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Low-Dose IL-2 for Treating Moderate to Severe Alopecia Areata: A 52-Week Multicenter Prospective Placebo-Controlled Study Assessing its Impact on T Regulatory Cell and NK Cell Populations

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TO THE EDITOR

The treatment of severe alopecia areata (AA) remains highly challenging. A breakdown of immune privilege of the hair follicle resulting in the development of an admixed immune infiltrate of antigen-presenting cells and $CD4^+$ and $CD8^+$ T lymphocytes is hypothesized to represent an important driver of AA (Pratt et al., 2017). A deficiency in T regulatory cells (Tregs) might facilitate the occurrence of this immune privilege breakdown. A growing corpus of data in animal models, as well as from blood and skin in patients with AA, emphasized the likely key role of Tregs in AA pathomechanisms (Conteduca et al., 2014; Hamed et al., 2019; McElwee et al., 2005; Petukhova et al., 2010; Shin et al., 2013; Tembhre and Sharma, 2013). IL-2 is essential for Treg homeostasis (Zorn et al., 2006). Low-dose IL-2 treatment results in Treg recovery and concomitant clinical improvement in patients with hepatitis C virus–induced vasculitis, graft-versus-host disease, lupus, and autoimmune thrombopenia (He et al., 2016; Koreth et al., 2011; Saadoun et al., 2011; Zhang et al., 2018). Conversely, low-dose IL-2 failed to improve type 1 diabetes while efficiently increasing the Tregs population (Hartemann et al., 2013). Using a similar approach, we reported partial hair regrowth in 4 of 5 patients with severe AA (Castela et al., 2014). We conducted a multicentric randomized placebo-controlled trial with a 52-week follow-up period in adult patients with severe AA of the scalp. The study was registered to the French Health Authorities (Agence Nationale de Sécurité du Médicament registration number: 150355A-42) and to the institutional review board of Sud Méditerranée V (registration number: 15.039). Written informed consent was obtained for all patients. Patients received a total of four cycles of subcutaneous low-dose IL-2 or saline serum. Severity of Alopecia Tool score was used as the primary criteria to assess efficacy. Treg and NK peripheral population analysis was carried out at baseline; the final day of the fourth cycle; and at 1, 3, 6, and 12 months (Supplementary Materials and Methods).

A total of 43 patients were randomized, of whom 21 were assigned to receive low-dose IL-2 and 22 to the placebo. Nine patients did not complete the study. The flow diagram of the study and the baseline characteristics of the population are presented in Supplementary Figure S1 and Supplementary Table S1, respectively. At 12 months after the end of the treatment, 50% reduction in Severity of Alopecia Tool score was achieved in 14.3% of the low-dose IL-2 group versus 9.1% in placebo group ($P = 0.66$) in the intention-to-treat analysis. The evolution of the Severity of Alopecia Tool score during treatment is presented in Table 1. No significant improvement was observed in both groups for body hair and nails. The Dermatology Life Quality Index and the satisfaction of the patients did not change significantly between baseline and 6 and 12 months after the end of the treatment in both groups, with no statistical difference between the two groups (Supplementary Tables S2 and S3). Adverse events encountered during the study are presented in

Abbreviations: AA, alopecia areata; Treg, T regulatory cell

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Table 1. Evolution of the SALT Score

	W0 (n = 22)	W3 (n = 22)	W6 (n = 22)	W9 (n = 22)	1 Month Follow-Up (n = 22)	3 Months Follow-Up (n = 22)	6 Months Follow-Up (n = 22)	12 Months Follow-Up (n = 12)
Placebo, median (IQR)	84 (56.6–100)	81.9 (61.9–100)	81 (68.4–100)	80.1 (67.4–100)	91.5 (44.8–100)	93 (44.8–100)	82.9 (48.2–100)	72.2 (44–100)
	W0 (n = 21)	**W3 (n = 21)**	**W6 (n = 21)**	**W9 (n = 21)**	**1 Month Follow-Up (n = 21)**	**3 Months Follow-Up (n = 21)**	**6 Months Follow-Up (n = 21)**	**12 Months Follow-Up (n = 21)**
Low-dose IL-2, median (IQR)	100 (76.4–100)	100 (76.4–100)	100 (76.4–100)	100 (69.5–100)	100 (61.2–100)	100 (64.4–100)	100 (90–100)	96.8 (70.3–100)

Abbreviations: IQR, interquartile range; LOCF, Last Observation Carried Forward; SALT, Severity of Alopecia Tool; W, week.
W0: Baseline; W3, W6, and W9: weeks 3, 6, and 9, respectively, after the onset of treatment. Data are imputed using LOCF.

