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Thèse

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Diplôme d'État

par

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Tofacitinib topique 2% versus placebo en adjonction du propionate de clobétasol 0,05% pour le traitement des pelades chez l'enfant de 4 à 17 ans : protocole pour un essai en add-on contrôlé, randomisé, en double-aveugle et multicentrique

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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
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Je donnerai mes soins gratuits à l'indigent,
et n'exigerai jamais un salaire au-dessus de mon travail.

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je rendrai à leurs enfants
l'instruction que j'ai reçue de leurs pères.

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si j'y manque.

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Table des matières

I. INTRODUCTION GÉNÉRALE 12

II. PROTOCOLE DE RECHERCHE TOPPER 19

1. RESUME EN FRANÇAIS 19

2. ARTICLE SCIENTIFIQUE EN ANGLAIS 21

Abstract *24*

Background *26*

Methods: participants, interventions, and outcomes *29*

Methods: assignment of interventions *34*

Methods: data collection, management and analysis *35*

Methods: monitoring *36*

Ethics and dissemination *37*

Discussion *40*

Declarations *43*

References *45*

Figures *49*

Additional files *53*

III. CONCLUSION GENERALE 68

I- INTRODUCTION GÉNÉRALE

La pelade est une cause bénigne et fréquente d'alopécie acquise non cicatricielle chez l'enfant et l'adulte. L'étiologie de cette pathologie auto-immune est complexe, probablement d'origine multifactorielle (1). L'incidence cumulative au cours de la vie est estimée à 2 % (2). Chez l'enfant, le pic d'incidence est d'environ 12 ans chez le garçon et 9 ans chez la fille (3). On distingue plusieurs formes cliniques : pelade en plaque unique ou plaques multiples (**Figure 1**), pelade ophiasis, pelade décalvante totale et pelade universelle.

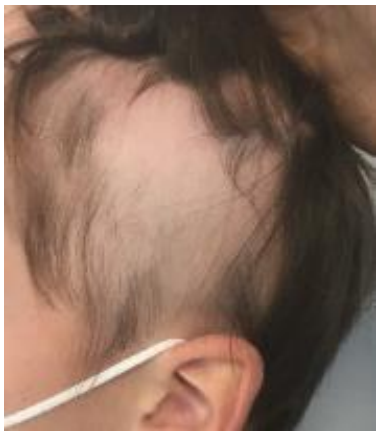

Figure 1 : Pelade en plaques.

Le diagnostic de pelade est fait lors de l'examen clinique. On observe une ou plusieurs plaques alopéciques bien délimitées avec un cuir chevelu sain. Le test de traction est positif. En trichoscopie, on observe des cheveux en point d'exclamation, des points noirs, des points jaunes et des cheveux coudés (**Figure 2**).

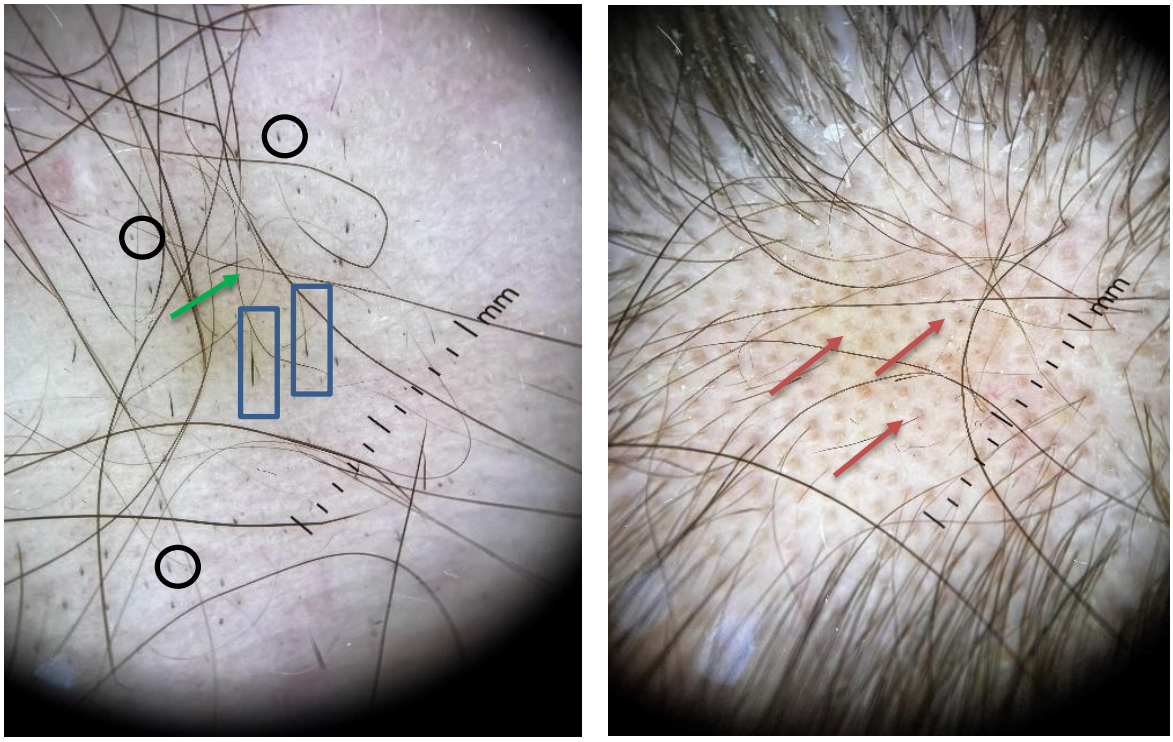

Figure 2 : Examen trichoscopique d'une plaque de pelade. Cheveux en points d'exclamation (rectangles bleus), points noirs (cercles noirs), points jaunes (flèches rouges) et cheveux coudés (flèche verte).

Des modifications non spécifiques des ongles peuvent être présentes dans 10 à 20% des patients comme par exemple des ponctuations unguéales en dé à coudre, des stries longitudinales, une trachyonychie, une lunule émiettée ou des onychodystrophies majeures (4). L'examen histologique, rarement nécessaire, montre un infiltrat lymphocytaire péri-bulbaire dense à la phase aiguë qui ressemble à un "essaim d'abeilles" (5). Son évolution est imprévisible.

Il n'existe pas de recommandations pour la prise en charge des pelades chez l'adulte et chez l'enfant. Les traitements actuellement proposés sont les dermocorticoïdes, les injections intra-lésionnelles de corticoïdes, le minoxidil, la PUVAthérapie, l'immunothérapie de contact

ou des traitements systémiques comme la corticothérapie générale et le méthotrexate. Le choix du traitement dépendra de l'étendue et de l'ancienneté de la pelade. Actuellement, les dermocorticoïdes sont le traitement de première intention pour les enfants atteints de pelade en plaques (6).

La voie de signalisation JAK/STAT (Janus Kinase/Transducteur et Activateur de Signal de la Transcription) jouant un rôle majeur dans la régulation du système inflammatoire et immunitaire, intervient dans la physiopathologie de la pelade (7). Les Janus kinase, appelées JAK, sont des enzymes à activité tyrosine kinase intracellulaires qui interagissent au niveau de la portion intracellulaire du récepteur cytokinique. Lorsque qu'une cytokine se fixe sur son récepteur spécifique, une cascade de phosphorylation se produit (phosphorylation des enzymes JAK puis des molécules STAT [*Signal Transducers and Activators of Transcription*]), induisant une translocation nucléaire des molécules STAT phosphorylées permettant la transcription et la régulation de l'expression de gènes spécifiques (**Figure 3**).

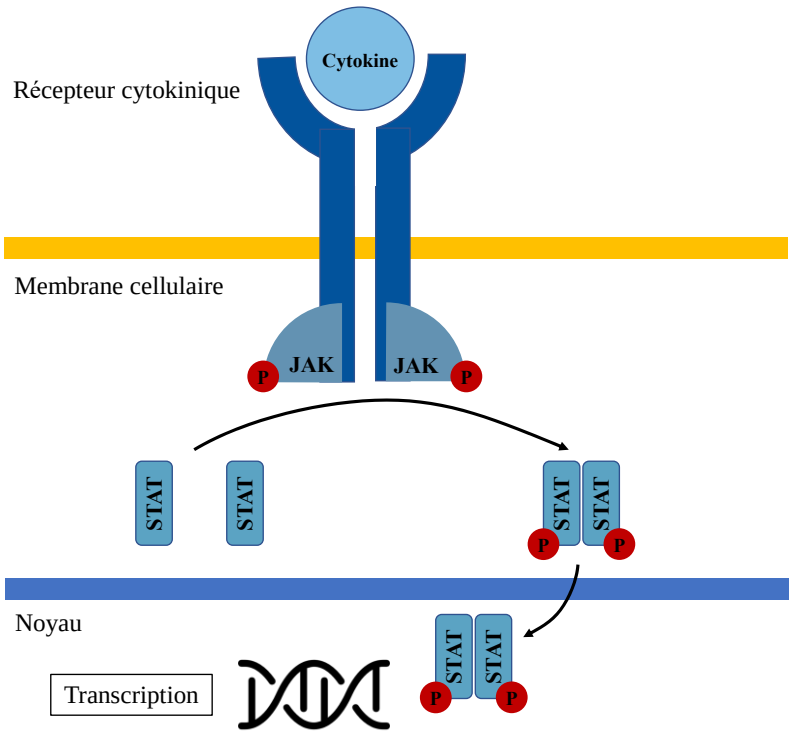

Figure 3 : Mécanisme d'action de la voie de signalisation JAK-STAT.

