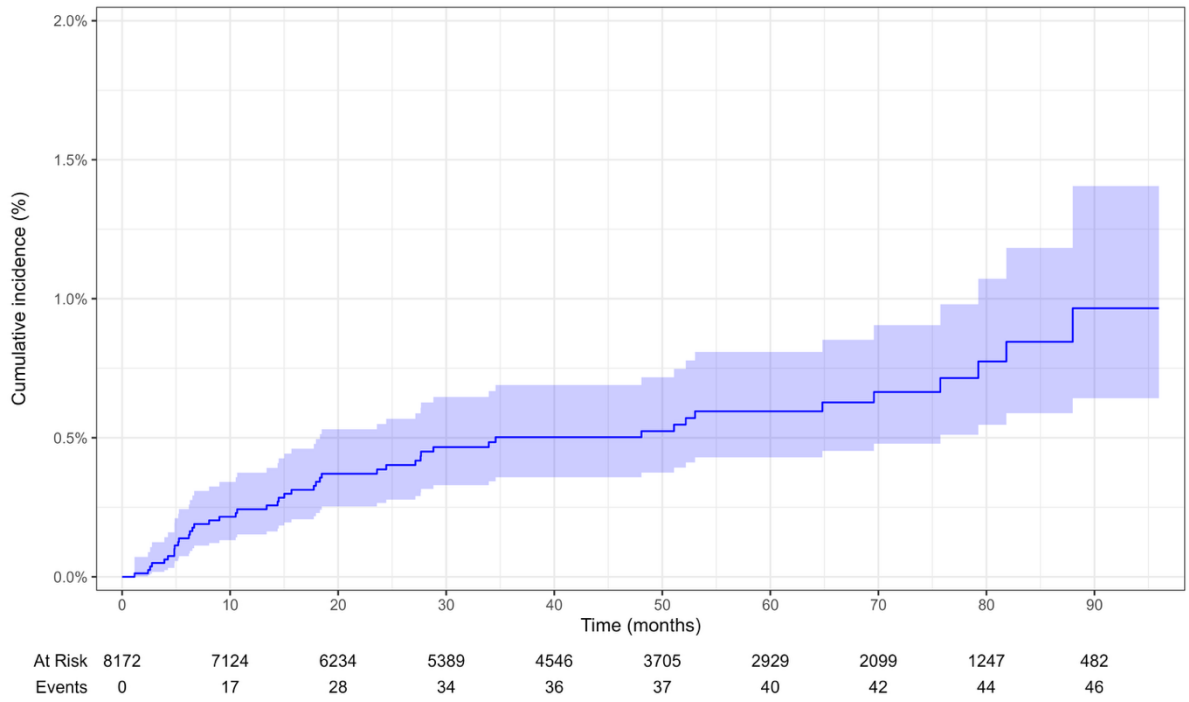

Figure S1. Eight-year cumulative incidence of acute myeloid leukemia in adults with primary immune thrombocytopenia with thrombopoietin receptor agonists. The vertical axis represents cumulative incidence. The horizontal axis represents time. The colored area represents the 95% confidence interval. The numbers of patients at risk for the event are indicated below the graph, as well as the numbers of patients who developed acute myeloid leukemia.

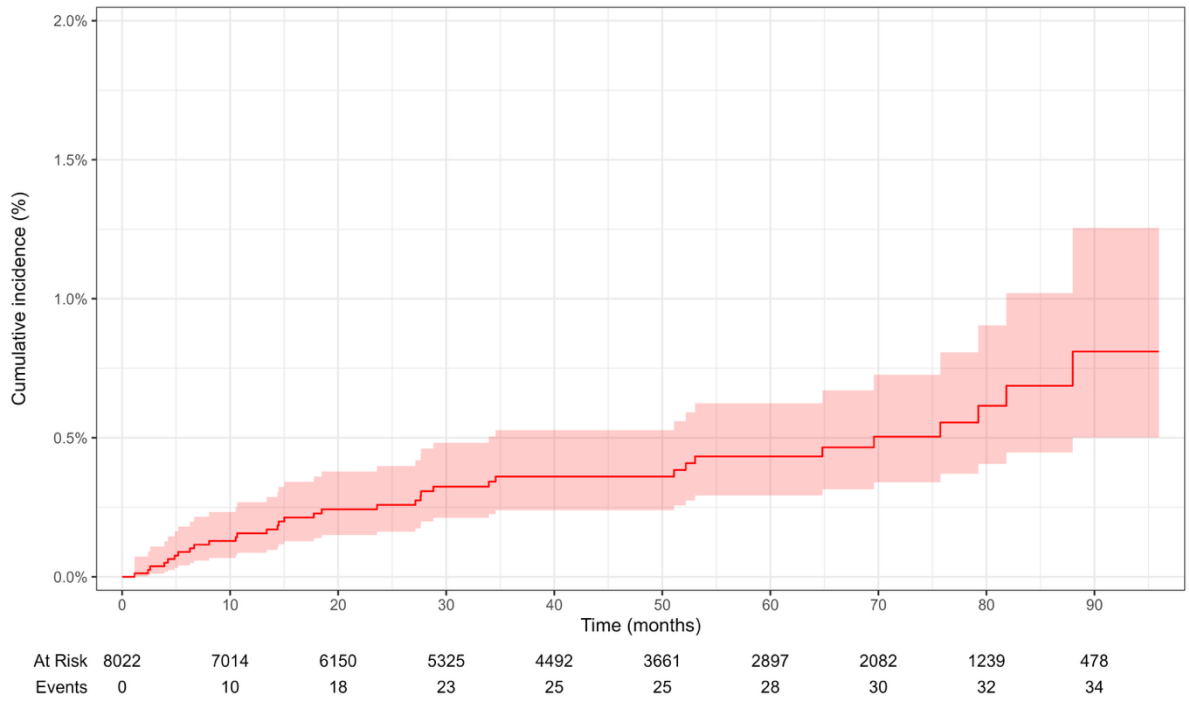

Figure S2. Eight-year cumulative incidence of acute myeloid leukemia in adults with primary immune thrombocytopenia with thrombopoietin receptor agonists after excluding previous diagnosis of myelodysplastic syndrome. The vertical axis represents cumulative incidence. The horizontal axis represents time. The colored area represents the 95% confidence interval. The numbers of patients at risk for the event are indicated below the graph, as well as the numbers of patients who developed acute myeloid leukemia.