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MINI REVIEW

Immunoadsorption in dermatology

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Abstract Immunoadsorption (IA), also termed immunoapheresis, has been established as effective and specific tool advantageous to plasmapheresis to remove immunoglobulin and immune complexes and in cytapheresis, immune cells from the circulation. IA was successfully used in various autoantibody-mediated diseases, e.g. acquired hemophilia, myasthenia gravis, dilated cardiomyopathy, and Guillain–Barré syndrome. In dermatology, IA has been applied as an effective adjuvant treatment for autoimmune bullous diseases. Autoimmune blistering disorders are a heterogeneous group of diseases that are associated with autoantibodies to desmosomal (pemphigus group) and basal membrane zone proteins (pemphigoid group, epidermolysis bullosa acquisita). Because the pathogenic relevance of autoantibodies was clearly demonstrated in the majority of these disorders, removal of autoantibodies, therefore, appears to be a rational therapeutic approach for these patients. IA has been shown to effectively lower the autoantibody levels and leads to rapid clinical responses in patients with immunobullous disorders. Here, clinical effects and adverse events of IA in more than 50 reported patients with autoimmune blistering disorders are reviewed. In addition, an overview of the available IA systems and treatment protocols is provided and guidelines of a recent consensus of German, Austrian, and Swiss experts for the use of IA in autoimmune bullous diseases are summarized.

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Introduction

The arrival of immunoadsorption (IA), also termed immunoapheresis, about 20 years ago [25] allowed the selective removal of Ig and immune complexes from patients' circulation. IA has been successfully used in patients with systemic lupus erythematosus, myasthenia gravis, multiple sclerosis, dilated cardiomyopathy, antibody-mediated graft rejection, Guillain–Barré syndrome, ABO-incompatible kidney transplantation, rheumatoid arthritis, idiopathic thrombocytopenic purpura, and hemophilia with inhibitors [12, 13, 15, 17, 24, 28, 37, 46, 49]. In the latter three disorders, IA has been approved by the US American Food and Drug Administration. IA depletes Ig irrespective of its specificity. Specific adsorbers have been developed for autoantibodies to the β1-adrenergic receptor in dilated cardiomyopathy (Coraffin®, Fresenius Medical Care), C1q in systemic lupus erythematosus (Miro®, Fresenius Medical Care), and to ABO blood group antigens [21, 29, 51, 74].

IA also comprises cytapheresis. In cytapheresis, leukocytes are depleted by filtration, a procedure termed leukocytapheresis, or granulocytes and monocytes/macrophages are removed using cellulose acetate beads (Adacolumn®, Jimro, Gunma, Japan). Cytapheresis is particularly employed in inflammatory bowel disease, but has also been applied in rheumatoid arthritis and systemic lupus erythematosus [39, 54, 55, 70].

In dermatology, IA has been increasingly used in patients with autoimmune bullous diseases. In addition, patients with psoriasis have been successfully subjected to cytapheresis [34] and most, recently, in patients with severe

atopic dermatitis and very high serum IgE levels, SCORAD could be halved following 10 IA procedures (TheraSorb®, Miltenyi, Bergisch Gladbach) [27].

The novel therapeutic principle was particularly attractive for autoimmune bullous disorders since the pathogenic relevance of autoantibodies has been clearly established in most of them, including pemphigus [1, 2, 4, 56], bullous pemphigoid [23, 32, 42, 57, 67], anti-laminin 332 mucous membrane pemphigoid [31], and epidermolysis bullosa acquisita [66, 68, 69, 77]. In the present review, the application of IA in autoimmune blistering diseases is discussed.

Autoimmune bullous diseases

Autoimmune bullous diseases are a heterogeneous group of disorders that can be subdivided according to the level of split formation into intraepidermally blistering pemphigus diseases and subepidermal bullous disorders, latter including pemphigoid diseases, epidermolysis bullosa acquisita, and dermatitis herpetiformis. In the pemphigus group (pemphigus vulgaris, pemphigus foliaceus, and paraneoplastic pemphigus), autoantibodies recognize desmoglein 1 and 3, while in paraneoplastic pemphigus, additional proteins of the plakin family are bound [5, 75]. In the pemphigoid group (bullous pemphigoid, linear IgA disease, pemphigoid gestationis, mucous membrane pemphigoid), type XVII collagen (BP180), BP230, laminin 332, and $\alpha 6\beta 4$ integrin are targeted. Autoantibodies in patients with epidermolysis bullosa acquisita react with type VII collagen in anchoring fibrils. In dermatitis herpetiformis, immune complexes containing IgA and epidermal transglutaminase are deposited in the upper dermis [61].

Within the group of autoimmune bullous skin diseases, in Central Europe and the USA, the most common are bullous pemphigoid and mucous membrane pemphigoid [6, 30, 36]. In other geographic regions, such as Iran and Israel, pemphigus is about 10 times more frequent as compared to Central Europe and the USA [9, 48], and in Africa, linear IgA disease is the second most common immunobullous disease, the most frequent being bullous pemphigoid [40].

In the majority of autoimmune bullous disorders, disease activity can be sufficiently controlled by systemic corticosteroids in combination with further immunosuppressants/immunomodulants, such as dapsone, doxycycline, methotrexate, azathioprine, or mycophenolate mofetil. However, adverse events of these therapeutic agents may significantly increase both morbidity and mortality [8]. In pemphigus, mucous membrane pemphigoid, and epidermolysis bullosa acquisita, treatment is challenging and only in a minority of patients, conventional immunosuppressive therapy induces clinical remission. Until recently, only cyclophosphamide and high-dose intravenous Ig had been available as potent second-line therapies. Meanwhile, IA and the monoclonal anti-CD20 antibody rituximab, which may also be used in combination, have been established as further therapeutic options.

Plasmapheresis

Before the introduction of IA, plasmapheresis was the sole therapeutic intervention that allowed the immediate decrease in pathogenic autoantibodies. In 1978, plasmapheresis was first employed in pemphigus [10]. Following promising reports on its successful application in pemphigus [52, 53, 71–73], the controlled prospective multicenter trial by Guillaume et al. was a major drawback for this treatment principle. In 34 pemphigus patients, treatment with prednisolone (tapering doses of 0.5 mg/kg/day with dose increases up to 2 mg/kg/day when required) was compared with the application of ten plasmapheresis procedures within 4 weeks in combination with the same prednisolone protocol. Although no differences were observed in clinical efficacy and cumulative prednisolone dose, in four patients of the plasmapheresis arm, a fatal sepsis occurred [18].

When compared with plasmapheresis, IA has several advantages: IA (1) more selectively removes Ig, (2) does not require the substitution of plasma components such as fresh-frozen plasma or human albumin (Fig. 1), (3) allows the processing of the two- to threefold plasma volume per treatment session, and (4) it is associated with a lower rate of adverse events, such as infections and allergic reactions [7]. When IA is available, it may thus preferentially be applied to selectively deplete Ig.

Immunoadsorption

Immunoadsorption systems differ with respect to ligands, matrix, volume of the columns, affinity to certain Ig classes and reusability. As an adsorber matrix, usually, sepharose is used, but cellulose and polyvinyl alcohol is also applied (Table 1). In single-use devices, phenylalanine, tryptophan, dextran sulfate, and hydrophobic amino acids serve as ligands. Adsorbers capable of being regenerated contain the ligands protein A, the synthetic peptide PGAM146, or sheep antibodies-directed against human Ig (Table 1). No differences in IgG depletion rates between the protein A-based and the anti-human Ig-based reusable systems have been observed [38].

