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REVIEW

Pyoderma Gangrenosum with Biological Agents Therapy: A Systematic Review

Bowen Tan*, Meng Chen*, Xinru Hu, Jia He, Lei Zhang, Shuang Du, Yunzhu Mou, Xincai Xiong, Xi Duan

Department of Dermatovenereology, Affiliated Hospital of North Sichuan Medical College, Nanchong, Sichuan, People's Republic of China

*These authors contributed equally to this work

Correspondence: Xi Duan, Department of Dermatovenereology, Affiliated Hospital of North Sichuan Medical College, Maoyuan South Road No. 1, Nanchong, 637000, People's Republic of China, Email dancing913@126.com

Background: Pyoderma gangrenosum (PG) is a rare disease causing painful skin ulcers, typically starting with tender pustules that quickly develop into painful ulcers. Traditional treatments like glucocorticoids and immunosuppressants often have adverse effects and limited efficacy, making them unsuitable for all patients. Recent evidence shows that biological agents are more effective and safer, leading to increased acceptance. However, selecting the most suitable biological agent from the many available options remains a significant challenge for both physicians and patients.

Objective: To systematically review the treatment outcomes of two biologics: TNF (tumour necrosis factors)-α inhibitors and IL (interleukin) inhibitors in pyoderma gangrenosum.

Methods: A search of Pubmed was conducted on September 7, 2024. A total of 107 studies were included using Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines.

Results: A total of 139 patients were included. Ninety-two were treated with TNF-α inhibitors and 47 with IL inhibitors. The number of included cases and the efficacy are Infliximab (n=52, 88.4%), Adalimumab (n=23, 91.3%), Etanercept (n=13, 84.6%), Certolizumab (n=3, 66.6%), Golimumab (n=1, 100.0%), Anakinra (n=11, 100.0%), Canakinumab (n=7, 100.0%), Secukinumab (n=5, 40.0%), Brodalumab (n=3, 100.0%), Ixekizumab (n=1, 100.0%), Ustekinumab (n=12, 100.0%), Spesolimab (n=3, 100.0%), Guselkumab (n=2, 100.0%), Tildrakizumab (n=2, 100.0%), Risankizuma (n=1, 100.0%). Among them, 46.0% (n=64) achieved complete remission, including 47 (33.8%) who used TNF-α inhibitors and 17 (12.2%) with IL inhibitors. And the total effective rate of IL- inhibitors (93.6%) was higher than that of TNF-α inhibitors (88.0%), but had no statistical significance ($p>0.05$). However, it takes less time for IL inhibitors to reach partial remission or complete remission. Additionally, in infliximab group, the number of adverse events that occurred was large and varied.

Conclusion: Difference in effective rate shows no statistical significance between two kinds of agents. However, IL inhibitors demonstrate an advantage with shorter treatment cycles. Additionally, Infliximab has a wider range of side effects and should be used with caution.

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Keywords: biological products, pyoderma gangrenosum, tumor necrosis factor inhibitors, interleukin inhibitors, cytokine inhibitors

Introduction

Pyoderma gangrenosum (PG) is a rare disease with an incidence of 5.8 cases per 100,000 adults,[1,2] which is a non-infectious neutrophilic dermatosis characterized by skin inflammation and ulcer.[1,3] The clinical manifestations of PG are diverse and can be divided into four subtypes: ulcerative, bullous, pustular, and vegetative.[4] The exact etiology of PG is unknown, and multiple inflammatory mediators and defects in neutrophil chemotaxis and hyperresponsiveness have been implicated in the pathogenesis of PG. In experiments, abnormalities in neutrophil migration have also been described. Thus, neutrophil dysfunction has been implicated in the pathogenesis of PG. Neutrophils are defective in chemotaxis, migration, phagocytosis and bactericidal activity. Recently, interleukin (IL)-1β and IL-α driven innate immune

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dysfunction has been demonstrated. Dysfunction, suggesting that autoinflammation plays a key role in PG pathogenesis. Autoinflammation plays a key role in the pathogenesis of PG, and adaptive immunity also plays a contributing role.[5] To date, there is still no gold standard for the treatment of PG. In addition, the histopathological examination of this disease lacks specificity, so it is often used to exclude other ulcerative diseases. Commonly, the treatments are systemic glucocorticoids, cyclosporine and anti-tumor necrosis factor-a.[6] Nowadays, new treatment methods have been developed, such as using biological agents (TNF-α inhibitor and IL-inhibitors). This study aims to investigate the efficacy of the two biological agents in treating pyoderma gangrenosum and to report potential adverse reactions that may occur during treatment.

