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Drug-induced immune thrombocytopenia: an updated list of suspected drugs using the World Health Organization pharmacovigilance database

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UNIVERSITÉ de CAEN NORMANDIE

UFR SANTÉ

FACULTÉ de MÉDECINE

Année 2020/2021

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DU GRADE DE DOCTEUR EN MÉDECINE

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Par

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TITRE DE LA THÈSE :

Purpura thrombopénique immunologique induit par les médicaments : actualisation de la liste des médicaments suspects à l'aide d'une base de pharmacovigilance internationale.

Drug-induced immune thrombocytopenia: an updated list of suspected drugs using the World Health Organization pharmacovigilance database.

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Abréviations

ADR Adverse Drug Reaction

CAMMS223 CAMpath-1H in Multiple Sclerosis international trial

CARE-MS I and II (Comparison of Alemtuzumab and Rebif[®] Efficacy in Multiple Sclerosis)

DITP Drug-induced Immune Thrombocytopenia

DTP Diphtheria Tetanus Poliomyelitis (vaccine)

EMA European Medicines Agency

FDA Food and Drug Administration

ICI Immune Checkpoint Inhibitor

ICSR Individual Case Safety Report

ITP Immune Thrombocytopenia

LLT Low Level Term

MedDRA Medical dictionary for Drug Regulatory Activities

MMR Measles Mumps and Rubella (vaccine)

ROR Reporting Odds Ratio

WHO World Health Organisation

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Introduction

Drug-induced thrombocytopenia is a common adverse effect that can be caused by various mechanisms, including myelotoxicity (chemotherapeutic agents, linezolid), interference with specific megakaryocyte function (bortezomib), thrombotic microangiopathy (tacrolimus, quinine or cyclosporine) and immune mechanisms. These immune mechanisms result from accelerating platelet destruction via drug-dependent platelet antibodies that can act by increasing platelet clearance (quinine) or inducing platelet activation (heparin) (1–3).

Immune thrombocytopenia (ITP) is mainly peripheral and mediated by autoantibodies. ITP can be a primary condition or be associated with several other causes and conditions whose management may have an impact on its treatment. Drug-induced immune thrombocytopenia (DITP) is caused by drug-dependent platelet antibodies resulting in increased platelet clearance within the reticuloendothelial system.

In DITP, the platelet count generally decreases from the 5th to the 7th day after the first exposure to the offending treatment, frequently reaching very low levels ($<20,000$ platelets / mm^3) and thus exposing the patient to potential severe bleeding and to possible fatal outcomes. In most cases, the withdrawal of the incriminated drug leads to a favourable outcome with rapid improvement as soon as 1 or 2 days, and a definite resolution of the thrombocytopenia in less than a week (4,5). However, the diagnosis of DITP remains challenging and difficult because of several reasons: the limited knowledge and evidence in this rare disease because of the lack of systematic and powerful studies on the field; the frequent comorbidities of involved patients who are thereby often exposed to several drugs and several underlying other diseases as possible causes of secondary ITP, leading to frequent misdiagnoses (4,6,7) or simply a lack of evocation of DITP. Moreover, the withdrawal of some drugs on a simple rare hypothesis can be highly challenging and deleterious.

The clinical entity of DITP was first described after the exposure to quinine more than a century ago (5). Since then, multiple DITP observations have been published incriminating several drugs or drug classes such as platelet inhibitors (abciximab, tirofiban), antibiotics (vancomycin among others), anticonvulsant agents (carbamazepine), diuretics (chlorothiazide), or analgesic agents (acetaminophen, diclofenac) (5). Some literature reviews have suggested a non-official list of suspected drugs, based on dozens of published case reports (4,8), and various national (9) and international (10) recommendations provide a short list of drugs incriminated in DITP, based on these not always recent data.

More recently, abnormal pharmacovigilance signals have been reported in studies based on national or local databases. A French team conducted a survey on DITP, based on 59 case reports extracted from the French pharmacovigilance database from 2007 to 2010 (11). The Berlin Case Control Surveillance Study (FAKOS) collected serious toxicities of drugs in 50 hospitals in Berlin for 10 years up to 2009, including DITP (12). However, the pharmacopoeia has noticeably evolved since then, as well as probably the spectrum of DITP. Indeed, the new paradigm of biological therapies provide an exponential increase in new drug classes that directly interfere with molecular, cytokine and immunological pathways, with a potential increase in autoimmune adverse effects.

We therefore propose to update the list of suspected drugs associated with ITP by analysing the World Health Organisation (WHO) Vigibase[®], an international pharmacovigilance database.

Materials and Methods

Study design

Our disproportionality analysis was based on the study of abnormal pharmacovigilance signals among the more than 20,000,000 Individual Case Safety Reports (ICSRs) notified by more than 130 countries in the WHO pharmacovigilance database, managed by the Uppsala Monitoring Centre in Sweden since 1967.

The registration of a record can be performed by different health actors: physicians, pharmacists, other health professionals, and patients. Each report included medical information (drugs taken with dosage, start and end dates and indication; adverse drug reactions (ADRs) types, seriousness and outcomes), patient characteristics (sex, age), and administrative data (country of origin, reporter qualification, date of reporting...). For all drugs, suspect/interacting or concomitant nature was specified (13).

A serious ADR was defined as an adverse effect that caused death, was life-threatening, required or prolonged hospitalisation, led to persistent or significant disability, congenital anomaly, birth defect or any other medically important condition.

