DR. DAGMAR SIMON (Orcid ID : 0000-0001-8965-9407)

PROF. SHIDA YOUSEFI (Orcid ID : 0000-0002-9855-4305)

Article type : Letter to the Editor

Editor : Claudia Traidl-Hoffmann

Mepolizumab failed to affect bullous pemphigoid: a randomized, placebo-controlled, double-blind phase 2 pilot study

Dagmar Simon[1], Shida Yousefi[2], Simone Cazzaniga[1,3], Christina Bürgler[1], Susanne Radonjic[1], Carine Houriet[1], Kristine Heidemeyer[1], Hans-Wilhelm Klötgen[1], Evelyne Kozlowski[2], Luca Borradori[1], Hans-Uwe Simon[2, 4]

[1]Department of Dermatology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland
[2]Institute of Pharmacology, University of Bern, Bern, Switzerland
[3]Centro Studi GISED, Bergamo, Italy
[4]Department of Clinical Immunology and Allergology, Sechenov University, Moscow, Russia

Corresponding author:
Dagmar Simon, M.D.
Department of Dermatology, Inselspital, 3010 Bern, Switzerland
Tel.: +41 31 632 2233
Email: dagmar.simon@insel.ch

Funding information: The study was supported by a research grant from GlaxoSmithKline. The immunofluorescence studies were supported by Swiss National Science Foundation (grant No. 310030_184816 to H.U.S).

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

To the Editor:

Bullous pemphigoid (BP) is the most common autoimmune blistering skin disease characteristically affecting the elderly.[1] The disease is due to an autoimmune response against hemidesmosomal antigens, involving autoreactive T and B cells. Interleukin (IL)-5 is abundantly expressed in lesional skin, and is associated with blood eosinophilia and eosinophil infiltration in the skin of BP patients.[2,3] There is evidence that eosinophils, following activation with IL-5 in the presence of BP antibodies, may directly contribute to blister formation.[4]

Superpotent topical and oral corticosteroids as well as doxycycline are currently used to treat BP patients.[1] Nevertheless, use of steroids is limited by their side effects, and after discontinuation of therapy, BP relapses in 85% of patients within 6 months.[5] Since eosinophils are characteristically found in the skin at early stages of the disease before blisters occur, targeting eosinophils by reducing their number and activation promised an alternative therapeutic approach. Anti-IL-5 antibody (mepolizumab) therapy has been shown to be effective in eosinophilic bronchial asthma and hypereosinophilic syndrome.[6-8]

The objective of the presented trial was to investigate the efficacy and safety of mepolizumab versus placebo as an add-on therapy to oral corticosteroids (OCS) in patients with an acute flare-up of BP. We conducted a randomized, placebo-controlled, double-blind, parallel-group, phase 2 pilot study at a single academic center (NCT01705795). The trial was approved by the cantonal ethics committee Bern and the regulatory agency Swissmedic. All the participants provided written informed consent prior to enrollment in the study.

After screening, participants were randomly assigned in a 2:1 ratio to receive intravenous mepolizumab at a dose of 750 mg or matching placebo every 4 weeks over 12 weeks in addition to standard care with OCS, and followed over a period of up to 6 months after treatment. The OCS dose was 0.5 mg prednisolone per kg body weight until no further blisters and/or BP lesions appeared, and was then tapered by 20% every 2 weeks. Enrolled patients presented with either a newly diagnosed disease or a relapse of BP.[1] The primary endpoint was the cumulative rate of relapse-free patients after initiating therapy. Additional information on the study design (Figure S1, Tables S1 and S2) and the statistical analyses is provided in this article's online supporting information.

In total, 32 patients were enrolled, and 30 underwent randomization and received at least one dose of the trial regimen and thus were included in the intention-to-treat population. The patients' characteristics and diagnostic findings at baseline are given in Table S3 in this article's online supporting information.

The proportion of patients free of BP relapse did not differ between mepolizumab and placebo groups as assessed 4 weeks after the end of treatment (week 16) and at the end of follow-up (week 36) (Table 1, Figure 1A). Moreover, there were no significant differences in median time until relapse between groups. Thereby, the trial failed to achieve the primary endpoint. In addition, the cumulative rates of patients achieving disease control and maintaining disease control did not show significant differences between mepolizumab and placebo groups (Figure 1B-C). Upon treatment, an overall improvement of BP clinical signs as indicated by a reduction of the severity score, and the intensity of pruritus were noted in both mepolizumab and placebo groups. Despite the fact that mepolizumab did not significantly affect the clinical outcome, we found significantly lower peripheral blood eosinophil levels in patients treated with mepolizumab compared to patients receiving placebo (Table 1).