Methods

Search Strategy and Eligibility

A comprehensive overview of articles published from inception to September 7, 2024. The relevant criteria are shown in Table 1. The following Boolean logic search: ("infliximab" OR "Monoclonal Antibody cA2" OR "Antibody cA2, Monoclonal" OR "MAb cA2" OR "Infliximab-dyyb") AND ("pyoderma gangrenosum") in title. Vocabulary and syntax were adapted to each database, and a similar strategy was used in the search for publications on another drugs. The study included patients with a diagnosis of PG and reported on the outcome of resolution of PG treated with the biologics studied, as well as two indicators, C-reactive protein (CRP) and neutrophilic infiltration of lesions.

Treatment Outcomes

1.Treatment efficacy of biological agents:

① Complete remission: The total resolution of lesions. The studies used the terms "complete remission", "near recovery", "almost remission", and "symptom-free".
② Partial remission: Some degree of improvement, but lesions not fully recovered. The studies used the terms "partial remission", "partial healed" and "improved".
③ No remission: No changes in lesions. The publications used the terms "no resolution" or "no response".
④ Deterioration: Deterioration of skin lesions.

2. Time to remission: The patient is treated with the biologic for a period of time until the lesion returns to the set standard. (If weeks were used as the unit of calculation in the study, 4 weeks was considered to be a month).
3. Adverse events: Diseases or unfavorable conditions caused by this biological agent.

Study Selection and Data Extraction

For each selected study, the following information was extracted into a spreadsheet: number of patients, age, elevated CRP, neutrophilic infiltration of lesions, previous therapy, concomitant therapy, outcome (complete remission, partial remission, no remission, deterioration), time to remission, and adverse events.

Quality Assessment

The measurement tool for assessment of multiple systematic reviews (AMSTAR) 2007 was used to quality of evidence.

Table 1 Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Written in English Participants used the selected drugs. The search term appears in the title	Written in other language Literature review or meta-analysis Unable to obtain the document. PG is caused by the biologics of study

Statistical Analyses

Data were analyzed using descriptive statistics. Categorical variables are expressed as numbers and percentages, and continuous variables are expressed as ranges. Categorical data were compared using the Chi-square test (p-values <0.05 were considered statistically significant differences) and point estimation. Analysis was performed using IBM SPSS Statistics 27 software.

Results

As shown in Figure 1, 659 articles were retrieved, 397 articles were excluded after article title screening, 14 articles were excluded after literature duplication moved, 141 articles were further excluded, and finally a total of 107 studies were included in the analysis. The infliximab group comprised 40 publications,[7–46] the adalimumab group had 20,[47–65] etanercept featured 8,[66–73] certolizumab included 3,[74–76] golimumab had 1,[77] anakinra had 9,[78–86] canakinumab had 3,[87–89] secukinumab included 4,[90–93] brodalumab and ixekizumab each had 1,[94,95] ustekinumab featured 10,[96–104] spesolimab included 2 publications,[105,106] 2 in guselkumab,[107,108] tildrakizumab had 2[109,110] and 1 of risankizumab.[110]

As shown in Tables 2–4 a total of 139 patients were included in this study, of which 52 were treated with Infliximab, 23 with Adalimumab, 13 with Etanercept, 3 with Certolizumab, 1 with golimumab,11 with Anakinra, 7 with Canakinumab, 5 with Secukinumab, 3 received Brodalumab, 1 received Ixekizumab, 12 received Ustekinumab, 3 received Spesolimab, 2 in guselkumab, 2 with tildrakizumab and risankizumab had 1. Of the 139 patients, 9 were minors (6.5%), 106 were middle-aged and young adults (76.3), and 15 were elderly (10.8%), 9 medical records did not report age (6.5%).

