Pyoderma Gangrenosum and Interleukin Inhibitors: A Semi-Systematic Review

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Keywords

Pyoderma gangrenosum · Anakinra · Ustekinumab · Canakinumab · Interleukin inhibitors

Abstract

Background: Pyoderma gangrenosum (PG) is a rare ulcerating skin disease associated with multiple comorbidities and increased mortality. In recent decades, newer biologics such as interleukin inhibitors have been used to treat PG; however, the literature is scarce, consisting predominantly of case reports and caseseries. The aim of our review was to evaluate the effectiveness and safety of interleukin inhibitors for the treatment of PG in adults. **Summary:** A literature search was conducted using search terms related to PG and interleukin inhibitors in databases such as PubMed, Embase, Scopus, Web of Science, and Cochrane Library. The study eligibility criteria included patients diagnosed with PG, over the age of 18, and treated with an interleukin inhibitor. Our study included 60 papers describing 81 patients fulfilling the eligibility criteria. The treatment with interleukin inhibitors resulted in 70% (95% CI 59–80%) response and 57% (95% CI 45–68%) complete response rates, and few (4%) mild adverse events, hence supporting the off-label use for the treatment of recalcitrant PG in adults. The response and complete response rates were 59% (17/29) and 38% (11/29) for anakinra, 64% (7/11) and 55% (6/11) for canakinumab, and 79% (27/34) and 71% (24/34) for ustekinumab, respectively. Limitations include publication bias that might have

overestimated the efficacy as successful cases responding to treatment are more likely to be reported than nonresponding cases. Additionally, the heterogeneity of the treatment groups does not allow conclusions of superiority or inferiority of the different interleukin inhibitors to be drawn. Further studies are needed to investigate the efficacy of the different interleukin inhibitors and to investigate the importance of underlying disease for treatment response.

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Introduction

Pyoderma gangrenosum (PG) is a rare immune-mediated ulcerative skin disease. PG is often associated with prior trauma or underlying disease [1, 2]. Neutrophils play a key role in the pathogenesis of PG and accumulate in the dermis. The immune dysregulation in PG has not yet been fully understood, but it involves T cells, neutrophils, and inflammatory mediators. Proinflammatory cytokines such as TNF α , interleukin-1 (IL-1), IL-6, IL-8, IL-17, and IL-23 are upregulated in the skin with PG [3–9]. The management of PG relies mainly upon immunosuppression with no acknowledged treatment guidelines, but systemic corticosteroids and oral cyclosporine are frequently used drugs [10]. In recent decades, biologics in the form of TNF α inhibitors have been used, and a recent

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semi-systematic review has demonstrated the effectiveness of TNF α inhibitors in the treatment of PG [11]. However, the effectiveness of newer biologics such as interleukin inhibitors remains unknown. Therefore, the aim of this paper was to review the therapeutic effectiveness and safety of interleukin inhibitors in adults with PG.

Methods

Our review has been reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [12]. However, all items were not applicable, thus the classification as a semi-systematic review, because the data were individual-level rather than group-level due to a paucity of larger studies. This review uses a similar approach to the study selection and data extraction as the semi-systematic review for TNF α inhibitors [11].

Search Strategy

The literature search included publications from 1998 to 2021 and was conducted in the following databases: PubMed, Embase, Scopus, Web of Science, and Cochrane Library. Moreover, literature was searched in World Health Organization International Clinical Trials Registry Platform, Trials Register of Promoting Health Interventions, The National Technical Information Service, NICE Local Practice Case Studies, Open Grey, NHS Evidence, and UK Clinical Trials Gateway. The search terms were related to PG and interleukin inhibitors and truncated to retrieve results with all word endings. There were no language restrictions (see online suppl. Table 1 for the full search strategy; for all online suppl. material, see www.karger.com/doi/10.1159/000519320). Additionally, citations were manually searched through the reference list of publications included in our review.

Study Selection

All publications identified through database searching were merged and duplicates were removed. Subsequently, a screening process based on examination of titles and abstracts led to relevant publications that were full-text assessed for inclusion. Inclusion criteria for studies and case reports were (1) patients diagnosed with PG, (2) over the age of 18, and (3) administered an interleukin inhibitor with the therapeutic response reported. Publications were excluded (1) if patients had been reported in a prior publication to prevent duplicates or (2) if PG occurred during interleukin inhibitor treatment because an assessment of treatment response was not possible.

Data Extraction

For each patient, the following data items were extracted: age, sex, number and location of PG lesions, duration and type of PG, comorbidities, previous and concomitant treatment, interleukin inhibitor agent, treatment response, time to response and complete healing, reoccurrence of PG after complete healing, and adverse events.

