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Efficacité et sécurité du Rituximab dans les manifestations classantes et non classantes du Syndrome des Anti-Phospholipides hors syndrome catastrophique

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Remerciements

A mon Père,
Tu aurais été très fier d'assister à ma thèse
Merci pour tout ce que tu m'as transmis
Tu me manques
Je pense chaque jour à toi

A ma mère, mes frères, mes grands-parents et à toute ma Famille qui m'ont toujours soutenu.

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Merci à Anna.

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Commenté [BC1]: numérotation à mettre

LISTE DES TABLEAUX ET FIGURES

Commenté [BC2]: pas sûr de l'utilité mais si tu le mets rajoutes la numérotation des pages

Commenté [BC3R2]:

Commenté [c4]: Débute la numérotation à la première page d'intro = page 1

Commenté [cg5R4]: Je n'ai pas réussi la manip désolé

Introduction

Le syndrome des anti-phospholipides (SAPL) est une maladie auto-immune rare, définie par la présence de manifestations dites classantes thrombotiques et/ou obstétricales et la présence d'anticorps anti-phospholipides dont la persistance est confirmée à 12 semaines d'intervalle (1). Il existe d'autres manifestations cliniques (neurologique, cardiaque, dermatologique, rénale, hématologique, pulmonaire) du SAPL dites non classantes qui font du SAPL une véritable maladie systémique (2).
En 2022, de nouveaux critères du SAPL ont été proposés englobant l'ensemble des manifestations de la maladie classantes ou non (3).

Il n'existe actuellement aucun traitement curatif du SAPL. Le traitement des thromboses repose sur l'utilisation d'un traitement anticoagulant au long cours par un Anti Vitamine K (AVK), en relais d'une héparinothérapie initiale (4).
Cependant, malgré un traitement anti-coagulant adapté, un tiers des patients présente au moins une récidive de thrombose (artérielle ou veineuse) sous traitement. Cette récidive peut survenir jusqu'à plusieurs années après le début de l'anticoagulation, selon les données de la cohorte « Europhospholipid » qui comprenait 1000 patients atteints de SAPL suivis pendant 10 ans (5). De plus le traitement anti coagulant semble moins efficace sur les manifestations non classantes de la maladie (6).

Commenté [c6]: Tu ne peux pas dire manifestations non thrombotiques car elles sont quasiment tout le temps thrombotiques

Les lymphocytes B jouent un rôle important dans la physiopathologie de l'auto-immunité et en particulier du SAPL (7). Le Rituximab est un anticorps monoclonal anti-CD20, dont l'action cytotoxique sur les lymphocytes B en fait un traitement potentiel pour le SAPL. Certains auteurs ont montré l'efficacité du Rituximab pour diminuer le taux des anticorps anti-phospholipides dans le sérum des patients (8). Par ailleurs, le Rituximab est utilisé comme traitement de seconde ligne dans le Syndrome Catastrophique des Anti-Phospholipides (CAPS) mais le niveau de preuves justifiant son utilisation reste faible (9).

Certains auteurs ont proposé le recours au Rituximab comme traitement des manifestations du SAPL. Plusieurs études observationnelles rétrospectives ou séries de cas ont montré une efficacité du Rituximab, avec une disparition des manifestions cliniques initiales (classantes ou non classantes), mais ces résultats n'ont pas été confirmés dans d'autres travaux (10,11,12). Dans une étude de phase II ouverte et non

Commenté [c7]: Fais des réf groupées

Commenté [cg8R7]: Je ne sais pas faire désolé

randomisée (étude RITAPS) portant sur 19 patients atteints de manifestations non classantes la moitié des patients traités par Rituximab présentait une réponse partielle ou complète (13). Dans une étude portant sur 42 patients atteints de SAPL traités par Rituximab, un bénéfice clinique a été observé chez 80% des patients avec une réponse complète dans 55% des cas (14).

Néanmoins le niveau de preuves permettant de justifier le recours au Rituximab comme traitement du SAPL reste actuellement faible et les données d'efficacité dans la littérature ne sont pas toutes convergentes. Des interrogations demeurent également sur le schéma thérapeutique optimal (15,16).

Dans ce travail, nous avons réalisé une revue de la littérature des données publiées sur l'efficacité et la sécurité du recours au Rituximab pour le traitement du SAPL en dehors du Syndrome Catastrophique des Anti-Phospholipides.

ARTICLE ORIGINAL

Efficacy and safety of Rituximab in Anti-Phospholipid Syndrome: A scoping Review

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Commenté [c9]: Ça reste à réfléchir.

Authors' contribution:

All authors designed the study. GC (Guidarelli Clément) and BC (Beuvon Clément) had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. GC and BC contributed substantially to the study design. GC collected the data. GC and BC drafted the manuscript. MM (Martin Mickaël), PM (Puyade Mathieu), MJP (Martellosio Jean-Philippe), LA (Le Houarno Anna), GF (Grand François) and (Roblot Pascal) critically revised the manuscript. All authors approved the manuscript.

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Word count: Abstract: 338 Text: 3938

Commenté [BC10]: n'oublies pas le compte des mots à la relecture définitive

Commenté [BC11R10]:

Abstract

BACKGROUND: There is currently no curative treatment for Anti-Phospholipid Syndrome (APS). Rituximab is an anti-CD20 monoclonal antibody, whose ability to deplete B cells makes it a potential treatment for APS. Few data are available on efficacy and safety of Rituximab use to treat APS.

OBJECTIVE: Assess the efficacy and safety of Rituximab to treat APS classifying and non-classifying manifestations excluding Catastrophic Anti-Phospholipid Syndrome.

DESIGN: We conducted a comprehensive scoping review of published data on Pubmed and Medline databases. Patients aged of 18 years or more, with primary APS or secondary APS related to Systemic Lupus Erythematosus (SLE), who received Rituximab for an APS classifying manifestation or non-classifying manifestation were included. Pediatrics patients, patient without APS or presenting a Catastrophic Antiphospholipid Syndrome (CAPS) or cancer were excluded. Clinical response was recorded for each APS manifestation. Follow-up data was recorded at 6 and 12 months when available. A pooled descriptive analysis of patients' data was performed.

RESULTS: Out of the 89 articles screened 28 were selected by both investigators. Among 121 patients included for analysis, 97/121 patients (80%) received around 2 g of Rituximab. At 6 months an overall favorable clinical response to Rituximab therapy was observed in 91/117 patients (78%); from with 38/42 patients (90%) initially had recurrent thrombosis; 21/31 patients (68%) had immune cytopenia; 10/12 patients (83%) had neurological involvement; 10/12 patients (83%) had cutaneous involvement; 7/10 patients (70%) had lung involvement; 3/3 patients (100%) had renal involvement; 1/5 patients (20%) had cardiac involvement and 1/2 patients (50%) had obstetrical manifestations. At 12 months, sustained favorable clinical response was reported in 69/89 patients (78%) whereas 4 patients (6%) relapsed. At 6 months 92/103 patients (90%) have persistence of at least one antiphospholipid antibody. Twenty per-cent of patients presented a serious side effects requiring hospitalization and 5 deaths occur.

CONCLUSIONS: Our study suggests an overall benefit of Rituximab in the treatment of the different manifestations of APS with an acceptable safety. Further studies are needed to confirm our results.

Commenté [BC12]: as-tu bien vérifié depuis que tu as changé les stats ?

Commenté [cg13R12]: Oui on est passé de 37/41 à 38/42

KEYWORDS: Anti-Phospholipid Syndrome, Systemic Lupus Erythematosus, Rituximab, Scoping Review

Commenté [c14]: Petits codes de mise en forme toujours des sauts de page entre les différentes parties

Commenté [cg15R14]: D'accord j'ai fait ça partout du coup

Introduction

Anti-Phospholipid Syndrome (APS) is a rare autoimmune disease, defined in 2006 according to the Sapporo criteria by the presence of thrombotic and/or obstetrical manifestations and confirmed persistence at 12-week intervals of anti-phospholipid antibodies (1).

Other clinical manifestations of APS such as neurological, cardiac, dermatological, renal, hematological, pulmonary involvement called non-classifying manifestations make APS a systemic disease (2). In 2022, new APS criteria encompassing all the different manifestations of the disease have been proposed (3).

There is currently no curative treatment for APS. The treatment of thromboses based on the use of long-term anticoagulant treatment with an Anti Vitamin K (VKA), in relay of an initial heparin therapy (4). However, despite appropriate anticoagulant treatment, a third of patients present a new thrombosis even after several years, according to data from the "Europhospholipid" cohort, which included 1,000 patients with APS followed up for 10 years (5). In addition, anticoagulant treatment is less effective on non-classifying manifestations of the disease (6).

