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Par

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TITRE

Indication d'une prophylaxie anti-pneumocystose chez les sujets ayant une anomalie vasculaire traitée par inhibiteurs de la voie PI3K/AKT/mTOR : enquête auprès d'experts et revue systématique de la littérature

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SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté,
de mes chers condisciples
et selon la tradition 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.

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TABLE DES MATIÈRES

I. INTRODUCTION GÉNÉRALE

Les anomalies vasculaires superficielles regroupent des entités nosologiques variées, dont certaines sont congénitales, chroniques, et à l'origine d'une morbidité importante. Selon la dernière classification de l'ISSVA (*International Society for the Study of Vascular Anomalies*), on les classe en « tumeurs vasculaires » ou « malformations vasculaires ». Depuis 2011, les inhibiteurs de la voie mTOR (*mammalian Target Of Rapamycin*), notamment le sirolimus (rapamycine), sont utilisés pour améliorer la symptomatologie ou les complications de certaines anomalies vasculaires complexes. Ils possèdent en effet des propriétés anti-angiogéniques et -lymphangiogéniques qui leur confèrent un intérêt dans leur prise en charge. Suite à la découverte de mutations génétiques somatiques activatrices du gène *PI3KCA* associées à certaines formes syndromiques de malformations vasculaires complexes (entités appartenant au spectre PROS [PIK3CA-Related Overgrowth Spectrum], les inhibiteurs de la PI3 kinase sont également de plus en plus utilisés.

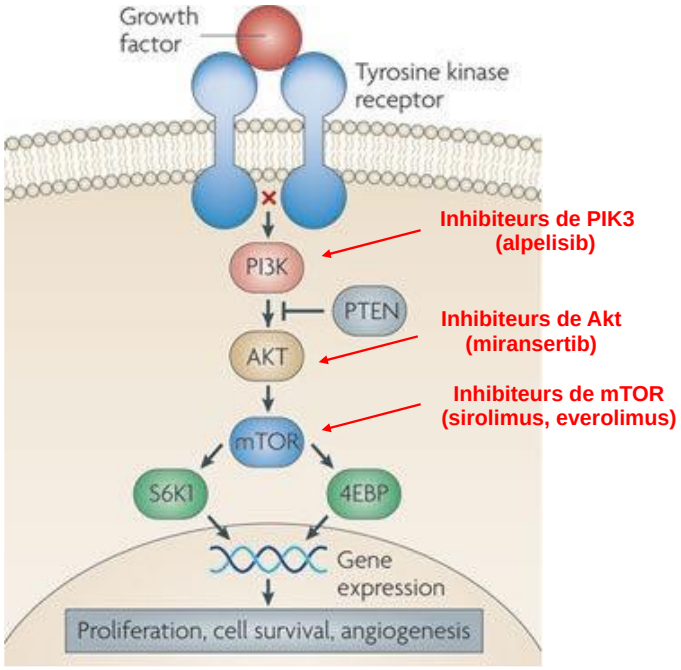
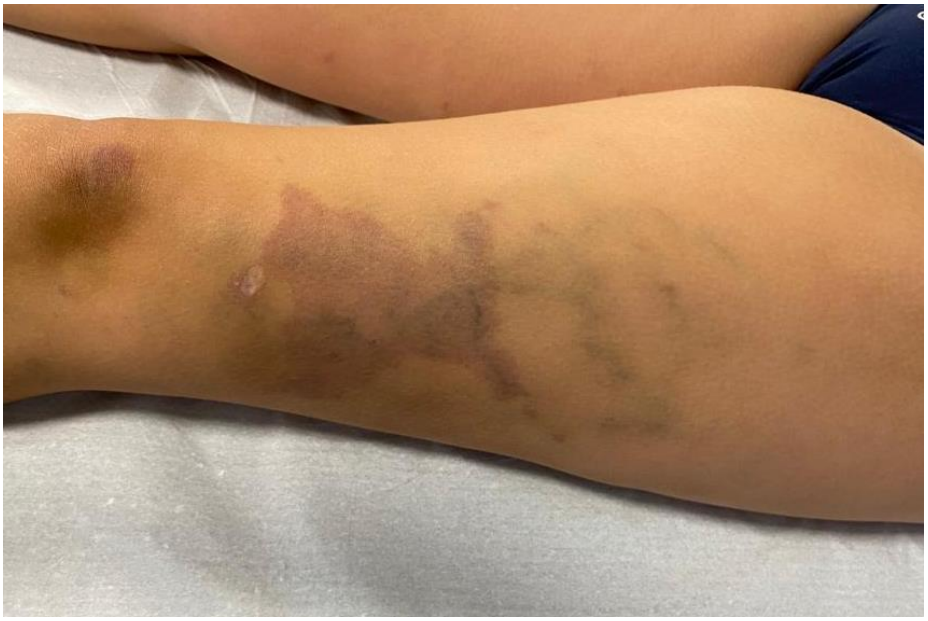
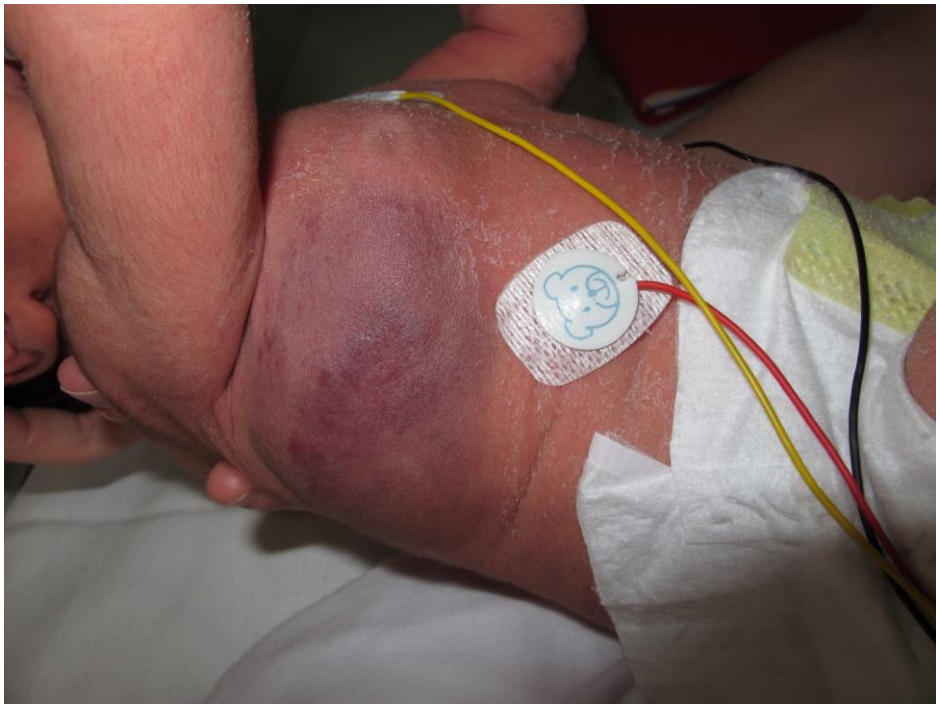


Schéma de la voie PIK3/Akt/mTOR

Le sirolimus est actuellement le plus prescrit d'entre les différentes molécules. Il a actuellement une autorisation de mise sur le marché pour prévenir le rejet de greffe chez les personnes ayant reçu une transplantation rénale. Dans le traitement des anomalies vasculaires, il est utilisé à des doses souvent proches de celles utilisées chez les patients transplantés. La particularité de son utilisation dans les anomalies vasculaires est son usage dans une population souvent pédiatrique, y compris en période néonatale, notamment pour traiter la coagulopathie du phénomène de Kasabach-Merritt compliquant certaines tumeurs vasculaires congénitales rares (hémangio-endothéliomes kaposiformes ou angiomes en touffes). Il a également un effet principalement suspensif sur les symptômes de certaines malformations vasculaires, notamment à composante lymphatique (saignements, suintements, douleurs), et est souvent initié pour une longue durée, de par le caractère chronique de ces affections.



Malformation vasculaire complexe (syndrome CLOVES) entrant dans le cadre du PROS



Hémangio-endothéliome kaposiforme compliqué de phénomène de Kasabach-Merritt

Pneumocystis jirovecii est un germe fongique opportuniste, touchant principalement les patients immunodéprimés : patients infectés par le VIH avec un taux de lymphocytes CD4+ < 200/mm^3. Les patients traités par immunosuppresseurs représentent également une population à risque. Par exemple, les patients transplantés, recevant plusieurs immunosuppresseurs, dont les inhibiteurs de mTOR reçoivent une prophylaxie anti-

pneumocystose. Celle-ci figure d'ailleurs dans le RCP (résumé des caractéristiques du produit) du sirolimus.

Il n'existe pas de données concernant la prévalence des pneumocystoses chez les patients présentant une anomalie vasculaire et recevant un traitement par un inhibiteur de la voie PI3K/AKT/mTOR, et pas de consensus ou de recommandations concernant la prescription d'un traitement prophylactique systématique.

L'objectif de ma thèse a donc été de mettre en évidence des données de prévalence d'infections à *Pneumocystis jirovecii* dans cette population, et d'identifier les arguments en faveur d'une prophylaxie systématique ou non. Le protocole, intitulé PROPHYLUS s'est articulé en 2 étapes.

