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

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Abstract

Autoimmune blistering diseases (AIBDs) encompass various skin conditions that involve the production of autoantibodies that attach to specific antigens found in the skin and mucous membranes. This systematic review examined the efficacy and safety of intravenous immunoglobulin (IVIG) therapy for AIBDs. The search included PubMed, Science Direct, Google Scholar, Wiley, and EBSCO using the following keyword combinations: (Pemphigus Vulgaris OR Bullous Pemphigoid OR Autoimmune Blistering Disease) AND (Intravenous Immunoglobulin OR IVIG) AND (Efficacy OR Long-term Outcomes) AND (Safety OR Adverse Effects OR Quality of Life). Of 617 papers, 12 articles were considered suitable for the systematic review and extracted through the database search. A meta-analysis demonstrated an efficacy of 85.0% (95% confidence interval [CI]: 75.5-92.3, $p<0.001$) for IVIG therapy in AIBDs. Subgroup analyses showed relapse rates of 18.2% (95% CI: 9.3-27.0, $p<0.001$) and adverse event rates of 48.0% (95% CI: 28.7-67.3, $p<0.001$). Rapid clinical responses occurred within 1-4 weeks, with sustained remission lasting up to 44 months. Corticosteroid use was reduced by 76-90%, and autoantibody titers declined significantly. While adverse events were common (26-88% of patients), most were mild, with severe complications (<5%). IVIG is effective for AIBDs, offering rapid control, durable remission, and significant steroid reduction. Standardized protocols for dosing and monitoring are needed, and future research should focus on large-scale trials to confirm long-term benefits.

Introduction

Autoimmune blistering disorders (AIBDs) encompass a diverse range of conditions marked by the presence of autoantibodies that bind to specific skin and mucous membrane antigens. These disorders can be divided into two main categories: pemphigoid diseases, characterized by subepidermal blisters due to autoantibodies targeting components of the dermal-epidermal junction (*e.g.*, BP180, BP230), and pemphigus, where autoantibodies are directed against desmosomal proteins (desmoglein 1 and 3) that connect neighboring keratinocytes, leading to intraepidermal acantholysis.[1,2] A notable form of AIBD is dermatitis herpetiformis, which involves autoantibodies that react against tissue and epidermal transglutaminase.[3,4]

Bullous pemphigoid (BP) is the most common AIBD in Europe, occurring at a rate of approximately 20 cases per million people per year. Following BP, mucous membrane pemphigoid and pemphigoid gestationis are also noteworthy, each with an incidence of about 2 cases per million annually.[5,6] BP predominantly affects elderly individuals (mean age ~70-80 years), with a slight male predominance in some cohorts. In pemphigus, the frequency varies by geographic location. In regions such as Central Europe and the United States, the estimated incidence is around 1 to 7 new cases per million

individuals each year.[7,8] Typically, pemphigus vulgaris (PV) occurs more frequently than pemphigus foliaceus, with reported ratios varying from 4:1 to 9:1.[9] PV usually presents at a younger age (40-60 years) than BP, and its sex distribution varies geographically, with some regions showing a female predominance.

AIBDs have a profound impact on many facets of a person's life, creating a considerable burden.[10,11] Treatment options like corticosteroids, whether used alone or in conjunction with steroid-sparing immunosuppressants (*e.g.*, azathioprine, mycophenolate mofetil, or rituximab), have effectively managed these conditions. Current international guidelines recommend systemic corticosteroids as first-line therapy, with rituximab approved for moderate-to-severe PV. However, these traditional therapies are associated with significant side effects and health complications, particularly when used over extended periods.[12,13] This ongoing issue has led dermatologists to seek the most effective treatments that minimize potential complications continually. Intravenous immunoglobulin (IVIG) is currently given to patients with severe or refractory AIBDs, particularly when conventional biological therapies are not advisable or cannot be tolerated.[14] It is important to note that IVIG is rarely used as monotherapy in real-world practice; it is often combined with other systemic therapies (*e.g.*, rituximab or immunosuppressants) as an adjunct or as part of a steroid-sparing strategy. IVIG exerts its immune-modulating effects through various mechanisms that are not mutually exclusive, primarily involving its immunoglobulin G (IgG) structure and its two active regions: the F(ab')2 and Fc domains.[15,16] The main actions of IVIG in managing autoimmune disorders include neutralizing circulating autoantibodies *via* the F(ab')2 fragment, as well as preventing tissue damage caused by complement activation and reducing the lifespan of circulating autoantibodies through the Fc domain. Consequently, IVIG helps to inhibit abnormal immune responses and promotes long-lasting clinical remission.[16,17]

