

Review Article

Immunoadsorption in Dermatology

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Abstract: Immunoadsorption (IA) has been successfully used in a large variety of autoantibody-mediated disorders. In dermatology, IA is increasingly applied as adjuvant treatment for severe and/or refractory autoimmune bullous diseases. These disorders are characterized by autoantibodies against structural proteins of the skin and/or mucous membranes and include, among others, pemphigus vulgaris, pemphigus foliaceus, and bullous pemphigoid. Autoimmune blistering diseases are associated with a high mortality (pemphigus) or morbidity (bullous pemphigoid) and in particular in pemphigus diseases, treatment is challenging.

The pathogenetic role of autoantibodies in most of the immunobullous diseases has been clearly demonstrated, therefore, removal of these autoantibodies is a rational therapeutic approach. IA has been shown to effectively lower the serum autoantibodies and to lead to rapid clinical responses. Most recently, IA has been successfully applied in patients with severe atopic dermatitis and high total serum IgE levels. Here, the different treatment protocols, clinical efficacy, and adverse events are summarized. **Key Words:** Atopic dermatitis, Autoantibody, Immunoadsorption, Pemphigoid, Pemphigus, Treatment.

Immunoadsorption (IA) has been successfully used in various autoantibody-mediated diseases such as systemic lupus erythematosus, myasthenia gravis, Guillain-Barré-syndrome, dilated cardiomyopathy, rheumatoid arthritis, idiopathic thrombocytopenic purpura, hemophilia with inhibitors, dermatomyositis, ABO-incompatible kidney transplantation, and autoimmune bullous disorders (1,2). The active principle of most available adsorber types is the non-specific removal of immunoglobulins (Ig) (3). Since the pathogenetic relevance of autoantibodies could be defined in various diseases, disease-specific adsorbers have been developed, for example, in dilated cardiomyopathy (β 1-adrenergic receptors), systemic lupus erythematosus (C1q) and to ABO blood group antigens (4–6). Beside its ability to selectively remove Ig from the patients' circulation, IA also clears immune complexes and comprises cytopheresis. By cytopheresis, inflammatory cells (granu-

locytes, monocytes, or lymphocytes) or platelets are depleted from the peripheral blood. Cytopheresis has been successfully applied in rheumatoid arthritis, systemic lupus erythematosus, and inflammatory bowel disease (7–9). In dermatology, patients with psoriasis and pyoderma gangrenosum have been successfully subjected to leukocytopheresis (10,11).

In the present review, the application of IA in autoimmune blistering diseases and atopic dermatitis is discussed.

AUTOIMMUNE BULLOUS DISEASES

Autoimmune bullous diseases represent a heterogeneous group of disorders associated with circulating autoantibodies against distinct adhesion molecules of the skin or/and mucosa. According to the level of split formation, the disorders can be divided into two groups: the intraepidermal blistering pemphigus and the subepidermal blistering pemphigoid diseases (12). The first group includes pemphigus vulgaris (PV), pemphigus foliaceus (PF), and paraneoplastic pemphigus.

Pemphigus vulgaris, a potentially fatal condition, is characterized by erosions of the mucous membranes

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and/or blisters and erosions of the skin. In contrast, pemphigus foliaceus is restricted to the skin and presents with erosions and hyperkeratotic scales. Paraneoplastic pemphigus is obligatorily associated with a neoplasia and a hemorrhagic stomatitis and a multiform-like exanthema is found (13,14). Remarkably, the first patient treated with IA in 1998 suffered from paraneoplastic pemphigus. He was sufficiently treated with a total of 10 IA combined with systemic glucocorticoids and surgical removal of the underlying cancer (15).