In the first step of IA, plasma and cellular components are separated by plasma filtration or centrifugation (Fig. 1). Single-use adsorbers are subjected to the patient plasma until their capacity is utilized. In reusable systems, a pair of adsorber columns is used. While one column is loaded with

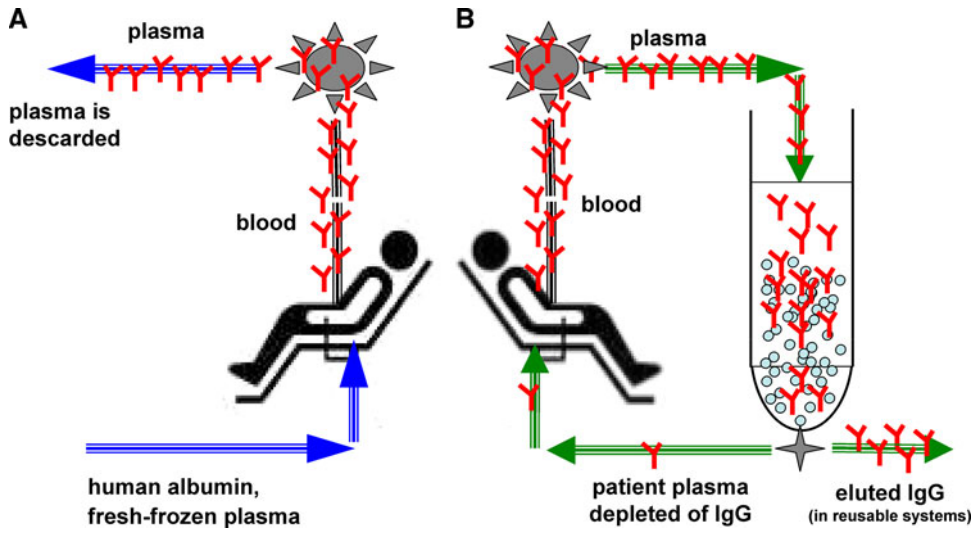

Fig. 1 Schematic diagram of plasmapheresis and immunoadsorption (IA). In both plasmapheresis (**a**) and IA (**b**), patient plasma is generated from the patients' blood by filtration or centrifugation. In plasmapheresis, the plasma is discarded and needs to be replaced by human albumin or fresh-frozen plasma (**a**). In contrast, in IA, the plasma is passed over a column that is loaded with an immunoglobulin (Ig)-specific ligand that binds the patient's Ig. The Ig-depleted plasma is then re-infused after supplementation with the previously separated patient cells (**b**). Single-use IA columns are exhausted after being charged with Ig from 2–3 l of plasma, whereas in regenerable systems, a pair of adsorber columns is used. While one column is loaded with plasma, in the other, antibodies are eluted by a sudden pH change allowing for a continuous apheresis process

Table 1 Commercially available adsorber for removal of immunoglobulin

Product	Regenerable adsorber[a]			Single-use adsorber		
	Immunosorba®	TheraSorb Ig/flex®[b]	Globaffin®	Prosorba®	Selesorb®	IM TR350® IM PH350®
Company	Fresenius Medical Care	Miltenyi Biotech	Fresenius Medical Care	Fresenius Medical Care	Kaneka	Asahi-Medical/Diamed
Ligand	Staphylococcal protein A	Polyclonal anti-human sheep antibody	Synthetic peptide PGAM146	Staphylococcal protein A	Dextran sulfate	Tryptophan (IM TR), phenylalanine (IM PH)
Matrix	Sepharose	Sepharose	Sepharose	Sepharose	Cellulose	Polyvinyl alcohol
Adsorbed proteins	IgG, IgA, IgM	IgG, IgA, IgM, IgE	IgG, IgA, IgM	IgG, IgA, IgM	Anti-ds DNA antibodies, lipids, fibrinogen	Immunoglobulins, fibrinogen, albumin, and others

Adopted from Zillikens et al. [78]

[a] for the same patient

[b] TheraSorb-Ig® can be used for 20 treatments, TheraSorb-Ig flex® for 10 treatments

plasma, the other is regenerated, i.e. the antibodies are flushed away, allowing for a continuous apheresis process. The three commercially available reusable adsorbers allow for up to 20 treatment sessions for the same patient.

Autoantibody levels can be lowered by 75% by a single IA procedure with a reusable system as exemplified by desmoglein-specific antibodies in patients with pemphigus for the initial 3 IA procedures (Fig. 2a). After three IA on three consecutive days, autoantibody levels can be decreased by about 95% (Fig. 2a). In contrast, a tryptophan adsorber achieves a 30% reduction [35]. In addition to its lower capacity, the latter has the side effect of a significant drop in fibrinogen levels. More importantly, a single IA procedure is less effective because autoantibodies re-diffuse from the tissue to the circulation and 24 h after the first IA, 40% of the initial levels are reached again (Fig. 2a). Interestingly, irrespective of the treatment protocol and adjuvant immunosuppression, lowering serum anti-desmoglein autoantibody levels by IA appeared to be sustainable. After 1 month of the first IA, autoantibody levels were decreased by nearly 80%, after 6 months, a reduction by 90% was observed. After 12 months, average reduction was still 90% as compared to the pre-IA anti-desmoglein levels with 30% of pemphigus patients in whom autoantibody levels were negative (Fig. 2b).

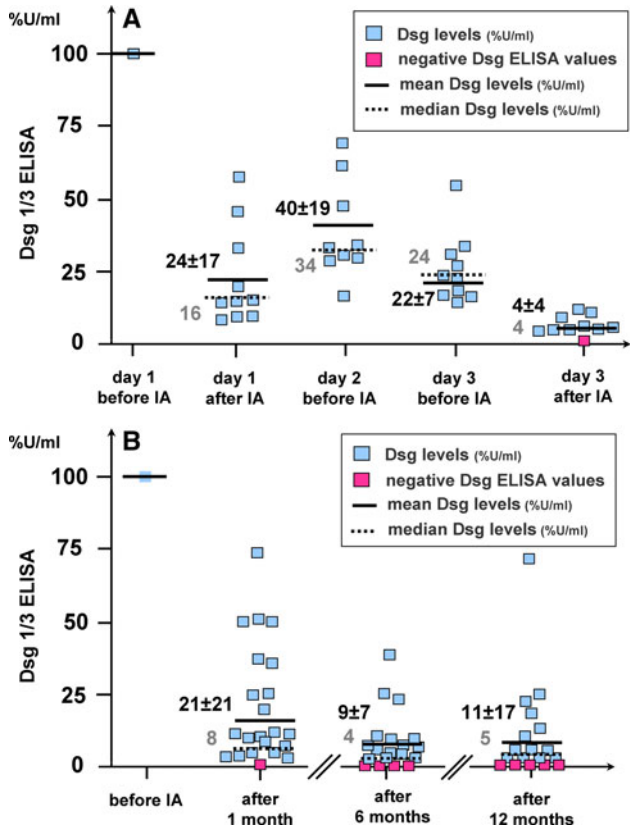

Fig. 2 Autoantibody levels during immunoadsorption (IA). Autoantibody levels during the initial 3-day-treatment cycle (**a**). Ten patients with severe and/or refractory pemphigus were subjected to 3 IA on three consecutive days using regenerable systems (Immunosorba®, TheraSorb®). Levels of anti-desmoglein (Dsg) antibodies were determined by ELISA (MBL, Nagoya, Japan). Autoantibody levels prior to the first IA were normalized to 100 and levels of subsequent analyses are given in percent of the initial levels (*light blue squares*). Autoantibody levels were measured directly before and directly after the individual IA. Negative ELISA values are indicated by *magenta squares*. Mean anti-desmoglein autoantibody levels (*black line*) ± standard deviation as well as median levels (*dotted line*) are indicated. After the first IA, autoantibody levels decreased by 76%. Owing to re-diffusion from the tissue, autoantibody levels increased again to 40% of the initial values on the next day. This observation necessitates the serial application of IA on consecutive days. After the third IA autoantibody levels were reduced by 96% compared with pre-IA levels. Autoantibody levels during a follow-up period of 12 months after the initial treatment cycle (**b**). The long-term effect of IA on the circulating autoantibody levels is visualized. Data are retrieved from 22 previously reported pemphigus patients treated according to protocol 1, 2 and 5 [58, 63, 64]. Anti-desmoglein antibody levels were determined by ELISA (MBL). Autoantibody levels prior to initiation of IA were normalized to 100 and levels of subsequent analyses are given in percent of the initial levels (*light blue squares*). Negative ELISA values are indicated by *magenta squares*. Mean anti-desmoglein autoantibody levels (*black line*) ± standard deviation as well as median levels (*dotted line*) are indicated. After 1 month of the first IA, autoantibody levels decreased by an average of 79% and 5 months later, by 91% compared with the initial levels. After 12 months, autoantibody levels remained low and were reduced to 11% of the pre-IA levels

Immunoadsorption in pemphigus

As soon as IA became available, this novel procedure has extensively been exploited in immunobullous diseases (Table 2). In 1998, IA was applied for the first time in these disorders, e.g. in a patient with paraneoplastic pemphigus [62]. In this patient, following the surgical removal of his retroclavicular myofibroblastic tumour, ten IA (Therasorb®) were performed over 4 weeks in conjunction with low-dose oral prednisolone that resulted in a complete remission defined as healing of all lesions and no further immunosuppression required [62]. Definitions of the clinical responses are given in Table 2.