Current therapies for AIBD often involve prolonged usage of corticosteroids, which may result in serious side effects. Therefore, alternative treatments with fewer adverse effects are essential. IVIG has emerged as a promising option due to its immunomodulatory effects and potential to reduce corticosteroid dependence. However, varied outcomes in studies highlight the need for a systematic review. This review aims to evaluate the efficacy and safety of IVIG therapy in patients with AIBD, focusing on its effects on disease remission, relapse rates, and adverse events to guide treatment decisions.

Materials and Methods

This systematic review was conducted using the guidelines established by the PRISMA framework for systematic reviews and meta-analyses and registered on PROSPERO (CRD420250628230).[18] No deviations from the registered protocol occurred.

Literature search strategy

The search was conducted across five electronic databases: PubMed, Science Direct, Google Scholar, Wiley Online Library, and EBSCOhost. The following search strings were applied to each database; PubMed: ("Pemphigus Vulgaris"[MeSH] OR "Bullous Pemphigoid"[MeSH] OR "Autoimmune Blistering Diseases"[MeSH]) AND ("Immunoglobulins, Intravenous"[MeSH] OR "IVIG" OR "IVIg") AND ("Treatment Outcome"[MeSH] OR "Efficacy" OR "Long-Term Outcomes") AND ("Drug-Related Side Effects and Adverse Reactions"[MeSH] OR "Safety" OR "Adverse Effects" OR "Quality of Life"); Science Direct, Wiley, EBSCO: (Pemphigus Vulgaris OR Bullous Pemphigoid OR Autoimmune Blistering Disease) AND (Intravenous Immunoglobulin OR IVIG) AND (Efficacy OR Long-term Outcomes) AND (Safety OR Adverse Effects OR Quality of Life); Google Scholar: the first 200 results were screened using the same keyword combination, with additional manual screening of references from included studies. No language or date restrictions were applied beyond the English language requirement. Duplicates were removed using reference management software (EndNote) before screening.

Inclusion and exclusion criteria

This systematic review examined studies on patients with AIBD, such as BP and PV. Eligible study designs included randomized controlled trials (RCTs), prospective/retrospective cohorts, case series, or case reports. Eligible interventions required IVIG as a primary or adjunctive therapy, with reported outcomes on efficacy (*e.g.*, disease control, relapse rates) or safety (*e.g.*, adverse events). Only studies published in English were considered to ensure accessibility and consistency in interpretation. Studies were excluded if they were published in non-English languages, lacked sufficient outcome data (*e.g.*, missing efficacy/safety metrics), or involved animal models, *in vitro* experiments, or review articles.

Selection of articles and data extraction

Two independent authors reviewed and screened the full text of eligible studies based on predefined criteria. Data were manually extracted into an Excel spreadsheet, capturing study characteristics such as the title, first author's last name, publication year, country of origin, study design, and journal name. Demographic details included patient age, sample size, number of groups, diagnosis (*e.g.*, BP, PV), and disease duration. Intervention specifics focused on IVIG regimens (dose, frequency, duration,

brand) and comparator treatments (*e.g.*, placebo). Outcome measures encompassed efficacy metrics (disease control rates, relapse rates, steroid reduction, autoantibody changes) and safety data (adverse events, mortality). Analytical techniques, such as enzyme-linked immunosorbent assay for autoantibody quantification, were also recorded. Discrepancies in extraction were resolved through consensus or consultation with a third reviewer.

