Drug-induced IgA vasculitis in children and adults: Revisiting drug causality using a dual pharmacovigilance-based approach

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ABSTRACT

OBJECTIVES

IgA vasculitis (IgAV) is an immune complex small-vessel vasculitis. Drug-induced IgAV cases were rarely reported in the literature. Drug causality assessment is challenging as many other etiological factors can be involved. We performed a pharmacovigilance study to identify the main drugs reported to induce IgAV.

METHODS

We used the French pharmacovigilance database (FPVD) and the WHO global individual case safety reports database (VigiBase) to retrieve IgAV cases. Cases from the FPVD were reviewed by two investigators using predefined criteria. Disproportionality analyses (case – non-case approach) were conducted in VigiBase to identify drugs significantly associated with IgAV reporting.

RESULTS

Of the 467 IgAV cases retrieved from the FPVD, 115 (47 children and 68 adults) have been assessed as definite or probable, reported with 178 suspected drugs. Overall IgAV cases were mainly male (58%), with a median age of 33.5 (8.0-63.3) years. No death was reported. Besides, we identified 1558 possible IgAV cases in VigiBase. Among them, 40 were associated with a disproportionality in IgAV reporting. Drugs were mainly vaccines, antibiotics and TNF-α blockers, these finding being consistent in both databases. IgAV reporting with TNF-α blockers was significantly associated with their use in inflammatory bowel diseases, psoriasis or ankylosing spondylitis compared to other indications.

CONCLUSIONS

Our systematic study enables the identification of culprit drugs in drug-induced IgAV. These results strengthen the immune pathophysiology of IgAV and the role of underlying disease. The list of suspected drugs may be useful for physicians to manage patients with IgAV and consider appropriate drug discontinuation.

KEY MESSAGES

What is already known about this subject?

IgA vasculitis has multifactorial etiology. To date, possible culprit drugs have been reported only in case reports.

What does this study add?

Using a dual pharmacovigilance-based approach, we identified drugs associated with the occurrence of IgA vasculitis, such as all types of vaccines, major antibiotics and immunomodulatory agents, mainly TNF-α blockers.

How might this impact on clinical practice or future developments?

Physicians should be aware of drug-induced IgA vasculitis and we provide evidence on the most frequent implicated drugs.

INTRODUCTION

Immunoglobulin A (IgA) vasculitis (IgAV), formerly called Henoch-Schonlein purpura, is an immune complex-mediated vasculitis firstly described in 1802 [1]. IgAV affects small vessels and is characterized by the presence of IgA1-dominant immune deposits [2]. The definition of this disease has been a matter of debate for years [3]. The disease most often presents with palpable purpura, frequently extensive with sometimes bullous or necrotic elements, arthralgia and/or arthritis, gastrointestinal (GI) involvement with severity ranging from mild abdominal pain to hemorrhage and/or bowel perforation, and renal involvement with glomerulonephritis [4–6]. Although more common in children, IgAV is usually more severe in adults and its prognosis is mainly related to GI and renal involvements. Benign forms require symptomatic care, especially in children, whereas in severe forms, more aggressive treatments based on glucocorticoids and immunosuppressive agents are necessary [7,8].

Although IgAV pathogenesis has not been yet fully elucidated, a key role of IgA is suspected, particularly because of its implication in innate immunity within the GI mucosal barrier where interactions with many pathogens take place. Some studies suggest that seasons – mainly autumn and winter – are associated with more frequent onset of the disease, possibly related to infectious agents [9]. Susceptibility genes were identified, some of them involving the HLA system. Overall, environment and genetic background could be key players in the pathophysiology of IgA vasculitis, and among exogenous agents, drugs could be potential triggers of the disease [10].

Scarce data in the literature suggest that some drugs may trigger IgAV. To date, only case reports have been published in the literature, as well as a single systematic review of the literature [11]. The assessment of drug causality is challenging as many other etiological factors can be involved. So far, no systematic pharmacovigilance study has been conducted. Therefore, we aimed to identify drugs associated with IgAV reporting using a pharmacovigilance-based data mining dual approach.

METHODS

Data sources and study design

Two different pharmacovigilance databases were used: the French Pharmacovigilance Database (FPVD) and VigiBase, the World Health Organization (WHO) global database of individual case safety reports (ICSR). In this dual approach, we analyzed detailed clinical description of drug-induced IgAV cases within the FPVD, combined with a disproportionality analysis within VigiBase, allowing the identification of main culprit drugs associated with IgAV.