For this observational retrospective study, we could not use a Preferred Term from the Medical Dictionary for Drug Regulatory Activities (MedDRA) terms (version 23.1) to collect all ADRs of interest, because none was specific enough. Therefore, we collected all ADRs registered in Vigibase[®] from 2006, date of the introduction of the following terms, to February 2021, with one of the following Low Level Term (LLT) according to the MedDRA: Immune thrombocytopenic purpura, Immune-mediated thrombocytopenic purpura, Persistent immune thrombocytopenic purpura, Primary immune thrombocytopenic purpura, Refractory immune thrombocytopenic purpura, Secondary immune thrombocytopenic purpura.

The selected drugs were those qualified as “suspect” or “interacting”. Among the drugs associated with a significant signal, we excluded the following at risk of indication or protopathic biases, considering their recognized use as first or second-line therapies in the management of ITP (10): Eltrombopag, Romiplostim, Rituximab, Prednisone, Dexamethasone, Vincristine, Cyclophosphamide.

According to the European Medicines Agency (EMA) recommendations about the screening for adverse reactions (14), a signal of disproportionate reporting was considered

only when there were at least 5 ICSRs with the same drug. Therefore, we excluded all drugs associated with 4 or less notifications.

The study was approved by the local ethics committee of Caen University Hospital (Comité Local d’Ethique de la Recherche en Santé, n°2224).

Statistical analysis

We performed a frequentist approach for the measure of disproportionality with the calculation of the Reporting Odds Ratio (ROR), which is based on a case/non case analysis for each drug of interest (15).

For the calculation, we used a contingency table describing the number of ADRs of interest or the number of all other ADRs reported since 2006, according to the studied drug, and according to all other drugs in the database (Table 1).

Exposure \ ADRs	ADR of interest “Cases”	Other ADRs “Non-cases”
Drug of interest	a	b
Other drugs	c	d

Table 1: Contingency table for a case/non case analysis. *ADR: Adverse drug reaction.*

A signal was defined by the demonstration of a difference of statistical distribution between cases and non-cases, called a disproportionality. To evaluate disproportionality, we used a ROR, confronting the reporting odd of the group exposed to the drug of interest, and the reporting odd of the group exposed to other drugs, which is calculated by the following formula:

$$\text{ROR} = (a/b) / (c/d)$$

A ROR was considered as statistically significant if the lower limit of its 95% confidence interval (CI95%) was strictly superior to 1, calculated by the following formula:

$$\text{ROR CI95\%} = \text{ROR} * e^{+1.96 \sqrt{(1/a+1/b+1/c+1/d)}}$$

Descriptive data were presented as median [25th-75th percentiles] or number (percentage).

For the calculation of the median delay between the introduction of the suspected drug and the occurrence of ITP, we considered only the ICSRs containing complete dates (year, month, and day of the month). By doing so, the data loss was estimated inferior to 5%.

Results

A total of 1932 ICSRs of potential DITP were retrieved between 2006 and February 2021 using Vigibase®. Among them, 1245 ICSRs incriminating at least one drug with significant signal (ROR CI95% > 1, > 4 ICSRs), accounting for a total of 61 drugs, were included after exclusion of drugs with potential indication or protopathic biases (Figure 1).

