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1 **Drug-induced IgA vasculitis in children and adults: revisiting drug causality using a**
2 **dual pharmacovigilance-based approach**

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33 antibiotics, pharmacovigilance

34
35

36 **ABSTRACT**

37

38 **OBJECTIVES**

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

43

44 **METHODS**

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

50

51 **RESULTS**

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

60

61 **CONCLUSIONS**

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

66

67

68 **KEY MESSAGES**

69 *What is already known about this subject?*

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

72

73 *What does this study add?*

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

77

78 *How might this impact on clinical practice or future developments?*

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

81

82

83 INTRODUCTION

84 Immunoglobulin A (IgA) vasculitis (IgAV), formerly called Henoch-Schonlein purpura, is an
85 immune complex-mediated vasculitis firstly described in 1802 [1]. IgAV affects small vessels
86 and is characterized by the presence of IgA1-dominant immune deposits [2]. The definition of
87 this disease has been a matter of debate for years [3]. The disease most often presents with
88 palpable purpura, frequently extensive with sometimes bullous or necrotic elements,
89 arthralgia and/or arthritis, gastrointestinal (GI) involvement with severity ranging from mild
90 abdominal pain to hemorrhage and/or bowel perforation, and renal involvement with
91 glomerulonephritis [4–6]. Although more common in children, IgAV is usually more severe
92 in adults and its prognosis is mainly related to GI and renal involvements. Benign forms
93 require symptomatic care, especially in children, whereas in severe forms, more aggressive
94 treatments based on glucocorticoids and immunosuppressive agents are necessary [7,8].
95 Although IgAV pathogenesis has not been yet fully elucidated, a key role of IgA is suspected,
96 particularly because of its implication in innate immunity within the GI mucosal barrier where
97 interactions with many pathogens take place. Some studies suggest that seasons – mainly
98 autumn and winter – are associated with more frequent onset of the disease, possibly related
99 to infectious agents [9]. Susceptibility genes were identified, some of them involving the
100 HLA system. Overall, environment and genetic background could be key players in the
101 pathophysiology of IgA vasculitis, and among exogenous agents, drugs could be potential
102 triggers of the disease [10].
103 Scarce data in the literature suggest that some drugs may trigger IgAV. To date, only case
104 reports have been published in the literature, as well as a single systematic review of the
105 literature [11]. The assessment of drug causality is challenging as many other etiological
106 factors can be involved. So far, no systematic pharmacovigilance study has been conducted.
107 Therefore, we aimed to identify drugs associated with IgAV reporting using a
108 pharmacovigilance-based data mining dual approach.

109 **METHODS**

110 **Data sources and study design**

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

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

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

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

136

137 **Descriptive study**

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

146

147 **Disproportionality analysis**

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

160 [15]. Thus, disproportionality analyses identified whether IgAV cases were differentially
161 reported with a suspected drug compared to all the other drug in the full database.
162 Furthermore, specifically for TNF- α blockers, we performed secondary disproportionality
163 analyses on the reporting of IgAV in patients with inflammatory bowel diseases, psoriasis or
164 ankylosing spondylitis (i.e. diseases associated with susceptibility genes and potential
165 environmental triggers, that could also be shared with IgA vasculitis [17]) compared to other
166 treatment indications.

167

168 **Statistical analysis**

169 Descriptive analysis was performed on the cases retrieved from the two databases.
170 Quantitative variables were expressed as median \pm interquartile range (IQR), and compared
171 using non-parametric analyses. Qualitative variables were expressed in figures and
172 percentages. RORs with their 95% CI were calculated for each different suspected drug.

173 Briefly, ROR [95% CI] are calculated as $ROR = \frac{ad}{bc} [e^{\pm 1.96 \sqrt{(\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d})}}$, where a is the
174 number of IgAV cases reported with a suspected drug, b is the number of non-cases (i.e. other
175 ADR reports) reported with a suspected drug, c is the number of IgAV cases reported with all
176 other drugs, and d is the number of non-cases (i.e. other ADR reports) reported with all other
177 drugs. To limit reporting bias, we only considered suspected drugs reported in at least three
178 ICSRs according to European Medicines Agency guidelines [18], and coming from three
179 different countries. Disproportionality in reporting for a suspected drug was considered when
180 the lower bound of the 95% CI of the ROR was superior to one (>1). ROR were expressed for
181 each suspected drugs and for each pharmacological classes. All analyses were performed
182 using Microsoft Excel software and Prism GraphPad.