The FPVD is a national database that encompasses all adverse drug reactions (ADRs) notified to the French Pharmacovigilance Network, comprising 31 regional pharmacovigilance centers. On each ICSR, causality assessment is made by clinical pharmacologists based on a national scoring system [12]. Since 1986, about 800,000 ICSRs originating from healthcare professionals or patients have been registered in this database, after drug causality assessment by pharmacologists. Each ICSR is classified as “non-serious” or “serious”, based on criteria as defined by the WHO such as death, life-threatening conditions, requiring/prolonging hospitalization or resulting in persistent or significant disability/incapacity [13]. ICSRs include information about reporting, patient, type of ADR according to the Medical Dictionary for Regulatory Activities (MedDRA), and suspected and concomitant drugs. Furthermore, regional implantation of pharmacovigilance centers within university hospitals allows the ability to have detailed narratives on clinical and biological events as well as on medical history for each ICSRs. ICSRs are fully anonymized in the FPVD, whose access is granted to each pharmacovigilance center.

VigiBase, the WHO pharmacovigilance database, gathers reports of suspected ADRs to medicinal products from national pharmacovigilance centers since 1968 [14]. To date, VigiBase includes about 20 millions of ICSRs from over 130 countries across the world. This

makes it very powerful to conduct disproportionality analyses and identify possible pharmacovigilance signal, i.e. new adverse effect-drug combination [15].

Descriptive study

Reports of IgAV cases registered in the FPVD until January 31th, 2019 were retrieved using the preferred term (PT) "Henoch-Schonlein purpura" as ADR. A case-by-case analysis of detailed narratives was performed by a pair of internal medicine physicians (CR, BT) and clinical pharmacologists (MT, LC) in order to categorize IgAV cases into definite, probable or excluded, according to predefined criteria (**Table 1**). Cases were selected if they had a plausible time to onset after suspected drug introduction, or after last infusion for cycle treatment such as Tumor Necrosis Factor alpha (TNF-α) blockers, defined as less than 3 months.

Disproportionality analysis

ICSRs reported as IgAV cases in VigiBase until January 31th, 2019 were retrieved using the lowest level terms (LLTs) "Rheumatic purpura", "Henoch-Shonlein purpura", "Henoch-Schonlein", "Henoch-Schonlein purpura", "Schoenlein-Henoch purpura", "Vasculitis Henoch-Schonlein like", "IgA vasculitis" and "IgA-associated vasculitis" as ADR. Other LLTs, included in the above PT "Henoch-Schonlein purpura" according to MedDRA hierarchical structure, such as "Allergic purpura" or "Anaphylactic vascular purpura" were not included as these terms does not referred to the IgAV definition and were not specific. We further only considered drugs reported in ICSRs as "suspect" or "interaction". All levels of causality assessment were included [12]. We used a case/non-case design to measure disproportionality of IgAV reporting among all drugs reported in VigiBase, using the odds ratio of reporting (ROR) and its 95% confidence interval (CI) [16]. This approach has been largely evaluated and used to perform signal detection among pharmacovigilance databases

[15]. Thus, disproportionality analyses identified whether IgAV cases were differentially reported with a suspected drug compared to all the other drug in the full database. Furthermore, specifically for TNF-α blockers, we performed secondary disproportionality analyses on the reporting of IgAV in patients with inflammatory bowel diseases, psoriasis or ankylosing spondylitis (i.e. diseases associated with susceptibility genes and potential environmental triggers, that could also be shared with IgA vasculitis [17]) compared to other treatment indications.

Statistical analysis

Descriptive analysis was performed on the cases retrieved from the two databases. Quantitative variables were expressed as median ± interquartile range (IQR), and compared using non-parametric analyses. Qualitative variables were expressed in figures and percentages. RORs with their 95% CI were calculated for each different suspected drug. Briefly, ROR [95% CI] are calculated as ROR = $\frac{ad}{bc}$ [$e^{\pm 1.96\sqrt{\left(\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}\right)}}$], where *a* is the number of IgAV cases reported with a suspected drug, *b* is the number of non-cases (i.e. other ADR reports) reported with a suspected drug, *c* is the number of IgAV cases reported with all other drugs, and *d* is the number of non-cases (i.e. other ADR reports) reported with all other drugs. To limit reporting bias, we only considered suspected drugs reported in at least three ICSRs according to European Medicines Agency guidelines [18], and coming from three different countries. Disproportionality in reporting for a suspected drug was considered when the lower bound of the 95% CI of the ROR was superior to one (>1). ROR were expressed for each suspected drugs and for each pharmacological classes. All analyses were performed using Microsoft Excel software and Prism GraphPad.

RESULTS

IgAV characteristics

Among 467 cases extracted from the FPVD, a total of 115 IgAV cases have been included according to the predefined diagnosis criteria, and categorized as definite (n=67) and probable (n=48) (**Figure 1**). These cases included overall 178 different suspected drugs.