The primary endpoint was treatment response and defined as either complete response (complete healing of PG lesions or major improvement within weeks without follow-up reported), partial

response (significant improvement of lesions and symptoms), or no response (minimal improvement, no change, or worsening of lesions and symptoms). Treatment response was assessed based on the findings reported in the publications. Moreover, the assessment of treatment response was based on all lesions rather than a single target lesion.

The outcome measures were response (percentage of patients with partial or complete response) and complete response rates (percentage of patients with complete response).

Patients administered multiple courses or different interleukin inhibitors were reported based on the initial treatment attempt in order to have interleukin inhibitor-naïve patients and reduce concomitant medication.

Statistical Analyses

Fisher's exact test was used to compare categorical data, whereas one-way ANOVA was used to compare means. Missing data were excluded from the analyses. p values <0.05 were considered statistically significant. The analyses were performed with the SAS 9.4 software.

Results

The literature search identified 1,151 unique publications (online suppl. Fig. 1 with flow diagram of the selection process). The screening based on examination of titles and abstracts excluded 789 citations, leaving 362 publications that underwent full-text assessment (online suppl. Table 2 with excluded publications with reasons of exclusion), resulting in the inclusion of 60 publications describing 81 patients (online suppl. Tables 3 and 4) [3, 5, 13–70].

Demographic and Clinical Characteristics

The mean age of the included 81 patients was 43.34 years, with a sex distribution of 49% females and 51% males (Table 1). The number of PG lesions was multiple (>1) in 68% of patients, and the lower limbs were the site of predilection (49%). A total of 22% of cases were not associated with underlying disease (idiopathic). The prevalence of idiopathic PG was significantly lower ($p = 0.0115$) among patients treated with anakinra (7%) compared to patients treated with canakinumab (45%) or ustekinumab (28%), whereas the prevalence of hidradenitis suppurativa or autoinflammatory syndromes was statistically significantly ($p < 0.0001$) higher among patients treated with either anakinra (59%) or canakinumab (45%) than among patients treated with ustekinumab (3%). The prevalence of inflammatory bowel disease was significantly higher ($p = 0.0029$) among patients treated with ustekinumab (50%) compared to patients treated with anakinra (14%) or canakinumab (9%). Overall, 18 and 6%

Table 1. Demographic and clinical characteristics of the included patients ($n = 81$) by overall and treatment group (anakinra, canakinumab, ustekinumab)

Characteristics	All	Anakinra	Canakinumab	Ustekinumab	<i>p</i> value
Age					
Mean $\pm$ SD, years	43.34 $\pm$ 14.99	39.24 $\pm$ 15.27	42.64 $\pm$ 18.94	46.41 $\pm$ 12.45	0.1899
Missing values	5	0	0	5	
Sex					
Female	49% (36/73)	35% (9/26)	36% (4/11)	62% (18/29)	0.1005
Male	51% (37/73)	65% (18/26)	64% (7/11)	38% (11/29)	
Missing values	8	3	0	5	
Location of PG					
Lower limb(s)	49% (31/63)	27% (6/22)	64% (7/11)	61% (14/23)	0.1094
Torso	16% (10/63)	18% (4/22)	27% (3/11)	13% (3/23)	
Other body parts ^a	13% (8/63)	23% (5/22)	0% (0/11)	4% (1/23)	
Multiple body parts ^b	22% (14/63)	32% (7/22)	9% (1/11)	22% (5/23)	
Missing values	18	7	0	11	
Number of PG lesions					
Single	32% (20/63)	32% (7/22)	27% (3/11)	30% (7/23)	1.0000
Multiple (>1)	68% (43/63)	68% (15/22)	73% (8/11)	70% (16/23)	
Missing values	18	7	0	11	
Associated diseases					
IBD	21% (21/79)	14% (4/29)	9% (1/11)	50% (16/32)	0.0029
Hematologic diseases	6% (5/79)	7% (2/29)	0% (0/11)	6% (2/32)	1.0000
HS or autoinflammatory disorders ^c	32% (25/79)	59% (17/29)	45% (5/11)	3% (1/32)	<0.0001
Rheumatic diseases	18% (14/79)	14% (4/29)	0% (0/11)	19% (6/32)	0.3895
No associated diseases	22% (17/79)	7% (2/29)	45% (5/11)	28% (9/32)	0.0115
Missing values	2	0	0	2	
Duration of PG					
<12 weeks	14% (7/49)	0% (0/12)	10% (1/10)	15% (3/20)	0.4441
>12 weeks	86% (42/49)	100% (12/12)	90% (9/10)	85% (17/20)	
Missing values	32	17	1	14	
Previous treatment					
Yes	100% (79)	100% (29)	100% (11)	100% (32)	
No	0% (0)	0% (0)	0% (0)	0% (0)	
Missing values	2	0	0	2	
Previous TNF α inhibitor treatment					
Yes	63% (50/79)	62% (18/29)	45% (5/11)	75% (24/32)	0.2053
No	37% (29/79)	38% (11/29)	55% (6/11)	25% (8/32)	
Missing values	2	0	0	2	

