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Efficacy and safety of coacillium in children and adolescents with moderate to severe alopecia areata: a randomised, double-blind, multicentre, phase 2-3 trial

Ulrike Blume-Peytavi*[1], Bianca Maria Piraccini[2], P. Reygagne[3], Bhaswati Mukherjee[4], Alexandre Guichard[5], William Pralong[5], Jiawei Liu[5], Saad Harti[5]

[1]Charité-Universitaetsmedizin, Department of Dermatology, Venereology and Allergology, Berlin, Germany, [2]Universitaria di Bologna, IRCCS Azienda Ospedaliero, Bologna, Italy,[3]St Louis Hospital, Centre Sabouraud, Paris, France, [4]CliniExperts Research Services, New Delhi, India, [5]Legacy Healthcare, Epalinges, Switzerland

Introduction & Objectives:

Alopecia areata (AA) is an autoimmune mediated disease characterized by rapid onset of hair loss often with chronic relapsing course. There is only one approved treatment for adults with severe AA, alopecia totalis (AT) and alopecia universalis (AU). No treatment is approved for children, adolescents or for patients with a moderate form of AA, albeit early-onset of AA may have a less favorable prognosis. We investigated the efficacy and safety of coacillium in children and adolescents with moderate to severe AA. Coacillium is a botanical drug composed of *Allium cepa, Citrus limon, Theobroma cacao* and *Paullinia cupana.*

Materials & Methods:

A randomised, double-blind, multicentre, phase 2–3 trial, RAAINBOW, was conducted at 12 sites in 4 countries. Patients aged 2 to 18 years with Severity of Alopecia Tool (SALT) score of 25-50 (moderate AA) and 50-95 (severe AA) were randomly assigned to coacillium 22.25% twice-daily (coacillium group), or placebo (placebo group)(2:1). The treatment period of 24 weeks was followed by a treatment-free period of 24 weeks to evaluate disease relapse after treatment discontinuation. No concomitant treatment for AA was allowed. Protocol details are registered with ClinicalTrials.gov, NCT03240627.

Results:

A total of 107 patients were randomly assigned to coacillium (71) or placebo (36). Average age was 11 years old, mean time since onset of disease was 3 years, 45% were female, 60% had severe AA, 40% moderate AA, 52% experienced their first episode of AA and 48% their second flare or more. The primary endpoint was the relative change in SALT score. After 24 weeks of treatment, the average change in coacillium group (+22.87%) was statistically significantly superior to the placebo group (-8.00%) ($p<0.0001$). 73% of coacillium-treated subjects who completed the 24 weeks treatment period responded to treatment. Of those, 96% kept improving after treatment discontinuation, while 4% only experienced disease relapse within the 24 weeks treatment-free period. At week 24, the percentage of patients with a SALT score of 20 or less was 21.2% in coacillium group and 5.3% in the placebo group. At week 48, including 24 weeks without treatment, the percentage of patients with a SALT score of 20 or less was 46.7% in coacillium group and 9.1% in the placebo ($p=0.0031$). Improvement of CDLQI was consistent with treatment effect; at week 48, CDLQI change in coacillium group was -2.52 while change in placebo group was +0.83 ($p=0.0313$). No serious adverse event was reported in the coacillium group. One case of severe transient eczema was reported, while all other AEs were mild or moderate, local and transient.

Conclusion:

In this phase 2-3 trial involving children and adolescents with moderate to severe alopecia areata, coacillium cutaneous solution 22.25% twice-daily was superior to placebo after 24 weeks of treatment and well tolerated.

Discontinuation of drug treatment triggered merely no disease relapse. Coacillium might be a suitable treatment option for children and adolescents with moderate to severe alopecia areata.