Most cases were male (n=68, 59%) with a median age of 33.5 (IQR 8-63.3) years, and 47 (41%) cases were children (**Table 2**). Main IgAV clinical characteristics were purpura (n=115, 100%), joint involvement (n=64, 56%), GI involvement (n=42, 37%) and renal involvement (n=38, 33%). Tissue biopsy was available in 52 (45%) patients corresponding to 34 definite and 17 probable IgAV diagnosis, and included renal biopsy in 8 patients and skin biopsy in 44. Among patients with available biopsy, the presence of IgA immune deposits was noted in 32 (67%). No vasculitis-specific treatment was required in 75 (65%) patients. In contrast, 36 (31%) patients received glucocorticoids, four (3.5%) colchicine and one (1%) cyclophosphamide. Outcome was favorable with complete recovery in 62 (67%) patients and 15 (16%) had sequelae, most frequently mild to moderate (two patients had persistent chronic renal failure). No death was reported during follow-up.

Suspected drugs

Main suspected drugs were vaccines (n=42, 24%), antibiotics (n=38, 21%) and TNF-α blockers (n=14, 8%) (**Tables 2, Figure 2, Supplementary Table S1**). All types of vaccines have been reported, such as live attenuated vaccines (mainly measles, rubella and mumps), inactivated vaccines (mainly influenza and poliomyelitis), and subunit vaccines (mainly diphtheria and tetanus). Among antibiotics, IgV cases were reported for beta-lactamines, fluoroquinolones and macrolides. Regarding TNF-α blockers, cases were only with adalimumab and infliximab; it is noteworthy that these cases only concerned patients treated for Crohn's disease or psoriasis and none for rheumatoid arthritis.

Median time from drug initiation and onset of vasculitis was 11 days (IQR 6-30), 10 days (IQR 6-30) and 23 months (IQR 6.3-30.5) for vaccines, antibiotics and TNF-α blockers, respectively.

Disproportionality analysis

Of the 18,578,924 ICSRs in VigiBase, we retrieve 1,558 ICSRs of possible IgAV reported with 397 different suspected drugs. Cases mainly originated from Americas (n=759, 48.7%) and Europe (n=650, 41.7%) (**Supplementary Table S2**). About half of the patients were female (n=767, 49.2%) and median age was 27.0 (IQR 5.0-50.8) years, including 434 (27.9%) children. Among these IgAV cases, 79 different suspected drugs have been reported in at least three cases originating from different countries. The case – non-case analysis showed that of 79 suspected drugs, 40 were associated with a significant disproportionality in IgAV reporting (**Table 3, Figure 2, Supplementary Table S3**). These drugs are mainly vaccines, antibiotics, and immunomodulatory agents. About all vaccine types are represented, including live-attenuated vaccines (measles, mumps, rubella, Japanese encephalitis, varicella zoster and yellow fever), inactivated vaccines (hepatitis A, rabies and tick bone encephalitis) and subunit vaccines (diphtheria, poliomyelitis, tetanus, pertussis, influenza, papillomavirus, meningococcal, hepatitis B, haemophilus influenzae B). The highest disproportionality is for tick borne vaccine (ROR 30.5 [95% CI: 20.0-46.5]). Others drugs include various classes of antibiotics (amoxicillin and derivatives, ciprofloxacin, clarithromycin, daptomycin, fusidic acid), immunomodulatory agents (montelukast, infliximab, adalimumab, certolizumab pegol, tocilizumab and tacrolimus) and other drugs (losartan, methylphenidate, isotretinoin and somatropin). Secondary disproportionality analysis showed that IgAV cases reporting for TNF-α blockers was significantly associated with their use in inflammatory bowel diseases, psoriasis or ankylosing spondylitis, compared to other indications (ROR 2.1 [95% CI: 1.4-3.2] (**Supplementary Table S4**).

DISCUSSION

We report here the first systematic study on drug-induced IgAV. Our analyses allowed the identification of suspected drugs reported to induce IgAV in pediatrics and adults, such as vaccines, antibiotics and immunomodulatory agents, mainly TNF-α blockers. The identification of suspected drugs was consistent between both analyses. This study also shows the relevance of this novel method based on a combined analysis of two pharmacovigilance databases: a qualitative analysis of IgAV cases from the FPVD based on an expert opinion case-by-case review and a quantitative analysis with a signal detection approach from the large international database VigiBase using disproportionality analyses.

The descriptive analysis showed that epidemiological characteristics of drug-induced IgAV was similar to epidemiological features of IgAV classically described [19]. Overall median age was 33.5 years and about 40% were pediatrics. Drug-induced IgAV cases mainly concerned male patients which is also a common characteristic of IgAV. As expected, cutaneous involvement was found in all drug-induced IgAV cases, followed by joint and GI involvements that constitutes the classic triad of IgAV. Glomerulonephritis was less common than in idiopathic forms, but was still present in one third of the studied population. Of note, most of the drug-induced cases had a favorable outcome with symptoms resolving quickly after drug discontinuation, and only a minority of patients requiring immunosuppressive agents. To date, only case reports [20–24] and one review [11] have been published on drug-induced IgAV. Review of literature also showed male predominance (53%) with a median age of 37.5 years (range 1-86), including 36% of children. Vasculitis-specific treatments were prescribed in 59% of the cases. Outcome was similar between this review and our study with a recovery achieved in 92% and only few complications or sequelae (four deaths and two chronic renal failure).