B lymphocytes play an important role in the pathophysiology of autoimmunity and in particular in APS (7). Rituximab is an anti CD-20 monoclonal antibody, whose ability to deplete B cells makes it a potential treatment for APS. Biologically, some authors have shown Rituximab to be effective to decrease the anti-phospholipid antibodies level in the serum of patients after treatment (8). Furthermore, in catastrophic anti-phospholipid syndrome (CAPS), Rituximab can be proposed as a second-line treatment (9).

Some authors have proposed Rituximab as a treatment for classifying and non-classifying manifestations of APS but level of evidence is currently low. Some small retrospective observational studies and case series have shown beneficial effects of Rituximab, however other studies have not confirmed these results (10,11,12).

Only one non-randomized phase II study (RITAPS study) reported an efficacy of Rituximab to treat non-classifying manifestations of APS with about a half of complete or partial responses (13).

Commenté [c16]: Sûr de ça ? Rare = < 1/2000 patients

Commenté [cg17R16]: Source site de la FAI2R (https://www.fai2r.org/les-pathologies-rares/syndrome-des-antiphospholipides/generalites/)
Le SAPL affecte principalement les femmes. Son incidence est approximativement de 5 nouveaux cas pour 100 000 personnes par an, sa prévalence est estimée à environ 20 à 50 cas pour 100 000 sujets.

Commenté [c18R16]: C'est fou j'aurais dit que c'était beaucoup plus fréquent

Commenté [c19]: Vérifie bien que tu écris toujours les termes de la même manière

Commenté [cg20R19]: Je mets toujours Rituximab avec R majuscule si ca te va

Commenté [c21R19]: Ok ça me va j'ai corrigé comme ça dans le reste du manuscrit

Commenté [c22]: Lesquelles ? Classantes ou non ? Si les deux alors il faut le dire

Commenté [cg23R22]: Pour les 2, je fais la précision

Commenté [c24]: Tu peux faire des citations groupées 9-10 sur Zotero.

Commenté [cg25R24]: Je ne sais pas faire désolé

Commenté [c26]: On s'en doute si ce sont des cases reports et des séries de cas

Commenté [cg27R26]: D'accord

Commenté [cg28R26]: Je supprime

Recently, the largest cohort of APS patients with classifying manifestations or not treated with Rituximab reported a clinical benefit in 80% of patients and a complete response in 55% of cases (14).
To date, little data is available on Rituximab use to treat APS manifestations and literature remains divided and heterogeneous.

Here we conducted a comprehensive scoping review of published data to assess the efficacy and safety of Rituximab to treat APS classifying and non-classifying manifestations excluding CAPS.

Commenté [c29]: Je me pose la question de coupler en une phrase les différentes études sans détailler et détailler davantage dans la discussion (c'est toujours la question avec l'intro, planter le décor sans trop en dire)

Commenté [cg30R29]: On peut proposer plus court si tu le souhaites :
Only one phase II study (RITAPS study) was conducted, which reports about a half of partial or complete responses.
Recently, the largest retrospective cohort reported a benefit in 80% of patients and a complete response in 55% of cases

Commenté [c31R29]: Motif faite dans le texte. C'est un peu mieux on ne fera pas plus court pour le moment.

Materials and Methods

A comprehensive scoping review was performed on Pubmed and Medline databases, following PRISMA-ScR (Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews) guidelines. A systematic search strategy was established before the review. A pooled analysis of available data was done.

Literature search and information sources

Literature search was performed from 12/07/2022 to 20/04/2023. All articles written in English or French, published from 2004 (date of appearance of the term Rituximab on the database) to January 2023 were assessed for eligibility. Relevant keywords and medical subject headings (MeSH) terms were used to select articles describing the use of Rituximab to treat any manifestation of APS. The terms used for the search strategy were: ("Rituximab"[Mesh]) AND ("Antiphospholipid Syndrome/diagnosis"[Mesh] OR "Antiphospholipid Syndrome/drug therapy"[Mesh] OR "Antiphospholipid Syndrome/therapy"[Mesh]) and the filter « Humans » was applied.

Eligibility criteria

Type of studies

Only case reports, case series, retrospective and prospective studies written in English or French were considered for eligibility. Articles not available in English or French and reviews were excluded.

Type of participants

Patients aged of 18 years or more, with primary APS or secondary APS related to Systemic Lupus Erythematosus (SLE), who received Rituximab for an APS classifying manifestation or non-classifying manifestation were included in the review.

Pediatrics patients, patient without APS or presenting a Catastrophic Antiphospholipid Syndrome (CAPS) or cancer were excluded.

APS was defined according to Sapporo criteria by combination of arterial and/or venous thrombosis, or obstetrical manifestations and persistent presence of antiphospholipid antibodies (aPL) such as lupus anticoagulant (LAC), antiβ2-glycoprotein I (antiβ2GPI) and anticardiolipin antibodies (aCL) (1) as described in Annex 1.

Non-classifying manifestations included Neurological, Cardiac, Pulmonary, Renal, Dermatological, and Haematological involvement. There were defined according to Uthman et al. (2) (Annex 2).

Commenté [c32]: Ça se discute de citer plutôt RITAPS

Screening process and article selection

Database screening was done separately by two independent investigators (GC and BC) in two steps. First, articles were selected according to predefined eligibility criteria on title keywords or after abstract or full-text reading if relevant keywords were not found. Then, a full-text review of all articles was performed to confirm eligibility of patients. In case of discrepancy in article selection or patient's eligibility, a consensus was obtained between authors (GC and BC) after discussion. Duplicates were excluded. No risk of bias assessment was performed because of the important proportion of case reports.

Commenté [c33]: Ce qui est discutable car j'ai découvert qu'il existe des outils pour cela. Peut-être à garder en tête pour la publication de même que l'enregistrement de la revue dans le registre international++

Commenté [cg34R33]: On laisse comme ça pour la thèse et on verra pour l'article si on doit modifier? Est-ce que ca te va?

Data extraction and collection

The demographic, clinical and biological data of each patient were extracted from case reports and case series and pooled with patients' data available from retrospective and prospective studies. Demographic data, clinical features, presence of associated SLE, positivity of APS, presence of classifying manifestation or not, concomitant therapies (i.e anticoagulation, platelet aggregation inhibitors, immunosuppressive therapy, plasma apheresis, intravenous immunoglobulins transfusion, red blood cells transfusion, thrombopoietin mimetic peptide, ilomedin perfusions) Rituximab protocol, Rituximab dose, outcomes and adverse effects were collected. Microsoft Excel software was used to synthetize collected data.

Outcomes

The main outcome was the clinical response of all APS manifestations to Rituximab therapy. In most cases individual patient data was not available in particular in retrospective or prospective studies. The good clinical response was considered if authors reported a clinical benefit in patients after Rituximab treatment for APS whatever the manifestation. As the definition of clinical response to Rituximab treatment was heterogeneous depending on the studies, we choose a definition for clinical response taking into consideration of these differences. No distinction has been done between complete or partial responses reported in some studies and patients have been only classified as responders or not.

For the classifying manifestations of APS, response to therapy was defined as follow:

- For the thrombotic manifestations as no further thrombosis or persistence of thrombosis and the non-response as new episode of thrombosis when available or as clinical success reported by authors at 6 months.
- For obstetrical manifestations, response to therapy was defined as viability of the fetus and the non-response as fetal death in utero.

For the non-classifying manifestations of APS, response to therapy was defined as full or partial resolution of initial APS manifestation achieved and maintained at 6 months.

The relapse was defined as a recurrence of APS manifestation at 12 months in patients with clinical response at 6 months.

aPL positivity levels were defined according to the international consensus statement on the classification criteria for definite anti-phospholipid syndrome (APS) (1). For the biological response, the success was defined by negativation of all aPL 6 month after Rituximab therapy. Treatment failure was defined by persistence at least one aPL 6 month after Rituximab therapy.

Statistical analysis

A pooled analysis of extracted data was performed. Descriptive statistics were used to summary data collected using continuous variables median and interquartile range (IQR) for continuous variables and numbers and proportions for categorical variables. Considering the design of the study and the large number of case reports expected no comparative analysis or meta-analysis analysis was performed.

Results

Screening and patients' selection

Out of the 89 records screened and assessed for eligibility, 28 were selected by both investigators. They were distributed as follows: 21 case reports, 6 retrospective studies, 1 clinical trial. From these records, 126 Patients were extracted and assessed for eligibility: 81 patients from retrospectives studies, 25 patients from case reports, 20 patients from one clinical trial.

Finally, after secondary exclusion of 4 CAPS patients and 1 pediatric patient; 121 patients were included in the analysis.

