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Designs utilisés dans les études thérapeutiques sur les anomalies vasculaires superficielles rares : une revue systématique

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SERMENT DE GALIEN

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L'étudiant
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Abréviations

CAVM	Malformations capillaires et artérioveineuses
CENTRAL	*Cochrane Central Register of Controlled Trials*
CLAVM	Malformations capillaires, lymphatiques et artérioveineuses
CLM	Malformations capillaires et lymphatiques
CLVM	Malformations capillaires, lymphatiques et veineuses
CONSORT	*CONsolidated Standards Of Reporting Trials*
CVM	Malformations capillaires et veineuses
DXA	*Dual-energy X-ray absorptiometry*
ESPD	*European Society for Pediatric Dermatology*
EUCTR	*European Union Clinical Trials Register*
FAVA-MULTI	Filière Santé Maladies Rares Maladies Vasculaires Rares avec atteinte Multi systémique
FIMARAD	Filière Santé Maladies Rares Dermatologiques
ISSVA	*International Society for the Study of Vascular Anomalies*
LM	*Lymphatic malformation*
LVM	Malformation lymphatiques et veineuses
NA	*Not applicable*

NRS	*Numerical rating scale*
PedsQL	*Pediatric Quality of Life Inventory*
PRISMA	*Preferred Reporting Items for Systematic and Meta-Analyses*
PROS	*PIK3CA-related Overgrowth Spectrum*
PROSPERO	*Prospective Register of Systematic Reviews*
Q1	*First quartile*
Q3	*Third quartile*
RCT	*Randomized controlled trial*
RPPD	*randomized placebo phase design*
SD	*Standard deviation*
SFDP	Société Française de Dermatologie Pédiatrique
SPIRIT	*Standard Protocol Items : Recommendations for Interventional Trials*
SWT	*stepped-wedge individual randomized trial*
TAPQOL	*TNO-AZL Preschool children Quality of Life*
TETECOU	Filière Santé Maladies Rares Malformations de la tête, du cou et des dents
VA / AV	*Vascular anomaly* / Anomalie vasculaire
VAS	*Visual analogue scale*
VM / MV	*Vascular malformation* / Malformation vasculaire
VT / TV	*Vascular tumor* / Tumeur vasculaire

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Chapitre 1

Introduction

Les anomalies vasculaires (AV) représentent un large panel de pathologies et sont classées par la Société Internationale pour l'Etude des Anomalies Vasculaires (ISSVA) en tumeurs vasculaires (TV) ou en malformations vasculaires (MV) selon leurs aspects cliniques, biologiques, radiologiques, pathologiques et caractéristiques moléculaires (Table 1.1). Les malformations vasculaires sont elles-mêmes subdivisées en MVs de haut débit et MVs de bas débit [1].

TABLEAU 1.1 – Classification des anomalies vasculaires par l'ISSVA

Anomalies vasculaires				
Tumeurs vasculaires	**Malformations vasculaires**			
	Simples	**Combinées°**	**Tronculaires**	**Associées à d'autres anomalies**
Bénignes Localement agressives/ borderline Malignes	Malformations capillaires Malformations lymphatiques Malformations artério-veineuses* Fistules artérioveineuses*	CVM, CLM, LVM, CLVM, CAVM*, CLAVM*, autres	Voir la liste proposée par l'ISSVA	Voir la liste proposée par l'ISSVA

° définies comme deux ou plusieurs malformations vasculaires trouvées dans une lésion
* lésions à haut débit
Abréviations : CVM, Malformations capillaires et veineuses, CLM, Malformations capillaires et lymphatiques, LVM, Malformation lymphatiques et veineuses, CLVM, Malformations capillaires, lymphatiques et veineuses, CAVM, Malformations capillaires et artérioveineuses, CLAVM, Malformations capillaires, lymphatiques et artérioveineuses.

Les TVs sont caractérisées par une prolifération ou une hyperplasie des cellules endothéliales, tandis que les MVs (1.1) résultent d'un défaut de la vasculogenèse embryonnaire qui pourrait être lié à des mutations génétiques somatiques ou germinales et impliquer les capillaires, les veines, les artères, le système lymphatique ou une combinaison de ceux-ci [2–4].

Tandis que l'hémangiome infantile est courant (environ 10% des nourrissons), autorégressif et de traitement simple, les autres anomalies vasculaires sont rares (<2% des naissances) et ne possèdent pas de recommandations quant à leur prise en charge [5, 6]. Quelques TVs (par exemple, l'hémangiendothéliome kaposiforme) et la plupart des MVs (à l'exception des taches de vin) sont des maladies chroniques rares.

En Europe, une maladie touchant moins de 1 personne sur 2 000 est considérée comme une maladie rare [7], alors qu'aux États-Unis, une maladie rare est définie comme une affection qui touche moins de 200 000 personnes [8]. Les MVs sont généralement congénitales et ont tendance à s'aggraver avec le temps.

Le diagnostic des AVs repose sur l'examen clinique – une biopsie peut être nécessaire pour confirmer –, qui peut être complété par des examens d'imagerie : échographie-Doppler (dépistage) et IRM (confirmation de la nature de la MV et visualisation de son extension) [9].

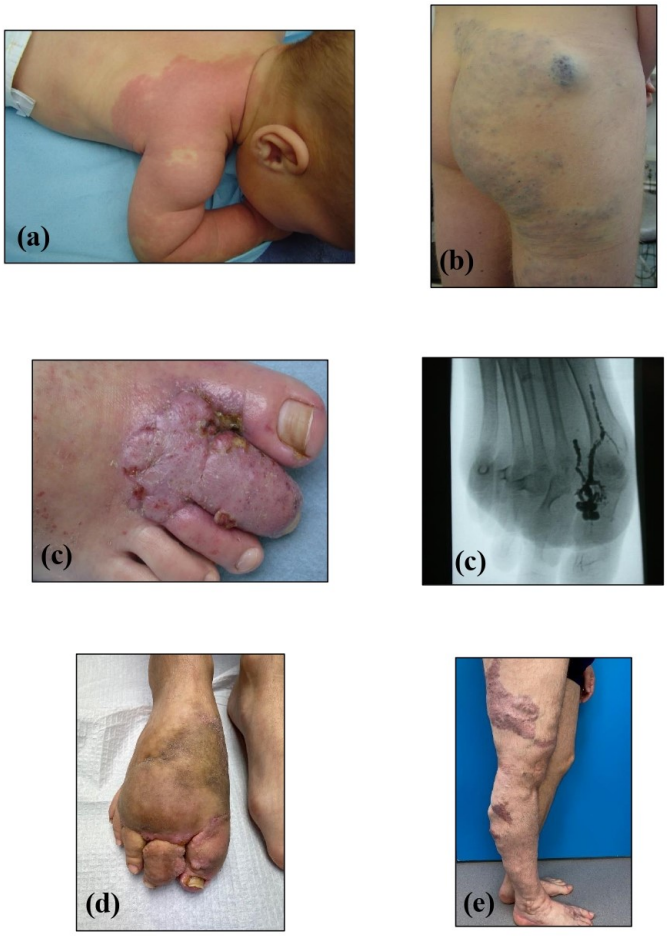

FIGURE 1.1 – Photos de différentes malformations vasculaires

(a) Malformation capillaire
(b) Malformation veineuse
(c) Malformations artério-veineuses
(d) Malformation lymphatique
(e) Syndrome de Klippel-Trenaunay

Leur prise en charge se décide en concertation pluridisciplinaire habituellement, et peut comprendre différentes modalités thérapeutiques aussi variées que la physiothérapie, la sclérothérapie/embolisation, la chirurgie, les méthodes physiques (lasers, ...), et certains médicaments (anticoagulants, inhibiteurs de mTOR, thérapies ciblées...). Souvent, les traitements sont instaurés dans l'enfance et reposent sur une approche personnalisée qui tient compte des objectifs de traitement du patient et nécessitent généralement des consultations multidisciplinaires. Il n'existe pas de recommandations validées pour le traitement des AVs rares [10]. En effet, les recommandations sont difficiles à élaborer compte tenu du large spectre et du nombre insuffisant d'études cliniques prospectives pour prouver l'efficacité du traitement [11–13].

Actuellement, l'essai contrôlé randomisé est le standard de l'évaluation thérapeutique et permet de guider la pratique clinique en fournissant des preuves de référence. Toutefois, les essais pour les maladies rares se heurtent à des problèmes de taille d'échantillon et nécessitent des designs adaptés.

Concernant les AVs rares, la conception des essais cliniques est difficile du fait de la difficulté cumulée de la rareté des maladies, de l'hétérogénéité des pathologies et souvent que la population d'intérêt est constituée d'enfants, ce qui, au-delà des questions de recrutement, pose des problèmes éthiques spécifiques (consentement des deux parents requis, acceptation par l'enfant, nombre limité de prélèvements et examens invasifs) [14, 15]. Pour pallier ces problèmes méthodologiques et éthiques, des conceptions alternatives ont émergé mais sont encore peu utilisées [16].

Le but de notre recherche était d'étudier les plans d'étude utilisés dans les études cliniques thérapeutiques des AVs rares par une revue systématique de la littérature.

Chapitre 2

Revue systématique de la littérature

2.1 Résumé en Français

Contexte Les anomalies vasculaires superficielles rares représentent un large panel de maladies. Leur prise en charge est difficile compte tenu de leur large spectre et du manque d'essais cliniques évaluant l'efficacité des traitements. Un essai clinique randomisé sur les anomalies vasculaires est difficile en raison de la rareté des maladies et est renforcé par la population d'intérêt qui est souvent composée d'enfants. Par conséquent, des designs appropriés sont nécessaires. Nous avons réalisé une revue systématique méthodologique pour identifier les designs mis en œuvre pour étudier le traitement des anomalies vasculaires superficielles rares.

