

Short communication

Anti-IL-5 recombinant humanized monoclonal antibody (Mepolizumab) for the treatment of atopic dermatitis

Background: Eosinophils may play an important role in the pathogenesis of atopic dermatitis (AD). Interleukin-5 is essential for eosinophil growth, differentiation and migration. A monoclonal antibody to human interleukin-5 (mepolizumab) was developed for atopic diseases. This study was designed to study the effect of mepolizumab in AD.

Methods: Two single doses of 750 mg mepolizumab, given 1 week apart, were studied in patients with moderate to severe AD using a randomized, placebo-controlled parallel group design. The primary endpoint of 'success' to treatment was defined as the percentage of patients with at least 'marked improvement' after 2 weeks as assessed by the Physician's Global Assessment of Improvement (PGA). Furthermore, SCORing AD (SCORAD), pruritus scoring, number of blood eosinophils and serum thymus and activation-regulated chemokine (TARC) values served as secondary endpoints. Fluticasone propionate cream 0.05%, once daily could be used as rescue medication from day 16 if no improvement was recorded.

Results: Eighteen patients received mepolizumab and 22 placebo treatment. Peripheral blood eosinophil numbers were significantly reduced in the treatment group compared with placebo ($P < 0.05$). No clinical success was reached by PGA assessment ($P = 0.115$), SCORAD ($P = 0.293$), pruritus scoring and TARC values in the mepolizumab-treated group compared with placebo. However, modest improvement ($< 50\%$ improvement) assessed by PGA was scored significantly more in the mepolizumab-treated group compared with placebo ($P < 0.05$).

Conclusion: Two single doses of 750 mg mepolizumab did not result in clinical success in patients with AD, despite a significant decrease in peripheral blood eosinophils.

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Eosinophils and T cells play a major role in the pathogenesis of atopic dermatitis (AD) (1). Interleukin 5 (IL-5) is the key cytokine in eosinophil differentiation and growth in the bone marrow (2) and stimulates eosinophil release into the peripheral circulation (3). Moreover, IL-5 renders eosinophils more sensitive for stimuli, a process called priming (4). A humanized monoclonal antibody to IL-5 (mepolizumab) has been developed (5) and tested in patients with allergic asthma (AA). No clinical benefit was reached in AA (6–8).

Importantly, the contribution of eosinophils in the pathogenesis of AD might be different from the contri-

bution of eosinophils in the pathogenesis of AA. Tissue and blood eosinophils are more activated in AD (9) and peripheral blood eosinophils of AD patients show a significantly more delayed programmed cell death compared to patients with AA (10). Therefore, it may be that, due to strong activation of eosinophils in AD, depletion of eosinophils by anti-IL-5 therapy will relieve AD symptoms. The current study is the first to evaluate anti-IL-5 treatment in AD patients.

Methods

Patients

Forty-three patients (20 male; 23 female, mean age 29, range 18–57) with AD, diagnosed according to Hanifin and Rajka criteria (11) were recruited. At inclusion, all patients experienced a flare of AD, defined as objective SCORing AD (SCORAD) (12) between 20 and

Abbreviations: AA, allergic asthma; AD, atopic dermatitis; APT, atopy patch test; IL-5, interleukin 5; SCORAD, SCORing atopic dermatitis; PGA, Physicians global assessment of improvement scale; VAS, visual analog scale; TARC, thymus and activation-regulated chemokine; CCR3, CC chemokine receptor 3.

40. Out of 43 patients, six had allergic rhinitis; 12 AA, eight both allergic rhinitis and asthma, 17 had solely AD. Eighteen patients showed eosinophilia (> 500 eosinophils/mm³).

Local and systemic treatment was discontinued at least 14 days before inclusion. All patients provided written informed consent and this study was approved by ethics committees of all participating centers.

Study design

This was a randomized double-blind, placebo-controlled, parallel group study based at six centers in Europe from January until July 2002 (Fig. 1). At screening a full medical history, physical examination, assessment of AD severity and laboratory investigations were taken. At day 0 patients received either mepolizumab (SB240563) 750 mg or placebo intravenously, with regular monitoring of vital signs. Two hours after the infusion, patients were discharged and returned at day 2 for blood analysis and clinical scoring. At day 7, a second dose was administered following the same procedure. At day 14 patients returned for blood analysis and clinical scoring. Patients were assigned as responders or nonresponders. Fluticasone propionate cream, 0.05% once daily, was given to nonresponders as rescue medication at day 16. At day 28, patients returned for clinical scoring and blood analysis. At day 30 all patients returned for a safety follow up visit. Patients did not use any other treatment during the entire study period, except for nonmedicated emollients and bath oil as needed. Topical hydrocortisone acetate 1% was allowed for eczema lesions on the face.