Quality assessment

The Cochrane risk-of-bias tool for randomized trials (RoB-2)[19] was used to evaluate methodological quality across six domains: selection bias (randomization/allocation), performance bias (blinding of participants/personnel), detection bias (blinding of outcome assessors), attrition bias (missing data handling), reporting bias (selective outcome reporting), and other biases (*e.g.*, conflicts of interest). Each domain is rated as low, high, or unclear, with the overall risk reflecting the highest bias level identified. Moreover, the methodological quality of non-randomized studies (retrospective, prospective, cohort, and case-control) was assessed using the Methodological Index for Non-Randomized Studies (MINORS) tool.[20] Each study was assigned a unique identifier and categorized by design. Twelve criteria were evaluated on a scale from 0 to 2, where 0 meant not reported, 1 indicated inadequate reporting, and 2 denoted adequate reporting. Criteria 1-8 applied to all studies, while items 9-12 were specific to comparative studies. Total scores ranged from 0 to 16 for non-comparative studies and from 0 to 24 for comparative designs, with higher scores indicating better methodological quality.

The Methodological Quality and Synthesis of Case Series and Case Reports tool was utilized for the case report and series study. This framework evaluates four key domains: selection (criteria for participant inclusion), ascertainment (accuracy in outcome measurement), causality (plausibility of cause-effect relationships), and reporting (completeness of methodological details). Each domain is assigned a score based on predefined criteria, with higher total scores indicating a lower risk of bias. Although there is no established cutoff to categorize risk levels as “low”, “moderate”, or “high”, we critically analyzed individual item scores and the overall score to assess reliability.

Statistical analysis

The meta-analysis was conducted using a random-effects model (DerSimonian-Laird method) due to anticipated clinical and methodological heterogeneity across studies. Proportions were transformed using the Freeman-Tukey double arcsine transformation to stabilize variances. For studies reporting zero events (*e.g.*, no relapses or no adverse events), a continuity correction of 0.5 was applied to enable pooling. Heterogeneity was quantified using the I^2 statistic, with values of 25%, 50%, and 75%

representing low, moderate, and high heterogeneity, respectively. All analyses were performed using OpenMetaAnalyst (version 1.0.25).[21] A leave-one-out sensitivity analysis was conducted for outcomes with high heterogeneity (I^2>50%) to assess the robustness of pooled estimates. Publication bias was not formally assessed due to the small number of included studies (<10) for most outcomes.

Results

A total of 617 papers were extracted from five databases (PubMed, Science Direct, Google Scholar, Wiley, and EBSCO). Twelve articles were considered suitable for the systematic review (Figure 1). Among these, five studies focused on BP (totaling approximately 78 patients), seven studies focused on PV (totaling approximately 90 patients), and two studies included mixed AIBDs. Due to incomplete disease-specific outcome reporting in the mixed studies, formal subgroup meta-analyses by disease type could not be performed for all outcomes; where separate data were available, results are reported for each disease individually. Baseline patient characteristics, including mean age, disease duration, and IVIG dosing regimens, are summarized in Table 1.[22-33]

The included studies reported clear criteria for initiating IVIG therapy. In 10 of 12 studies, IVIG was used for refractory disease (failure of at least two conventional therapies). Eight studies cited corticosteroid dependence or intolerance as an indication. Three studies used validated severity scores (Bullous Pemphigoid Disease Area Index or Pemphigus Disease Area Index) to select patients. Baseline autoantibody titers were reported in six studies, but were not consistently used as selection thresholds. Overall, IVIG was predominantly reserved for patients with severe, refractory, or steroid-intolerant disease.

Supplementary Table 1 summarizes the efficacy outcomes of IVIG therapy. A random-effects model with Freeman-Tukey double arcsine transformation was used; for studies reporting zero events, a continuity correction of 0.5 was applied. The pooled analysis demonstrated an overall disease control rate of 86.0% (95% confidence interval [CI]: 79.1-92.9, $p<0.001$) with low heterogeneity (I^2=31.1%) (Figure 2). When examined by disease type, BP response rates ranged from 84.8% to 100%, while PV response rates ranged from 62.5% to 90.5%. Initial clinical improvement was observed within 1 to 4 weeks, with complete remission achieved between 2 and 22 months. A marked corticosteroid-sparing effect was observed across studies, with dose reductions ranging from 76% to 90%. Autoantibody titers (anti-Dsg1/3 for PV; anti-BP180 for BP) declined significantly and correlated with clinical improvement in eight studies. Durable remission of IVIG was reported for 12 to 44 months. Notably, the definitions of key outcomes such as “disease control”, “remission”, and “relapse” varied across

studies, which may contribute to the observed heterogeneity and limit direct comparisons. No dose-response analysis could be performed due to inconsistent reporting of dosing schedules.