Screening process and patients' selection summarized in the flow chart (Figure 1).

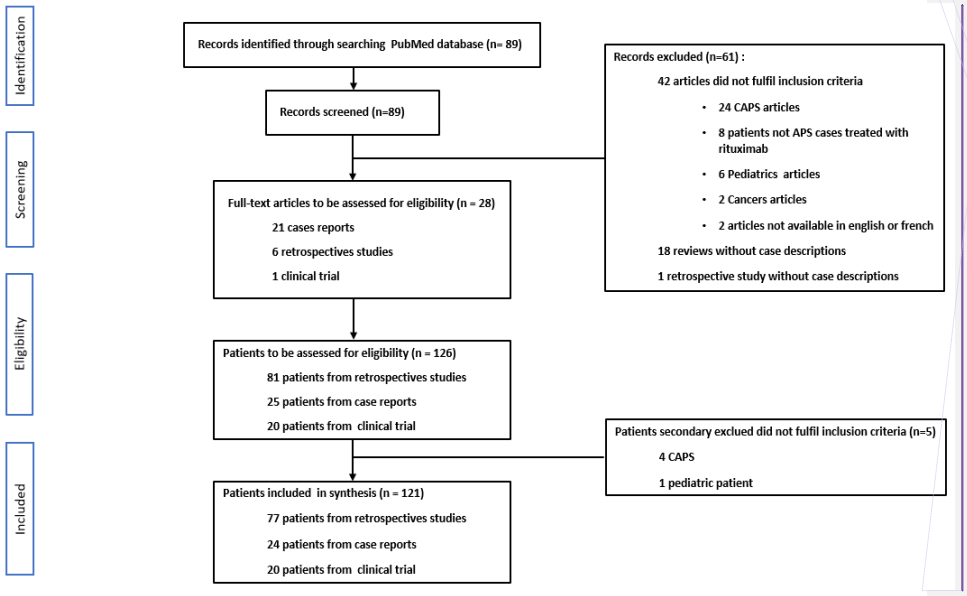

Fig. 1 Flow Chart

Abbrevation: APS Antiphospholipid Syndrome, CAPS Catastrophic Antiphospholipid Syndrom

Commenté [c35]: Très bien mais à mettre en plus grand sans cadre et 600 dpi de résolution

Commenté [c36R35]: Plus mettre les items de PRISMA à côté en bleu comme dans le flow chart prisme officiel

Commenté [cg37R35]: Dit moi si ca te convient comme cela

Commenté [c38R35]: Toujours pas :)

Commenté [c39]: Cf le ppt pour les corrections

Commenté [c40]: Je t'ai renvoyé le flow chart corrigé

Baseline characteristics

The mean age ± SD was 40.4 ± 13.3 years and 76 patients (63%) were female. APS was primary in 87 patients (72%) and secondary to SLE in 34 (28%). Forty-six patients (38%) presented classifying manifestation of APS and fulfill Sapporo Criteria for APS. aPL was noticed in 118 patients. 19 patients (16%) had single aPL positivity, 31 patients (26%) had double aPL positivity and 68 patients (58%) had triple aPL positivity. We cannot detail the percentage of patients who had positive Lupus Anticoagulant (LAC), positive anti-β_2GP1 antibody (IgM or IgG) or positive anticardiolipin (aCL) antibody (IgM or IgG) but at least ninety-nine patients (82%) of patients were classified at high-risk according to EULAR definition.

In detail, the clinical manifestations of APS for which Rituximab therapy was administered included 44 patients with recurrent thrombosis (37 patients, 84%, were anticoagulated mostly by VKA), 31 patients with cytopenia mainly thrombocytopenia (30 patients) but also 1 patient with autoimmune haemolytic anaemia, 12 patients with neurological manifestations, 12 patients with skin manifestations, 10 patients with diffuse alveolar haemorrhage (DAH), 6 patient with cardiac involvement, 4 patients with renal involvement and 2 patients with obstetrical manifestations.

Anticoagulation and Antiplatelet therapies were noticed in 119 patients. Ninety-seven patients received anticoagulation (82%) mostly VKA, 31 patients received platelet aggregation inhibitors (26%) and 23 patients received both therapies (19%), mostly due to sustained thrombosis. All obstetrical manifestations were treated with antiplatelets and VKA as recommended. Twenty-two patients (18%) did not receive anticoagulation therapy due to sustained severe thrombocytopenia.

Concomitant therapies were noticed in 121 patients. Ninety-six patients (79%) received at least one immunosuppressive therapy and 66 patients received hydroxychloroquine (55%). High dose glucocorticoids (GCs) were administered in 73 patients (68%; oral GCs at a dose up to 1 mg/kg/day in 54 patients), 500–1000 mg pulses of methylprednisolone/day in 12 patients.

Other immunosuppressants were prescribed in 38 patients (31%): azathioprine in 17 patients, cyclophosphamide in 15, mycophenolate mofetil in 10 patients, ciclosporine in 5 patients, vincristine 3 patients, disulone in 2 patients, tacrolimus in 2 patients, and belimumab in 1 patient.

Additionally, 27 patients (22%) underwent plasma apheresis and 28 patients (23%) received intravenous immunoglobulins' transfusion.

Commenté [c41]: A recalculer à partir de ta base. Pour les classer regarde la définition des recos (EULAR par exemple).

Commenté [cg42R41]: Je ne peux pas stratifier le risque des patients comme je n'ai pas le détail des anticorps APS

Commenté [cg43R41]: Au maximum je peux parler des high risk en regroupant le nombre de patients double et triple positif mais je ne peux pas parler des medium risk et des low risk

Commenté [c44]: Sous traitement anti coagulant ou non ?

Commenté [cg45R44]: 36 patients sur 43, je rajoute l'information dis moi si ca te va

Commenté [c46R44]: 36 ou 37 ?

Commenté [cg47R44]: 37 patients sur 44

Commenté [cg48]: Dont 12 patients plaquenil seul d'où la diminution 108-12 = 96 du nombre de patients avec au moins un traitement immunosuppresseur

Commenté [c49]: 1. Plaquenil c'est pas IS
2. Pars du plus gros nombre pour aller vers le plus petit

Commenté [cg50R49]: Je modifie en mettant le Plaquenil à part

The only patient with hemolytic anemia received red blood cells transfusion. Three patients with thrombocytopenia received thrombopoietin mimetic peptide and 2 patients with dermatologic manifestations received ilomedin perfusions.

The Rituximab protocol was described in 121 patients. Four different treatment regimens of Rituximab were reported. Standard protocols with 2 doses of 1000 mg (2 weeks apart) or a 375mg/m2 given once weekly for 4 weeks were mainly used.
In a recent study, 2 low dose regimens were used: 2 doses of 500 mg (2 weeks apart) or a protocol where less than 375mg/m2 given once weekly for 4 weeks (16).
The 2 doses of 1000 mg (2 weeks apart) regimen were used in 52 patients (43%) and the protocol of 375 mg/m2 given once weekly for 4 doses in 44 patients (36%). Nine patients (8%) received 2 doses of 500 mg (2 weeks apart) and 16 patients received less than 375mg/m2 given once weekly for 4 weeks (13%).
Ninety-seven patients (80%) received around 2 g of Rituximab, 13 patients (11%) received 1 g and 11 patients (9%) received less than 1 g.

Baseline characteristics of patients are summarized in Table I.

Commenté [c51]: Je ne vois pas la diff avec le deuxième

Commenté [cg52R51]: 10.3389/fimmu.2022.971366 "Low dose versus standard dose rituximab for the treatment of antiphospholipid syndrome: A pilot study from a tertiary medical center"

C'est les l' étude récente chinoise où dans des SAPL thrombotiques, les auteurs décident de faire 4 perfusions de rituximab, mais au lieu de mettre 375mg/m2 dans chaque perfusions ils font des doses plus faibles.
Les auteurs détaillent pour chaque patients la dose totale de rituximab reçue

Commenté [c53R51]: Regarde comment j'ai modifié. Parce qu'on ne peut pas écrire la même chose et dire que c'est différent.

Commenté [c54R51]: Ou alors tu mets le dosage vraiment reçu par les patients

Commenté [c55]: Je ne vois pas la diff avec le deuxième

Commenté [cg56R55]: 10.3389/fimmu.2022.971366 "Low dose versus standard dose rituximab for the treatment of antiphospholipid syndrome: A pilot study from a tertiary medical center"

C'est les l' étude récente chinoise où dans des SAPL thrombotiques, les auteurs décident de faire 4 perfusions de rituximab, mais au lieu de mettre 375mg/m2 dans chaque perfusions ils font des doses plus faibles.
Les auteurs détaillent pour chaque patients la dose totale de rituximab reçue

Commenté [c57R55]: Regarde comment j'ai modifié. Parce qu'on ne peut pas écrire la même chose et dire que c'est différent.