Supplementary Tables S4 and S5. Flu-like syndrome was the most frequent adverse event in the low-dose IL-2 group, with 66.7% of patients presenting these symptoms at least once compared with 13.6% in placebo group ($P = 0.0005$). Eosinophilia was observed in eight patients (38.1%) in the low-dose IL-2 arm versus none in the placebo arm ($P = 0.0014$). All side effects were transient. The total Treg peripheral population ($CD3^+CD4^+CD25^{++}CD127^{low}$) was significantly increased in the low-dose IL-2 group at all time points compared with baseline (except at 12 months); after the end of the last cycle ($P = 0.0063$); and after 1 month ($P < 0.0001$), 3 months ($P < 0.0001$), 6 months ($P = 0.0012$), and 12 months ($P = 0.084$) (Figure 1a). Conversely, no significant variation of the total Treg population was observed in the placebo arm at any time point compared with baseline. Similarly, the Treg to $CD8^+$ cells ratio was significantly increased at all time points in the low-dose IL-2 arm ($P = 0.0004$, $P < 0.0001$, $P < 0.0013$, $P < 0.0001$, and $P = 0.0051$ after the end of the last cycle and after 1, 3, 6, and 12 months, respectively) (Figure 1b). The increase of Tregs only involved the naive subpopulation ($CD45RA^+$ $CD197^+$) ($P = 0.005$, $P < 0.0001$, $P = 0.0123$, $P = 0.0077$, and $P = 0.08$ after the end of the last cycle and after 1, 3, 6, and 12 months, respectively) (Figure 1c). Conversely, the relative percentage of central memory ($CD45RA^-$ $CD197^+$) (Figure 1d), effector memory ($CD45RA^-$ $CD197^-$) (Figure 1e), and CLA^+ $CCR4^+$ $CCR10^+$ DR^+ Tregs (Figure 1f) were decreased in the low-dose IL-2 arm. Similarly, a significant increase of the absolute number of naive Tregs was observed in the IL-2 group at all time points, whereas no significant variation was observed in the other subtypes of Tregs. The total NK cells transiently increased in the IL-2 arm but only at the end of the treatment; however, the variation did not reach statistical significance ($P = 0.08$). The NK cell count then returned to levels comparable to baseline (Supplementary Figure S2a). Analysis of CD158 (KIR) and CD314 (NKG2D) markers showed that the NK $158^+/314^-$ subpopulation corresponded to the subset most influenced by low-dose IL-2, with a significant decrease at the end of the treatment ($P = 0.036$), whereas the NK $158^-/314^+$ population increased at the end of the treatment but without reaching a statistically significant level ($P = 0.23$) (Supplementary Figure S2b–e).

Despite encouraging results in the pilot study we initially conducted (Castela et al., 2014), the results of this large prospective randomized placebo-controlled trial did not further support the efficacy of low-dose IL-2 in treating severe AA, at least with the type and regimen of IL-2 used in this study. The analysis of Tregs in the blood of patients during and after treatment showed that low-dose IL-2 is likely to elicit a proliferation or a recruitment of Tregs. However, despite this significant increase of peripheral Tregs, the treatment failed to significantly stimulate hair regrowth. The mild and transient increase of NK cells does not support a significant involvement of NK cells in the failure of low-dose IL-2 treatment. The observed limitation of the overall increase of Tregs to the naive subset, with no expansion of the effector and memory populations with skin homing capabilities, probably explains, at least partially, the lack of clinical efficacy in patients with AA. New generations of long-lived IL-2 that are more specific for Tregs are currently developed and tested in early clinical stages for several autoimmune and inflammatory disorders (Peterson et al., 2018). Our results emphasize the importance for a more specific characterization of the different subsets of Tregs and the necessity of assessing if the expanded Tregs express tissue homing markers in the setting of organ-specific diseases.

Data availability statement

The raw data are available on reasonable request to Dr Eric Fontas (fontas.e@chu-nice.fr) for research purposes only. This study is registered at ClinicalTrials.gov (NCT01840046).

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CONFLICT OF INTEREST

Novartis provided Proleukin at a discounted price for this study. The authors state no conflicts of interest.