The pooled relapse rate was 18.2% (95% CI: 9.3-27.0, $p<0.001$) with no heterogeneity ($I^2=0\%$) (Figure 3). Relapses occurred in both BP and PV, but disease-specific pooled rates could not be calculated due to incomplete reporting. In studies that specified timing, relapses occurred only after IVIG discontinuation, not during active combination therapy. No baseline predictors of relapse could be reliably identified, although longer IVIG duration (≥12 cycles) appeared associated with lower relapse risk.

The pooled adverse event rate was 48.0% (95% CI: 28.7-67.3, $p<0.001$) with high heterogeneity ($I^2=86.8\%$) (Figure 4). A leave-one-out sensitivity analysis confirmed the robustness of this estimate. The most frequent adverse events included headache (25-44%), fatigue (33-44%), nausea (15-35%), transient blood pressure changes (~25%), and fever or chills (10-30%). Serious adverse events occurred in less than 5% of patients and included one case of hepatic failure, one deep vein thrombosis, and one tracheostomy requirement. Two deaths were reported, both unrelated to IVIG therapy. These safety data are summarized in Table 2.

Quality assessment showed low risk of bias for the three RCTs (*Supplementary Table 2*). The two non-randomized studies demonstrated moderate methodological quality, with MINORS scores of 8/16 and 9/16 (*Supplementary Table 3*). The case reports and case series showed strengths in reporting but had limitations in selection bias and causal inference, making them suitable for hypothesis generation (*Supplementary Table 4*).

Discussion

Our review revealed the efficacy of IVIG therapy in various forms of AIBD, including BP, PV, and their equivalents. Across multiple studies, IVIG has shown a high rate of disease control, a significant effect in reducing the need for steroids, and notable immunomodulatory effects. However, the response times and adverse event profiles can vary. Several studies have reported rapid induction of remission. Xiao *et al.* (2007) found that children with BP achieved complete remission within 1 week, with sustained benefits lasting over 2 years.[25] Similarly, Yu *et al.* (2020) observed initial improvement within 1 week, with complete remission achieved by 8 weeks, further supporting the rapid onset of action with IVIG monotherapy.[32] In contrast, other studies, such as those conducted by Segura *et al.* (2007) and Arnold *et al.* (2009), reported a more gradual improvement, with response times ranging from several months to more than 6 months.[24,27] Notably, while Ahmed *et al.* (2001) and Baum *et al.* (2006) reported disease control rates of 100% and 83%, respectively, the duration of remission varied

significantly, approximately 3 months in Ahmed *et al.*'s study compared to over 22 months in Baum *et al.*'s research.[22,23] This variability in the time course suggests that factors such as disease severity and IVIG dosing regimens may play a significant role in the treatment outcomes. Our pooled analysis shows that IVIG is highly effective in managing disease activity, achieving a disease control rate of 86.0% (95% CI: 79.1-92.9, $p<0.001$). This finding aligns with a recent systematic review by Kianfar *et al.* (2023), which reported remission rates of 78.6% for epidermolysis bullosa acquisita, 82.8-86.7 for pemphigus with rituximab combination, and 88.0% for BP with IVIG alone.[34]

Moreover, IVIG has frequently been used as a steroid-sparing agent. Ahmed *et al.* (2001) evidenced an 89.7% reduction in corticosteroid dose,[22] and similar steroid tapering was observed in studies by Baum *et al.* (2006) and Asarch *et al.* (2009), where responders either taper or completely discontinue prednisone.[23,28] Furthermore, multiple studies reported significant immunological effects: Amagai *et al.* (2009) documented a marked reduction in anti-Dsg1 and anti-Dsg3 IgG titers,[31] and Seidling *et al.* (2013) demonstrated declines in desmoglein levels that paralleled clinical improvements.[30] Even though Arnold *et al.* (2009) noted that the mean prednisolone dose during the IVIG phase was slightly higher than placebo, outcome measures such as autoantibody levels were improved, indicating that the biological effect of IVIG might precede, or even enable, later clinical benefits.[27]