Les inhibiteurs de JAK réduisent l'inflammation en empêchant l'action des cytokines inflammatoires par le blocage de l'enzyme JAK. Ils sont utilisés depuis plusieurs années dans le traitement de maladies inflammatoires digestives et rhumatismales (rectocolite hémorragique et polyarthrite rhumatoïde par exemple) et leurs indications sont en expansion constante. En dermatologie, dans le courant des années 2010, de nombreuses séries de cas et quelques essais ont étudié le tofacitinib dans le traitement de la pelade.

Le tofacitinib est un inhibiteur de JAK de 1ère génération ciblant principalement JAK1 et JAK3. L'efficacité du tofacitinib oral (administré à la dose de 5 mg deux fois par jour pendant 12 semaines) était bonne avec une réponse au traitement chez 64% des patients et 32% des patients ont présenté une amélioration de plus de 50 % de leur score SALT (*Severity ALopecia Tool*) en 3 mois (8). Des évènements indésirables ont été rapportés dans 7-22% des patients (9) avec principalement la survenue d'infections, notamment bactériennes et virales (herpès et zona). Des effets indésirables à type de céphalées, acné et perturbations du bilan hépatique ont également été décrits (10). Des événements thromboemboliques (thrombose veineuse profonde et embolie pulmonaire) ont été décrits chez des patients traités par tofacitinib pour une polyarthrite rhumatoïde (11) mais n'ont pas été rapportés dans les essais sur la pelade. Cependant, les effets secondaires systémiques des anti-JAK par voie orale limitent leur utilisation chez l'enfant.

L'utilisation topique des anti-JAK dans la pelade s'est développée depuis 2017 avec l'utilisation du tofacitinib topique, qui est le plus utilisé, et du ruxolitinib topique. Plusieurs cas cliniques et séries de cas pour le traitement de la pelade de l'enfant ont été rapportés. Bayart et al ont rapporté une série de cas de 6 patients pédiatriques avec une pelade traités par des inhibiteurs topiques de JAK (4 avec 2 % de tofacitinib topique et 2 avec 1 à 2 % de ruxolitinib topique). Pour 4 des 6 patients, une repousse partielle des cheveux a été rapportée (12). En 2018, Putterman et al ont rapporté une réduction de 32,3% du score SALT (*Severity*

of Alopecia Tool) chez 11 enfants âgés de 4 à 16 ans traités par tofacitinib topique 2% 2 fois par jour pendant 8 à 72 semaines. Aucun effet secondaire n'était rapporté en dehors d'une irritation sur le site d'application chez un patient. Cependant, seuls 3 patients sur 11 avaient une repousse cosmétiquement acceptable (13).

Il n'y a pas de données publiées sur l'association des inhibiteurs topiques de JAK et des corticoïdes topiques et aucun essai contrôlé randomisé n'a été conduit dans la population pédiatrique. En raison des résultats variés des inhibiteurs de JAK topiques en monothérapie, nous souhaitons évaluer l'efficacité d'une stratégie thérapeutique incluant des inhibiteurs de JAK topiques en adjonction aux corticoïdes topiques pour les pelades de l'enfant.
A ce jour, il n'existe pas de produit commercialisé pour le tofacitinib topique et consiste en une préparation magistrale à partir du tofacitinib en comprimés. La production de ce traitement sera réalisée à l'aide du laboratoire pharmaceutique américain ChemistryX (Philadelphie, USA, Dr Lars Brichta) qui a développé ce traitement aux États-Unis avec l'obtention d'une autorisation de la FDA *(Food and Drug Administration)*. Le tofacinitib topique a été évalué par l'équipe de ChemistryX dans plusieurs publications (12, 13). La production sera donc réalisée par les pharmaciens hospitaliers de la Pharmacie - Recherche Clinique & référent Médicament de Thérapie Innovante du CHU de Tours après une formation sur la production par le laboratoire ChemistryX.

Mon rôle dans ce projet a consisté en l'élaboration et la rédaction du protocole de recherche, avec l'aide du Centre d'Investigation Clinique (CIC) et de la Pharmacie - Recherche Clinique & référent Médicament de Thérapie Innovante du CHU de Tours.
Ce projet de recherche a été déposé à l'appel d'offre de la Direction Générale de l'Offre de Soins (DGOS) et a été retenu comme Programme Hospitalier de Recherche Clinique National (PHRC-N) en 2020.

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II. PROTOCOLE DE RECHERCHE TOPPER

1. Résumé en français

Rationnel : La pelade est une affection auto-immune fréquente, caractérisée par une alopécie non cicatricielle acquise. Il n'existe pas de recommandations pour la prise en charge de cette pathologie. Les inhibiteurs de la Janus Kinase (JAK) ont des propriétés anti-inflammatoires. Plusieurs études ont déjà évalué l'efficacité du tofacitinib oral dans le traitement de la pelade mais des effets indésirables limitent son administration chez les enfants. Les inhibiteurs de JAK topiques ont été utilisés dans plusieurs séries de cas avec une efficacité modérée dans le traitement de la pelade pédiatrique. L'objectif de cette étude est d'évaluer l'efficacité du tofacitinib topique 2% en adjonction au propionate de clobétasol pour les pelades de l'enfant.

Méthodes : Cette étude multicentrique, randomisée, en double aveugle, inclura 120 patients âgés de > 3 et < 18 ans, avec un diagnostic de pelade en plaque confirmé à la dermoscopie, stable ou avec une aggravation depuis plus de 2 mois, sans aucun signe de repousse spontanée. Les patients seront randomisés avec un ratio 1 :1 dans le groupe expérimental (tofacitinib topique à 2 % en en adjonction au propionate de clobétasol à 0,05 %) ou dans le groupe témoin (placebo en adjonction au propionate de clobétasol à 0,05 %). Le tofacitinib topique en crème et le placebo crème seront appliqués deux fois par jour, le propionate de clobétasol une fois par jour pendant une période de 12 semaines par le patient ou ses parents sur les zones affectées. A la fin de la période de 12 semaines, les traitements topiques seront arrêtés, le critère de jugement principal sera mesuré. A la semaine 24, les patients seront revus pour évaluer l'efficacité et la récidive. Le critère de jugement principal sera le pourcentage de sujets atteignant une repousse de 50 % des cheveux. Il sera évalué à l'aide du score international validé *Severity ALopecia Tool* (SALT). Le score sera évalué par un dermatologue dans chaque centre, en aveugle. La proportion de patients présentant une repousse complète, la variation du score SALT entre semaine 0 et semaine 12, l'efficacité du traitement évaluée par le patient ou ses parents et la

qualité de vie seront évalués en critères de jugement secondaires La tolérance clinique et biologique seront évaluées à la semaine 6 et 12.

Discussion : Actuellement, les traitements disponibles pour la pelade pédiatrique sont limités. Il existe un réel besoin de développer de nouveaux traitements, en particulier avec une administration topique. Si l'essai démontre l'efficacité et la sécurité du tofacitinib 2% topique ajouté au propionate de clobétasol, cela conduira à un réel changement thérapeutique et pourrait devenir un traitement de première ligne pour la pelade de l'enfant.

2. Article scientifique en anglais

Topical tofacitinib 2% versus placebo added to clobetasol propionate 0.05% for alopecia areata in children aged 4 to 17 years old (TOPPER): protocol for a multicentre randomised, double-blind, placebo-controlled add-on trial

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The authors declare no conflict of competing interests.

Trial registration

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EU Clinical Trials Register EudraCT Number: awaiting

Protocol version: version 1, March 4, 2021

Abstract

Background

Alopecia areata (AA) is a common autoimmune disorder, characterized by non-scarring hair loss with preservation of hair follicles. Therapeutic strategies for AA in children are lacking. Janus Kinase (JAK) inhibitors have anti-inflammatory properties. Topical JAK inhibitors have been proven effective and well-tolerated in pediatric AA in case reports. The objective is to assess the efficacy of 2% topical tofacitinib added to clobetasol propionate 0.05% in alopecia areata in children, versus vehicle and clobetasol propionate.