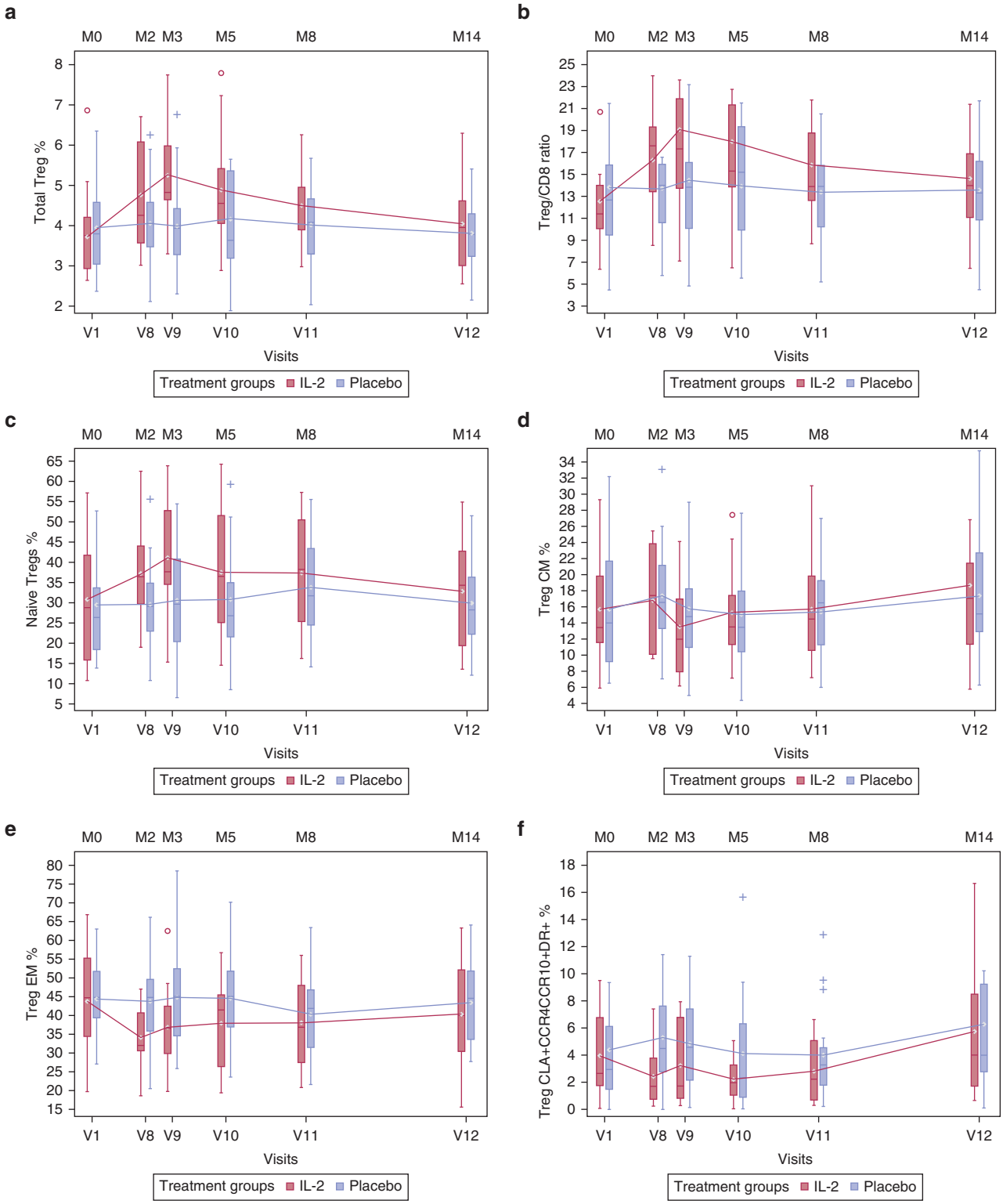

Figure 1. Monitoring of Treg populations over time. Flow cytometry analysis was performed at baseline (V1); at the end of the fourth cycle of treatment (V8); 1 month after the end of the cures (V9); and after 3 (V10), 6 (V11), and 12 months (V12). (**a**) Percentage of Tregs in the total lymphocyte population. (**b**) Tregs/CD8 ratio. (**c**) Naive Treg subsets. (**d**) CM Treg subsets. (**e**) EM Tregs. (**f**) Activated Tregs with cutaneous homing markers. CM, central memory; EM, effector memory; Treg, T regulatory cell.

