

Methotrexate Versus Cyclosporine in Adults with Moderate-to-Severe Atopic Dermatitis: A Phase III Randomized Noninferiority Trial



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What is already known about this topic? Methotrexate is currently used to treat atopic dermatitis in adults and has achieved clinical improvement in a randomized trial versus azathioprine for severe atopic eczema. Both treatments were safe in the short-term.

What does this article add to our knowledge? This noninferiority study, comparing methotrexate versus cyclosporine in patients with moderate-to-severe atopic dermatitis, shows that methotrexate improves less rapidly the patients than cyclosporine but with a better safety profile.

How does this study impact current management guidelines? Atopic dermatitis being a highly inflammatory disease, we recommend initiating subcutaneous methotrexate between 15 mg/wk and 25 mg/wk, depending on patient weight and severity of the disease.

BACKGROUND: Methotrexate is currently used to treat atopic dermatitis but has never been assessed versus cyclosporine in adults.

OBJECTIVE: This study evaluated the efficacy and safety of methotrexate versus cyclosporine in patients with moderate-to-severe atopic dermatitis.

METHODS: Patients were randomized to receive either oral methotrexate (15 mg/wk) or cyclosporine (2.5 mg/kg/d) for 8 weeks. The primary end point was a patient achieving 50% improvement in the SCORing Atopic Dermatitis index (SCORAD 50) at week 8. When the primary end point was not achieved, methotrexate was increased to 25 mg and cyclosporine

to 5 mg during the next 16 weeks. The secondary end points were a patient achieving a 50% reduction in the Eczema Area Severity Intensity index (EASI 50) and SCORAD 50 at each visit ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study?term=NCT00809172) no. NCT00809172).

RESULTS: A total of 97 patients received methotrexate 15 mg (n = 50) or cyclosporine 2.5 mg (n = 47). Regarding the primary end point at week 8, methotrexate was inferior to cyclosporine because the proportion of patients with SCORAD 50 was 8% (4 of 50) in the methotrexate arm versus 42% (18 of 43) in the cyclosporine arm. The difference in percentages for the 2 treatment groups (2-sided 90% CI) was -34% (-48% to -20%). At week 8, methotrexate and cyclosporine dosages

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Conflicts of interest: M. Viguier is on the boards for Lilly and Novartis; has received lecture fees from Lilly, Abbvie, and MSD; and has received travel support from Janssen, Novartis, and Abbvie. The rest of the authors declare that they have no relevant conflicts of interest.

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Abbreviations used

DLQI- Dermatology Life Quality Index (score ranging from 0 to 30, a higher score indicating a greater severity)

EASI index- Eczema Area Severity Intensity index (score ranging from 0 to 72, a higher score indicating a greater severity)

EASI 50- 50% improvement in the Eczema Area Severity Intensity index

SCORAD index- SCORing Atopic Dermatitis index (score ranging from 0 to 103, a higher score indicating a greater severity)

SCORAD 50- 50% improvement in the SCORing Atopic Dermatitis index

were increased in 56% and 49% of the patients, respectively. Regarding EASI 50, the noninferiority end point was reached at week 20 in 92% (22 of 24) of patients in the methotrexate arm and 87% (26 of 30) of patients in the cyclosporine arm. The treatment-related adverse events were more frequent with cyclosporine ($P < .0001$).

CONCLUSIONS: Methotrexate 15 mg/wk was inferior to cyclosporine 2.5 mg/kg/d at week 8. Increasing the doses of methotrexate to 25 mg/wk induced a significant improvement versus cyclosporine at week 20. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;6:562-9)

Key words: Atopic dermatitis; Methotrexate; Cyclosporine; Trial

Atopic dermatitis is characterized by skin barrier dysfunction and immunologic disturbance of the adaptive and innate immune system to exogenous (eg, house dust mite allergens) and endogenous factors.^{1,2} This frequent chronic inflammatory skin disorder affects 2% to 3% of adults³ of whom approximately 20% display a moderate-to-severe disease.⁴ Nonresponders to topical agents (corticosteroids, tacrolimus)⁵ need systemic treatments that are limited and difficult to deal with because of their side effects. Phototherapy has limitations related to patient availability and risk of carcinogenesis. Cyclosporine, licensed in many European countries, is associated with hypertension, renal impairment, and general immunosuppression. Furthermore, this treatment is not indicated for long-term treatments because of its cumulative toxicity.⁶ Methotrexate is a well-known drug that has been in use for more than 40 years in the treatment of psoriasis and more recently in atopic dermatitis.^{7,8} Its major side effects, which include bone-marrow suppression and liver toxicity, are prevented by regular biological follow-ups, dosage of procollagen III, and imaging. Previous studies have shown that methotrexate could improve moderate-to-severe atopic dermatitis.⁹⁻¹¹ In this respect, we have recently observed, in an open retrospective study in 20 patients, that 75% of patients were markedly improved by methotrexate at doses ranging from 7.5 mg/wk to 25 mg/wk.¹² We decided then to conduct a noninferiority clinical trial to better assess methotrexate efficacy and safety versus cyclosporine.

METHODS

Study design

This phase 3, randomized, multicenter, parallel-group, evaluator-blind, noninferiority trial comparing methotrexate with cyclosporine

was conducted at 8 centers in France. This study was registered under European Clinical Trials Database 2007-004652-36 and under ClinicalTrials.gov (no. NCT00809172) in December 2008. The study was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines. It was approved in July 2008 by the local research ethics committee and the French Health Products Safety Agency. All patients received a detailed description of the study and provided written informed consents. The design of the study is shown in [Figure E1](#) in this article's Online Repository at www.jaci-inpractice.org.

Patients

Eligible patients were those who presented a chronic moderate-to-severe atopic dermatitis as per the diagnostic criteria of the UK Working Party¹³ with a score of more than 15 on the SCORing Atopic Dermatitis (SCORAD) index and presented an inadequate response to a regimen of topical corticosteroids or tacrolimus. The major exclusion criteria were the use of systemic corticosteroids or an immunosuppressive treatment within 4 weeks before the inclusion visit and a contraindication to methotrexate or cyclosporine. The additional eligibility criteria are provided in [Table E1](#) in this article's Online Repository at www.jaci-inpractice.org. The prohibited treatments are listed in [Table E2](#) and the concomitant and rescue medications in [Table E3](#) in this article's Online Repository at www.jaci-inpractice.org. All the patients were examined by a dermatologist at the enrollment and baseline visits, then every 4 weeks during 24 weeks. At each visit, trained assessors, blind to the treatment allocation, evaluated the SCORAD index, the Eczema Area Severity Intensity (EASI) index, and the Dermatology Life Quality index (DLQI). The response to the treatment was the percentage of SCORAD index improvement compared with that of the baseline visit. The patient was considered as a nonresponder and discontinued the trial whenever, at 8 weeks of treatment, he or she experienced a decrease in the SCORAD index by more than 5% versus the baseline (SCORAD index $< -5\%$) and whenever at 12, 16, and 20 weeks of treatment he or she did not achieve at least a 5% reduction in the SCORAD index (SCORAD index $< +5\%$) (see [Table E4](#) in this article's Online Repository at www.jaci-inpractice.org).