To date, 48 pemphigus patients, 40 with pemphigus vulgaris, 7 with pemphigus foliaceus, and 1 with paraneoplastic pemphigus have been subjected to IA. In 38 patients, reusable systems were applied [11, 14, 19, 35, 45, 47, 58, 62–64] (Table 2). Assessing the real value of IA in immunobullous disorders is difficult, because no prospective controlled study has been performed yet. Indeed, all data are based on case reports and five case series of up to nine patients. In addition, different adsorbers and treatment protocols were applied. Below, the six reported treatment protocols are presented, the last one being currently applied in our patients with severe and/or refractory pemphigus.

Protocol 1

In a first protocol, repeated IA (Immunosorba®) was used in five refractory pemphigus patients in combination with tapering doses of methylprednisolone (initially, 0.5 mg/kg per day) and a single i.v. pulse of dexamethasone (100 mg on days 4–6) and cyclophosphamide (500 mg on day 4). IA was performed 19 times in each patient: on three consecutive days in the first week (days 1–3) and then four times in weekly, 2-weekly, 3-weekly, and 4-weekly intervals, respectively [58]. In all patients, after 12 weeks, autoantibody levels had decreased to <20% compared with pre-IA levels. Healing of all lesions was noted after 3–21 weeks [58]. After a follow-up period of 8–10 years, however, only one patient is still in clinical remission without relapse (unpublished data).

Protocol 2

In this approach, the same IA protocol was used in nine patients with pemphigus vulgaris. Unlike in the previous protocol, however, higher doses of methylprednisolone were given (initially 2.0 mg/kg per day) in conjunction with azathioprine (50–250 mg per day) or mycophenolate mofetil (2 g per day). The i.v. pulse with dexamethasone and

Table 2 Immunoadsorption in autoimmune bullous skin diseases: concomitant immunosuppression, clinical response and adverse events

Diagnosis	No. of patients/ references	Protocol[a]/ adsorber/no. of adsorptions	Concomitant immunosuppression	Clinical responses	Serious adverse events	Follow-up[b] (months)
Paraneoplastic pemphigus	1 [62]	Therasorb®/10[c]	Prednisolone 15 mg/day	CR	None	Not detailed
Pemphigus vulgaris	1 [45]	IM TR360®/11	Prednisolone 45 mg/day[d]	CliR	None	8
	4 [58]	Protocol 1 Immunosorba®/12–17	Initially: single pulse i.v. dexamethasone (3 × 100 mg) and i.v. cyclophosphamide (500 mg)[c]; prednisolone 0.5 mg/kg/day[d]	CR (n = 1), CliR (n = 3)	Single episode of hypotension and bradycardia (n = 1)	4–10
	7 [35]	Protocol 3 IM TR350®/2	Intravenous prednisolone 1.5 mg/kg on 2 days; prednisolone 0.5 mg/kg/day[d] plus azathioprine or mycophenolate mofetil or cyclophosphamide	PR (n = 7)	Anaphylaxis grade III during IA	6
	1 [14]	Immunosorba®/19[c]	Prednisolone 0.5 mg/kg/day[d] plus azathioprine 100 mg/day	PR	None	30
	9 [63]	Protocol 2 Immunosorba®/10–40	Prednisolone 2.0 mg/kg/day[d] plus azathioprine	CR (n = 1), CliR (n = 6), PR (n = 1)[e]	Perforating diverticulitis	18–38
	4 [11]	Protocol 4 Globaffin®/7 4–16	I.v. cyclophosphamide 750 mg/m^2 plus IVIG (10 g) pulses	CliR (n = 2), PR (n = 2)	None	9
	5 [64]	Protocol 5 Immunosorba®/6–17	Rituximab (4 × 375 mg/m^2) plus prednisolone 2.0 mg/kg/day[c] plus azathioprine 2.5 mg/kg/day or mycophenolate mofetil 2 g/day[c]	CR (n = 1), CliR (n = 4)	*Staphylococcus aureus* sepsis, *P. carinii* pneumonia, pulmonary embolism, deep venous thrombosis, herpes zoster infection	13–30
	1 [19]	Therasorb®/25[f]	Prednisolone plus mycophenolate mofetil 2 g/day	CliR	None	20
	1 [61]	Protocol 5, adopted Immunosorba®/5	Rituximab (4 × 375 mg/m^2) plus prednisolone 2.0 mg/kg/day[d] plus azathioprine 2.5 mg/kg/day	CR	Herpes zoster infection	22
	1 [61]	Immunosorba®/9[c]	Monthly i.v. dexamethasone pulses (3 × 100 mg) plus azathioprine 2.5 mg/kg/day	CliR	None	5
	6 [47]	Protocol 4, adopted Globaffin®/4–12	Prednisolone 0.5 mg/kg/day[c] plus azathioprine or mycophenolate mofetil 3 g/day	CliR (n = 3), PR (n = 3)	Myocardial infarction	12
Pemphigus foliaceus	1 [58]	Protocol 1 Immunosorba®/18	Initially: single pulse i.v. dexamethasone (3 × 100 mg) and i.v. cyclophosphamide (500 mg)[c]; prednisolone 0.5 mg/kg/day[d]; monthly IVIG (2 g/kg) for 3 months	CR	Deep venous thrombosis	27
	2 [35]	Protocol 3 IM TR350®/2	Intravenous prednisolone 1.5 mg/kg on 2 days; prednisolone 0.5 mg/kg/day[d] plus azathioprine	PR (n = 2)	None	6
	2 [11]	Protocol 4 Globaffin®/4	Single i.v. cyclophosphamide (750 mg/m^2) plus IVIG (10 g) pulse	CliR, PR	None	9
	2 [64]	Protocol 5 Immunosorba®/8, 14	Rituximab (4 × 375 mg/m^2) plus prednisolone 2.0 mg/kg/day[d] plus mycophenolate mofetil 2 g/day	CliR	None	20, 25

Table 2 continued

Diagnosis	No. of patients/ references	Protocol[a]/ adsorber/no. of adsorptions	Concomitant immunosuppression	Clinical responses	Serious adverse events	Follow-up[b] (months)
Bullous pemphigoid	2 [22]	Selesorb®/4, 6	Prednisolone 50 mg/day[d] plus dapsone; prednisolone 50 mg/day[c]	PR (n = 2)	None	3
	2 [20]	IM TR350®/2[c]	Methylprednisolone 2.0 mg/kg/day[d] plus dapsone 1.5 mg/kg/day; methylprednisolone 1.5 mg/kg/day[d] plus azathioprine 2.0 mg/kg/day plus IVIG (2 g/kg)	CliR	*Staphylococcus aureus* sepsis	3
Pemphigoid gestationis	1 [76]	Therasorb®/6[c]	Prednisolone 0.6 mg/kg/day[d]	PR	None	7
Anti-p200 pemphigoid	1 [26]	IM TR350®/2[c]	Doxycycline 200 mg/day plus topical clobetasol propionate 0.05%	CR	None	4
Epidermolysis bullosa acquisita	1 [33]	Protocol 2, adopted Immunosorba®/37[c]	Azathioprine 75 mg/day plus prednisolone 100 mg/day[d]	CliR	None	26
	2 [43]	Globaffin®/2[c]	Mycophenolate mofetil 2 g/day	PR (n = 2)	None	8, 12