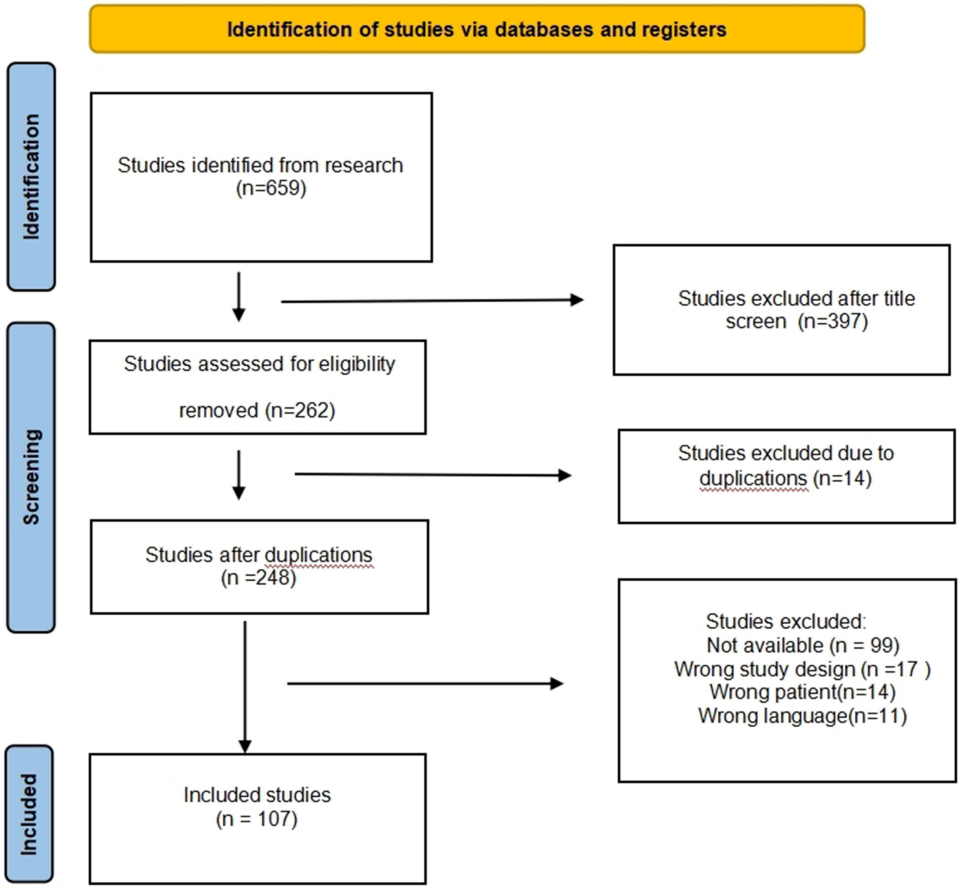

Figure 1 Flow chart of study selection following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.
Abbreviations: PG, Pyoderma gangrenosum; TNF, tumour necrosis factors; IL, interleukin; CRP, C-reactive protein; CR, Complete remission; PR, Partial remission; AE, Adverse event.

Table 2 Statistics of Patients Treated with TNF-αinhibitors (Infliximab, Adalimumab, Etanercept, Certolizumab, Golimumab

	Infliximab	Adalimumab	Etanercept	Certolizumab	Golimumab
Patients, n (%)	52 (100.0)	23 (100.0)	13 (100.0)	3 (100.0)	1 (100.0)
Age (year)					
0-17	4(7.7)	3(13.0)	0(0.0)	0(0.0)	0(0.0)
18-65	37(71.2)	17(74.0)	12(92.3)	3(100.0)	0(0.0)
>65	5(9.6)	1(4.3)	1(7.7)	0(0.0)	1 (100.0)
NR	6(11.5)	2(8.7)	0(0.0)	0(0.0)	0(0.0)
Efficacy, n (%)					
Complete remission	28(53.8)	11(47.8)	6(46.2)	1(33.3)	1 (100.0)
Partial remission	18(34.6)	10(43.5)	5(38.5)	1(33.3)	0(0.0)
No remission	2(3.8)	1(4.3)	NR	NR	0(0.0)
Deterioration	1(1.9)	1(4.3)	NR	NR	0(0.0)
Time to remission (month)					
Range	1.5-24	1.25-16	2-19	15~30	12.5
Mean (Complete remission)	10.1	6.5	5.5	30.0	12.5
Mean (Partial remission)	4.7	8.5	4.5	15.0	NR
Adverse events, n (%)					
Serum sickness	1(1.9)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Arthralgia and fever	1(1.9)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Anaphylactic shock	1(1.9)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Erysipelas	1(1.9)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Arthritis and myalgia	1(1.9)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Diarrhea and fever	1(1.9)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Thrombocytopaenia	1(1.9)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Leukopaenia	1(1.9)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Allergic reaction	1(1.9)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Plamoplantar pustules	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Neutrophilic infiltration of lesions					
Yes	14(27.0)	6(26.1)	5(38.5)	2(66.7)	1 (100.0)
Elevated CRP					
Yes	11(21.2)	6(26.1)	1(7.7)	NR	0(0.0)
Concomitant therapy, n (%)					
Cyclosporine	4(7.7)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Systemic corticosteroids	12(23.1)	7(30.4)	3(23.1)	3(100.0)	1 (100.0)
Methotrexate	7(13.5)	2(8.7)	0(0.0)	1(33.3)	0(0.0)
Azathioprine	4(7.7)	3(13.0)	0(0.0)	0(0.0)	0(0.0)
Cyclophosphamide	1(1.9)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Mycophenolate mofetil	2(3.8)	2(8.7)	0(0.0)	0(0.0)	0(0.0)
Antibiotic	6(11.5)	1(4.3)	2(15.4)	0(0.0)	0(0.0)
Adalimumab	1(1.9)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Tacrolimus	0(0.0)	2(8.7)	0(0.0)	1(33.3)	0(0.0)
Rifampicin	2(3.8)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Isoniazid	2(3.8)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Previous treatments, n (%)					
Cyclosporine	13(25.0)	6(26.1)	4(30.8)	1(33.3)	0(0.0)
Systemic corticosteroids	29(55.8)	10(43.5)	12(92.3)	3(100.0)	1 (100.0)
Mycophenolate mofetil	6(11.5)	4(17.4)	0(0.0)	1(33.3)	0(0.0)
Antibiotic	10(19.2)	7(30.4)	3(23.1)	2(66.7)	0(0.0)
Adalimumab	2(3.8)	0(0.0)	0(0.0)	1(33.3)	1 (100.0)
Methotrexate	8(15.4)	2(8.7)	1(7.7)	1(33.3)	0(0.0)

(*Continued*)

Table 2 (Continued).