Méthodes Nous avons effectué une recherche documentaire le 25 janvier 2021 dans les bases de données PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), Embase, ClinicalTrials.gov et European Union Clinical Trials Register. Cette recherche documentaire méthodologique systématique a été enregistrée au registre prospectif des revues systématiques (PROSPERO : CRD42021232449). Les essais randomisés et non randomisés ont été inclus s'ils remplissaient les critères suivants : étaient des études prospectives sur les traitements des anomalies vasculaires superficielles rares, concernaient des humains (adultes et enfants) et étaient publiés en anglais à partir de 2000. Nous avons exclu les rapports de cas/séries de cas rapportant moins de 10 patients, les revues, les études rétrospectives, les études animales, études d'anomalies vasculaires systémiques ou communes et études non thérapeutiques. Nous n'avons pas évalué le risque de biais dans les études incluses car notre revue était une revue méthodologique axée sur la conception utilisée. L'examen a fourni une analyse descriptive des caractéristiques pertinentes des études de recherche admissibles.

Résultats Sur 2046 articles identifiés, nous avons retenu 97 études (62 rapports et 35 protocoles) : 25 études contrôlées randomisées, 7 études comparatives non randomisées, 64 cohortes prospectives et 1 série de cas. Parmi les 32 études comparatives incluses, 21 ont utilisé une conception en groupes parallèles. Les 11 autres études ont utilisé des designs alternatifs qu'ils soient randomisés tels que les cross-over, randomized placebo phase, delayed-start, within-person, ou non (challenge-dechallenge-rechallenge

ou ont utilisé un groupe contrôle historique ou ont mis en place une période observationnelle de “run-in”).

Conclusion Notre recherche documentaire systématique met en évidence le manque d’essais contrôlés randomisés dans les anomalies vasculaires systémiques ou communes en raison de la rareté des patients et de leur hétérogénéité. De nouvelles conceptions méthodologiques émergent et peuvent surmonter les limites des essais en groupes parallèles.

Mots-clés : Designs, Essais contrôlés randomisés, Malformations vasculaires, Maladies rares

2.2 Article scientifique en Anglais

RESEARCH

Designs used in published therapeutic studies of rare superficial vascular anomalies: A systematic literature search

Aude Allemang-Trivalle[1,2*], Sophie Leducq[1,3], Annabel Maruani[1,2,3†] and Bruno Giraudeau[1,2†]

Abstract

Background: Rare superficial vascular anomalies represent a wide range of diseases. Their management is difficult given the broad spectrum and the lack of clinical trials assessing treatment efficacy. A randomized clinical trial of vascular anomalies is difficult because of the rarity of the diseases and is enhanced by the population of interest often being children. Therefore, suitable designs are needed. We conducted a methodological systematic literature search to identify designs implemented for investigating the treatment of rare superficial vascular anomalies.

Methods: We conducted a literature search on January 25, 2021, of the PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), Embase, ClinicalTrials.gov and European Union Clinical Trials Register databases. This systematic methodological literature search was registered at the Prospective Register of Systematic Reviews (PROSPERO: CRD42021232449). Randomized and non-randomized studies were included if they met the following criteria: were prospective studies of rare superficial vascular anomaly therapies, dealt with humans (adults and children) and were published in English from 2000. We excluded case reports/case series reporting fewer than 10 patients, reviews, retrospective studies, animal studies, studies of systemic or common vascular anomalies and non-therapeutic studies. We did not assess risk of bias in the included studies because our review was a methodological one focused on the design used. The review provided a descriptive analysis of relevant features of eligible research studies.

Results: From 2046 articles identified, we included 97 studies (62 reports and 35 ongoing studies): 25 randomized controlled studies, 7 non-randomized comparative studies, 64 prospective cohorts and 1 case series. Among the 32 comparative studies included, 21 used a parallel-group design. The 11 other studies used different designs such as cross-over, randomized placebo phase, delayed-start, within-person, or challenge–dechallenge–rechallenge or used a historical control group or an observational run-in period.

Conclusions: Our systematic literature search highlights the lack of randomized control trials in systemic or common vascular anomalies due to the rarity of patients and their heterogeneity. New designs are emerging and can overcome the limitations of testing treatments in parallel groups.

Keywords: Research Design; Randomized Controlled Trials; Vascular Malformations; Rare Diseases

Introduction

Vascular anomalies (VAs) represent a large panel of diseases and are classified according to their clinical, biological, radiological, pathological and molecular characteristics by the International Society for the Study of Vascular Anomalies (ISSVA) as vascular tumors (VTs), which might be benign, borderline or malignant, or vascular malformations (VMs) [1]. VTs are characterized by endothelial-cell proliferation or hyperplasia, whereas VMs result from a defect in embryonic vasculogenesis that might be linked to somatic or germinal gene mutations. VMs are classified according to the vessels involved (i.e., capillary VMs [port-wine stains], venous VMS, lymphatic VMs or arteriovenous VMs). They are considered "simple" when one type of vessel is involved and combined or syndromic if associated with other malformations [2–4]. This classification does not take into account the prevalence of the

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conditions, which might be common (port-wine stains, infantile hemangiomas) or rare. Rare vascular anomalies often are chronic conditions: in Europe, a disease affecting fewer than 1 in 2,000 people is considered a rare disease [5], whereas in the United States, a rare disease is defined as a condition that affects fewer than 200,000 people [6]. The natural history of most rare VAs is progressive worsening without therapeutic intervention.

Treatment of rare VAs includes different therapeutic modalities (i.e., physiotherapy, interventional radiology [sclerotherapy/embolization], surgery, interventions with device such as lasers, and drugs [anticoagulants, mammalian target of rapamycin inhibitors], including targeted therapeutic ones such as selective inhibitor of the phosphoinositol-3-kinase for CLOVES syndrome) [7–10]. Often, treatments are started in childhood. The management of rare VAs is based on a personalized approach that considers the patient's goals for treatment and usually requires multidisciplinary consultations. There are no validated guidelines for treatment of rare VAs [11]. Indeed, recommendations are difficult to develop given the broad spectrum and insufficient number of prospective clinical studies to prove the efficacy of treatment [7, 9, 12].

Randomized controlled trials (RCTs) provide gold-standard evidence to guide clinical practice. However, trials for rare diseases have recruitment issues and require tailored designs. Regarding rare VAs, the design of clinical trials is difficult because of the cumulative difficulty of the rarity of diseases, the heterogeneity of conditions and often that the population of interest is children, which, above recruitment issues, raises specific ethical issues (consent of both parents, acceptance by the child, limited number of samples and invasive exams) [13, 14]. To overcome these methodological and ethical problems, alternative designs have emerged but are still little used [15].

The aim of this study was to investigate the study designs used in therapeutic clinical studies of rare VAs by a systematic literature search.

Methods

Registration and protocol

This study was designed as a systematic methodological literature. It was registered at the Prospective Register of Systematic Reviews (PROSPERO: CRD42021232449).

Eligibility criteria

Reports of randomized and non-randomized studies were included if they met the following criteria: were prospective studies of rare superficial VA therapies, dealt with humans (adults and children) and were published in English from 2000. The different groups of VAs included were simple lymphatic malformations, simple venous malformations, slow-flow combined malformations including syndromic forms, arteriovenous malformations and rare vascular tumors. We included ongoing studies (i.e., studies, comparative or not, whose results were not published at the time of the electronic research on January 25, 2021). We excluded case reports/case series reporting fewer than 10 patients, reviews, retrospective studies, animal studies, studies of systemic or common VAs (prevalence greater than 1 in 2,000 people) and non-therapeutic studies. There was no minimum number of patients for clinical trials. To differentiate the prospective cohorts from case series, we followed the definition proposed by Dekkers et al. [16]: "in a cohort study, patients are sampled on the basis of exposure and are followed over time, and the occurrence of outcomes is assessed." In a case series, patients can be sampled according to both the specific outcome and specific exposure or only a specific outcome. To distinguish cohort studies from case series, we mainly considered the participant selection and sampling parameter (Is it linked to the outcome? to a specific exposure?) and to the presence of a follow-up period during which the outcome is assessed (cohort study criteria) [17]. Two authors reviewed the full text of each study, with blinding, to label them. Discrepancies were resolved by discussion between these two authors. Many studies that could have been initially defined as case series were reclassified as cohort studies.

Search strategy

The electronic search conducted on January 25, 2021, involved the databases PubMed, Embase (on Embase.com), and Cochrane Central Register of Controlled Trials (CENTRAL) and the registers ClinicalTrials.gov and European Union Clinical Trials Register (EUCTR). The search terms used can be found in the supplementary materials and methods file.

Selection process

According to the pre-defined criteria, two authors (AAT and SL) independently selected reports based on the title abstracts. Any discrepancies were resolved by the senior authors (AM and BG). The same two authors then examined the full texts of the selected reports. They excluded duplicate publications, general reviews, systematic reviews or reports with insufficient information as full text not accessible. Publication duplicates were detected by using first Zotero software and then Airtable. Duplicates between registers and publications were manually detected and resolved directly on Airtable.

Data collection process

For each selected study, two reviewers independently followed a standard template for data extraction. Any disagreements were resolved by discussion and if necessary by a senior author. Data were extracted to an Airtable spreadsheet (https://airtable.com/) and included publication metrics (name of the first author, journal, publication year, source and article type), study recruitment characteristics (continent and number of centres), study design (study type, randomization, trial design, design justification by the authors, blinding and important changes after trial beginning), study groups (number of groups, experimental treatment and control), primary outcome, characteristics of patients (type of VAs using the ISSVA classification system, age category), planned sample size, number of patients included and funding sources. Intervention type in the experimental group were extracted and classified as follows: parenteral drugs, enteral drugs, topical drugs, interventional radiology (i.e., image-guided minimally invasive treatment such as embolization or percutaneous sclerosis) and physiotherapy. Figure S1 (supplementary material) represents the designs used in comparative studies included in the final analysis.

