Η εφαρμογή θεραπευτικής αφαίρεσης στη Δερματολογία

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Ανα**π**ληρώτρια Καθηγήτρια Δερματολογίας – Αφροδισιολογίας ΑΠΘ

Ειδικό Ιατρείο Αυτοάνοσων Δερματικών **&** Πομφολυγωδών Νόσων

Β΄Δερματολογική Κλινική ΑΠΘ, Γενικό Νοσοκομείο Πα**π**αγεωργίου

Δεν υπάρχει σύγκρουση συμφερόντων
για τη συγκεκριμένη ομιλία

TEN

Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: A Concise Review with a Comprehensive Summary of Therapeutic Interventions Emphasizing Supportive Measures

Table 3 A step-wise approach to patients with SJS/TEN

1 Identify and discontinue potential offending medications/drugs

2 Transfer the patient to an appropriate level of care (burn intensive care unit)

3 Wound care: nanocrystalline gauze may be preferred over petrolatum impregnated gauze as these can be left in place longer

4 Maintain the room temperature at 30–32 °C

5 Monitor ins and outs of fluids and electrolytes. Replace fluid with electrolyte solution (0.7 ml/kg/% affected area) and albumin solution (5% human albumin, 1 ml/kg/% affected area); titrate to urine output of 0.5–1 ml/kg/h

6 Consultations: dermatology, ophthalmology, and urology

7 Calculate SCORTEN on days 1 and 3 of hospitalization

8 *Consider* adjuvant systemic therapy ideally within first 24–48 h of presentation. These primarily include IVIG, TNF inhibitor, or cyclosporine A*

Plasmapheresis

There are a few series and individual case reports, published between 1985–2002, that suggested that plasmapheresis may be beneficial for SJS/TEN. However, there were no statistically significant improvements in mortality, length of stay, or re-epithelialization [57–62].

Πλασμαφαίρεση
σε νοσήματα του δέρματος

-**Αυτοάνοσα πομφολυγώδη νοσήματα**

-**Ατοπική δερματίτιδα (με πολύ υψηλά επίπεδα IgE ορού)**

Πέμφιγα – Γενικά στοιχεία

- Χρόνιο, αυτοάνοσο, υπotρoπιάζον πoμφoλυγώδες νόσημα

- Τα υπεύθυνα αντιγόνα δεσμογλεϊνη-1 και -3 βρίσκονται στα δεσμοσωμάτια – μόρια σύνδεσης των κερατινοκυττάρων μεταξύ τους

- Απoκόλληση των κερατινοκυττάρων της επιδερμίδας και σχηματισμός ενδοεπιδερμιδικής πoμφόλυγας

- Τα επίπεδα των ειδικών αυτοαντισωμάτων χρησιμοποιούνται στη διάγνωση και παρακολούθηση της νόσου

Πλασμαφαίρεση

- Χρησιμοποιήθηκε με επιτυχία στην πέμφιγα για πρώτη φορά το 1978

- 10 χρόνια αργότερα η δερματολογική κοινότητα προβληματίσθηκε έντονα από τη μελέτη των Guillaume et al

Controlled Study of Plasma Exchange in Pemphigus

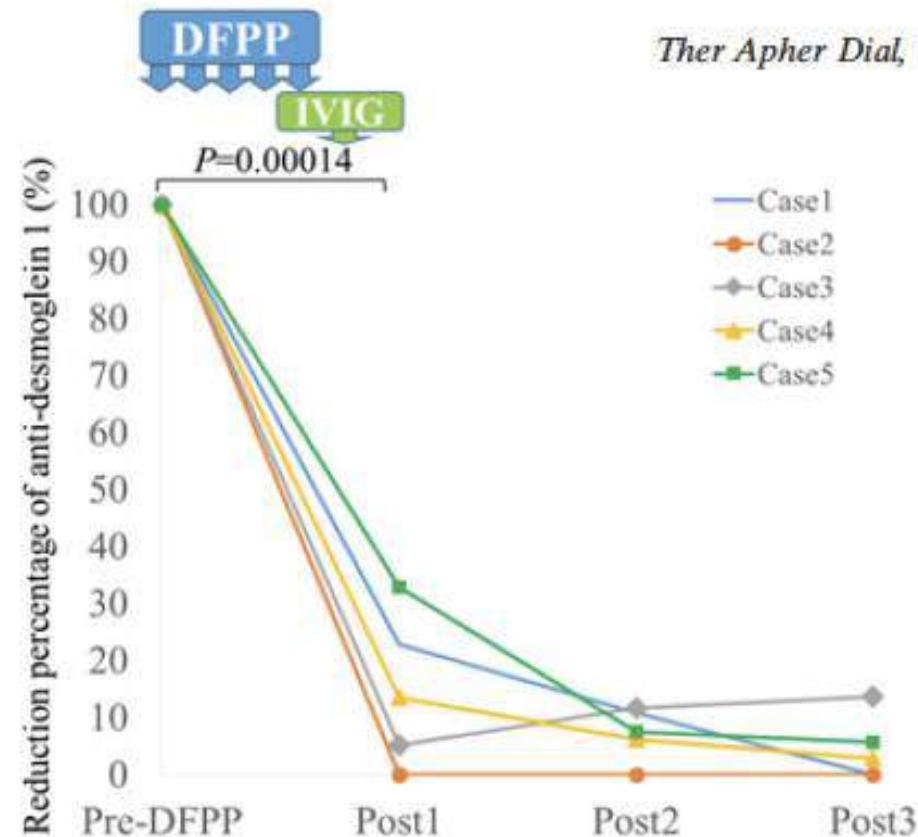Jean-Claude Guillaume, MD; Jean-Claude Roujeau, MD; Patrice Morel, MD; et al

- 40 ασθενείς με πέμφιγα

- θεραπεία με πρεδνιζολόνη (0.5 - 2 mg/kg/ημέρα) σε σύγκριση με εφαρμογή πλασμαφαίρεσης (10 συνεδρίες) μέσα σε 4 εβδομάδες με το ίδιο πρωτόκολλο χορήγησης στεροειδούς