IVIG intravenous immunoglobulin, *CliR* clinical remission (healing of clinical manifestations but further treatment required), *CR* complete remission (clinical remission and no further therapy needed), *PR* partial remission (healing of >50% of clinical manifestations), *SD* stable disease (<25% increase and <50% improvement)

[a] As detailed in sections Protocol 1 to 5 in the main document

[b] After first immunoadsorption (IA)

[c] Detailed in the text

[d] Only the initial dose is given; stepwise reduction according to clinical response did usually follow

[e] In one patient, IA had to be discontinued due to a perforating diverticulitis

[f] 12 IAs in weekly intervals followed by 13 IAs in monthly intervals

cyclophosphamide was omitted in this protocol. In eight patients, rapid clinical remissions were induced [63]. At present, after follow-up periods between 6 and 7 years, five patients have remained in clinical remission without relapses; one patient died after all lesions had healed 2 years after initiation of IA, one patient suffered from a severe relapse, and one patient was lost for follow-up (unpublished data). While the second protocol resulted in better long-term responses, the fourfold higher corticosteroid doses and addition of azathioprine or mycophenolate mofetil may have contributed to an increased risk of severe adverse events.

Protocol 3

This protocol applied a single-use absorber system (IM TR350®). Six patients with refractory and three with acute severe pemphigus were treated on days 1 and 3, followed by i.v. prednisolone (1.5 mg/kg) on the same days. On day 4, methylprednisolone (0.5 mg/kg per day) in combination with additional immunosuppressants, including azathioprine, mycophenolate mofetil, and cyclophosphamide were initiated [35]. When compared with the long-term protocol with reusable systems [58, 63], markedly less reduction in serum autoantibodies and shorter durations of clinical improvement were noted [35].

Protocol 4

This approach included the application of the reusable Globaffin® adsorber in four refractory patients with pemphigus vulgaris and in two with pemphigus foliaceus. IA was performed on four consecutive days followed by IVIG (10 g) and in some patients, i.v. cyclophosphamide (750 mg/m^2), on the fifth day. This procedure was repeated 4 weekly until all lesions had healed. Adjuvant immunosuppression consisted of prednisolone (1.0–2.0 mg/kg per day) and azathioprine (1.5–2.5 mg/kg per day)/mycophenolate mofetil (2–3 g per day). A rapid decline in serum autoantibodies was observed and most lesions cleared within a few weeks. During the follow-up period of 2 years, clinical remissions occurred in three patients while still on immunosuppressants. In the three others, partial remissions were induced [11].

Recently, six additional patients with pemphigus vulgaris, resistant to systemic corticosteroids combined with azathioprine or mycophenolate mofetil, were subjected to the same IA schedule [47]. IVIG and cyclophosphamide were omitted in these patients. In three patients, a clinical remission (defined as healing of all lesions, but further immunosuppression required) was achieved. The remaining three patients experienced partial remissions and were subsequently treated with rituximab [47].

Protocol 5

To have the patients benefit from both the rapid clinical response seen with IA and the striking long-term effect of rituximab [41, 59, 60], protocol 2 was modified as followed: IA (Immunosorba®) was performed on days 1, 2, 3, 8, 15, 22, 29, and then in 2-, 3-, and 4-weekly intervals as described [58, 63]; four rituximab infusions (375 mg/m^2) were administered on days 9, 16, 23, and 30, a schedule that was adopted from patients with B-cell non-Hodgkin lymphoma. Concomitantly, patients received tapering doses of oral prednisolone (2.0 mg/kg per day) plus azathioprine (2.5 mg/kg per day) or mycophenolate mofetil (2 g per day) [64]. Seven patients with severe pemphigus, six of them with treatment-resistant disease, were included. Within 1 month, in four patients, no new lesions appeared and in three patients, partial remissions were obtained. After 1 year, one patient had achieved complete remission, four were in clinical remission, and two had reached partial remission [64]. In all patients, serum autoantibodies decreased strikingly. Four patients suffered from severe adverse events, including *Staphylococcus aureus* sepsis, *P. carinii* pneumonia, herpes zoster infection, pulmonary embolism, and deep venous thrombosis [64]. To date, after follow-up periods of 3 to more than 4 years, one patient is in complete remission, two in clinical, and one in partial remission. In three patients, relapses occurred between 14, 30, and 34 months after initiation of this regimen (unpublished data).

Following the same protocol, another patient with pemphigus vulgaris has been treated with excellent outcome (Table 2). His lesions cleared 8 weeks after the first IA and currently, he is in complete remission while circulating and tissue-bound autoantibodies have become undetectable [61].

Current protocol

Based on these data, the strength of IA in pemphigus seemed to rely on the rapid induction of clinical remission by swift reduction of circulation autoantibodies during the first weeks of treatment rather then the influence of long-term outcome. To maximize this effect, we currently perform IA on three consecutive days (referred to as 1 cycle) followed by additional cycles 3 weeks later and then 4 weekly until lesions have healed for 90% and serum autoantibodies have dropped to 10% of original levels (Fig. 3). Rituximab is applied twice at a dose of 1 g on days 4 and 25. This schedule was based on the one for rheumatoid arthritis for which rituximab had meanwhile been licensed. Unlike the rituximab protocol for rheumatoid arthritis in pemphigus, the second IA cycle and the second rituximab infusion were performed 3 weeks after the initial infusion to avoid reducing rituximab levels by subsequent IA.

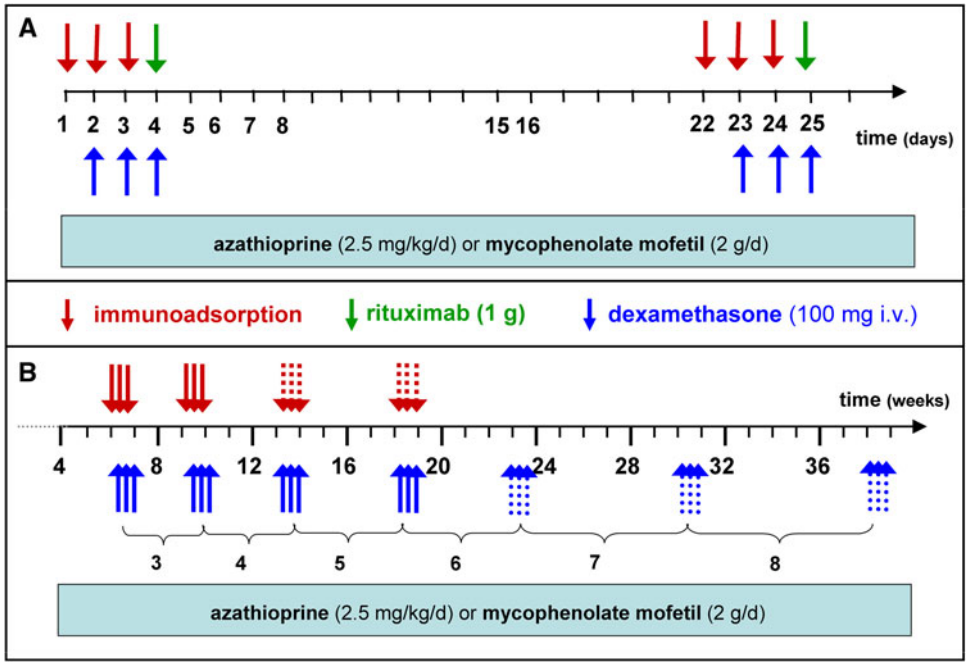

Fig. 3 Novel treatment protocol for patients with severe and/or refractory autoimmune bullous diseases combining the rapid clinical response following immunoadsorption (IA) and the excellent long-term effect of rituximab. IA (*red arrows*) is performed on three consecutive days representing one treatment cycle. IA cycles are repeated after 3 weeks and then 4 weekly until lesions have healed to about 90% and serum autoantibodies have dropped by about 90%. Rituximab (*green arrows*) is applied twice at a dose of 1 g on days 4 and 25. In addition, i.v. dexamethasone pulses (100 mg on 3 consecutive days; *blue arrows*) are administered in prolonging intervals of initially 3, and later of up to 8 weeks together with daily azathioprine (2.5 mg/kg per day with normal TPMT) or mycophenolate mofetil (2 g per day)

To decrease the rate of severe side effects encountered in Protocol 5 (see below), oral prednisolone was replaced by i.v. dexamethasone pulses (100 mg on 3 consecutive days) applied in conjunction with each IA. As in previous protocols, azathioprine or mycophenolate are also given (Fig. 3). Until now, 15 patients have been subjected to this protocol. Rapid clinical responses were seen (Fig. 4) while only two severe adverse events have occurred [65].

