Intravenous Immunoglobulin (IVIg) in Dermatology

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I have no relevant conflicts of interest to declare

What is IVIg?

IVIg = **i**ntra**v**enous **i**mmuno**g**lobulin

- Contains the pooled, polyvalent, IgG antibody extracted from the plasma of over 1000 blood donors
- Contains <2.5% IgA
- Mainly used as treatment in three major categories:
  - —immune deficiencies
  - —autoimmune diseases
  - —acute infections
- Can be used in pregnancy

Skin diseases treated with IVIg

Autoimmune connective tissue disorders

Cutaneous lupus erythematosus
Dermatomyositis
Mixed connective tissue disease
Nephrogenic fibrosing dermopathy
Scleroderma (Systemic sclerosis)

Autoimmune mucocutaneous blistering diseases

Bullous pemphigoid
Epidermolysis bullosa acquisita
Lichen planus pemphigoides
Linear IgA bullous disease
Mucous membrane (Cicatricial) pemphigoid
Paraneoplastic autoimmune multiorgan syndrome (Paraneoplastic pemphigus)
Pemphigoid (Herpes) gestationis
Pemphigus foliaceus
Pemphigus vulgaris

Skin diseases treated with IVIg

Vascular disorders

Anti-neutrophil cytoplasmic autoantibody (ANCA) positive vasculitides:
- Microscopic polyangiitis
- Wegener's granulomatosis

Behçet's disease
Churg–Strauss syndrome
Cutaneous polyarteritis nodosa
Degos' disease
Leukocytoclastic vasculitis
Livedoid vasculopathy

Drug-induced disorders

Anticonvulsant hypersensitivity syndrome
Erythema multiforme
Kaposi sarcoma due to immunosuppression
Methotrexate-induced acral erythema
Stevens–Johnson syndrome
Toxic epidermal necrolysis (Lyell's syndrome)

Skin diseases treated with IVIg

Miscellaneous dermatoses

Alopecia universalis
Atopic dermatitis
Calcinosis cutis
Chronic urticaria:
—*Angioedema with hypereosinophilia*
—*Autoimmune urticaria*
—*Chronic idiopathic urticaria*
—*Delayed pressure urticaria*
—*Solar urticaria*
Graft-versus-host disease
Hyper-IgE syndrome
Kawasaki's syndrome
Necrobiosis lipoidica diabeticorum
POEMS syndrome: *polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes*
Polymorphous light eruption
Pretibial myxedema
Psoriasis
Pyoderma gangrenosum
Scleroderma
Scleromyxedema
Sweet's syndrome
Wiskott–Aldrich syndrome

Skin diseases treated with IVIg

Skin infectious and infection-related diseases

Lyme disease
Measles
Necrotizing fasciitis
Rubella
Staphylococcal scalded skin syndrome (SSSS; Ritter's disease)
Streptococcal toxic shock syndrome (STSS)
Varicella

How is IVIg therapy given?

- Intravenously over several hours, gradually increasing the rate of infusion up to 200 ml/h.
- Daily for 2-5 days. Usually @400 mg/kg/day up to 2 g/kg per month = one cycle.
- Cycles can be repeated in 2-4 weeks, depending on circumstances (IgG half-life is 3-4 weeks).
- Multiple cycles are usually required: from 3-5 to 30-50 and more.
- Very expensive: ~$10,000 for one cycle.

Analysis of High-dose Intravenous Immunoglobulin Therapy in 16 Patients with Refractory Autoimmune Blistering Skin Disease: High Efficacy and No Serious Adverse Events

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High-dose intravenous immunoglobulin (IVIG) therapy is used in patients with severe autoimmune blistering diseases that are refractory to standard immunosuppressive therapy. To determine the efficacy and frequency of adverse events of IVIG therapy, we retrospectively analysed data for 16 patients with pemphigus vulgaris, pemphigus foliaceus, paraneoplastic pemphigus, bullous pemphigoid and paraneoplastic bullous pemphigoid. Frequency of adverse reactions and efficacy of IVIG were analysed over time with a scoring system for every 6 months of IVIG therapy. Headache (43.8%) and fatigue (43.8%) were the most common side-effects recorded; serious adverse reactions did not occur. There was good overall efficacy, as measured by clinical response rates using a clinical score, as well as indicated by a mean reduction of 75.8% in the starting steroid dose. ***Key words: high-dose intravenous immunoglobulin therapy; autoimmune mucocutaneous blistering disease; pemphigus vulgaris; pemphigus foliaceus; bullous pemphigoid.***

Patient characteristics

Disease (total No. of patients)	Sex M/F	Age at diagnosis, years	IVIG cycles, *n*
Pemphigus vulgaris ($n = 10$), mean ± SD	4/6	49.9 ± 13.6	40.9 ± 22.7
Paraneoplastic pemphigus ($n = 1$)	1/0	72	42
Pemphigus foliaceus ($n = 3$), mean ± SD	1/2	38.7 ± 11.9	29.7 ± 22.4
Bullous pemphigoid ($n = 1$)	1/0	58	32
Paraneoplastic bullous pemphigoid ($n = 1$)	1/0	61	45
Overall ($n = 16$), mean ± SD	8/8	50.4 ± 14.1	38.6 ± 20.0

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Impact of cost of IVIg on treatment

- Need to obtain clearance from insurance company before treatment can be given.
- Insurance company may not allow it, or may restrict frequency or duration of treatment.

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Comparison of cost of immune globulin intravenous therapy to conventional immunosuppressive therapy in treating patients with autoimmune mucocutaneous blistering diseases

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Abstract

Autoimmune mucocutaneous blistering diseases (AMBD) are a group of potentially fatal diseases that affect the skin and mucous membranes. AMBD have different target antigens as well as variable clinical presentation, course, and prognosis.

The mainstay of conventional immunosuppressive therapy (CIST) for AMBD is long-term high-dose systemic corticosteroids and immunosuppressive agents. Such therapy has proven effective in many patients; however, in some patients, the disease continues to progress with significant sequelae such as blindness, loss of voice, anal, and vaginal stenosis which causes poor quality of life. Furthermore, the CIST may have some serious side effects including opportunistic infections which may cause death.

Immune globulin intravenous (IGIV) therapy has been reportedly used in the management of patients with AMBD refractory to CIST. IGIV has shown to be more clinically beneficial than CIST by bringing about long-term clinical remission and less recurrence. The high cost of the IGIV is of concern to patients, physicians, and insurance companies.

In this report, we compare the cost of IGIV to that of CIST in treating a cohort of 15 mucous membrane pemphigoid (MMP), 10 ocular cicatricial pemphigoid (OCP), 15 bullous pemphigoid (BP), and 32 pemphigus vulgaris (PV) patients.

In each cohort of patients, CIST had significant side effects, many of which were hazardous and required prolonged and frequent hospitalizations. Some of these side effects were severe enough to require discontinuation of the treatment. We consider the total cost of CIST to be the actual cost of the drug, plus the cost of management of the side effects produced by CIST. In the same patient cohort, no significant side effects to IGIV were observed. None of the IGIV treated patients required physician visits, laboratory tests, or hospitalizations specifically related to IGIV therapy. Hence, the total cost of the IGIV therapy is the actual cost of the IGIV only. The mean total cost of treatment of IGIV therapy is statistically significantly less than that of CIST during the entire course of the disease and on an annual basis.

In conclusion, IGIV therapy is a safe, clinically beneficial, and a cost effective alternative treatment in patients with AMBD, non-responsive to CIST.

Comparison of cost of conventional immunosuppressive therapy (CIST) with IVIg therapy in patients with mucous membrane pemphigoid (MMP), ocular cicatricial pemphigoid (OCP), bullous pemphigoid (BP) and pemphigus vulgaris (PV).

	CIST	IGIV	Statistical analysis
Total cost of care			
MMP	$301,122	$134,400	$p<0.0005$
BP	$184,708	$67,520	$p=0.001$
PV	$337,904	$176,100	$p=0.005$
OCP	$1,107,487	$194,080	$p=0.005$
Annual cost of care			
MMP	$168,518	$65,190	$p<0.05$
BP	$78,229	$33,173	$p=0.01$
PV	$123,133	$76,249	$p=0.01$
OCP	$143,276	$84,923	$p=0.014$

Generic IVIg infusion protocol

- Administer IVIg product at 400-500 mg/kg/day on 4-5 consecutive days up to the total dose of 2 g/kg/month times ? number of months.
- Premedicate patient with 25 mg Benadryl (diphenhydramine) and 500 mg Tylenol (acetaminophen) 15-30 min prior to starting the infusion.
- Place peripheral i.v. and maintain with 0.9% sodium chloride.
- Infusion Rate: start at 0.5 ml/kg/h, then increase by 15 ml/h every 15 min until target rate of 150-200 ml/h, as tolerated. Maximum rate is 200 ml/h.
- Observe vital signs prior to infusion. Blood pressure and pulse every 30 min until stable infusion rate, then every hour.
- Watch for signs of fluid overload, cardiovascular symptoms, allergic reactions, skin rash, fever, and moderate to severe headache.
- For adverse events, stop the infusion. Can restart the infusion at the same or lower rate if the symptoms subside.

Immediate side effects

- Headache, flushing, chills, fever, nausea, vomiting, dizziness, sweating, hypertension, feelings of tightness in the chest, back pain, and muscle aches. Related to infusion rate.
- Aseptic meningitis. More common with history of migraine.
- Thrombosis/stroke. Related to infusion rate + dose. More common if history of cardiac disease, stroke, myocardial infarction, thrombosis, old age, hypercoagulation, limited mobility.
- Anaphylaxis. If IgA deficient.
- Acute renal failure: due to osmotic injury. More common with sucrose, dehydration, hypovolemia, sepsis, diabetes.