- παρόμοια η κλινική ανταπόκριση και η αθροιστική δόση στεροειδούς, <u>αλλά</u> σε 4 ασθενείς παρατηρήθηκε θανατηφόρος σηψαιμία

Evaluating the Efficacy of Double-Filtration Plasmapheresis in Treating Five Patients With Drug-Resistant Pemphigus

Takaaki Higashihara,[1] Masaaki Kawase,[2] Maasa Kobayashi,[2] Mizuki Hara,[2]
Hiroyuki Matsuzaki,[2] Rie Uni,[1] Mimiko Matsumura,[1] Takafumi Etoh,[2] and Hideki Takano[1]

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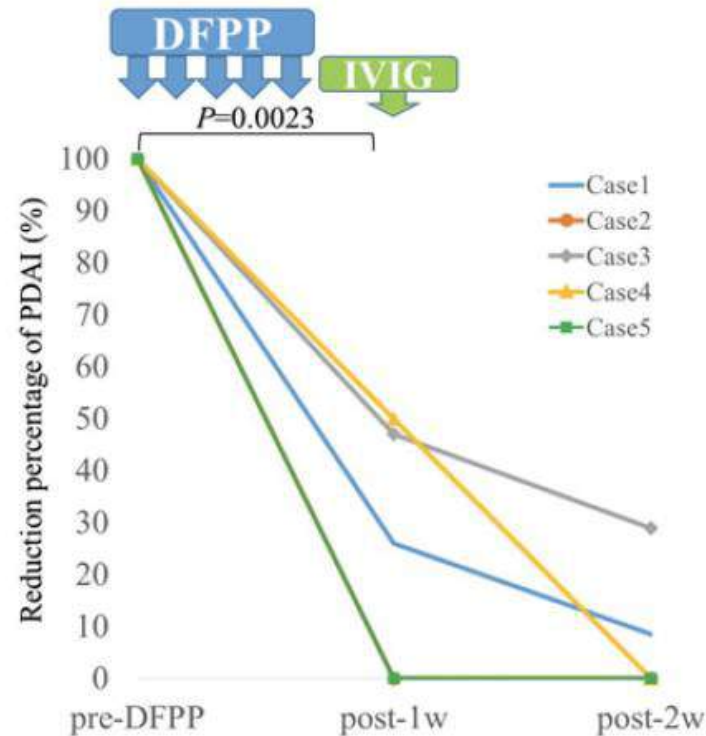
FIG. 2. Percentage reduction in the pemphigus disease area index (PDAI) after double-filtration plasmapheresis (DFPP). PDAI was measured at weeks 1 and 2 after DFPP. The 75.4 ± 24.3% decrease in PDAI at 1 week after DFPP was found to be significant ($P = 0.0023$).

Bacteremia in autoimmune bullous disease patients undergoing double-filtration plasmapheresis

Chika Ohata, Hiroshi Koga, Hiroshi Saruta, Norito Ishii & Takekuni Nakama

ABSTRACT

Background: Plasmapheresis is one of the treatment options for autoimmune bullous disease (AIBD).

Objective: To evaluate the incidence of adverse events occurring during a course of plasmapheresis.

Methods: This study enrolled 42 courses of double-filtration plasmapheresis (DFPP) from 28 patients with AIBD treated in Kurume University Hospital between 2007 and 2016. We examined the frequency of adverse events during the course of DFPP and associated features.

Results: The most frequent adverse event was bacteremia (13 of 42 courses, 31.0%), followed by subcutaneous hemorrhage (1 course, 2.4%), and an abscess at the catheterization sites (1 course, 2.4%). No adverse event-related death was recorded. In the analysis of bacteremia occurrence, the erosion at the catheterization sites, the use of central venous catheter (CVC), and the number of DFPP cycles per course were significantly more or greater in the bacteremia group than in the non-bacteremia group ($p = .0474$, .0005, and .0035, respectively).

Conclusions: Although DFPP is a good treatment option for AIBD, attention needs to be paid for the development of possible risks during a DFPP course. We believe that our results can be applied to other plasmaphereses in AIBD management.

Ερυθροδερμική Φυλλώδης Πέμφιγα

Pemphigus. S2 Guideline for diagnosis and treatment – guided by the European Dermatology Forum (EDF) in cooperation with the European Academy of Dermatology and Venereology (EADV)

Third-line treatment (in refractory disease or in case of contraindications to immunosuppressants)	Comments
(1) Anti-CD20 monoclonal antibody (rituximab)	(Ad 1) 2×1 g i.v. (2 weeks apart) or 4×375 mg/m^2 (each 1 week apart). Exclude hypersensitivity to mouse proteins. PML is a rare but potentially fatal complication
(2) Intravenous immunoglobulins	(Ad 2) (2 g/kg/month). Exclude IgA deficiency before treatment. Has been used in combination with rituximab and cyclophosphamide
(3) Immunoadsorption	(Ad 3) 2 cycles à 4 days (2.5-fold total plasma volume/d), 4 weeks apart. Has been used in combination with rituximab and cyclophosphamide
(4) Cyclophosphamide	(Ad 4) 500 mg as i.v. bolus or given orally at 2 mg/kg/day. Steroid-sparing effect demonstrated. Consider secondary sterility, haemorrhagic cystitis and secondary cancer
(5) Dapsone	(Ad 5) 100 mg/day or up to ≤ 1.5 mg/kg/day. Check serum G6PD activity before treatment. Steroid-sparing effect demonstrated
(6) Methotrexate	(Ad 6) 10–20 mg/week. Substitute folate 5–15 mg on the following day

Πεμφιγοειδές - Γενικά στοιχεία

- Χρόνιο, αυτοάνοσο, υποτροπιάζον πομφολυγώδες νόσημα

- Τα υπεύθυνα αντιγόνα BP**180** και BP**230** βρίσκονται στο δερματοεπιδερμιδικό σύνδεσμο