Data analysis

We did not assess risk of bias in the included studies. The review provided a descriptive analysis of relevant features of eligible research studies, focusing on designs used. The characteristics of each included clinical trial were summarized in tables using descriptive statistics. Categorical variables are presented as counts and proportions (n, %). Quantitative variables are presented as median and interquartile range (median [Q1-Q3]). To statistically analyze categorical variables, we used the chi-square test. To statistically analyze quantitative variables, we used the non-parametric Mann-Whitney U test. R-4.2.2 software was used for statistical analyses.

Results

In the initial database search, we identified 2 046 reports and finally included 97 studies (62 reports and 35 ongoing studies): 25 RCTs, 7 non-randomized comparative studies, 64 prospective cohort studies and 1 case series. Figure 1 presents the flow of articles in the review.

Characteristics of the included studies

Table 1 shows the epidemiology and reporting characteristics of the 97 included studies. Twenty studies that could have been initially defined as case series were reclassified as cohort studies [18–37].

Patient characteristics

Most of the included studies involved heterogeneous patients. First, about two thirds of studies included both children and adults [7, 19–21, 23–27, 29–34, 36, 38–84]. Second, nearly one third were of several diseases [7, 22, 27, 29, 30, 33, 38, 40, 45, 50, 52, 54, 55, 57, 58, 60, 64, 64, 65, 67, 68, 74, 77, 79, 84–86]. Most studies were of lymphatic malformations (LMs) and/or venous malformations [7, 18–34, 36–46, 48, 50–62, 64, 64–68, 71–80, 82–104], followed by rare VTs [7, 27, 29, 35, 40, 52, 55, 60, 63, 64, 67, 68, 105–110], arteriovenous malformations [29, 38, 45, 50, 52, 55, 58, 67–70, 84, 111, 112], and slow-flow combined malformations or syndromic malformations [7, 22, 38, 45, 47, 49, 50, 52, 54, 57, 58, 64, 64, 65, 68, 74, 77, 79, 81, 85, 86].

Experimental treatments

Overall, whatever the study type (comparative or non-comparative, randomized or non-randomized), the most evaluated experimental treatment was interventional radiology [18, 19, 21–27, 29, 30, 32–34, 36–42, 44–46, 50–57, 59–62, 66, 67, 72, 73, 75, 76, 78–80, 84, 87–94, 97, 98, 102, 104, 111–113] followed by enteral drugs [7, 20, 31, 47, 49, 63, 64, 64, 65, 68–70, 74, 77, 81, 82, 85, 96, 99–101, 107–110]. total of 14 studies offered a combination of treatments in the experimental arm. For 10, it was a combination of two interventional radiology treatments [19, 32, 36, 39, 42, 44, 56, 59, 83, 91]. Three studies investigated the combination of two enteral drugs [47, 63, 100] and one study combined sclerotherapy and surgery [66]. Thus, many included studies used interventional radiology to treat LMs [19, 21–27, 29, 30, 33, 37–40, 42, 44, 45, 50–52, 54, 55, 57, 60, 75, 84, 97, 98, 102, 104, 113] (32 studies) and venous malformations [18, 22, 27, 29, 30, 32–34, 36, 38, 41, 45, 46, 50, 52–57, 59, 61, 62, 66, 67, 72, 73, 76, 78–80, 84, 87–94] (40 studies).

Planned and achieved sample size

Most studies (n=57, 58.8%) did not report a planned sample size [18, 19, 21–30, 32–37, 39–41, 44–46, 51–57, 60–62, 66, 67, 72, 73, 75, 76, 78–80, 83, 84, 89, 91–94, 96–98, 100, 102, 104, 113]. A higher proportion of comparative studies [43, 48, 49, 59, 63, 65, 71, 74, 81, 85, 86, 88, 90, 99, 103, 105, 107, 109, 110] than non-comparative studies [7, 20, 31, 38, 42, 47, 50, 58, 64, 64, 68–70, 77, 82, 87, 101, 106, 108, 111, 112] had a planned sample size (n=19, 59.4% vs n=21, 32.3%, p=0.011). For more than half the studies, the median (Q1-Q3) planned sample size was 38 (25-61) patients per study. In the 62 reports, the median (Q1-Q3) number of included patients was 28 (15-44) Comparative studies are significantly larger than non-comparative studies (median [Q1-Q3] sample size 39 [28-90] vs 20

[14-43], p=0.008). Table 1 presents the intervention and sample size description of studies included in the final analysis.

Methodology of the studies

Comparative study design (32 studies)

Many of the comparative studies (n=21, 65.6%) used a classical design with parallel groups [41, 44, 57, 59, 60, 63, 67, 72, 80, 83, 86, 88–91, 97, 99, 105, 107, 109, 110]. Table 2 presents the methodological data for comparative studies included in the final analysis. The 11 other studies used different designs: cross-over [48, 65], randomized placebo phase [43, 85], delayed-start [47, 103], within-person [71], challenge–dechallenge–rechallenge [74], and observational run-in period [81] or used a historical control group [66, 73]. Table 3 reports the characteristics of these studies. Two studies had two stages: a pilot phase with a small sample size followed by a larger comparative trial [43, 88].

Among the 32 comparative studies, 14 (43.8%) had some form of blinding [43, 48, 49, 59, 67, 71, 80, 85, 86, 88, 91, 99, 103, 107]. These 14 studies were RCTs, representing 56% of RCTs included in the review. Blinded actors were outcome assessors (4 studies, 12.5%) [43, 85, 103, 107] or both participants and care providers (4 studies, 12.5%) [48, 71, 80, 86]. Three studies (9.4%) [49, 59, 99] exhibited triple blinding (participants, care provider and outcome assessor).

Design justification by the authors

For 6 of the 32 (18.8%) comparative studies, the authors justified their design in their report [43, 71, 73, 81, 85, 103]. Of these 6 studies, 4 were randomized [43, 71, 85, 103] and 2 were not [73, 81]. The first randomized study used a delayed-start design with an observational period of 6 months based on data suggesting that after this period, spontaneous regression was unlikely [103]. For the following 3 randomized studies [43, 71, 85], the authors explained that the population with the pathologies of interest was too rare to be able to set up a classic parallel-group trial. One used a within-person design because it allowed for reducing the number of patients to be included as well as inter-observation variability and all patients to receive the experimental treatment [71]. The other 2 randomized studies had a randomized placebo-phase design, which allowed for reducing the number of participants to include and increased acceptability (because every participant received the experimental intervention) and therefore ensured feasibility [43, 85]. For the non-randomized studies, the first used historical controls because randomization was judged too difficult to implement with the varying nature of VMs [73]. The second used an observational run-in period as a control and not a placebo because the experimental treatment was increasingly available and this would have compromised recruitment [81].

Important changes in the protocol after trial beginning

After the beginning of the clinical trial, 10 (10.3%) studies made important changes to their protocol [7, 47, 63–65, 81, 87, 99, 110, 114]. Changes concerned the addition, removal or change of the primary or secondary outcomes (6 studies) [7, 47, 64, 65, 81, 87], a decrease in estimated enrollment (3 studies) [63, 99, 114], a modification of the intervention (1 study) [110] and a modification of the inclusion criteria (1 study) [47].

Discussion

This methodological systematic literature search allowed identifying 62 reports and 35 ongoing studies representing 32 comparative and 65 non-comparative therapeutic studies of rare superficial VAs. Studies were frequently non-comparative cohorts, assessing interventional radiology in venous malformations or LMs. The proportion of experimental (i.e. randomized) studies was low. Our review showed that some authors used randomized designs distinct from the classical two-parallel group design, such as cross-over, within-person, randomized placebo-phase and delayed-start. We also noted in our review some designs of non-randomized studies that may be interesting for studying rare diseases such as the use of a historical control group or the challenge-dechallenge-rechallenge design [115].

This latter result is consistent with previously published results: in a systematic review of sirolimus treatment for LMs, among 20 studies, only one was an RCT, versus 19 retrospective case series or case reports [116]. Another review evaluating the efficacy of sirolimus for treating vascular abnormalities identified mostly single case reports (47 studies) and case series (22 studies) and very few prospective observational studies (n=2) or RCTs (n=2) [9]. Vascular anomalies are heterogeneous, which challenges the randomization (Is stratification desirable? possible?), outcome selection (Is there a relevant common outcome?) and results interpretation [9, 73, 121].

Thus, using a classical two parallel-group RCT presents a conundrum, and therefore, alternative designs involving intra-patient comparison are of high interest for clinical trials of rare pathologies because they can avoid some of the difficulties mentioned below [117–120, 122]. The rarity of these pathologies is also a difficulty [116, 123]. Thus, we observed a lower number of included patients as compared with the planned sample size, a result already acknowledged for

rare diseases [124, 125]. The most glaring example was one study that compared vincristine and sirolimus for treating high-risk VTs [63]. The authors had planned to enroll 50 patients, but the study had to stop because owing to the rarity of the pathology, only 4 patients had been recruited. Our observations seem consistent with the narrative review of Neto et al. which aimed to summarize Cochrane systematic review evidence on treatments for congenital vascular anomalies and hemangiomas. They had several difficulties including the limited number of existing systematic reviews, limited number of participants in the studies of these pathologies and heterogeneity of the participants [126]. To carry out therapeutic clinical trials on rare superficial VAs, the results of our review suggest to select a design that can limit the required sample size as much as possible. To have as low a required sample size as possible, investigators can promote intra-patient comparisons, thus increasing power. This option also allows for better accuracy because of the absence of inter-patient variability [127, 128]. In our review, we found three such designs: the cross-over design [129–131], the randomized placebo-phase design [132, 133] and the within-person design [134]. More so, the main advantage of this last design is that it eliminates confounding factors between the arms of the trial because the treatments to be compared are given at the same time and not successively as in the cross-over design or the randomized placebo-phase design. It is particularly suitable for dermatology (e.g., VAs) practice. However, the resulting problem is that these designs are more sensitive to dropouts and missing data because each participant is their own control; therefore, a dropout potentially affects both groups.