Study assessments and procedures

To determine efficacy, AD activity was measured at day 0, 2 and 14 by the physician's global assessment (PGA), objective SCORAD (12) and itch scoring. The PGA is an overall assessment from 0 to 5 of AD activity, taking into account quality and extent of lesions relative to the baseline [0 = clear (100%), 1 = almost clear (90–99% improvement), 2 = marked improvement (50–89%), 3 = modest improvement (<50%), 4 = no change and 5 = worse]. Responders were defined by PGA score 0–2 on day 14. Nonresponders were defined when 3–5 was scored on the PGA on day 14. The PGA at 14 days was defined as primary endpoint of treatment efficacy.

Diary cards were used to record pruritus intensity ranging from 0 to 3 (0 = no itching, 1 = occasional itch, 2 = fairly persistent itch and 3 = intolerable, constant itch). Also a visual analog scale (VAS) was recorded for itch from 0 to 10 (0 being 'no itch' and 10 being 'most intense itch imaginable').

Laboratory assessments included complete blood count, blood chemistry, urinalysis and pregnancy test for female participants. Peripheral blood eosinophil level was measured at day 0, 2, 7, 14 and 28. All parameters were measured in a central laboratory (Labor dr. Spranger, Ingolstadt, Germany) using standard procedures. Serum thymus and activation-regulated chemokine (TARC) was measured in a subgroup of patients at day 0 and 14 (13). TARC

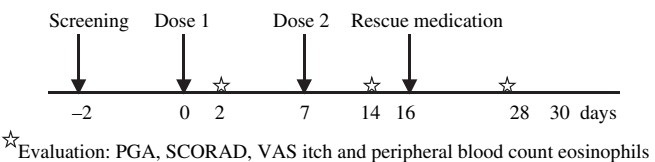


Figure 1. Study design.

is a new objective parameter for disease severity specific for AD and was measured as described before (14).

Statistical analysis

With a planned sample size of 48 (24 subjects per arm), the study had 90% power, based on a one-sided test, to detect a difference between the assumed placebo response rate of 22% and mepolizumab response rate of 66%. For primary efficacy (PGA) Fisher's exact test (one-sided) was used. For secondary efficacy (SCORAD, eosinophils, TARC) analysis of covariance was used. Summary statistics were performed for pruritus scores.

Results

Patients

Forty-three patients were eligible for this study. Twenty patients received mepolizumab and 23 placebo treatment (Fig. 2). Three patients (two mepolizumab, one placebo) withdrew before day 14 due to exacerbation or lack of therapeutic effect. At day 0 no significant differences were found considering SCORAD, itch scoring, blood eosinophils and TARC values between placebo and mepolizumab groups (Table 1).

Efficacy

Four of 18 (22.2%) patients in the mepolizumab-treated group responded to therapy by achieving 'marked improvement' on PGA at day 14. One of 22 (4.6%) patients responded in the placebo group. This difference in success was not significant ($P = 0.115$, Table 2). When all clinical 'improvement' parameters of the PGA (so also 'modest improvement') were included, a significant effect

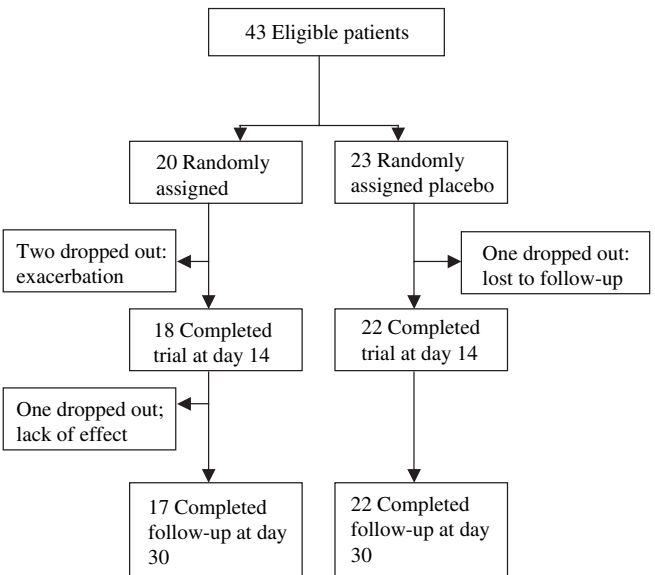


Figure 2. Trial profile. Rescue therapy from day 16 to day 30 was given in eight of 18 patients in the mepolizumab-treated group and in 15 of 22 in the placebo-treated group.

Table 1. Baseline characteristics of the Mepolizumab- and placebo-treated groups

	Mepolizumab (<i>n</i> = 20)	Placebo (<i>n</i> = 23)
Age (years)	32 (19–57)	27 (18–42)
Sex, M : F	10 : 10	10 : 13
SCORAD	36.3 (20.8–54.5)	32.5 (18.5–45.4)
Blood eosinophils/mm ³	521 (123–1251)	647 (74–1810)
VAS-pruritus	5.6 (1–10)	5.5 (0–10)
TARC-level (pg/ml)	1955 (215–4441) (<i>n</i> = 7)	2562 (246–14300) (<i>n</i> = 10)

SCORAD, SCORing atopic dermatitis; VAS, visual analogue scale; TARC, thymus and activation-regulated chemokine. Data are expressed as mean (minimum–maximum).