Drugs reported in this review based on cases reports were consistent with our findings. Among the 130 drug-related IgAV cases reported in 89 articles in the literature, 79%

belonged to one of the following classes: vaccines (n=31), mainly against influenza and measles, antibiotics (n=13), TNF-α blockers (n=10) or cardiovascular drugs (n=10). Using our approach, we found that all types of vaccines were associated with a significant disproportionality. IgAV exhibits a complex and multifactorial pathophysiology, with a leading theory that an environmental factor could trigger the disease in genetically predisposed individuals [4,25]. We can hypothesize that vaccines, by mimicking the immune response against pathogens to induce long-term antibodies, could represent an immunological trigger and promote the onset of IgAV.

The second most common drug class identified in our study was antibiotics. All pharmacological classes of antibiotics were reported as suspected drugs for IgAV which is in line with data from the literature. However, since infections were largely reported to act as an immunological trigger of IgAV [10,26–30], it could represent a possible confounder for antibiotics, reason why antibiotics causality should be interpreted cautiously.

The third most common therapeutic group of suspected drugs were immunomodulatory agents, especially TNF-α blockers. The latter were previously reported to be a potential inducer of vasculitis. In a French retrospective cohort on vasculitis induced by TNF-α blockers, only two out of 30 cases with available biopsy showed IgA deposits in the kidney [31]. In this study, the main underlying disease was rheumatoid arthritis. Other case reports revealed a potential association between IgAV and TNF-α blockers [32–35]. Our data mining analysis identified adalimumab, infliximab and certolizumab as suspected drugs, whereas no case was associated with etarnercept. Time to vasculitis onset after drug initiation was longer compared to other therapeutic classes, which is consistent with previous study showing a mean interval of 9.6 months [31]. Interestingly, among ICSR with TNF-α blockers in VigiBase, we found a disproportionality in IgAV reporting for patients with IBD, psoriasis or ankylosing spondylitis compared to other indications. Thus, it appears that IgAV cases with TNF-α blockers were associated with IBD, psoriasis or ankylosing spondylitis. These three

aforementioned conditions are known to share susceptibility genes and potential environmental triggers, that could also be shared with IgA vasculitis [17]. Besides, the link between these diseases could be related to the gut-synovial axis. Indeed, there are complementary theories that include the role of microbiota and especially dysbiosis with changes in gut bacteria with some type of bacteria that can induce autoimmunity probably related to molecular mimicry. Gut T-cells activated by these antigens in the Peyer's patches and the mesenteric lymph nodes, express specific adhesion molecules, which is responsible for the homing of these cells to the joint, thus, inducing inflammation [36]. TNF-α blockers could reveal the underlying vasculitis in this high-risk population. Finally, to explain vasculitis induced by TNF-α blockers, some studies suggested the formation of anti-TNF/TNF immune complexes that could deposit in small vessels [34,37,38].

Our study has some strengths and limitations. Our dual approach from two pharmacovigilance databases allows us to identified drugs reported to induce IgAV based on cases with an expert diagnosis. Also, we used predefined criteria and a case-by-case analysis after expert reviewing to improve the robustness of our diagnoses. We combined a data mining approach using a case – non-case method on the large WHO global safety database, allowing us to identify drugs associated with rare event such as IgAV. We included all reported cases, both from patients and health care professionals to increase the power of the study and identify new suspected drugs. However, pharmacovigilance analyses have inherent limitations, including primarily an under-reporting of ADRs. Second, information bias is possible, especially on patient reporting. However, IgAV is an expert diagnosis and patients reporting this reaction are likely to have received this diagnosis from physicians. Third, since clinical details are not available in VigiBase, it is not possible to provide the same level of informativeness, and retrieved ICSRs are only considered as possible IgAV. Nevertheless, since both analyses identified overall the same pharmacological groups of drugs, results of the disproportionality analysis appears reliable. Moreover, to limit wrong diagnosis in VigiBase

analysis, we restricted IgAV ICSR identification to cases reported with specific terms for this diagnosis.

In sum, we provide here the largest study on drug induced-IgAV, including pediatrics and adults. Our dual pharmacovigilance-based approach allowed us to identify suspected drugs that are represented by three main therapeutic classes: vaccines, antibiotics and immunomodulatory agents, mainly TNF-α blockers. These results strengthen the immune pathophysiology of IgAV. The list of suspected drugs may be useful for physicians to manage patients with IgAV and consider appropriate drug discontinuation.

INFORMATION STATEMENT

The information from VigiBase comes from a variety of sources, and the probability that the suspected adverse effect is drug-related is not the same in all cases. The information does not represent the opinion of the UMC, the World Health Organization or the French *Agence Nationale de Sécurité des Médicaments*, and only reflects the authors' opinion.