Methods

This multicenter randomized placebo-controlled double-blind add-on trial aims to include 120 patients aged > 3 years and < 18 years with a diagnosis of patchy AA of the scalp made on clinical examination and confirmed by dermoscopic examination, stable or worsening disease for more than 2 months with no evidence of spontaneous hair regrowth. Patients will be randomly allocated to the experimental group (topical tofacitinib 2% added to clobetasol propionate 0.05%) or to the control group (topical vehicle added to clobetasol propionate 0.05%) in a 1:1 ratio. Tofacitinib and placebo will be applied twice daily, clobetasol propionate once daily for a period of 12 weeks by the patient or parents on affected areas. At the end of the 12-week-treatment period, patients achieving 50% of scalp hair regrowth will be considered as successes (primary outcome). This will be evaluated using the validated international Severity ALopecia Tool score (proportion of patients reaching SALT 50). Scoring will be assessed by a dermatologist in each centre blinded to the treatment. At week 24, patients will be seen to evaluate efficacy and recurrence. Secondary outcomes will include efficacy using the SALT score, complete hair regrowth, patient-reported global efficacy, quality of life and pain assessment. Clinical and biological safety will be evaluated at weeks 6 and 12.

Discussion

Currently, treatments available for pediatric alopecia areata are limited. There is a real need to develop new treatments, particularly with a topical administration. If the trial demonstrates efficacy and safety of topical tofacitinib 2% added to clobetasol propionate, this will lead to a real therapeutic change and could become a first-line treatment for paediatric AA.

Keywords

Alopecia areata, Janus kinase inhibitors, tofacitinib, topical corticosteroids, children, topical, quality of life

Background

Background and rationale

Alopecia areata (AA) is a common autoimmune disorder, characterized by non-scarring hair loss with preservation of hair follicles. AA affects patients at different ages but most cases occur before the age of 20 years (1). The cumulative lifetime incidence of AA is estimated at 2% (2). Pediatric AA patients represented 18.1% of AA patients of all ages with a ratio of 1.25:1 (female to male ratio) (3). Most often, alopecia in children is mild to moderate in severity (less than 50% hair loss) (4). Approximately 80% of children aged 4-16 years with AA reported impaired health-related quality of life, with increased risk of anxiety, depression, and obsessive-compulsive disorder (1, 5).

Exact pathogenesis of AA is still unclear and its evolution unpredictable. AA originates from a peribulbar lymphocytic infiltrate in hair follicles produced by a cascade increase in inflammatory mediators (6,7). Diagnosis is made on physical examination and includes clinical findings, traction test and trichoscopy (8).

There are no guidelines for management of AA in children with current treatments and efficacy limited. Topical corticosteroids are the first-line treatment but are not sufficiently efficient in 70% of cases (9). Systemic drugs including corticosteroids or methotrexate are sometimes used as second line therapy (1) but have not shown high efficacy and expose to adverse effects in children. None of them are Food and Drug Administration (FDA) or European Medicines Agency (EMA) approved.

Janus Kinase (JAK) family consists of 4 members: JAK1, JAK2, JAK3, and Tyrosine kinase 2 (TYK2) (10). JAK pathway is an ubiquitous intracellular signaling network involved in many inflammatory and autoimmune diseases (11). Clinical studies have shown their efficacy on inflammatory skin disorders, such as atopic dermatitis and psoriasis (12, 13). Rationale for developing JAK inhibitors is therefore strong.

Several studies have shown that JAK inhibitors promote rapid hair regrowth (14). More recently, they have shown efficacy in several cases of AA in adults and children (15, 16). According to a systematic review and meta-analysis based on 14 studies, tofacitinib has reasonable effectiveness (17).

Nevertheless, oral JAK inhibitors are not without side effect. The most commonly reported side effects are upper respiratory infections and urinary tract infections, risk of VZV infection, headaches, dyslipidemia and mild increase in liver transaminase levels (18, 19). Oral tofacitinib is the first JAK inhibitor developed for the treatment of autoimmune disease (20), FDA and EMA approved for the treatment of rheumatoid arthritis, psoriatic arthritis and ulcerative colitis (10). Recently, in dermatology, FDA and EMA approved respectively oral upadacitinib (JAK1 inhibitor) (21) and oral baricitinib (JAK1/2 inhibitor) for moderate to severe atopic dermatitis in adult (22).

Topical JAK inhibitors have been proven effective and well-tolerated in pediatric AA in case reports (23). In a case series of 11 patients with paediatric AA treated with 2% topical tofacitinib, the average change in SALT score was a reduction of 32.3% (24).

Topical tofacitinib is the oldest and most used of topical JAK inhibitors (25), developed since 2013 first for psoriasis (26) and then for atopic dermatitis (13). Main side effects reported for topical tofacitinib are only mild symptoms: grade I and II infections, transient elevation of liver transaminase or cholesterol level (26,27). No severe side effects have been reported. Local adverse effects (pruritus, application side pain) were reported in less than 3% of patients (13).

There is no published data on the association of topical JAK inhibitors and topical corticosteroids and no randomised controlled trial conducted in paediatric population. Because of varied results of topical JAK inhibitors as a monotherapy, we would like to

evaluate the efficacy of a therapeutic strategy including topical JAK inhibitors added to topical corticosteroids for AA in children.

Objectives

We aim at running a clinical trial (Topical TOfacitinib versus Placebo added to clobetasol Propionate for alopEcia aReata TOPPER) to assess the efficacy (> 50% hair regrowth) of a 12-week application period of topical tofacitinib 2% added to clobetasol propionate 0.05% in alopecia areata in children, versus vehicle and clobetasol propionate.

Trial design

TOPPER is designed as a multicentre individually randomised (1:1 allocation), double-blind (patient, investigator and outcome assessor), vehicle-controlled, superiority add-on trial, comparing topical tofacitinib 2% added to topical corticosteroids (clobetasol propionate 0.05%) versus topical vehicle added to topical corticosteroids (**Figure 1**).

For each patient, topical treatments will be applied for a 12-week period by the patient or the parent to the affected areas (**Figure 2**). Parents/patients, investigators and outcome assessors are blinded to treatment. Parents will complete a daily notebook to assess therapeutic adherence.

At the end of the 12-week-period, topical treatments will be stopped, and the primary outcome will be measured.

At week 24, patients will be seen to evaluate efficacy and recurrence. In case of new flair or hair loss between week 12 and week 24, topical steroids will be prescribed, as a rescue treatment, and it will be mentioned in the daily notebook.

Methods: participants, interventions, and outcomes

Study setting

The study will involve 14 French centres, all involved in tertiary care centres for paediatric dermatology (**Additional file 1**).

Eligibility criteria

Inclusion criteria

Eligible patients will be > 3 years old and < 18 years and have a diagnosis of patchy AA of the scalp made on clinical examination and confirmed by dermoscopic examination with stable or worsening disease for more than 2 months with no evidence of spontaneous hair regrowth and at least one patchy AA ≥ 2 cm^2 and total scalp area < 75%. The patient must not have previous treatment oral or topical treatment (including topical superpotent corticosteroids) or must have a treatment stopped for at least 1 month to avoid biasing the results.

The age range of > 3 years and < 18 years was chosen because AA before the age of 4 is less common and we need a scalp area involved large enough to apply the topical treatments. We limited the trial to patchy AA and excluded patients with alopecia totalis or alopecia universalis because of variable responses that may occur between those patients. Moreover, although the dermal absorption of tofacitinib is limited, the risk of systemic passage will be increased for large surface scalp areas to treat.

Exclusion criteria

Participants will be excluded if they meet any of the following criteria: alopecia totalis or alopecia universalis; prior treatment with oral or topical JAK inhibitors within 12 months prior to the study; immunosuppression; ongoing neoplasia; active infection or chronic infectious disease; severe hepatic impairment; personal history of thromboembolism; dyslipidaemia; local fungal, viral or bacterial infection at the site of AA; known allergy to any

component of the topical tofacitinib or clobetasol preparation or vehicle and pregnancy or breastfeeding.

Intervention

Each patient will be randomly allocated to receive either topical tofacitinib 2% added to clobetasol propionate 0.05% or topical vehicle added to clobetasol propionate 0.05% applied for 12 weeks (**Figure 1**).

The formulation of topical experimental treatment is compounded in a liposomal base with 2% tofacitinib package in 30 g tube. Considering these small molecules are poorly soluble in water, JAK inhibitors might be effective when delivered in a liposomal base, which often consist of phospholipids mixed with water. Topical formulations of tofacitinib, coumpounding by Chemistry RX, were well tolerated and efficient for most patients in two recent publications (23,24). The vehicle formulation will be similar to the experimental treatment but will not contain tofacitinib.

With regard to topical corticosteroids, clobetasol propionate 0.05% cream will be used in its commercial form. Clobetasol propionate 0.05% is the most used for treatment of AA in both adults and children (28). Each 100 g tube contains 0.05 g of clobetasol propionate. Excipients with known effect are propylene glycol, cetostearyl alcohol and chlorocresol.

The 2% topical tofacitinib or the vehicle will be applied, at home, twice daily (in the morning and in the evening) and topical corticosteroids once daily (the application at noon seems difficult because of school, so we propose an application in the afternoon when returning from school), for 12 weeks by the patient or the parent to the affected areas (**Figure 2**). The 2 preparations will be applied using a glove, in massage until complete penetration of thin thickness. The amount to be applied will be defined using the fingertip unit (FTU) which is widely used in dermatology (29). One FTU is equivalent to 20-25 mm of cream squeezed onto the fingertip. One FTU is 0.5 g of cream and is enough to treat an area of skin twice the

size of adult's hand (included palm and fingers). Thus, amount of cream to be applied will be adjusted using the FTU depending on the size area. An information letter will be delivered to the nurses and patients/parents in which FTU is detailed.