Delayed side effects

- Anemia—*due to anti-AB antibodies (Type 0 = universal receiver)*
- Cardiac insufficiency—*due to fluid overload*
- Renal insufficiency—*due to immune complexes, sucrose*
- Viral infection—*less with detergent treatment or ultrafiltration*

Delayed side effects

- Anemia—*due to anti-ABO antibodies (Type 0 = universal receiver)*
- Cardiac insufficiency—*due to fluid overload*
- Renal insufficiency—*due to immune complexes, sucrose*
- Viral infection—*less with detergent treatment or ultrafiltration*

In contrast to conventional immunosuppressive therapy:

no immune suppression

no ovarian/testicular suppression

no carcinogenicity

What affects the safety of IVIg therapy?

VARIABLE	IMPACT
IgA content	Anaphylaxis, if patient is IgA deficient
Concentration	Fluid overload if dilute Osmotic overload if concentrated
Sugar content	Sucrose – nephropathy
Administration rate	Slow – fewer side effects
Frequency	Fewer side effects if given over 4-5 d

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Not All Intravenous Immunoglobulin Preparations are Equally Well Tolerated

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[1]Department of Dermatology, [2]Division of Pulmonary Medicine, and [3]Biostatistics Unit, Institute for Social and Preventive Medicine, University Hospital Zürich, Switzerland

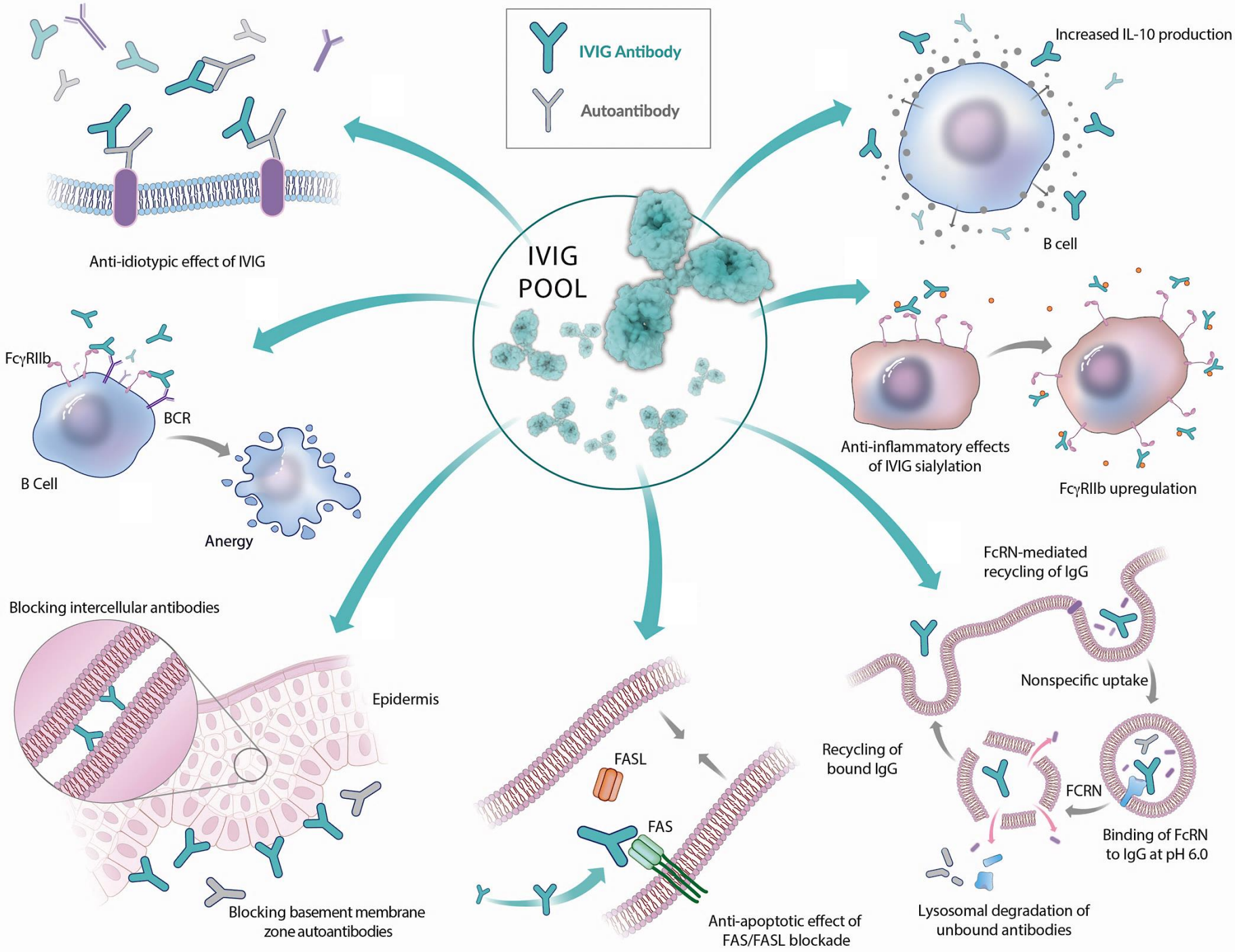
Numbers of patients and adverse events

IVIG preparation	Patients treated, *n*	Adverse events, *n* (%)
Redimune NF Liquid®	28	14 (100)
Octagam®	26	0 (0)

Commercially available IVIg products

Consideration	Gammagard Liquid 10%	Gamunex-C 10% & Gammaked	Privigen 10%	Flebogamma 10% DIF	Octagam 5%	Carimune NF
Manufacturer	Baxter Healthcare	Grifols (Talecris)	CSL Behring	Grifols	Octapharma USA	CSL Behring
Concentration	10%	10%	10%	10%	5%	6%
Form	liquid	liquid	liquid	liquid	liquid	lyophilized
Sodium Content	trace	not detectable	trace	trace	not detectable	0.9%
Stabilizer	glycine	glycine	proline	sorbitol	maltose	sucrose
Osmolality/ Osmolarity	240–300 mOsm/kg	258 mOsm/kg	240–440 mOsm/kg	240–370 mOsm/kg	310–380 mOsm/kg	690 mOsm/kg
IgA Content	37 mcg/mL	46 mcg/mL	<25 mcg/mL	<6 mcg/mL	<200 mcg/mL	>720 mcg/mL
pH	4.6–5.1	4–4.5	4.6–5	5.5	5.1–6	6.4–6.8
Supply Size (Grams)	30, 20, 10, 5, 2.5, 1	20, 10, 5, 2.5, 1	20, 10, 5	20, 10, 5	25, 10, 5, 2.5, 1	12, 6, 3
Shelf Life	24 months at room temp; 36 months refrigerated	6 months at room temp; 36 months refrigerated	36 months at room temp	24 months at room temp	24 months at room temp	24 months at room temp

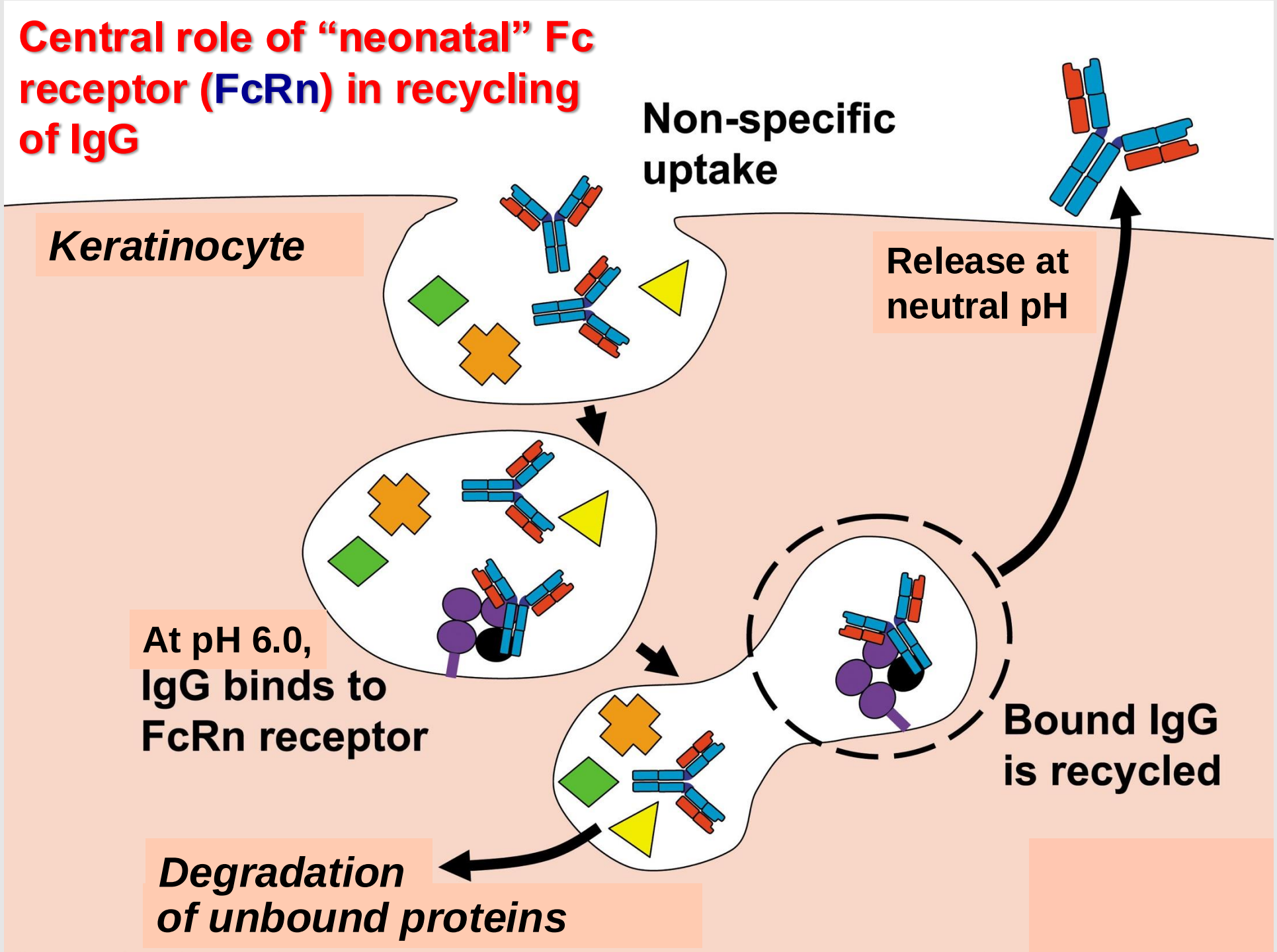
How does IVIg work in skin diseases?