	Infliximab	Adalimumab	Etanercept	Certolizumab	Golimumab
Azathioprine	8(15.4)	5(21.7)	1(7.7)	0(0.0)	0(0.0)
Tacrolimus	4(7.7)	0(0.0)	1(7.7)	1(33.3)	0(0.0)
Cyclophosphamide	1(1.9)	1(4.3)	0(0.0)	0(0.0)	0(0.0)

Table 3 Statistics of Patients Treated with IL-Inhibitors (Anakinra, Canakinumab, Scukinumab, Brodalumab, Ixekizumab

	Anakinra	Canakinumab	Secukinumab	Brodalumab	Ixekizumab
Patients, n (%)	11 (100.0)	7 (100.0)	5 (100.0)	3 (100.0)	1 (100.0)
Age (year)					
0-17	2(18.2)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
18-65	7(63.6)	5(71.4)	5(100.0)	3(100.0)	1(100.0)
>65	1(9.0)	2(28.6)	0(0.0)	0(0.0)	0(0.0)
NR	1(9.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Efficacy, n (%)					
Complete remission	5(45.5)	1(14.3)	1(20.0)	0(0.0)	0(0.0)
Partial remission	6(54.5)	6(85.7)	1(20.0)	3(100.0)	1(100.0)
No remission	0(0.0)	0(0.0)	NR	0(0.0)	0(0.0)
Deterioration	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Time to remission (month)					
Range	1-24	2~12	4~5	1-3	12
Mean (Complete remission)	8.3	4.0	5.0	NR	NR
Mean (Partial remission)	3.8	5.8	4.0	2.0	12.0
Adverse events, n (%)					
Serum sickness	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Arthralgia and fever	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Anaphylactic shock	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Erysipelas	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Arthritis and myalgia	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Diarrhea and fever	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Thrombocytopaenia	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Leukopaenia	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Allergic reaction	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Plamoplantar pustules	0(0.0)	0(0.0)	0(0.0)	1(33.3)	0(0.0)
Neutrophilic infiltration of lesions					
Yes	3(27.3)	1(14.3)	2(40.0)	NR	NR
Elevated CRP					
Yes	2(18.2)	1(14.3)	NR	NR	NR
Concomitant therapy, n (%)					
Cyclosporine	0(0.0)	0(0.0)	1(20.0)	0(0.0)	1(100.0)
Systemic corticosteroids	2(18.2)	5(71.4)	2(40.0)	1(33.3)	0(0.0)
Methotrexate	1(9.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Azathioprine	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Cyclophosphamide	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Mycophenolate mofetil	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Antibiotic	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Adalimumab	0(0.0)	0(0.0)	1(20.0)	0(0.0)	1(100.0)
Tacrolimus	0(0.0)	1(14.3)	0(0.0)	0(0.0)	0(0.0)
Rifampicin	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)

(*Continued*)

Table 3 (Continued).

	Anakinra	Canakinumab	Secukinumab	Brodalumab	Ixekizumab
Isoniazid	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Previous treatments, n (%)					
Cyclosporine	4(36.4)	0(0.0)	1(20.0)	0(0.0)	0(0.0)
Systemic corticosteroids	8(72.7)	7(100.0)	1(20.0)	2(66.7)	0(0.0)
Mycophenolate mofetil	2(18.2)	0(0.0)	1(20.0)	0(0.0)	0(0.0)
Antibiotic	5(45.5)	0(0.0)	1(20.0)	0(0.0)	1(100.0)
Adalimumab	4(36.4)	0(0.0)	4(80.0)	2(66.7)	0(0.0)
Methotrexate	3(27.3)	0(0.0)	0(0.0)	1(33.3)	0(0.0)
Azathioprine	0(0.0)	1(14.3)	1(20.0)	0(0.0)	0(0.0)
Tacrolimus	2(18.2)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Cyclophosphamide	1(9.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)

Table 4 Statistics of Patients Treated with IL-Inhibitors (Ustekinumab, Spesolimab, Guselkumab, Tildrakizumab, Risankizumab