Another difficulty is using a placebo. First, a sham intervention for surgery or interventional radiology is difficult [135], in particular for the ethical aspect because this fictitious intervention can cause excessive risk for participants. In general, invasive procedures such as surgeries should normally be tested against standard medical treatment or no treatment [136]. Then, it is important to limit the time spent on placebo, Limiting the time spent on placebo facilitates recruitment. For VAs, given that there are standard treatments, patients and physicians would be reluctant to have a real placebo-only control group. Therefore, there are designs that can limit this period under placebo, such as the randomized placebo-phase design. Nevertheless, to ensure the validity of the results, an effective placebo-phase duration must be established: short enough to avoid changes over time and long enough for valid measurements [15]. However, there is the risk of participants dropping out if the placebo-controlled phase is too long. Second, for rare diseases with a potentially shortened lifespan, parents may be reluctant to have their children receive a placebo [81, 137]. To overcome this, investigators can maximize on-treatment participants by giving each patient the experimental treatment at some point (this is the case in the cross-over design) or by ensuring that all patients end the study being exposed to the experimental treatment, which offers the opportunity to pursue this treatment (if possible) outside of the study context (this is the case in the delayed-start design [138] and the randomized placebo-phase design). Either way, maximizing on-treatment participants facilitates recruitment and increase acceptance and accrual. These types of design can be of interest if conducting a two-parallel group RCT would be difficult or unacceptable, for instance when assessing an experimental treatment for an incurable or fatal disease or when the disease affects the more fragile pediatric population (which is the case with VAs).

For investigators, using an observational run-in period allows for collecting useful clinical data, especially in the case of rare diseases such as VAs, screening out ineligible or non-compliant participants, and establishing baseline observations. However, it also has disadvantages, such as affecting the external validity of the study by excluding patients and affecting the internal validity by exaggerating the intention-to-treat effect (e.g., if a run-in period is used to exclude participants who do not tolerate the treatment, then potentially there will be only a large number of good responders in the following phase, which can give a too optimistic view of the treatment effect) [139]. It is also possible to integrate an “internal” pilot study (pilot phase) into a clinical trial that allows for integrating the pilot participants into the definitive study and therefore not “exhausting” the stock of patients eligible for the study. This is interesting in the case of rare diseases such as VAs. These pilot phases built into the trial do not require additional time or funds [15].

Our review highlighted the use of a historical control. Despite certain advantages such as avoiding the problem of recruiting patients, especially for studying rare diseases such as VAs, this design has several disadvantages: confounding effects [140] (baseline patient characteristic differences between treatment arms can prevent highlighting the treatment effect), selection bias [141, 142] (whereby patients receiving the experimental treatment are selected from a pool of ”good responders”, thus resulting in an overestimation of the treatment effect), performance, and detection bias [143, 144] (because there is no blinding). To overcome these, it would be interesting to use advanced methods to manage confusion in observational studies, such as stratifying patients on the estimated propensity scores

during the analysis of observational data [142]. The Bayesian statistical approach could also be of interest, combined with any design, although we could not find it in our review. This approach uses data from previous studies to form a prior probability distribution for treatment effect, combined with current trial data for a posterior distribution, from which conclusions can be drawn [13].

This systematic review has several limitations. First, it certainly does not present all the studies published on the subject given the use of several filters: we included only studies published in the English language and since the year 2000. In addition, most authors did not justify their choice of methodological scheme in their publication, which limited our collection of information on this subject. In addition, registry ongoing studies contain more missing data than do published articles. We can also consider limitations in the method we chose to follow by not looking at other methodological issues such as sequence generation and allocation concealment, which are issues of importance in randomized trials but probably of lower importance than blinding [145, 146].

Conclusions

Comparative studies are mandatory for assessing treatments or interventions, but RCTs are rare in these diseases. Classical two parallel-group ddekesigns are of limited use in rare pediatric diseases, notably with large between-patient variability. New designs, more adapted to this specific medical context, are emerging and can overcome the limitations of testing treatments in parallel groups. Their use is necessary for conducting trials with a high level of evidence.

Ethical approval and consent to participation
Not applicable.

Consent to publication
Not applicable.

Availability of data and material
The dataset supporting the conclusions of this article is available in the opensource online data repository hosted at Mendeley: doi: 10.17632/n2vs8spdhz.1 [147]

Competing interests
The authors declare that they have no competing interests.

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Author's contributions
Conceptualization: AAT, AM, BG; Formal Analysis: AAT; Investigation: AAT, SL; Methodology: AAT, AM, BG; Supervision: AM, BG; Validation: AAT, SL; Visualization: AAT; Writing–original draft: AAT; Writing–review & editing: AAT, AM, BG.

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Figures and Tables

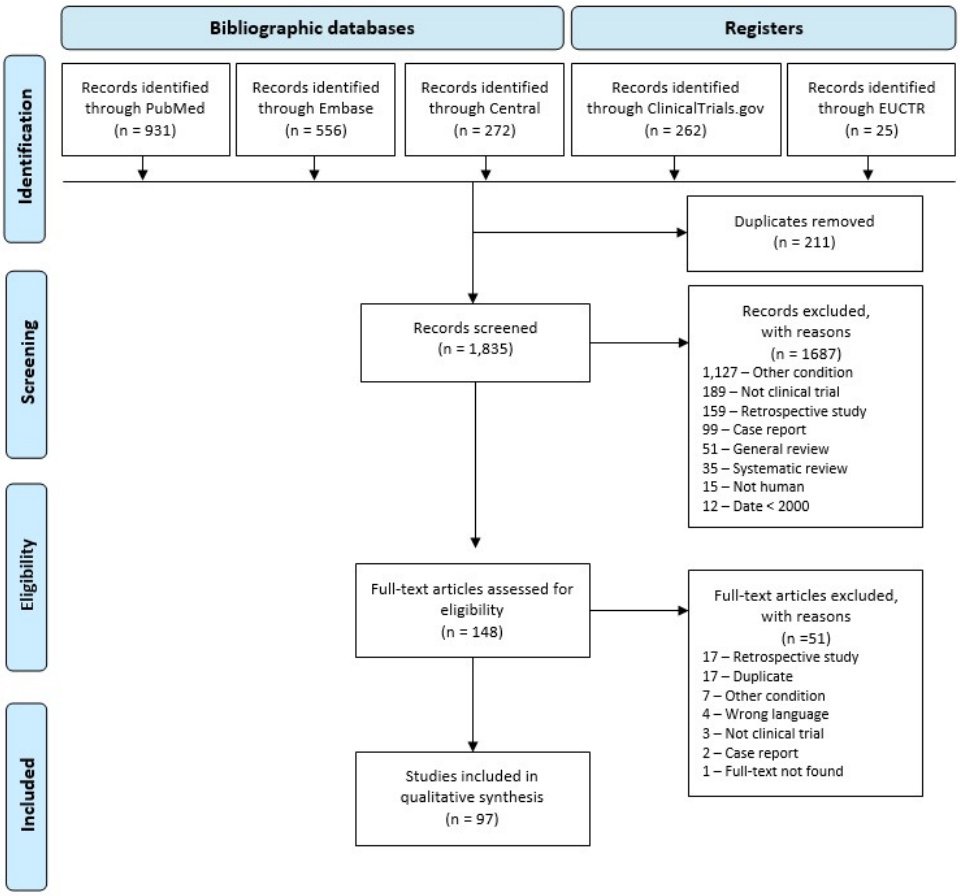


Figure 1: Flow of articles in the review

Table 1. Description of studies included in the final analysis

ALL STUDIES				
		TOTAL N=97	**REPORTS N=62**	**ONGOING STUDIES N=35**
SOURCE	Publication year, n (%)			
	2002–2010	20 (20.6)	17 (27.4)	3 (8.6)
	2011–2015	28 (28.9)	23 (37.1)	5 (14.3)
	2016–2020	49 (50.5)	22 (35.5)	27 (77.1)
	Source, n (%)			
	Bibliographic databases	70 (72.2)	62 (100.0)	8 (22.9)
	Registers	27 (27.8)	0	27 (77.1)
SETTING	International study, n (%)			
	Yes	9 (9.3)	3 (4.8)	6 (17.1)
	No	87 (89.7)	58 (93.6)	29 (82.9)
	Unclear	1 (1.0)	1 (1.6)	0
	Continent of study recruitment, n (%) [a]			
	North America	15 (15.5)	6 (9.7)	9 (25.7)
	South America	1 (1.0)	1 (1.6)	0
	Europe	26 (26.8)	12 (19.4)	14 (40.0)
	Asia	53 (54.6)	39 (62.9)	14(40.0)
	Africa	4 (4.1)	4 (6.5)	0
	Oceania	1 (1.0)	0	1 (2.9)
	Unclear	1 (1.0)	1 (1.6)	0
	Number of centres, n (%)			
	1	72 (74.2)	53 (85.5)	19 (54.3)
	2–5	14 (14.4)	5 (8.1)	9 (25.7)
	> 5	9 (9.3)	2 (3.2)	7 (20.0)
	Unclear	2 (2.1)	2 (3.2)	0
FUNDING	Funding body, n (%)			
	Public	43 (44.3)	13 (21.0)	30 (85.7)
	Private	6 (6.2)	1 (1.6)	5 (14.3)
	Both private and public	1 (1.0)	1 (1.6)	0
	No specific funding	4 (4.1)	4 (6.5)	0
	Not reported	43 (44.3)	43 (69.4)	0
DESIGN	Study type, n (%)			
	Comparative	32 (33.0)	15 (24.2)	17 (48.6)
	Prospective cohort	64 (66.0)	46 (74.2)	18 (51.4)
	Case series	1 (1.0)	1 (1.6)	0
PARTICIPANTS	Study population type, n (%)			
	Children	28 (28.9)	17 (27.4)	11 (31.4)
	Adults	5 (5.1)	0	5 (14.3)
	Both	63 (65.0)	44 (71.0)	19 (54.3)
	Unclear	1 (1.0)	1 (1.6)	0
	Included participant diseases, n (%) [a]			
	Simple lymphatic malformations	51 (52.6)	37 (59.7)	14 (40.0)
	Simple venous malformations	52 (53.6)	37 (59.7)	15 (42.9)
	Slow flow combined malformations including syndromic forms	21 (21.7)	10 (16.1)	11 (31.4)
	Arteriovenous malformations	14 (14.4)	7 (11.3)	7 (20.0)
	Rare vascular tumors	18 (18.6)	9 (14.5)	9 (25.7)
	Several diseases	27 (27.8)	18 (29.0)	9 (25.7)
		TOTAL N=97	**STUDY STATUS**	**STUDY OBJECTIVE**