La première a consisté en une revue systématique de la littérature, prenant en compte dans la recherche toutes les publications de patients ayant reçu un inhibiteur de la voie mTOR/PI3K/AKT pour une anomalie vasculaire, afin d'obtenir une prévalence de la pneumocystose d'après la littérature, et une estimation de la fréquence d'utilisation d'une prophylaxie. La seconde a consisté en la réalisation d'une enquête (sous la forme d'un questionnaire en langue anglaise, en ligne), que nous avons adressée, via les sociétés savantes (ISSVA, ESPD, SFDP), à un panel d'experts internationaux sur les anomalies vasculaires, concernant leurs habitudes et modalités de prescription vis-à-vis de ce risque infectieux.

Le protocole PROPHYLUS a reçu un financement de la filière FIMARAD (FIlière MAladies RAres en Dermatologie). Il est présenté sous la forme d'un article scientifique, qui sera soumis pour publication dans une revue anglophone.

II. RÉSUMÉ DU TRAVAIL EN FRANÇAIS

Indication d'un traitement prophylactique anti-pneumocystose chez les sujets ayant une anomalie vasculaire traitée par inhibiteurs de la voie PIK3/AKT/mTOR : enquête auprès d'experts et revue systématique de la littérature

Introduction

Les anomalies vasculaires (AV) sont de plus en plus souvent traitées par des inhibiteurs de la voie PI3K/AKT/mTOR afin d'améliorer les complications et de prévenir leur aggravation. Ces médicaments ont des propriétés immunosuppressives, et donc théoriquement surexposent les patients aux infections opportunistes, notamment à la pneumonie à *Pneumocystis jiroveci* (PJP). Il n'existe actuellement aucun consensus sur l'utilisation d'une prophylaxie anti-pneumocystose. L'objectif de cette étude a été d'étudier la prévalence de la PJP opportuniste chez les patients recevant des inhibiteurs de la voie PI3K/AKT/mTOR pour une VA, et de déterminer s'il y a une indication d'une prophylaxie de la pneumocystose dans cette population.

Méthodes

Cette étude a été menée en 2 parties : 1) enquête adressée à un panel d'experts internationaux des AVs, leur demandant leurs modalités d'utilisation des médicaments de prophylaxie de la pneumocystose ; 2) revue systématique de la littérature sur tous les cas publiés de patients recevant ces médicaments pour une AV, dans le but d'estimer la prévalence de la PJP dans cette population.

Résultats

Quatre-vingt médecins ont répondu à l'enquête, parmi lesquels 68 (85,0%) avaient déjà prescrit du sirolimus et ont été retenus dans l'analyse. A la question de savoir s'ils prescrivaient une prophylaxie de la PJP associée aux inhibiteurs de mTOR, 21 (30,9%) ont répondu toujours, 20 (29,4%) au cas par cas, 27 (39,7%) jamais.
Concernant la revue systématique, parmi les 3394 rapports examinés, 217 ont été inclus, concernant 1189 patients (1143 ayant reçu du sirolimus, 38 de l'everolimus, 4 de l'alpelisib, 4 du miransertib). Deux cas de PJP ont été signalés parmi les 1 189 cas (0,2 %), l'un recevant du sirolimus et l'autre de l'évérolimus. Aucun n'avait reçu de médicaments prophylactiques contre la PJP. Ainsi, la prévalence de la PJP a été calculée à 0,88 cas/1000 patients sous sirolimus, IC95 [-0,84;2,59] et 26,31 cas/1000 sous évérolimus, IC95 [-24,58;77,18]. Il n'y a pas eu de PJP sous alpelisib et miransertib. Une prophylaxie de la PJP a été administrée dans 218 cas (18,3 %), plus fréquemment chez les enfants (91,3 % vs 77,2 %, p=0,012), le plus souvent en utilisant le triméthoprime-sulfaméthoxazole (TMP-SMX) (186 patients, 85,3 %).

Conclusions et pertinence

Notre étude montre que, même si la PJP est un événement rare, elle peut survenir chez les patients atteints d'une AV traitée par un inhibiteur de mTOR. Elle ne permet pas d'émettre de recommandations, mais suggère qu'une prophylaxie par TMP-SMX devrait certainement être administrée à un sous-groupe de patients présentant des facteurs de risque plus élevés de PJP (patients très jeunes, ayant des comorbidités ou prenant d'autres immunosuppresseurs, recevant un inhibiteur de mTOR depuis très longtemps, ayant un taux de lymphocytes abaissé).

Mots-clés : Anomalies vasculaires ; Inhibiteurs de la voie PI3K/AKT/mTOR ; Malformations vasculaires ; Pneumocystis jirovecii pneumonia

III. RÉSUMÉ DU TRAVAIL EN ANGLAIS

Indication for a pneumocystis prophylaxis therapy in patients with vascular anomalies treated with PIK3/AKT/mTOR pathway inhibitors: experts' opinion and systematic review from the literature

Importance

Vascular anomalies (VAs) are increasingly being treated with PI3K/AKT/mTOR pathway inhibitors to prevent complications and disease worsening. These drugs have immunosuppressive properties and thus theoretically overexpose patients to opportunistic infections, especially *Pneumocystis jiroveci* pneumonia (PJP). PJP prophylaxis use lacks consensus.

Objectives

To investigate the prevalence of opportunistic PJP in patients receiving PI3K/AKT/mTOR inhibitors for VAs and determine any indication for pneumocystis prophylaxis in this population.

Methods

The study was conducted in 2 parts. First, we sent a survey to a panel of international experts of VAs asking about their use of pneumocystis prophylaxis drugs. Then, we performed a systematic review of the literature of all published cases of patients receiving these drugs for VA to estimate the prevalence of PJP in this population.

Results

Overall, 80 physicians answered the survey; 68 (85.0%) already prescribed sirolimus and were retained in the analysis. When asking whether experts added PJP prophylaxis when prescribing mTOR inhibitors, 21 (30.9%) answered always, 20 (29.4%) case by case, and 27 (39.7%) never. For the systematic review, among 3 053 reports screened, 217 were included (1 189 patients: 1143 received sirolimus, 38 everolimus, 4 alpelisib, 4 miransertib). Among the 1 189 cases, 2 (0.2%) of PJP were reported: one was treated with sirolimus and one everolimus. Thus, the prevalence of PJP was estimated at 0.88 cases/1000 patients under sirolimus (95% CI -0.84 to 2.59) and 26.31 cases/1000 under everolimus (95% CI -24.58 to 77.18). No patient with PJP received prophylaxis drugs. We found no PJP cases under alpelisib and miransertib. PJP prophylaxis was given in 218 (18.3%) cases, more frequently for children (91.3% vs 77.2% in the non-prophylaxis group, p=.012), mostly trimethoprim-sulfamethoxazole (TMP-SMX) (n=186 patients, 85.3%).

Conclusions and Relevance:

Our study shows that even if PJP is a rare event, it may occur in patients with VAs treated with an mTOR inhibitor. Although our results cannot allow for revising guidelines, prophylaxis with TMP-SMX might be appropriate for a subgroup of patients with risk factors for PJP.

Keywords: Vascular anomalies; PI3K/AKT/mTOR pathway inhibitors; Pneumocystis prophylaxis therapy; Vascular malformations; Pneumocystis jirovecii pneumonia.

IV. ARTICLE SCIENTIFIQUE

Indication for a pneumocystis prophylaxis therapy in patients with vascular anomalies treated with PIK3/AKT/mTOR pathway inhibitors: experts' opinion and systematic review from the literature

Short title: Sirolimus for vascular malformations and pneumocystis prophylaxis

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Drs Navarro and Tarik Zejli, Mrs Edée and Prof. Maruani selected and extracted data; Drs Jonville-Bera and Maurier searched pharmacovigilance databases; Prof. Maruani and Mrs Herchaoui designed the survey and disseminated it to experts; Mrs Allemang-Trivalle and Prof. Giraudeau performed statistical analyses. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Abbreviations:

CLOVES: congenital lipomatous (fatty) overgrowth, vascular malformations, epidermal nevi and scoliosis/skeletal/spinal anomalies

KMP: Kasabach-Merritt phenomenon

mTOR: mammalian target of rapamycin

PIK3: phosphoinositide-3-kinase

PIK3CA: phosphoinositide-3-kinase, catalytic subunit alpha

PJP: *Pneumocystis jirovecii* pneumonia

PROS: *PIK3CA*-related overgrowth spectrum

TMP-SMX: trimethoprim-sulfamethoxazole

VAs: vascular anomalies

VMs: vascular malformations

Abstract

Vascular anomalies (VAs) are increasingly being treated with PI3K/AKT/mTOR pathway inhibitors to prevent complications and disease worsening. These drugs have immunosuppressive properties and thus theoretically overexpose patients to opportunistic infections, especially *Pneumocystis jiroveci* pneumonia (PJP). PJP prophylaxis use lacks consensus. The objective of the study was to investigate the prevalence of opportunistic PJP in patients receiving PI3K/AKT/mTOR inhibitors for VAs and determine any indication for pneumocystis prophylaxis in this population.

It was conducted in 2 parts. First, we sent a survey to a panel of international experts of VAs asking about their use of pneumocystis prophylaxis drugs. Then, we performed a systematic review of the literature of all published cases of patients receiving these drugs for VA to estimate the prevalence of PJP in this population.