IVIG Antibody
Autoantibody
IVIG POOL
Anti-idiotypic effect of IVIG
Increased IL-10 production
B cell
FcγRIIb
BCR
B Cell
Anergy
Anti-inflammatory effects of IVIG sialylation
FcγRIIb upregulation
Blocking intercellular antibodies
Epidermis
Blocking basement membrane zone autoantibodies
FASL
FAS
Anti-apoptotic effect of FAS/FASL blockade
FcRN-mediated recycling of IgG
Nonspecific uptake
Recycling of bound IgG
FCRN
Binding of FcRN to IgG at pH 6.0
Lysosomal degradation of unbound antibodies

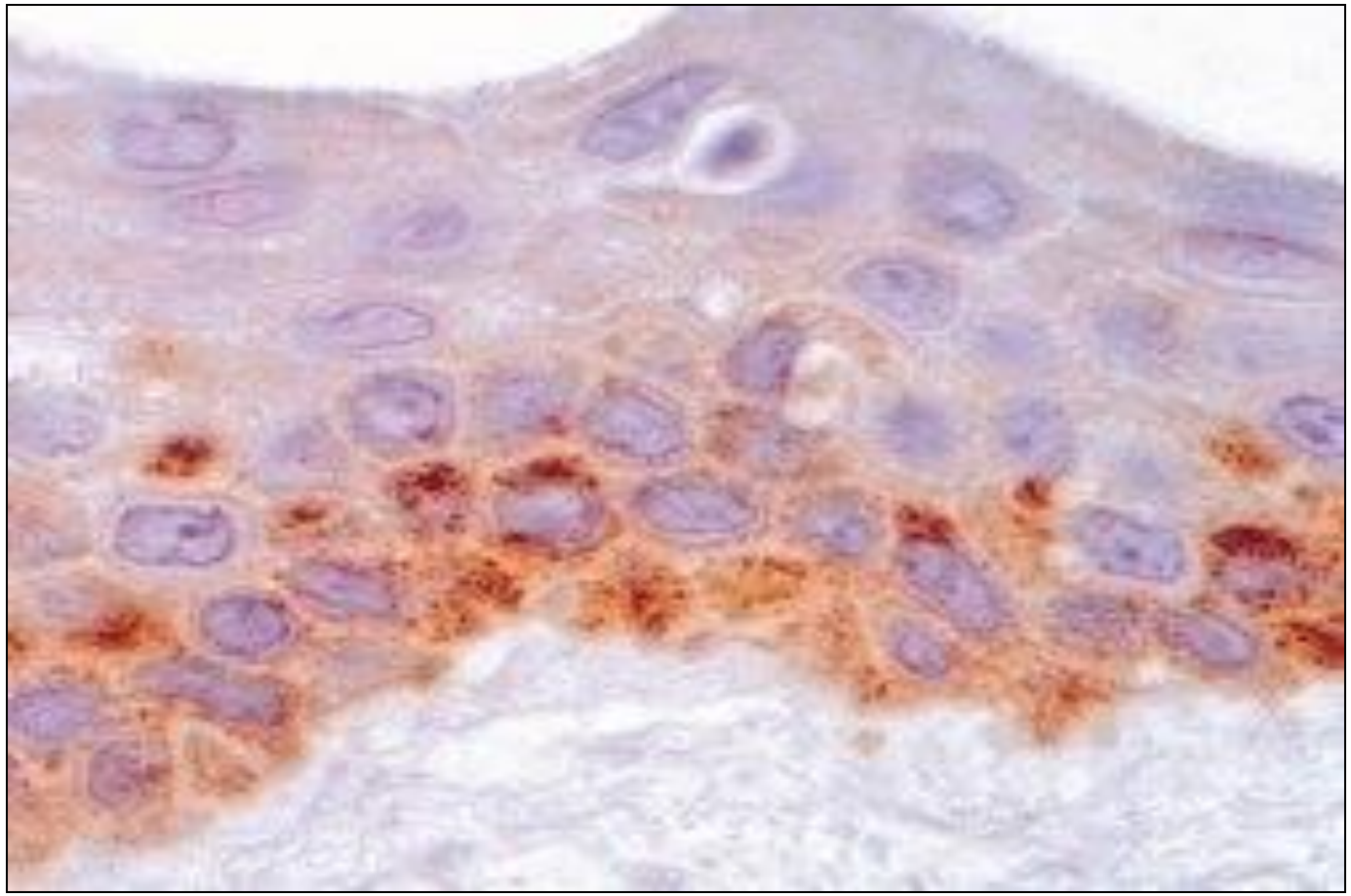
Mechanisms of therapeutic action of IVIg

- **selective elimination of pathogenic antibodies due to blocking (saturation) of the neonatal Fc receptor (FcRn) that protects IgG molecules from lysosomal degradation**
- **anti-inflammatory action of sialylated IgG species that upregulate expression of the inhibitory FcγR (FcγRIIB) receptor on immune cells**
- **inactivation of pathogenic antibodies by the anti-idiotypic antibodies present in IVIg preparations**
- **activation of anergic/apoptotic program in B cells by anti-idiotypic antibodies**
- **increase of B cells producing the immunosuppressive cytokine IL-10**
- **protection of self-antigens targeted by autoimmunity by the blocking antibodies present within donors' IgGs**
- **anti-apoptotic and anti-oncotic effects on keratinocytes**