			REPORTS N=62	ONGOING STUDIES N=35	COMPARATIVE STUDIES N=32	NON-COMPARATIVE STUDIES N=65
INTERVENTION	Intervention type in the experimental group, n (%) [a]					
	Parenteral drugs	3 (3.1)	2 (3.2)	1 (2.9)	2 (6.3)	1 (1.5)
	Enteral drugs	25 (25.8)	6 (9.7)	19 (54.3)	10 (31.3)	15 (23.1)
	Topical drugs	5 (5.2)	0	5 (14.3)	3 (9.4)	2 (3.1)
	Interventional radiology	61 (62.9)	52 (83.9)	9 (25.7)	15 (46.9)	46 (70.8)
	Physiotherapy	3 (3.1)	2 (3.2)	1 (2.9)	2 (6.3)	1 (1.5)
	Surgery	0	0	0	0	0
	Combined treatment	14 (14.4)	10 (16.1)	4 (11.4)	0	0
SAMPLE SIZE	Planned sample size, n (%)					
	≤ 10 [b]	3 (3.1)	1 (1.6)	2 (5.7)	0	3 (4.6)
	11–24	6 (6.2)	1 (1.6)	5 (14.3)	3 (9.4)	3 (4.6)
	25–49	12 (12.4)	1 (1.6)	11 (31.4)	6 (18.8)	6 (9.2)
	50–99	12 (12.4)	2 (3.2)	10 (28.6)	6 (18.8)	6 (9.2)
	≥ 100	7 (7.2)	1 (1.6)	6 (17.1)	4 (12.5)	3 (4.6)
	Not planned	57 (58.8)	56 (90.3)	1 (2.9)	13 (40.6)	44 (67.7)
	Number of patients included					
	Median	27.5	27.5	NA	39.0	20.0
	[Q1; Q3]	[15.0 ; 43.8]	[15.0 ; 43.8]	NA	[28.0 ; 89.5]	[13.5 ; 43.0]
	Number of patients included, n (%)					
	≤ 10	5 (5.2)	5 (8.1)	NA	0	5 (7.7)
	11–24	24 (24.7)	24 (38.7)	NA	2 (6.3)	22 (33.8)
	25–49	18 (18.6)	18 (29.0)	NA	8 (25.0)	10 (15.4)
	50–99	9 (9.3)	9 (14.5)	NA	2 (6.3)	7 (10.8)
	≥ 100	6 (6.2)	6 (9.7)	NA	3 (9.4)	3 (4.6)
	NA	35 (36.1)	35 (36.1)	NA	17 (53.1)	18 (27.7)

[a]Not exclusive

[b]Case reports/case series reporting fewer than 10 patients were excluded

Abbreviations: NA, not applicable; Q1, first quartile; Q3, third quartile

Table 2. Methodological data for comparative studies included in the final analysis

COMPARATIVE STUDIES				
		TOTAL N= 32	**RANDOMIZED N= 25**	**NON-RANDOMIZED N= 7**
DESIGN	Trial design, n (%)			
	Parallel groups	21 (65.6)	19 (76.0)	2 (28.6)
	Cross-over	2 (6.3)	1 (4.0)	1 (14.3)
	Randomized placebo phase	2 (6.3)	2 (8.0)	0
	Within-person	1 (3.1)	1 (4.0)	0
	Delayed-start design	2 (6.3)	2 (8.0)	0
	Observational run-in period	1 (3.1)	0	1 (14.3)
	Challenge–dechallenge–rechallenge	1 (3.1)	0	1 (14.3)
	Use of a historical control group	2 (6.3)	0	2 (28.6)
	Studies reported design justifications, n (%)*			
	Yes	6 (18.8)	4 (16.0)	2 (28.6)
	No	26 (81.3)	21 (84.0)	5 (71.4)
	Blinding, n (%)			
	Participants only	2 (6.3)	2 (8.0)	0
	Participants and care provider	4 (12.5)	4 (16.0)	0
	Participants, care provider and outcome assessor	3 (9.4)	3 (12.0)	0
	Outcome assessor only	4 (12.5)	4 (16.0)	0
	Participants and outcome assessor	1 (3.1)	1 (4.0)	0
	No blinding	10 (31.3)	7 (28.0)	3 (42.9)
	Not specified	8 (25.0)	4 (16.0)	4 (57.1)
TREATMENT GROUPS	Number of groups, n (%)			
	1	8 (25.0)	8 (32.0)	NA
	2	15 (46.9)	15 (60.0)	NA
	3**	2 (6.3)	2 (8.0)	NA
	Intervention type in the experimental group, n (%)			
	Parenteral drugs	2 (6.3)	2 (8.0)	0
	Enteral drugs	10 (31.3)	7 (28.0)	3 (42.9)
	Topical drugs	3 (9.4)	3 (12.0)	0
	Interventional radiology	15 (46.9)	11 (44.0)	4 (57.1)
	Physiotherapy	2 (6.3)	2 (8.0)	0
	Control group treatment (n=31)[a], n (%)			
	Placebo, sham interventions	4 (12.5)	4 (16.0)	0
	Active drugs	5 (15.6)	5 (20.0)	0
	Interventional radiology	13 (40.6)	11 (44.0)	2 (28.6)
	Physiotherapy	0	0	0
	Surgery	1 (3.1)	0	1 (14.3)
	Interventional radiology and surgery	1 (3.1)	0	1 (14.3)
	No treatment	7 (21.9)	5 (20.0)	2 (28.6)

[a]One study did not have control group but had 2 experimental groups.

* Whether the authors explained and/or justified the use of their study design/methodology in their protocol or publication.

** For one, it was different concentrations of the same treatment and for the other, the groups were composed as follows: treatment 1 vs treatment 2 vs both treatments 1 and 2.

Table 3. Characteristics of 11 comparative studies with a non-parallel design

	FIRST AUTHOR	DESIGN	YEAR	POPULATION	INTERVENTION	COMPARISON	PRIMARY OUTCOME
RANDOMIZED	Mükke	Cross-over [48]	2020	Venous malformation Adults and children	Physiotherapy (compression stockings)	No treatment	Change in volume of the malformation measured non-invasively by MRI.
	Luo	Delayed-start [20]	2020	PROS Adults and children	Enteral drug (alpelisib)	Placebo	Change in the target lesion volumes assessed by MRI.
	Maruani	Randomized placebo phase [43]	2019	Lymphatic malformations Adults and children	Topical drug (sirolimus)	No treatment	Evaluation of global severity of the lingual microcystic lymphatic malformation using Physical Global Assessment (PGA).
	Leducq	Within-person [71]	2019	Lymphatic malformations Adults and children	Topical drug (sirolimus)	Placebo	Evaluation of cutaneous microcystic lymphatic malformation versus topical vehicle using PGA.
	Maruani	Randomized placebo phase [85]	2018	Vascular malformation Children	Enteral drug (sirolimus)	No treatment	Change in the volume of the vascular malformation seen on MRI.
	Smith	Delayed-start [103]	2009	Lymphatic malformations Children	Parenteral drug (picibanil)	No treatment	Change in volume/size of the malformation evaluated by CT or MRI.
NON-RANDOMIZED	te Loo	Challenge–dechallenge–rechallenge [74]	2019	Vascular malformation Adults and children	Enteral drug (sirolimus)	No treatment	Evaluation of the quality of life measured by TAPQOL, PedsQL and Research and development Rand-36. Evaluation of the pain using VAS score and NRS score.
	Parker	Observational run-in period [81]	2019	PROS Adults and children	Enteral drug (sirolimus)	No treatment	Percent change in unaffected and affected fibrofatty tissue measured by DXA and MRI scan.
	Hammer	Cross-over[a] [65]	2018	Vascular malformation Adults and children	Enteral drug (sirolimus)	Patient's long term history (Surgery, interventional radiology etc.)	Physical, functional, biological, radiological and quality of life evaluations.

	Weitz-Tuoretmaa	Historical control group [73]	2017	Venous malformation Adults and children	Sclerotherapy (polidocanol)	Sclerotherapy (ethanol)	Severity evaluation of symptoms by a self-evaluation questionnaire.
	James	Historical control group [66]	2011	Venous malformation Adults and children	Sclerotherapy	Surgery	Evaluation of lesions dimensions by MRI, surgical parameters, and duration of hospital stay.

