Prediction of long-term scalp hair regrowth at 24 months in patients with alopecia areata receiving ritlecitinib treatment in the ALLEGRO clinical trial program

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BACKGROUND

- Alopecia areata (AA) is an autoimmune disease that has an underlying immuno-inflammatory pathogenesis and is characterized by nonscarring hair loss, ranging from small bald patches to complete scalp, face, and/or body hair loss[1]
- Ritlecitinib, an oral JAK3/TEC family kinase inhibitor, demonstrated efficacy and safety up to 48 weeks in patients aged ≥12 years with AA in the ALLEGRO phase 2b/3 study (NCT03732807)[2]
- ALLEGRO-LT (NCT04006457) is an ongoing phase 3, open-label study, investigating the long-term safety and efficacy of ritlecitinib in patients aged ≥12 years with AA[3]
- Since AA requires long-term treatment to establish its full therapeutic effect, predicting treatment outcomes based on patient characteristics and early response pattern could enhance clinical decision-making

OBJECTIVE

- To evaluate the predictive value of demographic and disease characteristics, and early response pattern to determine Severity of Alopecia Tool (SALT) score ≤20 response at Month 24 in patients with AA receiving ritlecitinib in the ALLEGRO clinical trial program

METHODS

Study design and patients

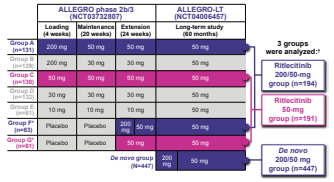
ALLEGRO-LT enrolled patients into two arms:

- Patients aged ≥12 years with ≥50% scalp hair loss due to AA who received ritlecitinib in either the ALLEGRO phase 2a study (NCT02974868) or ALLEGRO-2b/3
- *De novo* patients aged ≥12 years with ≥25% scalp hair loss

This post-hoc analysis of ALLEGRO-2b/3 and ALLEGRO-LT included (**Figure 1**):

- Patients who received an initial 4-week loading dose of 200-mg ritlecitinib once daily (QD) followed by ritlecitinib 50-mg QD
- Patients who received 50-mg ritlecitinib QD without a loading dose
- *De novo* patients who received an initial 4-week loading dose of 200-mg ritlecitinib QD followed by ritlecitinib 50-mg QD

Figure 1. ALLEGRO-2b/3 and ALLEGRO-LT study designs and patients included in the post-hoc analysis



*Data while on placebo were not included in this analysis; data from patients in Groups F and G were re-baselined from the start of treatment with ritlecitinib.
‡Patients who rolled over from ALLEGRO-2b/3 to ALLEGRO-LT were aged ≥12 years with ≥50% scalp hair loss. Patients in the *de novo* group were aged ≥12 years with ≥25% scalp hair loss.

Statistical analysis

- To predict SALT ≤20 response at Month 24, random forest analyses with 5-fold cross-validation with 3 repetitions were performed under two scenarios:

Scenario 1:
- Using baseline demographic and disease characteristics covariates

Scenario 2:
- Using baseline demographic and disease characteristics covariates, along with Month 6 SALT, Eyebrow Assessment (EBA) and Eyelash Assessment (ELA) scores

- Baseline demographic and disease characteristics listed in **Table 1**, along with the use of loading dose were covariates included in the models. While covariates for gender, race, type of AA, prior pharmacological treatment for AA, comorbid conditions and use of loading dose were treated as categorical, the remainder of the covariates were treated as continuous
- Each model included only patients with a complete set of observations, defined as having non-missing values for all covariates and SALT responses, with no data imputation performed
- Data are presented for:
  - Area under the receiver operating characteristic curve (AUROC)
    - AUROC is a continuous value from 0 to 1, with higher values indicating a better predictive capacity of the model
  - Mean accuracy
- Importance of covariates was assessed based on the whole population of patients
  - This was determined by the mean decrease in accuracy when covariate values were randomly permuted, with larger decreases indicating a significant contribution of the covariate to the model's accuracy
- Data cutoff was December 9, 2022

RESULTS

- Baseline demographics and disease characteristics are shown in **Table 1**

Table 1. Demographic and baseline disease characteristics in patients included in the analysis

	All patients (N=832)
Age, mean (SD), years	33.2 (14.2)
Female, n (%)	520 (62.5)
Race, n (%)	
White	570 (68.5)
Asian	200 (24.0)
Other	62 (7.5)
BMI, mean (SD), kg/m²	24.9 (5.3)
Type of AA	
AT/AU*	315 (37.9)
Other	517 (62.1)
Baseline SALT score, mean (SD)†	82.3 (23.6)
Eyebrow involvement, n (%)†‡	649 (78.0)
Eyelash involvement, n (%)†‡	588 (70.7)
Number of AA episodes, mean (SD)	2.9 (5.1)
Duration of current AA episode at baseline§, years, mean (SD)	3.1 (2.7)
Duration of AA since diagnosis, years, mean (SD)	9.8 (10.4)
Duration of significant (≥50%) scalp hair loss at baseline§, mean (SD), years	2.9 (3.3)
Prior pharmacological treatment for AA, n (%)	559 (67.2)
Comorbid conditions, n (%)	
Asthma	99 (11.9)
Autoimmune thyroiditis	43 (5.2)
Atopic dermatitis	109 (13.1)
Allergic rhinitis	70 (8.4)

AA, alopecia areata; AT, alopecia totalis; AU, alopecia universalis; BMI, body mass index; EBA, Eyebrow Assessment; ELA, Eyelash Assessment; SALT, Severity of Alopecia Tool.
*Participants in the AT and AU categories had a SALT score of 100 (complete scalp hair loss) at baseline and a clinical diagnosis of AT or AU by the investigator.
†Covariate assessed at baseline and at Month 6 for the analysis of Scenario 2. ‡Eyebrow and eyelash involvement were based on the EBA/ELA scores, which are 4-point scales with clinician-reported scores that represent the extent of eyebrow or eyelash hair: 0 (none), 1 (minimal), 2 (moderate), and 3 (normal). EBA/ELA analyses at baseline only include participants with scores of 0, 1 or 2. §As assessed by the investigator. ¶The time since the patient last had substantial scalp hair, regardless of whether that hair growth occurred spontaneously or was the result of the interventional treatment, with a maximum duration of ≤10 years.

