Study Protocol

Vitamin D as an Adjunct to Janus Kinase Inhibitors for Alopecia Areata: A Randomized Controlled Trial

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Ethics Approval	Institutional Review Board (IRB), King Hussein Hospital, Jordanian Royal Medical Services Approval No. 18/2024

1. Administrative Information

1.1 Roles and Responsibilities: The Principal Investigator (Dr. Asem Aldebei) is responsible for the overall conduct of the trial, protocol adherence, and final approval of the manuscript. Co-investigators contributed to study design, data acquisition, statistical analysis, interpretation of results, and manuscript drafting and revision. All authors approved the final protocol and accept accountability for the integrity of the work.

1.2 Funding: The authors received no specific funding for this work from any funding agency in the public, commercial, or not-for-profit sectors.

1.3 Confidentiality: All participant data were anonymized prior to analysis. Data are stored securely and are available from the corresponding author upon reasonable request.

2. Introduction

2.1 Background and Rationale

Alopecia areata (AA) is a chronic, immune-mediated disorder affecting hair follicles, causing non-scarring hair loss in forms such as patchy alopecia, alopecia totalis (AT), or alopecia universalis (AU). Its lifetime incidence is approximately 2%, with onset most commonly in the third and fourth decades of life. The disease course is unpredictable, with spontaneous remission and relapse, and imposes a significant psychosocial burden due to its effects on appearance and self-esteem.

Janus kinase inhibitors (JAKI), such as baricitinib and tofacitinib, have emerged as effective treatments for AA by blocking pathogenic cytokine signaling, inducing substantial regrowth even in severe or long-standing cases. However, response rates are variable, particularly in AT and AU.

Vitamin D, assessed as serum 25-hydroxyvitamin D [25(OH)D], has immunomodulatory properties relevant to AA. Deficiency is common and has been linked to greater disease severity and poorer treatment response — a concern of particular relevance in Jordan, where a national survey found low vitamin D status in 89.7% of adults. Given that both JAK inhibition and vitamin D affect overlapping immune pathways, a synergistic benefit from combination therapy is biologically plausible but has not been well characterized in a controlled trial.

2.2 Objectives

Primary objective: To assess whether JAKI plus vitamin D supplementation improves hair regrowth and quality of life compared with JAKI monotherapy in patients with AA.

Secondary objective: To monitor serum vitamin D changes with or without supplementation, exploring the effect of JAKI therapy on vitamin D metabolism.

2.3 Trial Design

This is a 12-month, single-center, randomized, controlled, open-label trial with a 1:1 allocation ratio and two parallel arms: (1) JAK inhibitor plus vitamin D supplementation, and (2) JAK inhibitor monotherapy. The trial was conducted at the Royal Medical Services dermatology clinics, Jordan, with reporting following the CONSORT guidelines for randomized trials.

3. Methods: Participants, Interventions, and Outcomes

3.1 Study Setting

Participants were recruited from dermatology clinics within the Jordanian Royal Medical Services. Patient recruitment and follow-up spanned from 2024, following institutional ethical approval, until January 1, 2026.

3.2 Eligibility Criteria

Inclusion criteria:

- Age 18–60 years.
- Diagnosis of alopecia areata, totalis, or universalis.
- No JAK inhibitor use in the past 6 months.
- Willingness to comply with visits and treatment protocol.

Exclusion criteria:

- Pregnancy or breastfeeding.
- Active autoimmune disease contraindicating JAK inhibitor use.
- Not suitable for JAK inhibitor therapy based on baseline labs: positive Quantiferon, positive hepatitis profile, elevated lipids (LDL > 150 mg/dL, triglycerides > 200 mg/dL, cholesterol > 200 mg/dL), abnormal liver enzymes (AST > 37 U/L, ALT > 37 U/L).

- Hypercalcemia, vitamin D toxicity, recent malignancy, or systemic infection.
- Current immunosuppressant use (e.g., corticosteroids) or known secondary vitamin D deficiency.

3.3 Interventions

Combination Therapy Arm: JAK inhibitor (baricitinib 4 mg daily or tofacitinib 5 mg twice daily) plus cholecalciferol supplementation, with dose tailored to each participant's baseline vitamin D level:

- < 25 nmol/L: 50,000 IU weekly for 6–8 weeks, then 800 IU/day.
- 25–50 nmol/L: 800 IU/day.
- ≥ 50 nmol/L: 400–600 IU/day (maintenance dose).