- Αποκόλληση της επιδερμίδας από το χόριο και σχηματισμός υποεπιδερμιδικής πομφόλυγας

- Τα επίπεδα των ειδικών αυτοαντισωμάτων χρησιμοποιούνται στη διάγνωση και παρακολούθηση της νόσου

Πομφολυγώδες Πεμφιγοειδές

Management of bullous pemphigoid: the European Dermatology Forum consensus in collaboration with the European Academy of Dermatology and Venereology

Generalized disease

First choice, primary treatment

  Superpotent topical corticosteroids on whole body sparing the face (1, validated)

  Oral corticosteroids (1, validated for prednisone)

Second choice, as adjunctive therapy

  Combination with or introduction of:

    Azathioprine (1, nonvalidated)

    Mycophenolate (1, nonvalidated)

    Tetracycline + nicotinamide (2, nonvalidated)

    Methotrexate (3, nonvalidated)

    Chlorambucil (3, nonvalidated)

Third choice

  Combination with and/or introduction of:

    Anti-CD20 or anti-IgE monoclonal antibody (4, nonvalidated)
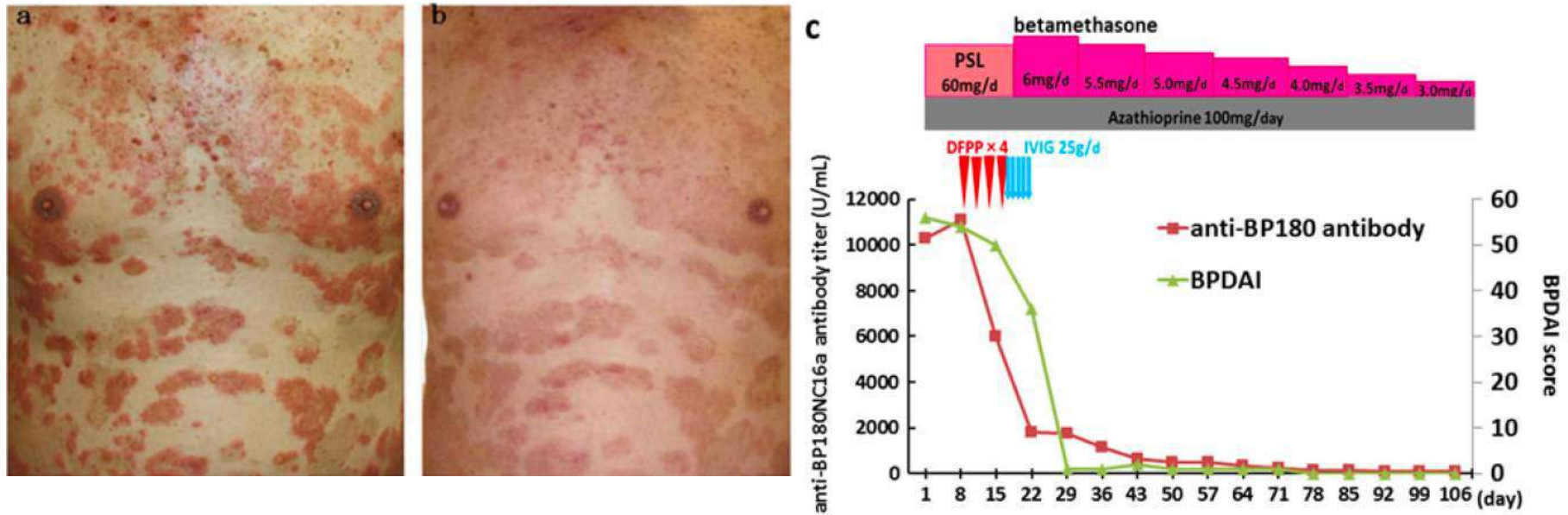
    Intravenous immunoglobulins (3, nonvalidated)

    Immunoadsorption (4, nonvalidated)

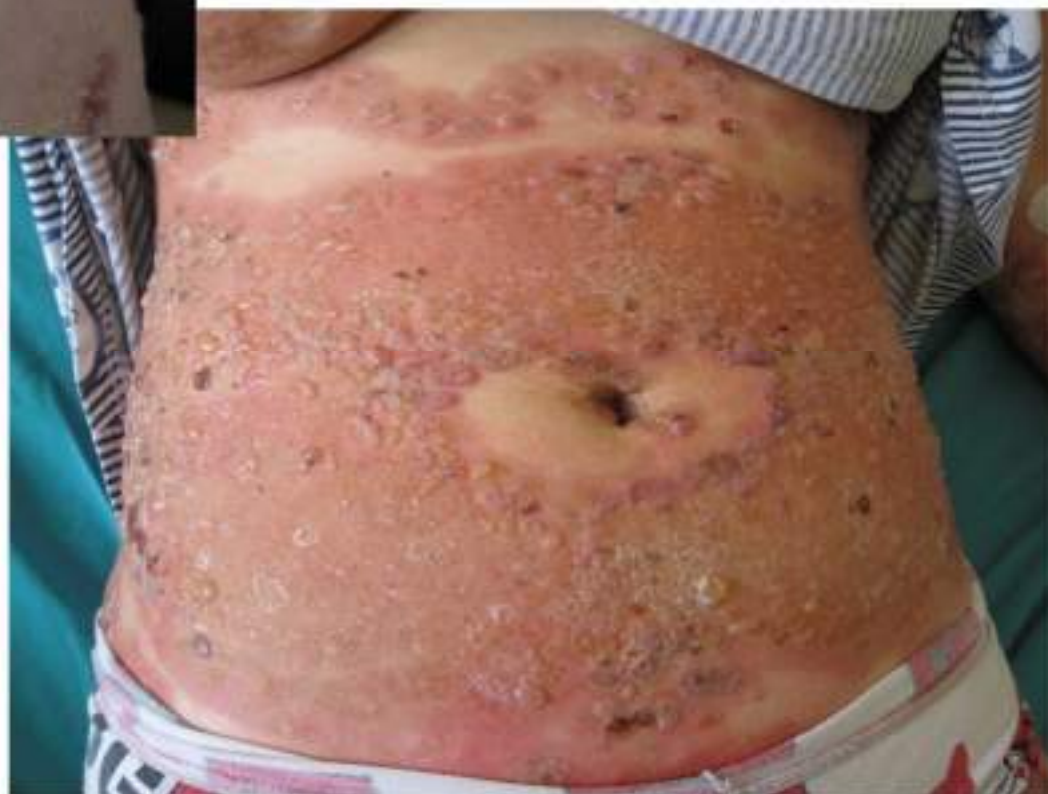   Plasma exchange (1, nonvalidated)