Treatment regimens

Eligible patients were assigned in a 1:1 ratio to receive either methotrexate (15 mg/wk in a single oral dose) or cyclosporine (2.5 mg/kg of body weight/d divided in 2 oral doses). The randomization was performed centrally using computer-generated random numbers using random fixed permuted blocks with stratification on the center and the disease severity (severe = SCORAD index > 40). After 8 weeks of treatment, these doses were, respectively, increased to 25 mg/wk and 5 mg/kg of body weight/d for 16 more weeks in the patients who did not achieve 50% reduction in the SCORAD index (SCORAD 50). Patients randomized to methotrexate received 5 mg folate daily, except on the day of methotrexate intake. Topical corticosteroids and tacrolimus were allowed only during the first 4 weeks of the systemic treatment. The patients had to use their personal moisturizer during the whole study. Only the assessors were blind to the treatment allocation. Patients on methotrexate had weekly complete blood cell counts during the 12 first weeks, then every 4 weeks until week 24. Liver enzymes and serum creatinine were assessed every 4 weeks. Patients on cyclosporine had blood analyses every 4 weeks (including a complete blood cell count, serum creatinine, liver enzymes). In addition, electrolytes, bilirubin, uric

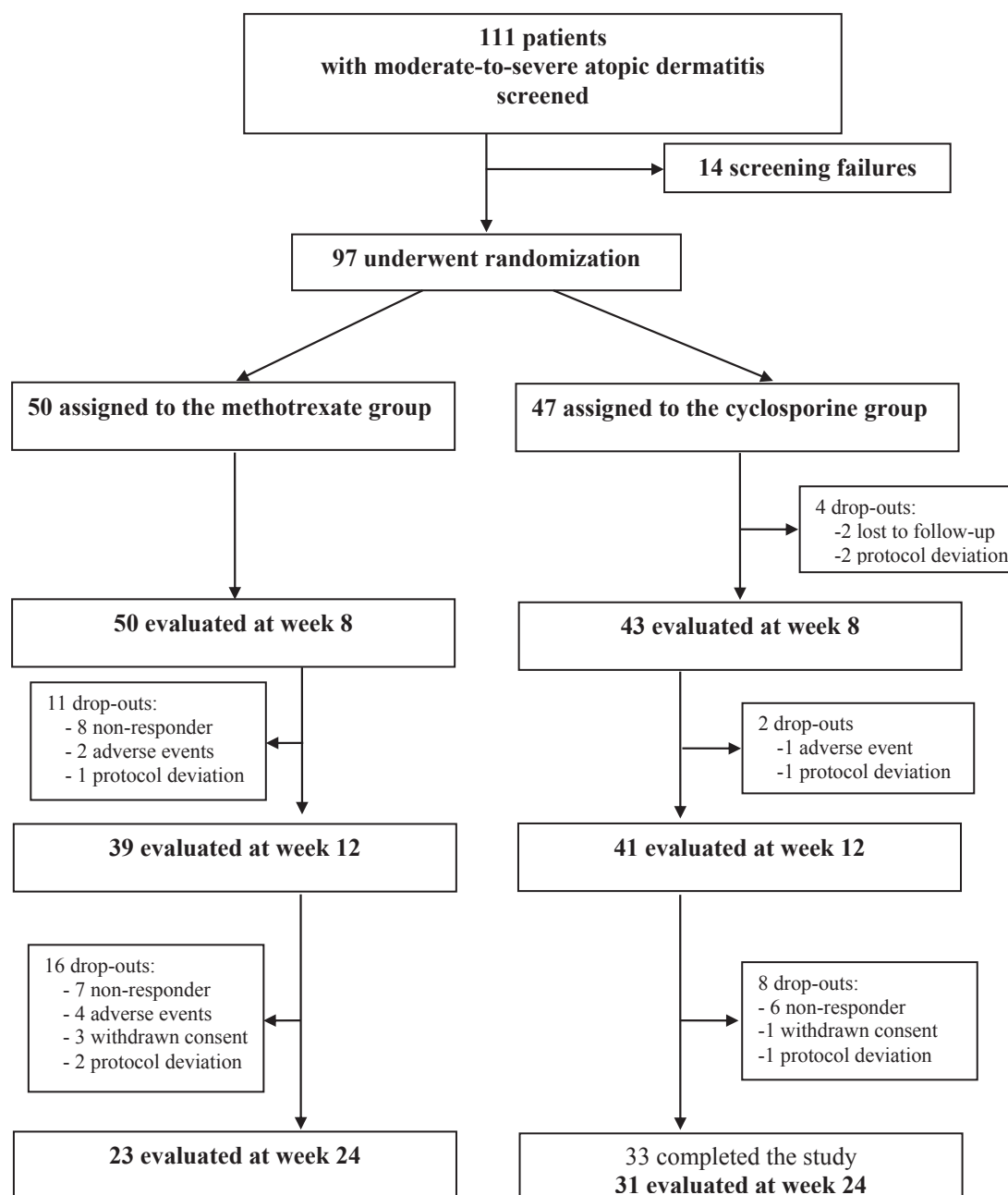


FIGURE 1. Trial profile.

acid, blood glucose tests, and urine analyses were carried out every 12 weeks.

Outcomes

Efficacy. The primary end point was a patient achieving SCORAD 50 at 8 weeks of treatment. The secondary end points were patients achieving 50% improvement in the Eczema Area Severity Intensity index (EASI 50) and a DLQI value of 5 or less at 8 weeks of treatment and patients achieving these 3 scores at 12, 16, 20, and 24 weeks of treatment. The secondary end point regarding safety was the number of clinical and biological events (probably or possibly) related to the study treatments.

Safety was monitored through physical examination, surveillance of adverse events, and laboratory tests. A *serious adverse event* was defined as a life-threatening event and events that resulted in death, hospitalization, disability, or permanent damage. The intensity of the adverse events was described as mild, moderate, or severe. The dermatologist qualified the adverse events as not, possibly, or probably related to the treatment.