	Ustekinumab	Spesolimab	Guselkumab	Tildrakizumab	Risankizumab
Patients, n (%)	12 (100.0)	3 (100.0)	2(100.0)	2(100.0)	1 (100.0)
Age (year)					
0-17	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
18-65	11(91.7)	2(66.7)	2(100.0)	0(0.0)	1 (100.0)
>65	1(8.3)	1(33.3)	0(0.0)	2(100.0)	0(0.0)
NR	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Efficacy, n (%)					
Complete remission	7(58.3)	2(66.7)	0(0.0)	1(50.0)	0(0.0)
Partial remission	5(41.7)	1(33.3)	2(100.0)	1(50.0)	1 (100.0)
No remission	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Deterioration	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Time to remission (month)					
Range	2-24	1-1.25	12-15	7-20.5	12
Mean (Complete remission)	8.8	1.0	NR	7.0	NR
Mean (Partial remission)	3.0	1.1	13.5	20.5	12.0
Adverse events, n (%)					
Serum sickness	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Arthralgia and fever	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Anaphylactic shock	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Erysipelas	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Arthritis and myalgia	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Diarrhea and fever	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Thrombocytopaenia	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Leukopaenia	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Allergic reaction	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Plamoplantar pustules	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Neutrophilic infiltration of lesions					
Yes	4(33.3)	1(33.3)	NR	1(50.0)	NR
Elevated CRP					
Yes	NR	1(33.3)	NR	2(100.0)	NR
Concomitant therapy, n (%)					
Cyclosporine	2(16.7)	1(33.3)	1(50.0)	0(0.0)	0(0.0)
Systemic corticosteroids	4(33.3)	1(33.3)	1(50.0)	0(0.0)	1 (100.0)
Methotrexate	1(8.3)	0(0.0)	0(0.0)	1(50.0)	0(0.0)

(*Continued*)

Table 4 (Continued).

	Ustekinumab	Spesolimab	Guselkumab	Tildrakizumab	Risankizumab
Azathioprine	1(8.3)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Cyclophosphamide	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Mycophenolate mofetil	3(25.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Antibiotic	3(25.0)	0(0.0)	1(50.0)	0(0.0)	0(0.0)
Adalimumab	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Tacrolimus	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Rifampicin	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Isoniazid	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Previous treatments, n (%)					
Cyclosporine	5 (41.7)	3(100.0)	1(50.0)	2(100.0)	1 (100.0)
Systemic corticosteroids	10 (83.3)	3(100.0)	2(100.0)	2(100.0)	1 (100.0)
Mycophenolate mofetil	1 (8.3)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Antibiotic	2 (16.7)	0(0.0)	2(100.0)	1(50.0)	0(0.0)
Adalimumab	3(25.0)	2(66.7)	2(100.0)	0(0.0)	1 (100.0)
Methotrexate	0(0.0)	0(0.0)	0(0.0)	1(50.0)	1 (100.0)
Azathioprine	2(16.7)	0(0.0)	0(0.0)	0(0.0)	1 (100.0)
Tacrolimus	2(16.7)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Cyclophosphamide	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)

Comprehensive Analysis of Biological Agents for Pyoderma Gangrenosum

This article examines multiple biological agents for treating pyoderma gangrenosum. Table 5 below consolidates key data across different biological agent categories, highlighting sample characteristics, baseline features, treatment history, efficacy, and safety.

Class-Specific Key Findings

TNFα Inhibitors

This class includes the largest sample sizes (eg, n=52 for Infliximab) and shows high overall efficacy (CR+PR: 88.4% for Infliximab, 91.3% for Adalimumab). A critical distinction is safety: Infliximab is associated with diverse AEs (serum sickness,[14] arthralgia and fever,[14] anaphylactic shock,[20] erysipelas,[22] arthritis and myalgia,[22] diarrhea and fever,[30] thrombocytopaenia,[30] leukopaenia[30] and allergic reaction[38]), while Adalimumab, Etanercept, Certolizumab, and Golimumab have no reported AEs. Systemic corticosteroids are the most common prior/concurrent medication (43.5–-100% across agents).

IL1 Inhibitors

Both Anakinra (CR+PR: 100%) and Canakinumab (CR+PR: 100%) achieve full remission in all patients, with no AEs reported. Anakinra has a broader age distribution (including minors), while Canakinumab primarily treats middle-aged /older adults. Prior use of systemic corticosteroids is nearly universal (72.7–100%).

IL17 Inhibitors

Efficacy varies (CR+PR: 40% for Secukinumab, 100% for Brodalumab/Ixekizumab), and Brodalumab is the only agent in this class with an AE (1 case of palmoplantar pustules).[94] Adalimumab is a common prior medication (66.7–80%), reflecting use in refractory cases.

IL12/23 Inhibitors (Ustekinumab)

With a high CR rate (58.3%) and no AEs, Ustekinumab demonstrates strong efficacy and safety. Over 80% of patients had prior systemic corticosteroid use, consistent with its role in steroid-refractory PG.