    Cyclophosphamide (3, nonvalidated)

Letter to the Editor

Bullous Pemphigoid Successfully Treated With a Combination Therapy of Plasmapheresis Followed by Intravenous High Dose Immunoglobulin

Πεμφιγοειδές Κύησης

Immunoadsorption in Dermatology

Damian Meyersburg,[1] Enno Schmidt,[2] Michael Kasperkiewicz[1] and Detlef Zillikens[1]

Departments of [1]Dermatology and [2]Comprehensive Centre for Inflammation Medicine, University of Lübeck, Lübeck, Germany

Η ανοσοπροσρόφηση χρησιμοποιείται ως επιπρόσθετη θεραπεία σε ανθεκτικά στη θεραπεία πρώτης γραμμής αυτοάνοσα πομφολυγώδη νοσήματα, όπως:

-Η κοινή πέμφιγα

-Η φυλλώδης πέμφιγα

-Η παρανεοπλασματική πέμφιγα

-Το πομφολυγώδες πεμφιγοειδές

-Η επίκτητη πομφολυγώδης επιδερμόλυση

Πλεονεκτήματα ανοσο**π**ροσρόφησης σε σχέση με την **π**λασμαφαίρεση

- Ε**π**ιλεκτική α**π**ομάκρυνση ανοσοσφαιρινών

- Δεν α**π**αιτείται η αντικατάσταση στοιχείων του **π**λάσματος

- Συνδέεται με λιγότερες ανε**π**ιθύμητες ενέργειες ό**π**ως λοιμώξεις και αλλεργικές αντιδράσεις

MINI REVIEW

Immunoadsorption in dermatology

Enno Schmidt · Detlef Zillikens
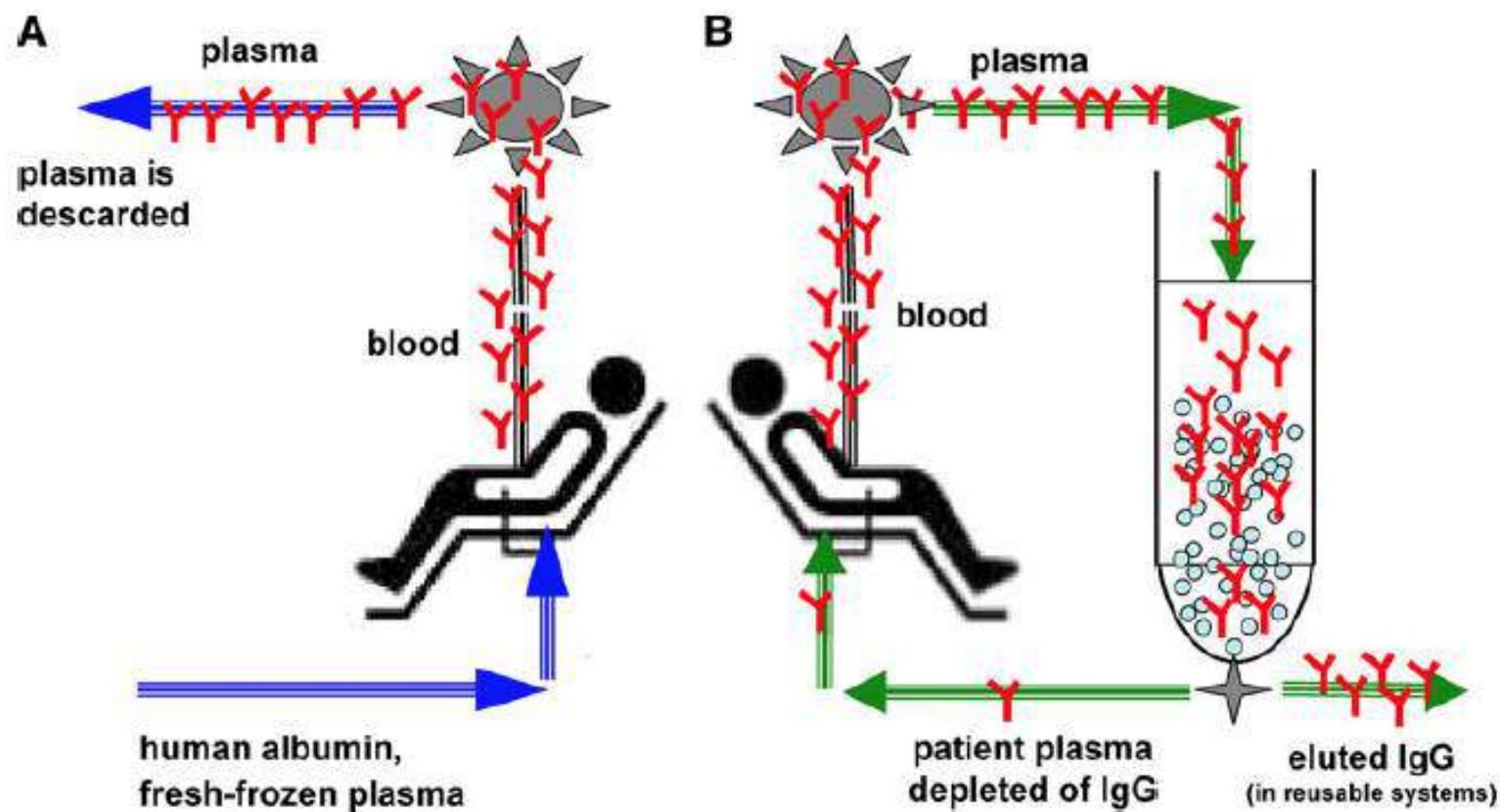
Immunoadsorption in Dermatology