183

184

185 RESULTS

186 IgAV characteristics

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

190 Most cases were male (n=68, 59%) with a median age of 33.5 (IQR 8-63.3) years, and 47
191 (41%) cases were children (**Table 2**). Main IgAV clinical characteristics were purpura
192 (n=115, 100%), joint involvement (n=64, 56%), GI involvement (n=42, 37%) and renal
193 involvement (n=38, 33%). Tissue biopsy was available in 52 (45%) patients corresponding to
194 34 definite and 17 probable IgAV diagnosis, and included renal biopsy in 8 patients and skin
195 biopsy in 44. Among patients with available biopsy, the presence of IgA immune deposits
196 was noted in 32 (67%). No vasculitis-specific treatment was required in 75 (65%) patients. In
197 contrast, 36 (31%) patients received glucocorticoids, four (3.5%) colchicine and one (1%)
198 cyclophosphamide. Outcome was favorable with complete recovery in 62 (67%) patients and
199 15 (16%) had sequelae, most frequently mild to moderate (two patients had persistent chronic
200 renal failure). No death was reported during follow-up.

201

202 Suspected drugs

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

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

214

215 **Disproportionality analysis**

216 Of the 18,578,924 ICSRs in VigiBase, we retrieve 1,558 ICSRs of possible IgAV reported
217 with 397 different suspected drugs. Cases mainly originated from Americas (n=759, 48.7%)
218 and Europe (n=650, 41.7%) (**Supplementary Table S2**). About half of the patients were
219 female (n=767, 49.2%) and median age was 27.0 (IQR 5.0-50.8) years, including 434 (27.9%)
220 children. Among these IgAV cases, 79 different suspected drugs have been reported in at least
221 three cases originating from different countries. The case – non-case analysis showed that of
222 79 suspected drugs, 40 were associated with a significant disproportionality in IgAV reporting
223 (**Table 3, Figure 2, Supplementary Table S3**). These drugs are mainly vaccines, antibiotics,
224 and immunomodulatory agents. About all vaccine types are represented, including live-
225 attenuated vaccines (measles, mumps, rubella, Japanese encephalitis, varicella zoster and
226 yellow fever), inactivated vaccines (hepatitis A, rabies and tick bone encephalitis) and subunit
227 vaccines (diphtheria, poliomyelitis, tetanus, pertussis, influenza, papillomavirus,
228 meningococcal, hepatitis B, haemophilus influenzae B). The highest disproportionality is for
229 tick borne vaccine (ROR 30.5 [95% CI: 20.0-46.5]). Others drugs include various classes of
230 antibiotics (amoxicillin and derivatives, ciprofloxacin, clarithromycin, daptomycin, fusidic
231 acid), immunomodulatory agents (montelukast, infliximab, adalimumab, certolizumab pegol,
232 tocilizumab and tacrolimus) and other drugs (losartan, methylphenidate, isotretinoin and
233 somatropin). Secondary disproportionality analysis showed that IgAV cases reporting for
234 TNF- α blockers was significantly associated with their use in inflammatory bowel diseases,
235 psoriasis or ankylosing spondylitis, compared to other indications (ROR 2.1 [95% CI: 1.4-
236 3.2] (**Supplementary Table S4**).