Statistical analysis

The sample size calculation was based on a 1-sided alpha risk of 5%, a power of 80% (beta risk = 0.2), a 80% proportion of success in the cyclosporine arm, and a noninferiority limit of -20% (1-sided CI, left limit) for the difference in success proportions (methotrexate

TABLE I. Baseline characteristics of the intention-to-treat population

Characteristic	Cyclosporine	Methotrexate	P value
No.	47	50	
Age (y)	33 ± 10	32 ± 9	.37
Males	31 (66)	28 (57)	.38
Weight (kg)	74 ± 14	69 ± 11	.02
Disease duration (y)	23 (19-29)	24 (14-29)	.81
EASI	19 ± 12	18 ± 0	.61
SCORAD index	58 ± 15	53 ± 14.2	.07
Patients with SCORAD index >40	41 (87)	40 (80)	.42
Affected body surface area	43 ± 28	38 ± 25	.32
Pruritus (SCORAD visual analogic scale)	6.7 ± 2	6.4 ± 3	.50
DLQI	12 ± 6	13 ± 8	.50

Data are number (%) or mean. ± SD, or median (25th-75th percentile).

vs cyclosporine). At the time of the study, there were no references regarding the noninferiority margin. The −20% limit was thus chosen on the basis of the following 3 facts: (1) cyclosporine decreased the intensity of symptoms of atopic dermatitis in 78% to 88% of patients after 6 weeks of treatment¹⁴; (2) a good clinical response was seen in more than 80% of patients with psoriasis on cyclosporine¹⁵; and (3) in a previous retrospective study,¹² 65% of patients with atopic dermatitis showed a significant clinical response within 8 weeks on methotrexate. We finally estimated that a −20% limit was acceptable because methotrexate is better tolerated than cyclosporine. One hundred patients were required to reject the null hypothesis of greater than 20% less efficacy in the methotrexate arm versus the cyclosporine arm. According to the “Intention-to-treat” principle, the primary analysis was performed on all randomized and evaluated subjects using the 95% unilateral lower confidence limit (equal to a 90% bilateral lower confidence limit) to reject the noninferiority. In a secondary analysis, a logistic regression model was used to estimate the difference in proportions between the 2 treatment arms taking into account the center and considering the stratification variables as adjustment variables. The center was introduced either as a random effect or as a fixed effect after merging the small centers and the other variables (severity strata or baseline SCORAD index) as fixed effects. A per-protocol analysis was also conducted to avoid promoting the equivalence of treatments. The per-protocol population analysis was carried out after excluding data with major deviations from the protocol found at the blind review of the data set (missing main end point, deviation from the protocol dosages, and use of nonauthorized treatments). The real allocated treatment was the random allocated treatment for all patients (no deviation from the intention-to-treat principle). One missing SCORAD index value at week 8 was replaced by interpolation between week 4 and week 12 values. Two sensibility analyses were performed replacing the missing primary end point by either a success or a failure. The secondary efficacy outcomes were analyzed with the same statistical methods and data on all patients evaluated at 4, 8, 12, 16, 20, and 24 weeks of treatment. Patients who stopped the study at week 8 for nonresponse, adverse events, or other reasons were not evaluated later within the study protocol. Adverse events were analyzed in all patients by arm (number of events and number of patients) and compared with Fischer exact test.

RESULTS

From December 2008 to March 2012, 111 patients were screened for the present study. Of these, 97 underwent randomization: 50 patients in the methotrexate arm and 47 in the cyclosporine arm (Figure 1). The baseline characteristics of the patients are presented in Table I. The demographic characteristics were well balanced between the 2 arms. The median duration of the disease was 23 years or more in the 2 arms. Severe disease (SCORAD index >40) was present in 80% or more patients. Within the first 8 weeks of treatment, 2 patients in the cyclosporine arm were lost to follow-up and 2 excluded for protocol deviation. The primary end point was then analyzed in 50 patients in the methotrexate arm and 43 patients in the cyclosporine arm. After stopping topical steroids, which were authorized only during the first 4 weeks, the number of eczema flares recorded between week 4 and week 8 was 8 in the methotrexate arm versus 4 in the cyclosporine arm (see Table E5 in this article's Online Repository at www.jaci-inpractice.org). The methotrexate dose was increased to 25 mg/wk in 56% of patients in the methotrexate arm (28 of 50) and the cyclosporine dose to 5 mg/kg of body weight/d in 49% of patients in the cyclosporine arm (21 of 43). Finally, 23 patients (46%) in the methotrexate arm and 33 patients (77%) in the cyclosporine arm received their treatments for 24 weeks and completed the study. In both arms, nonresponse was the main reason for treatment discontinuation (see Table E6 in this article's Online Repository at www.jaci-inpractice.org). Regarding the primary end point, 8% (4 of 50) of patients in the methotrexate arm compared with 42% (18 of 43) of patients in the cyclosporine arm achieved SCORAD 50 response at week 8. The 2-sided 90% CI for the difference in percentages for the 2 treatment groups was −48% to −20%, and so the noninferiority of methotrexate to cyclosporine was not demonstrated when compared with the −20% noninferiority limit. Moreover, the results show that methotrexate is inferior to cyclosporine because the CI does not include zero. The sensibility analysis replacing the 4 missing data at week 8 by either a success or a failure did not change the conclusion, the difference in percentages for the 2 treatment groups (90% CI) being, respectively, −39% (−52% to −25%) and −30% (−44% to −17%). An analysis adjusted on variables “center” and “severity” or on the baseline SCORAD index did not change the primary result. The per-protocol analysis also gave a similar result, that is, −30% (−45% to −15%) regarding the main end point. Inferiority regarding the secondary end point of efficacy at 8 weeks was also accepted (Table II). EASI 50 was achieved in 35% of methotrexate arm subjects versus 68% of cyclosporine arm subjects; the difference was −34% (−50% to −17%). The DLQI value of 5 or less was achieved in 31% versus 56%, respectively; the difference was −25% (−42% to −9%). The percentage of methotrexate patients achieving SCORAD 50, EASI 50, and the DLQI value of 5 or less increased dramatically after week 12 (Figure 2), that is, after increasing the drug doses in patients who did not reach sufficient improvement at week 8. At week 20, the clinical improvement obtained with methotrexate 25 mg/wk was similar to that obtained with cyclosporine 5 mg/kg/d for EASI 50, one of the secondary end points, which was reached by 92% (22 of 24) of methotrexate patients versus 87% (26 of 30) of cyclosporine patients. The 5% (−9% to 19%) difference was maintained at week 24; precisely, the difference was 6% (−10% to 23%) between patients still in the study (54 of the 97 participants).