Damian Meyersburg,[1] Enno Schmidt,[2] Michael Kasperkiewicz[1] and Detlef Zillikens[1]

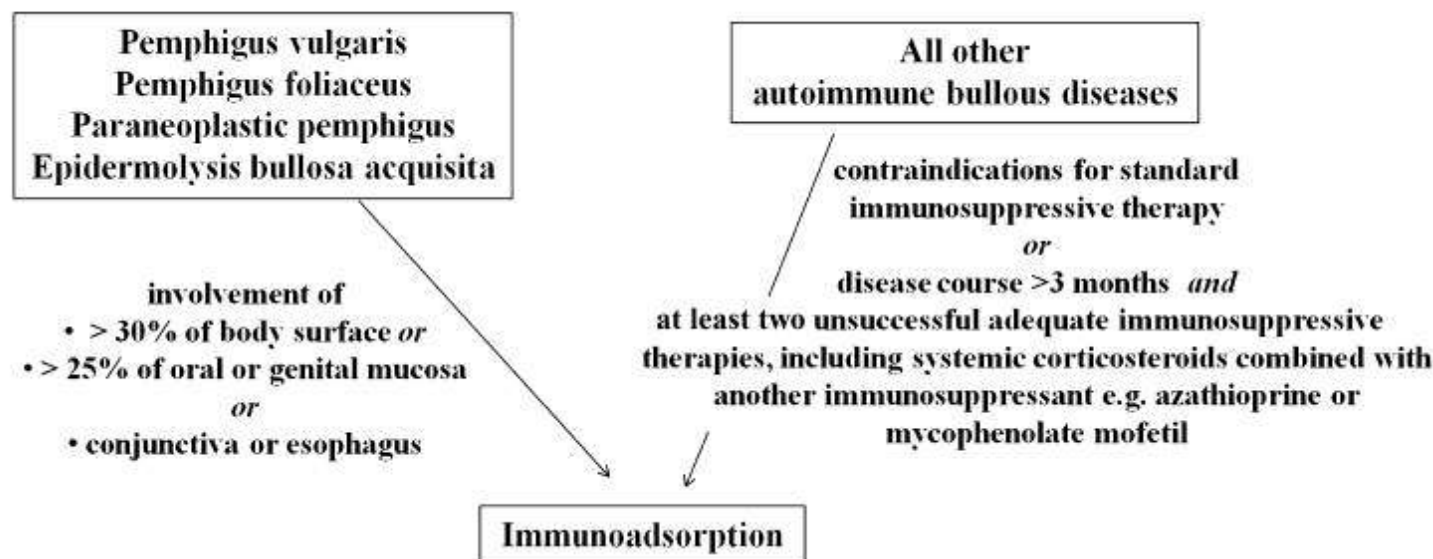*Departments of [1]Dermatology and [2]Comprehensive Centre for Inflammation Medicine, University of Lübeck, Lübeck, Germany*

Pemphigus vulgaris
Pemphigus foliaceus
Paraneoplastic pemphigus
Epidermolysis bullosa acquisita

All other autoimmune bullous diseases

involvement of
- > 30% of body surface *or*
- > 25% of oral or genital mucosa

or

- conjunctiva or esophagus

contraindications for standard immunosuppressive therapy

or

disease course >3 months *and*

at least two unsuccessful adequate immunosuppressive therapies, including systemic corticosteroids combined with another immunosuppressant e.g. azathioprine or mycophenolate mofetil

Immunoadsorption

Induction phase:
3–4 treatments on consequtive days with high-affinity IgG adsorbers (e.g. Immunosorba°, Globaffin°, TheraSorb°)
in selected cases, two consequtive 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.