The first application will be made by a nurse during visit 1 to show the patient/parent how to apply the preparations properly. If necessary, showering will have to be undertaken at least two hours after the application of the topical treatment. No other cream will have to be applied within two hours. Parents will complete a daily notebook to assess therapeutic adherence.

In case of severe local adverse event and unexpected event, temporary discontinuation of the treatment will be recommended until next visit.

In case of new patches of alopecia areata between 2 visits, topical experimental treatment and topical corticosteroids will be applied on these new lesions.

Concerning concomitant cares, systemic and intralesional steroids, contact sensitizers, topical and systemic immunosuppressive drugs, immunotherapy and light therapy, topical minoxidil, surgery and laser excimer of the scalp, PUVAtherapy and oral JAK inhibitors will be prohibited. Artificial hair fibers to cover patch of alopecia, oral vitamins (vitamin B12, B9, zin etc), shampoo and cosmetics will be authorized.

Outcomes

Primary outcome

The primary outcome will be the percentage of subjects achieving 50% of scalp hair regrowth at the end of the 12 weeks treatment period. This will be evaluated using the validated international Severity ALopecia Tool score (SALT score) (proportion of patients reaching SALT 50). Scoring will be assessed by the assessor in each centre at baseline and week 12.

The SALT score is a tool used for determining degree of hair loss based on the percentage of scalp surface area involved (30). The SALT score was chosen as the primary outcome as it is a validated scale that has been recommended as part of the core outcome set for use in alopecia areata trials (31) (**Additional file 2**). Moreover, to reduce inter and intra-observer variation, we decide to carry out training, at the beginning of the study, on the use of the SALT score for all dermatologists involved in the study.

Secondary outcomes

Secondary outcomes are clinical assessments of the efficacy of tofacitinib, the impact on the quality of life as well as the pain induced by the treatment.

Clinical efficacy and impact on quality of life will be assessed by different endpoints (**Additional files 2 and 3**).

- Evaluation of the SALT score relative variation between baseline and week 12 then baseline and week 24
- Percentage of subjects achieving 50% of scalp hair regrowth at week 12
- Complete regrowth at week 12
- Percentage of subjects who received rescue treatment between baseline and week 24 will be assessed by each investigator in each centre
- Quality of life will be self-assessed using the validated Child-DLQI scale at week 12 compared to baseline (**Additional file 3A**)
- Pain using a Visual Analog Scale (VAS) from 0 to 10 by the children at week 12 (0 no pain and 10 extreme pain)

Safety

Topical JAK inhibitors have been reported in several case reports/series to be very well-tolerated in pediatric AA unlike the oral JAK inhibitors that give upper respiratory infections and urinary tract infections, risk of VZV infection, headaches, dyslipidemia and mild increase in liver transaminase levels (18, 19). Tofacitinib oral decreases in neutrophil counts and hemoglobin, increases in cholesterol, triglycerides, and transaminases (25). On the other hand, for the topical form, the low incidence of adverse effects and the global stability of the biological markers described so far seem to show an absence of systemic toxicity.

Therefore, to confirm this good tolerance, cutaneous and general side effects at weeks 6, 12 and 24 will be recorded (**Table**). Evaluation of biological safety will be checked at weeks 6 and 12 compared to baseline (we will perform biological measurements that required for assessing safety of oral JAK inhibitors: blood cell count, liver and renal function, ionogram, lipids and glycemia).

Participant timeline

The duration of participation will be 24 weeks for each patient. The **Figure 1** displays the flow chart of the study, from inclusion visit to the end of the study.

Sample size

We hypothesize that 10% of the control group and 30% of the experimental group would achieve the primary endpoint, i.e. 50% regrowth. To achieve an 80% power with a two-sided type I error rate of 5%, we need 59 patients per group. Thus, our target sample size is 120 patients.

Recruitment

The recruitment of children with AA will be possible thanks to the 14 French hospital centres which all involved in tertiary care centres for paediatric dermatology. The recruitment period is estimated at 36 months.

Methods: assignment of interventions

Allocation

Sequence generation and allocation concealment mechanism

Participants will be randomly assigned to either the control or experimental group with a 1:1 ratio allocation per a computer (SAS based) generated randomisation schedule using permuted blocks of random sizes. The block sizes will not be disclosed to study investigators. Participants will be randomised using Ennov Clinical©, an online central randomisation procedure. To ensure allocation concealment, the randomisation procedure will not be possible until the participant has been recruited into the trial. Notably all selection criteria must be collected and met.

Implementation

An allocation sequence will be generated by a statistician not involved in the recruitment or follow-up of the participants.

Blinding

Patients, parents and investigators will be blinded for the treatment allocated to each patient, during all the study.

To ensure blinding, packaging will be performed in such manner that patients and parents will be unable to determine to which arm they are assigned. Their appearance will be similar, thus the active drug (topical tofacitinib) and placebo (vehicle) cannot be distinguished at drug allocation. Furthermore, the consistency of the cream is similar.

In previous studies, were no serious adverse events and AEs included mild laboratory abnormalities that normalized after 3 months of treatment, unknown if related to treatment (25). Therefore, patients will not be able to determine to which arm they are assigned.

Last, outcome assessors will also be blinded.

Unblinding will be requested for any reason considered essential by the investigating physician following the procedure determined in advance.

Methods: data collection, management and analysis

Data collection methods

The **Table** represents data collection (schedule of enrolment, interventions and assessments) from inclusion to final follow-up.

Data management

Data management will be performed by the INSERM CIC-P 1415. An electronic case report form (eCRF) will be developed using the Ennov Clinical® software. The management of the eCRF will be done in agreement with the INSERM CIC-P 1415 standardized operating procedures (SOP). The clinical research associate (CRA) in charge of the study will be trained to use the eCRF and will be in charge of the investigator's training. Data will be entered in investigating centers through a secure web site, monitored by CRAs and potential queries will be edited by data managers, in agreement with a specified data management plan. A data review will be done prior locking the database. The database will be locked in agreement with the INSERM CIC-P 1415 SOPs and data will be extracted in a SAS format or other, according to statistical requirements.

Statistical methods

Statistical analyses will be performed by the methodological and biostatistics unit, INSERM CIC-P 1415 University Hospital Center of Tours.

A detailed analysis plan will be *a priori* defined. SAS 9.4 and R 3.6.1 (or latest versions) software will be used. The level of statistical significance will be set at 5%.

All patients will be analyzed in the group allocated by randomisation. Nevertheless, patients who did not receive any dose of the study treatment will be discarded. Participants who

withdrew their consent to study participation will also be discarded, in case they explicitly refuse that their collected data be used, as required by the French legislation.
The number of participants with missing data for each variable of interest will be indicated.

Baseline characteristics will be reported per group using descriptive statistics. No statistical test will be performed on baseline measures.

For the primary analysis, the proportion of patients reaching SALT 50 at week 12 will be compared between groups using a chi-square test.
For secondary outcomes, the evaluation of the SALT score relative variation between baseline and week 12 then baseline and week 24 will be compared by Student's *t* test or Wilcoxon test. Considering the self-assessment of quality of life and the pain, they will be analysed using a t-test. Percentage of subjects with a complete regrowth and percentage of patients with rescue treatment between week 12 and 24 will be compared between the 2 groups using a chi-square test or Fisher exact test. Safety data will be analysed using descriptive analysis.

Methods: monitoring

Data monitoring

A clinical research assistant (CRA) will be responsible for coordinating the study: the assistant will be responsible for the logistics of and monitoring the study, producing reports concerning its state of progress, verifying that the e-CRFs are updated (request for additional information, corrections, etc.) and transmitting severe adverse events (AEs) to the sponsor (**Additional file 4**).

A data safety monitoring board (DSMB) will be composed of three medical doctors specialized in pharmaco-dermatology and dermatology. The DSMB will be systematically contacted 1) at any time by the sponsor for each case of expected serious adverse reaction or for a suspected unexpected serious adverse drug reaction (SUSAR); 2) before each

development safety update report is sent to the French Agency for the Safety of Health Products (ANSM); and 3) if data may change the benefit/risk ratio during the clinical trial.

Harms

All AEs will be monitored until they are completely resolved. The investigator will immediately notify the sponsor of any serious AE. The sponsor will report all SUSARs to the Eudravigilance (European pharmacovigilance database), French health authorities (ANSM), and the investigators within the regulatory time periods for reporting.

Auditing

An audit may be performed at any time by people appointed by the sponsor who are independent to those responsible for the study. The audit's aim is to ensure the good quality of the study and that the law and regulations in force are being accounted for.

The investigators agree to comply with the requirements of the sponsor and the relevant authority for an audit or an inspection of the study.

The audit can apply to all stages of the study, from development of the protocol to publication of the results, filing the data used or produced in the study.