TABLE II. Score and percent decrease in score between treatment arms

End point	Week	N	Methotrexate arm			Cyclosporine arm			Mean difference % between arms (90% CI)	
			Value	% decrease	% patients achieving end point	N	Value	% decrease		% patients achieving end point
SCORAD primary										
end point: $\geq 50\%$ decrease										
	0	50	52.6 $\pm$ 14.2	NA	NA	47	57.9 $\pm$ 15.0	NA	NA	NA
	4	49	44.9 $\pm$ 15.1	12.4 $\pm$ 26.9	8.2	46	35.8 $\pm$ 16.0	37.5 $\pm$ 23.5	30.4	NA
	8	50	44.6 $\pm$ 16.6	12.6 $\pm$ 33.6	8.0	43	32.5 $\pm$ 15.7	43.8 $\pm$ 22.7	41.9	−34 (−48 to −20)
	12	36	36.6 $\pm$ 13.7	27.8 $\pm$ 23.5	19.4	41	29.6 $\pm$ 16.3	49.4 $\pm$ 25.2	51.2	−31 (−49 to −15)
	16	28	28.7 $\pm$ 11.5	43.3 $\pm$ 17.3	42.9	34	27.0 $\pm$ 15.6	54.8 $\pm$ 23.2	61.8	−19 (−39 to 2)
	20	25	26.0 $\pm$ 8.0	46.8 $\pm$ 17.1	48.0	32	24.2 $\pm$ 12.9	56.6 $\pm$ 23.3	65.6	−18 (−39 to 4)
	24	23	26.9 $\pm$ 11.6	47.9 $\pm$ 18.3	39.1	31	24.9 $\pm$ 15.5	55.9 $\pm$ 28.2	71.0	−32 (−53 to −10)
EASI, secondary										
end point: $\geq 50\%$ decrease										
	0	50	18.6 $\pm$ 10.1	NA	NA	47	19.3 $\pm$ 11.8	NA	NA	NA
	4	49	12.6 $\pm$ 8.1	12.9 $\pm$ 71.2	32.0	46	9.3 $\pm$ 8.8	50.1 $\pm$ 28.8	54.6	NA
	8	49	12.9 $\pm$ 9.6	10.4 $\pm$ 105.3	34.7	41	8.1 $\pm$ 8.1	58.2 $\pm$ 28.3	68.3	−34 (−50 to −17)
	12	37	9.8 $\pm$ 5.6	31.7 $\pm$ 45.0	43.2	41	7.0 $\pm$ 7.3	62.6 $\pm$ 32.8	75.6	−32 (−50 to −15)
	16	27	6.3 $\pm$ 4.6	57.0 $\pm$ 27.6	66.7	34	6.1 $\pm$ 6.9	68.2 $\pm$ 23.9	79.4	−13 (−31 to 6)
	20	24	4.8 $\pm$ 2.5	66.8 $\pm$ 25.2	91.7	30	4.9 $\pm$ 5.8	69.8 $\pm$ 35.7	86.7	+5 (−9 to 19)*
	24	23	5.0 $\pm$ 3.6	67.7 $\pm$ 24.4	87.0	31	5.4 $\pm$ 5.0	67.4 $\pm$ 30.0	80.7	+6 (−10 to 23)*
DLQI, secondary										
end point: DLQI ≤ 5										
	0	50	12.3 $\pm$ 6.3	NA	14.0	47	13.2 $\pm$ 7.5	NA	19.1	−5 (−18 to 7)
	4	49	8.4 $\pm$ 6.2	NA	44.0	46	6.2 $\pm$ 5.6	NA	60.9	−17 (−33 to 0)
	8	50	10.8 $\pm$ 7.8	NA	30.6	43	6.5 $\pm$ 6.3	NA	56.1	−25 (−42 to −9)
	12	36	7.2 $\pm$ 5.5	NA	41.7	41	5.4 $\pm$ 5.6	NA	68.3	−27 (−45 to −9)
	16	28	5.1 $\pm$ 3.5	NA	60.7	34	4.3 $\pm$ 5.4	NA	77.1	−16 (−36 to 3)
	20	25	4.4 $\pm$ 4.1	NA	72.0	32	3.7 $\pm$ 5.1	NA	87.5	−16 (−33 to 2)
	24	23	5.0 $\pm$ 4.6	NA	65.2	31	3.3 $\pm$ 4.4	NA	80.6	−15 (−35 to 5)

NA, Not applicable/available.

The values are means $\pm$ SDs.

*Noninferiority achieved.

However, the noninferiority of methotrexate versus cyclosporine was not reached for the other end points. The total number of adverse events was balanced between the methotrexate and cyclosporine arms (Table III) but the number of treatment-related adverse events was significantly lower in the methotrexate arm than in the cyclosporine arm (30% vs 55%, respectively, $P < .0001$). Hypertension was recorded in 3 of the subjects who were treated with cyclosporine; 16 neuromuscular disorders and 11 dermatological disorders occurred in the cyclosporine arm versus, respectively, 7 and 1 in the methotrexate arm. One serious adverse event (hospitalization due to eczema flare) occurred in the cyclosporine arm. No myelosuppression occurred in the methotrexate arm. Discontinuation due to treatment-related adverse events was required in 2 patients of the methotrexate arm: elevation in liver enzymes in 1 patient with 15 mg at week 8 and lymphocytopenia in another patient with 25 mg at week 12.

DISCUSSION

This study is the first head-to-head comparison of methotrexate versus cyclosporine in adults with moderate-to-severe atopic dermatitis. We show that cyclosporine (2.5 mg/kg/d) is more effective than methotrexate (15 mg/wk) to treat moderate-

to-severe atopic dermatitis. Indeed, the primary and secondary end points were not met at weeks 8, 12, and 16. Later on (by week 20), after an increase in doses in the nonresponding patients at week 8, differences between the 2 agents were no longer present, at least as far as EASI 50 responses are concerned. These data confirm the rapid efficacy of cyclosporine in atopic dermatitis and further suggest that methotrexate at high doses may be valuable in the treatment of atopic dermatitis. The determination of the dosage of the study drugs relied on several observations. Methotrexate is usually prescribed at a dose ranging from 5 mg/wk to 25 mg/wk. The initial dose of 15 mg was selected by analogy to its use in psoriasis, to limit toxicity.^{16,17} The 2.5 mg cyclosporine dose was chosen according to the labeling of the drug for atopic dermatitis, 5 mg being indicated for the most severe forms. The choice of 8 weeks for the primary end point was based on the results obtained in 3 previously published clinical studies: (1) our retrospective study on methotrexate in atopic dermatitis¹² showed a marked improvement in skin symptoms at week 8 in 14 of 20 patients with atopic dermatitis; of note, most of these patients received high (25 mg/wk) drug doses administered intramuscularly and the patients had a less severe atopic dermatitis than did those in the present study; (2) the recently published pediatric study of El-Khalawany et al¹⁸