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Table 5 Comparative Analysis of Biologic Agents in PG Treatment

Drug Class	Specific Agent	Sample Size (n)	Age Distribution (Predominant Group)	Key Baseline Features (Neutrophilic Infiltration/CRP Elevation, %)	Prior Medications (Most Common, %)	Concurrent Medications (Most Common, %)	Treatment Duration Range (Months)	Efficacy (CR/PR, %)	Adverse Events (AEs) [Reference No.]
TNFα Inhibitors	Infliximab	52	Middle-aged adults (71.2%)	27.0% / 21.2%	Systemic corticosteroids (55.8%)	Systemic corticosteroids (23.1%)	1.5–24	53.8% / 34.6%	1 case each of serum sickness,[14] arthralgia and fever,[14] anaphylactic shock,[20] erysipelas,[22] arthritis and myalgia,[22] diarrhea and fever,[30] thrombocytopaenia,[30] leukopaenia,[30] allergic reaction[38]
	Adalimumab	23	Middle-aged adults (74.0%)	26.1% / 26.1%	Systemic corticosteroids (43.5%)	Systemic corticosteroids (30.4%)	1.25–16	47.8% / 43.5%	No reported AEs
	Etanercept	13	Middle-aged adults (92.3%)	38.5% / 7.7%	Systemic corticosteroids (92.3%)	Systemic corticosteroids (23.1%); Antibiotics (15.4%)	2–19	46.2% / 38.5%	No reported AEs
	Certolizumab	3	Middle-aged adults (100%)	66.7% / Data not available (DNA)	Systemic corticosteroids (100%)	Systemic corticosteroids (100%)	15–30	33.3% / 33.3%	No reported AEs
	Golimumab	1	Older adults (100%)	100% / DNA	Systemic corticosteroids (100%); Adalimumab (100%)	Systemic corticosteroids (100%)	12.5	100% / 0%	No reported AEs
IL1 Inhibitors	Anakinra	11	Middle-aged adults (63.6%)	23.7% / 18.2%	Systemic corticosteroids (72.7%)	Systemic corticosteroids (18.2%); Methotrexate (9.0%)	1–24	45.5% / 54.5%	No reported AEs
	Canakinumab	7	Middle-aged adults (71.4%)	14.3% / 14.3%	Systemic corticosteroids (100%)	Systemic corticosteroids (71.4%)	2–12	14.3% / 85.7%	No reported AEs
IL17 Inhibitors	Secukinumab	5	Middle-aged adults (100%)	40.0% / DNA	Adalimumab (80.0%)	Systemic corticosteroids (40.0%)	4–5	20.0% / 20.0%	No reported AEs (2 cases unreported)
	Brodalumab	3	Middle-aged adults (100%)	DNA / DNA	Systemic corticosteroids (66.7%); Adalimumab (66.7%)	Systemic corticosteroids (33.3%)	1–3	0% / 100%	1 case of palmoplantar pustules[94]
	Ixekizumab	1	Middle-aged adults (100%)	DNA / DNA	Antibiotics (100%)	Cyclosporine; Adalimumab	12	0% / 100%	No reported AEs
IL12/23 Inhibitors	Ustekinumab	12	Middle-aged adults (91.7%)	33.3% / DNA	Systemic corticosteroids (83.3%)	Systemic corticosteroids (25%); Antibiotics (25%)	2–24	58.3% / 41.7%	No reported AEs
IL23 Inhibitors	Guselkumab	2	Middle-aged adults (100%)	0% / 0%	Systemic corticosteroids (100%); Adalimumab (100%)	Systemic corticosteroids (50%); Cyclosporine (50%)	12–15	0% / 100%	No reported AEs
	Tildrakizumab	2	Older adults (100%)	50.0% / 100%	Systemic corticosteroids (100%); Cyclosporine (100%)	Methotrexate (50%)	7–20.5	50.0% / 50.0%	No reported AEs
	Risankizumab	1	Middle-aged adults (100%)	0% / 0%	Systemic corticosteroids (100%); Adalimumab (100%)	Systemic corticosteroids (100%)	12	100% / 0%	No reported AEs
IL36R Inhibitors	Spesolimab	3	Middle-aged adults (66.7%)	33.3% / 33.3%	Systemic corticosteroids (100%); Cyclosporine (100%)	Systemic corticosteroids (33.3%); Cyclosporine (33.3%)	1–1.25	66.7% / 33.3%	No reported AEs

Table 6 Statistical results of the Chi-Square Analysis of the Efficacy of the Two Types of Biologics

	Biologics	Efficacy (%)			Total Efficacy (%)	χ2	p
		Partial Remission	Complete Remission	No Remission			
Groups	IL inhibitors	27(57.45)	17(36.17)	3(6.38)	93.6	5.44	0.07
	TNF-α inhibitors	34(36.96)	47(51.09)	11(11.96)	88.0		

Table 7 Average Period of Treatment with Two Types of Biologics

Time to Remission(month)	TNF-α Inhibitors	IL Inhibitors
Mean (Complete remission)	9.1	7.1
Mean (Partial remission)	6.1	5.7

IL23 Inhibitors

Guselkumab, Tildrakizumab, and Risankizumab all show favorable safety (no AEs) and efficacy (CR+PR: 100%). Tildrakizumab is unique in having 100% CRP elevation at baseline, suggesting utility in inflammatory PG phenotypes.