IA treatment of three additional patients with refractory pemphigus vulgaris has been reported [14, 19, 45]. Among them, one patient received monthly IA for almost 2 years [14]. Further details are presented in Table 2.

IA in pemphigoid diseases and epidermolysis bullosa acquisita

Immunoadsorption has also been successfully performed in four refractory patients with bullous pemphigoid, three with epidermolysis bullosa acquisita, and one patient with

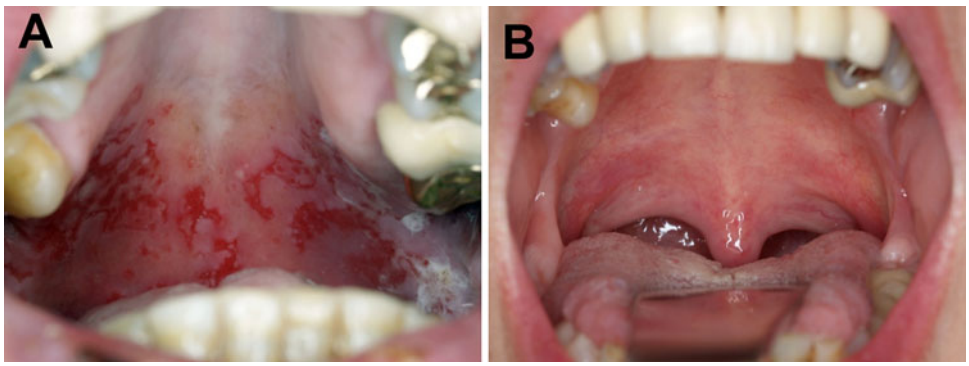

Fig. 4 Clinical response in a patient with refractory pemphigus vulgaris treated with immunoadsorption (IA), rituximab, i.v. dexamethasone pulses, and azathioprine. Multiple erosions on the palate before (**a**) and healing of all lesions after 18 IA (6 treatment cycles of 3 IA) and 5 months after initiation of the combination regimen including protein A immunoadsorption, rituximab, i.v. dexamethasone pulses and azathioprine (**b**). For further details of the treatment protocol refer to the section current protocol and Fig. 3

pemphigoid gestationis and anti-p200 pemphigoid, respectively (Table 2).

In 2 patients with bullous pemphigoid and high-serum levels of anti-BP180 autoantibodies (312 and 10,226 U/ml) who were unresponsive to methylprednisolone (0.5 mg/kg per day) plus dapsone (1.5 mg/kg per day) and methylprednisolone (1.5 mg/kg per day) plus azathioprine (2.0 mg/kg per day), respectively, two single IA on consecutive days using the tryptophan-linked matrix IM TR350® resulted in dramatic clinical responses within 2 weeks after initiation of IA and sharp decreases of circulating autoantibodies [20]. The other two patients with bullous pemphigoid were treated with four and six IA by the use of dextran sulphate conjugated cellulose columns (Selesorb®) during a 2-week period. Skin lesions improved considerably and serum autoantibodies decreased [22].

In one relapsed patient with the inflammatory variant of epidermolysis bullosa acquisita, IA (Immunosorba®) was performed following Protocol 2 with some modifications [63]. After 26 months and 37 IA that were performed in finally monthly intervals, clinical remission was achieved while prednisolone could be reduced to 4 mg per day [33]. In two patients with the mechanobullous variant of epidermolysis bullosa acquisita, 2 IA (Globaffin®) were combined with rituximab and mycophenolate mofetil leading to partial remissions [43].

In an 18-year-old woman with pemphigoid gestationis, 6 IA (Therasorb®) applied between the 30th and 34th week of gestation in conjunction with prednisolone (0.6 mg/kg per day) controlled her disease. She had previously been unresponsive to methylprednisolone (1.0 mg/kg per day). In parallel with the clinical response anti-BP180 autoantibodies decreased by 70% and the prednisolone dose could be reduced to 0.3 mg/kg per day [76].

Very recently, we have described a 70-year-old male patient with anti-p200 pemphigoid in whom 2 IA with IM TR-350® combined with oral doxycycline 200 mg per day and topical clobetasol propionate 0.05% twice daily resulted in a clinical response within 2 weeks without adverse events [26]. This treatment regimen was chosen due to the severity of skin lesions, relatively high autoantibody levels, and an active duodenal ulcer accompanied with hematochezia refraining us from employing systemic corticosteroids. Eighteen weeks later, 2 weeks after the discontinuation of doxycycline, a severe relapse occurred. Interestingly, the relapse was associated with autoantibodies to both the p200 antigen and BP180 [26].

Adverse events

Of the 14 pemphigus patients treated in Protocol 1 and Protocol 2, only two severe adverse events were noted, including a deep venous thrombosis and a perforating diverticulitis [58, 63]. In Protocol 5, that combined high-dose oral prednisolone with IA, rituximab, and azathioprine/mycophenolate mofetil, four of seven patients suffered from severe adverse events [64] (Table 2). In our current protocol (Fig. 3), high-dose oral prednisolone was replaced by i.v. dexamethasone pulses and only two severe adverse events were noted in 15 pemphigus patients [65]. The relatively high rate of severe unwanted events in Protocol 5 [64] may be related to prolonged administration of high dose of oral prednisolone.

Excluding the patients treated in Protocol 5, in only 6 of the remaining 50 patients with immunobullous disorders treated with IA, severe adverse events were observed. Of all adverse events, only four appear to be directly related to IA: a single episode of hypotension and bradycardia as well as a grade III anaphylactic reaction during the IA procedure and *Staphylococcus aureus* sepsis after infection of the central venous catheter in two patients (Table 2). In addition, venous access was sometimes difficult and temporary paraesthesia of hands and lips that rapidly resolved after administration of calcium did occur. The relatively low incidence of adverse events seen in autoimmune blistering diseases is in line with data from the Swedish Apheresis Group that reported adverse events in <1% of procedures [44].

Recommendations

Below, recommendations for the use of IA in the treatment of autoimmune bullous diseases that have been published following a consensus meeting of German, Austrian, and Swiss physicians experienced in IA are summarized [78].

(Contra-) indications

Immunoadsorption may be performed as first-line treatment in pemphigus or epidermolysis bullosa acquisita patients with acute and severe disease [defined as involvement of (1) >30% of the body surface or (2) >25% of oral or genital mucous membranes or (3) conjunctiva or (4) esophagus]. In patients with other autoimmune blistering disorders, IA should be reserved for refractory patients with disease courses of more than 3 months and at least two adequate immunosuppressive therapies (Fig. 5). IA may not be performed in patients with known hypersensitivity to column material, severe cardiovascular disease, extreme bleeding tendency during anticoagulation, treatment with ACE inhibitors (discontinue drugs at least 72 h before IA), and children under 15 kg of body weight.