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AUTHOR CONTRIBUTIONS

Conceptualization FLD, MT, JPL, TP; Data Curation: FLD, EF, TP; Formal Analysis: EF, MT, TP; Funding Acquisition: TP; Investigation: FLD, JDB, MT, MV, OD, PR, HM, SM, MAR; Methodology: EF; Project Administration: TP; Resources: TP; Software: EF; Supervision: TP; Validation: TP; Writing - Original Draft Preparation: TP;

Writing - Review and Editing: FLD, JDB, MT, MV, OD, PR, HM, SM, MAR, EF, JPL, TP

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SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at www.jidonline.org, and at https://doi.org/10.1016/j.jid.2020.08.015.

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Induction of Regulatory T Cells in *Leishmania major*–Infected BALB/c Mice Does Not Require Langerin+ Dendritic Cells

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TO THE EDITOR

Cutaneous leishmaniasis is a disease caused by the protozoan parasite *Leishmania major* and transferred to humans by infected phlebotomine sand flies. Cutaneous leishmaniasis manifests in lesion formation of the infected skin and poses a severe health burden with 1 million cases reported in the past 5 years. In healthy individuals and murine experimental leishmaniasis of resistant C57BL/6 mice, the cutaneous disease can be controlled through T helper (Th)1– and/or cytotoxic T-lymphocyte–mediated immune responses that are characterized by IFN-γ–driven macrophage activation and parasite killing, which induces lifelong memory and protection. In contrast, Th2- and/or Th17-governed immune responses in immune-compromised individuals and susceptible BALB/c mice lead to uncontrolled disease progression (Peters and Sacks, 2006).

Lesion-associated dendritic cells (DCs) contribute to effective T-cell

Abbreviations: DC, dendritic cell; LC, Langerhans cell; Th, T helper; Treg, regulatory T cell

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SUPPLEMENTARY MATERIALS AND METHODS

Type of study

We conducted a nationwide multicentric prospective randomized placebo-controlled study in the Departments of Dermatology of Nice, Paris, Marseille, Reims, and Montpellier University Hospitals from January 2016 to February 2019. The study was registered to the French Health Authorities (ANSM registration number: 150355A-42) and to the institutional review board of Sud Méditerranée V (registration number: 15.039). Written informed consent was obtained for all the patients. The study was registered at ClinicalTrials.gov (registration number: NCT01840046).

Objectives

The main objective was to compare the clinical efficacy of low doses of IL-2 versus placebo in severe alopecia areata (AA) after 1 year of follow-up.

The secondary objectives were to study the evolution of peripheral T regulatory cell and NK cell populations during treatment. QOL, patient's satisfaction, regrowth of body hair, and tolerance were also assessed.

Population

Patients with a clinical diagnosis of AA (ophiasis, totalis, or universalis forms) defined as severe, that is, affecting at least 50% of the scalp and aged between 18 and 60 were considered for inclusion. The last flare of AA must have occurred less than 2 years before inclusion. Any topical treatment of AA (topical steroids, topical calcineurin inhibitors, or minoxidil) should have been discontinued at least 1 month before inclusion. Phototherapy and any systemic treatments of AA (systemic steroids, ciclosporin, methotrexate, or any other immunosuppressive drugs) should have been stopped at least 3 months before inclusion. Contraindication to IL-2; pregnant or breast feeding women; positive status for HIV, hepatitis C virus, and hepatitis B virus; kidney or liver insufficiency; and any active infection were also exclusion criteria.

Treatments

Patients received a total of four cycles of low-dose IL-2 or saline serum. Each cycle included five consecutive days of subcutaneous injections of either aldesleukin (Proleukin, Novartis, Basel, Switzerland) or saline serum according to randomization, followed by 16 days with no additional injection. During the first cycle, 1.5 MUI/day of aldesleukin was used, and 3 MUI/day was used for the three other cycles.