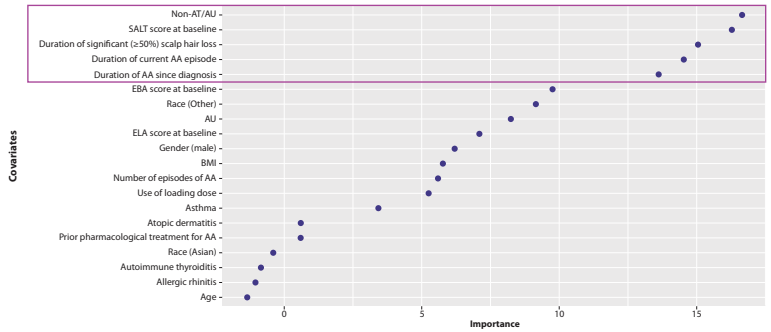
Scenario 1: using baseline demographic and disease characteristics covariates (**Figure 2**)

- The AUROC ranged from 0.769 to 0.784
  - A maximum value for mean accuracy of 75.5% was obtained at a cutoff of 0.6 for the predicted probability of SALT ≤20 response at Month 24 in the best random forest model (AUROC = 0.784)
  - The most important covariates for predicting the probability of SALT ≤20 response at Month 24 were:
    - Non-AT/AU
    - Baseline SALT score
    - Duration of significant (≥50%) scalp hair loss at baseline
    - Duration of current AA episode at baseline
    - Duration of AA since diagnosis

Scenario 2: using baseline demographic and disease characteristics covariates, along with Month 6 SALT, EBA and ELA scores (**Figure 3**)

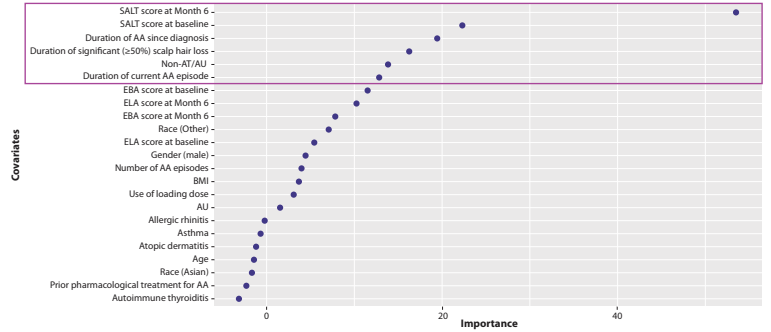
- The AUROC ranged from 0.826 to 0.836
  - A maximum value for mean accuracy of 79.6% was obtained at the 0.5 cutoff for the predicted probability of SALT ≤20 response at Month 24 in the best random forest model (AUROC = 0.836)
  - The most important covariates for predicting SALT ≤20 response at Month 24 were similar to Scenario 1 with the addition of SALT score at Month 6:
    - SALT score at Month 6
    - Baseline SALT score
    - Duration of AA since diagnosis
    - Duration of significant (≥50%) scalp hair loss at baseline
    - Non-AT/AU
    - Duration of current AA episode at baseline

Figure 2. Importance of covariates for predicting SALT ≤20 response at Month 24 from the best random forest model in Scenario 1



AA, alopecia areata; AT, alopecia totalis; AU, alopecia universalis; BMI, body mass index; EBA, Eyebrow Assessment; ELA, Eyelash Assessment; SALT, Severity of Alopecia Tool.
Importance of covariates was determined by the mean decrease in accuracy when covariate values were randomly permuted, with larger decreases indicating a significant contribution of the covariate to the model's accuracy.

Figure 3. Importance of covariates for predicting SALT ≤20 response at Month 24 from the best random forest model in Scenario 2



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Importance of covariates was determined by the mean decrease in accuracy when covariate values were randomly permuted, with larger decreases indicating a significant contribution of the covariate to the model's accuracy.

CONCLUSIONS

- Specific demographic and disease characteristics, such as SALT score at baseline and Month 6, non-AT/AU, duration of AA since diagnosis, duration of significant (≥50%) scalp hair loss at baseline, and duration of current AA episode at baseline, are useful for the estimation of the probability of a SALT ≤20 response at Month 24 with ritlecitinib treatment in patients with AA
- The predictive capacity of these covariates may be valuable for optimizing treatment decisions in AA, potentially improving outcomes by identifying patients who are more likely to respond favorably to treatment
- However, the models are limited by the available covariates in the clinical trials and by the specific trial designs, which may not fully represent real-world patient populations
- As covariate importance shows significance without indicating effect direction, future analyses should investigate whether the effects are positive or negative
- As such, the models are not validated for use in clinical practice and should not be used as a substitute for professional medical judgement or decision-making

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DISCLOSURES

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