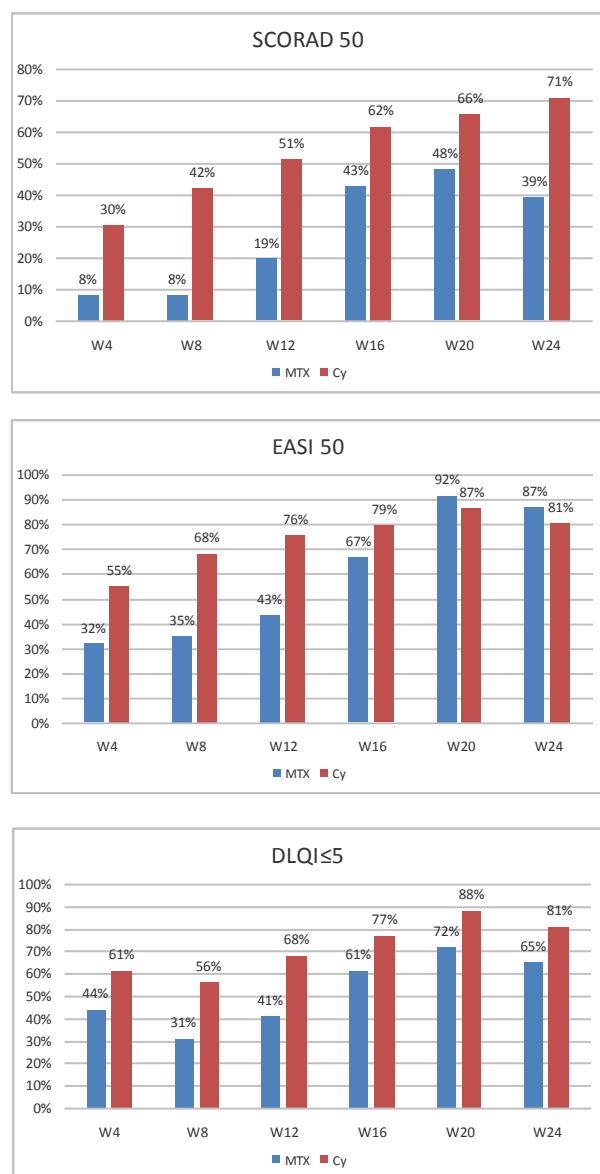


FIGURE 2. Proportions of patients with SCORAD 50, EASI 50, and DLQI value of 5 or less. The percentages are the proportions of patients who achieved SCORAD 50 or EASI 50, or met the criterion of DLQI value being 5 or less. The primary end point (SCORAD 50) was not met at week 8: the difference between the 2 treatment arms exceeded the prespecified noninferiority margin by 28% (unilateral confidence limit = -0.48 or -48% ; ie, lower than the -20% limit in the intention-to-treat analysis, $P = .95$). The per-protocol analysis and the analysis adjusted on the center and disease severity did not change the above conclusion. The secondary end point was achieved with EASI 50 at week 20 (unilateral confidence limit = -0.09 or -9% ; ie, lower than the -20% limit) and maintained at week 24 (unilateral confidence limit = -0.01 or -10%). Cy, Cyclosporine; MTX, methotrexate; W, week.

comparing methotrexate and cyclosporine in children with atopic dermatitis showed that the onset of action of methotrexate was between 3 and 5 weeks; and (3) the study of Heydendael et al¹⁶

TABLE III. Adverse events

Variable	Cyclosporine	Methotrexate	Total
Subjects	47	50	97
Total no. of adverse events*	123	117	240
Adverse events related to study drug (%)†	68 (55)	35 (30)	103
Serious adverse events	1‡	0	1
Treatment nonrelated adverse events leading to discontinuation	0	4	4
Treatment-related adverse events leading to discontinuation	1‡	2§	3
Subjects with at least 1 adverse event	37 (79)	41 (82)	78 (80)
Subjects with treatment-related adverse events	25 (53)	20 (40)	45 (46)
Subjects with adverse events leading to discontinuation	1	2	3
Adverse events of special interest			
Infections			
Nonskin infections	10	6	16
Skin infections	5	6	11
Gastrointestinal disorders	11	9	20
Neuromuscular disorders			
Headache	5	1	6
Fatigue	4	6	10
Cramps	3	0	3
Paresthesia	4	0	4
Dermatological disorders			
Hypertrichosis	5	0	5
Gingival hyperplasia	3	0	3
Other (acne, virus papilloma)	3	1	4
Hypertension	3	0	3

* $P = .58$.

† $P < .0001$.

‡One serious adverse event was hospitalization for severe eczema flare at week 12 in a patient on 2.5 mg/kg/d cyclosporine.

§One patient on 15 mg/wk methotrexate discontinued the study at week 8 because of elevation in liver enzymes (4 times past the normal limit) and another patient on 25 mg/wk methotrexate discontinued at week 12 because of lymphopenia (900 cells/ μ L vs 1500 cells/ μ L as normal count).

on adult psoriasis comparing 15 mg methotrexate and 3 mg cyclosporine that reported a marked clinical improvement in both arms, as early as week 4. In the present study, the drug doses were increased, if necessary, after 8 weeks of treatment in accordance with recommendations for the use of methotrexate^{19,20} and cyclosporine.^{21,22} Therefore, patients who did not reach 50% clinical improvement at week 8 were given methotrexate 25 mg/wk or cyclosporine 5 mg/kg/d from week 8 to week 24. The noninferiority of 15 mg of oral methotrexate versus 2.5 mg of cyclosporine was not demonstrated at week 8. Concerning cyclosporine, our data confirm its rapid efficacy in the control of atopic dermatitis with response rates at week 8 (44% decrease in the mean SCORAD index) in the range of previously published studies.²¹ The sample size of screened patients was based on the proportion of subjects achieving SCORAD 50 at week 8 being 80% for the cyclosporine group: the observed proportion being lower (42%), the power was probably overestimated to reject the noninferiority. The discrepancy between the estimation and the result is due to the

