Dermatology Reports

The efficacy and safety of intravenous immunoglobulin in pemphigus vulgaris and bullous pemphigoid: a systematic review and meta-analysis

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SUPPLEMENTARY MATERIAL

Supplementary Table 1. Efficacy and safety outcomes of IVIG therapy in AIBDs.

First author, year	Disease	Disease control rate and time	Reduction in corticosteroid use	Autoantibody titers	Relapse rate	Duration of remission	Adverse events	Conclusion
Ahmed et al., 2001[22]	BP	Rate: 100% (10/10) Time: 2.9 months (range: 2.0–4.0)	- Pre-IVIG: Mean prednisone dose = 18,212 (10,650-38,820) mg - Post-IVIG: Mean dose = 1,865 (850-2750) mg (89.7% reduction)	NA	-Pre-IVIG: 4.1 (1-7) -Post-IVIG: 0.9 (0-3)	22.9 months (range: 14–44)	5/15 (33.3%) [Headaches, nausea, fatigue]	IVIG led to sustained remission in refractory bullous pemphigoid, reduced steroid use, improved quality of life, and caused minimal side effects. Gradual withdrawal is crucial for maintaining remission.
Baum et al., 2006[23]	PV	Rate: 83% (10/12 patients: 50% complete remission, 33% partial response) Time: ~6 months (after six cycles)	Baseline prednisone: reduced in 10/12 patients	NA	2/12 (17%) did not respond;	22 months (range 8–81 months	2/12 [Mild headache (1), syncope (vaso-vagal, 1)]	IVIG demonstrated steroid-sparing efficacy in severe PV with minimal adverse effects.
Segura et al., 2007[24]	Mixed (10 PV, 9 other)	Rate: 74% (14/19) [21% complete response, 53% partial response] Time: 20-22 months	Prednisone was tapered or discontinued in responders	Declined in 5/19	NR	12–18 months	-Adverse events: 5/19 (26.3%) [Headache, fever, chills, nausea, vomiting, diarrhea, DVT, bradycardia, hypertension, epistaxis] -Discontinuation Due to AEs: 3/19 [DVT and gastroenterologic symptoms] Mortality: 1/19 [due to metastatic lung cancer, unrelated to IVIG]	The effectiveness of IVIG appeared to be lower than documented in past studies. This variation may be due to the specific preparations used, the severity of the condition, or the unique responses of each patient based on polymorphisms in the Fc receptor gamma.
Xiao et al., 2007[25]	BP	Rate: 100% Time: 1 week	NA (steroids not used)	BP180: 57.0 U/mL (elevated)	Mild relapses within 1 year	No relapses for 2 years post-treatment	0	IVIG quickly induced remission in childhood BP without significant adverse effects. Mild relapses occurred but were manageable.
Amagai et	PV	Rate: 90.5% (19/21	NA	Significant	NA	NA	400mg group: 6/21 (28.6%)	