Ethics and dissemination

Research ethics approval

The sponsor and the investigator or investigators undertake to conduct the study in compliance with the French law in force (*Code de Santé Publique*), the recommendations of French and international Good Clinical Practices (ICH), the Helsinki Declaration (Ethical Principles for Medical Research involving Human Subjects), and the European regulations related to clinical research.

The study will be conducted in accordance with this protocol. With the exclusion of emergency situations necessitating specific therapeutic actions to take place, the investigators

guarantee to follow the protocol in all respects, in particular in regard to obtaining consent and the reporting and follow-up of serious adverse events.

This research will be registered in the European EudraCT database in accordance with art. L1121.15 of the French Public Health Act. The protocol will be submitted to the French institutional review board.

Protocol amendments

Important protocol modifications will be submitted for approval to the French institutional review board and will be communicated to coinvestigators.

Consent and assent

The written informed consent of the patient and parents must be dated and signed by both the patient/parents and the investigator prior to any further intervention in the study. At the inclusion visit, the patient and parents will receive a copy of the signed written consent and information letter. The original information letter and consent form will be kept by the investigator (even if the patient moves to a new house during the study period) in a safe place that is inaccessible to third parties.

Parents will give their informed signed consent after their child has consented (if able). Children ≥ 16 years old must also consent to use of their data according to article 89 (Regulation [EU] 2016/679 - RGPD). For minor participants becoming adults (18 years) during the study, the consent of the participant will be collected again.

Confidentiality

During the study or once it is over, the information collected on the people taking part in it and forwarded to the sponsor by the investigators (or any other specialized staff member involved) will be made anonymous. Under no circumstances may the uncoded names or addresses of the people concerned appear in it. The sponsor will ensure that each participant

taking part in the study has given his agreement in writing for access to the individual data concerning him, which is strictly necessary for the quality control of the study.

Access to data

The sponsor is responsible for obtaining the agreement of all the parties involved in the study in order to guarantee direct access to source data, source documents and reports in all the sites where the study is being conducted, so that he can control their quality and audit them. He is responsible for all information collected on participants enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator.

The investigators will make available to people with a right of access according to the legislative and regulatory provisions in force (articles L.1121-3 and R.5121-13 of the French Public Health Act) the documents and individual data strictly necessary for monitoring, carrying out quality control and auditing the biomedical research.

Dissemination policy

Any written or oral communication of the results of the study will be previously agreed by the coordinating investigator and, if necessary, by the scientific committee constituted for the study.

Publication of the main results will mention the sponsor and the funding source. We will follow the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (updated in December 2014) from the International Committee of Medical Journal Editors (ICMJE). All investigators not-cited in the authorship will be listed as non-author contributors. Participants will be informed, at their request, of the overall results of the study.

SPIRIT

This protocol has been written in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines. The SPIRIT checklist is in **Additional file 5.**

Discussion

This individual, add-on, blinded RCT aims to compare topical tofacitinib 2% added to topical superpotent corticosteroids with topical vehicle in AA in children aged 4-17 years.

Considering unsatisfied efficacy of current treatment of AA and the significant impact of this condition on quality of life, therapeutic strategies are needed. The implementation of a multicentre randomised placebo-controlled therapeutic trial evaluating topical JAK inhibitors associated with clobetasol propionate (first-line treatment in AA) is innovative and competitive. Topical JAK inhibitors are currently evaluated in adult for AA but there is not current clinical trial posted on registry (Clinicaltrials.gov) for paediatric AA.

In the literature, modalities of use of topical JAK inhibitors are highly heterogeneous. We decided to evaluate topical tofacitinib applied twice daily because i) is the most common topical treatment reported and ii) tofacitinib is the first JAK inhibitor developed for the treatment of autoimmune disease.

During the double-blind 12 week-period, we have planned that patient/parent will apply both topical treatments at home, with 3 applications per day. We believe that, despite the number of applications per day, the adherence and compliance will be high, because of the impact of this condition on quality of life and the need for the patients of an effective treatment. Moreover, for most of the children, topical treatments will be applied by the parents, which will improve treatment compliance.

The SALT score was chosen as the primary outcome as it is a validated scale that has been recommended as part of the core outcome set for use in alopecia areata trials. It will be

assessed at 12 weeks, in accordance with the recommendations (31). The adjudication of the primary outcome for greater consistency by 3 independent dermatologic experts blinded to the treatment using standardized photographs was discussed. Finally, because, of the difficulty to provided good standardized photographs of the scalp in children, we decided to not retain this option. To limit inter and intra observer variability, we decided to carry out a training, at the beginning of the study, on the use of the SALT score for all dermatologists involved in the study. Because current treatments for AA have limited efficacy, patients are rapidly referred to tertiary care centers in pediatric dermatology, where recruitment of AA patients is high. For this reason, dermatologists who will be co-investigators in this trial are frequently involved in the management of hair diseases in pediatric dermatology.

Currently, treatments available for pediatric alopecia areata are limited. There is a real need to develop new treatments, particularly with a topical administration. If the trial demonstrates efficacy and safety of topical tofacitinib 2% added to clobetasol propionate, this will lead to a real therapeutic change and could become a first-line treatment for pediatric AA.

Trials status

Regulatory applications will be submitted (French institutional review board and ANSM).

The protocol will be registered on ClinicalTrials.gov.

Abbrevations

AA	Alopecia areata
AEs	Adverse Events

ANSM	Agence Nationale de Sécurité du Médicament
CRA	Clinical Research Assistant
Child-DLQI	Children’s Dermatology Life Quality Index
DLQI	Dermatology Life Quality Index
DSMB	Data Safety Monitoring Board
e-CRF	Electronic Case Report Form
EMA	European Medicines Agency
FDA	Food and Drug Administration
FTU	Finger Tip Unit
GCP	Good Clinical Practices
INSERM	Institut National de la Santé et de la Recherche Médicale
JAK	Janus Kinase
RCT	Randomised Controlled Trial
SOP	Standard Operating Procedures
SUSAR	Suspected Unexpected Serious Adverse Reaction
VAS	Visual Analog Scale

Declarations

Ethical Approval and Consent to participate

Regulatory applications will be submitted (French institutional review board and ANSM). Written and oral informed consent will be obtained from all participants before enrolment.

Consent for publication

We will be obtained informed consent for publication of the dataset from patients at the point of recruitment to the trial. All patient details will be fully anonymous.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

The study is funded by the French Ministry of Social Affairs and Health (French National Program of Clinical Research [PHRC-N], 2020). No industry support is involved.

Authors's contributions

CLH, SL, PP, LZ, MA and AM conceived of the study. SB, DB, CB, CD, ALD, EM, SM, JM, JMH and PV participated in its design and coordination. PP will perform the statistical calculations. CLH, SL and AM will write the manuscript. All authors will read and approve the final manuscript.

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Additional files

Additional file 1. List of study sites

Additional file 2. Severity ALopecia Tool score (SALT score)

Additional file 3A. Dermatology Life Quality Index (DLQI) – French version

B. Dermatology Life Quality Index (DLQI) for patients ≥ 16 years and < 18 years – French version

Additional file 4A. Safety evaluation terminology. B. Severity evaluation of non-serious adverse events. C. Causal relationship evaluation

Additional file 5. SPIRIT checklist

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Figures

Figure 1. Flow chart of the study procedure

The figure 1 displays the flow chart of the study, from inclusion visit (visit 0) to the end of the study (visit 4 at 24 weeks).