($P < 0.05$) could be calculated in favor of the mepolizumab-treated group (72% improvement) vs placebo (41% improvement) (Table 2).

SCORAD and pruritus scores were secondary clinical endpoints. A larger decrease in SCORAD was recorded in the mepolizumab group compared with placebo at day 14, although not significantly different ($P = 0.293$, Table 2). No difference in pruritus score was reached between groups. VAS itch at day 2 and 14 showed a slightly larger decrease in itch in the mepolizumab group compared with placebo (day 14: mean decrease of 2.6 cm in the mepolizumab group compared with 1.3 cm in the placebo group).

Peripheral blood eosinophils and serum TARC

At all post-baseline visits a significant decrease ($P < 0.001$) of blood eosinophils in the mepolizumab-treated group was reached (Table 2). Serum TARC levels were determined in seven mepolizumab and 10 placebo-treated patients, showing no significant differences.

Safety

Mepolizumab therapy caused some side effects of mild and temporary nature, showing no differences from side effects reported in the placebo group.

Discussion

This study was designed to assess the clinical benefit of mepolizumab therapy in AD. A significant reduction

of peripheral blood eosinophils was reached in the mepolizumab group compared with placebo at all efficacy time points. Results for PGA indicate that mepolizumab may have some benefit over placebo, however the observed difference in treatment effect of 17.7% failed to achieve statistical significance ($P = 0.115$, Table 2). If 'modest improvement' would have been assigned as a 'successful response', a significant improvement was seen in the mepolizumab-treated group compared with placebo ($P = 0.0476$). Furthermore, the current study showed a tendency of reduction in SCORAD and itch measurements in the mepolizumab group.

Lack of clinical benefit of mepolizumab therapy can be explained in different ways.

First, peripheral blood eosinophil depletion might not be translated into adequate depletion of eosinophils in the skin within this 2-week time frame. Significant reduction of tissue eosinophils may take longer.

Second, remaining blood eosinophils can still migrate into the tissue by selective chemotaxis. Eotaxin and RANTES are chemoattractants for eosinophils trafficking from blood into tissue. Eosinophils carry the CC chemokine receptor 3 (CCR3), which has eotaxin and RANTES (15) as ligands. Eotaxin is mainly responsible for chemoattraction of peripheral eosinophils into the tissue (16). This is an attractive explanation for anti-IL-5 therapy alone not being sufficient for acute AD and might suggest clinical benefit of a combination therapy of IL-5-antagonist and CCR3 antagonists (17).

Third, the current mepolizumab dose is insufficient for complete depletion of blood eosinophils (Table 2). Titration of mepolizumab therapy in correlation with the amount of blood eosinophils may be needed. When eosinophils are completely depleted in blood, a preventive effect of disease exacerbations can be expected. It would therefore be interesting to investigate the number of eczema flares when anti-IL-5 is administered as preventive therapy.

Finally, eosinophils might have a less important role in the pathogenesis of AD. The cellular infiltrate in AD is characterized not only by eosinophils, but also T cells, macrophages and other cells. T cells are not affected by anti-IL-5 (8).

Concluding, in spite of a clear reduction in blood eosinophils by mepolizumab therapy in AD patients, no

Table 2. Study-specific parameters

Parameter	Day 0		Day 2		Week 2		<i>P</i> -value (week 2–day 0)
	Mepo	Placebo	Mepo	Placebo	Mepo	Placebo	
Blood eosinophils, mean ($\pm$ SEM)	521 $\pm$ 79	647 $\pm$ 81	144 $\pm$ 28	537 $\pm$ 94	203 $\pm$ 54	679 $\pm$ 80	<0.05 (<i>n</i> = 40)
PGA success (<i>n</i>)	–	–	3	1	4	1	0.115 (<i>n</i> = 40)
SCORAD, mean ($\pm$ SD)	36.3 $\pm$ 9	32.4 $\pm$ 7	32.9 $\pm$ 8	31.8 $\pm$ 8	29.0 $\pm$ 12	30.4 $\pm$ 10	0.293 (<i>n</i> = 40)
TARC (<i>n</i> = 17), mean (min–max)	1955 (215–4441)	2563 (246–14300)	–	–	2935 (141–8601)	2658 (239–9325)	0.813 (<i>n</i> = 17)

Mean values of peripheral blood eosinophils/mm³, SCORAD values, amount of patients showing success and improvement at day 0, 2 and 14. *P*-values are calculated on day 14 compared with baseline.

significant clinical improvement in AD symptoms after 2 weeks of therapy was reached. Future investigations have to reveal whether prolonged follow-up, preventive therapy or mepolizumab dose-dependent treatment related to the amount of peripheral eosinophilia will lead to clinical improvement.

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