In all patients, the diagnosis needs to be based on characteristic clinical findings, direct immunofluorescence microscopy

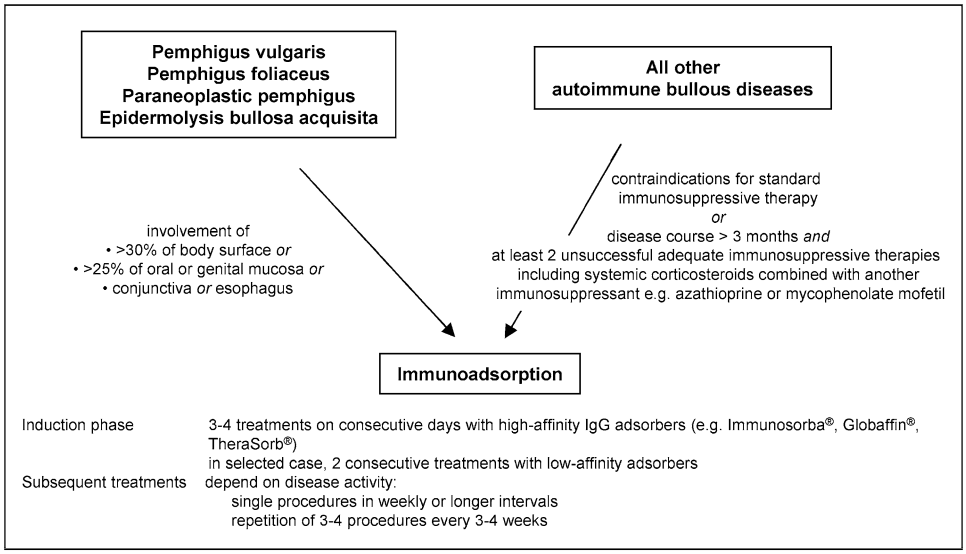

Fig. 5 Algorithm for the use of immunoadsorption in autoimmune bullous skin disorders as recommended by a Consensus meeting of German, Austrian, and Swiss physicians experienced in this therapy [78]

and/or the detection of typical serum autoantibodies. IA should be performed in centers experienced in extracorporal circulation on an in-patient basis. It is advisable to obtain written informed consent of the patients. Owing to the higher rate of infections in patients with central venous catheters a peripheral venous access may be chosen whenever possible [78].

Treatment protocol

An induction phase comprises three to four IA procedures on consecutive days with high-affinity adsorbers (e.g. Immunosorba®, Globaffin®, Therasorb®) or in selected cases, two consecutive treatments with low-affinity columns (e.g. IM TR350®, IM PH350®, Selesorb®). Subsequent treatments depend on the clinical activity and may consist of weekly single IA or monthly IA on three or four consecutive days. To document efficacy of IA autoantibody levels should be monitored before and after each IA. Adjuvant immunosuppression is obligatory and tapering doses of prednisolone (1.0–2.0 mg/kg per day) combined with azathioprine (2.5 mg/kg per day with normal TPMT) or mycophenolate mofetil (usually 2 g per day) are standard regimens. The application of i.v. cyclophosphamide pulses (500–750 mg/m^2) or rituximab is also possible [78].

Perspectives

Regarding all available data, IA appears to be a rational, effective, and relatively safe adjuvant therapy for severe and/or treatment-resistant autoimmune bullous disorders. IA allows the rapid reduction of serum autoantibodies which is reflected by rapid clinical responses. In our experience, the rapid clinical effect following IA obtained in most of these patients is, for the time being, ideally complemented with the B-cell depleting agent rituximab. The combination of IA and rituximab has also been successfully applied in demyelinating polyneuropathy and is currently increasingly used in ABO-incompatible organ transplantations [16, 50].

A major drawback in the treatment of autoimmune bullous disorders has always been the rarity of high-quality prospective controlled studies. Prospective controlled trials in pemphigus have recently been published for the use of IVIG [3] and initiated for rituximab (www.clinicaltrial.gov). Most recently, support for a multicenter prospective controlled trial to explore the value of IA in pemphigus has been granted by the German Research Foundation. In this trial, 82 pemphigus patients will either receive tapering doses of prednisolone 1.0 mg/kg/day p.o plus azathioprine/mycophenolate mofetil or the same regimen in combination with IA. Two to four IA cycles of four IA on consecutive days are scheduled with a 3-week interval. This trial may also open the avenue for the development of adsorbers specific for the relevant target antigens.

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References

1. Amagai M, Hashimoto T, Shimizu N, Nishikawa T (1994) Absorption of pathogenic autoantibodies by the extracellular domain of pemphigus vulgaris antigen (Dsg3) produced by baculovirus. J Clin Invest 94(1):59–67
2. Amagai M, Hashimoto T, Green KJ, Shimizu N, Nishikawa T (1995) Antigen-specific immunoadsorption of pathogenic autoantibodies in pemphigus foliaceus. J Invest Dermatol 104(6):895–901