Monotherapy Arm: JAK inhibitor only, at the same dosing as above.

Safety Considerations: JAK inhibitors carry potential risks including infections (upper respiratory, herpes zoster, serious infections), thromboembolic events (DVT, pulmonary embolism), anemia, neutropenia, elevated liver enzymes, and lipid increases. Vitamin D supplementation carries potential risks of hypercalcemia (nausea, arrhythmias, confusion), kidney stones, and interactions with drugs such as diuretics. Interactions between JAK inhibitors and vitamin D are not well characterized and necessitate close monitoring.

3.4 Outcomes

Primary outcome: Hair growth rate, measured by change in Severity of Alopecia Tool (SALT) score from baseline to 6 and 12 months.

Secondary outcomes: Change in Dermatology Life Quality Index (DLQI; 10 items, score range 0–30, higher scores indicating poorer quality of life) from baseline to 6 and 12 months; change in serum vitamin D levels from baseline to 6 and 12 months.

Assessment schedule: Participants were monitored bimonthly during treatment for adherence, progress, and adverse effects. Post-treatment, monthly visits assessed hair regrowth, density, and DLQI changes. Baseline and periodic laboratory monitoring included blood counts, liver function tests, lipid profiles, calcium, and vitamin D levels, with adverse events recorded at biweekly visits.

3.5 Sample Size

Assuming an effect size of 0.488, $\alpha = 0.05$, and power = 0.80, ANCOVA was calculated to require 66 participants (33 per group) with a 95% confidence interval. Adding 10% to account for attrition yielded a target enrollment of 73 participants.

4. Methods: Assignment of Interventions

4.1 Sequence Generation

Randomization was performed using a computer-generated block randomization sequence in a 1:1 ratio.

4.2 Allocation Concealment Mechanism

Allocation concealment was achieved through a centralized electronic randomization system, preventing foreknowledge of group assignment prior to enrolment.

4.3 Blinding

This was an open-label trial: given the visible nature of oral cholecalciferol supplementation, patients and treating physicians were not blinded to treatment allocation. However, SALT and DLQI outcome assessments were performed by a physician independent of the treating physician and blinded to treatment allocation, reducing the risk of assessment bias despite the open-label nature of treatment delivery.

5. Methods: Data Collection, Management, and Analysis

5.1 Data Collection Methods

Demographic, clinical, and laboratory data were collected at baseline and at scheduled follow-up visits as described in Section 3.4, using standardized case report forms.

5.2 Statistical Methods

Categorical data are summarized as frequencies and percentages; continuous data as mean ± standard deviation. ANCOVA was used to compare mean SALT and DLQI scores between groups at 6 and 12 months, adjusting for baseline covariates. Repeated-measures ANOVA was used to assess within-group change over time. Assumptions of normality, homogeneity of variance, multivariate outliers, and sphericity were tested prior to analysis. Statistical significance was set at $p < 0.05$. Analyses were conducted using SPSS v28 (IBM Corp.).

6. Methods: Monitoring

6.1 Data Monitoring

Adverse events were recorded at biweekly visits, with appropriate clinical interventions to ensure participant safety. Baseline and periodic laboratory monitoring (blood counts, liver function tests, lipid profiles, calcium, and vitamin D levels) were used to detect emerging safety concerns.

6.2 Harms

All adverse events were documented and assessed by the study team for relatedness to study interventions, in accordance with the safety considerations outlined in Section 3.3.

7. Ethics and Dissemination

7.1 Research Ethics Approval

This study was approved by the Institutional Review Board (IRB) of King Hussein Hospital, Jordanian Royal Medical Services (Approval No. 18/2024), and was conducted in accordance with the Declaration of Helsinki. Approval was obtained prior to data collection.

7.2 Consent

Written informed consent was obtained from all individual participants prior to enrollment, following a full explanation of the study's procedures, potential risks, and benefits. Participants were informed of their right to withdraw at any time without effect on their ongoing clinical care.

7.3 Confidentiality

All participant data were anonymized prior to analysis and stored securely, accessible only to the study team.

7.4 Dissemination Policy

Results of this trial are intended for publication in a peer-reviewed journal. The data that support the findings of this study are available from the corresponding author upon reasonable request.