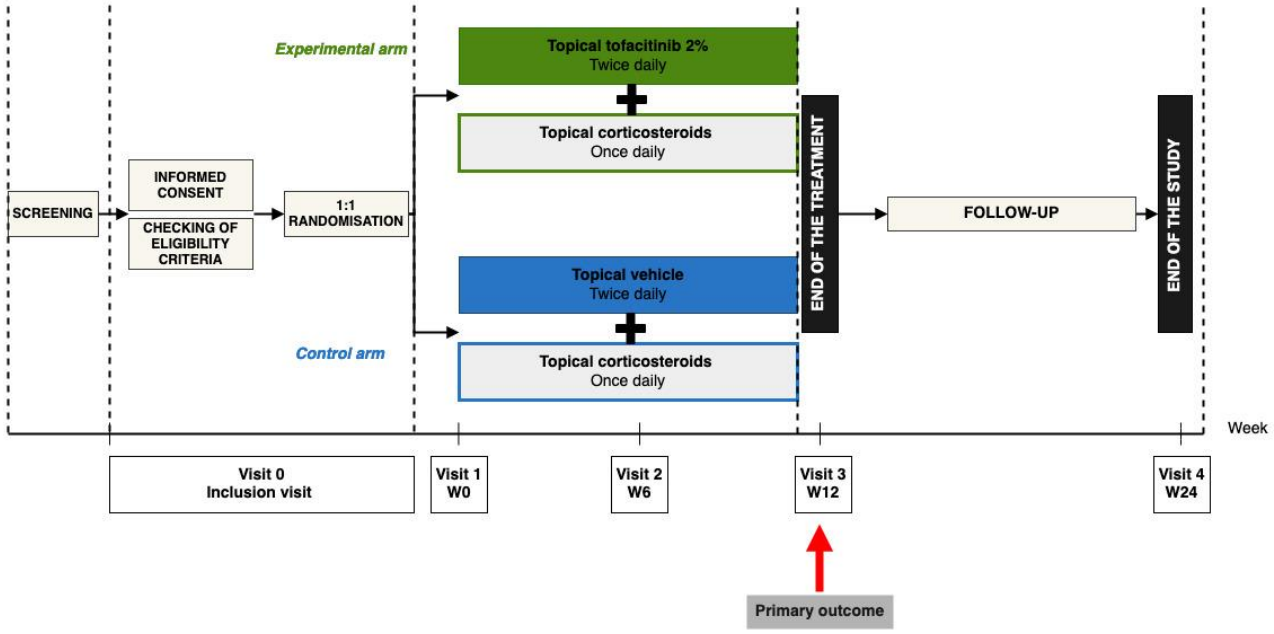
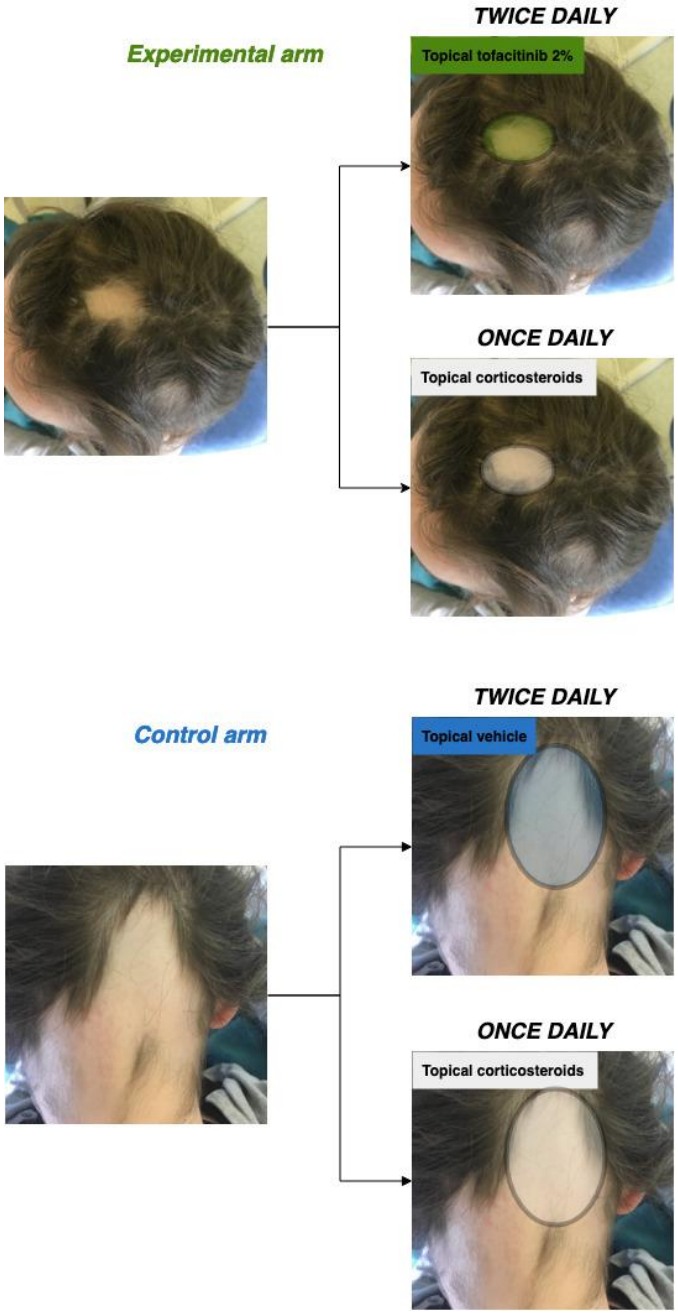


Figure 2. Examples of patches of alopecia areata in 2 patients allocated to the experimental and control arm. Experimental treatment (topical tofacitinib or placebo [topical vehicle]) will be applied twice daily, added to topical corticosteroids applied once daily. The figure 2 shows how the child or his/her parents will apply the experimental treatment or placebo, both added to topical corticosteroids.



Table

Table. *Schedule of enrolment, interventions and assessments*

STUDY PERIOD					
	Inclusion	Administration of treatment and visit	Follow-up		
	V0	**D1 (V1)**	**W6 (V2)**	**W12 (V3)**	**W24 (V4)**
TIMEPOINT	*15-30 days just before treatment initiation*	-	+/- 3 days	+/- 3 days	+/- 3 days
DRUG ADMINISTRATION					
Topical tofacitinib or topical vehicle		<----------twice daily ---------->			
Topical corticosteroids		<----------once daily ---------->			
ENROLMENT					
Eligibility screening	X				
Informed consent	X				
Control of inclusion and non-inclusion criteria	X				
Preparations ordering	X				
Randomisation	X				
MEASUREMENTS					
Physical examination	X	X	X	X	X
Height and weight	X				
Vital signs (cardiac frequency, arterial pressure)	X	X	X	X	X
Blood test*	X		X	X	
Tuberculosis test**	X				
Check of vaccination	X				
Urinary pregnancy test***	X	X	X	X	

STUDY PERIOD					
	Inclusion	Administration of treatment and visit	Follow-up		
	V0	**D1 (V1)**	**W6 (V2)**	**W12 (V3)**	**W24 (V4)**
TIMEPOINT	*15-30 days just before treatment initiation*	-	+/- 3 days	+/- 3 days	+/- 3 days
Measure of scalp surface area involved	X				
Application by research nurse		X	X		
Teaching video		X			
Cutaneous effects			X	X	X
Adverse events			X	X	X
INTERVENTIONS					
Delivery of topical tofacitinib		X	X		
Delivery of vehicle		X	X		
Treatment returns			X	X	
ASSESSMENTS					
SALT score		X		X	X
Percentage of subjects with a complete regrowth				X	
VAS for self-assessment				X	
Dermatology Life Quality Index		X		X	
Use of rescue treatment, if any					X
Biological measurements	X		X	X	
Daily notebook			X	X	X

*Blood test: blood cell count, liver function, renal function, ionogram, lipids, glycemia and only at baseline hepatitis B, C and HIV serologies if not provided

**Tuberculosis test (with the tuberculin skin test or an interferon γ release assay) for patients with tuberculosis risk factors

***An urinary pregnancy test will be performed for women and girls of childbearing potential

Additional files

Additional file 1. List of study sites

Name	Specialty	Health Facility	Address
BARBAROT	Sebastien	Nantes	CHU Nantes
BESSIS	Didier	Montpellier	CHU Montpellier
BODEMER	Christine	Paris	APHP-Hôpital Necker
BORALEVI	Franck	Bordeaux	CHU Bordeaux
BURSZTEJN	Anne-Claire	Nancy	CHU Nancy
CHIAVERINI	Christine	Nice	CHU Nice
DROITCOURT	Catherine	Rennes	CHU Rennes
LASEK-DURIEZ	Audrey	Lille	CHU Lille
MAHE	Emmanuel	Argenteuil	CH Argenteuil
MALLET	Stéphanie	Marseille	CHU Marseille
MIQUEL	Juliette	La Réunion	CHU La Réunion
MARUANI	Annabel	Tours	CHU Tours
MAZEREEUW-HAUTIER	Juliette	Toulouse	CHU Toulouse
VABRES	Pierre	Dijon	CHU Dijon-Bourgogne

Additional file 2. Severity ALopecia Tool score (SALT score)

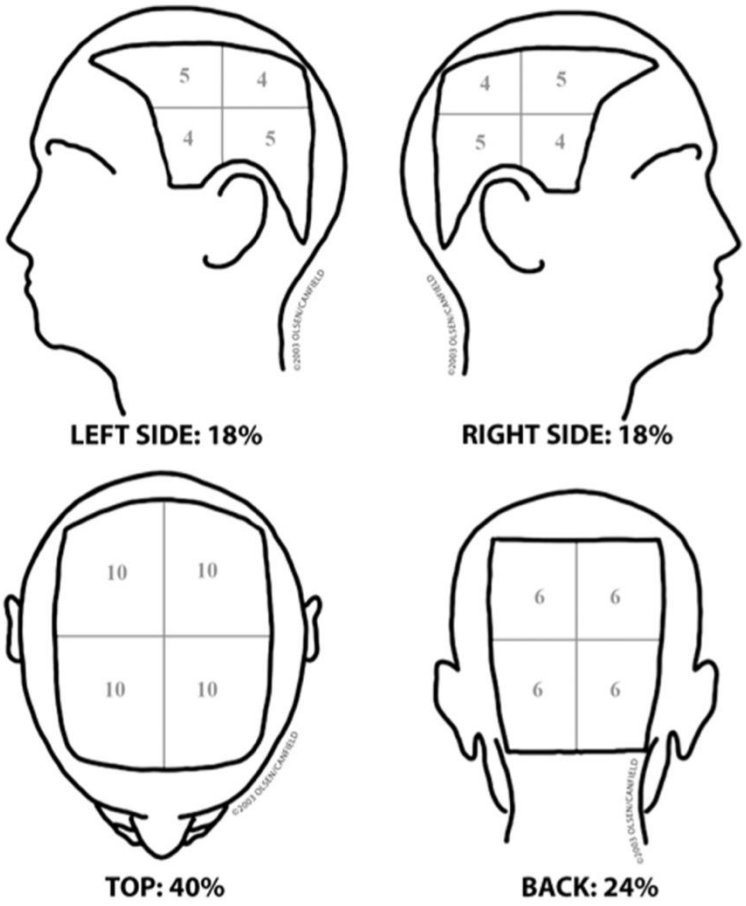


Fig 1. SALT I aid for determining scalp surface area.