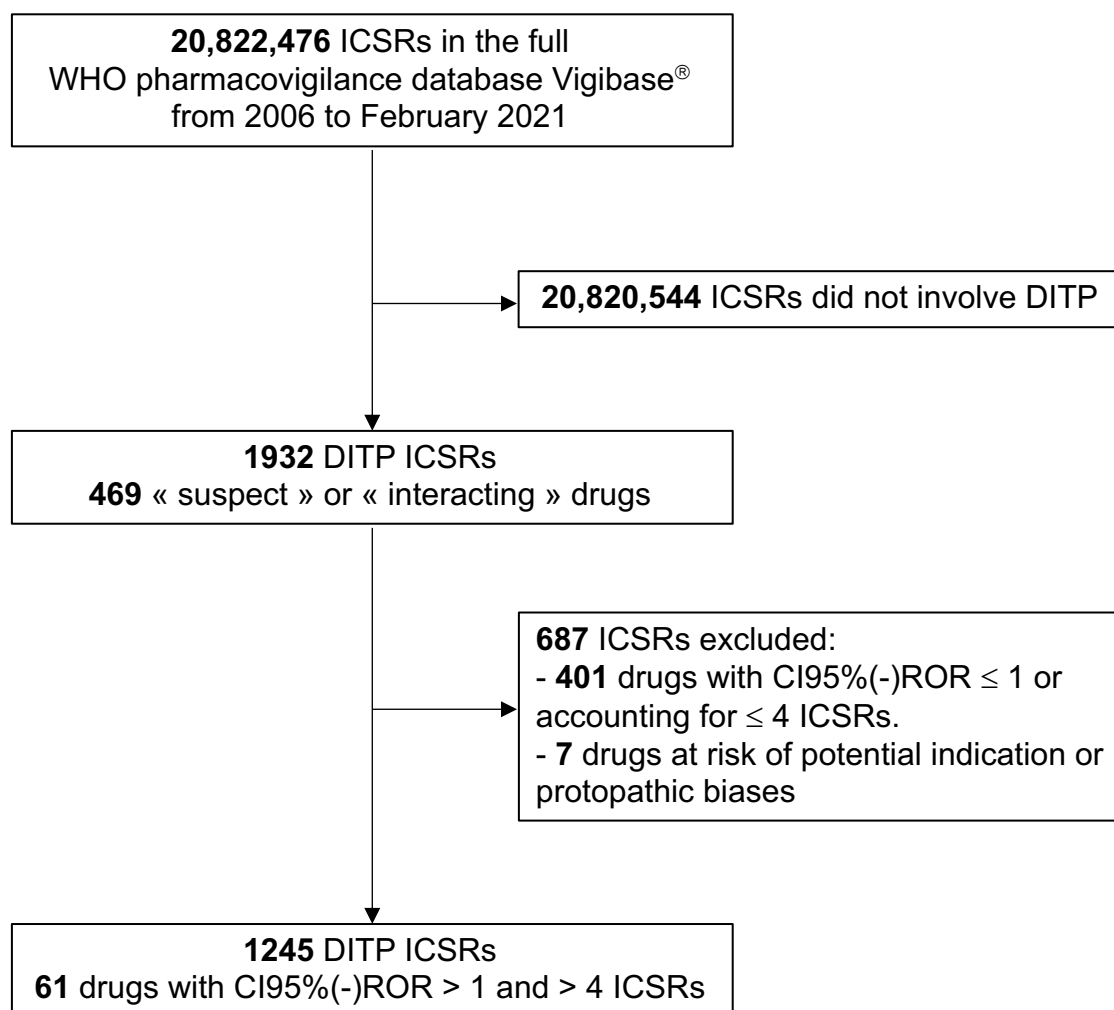


Figure 1: Flowchart of the selection of the ICSRs of interest

ICSR: Individual Case Safety Report; WHO: World Health Organisation; DITP: Drug-induced Immune Thrombocytopenia; CI95%(-)ROR: inferior limit of the 95% confidence interval

These 1245 ICSRs, of which for all data were available, have been notified in 29 different countries, mostly United States of America (n=912, 73%), and in Europe (n=222, 18%). The report was ensured by physicians or other health professionals in most cases (n=402, 50% and n=208, 26% respectively) (Table 2).

DITP occurred in 572 (51%) women (data available for 1130 ICSRs, 91%); the median age at onset was 32 [1.6 – 58] years, including 43% of children (data available for 893 ICSRs, 72%) (Table 2). The age distribution was marked by 2 peaks of incidence, notably at the first

years of age and between 10 and 14 years whatever the gender. The distribution of the number of cases was relatively homogeneous between 40 and 70 years, followed by a slight decrease in the oldest (Figure 2).

	n	%
Gender (n = 1130)		
Women	572	51
Men	558	49
Age (n = 893)		
Median age	32 years [1.58 - 58]	
Adults	512	57
Children	381	43
Country of primary source (n = 1245)		
USA	912	73.3
Europe, including:	222	17.8
<i>France</i>	57	4.6
<i>UKGBNI</i>	32	2.6
<i>Spain</i>	32	2.6
<i>Germany</i>	27	2.2
<i>Italy</i>	21	1.7
<i>Netherlands</i>	8	0.6
<i>Belgium</i>	7	0.6
<i>Switzerland</i>	5	0.4
<i>Portugal</i>	5	0.4
<i>Greece</i>	5	0.4
<i>Norway</i>	4	0.3
<i>Ireland</i>	4	0.3
<i>Hungary</i>	3	0.2
<i>Denmark</i>	3	0.2
<i>Austria</i>	3	0.2
<i>Slovenia</i>	2	0.2
<i>Czech Republic</i>	2	0.2
<i>Sweden</i>	1	0.1
<i>Finland</i>	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	100

Table 2: Characteristics of the ICSRs (n=1245)
UKGBNI: United Kingdom of Great Britain and Northern Ireland