In pemphigus, IgG autoantibodies are directed against the desmosomal structural proteins, namely desmoglein 1 and 3 (Dsg 1 and 3); additionally, in paraneoplastic pemphigus, proteins of the plakin family are targeted. The binding of autoantibodies results in the loss of epidermal adhesive properties and clinically, in blisters and erosions. The pathogenic importance of pemphigus autoantibodies could be clearly demonstrated both in vitro and in vivo (16–18), for example, the injection of patients' sera and purified IgG in mice reproduced the major immunopathological and clinical features of pemphigus, that is, binding of autoantibodies to the epidermal desmosomes, loss of cell-cell adhesion (acantholysis), and clinical blisters (19,20).

The pemphigoid group usually presents with tense blisters, urticarial plaques, and prurigo-like eczematous lesions. In central Europe and the UK, bullous pemphigoid is the most common dermatosis, followed by mucous membrane pemphigoid, pemphigoid gestationis, linear IgA disease, anti-p200 pemphigoid, and epidermolysis bullosa acquisita (21–23). In this group, type XVII collagen, also termed BP180 and BP230 (in bullous pemphigoid, mucous membrane pemphigoid, pemphigoid gestationis, and linear IgA disease), laminin 332 and $\alpha 6\beta 4$ integrin (in mucous membrane pemphigoid), laminin $\gamma 1$ (in anti-p200 pemphigoid), and type VII collagen (in epidermolysis bullosa acquisita) are targeted (12). The pathogenic effect of autoantibodies against BP180, type VII collagen, and laminin 332 has been univocally shown both in vitro and in vivo (24–31). In dermatitis herpetiformis, immune complexes containing IgA and epidermal transglutaminase as well as autoantibodies against endomysium, tissue transglutaminase and epidermal transglutaminase are responsible for clinical signs (32,33).

Among autoimmune bullous diseases, treatment of patients with pemphigus, mucous membrane pemphigoid, and epidermolysis bullosa is most challenging (12,34–39). In these diseases, systemic corticosteroids (0.5–2.0 mg prednisolone/kg per day) are the therapeutic backbone and are usually com-

bined with additional immunosuppressants or immunomodulants such as azathioprine, mycophenolate mofetil, cyclophosphamide, and dapsone. However, a significant part of the mortality and morbidity is related to side-effects and in a considerable number of patients, disease activity cannot be controlled by conventional therapy. In these cases, adjuvant high-dose intravenous immunoglobulins and the anti-CD20 antibody rituximab have been successfully applied (40–49). For the use of both regimens in the treatment of immunobullous diseases, experts' opinions have been published (50,51). Due to the clear evidence for the pathogenic role of autoantibodies in the major autoimmune blistering disorders, IA is a tempting therapeutic option.

IMMUNOADSORPTION IN PEMPHIGUS

At present, various immunoadsorption systems and protocols are used to reduce the circulating autoantibodies in plasma. Specific pemphigus anti-desmoglein IgG autoantibody levels decline by about 75% within a single IA procedure with the reusable systems Immunosorba and Therasorb (1). Interestingly, due to most likely re-diffusion from the tissue and, to a lesser extent, to further production, autoantibody levels increase again to 40% of the initial values on the next day. When IA is used on three consecutive days (one cycle), autoantibody levels were reduced by 95% compared with pre-IA levels (1). In contrast, other data indicate that the Globaffin adsorber system effectively reduces the same antibodies by an average of 50–70% per IA cycle consisting of four treatments (52). A tryptophan adsorber achieved a 30% reduction (53). No differences in IgG depletion rates between the protein A-based and the anti-human Ig-based reusable systems have been demonstrated (54). To obtain durable effects of the rapid decrease in circulating autoantibodies and immune complexes, IA has to be combined with existing standard immunosuppressant treatment. By this approach, one month after the first IA, autoantibodies decreased by nearly 80%. After 6 and 12 months, a reduction by 91% and 89%, respectively, were achieved (1).

