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Drug-induced antiphospholipid syndrome: analysis of from the WHO international database

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Abstract

Objective

As with drug-induced lupus, some drugs may induce an antiphospholipid syndrome (APS). With the always growing numbers of new molecules, the list of the liable treatments evolves rapidly. We herein analyzed Vigibase, the international pharmacovigilance database, to identify drugs suspected of inducing APS.

Methods

All the reported cases associated with "anti-phospholipid syndrome" using the preferred term level of medDRA (dictionary of regulated drug activity) when associated with anti-phospholipid antibodies in Vigibase were analyzed. For each treatment, a Bayesian disproportionality indicator (i.e. information component, IC) was calculated. A drug was significantly associated with APS if the 95% lower-end of the IC credibility interval was positive ($IC_{0.25} > 0$). Drugs with potential protopathic bias were excluded.

Results

From 01/11/2000 to 25/07/2021, 790 reports of suspected drug-induced APS were found in Vigibase. After excluding drugs reported by a single country and drugs with *protopathic bias*, fourteen drugs (n= 359 reports) were associated with APS with an $IC_{0.25} > 0$. These drugs were hormones : ethinylestradiol-etonogestrel and drospirenone-ethinylestradiol ; platelet growth factors : eltrombopag, romiplostim ; vaccines : Human Papillomavirus vaccine, hepatitis A and B vaccines and typhoid vaccine ; antibiotics : minocycline ; nonsteroidal anti-inflammatory : rofecoxib ; biotherapy : interferon beta-1-a, etanercept ; anti-hypertensive drug : hydralazine ; bisphosphonates : alendronic acid and antipsychotic : olanzapine. The mean age at diagnosis of drug-induced APS was 39.2 years [29.3;47.9] and there were 63.5% of female patients. The mean delay from first exposition to drug-induced APS was 19.7 months [4.5; 38.8]. Drug-induced APS was reported as a severe side effect in 66.3% of cases: 8.4% with a life-threatening event and 2.5% of death (n=9). A third (n = 118, 32.9%) pulmonary embolism events were reported and 4.2% (15) cerebral infarctions. 14.8% (53) cases were associated with a systemic lupus, a sub-analysis without lupus cases showed the same severity of cases.

Conclusion

This study identified 14 drugs potentially associated with drug-induced APS that may prove useful in the investigational work-up in any new diagnosis of APS.

Introduction

Antiphospholipid syndrome (APS) is an autoimmune systemic disease, characterized by venous/arterial thrombosis and/or obstetrical adverse events [1]. Even if usually APS is primary or associated with autoimmune disease such as systemic lupus erythematosus (SLE), in some cases a recent infection or drug-related induced disease could be found [2]. Martirosyan et al [6] reviewed the possible environmental triggers inducing APS, and showed that infections, in particular from viral origin, combined to genetic background can be responsible for APS. Several drugs have been previously reported to induce antiphospholipid antibodies and, in some cases, clinical APS, such as antiarrhythmics, anti-epileptic, antibiotics and anti-hypertensive drugs. Among the various drugs susceptible to induce lupus anticoagulant, several drugs have been previously listed such as antiarrhythmic: procainamide; natural alkaloid: quinine; antipsychotics: haloperidol, fluphenazine, perphenazine, clozapine; tricyclic antidepressant: doxepin; anti-epileptic drugs: phenytoin, valproic acid, biotherapy: interferon- α , etanercept, infliximab, adalimumab; anti-hypertensive drugs: hydralazine, acebutolol; antibiotics: penicillin etc. [22].

Concerning vaccines, influenza vaccines combined with adjuvant drugs could induce APS [6]. The risk to develop thrombosis and antiphospholipid antibodies (aPL) after influenza A H1/N1 vaccine without adjuvant was not significantly different in 45 APS patients compared to 33 healthy controls .[15] The role of vaccines adjuvants has been described as so-called ASIA syndrome (Autoimmune/auto-inflammatory syndrome induced by adjuvant), which could result from the association of genetic predisposition, for instance patients carrying HLA-DRB1*01 or HLA-DRB4 and vaccine adjuvant exposure [16, 17]. The tetanus toxoid and seasonal influenza vaccines were found to be associated with aPL production and APS syndrome, but the exact prevalence of ASIA syndrome is not determined [20, 21]. Despite some case reports on APL after HPV vaccination, a meta-analysis involving 20 studies and 169000 various auto-immune disorders did not showed an increased risk of auto-immune disorders after HPV vaccination (Odds-ratio 1.003, 95% CI : [0.95-1.06]) [18] [19]. Large data about the prevalence of drug and vaccine induced APS are still lacking.