intensity of the disease: most of the patients in the cyclosporine arm had a severe atopic dermatitis (87% patients with SCORAD index >40). Alternatively, methotrexate had a poor efficacy at 15 mg and at week 8. Actually, we observed a slow onset of response to methotrexate with only a 13% reduction in the mean EASI at week 4, versus 50% in patients on cyclosporine. The delay in methotrexate-induced clinical improvement during the first weeks of treatment was responsible for (1) an increased number of eczema flares, after stopping topical corticoids at week 4, that were twice as frequent in the methotrexate arm as in the cyclosporine arm, and (2) higher numbers of early drug discontinuation in the methotrexate group. Therefore, methotrexate 15 mg/wk is not the appropriate dose to control moderate-to-severe atopic dermatitis in adults. In this respect, it is noteworthy that adult atopic dermatitis is apparently more resistant than childhood atopic dermatitis to methotrexate because a recent study reported that low-dose methotrexate (7.5 mg/wk) was as effective as cyclosporine (2.5 mg/kg/d) in severe (SCORAD index >50) atopic dermatitis in children.¹⁸ The noninferiority of methotrexate 25 mg/wk was then shown at week 20 for the secondary end point EASI 50, but not for SCORAD 50. The EASI score is an objective measure of the physician's estimate of disease extent and severity.²² The SCORAD incorporates both objective physician's estimates and subjective patient's assessment of itch and sleep loss.²³ Therefore, the EASI 50 probably represents a better tool to analyze the extent and severity of the atopic dermatitis skin inflammation. In this respect, it is currently the reference score used in clinical trials with new therapies in atopic dermatitis.²⁴⁻²⁶ At week 20, that is, 12 weeks after increasing the doses of both drugs in previously nonresponder patients, the clinical improvement observed with 25 mg/wk methotrexate was similar to that induced by 5 mg/kg/d cyclosporine, with 92% and 87% of patients reaching EASI 50, respectively. This observation confirms that methotrexate 25 mg/wk is a good option for the systemic treatment of atopic dermatitis. That higher doses of methotrexate are needed to improve atopic dermatitis is in sharp contrast to the data obtained in psoriasis. Indeed, Heydendael et al¹⁶ have shown that methotrexate 15 mg/wk induced a 40% improvement in moderate-to-severe psoriasis that was observed as early as week 4, a figure very close to the 50% improvement observed in patients treated with 3 mg/kg/d of cyclosporine. This difference between atopic dermatitis and psoriasis in terms of clinical response to methotrexate could be explained by the recently recognized highly inflammatory nature of atopic dermatitis. Indeed, Czarnecki et al²⁷ have reported that both skin-homing and systemic T-cell subsets show higher activation status in atopic dermatitis than in psoriasis. Because the immunosuppressive effect of methotrexate is considered to be mediated by its ability to induce apoptosis and clonal deletion of activated T cells,²⁸ it is therefore logical that higher doses of methotrexate are needed to obtain a clinically relevant anti-inflammatory effect in atopic dermatitis versus psoriasis. On the basis of results of the present study and on the points discussed above, in a future clinical trial we would recommend initiating methotrexate between 15 mg/wk and 25 mg/wk (depending on the patient's weight and the severity of the disease) and using the subcutaneous way to increase both bioavailability and efficacy.²⁹ Regarding safety, the adverse events of both drugs were in agreement with the current literature. The number of treatment-related adverse events was significantly higher in the cyclosporine arm. Importantly, the higher dose of

methotrexate did not lead to increased numbers of side effects in this population. No serious adverse event occurred in the methotrexate arm. This is in favor of a better safety profile of methotrexate than cyclosporine.

Strengths and limitations

Important strengths of our study are as follows: (1) the first head-to-head comparison between methotrexate and cyclosporine in adults with moderate-to-severe atopic dermatitis; (2) the use of validated outcome criteria, SCORAD 50 and EASI 50, instead of mean reduction in SCORAD index; and (3) 2 doses of drugs instead of the wide ranges of doses in previously published studies.⁹⁻¹¹ The major limitation of this study was the high number of early treatment discontinuations. Indeed, by week 8 only 80 out of 97 patients (39 of 50 in the methotrexate arm and 41 of 47 in the cyclosporine arm) were still enrolled in the study. Several factors could explain the high study dropout rate: (1) the baseline severity of the disease (SCORAD index >40 in 80% of patients) could account for the insufficient early improvement in patients under either cyclosporine or methotrexate; (2) the slow onset of oral methotrexate efficacy, already discussed; and (3) the withdrawal of the topical steroid therapy after week 4: that was decided to better evaluate the true efficacy of the 2 medications. The presence of allergic contact dermatitis was not captured in the study and represents another limitation of this work.

CONCLUSIONS

Methotrexate 15 mg/wk is less efficient than cyclosporine 2.5 mg/kg/d to improve moderate-to-severe atopic dermatitis at week 8. However, increasing the dose of methotrexate to 25 mg/wk yielded significant improvement in atopic dermatitis symptoms at week 20 comparable to that observed with cyclosporine and with a better safety profile. Additional studies using methotrexate 25 mg/wk orally or as subcutaneous injections are needed to confirm the value of the drug as a first-line systemic treatment for moderate-to-severe chronic atopic dermatitis.³⁰⁻³²

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REFERENCES

- Novak N, Leung DY. Advances in atopic dermatitis. *Curr Opin Immunol* 2011; 23:778-83.
- Bieber T. Atopic dermatitis. *N Engl J Med* 2008;358:1483-94.
- Margolis JS, Abuabara K, Bilker W, Hoffstad O, Margolis DJ. Persistence of mild to moderate atopic dermatitis. *JAMA Dermatol* 2014;150:593-600.
- DaVeiga SP. Epidemiology of atopic dermatitis: a review. *Allergy Asthma Proc* 2012;33:227-34.
- Simon D, Bieber T. Systemic therapy for atopic dermatitis. *Allergy* 2014;69: 46-55.
- Behnam SM, Behnam SE, Koo JY. Review of cyclosporine immunosuppressive safety data in dermatology patients after two decades of use. *J Drugs Dermatol* 2005;4:189-94.
- Politek K, Schaft JV, Coenraads PJ, de Bruin-Weller MS, Schuttelaar MLA. Drug survival for methotrexate in a daily practice cohort of adult patients with severe atopic dermatitis. *Br J Dermatol* 2016;174:201-3.