Central role of “neonatal” Fc receptor (FcRn) in recycling of IgG

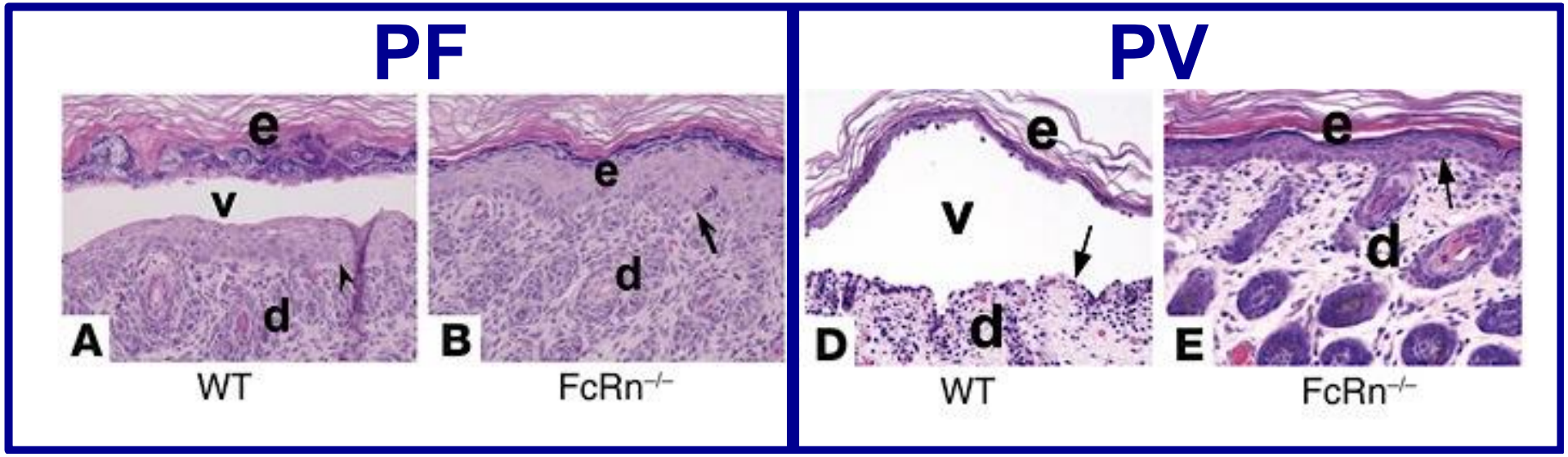


FcRn in human epidermis



Cauza et al, J Invest Dermatol 124:132 –139, 2005

FcRn-deficient mice are resistant to experimental PF and PV



Li et al, J Clin Invest 115:3440-3450, 2005

Mechanisms of therapeutic action of IVIg

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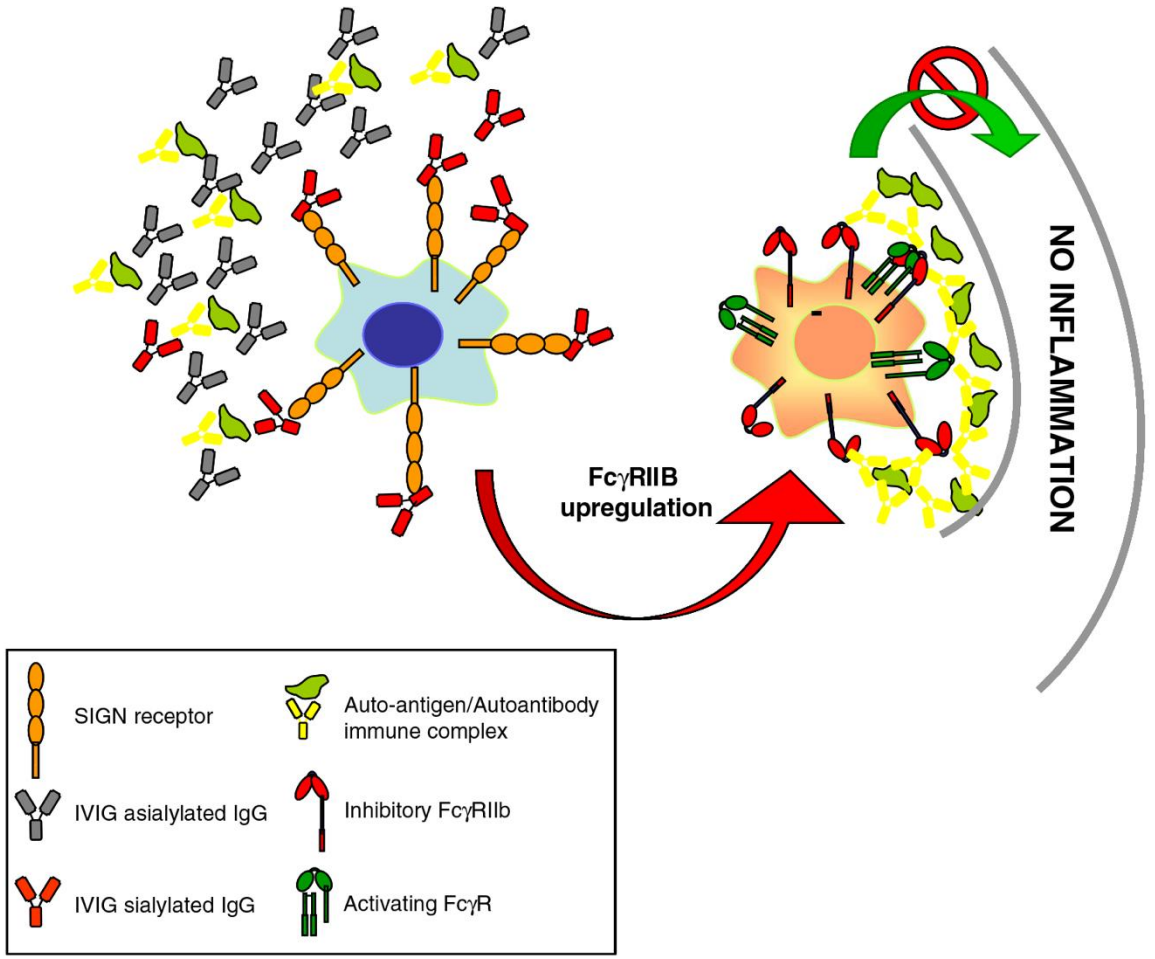
Anti-inflammatory effect of IVIg sialylation



A model for the anti-inflammatory activity of α2,6 sialylated Fc. α2,6 sialylated Fcs, found in preparations of intravenous gamma globulin (IVIG), engage a lectin on the surface of a regulatory macrophage population (*blue*) in the spleen found in the marginal zone, now identified as SIGN-R1. Engagement of this lectin induces a cellular program that results in the secretion of anti-inflammatory, soluble mediators that target effector macrophages (*orange*) found at the site of tissue inflammation where pathogenic immune complexes are deposited. These effector macrophages respond to the anti-inflammatory mediators by increasing surface expression of the inhibitory FcγRIIB receptor. This alters the threshold concentration of immune complexes necessary to trigger macrophage activation and subsequent inflammation. This pathway's net result is to attenuate autoantibody-mediated inflammation and tissue pathology.

Anthony & Ravetch, 2010

Mechanisms of therapeutic action of IVIg

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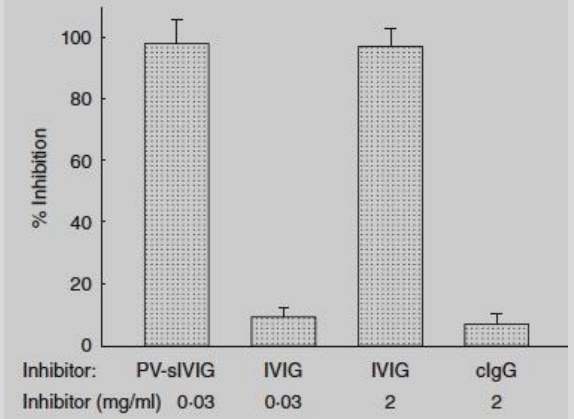

Fig. 2. Enzyme-linked immunosorbent assay competition assay demonstrating the single-chain variable fragment binding neutralization activity of pemphigus vulgaris-specific intravenous immunoglobulin (PV-sIVIG), low-dose intravenous immunoglobulin (IVIG) (98% compared to 9%, respectively, $P < 0{\cdot}001$), normal dose IVIG (97% inhibition) and control immunoglobulin G (cIgG) (7% inhibition) to desmoglein 3.

Clinical and Experimental Immunology

Efficacy of intravenous immunoglobulin (IVIG) affinity-purified anti-desmoglein anti-idiotypic antibodies in the treatment of an experimental model of pemphigus vulgaris

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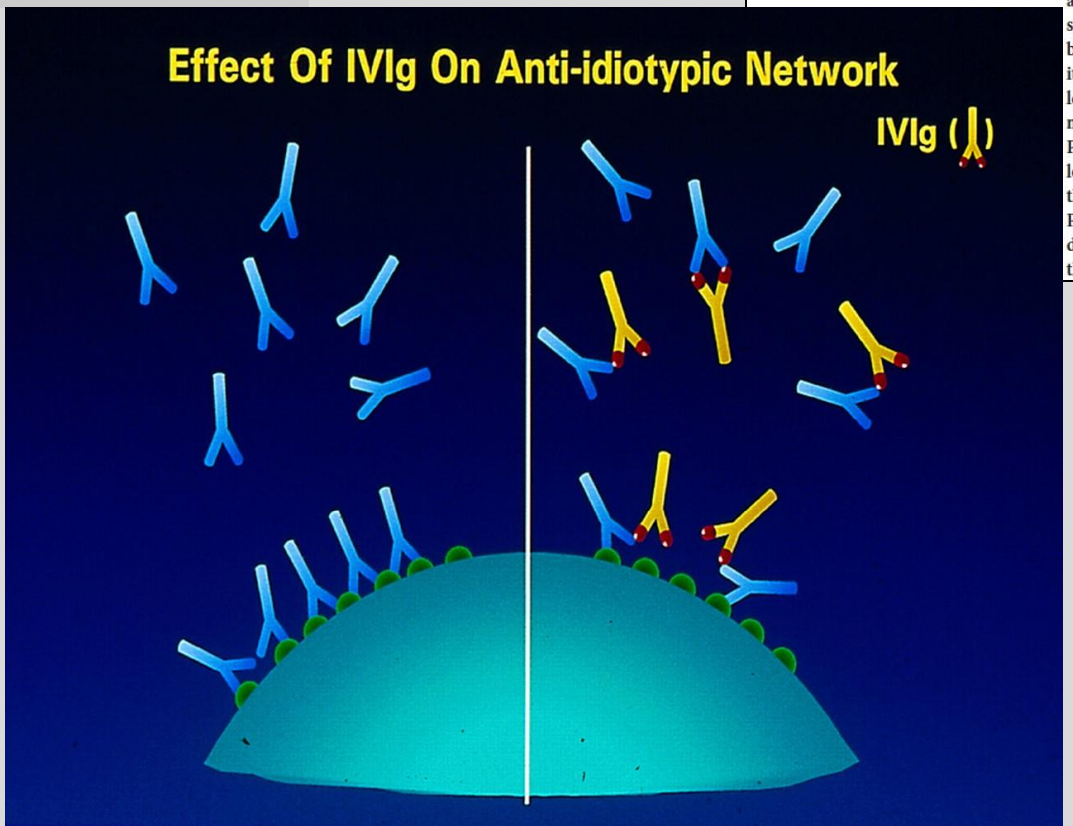
Summary

Pemphigus vulgaris is a rare life-threatening autoimmune bullous disease caused by immunoglobulin G (IgG) autoantibodies directed against desmogleins 1 and 3. Previously, we showed that intravenous immunoglobulin (IVIG) ameliorates anti-desmoglein-induced experimental pemphigus vulgaris in newborn naive mice. The aim of this study was to examine the efficacy of anti-anti-desmoglein-specific IVIG in a similar model. Pemphigus-vulgaris-specific IVIG (PV-sIVIG) was affinity-purified from IVIG on a column of single-chain variable fragment (scFv) anti-desmogleins 1 and 3. The anti-idiotypic activity of PV-sIVIG was confirmed by enzyme-linked immunosorbent assay, inhibition assay. After induction of pemphigus by injection of anti-desmogleins 1 and 3 scFv to newborn mice, the animals were treated with PV-sIVIG, IVIG (low or high dose) or IgG from a healthy donor ($n = 10$ each). The skin was examined 24–48 h later, and samples of affected areas were analysed by histology and immunofluorescence. *In vitro* study showed that PV-sIVIG significantly inhibited anti-desmogleins 1 and 3 scFv binding to recombinant desmoglein-3 in a dose-dependent manner. Specificity was confirmed by inhibition assay. *In vivo* analysis revealed cutaneous lesions of pemphigus vulgaris in mice injected with normal IgG (nine of 10 mice) or low-dose IVIG (nine of 10 mice), but not in mice treated with PV-sIVIG (none of 10) or high-dose IVIG (none of 10). On immunopathological study, PV-sIVIG and regular IVIG prevented the formation of acantholysis and deposition of IgG in intercellular spaces. In conclusion, the PV-sIVIG preparation is more effective than native IVIG in inhibiting anti-desmoglein-induced pemphigus vulgaris in mice and might serve as a future therapy in patients with the clinical disease.