Efficacy and Safety of Coacillium in Children and Adolescents with Moderate to Severe Alopecia Areata: a Randomised, Double-blind, Multicentre, Phase 2-3 Trial

Ulrike Blume-Peytavi,[1] Bianca-Maria Piraccini,[2] Pascal Reygagne,[3] Bhaswati Mukherjee,[4] Alexandre Guichard,[5] Jiawei Liu,[5] William Pralong,[5] Saad Harti[5]

[1]Department of Dermatology, Venereology and Allergology, Charité-Universitaetsmedizin, Berlin, Germany; [2]Dermatology Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy; [3]Centre Sabouraud, St Louis Hospital, Paris, France; [4]CliniExperts Research Services Pvt. Ltd, Delhi, India; [5]Legacy Healthcare, Epalinges, Switzerland

BACKGROUNG

- Alopecia areata (AA) is an autoimmune disease driven by the trafficking of cytotoxic T lymphocytes, from the circulation to peri- and intra-follicular regions, mediated mainly by adhesion molecules expressed by activated endothelial cells (EC). AA is characterized by rapid onset of hair loss, with chronic relapses due to tissue-resident memory T cells, primed by interaction with activated EC.
- Two JAK inhibitors were recently approved representing a major advance. However, they are restricted to severe AA, in adults and adolescents,.
- Early intervention, when the disease is still moderate, may prevent disease progression to a severe stage. Also, early intervention after first manifestation in infancy might possibly prevent disease progression or chronicity. Last, discontinuation of JAK-inhibitors' treatment leads to disease relapse.

OBJECTIVE

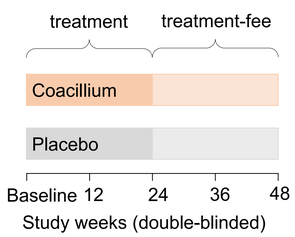
- Coacillium cutaneous solution is a botanical drug composed of Allium cepa, Citrus limon, Theobroma cacao and Paullinia cupana. Its multiple components have shown to act positively on both hair follicle cycling and EC activation.
- We investigated Coacillium safety and efficacy in children and adolescents with moderate to severe AA

METHODS

Study design

- RAAINBOW study is an international, double-blind, placebo-controlled, randomised, multi-centre study (Figure 1)
- Patients received twice-daily Coacillium cutaneous solution or placebo for 24 weeks.
- The treatment period was followed by a 24-weeks treatment-free follow-up to assess disease relapse,
- No concomitant treatment for AA was allowed

Figure 1: study design



Key eligibility criteria

- Patients were aged 2-18, with a diagnosis of AA, and hair loss involving 25-50% (moderate) or 50%-95% (severe) of the scalp, with a current AA episode duration of 6 months to 3 years.
- Hair loss was measured by Severity of Alopecia Tool (SALT) (Olsen, 2004)

Endpoints

- Primary endpoint is the relative change in SALT after 24 weeks of treatment
- Change in CDLQI, EQ-VAS and duration of treatment effect from end of treatment after 12 weeks and 24 weeks of treatment-free period were evaluated
- Percentage of patients achieving SALT ≤ 20 was measured post-hoc

Statistical analysis

- All analyses were conducted with two-sided significance level of 0.05 on relative change in SALT score as the dependent variable, and treatment, visit, and treatment-by-visit-interaction as fixed effects, and baseline SALT score (severity) as covariate.
- A generalized linear model (GLIMMIX procedure in SAS) was used for efficacy analysis (focused on the FAS data, confirmed in ITT data).
- Confirmatory testing of the hypotheses for the key secondary endpoints was tested hierarchically once the primary endpoint was established.
- The safety set included all randomized patients with at least one application.

Olsen EA et al. Alopecia areata investigational assessment guidelines--Part II. National Alopecia Areata Foundation. J Am Acad Dermatol. 2004 Sep;51(3):440-7

RESULTS

- At baseline, mean SALT score was 58 and was generally consistent across treatment groups (Table 1)

Table 1: baseline characteristics

Item	Total	Coacillium	Placebo
N (ITT)	107	71 (66%)	36 (34%
N (FAS)*	62	42 (68%)	20 (32%)
Severe	37 (60%)	24 (57%)	13 (65%)
Moderate	25 (40%)	18 (43%)	7 (35%)
Average SALT at V1	58	56.1	61.8
Average age	11	11.1	10.1
Time since onset of AA	3 years	3.3 years	2.5 years
Female	34 (55%)	22 (52%)	12 (60%)
Patients with several flares	30 (48%)	21 (50%)	9 (45%)

* FAS population consists of patients assessed as SALT 25-95 at baseline by both investigator and independent expert