[a] According to the authors, this study is a "crossover trial using patient's long-term clinical, biological and radiological history before sirolimus treatment as control"
Abbreviations: DXA, dual-energy X-ray absorptiometry; NRS, numerical rating scale; PedsQL, Pediatric Quality of Life Inventory; PROS, PIK3CA-related Overgrowth Spectrum; TAPQOL, TNO-AZL Preschool children Quality of Life; VAS, visual analogue scale

2.3 Dossier complémentaire

2.3.1 PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Pages 1-2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Pages 1-2
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 2
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.	Page 2
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Supplementary file
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.	Page 2
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.	Page 3
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.	Page 3
	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.	Page 3
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.	N/A
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.	N/A
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)).	Page 3
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 3
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 3
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the	Page 3

Section and Topic	Item #	Checklist item	Location where item is reported
		model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	N/A
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	N/A
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	N/A
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.	Page 3
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Figure 1
Study characteristics	17	Cite each included study and present its characteristics.	Pages 3-4 + Tables 1,2,3
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	N/A
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.	Pages 3-4 + Tables 1,2,3
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	N/A
	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.	N/A
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	N/A
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	N/A
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	N/A
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Pages 4-6
	23b	Discuss any limitations of the evidence included in the review.	Pages 4-6
	23c	Discuss any limitations of the review processes used.	Pages 4-6
	23d	Discuss implications of the results for practice, policy, and future research.	Pages 4-6
OTHER INFORMATION			

Section and Topic	Item #	Checklist item	Location where item is reported
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 2
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 2
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 6
Competing interests	26	Declare any competing interests of review authors.	Page 6
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.	Page 6

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

2.3.2 Research terms

Pubmed

("Vascular anomal*" OR "Vascular malformation*" OR "Vascular tumor*" OR "Kasabach-Merritt" OR "Lymphangiom*" OR "Lymphatic malformation*" OR "Venous malformation*" OR "PIK3CA-related overgrowth spectrum" OR “Klippel-Trenaunay syndrome” OR “CLOVES”) AND (“Efficac*” OR "Trial*" OR "Random*” OR "Therapeutic stud*") NOT (Case report*[TI]) NOT(cancer*[TI]) NOT(retrospectiv*[TI])

Central

("Vascular anomal*" OR "Vascular malformation*" OR "Vascular tumor*" OR "Kasabach-Merritt" OR "Lymphangiom*" OR "Lymphatic malformation*" OR "Venous malformation*" OR "PIK3CA -related overgrowth spectrum" OR “Klippel-Trenaunay syndrome” OR “CLOVES”) in Title Abstract Keyword AND ("Efficac" OR "Trial*" OR "Random* " OR "Therapeutic*") in Title Abstract Keyword NOT "Cancer* ", "Case report*", "Retrospectiv*" in Record Title - (Word variations have been searched)

Embase

('vascular anomal*' :ab,ti OR 'vascular malformation*' :ab,ti OR 'vascular tumor*' :ab,ti OR 'kasabach-merritt' :ab,ti OR 'lymphangiom*' :ab,ti OR 'lymphatic malformation*' :ab,ti OR 'venous malformation*' :ab,ti OR 'pik3ca-related overgrowth spectrum' :ab,ti OR 'klippel-trenaunay syndrome' :ab,ti OR 'cloves' :ab,ti) AND ('efficac*' :ab,ti OR 'trial*' :ab,ti OR 'random*' :ab,ti OR 'therapeutic stud*' :ab,ti) NOT 'case report*' :ti NOT cancer* :ti NOT retrospectiv* :ti AND [english]/lim AND [2000-2021]/py AND [humans]/lim AND [embase]/lim NOT [medline]/lim

ClinicalTrials.gov

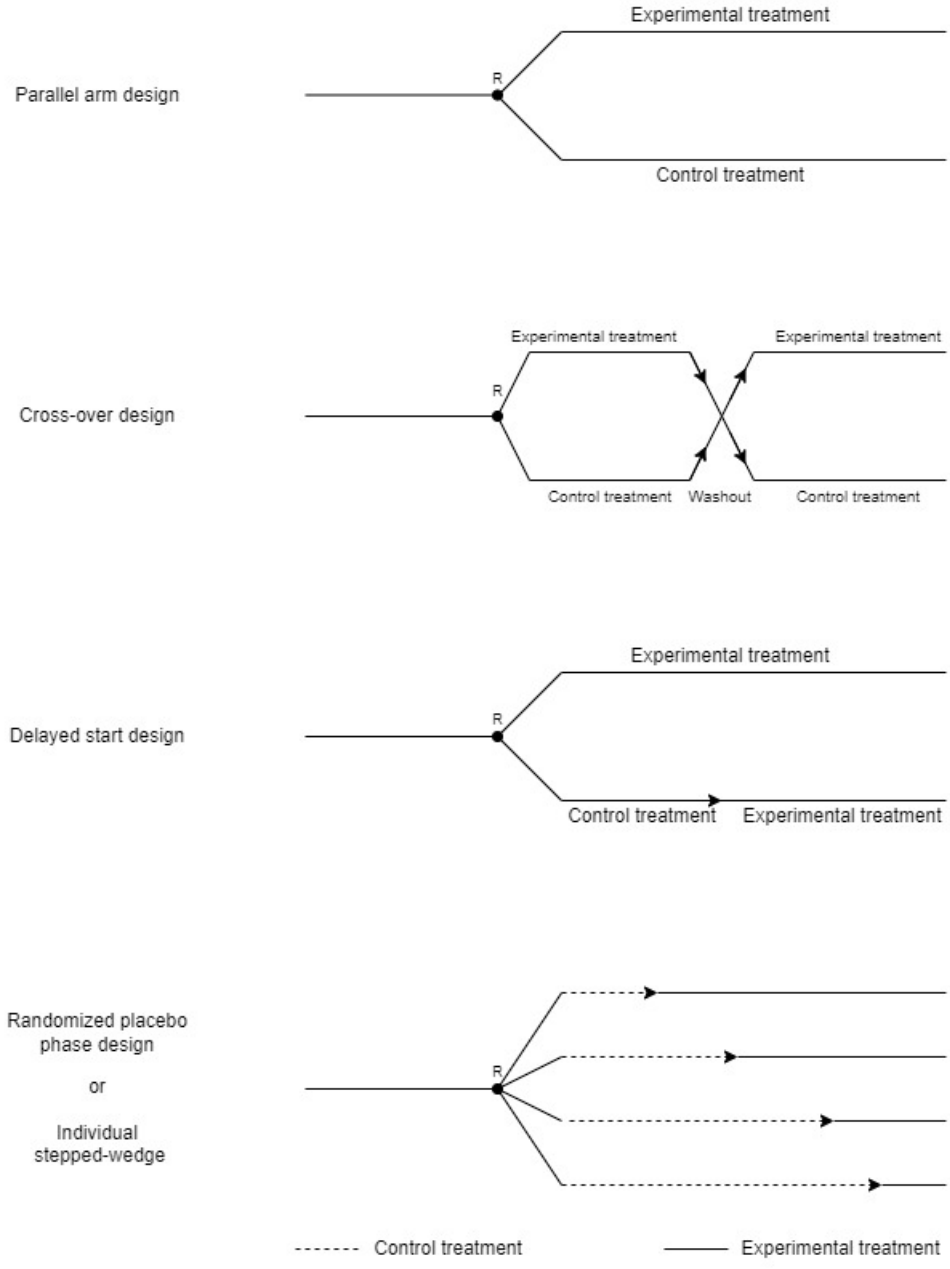
Condition or disease : "Vascular anomalies" OR "Vascular malformations" OR "Vascular tumors" OR "Kasabach-Merritt" OR "Lymphangiomas" OR "Lymphatic malformations" OR "Venous malformations" OR "PIK3CA-related overgrowth spectrum" OR

"Klippel-Trenaunay syndrome" OR "CLOVES" Other therms : "Efficacy" OR "Trials" OR "Randomized" OR "Therapeutic studies" NOT "case reports" NOT "retrospective" NOT "cancers" First posted : 01/01/2000 – 01/25/2021

EU-CTR

(CLOVES AND Efficacy) OR (CLOVES AND Trials) OR (CLOVES AND Randomized) OR (CLOVES AND Therapeutic studies) OR (Vascular anomalies AND Efficacy) OR (Vascular anomalies AND Trials) OR (Vascular anomalies AND Randomized) OR (Vascular anomalies AND Therapeutic studies) OR (Vascular malformations AND Efficacy) OR (Vascular malformations AND Trials) OR (Vascular malformations AND Randomized) OR (Vascular malformations AND Therapeutic studies) OR (Vascular tumors AND Efficacy) OR (Vascular tumors AND Trials) OR (Vascular tumors AND Randomized) OR (Vascular tumors AND Therapeutic studies) OR (Kasabach-Merritt AND Efficacy) OR (Kasabach-Merritt AND Trials) OR (Kasabach-Merritt AND Randomized) OR (Kasabach-Merritt AND Therapeutic studies) OR (Lymphangioma AND Efficacy) OR (Lymphangioma AND Trials) OR (Lymphangioma AND Randomized) OR (Lymphangioma AND Therapeutic studies) OR (Lymphatic malformations AND Efficacy) OR (Lymphatic malformations AND Randomized) OR (Lymphatic malformations AND Therapeutic studies) OR (Venous malformations AND Efficacy) OR (Venous malformations AND Trials) OR (Venous malformations AND Randomized) OR (Venous malformations AND Therapeutic studies) OR (Klippel-Trenaunay syndrome AND Efficacy) OR (Klippel-Trenaunay syndrome AND Trials) OR (Klippel-Trenaunay syndrome AND Randomized) OR (Klippel-Trenaunay syndrome AND Therapeutic studies) OR (PIK3CA-related overgrowth spectrum AND Efficacy) OR (PIK3CA-related overgrowth spectrum AND Trials) OR (PIK3CA-related overgrowth spectrum AND Randomized) OR (PIK3CA-related overgrowth spectrum AND Therapeutic studies) NOT(cancer) NOT(retrospective) NOT(case report)

2.3.3 Designs used in comparative studies included in the final analysis


Parallel arm design
R
Experimental treatment
Control treatment
Cross-over design
R
Experimental treatment
Experimental treatment
Control treatment
Washout
Control treatment
Delayed start design
R
Experimental treatment
Control treatment
Experimental treatment
Randomized placebo phase design
or
Individual stepped-wedge
R
Control treatment
Experimental treatment
Within-person design
Within
each participant
R
Experimental treatment
Site 1
Site 2
Control treatment
R
Randomisation
Switch