To date 82 pemphigus patients, 76 with pemphigus vulgaris, 13 with pemphigus foliaceus, and one with paraneoplastic pemphigus were reported to have been subjected to IA (Table 1) (15,52,53,55–58,60,63–66). In most patients, reusable systems on the basis of protein A (Immunosorba) were applied (41 patients) followed by the Globaffin adsorber column, containing the peptide PGAM146 (12 patients), the Therasorb adsorber system with polyclonal

TABLE 1. Immunoadsorption in autoimmune bullous skin diseases: clinical response and adverse events

Diagnosis	No. patients (reference)	Adsorbent/No. adsorptions	Clinical responses	Serious adverse events	Follow-up† (months)
Paraneoplastic pemphigus	1 (15)	Therasorb/10	CR	None	Not detailed
Pemphigus vulgaris	1 (55)	IM TR360/11	CliR	None	8
	4 (56)	Immunosorb/12–17	CR (n = 1), CliR (n = 3)	Single episode of hypotension and bradycardia (n = 1)	4–10
	7 (53)	IM TR350/2	PR (n = 7)	Anaphylaxis grade III during IA	6
	1 (57)	Immunosorb/19	PR	None	30
	9 (58)	Immunosorb/10–40	CR (n = 1), CliR (n = 6), PR (n = 1)	Perforating diverticulitis	18–38
	4 (59)	Globalfin 7 4–16	CliR (n = 2), PR (n = 2)	None	9
	5 (60)	Immunosorb/6–17	CR (n = 1), CliR (n = 4)	<i>Staphylococcus aureus</i> sepsis, <i>P. carinii</i> pneumonia, pulmonary embolism, deep venous thrombosis, herpes zoster infection	13–30
	1 (61)	Therasorb/25	CliR	None	20
	1 (62)	Immunosorb/5	CR	Herpes zoster infection	22
	1 (62)	Immunosorb/9	CliR	None	5
	6 (63)	Globalfin/4–12	CliR (n = 3), PR (n = 3)	Myocardial infarction	12
	1 (64)	Therasorb/12	CR	None	12
	10 (65)	Globalfin/8–16	CliR (n = 6)	None	12
			PR (n = 1)		
			Relapse (n = 1)		
	17 (66)	Immunosorb/Therasorb/12–18	CR (n = 6)	<i>Staphylococcus aureus</i> sepsis, Herpes simplex virus infection	11–43
			CliR (n = 8)		
			PR (n = 2)		
Pemphigus foliaceus	6 (66)	Immunosorb/Therasorb/12–18	CR (n = 1)	None	11–43
			CliR (n = 4)		
			PR (n = 1)		
	1 (56)	Immunosorb/18	CR	Deep venous thrombosis	27
	2 (53)	IM TR350/2	PR (n = 2)	None	6
	2 (59)	Globalfin/4	CliR, PR	None	9
	2 (60)	Immunosorb/8, 14	CliR	None	20, 25
Bullous pemphigoid	2 (67)	Selesorb/4, 6	PR (n = 2)	None	3
	2 (68)	IM TR350/2	CliR	<i>Staphylococcus aureus</i> sepsis	3
	1 (69)	Immunosorb/12	CliR	None	19
Mucous membrane pemphigoid (anti-laminin 332)					
Pemphigoid gestationis	1 (70)	Therasorb/6	PR	None	7
	1 (64)	Therasorb/15	CR	None	2
Anti-p200 pemphigoid	1 (71)	IM TR350/2	CR	None	4
Epidermolysis bullosa acquisita	1 (72)	Immunosorb/37	CliR	None	26
	2 (73)	Globalfin/2	PR (n = 1)	None	8, 12
	1 (74)	Immunosorb/7	CR	None	4

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). †After first immunoadsorption (IA). From Schmidt et al. (1). With kind permission from Springer Science and Business Media.

sheep antibodies coupled to a sepharose matrix (10 patients), and the single use tryptophan adsorber IM TR350 (12 patients).