237 **DISCUSSION**

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

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

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

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

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

276 The third most common therapeutic group of suspected drugs were immunomodulatory
277 agents, especially TNF- α blockers. The latter were previously reported to be a potential
278 inducer of vasculitis. In a French retrospective cohort on vasculitis induced by TNF- α
279 blockers, only two out of 30 cases with available biopsy showed IgA deposits in the kidney
280 [31]. In this study, the main underlying disease was rheumatoid arthritis. Other case reports
281 revealed a potential association between IgAV and TNF- α blockers [32–35]. Our data mining
282 analysis identified adalimumab, infliximab and certolizumab as suspected drugs, whereas no
283 case was associated with etanercept. Time to vasculitis onset after drug initiation was longer
284 compared to other therapeutic classes, which is consistent with previous study showing a
285 mean interval of 9.6 months [31]. Interestingly, among ICSR with TNF- α blockers in
286 Vigibase, we found a disproportionality in IgAV reporting for patients with IBD, psoriasis or
287 ankylosing spondylitis compared to other indications. Thus, it appears that IgAV cases with
288 TNF- α blockers were associated with IBD, psoriasis or ankylosing spondylitis. These three

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

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

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

317

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

324

325

326 **INFORMATION STATEMENT**

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

331

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333 None for all authors

334

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338

339 **AUTHORSHIP CRITERIA**

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

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

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

344 All authors fulfill authorship criteria.

345

346

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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.

472

Diagnosis	Pediatrics	Adults
Definite IgAV	<p><u>Any purpura associated with at least one of the following:</u></p> <p>Renal, gastrointestinal or musculoskeletal involvement</p> <p><u>and/or</u></p> <p>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)</p>	<p>Any purpura without further organ damage associated with histological evidence of leukocytoclastic vasculitis with IgA immune deposits on skin biopsy</p> <p><u>or</u></p> <p>Any purpura associated with at least another organ involvement</p> <p><u>and</u> confirmed by histology from any other part than skin.</p>
Probable IgAV	<p><u>At least 2 criteria among:</u></p> <p>Age <20 years</p> <p>Evocative vascular purpura</p> <p>Acute abdominal pain</p> <p>Leukocytoclastic vasculitis on skin biopsy (meeting ACR criteria only)</p> <p>Rheumatoid purpura both coded and mentioned in the narrative</p>	<p>Presence of evocative purpura (or leukocytoclastic vasculitis in case of biopsy) associated with another clinical organ involvement but without confirmation of IgA deposits.</p> <p>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.</p>

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

477

478 * among patients who had a biopsy.

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

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

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

486 DTP, diphtheria tetanus pertussis; HBV, Hepatitis B Virus; TNF, Tumor Necrosis Factor;

487 NSAID, Non Steroidal Anti-inflammatory Drug

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

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

497

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

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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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505 **FIGURE LEGENDS**

506

507 **Figure 1. Flowchart of the dual approach analysis based on the French**
508 **Pharmacovigilance Database and Vigibase, the WHO global database of individual case**
509 **safety reports.**