Criteria of evaluation

The main criteria used to assess the clinical efficacy was the Severity of Alopecia Tool score (Olsen et al., 2004). This score was assessed by two independent physicians on standardized pictures on a consensus-based matter (HM, TP). A 50% reduction in the Severity of Alopecia Tool score was considered the main indicator of success, and the percentage of patients reaching a 50% reduction in the Severity of Alopecia Tool score 12 months after treatment completion was calculated and compared in both arms as a primary endpoint. The regrowth of body hair and nail improvement (when applicable) was assessed by an investigator global assessment using a semiquantitative scale: −1, worsening; 0, no change; 1, slight improvement; 2, moderate improvement; 3, marked improvement; and 4, complete regrowth. The quality of life was assessed by Dermatology Life Quality Index calculation. The satisfaction was graded by the patients at month 12 on a visual analog scale. Adverse events were reported and graded at each visit according to the National Institute of Health classification.

Blood samples were obtained before each cycle and after 5 days of injections. Additional analyses were performed 1, 3, 6, and 12 months after the end of the last cycle. Blood cell count, liver test, urea, and creatinemia were analyzed at all time points. Flow cytometry analysis of lymphocyte, T regulatory cell, and NK cell populations was carried out before treatment; at the last day of the fourth cycle; and 1, 3, 6, and 12 months after the end of the last cycle.

Flow cytometry analysis

Flow cytometry analysis was performed on blood collected with EDTA and labeled within 48 hours. Briefly, immunophenotypical analysis was performed using 8-color flow cytometry (FACSCanto II, BD Biosciences, San Jose, CA). The following antibodies were used in this study: FITC-conjugated CD16, CD56, CD8, and CD162; phycoerythrin-conjugated CD25 and CD152b; peridinin chlorophyll protein-Cy5.5—conjugated CD4; phycoerythrin-Cy7—conjugated CD19 and CD127; allophycocyanin-conjugated CD45RA, HLA-DR, and CD314; allophycocyanin-H7—conjugated CD3; V450-conjugated CD197; BV421-conjugated CD8, CD194, and CCR10; and V500-conjugated CD45, all purchased from BD Biosciences. Instrument set up was performed according to the France Flow Standard Operating Procedures (Solly et al., 2019). Identification of lymphocytes was done using a combination of side scatter and forward scatter properties and CD45 expression. The gating strategy for T regulatory cells was based on the gating of $CD3^+CD4^+$ and $CD3^+CD8^+$ lymphocytes, the gate $CD127wkCD25^+$ being set on $CD3^+CD4^+$ T cells using the $CD3^+CD8^+$ T cells as a negative control (Liu et al., 2006). Subpopulations of naive, memory, effector, and effector memory T regulatory cells were identified according to the expression of CD45RA and CD197 (Maecker et al., 2012).

Sample size calculation

According to the literature, we anticipated a success rate of 10% at month 12 in the placebo group (Delamere et al., 2008). Assuming a success rate of 50% in the IL-2 group based on our preliminary study (Castela et al., 2014), with 80% power, a 5% type I error, and a bilateral hypothesis, we calculated that 25 patients per arm were needed. Assuming 10% lost to follow-up, a final overall effective number of 56 patients was retained.

Randomization

Patients were randomly assigned in a 1:1 ratio to either the IL-2 or placebo arm. The randomization process was centralized and performed in the methodological center of Nice University Hospital. The randomization list was established using the blocks method with nQuery Advisor v7.0.

Statistical analysis

Analysis of the primary outcome was performed on a modified intention-to-

treat principle. All patients who underwent randomization and took at least one dose of medication were submitted to analysis. Missing values were imputed according to the Last Observation Carried Forward procedure. Per-protocol analyses were also performed, considering only patients who completed the entire study without violation of the protocol and with an adequate compliance (at least 16 injections out of 20 scheduled).

First, the rate of success (50% reduction in Severity of Alopecia Tool score 12 months after last infusion) was compared between treatment arms using the Fisher exact test. Then, the investigator global assessment for regrowth of body hair and nails was compared at month 6 and month 12 using the Wilcoxon rank sum test. Covariance analysis was used to compare quality of life improvement between inclusion and month 6 and month 12, adjusted to the baseline value of the Dermatology Life Quality Index score. Satisfaction was measured with Student's *t*-test, and the rates of main adverse effects were compared between groups with Fisher exact test. All analyses of lymphocyte subpopulations were performed using the Student's *t*-test for paired data.

Two-sided *P*-values < 0.05 were considered statistically significant. Statistical analyses were performed using SAS Enterprise Guide software, version 7.1 (SAS Institute, Inc, Cary, NC).

