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Efficacy and safety of adjuvant immunoadsorption in pemphigus vulgaris and pemphigus foliaceus (IA-Pem Study): a multicentre randomized controlled trial

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Abstract

Background Pemphigus vulgaris (PV) and pemphigus foliaceus (PF) are potentially life-threatening autoimmune blistering diseases. Treatment is based on long-term immunosuppression with high doses of glucocorticosteroids in combination with potentially corticosteroid-sparing agents and/or rituximab. Immunoadsorption (IA) has emerged as a fast-acting adjuvant treatment option.

Objectives To assess the clinical efficacy of IA in addition to best medical treatment (BMT).

Methods We conducted a multicentre (26 centres from Germany and Austria) randomized controlled trial in 72 patients with newly diagnosed, relapsed or chronic active PV or PF (34 female patients and 38 male patients, aged 42–72 years) comparing BMT (prednisolone 1.0 mg kg^{-1} per day plus azathioprine or mycophenolate) with adjuvant IA (BMT + IA). Central 1 : 1 randomization was done at the coordinating centre for clinical trials (KKS Marburg). The primary endpoint was analysed using Kaplan–Meier and Cox regression methods.

Results The study was ended prematurely owing to safety concerns after random allocation of 72 patients to BMT + IA ($n=34$) or BMT ($n=38$). The primary endpoint, time to complete remission on therapy, was not significantly different for the two groups [hazard ratio (HR) 1.35, 95% confidence interval (CI) 0.68–2.69; $P=0.39$]. The cumulative dose of prednisolone was significantly lower in the BMT + IA group compared with BMT alone (difference −1214, 95% CI −2225 to −70; $P=0.03$). In a post hoc analysis, patients with more extensive PV/PF showed a tendency towards a shorter time to remission in the BMT + IA group compared with the BMT group (HR 1.87, $P=0.17$ in patients with baseline Pemphigus Disease Area Index ≥ 15). While more adverse events were observed in patients in the BMT group (29 vs. 25), severe adverse events were more frequent in patients in the BMT + IA group (17 events in 10 patients vs. 11 events in 8 patients).

Conclusions In this study, adjuvant IA did not demonstrate a shorter time to clinical remission, but a corticosteroid-sparing effect was observed. In patients with extensive PV/PF, post hoc analysis suggests that adjuvant IA may lead to earlier remission, but potential adverse events must be carefully weighed against the expected benefits.

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Lay summary

Pemphigus vulgaris and pemphigus foliaceus are potentially life-threatening autoantibody-driven blistering diseases, which present with erosions or blisters on skin and/or mucous membranes. Treatment is based on long-term immunosuppressive agents. Immunoadsorption (IA) is a procedure that removes autoantibodies from the blood and has emerged as a fast-acting treatment option for pemphigus.

We conducted a trial comparing best medical treatment (BMT) (prednisolone 1.0 mg kg per day plus azathioprine or mycophenolate) with best medical treatment plus IA (BMT + IA). A total of 26 centres from Germany and Austria recruited 72 patients with active pemphigus (34 women and 38 men, aged 42–72 years) who were randomly allocated in a ratio of 1 : 1 to the treatment groups.

Following inclusion of 72 patients in the BMT + IA (n = 34) or BMT (n = 38) groups, the study ended prematurely owing to safety concerns. The main outcome, time to complete remission (relief of all symptoms) while still receiving therapy, was not significantly different for the two groups. In contrast, the cumulative dose of prednisolone was significantly lower in the BMT + IA compared with BMT alone.

In an additional analysis, patients with more extensive pemphigus showed a tendency towards a shorter time to remission in the BMT + IA group compared with the BMT group. While more adverse events were observed in the BMT group (29 vs. 25), severe adverse events were more frequent in the BMT + IA group (17 vs. 11).

In this study, IA did not show a shorter time to clinical remission, but a prednisolone-sparing effect was observed. In patients with extensive pemphigus, adjuvant IA may possibly lead to earlier remission, but potential adverse events must be carefully weighed against the expected benefits.

What is already known about this topic?

- For pemphigus vulgaris and pemphigus foliaceus, potentially life-threatening autoimmune diseases affecting the skin and/or mucous membranes, immunoadsorption (IA) has been proposed as a fast and effective adjuvant treatment option in a number of case reports and case series, but a randomized controlled trial has not yet been reported.

What does this study add?

- In this randomized controlled trial, IA combined with best medical treatment, i.e. oral prednisolone and azathioprine or mycophenolate, was compared with best medical treatment alone.
- A statistically significant difference was not found between the two groups in relation to the primary endpoint, i.e. time to clinical remission.
- The cumulative prednisolone dose was significantly lower in the IA group, and in patients with extensive disease a tendency towards faster remission was observed in the IA arm.
- Adjuvant IA may be valuable in the initial treatment phase of patients with severe pemphigus.