Commenté [c58R55]: Ou alors tu mets le dosage vraiment reçu par les patients

Commenté [c59]: 1. Plutôt en word mais si t'as pas le temps ça passera comme ça
2. Simple positifs à mettre non ?
3. Indications : dans l'ordre numérique ++ 44 puis 31 puis 12…
Le reste très bien
4. Dissocie la légende du titre et des abréviations stp

Table I. Demographics and clinical manifestations of patients with APS treated with Rituximab.

Parameter	Patients with APS (n=121)
Age (in years) mean ± SD	40,4 (±13,3)
Gender (Female/Male) n (%)	76 (63%) / 45 (37%)
Primary APS / APS secondary to SLE n (%)	87 (72%) / 34 (28%)
*Triple positive aPLs n (%)	68 (58%)
*Double positive aPLs n (%)	31 (26%)
*Single positive aPL n (%)	19 (16%)
Indications for rituximab therapy n (%)	
Recurrent Thrombosis	44 (36%)
Cytopenia (i.e. thrombocytopenia, anemia)	31 (26%)
Neurological manifestations	12 (10%)
Skin manifestations	12(10%)
Diffuse alveolar haemorrhage	10 (8%)
Cardiac involvement	6 (5%)
Renal involvement	4 (3%)
Obstetrical Manifestations	2 (2%)
Anticoagulation n (%) / Antiplatelet n (%)	97 (82%) / 31 (26%)
Anticoagulation and Antiplatelet n (%)	23 (19%)
Immunosuppressant n (%)	96 (79%)
Corticotherapy n (%)	73 (68%)
oraly/pulse/both	54 (74%) / 12 (16%) / 7 (10%)
Other immunosuppresant n (%)	38 (31%)
Other medications n (%):	
Hydroxychloroquine	66 (55%)
Immunoglobulin infusion	28 (23%)
Plasmatic exchange	27 (22%)
Thrombopoietin mimetic peptide	3 (2%)
Ilomedin infusion	2 (2%)
Red Blood cells transfusion	1 (1%)
Platelet transfusion	0 (0%)
Rituximab protocol n (%)	
1000mg x 2	52 (43%)
375mg/m^2 x 4	44 (36%)
< 375mg/m^2 x 4	16 (13%)
500 mg x2	9 (8%)
Rituximab dose n (%) 2g / 1g / <1g	97 (80%) / 13 (11%) / 11 (9%)

Data is presented as mean± standard deviation or number of patients (percentage)
Abbrevation : APS Antiphospholipid Syndrom SLE Systemic Lupus Erythematosus aPL antiphospholipid antibody

Response to Rituximab therapy

The response to Rituximab can be analyzed in 117 patients; 4 patients were lost to follow-up (Two without explanation in patients with thrombosis and 2 discontinuations of treatment for adverse reaction after the first infusion of Rituximab. The first in a patient with cardiac involvement. The second in a patient with renal manifestation). Follow-up data was reported and available in 117 patients (100%) at 6 month and 89 patients at 12 months after Rituximab infusion.

Commenté [cg60]: J'ai réécrit la partie pour enlever le surlignage

At 6 month the clinical response to Rituximab therapy was favorable in 91/117 patients (78%), while 26/117 patients (22%) did not respond including 5 deaths (4%).
A favorable outcome at 12 months was reported in 89 patients and was sustained in 69 patients (78%). Twenty patients were non-responders (22%) including 4 relapses (6%).

Commenté [cg61]: J'ai enlevé la notion de répondeurs complets, dis moi si ca te va

About the biological response, aPL were described in 103 patients at 6 months and in 102 patients at 12 months.
At 6 months 92 patients (90%) have persistence of at least one aPL. Only 11 patients (10%) presented a negativation of all aPL.
This biological response remains stable between 6 and 12 months. Only one patient with antibody positive at 6 months turns negative at 12 months, while 1 patient with antibody negative at 6 months turns positive at 12 months.

Clinical and Biological response to Rituximab Therapy is summarized in Table II.

Table II. Clinical and Biological response to Rituximab.

Parameter	Patients with APS
Clinical response all APS patients	
At M6 (n = 117)	
Responder n (%)	91 (78%)
No Responder including death n (%)	26 (22%) / 5 (4%)
At M12 (n = 89)	
Sustained response	69 (78%)
No Responder including death	20 (22%)
Late Responder	1 (6%)
Relapse	4 (6%)
Biological response all APS patients	
At M6 (n= 103)	
Persistence at least one aPL	92 (90%)
Negativation all aPL	11(10%)
At M12 (n=102)	
Positive aPL at M6 whose negatived at M12	1 (1%)
Negative aPL at M6 whose positived at M12	1 (1%)

Data is presented as number of patients (percentage).
Abbrevation : APS Antiphospholipid Syndrom, aPL antiphospholipid antibody

Commenté [c62]: Même commentaire pour les légendes Retire le gras et le souligné

Clinical response to Rituximab for each APS manifestation

Commenté [cg63]: J'ai enlevé la notion de réponse complète dans chaque manifestation clinique

Thrombotic manifestations and thrombocytopenia were the most frequent indications for using Rituximab to treat APS manifestations representing 60% of indications.

Commenté [cg64]: Comme j'ai ajouté un patient qui avait une manifestation thrombotique et non vasculaire ca fait 42 thrombose et 31 cytopénies soit 73 patients en tout 73/121 = 60,3%

Out of 42 patients with arterial or venous thrombotic event related to APS, the nature of thromboses was detailed in fourteen patients: Four patients had only veinous thrombosis, four patients had only arterial thrombosis, six patients had arteriovenous thrombosis. Thirty-eight patients (90%) were responders at 6 months, and 4 patients (10%) were non-responders including 1 death. This response was sustained in 23/25 patients at M12 (92%), and 2 patients (8%) presented a relapse.

Commenté [c65]: Il va falloir dire le nombre de manifestations artérielles et veineuses

Commenté [cg66R65]: Je rajoute le détail :
Statut connu chez 14 patients sur 42
Veineuse seule : 4 patients
Artérielle : 4 patients
Artério-veineuse : 6 patients

Among 31 patients with cytopenia, 21 patients (68%) were responders at 6 months, and 10 patients (32%) were non-responders without any death. This response was sustained in 20/20 patients at M12 (100%). No patient relapsed, and one patient presented a late response after 12 month (10%).

Out of 12 patients with neurological manifestations 10 (83%) responds at 6 months. Two patients (17%) were non-responders including 1 death. This response was sustained in 6/7 patients at M12 (86%) and no patient relapsed.

Commenté [c67]: Il faut détailler le type de manifestation si tu peux

Commenté [cg68R67]: Je n'ai pas le détail, patients majoritairement issus de l'étude rétrospective israélienne

Commenté [c69R67]: Ok

From 12 patients presented APS with cutaneous manifestations 10 (83%) were responders at 6 months. Two patients (17%) were non-responders without death. This response was maintained in 9/10 patients at M12 (90%).

Commenté [cg70]: Comme pour les manifestations neurologiques, je n'ai pas le détail

Commenté [c71R70]: Ok

Among 10 patients with lung involvement, 7 (70%) were responders at 6 months. Among the 3 non responder patients 2 deaths occur. The response was sustained in 6/7 patients at M12 (86%) and only 1 patient relapsed.

Five patients presented cardiac involvement treated by Rituximab but only one patient (20%) was responder at 6 months and the response was sustained at 12 months.

The 3 patients with renal manifestation were responders at 6 months (100%). This response was maintained for all patients at M12 without relapse.

Two patients presented obstetric manifestations 1 patient was responder with birth at term without complication and 1 patient was non-responder with a fetal death in utero at 21 weeks.

Figure 2 summarized clinical response to Rituximab for each APS manifestation.