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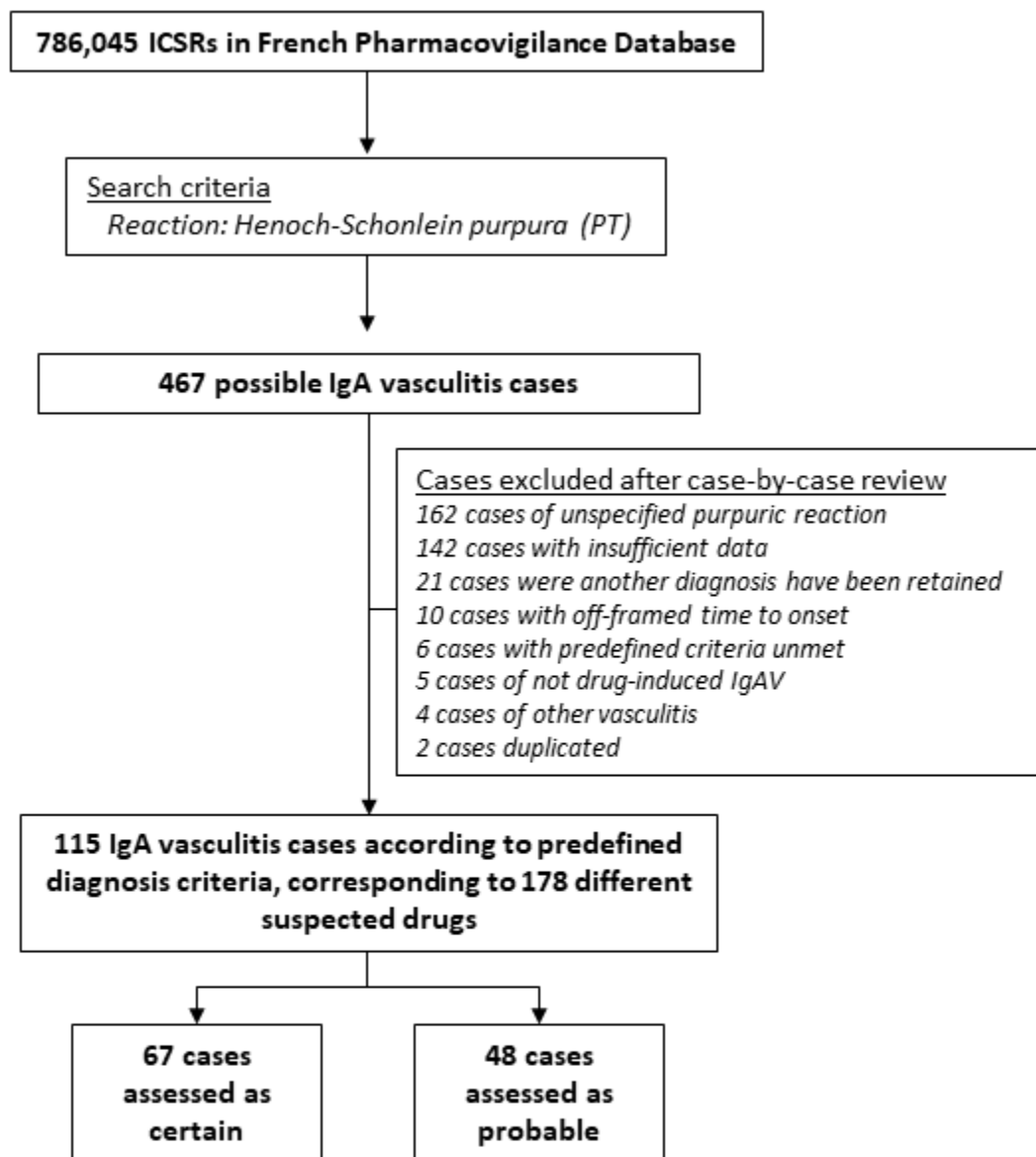
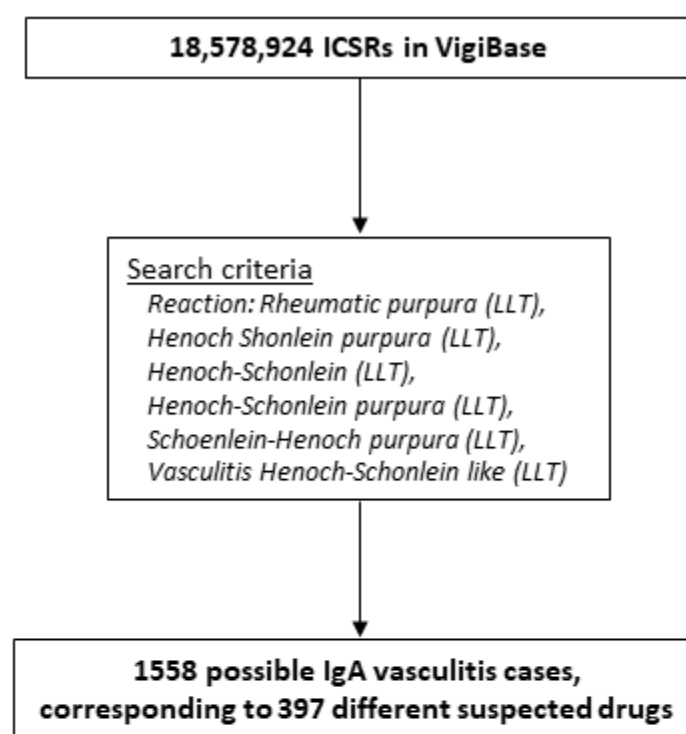
514 **Figure 2. Suspected drugs in IgA vasculitis cases with definite or probable diagnosis,**
515 **and their odds-ratio of reporting for IgA vasculitis in the WHO global database of**
516 **individual case safety reports.**

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

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

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

528

A**B**

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)	-