From VigiBase, the WHO international global database, we sought to assess and describe drug-induced antiphospholipid syndrome.

METHODS

Data source

This study is based on VigiBase, a WHO global individual case-safety reports (ICSR) database, with to date more than 130 countries which actually contributes to adversarial reported events declaration [8,9]. There are currently over 29 million deduplicated ICSRs submitted from national pharmacovigilance centers that come from different sources such as healthcare professionals, patients and pharmaceutical companies.

Data assessment

In this observational retrospective study, we included all ADRs reported as ‘anti-phospholipid syndrome’ according to the Medical Dictionary for Drug Regulatory Activities (MedDRA) term (preferred term [PT] : “Antiphospholipid antibodies positive” and “Antiphospholipid syndrome”) in VigiBase, from inception (January 1, 1981) to July 25, 2021. The drugs considered in the analysis were those notified as suspected or interacting treatments. Drugs for which all cases of APS were reported in a single country and those used to treat APS - i.e. with protopathic bias - were excluded (rituximab, hydroxychloroquine, mycophenolic acid *etc.*). Patients on anticoagulants and antithrombotic treatments were excluded from the analysis (heparin, enoxaparin, warfarin, rivaroxaban, apixaban, edoxaban, acetylsalicylic acid). The flowchart of the overall extraction is shown in **figure 1**.

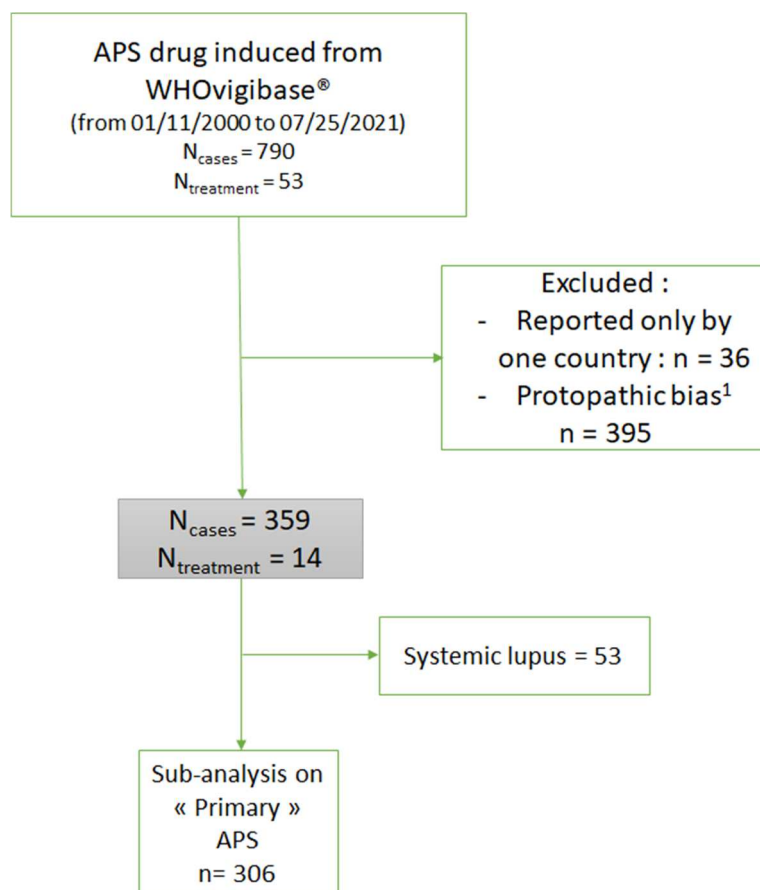


Figure 1 : Flowchart. Treatment excluded because of the protopathic bias were : Aspirin, Fondaparinux, Clopidogrel, Warfarin, Heparin, Enoxaprin, Apixaban, Rivaroxavin, Eculizumab, Azathioprine, Adalimumab, Indlixumab, Hydroxychloroquine, Rituximab, Belimumab, Edoxaban, Mycophenolic acid, Prednisone