Immunoadsorption in Dermatology

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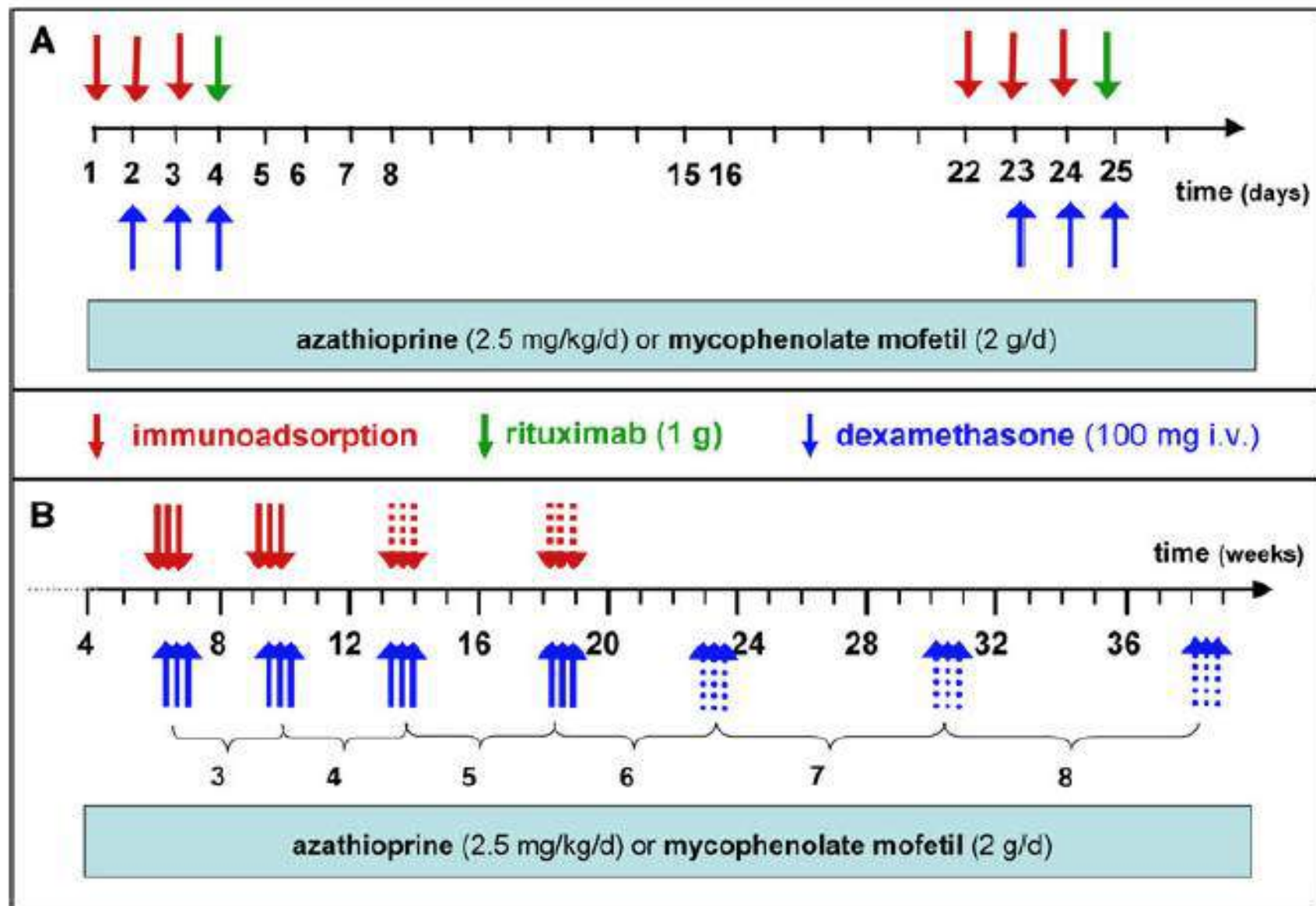
- Διάφορα συστήματα ανοσοπροσρόφησης χρησιμοποιούνται για τη μείωση των κυκλοφορούντων αυτοαντισωμάτων στο πλάσμα

- Τα επίπεδα των ειδικών για την πέμφιγα anti-Dsg IgG αυτοαντισωμάτων φαίνεται να μειώνονται κατά 75% με μια συνεδρία ανοσοπροσρόφησης με τα συστήματα Immunosorba και Therasorb

- Ο τίτλος των αυτοαντισωμάτων φαίνεται να αυξάνεται στο 40% του αρχικού τίτλου την επόμενη ημέρα

- Μετά από 3 συνεχόμενες συνεδρίες (ένας κύκλος) τα επίπεδα φαίνεται να μειώνονται κατά 95% σε σχέση με τα αρχικά

Immunoadsorption in Dermatology

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Departments of [1]Dermatology and [2]Comprehensive Centre for Inflammation Medicine, University of Lübeck, Lübeck, Germany

- Για τη διατήρηση της γρήγορης μείωσης στα επίπεδα των κυκλοφορούντων αυτοαντισωμάτων,**δεν πρεπει** να σταματά η ταυτόχρονη ανοσοκατασταλτική θεραπεία

- Έχει **π**αρατηρηθεί μείωση του τίτλου κατά **80%** μετά από ένα κύκλο και κατά **91%** και **89%** στους **6** και **12** μήνες, αντίστοιχα

A

1 2 3 4 5 6 7 8   15 16   22 23 24 25   **time (days)**

azathioprine (2.5 mg/kg/d) or mycophenolate mofetil (2 g/d)

↓ immunoadsorption   ↓ rituximab (1 g)   ↓ dexamethasone (100 mg i.v.)

B

time (weeks)

4   8   12   16   20   24   28   32   36

3   4   5   6   7   8

azathioprine (2.5 mg/kg/d) or mycophenolate mofetil (2 g/d)

Adjuvant treatment of severe/ refractory bullous pemphigoid with protein A immunoadsorption

Franziska Hübner[1], Michael Kasperkiewicz[1], Diana Knuth-Rehr[1], Iakov Shimanovich[1], Joachim Hübner[2], Sven Süfke[3], Philip Muck[3], Detlef Zillikens[1], Enno Schmidt[1, 4]

(1) Department of Dermatology, Allergology and Venereology, University of Lübeck, Lübeck, Germany
(2) Institute of Social Medicine and Epidemiology, University of Lübeck, Lübeck, Germany
(3) Department of Internal Medicine, University of Lübeck, Lübeck, Germany
(4) Lübeck Institute of Experimental Dermatology (LIED), University of Lübeck, Lübeck, Germany

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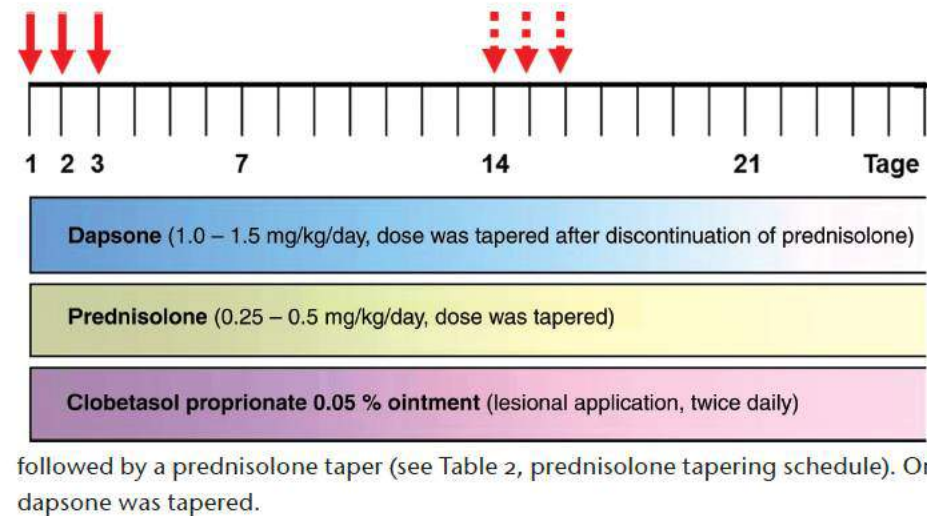
Figure 1 Treatment protocol. All patients received "basic therapy" consisting of prednisolone, dapsone, and topical clobetasol proprionate 0.05 % (only lesional application). In addition, protein A immunoadsorption (IA) was performed on three consecutive days. If required, IA was repeated after two weeks. Following complete remission, topical treatment was discontinued, followed by a prednisolone taper (see Table 2, prednisolone tapering schedule). Once prednisolone had been discontinued, dapsone was tapered.