3. Amagai M, Ikeda S, Shimizu H, Iizuka H, Hanada K, Aiba S, Kaneko F, Izaki S, Tamaki K, Ikezawa Z, Takigawa M, Seishima M, Tanaka T, Miyachi Y, Katayama I, Horiguchi Y, Miyagawa S, Furukawa F, Iwatsuki K, Hide M, Tokura Y, Furue M, Hashimoto T, Ihn H, Fujiwara S, Nishikawa T, Ogawa H, Kitajima Y, Hashimoto K (2009) A randomized double-blind trial of intravenous immunoglobulin for pemphigus. J Am Acad Dermatol 60(4):595–603
4. Anhalt GJ, Labib RS, Voorhees JJ, Beals TF, Diaz LA (1982) Induction of pemphigus in neonatal mice by passive transfer of IgG from patients with the disease. N Engl J Med 306(20):1189–1196
5. Anhalt GJ (2004) Paraneoplastic pemphigus. J Investig Dermatol Symp Proc 9(1):29–33
6. Bertram F, Brocker EB, Zillikens D, Schmidt E (2009) Prospective analysis of the incidence of autoimmune bullous disorders in Lower Franconia, Germany. J Dtsch Dermatol Ges 7(5):434–440
7. Braun N, Bosch T (2000) Immunoadsorption, current status and future developments. Expert Opin Investig Drugs 9(9):2017–2038
8. Bystryn JC, Steinman NM (1996) The adjuvant therapy of pemphigus: an update. Arch Dermatol 132(2):203–212
9. Chams-Davatchi C, Valikhani M, Daneshpazhooh M, Esmaili N, Balighi K, Hallaji Z, Barzegari M, Akhiani M, Ghodsi Z, Mortazavi H, Naraghi Z (2005) Pemphigus: analysis of 1209 cases. Int J Dermatol 44(6):470–476
10. Cotterill JA, Barker DJ, Millard LG (1978) Plasma exchange in the treatment of pemphigus vulgaris. Br J Dermatol 98(2):243
11. Eming R, Rech J, Barth S, Kalden JR, Schuler G, Harrer T, Hertl M (2006) Prolonged clinical remission of patients with severe pemphigus upon rapid removal of desmoglein-reactive autoantibodies by immunoadsorption. Dermatology 212(2):177–187
12. Felix SB, Staudt A (2008) Immunoadsorption as treatment option in dilated cardiomyopathy. Autoimmunity 41(6):484–489
13. Freedman J, Garvey MB (2004) Immunoadsorption of factor VIII inhibitors. Curr Opin Hematol 11(5):327–333
14. Frost N, Messer G, Fierlbeck G, Risler T, Lytton SD (2005) Treatment of pemphigus vulgaris with protein A immunoadsorption: case report of long-term history showing favorable outcome. Ann N Y Acad Sci 1051:591–596
15. Gaubitz M, Schneider KM (2003) Immunoadsorption in systemic lupus erythematosus: different techniques and their current role in medical therapy. Ther Apher Dial 7(2):183–188
16. Genberg H, Kumlien G, Wennberg L, Tyden G (2007) Long-term results of ABO-incompatible kidney transplantation with antigen-specific immunoadsorption and rituximab. Transplantation 84(12 Suppl):S44–S47
17. Genberg H, Kumlien G, Wennberg L, Berg U, Tyden G (2008) ABO-incompatible kidney transplantation using antigen-specific immunoadsorption and rituximab: a 3-year follow-up. Transplantation 85(12):1745–1754
18. Guillaume JC, Roujeau JC, Morel P, Doutre MS, Guillot B, Lambert D, Lauret P, Lorette G, Prigent F, Triller R et al (1988) Controlled study of plasma exchange in pemphigus. Arch Dermatol 124(11):1659–1663
19. Gunther C, Laske J, Frind A, Julius U, Pfeiffer C (2008) Successful therapy of pemphigus vulgaris with immunoadsorption using the TheraSorbtrade mark adsorber. J Dtsch Dermatol Ges
20. Herrero-Gonzalez JE, Sitaru C, Klinker E, Brocker EB, Zillikens D (2005) Successful adjuvant treatment of severe bullous pemphigoid by tryptophan immunoadsorption. Clin Exp Dermatol 30(5):519–522
21. Hiepe F, Pfuller B, Wolbart K, Bruns A, Leinenbach HP, Hepper M, Schossler W, Otto V (1999) C1q: a multifunctional ligand for a new immunoadsorption treatment. Ther Apher 3(3):246–251
22. Ino N, Kamata N, Matsuura C, Shinkai H, Odaka M (1997) Immunoadsorption for the treatment of bullous pemphigoid. Ther Apher 1(4):372–376
23. Iwata H, Kamio N, Aoyama Y, Yamamoto Y, Hirako Y, Owaribe K, Kitajima Y (2009) IgG from patients with bullous pemphigoid depletes cultured keratinocytes of the 180-kDa bullous pemphigoid antigen (type XVII collagen) and weakens cell attachment. J Invest Dermatol 129(4):919–926
24. Kaczmarek I, Deutsch MA, Sadoni S, Brenner P, Schmauss D, Daebritz SH, Weiss M, Meiser BM, Reichart B (2007) Successful management of antibody-mediated cardiac allograft rejection with combined immunoadsorption and anti-CD20 monoclonal antibody treatment: case report and literature review. J Heart Lung Transplant 26(5):511–515
25. Kadar JG, Borberg H (1990) Biocompatibility of extracorporeal immunoadsorption systems. Transfus Sci 11(2):223–239
26. Kasperkiewicz M, Hoppe U, Zillikens D, Schmidt E (2009) Relapse-associated autoantibodies to BP180 in a patient with anti-p200 pemphigoid. Clin Exp Dermatol (in press)
27. Kasperkiewicz M, Schmidt E, Rose C, Frambach, Anemüller W, Grabbe J, Ludwig R, Zillikens D (2009) Immunadsorption bei Patienten mit schwerster atopischer Dermatitis und exzessiv erhöhten peripheren Serum-IgE-Spiegeln. 82. Jahrestagung der Norddeutschen Dermatologischen Gesellschaft. 02.04.09.2009, Halle (Saale) (abstract)
28. Knobl P, Derfler K (1999) Extracorporeal immunoadsorption for the treatment of haemophilic patients with inhibitors to factor VIII or IX. Vox Sang 77(Suppl 1):57–64
29. Kumlien G, Ullstrom L, Losvall A, Persson LG, Tyden G (2006) Clinical experience with a new apheresis filter that specifically depletes ABO blood group antibodies. Transfusion 46(9):1568–1575
30. Langan SM, Smeeth L, Hubbard R, Fleming KM, Smith CJ, West J (2008) Bullous pemphigoid and pemphigus vulgaris–incidence and mortality in the UK: population based cohort study. BMJ 337:a180
31. Lazarova Z, Yee C, Darling T, Briggaman RA, Yancey KB (1996) Passive transfer of anti-laminin 5 antibodies induces subepidermal blisters in neonatal mice. J Clin Invest 98(7):1509–1518
32. Liu Z, Diaz LA, Troy JL, Taylor AF, Emery DJ, Fairley JA, Giudice GJ (1993) A passive transfer model of the organ-specific autoimmune disease, bullous pemphigoid, using antibodies generated against the hemidesmosomal antigen, BP180. J Clin Invest 92(5):2480–2488
33. Liu Z, Diaz LA, Swartz SJ, Troy JL, Fairley JA, Giudice GJ (1995) Molecular mapping of a pathogenically relevant BP180 epitope associated with experimentally induced murine bullous pemphigoid. J Immunol 155(11):5449–5454
34. Liumbruno GM, Centoni PE, Molfettini P, Ceretelli S, Ceccarini M, Bachini L, Pomponi A, Bagnoni G, Vitolo M, Eberle O, Biondi A, Sodini ML (2006) Lymphocytapheresis in the treatment of psoriasis vulgaris. J Clin Apher 21(3):158–164
35. Luftl M, Stauber A, Mainka A, Klingel R, Schuler G, Hertl M (2003) Successful removal of pathogenic autoantibodies in pemphigus by immunoadsorption with a tryptophan-linked polyvinylalcohol adsorber. Br J Dermatol 149(3):598–605
36. Marazza G, Pham HC, Scharer L, Pedrazzetti PP, Hunziker T, Trueb RM, Hohl D, Itin P, Lautenschlager S, Naldi L, Borradori L (2009) Incidence of bullous pemphigoid and pemphigus in Switzerland: a 2-year prospective study. Br J Dermatol 161(4):861–868
37. Marn Pernat A, Buturovic-Ponikvar J, Svigelj V, Ponikvar R (2009) Guillain–Barre syndrome treated by membrane plasma exchange and/or immunoadsorption. Ther Apher Dial 13(4):310–313
38. Matic G, Hofmann D, Winkler R, Tiess M, Michelsen A, Schneidewind JM, Hebestreit G, Keysser M, Muller W, Kinze EM, Ramlow W (2000) Removal of immunoglobulins by a protein A versus an antihuman immunoglobulin G-based system: evaluation of 602 sessions of extracorporeal immunoadsorption. Artif Organs 24(2):103–107