Long-term follow-up data reported in several studies support the durability of IVIG-induced remission. For example, Asarch *et al.* (2009) found that remission in PV was largely sustained over a mean period of approximately 30 months,[28] and Gaitanis *et al.* (2012) noted that IVIG, when initiated early in BP, led to sustained responses with a relatively low relapse rate.[29] However, while some studies (Xiao *et al.*, 2007, and Yu *et al.*, 2020) reported 100% remission with minimal relapse,[25,32] and Segura *et al.* (2007) documented a modest relapse rate.[24] These findings underscore the importance of tailoring IVIG regimens to patient-specific factors and the underlying disease course. This further emphasizes its role in maintaining disease control over time.

The overall safety profile of IVIG in these studies appears favorable. Common adverse events included headaches, nausea, fatigue, and transient blood pressure changes; these were typically mild and manageable. In contrast, rare serious adverse events such as the hepatic failure reported in the 200 mg group by Amagai *et al.* (2009) and a case requiring tracheostomy noted by Spałek *et al.* (2023) emphasize the need for vigilant monitoring, especially in older patients or those with underlying comorbidities.[31,33] It is worth noting that adverse events were not universal, and most patients across studies tolerated IVIG well, reinforcing its potential as a viable therapeutic option for refractory cases. Similarly, a systematic review highlighted several notable side effects associated with the condition. Headaches were reported frequently, along with fever and chills, nausea and vomiting, and episodes of hyper/hypotension. Fatigue was also mentioned as a common issue, while occurrences of anemia

and skin-related symptoms were less prevalent. Muscle pain was observed in a smaller portion of cases. Thromboembolic events were rare, with incidents of deep vein thrombosis, transient strokes, and strokes noted in very few individuals.[34] This review aligned with findings of the studies by Ahmed *et al.* (2001), Baum *et al.* (2006), and Asarch *et al.* (2009).[22,23,28] However, rare but serious events like thromboembolic complications, including deep vein thrombosis (1.0%), transient ischemic strokes, and full strokes, emphasize the need for careful patient monitoring, especially in those with predisposing risk factors. Segura *et al.* (2007) and Amagai *et al.* (2009) similarly reported adverse events, such as bradycardia and hepatic failure, although these were isolated occurrences.[24,26] Despite the variability in safety profiles, the consistent efficacy of IVIG in achieving significant steroid-sparing effects and durable remission highlights its therapeutic importance. This reinforces the need for personalized patient management and careful monitoring to minimize risks.

This review is limited by the heterogeneity of the included studies, which vary in design (including case reports, small cohorts, and RCTs), IVIG dosing protocols, and definitions of outcomes. These differences complicate direct comparisons across studies. Many of the studies had small sample sizes, short follow-up periods, or did not include control groups, which reduces the generalizability of the findings. Additionally, publication bias may lead to an overestimation of efficacy, and safety data were reported inconsistently, likely underrepresenting rare adverse events. To address these shortcomings, future research should focus on conducting large, multicentre RCTs with standardized IVIG regimens, uniform outcome measures, and long-term follow-up.

Conclusions

This systematic review and meta-analysis demonstrates that IVIG therapy is effective in managing AIBDs, particularly PV and BP. IVIG achieves significant disease control (86.0% pooled efficacy), reduces corticosteroid dependence by 76-90%, and can induce durable remission lasting up to 44 months. However, the available evidence is predominantly derived from non-randomized studies, case series, and small RCTs, which limits the strength of causal inferences regarding definitive efficacy. It is important to emphasize that IVIG is not a universal first-line therapy but rather a valuable option for specific patient subgroups, including those with refractory disease unresponsive to conventional therapies, contraindications or intolerance to standard treatments, or severe disease requiring rapid control. Furthermore, access to IVIG remains limited in certain countries due to high costs, variable regulatory approval, and supply constraints, which may restrict its practical use despite demonstrated efficacy. While adverse events are common (approximately 48%), they are generally mild and manageable; severe complications are rare (<5%). The substantial heterogeneity in IVIG dosing

protocols, outcome definitions, and study designs across the literature underscores the need for standardization. Future research should prioritize large, multicenter RCTs with uniform dosing regimens, disease-specific outcome measures, and long-term follow-up to confirm long-term benefits and establish optimal patient selection criteria.