Overall, 80 physicians answered the survey; 68 (85.0%) already prescribed sirolimus and were retained in the analysis. When asking whether experts added PJP prophylaxis when prescribing mTOR inhibitors, 21 (30.9%) answered always, 20 (29.4%) case by case, and 27 (39.7%) never. For the systematic review, among 3 053 reports screened, 217 were included (1 189 patients: 1143 received sirolimus, 38 everolimus, 4 alpelisib, 4 miransertib). Among the 1 189 cases, 2 (0.2%) of PJP were reported: one was treated with sirolimus and one everolimus. Thus, the prevalence of PJP was estimated at 0.88 cases/1000 patients under sirolimus (95% CI -0.84 to 2.59) and 26.31 cases/1000 under everolimus (95% CI -24.58 to 77.18). No patient with PJP received prophylaxis drugs. We found no PJP cases under alpelisib and miransertib. PJP prophylaxis was given in 218 (18.3%) cases, more frequently for children (91.3% vs 77.2% in the non-prophylaxis group, p=.012), mostly trimethoprim-sulfamethoxazole (n=186 patients, 85.3%).

Our study shows that even if PJP is a rare event, it may occur in patients with VAs treated with an mTOR inhibitor. Although our results cannot allow for revising guidelines, prophylaxis with trimethoprim-sulfamethoxazole might be appropriate for a subgroup of patients with risk factors for PJP.

Introduction

Vascular anomalies (VAs) are classified according to the International Society for the Study of Vascular Anomalies (ISSVA) as vascular tumors and vascular malformations (VMs).[1] VMs are chronic conditions that are congenital or acquired and might involve one or several types of vessels. High-flow VMs include arteriovenous VMs and fistulae, and slow-flow VMs are capillary malformations, lymphatic VMs, venous VMs, and combinations of these. For some VMs, somatic activating mutations of genes were evidenced, especially *PIK3CA*, and these entities belong to the spectrum of *PIK3CA*-related overgrowth syndrome (PROS).[2,3] These are chronic conditions that cause morbidity and mortality and require a multidisciplinary approach.[4]

Mammalian target of rapamycin (mTOR) inhibitors[5-8] and specific inhibitors of phosphoinositide-3-kinase (PI3K)[9,10] are increasingly being used to improve symptoms or prevent complications of certain complex VAs, in particular vascular tumors complicated by Kasabach-Merritt phenomenon (KMP), and VMs complicated by pain, functional impairment, oozing or bleeding. Sirolimus is the most widely used inhibitor. It directly inhibits mTOR, which is regulated by PI3K, and has anti-angiogenic and -lymphangiogenic properties that make it useful for treating these VAs,[11] especially those with a lymphatic component. It also has other properties, notably immunosuppression.[12] This drug is currently EU- and US-FDA-approved for preventing transplant rejection in organ transplant patients,[13] and also in sporadic lymphangioleiomyomatosis with lung involvement, which is a rare condition.

The most common reported adverse events with sirolimus and other mTOR inhibitors are mucositis/mouth ulcers, asthenia, gastrointestinal disorders, headache, hypercholesterolemia/hypertriglyceridemia, hyperglycemia, hematologic abnormalities (including lymphopenia), and various infections (including opportunistic ones).[5-7,14] In VAs, sirolimus is used at heterogeneous doses but generally close to those used in patients undergoing transplantation, with a target residual concentration of 4 to 12 μg/ml. It is used in both adult and pediatric populations, including in the neonatal period, and for a long duration because of

the chronic condition.[8,15]

Pneumocystis jirovecii is a fungus that can colonize healthy people, but the prevalence of colonization among patients with chronic pulmonary conditions, without clinical manifestations, is high.[16,17] *P. jirovecii* pneumonia (PJP) usually occurs in immunocompromised individuals and is a potentially life-threatening infection. It is predominantly seen in HIV-infected patients with T-helper cell count (CD4) < 200 cells/mm^3.[18-20] Trimethoprim-sulfamethoxazole (TMP-SMX) is the first-line drug for treatment and prophylaxis.[21] Immunocompromised HIV-negative patients are increasingly identified as being at risk for PJP.[19,22] In this population, PJP typically presents fulminant respiratory failure associated with fever and dry cough. Immunosuppressive therapies and associated defective cellular immunity are among the main contributing risk factors, such as for organ transplant patients receiving mTOR inhibitors.[22] With the advent of prophylaxis, the incidence of PJP has decreased greatly in these patients.[23] Therefore, this rare adverse event is currently described in the package insert of mTOR inhibitors.

To our knowledge, there are no data on the prevalence of PJP in patients with VAs treated with PI3K/AKT/mTOR inhibitors and no consensus on practices regarding the concomitant prescription of preventive treatment for PJP. PJP events have been very rarely reported to pharmacovigilance authorities, as only 3 cases are recorded in the WHO's global ICSR (Individual Case Safety Reports) database, VigiBase®, in patients treated with Pi3K/AKT/mTOR for VMs, all 3 with sirolimus.[24] However, PJP in this population might be largely under-reported.

The aim of this study was to investigate the prevalence of opportunistic pneumocystis infection in patients receiving PI3K/AKT/mTOR inhibitors for VAs and determine any indication for pneumocystis prophylaxis in this population.

Methods

This study was conducted in 2 parts: 1) a survey of a panel of international experts of VAs about mTOR/PI3K inhibitors, risks for PJP and how they use pneumocystis prophylaxis drugs and 2) a systematic review of the literature of all published cases of patients receiving these drugs for a VA to estimate the prevalence of PJP in this population.

Part 1 - Survey of international experts of VAs

Experts were contacted via scientific societies such as the ISSVA, European Society for Pediatric Dermatology (ESPD), *Societé Française de Dermatologie Pédiatrique* (SFDP), and *FIlière MAladie RAres en Dermatologie* (FIMARAD). In May-June 2022, experts were sent a questionnaire via a Sphinx ONLINE 4.26 link. The questionnaire contained 72 items that asked about characteristics of responders, their activities regarding VAs and their prescription of mTOR/PI3K inhibitors, and pneumocystis prophylaxis (if they added it when prescribing mTOR or PI3K inhibitors, for which cases and which drugs) and finally whether they already had a case of PJP and to provide a description.

Part 2 - Systematic review

Searching

This review was conducted according to the Cochrane Collaboration statement for systematic reviews. The databases MEDLINE (PubMed), Embase and CENTRAL (Cochrane) were searched on April 2021 to screen articles from January 2011 until March 2021. The search equations included “mTOR inhibitors”, “sirolimus”, “rapamycin”, “alpelisib”, “everolimus” AND “vascular anomalies”, “venous malformation”, “lymphatic malformation”, “PROS”, “CLOVES”, “Klippel-Trenaunay”, “Sturge-Weber”, “Kasabach-Merritt”. Also, we used equations combining the keywords for treatment and those for pneumocystis with “Pneumocystis” and “Pneumocystis jiroveci pneumonia”.

Selection of articles

Two authors (M.N., T.Z.) independently selected articles, first on titles and abstracts then on full texts. Eligibility criteria were all original reports of prospective or retrospective studies and case reports describing patients receiving an PI3K/AKT/mTOR inhibitor for VAs in any age

group. Exclusion criteria were non-original articles (general reviews etc.), studies of animals or *in vitro* studies, studies of other immunosuppressive treatments or other conditions, and reports with too few data to analyze.

Data extraction

Two authors (M.N., A.E.) independently extracted data from included studies. Disagreements were resolved with a third author (A.M.) when necessary. The following data were collected: data on the article and the study or case; data on subjects of the reports, the VA and treatment; laboratory results, especially lymphocyte count; duration of treatment; occurrence of severe adverse events, including PJP and death; and administration of PJP prophylaxis.

Data analysis

For descriptive analysis, categorical variables are expressed with number (percentage) and quantitative variables with mean ± standard deviation (SD) or median (interquartile range [IQR]). For comparing groups, chi-squared or Fisher exact tests were used. $P < .05$ was considered statistically significant. Prevalence of PJP was calculated with 95% confidence intervals (CIs). We used R 4.2.0 for analysis.

Results

Part 1 - Survey of international experts of VAs

In total, On the > 300 physicians that received the link, 80 answered the survey; 68 (85.0%) prescribed sirolimus and were retained in the analysis (**Supplemental File 1: survey answers**). Overall, 45/68 (66.2%) were women, and the most represented age range was 36 to 45 years (n=24, 35.3%); 28 (41.2%) were dermatologists, 20 (29.4%) onco-hematologists, 7 (10.3%) pediatricians and the others surgeons, geneticists or others. They came from 15 different countries, mainly Europe (n=41, 60.3%) and North America (n=24, 35.3%). Most (n=42, 61.8%) cared for both children and adults and were involved in multidisciplinary consultations (n=63, 92.6%). In all, 22 (32.4%) physicians cared for 26 to 50 patients with complex VAs (most represented range) in the past year. All already prescribed sirolimus, 10 (14.7%) everolimus, and 33 (48.5%) alpelisib. Most (n=63, 92.6%) reported that they asked for

laboratory results before initiating mTOR inhibitors, and almost all (n=67) monitored mTOR inhibitors by dosing sirolimus residual concentrations (with a target concentration of 3 to 15 ng/ml for all but one), and 58 (86.6%) monitored lymphocyte counts.

When asked if they added prophylactic treatment for pneumocystis when prescribing mTOR inhibitors, 21 (30.9%) answered always, 20 (29.4%) on a case-by-case basis, and 27 (39.7%) never; with alpelisib, 27/36 (75.0%) answered never, 4 always and 5 on a case-by-case basis.

For the 41 who already prescribed prophylactic drugs, all used TMP-SMX and 5 (12.2%) sometimes alternatively used pentamidine. Identified factors that could influence prescription of prophylaxis were age of the patient (n=12), comorbidities of the patient (n=6), and lymphopenia or neutropenia < 1000 cells/mm^3 (n=3). The type of VA and duration of mTOR inhibitor treatment did not influence the prescription.