With regard to the different adsorber systems applied in combination with corticosteroids and the other immunosuppressants, different cohort studies with up to 23 patients have been published documenting the effective use of IA in the treatment of severe and recalcitrant pemphigus. Most studies showed a sharp decline in circulating autoantibody levels after each IA procedure in conjunction with clinical improvement of cutaneous and mucosal erosions. However, in about 26% of patients, relapses were noted after an average time of 11–43 (mean 29) months after the initial IA in combination with rituximab (52,56,60,63,66). Interestingly, Kwon et al. showed that in a considerable percentage of pemphigus patients in clinical remission, high serum levels of autoantibodies persist. These autoantibodies appear to be non-pathogenic and to have replaced the initial pathogenic autoantibody fraction following an epitope spreading process (65,75).

To date, about eight different IA protocols have been applied in pemphigus. In all protocols, IA was used in an adjuvant manner in combination with systemic corticosteroids and a second immunosuppressive drug, usually azathioprine, mycophenolate mofetil or cyclophosphamide. In most treatment resistant patients, the preceding medication was continued when IA was initiated. In recent studies, IA was given in conjunction with rituximab to combine the rapid effect of IA with a sustained long-term effect of rituximab.

In the first protocol in 2003, IA was applied in five refractory pemphigus patients with a relatively low dose of methylprednisolone (0.5 mg/kg per day tapering) and one single cycle of i.v. cyclophosphamide (500 mg) and i.v. dexamethasone (100 mg on 3 consecutive days). IA was applied all together 19 times (after the three initial IAs on consecutive days, four times in weekly intervals, four times in 2-weekly, 3-weekly, and 4-weekly, respectively) (56). To optimize the response rates, Shimanovich et al. then used the same IA protocol, but in combination with a conventional pemphigus treatment comprising methylprednisolone at an initial dose of 2.0 mg/kg per day combined with azathioprine or mycophenolate mofetil (2 g per day). In the follow-up of 5 years, five of nine patients remained in clinical remission and one patient died 2 years after initiation of the IA protocol (58). Subsequently, Shimanovich et al. introduced rituximab into the protocol and performed IA more vigorously in the initial phase. In four of the eight treated patients, however, severe adverse reac-

tions were noticed, that is, bacterial and viral infections as well as thromboembolic events (1,60). Additional IA protocols were published using tryptophan-based and Globaffin adsorbers (52,53).

Current protocols

In our most recent protocol, to maximize the effect of IA, one IA cycle on three consecutive days was followed by additional cycles after 3 weeks and then in 4-week intervals until lesions had healed by 90%. In 17 pemphigus patients, protein A IA (Immunosorba) was performed, in six patients the Therasorb adsorber system was used (66). To decrease the rate of severe side-effects encountered in the previous protocol, the high-dose oral prednisolone was replaced by i.v. dexamethasone pulses. One pulse comprised three infusions on three consecutive days and was given in conjunction with IA. When IA was omitted, intervals were stretched to up to 8 weeks according to disease activity. Rituximab (1 g) was given on days 4 and 25 together with daily azathioprine (2.5 mg/kg per day with normal Thiopurine methyltransferase [TPMT] activity) or mycophenolate mofetil (2 g/day). Already between the first two IA cycles, autoantibody levels decreased by more than 50%. After 3 months, nine (39%) patients were free of pemphigus lesions, three (13%) had minimal disease, and in the remaining 11 (48%) patients, partial remission on therapy was achieved. After 8.9 months of protocol treatment, 22 (96%) patients showed a complete remission on therapy (Fig. 1). In about a quarter of patients, relapses occurred between 4 and 24 months after initiation of the protocol. Re-administration of rituximab or the full protocol resulted in complete remission on/off-therapy in 80% (four of five) of the patients. The overall complete remission rate was 91% after a total follow-up period of up to 50 months with a mean follow-up time of 33 months (66). Serious adverse events were observed in two (9%) patients including a *Staphylococcus aureus* sepsis due to an infected central intravenous line and an extensive *Herpes simplex virus* infection (66). The rate of severe adverse events is in line with pemphigus patients treated with rituximab and additional immunosuppressants (41). Based on these data, currently, all patients with severe and refractory pemphigus are treated according to this protocol in our department.