8. Védie AL, Ezzedine K, Amazan E, Boralevi F, Milpied B, Taïeb A, et al. Long-term use of systemic treatments for moderate-to-severe atopic dermatitis in adults: a monocentric retrospective study. *Acta Derm Venereol* 2016;96:802-6.
9. Weatherhead SC, Wahie S, Reynolds NJ, Megitt SJ. An open-label, dose-ranging study of methotrexate for moderate-to-severe adult atopic eczema. *Br J Dermatol* 2007;156:346-51.
10. Lyakhovitsky A, Barzilai A, Heyman R, Baum S, Amichai B, Solomon M, et al. Low-dose methotrexate treatment for moderate-to-severe atopic dermatitis in adults. *J Eur Acad Dermatol Venereol* 2010;24:43-9.
11. Schram A, Roekevisch E, Leeflang MM, Bos JD, Schmitt J, Spuls PI. A randomized trial of methotrexate versus azathioprine for severe atopic eczema. *J Allergy Clin Immunol* 2011;128:353-9.
12. Goujon C, Bérard F, Dahel K, Guillot I, Hennino A, Nosbaum A, et al. Methotrexate for the treatment of adult atopic dermatitis. *Eur J Dermatol* 2006;16:155-8.
13. Williams HC, Burney PG, Pembroke AC, Hay RJ. The U.K. Working Party's Diagnostic Criteria for Atopic Dermatitis, III: independent hospital validation. *Br J Dermatol* 1994;131:406-16.
14. Granlund H, Erkkö P, Sinisalo M, Reitamo S. Cyclosporin in atopic dermatitis: time to relapse and effect of intermittent therapy. *Br J Dermatol* 1995;132:106-12.
15. Ozawa A, Sugai J, Ohkido M, Ohtsuki M, Nakagawa H, Kitahara H, et al. Cyclosporin in psoriasis: continuous monotherapy versus intermittent long-term therapy. *Eur J Dermatol* 1999;9:218-23.
16. Heydendaal VM, Spuls PI, Opmeer BC, de Borgie CA, Reitsma JB, Goldschmidt WF, et al. Methotrexate versus cyclosporine in moderate-to-severe chronic plaque psoriasis. *N Engl J Med* 2003;349:658-65.
17. Menting S, Dekker P, Limpens J, Hooft L, Spuls P. Methotrexate dosing regimen for plaque-type psoriasis: a systematic review of the use of test-dose, start-dose, dosing scheme, dose adjustments, maximum dose and folic acid supplementation. *Acta Derm Venereol* 2016;96:23-9.
18. El-Khalawany MA, Hassan H, Shaaban D, Ghonaim N, Eassa B. Methotrexate versus cyclosporine in the treatment of severe atopic dermatitis in children: a multicenter experience from Egypt. *Eur J Pediatr* 2013;172:351-6.
19. Montaudie H, Sbidian E, Paul C, Maza A, Gallini A, Aractingi S, et al. Methotrexate in psoriasis: a systematic review of treatment modalities, incidence, risk factors and monitoring of liver toxicity. *J Eur Acad Dermatol Venereol* 2011;25:12-8.
20. Mrowietz U, De Jong EM, Kragballe K, Langley R, Nast A, Puig L, et al. A consensus report on appropriate treatment optimization and transitioning in the management of moderate-to-severe plaque psoriasis. *J Eur Acad Dermatol Venereol* 2014;28:438-53.
21. Schmitt J, Schmitt N, Meurer M. Cyclosporin in the treatment of patients with atopic eczema—a systematic review and meta-analysis. *J Eur Acad Dermatol Venereol* 2007;21:606-19.
22. Hanifin JM, Thurston M, Omoto M, Cherill R, Tofte SJ, Graeber M. The Eczema Area and Severity Index (EASI): assessment of reliability in atopic dermatitis. *Exp Dermatol* 2001;10:11-8.
23. Kunz B, Oranje AP, Labrèze L, Stalder JF, Ring J, Taieb A. Clinical validation and guidelines for the SCORAD index: consensus report of the European Task Force on Atopic Dermatitis. *Dermatology* 1997;195:10-9.
24. Schmitt J, Lagan S, Williams HC. What are the best outcome measurements for atopic eczema? A systematic review. *J Allergy Clin Immunol* 2007;120:1389-98.
25. Chalmers J, Deckert S, Schmitt J, Harmonising Outcome Measures for Atopic Dermatitis (HOME) Initiative Executive Board. Reaching clinically relevant outcome measures for new pharmacotherapy and immunotherapy of atopic eczema. *Curr Opin Allergy Clin Immunol* 2015;15:227-33.
26. Beck LA, Thaci D, Hamilton JD, Graham NM, Bieber T, Rocklin R, et al. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. *N Engl J Med* 2014;371(2):130-9.
27. Czarnecki T, Malajian D, Shemer A, Fuentes-Duculan J, Gonzalez J, Suárez-Fariñas M, et al. Skin-homing and systemic T-cell subsets show higher activation in atopic dermatitis versus psoriasis. *J Allergy Clin Immunol* 2015;136:208-11.
28. Genestier L, Paillot R, Fournel S, Ferraro C, Miossec P, Revillard JP. Immunosuppressive properties of methotrexate: apoptosis and clonal deletion of activated peripheral T cells. *J Clin Invest* 1998;102:322-8.
29. Chiaravalloti AJ, Strober BE. The use of self-administered subcutaneous methotrexate for the treatment of psoriasis. *J Drugs Dermatol* 2014;13:929-31.
30. Madhok V, Futamura M, Thomas KS, Barbarot S. What's new in atopic eczema? An analysis of systematic reviews published in 2012 and 2013, part 1: epidemiology, mechanisms of disease and methodological issues. *Clin Exp Dermatol* 2015;40:238-42.
31. Ring J, Alomar A, Bieber T, Deleuran M, Fink-Wagner A, Gelmetti C, et al. Guidelines for treatment of atopic eczema. *J Eur Acad Dermatol Venereol* 2012;26:1045-60.
32. Sidbury R, Davis DM, Cohen DE, Cordoro KM, Berger TG, Bergman JN, et al. Guidelines of care for the management of atopic dermatitis: management and treatment with phototherapy and systemic agents. *J Am Acad Dermatol* 2014;71:327-49.

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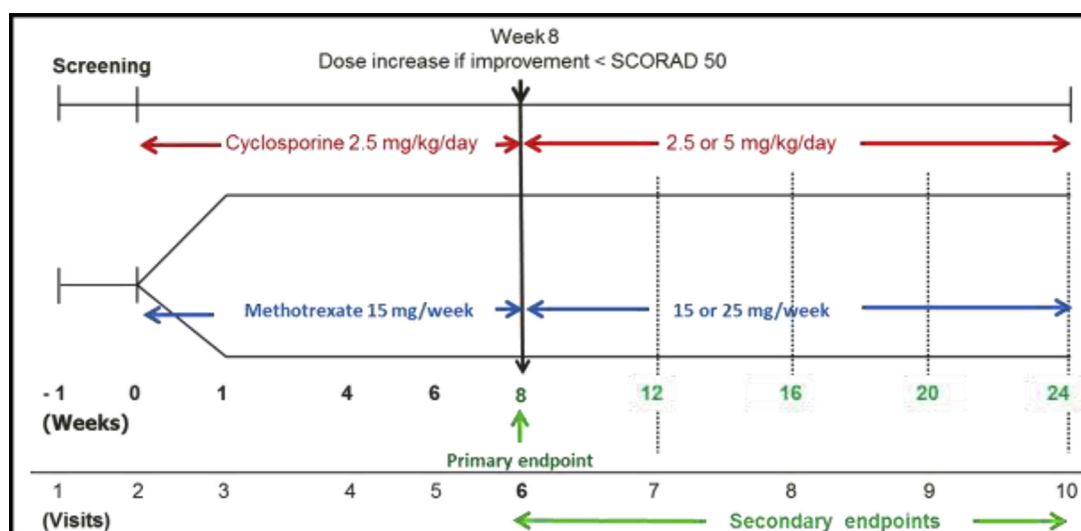
**FIGURE E1.** Design of the study.