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Figure 1. Schematic representation of the criteria for selecting studies in the systematic review.

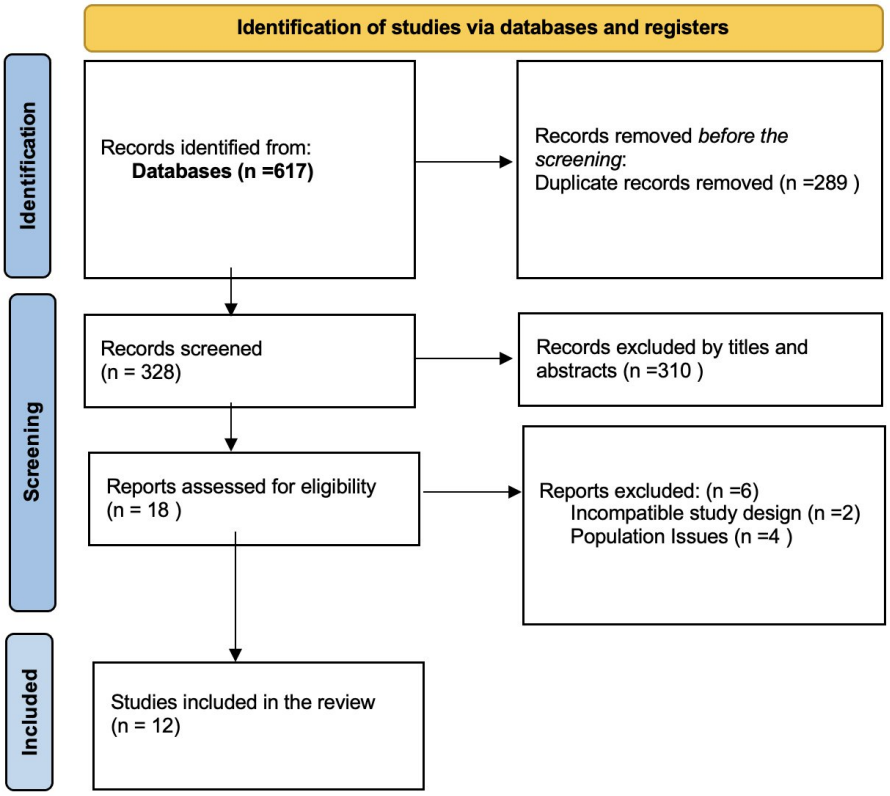


Table 1. Study characteristics and IVIG regimens for AIBDs.