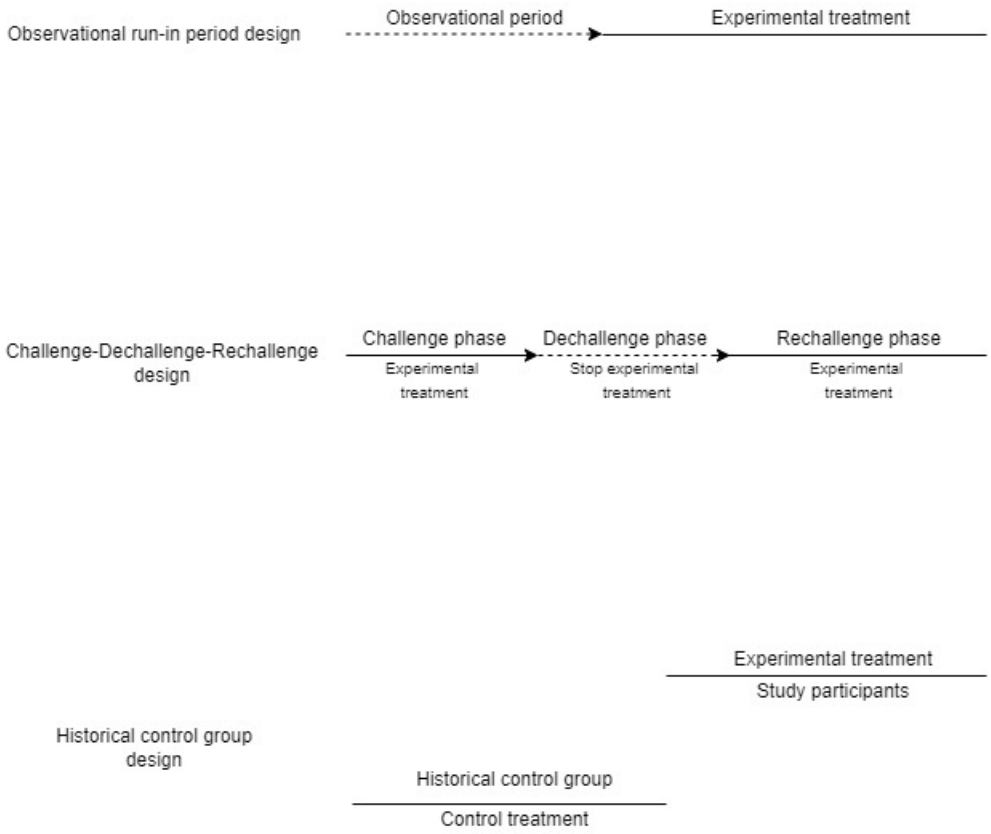


Fig. S1 Designs used in comparative studies included in the final analysis Parallel-group, cross-over, delayed-start, within-person and individual stepped-wedge designs are randomized designs. The observational run-in period, challenge–dechallenge–rechallenge and historical control group designs are not randomized. "R" refers to the randomization and the triangle to the switch between the control treatment and the experimental treatment or vice versa.

Chapitre 3

Discussion générale

Notre revue systématique a mis en évidence plusieurs points intéressants concernant les études sur les AVs. Tout d'abord, il y avait une majorité d'études non comparatives, principalement publiées entre 2011 et 2015 et dont le traitement expérimental était plus « classique » comme la radiologie interventionnelle. La plupart de ces études étaient des cohortes présentant donc un faible niveau de preuves pour évaluer l'efficacité du traitement.

A partir de 2016 sont apparues davantage d'études comparatives dans le but de tester des traitements oraux et utilisant des designs plus innovants, dits « alternatifs » : randomized placebo-phase, within-person and delayed-start.

Plusieurs difficultés provenant de la population d'intérêt ont été mises en exergue et confirmées par notre revue systématique :

- L'hétérogénéité des AVs, remettant en question la randomisation (la stratification est-elle souhaitable ? possible ?), la sélection des résultats (existe-t-il un résultat commun pertinent ?) et l'interprétation des résultats [13, 17, 18].
- La rareté de ces maladies, ce qui implique souvent un nombre inférieur de patients inclus par rapport à la taille d'échantillon prévue [19, 20].
- La difficulté à utiliser un placebo, pour plusieurs raisons :
  - i Simuler une intervention chirurgicale ou radiologique interventionnelle est difficile [21].
  - ii La réticence des parents à ce que leurs enfants reçoivent un placebo étant donnée une durée de vie potentiellement raccourcie par la maladie [22, 23].
  - iii La vulnérabilité des patients étant donné que ce sont principalement des enfants, rendant difficile la réalisation d'examens « inutiles » à plusieurs reprises [7, 24] .

Pour surmonter les problèmes méthodologiques et éthiques cités précédemment, des schémas méthodologiques alternatifs ont été développés mais sont encore peu utilisés en pratique. Ils nécessitent des conditions et situations particulières à leur mise en place que nous présentons dans le tableau 3.1 suivant, accompagnés de leurs avantages et inconvénients.

Globalement, l'utilisation de ces designs alternatifs présente plusieurs avantages :

- La réalisation de comparaisons intra-patients évite la variabilité inter-patients et diminue par conséquent la taille d'échantillon nécessaire,
- Limitation du temps passé sous placebo,
- Tous les participants reçoivent le traitement expérimental avant la fin de l'essai, ce qui évite un rejet des parents et/ou participants lors du recrutement.

TABLEAU 3.1 – Avantages, inconvénients et conditions/situations d'utilisation des designs alternatifs

	DESIGNS ALTERNATIFS	AVANTAGES	INCONVENIENTS	CONDITIONS/SITUATIONS
RANDOMISÉS	**Cross-over**	Taille d'échantillon plus faible que pour un essai en deux bras parallèles. Tous les patients reçoivent le traitement expérimental. Prend en compte la variabilité intra-individuelle et non inter-individuelle.	Risque de l'effet carry-over (effet du traitement expérimental sur la période contrôle). Durée de suivi des patients plus longue : augmente le risque de perdu de vue compromettant la puissance de l'étude. Sensibilité aux abandons et données manquantes.	Etude de maladies chroniques d'évolution stable. Evaluation de traitements dont le délai d'action est relativement rapide. L'effet des traitements doit être réversible. Période de sevrage suffisamment longue.
	Delayed start	Facilité de recrutement des patients : garantie que tous les patients reçoivent le traitement expérimental à la fin de l'étude. Possibilité de poursuivre le traitement en dehors du contexte de l'étude.	Absence d'aveugle de la 2nde période. Absence de comparabilité des deux groupes en début de 2nde période, rendant difficile l'interprétation des résultats.	Evaluation du critère de jugement avant le début de la seconde période. Evaluation de la 2nde période limitée aux résultats secondaires, ce qui ne modifiera pas la conclusion de l'étude.
	Randomized placebo-phase	Taille d'échantillon plus faible que pour un essai en deux bras parallèles. Facilité de recrutement des patients : garantie que tous les patients reçoivent le traitement expérimental à la fin de l'étude. Prend en compte la variabilité intra-individuelle et non inter-individuelle.	Risque d'abandon des participants si la phase contrôlée sous placebo est trop longue. Capacité limitée à estimer l'ampleur de l'effet pour les thérapies de faible puissance. Plus la thérapie est de faible puissance plus il sera nécessaire d'avoir un grand nombre de participants pour détecter l'effet traitement.	Phase de contrôle suffisamment courte pour éviter les variations dans le temps et suffisamment longue pour avoir des mesures valides. Evaluation de traitements de fond ou de thérapies induisant une rémission à l'aide de paramètres de survie. Dans le cas de maladies à évolution rapide et défavorable. Convient mieux au début du développement d'un nouveau traitement et/ou dans le cas où la réalisation d'un essai contrôlé randomisé serait difficile ou inacceptable.
	Within-person	Elimination des facteurs de confusion entre les bras de l'essai. Caractéristiques à *baseline* identique entre les deux bras : évite la variabilité inter-patient.	Application limitée aux traitements locaux sans effet systémique (sinon effet *carry-over*). Difficulté à mettre en place l'aveugle de l'investigateur.	Surtout utilisé en dermatologie et ophtalmologie. Evaluation de traitements à action locale principalement.

TABLEAU 3.1 – Avantages, inconvénients et conditions/situations d'utilisation des designs alternatifs (suite)

			Difficulté de l'analyse statistique en cas de plus de 2 observations par patient. Influence potentielle du traitement expérimental d'une partie du corps à une autre partie de la même entité (effet *carry-across*). Evènements indésirables systémiques possiblement masqués.	
NON RANDOMISES	**Contrôle historique**	Facilité de recrutement des patients.	Caractéristiques initiales des patients des 2 groupes différentes : empêche de mettre en évidence l'effet traitement (effets confondants). Biais de sélection : les patients recevant le traitement expérimental pourraient avoir été sélectionné dans un pool de patients « bon répondeurs » (surestimation de l'effet traitement). Absence d'aveugle : biais de performance et de détection. Différences possibles dans la méthodologie d'évaluation des *outcomes* entre les deux groupes. Evolution des *outcomes* au cours du temps.	Utilisation principalement dans le cas de maladies rares.
	Challenge-dechallenge-rechallenge	Identification rapide de l'agent à l'origine des symptômes. Confirmation de l'efficacité d'un traitement spécifique : fournit les preuves solides d'une relation causale entre une intervention et un *outcome*.	Facteurs et biais de confusion. Préoccupations éthiques liées au fait de « challenger » et « dé-challenger » les patients.	Applicable à certains types d'intervention. Non réalisation dans tous les contextes cliniques. Principalement utilisé en pharmacovigilance.
	Période observationnelle de « run-in »	Collecte de données cliniques utiles. Dépistage des patients inéligibles ou non conformes.	Validités externe et interne affectées : l'exclusion de patients peut provoquer l'exagération de l'effet en intention de traiter (groupe de bons répondeurs favorable à l'effet traitement).	