Figure from Olsen EA, Canfield D. SALT II: A new take on the Severity of Alopecia Tool (SALT) for determining percentage scalp hair loss. J Am Acad Dermatol. 2016;75(6):1268-70.

How to calculate SALT score?

1- For each zone (left side, right side, front and back), first evaluate the percentage of hair loss (from 0 to 100%)

2- Multiply it by percent surface area of the scalp in that area to obtain the score for each zone. For the right side and the left side, the percent surface area is 0.18. For the vertex, it is 0.40 and for the back, 0.24.

3- All SALTs obtained in each zone are added to obtain the final SALT score.

For example, if the percentage hair loss in vertex, back, right side, left side is 50, 25, 25 and 10% respectively; then the SALT score = (50 × 0.4) + (10 × 0.24) + (25 × 0.18) + (25 × 0.18) = 20 + 2.4 + 4.5 + 4.5 = 31.4.

Additional file 3A. Dermatology Life Quality Index (DLQI) – French version

QUESTIONNAIRE QUALITE DE VIE –DERMATOLOGIE DE L'ENFANT*

Ces questions ont pour but de mesurer à quel point tu as été gêné par tes problèmes de peau au cours de la semaine dernière.

Pour chaque question, réponds en mettant une croix dans une seule case.

1	Au cours de la semaine dernière, est-ce que ta peau t'a démangé, « gratté », ou t'a fait mal ?		Enormément Beaucoup Un peu Pas du tout	□ □ □ □
2	Au cours de la semaine dernière, est-ce que tu as été gêné ou mal à l'aise, malheureux ou triste à cause de tes problèmes de peau ?		Enormément Beaucoup Un peu Pas du tout	□ □ □ □
3	Au cours de la semaine dernière, est-ce que tes problèmes de peau ont changé tes relations avec tes copains ?		Enormément Beaucoup Un peu Pas du tout	□ □ □ □
4	Au cours de la semaine dernière, est-ce que tu as dû te changer ou porter des chaussures ou des vêtements différents ou spéciaux à cause de tes problèmes de peau ?		Enormément Beaucoup Un peu Pas du tout	□ □ □ □
5	Au cours de la semaine dernière, est-ce que tes problèmes de peau t'ont gêné pour sortir, jouer, ou faire les choses qui t'intéressent ?		Enormément Beaucoup Un peu Pas du tout	□ □ □ □
6	Au cours de la semaine dernière, est-ce que tu as évité d'aller nager ou de faire du sport à cause de tes problèmes de peau ?		Enormément Beaucoup Un peu Pas du tout	□ □ □ □
7	Avais-tu école la semaine dernière ? OU Etais-tu en vacances ?	Si tu avais école : au cours de la semaine dernière, est-ce que tes problèmes de peau ont eu des conséquences sur ton travail à l'école ? Si tu étais en vacances : au cours de la semaine dernière, est-ce que tes problèmes de peau t'ont empêché de passer de bonnes vacances ?	A cause de mes problèmes de peau, je n'ai pas pu aller à l'école <u>OU</u> Enormément Beaucoup Un peu Pas du tout Enormément Beaucoup Un peu Pas du tout	□ □ □ □ □ □ □ □ □

8	Au cours de la semaine dernière, est-ce qu'à cause de tes problèmes de peau tu as été embêté par les autres : ils te donnaient de drôles de noms, te taquinaient, cherchaient la bagarre, te posaient des questions, ou t'évitaient ?	Enormément Beaucoup Un peu Pas du tout	□ □ □ □
9	Au cours de la semaine dernière, est-ce que tu as mal dormi à cause de tes problèmes de peau ?	Enormément Beaucoup Un peu Pas du tout	□ □ □ □
10	Au cours de la semaine dernière, est-ce que le traitement pour ta peau t'a posé des problèmes ?	Enormément Beaucoup Un peu Pas du tout	□ □ □ □

Date à laquelle le questionnaire a été rempli : I_I_I / I_I_I / I_I_I_I_I Score : /30
Vérifie bien que tu as bien répondu à TOUTES les questions. Merci.

Additional file 3B. Dermatology Life Quality Index (DLQI) for patients ³ 16 years and < 18 years – French version

QUESTIONNAIRE QUALITE DE VIE –DERMATOLOGIE

1.	Au cours des 7 derniers jours, votre peau vous a-t-elle **démangé(e), fait souffrir** ou **brûlée ?**	Enormément Beaucoup Un peu Pas du tout	□ □ □ □	
2.	Au cours des 7 derniers jours, vous êtes-vous senti(e) **gêné(e)** ou **complexé(e)** par votre problème de peau ?	Enormément Beaucoup Un peu Pas du tout	□ □ □ □	
3.	Au cours des 7 derniers jours, votre problème de peau vous-a-t-il gêné(e) pour **faire des courses**, vous **occuper** de votre maison ou pour **jardiner** ?	Enormément Beaucoup Un peu Pas du tout	□ □ □ □	Non concerné(e) □
4.	Au cours des 7 derniers jours, Votre problème de peau vous a-t-il influencé(e) dans le **choix des vêtements** que vous portiez ?	Enormément Beaucoup Un peu Pas du tout	□ □ □ □	Non concerné(e) □
5.	Au cours des 7 derniers jours, Votre problème de peau a-t-il affecté **vos activités avec les autres** ou vos **loisirs** ?	Enormément Beaucoup Un peu Pas du tout	□ □ □ □	Non concerné(e) □
6.	Au cours des 7 derniers jours, avez-vous eu du mal à faire du **sport** à cause de votre problème de peau ?	Enormément Beaucoup Un peu Pas du tout	□ □ □ □	Non concerné(e) □
7.	Au cours des 7 derniers jours, votre problème de peau vous a-t-il complètement empêché(e) de **travailler** ou d'**étudier** ? Si la réponse est « non » : au cours des 7 derniers jours, votre problème de peau vous a-t-il gêné(e) dans votre **travail** ou dans vos **études** ?	Oui non Beaucoup Un peu Pas du tout	□ □ □ □ □	Non concerné(e) □
8.	Au cours des 7 derniers jours, votre problème de peau a-t-il rendu difficiles vos relations avec votre **conjoint**(e), vos **amis proches** ou votre **famille** ?	Enormément Beaucoup Un peu Pas du tout	□ □ □ □	Non concerné(e) □

9.	Au cours des 7 derniers jours, votre problème de peau a-t-il rendu votre **vie sexuelle difficile** ?	Enormément Beaucoup Un peu Pas du tout	□ □ □ □	Non concerné(e) □
10.	Au cours des 7 derniers jours, le **traitement** que vous utilisez pour votre peau a-t-il posé un problème, par exemple, par exemple en prenant trop de votre temps ou en salissant votre maison ?	Enormément Beaucoup Un peu Pas du tout	□ □ □ □	Non concerné(e) □

Date à laquelle le questionnaire a été rempli : I_I_I / I_I_I / I_I_I_I_I Score : /30

Additional file 4A. Safety evaluation terminology

- ✓ **Adverse Event (AE)** (article R.1123-46of the French Public Health Act)**:** any harmful event occurring in a person taking part in a research study involving individuals, whether or not that event is linked to the study or to the product being investigated in the study.
- ✓ **Serious Adverse Event (SAE)** (article R.1123-46 of the Public Health Act and the ICH E2B guide): the severity is defined by one of the following observations:
  - death,
  - life-threatening for the person taking part in the research study (directly life-threatening at the time of the event, regardless of the consequences of corrective or palliative therapy),
  - disability or significant or lasting handicap,
  - hospitalization,
  - prolongation of hospitalization,
  - malformation/birth defect,
  - potentially serious event (adverse clinical event or laboratory test result considered serious by the investigator).
- ✓ **Adverse Reaction (AR)**: any untoward and unintended reaction to an investigational medicinal product, whatever the dose administered.
- ✓ **Serious Adverse Reaction (SAR)**: serious adverse events potentially caused by a medicinal product.
- ✓ **Suspected Unexpected Serious Adverse Reaction** (**SUSAR**) (article R.1123-46 of the French Public Health Act): serious adverse reaction, the type, severity, frequency or outcome in which it is inconsistent with the information contained in the summary of product characteristics for an authorized medicinal product or, in the case of an unauthorized medicinal product, in the investigator's brochure.
- ✓ **New fact** (article R.1123-46 12°of the French Public Health Act)**:** New information which could lead to:
  - A re-evaluation of the benefit/risk ratio of the study or the investigational product,
  - Modifications, due to its foreseen sufficiency in making changes in the way the product is used, to documents concerning the study, or if necessary to the way the study is conducted,
  - A suspension, interruption or modification of the research protocol or similar research.