COMPETING INTERESTS AND FUNDING

None for all authors

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AUTHORSHIP CRITERIA

(1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data,

(2) drafting the article or revising it critically for important intellectual content,

(3) final approval of the version to be submitted.

All authors fulfill authorship criteria.

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464 **TABLES**

465

466 **Table 1. Predefined criteria used for the assessment of definite or probable IgA**
467 **Vasculitis (IgAV) cases among pediatric and adult patients.** According to these criteria,
468 histological analysis is predominant for IgAV in adults and are not essential in pediatrics.
469 ACR, American College of Rheumatology; EULAR, European League Against Rheumatism;
470 PRINTO, Paediatric Rheumatology International Trials Organisation; PRES, Paediatric
471 Rheumatology European Society.

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Diagnosis	Pediatrics	Adults
Definite IgAV	Any purpura associated with at least one of the following: Renal, gastrointestinal or musculoskeletal involvement **and/or** Histological confirmation of vasculitis with IgA-dominant immune deposits (compatible with ACR and EULAR/PRINTO/PRES criteria commonly used in children and/or the 2012 Chapel Hill criteria)	Any purpura without further organ damage associated with histological evidence of leukocytoclastic vasculitis with IgA immune deposits on skin biopsy **or** Any purpura associated with at least another organ involvement **and** confirmed by histology from any other part than skin.
Probable IgAV	At least 2 criteria among: Age <20 years Evocative vascular purpura Acute abdominal pain Leukocytoclastic vasculitis on skin biopsy (meeting ACR criteria only) Rheumatoid purpura both coded and mentioned in the narrative	Presence of evocative purpura (or leukocytoclastic vasculitis in case of biopsy) associated with another clinical organ involvement but without confirmation of IgA deposits. Of note, evocative purpura in IgAV is commonly described as an extensive palpable purpura that can affect all the limbs and the abdomen with sometimes bullous or necrotic elements.

473 **Table 2. Characteristics of pediatric and adult IgA vasculitis cases from the French**

474 **pharmacovigilance database.**

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	Pediatrics (n = 47)	**Adults** (n = 68)	**Overall (n=115)**
Age, median, years	6 (5-9.3)	60 (39-71.3)	33.5 (8.0-63.3)
Gender, male:female	26:21	41:27	68:47 (59%)
IgA vasculitis diagnosis			
Definite	35 (74.5%)	32 (47.1%)	67 (58.2%)
Probable	12 (26.1%)	36 (52.9%)	48 (41.8%)
Vasculitis characteristics			
Cutaneous involvement	47 (100.0%)	68 (100.0%)	115 (100.0%)
Articular involvement	27 (57.4%)	37 (54.4%)	64 (55.7%)
Gastrointestinal involvement	21 (44.6%)	21 (30.9%)	42 (36.5%)
Renal involvement	13 (27.7%)	25 (36.8%)	38 (33.3%)
Histology*	3 (6.4%)	49 (72.1%)	52 (45.2%)
Kidney biopsy	2 (66.7%)	6 (12.5%)	8 (15.7%)
Skin biopsy	1 (33.3%)	43 (87.8%)	44 (84.6%)
IgA deposits	3 (100.0%)	29 (60.4%)	32 (62.7%)
Treatment			
Glucocorticoids	12 (25.5%)	20 (29.4%)	32 (27.9%)
Glucocorticoids plus colchicine	-	3 (4.4%)	3 (2.6%)
Glucocorticoids plus cyclophosphamide	-	1 (1.5%)	1 (0.9%)
Colchicine	-	1 (1.5%)	1 (0.9%)
Azathioprine	-	1 (1.5%)	1 (0.9%)
None	34 (72.3%)	41 (60.3%)	75 (65.2%)
Unknown	1 (2.1%)	1 (1.5%)	2 (1.7%)
Outcome			
Complete recovery	29 (61.6%)	33 (48.5%)	62 (53.9%)
Sequelae	6 (12.8%)	9 (13.2%)	15 (13.0%)
Not recovered	6 (12.8%)	11 (16.1%)	17 (14.9%)
Unknown	6 (12.8%)	15 (22.1%)	21 (18.2%)
Reported drugs**			
Vaccines			*42 (23.6%)*
Influenza vaccines	6	5	11
DTP and other associations	6	4	10
Measles and other associations	8	0	8
HBV and other associations	6	0	6
Other vaccines	6	1	7
Antibiotics			*38 (21.4%)*
Beta-lactamines	4	10	14
Fluoroquinolones	0	4	4
Macrolides	0	4	4
Sulfamides	0	3	3

Other antimicrobial drugs	4	7	13
TNF-α blockers			*14 (7.9%)*
Adalimumab	0	9	9
Infliximab	0	5	5
Anti-hypertensive drugs	0	10	*10 (5.6%)*
Analgesics	1	9	*10 (5.6%)*
Anticoagulant and antiplatelet agents	0	9	*9 (5.1%)*
NSAID	2	7	*9 (5.1%)*
Other immunomodulators	3	3	*6 (3.4%)*
Psycholeptics and psychoanaleptics	1	4	*5 (2.8%)*
Antidiabetics	0	3	*3 (1.7%)*
Other drugs	12	20	*32 (18.0%)*

* among patients who had a biopsy.