Next, we were interested whether mepolizumab would have an effect on skin inflammation (Table S4, Figure S2 in this article's online supporting information). In both groups, the mean number of skin infiltrating eosinophils was reduced upon therapy. The mean difference in eosinophil numbers was higher in the mepolizumab

compared with the placebo group (-62.8 versus -45.9; p=0.68). The number of cells expressing IL-5 did not decrease in either mepolizumab or placebo groups. Furthermore, we did not observe any significant differences in the numbers of T cell, mast cells, and cells expressing IL-13 or IFN-γ.

The overall percentage of patients with adverse and serious adverse events was considerable, something which can be accounted for by the age of the patients and their various co-morbidities. Despite the relatively high number of serious adverse events, none of them was related to mepolizumab. The uncontrolled diabetes observed in one patient was most likely due to the OCS therapy. Five patients discontinued the study medication because of a lack of efficacy (Figure S1 and Table S5 in this article's online supporting information).

Based on the observation that eosinophils are present in BP lesions and are capable of splitting the skin at the dermal-epidermal junction in an ex vivo model,[4] we launched this investigator-initiated trial to study the effect of mepolizumab, an anti-IL-5 antibody, that might reduce the number and activity of eosinophils in patients with active BP. Unfortunately, we could not demonstrate any superiority of mepolizumab therapy over placebo in terms of the clinical and serological outcomes.

What reasons might explain the failure of mepolizumab to significantly improve BP? 1. The total number of patients enrolled in this proof-of-concept study, was modest. It can be assumed that small effects of mepolizumab might have been detectable in a larger cohort and by calculating a higher study power. 2. Since we could not estimate the effect of mepolizumab in these elderly patients in advance, for ethical reasons, we chose an add-on therapy, i.e. mepolizumab or placebo were administered in addition to the standardized therapy with OCS. This design may have obscured possible effects of mepolizumab. 3. The treatment period with the study drug was limited to 12 weeks. This time-period may have been rather short to achieve long-term control of BP.

As expected, mepolizumab significantly decreased blood eosinophil numbers. However, it did not significantly affect tissue eosinophil infiltration. Even after therapy, eosinophils were detectable in the skin both in patients with and without relapse of BP. The observation that mepolizumab insufficiently controls tissue eosinophil numbers has been reported in other trials with bronchial asthma and eosinophilic esophagitis.[7, 8]

Based on the experimental observations of a role for eosinophils in BP[4], we would still argue for continuing investigation of therapeutic strategies targeting eosinophil activity and/or numbers. In this context, novel therapeutic antibodies against the IL-5 receptor alpha subunit would seem to be promising since they mediate antibody-dependent cell-mediated cytotoxicity of both eosinophils and basophils.[9] Moreover, bertilimumab, an anti-eotaxin antibody, has recently been designated as an orphan drug for the treatment of BP by the Food and Drug Administration.

CONFLICT OF INTEREST

The authors declare that they have no relevant conflicts of interest.

ACKNOWLEDGMENT

The study drug mepolizumab was provided by GlaxoSmithKline.

FUNDING INFORMATION

The study was supported by a research grant from GlaxoSmithKline. The immunofluorescence studies were supported by Swiss National Science Foundation (grant No. 310030_184816 to H.U.S).

Keywords

bullous pemphigoid, eosinophil, interleukin-5, mepolizumab

Dagmar Simon[1]

Shida Yousefi[2]

Simone Cazzaniga[1,3]

Christina Bürgler[1]

Susanne Radonjic[1]

Carine Houriet[1]
Kristine Heidemeyer[1]
Hans-Wilhelm Klötgen[1]
Evelyne Kozlowski[2]
Luca Borradori[1]
Hans-Uwe Simon[1,4]

[1]Department of Dermatology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland
[2]Institute of Pharmacology, University of Bern, Bern, Switzerland
[3]Centro Studi GISED, Bergamo, Italy
[4]Department of Clinical Immunology and Allergology, Sechenov University, Moscow, Russia

Correspondence
Dagmar Simon, Department of Dermatology, Inselspital, 3010 Bern, Switzerland
E-Mail: dagmar.simon@insel.ch