Pemphigus vulgaris (PV) and pemphigus foliaceus (PF) are severe autoimmune blistering skin diseases characterized by IgG autoantibodies against the two desmosomal proteins Desmoglein (Dsg)1 and Dsg3.[1,2] In addition, autoantibodies to other target antigens, including cholinergic receptors and annexins, have been reported.[3,4] Pemphigus is a potentially fatal condition with erosions on surface-close mucous membranes, i.e. mouth, nose, pharynx, larynx, perianal area and vulva/penis in PV, and flaccid blisters, erosions and crusts in PF and the mucocutaneous form of PV.[1] The incidence of pemphigus considerably differs among different ethnic groups, ranging from 0.6 to 1.0 per million per year in Northern Europe and 4.0 to 8.0 per million per year in the UK, Southern and Eastern Europe, the USA and India. The highest incidences, 16.1 and 32 per million per year, were found in populations of Jewish decent.[5] Before the introduction of corticosteroids in the therapy of pemphigus, mortality was as high as 70% and is still two to three times higher compared with control populations.[5–7] To reduce the high doses of corticosteroids (initial dose, prednisolone 1.0–2.0 mg kg^{-1} day) and their associated, often-devastating, side-effects further immunosuppressants such as azathioprine or mycophenolate are usually added.[8,9] However, their beneficial effect in pemphigus has not unequivocally been shown.[8,9] Recently, rituximab has substantially improved the treatment of PV and PF and was approved for moderate and severe PV by the European Medicines Agency and the US Food and Drug Administration.[8–12] One of the caveats of rituximab is the time until it exerts clinical efficacy, with complete remission not being achieved before 4 months after its initiation.[11,13]

In contrast to many other autoimmune diseases, in pemphigus, the direct pathogenic effect of anti-Dsg1 and anti-Dsg3 autoantibodies has been clearly demonstrated[2,14–17] and levels of serum autoantibodies often parallel disease in individual patients.[18,19] Therefore, in pemphigus the removal of autoantibodies appears to be an attractive and rational therapeutic approach to rapidly reduce pathogenic autoantibodies.

Plasmapheresis has been applied in patients with severe or refractory pemphigus with variable success.[20,21] Since the early 2000s, adjuvant immunoadsorption (IA) has successfully been used in more than 100 reported cases of severe and/or refractory PV and PF employing various treatment protocols.[22–29] IA has several advantages over plasmapheresis

as it selectively removes immunoglobulins from the circulation, does not require substitution of plasma components, and allows the processing of two to three times more plasma volume per treatment session. IA systems differ with respect to ligands, matrix, volume of the columns, affinity to certain immunoglobulin isotypes, and reusability.[21,30]

In previous case series with adjuvant IA, Dsg-specific serum autoantibody levels were lowered by 75% following a single IA procedure and decreased by about 95% when applied on three consecutive days.[21,24] The therapeutic principle of removal of pathogenic autoantibodies from the circulation is also exerted by high-dose intravenous IgG and neonatal Fc receptor inhibitors. Both approaches have been applied successfully in PV/PF in phase II studies.[31–33]

The Immunoadsorption in Pemphigus (IA-Pem) clinical trial evaluated whether IA in combination with a standard immunosuppressive regimen of oral prednisolone (1.0 mg kg^{-1} day) plus azathioprine or mycophenolate leads to a faster complete remission on therapy while not being associated with more severe adverse events compared with the standard immunosuppressive regimen.

Patients and methods

Trial design, setting and randomization

The study was conducted as a multicentre randomized controlled trial (RCT) with equal randomization stratified for patients' status (newly diagnosed vs. chronic active vs. relapsed) and 1 : 1 allocation to best medical treatment (BMT) and interventional group (BMT + IA, see Interventions) in 26 dermatology departments that served as secondary or tertiary transferal centres for patients with pemphigus in Germany ($n = 25$) and Austria ($n = 1$). The randomization algorithm used permuted blocks of random sizes. Central randomization at the coordinating centre for clinical trials (KKS Marburg) guaranteed concealment of allocation. The trial was registered at Deutsches Register Klinischer Studien (DRKS 00000566).

Participants

The following inclusion criteria were applied:

- Patients with clinical active PV/PF presenting with lesions covering > 1.0% of body surface area or > 2 cm^2 of mucous membranes. Diagnosis of PV/PF was based on compatible clinical features such as blisters and/or erosions on the skin and/or mucous membranes and direct immunofluorescence (IF) microscopy of perilesional skin/mucous membrane showing cell surface staining of epidermis/epithelium for IgG and/or C3 and indirect IF microscopy on monkey oesophagus demonstrating cell surface staining of epithelium for IgG or IgG reactivity against Dsg3/Dsg1 by enzyme-linked immunosorbent assay[34]
- Newly diagnosed, chronic refractory or relapsed PV/PF
- Signed written informed consent
- Age ≥ 18 years
- Washout periods:
- Rituximab, leflunomide ≥ 1 year; plasmapheresis/IA ≥ 3 months; intravenous immunoglobulin ≥ 2 months; monoclonal antibodies against tumour necrosis factor-α ≥ 4 weeks; methotrexate, cyclophosphamide, ciclosporin A, dapsone, tetracyclines ≥ 1 week. Patients with chronic refractory disease (> 6 months) and relapsed patients on azathioprine may be switched to mycophenoles.