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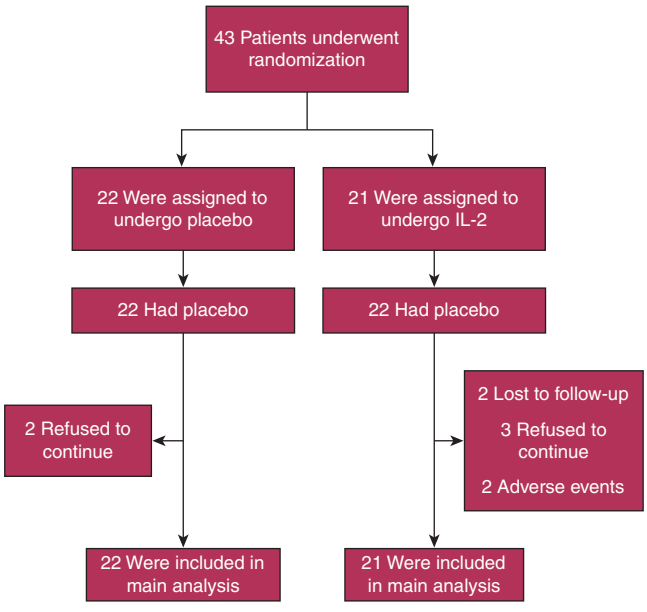
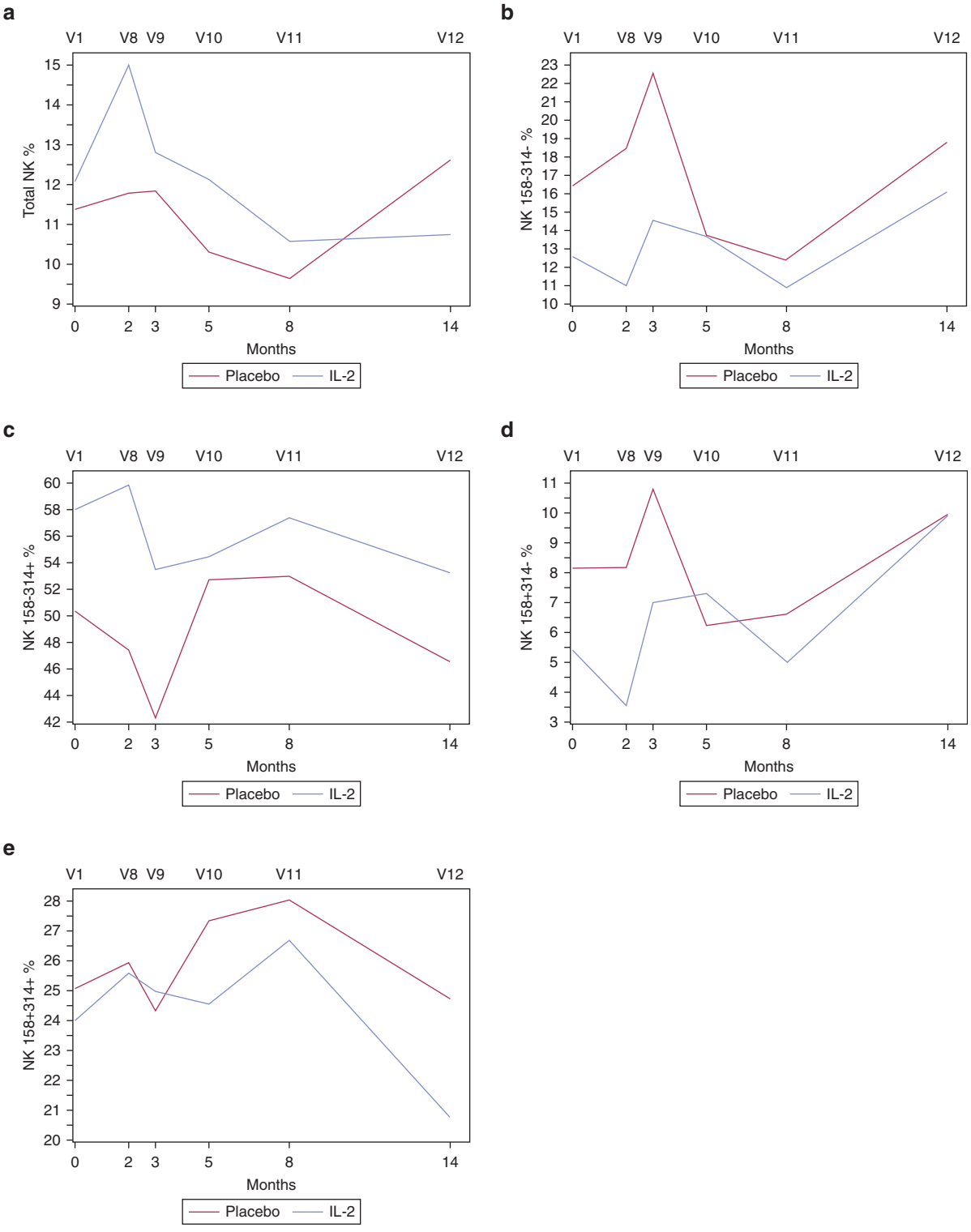


