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Letters to *Blood*



TO THE EDITOR:

# An updated list of drugs suspected to be associated with immune thrombocytopenia based on the WHO pharmacovigilance database

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Iatrogenic thrombocytopenia is a common adverse drug reaction (ADR) that can be caused by various mechanisms, including drug-associated immune thrombocytopenia (DITP), whose prognosis is generally favorable when the suspected drug is withdrawn.[1-4] However, the diagnosis of DITP remains challenging for several reasons. First, there is limited evidence about this rare disease because of a lack of recent powerful studies.[2-6] Second, the involved patients frequently have comorbidities and are thereby often exposed to several drugs, which may be possible causes of secondary immune thrombocytopenia (ITP) leading to frequent misdiagnoses.[2,7,8] Moreover, the withdrawal of some drugs can be highly challenging and deleterious. For these reasons, and because the pharmacopoeia has noticeably evolved these past 10 years, we propose to update the list of drugs associated with ITP by analyzing the World Health Organization pharmacovigilance database: Vigibase.

Vigibase is an international pharmacovigilance database gathering data from national pharmacovigilance databases of more than 130 countries. Each report included medical information (drug start and end dates and indication; ADR types and severity), patient characteristics, and administrative data. We collected all individual case safety reports (ICSRs) of suspected DITP registered in Vigibase from 2006 to February 2021, with 1 of the following low-level terms according to the Medical Dictionary for Drug Regulatory Activities: immune thrombocytopenic purpura; immune-mediated thrombocytopenic purpura; persistent immune thrombocytopenic purpura; primary immune thrombocytopenic purpura; refractory immune thrombocytopenic purpura; and secondary immune thrombocytopenic purpura. The selected drugs were those qualified as "suspect" or "interacting." Among the drugs associated with a significant disproportionality signal, we excluded drugs at risk of indication or protopathic biases (prescription of the drug in response to some early symptoms of the disease), considering their recognized use as first- or second-line therapies in the management of ITP.[9] The study was approved by the local ethics committee of Caen University Hospital (Comité Local d'Ethique de la Recherche en Santé, no. 2224). We performed a case/noncase analysis[10] for each drug of interest. Noncases were defined as all non-ITP reports in the database. Disproportionality was assessed by the calculation of the reported odds ratio (ROR) for drugs that had ≥5 reported cases of ITP.[11] A significant disproportionality was defined by a lower limit of the ROR 95% confidence interval (95% CI) > 1.

Overall, 1245 ICSRs were included (1238 [99%] with the term immune thrombocytopenic purpura), accounting for 1787 notifications (several drugs could be notified in the same ICSR), and 61 drugs (supplemental Figure 1). DITP occurred in 572 (51%) females. The median age at onset was 32 (1.6-58) years, and 43% of all cases involved children (Table 1). The age distribution was marked by a peak of incidence at the first years of life, regardless of sex (supplemental Figure 2). Alemtuzumab was the most frequently reported drug and had the strongest signal (n = 239/1787, 13%; ROR = 161.5 [95% CI, 140.9-185.1]). Seven of the 10 strongest signals (ROR >10) involved vaccines, including against *Haemophilus influenzae* type b, rabies, hepatitis B and A and measles, and mumps and rubella (MMR) vaccine. The median age for all vaccine-related ITPs was 12 (3-14) years. The most represented pharmaceutical classes were, in decreasing order, vaccines (n = 954/1787, 53%), multiple sclerosis immunomodulatory agents (n = 276/1787, 15%), and anticancer drugs (n = 243/1787, 14%), including checkpoint inhibitors (n = 88/1787, 5%). The median onset of ITP was 12 (10.5-33.5) days (data available for 488 ICSRs, Table 2).