- ✓ **Causal relationship:** relationship between the adverse event and the treatment. An adverse event related to an investigational medicinal product will be classified as an adverse reaction. Factors to consider when determining the cause of an adverse event are:
  - the chronological order of events,
  - the disappearance of the AE at the time of drug discontinuation and/or the reappearance upon re-administration,
  - the pharmacodynamic and pharmacokinetic properties of the drug,

- history of a similar event occurring during the administration of the drug or a drug of the same class,
- other potential causes of the AE.

Additional file 4B. Severity evaluation of non-serious adverse events

Severity **(Toxicity Grade)**	**Description**
Mild	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The participant may be aware of the sign or symptom but tolerates it reasonably well.
Moderate	Mild to moderate limitation in activity, no or minimal medical intervention/therapy required.
Severe or life threatening	Marked limitation in activity, medical intervention/therapy required, hospitalizations possible. The participant is at risk of death due to the adverse experience as it occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe.

Additional file 4C. Causal relationship evaluation

In accordance with ICH guidelines on the management of adverse events in clinical trials- ICHE2B(R3)12 May 2005 version- the relationship between all notified SAE and the research must be assessed.

The method used to evaluate the relationship of the event is as follows:

- ✓ **Unrelated**: the event occurred within a time period that is not compatible with the administration of the medicinal product, and/or sufficient information exists showing that the observed reaction is unrelated to the medicinal product, and/or a probable alternative explanation exists.
- ✓ **Doubtful**: the timing of the event (occurrence, outcome) is inconsistent with the administration of the medicinal product. The event is most likely related to factors other than the medicinal product such as the participant's clinical condition or concomitant administration of other medicinal products.
- ✓ **Possible**: the event occurred within a period that is compatible with the administration of the medicinal product. Although a causal effect of the product cannot be ruled out, other factors can be implicated, such as the participant's clinical condition or the concomitant administration of other medicinal products. Information about the outcome upon discontinuation of the studied treatment can be absent or inconclusive.
- ✓ **Probable**: the event occurred within a period that is compatible with the administration of the medicinal product. It cannot reasonably have been caused by another factor, such as the participant's clinical condition or the concomitant administration of other medicinal products. The outcome upon discontinuation of the medicinal product must be clinically compatible. Information about re-challenge with the medicinal product is not essential.
- ✓ **Highly probable**: the event occurred within period that is highly compatible with the administration of the medicinal product. It cannot be explained by another factor such as the participant's clinical condition or the concomitant administration of other medicinal products. The outcome upon discontinuation of the medicinal product must be clinically compatible. The event should have a pharmacological or pathophysiological explanation, or recurs upon re-challenge with the medicinal product.

Additional file 5. SPIRIT checklist

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page Number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	21
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Awaiting
	2b	All items from the World Health Organization Trial Registration Data Set	Awaiting
Protocol version	3	Date and version identifier	Awaiting
Funding	4	Sources and types of financial, material, and other support	Awaiting
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Awaiting
	5b	Name and contact information for the trial sponsor	Awaiting
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Awaiting
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Awaiting

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	26-27
	6b	Explanation for choice of comparators	27-28
Objectives	7	Specific objectives or hypotheses	28
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	28

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	29
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	29
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	29-30
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	30-31
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	30
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	31

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	31-32
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	33 + Figure 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	33
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	33
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	34
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	34
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	34
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	34

	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	35

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	35 + Table
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	36
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	35
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	35-36
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	36
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	35-36

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	36

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	36-37
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	37
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	37
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	37-38
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	38
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	38
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	38
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	23-43
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	39
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	39
	31b	Authorship eligibility guidelines and any intended use of professional writers	Awaiting
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	44
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Awaiting
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

III. CONCLUSION GENERALE

Actuellement, les inhibiteurs de JAK font partie intégrante des thérapeutiques innovantes en dermatologie. Des séries de cas ont rapporté une efficacité des anti-JAK topiques dans le traitement de la pelade mais seulement sur de petits effectifs. Des études randomisées et contrôlées sont donc nécessaires pour évaluer réellement leur efficacité dans le traitement de la pelade chez l'enfant.

Cette étude randomisée et contrôlée, nationale impliquant les centres de dermato-pédiatrie en France, permettra d'évaluer l'efficacité et la tolérance du tofacitinib topique dans le traitement de la pelade.

Le traitement par tofacitinib topique 2% n'est pas commercialisé et la production de la formulation topique sera réalisée au CHRU de Tours. Si l'efficacité du tofacitinib topique 2% en adjonction aux dermocorticoïdes d'activité très forte est démontrée, ce traitement pourrait être proposé en 1ère ou 2ème intention dans les pelades en plaques de l'enfant. La production de cette formulation pourrait être alors poursuivie au sein de notre CHRU et dispensée dans les autres CHU.

La rédaction de ce protocole a été un très travail très enrichissant et m'a permis de découvrir le monde de la recherche clinique. Je souhaite pouvoir poursuivre ce projet de recherche au cours de mon assistanat au CHRU de Tours et participer au recrutement et suivi des patients.

Vu, le Directeur de Thèse

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

université de TOURS | Faculté de médecine

Thèse 2021/2022

DOCTORAT en MEDECINE

Diplôme d'Etat

D.E.S. de Dermatologie et Vénéréologie
Présentée et Soutenue le 5 mai 2022
Dépôt de sujet de thèse, proposition de jury,

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Titre de la Thèse : Tofacitinib topique 2% versus placebo en adjonction du propionate de clobétasol 0,05% pour le traitement des pelades chez l'enfant de 4 à 17 ans : protocole pour un essai en add-on contrôlé, randomisé, en double-aveugle et multicentrique

JURY

Président : Professeur Annabel MARUANI, Dermatologie-Vénéréologie, Faculté de Médecine - Tours

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Docteur Juliette ROBERT, Dermatologie-Vénéréologie, AH, CHU - Tours

Avis du Directeur de Thèse
À Tours, le 14/03/2022
Signature

Avis du Directeur de l'U.F.R. Tours
à Tours, le 18.3.22
Signature

LE HELLOCO Claire
71 pages – 1 tableau – 2 figures – 5 annexes

Résumé : *Rationnel.* La pelade est une maladie auto-immune fréquente de l'adulte et de l'enfant. Son traitement est mal codifié avec des résultats le plus souvent décevants. De nouvelles thérapeutiques émergent de plus en plus ; notamment avec les inhibiteurs de Janus kinase (anti-JAK) qui voient leurs indications en constante expansion. L'efficacité du tofacitinib oral (inhibiteur de JAK de 1ère génération ciblant principalement JAK1 et JAK3) a été utilisé avec efficacité pour le traitement de pelade modérée à sévère chez l'adulte avec une bonne tolérance. Concernant le tofacitinib topique, des séries de cas ont déjà évalué son efficacité chez l'enfant mais il n'existe ni d'étude randomisée et contrôlée réalisée au sein de la population pédiatrique ni de données publiées sur l'association des anti-JAK topiques et des corticostéroïdes topiques d'activité très forte.
Méthodes. L'objectif de cette étude de phase 2, multicentrique, randomisée, contrôlée, en double aveugle, est d'évaluer l'efficacité et la sécurité du tofacitinib topique 2% versus un placebo en adjonction d'un dermocorticoïde d'activité très forte (propionate de clobétasol) dans la pelade de l'enfant de 4 à 17 ans. Le tofacitinib topique 2% (ou placebo) sera appliqué deux fois par jour et le propionate de clobétasol une fois par jour pendant une période de 12 semaines par le patient ou les parents sur les zones affectées. Le critère de jugement principal sera le pourcentage de sujets obtenant une repousse de 50 % des cheveux du cuir chevelu. Il sera évalué à l'aide du score international validé du *Severity ALopecia Tool*. La qualité de vie, l'évaluation de la variation relative du score SALT et le taux de repousse complète à la semaine 12 seront également évalués.
Discussion. Les traitements actuellement disponibles dans la pelade de l'enfant sont limités. Il existe un réel besoin de développer de nouveaux traitements, notamment topiques. Si l'essai démontre l'efficacité et la sécurité du tofacitinib topique 2% en adjonction aux dermocorticoïdes d'activité très forte dans la pelade de l'enfant, cela conduirait à un réel changement dans la prise en charge de cette pathologie fréquente.

Mots clés : pelade - inhibiteur de Janus kinase - tofacitinib - dermocorticoïdes - enfant

Jury :

Président du Jury :	Professeur Annabel Maruani
Directeur de thèse :	Docteur Sophie Leducq
Membres du Jury :	Professeur Mahtab Samimi, Professeur Juliette Mazereeuw-Hautier, Docteur Saloua Mammou Mraghni, Docteur Juliette Robert

Date de soutenance : le 5 mai 2022