REFERENCES

1. Feliciani C, Joly P, Jonkman MF, Zambruno G, Zillikens D, Ioannides D, Kowalewski C, Jedlickova H, Kárpáti S, Marinovic B, Mimouni D, Uzun S, Yayli S, Hertl M, Borradori L. Management of bullous pemphigoid: the European Dermatology Forum consensus in collaboration with the European Academy of Dermatology and Venereology. *Br J Dermatol. 2015*;172:867-877.
2. Rico MJ, Benning C, Weingart ES, Streilein RD, Hall RP 3rd. Characterization of skin cytokines in bullous pemphigoid and pemphigus vulgaris. *Br J Dermatol*. 1999;140:1079-1086.
3. Wakugawa M, Nakamura K, Hino H, Toyama K, Hattori N, Okochi H, Yamada H, Hirai K, Tamaki K, Furue M. Elevated levels of eotaxin and interleukin-5 in blister fluid of bullous pemphigoid: correlation with tissue eosinophilia. *Br J Dermatol*. 2000;143:112-116.

4. de Graauw E, Sitaru C, Horn M, Borradori L, Yousefi S, Simon HU, Simon D. Evidence for a role of eosinophils in blister formation in bullous pemphigoid. *Allergy*. 2017;72:1105-1113.
5. Bernard P, Reguiai Z, Tancrède-Bohin E, Cordel N, Plantin P, Pauwels C, Vaillant L, Grange F, Richard-Lallemand MA, Sassolas B, Roujeau JC, Lok C, Picard-Dahan C, Chosidow O, Vitry F, Joly P. Risk factors for relapse in patients with bullous pemphigoid in clinical remission: a multicenter, prospective, cohort study. *Arch Dermatol.* 2009;145:537-542.
6. Radonjic-Hoesli S, Valent P, Klion AD, Wechsler ME, Simon HU. Novel targeted therapies for eosinophil-associated diseases and allergy. *Annu Rev Pharmacol Toxicol*. 2015;55:633-656.
7. Flood-Page PT, Menzies-Gow AN, Kay AB, Robinson DS. Eosinophil's role remains uncertain as anti-interleukin-5 only partially depletes numbers in asthmatic airway. *Am J Respir Crit Care Med*. 2003;167:199-204.
8. Straumann A, Conus S, Grzonka P, Kita H, Kephart G, Bussmann C, Beglinger C, Smith DA, Patel J, Byrne M, Simon HU. Anti-interleukin-5 antibody treatment (mepolizumab) in active eosinophilic oesophagitis: a randomised, placebo-controlled, double-blind trial. *Gut*. 2010;59:21-30.
9. Kolbeck R, Kozhich A, Koike M, Peng L, Andersson CK, Damschroder MM, Reed JL, Woods R, Dall'acqua WW, Stephens GL, Erjefalt JS, Bjermer L, Humbles AA, Gossage D, Wu H, Kiener PA, Spitalny GL, Mackay CR, Molfino NA, Coyle AJ. MEDI-563, a humanized anti-IL-5 receptor alpha mAb with enhanced antibody-dependent cell-mediated cytotoxicity function. *J Allergy Clin Immunol*. 2010;125:1344-1353.