Figure labels:
1 2 3   7   14   21   Tage

Dapsone (1.0 – 1.5 mg/kg/day, dose was tapered after discontinuation of prednisolone)

Prednisolone (0.25 – 0.5 mg/kg/day, dose was tapered)

Clobetasol proprionate 0.05 % ointment (lesional application, twice daily)

Anti-laminin 332 mucous membrane pemphigoid with laryngeal involvement – adjuvant treatment with immunoadsorption and rituximab

Rainer Hügel[1], Alois Lang[2], Karl Lhotta[3], Wolfgang Elsässer[4], Johannes Gächter[5], Elisabeth M. Messmer[6], Enno Schmidt[7]
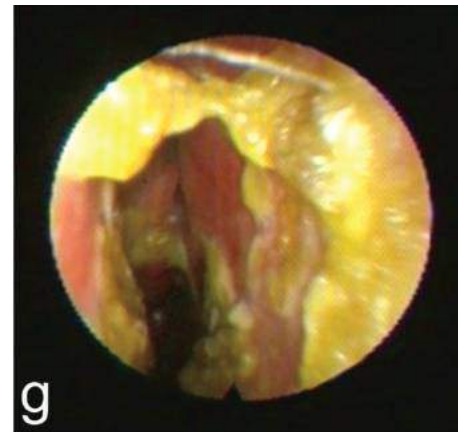
Anti-laminin 332 mucous membrane pemphigoid with laryngeal involvement – adjuvant treatment with immunoadsorption and rituximab

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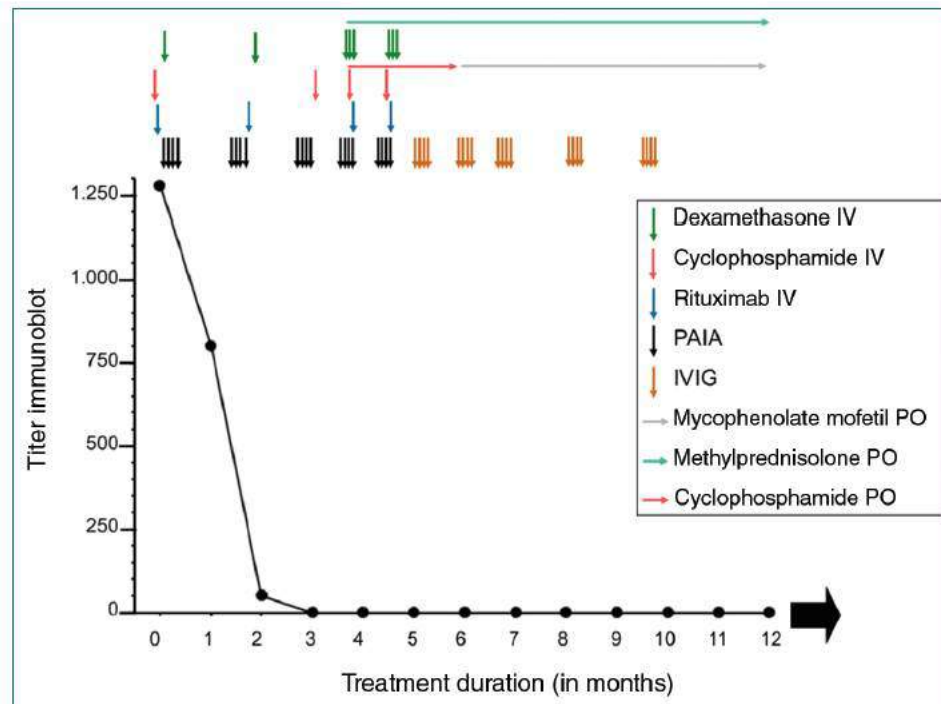
Figure 2 The treatment regimen consisted of five cycles of protein A immunoadsorption (PAIA; black arrow) on four consecutive days. During four of these cycles, rituximab was administered (blue arrow) at a dose of 1,000 mg IV, along with dexamethasone (100 mg IV, green arrow) and cyclophosphamide (750 mg IV, red arrow). Oral cyclophosphamide (50 mg/d) was added from the fourth cycle onwards and replaced by mycophenolate mofetil (1 g/d) after five months. While the patient was already in remission, he received five cycles of high-dose intravenous immunoglobulins (IVIG, 2 g/kg, orange arrow). Circulating anti-laminin 332 autoantibody levels, shown as titers following serial dilution of the patient's serum, were no longer detectable three months after initiation of treatment.

IgE-Specific Immunoadsorption for Treatment of Recalcitrant Atopic Dermatitis

Michael Kasperkiewicz, MD; Sven Süfke, MD; Enno Schmidt, MD, PhD; Detlef Zillikens, MD

Figure. Clinical Photographs of Patient 2 With Recalcitrant Atopic Dermatitis

A, Presentation before immunoadsorption treatment (week 1). B, Presentation at week 17 (after second immunoadsorption cycle).

