Multimodal Treatment of Pemphigus & Multi- vs. Monofactorial Pathogenesis of Pemphigus

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Abstract

BACKGROUND:
Pemphigus vulgaris (PV) is a life-long IgG autoantibody mediated blistering disease affecting the mucosal surfaces lined by the stratified epithelium (oral, nasal, genital) and sometimes also the skin. While corticosteroid treatment is life-saving, the high dose and prolonged courses required for disease control are associated with significant adverse effects, including death. Although introduction of rituximab (RTX) provided for a favorable outcome, the high relapse rate, that is, up to 80%, precludes successful use of RTX as a monotherapy. Intravenous immunoglobulin (IVIg) is being increasingly utilized as off-label therapy for a variety of autoimmune and inflammatory diseases, including PV and pemphigus foliaceus (PF).

AIMS:
The goal of pemphigus research is to develop an effective treatment modality that would allow patients to achieve and maintain a stable remission without the need for additional treatments, or cure.

MATERIALS AND METHODS:
This article summarizes clinical outcome of 123 pemphigus patients treated with a combination of IVIg, an immunosuppressive cytotoxic drug (ICD) and mitochondrion-protecting drugs in the Blistering Disease Clinic at the University of California, Irvine from 2007 to 2017.

RESULTS:
The mean time to disease control was 0.2 months and time to complete remission - 1.7 months. Duration of complete remission on drugs until relapse or end of treatment was 19.3 months. The mean duration of complete remission off drugs until relapse was 15.8 months. That until end of follow up was 48.4 months, with a minimum of 14 and a maximum of 91 months.

The overall complete remission rate off all drugs was 100%, with 12% overall relapse rate. Most relapses, 8.1 vs. 3.3%, occurred during the time of treatment, compared to posttreatment. No patients had more than a single relapse. The duration of the posttreatment follow-up ranged from 9 to 97 months with a mean of 64.8 months, or 5.4 years. The total number of IVIg cycles ranged from 26 in patients without a relapse to 37 in patients with a relapse. The clinical outcome in patients that received IVIg with RTX or another ICD were found to be very similar.

DISCUSSION:
Thus, the multidrug IVIg regimen allowed to achieve three principal treatment objectives: (i) rapid control of pemphigus symptoms; (ii) stable disease remission; and (iii) overall safety of treatment.

CONCLUSIONS:
While the individualized therapeutic approaches to eradicate the autoreactive B cell clones causing disease in each particular PV or PF patient are being developed, all pemphigus patients can benefit from the treatment protocol described in this study.

Theoretical premises for development of curative treatment of pemphigus

- Need to keep disease in full remission until clones of autoantibody (AuAb) producing cells die off:
  - relapse rate in pemphigus patients is higher if the remission-maintaining drugs are discontinued after <2 years of treatment
  - estimated longevity of memory B-cells/plasma cells in mice is 1-3 years

- Each relapse of pemphigus is associated with production of additional AuAbs, due to self-immunization with sequestered antigens released from damaged keratinocytes, which is comparable to booster injection of tetanus toxoid

- Each relapse "resets the clock" for cure for additional 2-3 years

Multidrug treatment of pemphigus

- systemic corticosteroids: prednisone taper
- — mitochondrion protection: minocycline (doxycycline) + niacinamide (nicotinamide)
- — IVIg or plasmapheresis or plasma exchange
- prevention of AuAb production

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Methylprednisolone increased the protein levels of E-cadherin and Dsg 1 and 3 by 300, 180, and 40%, respectively.

Some patients respond well to moderate doses of prednisone (1 mg/kg/day), others require higher doses. If there is an insufficient response after 10 days, the dose is increased by 30%.

Once control of disease is achieved (lack of new lesions, epithelialization of existing erosions and negative Nikolsky sign), the prednisone dose is decreased in a "logarithmic fashion" by 25% of the current dose every 3 weeks.

Mechanisms of Mitochondrial Damage in Keratinocytes by Pemphigus Vulgaris Antibodies

Critical Role of the Neonatal Fc Receptor (FcRn) in the Pathogenic Action of Antimitochondrial Autoantibodies Synergizing with Anti-desmoglein Autoantibodies in Pemphigus Vulgaris

Antimitochondrial Autoantibodies in Pemphigus Vulgaris: A Missing Link in Disease Pathophysiology

IVIg
**Major principles of curative treatment of pemphigus**

- Systemic corticosteroid therapy remains an indispensable component of treatment of pemphigus, as it increases adhesive properties of keratinocytes. Each patient is unique in his/her response to prednisone

- IVIg is a safe and effective drug to maintain clinical remission via several therapeutic mechanisms, including selective elimination of AuAbs
Major principles of curative treatment of pemphigus

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- IVIg is a safe and effective drug to maintain clinical remission via several unique in his/her response to prednisone
- The "rebound effect" can be prevented through inhibition of a compensatory therapeutic mechanisms, including s

"Non-desmoglein pemphigus"

If non-desmoglein (Dsg) antibodies alone were responsible for some cases of pemphigus vulgaris (PV), one would expect to see a certain number of cases of acute PV with negative anti-keratinocyte antibodies by direct and/or indirect immunofluorescence but negative by Dsg 1/3 ELISA.