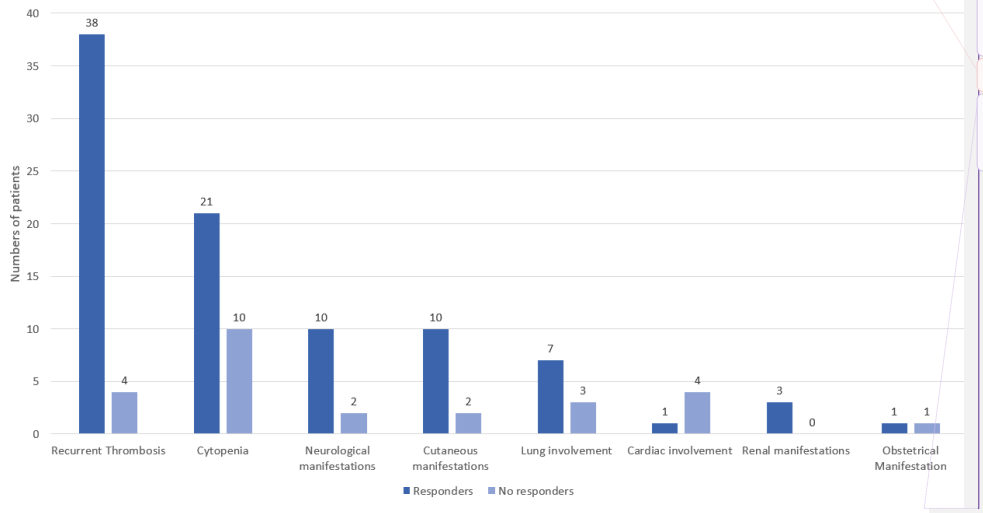

Fig. 2 Clinical response to rituximab according APS manifestations.

Abbrevation : APS Antiphospholipid Syndrom

Clinical response at 6 months in recurrent thrombosis according Rituximab doses (2 g, 1 g, < 1g)

In 42 patients with thrombotic manifestations, 22 patients (52%) received around 2 g of Rituximab. At 6 months 19/22 patients (86%) were responders, and 3 patients were non-responders (14%) without death. Eleven patients (27%) received 1 g of Rituximab. At 6 months all patients were responders (100%).

Commenté [c72]: Tu avais mis 100% mais 3/4 = 75% … A vérifier avec ta table

Commenté [cg73R72]: J'ai un patient avec atteinte rénale est perdu de vue à cause d'une réaction à la première perfusion de rituximab d'où le passage de 4 dans la population décrite à 3 patients dans la population analysée

Commenté [c74]: Je ne suis pas certain de l'intérêt. Si on veut avoir le détail par manifestation il y a ce que tu as mis au dessus. Pas d'intérêt clinique je pense à groupe les thromboses et les cytopénies.

Commenté [cg75R74]: Je supprime

Commenté [c76]: On reverra avec Mathieu si on met les décès sur le graphe je trouve qu'on a l'impression qu'ils sont comptés en plus.

Commenté [c77]: Alors là peut-être préciser d'où viennent les données

Commenté [cg78R77]: Je mets la référence bibliographique des 2 articles chinois qui ont proposé des doses réduites de rituximab si ca ta va?

Nine patients (22%) received less than 1 gramme of Rituximab. At 6 month, 7 patients (78%) were responders. 2 patients were non-responders (22%) with 1 death.

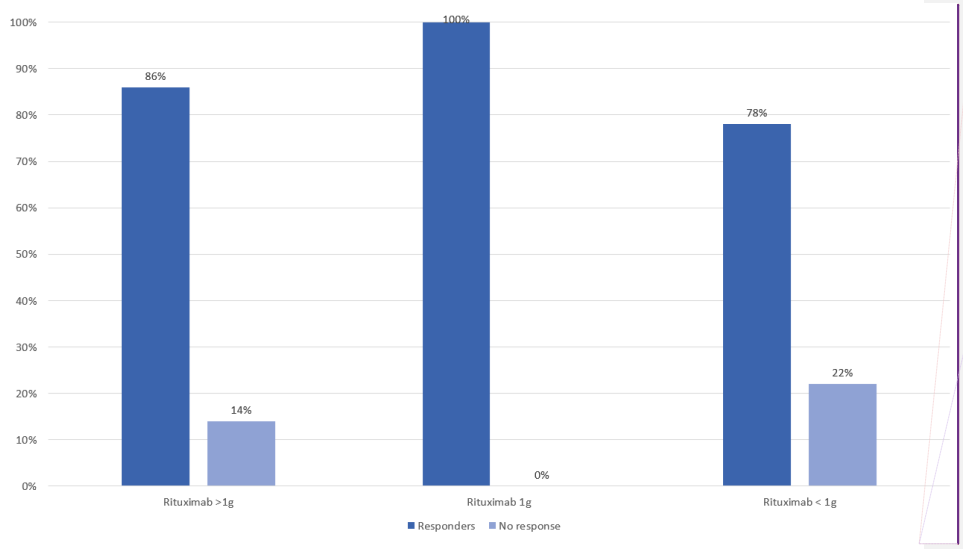

Fig. 3 Clinical response in recurrent thrombosis according rituximab doses.

Abbrevation : APS Antiphospholipid Syndrom

Safety

Among 121 patients treated with Rituximab, 24 serious side effects (20%) requiring hospitalization were reported, including 7 infections, 1 neutropenia without infection and 2 hypersensitivity reactions requiring treatment to be stopped.

Five deaths were reported. Three patients died of infections. Two patients died of uncontrolled disease, the first died of a progression of his neurological APS. The second died of Haemophagocytic Lymphohistiocytosis Syndrome.

Fifty-seven non-serious side effects (47%) were reported, including 21 non-serious infections (17%) and 8 reactions (7%) after Rituximab infusion. The other most common reaction was musculoskeletal disorders (9%), almost arthralgia.

Serious and non-serious adverse event are summarized in Table III.

Commenté [cg79]: Pour les graphiques, est ce que je fais seulement répondeur/ non répondeur, ou je rajoute une colonne décès ?

Ca met plus en valeur la mortalité mais ca donne des stats légérement différentes du texte

(J'ai retiré de la colonne non répondeurs, le nombre de patient décédés et je les ai mis à part pour être plus lisible)

Exemple : Ici dans le graph rituximab 1g, j'ai fait 7 répondeurs, 1 non répondeur et 1 décès pour que les pourcentages soit égaux à 100%

Commenté [c80R79]: Mets juste répondeurs non répondeurs ++ Si tu mets les décès à part c'est faux parce que depuis le début tu les inclus dans les non répondeurs !

Commenté [c81]: Je comprends pas : infection ou hémorragie alvéolaire ?

Commenté [cg82R81]: Je voulais dire que parmi les 3 patients décédés, 2 d'entre eux avaient une attente pulmonaire du SAPL et 1 patient avait une atteinte cardiaque.

Mais j'ai déjà précisé dans la sous partie réponse selon les manifestations cliniques, la porportion de patient décédes c'est redondant et ca n'apporte rien de nouveau

J'enlève pour plus de clarté si ca te va

Commenté [c83R81]: Ok mais ce n'est pas du tout ce qui est écrit tu mets :
5 décès au total dont 3 infections + 2 maladies non contrôlées (1 SAM et une atteinte neuro du lupus) donc je ne comprends toujours pas

Commenté [c84]: Je trouve que ça manque un peu de clarté

Commenté [cg85R84]: J'ai réécrit plus simplement en enlevant la manifestation clinique pour laquelle chaque patient était initialement traité par rituximab

Ca n'apporte rien et si jamais on me demande le détail lors de la soutenance je pourrais le rajouter à l'oral

Dis moi si tu trouves cela plus lisible

Commenté [c86]: En fait c'est la définition. Serious adverse event = hospitalisé

Commenté [cg87R86]: D'accord je note!

Table III. Serious and non serious adverse event.

Parameter	Patients with APS (n=121)
Serious (hospitalization) n (%)	24 (20%)
Infections	7 (6%)
Death	5 (4%)
Discontinuation of treatment due to perfusion reaction	2 (2%)
Neutropenia without infection	1 (1%)
Other	9 (7%)
Non serious n (%)	57 (47%)
Infection	21 (17%)
Muskuloskeletal	11 (9%)
Reaction after Rituximab perfusion	8 (7%)
Cardiovascular	8 (7%)
Neuropsychiatric	4 (3%)
Gastrointestinal	3 (2%)
Hematologic	2 (2%)

Data is presented as number of patients (percentage)
Abbrevation : APS Antiphospholipid Syndrom

Commenté [c88]: Ok mais mets par ordre de fréquence ++

Discussion

This scoping review with pooled analysis suggests an overall benefit of Rituximab in the treatment of the different manifestations of APS with a clinical response at 6 months in 78% of patients. This response was maintained at 12 months in 78% of patients initially responding at 6 months but 6% of treated patients experienced a relapse at 12 months after treatment and 4% mortality was observed which suggests the need for follow-up of patients.

The population of our study is consistent with those described in previous cohort studies (5,18). The mortality rate of 4% observed in our study is lower than in the "Europhospholipid" cohort where the 10-year mortality was 9.3%. However, in the majority of reported cases, the follow-up was shorter and stopped on average at 12 months, which may explain underestimating the mortality rate of our pooled analysis.