First author, year	Study design	Disease (n)	Mean age (years)	Male /Female	Mean disease duration	IVIG regimen
Bullous pemphigoid						
Ahmed *et al*., 2001[22]	Prospective	BP (15)	76 (61-89)	10/5	28.3 months	2 g/kg/cycle every 4 weeks; mean 14.7 cycles (10-18); duration 20-30 months
Xiao *et al*., 2007[25]	Case report	BP (1)	3.5 months	1/0	1 week	400 mg/kg/day × 4 days (single cycle)
Gaitanis *et al.*, 2012[29]	Case series	BP (5)	59-89	1/4	1.95 months	2 g/kg/cycle over 5 days every 4 weeks; 1-19 cycles
Amagai *et al.*, 2017[31]	RCT	BP (29 IVIG, 27 placebo)	IVIG: 64.0 ±11.7; Placebo: 66.3 ±14.4	19/37 total	NR	400 mg/kg/day × 5 days (single cycle)
Yu *et al.*, 2020	Case report	BP (1)	76	0/1	≥4 weeks of symptoms	400 mg/kg/day × 5 days (single cycle)
Pemphigus vulgaris						
Baum *et al.*, 2006[23]	Case series	PV (12)	51 (30-67)	7/5	2 years (4 mo-6 y)	2 g/kg/cycle every 4 weeks × 6 cycles; then intervals 6-8 weeks
Amagai *et al.*, 2009[26]	RCT	PV (61: 400 mg=21, 200 mg=20, placebo=20)	400 mg: 57.8±11.6; 200 mg: 57.0±14.6; placebo: 50.1±11.7	27/34	Placebo: 16.1±13.6 mo; 200 mg: 28.6±32.3 mo; 400 mg: 28.5±46.9 mo	200 or 400 mg/kg/day × 5 days (single cycle)
Arnold *et al.*, 2009[27]	RCT crossover	PV (1)	33	1/0	15 years	1 g/kg/month (trial) or 2 g/kg/ (open phase) × 6 cycles
Asarch *et al.*, 2009[28]	Retrospective case series	PV (8)	15.5 (15-18)	2/6	16.8 months	2 g/kg/cycle divided over 3 days monthly, then intervals up to 16 weeks; mean 28.5 cycles
Mixed or other AIBDs						
Segura et al., 2007[24]	Retrospective	PV (10), other (9)	23-80	8/11	6-252 months	2 g/kg/cycle monthly; 3-27 cycles
Seidling et al., 2013[30]	Retrospective	PV (10), BP (2), other (4)	50.4±14.4	8/8	40.8 months	2 g/kg/cycle every 4 weeks; mean 38.6 cycles/patient
Spałek et al., 2023[33]	Retrospective case series	PV (5), BP (1), other (4)	58.5±14.7	5/5	1.76±1.85 years	2 g/kg/cycle (400 mg/kg/day ×5) every 4 weeks; 4-12 cycles

BP, bullous pemphigoid; PV, pemphigus vulgaris; RCT, randomized controlled trial; NR, not reported; IVIG, intravenous immunoglobulin; AIBDs, autoimmune blistering diseases.

Table 2. Summary of adverse events associated with IVIG therapy in AIBDs.

Adverse event	Studies reporting the event (n)	Range of incidence (%)	Most common severity
Headache	6/12	25-44	Mild to moderate
Fatigue	5/12	33-44	Mild
Nausea/vomiting	4/12	15-35	Mild
Blood pressure changes (hyper/hypotension)	3/12	25 (transient)	Mild
Fever/chills	3/12	10-30	Mild
Back pain	2/12	31	Mild
Leukopenia	1/12	Not reported precisely	Mild
Hepatic dysfunction	2/12	1 case each (Amagai, 2009; Amagai, 2017)	Severe (1 hepatic failure)
Thromboembolic events (DVT)	1/12	1 case (Segura, 2007)	Severe
Tracheostomy requirement	1/12	1 case (Spałek, 2023)	Severe

DVT, deep vein thrombosis.

Figure 2. Forest plot of the disease control rate of IVIG therapy for AIBDs. Proportions were pooled using a random-effects model (DerSimonian-Laird method) with the Freeman-Tukey double arcsine transformation. Heterogeneity: I^2=31.1%, p=0.170.