IL36R Inhibitors (Spesolimab)

Despite a short treatment duration (1–1.25 months), Spesolimab achieves high CR (66.7%) with no AEs, highlighting potential for rapid response in select patients.

Analysis of the Efficacy of IL Inhititors and TNF-αinhititors

As showing in Table 6, 93.6% of the patients in IL inhibitors of total efficacy and 88.0% in TNF-α inhibitors, and it shows that there are no differences of effect between two categories of biologics that are statistically significant ($p>0.05$). We compared the efficacy of them in terms of treatment period as shown in Table 7. The average length of time to complete cure was 9.1 months for TNF-α inhibitors, compared with 7.1 months for IL inhibitors; the average length of time to partial cure was 6.1 months for TNF-α inhibitors, compared with 5.7 months for IL inhibitors. In both cases, IL inhibitors show a shorter treatment period.

Reporting Biases

Limitations include small sample size and lack of a control group. In addition, publication bias was another limitation, as studies with negative results were less likely to be published, ie, not reported. The data reported in this systematic review were affected by publication bias of the underlying included studies. In addition, the severity of PG and adjunctive therapeutic agents may influence the efficacy of various biologic treatments. Differences in the study methodology of the included literature hindered further accurate analysis.

Discussion

There are many challenges in the treatment of PG, mainly including the difficulty of diagnosis, variable response to treatment, susceptibility to recurrence, and side effects during treatment. In this context, the application of biologics has emerged, which effectively reduce the inflammatory response by precisely targeting specific inflammatory mediators, such as tumor necrosis factor and interleukin. This provides a new strategy for more efficient treatment with fewer side effects for patients with PG, especially those with refractory PG who are refractory to conventional treatments. Current biologics for the treatment of PG are mainly TNF-α inhibitors and interleukin-based biologics, the latter covering subclasses of inhibitors such as IL-1, IL-17, IL-12/23, IL-36R, IL-23 and others, which are inflammatory mediators presenting high levels in vivo at the onset of PG.[111] A total of 139 patients were included in this systematic review, most of them were distributed between 18 and 65 years of age, which is in the favored age for GP. Ninety-two patients were

treated with TNF-α inhibitors and 47 patients with IL-like inhibitors, all of whom experienced remission to varying degrees, with advantages and disadvantages of the different treatments. In our review, the total efficacy rates of 88.0% to TNF-α inhibitors were lower than 93.6% to IL inhibitors showed that there are no statistical significance, but IL inhibitors show a shorter treatment period. The number and variety of adverse reactions that occur during treatment with infliximab are higher, while relatively few side effects have been reported in patients treated with interleukin-based biologics, and patients treated with IL biologics still need to pay attention to the safety. Although relatively few side effects have been reported, fewer patients have been treated with IL biologics for PG in published studies, which is unfavorable for the evaluation of the efficacy.

In TNF-α inhibitors, infliximab is currently the only biologic that has been validated in randomized, double-blind, placebo-controlled trials as effective in the treatment of classical PG; however, their safety considerations should not be overlooked, as studies have shown an increased risk of adverse events after infliximab and adalimumab treatment, including heart failure, infections, and malignancy, among others.[112,113] Infliximab, adalimumab and etanercept groups included more number of cases, and among them infliximab achieved the highest rate of complete remission (53.8%). The remaining two drugs had too few cases for the cure rate to be sufficiently representative, although golimumab had a 100% cure rate (n=1). The average treatment period to achieve complete remission from this type of biologics is 9.1 months; the average time to achieve partial remission is 6.1 months. The treatment cycle for etanercept is the shortest among these biologic agents, with an average duration of 5.5 months. In addition, previous work has empirically combined adalimumab in combination with infliximab with promising efficacy in PG patients who are resistant to conventional immunosuppressants and systemic steroids.[114] A patient who developed a psoriasiform rash on PG treated with adalimumab switched to secukinumab, which controlled both the skin lesions and PG, revealing the individual variability of treatment with adalimumab as a TNF-α inhibitor. Of the 92 patients treated with these agents, 88.0% (n=81) of the patients improved, with complete recovery occurring in 51.1% (n=47). The advantages were the satisfactory cure rate and the prevalence of use. However, many adverse events have occurred, including serum sickness, arthralgia and fever, anaphylactic shock, erysipelas, arthritis and myalgia, diarrhea and fever, thrombocytopaenia, leukopaenia and allergic reaction.