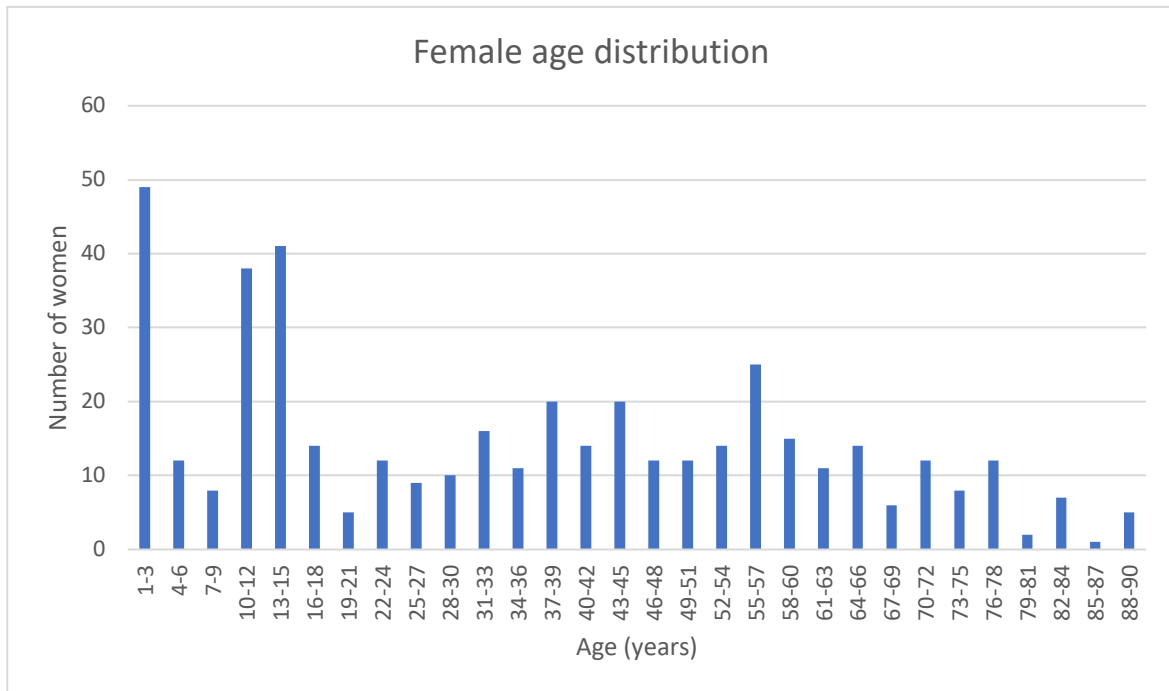
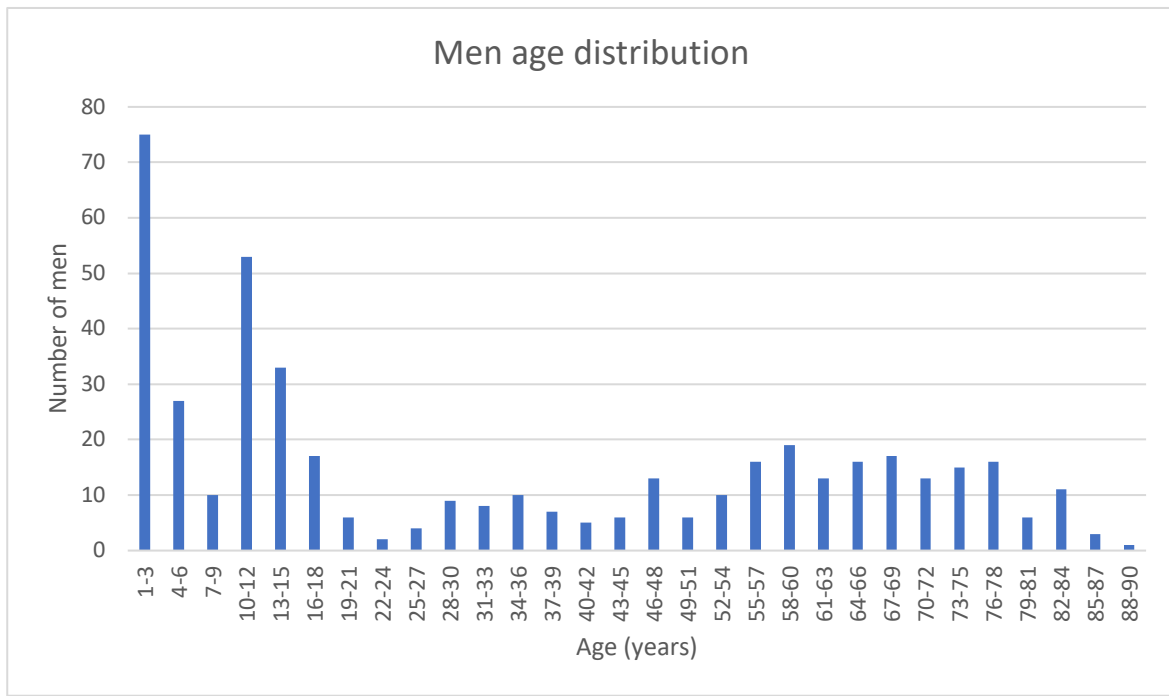


Figure 2: Age distribution of the individual case safety reports

The 61 suspected drugs included 1787 notifications, accounting for the 1245 ICSRs of interest (several suspected drugs could be reported in the same ICSR). Alemtuzumab was the most frequently reported drug, and with the strongest signal (n=239, 19% of ICSRs, and 12% of all notifications; ROR=161.5 [CI95%: 140.9-185.1]). The second and third highest disproportionate reporting were the human rabies immunoglobulin, with 8 cases, and guanfacine, with 10 cases (ROR=83.4 [CI95%: 41.5-167.5] and ROR=39.4 [CI95%: 21.1-73.3], respectively) (Table 3).

Seven of the 10 strongest signals (ROR > 10) involved vaccines, including *Haemophilus influenzae B* vaccine (n=68, 4%), rabies vaccine, (n=14, 1%), hepatitis B and A vaccines (n=76, 4% and n=43, 2%, respectively) and combined measles, mumps and rubella (MMR) vaccine (n=114, 6%). The median age for all vaccine-related ITP was 12 [3-14] years.

The most represented pharmaceutical classes were, in decreasing order: vaccines (n=954/1985, 48%); multiple sclerosis immunomodulatory agents including alemtuzumab, fingolimod, teriflunomide (n=276/1985, 14%); and anticancer drugs (n=243/1985, 12%), including checkpoint inhibitors (n=88/1985, 4%) (Table 3).

ITP was considered as a serious ADR in 1123 ICSRs (91%, data available for 1231 ICSRs, 99%), and at the time of reporting, fatal outcomes were registered in 40 ICSRs (Table 2).

The median time to onset between the introduction of the suspected drug and the occurrence of ITP was 12 days [10.5-33.5] (data available for 488 ICSRs, 39%; or 823 notifications, 46%) (Table 3).