Parmi ces schémas méthodologiques se trouve le « stepped-wedge individual randomized trial » (SWT) aussi appelé « randomized placebo phase design » (RPPD).

Ce design a été mis en œuvre dans l'essai PERFORMUS afin d'évaluer l'efficacité du sirolimus dans le traitement des malformations vasculaires de bas-débit chez l'enfant [5, 25]. Il s'agissait d'un essai clinique randomisé multicentrique, ouvert, qui a inclus 59 enfants âgés de 6 à 18 ans présentant une malformation vasculaire à bas débit entre 2015 et 2018. Les patients ont débuté l'essai par une période d'observation, puis sont passés à une période interventionnelle durant laquelle ils ont reçu du sirolimus par voie orale. La date de switch entre ces deux périodes a été randomisée entre les mois 4 et 8. Au final, l'étude a duré 12 mois pour chaque patient.

En effet, dans un SWT, les patients sont alloués de façon aléatoire à une séquence, chaque séquence étant la succession d'une période contrôle (pas de traitement, un traitement standard ou un placebo) et une période avec traitement à l'étude. Ce qui différencie les séquences est la date du switch entre la période contrôle et la période expérimentale. Ce design permet qu'à la fin de l'essai tous les patients reçoivent le traitement expérimental mais avec une durée variable de période contrôle et donc également une durée variable de période expérimentale. Ce design présente des avantages comme un nombre de sujets nécessaire inférieur à un schéma en deux groupes parallèles, et une facilité de recrutement car tous les patients reçoivent finalement le traitement expérimental [14, 16, 26–28]. Cependant, sa mise en place nécessite des conditions méthodologiques particulières devant être clairement définies.

C'est pourquoi, dans le cadre de ma thèse d'université, je poursuis mes recherches sur ce design à travers un travail statistique de simulation dont l'objectif sera de clairement définir et valider la formule de calcul d'effectif dans le cadre d'un SWT. Cette formule sera validée à l'aide d'une étude de simulations.

Chapitre 4

Conclusion et perspectives

Ma thèse d'université se poursuivra par un travail méthodologique conduit en s'appuyant sur une méthode de consensus Delphi international. Il s'agira de déterminer pour plusieurs situations cliniques le schéma méthodologique le plus approprié, en s'intéressant particulièrement aux designs alternatifs relevés dans notre revue systématique. Les différentes situations présentées sous forme de vignettes seront restreintes aux malformations vasculaires et à certains types de prise en charge (traitements *per os*, injectables et topiques, chirurgie et radiologie interventionnelle). Nous pourrons ensuite formuler des propositions qui seront envoyées pour validation auprès d'un groupe d'experts mais aussi de patients et d'aidants. Ces experts seront sollicités par mail via les sociétés savantes (ISSVA, SFDP, ESPD) et les filières maladies rares (FIMARAD, FAVA-MULTI, TETECOU).

Ce travail méthodologique permettra d'attribuer à différentes situations cliniques fixées un schéma méthodologique particulier, qui aura été jugé pertinent et acceptable par les différents acteurs concernés.

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Annexe A

Formulaire d'extraction des données

Extractor name

For all items where this is not applicable, write NA.

A. GENERALITIES

A1. First author

For protocols, note the principal investigator.

A2. Publication year

For protocols, note the date of protocol's publication on the clinical trials register.

A3. Journal

A4. Source :

1	ClinicalTrials.gov
2	Medline
3	Embase
4	Central
5	European Union Clinical Trials

A5. Article type :

1	Report
2	Protocol

A6. Registration number :

A7. International study : ☐ Yes ☐ No ☐ Unclear

A8. Subcontinent of study recruitment:

1	North America
2	South America
3	Europe
4	Asia
5	Middle East
6	North Africa
7	Sub-Saharan Africa
8	Oceania
9	Unclear

A9. Multicenter study : ☐ Yes ☐ No ☐ Unclear

A10. If A9= yes, number of centres:

B. STUDY CHARACTERISTICS

B1. Is it a comparative study? ☐ Yes ☐ No

B2. If B1 = yes, what is the objective?

1	Superiority
2	Non inferiority or equivalence
3	Unclear

B3. If B1 = no, what type of study is it?

Select prospective cohort if specified as such, otherwise select case series.

1	Prospective cohort
2	Case series
3	Unclear

For B4 to B6 and B8 to B10 cases, fill in only if B1 = yes.

B4. Is it a randomized study? ☐ Yes ☐ No

B5. If B4 = yes, what is the type of randomisation?

1	Simple
2	Block
3	Stratified
4	Unequal
5	Not described

B6. If B4 = yes, what is the trial design?

1	Parallel arms
2	Cross-over
3	N-of-1 or series of N-of-1
4	Randomized placebo phase
5	Withdrawal
6	Factorial
7	Cluster stepped wedge
8	Within-person
9	Other
10	Unclear

B7. Design description by the author.

B8. If B4 = yes, what is the number of treatments compared?

B9. If B4 = yes, and if adapted, what is the allocation ratio?

B10. Design justification by the authors

B11. Are there any important changes after trial beginning? ☐ Yes ☐ No ☐ NA

Check the protocol if the registration number is specified.

Ex: longer study period, design modification, modified selection criteria, etc ...

B12. If B10 = yes, describe the changes and the reasons.

B13. Is one of these actors blinded?
Select the actors concerned, otherwise check "No" (no blind) or "NA" (not specified or not concerned).

1	Participants
2	Care provider
3	Outcome assessor
4	No
5	NA

B14. For the experimental group, what is the intervention type?

1	Parenteral drug
2	Enteral drug
3	Topical drug
4	Interventional radiology
5	Physical
6	Surgery
7	Other

B15. If B1 = yes, for the control group, what is the standard treatment? *If none, select placebo.*

1	Placebo, sham intervention
2	Active drug
3	Interventional radiology
4	Active physical intervention
5	Surgery
6	No treatment

C. PARTICIPANTS CHARACTERISTICS

C1. What are the included participants diseases?

1	Simple lymphatic malformations
2	Simple venous malformations
3	Arteriovenous malformations
4	Slow flow combined malformations or syndromic
5	Rare vascular tumors

C2. What is the type of study population?

1	Paediatric
2	Adult
3	Both
4	NA

D. STATISTICAL CONSIDERATIONS

D1. If specified, what was the estimated sample size? ____

D2. What is the number of patients included? ____

Note the total number of patients included and the number of patients included with the pathology of interest.

E. FUNDING BODY

What was the funding sources of the study ?
If the treatment is given free of charge by a laboratory: do not consider it as private funding.

1	Private
2	Public
3	Both private and public
4	No specific funding
5	Not reported

F. COMMENTS

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Je, soussignée Aude ALLEMANG--TRIVALLE

Déclare être pleinement conscient(e) que le plagiat de documents ou d'une partie d'un document publiés constitue une violation des droits d'auteur ainsi qu'une fraude caractérisée. *(Décret n°92-657 du 13 juillet 1992)*

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SIGNATURES DU DIRECTEUR DE THESE ET DU DOYEN

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Sujet : Designs utilisées dans les études thérapeutiques sur les anomalies vasculaires superficielles rares : une revue systématique

Tours, le : 15/06/2023

Le(s) Directeur(s) de Thèse :

Vu et Transmis :
Le Doyen Le directeur de la Faculté des Sciences Pharmaceutiques

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TITRE DE LA THÈSE

Designs utilisés dans les études thérapeutiques sur les anomalies vasculaires superficielles rares : une revue systématique

RÉSUMÉ DE LA THÈSE

Les anomalies vasculaires superficielles rares représentent un large panel de maladies. Leur prise en charge est difficile compte tenu de leur large spectre et du manque d'essais cliniques évaluant l'efficacité des traitements. Un essai clinique randomisé sur les anomalies vasculaires est difficile à mettre en place en raison de la rareté des maladies sans compter que la population d'intérêt est souvent composée d'enfants. Par conséquent, des designs appropriés sont nécessaires. Nous avons réalisé une revue systématique méthodologique pour identifier les designs mis en œuvre pour étudier le traitement des anomalies vasculaires superficielles rares.

Nous avons effectué une recherche documentaire le 25 janvier 2021 dans les bases de données PubMed, CENTRAL, Embase, ClinicalTrials.gov et European Union Clinical Trials Register. Sur 2046 articles ou enregistrements identifiés, nous avons retenu 97 études (62 rapports et 35 protocoles) : 25 études contrôlées randomisées, 7 études comparatives non randomisées, 64 cohortes prospectives et 1 série de cas. Parmi les 32 études comparatives incluses, 21 ont utilisé un schéma en groupes parallèles. Les 11 autres études ont utilisé des designs alternatifs qu'ils soient randomisés tels que les cross-over, randomized placebo phase, delayed-start, within-person, ou non (challenge-dechallenge-rechallenge ou ont utilisé un groupe contrôle historique ou ont mis en place une période observationnelle de “run-in”).

Notre revue systématique met en évidence le manque d'essais contrôlés randomisés dans les anomalies vasculaires superficielles rares en raison de la rareté des patients et de leur hétérogénéité. Cependant, de nouvelles conceptions émergent et peuvent surmonter les limites des schémas en groupes parallèles.

MOTS-CLÉS SIGNIFICATIFS DE SON CONTENU, ATTIBUÉS PAR LE CANDIDAT EN LIAISON AVEC LA BIBLIOTHÈQUE UNIVERSITAIRE ET LES MEMBRES DU JURY
Designs, Méthodologie, Essais cliniques, Anomalies vasculaires superficielles, Maladies rares

JURY

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