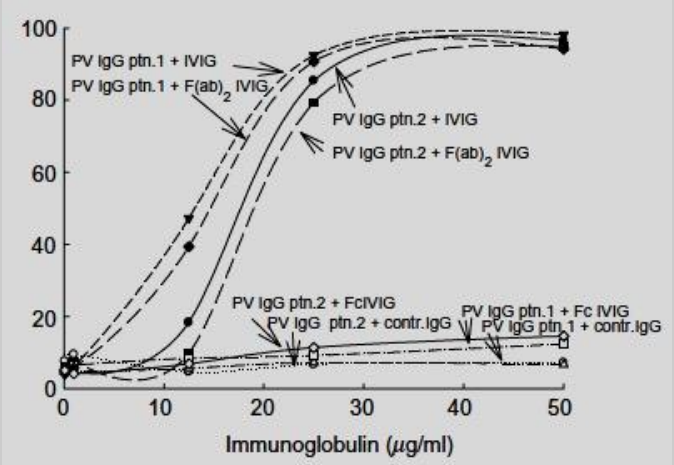


Fig. 2. Inhibition of pemphigus vulgaris (PV)-IgG binding to recombinant.desmoglein-3 (r.desmoglein-3) by IVIG: inhibition assay demonstrating the neutralization activity of IVIG and its $F(ab)_2$ portion on the PV-IgG binding to r.desmoglein-3. The data are presented in OD at 405 nm, mean ± s.d. of three separate experiments.

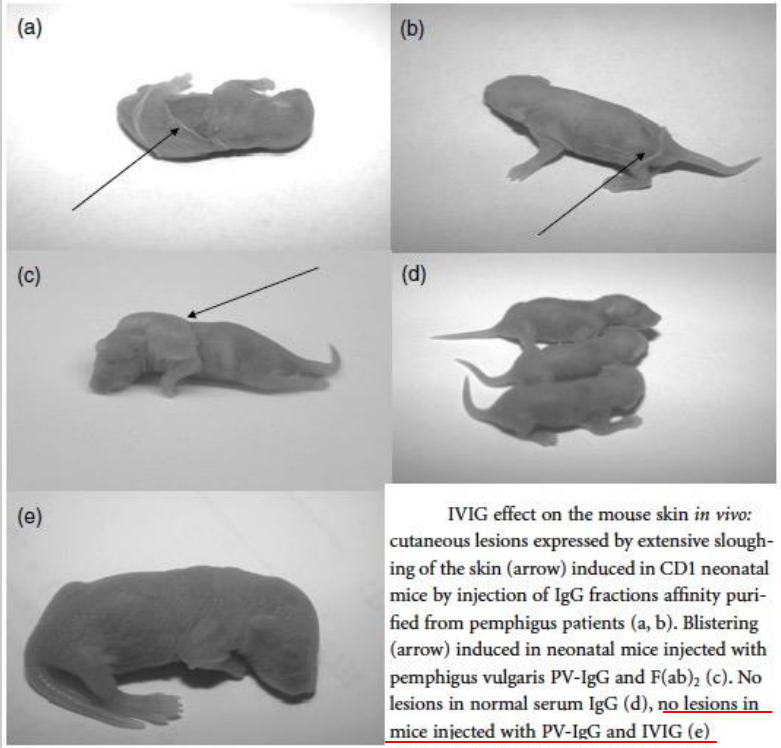
Clinical and Experimental Immunology

Protective effect of intravenous immunoglobulin (IVIG) in an experimental model of pemphigus vulgaris

D. Mimouni,*†‡‡ M. Blank,*‡‡
L. Ashkenazi,* Y. Milner,‡
M. Frusic-Zlotkin,‡ G. J. Anhalt,§
M. David† and Y. Shoenfeld*¶
*Department of Medicine B and Center for Autoimmune Diseases, Sheba Medical Center, Tel Hashomer, and the Sackler Faculty of Medicine, Tel Aviv University, Israel, †Department of Dermatology, Rabin Medical Center, Petah Tiqva and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel, ‡Myers Skin Biochemistry Laboratory, Department of Biological Chemistry, The Hebrew University, Givat Ram, Jerusalem, Israel, §Department of Dermatology, School of Medicine, Johns Hopkins University, Baltimore, Maryland, USA, and ¶Incumbent of the Laura Schwarz-Kipp Chair for Autoimmunity, Tel Aviv University, Israel

Summary

Uncontrolled studies have found intravenous immunoglobulin (IVIG) to be effective in the treatment of pemphigus vulgaris (PV). The aim of this study was to evaluate the role of IVIG in preventing IgG autoantibodies binding to desmoglein-3 and blister formation using a controlled experimental design. The ability of IVIG to affect the binding of IgG affinity purified from two patients with PV to desmoglein-3 in comparison to IgG from one donor, was conducted by enzyme-linked immunosorbent assay (ELISA). The specificity was confirmed by competition assay. We assessed the effect of IVIG on the induction of experimental-PV in CD1 newborn mice by subcutaneous subjection of IgG affinity purified from two patients with PV. The treatment was conducted by subcutaneous administration of IVIG together with IgG from the pemphigus patients or appropriate control. The skin of the newborns was examined 24–48 h later for blisters, and samples of the affected areas were analysed by immunohistochemistry. IVIG as a whole molecule and its $F(ab)_2$ portion inhibited the binding of anti-desmoglein-3 antibody to recombinant desmoglein-3 in a dose-dependent manner. The specificity was confirmed by competition assays. *In-vivo*, IVIG and its $F(ab)_2$ portion prevented blister formation in the newborn mice. Cutaneous lesions were noted only in the groups of newborn mice who were injected with IgG fractions from the PV patients. Immunopathological evaluation revealed that IVIG prevented the formation of acanthylosis with IgG deposition in the intercellular spaces. These results point to the efficacy of IVIG in the prevention of blister formation in an experimental PV model.



IVIG effect on the mouse skin *in vivo:* cutaneous lesions expressed by extensive sloughing of the skin (arrow) induced in CD1 neonatal mice by injection of IgG fractions affinity purified from pemphigus patients (a, b). Blistering (arrow) induced in neonatal mice injected with pemphigus vulgaris PV-IgG and $F(ab)_2$ (c). No lesions in normal serum IgG (d), no lesions in mice injected with PV-IgG and IVIG (e)

Mechanisms of therapeutic action of IVIg

- selective elimination of pathogenic antibodies due to blocking (saturation) of the neonatal Fc receptor (FcRn) that protects IgG molecules from lysosomal degradation
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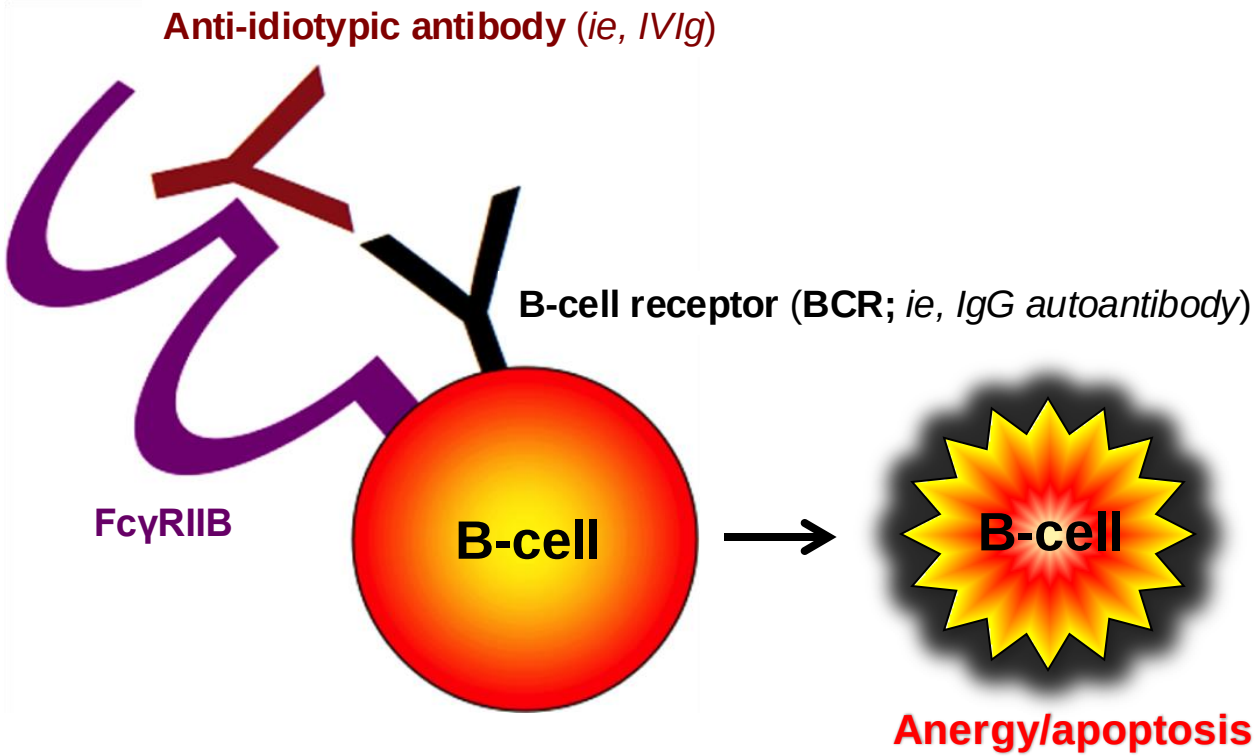
Protective role of anti-idiotypic antibodies in autoimmunity – Lessons for type 1 diabetes

CHRISTIANE S. HAMPE

Autoimmunity, June 2012; 45(4): 320–331



Co-ligation of FcγRIIB with the BCR. The Fc portion of anti-Id binds to the B lymphocyte's FcγRIIB. Simultaneously the Fab portion of anti-Id binds to the BCR, thereby co-ligating these two membrane proteins. Co-ligation of the FcγRIIB to the BCR abolishes the BCR-induced stimulation of antibody secretion.