Only 1/55 (1.8%) experts mentioned that he already had one case of VA treated with an mTOR inhibitor that was complicated by PJP. The case was a < 2-year-old infant with another comorbidity who received sirolimus for 1 to 3 months before the pneumocystis infection. The lymphocyte count was normal. The child recovered after treatment for PJP and withdrawal of sirolimus.

Part 2 - Systematic review

Among 3 994 publications screened, 217 (1 189 patients) were included in the final analysis (Figure 1): 163 (75.1%) case reports, 33 (15.2%) retrospective studies, and 21 (9.7%) prospective studies.

*Characteristics of patients (**Table 1**)*

The median age of patients was 6.5 years (IQR 2 to 11; mean age 9.2 ± 10.0 years), and 369 (31.0%) were children; 554 (46.6%) were females. Among the 1 189 patients, 1 181 (99.3%) received an mTOR inhibitor (1 143 [96.1%] sirolimus and 38 [3.2%] everolimus), 4 (0.3%) a PI3K inhibitor (alpelisib) and 4 (0.3%) an Akt1 inhibitor (miransertib). Thirteen different types of VAs were represented, the most frequent being cystic lymphatic malformations (n=343, 28.9%) and tumors complicated by KMP (n=278, 23.4%).

In the population using sirolimus, the mean dose was 2.1 ± 1.2 mg/day (range: 1 to 5) or 1.6 ± 0.4 mg/m^2. The mean dose of everolimus used was 3.3 ± 1.4 mg/day. Among the 1 143 patients receiving sirolimus, 152 (13.3%) also took systemic corticosteroids. No other concomitant immunosuppressive treatment was given.

Treatment and prophylaxis

Among all participants, 218 (18.3%) received pneumocystis prophylaxis, essentially TMP-SMX in 186 (85.3%) and pentamidine in 2 (0.9%); the drug used was not mentioned in the remaining 30 cases. No prophylaxis was given in 951 (80.0%) cases.

Pneumocystis infection

Among the 1 189 cases, 2 (0.2%) cases of PJP were reported, one receiving sirolimus and one everolimus. Thus, the calculated prevalence of PJP for patients with VAs treated with sirolimus was 1*100/1143 = 0.088% (i.e., 0.88 cases/1000 patients under treatment, 95% CI -0.84 to 2.59) and under everolimus was 1*100/38 = 2.631% (i.e., 26.31 cases/1000 patients under treatment, 95% CI -24.58 to 77.18).

None of the 2 cases had PJP prophylaxis. The first was a 63-year-old woman who received everolimus (2.5 mg/day escalated to 10 mg/day) for lymphangioleiomyomatosis. Pulmonary infection due to *P. jirovecii* occurred after 309 days of treatment (dosage 10 mg/day). She had CD4+ lymphopenia. The infection was treated successfully with oxygen and antimicrobiotic treatment.[25]

The second case was a 4-month-old boy with kaposiform hemangioendothelioma complicated by KMP that was treated successively with prednisolone 2 mg/kg/day, propranolol and 3 courses of vincristine (0.025 mg/kg/week) at age 2 months; propranolol and vincristine were discontinued and sirolimus 0.05 mg/kg twice a day was started at age 3 months (target 8 to 15 ng/ml), with tapering of corticosteroids. PJP developed after 4 weeks. At this time, sirolimus concentration was 16.2 ng/ml and prednisolone nearly ended. The absolute lymphocyte blood count was normal. The boy was hospitalized in a critical care unit; received TMP-SMX for 3 weeks as well as methylprednisolone, vancomycin, cefepime and azithromycin; and received extracorporeal membrane oxygenation for 7 days. He was discharged on day 32. Sirolimus was

re-introduced 3 weeks later, with prophylactic TMP-SMX for 3 days/week.[26]

Cases of death

Overall, 14 (1.2%) deaths were reported in patients receiving treatment for VAs. All patients received sirolimus (**Table 2**). Thus, the prevalence of death under sirolimus was 14*100/1143=1.23% (95% CI 0.59 to 1.87).

Comparison of groups with and without PJP prophylaxis

There was no case of PJP in the prophylaxis group. The proportion of children was significantly higher in the prophylaxis than non-prophylaxis group (91.3% vs 77.2%, p=.012), and patients with than without prophylaxis more often had a cystic lymphatic malformation (70.2% vs 19.6%; p<.001). All patients in the prophylaxis group received sirolimus (100% vs 95.2%, p=.002).

Discussion

PJP may occur in patients with VAs treated with an mTOR inhibitor but is rare. The prevalence of PJP with everolimus was 26.3 cases/1000 patients and with sirolimus 0.9 cases/1000 patients, but everolimus was much less used in VAs than sirolimus. All patients with PJP did not receive prophylaxis drugs. No cases of PJP infections were reported with alpelisib and miransertib, but the reports of patients receiving these molecules were low. Experts gave heterogeneous answers regarding the prescription of PJP prophylaxis associated with mTOR inhibitors, but with alpelisib, most did not prescribe PJP prophylaxis. In the 217 reports from the literature, 218 (18.3%) patients received PJP prophylaxis, especially children and patients with co-morbidities. We found 14 deaths linked to other infections or the diseases, all with sirolimus treatment.

Although mTOR inhibitors are used with moderate dosage in VAs, the PJP risk exists. According to the literature, the main risk factor for PJP in HIV-infected patients is a CD4+ lymphocyte count <200 cells/mm^3, which is an indication to start prophylaxis.[20,27] However, several authors have indicated that CD4+ cell count cannot be the only criteria for giving PJP prophylaxis. For example, Baulier et al. reported that half of their patients with PJP and an auto-immune/inflammatory disease had a CD4+ cell count > 200 cells/mm^3, although the CD4+ cell

count was significantly lower in patients with HIV than other patients (average 19 cells/mm^3).[28] After solid organ transplantation, the early infection incidence decreases due to effective prophylaxis, but late infections still occur.[18,29,30] Recently, a case–control study showed that PJP occurred at a median of 3 years after solid organ transplantation, and independent risk factors associated with PJP were low total lymphocyte count 1 year before PJP, mTOR inhibitors used as chronic maintenance immunosuppressive drugs, and corticosteroid bolus administration. A total lymphocyte count threshold <1000/µL also showed good predictive value for PJP occurrence.[31] However, patients with VAs in our systematic review were much younger on average than those in studies of solid organ transplantation and usually had no additional immunosuppressive therapy, except for several children with KMP who received corticosteroids boluses.

According to the experts questioned and the systematic review, the main pneumocystis prophylaxis drug used was TMP-SMX. In the non-HIV population (solid organ transplantation and hematologic cancers), guidelines consider it as first-line treatment; second lines include pentamidine, dapsone, or atovaquone.[32,33] In this population, a meta-analysis of 12 randomized trials showed that TMP-SMX allowed for a 91% reduction in the occurrence of PJP. Treatment was well tolerated in children but was withdrawn in 3.1% of adults because of adverse events.[33] Indeed, the benefit/risk balance of introducing TMP-SMX must be carefully considered because this drug might be responsible for toxic epidermal necrolysis syndrome.[34]

Our study is the first to investigate the risk of PJP and the interest of PJP prophylaxis in patients with VAs treated with PI3K/AKT/mTOR inhibitors. It has some limitations due to publication bias: not all cases of VAs that were treated and in whom PJP developed were published, which leads to probably undererestimating the prevalence of PJP in this population. Also, we found a lot of missing data in the reports, and very few data were available for alpelisib and miransertib, because they are more recently used. Finally, 218 patients had prophylaxis for PJP, but samples were not large enough to calculate the number needed to treat to avoid PJP.

In conclusion, although the results of our survey and systematic review cannot allow for revising guidelines on PJP prophylaxis in people with VAs treated with mTOR inhibitors,

alpelisib or miransertib, they do suggest that prophylaxis with TMP-SMX might be appropriate for a subgroup of patients with risk factors for PJP: patients with chronic lymphocyte count < 1000 cells/mm^3, long-term treatment with mTOR inhibitors, or association with other immunosuppressive drugs, including systematic corticosteroids. We currently lack data from registries and expert guidelines on this issue.

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Tables

Table 1. Characteristics of patients included in the systematic review.

Characteristics	Total N=1 189	Missing or unclear data
Sex, n (%)		114 (9.6)
Female	554 (46.6)	
Male	521 (43.8)	
Age (year)		728 (61.2)
Mean ± SD	9.2 ± 10.0	
Median [interquartile range], years	6.5 [2 to 11]	
Vascular anomaly types, n (%)		102 (8.6)
Cystic lymphatic malformation	343 (28.9)	
KHE/Tufted angioma/KMP	278 (23.4)	
Lymphangiomatosis (KLA/GSD/LLM)	174 (14.6)	
Venous malformation	96 (8.1)	
PIK3CA-related overgrowth spectrum	94 (7.9)	
Combined vascular anomaly	46 (3.9)	
Arteriovenous malformation	25 (2.1)	
PTEN-linked syndrome	15 (1.3)	
Sturge-Weber syndrome	8 (0.7)	
Complicated infantile hemangioma	5 (0.4)	
MLT	3 (0.3)	
Fibro-adipose vascular anomaly	2 (0.2)	
Lymphedema	2 (0.2)	
Treatment used for the vascular anomaly, n (%)		0
Sirolimus	1143 (96.1)	
Everolimus	38 (3.2)	
Alpelisib	4 (0.3)	
Miransertib	4 (0.3)	
Prophylaxis drugs, n (%)		20 (1.7)
Yes	218 (18.3)	
No	951 (80.0)	

KHE: kaposiform hemangioendothelioma; KMP: Kasabach-Merritt phenomenon; KLA: kaposiform lymphangiomatosis; GSD: Gorham Stout disease; LLM: lymphangioleiomatosis; PIK3CA: phosphoinositide-3-kinase, catalytic subunit alpha; PTEN: phosphatase and TENsin homolog; MLT: multifocal lymphangioendotheliomatosis with thrombopenia

Table 2. Characteristics of the 14 patients in the literature who received an mTOR inhibitor for vascular anomalies and who died.