The information from each report are as followed: general characteristics (country of origin, date of reporting, sex, age), data about drugs (characterization according to the Anatomical Therapeutic Chemical) (ATC) classification system [13], reason of prescription, date of first intake, date of interruption, dosage regimen and administration mode), and adverse events information (reported terms, MedDRA classification terms, onset date, end date, seriousness, final outcome).

A serious adverse event was defined as an adverse reaction that causes death, life threatening, requires hospitalization (initial or prolonged), leads to persistent or significant disability, congenital abnormalities, birth defect or to any other medically important conditions.

Statistics

For each drug (suspected or interacting treatment) associated with APS in VigiBase, a case–non-case analysis was performed [29]. This method compares the proportion of specific ADR reported for a single drug with the proportion of the same ADR for all other treatments in VigiBase. In this case–non-case study, the specific ADRs studied (ADS) were considered as

cases and all other reports were considered as non-cases. For this, we extracted from VigiBase the information component (IC), an indicator value for disproportionate reporting that compares observed and expected values with drug-adverse effect combinations that have been reported more often than one would expect [10, 11]. The IC is computed as: $IC = \log_2((N_{\text{observed}} + 0.5) / (N_{\text{expected}} + 0.5))$, where $N_{\text{expected}} = (N_{\text{drug}} \times N_{\text{effect}}) / N_{\text{total}}$, with N_{observed} being the actual number of case reports for the drug–effect combination; N_{expected} the number of case reports expected for the drug–effect combination; N_{drug} the number of case reports for the drug, regardless of effects; N_{effect} the number of case reports for the effect, regardless of drug; and N_{total} the total number of case reports in the database. We also report the IC025, which is the lower end of the 95% credibility interval for the IC. A positive IC025 value is the threshold used in statistical signal detection in VigiBase [9].

The extracted data are presented as median (25th–75th percentile, IQR) or number (percentage). Analyses were performed using the JMP V.13 software (SAS Institute, Cary, North Carolina, USA). This methodology was previously used by our group for the study of other diseases such as drug-induced capillary leak syndrome [12], or drug-induced lupus [7].

For the calculation of the median delay between start of medication and APS onset, we considered the 15th of the given month when the month but not the exact day was available.

Acknowledgements

The supplied data came from a variety of sources. The likelihood of a causal relationship was not the same in all cases. The information does not represent the opinion of the World Health Organization.

RESULTS

During the study period, 717 cases of drug-induced APS were reported. From these 717 cases, 322 were treated with APS-related medications and 5 treatments (corresponding to 36 cases) were reported only from one country, those treatments therefore excluded. Finally, after exclusion of the drugs with a non-significant IC025 (18 drugs), 359 drug-induced APS had a significant IC025 score, corresponding to 11 drugs and 3 vaccines, leading to the repartition shown in **figure 2**.