TABLE E1. Inclusion and exclusion criteria

Inclusion criteria

- Male or female patient older than 18 y
- Subject presenting with atopic dermatitis according to the diagnostic criteria of the UK Working Party
- Moderate-to-severe atopic dermatitis eligible for systemic treatment
- SCORAD index >15
- Patients were on an effective regimen of contraception, which had to be continued for 3 mo in female patients and 5 mo in male patients following the end of the trial (regarding the indications of methotrexate labeling)
- Subject agreeing to refrain from using topical or systemic treatments other than those to be used in the trial
- Subject able to understand the trial's objectives and provide written consent to take part in the trial
- Subject with national health insurance or similar coverage

Exclusion criteria

- Pregnant or nursing female patient
- Patient planning to have a conception during the trial period
- Subject with a contraindication to methotrexate: liver chronic disease, chronic respiratory impairment, hematologic disease, alcohol abuse, mouth ulcerations and peptic ulcer, methotrexate hypersensitivity
- Subject with a contraindication to cyclosporine: cyclosporine hypersensitivity, uncontrolled hypertension, renal impairment, poorly controlled infections, uveitis, history of malignancy or progressive malignancy, history of bowel obstruction
- Subject with active herpes
- Subject already treated with high doses of ultraviolet (total dose received >2000 J/cm²)
- Subject treated with methotrexate, cyclosporine, or other systemic immune-suppressants during the 30 d before the inclusion visit
- Subject treated with local immune-suppressants during the 7 d before the inclusion visit
- Subject who has followed treatment with systemic corticosteroids during the 30 d before the inclusion visit
- Subjects on the following medications within the week before the inclusion visit: probenecide, trimethoprim, nonsteroidal anti-inflammatory drugs, calcium inhibitors, potassium-saving diuretics, colchicine, amiodarone, anticonvulsant drug with enzymatic inhibition, danazol, bosentan, rosuvastatine
- Subjects taking, on a daily basis, grapefruit, potassium salt, and St John's wort
- Subject with congenital galactosemy, glucose or galactose malabsorption syndrome, or lactase deficit
- Subject with an acute and evolutive disease and/or taking antibiotics (macrolides, fusidic acid, pristinamycin, clindamycin) or systemic antifungal drugs at the inclusion visit
- Subject on simvastatin with a dosage of >10 mg/d at the inclusion visit
- Subjects treated with a live vaccine within 30 d before the inclusion visit or planning a live vaccine during the study or 1 mo after the end of the study
- Subject with a contraindication according to the investigator
- Subject deprived of freedom because of a court or administrative decision, under supervision or guardianship, or an adult subject protected by law or admitted to a health or social establishment
- Subject in an emergency situation
- Subject with a linguistic or psychiatric inability to give informed consent
- Subject in an exclusion period after having taken part in another clinical trial

TABLE E2. Prohibited treatments

- Treatments notified in the exclusion criteria
- Topical tacrolimus and corticosteroids (except during the first 4 wk of the protocol)
- Systemic corticosteroids
- Immunosuppressant treatment
- Treatment with a live vaccine
- Phototherapy

TABLE E3. Concomitant treatments

- Antihistamines
- Oral antibiotics except those mentioned in the exclusion criteria

TABLE E4. Evaluation response to treatment

Week 8

Response to treatment: R = % SCORAD index improvement in comparison with baseline SCORAD index

Response to treatment	Treatment	Dose decision	Study decision
$R \geq 90\%$ (good responder)	Methotrexate Cyclosporine	Treatment stopped	Continuation
$50\% \leq R < 90\%$	Methotrexate Cyclosporine	Same dose	Continuation
$-5\% \leq R < 50\%$	Cyclosporine	Dose increased to 5 mg/kg/d	Continuation
	Methotrexate	Dose increased to 25 mg/wk	Continuation
$R < -5\%$ (nonresponder)	Methotrexate Cyclosporine	Treatment stopped	Early discontinuation

Weeks 12, 16, 20

Response to treatment: R = % SCORAD index improvement in comparison with inclusion baseline

Response to treatment	Treatment	Dose decision	Study decision
$R \geq 90\%$ (good responder)	Methotrexate Cyclosporine	Treatment stopped	Continuation
$+5\% \leq R < 90\%$	Methotrexate Cyclosporine	Same dose	Continuation
$R < +5\%$ (nonresponder)	Methotrexate Cyclosporine	Treatment stopped	Early discontinuation

Nonresponse is $R < -5\%$ at week 8 or $R < +5\%$ at weeks 12, 16, and 20. No patient was a good responder.

TABLE E5. Flare of eczema: Patients with eczema flare, defined by the worsening of the evaluated SCORAD index in comparison with the SCORAD index at the last visit

Eczema flare over time	Methotrexate			Cyclosporine		
	N*	Discontinuation		N*	Discontinuation	
		Patients, due to eczema flare, n (%)	flare, n		Patients, due to eczema flare, n (%)	flare, n
W0-W4	50	2 (4)	0	47	5 (11)	0
W4-W8	50	8 (16)	0	43	4 (16)	0
W8-W12	39	2 (5)	0	43	1 (2)	1
W12-W16	29	3 (10)	1	41	2 (4)	0
W16-W20	25	4 (16)	0	37	3 (9)	0
W20-W24	23	3 (13)	0	33	0	0
Total		22	1		15	1

W, Week.

*Number of patients present in the study.

TABLE E6. Patient discontinuation

Patient disposition	Methotrexate	Cyclosporine
Subjects randomized and treated, n	50	47
Discontinuations, n (%)	27 (54)	14 (23)
Reasons for discontinuation, n (%)		
Lost to follow-up	0	2 (4)
Withdrawal of patient	3 (6)	1 (1)
Protocol deviation	3 (6)	4 (8)
Adverse event	6 (12)	1 (2)
Nonresponse	15 (28)	6 (13)
Subjects who completed the study, n (%)	23 (46)	33 (77)

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