** each IgA vasculitis case can be reported with more than one suspected drug

Data are shown as median (IQR) or n (%)

Other drugs were allopurinol, wasp venom proteins, ranitidine, omeprazole, esomeprazole, loperamide, potassium chloride, anethole trithione, buflomedil, troxerutin, calcitonin, leuprorelin, chondroitin sulfate, fenspiride, ambroxol, buzepide, clonicizine, pholcodine, mequitazine, dorzolamide, timolol, tuberculin, amylmetacresol dichlorobenzyl alcohol, biclotymol.

DTP, diphtheria tetanus pertussis; HBV, Hepatitis B Virus; TNF, Tumor Necrosis Factor; NSAID, Non Steroidal Anti-inflammatory Drug

Table 3. Suspected drugs in possible IgA vasculitis cases identified in the WHO global database of individual case safety reports, and their odds-ratio of reporting.

This table shows drugs associated with a disproportionality in IgA vasculitis reporting, i.e lower bound of ROR 95% IC superior to one. Complete table that includes all the reported drugs in possible IgA vasculitis ICSRs identified in VigiBase is presented in Supplementary data (Table S3).

IgV, IgA vasculitis; NSAIDs, Nonsteroidal anti-inflammatory drugs; TNF-α, Tumor Necrosis Factor-α; ROR, Reporting Odds Ratio; CI, Confidence Interval

Reported drug	Pharmacological group	IgAV cases	Non-cases	ROR [95%CI]
Encephalitis, tick borne, inactivated, whole virus vaccine	Vaccine	22	8490	30.5 [20.0-46.5]
Hepatitis combinations vaccine	Vaccine	20	9074	25.9 [16.7-40.3]
Diphtheria-poliomyelitis-tetanus vaccine	Vaccine	10	5933	19.7 [10.6-36.7]
Japanese encephalitis (inactivated and live attenuated) vaccine	Vaccine	5	3374	17.3 [7.2-41.6]
Measles, combinations with mumps, rubella and varicella, live attenuated vaccine	Vaccine	21	17,895	13.8 [9.0-21.2]
Papillomavirus vaccine	Vaccine	94	90,278	12.8 [10.4-15.8]
Rabies, inactivated, whole virus vaccine	Vaccine	9	9784	10.7 [5.6-20.7]
Meningococcal vaccine	Vaccine	71	81,555	10.5 [8.3-13.4]
Measles, combinations with mumps and rubella, live attenuated vaccine	Vaccine	104	129,177	9.9 [8.1-12.1]
Ampicillin and beta-lactamase inhibitor	Antibiotics	6	7,068	9.9 [4.4-22.1]
Hepatitis A, inactivated, whole virus vaccine	Vaccine	31	38,097	9.6 [6.7-13.7]
Influenza A(H1N1)pdm09 vaccine	Vaccine	40	52,034	9.1 [6.7-12.5]
Diphtheria-pertussis-poliomyelitis-tetanus vaccine	Vaccine	38	50,942	8.9 [6.4-12.2]
Hepatitis B, purified antigen vaccine	Vaccine	64	91,997	8.4 [6.5-10.7]
Influenza vaccine	Vaccine	134	203,158	8.3 [6.9-9.9]
Daptomycin	Antibiotics	4	5816	8.0 [3.0-21.4]