In this pharmacoepidemiological study, we aimed to establish what we believe is the first list of drugs potentially associated with ITP using a worldwide pharmacovigilance database. Our study first reported the different demographic characteristics of patients experiencing DITP vs primary ITP, including sex and age distribution differences.[12] Indeed, there is a slightly higher rate of females in primary ITP, with a sex ratio of 0.8 instead of 1 in our study. In addition, the incidence rate has a bimodal distribution among males, being highest among boys younger than age 18 years and men from 75 to 85 years of age, whereas the incidence rates were relatively stable in females from childhood to 60 years old and increased thereafter. In our study, the distribution exhibited a peak of incidence during childhood in both sexes. This distribution in DITP may be related to vaccine-related ADRs.

**Table 1. Characteristics of the ICSRs (n = 1245)**

| | n | % |
|---|---|---|
| **Sex (n = 1130)** | | |
| Female | 572 | 51 |
| Male | 558 | 49 |
| **Age (n = 893), y** | | |
| Median age | 32 (1.58-58) | |
| Adults | 512 | 57 |
| Children | 381 | 43 |
| **Country of primary source (n = 1245)** | | |
| United States | 912 | 73.3 |
| Europe, including: | 222 | 17.8 |
| France | 57 | 4.6 |
| United Kingdom of Great Britain and Northern Ireland | 32 | 2.6 |
| Spain | 32 | 2.6 |
| Germany | 27 | 2.2 |
| Italy | 21 | 1.7 |
| Netherlands | 8 | 0.6 |
| Belgium | 7 | 0.6 |
| Switzerland | 5 | 0.4 |
| Portugal | 5 | 0.4 |
| Greece | 5 | 0.4 |
| Norway | 4 | 0.3 |
| Ireland | 4 | 0.3 |
| Hungary | 3 | 0.2 |
| Denmark | 3 | 0.2 |
| Austria | 3 | 0.2 |
| Slovenia | 2 | 0.2 |
| Czech Republic | 2 | 0.2 |
| Sweden | 1 | 0.1 |
| Finland | 1 | 0.1 |
| Japan | 61 | 4.9 |
| Australia | 29 | 2.3 |
| Canada | 10 | 0.8 |
| Turkey | 4 | 0.3 |
| Indonesia | 2 | 0.2 |
| India | 2 | 0.2 |
| Philippines | 1 | 0.1 |
| Mexico | 1 | 0.1 |
| Malaysia | 1 | 0.1 |
| **Reporter qualification (n = 805)** | | |
| Physician | 364 | 45 |
| Other health professional | 205 | 26 |
| Consumer/Non health professional | 163 | 20 |
| Pharmacist | 31 | 4 |
| Others | 42 | 5 |
| **Serious adverse drug reactions (n = 1231)** | | |
| Yes | 1123 | 91 |
| No | 108 | 9 |
| Fatal outcomes | 40 | — |

Alemtuzumab showed the strongest signal for DITP in our study, in contrast with older literature reviews,[1,13] and may be explained by its recent approval in multiple sclerosis.

Unlike previous studies,[2,13] ours included pediatric patients and therefore clearly incriminated vaccines, and particularly *H influenzae* type b vaccine, hepatitis B and A vaccines, and the MMR vaccine. In a French study published in 2012,[5] 45% of the DITP involved vaccines, the 3 first reported being the combined diphtheria, tetanus, and polio vaccine; the influenza vaccine; and the MMR vaccine. The median age at diagnosis was 16 years, which is close to our age of 12 (3-14) years. In the literature, it seems that all vaccines have been related to DITP, at least in case reports.[5,14] However, the only vaccine incriminated with causal association in comparative studies is the MMR vaccine.[15,16] Notably, we did not find any report incriminating the SARS-CoV-2 vaccine because our inclusion period ended in February 2021. However, in the literature, several publications reported SARS-CoV-2 vaccine-induced ITP[17] or primary ITP relapses induced by a SARS-CoV-2 vaccine.[18] Given these data, international and national guidelines[19,20] have proposed performing SARS-CoV-2 vaccination in all stable ITP patients, followed by platelet count control in the following week because the risk of a severe form of COVID-19 exceeds the risk of ITP relapse or vaccine-induced ITP.