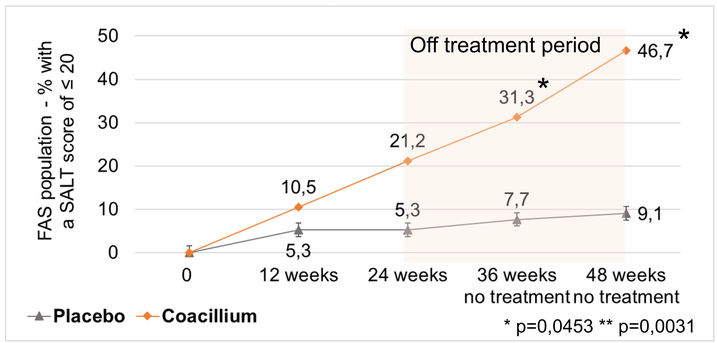
Relative change in SALT score after 24 weeks of treatment

- Mean change in Coacillium group (FAS) was 22,87% (improvement)
- Mean change in placebo group (FAS) was -8,00% (worsening)
- Difference was statistically significant (p<0,0001)
- Difference was statistically significant in ITT population also (p<0,0001)

Change in CDLQI and EQ-VAS

- Change in both CDLQI and EQ-VAS was positively correlated by change in SALT score, at 12 weeks, 24 weeks, and after treatment discontinuation.

Proportion of subjects achieving SALT ≤ 20



Safety

- No drug-related Serious adverse event (AEs) was reported
- One transient case of severe Treatment Emergent AE (acute eczema)
- Other AEs are mild-moderate, local and transient
- No immunosuppressant-like AEs and no steroid-like AEs
- Compliance was good, as seen in other trials with the drug candidate

Change in SALT score during treatment and after discontinuation

After 24 weeks (V3), treatment is discontinued. 82% of Coacillium-treated patients experienced hair growth between V3 (end of treatment) and V5 (24-weeks after end of treatment), versus 37% in Placebo-group.

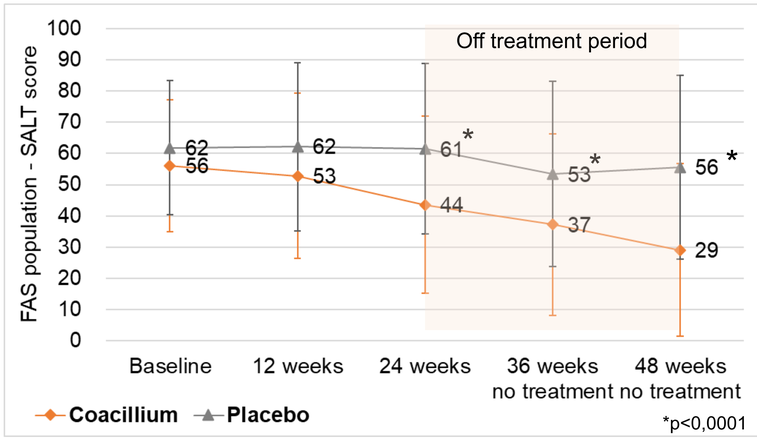
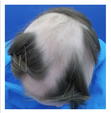
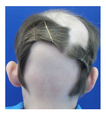
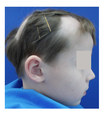
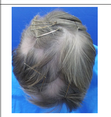
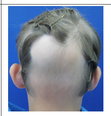
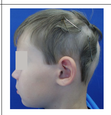
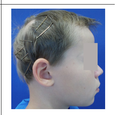
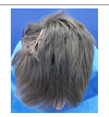
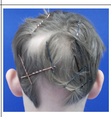
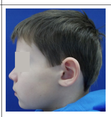
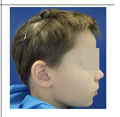


Figure 2: patient with SALT change at 24 weeks consistent with mean responders

Visit	Timeline	SALT score	Top	Posterior	Left side	Right side
V1	**Baseline**	**60**				
V3	**After 24 weeks of treatment**	**33**				
V5	**24 weeks after discontinuation of treatment**	**8**				

CONCLUSION

- Coacillium was superior to placebo, and well tolerated
- Most drug-responders experienced durable response during the 6-months treatment-free follow-up period
- To our knowledge, Coacillium is among the first drugs to show sustained remission off-treatment in an autoimmune-mediated disease, without immune-altering side-effects
- Coacillium might be a suitable treatment option for children and adolescents with moderate to severe alopecia areata
- Larger trials are warranted

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