Authors (year)	Sex	Age of death	Vascular condition	Site involved	Sirolimus dosage (blood level)	Sirolimus duration before adverse event	Comorbidities/ history/ concomitant treatment	Antibiotic prophylaxis	Cause of the death	Relation to treatment
Rössler et al. (2021)	NR	3 m	Microcystic LM	Face	0.8 mg/m²/d (6.9 ng/ml)	2 m	NR	None	Pulmonary infection metapneumovirus	🔴
Rössler et al. (2021)	NR	28 m	GLA	Diffuse (lung, bowel, spleen)	0.4 mg/m²/d (8 ng/ml)	24 m	History of pneumococcal infection	Penicillin daily	Acute ileus accompanied by adenovirus respiratory infection	🔴
Brill et al. (2021)	NR	8 d	KHE/ KMP	NR	NR	6 d	Embolization before sirolimus	NR	Complications of the vascular condition (heart failure)	🟢
Brill et al. (2021)	NR	11.5 m	KHE/ KMP	NR	NR	NR	Embolization before sirolimus	NR	Complications of the vascular condition	🟢
Wang et al. (2020)	M	Almost 4 m	KHE/ KMP	Neck	1.4 mg/m²/d	15 d	Methylprednisolone then prednisone 40 mg/d	NR	Fungal pulmonary infection	🔴
Alomar et al. (2020)	M	Almost 15 m	CLOVES	Right abdomen and right lower limb	2.2 mg/m²/d	5 m	History of recurrent infections in early childhood	None	Undetermined cause (acute fever)	🔴
Piacitelli et al. (2018)	M	62 d	PROS	Pelvis and lower limb, gastroenteral bleeding and brain anomalies	0.2 mg/m²/dose	15 d	History of recurrent neonatal *Escherichia coli* infection	None	*Escherichia coli* pulmonary infection, ascites, multiorgan failure	🟡
Ying et al. (2018)	F	3,5 m	KHE/ PKM	Face	0.1 mg/kg/d	2 m + 10 d	None	None	Sepsis including diarrhea and pneumonia	🔴
Ying et al. (2018)	M	5 m	KHE/ KMP	Left forearm	0.1 mg/kg/d	1 m + 10 d	Prednisone 3 mg/kg/d then methylprednisolone 2 mg/kg/d and propranolol	None	*Pneumonia mycoplasma* pneumonia	🔴
Czechowicz et al. (2017)	M	9 d	KHE/ KMP	Lateral chest	0.8 mg/m²/12 hr (15 ng/ml)	3 d	Embolization prior to sirolimus Methylprednisolone	None	Complication of the disease (cerebral hemorrhage)	🟢
Hutchins et al. (2017)	F	40 m	DNH	Skin, liver, spleen, lungs	0.8 mg/m²/12 hr	2 m	Propranolol, prednisone, sildenafil	None	Hypoglycemia after catheterization	🟢
Triana et al. (2017)	M	NR	KLA	Thorax	0.8 mg/m²/12 hr	NR	NR	NR	Complication of the disease (respiratory failure due to bilateral chylothorax)	🟢
Adams et al. (2016)	F	NR	CVLM	NR	0.8 mg/m²/12 hr (10-12 initially then < 2)	> 12 m	History of recurrent cellulitis	None	Sepsis	🔴
Situma et al. (2012)	M	10 y	Gorham's disease	Pelvis and L3-L5 vertebral bodies	NR	4 w	Sclerotherapy using bleomycin prior to sirolimus	NR	Complication of the disease (respiratory failure due to right sided chylothorax)	🟢

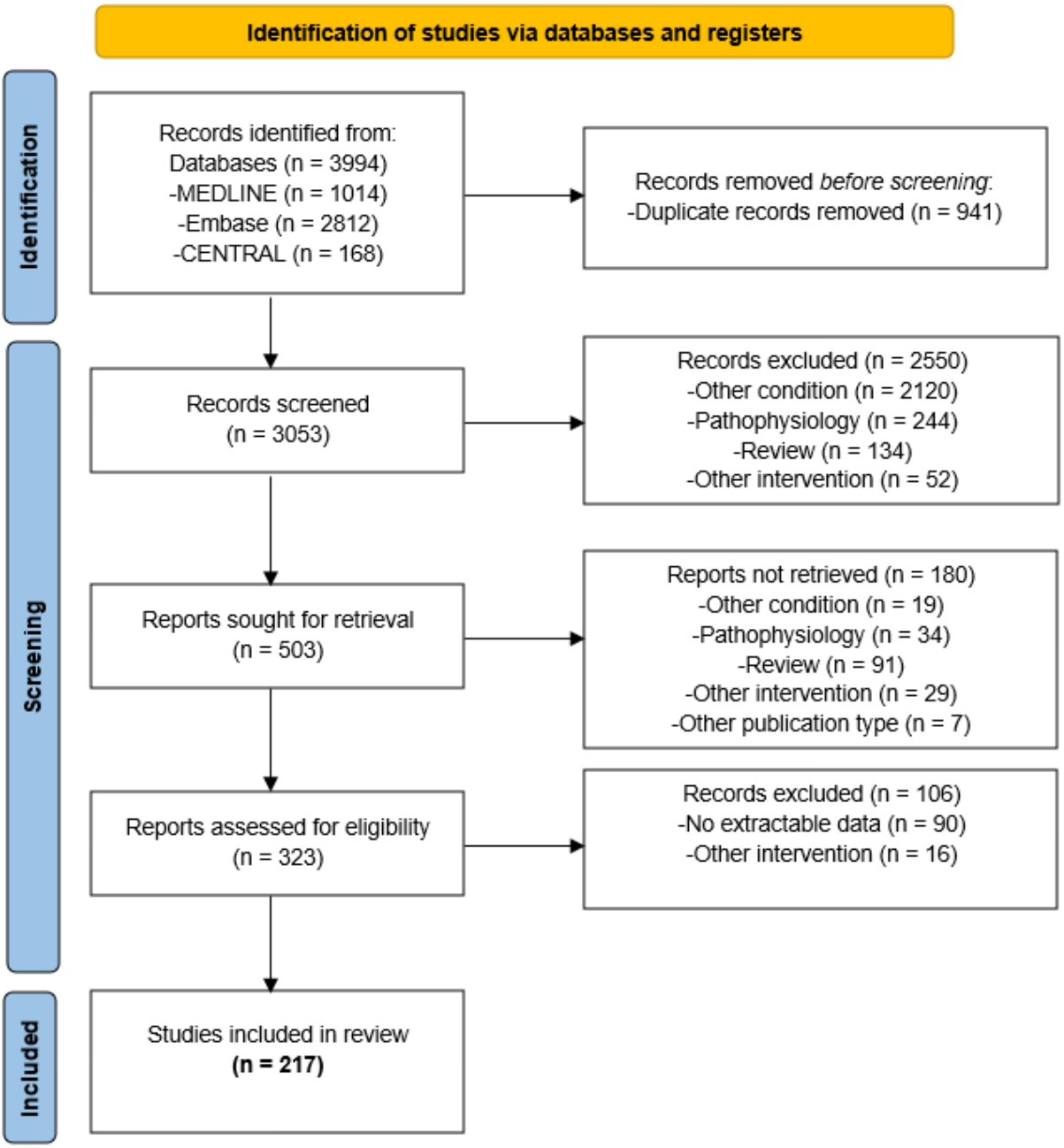
M: male; F: female; d: days; m: months; y: years; w: weeks; NR: not reported

CLOVES: congenital lipomatous overgrowth, vascular malformation, epidermal nævi, spinal/skeletal anomalies/scoliosis; CLVM: capillaro-lymphatic-venous malformation; DNH: diffuse neonatal hemangiomatosis; GLA: generalized lymphatic anomaly; KHE: kaposiform hemangio-endothelioma; KLA: kaposiform lymphangiomatosis; KMP: Kasabach-Merritt phenomenon; LM: lymphatic malformation; PROS: PIK3CA-related overgrowth spectrum

🟢 : *Not related to sirolimus* 🔴 : *Possibly related to sirolimus* 🟡 : *Uncertain*

Figure legends

Figure 1. Flow chart of included reports



Supplemental File 1. Detailed answers from the survey

Are you a specialist of vascular anomalies management AND have you already prescribed sirolimus for vascular anomalies?