"SUSPECT"/ "INTERACTING" drug	n ITP/drug	ROR	CI95%-	CI95%+	MD between the introduction of the drug and the occurrence of ITP	
					MD (days)	Data available for n patients
Alemtuzumab	239	161.5	140.9	185.1	352	33 (14%)
Immunoglobulin human anti-rabies	8	83.4	41.5	167.5	/	/
Guanfacine	10	39.4	21.1	73.3	/	/
Measles and rubella vaccine	10	22.7	12.2	42.3	16	9 (90%)
HIB vaccine	68	16.8	13.2	21.4	8	55 (81%)
Measles, mumps, rubella and varicella zoster vaccine	39	16.1	11.7	22.2	21	32 (82%)
Rabies vaccine	14	16.1	9.5	27.2	0	1 (7%)
Hepatitis b vaccine	76	15.0	11.9	18.8	12	57 (75%)
Hepatitis a vaccine	43	11.3	8.4	15.3	16.5	36 (84%)
Measles, mumps and rubella vaccine	114	10.9	9.0	13.2	19	93 (82%)
Nivolumab	47	10.5	7.8	14.0	89.5	6 (13%)
Fludarabine	11	10.1	5.6	18.3	9	1 (9%)
Busulfan	5	10.1	4.2	24.3	/	/
Temozolomide	13	9.7	5.6	16.8	/	/
Rotavirus vaccine	54	9.5	7.3	12.5	10	44 (81%)
Pembrolizumab	24	9.4	6.3	14.1	213	5 (21%)
Meningococcal vaccine	73	8.6	6.8	10.8	9.5	54 (74%)
Ipilimumab	17	8.5	5.3	13.7	23	1 (6%)
Typhoid vaccine	9	8.3	4.3	15.9	12	5 (56%)
Folinic acid	15	8.1	4.9	13.5	/	/
Pneumococcal vaccine	136	7.4	6.2	8.8	9.5	108 (79%)
Ibrutinib	27	7.1	4.9	10.4	/	/
Irinotecan	23	6.9	4.6	10.4	/	/
Losartan	13	6.7	3.9	11.6	37	1 (8%)
Venetoclax	8	6.2	3.1	12.3	130	1 (13%)
Doxycycline	15	6.0	3.6	10.0	20.5	2 (13%)
Melphalan	5	5.9	2.5	14.2	357	1 (20%)

Diphtheria, pertussis, polio, and tetanus vaccine	26	5.9	4.0	8.7	13	19 (73%)
Polio vaccine	38	5.9	4.3	8.1	7	33 (87%)
HPV vaccine	58	5.8	4.4	7.5	14	47 (81%)
Filgrastim	6	4.8	2.2	10.7	/	/
Eculizumab	18	4.7	2.9	7.5	/	/
Tacrolimus	24	4.4	2.9	6.5	42	3 (13%)
Oxaliplatin	35	4.3	3.0	5.9	2	1 (3%)
Diphtheria, hepatitis b, HIB, pertussis, polio and tetanus vaccine	18	4.2	2.6	6.7	11	16 (89%)
Vancomycin	22	4.2	2.8	6.4	/	/
Cefalexin	7	4.2	2.0	8.7	/	/
Ifosfamide	5	4.0	1.7	9.7	/	/
Ondansetron	6	3.9	1.7	8.6	/	/
Fingolimod	30	3.7	2.6	5.4	983	2 (7%)
Aciclovir	6	3.7	1.7	8.3	/	/
Sofosbuvir	7	3.7	1.8	7.8	/	/
Yellow fever vaccine	8	3.6	1.8	7.2	14	3 (38%)
Diphtheria, pertussis and tetanus vaccine	47	3.5	2.6	4.7	10	41 (87%)
Influenza vaccine	70	3.4	2.6	4.3	11	52 (74%)
Bisoprolol	6	3.3	1.5	7.3	33	1 (17%)
Sulfamethoxazole;Trimethoprim	22	3.1	2.1	4.8	11.5	6 (27%)
Peginterferon alfa-2b	5	3.0	1.3	7.3	/	/
Varicella zoster vaccine	45	3.0	2.2	4.0	14	39 (87%)
Clopidogrel	17	3.0	1.8	4.8	21	1 (6%)
Ticagrelor	6	2.9	1.3	6.4	19.5	2 (33%)
Diphtheria, HIB, pertussis, polio and tetanus vaccine	8	2.8	1.4	5.7	5.5	6 (75%)
Sunitinib	9	2.8	1.4	5.3	55	2 (22%)
Ethinylestradiol;Etonogestrel	6	2.7	1.2	6.0	/	/
Peginterferon alfa-2a	12	2.7	1.5	4.7	/	/
Rivaroxaban	33	2.5	1.8	3.5	34	1 (3%)
Vedolizumab	5	2.4	1.0	5.8	/	/
Ribavirin	19	2.4	1.5	3.7	/	/
Teriflunomide	7	2.2	1.1	4.7	/	/
Doxorubicin	14	2.0	1.2	3.4	/	/
Acetylsalicylic acid	26	1.8	1.2	2.7	20	3 (12%)
Total	1787 notifications 1245 ICSRs				12 [10.5-33.5]	823 notifications (46%) 488 ICSRs (39%)

Table 3: List of 61 drugs associated with ITP with significant disproportional reporting, classified by decreasing ROR