Fusidic acid	Antibiotics	3	4455	7.9 [2.5-24.3]
Losartan	Antihypertensive	11	19,642	6.5 [3.6-11.8]
Montelukast	Leucotriene receptor antagonist	11	20,893	6.2 [3.4-11.1]
Pneumococcal vaccine	Vaccine	78	167,226	5.6 [4.5-7.1]
Vancomycin	Antibiotics	24	52,157	5.4 [3.6-8.1]
Hemophilus influenzae B vaccine	Vaccine	29	65,176	5.5 [3.6-7.6]
Varicella zoster vaccine	Vaccine	47	122,031	4.6 [3.4-6.1]
Infliximab	TNF-α blocker	54	142,615	4.5 [3.4-5.9]
Clarithromycin	Antibiotics	16	41,864	4.5 [2.7-7.3]
Poliomyelitis vaccine	Vaccine	36	95,391	4.5 [3.2-6.2]
Diphtheria-hemophilus influenzae B-pertussis-poliomyelitis-tetanus vaccine	Vaccine	9	24,647	4.3 [2.2-8.2]
Diphtheria-pertussis-tetanus vaccine	Vaccine	60	182,598	3.9 [3.0-5.1]
Yellow fever, live attenuated vaccine	Vaccine	5	16,142	3.6 [1.5-6.7]
Methylphenidate	Centrally acting sympathomimetics	11	39,848	3.2 [1.8-5.8]
Isotretinoin	Retinoids	15	59,513	3.0 [1.8-4.9]
Tocilizumab	Interleukin 6 inhibitor	8	33,010	2.8 [1.4-5.7]
Tetanus toxoid, combinations with diphtheria toxoid vaccine	Vaccine	10	43,292	2.7 [1.5-5.0]
Somatropin	Anterior pituitary lobe hormone	7	30,665	2.7 [1.3-5.6]
Certolizumab pegol	TNF-α blocker	7	31,765	2.6 [1.2-3.6]
Amoxicillin and beta-lactamase inhibitor	Antibiotics	23	110,738	2.4 [1.6-3.7]
Amoxicillin	Antibiotics	20	106,823	2.2 [1.4-3.4]
Tacrolimus	Calcineurin inhibitor	9	48,485	2.2 [1.1-4.2]
Ciprofloxacin	Antibiotics	14	92,730	1.7 [1.0-2.9]
Adalimumab	TNF-α blocker	62	425,212	1.7 [1.3-2.2]

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FIGURE LEGENDS

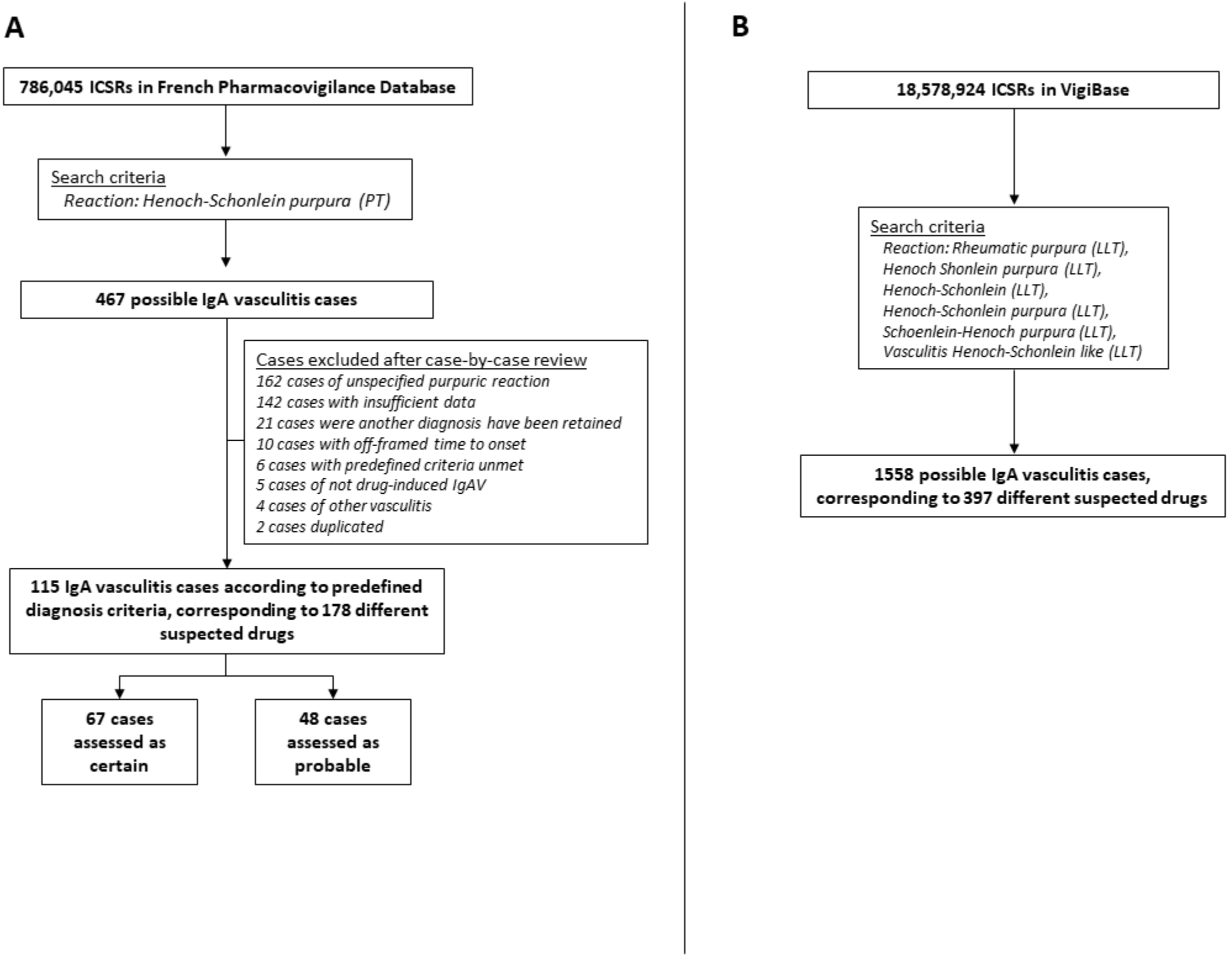
Figure 1. Flowchart of the dual approach analysis based on the French Pharmacovigilance Database and VigiBase, the WHO global database of individual case safety reports.