The following exclusion criteria were applied:

- Allergy to materials and/or medication used in the study, mandatory treatment with angiotensin-converting enzyme inhibitors
- Coagulopathy, severe cardiovascular disease (New York Heart Association IV, myocardial infarction within the last 3 months)
- Severe acute or chronically active systemic infections [i.e. hepatitis B surface antigen-positive chronically active hepatitis B, hepatitis C, HIV infection, patient history of tuberculosis infection, acute viral infections (i.e. varicella zoster virus, severe herpes simplex virus infection)]
- Fertile women not using adequate contraceptive methods, women who were pregnant or breastfeeding
- Severe reduction of liver or renal function (serum aspartate aminotransferase > threefold of normal value, serum creatinine > threefold of normal value), Hb < 9 g dL^{-1} or leucopenia < 3000 μL^{-1} or thrombocytopenia < 100 000 μL^{-1} owing to reduced bone marrow function
- Severe congenital immunodeficiency, active gastroduodenal ulcer, acute or unstable psychiatric diseases with a high risk of exacerbation owing to high-dose prednisolone
- Active or progressive malignancy or malignancy currently treated with chemotherapy/immunosuppressants or immunotherapy. In cases of patients with preceding malignancy who are in complete remission, an oncologist should be consulted prior to inclusion
- Illiteracy or insufficient language skills (German) to complete the questionnaires
- Simultaneous participation in another clinical trial, with the exception that it does not affect the study as approved and documented by the steering committee.

Interventions

Best medical treatment (control intervention)

Patients in the BMT arm received prednisolone at an initial dose of 1.0 mg kg^{-1} per day plus azathioprine (1.5–2.5 mg kg^{-1} per day; according to serum thiopurine methyltransferase activity) or mycophenolate, i.e. mycophenolate mofetil (2 g per day) or mycophenolate sodium (1440 mg per day), in the case of intolerance to azathioprine.

Experimental intervention (adjuvant immunoadsorption)

Patients in the BMT + IA arm received IA on four consecutive days (one treatment cycle) using Immunosorba® (Fresenius Medical Care, Bad Homburg, Germany). A total of two to four cycles required to achieve a clinical response were performed in 3-week intervals in addition to BMT.

Both best medical treatment and best medical treatment plus immunoadsorption

Patients received tapering doses of prednisolone, reduced by 25% each week if no new lesions occurred until a dose of 30 mg per day has been reached, daily doses then being reduced by 5 mg every 2 weeks until 10 mg per day was reached, followed by reductions of 2.5 mg every 2 weeks until prednisolone was omitted. Subsequently, daily doses of azathioprine or mycophenolate mofetil or mycophenolate sodium were reduced every 8 weeks by 50 mg, 500 mg or 360 mg, respectively.

Outcome measures

The primary outcome measure was the time from randomization to complete remission on therapy, also termed clinical remission, defined as healing of all blisters and erosions. Secondary endpoints included cumulative doses and time until omission of systemic corticosteroids and immunosuppressants; longitudinal analysis of Pemphigus Disease Area Index (PDAI)[35] and Autoimmune Blistering Skin Disorder Intensity Score (ABSIS)[36] (two validated scores to quantify disease activity in pemphigus); Dermatology Life Quality Index (DLQI); circulating anti-Dsg 1/3 IgG levels; and proportion of patients with a prednisolone dose <7.5 mg per day; time to reach minimal disease, defined as lesions covering $<0.5\%$ of body surface area or <1 cm² of mucous membranes and duration of clinical remission. The number and intensity of adverse events (AEs) were recorded and classified using system organ classes and preferred terms according to MedDRA and assessed for relatedness to the interventions.

Sample size

Based on Beissert *et al.*[37] we estimated a median time to remission of 80 days in the BMT group. Assuming an accrual period of 2 years, follow-up of 1 year and a true hazard ratio of 2 (i.e. a median time to remission of 40 days in the BMT + IA group), we calculated that 74 patients (37 per group) were needed to observe 65 events (remissions), which would provide a power of 80% in a two-sided log-rank test with a significance level of 0.05. To account for a potential 10% dropout, we initially planned to recruit 82 patients. The power calculations were performed using PASS (www.ncss.com). During the course of the trial, the dropout rate proved to be higher (about 20%) and the protocol was amended to recruit 92 patients. At the time when 72 patients were recruited, the data safety and monitoring board requested an interim analysis after a death of unknown cause in the BMT + IA group. The interim analysis revealed a higher number of severe AEs in the BMT + IA group and a smaller clinical effect than initially assumed. Thus, the recruitment of new patients was stopped. All analyses are based on the 72 patients included in the study.

Statistical methods and additional methods

Time to clinical remission and time to minimal disease were calculated with randomization as the starting point and were censored at the earlier of last contact date or 365 days after randomization for patients who did not experience the event. Duration of remission was calculated from the first reported date of remission until relapse or censoring date (last status report). Kaplan–Meier and Cox regression methods were used for the time to event analysis.[38,39] The log-rank test stratified for randomization strata was used for the confirmatory analysis of the primary endpoint in the intention-to-treat population. For Cox regression analyses, BMT was used as the reference class (hence, for time to remission and time to minimal disease, hazard ratios >1 favour BMT + IA and for duration of remission hazard ratios <1 favour BMT + IA). Post hoc subgroup analyses of time to clinical remission were performed in patients with significant/extensive pemphigus at baseline (ABSIS ≥ 17, PDAI ≥ 15), as defined by Boulard *et al.*[40] Analysis of further endpoints used the χ^2-test and WilcoxonMann–Whitney *U*-test together with Hodges–Lehmann (HL) estimates of location shift as appropriate. For longitudinal analyses of scores (PDAI, ABSIS), mixed models with restricted maximum likelihood estimation were applied, with repeated measurements within patients and the treatment variable and its interaction with time as factors.