Mechanisms of therapeutic action of IVIg

- selective elimination of pathogenic antibodies due to blocking (saturation) of the neonatal Fc receptor (FcRn) that protects IgG molecules from lysosomal degradation
- anti-inflammatory action of sialylated IgG species that upregulate expression of the inhibitory FcγR (FcγRIIB) receptor on immune cells
- inactivation of pathogenic antibodies by the anti-idiotypic antibodies present in IVIg preparations
- activation of anergic/apoptotic program in B cells by anti-idiotypic antibodies
- **increase of B cells producing the immunosuppressive cytokine IL-10**
- protection of self-antigens targeted by autoimmunity by the blocking antibodies present within donors' IgGs
- anti-apoptotic and anti-oncotic effects on keratinocytes

Japanese Dermatological Association
The Journal of Dermatology
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Journal of Dermatology 2016; ●●: 1–4

CONCISE COMMUNICATION

Increase of interleukin-10-producing B cells associated with long-term remission after i.v. immunoglobulin treatment for pemphigus

Miho KABUTO, Noriki FUJIMOTO, Toshihiro TANAKA

Department of Dermatology, Shiga University of Medical Science, Shiga, Japan

ABSTRACT

We present a refractory case of pemphigus vulgaris that achieved long-term remission after i.v. immunoglobulin treatment (IVIG). We evaluated the fluctuation of circulating interleukin-10-producing B cells (B10 cells) during the course in our case and other three patients with pemphigus treated with IVIG without clinical remission. B10 cells were observed predominantly in $CD1d^-$, $CD5^-$, $CD9^-$ and $CD27^+$ populations among $CD19^+$ cells in healthy controls, as well as in patients with pemphigus. The frequency of B10 cells among $CD19^+$ cells increased in our case, but not in the other three patients without clinical remission, which leads to speculation on the association between the increase of B10 cells and the achievement of long-term remission after IVIG treatment.

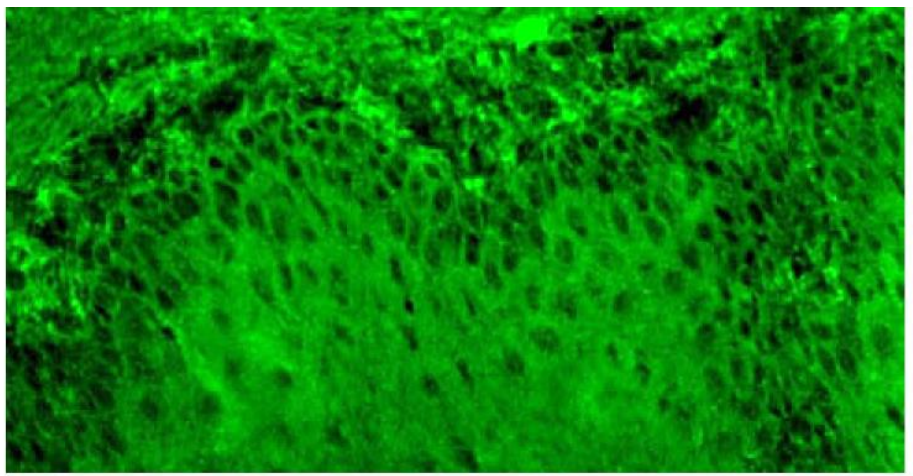
Mechanisms of therapeutic action of IVIg

- selective elimination of pathogenic antibodies due to blocking (saturation) of the neonatal Fc receptor (FcRn) that protects IgG molecules from lysosomal degradation
- anti-inflammatory action of sialylated IgG species that upregulate expression of the inhibitory FcγR (FcγRIIB) receptor on immune cells
- inactivation of pathogenic antibodies by the anti-idiotypic antibodies present in IVIg preparations
- activation of anergic/apoptotic program in B cells by anti-idiotypic antibodies
- increase of B cells producing the immunosuppressive cytokine IL-10
- **protection of self-antigens targeted by autoimmunity by the blocking antibodies present within donors' IgGs**
- anti-apoptotic and anti-oncotic effects on keratinocytes

Both autoantibodies and pathogen-specific antibodies are present in immunoglobulin preparations and reflect characteristics of the donor population

Sujoy Khan, MD,[a,b] Sue Sims, MSc,[a] Don Raine, MSc,[b] and William A. C. Sewell, MD[a,c]

J Am Acad Dermatol December 2008 **1089**



Pemphigus-associated antidesmosomal antibodies by indirect immunofluorescence using monkey esophagus as substrate with intravenous immunoglobulin preparation (diluted 1:10).

Mechanisms of therapeutic action of IVIg

- selective elimination of pathogenic antibodies due to blocking (saturation) of the neonatal Fc receptor (FcRn) that protects IgG molecules from lysosomal degradation
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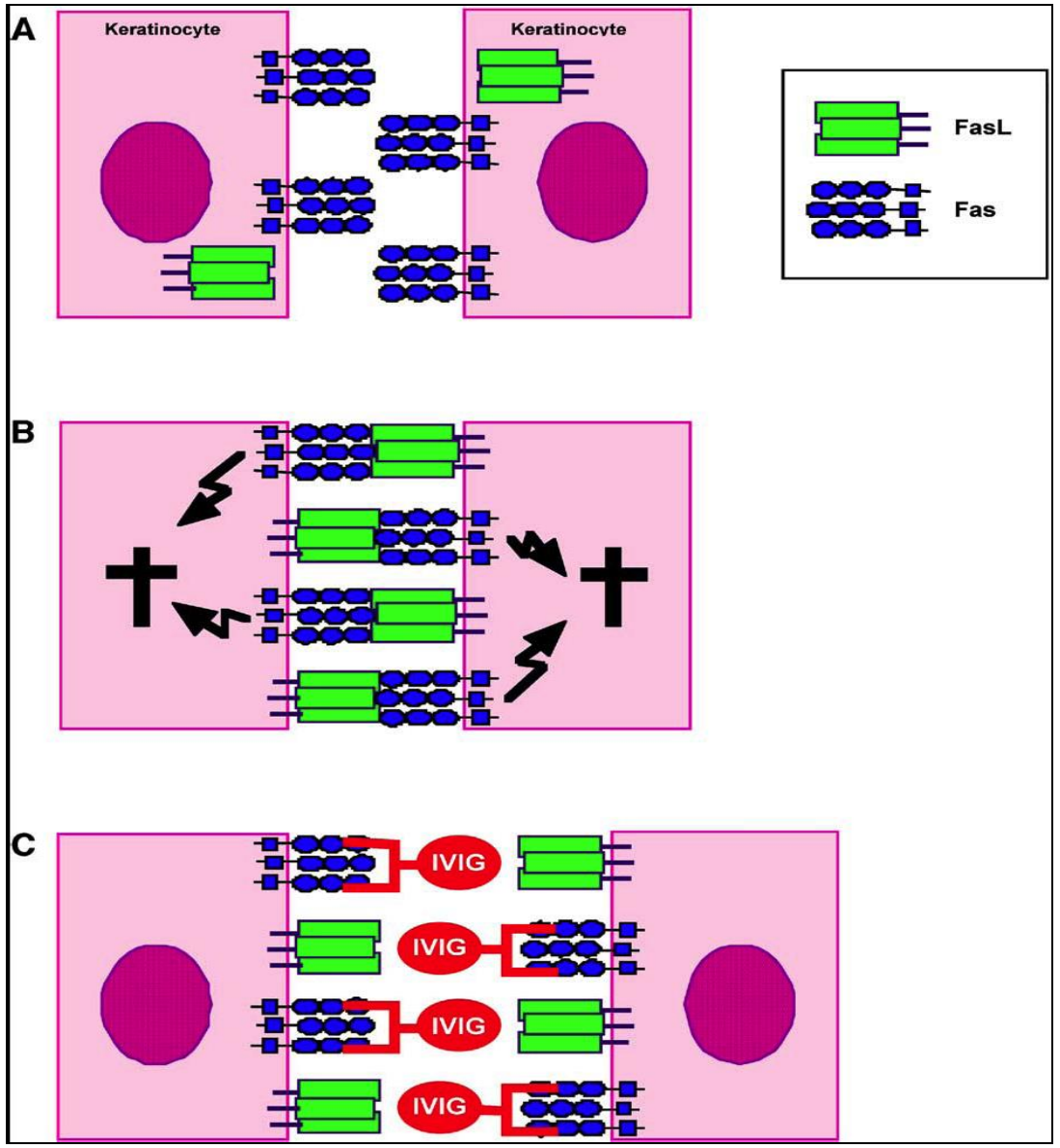
- inactivation of pathogenic antibodies by the anti-idiotypic antibodies present in IVIg preparations
- activation of anergic/apoptotic program in B cells by anti-idiotypic antibodies
- increase of B cells producing the immunosuppressive cytokine IL-10
- protection of self-antigens targeted by autoimmunity by the blocking antibodies present within donors' IgGs
- **anti-apoptotic effects on keratinocytes**