Despite a significant overall response rate to Rituximab we could observed different clinical efficacy according APS manifestations. Thrombotic manifestations and thrombocytopenia were the most frequent indication for Rituximab use because of inefficacy of VKA. We could distinguish different response profiles depending on the initial manifestation.

The highest rate of favorable response was observed in thrombotic manifestations with 90% of patients responding at 6 months and but with a significant relapse rate of 8% at 12 months. Currently, in recurrent thrombosis, the therapeutic strategy consists of increasing the INR threshold to 3-4, adding aspirin treatment or adding hydroxychloroquine treatment as proposed by Garcia et al. (17).

The effect of hydroxychloroquine is based on in vitro results only (19) and the antithrombotic effect of hydroxychloroquine has not been confirmed in prospective studies or meta-analysis (20). Rituximab could therefore be an interesting therapeutic solution to offer to the 30% of patients presenting with recurrent thrombotic manifestations (5).

The response to obstetric manifestations cannot be apprehended by this work, only 2 cases having been reported with one success and one failure (21,22). In the largest cohort of obstetric APS "EUROAPS", no patient had been treated with Rituximab (23).

Commenté [c89]: Je le décalerai au dessus au premier paragraphe

Commenté [cg90R89]: C'est mieux à cette place là?

J'ai laissé le premier paragraphe sur le rappel de notre résultat principal

Commenté [c91]: J'ai retiré 3 profiles car je pense que c'est assez artificiel (il n'y a pas vraiment de clusters identifiés). Commente plutôt par manifestation.

Commenté [c92]: Tu peux laisser comme ça pour la thèse mais il me semble plus approprié de citer des repos internationales type EULAR ou ACR

Commenté [cg93]: Qu'est ce que tu penses de ça comme paragraphe sur les indications d'intérêt par rapport aux taux de rechute et aux difficultés à traiter (30% de récurrence de thrombose)

In hematological manifestations, the response rate was lower (68%) but systematically sustained at 12 months, without relapse and in most of articles authors evoked in the majority of cases a possible withdrawal of immunosuppressant.
For other manifestations the responses reported were heterogeneous and the results should be taken with caution because of the low number of patients reported. The benefit of Rituximab seems to be greater in renal (100% of patient's responders) dermatological and neurological APS involvements (83% of patients responding for each).
Conversely, the most difficult condition to treat seems to be cardiac damage.

In 2018, Garcia et al. positioned Rituximab as a therapeutic option in cytopenias, dermatological manifestations and renal manifestations (17).
Since 2018, new published data suggests the interest of Rituximab in cytopenia, dermatological manifestations and renal manifestations but the number of patients we could include in the pooled analysis remains low (14,15,16).

The beneficial effects of Rituximab on APS that we described was already known in CAPS. In an open series of 20 patients from the international CAPS registry, the use of Rituximab seemed interesting in case of CAPS refractory to first-line treatment or in case of recurrent CAPS, 75% of patients recovering from the episode (24).

The therapeutic regimens reported in this review were heterogeneous. The regimen with 1g of Rituximab Day 1 and Day 15 was the main used in particular in RITAPS study (13). In another study Agmon-Levin et al. did not found any difference between the 1g D1-D15 regimen or that of 375mg/m^2 weekly for 4 weeks (14).

Two recent retrospective studies have proposed reduced dose regimens to treat the thrombotic APS (15,16).
They found a similar efficacy of Rituximab at a dose of 1g versus the usual standard regimens with cumulative dose around 2g (1g x 2 or 375mg/m^2 weekly for 4 weeks); with a response rate of 100% to 86% compared to a standard dose. However, Rituximab seems less effective below 1g; with a higher number of non-responders (22%) which could reflect a disease that is less controlled.
Regarding the biological response, our study suggests that the disappearance of antiphospholipid antibodies under treatment does not seem to be an achievable

Commenté [c94]: Par contre développer un paragraphe sur les indications d'intérêt par rapport aux taux de rechute et aux difficultés à traiter (30% de récurrence de thrombose notamment) ça me semble important

Commenté [cg95]: Je ne sais pas faire de citations groupées

Commenté [cg96]: J'ai trouvé ca sur le rituximab dans le CAPS ca date de 2013
Rituximab use in the catastrophic antiphospholipid syndrome: Descriptive analysis of the CAPS registry patients receiving rituximab

Dans les dernières données du CAPS registry publiés en 2015, il parle de 33 patients mais je n'ai pas les données sur la réponse
doi: 10.1016/j.autrev.2016.09.010. Epub 2016 Sep 15.
Catastrophic antiphospholipid syndrome (CAPS): Descriptive analysis of 500 patients from the International CAPS Registry

Commenté [c97]: Ref groupées n'oublie pas partout dans le doc

Commenté [cg98R97]: Je ne sais pas faire désolé

Commenté [cg99]: J'ai enlevé la notion de réponse complète

objective; with the persistence at 12 months of at least one aPL in 90% of our population. In the phase II Ritaps study, it was already pointed out that in all patients who had positive circulating lupus anticoagulant antibodies, anti-cardiolipins anti-β2GPI IgG; antibodies remained positive at 6 months and 12 months (13). In Agmon-Levin et al. study, an overall decrease in aPL levels was found in all patients under treatment, but no significant differences between responder and non-responder patients (14).

Here, we report concomitant immunosuppressive treatments in association with Rituximab which could modified the outcomes.

In patients with thrombotic manifestations, the concomitant immunosuppressive treatments reported are mainly intravenous or per os glucocorticoids (68%) and intravenous immunoglobulins (23%), as proposed by some experts (17).

Finally, in the most serious manifestations, plasma exchanges were carried out (22%) mainly by analogy to the treatment of the catastrophic syndrome of anti-phospholipids and the data of the "CAPS registry" (9).

In the majority of cases, Rituximab was administrated in refractory clinical situations after failure of corticosteroids, immunoglobulins or plasmatic exchange. Due to the faster onset of action of these treatments compared to Rituximab, the risk of confounding bias seems to be low.

It should be notice that 3/31 patients with cytopenia (10%) received additional treatment with a thrombopoietin agonist for thrombocytopenia; without clinical improvement in 66% of cases (13,25,26). Due to the rarity of the situation and the lack of improvement after Rituximab, the risk of favorable confounding bias is low.

Infections were the main adverse effect reported in 23.9% of patients and 6% had a serious infection. A hypersensitivity reaction to Rituximab infusion occurs in 10 patients (8%) and the treatment had to be stopped only in 2 severe cases (1.6%).

These data are consistent with the known safety data for Rituximab. In a pooled analysis of 2,578 patients with rheumatoid arthritis who received Rituximab for 6 months, 39% developed an infection. The rate of serious infections was 4.31 per 100 patient-years (Annex 3). Furthermore, in an analysis of 99 patients with ANCA vasculitis who received Rituximab for 6 months, 12% of patients experienced a

Commenté [c100]: Tu ne vas pas assez loin dans l'interprétation du biais que ça peut constituer sur l'effet du Ritux. Est ce qu'on en avait beaucoup, est ce que ça a un sens ? Est ce que ça reste une limite ?

Commenté [cg101R100]: intravenous immunoglobulins (28patients 23%)
plasma exchanges (27 patients 22%)

Commenté [cg102R100]: Qu'est ce que tu penses de ça
Dans la majorité des cas le Rituximab était administré après échecs des corticoïdes, des immunoglobulines ou des echanges plasmatiques.
En raison de leur court délai d'action de ces traitements comparé au Rituximab le risque de biais de confusion est faible.

Commenté [cg103]: Dis moi si tu trouves ça pertinent sinon j'enlève

Commenté [c104R103]: Tu peux avancer cette hypothèse ça me choque pas mais je pense que le principal argument est de dire que ce sont des patients réfractaires (j'ai rajouté)

Commenté [cg105]: Je ne sais pas faire de références groupées

Commenté [c106]: Je ne comprends pas ce 8%

Commenté [cg107R106]: 10 réactions à la première perfusion, 2 graves avec arrêt de traitement et 8 non graves avec poursuite du traitement
10/121 = 8,26%

reaction to the first infusion (Annex 4). A solution to reduce the risk of infection could be to reduce the dose of Rituximab to 1g as proposed in 2 recent studies (15,16).

Commenté [c108]: Ok mais seulement pour les infections

Our scoping review has several limitations. Due to its retrospective design and the heterogeneity of the quality of the published data, our data analysis can only remain descriptive. Moreover, the pooled analysis has been done from published data and was not patient based. It does not provide strong scientific evidence in favor of the use of Rituximab, not define the predictive factors of the therapeutic response. The biological response is also difficult to assess, in the absence of a consensus for monitoring antiphospholipid antibodies.