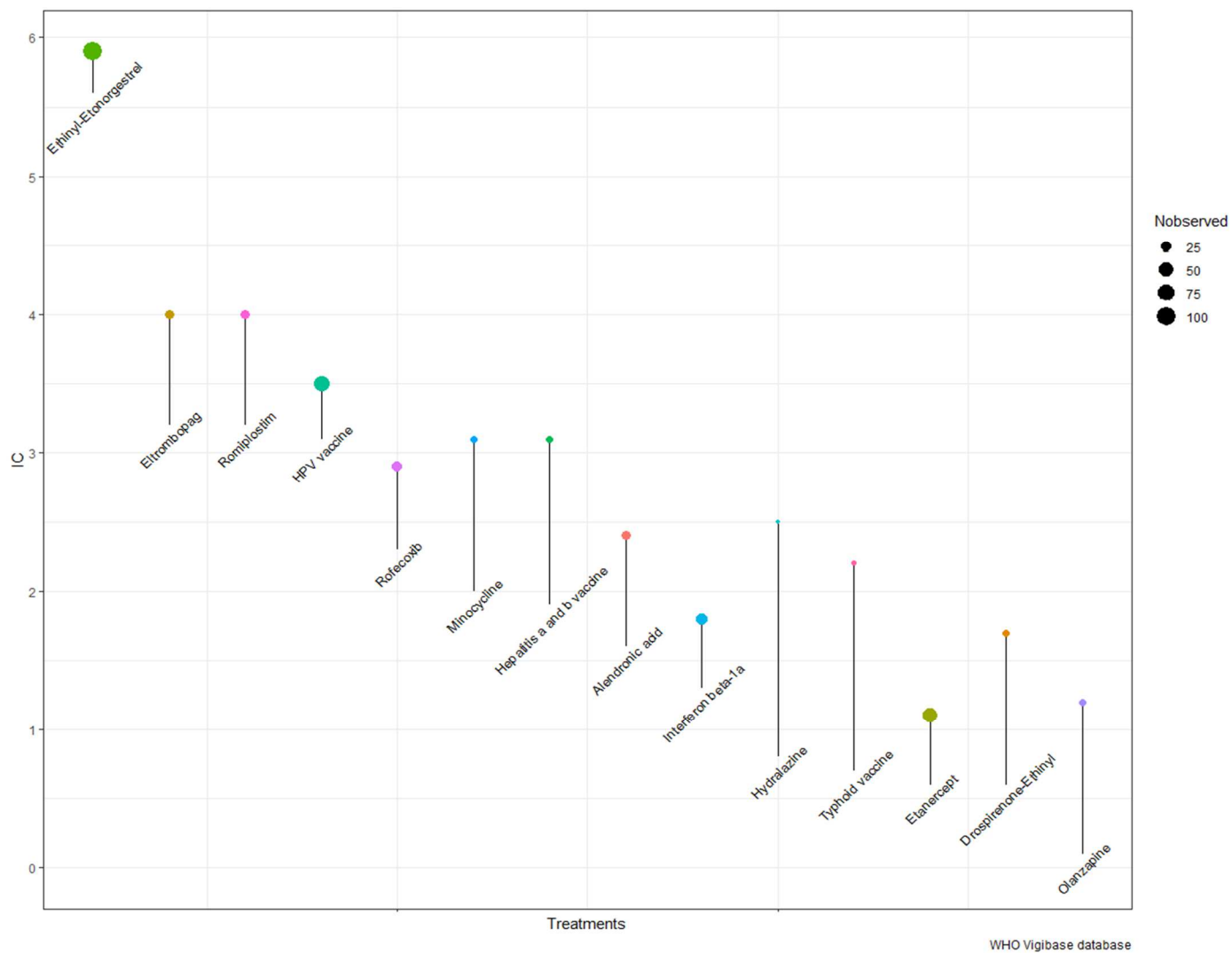


Figure 2 : Repartition of drugs according to their IC lowest points of each black segment correspond to each IC025. The size of the circles corresponds to the number of cases declared (from 4 for hydralazine to 100 for ethinylestradiol-etonogestrel).