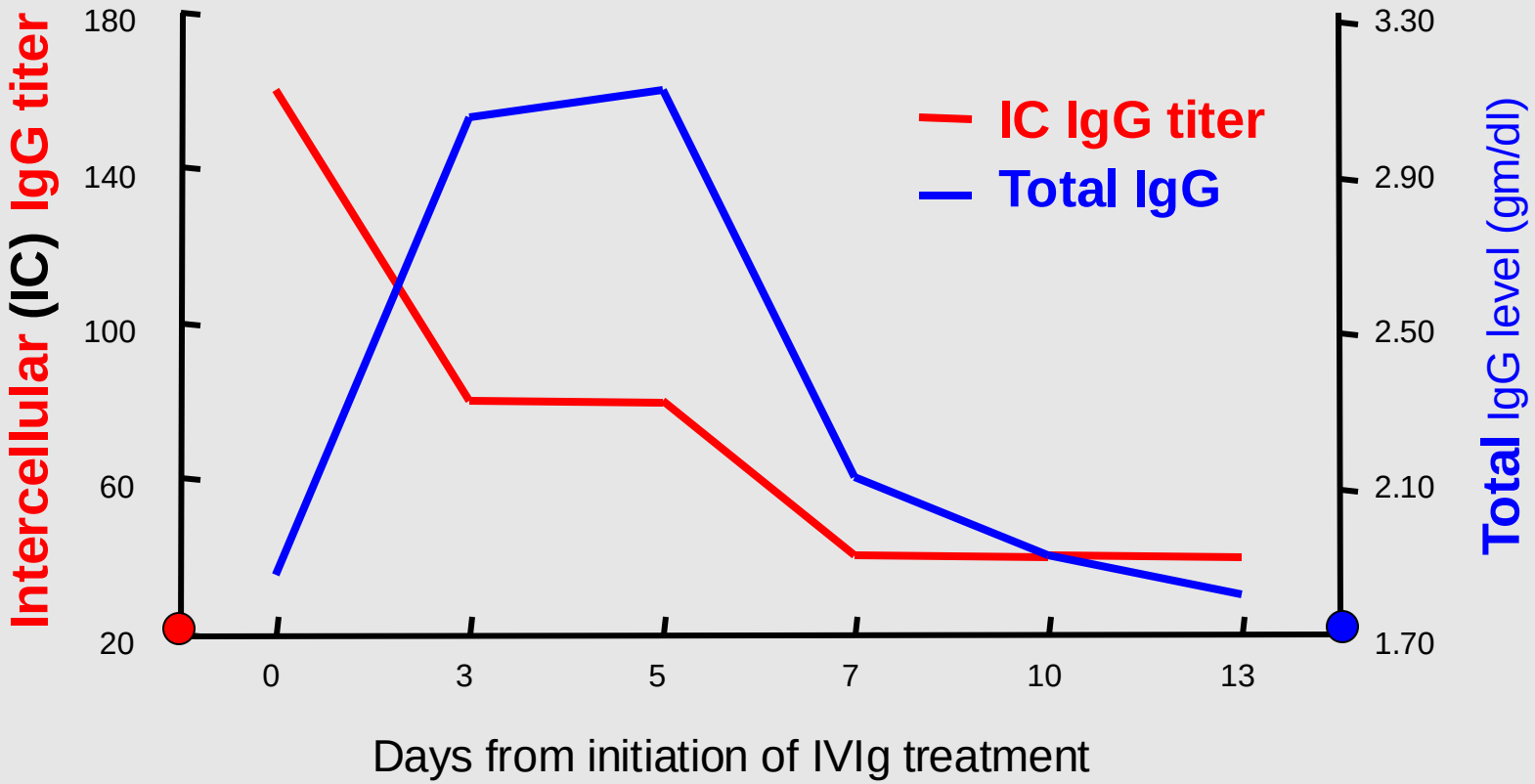
Inhibition of keratinocyte apoptosis by blockade of Fas by anti-Fas antibody present in IVIg



French *et al.*, 2006

Can IVIg be made to work better?

Effect of IVIg on levels of pemphigus (intercellular; IC) and total IgG antibodies



Bystryn, 2004

Current Eye Research
2000, Vol. 21, No. 2, pp. 646–654

0271-3683/00/2102-0646 $15.00
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Influence of intravenous immunoglobulin therapy on serum levels of anti-β4 antibodies in ocular cicatricial pemphigoid

A correlation with disease activity

A preliminary study

Erik Letko[1,2], Kailash Bhol[2], C. Stephen Foster[1] and A. Razzaque Ahmed[2]

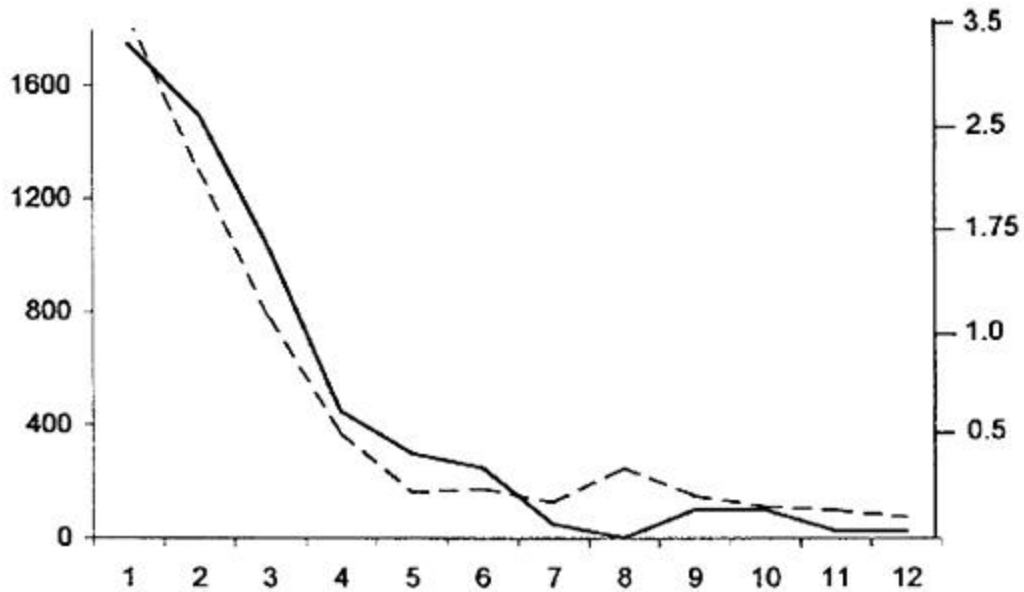


Figure 3. Correlation between disease activity and serum levels of antibodies to β4-integrin in patients with OCP during a consecutive 12 month period. Left hand Y axis demonstrates mean serum titers of anti-β4-integrin antibodies (solid line). Right hand Y axis demonstrates mean disease activity (dash line). "0" represents baseline levels prior to initiation of IVIg therapy. A decline in disease activity parallels a decline in titers of anti-β4 antibodies.

Therapeutic implications of mechanism of IVIg action

- Feedback mechanism maintains individual antibodies at a constant serum level.

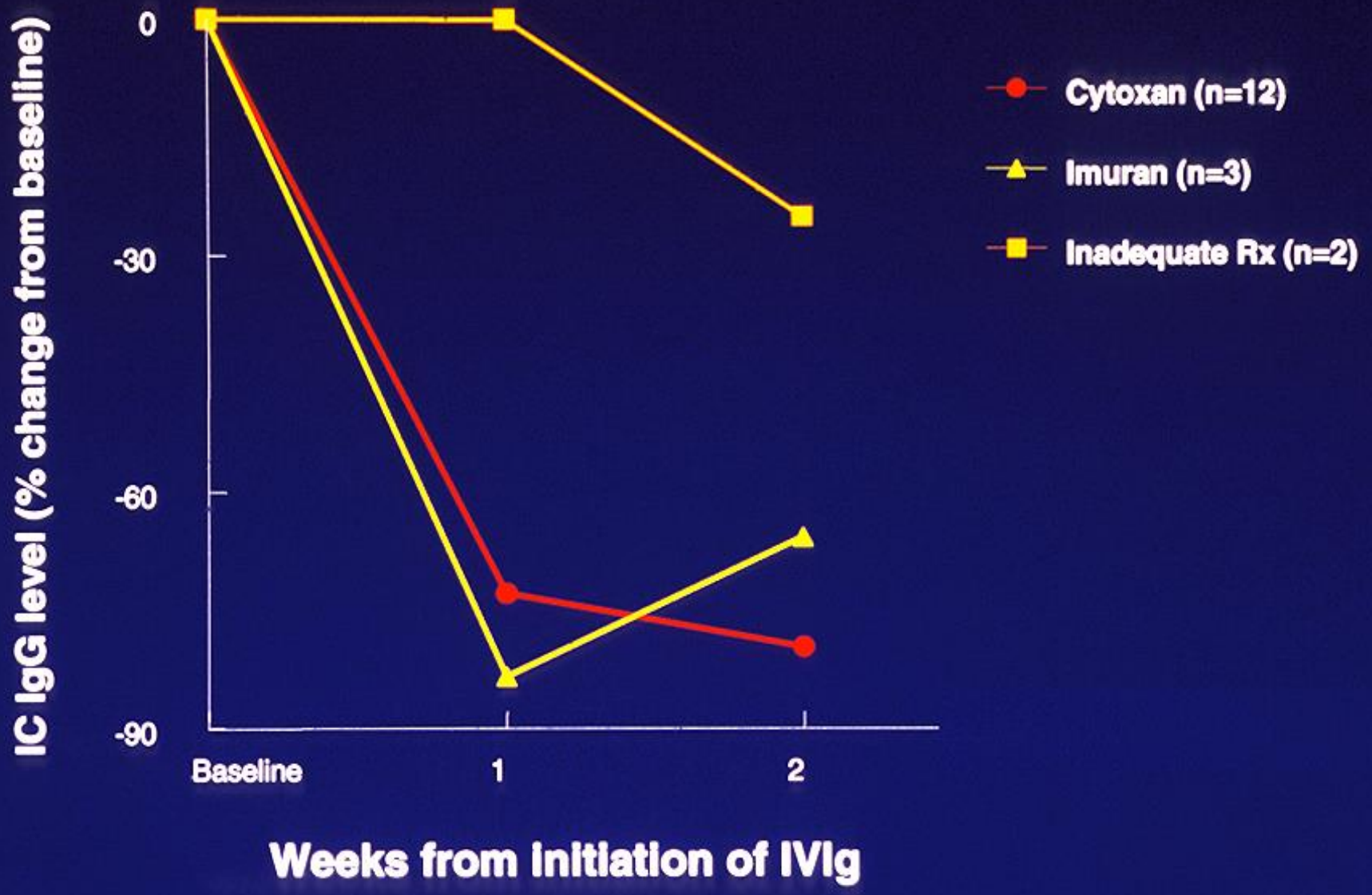
Therapeutic implications of mechanism of IVIg action