39. Mitsuyama K, Sata M (2009) Therapeutic leukocytapheresis in inflammatory bowel disease: clinical efficacy and mechanisms of action. Cytotherapy 11(2):229–237
40. Mulyowa GK, Jaeger G, Kabakyenga J, Brocker EB, Zillikens D, Schmidt E (2006) Autoimmune subepidermal blistering diseases in Uganda: correlation of autoantibody class with age of patients. Int J Dermatol 45(9):1047–1052
41. Nagel A, Hertl M, Eming R (2009) B-cell-directed therapy for inflammatory skin diseases. J Invest Dermatol 129(2):289–301
42. Naito K, Morioka S, Ogawa H (1982) The pathogenic mechanisms of blister formation in bullous pemphigoid. J Invest Dermatol 79(5):303–306
43. Niedermeier A, Eming R, Pfutze M, Neumann CR, Happel C, Reich K, Hertl M (2007) Clinical response of severe mechanobullous epidermolysis bullosa acquisita to combined treatment with immunoadsorption and rituximab (anti-CD20 monoclonal antibodies). Arch Dermatol 143(2):192–198
44. Norda R, Stegmayr BG (2003) Therapeutic apheresis in Sweden: update of epidemiology and adverse events. Transfus Apher Sci 29(2):159–166
45. Ogata K, Yasuda K, Matsushita M, Kodama H (1999) Successful treatment of adolescent pemphigus vulgaris by immunoadsorption method. J Dermatol 26(4):236–239
46. Ohji S, Nomura K (2008) The indication of steroid pulse therapy and apheresis therapy for multiple sclerosis. Nippon Rinsho 66(6):1127–1132
47. Pfutze M, Eming R, Kneisel A, Kuhlmann U, Hoyer J, Hertl M (2009) Clinical and immunological follow-up of pemphigus patients on adjuvant treatment with immunoadsorption or rituximab. Dermatology 218(3):237–245
48. Pisanti S, Sharav Y, Kaufman E, Posner LN (1974) Pemphigus vulgaris: incidence in Jews of different ethnic groups, according to age, sex, and initial lesion. Oral Surg Oral Med Oral Pathol 38(3):382–387
49. Poullin P, Announ N, Mugnier B, Guis S, Roudier J, Lefevre P (2005) Protein A-immunoadsorption (Prosorba column) in the treatment of rheumatoid arthritis. Joint Bone Spine 72(2):101–103
50. Rech J, Hueber AJ, Kallert S, Leipe J, Kalden JR, Beck M, Schett G, Schulze-Koops H (2008) Remission of demyelinating polyneuropathy with immunoadsorption, low dose corticosteroids and anti-CD20 monoclonal antibody. Ther Apher Dial 12(3):205–208
51. Ronspeck W, Brinckmann R, Egner R, Gebauer F, Winkler D, Jekow P, Wallukat G, Muller J, Kunze R (2003) Peptide based adsorbers for therapeutic immunoadsorption. Ther Apher Dial 7(1):91–97
52. Roujeau JC, Revuz J, Touraine R, Joneau-Fabre M, Mannoni P (1979) Cortico-resistant bullous pemphigoid: favorable results with plasmapheresis. Nouv Presse Med 8(41):3362
53. Roujeau JC, Andre C, Joneau Fabre M, Lauret P, Flechet ML, Kalis B, Revuz J, Touraine R (1983) Plasma exchange in pemphigus: uncontrolled study of ten patients. Arch Dermatol 119(3):215–221
54. Sakai Y, Sakai S, Otsuka T, Ohno D, Murasawa T, Munakata K, Mizuno K (2009) Efficacy of high-throughput leukocytapheresis for rheumatoid arthritis with a reduced response to infliximab. Ther Apher Dial 13(3):179–185
55. Sawada K, Muto T, Shimoyama T, Satomi M, Sawada T, Nagawa H, Hiwatashi N, Asakura H, Hibi T (2003) Multicenter randomized controlled trial for the treatment of ulcerative colitis with a leukocytapheresis column. Curr Pharm Des 9(4):307–321
56. Schiltz JR, Michel B (1976) Production of epidermal acantholysis in normal human skin in vitro by the IgG fraction from pemphigus serum. J Invest Dermatol 67(2):254–260
57. Schmidt E, Obe K, Brocker EB, Zillikens D (2000) Serum levels of autoantibodies to BP180 correlate with disease activity in patients with bullous pemphigoid. Arch Dermatol 136(2):174–178
58. Schmidt E, Klinker E, Opitz A, Herzog S, Sitaru C, Goebeler M, Mansouri Taleghoni B, Brocker EB, Zillikens D (2003) Protein A immunoadsorption: a novel and effective adjuvant treatment of severe pemphigus. Br J Dermatol 148(6):1222–1229
59. Schmidt E, Brocker EB, Goebeler M (2008) Rituximab in treatment-resistant autoimmune blistering skin disorders. Clin Rev Allergy Immunol 34(1):56–64
60. Schmidt E, Goebeler M, Zillikens D (2009) Rituximab in severe pemphigus. Ann N Y Acad Sci 1173(9):683–691
61. Schmidt E, Zillikens D (2009) Research in practice: diagnosis of subepidermal autoimmune bullous disorders. J Dtsch Dermatol Ges 7(4):296–300
62. Schoen H, Foedinger D, Derfler K, Amann G, Rappersberger K, Stingl G, Volc-Platzer B (1998) Immunoapheresis in paraneoplastic pemphigus. Arch Dermatol 134(6):706–710
63. Shimanovich I, Herzog S, Schmidt E, Opitz A, Klinker E, Brocker EB, Goebeler M, Zillikens D (2006) Improved protocol for treatment of pemphigus vulgaris with protein A immunoadsorption. Clin Exp Dermatol 31(6):768–774
64. Shimanovich I, Nitschke M, Rose C, Grabbe J, Zillikens D (2008) Treatment of severe pemphigus with protein A immunoadsorption, rituximab and intravenous immunoglobulins. Br J Dermatol 158(2):382–388
65. Shimanovich I, Bohmke AK, Westermann L, Kramer J, Zillikens D, Schmidt E (2009) Successful treatment of severe pemphigus with the combination of immunoadsorption and rituximab. J Invest Dermatol 129:S97
66. Sitaru C, Kromminga A, Hashimoto T, Brocker EB, Zillikens D (2002) Autoantibodies to type VII collagen mediate Fcgamma-dependent neutrophil activation and induce dermal-epidermal separation in cryosections of human skin. Am J Pathol 161(1):301–311
67. Sitaru C, Schmidt E, Petermann S, Munteanu LS, Brocker EB, Zillikens D (2002) Autoantibodies to bullous pemphigoid antigen 180 induce dermal–epidermal separation in cryosections of human skin. J Invest Dermatol 118(4):664–671
68. Sitaru C, Mihai S, Otto C, Chiriac MT, Hausser I, Dotterweich B, Saito H, Rose C, Ishiko A, Zillikens D (2005) Induction of dermal-epidermal separation in mice by passive transfer of antibodies specific to type VII collagen. J Clin Invest 115(4):870–878
69. Sitaru C, Chiriac MT, Mihai S, Buning J, Gebert A, Ishiko A, Zillikens D (2006) Induction of complement-fixing autoantibodies against type VII collagen results in subepidermal blistering in mice. J Immunol 177(5):3461–3468
70. Soerensen H, Schneidewind-Mueller JM, Lange D, Kashiwagi N, Franz M, Yokoyama T, Ramlow W (2006) Pilot clinical study of Adacolumn cytapheresis in patients with systemic lupus erythematosus. Rheumatol Int 26(5):409–415
71. Sondergaard K, Carstens J, Jorgensen J, Zachariae H (1995) The steroid-sparing effect of long-term plasmapheresis in pemphigus. Acta Derm Venereol 75(2):150–152
72. Tan-Lim R, Bystryn JC (1990) Effect of plasmapheresis therapy on circulating levels of pemphigus antibodies. J Am Acad Dermatol 22(1):35–40
73. Turner MS, Sutton D, Sauder DN (2000) The use of plasmapheresis and immunosuppression in the treatment of pemphigus vulgaris. J Am Acad Dermatol 43(6):1058–1064
74. Wallukat G, Muller J, Hetzer R (2002) Specific removal of beta1-adrenergic autoantibodies from patients with idiopathic dilated cardiomyopathy. N Engl J Med 347(22):1806
75. Waschke J (2008) The desmosome and pemphigus. Histochem Cell Biol 130(1):21–54
76. Wohrl S, Geusau A, Karlhofer F, Derfler K, Stingl G, Zillikens D (2003) Pemphigoid gestationis: treatment with immunoapheresis. J Dtsch Dermatol Ges 1(2):126–130

77. Woodley DT, Ram R, Doostan A, Bandyopadhyay P, Huang Y, Remington J, Hou Y, Keene DR, Liu Z, Chen M (2006) Induction of epidermolysis bullosa acquisita in mice by passive transfer of autoantibodies from patients. J Invest Dermatol 126(6):1323–1330
78. Zillikens D, Derfler K, Eming R, Fierlbeck G, Goebeler M, Hertl M, Hofmann SC, Karlhofer F, Kautz O, Nitschke M, Opitz A, Quist S, Rose C, Schanz S, Schmidt E, Shimanovich I, Michael M, Ziller F (2007) Recommendations for the use of immunoapheresis in the treatment of autoimmune bullous diseases. J Dtsch Dermatol Ges 5(10):881–887

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79. Abreu-Velez AM, Howard MS, Hashimoto K, Hashimoto T (2009) Autoantibodies to sweat glands detected by different methods in serum and in tissue from patients affected by a new variant of endemic pemphigus foliaceus. Arch Dermatol Res 301:711–718
80. Gaines E, Werth VP (2008) Development of outcome measures for autoimmune dermatoses. Arch Dermatol Res 300:3–9
81. Leighty L, Li N, Diaz LA, Liu Z (2007) Experimental models for the autoimmune and inflammatory blistering disease: bullous pemphigoid. Arch Dermatol Res 299:417–422
82. Nancy AL, Yehuda S (2009) Prediction and prevention of autoimmune skin disorders. Arch Dermatol Res 301:57–64