On the other hand, as our study is observational, the response to Rituximab may be biased by other immunosuppressive therapies concomitant interventions. Another issue was that we could not provide results on complete or partial responses to Rituximab because criteria used to define response were not the same between studies. Then, we choose to classify patients only as responders or not.

Nevertheless, given the rarity of APS, the absence of randomized controlled trials and the large number of newly reported cases we believe that the data from this scoping review can be contributive.

Commenté [c109]: Elle est super cette phrase je trouve

Conclusion

Our study, the first scoping review about the treatment by Rituximab for APS provides some arguments for the benefit of the treatment with an acceptable safety.

In regard of the retrospective and observational design of our study, further studies e.g. clinical trials are needed to confirm these results.

Several questions remain unanswered, the preferred therapeutic regimen, the strategy in the event of treatment failure or that of the need for a maintenance perfusion.

LIST OF ABREVIATIONS

- antiβ2GPI : antiβ2-glycoprotein I
- aCL : anticardiolipin antibodies
- ACR : American College of Rheumatology
- ANCA : Antineutrophil Cytoplasmic Antibodies
- aPL : Antiphospholipid Antibody
- APS : Anti-Phospholipid Syndrome
- CAPS : Catastrophic Anti-Phospholipid Syndrome
- DAH : Diffuse Alveolar Haemorrhage
- EULAR : European Alliance of Associations for Rheumatology
- GCs : Glucocorticoids
- INR : International Normalized Ratio
- IQR : Interquartile Range
- LAC : Lupus Anticoagulant
- NEJM : New England Journal of Medicine
- PRISMA-ScR : Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews
- SD : Standard Deviation
- SLE : Systemic Lupus Erythematosus
- VKA : Anti Vitamin K

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Commenté [cg110]: J'ai remplacé la référence 26 "celle du labo genetech"par les annexes 3 et 4 en mettant en évidence les passages que je cite, dis moi si ca te va

Commenté [c111]: Je peux pas mettre de commentaire en détail. Vancouver. La citation des noms de la 7 et de la 16 me semblent bizarres

Commenté [cg112R111]: Avec les changements dans la discussions ca correspond maintenant aux artibles 8 et 23, j'ai fait les modifications dis moi ce que tu en penses

Annexes

Annexe 1 Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost JTH. févr 2006;4(2):295-306.

Table 2 Revized classification criteria for the antiphospholipid syndrome

Antiphospholipid antibody syndrome (APS) is present if at least one of the clinical criteria and one of the laboratory criteria that follow are met*

Clinical criteria

1. Vascular thrombosis†

One or more clinical episodes‡ of arterial, venous, or small vessel thrombosis§, in any tissue or organ. Thrombosis must be confirmed by objective validated criteria (i.e. unequivocal findings of appropriate imaging studies or histopathology). For histopathologic confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall.

2. Pregnancy morbidity

(a) One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus, or

(b) One or more premature births of a morphologically normal neonate before the 34th week of gestation because of: (i) eclampsia or severe pre-eclampsia defined according to standard definitions [11], or (ii) recognized features of placental insufficiency¶, or

(c) Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded.

In studies of populations of patients who have more than one type of pregnancy morbidity, investigators are strongly encouraged to stratify groups of subjects according to a, b, or c above.

Laboratory criteria**

1. Lupus anticoagulant (LA) present in plasma, on two or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Haemostasis (Scientific Subcommittee on LAs/phospholipid-dependent antibodies) [82,83].
2. Anticardiolipin (aCL) antibody of IgG and/or IgM isotype in serum or plasma, present in medium or high titer (i.e. > 40 GPL or MPL, or > the 99th percentile), on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA [100,129,130].
3. Anti-β_2 glycoprotein-I antibody of IgG and/or IgM isotype in serum or plasma (in titer > the 99th percentile), present on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA, according to recommended procedures [112].

*Classification of APS should be avoided if less than 12 weeks or more than 5 years separate the positive aPL test and the clinical manifestation. †Coexisting inherited or acquired factors for thrombosis are not reasons for excluding patients from APS trials. However, two subgroups of APS patients should be recognized, according to: (a) the presence, and (b) the absence of additional risk factors for thrombosis. Indicative (but not exhaustive) such cases include: age (> 55 in men, and > 65 in women), and the presence of any of the established risk factors for cardiovascular disease (hypertension, diabetes mellitus, elevated LDL or low HDL cholesterol, cigarette smoking, family history of premature cardiovascular disease, body mass index ≥30 kg m^{-2}, microalbuminuria, estimated GFR < 60 mL min^{-1}), inherited thrombophilias, oral contraceptives, nephrotic syndrome, malignancy, immobilization, and surgery. Thus, patients who fulfil criteria should be stratified according to contributing causes of thrombosis. ‡A thrombotic episode in the past could be considered as a clinical criterion, provided that thrombosis is proved by appropriate diagnostic means and that no alternative diagnosis or cause of thrombosis is found. §Superficial venous thrombosis is not included in the clinical criteria. ¶Generally accepted features of placental insufficiency include: (i) abnormal or non-reassuring fetal surveillance test(s), e.g. a non-reactive non-stress test, suggestive of fetal hypoxemia, (ii) abnormal Doppler flow velocimetry waveform analysis suggestive of fetal hypoxemia, e.g. absent end-diastolic flow in the umbilical artery, (iii) oligohydramnios, e.g. an amniotic fluid index of 5 cm or less, or (iv) a postnatal birth weight less than the 10th percentile for the gestational age. **Investigators are strongly advised to classify APS patients in studies into one of the following categories: I, more than one laboratory criteria present (any combination); IIa, LA present alone; IIb, aCL antibody present alone; IIc, anti-β_2 glycoprotein-I antibody present alone.

Annexe 2 : Uthman I, Noureldine MHA, Ruiz-Irastorza G, Khamashta M. Management of antiphospholipid syndrome. Ann Rheum Dis. févr 2019;78(2):155-61.

Box 1 A comprehensive list of organ system-based, criteria clinical manifestations of antiphospholipid syndrome

Criteria clinical manifestations of the antiphospholipid syndrome.
Neurological:
- Cerebral venous thrombosis
- Multi-infarct dementia
- Stroke
- Transient ischaemic attack

Ophthalmic:
- Amaurosis fugax
- Optic neuropathy
- Retinal artery/vein thrombosis

Endocrine:
- Adrenal infarction

ENT:
- Nasal septum ischaemia/perforation

Cardiac:
- Intracardiac thrombus
- Myocardial infarction

Obstetrical:
- ≥1 unexplained fetal* death ≥10 WG
- ≥1 premature birth* at *or* <34 WG due to:
  - Severe pre-eclampsia
  - Eclampsia
  - Severe placental insufficiency
- ≥3 unexplained consecutive spontaneous abortions† at *or* <10 WG

Pulmonary:
- Pulmonary embolism
- Pulmonary artery thrombosis

Gastrointestinal:
- Budd-Chiari syndrome
- Oesophageal ischaemia
- Hepatic vein thrombosis
- Mesenteric ischaemia
- Pancreatic infarction
- Splenic infarction

Renal:
- Renal artery/vein thrombosis

Dermatological:
- Digital gangrene

Vascular‡:
- Arterial/Venous thrombosis (upper extremity)
- Arterial thrombosis (lower extremity)
- Deep vein thrombosis
- Jugular vein thrombosis
- Subclavian vein thrombosis
- Superficial venous thrombosis/thrombophlebitis

*Confirmed normal morphology.
†Absence of maternal anatomical/hormonal and maternal/paternal chromosomal abnormalities.
‡Any other vessel is at risk of developing thrombotic disease.
ENT, ear, nose and throat; WG, weeks of gestation.