ITP: immune thrombocytopenia; ROR: reporting odds ratio; CI95%-: inferior limit of the 95% confidence interval; CI95%+: superior limit of the 95% confidence interval; HPV: human papillomavirus; HIB: Haemophilus influenzae B type; ICSR: Individual Case Safety Report; MD: Median delay

For exploratory purposes, we calculated in a separate table (supplementary Table) the RORs of the excluded drugs because of potential indication or protopathic biases. Rituximab, dexamethasone, vincristine, and cyclophosphamide had a significant signal, all indications combined, that remained significant even after excluding cases for which the indication for the drug of interest was ITP or was unknown (ROR=3.7 [CI95% 2.6-5.3], ROR=1.9 [CI95% 1.1-3.3], ROR =2.6 [CI95% 1.3-4.9], ROR=1.9 [CI95% 1.2-3.1], respectively).

"SUSPECT"/ "INTERACTING" drug	n ITP/drug	ROR	CI95%-	CI95%+
Eltrombopag				
<i>x any indication combined</i>	62	50.4	39.1	64.9
<i>x after exclusion of ITP and unknown indications</i>	2	1.6	0.4	6.3
Romiplostim				
<i>x any indication combined</i>	23	24.6	16.3	37.2
<i>x after exclusion of ITP and unknown indications</i>	1	1.1	0.2	7.5
Rituximab				
<i>x any indication combined</i>	50	6.2	4.7	8.2
<i>x after exclusion of ITP and unknown indications</i>	30	3.7	2.6	5.3
Prednisone				
<i>x any indication combined</i>	16	2.8	1.7	4.6
<i>x after exclusion of ITP and unknown indications</i>	3	0.5	0.2	1.6
Dexamethasone				
<i>x any indication combined</i>	19	2.8	1.8	4.4
<i>x after exclusion of ITP and unknown indications</i>	13	1.9	1.1	3.3
Vincristine				
<i>x any indication combined</i>	9	2.6	1.3	4.9
<i>x after exclusion of ITP and unknown indications</i>	9	2.6	1.3	4.9
Cyclophosphamide				
<i>x any indication combined</i>	19	2.1	1.3	3.2
<i>x after exclusion of ITP and unknown indications</i>	18	1.9	1.2	3.1

Supplementary table: List of excluded drugs for potential indication or protopathic biases

ITP: immune thrombocytopenia; ROR: reporting odds ratio; CI95%-: inferior limit of the 95% confidence interval; CI95%+: superior limit of the 95% confidence interval

Discussion

With this pharmacoepidemiological study, we aimed to establish, as far as we know, the first list of potential drugs associated with ITP using a worldwide pharmacovigilance database. We found herein some new suspect therapeutics such as guanfacine, eculizumab, or doxycycline, and we confirmed and first quantified the signal strength of previous incriminated drugs in DITP, including vaccines, some antibiotics, irinotecan and mostly alemtuzumab that exhibited the greatest risk. Moreover, using this large database, our study first reported different demographic characteristics in DITP than in ITP for gender and age distribution.

The epidemiology of DITP was different from that of primary ITP. Indeed, Kholi *et al.* (16) described, based on several large epidemiological studies, a slightly higher rate of primary ITP in women, with a sex-ratio of 0.8 instead of 1 in our study. In addition, the authors described a bimodal distribution among males, with incidence rates highest among boys under 18 years old and men from 75 to 85 years; on the other hand, incidence rates were relatively stable in women from childhood to 60 years and increased thereafter. On the contrary, in our study, the distribution exhibited 2 peaks of incidence during the childhood in both sexes. This younger distribution in DITP should be related to vaccine-related ADRs.

Comparing our results to the DITP literature, we found profound changes in the list of incriminated drugs (1,2,8,17,18).

First, alemtuzumab, showed the strongest signal for DITP in our study, in contrary to the old literature reviews (1,8,17,18) that did not mention this drug. This biological therapy, an anti-CD52 monoclonal antibody that targets T, B and other immunological cells, received the marketing authorisation by the Food and Drug Administration (FDA) in 2001 (20), and by the EMA in 2013 (21) for the treatment of multiple sclerosis. More recently in 2020, the work by Cuker *et al.*, which gathered the data from several randomized studies with alemtuzumab, including CAMMS223 (Campath[®]-1H in multiple sclerosis international trial) and CARE-MS I and II (Comparison of Alemtuzumab and Rebif[®] Efficacy in Multiple Sclerosis) trials, reported alemtuzumab as a serious candidate for DITP. After a median follow-up of 6.1 years, 33 of 1485 alemtuzumab-treated patients (2.2%) developed ITP (22).

Second, unlike previous studies (8,18) that mainly focused on adults, and therefore did not find vaccines as a risk for DITP, our pharmacovigilance study that also includes paediatric patients clearly incriminated this pharmacological class. Indeed, the most reported drug class were vaccines that were responsible for 7 of the 10 strongest signals (ROR > 10), including *Haemophilus influenzae* B vaccine, hepatitis B and A vaccines and MMR vaccine. Moreover,

in a French pharmacoepidemiological study published in 2012 (11), 45% of the drugs involved in potential DITP were also vaccines; the median age at diagnosis was 16 years, which is closed to ours of 12 [3-14] years. Another literature review that focused on vaccine-related ITP case reports found similar findings to ours regarding main incriminated vaccines (19).