Subsequently, Behzad et al. reported on 10 pemphigus patients in whom IA (Globaffin) was also combined with rituximab. Two to four cycles consisting of four treatments at 4-week intervals were combined with systemic corticosteroids (1 mg/kg per day, initially) and azathioprine, mycophenolate



FIG. 1. Patient with pemphigus foliaceus subjected to the combination of immunoadsorption, rituximab, i.v. dexamethasone pulses, and azathioprine according to the current protocol (1,66) before initiation of the protocol (a) and 5 weeks (b) and 11 weeks later (c).

mofetil, cyclophosphamide, or dapsone. Rituximab was administered not before 1–6 months after the first IA cycle. Three months after combined IA and rituximab treatment, two thirds of the patients were in complete remission on therapy. After 6 and 12 months, 80% and 75% of patients showed complete remissions, respectively (65).

Prospective controlled multicenter study

To explore efficacy and adverse events of IA in pemphigus, a prospective controlled multicenter study was initiated supported by the program “Clinical Studies” of the German Research Council (DFG). The trial involves 25 study centers and compares the “best medical treatment”, that is, prednisolone 1.0 mg/kg per day plus azathioprine (1.5–2.5 mg/kg per day) or mycophenolate mofetil (2 g/day)/mycophenolate sodium (1440 mg/day) in case of intolerance to azathioprine with the same regimen in conjunction with IA. IA is performed on four consecutive days (day 1–4 comprising one cycle) followed by the second cycle on days 22–24. Depending on the

clinical response, two additional cycles may be given in 3-week intervals (Fig. 2). The major inclusion criteria are summarized in the same figure. The primary endpoint is the time to clinical remission, defined as complete healing of blistering and erosive lesions. Secondary endpoints include: (i) the duration of clinical remission; (ii) number of patients in remission after 6 and 12 months; (iii) cumulative doses of systemic corticosteroids and immunosuppressants until clinical remission; (iv) decrease in circulating desmoglein 1-/3-reactive IgG autoantibodies after 3, 6, 9 and 12 months; and (v) time until prednisolone and azathioprine or mycophenolate mofetil/sodium is omitted, respectively. The final analysis is expected in 2013 and will certainly help to understand the potential of IA in pemphigus.

IMMUNOADSORPTION IN PEMPHIGOID DISEASES

Immunoadsorption has also been successfully used in patients with refractory bullous pemphigoid