Ethics

The study was conducted following the Declaration of Helsinki and the Medical Product law, and was approved by the Ethics committee of the University of Marburg (AZ: 183/10) and, subsequently, all participating centres.

Results

Patients

From 7 March 2011 to 18 February 2014, 72 patients were randomly allocated to BMT + IA ($n=34$) or BMT ($n=38$) (Figure 1). Further recruitment was prevented by premature ending of the study as described above. Patient characteristics at randomization were well balanced and showed no statistically significant differences (Table 1).

Primary outcome measure

In the BMT + IA group, 16 of 34 patients (47%) experienced a clinical remission compared with 17 of 38 patients (45%) in the BMT group. The median time to clinical remission was 6.1 months in the BMT + IA group; in the BMT group, the median time to clinical remission could not be estimated. The log-rank test stratified for randomization strata showed no statistically significant difference in time to clinical remission ($P=0.39$) (Figure 2). The hazard ratio (HR) was 1.35 [95% confidence interval (CI) 0.68–2.69]. As a sensitivity analysis to the primary endpoint, time to clinical remission was censored for patients who switched from randomized therapy. This analysis did not show statistical significance either (HR 1.22, 95% CI 0.58–2.58; $P=0.60$).

Secondary outcome measures

The cumulative dose of prednisolone was significantly lower in the BMT + IA group (median 3055 mg) compared with the

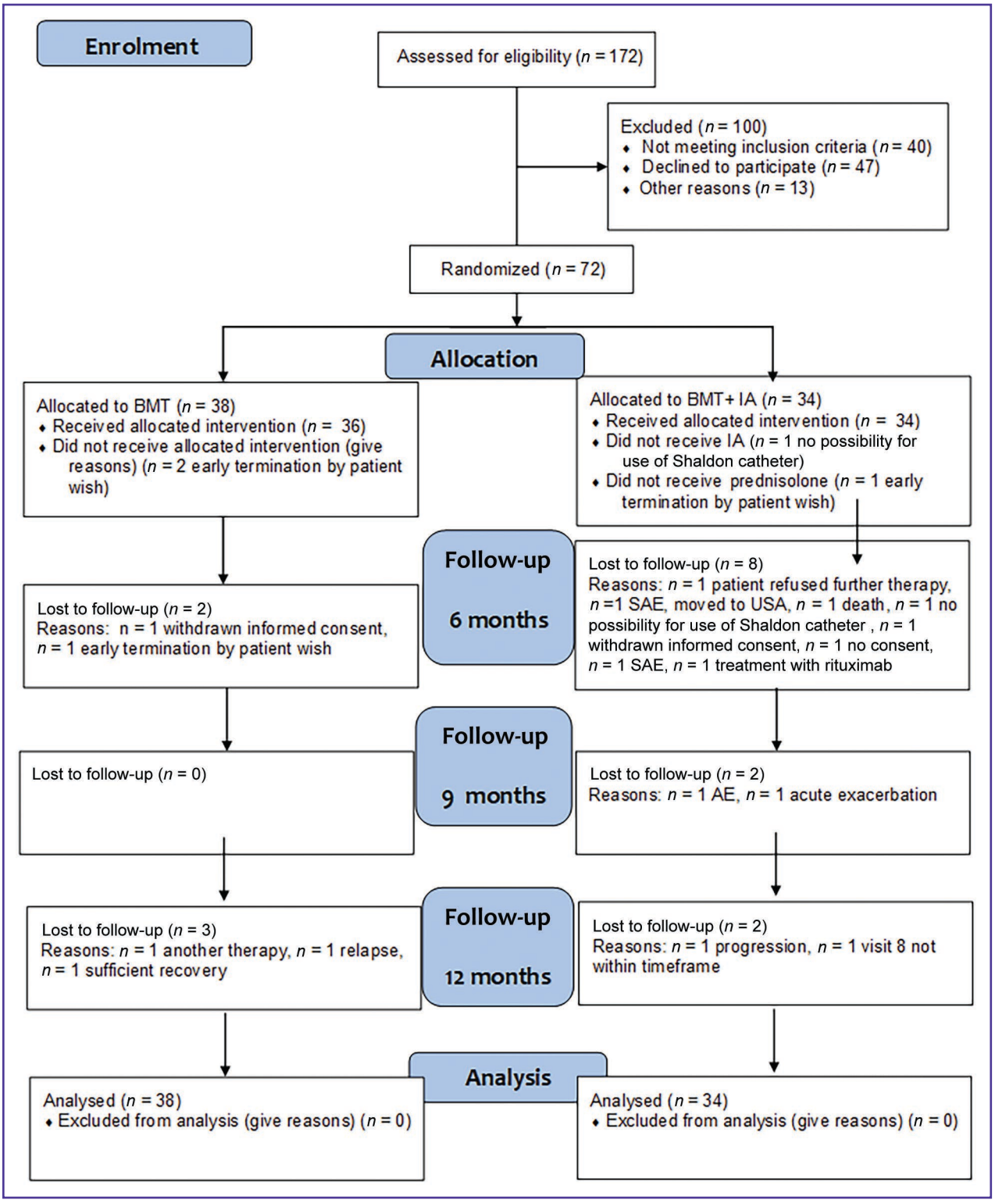

Figure 1 CONSORT flowchart. AE, adverse event; BMT, best medical treatment; SAE, serious AE.