Third, to our knowledge, it was the first time that guanfacine was mentioned as being potentially responsible of DITP, although only 10 cases were retrieved in our study. Guanfacine is an adrenergic alpha-agonist that recently received a marketing authorization (FDA 2009 (23), EMA 2015 (24)) for the treatment of attention deficit or hyperactivity disorders. This new indication probably explains the rebound of ADR notifications for this old drug previously used in the treatment of arterial hypertension.

Antibiotics were surprisingly poorly represented in our analysis, although highly mentioned in previous studies on DITP (2,11,12). Like most of them, we found a significant overreporting for vancomycin and sulfamethoxazole-trimethoprim. Doxycycline had the strongest signal among antibiotics. However, these results should be interpreted with caution, considering the frequent associations of antibiotics with other suspected drugs such as rabies prophylaxis, or the potential protopathic bias related to their indications.

In the same way, several drugs highly mentioned in the literature (1,2,8,17,18) were not significantly associated with DITP in our analysis, such as quinine, platelet inhibitors (abciximab, tirofiban), anticonvulsant agents (carbamazepine, phenytoin, valproic acid), diuretics (chlorothiazide) or some antibiotics (rifampicin). Some of them, like quinine, abciximab, tirofiban, phenytoin, and chlorothiazide, are less and less used nowadays because they are substituted by novel therapeutics since about fifteen years, whereas our analysis only included ICSRs since 2006. On the other hand, some of these substitute drugs were significantly associated with DITP in our study, such as losartan, bisoprolol, clopidogrel, ticagrelor, which justifies this update.

In order to prevent the indication or protopathic biases, we excluded from the main analysis drugs used to treat ITP as first- or second-line agents according to the international consensus report of management of ITP (10). However, as several cases of ITP induced by these drugs have previously been reported (25–35), we calculated for exploratory purposes the pharmacovigilance signals associated with these drugs. The ROR remained significant after exclusion of ITP and unknown indications for rituximab, strengthening the previously described associations (25–33). The same trends for significant ROR were also observed for dexamethasone, vincristine, and cyclophosphamide, but these associations were more poorly supported by the literature (34,35). On the contrary, methylprednisolone has been reported

several times as being responsible for DITP (36,37), but this association was not significant in our analysis.

Some hypotheses have been formulated to explain the pathophysiology of DITP. Molecular mimicry seems to be the classic mechanism responsible for vaccine-induced ITP, through infective components of the vaccine or other constituents such as adjuvants (19). For example, the culprit protein of molecular mimicry in influenza vaccine is probably the hemagglutinin, which is a major surface glycoprotein of the influenza virus used for binding to cells of interest. This molecule is highly targeted by neutralizing antibodies, including those induced by influenza vaccines; and it has been demonstrated that hemagglutinin also binds to platelets, triggering potential complement activation and platelet destruction through anti-hemagglutinin antibodies (19).

The mechanisms inducing ITP following vancomycin or trimethoprim/sulfamethoxazole treatment have been evocated a long time ago (38). The model of “drug-dependent” antibodies refers to antibodies that have low affinity for platelet glycoproteins; however, the binding of these antibodies to platelets strengthens in presence of the drug, inducing platelet destruction in the reticuloendothelial system only in presence of the drug (39). The main glycoprotein targeted by vancomycin and trimethoprim/sulfamethoxazole is glycoprotein IIb/IIIa (39).

There are a lot of recent publications regarding the new drugs of immune checkpoint inhibitors (ICI) class. Several related adverse effects have been reported, including haematological adverse effects that represent 3.6% of adverse effects with these drugs, including DITP that appears as the most frequent (40). The pathophysiology of this adverse reaction is directly related to the mode of operation of this drug class. As a reminder, ICIs are mainly used to fight tumour cells by disrupting the immunoinhibitory signals mediated by programmed cell death protein-1 or ligand-1, and/or cytotoxic T-lymphocyte-associated protein 4; the inhibition of the blocking signals offered by these proteins consequently releases the power of the immune system (41). Therefore, immune ADRs are expected, and the need for discontinuation of the ICI depends on the benefit-risk balance between the severity of the ADR and the expected benefit for the targeted disease. In addition to the involvement of the cellular immunity, some cases of DITP related to ICIs have been associated with anti-platelet autoantibodies (40), which implies the participation of humoral mechanisms.

Of note, the clinical presentation and probably the pathophysiology of alemtuzumab-induced ITP differ from that of other DITPs. Indeed, while with other drugs DITP classically appears within a few days following the exposure to the drug of interest, with alemtuzumab the related DITP rather emerge several months following the initiation of the drug. This DITP appears to be highly responsive to conventional therapies, and rarely evolves through a

chronic form (42,43). The timeline for the onset evokes a mechanism not directly related to the drug, but maybe to the consequence of its action, namely a dysregulation of the lymphocyte repopulation after drastic alteration of circulating lymphocyte pool. It could be, as suggested in Cuker *et al.* (42), a consequence of defects in central tolerance checkpoints during lymphocyte reconstitution.