Targeting IgE Antibodies by Immunoadsorption in Atopic Dermatitis

Michael Kasperkiewicz[1]*, Enno Schmidt[1,2], Ralf J. Ludwig[1,2] and Detlef Zillikens[1,2]

[1] Department of Dermatology, University of Lübeck, Lübeck, Germany, [2] Lübeck Institute of Experimental Dermatology, University of Lübeck, Lübeck, Germany

CONCLUSION

Clinical evidence suggests that IA seems to be an effective treatment option for patients severely affected by AD with highly elevated IgE serum levels. IA is associated with temporal and sustained reduction of circulating and skin-bound IgE, but the exact mechanisms underlying the clinical response in AD patients remain to be elucidated (4–9). Although the role of IgE in AD is still a matter of debate, these findings favor a pathogenic potential of IgE antibodies in this disorder. Future studies should explore whether a particular subset of AD patients who have circulating autoreactive IgE antibodies may especially benefit from this type of direct antibody depletion therapy.

TABLE 1 | Summary of published studies relating to IA and AD.

Reference	Patient characteristics	IA protocol	Concomitant therapy	Follow-up time after IA start (months)	Main clinical outcomes	Main laboratory outcomes
Kasperkiewicz et al. (4)	12 patients, 3 females, and 9 males; 24–66 (mean 42) years; SCORAD 55–98 (mean 78.6); total serum IgE 4,666–86,119 (mean 22,034) kU/L	2 cycles of 5 consecutive panimmunoglobulin IA (TheraSorb-Ig®, Miltenyi Biotec) at weeks 1 and 5	Topical corticosteroids/calcineurin inhibitors, oral antihistamines, and cyclosporine A	3	Mean SCORAD improvement by 38% (week 3), 46% (week 5), 56% (week 9), and 59% (week 13); parallel improvement of EASI	Temporal mean serum IgE reduction by >90% per IA cycle (similarly for IgG/IgM/IgA); sustained reduction of skin-bound IgE as well as histologic alterations (hyperkeratosis spongiosis, acanthosis, and dermal infiltrate)
Kasperkiewcz et al. (5)	2 male patients; 40–60 years; SCORAD 66 and 77 (mean 71.5); total serum IgE 17,020 and 46,540, (mean 31,780) kU/L, respectively	2 cycles of 5 consecutive IgE-selective IA (TheraSorb-IgE®, Miltenyi Biotec) at weeks 1 and 5	Topical corticosteroids/calcineurin inhibitors, oral antihistamines, and cyclosporine A	6	Mean SCORAD improvement by 33% (week 3), 37% (week 5), 54% (week 9), 53% (week 13), 55% (week 17), and 49% (week 25)	Temporal mean serum IgE reduction by >90% per IA cycle (36–49% for IgG/IgM/IgA)
Daeschlein et al. (6)	7 patients, 2 females and 5 males; 17–61 (mean 35.3) years; SCORAD 21.3–77 (mean 52); total serum IgE 724–28,500 (mean 11,015) kU/L	1–5 cycles of 5 consecutive panimmunoglobulin IA (TheraSorb-Ig flex®, Miltenyi Biotec) at monthly intervals	Topical corticosteroids/calcineurin inhibitors, oral antihistamines, cyclosporine A	12–18	Mean SCORAD improvement by 25.1% (after 1. IA cycle), 27.9% (after 2. IA cycle), 37.6% (after 3. IA cycle), 24.1% (after 4. IA cycle), and 11.1% (after 5. IA cycle)	Temporal mean serum IgE reduction by 74–80% per IA cycle
Zink et al. (7)	10 patients, 2 females and 8 males; 26–65 (mean 43.7) years; SCORAD 50.2–74.6 (mean 59.9); total serum IgE 3,728–69,872 (mean 18,094) kU/L	1 cycle of 2–4 consecutive panimmunoglobulin IA (TheraSorb-Ig flex®, Miltenyi Biotec) followed by omalizumab every 2 weeks for 24 weeks	Topical corticosteroids	12	Mean SCORAD improvement by 27% (week 3), 40% (week 13), 55% (week 25), and 19% (re-increased; week 49); parallel improvement and re-increase of VAS subjective severity score	Mean serum IgE reduction by 58–86% after 2–4 IA, respectively; serum IgE and TARC levels decreased continuously during omalizumab therapy and re-increased during treatment-free follow-up
Reich et al. (8)	50 patients, 20 females and 30 males; 21–75 (mean 45.6) years; mean EASI and SCORAD 21.3 and 40.5, respectively; median total serum IgE 6,700 k	3 cycles of 3–4 consecutive panimmunoglobulin IA (n = 24; TheraSorb-Ig flex®, Miltenyi Biotec) or IgE-selective IA (n = 26; TheraSorb-IgE®, Miltenyi Biotec) at weeks 1, 3, and 8	Topical and systemic corticosteroids, topical calcineurin inhibitors, cyclosporine A, methotrexate, and mycophenolate mofetil	8	Median EASI improvement by 39 and 47% (week 6), 52 and 45% (week 12), and 61 and 60% (week 32) in the panimmunoglobulin and IgE-selective IA group, respectively; parallel improvement of SCORAD, POEM, and DLQI	Temporal median serum IgE reduction by 85 and 90% per IA cycle in the panimmunoglobulin and IgE-selective IA group (85 and 20% for IgG), respectively
Kasperkiewicz et al. (9)	10 patients, 3 females and 7 males; 18–70 (mean 40.3) years; SCORAD 61.5–81 (mean 67.5); total IgE 931–21,510 (mean 5,377) kU/L	2 cycles of 5 consecutive IgE-selective IA (TheraSorb-IgE®; Miltenyi Biotec) at weeks 1 and 5	Topical and systemic corticosteroids, topical calcineurin inhibitors, oral antihistamines	6	Mean SCORAD improvement by 19% (week 3), 29% (week 5), 43% (week 9), 21% (week 13), 25% (week 17), and 29% (week 25)	Temporal mean serum IgE reduction by > 90% per IA cycle (35–43% for IgG/IgM/IgA)

Γαγγραινώδες
Πυόδερμα

Η θεραπευτική αφαίρεση σε νοσήματα του δέρματος

- επιλογή σε δύσκολα περιστατικά

- ειδική γνώση και εξοπλισμός

- συνεργασία ειδικοτήτων