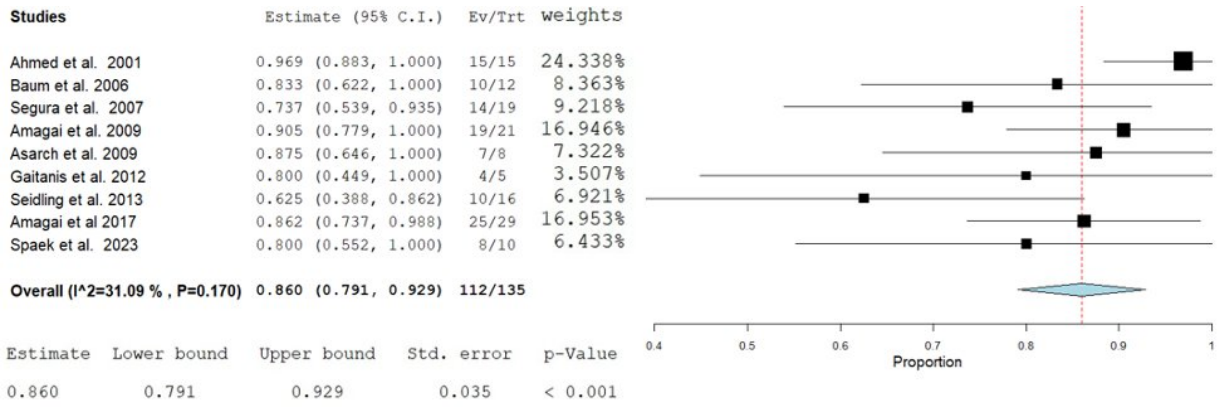


Figure 3. Forest plot of the relapse rate of IVIG therapy for AIBDs. Proportions were pooled using a random-effects model (DerSimonian-Laird method) with the Freeman-Tukey double arcsine transformation; a continuity correction of 0.5 was applied for studies with zero events. Heterogeneity: I^2= 0%, p=0.793.

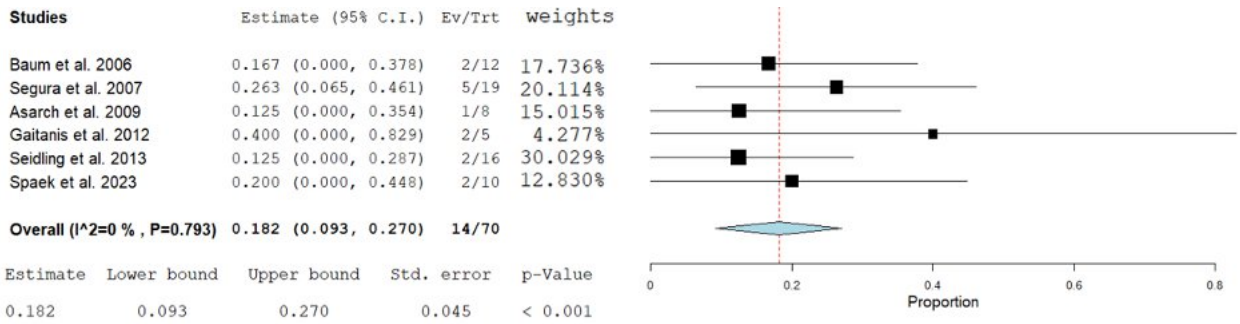
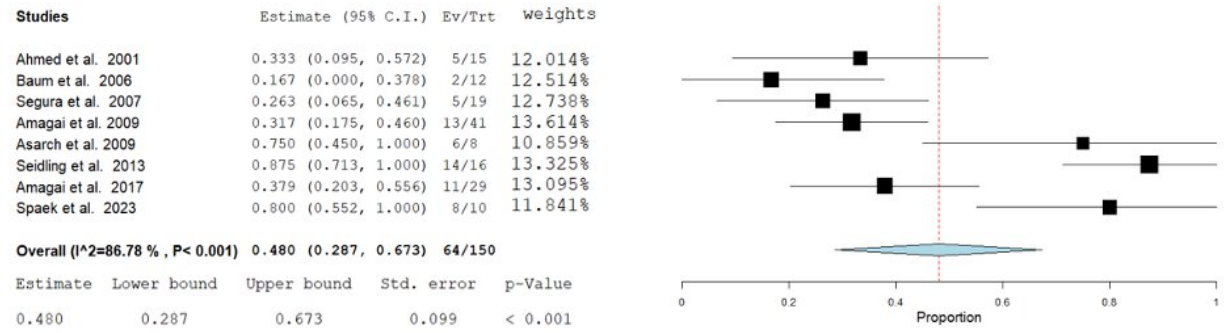


Figure 4. Forest plot of adverse events of IVIG therapy for AIBDs. Proportions were pooled using a random-effects model (DerSimonian-Laird method) with the Freeman-Tukey double arcsine transformation. Heterogeneity: I^2=86.8%, p<0.001.



Online supplementary material:

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

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.

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

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