group who received BMT alone (median 4835 mg) [HL estimate −1214, 95% CI −2225 to −70; $P=0.03$ (*U*-test)] (Table 2), while no difference was seen in the time to reach a daily dosage lower than 7.5 mg (stratified log-rank test, $P=0.51$) or in the cumulative dosage of other immunosuppressants azathioprine (*U*-test, $P=0.99$) or mycophenolate (*U*-test, $P=0.47$).

Disease activity of patients was assessed using the standardized clinical scoring measures ABSIS and PDAI and is shown in Figure 3 and Figure S1 (see Supporting

Table 1 Patient characteristics at baseline[a]

	BMT + IA ($n=34$)	BMT ($n=38$)
Age in years	50.0 (42.0–68.0)	55.0 (48.0–72.0)
Female	18 (53)	17 (45)
Male	16 (47)	21 (55)
White	31 (91)	37 (97)
Non-White	3 (9)	1 (3)
Pemphigus vulgaris	25 (74)	33 (87)
Pemphigus foliaceus	9 (26)	5 (13)
Newly diagnosed active pemphigus	17 (50)	16 (42)
Relapsed pemphigus	8 (24)	10 (26)
Chronic refractory pemphigus	9 (26)	12 (32)
ABSIS	31.75 (13.5–40.0)	19.5 (11.0–33.0)
PDAI	23.1 (12.0–42.3)	18.6 (12.0–29.3)
Anti-Dsg 1 IgG	77.0 (13.0–169.0)	64.0 (4.0–199.0)
Anti-Dsg 3 IgG	130.5 (4.5–481.5)	150.0 (26.0–718.0)
Time since first lesion, months		
Newly diagnosed active	4.3 (3.0–9.1)	3.2 (1.5–6.2)
Chronic refractory	32.5 (27.5–37.2)	35.4 (12.7–100.7)
Relapsed	51.5 (36.8–81.5)	66.8 (51.8–109.5)
Time since first lesion to diagnosis, months		
Newly diagnosed active	3.6 (2.0–8.2)	2.9 (1.0–5.7)
Chronic refractory	6.5 (1.6–11.5)	2.5 (1.0–11.4)
Relapsed	1.5 (0.5–5.0)	1.0 (0–4.4)
Time since first diagnosis, months		
Newly diagnosed active	0.4 (0.2–1.2)	0.1 (0.1–0.7)
Chronic refractory	19.4 (14.9–33.0)	28.7 (6.8–91.0)
Relapsed	42.8 (20.9–56.0)	64.6 (50.9–109.5)
Time since relapse, months		
Newly diagnosed active	0	0
Chronic refractory	0	1.6 (1.4–2.9)
Relapsed	2.1 (0.6–3.0)	2.6 (0.7–3.3)

ABSIS, Autoimmune Blistering Skin Disorder Index; BMT, best medical treatment; Dsg, Desmoglein; IA, immunoadsorption; PDAI, Pemphigus Disease Area Index. [a]Age and times are reported as median interquartile range (IQR) (first quartile, third quartile). Category variables are reported as *n* (%) within randomized group. No statistically significant differences in patient characteristics were observed. The smallest *P*-value was 0.08 for the difference of time since first diagnosis in patients with relapsed pemphigus.

Information). Statistically significant clinical improvements were seen at 3, 6, 9 and 12 months compared with baseline (all $P<0.001$) for the whole group. However, there was no statistically significant difference in improvement between the two treatment groups.

Time to reach minimal disease in the BMT + IA group (median of 5.8 months) was shorter, although not significantly, compared with the BMT group (median of 8.9 months) resulting in an HR of 1.36 (95% CI 0.73–2.53, $P=0.34$). There was no significant difference between the two treatment arms with regard to duration of clinical remission, DLQI and serum anti-Dsg 1/3 IgG levels at any measurement timepoint (data not shown).

Safety

After a death in the BMT + IA group the data safety and monitoring board initiated an interim analysis. Subsequently, further recruitment was prematurely terminated. A total of 220 AEs have been registered throughout the study, encompassing 136 different AE terms, in 54 of 72 patients (75%), which were mainly mild ($n=92$, 42%) or moderate ($n=98$, 45%) (Table S1; see Supporting Information). The number of patients with any AEs and severe AEs categorized by MedDRA system organ classes in both treatment groups is shown in Table 3. While AEs were more frequent in the BMT group, severe AEs were more frequent in the BMT + IA group (17 events in 10 patients, of which 7 events account for infections and investigations, e.g. abnormal blood and urine values and one death) compared with the BMT arm (11 events in 8 patients, of which 4 were gastrointestinal disorders) (Tables 3 S1, S2; see Supporting Information). The death in the BMT + IA group occurred in a 45-year-old male patient without known comorbidities 1 day after the second cycle of IA. Of note, all forensic investigations including postmortem analysis led by the public prosecutor's office did not find the cause of death or any causal relation to IA or BMT.