Box 2 A comprehensive list of organ system-based, extra-criteria clinical manifestations of antiphospholipid syndrome

Extra-criteria clinical manifestations of the antiphospholipid syndrome.
Neurological:
- Acute encephalopathy
- Cerebellar ataxia
- Chorea
- Cognitive dysfunction (in the absence of cerebral thrombosis)
- Epilepsy and seizures
- Guillain-Barre syndrome
- Hemiballismus
- Migraine
- Multiple sclerosis-like lesions
- Sensorineural hearing loss
- Transverse myelitis

Cardiac:
- Angina
- Cardiac valve disease
- Valve thickening
- Valve dysfunction
- Cardiomyopathy

Obstetrical:
- Late pre-eclampsia
- Late premature birth
- Placental abruption
- 3 non-consecutive miscarriages
- 2 unexplained miscarriages
- ≥2 unexplained in vitro fertilisation failures

Pulmonary:
- Alveolitis with alveolar haemorrhage
- Fibrosing alveolitis
- Pulmonary hypertension

Renal:
- Glomerulonephritis:
  - Membranous
  - Proliferative
- Thrombotic microangiopathy

Dermatological:
- Livedo reticularis
- Livedo racemosa
- Pseudovasculitic lesions
- Skin ulceration and necrosis
- Splinter haemorrhages

Vascular:
- Accelerated atherosclerosis
- Arterial stenosis (renal, coeliac, cerebral and so on)

Haematological:
- Evans syndrome
- Haemolytic anaemia
- Thrombocytopaenia

Musculoskeletal:
- Arthralgia
- Arthritis
- Avascular necrosis of bone
- Bone marrow necrosis
- Non-traumatic fractures

assessment are not clearly elucidated yet. Many new antibodies have been proposed so far; antidomain I β2GPI (anti-β2GPI DI) and anticomplex phosphatidylserine-prothrombin (anti-PS/PT) are the two most promising to become clinically relevant aPL.[18] Moreover, while aPL positivity has always been critical to diagnose APS, a new entity—seronegative APS (SNAPS)—was introduced in 2003.[19] Patient candidates for the diagnosis of SNAPS show several clinical manifestations suggestive of APS, with persistently negative aCL, anti-β2GPI and LAC, but not for

Annexe 3 rituxan_prescribing.pdf [Internet].

Disponible sur: https://www.gene.com/download/pdf/rituxan_prescribing.pdf

Infections

In the pooled, placebo-controlled studies, 39% of patients in the RITUXAN group experienced an infection of any type compared to 34% of patients in the placebo group. The most common infections were nasopharyngitis, upper respiratory tract infections, urinary tract infections, bronchitis, and sinusitis.

The incidence of serious infections was 2% in the RITUXAN-treated patients and 1% in the placebo group.

In the experience with RITUXAN in 2578 RA patients, the rate of serious infections was 4.31 per 100 patient years. The most common serious infections (greater than or equal to 0.5%) were pneumonia or lower respiratory tract infections, cellulitis and urinary tract infections. Fatal serious infections included pneumonia, sepsis and colitis. Rates of serious infection remained stable in patients receiving subsequent courses. In 185 RITUXAN-treated RA patients with active disease, subsequent treatment with a biologic DMARD, the majority of which were TNF antagonists, did not appear to increase the rate of serious infection. Thirteen serious infections were observed in 186.1 patient years (6.99 per 100 patient years) prior to exposure and 10 were observed in 182.3 patient years (5.49 per 100 patient years) after exposure.

Annexe 4 rituxan_prescribing.pdf [Internet].

Disponible sur: https://www.gene.com/download/pdf/rituxan_prescribing.pdf

Incidence of All Adverse Reactions
Occurring in greater than or equal to 10% of RITUXAN-treated Patients with active GPA and MPA in the GPA/MPA Study 1 Up to Month 6*

Adverse Reaction	RITUXAN N=99 n (%)	Cyclophosphamide N=98 n (%)
Nausea	18 (18%)	20 (20%)
Diarrhea	17 (17%)	12 (12%)
Headache	17 (17%)	19 (19%)
Muscle spasms	17 (17%)	15 (15%)
Anemia	16 (16%)	20 (20%)
Peripheral edema	16 (16%)	6 (6%)
Insomnia	14 (14%)	12 (12%)
Arthralgia	13 (13%)	9 (9%)
Cough	13 (13%)	11 (11%)
Fatigue	13 (13%)	21 (21%)
Increased ALT	13 (13%)	15 (15%)
Hypertension	12 (12%)	5 (5%)
Epistaxis	11 (11%)	6 (6%)
Dyspnea	10 (10%)	11 (11%)
Leukopenia	10 (10%)	26 (27%)
Rash	10 (10%)	17 (17%)

*The study design allowed for crossover or treatment by best medical judgment, and 13 patients in each treatment group received a second therapy during the 6 month study period.

Infusion-Related Reactions

Infusion-related reactions in GPA/MPA Study 1 were defined as any adverse event occurring within 24 hours of an infusion and considered to be infusion-related by investigators. Among the 99 patients treated with RITUXAN, 12% experienced at least one infusion-related reaction, compared with 11% of the 98 patients in the cyclophosphamide group. Infusion-related reactions included cytokine release syndrome, flushing, throat irritation, and tremor. In the RITUXAN group, the proportion of patients experiencing an infusion-related reaction was 12%, 5%, 4%, and 1% following the first, second, third, and fourth infusions, respectively. Patients were pre-medicated with antihistamine and acetaminophen before each RITUXAN infusion and were on background oral corticosteroids which may have mitigated or masked an infusion-related reaction; however, there is insufficient evidence to determine whether premedication diminishes the frequency or severity of infusion-related reactions.

Conclusion

Notre étude, la première scoping review réalisée sur le traitement par Rituximab du SAPL apporte des arguments en faveur d'un bénéfice du traitement avec un profil de tolérance acceptable.

En raison du caractère rétrospectif et observationnel de notre étude, davantage d'études en particulier des essais contrôlés randomisés sont nécessaires pour confirmer ces résultats.

Plusieurs questions restent sans réponses, en particulier, le protocole thérapeutique à privilégier, la stratégie en cas d'échec thérapeutique et la nécessité d'une perfusion d'entretien

SERMENT

⌘⌖⌘⌖⌘

En présence des Maîtres de cette école, de mes chers condisciples et devant l'effigie d'Hippocrate, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la médecine. Je donnerai mes soins gratuits à l'indigent et n'exigerai jamais un salaire au-dessus de mon travail. Admis dans l'intérieur des maisons mes yeux ne verront pas ce qui s'y passe ; ma langue taira les secrets qui me seront confiés, et mon état ne servira pas à corrompre les mœurs ni à favoriser le crime. Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime si je suis fidèle à mes promesses ! Que je sois couvert d'opprobre et méprisé de mes confrères si j'y manque !

⌘⌖⌘⌖⌘

Résumé

INTRODUCTION : Il n'y a actuellement pas de traitement curatif pour les patients atteints de Syndrome des Anti-Phospholipides (SAPL). Le Rituximab est un anticorps monoclonal anti-CD20, dont la capacité à dépléter les lymphocytes B en fait un traitement potentiel du SAPL. Peu de données sont disponibles sur l'efficacité et la tolérance du Rituximab dans le traitement du SAPL.

OBJECTIF : Évaluer l'efficacité et la tolérance du Rituximab dans les manifestations classantes et non classantes du SAPL en dehors du Syndrome Catastrophique.

METHODES : Nous avons réalisé une revue de la littérature des données publiées sur les bases de données Pubmed et Medline; les patients âgés de 18 ans et plus, présentant un SAPL primaire ou secondaire à un Lupus Érythémateux Systémique, qui ont reçus du Rituximab pour manifestation classante ou non du SAPL ont été inclus dans notre étude. Les patients pédiatriques, ceux présentant un syndrome catastrophique des anti-phospholipides un cancer ainsi que les patients ne présentant pas de SAPL étaient exclus. La réponse clinique a été recueillie pour chaque manifestation du SAPL. Les données de suivi ont été recueillies à 6 mois et à 12 mois lorsqu'elles étaient disponibles. Une analyse descriptive des données des patients issus des articles a été réalisée.

RESULTATS : Des 89 articles identifiés, 28 ont été sélectionnés par chacun des deux investigateurs. Parmi les 121 patients inclus dans notre étude 97/121 patients (80%) ont reçus environ 2 g de Rituximab. A 6 mois, une réponse clinique globale favorable au traitement par Rituximab a été observée chez 91/117 patients (78%); dont 38/42 patients (90%) qui avaient une thrombose récidivante; 21/31 patients (68%) qui avaient des cytopénies auto-immunes; 10/12 patients (83%) avec une atteinte neurologique; 10/12 patients (83%) avec une atteinte cutanée; 7/10 patients (70%) avec une atteinte pulmonaire; 3/3 patients (100%) avec une atteinte rénale; 1/5 patients (20%) avec une atteinte cardiaque et 1/2 patients (50%) avec une atteinte obstétricale. A 12 mois, une réponse clinique favorable était maintenue chez 69/89 patients (78%) tandis que 4 patients (6%) étaient en rechute. Chez 92/103 patients (90%), au moins un anticorps anti-phospholipides restait positif à 6 mois du traitement par Rituximab. Vingt pour cent des patients ont présentés un effet secondaire grave ayant nécessité une hospitalisation, et 5 décès ont été rapportés.

CONCLUSION : Notre étude suggère un bénéfice global du Rituximab dans les différentes manifestations du SAPL avec un profil de tolérance acceptable. D'avantages d'études sont nécessaires pour confirmer nos résultats.

MOTS CLES : Syndrome des Anti-Phospholipides, Lupus Erythémateux Disséminé, Rituximab, Revue de Littérature