- Feedback mechanism maintains individual antibodies at a constant serum level.
- Rapid decrease in autoantibodies will trigger new autoantibody synthesis and a “rebound” in their serum level.

Therapeutic implications of mechanism of IVIg action

- Feedback mechanism maintains individual antibodies at a constant serum level.
- Rapid decrease in autoantibodies will trigger new autoantibody synthesis and a “rebound” in their serum level.
- “Rebound” can be prevented by cytotoxic drugs.

Effect of cytotoxic drug on IVIg induced decrease in IC Ab



Bystryn, 2004

Autoimmunity, February 2012; 45(1): 111–118
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Intravenous immunoglobulin in the treatment of autoimmune bullous dermatoses: An update

ANNETTE CZERNIK[1], SIAVASH TOOSI[2], JEAN-CLAUDE BYSTRYN[2], & SERGEI A. GRANDO[1]

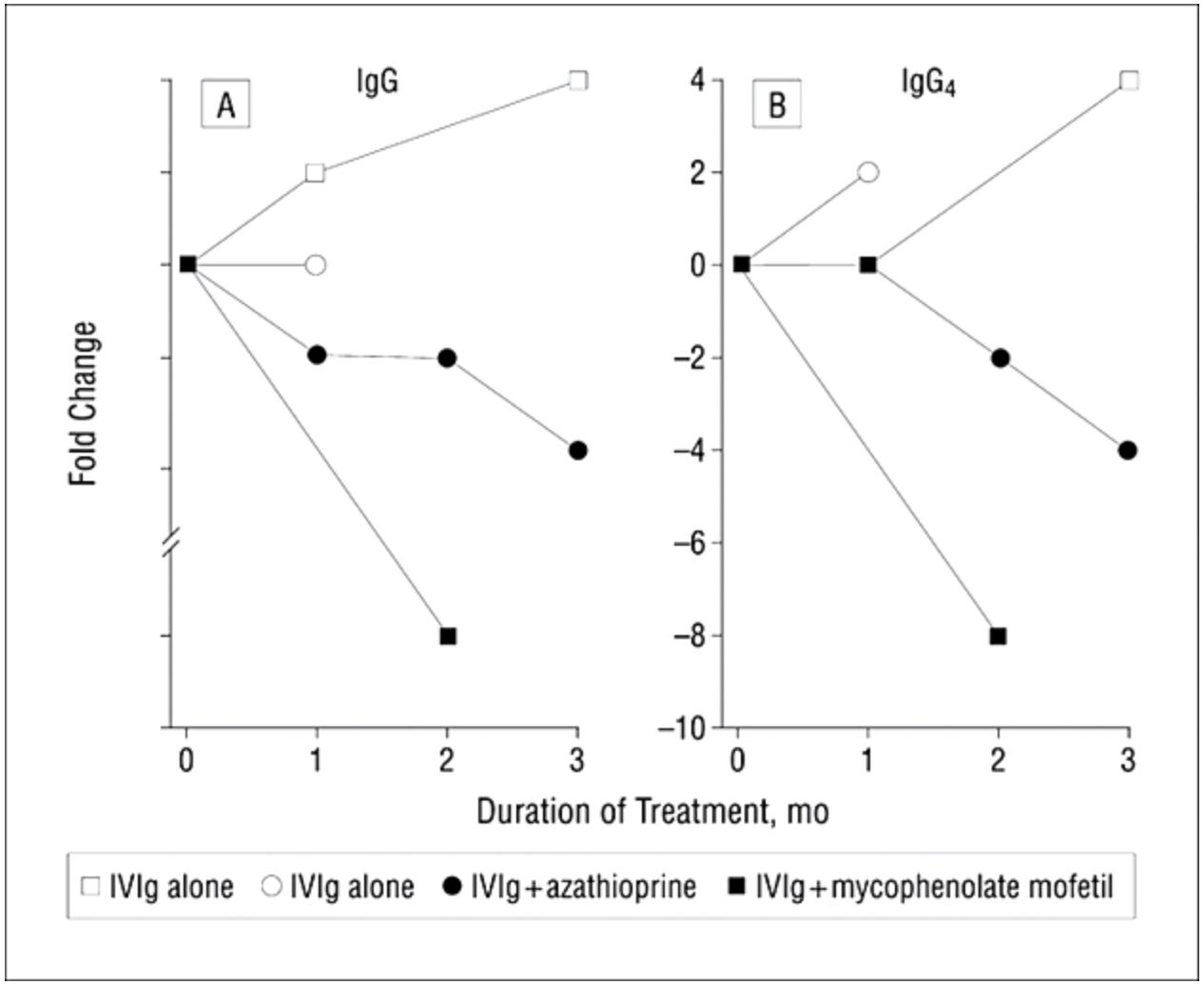
[1]*Department of Dermatology, University of California, Irvine, CA, USA, and* [2]*The Ronald O. Perelman Department of Dermatology, New York University School of Medicine, New York, NY, USA*

Effect of IVIg vs. IVIg plus cyclophosphamide in pemphigus.

	# pts	Anti-Dsg 1		Anti-Dsg 3		Prednisone dose (%)	Disease severity (%)
		IgG1 (%)	IgG4 (%)	IgG1 (%)	IgG4 (%)		
IVIg	4	−34	−33	−27	−66	−7	−15
IVIg + cyclophosphamide	3	−71	−72	−55	−47	−21	−38

Patients unresponsive to conventional therapy were randomized to receive IVIg 500 mg/kg/day for 4 days every 2 weeks, for a total of four cycles with or without oral cyclophosphamide 50 mg three times a day.

Comparison of effects of IVIg administered with and without an immunosuppressive drug on serum levels of pemphigoid IgG (A) and IgG4 (B) autoantibody levels



Czernik, A. et al. Arch Dermatol 2008;144:658-661.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Treatment of Pemphigus Vulgaris with Rituximab and Intravenous Immune Globulin

A. Razzaque Ahmed, M.D., Zachary Spigelman, M.D., Lisa A. Cavacini, Ph.D., and Marshall R. Posner, M.D.

ABSTRACT

BACKGROUND

Pemphigus vulgaris is a potentially fatal autoimmune mucocutaneous blistering disease. Conventional therapy consists of high-dose corticosteroids, immunosuppressive agents, and intravenous immune globulin.

METHODS

We studied patients with refractory pemphigus vulgaris involving 30% or more of their body-surface area, three or more mucosal sites, or both who had inadequate responses to conventional therapy and intravenous immune globulin. We treated the patients with two cycles of rituximab (375 mg per square meter of body-surface area) once weekly for 3 weeks and intravenous immune globulin (2 g per kilogram of body weight) in the fourth week. This induction therapy was followed by a monthly infusion of rituximab and intravenous immune globulin for 4 consecutive months. Titers of serum antibodies against keratinocytes and numbers of peripheral-blood B cells were monitored.

RESULTS

Of 11 patients, 9 had rapid resolution of lesions and a clinical remission lasting 22 to 37 months (mean, 31.1). All immunosuppressive therapy, including prednisone, could be discontinued before ending rituximab treatment in all patients. Two patients were treated with rituximab only during recurrences and had sustained remissions. Titers of IgG4 antikeratinocyte antibodies correlated with disease activity. Peripheral-blood B cells became undetectable shortly after initiating rituximab therapy but subsequently returned to normal values. Side effects that have been associated with rituximab were not observed, nor were infections.

CONCLUSIONS

The combination of rituximab and intravenous immune globulin is effective in patients with refractory pemphigus vulgaris.

1st Month – Week 1, 2, 3, 4 → RTX 375 mg/m²
Week 4 → IVIg cycle

2nd Month – Week 5, 6, 7, 8 → RTX 375 mg/m²
Week 8 → IVIg cycle

3rd, 4th, 5th, 6th Months → Once a month RTX + IVIg

IVIg for skin diseases: *Summary*

- IVIg is a safe and effective drug to induce and maintain a prolonged clinical remission
- it can rapidly and effectively control autoimmune skin diseases
- it has a corticosteroid-sparing effect
- its early use is of significant benefit in patients who may experience life-threatening complications from corticosteroids and immunosuppression
- IVIg works better if given together with a cytotoxic drug like Rituxan, Cytoxan, CellCept or Imuran