Post hoc subgroup analyses

Subgroup analyses in patients with significant/extensive pemphigus at baseline as defined by Boulard *et al.*[40] showed a tendency towards a shorter time to clinical remission in the BMT + IA group compared with the BMT group (HR 1.87, $P=0.17$ in patients with baseline PDAI ≥ 15). In these patients, who were severely affected, anti-Dsg 1/3 IgG did not differ significantly between randomized groups. Similar analyses in patients with baseline ABSIS ≥ 17 are shown in Figure S1.

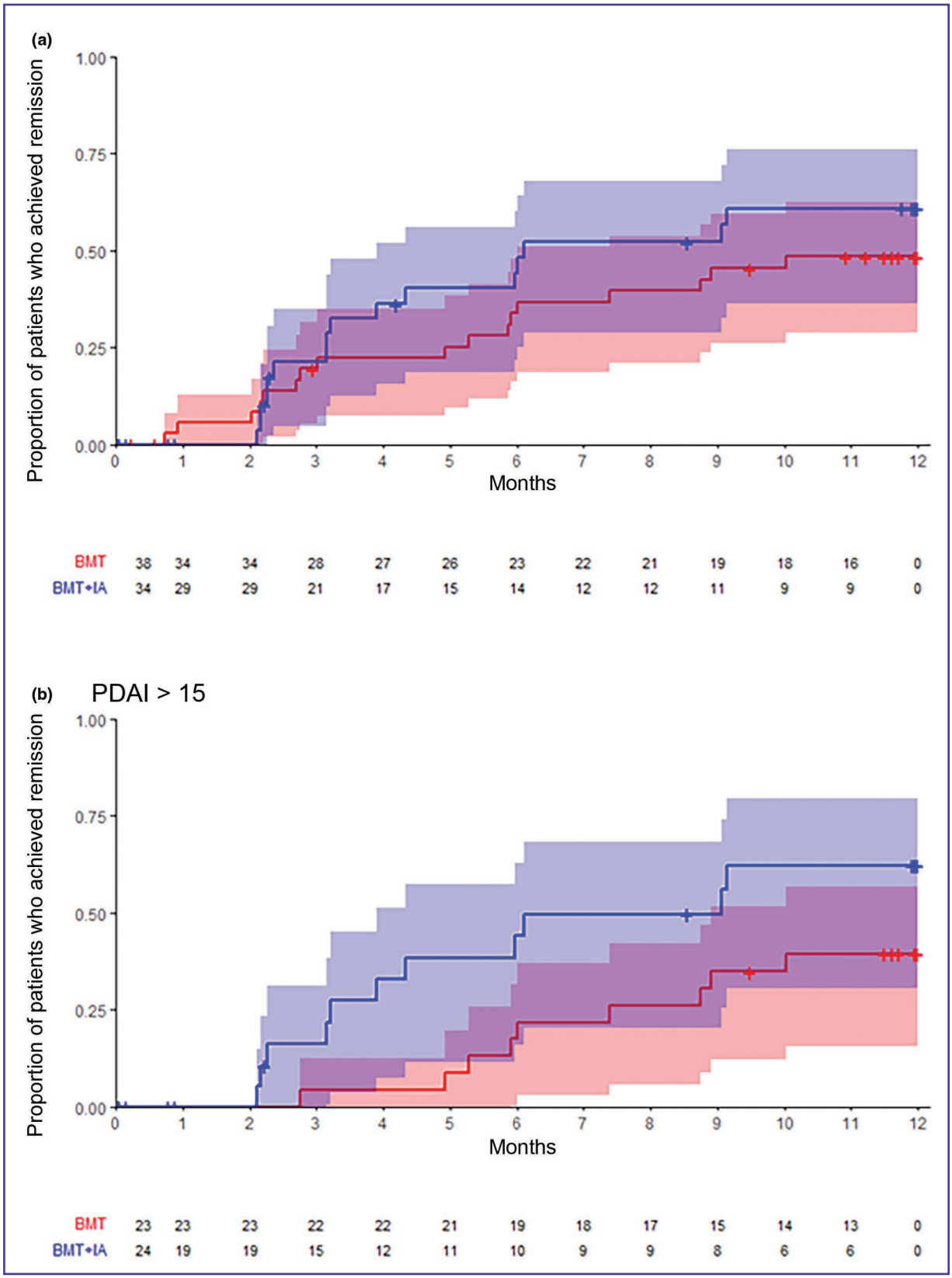

Figure 2 Time to complete remission on therapy (also termed clinical remission) (the primary endpoint of the study). (a) Time to clinical remission is shown using a Kaplan–Meier plot for all patients. No significant differences were observed between the two groups. (b) In a subgroup analysis of patients severe with disease (PDAI > 15), a tendency towards faster remission was observed. BMT, best medical treatment. PDAI, Pemphigus Disease Area Index.

Table 2 Cumulative dose of prednisolone (mg)

Arm	*n*	Missing	Median	IQR	Range
BMT + IA	33	1	3055	2135–5377	160–25 620
BMT	36	2	4835	3626–6428	1140–14 840

BMT, best medical treatment; IA, immunoadsorption; IQR, interquartile range. Cumulative dose of prednisolone intake (mg) throughout the study duration; two-sided Wilcoxon–Mann–Whitney *U*-tests ($P=0.03$).