	N	% Obs.
Yes	68	85%
No	12	15%
Total	**80**	**100%**

Your sex

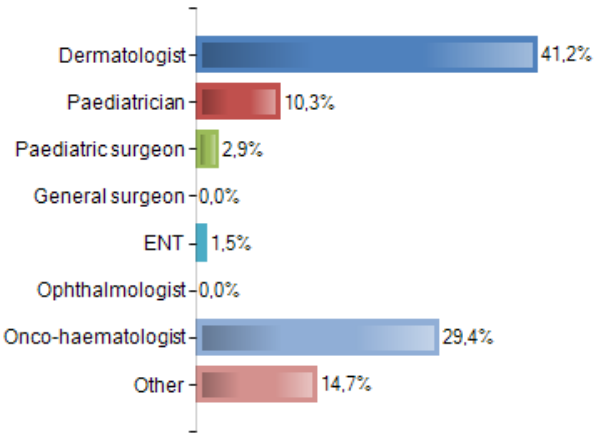
	N	% Obs.
Male	23	33.8%
Female	45	66.2%
No definite sex	0	0%
Total	**68**	**100%**

What is your age range?

	N	% Obs.
25-35 years	11	16.2%
36-45 years	24	35.3%
46-55 years	14	20.6%
56-65 years	19	27.9%
> 65 years	0	0%
Total	**68**	**100%**

What is your speciality?

	N	% Obs.
Dermatologist	28	41.2%
Pediatrician	7	10.3%
Pediatric surgeon	2	2.9%
General surgeon	0	0%
ENT	1	1.5%
Ophthalmologist	0	0%
Onco-hematologist	20	29.4%
Other	10	14.7%
Total	**68**	**100%**



Do you care for?

	N	% Obs.
Children and adults	42	61.8%
Children only	25	36.8%
Adults only	1	1.5%
Total	**68**	**100%**

In which country do you work?

	N	% Obs.
England	0	0%
Afghanistan	0	0%
Albania	0	0%
Algeria	1	1.5%
Andorra	0	0%
Antigua and Barbuda	0	0%
Argentina	0	0%
Armenia	0	0%
Australia	1	1.5%
Austria	0	0%
Azerbaijan	0	0%
Bahamas	0	0%
Bahrain	0	0%
Bangladesh	0	0%
Barbados	0	0%
Belarus	0	0%
Belgium	0	0%
Belize	0	0%
Benin	0	0%
Bhutan	0	0%
Bolivia	0	0%
Bosnia and Herzegovina	0	0%
Botswana	0	0%
Brazil	0	0%
Brunei	0	0%
Bulgaria	0	0%
Burkina Faso	0	0%
Burundi	0	0%
Côte d'Ivoire	0	0%
Cabo Verde	0	0%
Cambodia	0	0%
Cameroon	0	0%
Canada	1	1.5%
Central African Republic	0	0%
Chad	0	0%
Chile	0	0%
China	0	0%
Colombia	0	0%
Comoros	0	0%

Congo (Congo-Brazzaville)	0	0%
Costa Rica	0	0%
Croatia	0	0%
Cuba	0	0%
Cyprus	0	0%
Czechia (Czech Republic)	1	1.5%
Democratic Republic of the Congo	0	0%
Denmark	0	0%
Djibouti	0	0%
Dominica	0	0%
Dominican Republic	0	0%
Ecuador	0	0%
Egypt	0	0%
El Salvador	0	0%
Equatorial Guinea	0	0%
Eritrea	0	0%
Estonia	0	0%
Eswatini (fmr. "Swaziland")	0	0%
Ethiopia	0	0%
Fiji	0	0%
Finland	0	0%
France	28	41.2%
Gabon	0	0%
Gambia	0	0%
Georgia	0	0%
Germany	2	2.9%
Ghana	0	0%
Greece	1	1.5%
Grenada	0	0%
Guatemala	0	0%
Guinea	0	0%
Guinea-Bissau	0	0%
Guyana	0	0%
Haiti	0	0%
Holy See	0	0%
Honduras	0	0%
Hungary	0	0%
Iceland	0	0%
India	0	0%
Indonesia	0	0%
Iran	0	0%
Iraq	0	0%
Ireland	0	0%
Israel	1	1.5%
Italy	1	1.5%
Jamaica	0	0%
Japan	0	0%
Jordan	0	0%
Kazakhstan	0	0%
Kenya	0	0%

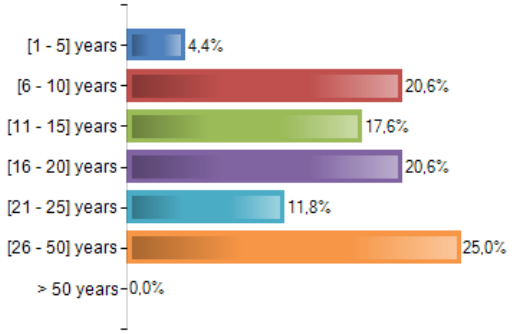
Kiribati	0	0%
Kuwait	0	0%
Kyrgyzstan	0	0%
Laos	0	0%
Latvia	0	0%
Lebanon	0	0%
Lesotho	0	0%
Libya	0	0%
Liechtenstein	0	0%
Lithuania	0	0%
Luxembourg	0	0%
Madagascar	0	0%
Malawi	0	0%
Malaysia	0	0%
Maldives	0	0%
Mali	0	0%
Malta	0	0%
Marshall Islands	0	0%
Mauritania	0	0%
Mauritius	0	0%
Mexico	0	0%
Micronesia	0	0%
Moldova	0	0%
Monaco	0	0%
Mongolia	0	0%
Montenegro	0	0%
Morocco	0	0%
Mozambique	0	0%
Myanmar (formerly Burma)	0	0%
Namibia	0	0%
Nauru	0	0%
Nepal	0	0%
Netherlands	0	0%
New Zealand	0	0%
Nicaragua	0	0%
Niger	0	0%
Nigeria	0	0%
North Korea	0	0%
North Macedonia	0	0%
Norway	0	0%
Oman	0	0%
Pakistan	0	0%
Palau	0	0%
Palestine State	0	0%
Panama	0	0%
Papua New Guinea	0	0%
Peru	0	0%
Paraguay	0	0%
Philippines	0	0%
Poland	0	0%

Portugal	0	0%
Qatar	0	0%
Romania	0	0%
Russia	1	1.5%
Rwanda	0	0%
Saint Kitts and Nevis	0	0%
Saint Lucia	0	0%
Saint Vincent and the Grenadines	0	0%
Samoa	0	0%
San Marino	0	0%
Sao Tome and Principe	0	0%
Saudi Arabia	0	0%
Senegal	0	0%
Serbia	0	0%
Seychelles	0	0%
Sierra Leone	0	0%
Singapore	0	0%
Slovakia	0	0%
Slovenia	0	0%
Solomon Islands	0	0%
Somalia	0	0%
South Africa	0	0%
South Korean	0	0%
South Sudan	0	0%
Spain	3	4.4%
Sri Lanka	0	0%
Sudan	0	0%
Suriname	0	0%
Sweden	1	1.5%
Switzerland	2	2.9%
Syria	0	0%
Tajikistan	0	0%
Tanzania	0	0%
Thailand	0	0%
Timor-Leste	0	0%
Togo	0	0%
Tonga	0	0%
Trinidad and Tobago	0	0%
Tunisia	0	0%
Turkey	0	0%
Turkmenistan	0	0%
Tuvalu	0	0%
Uganda	0	0%
Ukraine	0	0%
United Arab Emirates	0	0%
United Kingdom	1	1.5%
United States of America	23	33.8%
Uruguay	0	0%
Uzbekistan	0	0%
Vanuatu	0	0%

Venezuela	0	0%
Vietnam	0	0%
Yemen	0	0%
Zambia	0	0%
ZImbabwe	0	0%
Total	**68**	**100%**

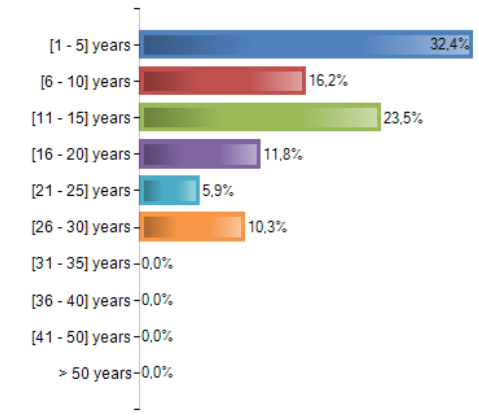
What is the duration of your medical practice?

	N	% Obs.
1-5 years	3	4.4%
6-10 years	14	20.6%
11-15 years	12	17.6%
16-20 years	14	20.6%
21-25 years	8	11.8%
26-50 years	17	25%
> 50 years	0	0%
Total	**68**	**100%**



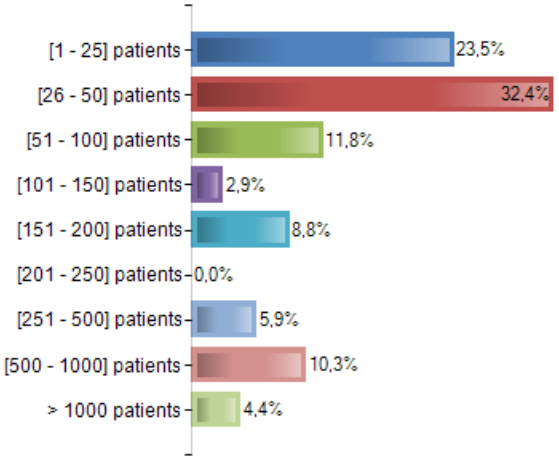
What is your duration of managing vascular anomalies?

	N	% Obs.
1-5 years	22	32.4%
6-10 years	11	16.2%
11-15 years	16	23.5%
16-20 years	8	11.8%
21-25 years	4	5.9%
26-30 years	7	10.3%
31-35 years	0	0%
36-40 years	0	0%
41-50 years	0	0%
> 50 years	0	0%
Total	**68**	**100%**



What is the approximate number of patients with vascular anomalies (excluding infantile hemangioma) that you managed in the past year?