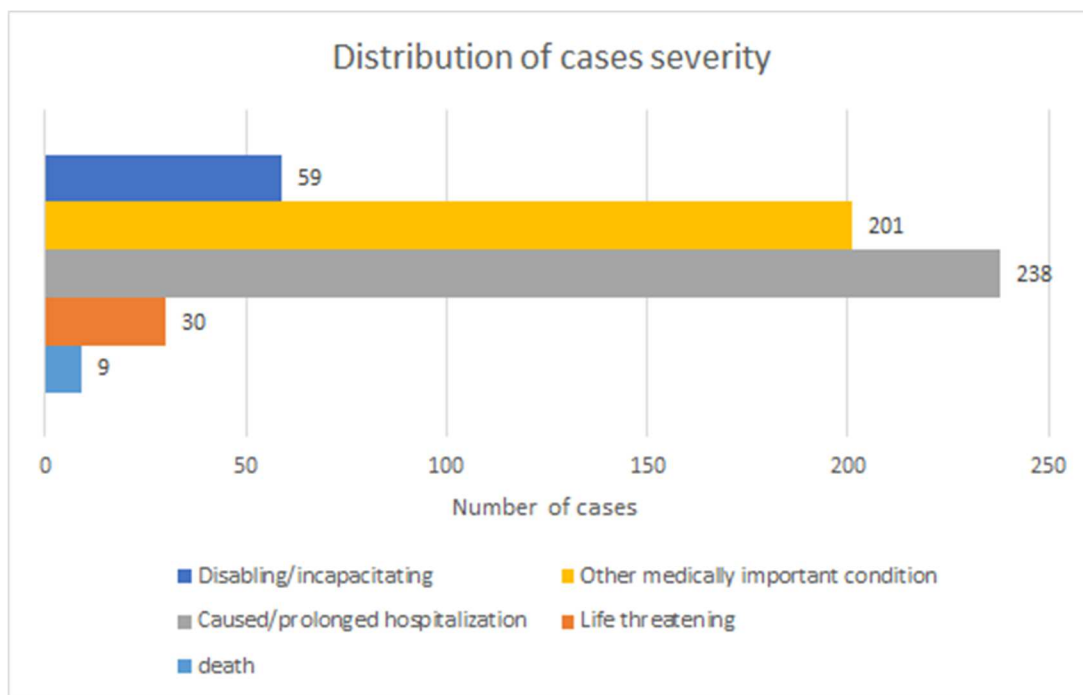


Figure 3 : Seriousness criteria repartition : 9 deaths were registered and 30 Life threatening events

The median age at diagnosis of these 359 suspected drug-induced APS was 39.2 years [29.3; 47.9] with 63.5 % of female cases. The mean time to onset of APS diagnosis after the drug initiation was 19.7 months [4.5; 38.8]. Severe adverse effects were reported in 66.3% cases (n = 238) with 8.4 % of life-threatening (n =30) and 2.5% death related to the events (n=9) with 32.9 % of pulmonary embolism (n = 118) and 4.2% of arterial cerebrovascular infarction (n = 15). Detailed reported effects can be found in **figure 3 and 4**.

Lupus association

APS syndrome was associated with Lupus in 53 cases (14.8%), among which 28 (54.5%) were also attributed to an HPV vaccine as co-suspect drug, as shown in **figure 5**.

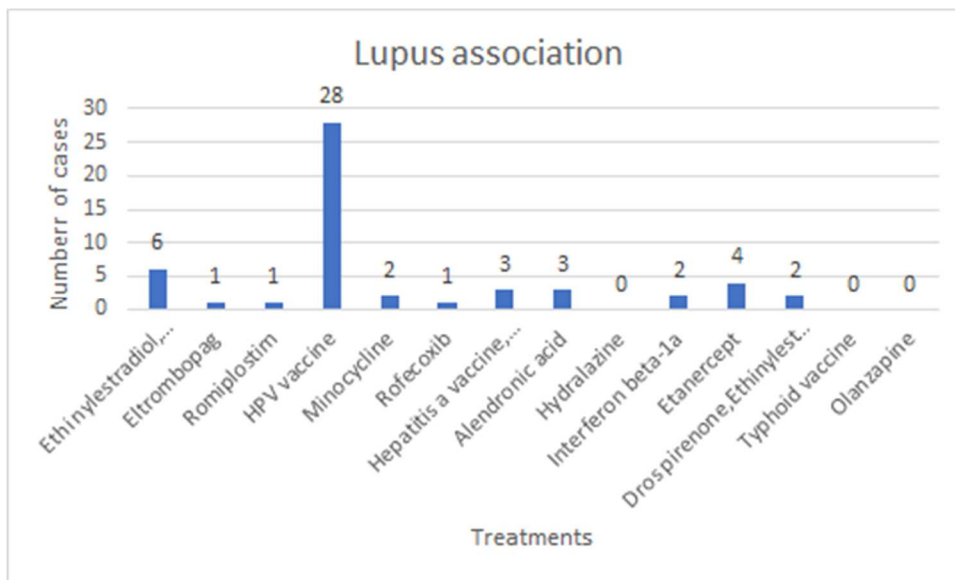


Figure 5 : Lupus association repartition.