Some hypotheses have been formulated to explain the pathophysiology of DITP. Molecular mimicry seems to be the classic mechanism responsible for vaccine-induced ITP.[14] The old model of "drug-dependent" antibodies, referring to antibodies with high affinity for platelet glycoproteins only in the presence of the drug, can be used for some antibiotics such as vancomycin or trimethoprim/sulfamethoxazole.[21,22] The pathophysiology of checkpoint inhibitor-associated ITP is directly related to their mode of operation: the block of the immunoinhibitory signals releases the immune system and immune ADRs are therefore expected.[23] The median onset of ITP after starting alemtuzumab is much longer (several months) than with other drugs, evoking a different pathophysiology.[24,25] The mechanism could not be directly related to the drug but perhaps to the consequence of its action, namely, a dysregulation of lymphocyte repopulation, after drastic alteration of the circulating lymphocyte pool. It could be, as suggested by Cuker et al,[25] a consequence of defects in central tolerance checkpoints during lymphocyte reconstitution.

Despite the statistical associations and the pathophysiological hypotheses suggested here, this list of suspected drugs has to be considered with caution given the alternative causes that can

**Table 2. List of 61 drugs associated with ITP with significant disproportional reporting, classified by decreasing ROR**

| "Suspect"/ "interacting" drug | n ITP/drug | ROR (95% CI) | Median onset of ITP after starting drug | | Fatal outcomes |
|---|---|---|---|---|---|
| | | | Median onset (days) | Data available for n notifications | n (%) |
| Alemtuzumab | 239 | 161.5 (140.9-185.1) | 352 (221-492) | 33 (14%) | 9 (4) |
| Immunoglobulin human anti-rabies | 8 | 83.4 (41.5-167.5) | — | — | 0 |
| Guanfacine | 10 | 39.4 (21.1-73.3) | — | — | 0 |
| Measles and rubella vaccine | 10 | 22.7 (12.2-42.3) | 16 (7-22) | 9 (90%) | 0 |
| HIB vaccine | 68 | 16.8 (13.2-21.4) | 8 (2-15) | 55 (81%) | 0 |
| Measles, mumps, rubella, and varicella-zoster vaccine | 39 | 16.1 (11.7-22.2) | 21 (11.75-27) | 32 (82%) | 0 |
| Rabies vaccine | 14 | 16.1 (9.5-27.2) | < 1 | 1 (7%) | 0 |
| Hepatitis B vaccine | 76 | 15.0 (11.9-18.8) | 12 (7-24) | 57 (75%) | 0 |
| Hepatitis A vaccine | 43 | 11.3 (8.4-15.3) | 16.5 (7.75-30.75) | 36 (84%) | 1 (2) |
| Measles, mumps, and rubella vaccine | 114 | 10.9 (9.0-13.2) | 19 (9-24) | 93 (82%) | 2 (2) |
| Nivolumab | 47 | 10.5 (7.8-14.0) | 89.5 (32-237) | 6 (13%) | 8 (17) |
| Fludarabine | 11 | 10.1 (5.6-18.3) | 9 | 1 (9%) | 2 (18) |
| Busulfan | 5 | 10.1 (4.2-24.3) | — | — | 2 (40) |
| Temozolomide | 13 | 9.7 (5.6-16.8) | — | — | 1 (8) |
| Rotavirus vaccine | 54 | 9.5 (7.3-12.5) | 10 (3.75-13.75) | 44 (81%) | 0 |
| Pembrolizumab | 24 | 9.4 (6.3-14.1) | 213 (77-441) | 5 (21%) | 3 (13) |
| Meningococcal vaccine | 73 | 8.6 (6.8-10.8) | 9.5 (5.25-20) | 54 (74%) | 0 |
| Ipilimumab | 17 | 8.5 (5.3-13.7) | 23 | 1 (6%) | 2 (12) |
| Typhoid vaccine | 9 | 8.3 (4.3-15.9) | 12 (2-14) | 5 (56%) | 0 |
| Folinic acid | 15 | 8.1 (4.9-13.5) | — | — | 0 |
| Pneumococcal vaccine | 136 | 7.4 (6.2-8.8) | 9.5 (2-22) | 108 (79%) | 0 |
| Ibrutinib | 27 | 7.1 (4.9-10.4) | — | — | 2 (7) |
| Irinotecan | 23 | 6.9 (4.6-10.4) | — | — | 0 |
| Losartan | 13 | 6.7 (3.9-11.6) | 37 | 1 (8%) | 0 |
| Venetoclax | 8 | 6.2 (3.1-12.3) | 130 | 1 (13%) | 0 |
| Doxycycline | 15 | 6.0 (3.6-10.0) | 20.5 (15.75-25.25) | 2 (13%) | 0 |
| Melphalan | 5 | 5.9 (2.5-14.2) | 357 | 1 (20%) | 0 |