al., 2009[26]		in 400mg group		reduction in anti-Dsg1 and Dsg3 IgG titers (days 43, 85)			200mg group: 7/20 (35.0%) Placebo group: 5/20 (25.0%) [Headache, aggravated hepatitis C, decreased lymphocytes, palpitations, hepatic dysfunction, nausea, hypertension] SAEs: 1 death (hepatic failure in 200mg group)	
Arnold et al., 2009[27]	PV	Partial improvement (mean overall score: 116 vs. 206 on placebo, $P < 0.0001$). Time: over a 6-month treatment phase	No significant reduction: mean prednisolone dose was higher during IVIG (358 mg vs. 337 mg on placebo).	During the IVIG phase, there was a significant reduction in anti-Dsg1 ($P=0.004$) and anti-Dsg3 ($P=0.004$).	The disease worsened during the placebo phase. The patient switched to rituximab post-trial.	NA	Prior mild AEs: fatigue, insomnia, chills	IVIG showed a biological effect in refractory pemphigus vulgaris, with improvements in autoantibody levels and patient-reported outcomes, although clinical improvement was mild. This study highlights the necessity for larger trials to confirm the efficacy of IVIG. The patient later achieved remission with rituximab.
Asarch et al., 2009[28]	PV	Rate: 87.5% (7/8) Time: 6 months	Prednisone tapered/discontinued post-IVIG response.	Improved anti-Dsg1 and Dsg3 levels	1/8 patient had recurrences; others sustained remission.	Mean 29.8 months post-IVIG discontinuation.	6/8 [Headaches (6), mild nausea (1), fatigue (1)]	IVIG is a safe and effective treatment for juvenile pemphigus vulgaris, often inducing sustained remission with minimal side effects. It acts as a steroid-sparing agent, especially for patients who do not respond to or cannot tolerate standard immunosuppressive therapies. Long-term follow-up showed durable remission in 7 out of 8 patients.
Gaitanis et al., 2012[29]	BP	Rate: 4/5 Time: 0.5 to 2.5 months	Steroids were tapered in all responders	Anti-BP180 titers decreased	2/5	Up to 24 months	1 death (unrelated to IVIG; due to pneumonia).	IVIG effectively manages bullous pemphigoid, particularly when initiated early, with 80.5% of patients achieving remission. Early treatment correlated with faster and more sustained responses. IVIG allowed corticosteroid tapering and showed a favorable safety profile, though infections remained a concern.
Seidling et al., 2013[30]	Mixed (10 PV, 2 BP, 4 other)	Rate: 62.5% (10/16 achieved remission/significan	Mean (SD) %: 75.8 ± 15.3 reduction in steroid dose	Desmoglein Dsg3 (PV): ~130 → ~50	12.5% (2/16)	Sustained over a 24-month observation	14/16 (87.5%) [Headache (43.8%), fatigue (43.8%), back pain (31.3%),	High-dose IVIG can effectively alleviate clinical symptoms in patients with refractory AIBD,

		t improvement) Time: 24 months		U/mL Dsg1 (PF): ~120 → ~40 U/mL (ELISA data)			blood pressure changes (25%), nausea, blurred vision, petechiae]	allowing for a gradual reduction in corticosteroid use. Unlike many other treatments, such as chemotherapy, IVIG is associated with minimal to severe side effects.
Amagai et al., 2017[31]	BP	Rate: 84.8% (25/29) reached treatment reduction (vs. 53.0% in placebo) Time: by day 57	Steroid dose remained stable in the IVIG group.	Anti-BP180 titer reduced by 53.7% in the IVIG group vs. 35.4% in the placebo (not statistically significant.	NA	NA	11/29 (37.9%) in IVIG group; 5/27 (18.5%) in placebo group. [Headache, hepatic dysfunction, fever, platelet decrease, injection site reactions.]	IVIG showed therapeutic benefits for steroid-resistant bullous pemphigoid, especially in severe cases (DAS ≥40), reducing disease activity and corticosteroid use. Adverse events were manageable, with no serious safety concerns, making IVIG a viable option for unresponsive BP patients.
Yu et al., 2020[32]	BP	Rate: 100% (achieved remission). Time: 1 week (initial improvement), 8 weeks (complete remission)	No systemic corticosteroids were used; topical mometasone furoate was tapered.	Anti-BP180 antibody decreased from 2730 U/mL to 104 U/mL post-IVIG.	0% (no relapse)	3 years	0 (no IVIG-related AEs reported).	IVIG monotherapy induced rapid and long-term disease control, suggesting it is a viable treatment option even for BP patients with complications.
Spałek et al., 2023[33]	Mixed (5 PV, 1 BP, 4 others)	Rate: 8/10 Time: Initial improvement after the first cycle	Baseline: 30.56 mg ± 21.14. Post-IVIG: 10.56 mg (2 months), 7.22 mg (12 months) (76.37% reduction).	Desmoglein 3 IgG decreased in PV patients	20% at 12 months	Sustained for 12 months in responders.	8/10 [Leukopenia (most common), headaches, hypotension, fungal infections, nausea, 1 patient required tracheostomy]	IVIG therapy can sustain remission for a year in some patients with AIBD unresponsive to first-line treatments, though it isn't universally effective. The treatment has a favorable safety profile, with mild side effects that typically don't necessitate discontinuation. Older patients may benefit from more frequent IVIG treatments due to potentially diminished responses.