	N	% Obs.
1-25 patients	16	23.5%
26-50 patients	22	32.4%
51-100 patients	8	11.8%
101-150 patients	2	2.9%
151-200 patients	6	8.8%
201-250 patients	0	0%
251-500 patients	4	5.9%
500-1000 patients	7	10.3%
> 1000 patients	3	4.4%
Total	**68**	**100%**

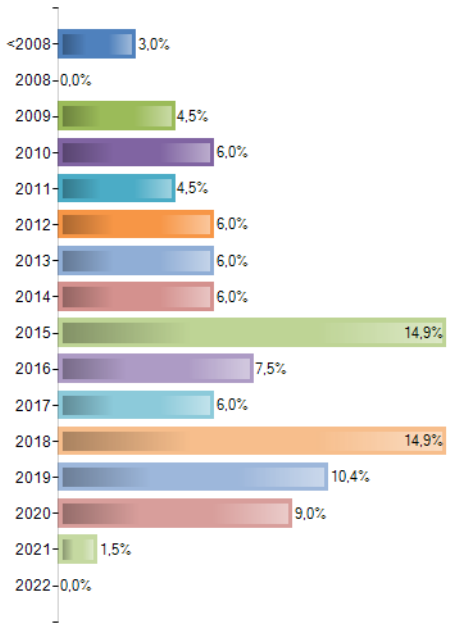


Are you involved in multidisciplinary consultations dedicated to vascular anomalies?

	N	% Obs.
Yes	63	92.6%
No	5	7.4%
Total	**68**	**100%**

Which year did you start prescribing an mTOR inhibitor (sirolimus/everolimus) for any vascular anomaly?

	N	% Obs.
<2008	2	3%
2008	0	0%
2009	3	4.5%
2010	4	6%
2011	3	4.5%
2012	4	6%
2013	4	6%
2014	4	6%
2015	10	14.9%
2016	5	7.5%
2017	4	6%
2018	10	14.9%
2019	7	10.4%
2020	6	9%
2021	1	1.5%
2022	0	0%
Total	**67**	**100%**



Have you ever prescribed everolimus for vascular anomalies?

	N	% Obs.
Yes	10	14.7%
No	58	85.3%
Total	**68**	**100%**

Have you ever prescribed a PI3K inhibitor (alpelisib) for vascular anomalies?

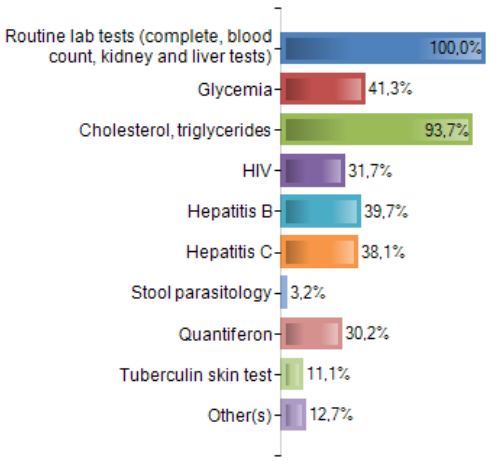
	N	% Obs.
Yes	33	48.5%
No	35	51.5%
Total	**68**	**100%**

Before initiating mTOR inhibitor therapy (sirolimus/everolimus), do you ask for laboratory results?

	N	% Obs.
Yes	63	92.6%
No	5	7.4%
Total	**68**	**100%**

If yes, which one(s):

	N	% Obs.
Routine lab tests (complete, blood count, kidney and liver tests)	63	100%
Glycemia	26	41.3%
Cholesterol. triglycerides	59	93.7%
HIV	20	31.7%
Hepatitis B	25	39.7%
Hepatitis C	24	38.1%
Stool parasitology	2	3.2%
Quantiferon	19	30.2%
Tuberculin skin test	7	11.1%
Other(s)	8	12.7%
Total	**63**	



During mTOR inhibitor therapy (sirolimus/everolimus), do you regularly monitor therapeutic residual concentration?

	N	% Obs.
Yes	67	98.5%
No	1	1.5%
Total	**68**	**100%**

If yes, what the residual concentration that your target is closest to:

	N	% Obs.
< 3 ng/ml	1	1.5%
3-10 ng/ml	21	31.8%
4-12 ng/ml	27	40.9%
5-15 ng/ml	17	25.8%
> 15 ng/ml	0	0%
Total	**66**	**100%**

During mTOR inhibitor therapy (sirolimus/everolimus), do you always monitor lymphocyte count?

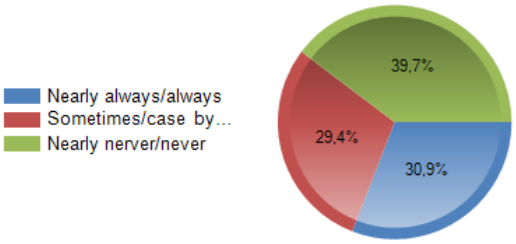
	N	% Obs.
Yes	58	86.6%
No	9	13.4%
Total	**67**	**100%**

During mTOR inhibitor therapy (sirolimus/everolimus), do you routinely screen for opportunistic infections (apart from physical examination)?

	N	% Obs.
Yes	3	4.4%
No	65	95.6%
Total	**68**	**100%**

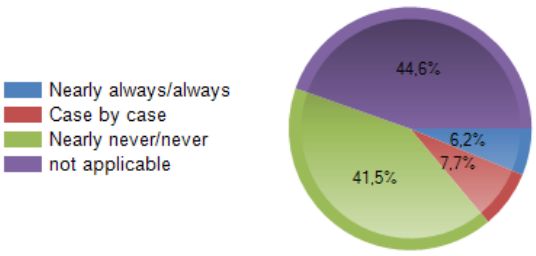
When prescribing mTOR inhibitors (sirolimus/everolimus), do you add treatment for pneumocystis prophylaxis?

	N	% Obs.
Nearly always/always	21	30.9%
Sometimes/case by case	20	29.4%
Nearly never/never	27	39.7%
Total	**68**	**100%**



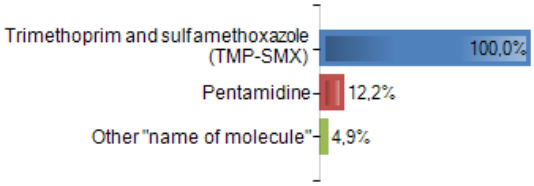
When prescribing PI3K inhibitors (alpelisib), do you add treatment for pneumocystis prophylaxis?

	N	% Obs.
Nearly always/always	4	6.2%
Case by case	5	7.7%
Nearly never/never	27	41.5%
not applicable	29	44.6%
Total	**65**	**100%**



If you add treatment for pneumocystis prophylaxis, which drug(s) do you use?

	N	% Obs.
Trimethoprim and sulfamethoxazole (TMP-SMX)	41	100%
Pentamidine	5	12.2%
Other "name of molecule"	2	4.9%
Total	**41**	



Does your prescription of treatment for pneumocystis prophylaxis depend on the age of the patient (infants or older people)?

	N	% Obs.
Yes	12	27.3%
No	32	72.7%
Total	**44**	**100%**

If yes,

	N	% Obs.
< 12 months	6	66.7%
< 24 months	1	11.1%
Child <12 years	0	0%
Child < 18 years	2	22.2%
Adult < 65 years	0	0%
Adults > 65 years	0	0%
Not specifically	0	0%
Total	**9**	**100%**

Does your prescription of treatment for pneumocystis prophylaxis depend on the comorbidities of the patient?

	N	% Obs.
Yes	6	66.7%
No	3	33.3%
Total	**9**	**100%**

If yes, which one(s):

	N	% Obs.
Other immunosuppressant drugs	5	83.3%
Diabetes or other diseases	1	16.7%
Weight (overweight or underweight)	0	0%
Other(s)	0	0%
Total	**6**	**100%**

Does your prescription of treatment for pneumocystis prophylaxis depend on the condition (vascular anomaly) of the patient?

	N	% Obs.
Yes	2	22.2%
No	7	77.8%
Total	**9**	**100%**

If yes, for which one(s) would you add pneumocystis prevention therapy?

	N	% Obs.
Venous malformations	11	44%
Lymphatic malformations	13	52%
Arteriovenous malformations	8	32%
Syndromic malformations (CLOVES/Klippel-Trenunay)	15	60%
Kasabach-Merritt phenomenon	11	44%
Other	9	36%
Total	**25**	

Does your prescription of treatment for pneumocystis prophylaxis depend on laboratory results?

	N	% Obs.
Yes	3	33.3%
No	6	66.7%
Total	**9**	**100%**

If yes, which one(s) would require pneumocystis prophylaxis therapy according to you?

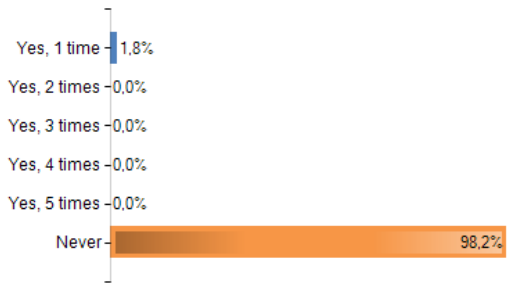
	N	% Obs.
Neutropenia <1000	2	66.7%
Neutropenia <500	0	0%
Lymphopenia <1000	2	66.7%
Lymphopenia <800	0	0%
Lymphopenia <600	1	33.3%
Lymphopenia <400	0	0%
Total	**3**	

Does your prescription of treatment for pneumocystis prophylaxis depend on how long you use mTOR or PIK3 inhibitors?