Our study had several limitations, including the biases associated with a case - non case study related to spontaneous notifications (under-notification, selective declaration, Weber effect, risk of duplication), missing data (information bias), and accountability (confounding factors, protopathic bias) (13,15). We tried to prevent the indication and protopathic biases by excluding all drugs used as first or second-line therapies in primary ITP from the analysis. It is also important to remember that pharmacoepidemiological studies based on large databases such as Vigibase are meant, not to assess causality, but to detect significant signals to guide studies of higher level of evidence with rechallenge or laboratory data (e.g. detection of drug-dependent platelet antibodies) as in the Reese *et al.* study (8). Moreover, for several suspect drugs mentioned for the first time in our study, the strength of the related signal is hard to assess because of all other possible associated mechanisms that can be involved in drug-induced thrombocytopenia, including myelotoxicity; because of other drugs that are frequently associated with the drug of interest; or because of underlying diseases, including autoimmune disorders, that may be responsible for secondary ITP and may be treated by the suspected drugs.

Conclusion

To conclude, this large pharmacovigilance database updated the list of drugs potentially responsible for DITP, focusing on therapeutics used these last 15 years. In addition to corroborate old signals for DITP mentioned in previous literature, this study also retrieved new suspect associations with more recently engineered or repositioned drugs, like alemtuzumab and guanfacine, respectively. If the time between the introduction of the incriminated drug and DITP occurrence is approximately 2 weeks, some DITP may be observed after more than a year, especially for alemtuzumab and checkpoint inhibitors, suggesting a different pathophysiology for these latter classes. Prospective large observational and experimental studies are required to strengthen the associations for the highest pharmaco-epidemiological signals.

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Pour le Président
de l'Université de CAEN et P.O

Le Doyen

ANNEE DE SOUTENANCE : 2021

NOM ET PRENOM DE L'AUTEUR : FUENTES Ségolène

TITRE DE LA THESE : Purpura thrombopénique immunologique induit par les médicaments : actualisation de la liste des médicaments suspects à l'aide d'une base de pharmacovigilance internationale.

RESUME DE LA THESE EN FRANÇAIS :

Contexte : Une thrombopénie est un effet indésirable (EI) médicamenteux fréquent pouvant notamment être secondaire au développement d'un purpura thrombopénique immunologique induit par les médicaments (PTIM) dont le pronostic est généralement favorable à l'arrêt du médicament incriminé. Étant donné l'évolution de la pharmacopée, nous proposons d'actualiser la liste des médicaments associés aux PTIM en analysant la base de données de pharmacovigilance de l'organisation mondiale de la santé : Vigibase®.

Méthodes : Nous avons collecté tous les rapports de sécurité individuels (RSI) suspectant un PTIM dans Vigibase®. Une analyse cas-non cas a été réalisée pour chaque médicament « suspect » ou « interacting ». Un signallement disproportionné était mis en évidence par le calcul du « reporting odds ratio » (ROR). Un signal était considéré significatif s'il concernait au moins 5 RSI et si la limite inférieure de l'intervalle de confiance à 95% du ROR était strictement supérieure à 1.

Résultats : Au total, 61 médicaments suspects avaient un signal significatif représentant 1245 RSI (572 femmes (51%), âge médian au diagnostic : 32 ans [1,6-58]). Le délai médian entre l'introduction du médicament et le diagnostic de PTIM était de 12 jours [10,5-33,5]. Le médicament le plus rapporté et avec le signal le plus fort était l'alemtuzumab (ROR=161,5), et la classe pharmaceutique la plus représentée était les vaccins, comprenant 7 des 10 signaux les plus forts. Le PTIM était considéré comme un EI grave dans 1123 RSI (91%).

Conclusion : Cette étude renforce de précédents signaux décrits et a identifié de nouveaux médicaments suspects, en lien avec l'évolution constante de la pharmacopée.

MOTS CLES : Purpura thrombopénique immunologique ; pharmacovigilance ; Vigibase® ; iatrogénie ; étude cas-non cas ; ROR.

TITRE DE LA THESE EN ANGLAIS : Drug-induced immune thrombocytopenia: an updated list of suspected drugs using the World Health Organization pharmacovigilance database.

RESUME DE LA THESE EN ANGLAIS :

Context: Thrombocytopenia is a common drug adverse effect that can be caused by various mechanisms, including drug-induced immune thrombocytopenia (DITP), whose prognosis is generally favourable when the suspected drug is withdrawn. As the pharmacopoeia has noticeably evolved, we propose to update the list of suspected drugs associated with DITP by analysing the World Health Organisation pharmacovigilance database: Vigibase®.

Methods: We collected all individual case safety reports (ICSRs) of suspected DITP registered in the Vigibase®. A case-non case analysis was performed for each "suspect" or "interacting" drug, and disproportionate reporting was assessed by calculating the reporting odds ratio (ROR). A signal was considered significant if it concerned at least 5 ICSRs, and if the inferior limit of the 95% confidence interval of the ROR was strictly superior to 1.

Results: A total of 1245 ICSRs of DITP were selected, accounting for 61 suspect drugs with a significant signal. DITP occurred in 572 (51%) women and the median age at onset was 32 years [1.6 – 58] with 43% of children. The median time to onset between the introduction of the suspected drug and the occurrence of ITP was 12 days [10.5-33.5]. The most frequently reported drug and with the strongest signal was alemtuzumab (ROR=161.5), and the most represented pharmaceutical class was vaccines, accounting for 7 of the 10 strongest signals. DITP was considered as a serious adverse drug reaction in 1123 ICSRs (91%).

Conclusion: This study strengthens some previous signals and found some new suspect drugs that are consistent with the evolution of the pharmacopoeia.

KEY WORDS: immune thrombocytopenia; drug-induced immune thrombocytopenia; pharmacovigilance; Vigibase®; case-non case analysis; ROR.