In order to focus specifically on primary APS, a sub analysis is performed without the 53 systemic lupus associated cases. Without lupus cases, the death proportion was similar (2.3% vs 2.5%).

Repartition of the clinical events with and without lupus cases are shown in **figure 4**. A Chi-squared test was performed with and without lupus showing no statistical differences between the two distributions ($p = 0.60$).

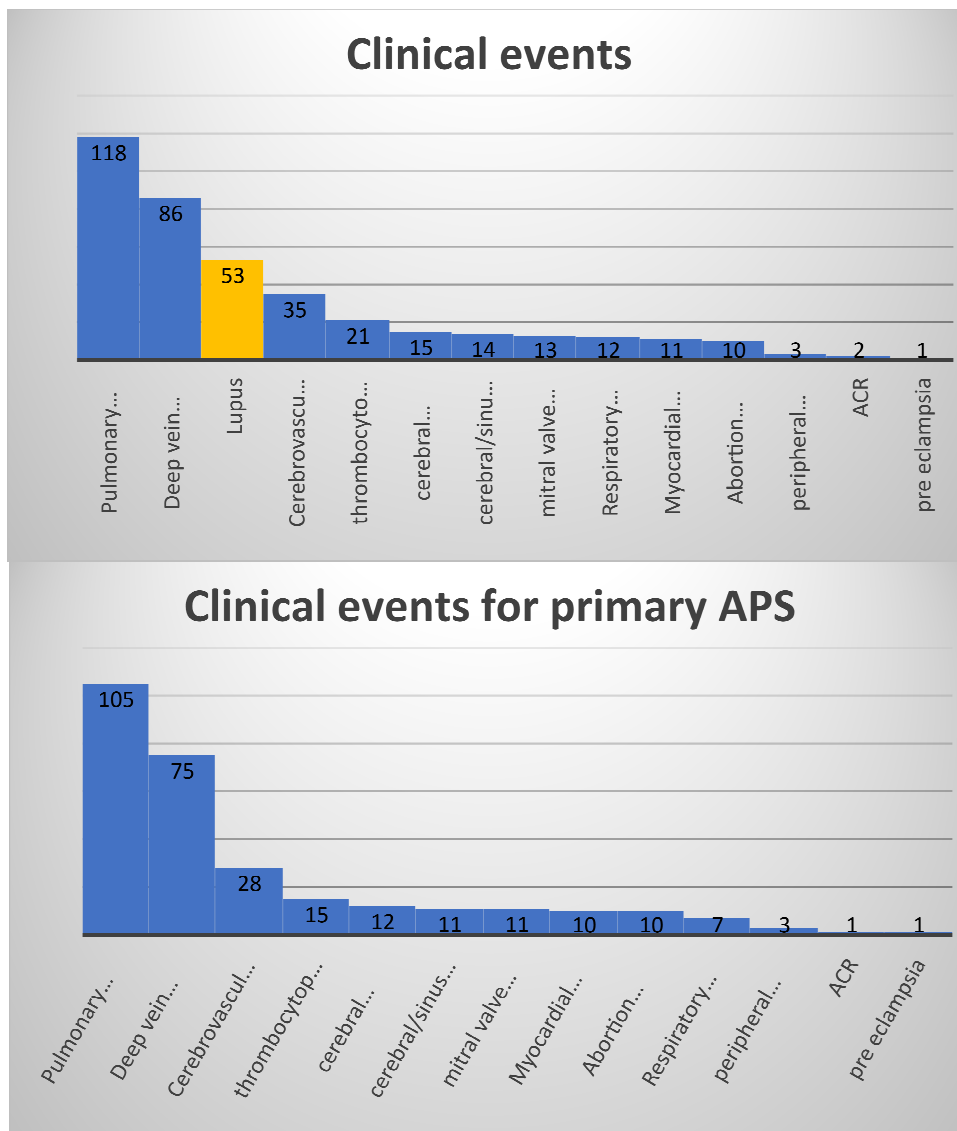


Figure 4 : Clinical events repartition with (above) and without lupus cases. Overall distribution does not differ if we integrate lupus cases. For all clinical events, Chi-squared test was above 0.97 in comparison with and without lupus.