Supplementary Figure S1. Flow diagram of the study.



Supplementary Figure S2. Monitoring of NK populations over time. Flow cytometry analysis was performed at baseline (V1); at the end of the fourth cycle of treatment (V8); 1 month after the end of the cures (V9); and after 3 (V10), 6 (V11), and 12 months (V12). (**a**) Percentage of total NK cell count. (**b**) Percentage of NK CD158 (KIR)$^{-}$/CD314 (NKG2D)$^{-}$ subpopulation. (**c**) Percentage of NK CD158^{-}/CD314^{+} subpopulation. (**d**) Percentage of NK CD158^{+}/CD314^{-} subpopulation. (**e**) Percentage of NK CD158^{+}/CD314^{+} subpopulation.

Supplementary Table S1. Characteristics of the Population

Characteristics	n	Placebo (n = 22), %	n	Low-Dose IL-2 (n = 21), %
Age (y), mean (±SD)	22	38.4 (13.0)	21	37.1 (9.9)
Sex				
Male	10	45.4	3	14.3
Female	12	54.6	18	85.7
Time since alopecia diagnosis (y), mean (±SD)	21	22.7 (15.0)	21	16.3 (13.0)
Time since last flare (y), mean (±SD)	22	0.9 (0.6)	21	0.6 (0.5)

Supplementary Table S2. Comparison of the Evolution of DLQI Scores at 6 and 12 Ms

DLQI Score	V1 (D0) (n = 22)	V11 (M6) (n = 19)	Diff_D0/M6 (n = 19)	*P*
Placebo, mean ± SD	6.64 ± 5.92	5.63 ± 6.71	−0.84 ± 5.59	0.6056
	V1 (D0) (n = 21)	**V11 (M6) (n = 17)**	**Diff_D0/M6 (n = 17)**	
Low-dose IL-2, mean ± SD	7.33 ± 5.59	5.18 ± 5.66	−1.71 ± 3.00	
DLQI Score	**V1 (D0) (n = 22)**	**V12 (M12) (n = 20)**	**Diff_D0/M12 (n = 20)**	***P***
Placebo, mean ± SD	6.64 ± 5.92	4.45 ± 5.87	−2.30 ± 3.70	0.7915
	V1 (D0) (n = 21)	**V12 (M12) (n = 16)**	**Diff_D0/M12 (n = 16)**	
Low-dose IL-2, mean ± SD	7.33 ± 5.59	4.63 ± 6.41	−1.81 ± 5.73	

Abbreviations: D, day; Diff, difference; DLQI, Dermatology Life Quality Index; M, month.
D0 represents day 0. M6 represents 6-month follow-up, whereas M12 12-month follow-up.

Supplementary Table S3. Comparison of Satisfaction at 3 and 12 Ms

Satisfaction	V10 (M3) (n = 18)	V12 (M12) (n = 19)
Placebo, mean ± SD	4.79 ± 3.35	4.30 ± 2.87
Satisfaction	**V10 (M3) (n = 19)**	**V12 (M12) (n = 15)**
Low-dose IL-2, mean ± SD	3.46 ± 3.17	3.68 ± 2.95
P-value	0.2209	0.5437

Abbreviations: M, month.
M3 represents 3-month follow-up, whereas M12 represents 12-month follow-up.

Supplementary Table S4. Adverse Events of Interest

Adverse Event	Low-Dose IL-2, n (%)	Placebo, n (%)	*P*-value
Flu-like syndrome	14 (66.7)	3 (13.6)	0.0005
Eosinophilia	8 (38.1)	0 (0)	0.0014
Reaction at the injection site	15 (71.4)	1 (4.6)	<0.0001
Asthenia	13 (61.9)	7 (31.8)	0.0480
Elevated liver enzymes	7 (33.3)	2 (9.1)	0.07
Digestive symptoms (pain and/or diarrhea)	9 (42.9)	7 (31.8)	0.4541
Upper track infection	8 (38.1)	5 (22.7)	0.2727
Headache	10 (47.6)	8 (36.4)	0.4545

n = number of patients who presented at least once with the adverse event.