HIB, *Haemophilus influenzae* type b; HPV, human papillomavirus.

**Table 2. (continued)**

| "Suspect"/ "interacting" drug | n ITP/drug | ROR (95% CI) | Median onset of ITP after starting drug | | Fatal outcomes |
|---|---|---|---|---|---|
| | | | Median onset (days) | Data available for n notifications | n (%) |
| Diphtheria, pertussis, polio, and tetanus vaccine | 26 | 5.9 (4.0-8.7) | 13 (4-21.5) | 19 (73%) | 0 |
| Polio vaccine | 38 | 5.9 (4.3-8.1) | 7 (2-11) | 33 (87%) | 0 |
| HPV vaccine | 58 | 5.8 (4.4-7.5) | 14 (5.5-40.5) | 47 (81%) | 0 |
| Filgrastim | 6 | 4.8 (2.2-10.7) | — | — | 0 |
| Eculizumab | 18 | 4.7 (2.9-7.5) | — | — | 1 (6) |
| Tacrolimus | 24 | 4.4 (2.9-6.5) | 42 (36-164) | 3 (13%) | 1 (4) |
| Oxaliplatin | 35 | 4.3 (3.0-5.9) | 2 | 1 (3%) | 0 |
| Diphtheria, hepatitis B, HIB, pertussis, polio and tetanus vaccine | 18 | 4.2 (2.6-6.7) | 11 (3.75-18) | 16 (89%) | 0 |
| Vancomycin | 22 | 4.2 (2.8-6.4) | — | — | 0 |
| Cephalexin | 7 | 4.2 (2.0-8.7) | — | — | 0 |
| Ifosfamide | 5 | 4.0 (1.7-9.7) | — | — | 0 |
| Ondansetron | 6 | 3.9 (1.7-8.6) | — | — | 0 |
| Fingolimod | 30 | 3.7 (2.6-5.4) | 983 (706-1155.5) | 2 (7%) | 1 (3) |
| Acyclovir | 6 | 3.7 (1.7-8.3) | — | — | 0 |
| Sofosbuvir | 7 | 3.7 (1.8-7.8) | — | — | 0 |
| Yellow fever vaccine | 8 | 3.6 (1.8-7.2) | 14 (7-14) | 3 (38%) | 0 |
| Diphtheria, pertussis, and tetanus vaccine | 47 | 3.5 (2.6-4.7) | 10 (7-16) | 41 (87%) | 0 |
| Influenza vaccine | 70 | 3.4 (2.6-4.3) | 11 (4.75-22.25) | 52 (74%) | 2 (3) |
| Bisoprolol | 6 | 3.3 (1.5-7.3) | 33 | 1 (17%) | 0 |
| Sulfamethoxazole; trimethoprim | 22 | 3.1 (2.1-4.8) | 11.5 (7.75-25) | 6 (27%) | 2 (9) |
| Peginterferon alfa-2b | 5 | 3.0 (1.3;7.3) | — | — | 0 |
| Varicella-zoster vaccine | 45 | 3.0 (2.2-4.0) | 14 (8.5-23) | 39 (87%) | 1 (2) |
| Clopidogrel | 17 | 3.0 (1.8-4.8) | 21 | 1 (6%) | 0 |
| Ticagrelor | 6 | 2.9 (1.3-6.4) | 19.5 (15.25-23.75) | 2 (33%) | 0 |
| Diphtheria, HIB, pertussis, polio, and tetanus vaccine | 8 | 2.8 (1.4-5.7) | 5.5 (1-12.25) | 6 (75%) | 0 |
| Sunitinib | 9 | 2.8 (1.4-5.3) | 55 (54.5-55.5) | 2 (22%) | 1 (11) |

HIB, *Haemophilus influenzae* type b; HPV, human papillomavirus.