AIBDs, autoimmune blistering diseases; BP, bullous pemphigoid; DAS, Disease Activity Score; Dsg, desmoglein (autoantigen in pemphigus); DVT, deep vein thrombosis; ELISA, enzyme-linked immunosorbent assay; IVIG, intravenous immunoglobulin; NA, not available/not applicable; PF, pemphigus foliaceus; PV, pemphigus vulgaris; SAEs, serious adverse events; SD, standard deviation.

Supplementary Table 2. Quality assessment for three RCT studies evaluated using the RoB-2 quality assessment tool. All three studies showed a low risk of bias.

Study ID	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Other Bias	Overall RoB
Amagai et al., 2009	Low	Low	Low	Low	Low	Low	Low
Amagai et al., 2017	Low	Low	Low	Low	Low	Low	Low
Arnold et al., 2009	Low	Low	Low	Low	Unclear	Unclear	Low

The Methodological index for non-randomized studies (MINORS) quality assessment of the two non-randomized studies reveals moderate methodological quality, with Segura (2006) scoring 8/16 and Seidling (2013) scoring 9/16, as shown in *Supplementary Table 3.*

Supplementary Table 3. MINORS quality assessment of non-randomized studies.

Study ID	A clearly stated aim	Inclusion of consecutive patients	Prospective collection of data	Endpoints appropriate to the aim of the study	Unbiased assessment of the study endpoint	Follow-up period appropriate to the aim of the study	Loss to follow-up was less than 5%	Prospective calculation of the study size	Total score
Segura, 2006	2	0	0	2	0	2	2	0	8/16
Seidlin, 2013	2	2	0	2	0	2	1	0	9/16

The Methodological Quality and Synthesis of Case Series and Case Reports (MMS) quality assessment of case reports and series studies reveals strengths and limitations. While most studies effectively reported exposures and outcomes, indicating transparency in methodology, concerns about selection bias were common due to unclear patient experiences and criteria representation. Weak causal inference was prevalent, as studies often lacked exploration of alternative explanations, re-challenge evidence, and dose-response analyses. Although follow-up duration was generally adequate, the gaps in addressing confounding factors suggest these studies are better suited for generating hypotheses rather than confirming therapeutic effects, as shown in *Supplementary Table 4.*

Supplementary Table 4. MMS quality assessment of case reports and series studies.

Items	Selection	Ascertainment		Causality		Reporting		
Study ID	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8
Yue Yu, 2020	Unclear	Yes	Yes	No	No	No	Yes	Yes
Asarch, 2009	Unclear	Yes	Yes	No	No	No	Yes	Yes
Spalek, 2023	Yes	Yes	Yes	No	No	No	Yes	Yes
Xiao, 2007	No	Yes	Yes	Yes	No	No	Yes	Yes
Gaitanis, 2012	Yes	Yes	Yes	No	No	No	yes	Yes
Ahmed, 2001	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Baum, 2006	Yes	Yes	Yes	No	No	No	Yes	Yes

Selection: [question 1]. Do the patient(s) represent the whole experience of the investigator (center), or is the selection method unclear to the extent that other patients with similar presentations may not have been reported?
Ascertainment: [question 2]. Was the exposure adequately ascertained? [question 3]. Was the outcome adequately ascertained?
Causality: [question 4]. Were other alternative causes that may explain the observation ruled out? [question 5]. Was there a challenge/re-challenge phenomenon? [question 6]. Was there a dose-response effect? [question 7]. Was the follow-up long enough for outcomes to occur?
Reporting: [question 8] Are the cases described with sufficient details to allow other investigators to replicate the research or enable practitioners to make inferences about their practice?

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