Figure 2. Suspected drugs in IgA vasculitis cases with definite or probable diagnosis, and their odds-ratio of reporting for IgA vasculitis in the WHO global database of individual case safety reports.

The left table includes drugs that have been reported in the French Pharmacovigilance Database as suspected drug in more than two cases related to a diagnosis of definite or probable IgA vasculitis, after case-by-case review. Odds-ratios of reporting result from the WHO global database of individual case safety reports (VigiBase) disproportionality analyses. Drugs in bold refer to those which are associated with a disproportionality of reporting in VigiBase.

Complete table that includes all the reported drugs in cases related to a diagnosis of definite or probable IgA vasculitis from the French Pharmacovigilance Database is in Supplementary data (Table S1).

IgV, IgA vasculitis; NSAIDs, Nonsteroidal anti-inflammatory drugs; TNF-α, Tumor Necrosis Factor-α; ROR, Reporting Odds Ratio; CI, Confidence Interval.


A
786,045 ICSRs in French Pharmacovigilance Database
Search criteria
Reaction: Henoch-Schonlein purpura (PT)
467 possible IgA vasculitis cases
Cases excluded after case-by-case review
162 cases of unspecified purpuric reaction
142 cases with insufficient data
21 cases were another diagnosis have been retained
10 cases with off-framed time to onset
6 cases with predefined criteria unmet
5 cases of not drug-induced IgAV
4 cases of other vasculitis
2 cases duplicated
115 IgA vasculitis cases according to predefined diagnosis criteria, corresponding to 178 different suspected drugs
67 cases assessed as certain
48 cases assessed as probable
B
18,578,924 ICSRs in VigiBase
Search criteria
Reaction: Rheumatic purpura (LLT),
Henoch Shonlein purpura (LLT),
Henoch-Schonlein (LLT),
Henoch-Schonlein purpura (LLT),
Schoenlein-Henoch purpura (LLT),
Vasculitis Henoch-Schonlein like (LLT)
1558 possible IgA vasculitis cases, corresponding to 397 different suspected drugs

Reported drugs	Number of IgAV cases (definite/probable)	VigiBase ROR [95% CI]
Vaccines		
measles, mumps and rubella, live attenuated vaccine	8 (6/2)	9.9 [8.1-12.1]
hepatitis B, purified antigen vaccine	6 (5/1)	8.4 [6.5-10.8]
influenza, inactivated, or surface antigen vaccine	6 (3/3)	8.3 [6.9-9.9]
influenza A(H1N1)pdm09 vaccine	5 (2/3)	9.1 [6.7-12.5]
diphtheria-pertussis-poliomyelitis-tetanus vaccine	5 (5/0)	8.9 [6.4-12.2]
hepatitis A, inactivated, whole virus vaccine	3 (2/1)	9.6 [6.7-13.7]
diphtheria-poliomyelitis-tetanus vaccine	3 (2/1)	19.7 [10.6-36.7]
meningococcal vaccine	2 (1/1)	10.5 [8.3-13.4]
Antibiotics		
amoxicillin	4 (4/0)	2.2 [1.4-3.4]
amoxicillin and beta-lactamase inhibitor	2 (2/0)	2.4 [1.6-3.7]
ceftriaxone	3 (2/1)	0.5 [0.2-1.3]
clarithromycin	2 (2/0)	4.5 [2.7-7.3]
ciprofloxacin	2 (0/2)	1.8 [1.0-2.9]
norfloxacin	2 (0/2)	1.8 [0.5-7.1]
sulfamethoxazole and trimethoprim	3 (2/1)	0.9 [0.4-1.8]
doxycycline	2 (1/1)	1.3 [0.4-3.9]
pristinamycin	2 (0/2)	2.6 [0.4-18.1]
TNF-α inhibitors		
adalimumab	9 (6/3)	1.7 [1.3-2.2]
infliximab	5 (4/1)	4.5 [3.4-6.0]
Other drugs		
furosemide	2 (0/2)	0.7 [0.2-2.2]
paracetamol	7 (2/5)	1.3 [0.2-2.2]
ketoprofen	3 (1/2)	2.0 [0.8-4.9]
niflumic acid	2 (1/1)	-
allopurinol	3 (2/1)	1.9 [0.8-4.5]
wasp venom proteins	2 (2/0)	-