	N	% Obs.
Yes	0	0%
No	9	100%
Total	**9**	**100%**

Have you ever observed pneumocystis infections under mTOR inhibitors or PIK3 inhibitors?

	N	% Obs.
Yes, 1 time	1	1.8%
Yes, 2 times	0	0%
Yes, 3 times	0	0%
Yes, 4 times	0	0%
Yes, 5 times	0	0%
Never	54	98.2%
Total	**55**	**100%**



If yes, were the case(s) declared to a pharmacovigilance center?

	N	% Obs.
Yes	0	0%
No	1	100%
Total	**1**	**100%**

Pneumocystic infection occurred after how many months of sirolimus/everolimus/alpelisib?

	N	% Obs.
< 1 month	0	0%
1-3 months	1	100%
3-6 months	0	0%
6-12 months	0	0%
12-24 months	0	0%
24-48 months	0	0%
> 48 months	0	0%
If > 48 months, how long?	0	0%
Total	**1**	**100%**

What was the age of the patient when the pneumocystis infection occurred?

	N	% Obs.
1-2 years	1	100%
3-6 years	0	0%
6-12 years	0	0%
12-18 years	0	0%
18-30 years	0	0%
30-50 years	0	0%
50-70 years	0	0%
> 70 years	0	0%
Total	**1**	**100%**

What was the treatment for the vascular anomaly?

	N	% Obs.
Sirolimus	1	100%
Everolimus	0	0%
Alpelisib	0	0%
Total	**1**	**100%**

Did the patient have another immunosuppressive factor?

	N	% Obs.
No	0	0%
Yes	1	100%
Total	**1**	**100%**

What was the approximate lymphocyte count of the patient when pneumocystis infection occurred?

	N	% Obs.
Normal range	1	100%
400-1000 lymphocytes/mm3	0	0%
200-400 lymphocytes/mm3	0	0%
< 200 lymphocytes/mm3	0	0%
Total	**1**	**100%**

In addition to treatment of pneumocystis infection, did you withdraw sirolimus/everolimus/alpelisib?

	N	% Obs.
Yes	1	100%
No	0	0%
Total	**1**	**100%**

Which treatment did you use for pneumocystis prevention?

	N	% Obs.
Cotrimoxazole sulfamethoxazole-trimethoprim	0	0%
Pentamidine	0	0%
Both: cotrimoxazole sulfamethoxazole-trimethoprim and pentamidine	0	0%
Other(s)	1	100%
Total	**1**	**100%**

Did the patient recover?

	N	% Obs.
Yes	1	100%
No	0	0%
Total	**1**	**100%**

Did you observe a second case of opportunistic pneumocystis infection in a patient with a vascular anomaly treated with an mTOR/PIK3 inhibitor?

	N	% Obs.
Yes	0	0%
No	1	100%
Total	**1**	**100%**

V. CONCLUSION GÉNÉRALE

L'infection opportuniste à pneumocystose survenant chez les patients ayant une anomalie vasculaire traitée par inhibiteurs de la voie mTOR/PI3K/AKT est un événement rare, potentiellement grave, mais qui existe.

La revue systématique de la littérature, a mis en évidence 2 cas d'infection pulmonaire à pneumocystose, non fatale. La prévalence calculée de la pneumocystose (sur 1189 patients traités au total) est ainsi estimée à 1,68/1000. Les 2 patients étaient traités par des inhibiteurs du mTOR (sirolimus pour l'un et éverolimus pour l'autre). Nous n'avons pas rapporté de cas d'infection à pneumocystose chez les patients recevant des inhibiteurs du PI3K (alpelisib) et AKT (miransertib), mais le nombre de patients concernés était anecdotique. Aucun cas n'est survenu lorsqu'une prophylaxie était associée.

Les réponses des experts à l'enquête ainsi que les données de la revue systématique confirment des pratiques très hétérogènes concernant la prescription concomitante d'une prophylaxie anti-pneumocystose. Il semblerait qu'elle soit plus souvent utilisée si un traitement par inhibiteur de mTOR est prescrit qu'un inhibiteur de la PI3K ou de Akt. Le triméthoprim-sulfametoxazole est la molécule la plus utilisée.

Ce travail est, à notre connaissance, la première étude à s'intéresser au risque de pneumocystose ainsi qu'à l'intérêt d'une prophylaxie chez les patients présentant une anomalie vasculaire traitée par inhibiteur de la voie mTOR/PI3K/AKT.

Cette étude présente cependant quelques limites. Tout d'abord, concernant la revue systématique, il existe un biais de sélection lié au fait que tous les patients traités pour une anomalie vasculaire, ou ayant présenté une infection ne sont pas systématiquement publié. Il est possible que la prévalence d'infection à pneumocystose estimée soit sous-estimée. Ensuite, trop peu de patients inclus étaient traités par inhibiteurs du PI3K et de l'Akt, puisqu'il s'agit de traitements dont l'utilisation est récente, bien que de plus en plus utilisés.

Bien que notre travail ne permette pas d'éditer des recommandations officielles, il suggère, en accord avec les données de la littérature, qu'un traitement prophylactique, par

triméthoprim-sulfametoxazole, pourrait être donné de manière systématique aux patients présentant certains facteurs de risques : lymphopénie < 1000/mm3, traitement par inhibiteurs de mTOR sur une longue période, comorbidité ou association à d'autres immunosuppresseurs, tels que les corticoïdes à forte dose.

VI. ANNEXES

Fichier 1 : Prisma check list

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title page
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	P. 5
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	P. 6-7
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	P. 7
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	P. 9
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	P. 8
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	P. 8
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	P. 9
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	P. 9
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	P. 9
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	P. 9
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	NA
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	NA
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	NA
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	NA
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	NA
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	NA
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	NA
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	NA
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	NA
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	NA

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	NA
Study characteristics	17	Cite each included study and present its characteristics.	NA
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	NA
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	P. 11
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	NA
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	P. 11
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	NA
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	NA
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	NA
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	NA
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	P. 13
	23b	Discuss any limitations of the evidence included in the review.	P. 14
	23c	Discuss any limitations of the review processes used.	P. 14
	23d	Discuss implications of the results for practice, policy, and future research.	P. 14-15
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Title page
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	NA
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	P. 19
Competing interests	26	Declare any competing interests of review authors.	P. 19
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	P. 19

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Vu, le Directeur de Thèse

Vu, le Doyen
De la Faculté de Médecine de
Tours Tours, le

NAVARRO Maxime

56 pages –2 tableaux –1 figure – 1 fichier supplémentaire

Indication d'un traitement prophylactique anti-pneumocystose chez les sujets ayant une anomalie vasculaire traitée par inhibiteurs de la voie PIK3/AKT/mTOR : enquête auprès d'experts et revue systématique de la littérature

Introduction. Les anomalies vasculaires (AV) sont de plus en plus souvent traitées par des inhibiteurs de la voie PI3K/AKT/mTOR afin d'améliorer les complications et de prévenir leur aggravation. Ces médicaments surexposent les patients aux infections opportunistes, notamment à la pneumonie à *Pneumocystis jiroveci* (PJP). Il n'existe actuellement aucun consensus sur l'utilisation d'une prophylaxie anti-pneumocystose. L'objectif de cette étude a été d'étudier la prévalence de la PJP opportuniste dans cette population et de déterminer s'il y a une indication d'une prophylaxie de la pneumocystose dans cette population.

Méthodes. Cette étude a été menée en 2 parties : une enquête adressée à un panel d'experts internationaux des AVs, leur demandant leurs modalités d'utilisation des médicaments de prophylaxie de la pneumocystose, et une revue systématique de la littérature sur tous les cas publiés de patients recevant ces médicaments.

Résultats. Quatre-vingt médecins ont répondu à l'enquête, parmi lesquels 68 (85,0%) avaient déjà prescrit du sirolimus et ont été retenus dans l'analyse. A la question de savoir s'ils prescrivaient une prophylaxie de la PJP associée aux inhibiteurs de mTOR, 21 (30,9%) ont répondu toujours, 20 (29,4%) au cas par cas, 27 (39,7%) jamais. Concernant la revue systématique, parmi les 3394 rapports examinés, 217 ont été inclus, concernant 1189 patients. Deux cas de PJP ont été signalés parmi les 1 189 cas (0,2 %), l'un recevant du sirolimus et l'autre de l'évérolimus. Aucun n'avait reçu de médicaments prophylactiques contre la PJP.

Conclusion. Notre étude montre que, même si la PJP est un événement rare, elle peut survenir chez les patients atteints d'une AV traitée par un inhibiteur de mTOR. Elle ne permet pas d'émettre de recommandations, mais suggère qu'une prophylaxie par triméthoprim-sulfamétoxazole devrait certainement être administrée à un sous-groupe de patients présentant des facteurs de risque plus élevés de PJP.

Mots clés : Anomalies vasculaires ; Sirolimus ; Everolimus ; Miransertib ; Alpelisib ; PI3K ; mTOR ; Malformations vasculaires ; *Pneumocystis jirovecii*

Jury :
Président du Jury : Professeur Gérard LORETTE
Directeur de thèse : Professeur Annabel MARUANI
Membres du Jury : Docteur Sophie LEDUCQ
Docteur Maella SEVERINO-FREIRE

Date de soutenance : le 03 octobre 2022