**Table 2. (continued)**

| "Suspect"/ "interacting" drug | n ITP/drug | ROR (95% CI) | Median onset of ITP after starting drug | | Fatal outcomes |
|---|---|---|---|---|---|
| | | | Median onset (days) | Data available for n notifications | n (%) |
| Ethinylestradiol; etonogestrel | 6 | 2.7 (1.2-6.0) | — | — | 0 |
| Peginterferon alfa-2a | 12 | 2.7 (1.5-4.7) | — | — | 1 (8) |
| Rivaroxaban | 33 | 2.5 (1.8-3.5) | 34 | 1 (3%) | 5 (15) |
| Vedolizumab | 5 | 2.4 (1.0-5.8) | — | — | 0 |
| Ribavirin | 19 | 2.4 (1.5-3.7) | — | — | 1 (5) |
| Teriflunomide | 7 | 2.2 (1.1-4.7) | — | — | 0 |
| Doxorubicin | 14 | 2.0 (1.2-3.4) | — | — | 0 |
| Acetylsalicylic acid | 26 | 1.8 (1.2-2.7) | 20 (16.5-895) | 3 (12%) | 1 (4) |
| Total | 1787 notifications<br>1245 ICSRs | | 12<br>(10.5-33.5) | 823 notifications<br>(46%)<br>488 ICSRs (39%) | 49 notifications<br>40 ICSRs<br>Data available for<br>1231 ICSRs (99%) |

HIB, *Haemophilus influenzae* type b; HPV, human papillomavirus.

be responsible for thrombocytopenia, and particularly for the rarest associations. We remind readers that pharmacovigilance studies aim to refer signals, but not to assess causality, which would require further studies.

To conclude, using a large pharmacovigilance database, we updated the list of drugs associated with ITP. In addition to corroborating and quantifying old signals for DITP mentioned in previous studies, this study also identified new drugs, such as alemtuzumab. The different delay between the introduction of the incriminated drug and DITP occurrence suggests different pathophysiologic mechanisms. Prospective large observational and experimental studies are required to confirm these associations.

## Acknowledgment

The results from this study do not represent the opinion of the World Health Organization or of the Uppsala Monitoring Center.

## Authorship

Contribution: S.F. and S.D. designed the study and drafted the letter; and all authors were involved in the acquisition, analysis, and interpretation of the data, and critically reviewed and approved the final version of the manuscript.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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## Footnotes

Submitted 14 February 2022; accepted 29 June 2022; prepublished online on *Blood* First Edition 8 July 2022.

The data that support the findings of this study are available from the corresponding author upon reasonable request.

The online version of this article contains a data supplement.

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DOI 10.1182/blood.2022015936





**TO THE EDITOR:**

# Ruxolitinib is more effective than other JAK inhibitors to treat VEXAS syndrome: a retrospective multicenter study

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VEXAS syndrome (vacuoles in myeloid progenitors, E1 ubiquitin-activating enzyme, X-linked, autoinflammatory manifestations, and somatic) is the consequence of the expansion of hematopoietic stem and/or progenitor cells with somatically acquired *UBA1* (ubiquitin-like modifier activating enzyme 1) mutations.[1,2] Patients present with a variety of autoinflammatory manifestations, and approximately half of them have an associated hematological malignancy, mainly myelodysplastic syndrome (MDS) and/or monoclonal gammopathy.[3,4] Long-term use of high doses in this steroid-dependent disease is often associated with unacceptable side effects. Retrospective studies have underlined the poor response of VEXAS patients to a variety of therapeutic strategies, except for a few patients exposed to Janus kinase inhibitors (JAKi).[2,5] Here, we present the results of