This was indeed the case in a number of studies. Different authors reported 5% (1), 6% (2), 9% (3), 10% (4), 17% (5), 19% (6) and even 33% (7) of PV patients lacking both anti-Dsg 1 and anti-Dsg 3 antibodies by ELISA.

Synergy among non-desmoglein antibodies contributes to the immunopathology of desmoglein antibody-negative pemphigus vulgaris.

Chernyavsky A, Amber KT, Agnoletti AF, Wang C, Grando SA.

Abstract

Pemphigus vulgaris (PV) is a potentially lethal mucocutaneous blistering disease characterized by IgG autoantibodies (AuAbs) binding to epidermal keratinocytes and inducing this devastating disease. We show that non-Dsg (Dsg) AuAbs (AuAbs) in a certain number of patients with the Dsg1/3 AuAbs-negative acute PV are pathogenic, since they induced skin blistering in neonatal mice due to suprabasal cell detachment. Serum levels of AuAbs to desmocollin 3 (Dsc3), M3 muscarinic acetylcholine receptor (M3AR), and secretory pathway Ca2+/Mn2+ ATPase isoform 1 (SPCA1) correlated with the disease stage of PV. Moreover, AuAbs absorption on recombinant Dsc3, M3AR, or SPCA1 prevented both skin blistering in the passive transfer of AuAbs model of PV in BALB/c mice and significantly decreased the extent of acantholysis in a neonatal mouse skin explant model. Although acantholytic activities of each of these immunoinhibitory-purified AuAbs could not induce a PV-like phenotype, their mixture produced a synergistic effect manifested by a positive Nikolsky sign on the skin of neonatal mice. The downstream signaling of all pathogenic non-Dsg AuAbs involved JNK-mediated phosphorylation and elevation of cytochrome c release and caspase 9 activity. Anti-Dsc3 and anti-SPCA1 AuAbs also activated SIRT proto-oncogene, non-receptor tyrosine kinase (SIRT). Of note, although a constellation of non-Dsg AuAbs apparently disrupt epidermal integrity, elimination of a single pathogenic AuAbs could prevent keratinocyte detachment and blistering. Therefore, anti-Dsg1/3 AuAbs-free PV can be a model for elucidating the roles of non-Dsg antigen-specific AuAbs in the physiological regulation of keratinocyte cell-cell adhesion and blister development.
Synergy among non-desmoglein antibodies contributes to the immunopathology of desmoglein antibody-negative pemphigus vulgaris.


Abstract

Pemphigus vulgaris (PV) is a potentially lethal mucocutaneous blistering disease characterized by IgG autoantibodies (AuAbs) binding to epidermal keratinocytes and inducing this devastating disease. Here, we observed that non-desmoglein (Dsg) AuAbs in serum of individuals with Dsg1/3 AuAbs-negative acute PV are pathogenic, since IgGs from these patients induced skin blistering in neonatal mice due to super basal acantholysis. Serum levels of AuAbs to desmogleins 1/3 (Dsc3), M3 muscarinic acetylcholine receptor (M3AR), and secretory pathway Ca2+-Mn2+-ATPase isoform 1 (SPCA1) correlated with the disease stage of PV. Moreover, AuAbs absorption on recombinant Dsc3, M3AR, or SPCA1 prevented both skin blistering in the passive transfer of AuAbs model of PV in BALB/c mice and significantly decreased the extent of acantholysis in a neonatal mouse skin explant model. Although acantholytic activities of each of these immunofluorescence-stained AuAbs could not induce a PV-like phenotype, their mixture produced a synergistic effect manifested by a positive Nikolsky sign in the skin of neonatal mice. The downstream signaling of all pathogenic non-Dsg AuAbs involved p38 mitogen-activated protein kinase (MAPK)-mediated phosphorylation and elevation of cytochrome c release and caspase 9 activity. Anti-Dsc3 and anti-SPCA1 AuAbs also activated SRC proto-oncogene, non-receptor tyrosine kinase (SRC), Of note, although a constellation of non-Dsg AuAbs apparently disrupted epidermal integrity, elimination of a single immunofluorescence-stained Dsg antigen did not induce skin detachment and blistering. Therefore, anti-Dsg1/3 AuAbs-negative PV can be a model for elucidating the roles of non-Dsg antigen-specific AuAbs in the physiological regulation of keratinocyte cell-cell adhesion and blister development.

The effect of absorption of sera of the Dsg1/3 AuAb-negative acute PV patients with recombinant self-antigens on skin blistering in the passive transfer of disease model of PV in BALB/c mice

Dsc3-absorbed M3AR-absorbed SPCA1-absorbed cAR-absorbed

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Non-Dsg PV AuAbs are pathogenic in neonatal BALB/c mice

The IgG fractions from sera of 12 anti-Dsg1/3 Dsg PV AuAbs are pathogenic in neonatal BALB/c mice, and the pups were examined 24 hrs later.
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Conclusions on non-Dsg pemphigus

- Non-Dsg AuAbs present in serum of the Dsg1/3 antibody-negative acute PV patients are pathogenic
- There is a synergy of the pathogenic actions of individual specificities of AuAbs
- A simultaneous hit by different species of non-Dsg AuAbs is required to overcome the integrity of epidermis and cause acantholysis
- Although a constellation of non-Dsg AuAbs is required to disrupt epidermal integrity, elimination of a single pathogenic AuAb type can prevent acantholysis and skin blistering