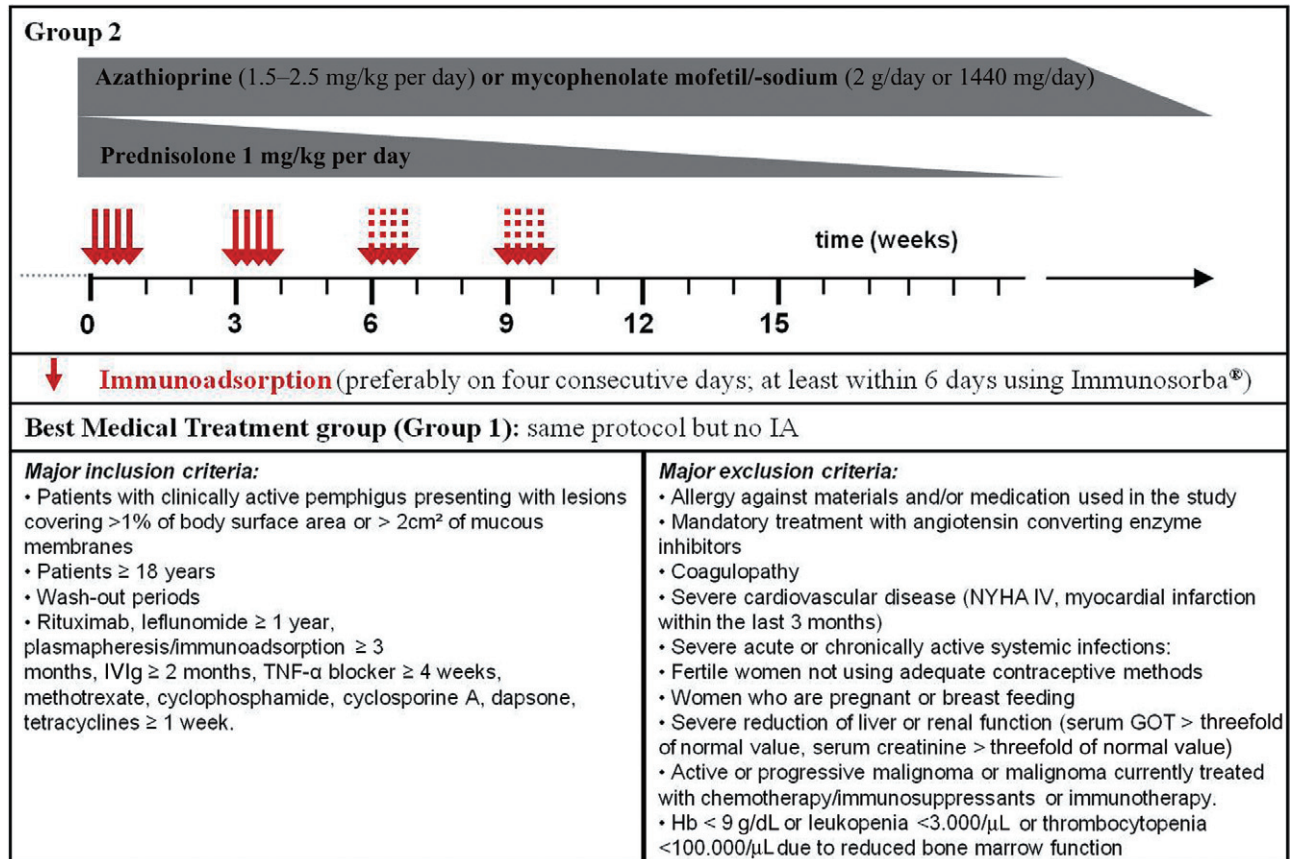


FIG. 2. Schematic diagram of the treatment protocol and major eligibility criteria of the current controlled prospective multicenter study to heal pemphigus. Immunoadsorption (IA) (arrows) is performed on four consecutive days, representing one treatment cycle. A total of two to four IA cycles, depending on clinical response, will be performed in 3-week intervals plus prednisolone at an initial dose of 1 mg/kg per day plus azathioprine (1.5–2.5 mg/kg per day; according to serum Thiopurine methyltransferase [TPMT] activity) or mycophenolate mofetil (2 g/day)/mycophenolate sodium (1440 mg/day). Reduction of prednisolone will be performed, according to the protocol, by 25% when no lesions have formed for 1 or 2 weeks, respectively. Eight weeks after prednisolone has been omitted the other immunosuppressants will be reduced every 8 weeks. IVIg intravenous immunoglobulin; TNF-α, tumor necrosis factor-α.

($n = 4$), epidermolysis bullosa acquisita ($n = 4$), pemphigoid gestationis ($n = 3$), mucous membrane pemphigoid ($n = 1$), and anti-p200 pemphigoid ($n = 1$) (59,64,67,68,70–74).

Bullous pemphigoid is the most common autoimmune bullous disease in Central Europe and the UK with an annual incidence of about 13 to 42 new cases per 1 million (21–23). Bullous pemphigoid frequently involves a premonitory stage with pruritic urticarial erythema and eczematous lesions followed by the classical bullous stage with tense blisters, erosions, and crusts (76). Bullous pemphigoid usually has a milder clinical course compared with pemphigus with a good response to high-potency topical corticosteroids, which are usually combined with dapsone, doxycycline, methotrexate, or azathioprine (76).