Interleukin-based biologics have also shown great potential for the treatment of PG. In the present study, a total of 47 individuals were treated with this category of agents and had an efficacy rate of 93.6% (n=44), with 36.2% (n=17) in complete remission. Except for IL-17 Inhibitors, which had an efficacy rate of 66.7% (n=6), all the other interleukin subpopulation inhibitors had an efficacy rate of 100%, and all of them were able to achieve complete remission or partial remission within a certain number of treatment cycles, or even rapid remission within a shorter treatment period. One patient receiving brodalumab developed palmoplantar pustules during treatment. The average treatment period to achieve full recovery from this type of biologics is 7.1 months; the average time to achieve partial recovery is 5.7 months. In addition, among patients who achieved complete recovery, spesolimab had the shortest average treatment period of 1 month. However, this seemingly objective number does not indicate that they are foolproof in the treatment of patients with PG. Small samples or individual case reports make this result insufficiently supportive, and future more more clinical studies are needed in the future to prove their reliability.

Among the patients treated with biological agents, about 46.0% (n=64) achieved complete recovery, including 47 patients (33.8%) who used TNF-α inhibitors and 17 patients (12.2%) with IL inhibitors. We found that the vast majority of these patients did not initially choose biological agents for treatment, but instead used systemic corticosteroids such as prednisone and immunosuppressants like cyclosporine. Furthermore, in subsequent treatment stages, patients continued to use systemic steroids and cyclosporine in combination with biological agents, while a small number of patients also added methotrexate or mycophenolate mofetil. Some patients even switched to another biological agent after the current one showed poor efficacy. This indicates that, despite the increasing use of biological agents this year, corticosteroids and immunosuppressants remain the first-line drugs when treating PG. A real-world data on biologic applications for PG indicate that patients treated with glucocorticoids are prone to developing resistance. While glucocorticoids deliver faster initial therapeutic responses and effectively shorten the short-term duration of ulcers, they carry significant long-term risks. In contrast, biologics demonstrate progressive improvement, manifested by sustained increases in epithelialization rates and continuous reductions in ulcer area. This characteristic supports their long-term role in PG treatment and

underscores the urgent clinical need for safer alternative therapies, as well as the necessity of developing PG replacement treatment options that balance efficacy and safety.[115]

We noted one case each of infliximab and adalimumab in which a patient deteriorated on treatment. The patient treated with infliximab was 60 years old and developed three large ulcers (the largest one measuring 19×12 cm), and after treatment developed sepsis caused by staphylococcus aureus and pseudomonas aeruginosa, and the patient eventually died of septic shock,[30] adalimumab-treated patients diagnosed with juvenile PG and experiencing a worsening of the disease may have been associated with their development of pertussis at 16 months of age, a genetic mutation resulting in interleukin deficiency, and an inadequate response to biologics, with poor efficacy leading to further deterioration. In addition, in the early stages he was treated with oral cyclosporine, methotrexate and prednisolone, which improved the ulcers, but eventually caused intolerable side-effects such as nausea, steroid-induced myositis and retarded skeletal growth.[60] We found that both of the above patients received cyclosporine and prednisolone prior to or concurrently with biologic therapy. The use of immunosuppressants and systemic steroids may lead to a significant increase in the risk of infections and tumors while enhancing the efficacy of the treatment.

This study reported seven adverse events. Six occurred after infliximab: a female patient developed serum sickness after bilateral mammoplasty and a septic infection treated with antibiotics; the other woman with ulcerative colitis had anaphylactic shock due to a hypersensitivity reaction; one patient experienced erysipelas, while another had arthritis and myalgia; a male patient had severe symptoms (diarrhea, fever, thrombocytopenia, and leukopenia), possibly from an allergic reaction related to his PG condition, which included multiple large ulcers (19x12 cm) and led to death despite cyclosporine treatment; another male developed a splenic abscess before an allergic reaction. One female on brodalumab developed palmoplantar pustules and COVID-19. Five of these patients had used steroids, which may have compromised autoimmunity and immunity, increasing the risk of adverse events, especially given the concurrent use of immunosuppressants and antibiotics.

Conclusion

The total effective rate of interleukin inhibitors and TNF-α inhibitors shows no statistical significance. However, both complete and partial cure times for IL-inhibitors are shorter than TNF-α inhibitors. Therefore, in this study, it can be assumed that IL-inhibitors have a higher efficacy in patients. In addition, besides the patient's own disease progress and basic diseases, the patient's remission state should also consider the treatment compliance, the control of complications and the control of the dosage and duration of combined medication. We found infliximab resulted in more adverse events. Further trials are needed in the future to demonstrate the efficacy and safety of these biologics.

Data Sharing Statement

The original data presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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