Supplementary Table S5. Reported Adverse Events

Type of Adverse Event	Total Count of Events	Number of Patients	Percentage of Patients
Placebo			
Asthenia	11	7	31.82
Digestive symptoms (pain and/or diarrhea)	11	7	31.82
Cephalalgia	11	8	36.36
Upper track infection	9	5	22.73
Hot flushes	4	2	9.09
Infection (other)	4	4	18.18
Pruritus	4	4	18.18
Flu-like syndrome	4	3	13.64
Arthralgia	2	1	4.55
Hepatic cytolysis	2	2	9.09
Eczema / Rhinitis / Allergic conjunctivitis	2	2	9.09
Hyperthermia	2	2	9.09
Febrile sensation	2	1	4.55
Cutaneous and/or mucosal xerosis	2	1	4.55
Tinnitus	1	1	4.55
Prostatic adenoma	1	1	4.55
Increased gamma-glutamyl transferase	1	1	4.55
Keratocone (evolution)	1	1	4.55
Exanthema	1	1	4.55
Microscopic hematuria	1	1	4.55
Depressive mood	1	1	4.55
Hypoeosinophilia	1	1	4.55
Lichen planus	1	1	4.55
Leg heaviness	1	1	4.55
Lymphopenia	1	1	4.55
Myalgia	1	1	4.55
Mycosis	1	1	4.55
Neutropenia	1	1	4.55
Neutrophilia	1	1	4.55
Thyroid nodule	1	1	4.55
Leg edema	1	1	4.55
Injection site reaction	1	1	4.55
Feeling of blocked ear	1	1	4.55
Sweating	1	1	4.55
Carpal tunnel syndrome	1	1	4.55
Accidental trauma	1	1	4.55
Sleep disorders	1	1	4.55
Low-dose IL-2			
Reaction at the injection site	40	15	71.43
Digestive symptoms (pain and/or diarrhea)	37	9	42.86
Flu-like syndrome	36	14	66.67
Asthenia	23	13	61.90
Hypereosinophilia	17	8	38.10
Cephalalgia	14	10	47.62
Infection (other)	12	9	42.86
Hepatic cytolysis	11	7	33.33
Upper track infections	11	8	38.10
Hyperthermia	7	4	19.05
Eczema/rhinitis/allergic conjunctivitis	5	4	19.05
Neuropathy	5	3	14.29
Leg edema	5	4	19.05
Arthralgia	4	2	9.52
Pruritus	4	4	19.05
Cough	4	2	9.52
Accidental trauma	4	3	14.29
Urticaria	3	1	4.76
Cutaneous and/or mucosal xerosis	3	2	9.52
Anorexia	2	2	9.52

(*continued*)

Supplementary Table S5. Continued

Type of Adverse Event	Total Count of Events	Number of Patients	Percentage of Patients
Breathing difficulty	2	2	9.52
Microscopic hematuria	2	2	9.52
Depressive mood	2	2	9.52
Weight gain	2	2	9.52
Anemia	1	1	4.76
Spider angioma	1	1	4.76
Aphtous ulcer	1	1	4.76
Increased C-reactive protein	1	1	4.76
Increased gamma-glutamyl transferase	1	1	4.76
Presternal burn	1	1	4.76
Sunburn	1	1	4.76
Groin pain	1	1	4.76
Dyspnea	1	1	4.76
Ecchymose	1	1	4.76
Exanthema	1	1	4.76
Gingivorrhagia	1	1	4.76
Hypercorticis	1	1	4.76
Malodorous hyperhidrosis	1	1	4.76
Lymphopenia	1	1	4.76
Melanonychia	1	1	4.76
Monocytosis	1	1	4.76
Mycosis	1	1	4.76
Eyelid edema	1	1	4.76
Weight loss	1	1	4.76
Photosensitivity	1	1	4.76
Psoriasiform lesions of the scalp	1	1	4.76
Febrile sensation	1	1	4.76
Tachycardia	1	1	4.76
Sleep disorders	1	1	4.76
Dizziness	1	1	4.76