Discussion

This study was performed to evaluate the efficacy and safety of the standard BMT at the time of study initiation[41] comprising prednisolone 1 mg per kg bodyweight and a potentially corticosteroid-sparing agent compared with the same regimen combined with IA. The undisputed direct pathogenic effect of pemphigus autoantibodies, the immediate mode of action of IA, the relatively few adverse reactions of IA in the reported case series and the high medical need for effective treatment options in PV/PF provided the rationale for this trial.

Owing to a sudden death of unknown cause, the data safety and monitoring board requested an interim data analysis. As more severe AEs were observed in the BMT + IA group ($n=17$) compared with the BMT group ($n=11$), recruitment of new patients was stopped. Follow-up visits were continued, which resulted in 72 patients who could be evaluated. All forensic investigations did not find any medical cause of the patient's death. As such, it remained unclear whether the death was related to the previous IA procedure.

Previous observational studies and case series in PV and PF have used IA in combination with a variety of additional immunosuppressants/immunomodulants, a variable number of IA procedures and different adsorbers.[23–28,42–48] A cycle of three IA treatments on consecutive days led to the reduction of anti-Dsg 1/3 serum levels by 90%, and treatment protocols combining IA with rituximab resulted in complete remission rates of 80–90% in patients with severe and/or refractory PV/PF.[21,23,24,28] Based on these observations and the central pathogenic role of anti-Dsg 1/3 IgG, the present study was initiated to define the value of adjuvant IA in the treatment of PV and PF.

In the present study, we could not show a significant benefit of BMT + IA over BMT with regard to the primary outcome measure, i.e. time to clinical remission. In the BMT + IA group, a faster (not statistically significant) decrease of PDAI and ABSIS within the first 3 months of treatment was observed (Figures 3, S1). This observation corresponds with the expectation that any clinical effect of IA will be seen at an early timepoint, most likely during the time IA is being performed.[22–27,29,43–47,49] In accordance with this, the time to reach minimal disease was shorter in the BMT + IA arm compared with BMT, although this finding was not statistically significant.

Systemic corticosteroids have been the therapeutic backbone in the treatment of PV/PF and have led to an enormously reduced mortality compared with the precorticosteroid era.[7] However, systemic corticosteroids are associated with a high number of AEs, and minimizing the required corticosteroid dose is one of the main concerns in pemphigus therapy.[8,50] Importantly, we observed a significant reduction of the cumulative prednisolone dose in the BMT + IA group (median 3.055 mg) compared with BMT alone (median 4.835 mg). Apart from the two RCTs that used rituximab in the treatment of PV/PF, this is the only RCT that demonstrated a corticosteroid-sparing effect of a therapeutic approach in pemphigus.[11,12]

However, this effect must be weighed against potential safety risks of IA. Previous reports have evaluated IA as

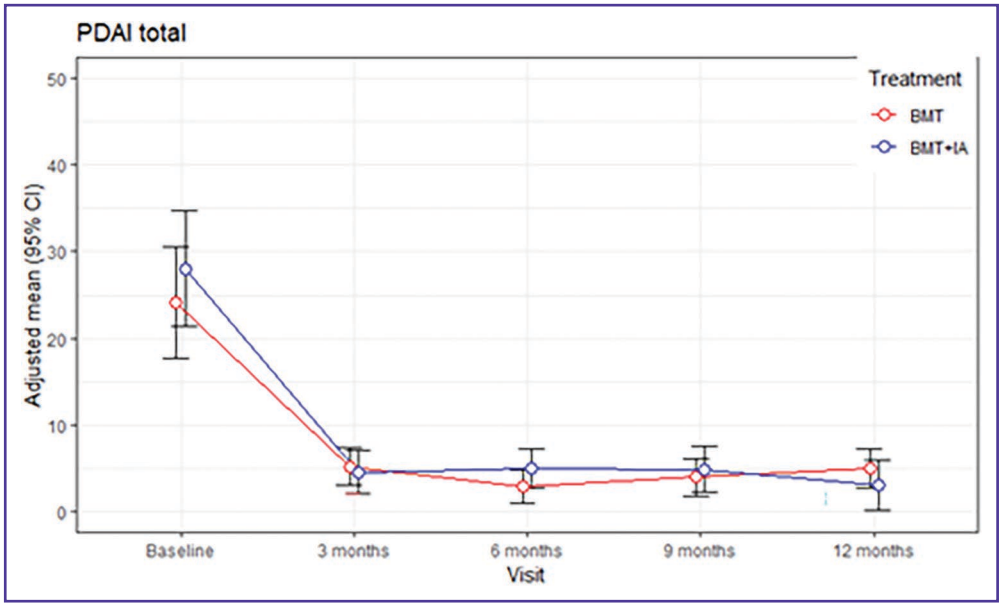

Figure 3 Improvement of disease activity measured using the PDAI. Disease severity was measured using the PDAI and showed a similar improvement of disease activity for best medical treatment alone (BMT, red lines) compared with additional IA (BMT + IA, blue lines). In the BMT + IA arm, a stronger, although not significantly different, decrease in disease activity within the first 3 months was observed. BMT, best medical treatment; CI, confidence interval, IA, immunoadsorption; PDAI, Pemphigus Disease Area Index.