APS phenotype

Among all complications, only one miscarriage was reported and 10 spontaneous abortion (including 8 with contraceptive treatments) and one pre-eclampsia with ethynestradiol-etonorgestrel.

Concerning the arterial and venous complications repartition, ethynilestradiol induced 128 complications whereas other treatments did not induce more than 20 events. Arterial complications were more frequent for rofecoxib treatment. Repartition of venous and arterial complications are shown in **figure 6**.

We performed a Chi-squared test to compare the venous and arterial complications for each treatment. We found that ethinylestradiol-etonorgestrel and eltrombopag induced significantly more venous complications with a p of 0.01 and 0.03, respectively. Rofecoxib tends to present more arterial complications but not statistically significant.

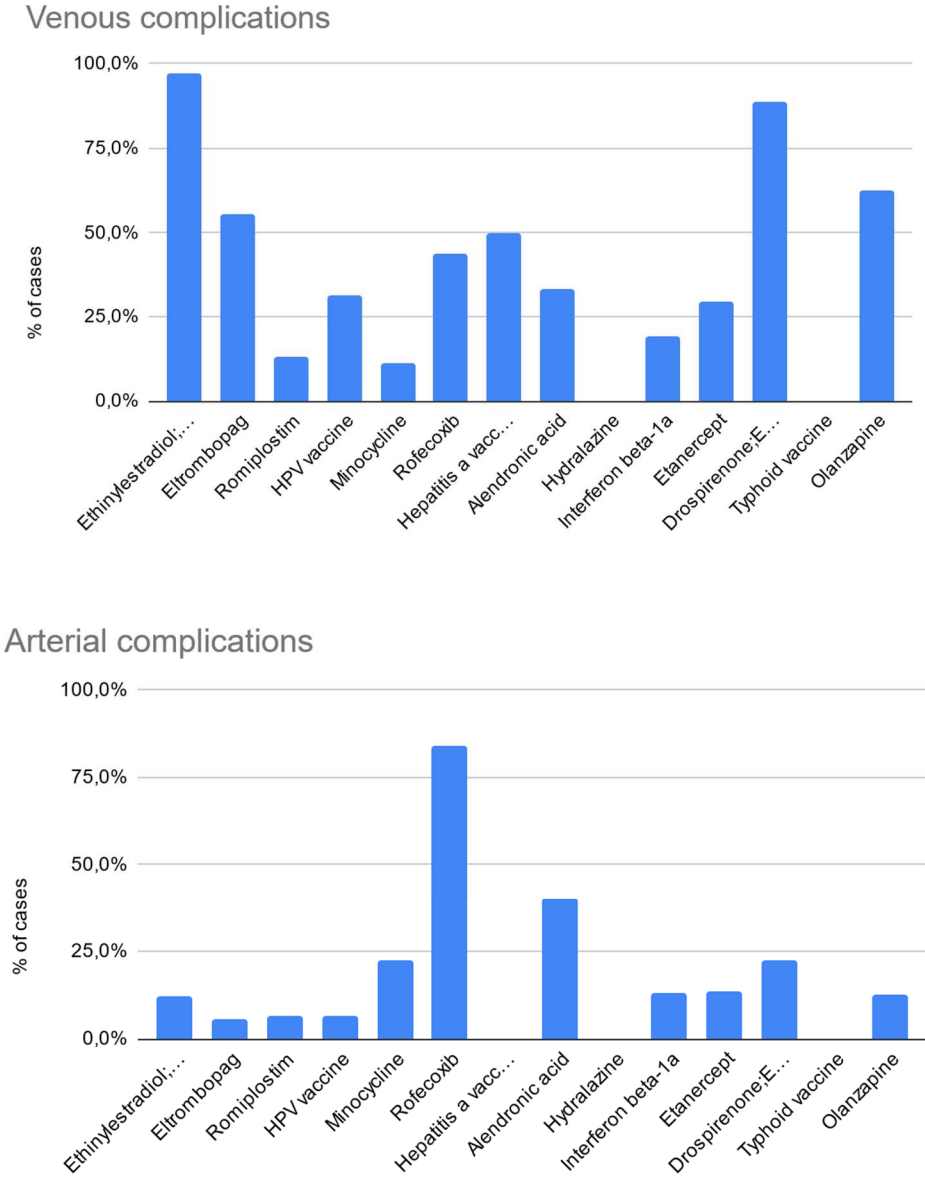


Figure 6 : Distribution of venous (upper figure) and arterial complications (lower figure). Venous complications were searched in the database as follow: “Pulmonary embolism”, “deep vein thrombosis”, “vena cava thrombosis”, “jugular thrombosis”, “portal thrombosis”, “cerebral thrombosis”, “transverse sinus thrombosis”, “sagittal sinus thrombosis”. Arterial complications were searched as: “myocardial infarction”, “cerebrovascular infarction”, “cerebrovascular accident”, “periphery arterial thrombosis”, “coelic ischaemic”.

DISCUSSION

To our knowledge, this is the largest series released to date. Our study described drugs and vaccines that could induce APS, extracted from the Vigibase, the WHO global ICRS database. Based on the Vigibase reports 11 drugs and 3 vaccines among ethinylestradiol/etonogestrel, eltrombopag, romiplostim, HPV vaccine, minocycline, rofecoxib, hepatitis A and B vaccine, alendronic acid, hydralazine, interferon beta-1-a, etanercept, drospirenone, typhoid vaccine and olanzapine have significant statistical association with APS. Antiphospholipid syndrome is not listed in the RCP for any of those treatments. Those a new pharmacovigilance signals require scrutiny for further confirmation.

Particular attention is required for ethinylestradiol-etonogestrel and drospirenone-ethinylestradiol, estrogen based oral contraception, which have a high IC₀₂₅ score and could be important to consider in the context of thrombosis. The link with estrogen and thrombosis is well-established. And Ahmed et al. [14] showed that orchidectomized mice given estrogen developed anti-cardiolipin antibodies with an incidence of 62,7% vs 20% (p <0,005). Biological targeting drugs have been also previously noted to be associated with APL antibodies, In particular etanercept [23, 22]. Concerning vaccines, tetanus toxinoid or seasonal influenza vaccines were not associated with a significant risk to develop APS, and data are too scarce about HPV, hepatitis A and B to conclude to the potential risk of vaccine induced APS from our data [17, 18, 19, 20, 21].