In two patients with bullous pemphigoid and high-serum levels of anti-BP180 autoantibodies (312 and 10 226 U/mL) who were unresponsive to

methylprednisolone (2 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), dapsone (1.5 mg/kg per day) and topical clobetasol propionate, respectively, two single IA on consecutive days using the tryptophan-linked matrix IM TR350 resulted in rapid clinical responses within 2 weeks after initiation of IA and sharp decreases of circulating autoantibodies (68). The other two patients with bullous pemphigoid were treated with four and six IA by the use of dextran sulfate conjugated cellulose columns (Selesorb) during a 2-week period. Skin lesions improved considerably and serum autoantibodies decreased (67) (Table 1).

In epidermolysis bullosa acquisita (EBA), IA was performed in four patients, two patients with the inflammatory variant and two with the mechanobullous subtype. In one case, remission on therapy was achieved after 37 IAs (Immunosorba) in combi-

nation with azathioprine and tapering doses of prednisolone over a period of 26 months. The other patient was sufficiently treated by seven cycles of IA in combination with azathioprine and prednisolone and additional administration of rituximab (72,74). In the subgroup of mechanobullous EBA, in one patient partial remission was observed after two courses of IA (Globaffin) in combination with rituximab and mycophenolate mofetil, while IA resulted in a stable disease in the other patient (73).

Pemphigoid gestationis arises in the second or third trimester or the immediate postpartum period and almost always spontaneously clears some weeks or few months after birth. Due to the natural self-limiting course of this disease, it is ideally suitable for IA. The removal of autoantibodies can in fact reduce clinical disease and does not necessarily need to be combined with immunosuppressants. In two pregnant women with pemphigoid gestationis, IA (Therasorb) resulted in dramatic clinical responses performing 6 and 15 IA treatments within 4 and 7 weeks, respectively. The good clinical condition could be maintained in both cases with low-dose corticosteroids until childbirth (64,70). In one patient, IA was applied 10 times in the post partum period because of a severe flare-up of the disease accompanied by very high serum levels of anti-BP180 antibodies despite high prednisolone dosage of 60 mg/day. Complete remission on therapy was induced within 8 weeks, prednisolone could be reduced to 7.5 mg/day within 5 weeks enabling the continuation of breast-feeding (59).

Recke et al. reported the first successful use of adjuvant immunoadsorption (Immunosorba) in

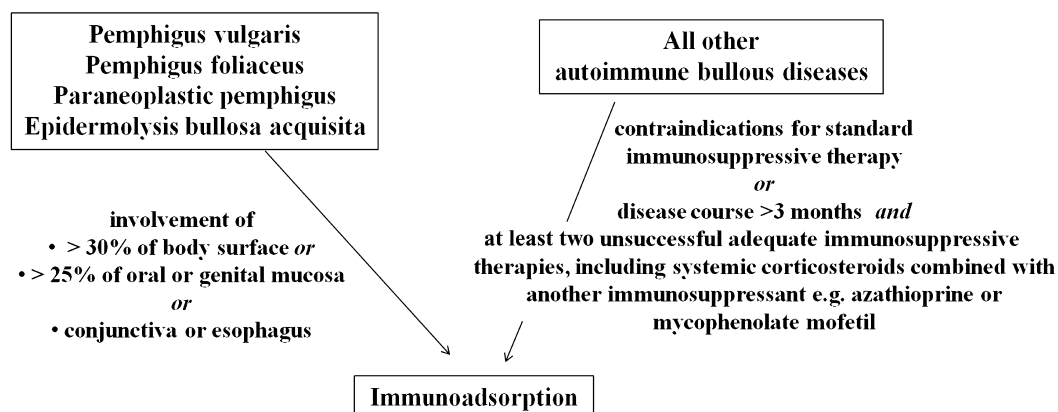
anti-laminin 332 mucous membrane pemphigoid that was previously treatment-refractory to i.v. dexamethasone-cyclophosphamide pulses combined with oral cyclophosphamide. IA was performed according to a protocol originally established for the treatment of pemphigus (1,66). After four cycles of IA and about 3 months after the second rituximab infusion, complete clinical remission was achieved. Concurrently, circulating anti-laminin 332 autoantibodies decreased by more than 90% and became undetectable 3 months later. Two months after initiating IA, oral cyclophosphamide was replaced by mycophenolate mofetil and cyclophosphamide pulses were omitted after a total of 10 cycles. No severe adverse events were observed (69).