TABLE 1. Intention-to-treat analysis of efficacy

	Mepolizumab (N=20)		Placebo (N=10)		P*
	N events	Cumulative survival rate (95% CI)	N events	Cumulative survival rate (95% CI)	
Cumulative relapse-free survival rates					
End of treatment (16 weeks)	6	66.7% (44.9 - 88.5)	4	55.6% (23.1 - 88.1)	0.74
End of follow-up (36 weeks)	14	20.0% (0.6 - 39.4)	6	33.3% (2.5 - 64.1)	0.53
Median survival time (weeks)		20.0 (8.4 - 31.6)		24.6 (0.0 - 51.3)	
Cumulative rates of patients reaching disease control					
First 2 weeks	15	86.1% (69.0 - 100)	8	80.0% (55.3 - 100)	0.27
End of treatment (16 weeks)	17	100% (nc)	10	100% (nc)	0.24
Median time (weeks)		1.14 (1.03 - 1.26)		1.71 (1.42 - 2.00)	
Cumulative rates of patient maintaining disease control**					
End of treatment (16 weeks)	5	68.6% (45.7 - 91.5)	4	50.0% (15.3 - 84.7)	0.48
End of follow-up (36 weeks)	13	21.2% (0.8 - 41.6)	6	33.3% (2.5 - 64.1)	0.73
Median time (weeks)		19.0 (10.7 - 27.3)		16.0 (8.1 - 23.9)	
ABSI score reduction from baseline	Mean (95% CI)***		Mean (95% CI)***		
Average in the first 16 weeks	25.6 (18.1 - 33.2)		21.6 (11.1 - 32.2)		0.52
Average in the overall study period (36 weeks)	28.1 (20.3 - 35.9)		32.8 (14.8 - 50.8)		0.43
Pruritus NRS reduction from baseline	Mean (95% CI)***		Mean (95% CI)***		
Average in the first 16 weeks	4.5 (3.4 - 5.5)		4.4 (2.9 - 5.8)		0.90
Average in the overall study period (36 weeks)	4.3 (3.2 - 5.4)		4.8 (3.3 - 6.3)		0.62
Cumulative dose of systemic corticosteroids until clinical remission	Mean (95% CI)		Mean (95% CI)		
	257.5 (185.3 - 329.7)		445.0 (167.5 - 722.5)		0.16****
Peripheral blood eosinophils	Mean (95% CI) *****		Mean (95% CI) *****		
Average in the first 16 weeks	0.04 (0.00 - 0.09)		0.16 (0.09 - 0.22)		**0.007**
Average in the overall study period (36 weeks)	0.05 (0.01 - 0.10)		0.26 (0.20 - 0.33)		**<0.001**
ELISA BP 180 AB	Mean (95% CI) *****		Mean (95% CI) *****		

(RU/ml)			
Average in the first 16 weeks	10.0 (-12.9 - 33.1)	6.6 (-21.6 - 34.8)	0.66
Average in the overall study period (36 weeks)	14.9 (-3.3 - 33.1)	7.5 (-20.5 - 35.5)	0.65
ELISA BP 230 AB (RU/ml)	Mean (95% CI) *****	Mean (95% CI) *****	
Average in the first 16 weeks	3.9 (-1.6 - 9.4)	-0.3 (-7.2 - 6.7)	0.52
Average in the overall study period (36 weeks)	4.5 (0.2 - 8.7)	-0.7 (-7.7 - 6.3)	0.52

ABSI: autoimmune bullous skin disorder intensity, CI: confidence interval, NRS: numerical rating scale, ELISA: enzyme-linked immunosorbent assay, BP180 AB, BP230 AB: antibodies to bullous pemphigoid hemidesmosomal antigens BP180 and BP230, RU: relative units.

* Log-rank test

** Comparisons were performed on patients who had achieved disease control (17 in the mepolizumab and 10 in the placebo groups)

*** Estimated marginal means from mixed linear regression models

**** Mann-Whitney U test

***** Estimated marginal means from mixed linear regression models including baseline levels of each parameter as adjustment factors

Figure legend

FIGURE 1 Rates of BP patients free of relapse, achieving disease control, and maintaining disease control. The Kaplan-Meier curves show (A) the cumulative relapse-free survival, (B) the cumulative disease-control rate, and (C) the disease-control maintenance rate in the mepolizumab (solid line) and placebo groups (dashed line).

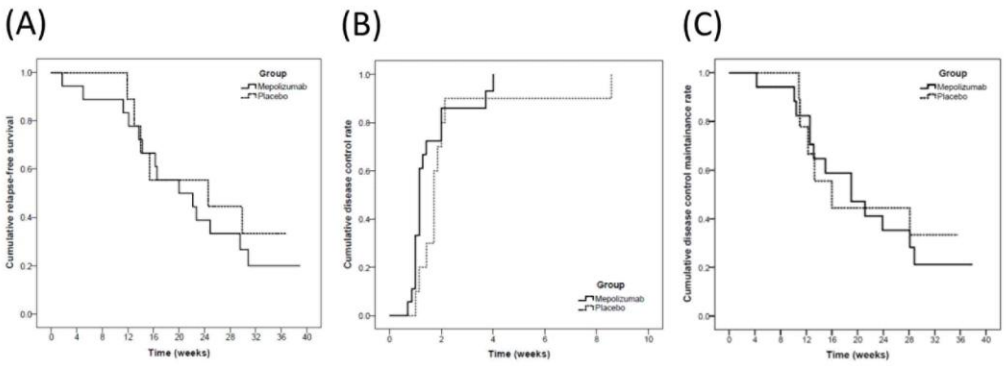

Figure 1