Interestingly, primary APS cases were as severe as cases associated with a lupus with no statistical differences in the two groups. Furthermore, we observed that some treatments tend to induce more venous complications than others, particularly regarding ethinylestradiol-etonogestrel and eltrombopag.

Very few obstetrical cases were reported (only one miscarriage and 8 out of 10 spontaneous abortions were reported under contraceptive treatments). These particularities confirm the point of view exposed by Meroni et al. [28] that different APS phenotypes are observed. Drug-induced APS seems to lead to more vascular phenotypes.

The main limitations of our analysis are those of retrospective pharmacovigilance studies from databases. Indeed, current post marketing pharmacovigilance is strongly based on spontaneous notification and presents well-known bias. Among these, the main bias concerns the lack of information and the under-notification [26, 27]. In particular, the genetic predisposition of the patient and his family is not known as well as the clinical context. Type

of antiphospholipid antibody, or the triple positivity was not mentioned, although this information is prognostic. For instance, the information of an infectious trigger that could play a part in APS development is not known. Specifically, SARS-COV2 infection may induce autoantibodies as shown in Damoiseaux et al [33], Mahroum et al [34], Lee et al. [35] and Bertin et al [36] in the case of post-COVID syndrome.

Our analysis did not find statistical association between Covid-19 vaccines. Although many authors have pointed out a possible link between vaccination and antiphospholipid syndrome, especially catastrophic antiphospholipid syndrome [30, 31, 32]. This can be explained by the fact that our data extraction stops in July 2021 which was still relatively early in the vaccination campaign, with significant differences in start date and vaccination rates depending on the country.

CONCLUSION

To conclude, from Vigibase worldwide database several drugs could be potentially responsible for drug-induced APS, and large specific studies are necessary to confirm these preliminary data.

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