EXPERT RECOMMENDATIONS ON THE USE OF IMMUNOADSORPTION IN IMMUNOBULLOUS DISEASES

Figure 3 summarizes the 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 (77).

IMMUNOADSORPTION IN ATOPIC DERMATITIS

Atopic dermatitis (AD) is a chronic, multifaceted, recurrent inflammatory skin disease that clinically presents with eczematous lesions. The major symptom is pruritus and dry, sensitive skin, which can



Induction phase:

3–4 treatments on consecutive days with high-affinity IgG adsorbers (e.g. Immunosorba®, Globaffin®, TheraSorb®) in selected cases, two consecutive treatments with low-affinity adsorbers

Subsequent treatments:

depending on disease activity: single procedure in weekly or longer intervals/repetition of 3–4 procedures every 3–4 week

FIG. 3. Algorithm for the use of immunoadsorption in autoimmune bullous skin disorders as recommended by German, Austrian, and Swiss physicians experienced in this therapy (77). Used with permission from John Wiley & Sons.



FIG. 4. Clinical response in a patient with refractory atopic dermatitis treated with immunoadsorption. Generalized papules and erosions on the trunk, neck and arms before (a) and 2 weeks after five daily immunoadsorptions (b).

impair patient quality of life. It has a multifactorial pathogenesis, which includes genetic components and environmental triggering factors. Patients with the extrinsic form of AD have been found to have increased serum IgE levels and high-affinity receptors for IgE. Thus, it can be assumed that depletion of the IgE antibodies may decrease clinical manifestations and disease activity (78).

Therapy with the anti-IgE antibody omalizumab has been shown to be effective in a subset of patients with recalcitrant AD, but extremely high total serum IgE levels may limit efficacy of this treatment (79,80). Very recently, we have investigated the effect of IA (Therasorb Ig) in 12 refractory patients with very high serum IgE levels (>4500 kU/L) and unresponsive to treatment with topical corticosteroids/calcineurin inhibitors, ultraviolet light therapy, systemic corticosteroids and cyclosporine A. Significant and continuous clinical improvement, measured by means of three different scoring tools (SCORAD, EASI and pruritus score) was achieved after five IA on consecutive days at week 1 and 5 (total 10 IA) (Fig. 4). Of note, only a short-term decrease of serum IgE, followed by fast recovery within 3 weeks after discontinuation of IA, was observed, whereas skin-bound IgE in the dermis and epidermis was reduced until the end of the observation period, 13 weeks after the initial IA. In parallel, decreased skin infiltration by inflammatory cells and an improved skin architecture were observed. One severe adverse event, a *Staphylococcus aureus* septicemia, originating from a central intravenous catheter was observed (81).

Most recently, a new IgE-specific adsorber (Therasorb IgE) has been approved. Data on the treatment

of severe AD and allergic asthma with pathologically elevated IgE levels are being awaited.

OUTLOOK

Immunoadsorption represents a rational, effective, and relatively safe treatment option in several autoimmune blistering diseases. It has been demonstrated that IA leads to a rapid clinical response by eliminating circulating immunoglobulins and immune complexes. IA may be applied as adjuvant first-line therapy in severe pemphigus or in refractory patients with immunobullous disorders. In order to combine the rapid clinical response of IA with a durable remission, IA may be applied in combination with the B-cell depleting agent rituximab. Further, IA has a relatively low incidence of adverse events with approximately $<1\%$ of all procedures (1). The results of the current prospective controlled trial in pemphigus will certainly yield important information on efficacy and safety of IA in pemphigus. Additional prospective controlled trials are needed to fully appreciate its therapeutic use in other immunobullous diseases and in AD.

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