Table 3 Adverse events

	BMT+IA ($n=34$)		BMT ($n=38$)	
Intensity	Any intensity	Severe	Any intensity	Severe
Any adverse event	25 (74)	10 (29)	29 (76)	8 (21)
System organ classes				
General disorders and administration site conditions	10 (29)	3 (9)	6 (16)	3 (8)
Metabolism and nutrition disorders	5 (15)	0 (0)	6 (16)	1 (3)
Nervous system disorders	4 (12)	1 (3)	8 (21)	0 (0)
Gastrointestinal disorders	7 (21)	0 (0)	3 (8)	2 (5)
Renal and urinary disorders	4 (12)	1 (3)	2 (5)	0 (0)
Injury, poisoning and procedural complications	2 (6)	0 (0)	3 (8)	0 (0)
Blood and lymphatic system disorders	5 (15)	0 (0)	0 (0)	0 (0)
Others[a]	23 (68)	7 (21)	26 (68)	4 (11)

Overview of adverse events by study arm and maximum intensity. Adverse events are coded according to the MeDRA system organ classes (SOCs). Data show the number of patients and corresponding percentages. Each patient is counted only once according to the highest intensity they experienced in the respective SOC. [a]Details about the SOCs categorized as 'others' here are shown in Table S2 (see Supporting Information).

a rather safe adjuvant therapy.[26,28,29,47,51] Difficult peripheral venous access in addition to dizziness and paranaesthesia during the IA procedure owing to citrate-induced hypercalcaemia are well-known mild AEs that occur with IA. Previously reported severe AEs in patients with pemphigus who underwent adjuvant IA included infections or thrombotic events such as *Staphylococcus aureus* sepsis, *Pneumocystis carinii* pneumonia and herpes zoster infection in addition to pulmonary embolism and deep vein thrombosis.[28,46] Severe AEs were observed less frequently in patients with pemphigus who received IA combined with intravenous dexamethasone pulses rather than long-term oral corticosteroids and in those with peripheral venous access compared with central venous access for IA.[24]

In the present study, the total number of patients who experienced AEs was higher in the BMT group compared with the BMT+IA arm. In contrast, more patients treated with BMT+IA experienced at least one severe AE. Of note, four patients treated with IA experienced severe infections or abnormal laboratory values (one patient with septicaemia, endocarditis, increased body temperature; one patient with increased transaminases; one patient with atypical pneumonia; one patient with bacterial infection) compared with none in the BMT group. In the patient with septicaemia, central venous access was employed. A higher rate of septicaemia has already been associated with patients with pemphigus who were treated with IA using central venous access compared with peripheral venous access.[24,28]

So far, IA has almost exclusively been applied in patients with extensive and/or refractory PV/PF.[28] Here, to demonstrate the general efficacy of IA in PV and PF, patients with mild and moderate disease activity were also included. In a post hoc analysis, patients with higher PDAI/ABSIS scores showed a tendency towards a shorter time to clinical remission compared with the BMT group. This observation underscores the value of IA in patients with PV/PF who had severe disease compared with those who had mild/moderate disease and, at the same time, may indicate one of the limitations of this trial. Exclusion of patients with mild and moderate disease would have reflected the real-world application of IA and the future target population. Another limitation of our study included the lack of blinding. Sham infusions required for blinding were avoided owing to ethical concerns. Additionally, investigators could freely choose between central and peripheral venous access rather than using only a central venous approach in those patients with difficult peripheral access. Furthermore, although IAs were performed in departments of nephrology or transfusion medicine by trained personnel, the experience with IA in pemphigus was highly heterogeneous between the different centres. In fact, two of the three patients with severe infections in the BMT+IA group were dealt with in a centre that had not practised IA for pemphigus prior to the trial.

In summary, our study does not show a clear clinical benefit of IA in pemphigus and indicates that IA may be associated with severe infections. Secondary endpoints and post hoc analyses suggest that IA has a corticosteroid-sparing effect and, in the group of patients with severe PV/PF, may possibly lead to more rapid complete remission on therapy. Based on these results, we propose IA as an adjuvant treatment option for patients with severe PV/PF, i.e. with extensive skin involvement, as induction therapy to rapidly reduce serum autoantibodies after carefully weighing expected benefits against potential side-effects. The combination with rituximab, given immediately after the first IA cycle, is particularly attractive in order to narrow the treatment response gap seen with rituximab, which was shown not to induce complete remission on therapy within the first 2 months after the first infusion.[11,12]

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Conflicts of interest

N.v.B. has a joint project and a patent pending with Euroimmun and received honoraria from Fresenius Medical Care. E.S. has a scientific cooperation arrangement with Fresenius Medical Care and received honoraria from this company. M.H. and R.E. have received honoraria from Fresenius Medical Care.

Data availability

Anonymized individual patient data will be made available to the scientific community with as few restrictions as feasible. However, until the publication of major outcomes, exclusive use will be retained. Data requests to be considered by the trial steering committee should be submitted by qualified researchers to the corresponding author.

Ethics statement

The study was conducted following the Declaration of Helsinki, the Medical Product law and was approved by the Ethics committee of the University of Marburg (AZ: 183/10) and, subsequently, all participating centres.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website.

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