Data are presented as % (n) of patients, unless otherwise specified. Missing values were excluded from the statistical analyses. HS, hidradenitis suppurativa; IBD, inflammatory bowel disease; PG, pyoderma gangrenosum; SD, standard deviation. ^a Body parts including upper limb(s), anogenital region, and head region. ^b PG located at least on two of the following body parts: upper limb(s), lower limb(s), torso, anogenital area, extracutaneous area, or head region. ^c Including PAPA, PAMI, PASH, PAPASH, PASS, and PAC syndromes.

of PG cases were associated with rheumatologic and hematologic diseases, respectively, but no significant differences were observed between the groups of patients treated with anakinra, canakinumab, or ustekinumab. The duration of PG lesions was more >12 weeks in 86% of patients. Before treatment with interleukin inhibitors, all patients had tried another treatment: 97,5% of patients had tried systemic treatment, mainly immunosuppressives in the form of corticosteroid steroids, cyclosporine,

methotrexate, or biologics, and 63% of patients had tried TNF α inhibitors.

Treatment and Response

A total of 34 patients were treated with ustekinumab (anti-IL-12/23), 29 patients with anakinra (IL-1 receptor antagonist), and 11 patients with canakinumab (anti-IL-1 β) (Table 2). Moreover, 3 patients were treated with secukinumab (anti-IL-17A), whereas 2 patients were

Table 2. Response and complete response rates to interleukin inhibitors with subgroup analyses based on interleukin inhibitor agent, associated disease, and duration of PG ($n = 81$)

	Response rate	Complete response rate	p value ^a	p value ^b
No stratification	70% (57/81) (95% CI 59–80%)	57% (46/81) (95% CI 45–68%)		
Interleukin inhibitor				
Anakinra	59% (17/29)	38% (11/29)	0.1269	0.0185
Canakinumab	64% (7/11)	55% (6/11)	0.7241	1.0000
Ustekinumab	79% (27/34)	71% (24/34)	0.1473	0.0420
Missing values	0	0		
Associated disease				
IBD	67% (14/21)	62% (13/21)	0.7850	0.6188
Hematologic diseases	60% (3/5)	60% (3/5)	0.6368	1.0000
HS or autoinflammatory disease ^c	56% (14/25)	36% (9/25)	0.1133	0.0146
Rheumatic disease	64% (9/14)	57% (8/14)	0.7502	1.0000
No associated diseases	94% (16/17)	76% (13/17)	0.0158	0.0971
Missing values	2	2		
Duration of PG				
<12 weeks	86% (6/7)	71% (5/7)		
>12 weeks	79% (33/42)	60% (25/42)	1.0000	0.6909
Missing values	32	32		

Data are presented as % (n) of patients, unless otherwise specified. Missing values were excluded from the statistical analyses. HS, hidradenitis suppurativa; IBD, inflammatory bowel disease; PG, pyoderma gangrenosum.

^a Calculated by Fisher's exact test for response rates (the percentage of patients with partial or complete response).

^b Calculated by Fisher's exact test for complete response rates (the percentage of patients with complete response).

^c Including PAPA, PAMI, PASH, PAPASH, PASS, and PAC syndromes.

treated with brodalumab (anti-IL-17 receptor), 1 patient with tocilizumab (anti-IL-6 receptor), and 1 patient with tildrakizumab (anti-IL-23). Overall, the response and complete response rates to interleukin inhibitors were 70% (95% CI 59–80%) and 57% (95% CI 45–68%), respectively.

The complete response rate for anakinra (38%) was significantly lower ($p = 0.0185$) compared to the other interleukin inhibitors, while that for ustekinumab (71%) was significantly higher ($p = 0.0420$).

Patients without associated diseases showed higher complete response rates and statistically significantly higher response rates than patients with associated comorbidity ($p = 0.0158$). Patients with hidradenitis suppurativa or autoinflammatory syndrome showed less favorable response (56%, $p = 0.1133$) and complete response (36%, $p = 0.0146$) compared to other patients without hidradenitis suppurativa or autoinflammatory syndrome. No other statistically significant differences were found in the subgroup analyses of comorbidities or duration of PG. No severe adverse events were reported (Table 3), but 4% (3/78) reported mild adverse events (painful nodules at injection sites, erysipelas, or arthralgia).

Table 3. Additional clinical characteristics

Clinical characteristics	
Adverse effects	4% (3/78)
Missing values	3
Reoccurrence of PG	7% (3/45)
Missing values	1
Mean time (SD) and range to complete healing, weeks	24.32 (21.54), 3–104 (range)
Missing values	12

PG, pyoderma gangrenosum; SD, standard deviation.

Discussion

Findings

The treatment with interleukin inhibitors provided 70% (95% CI 59–80%) response and 57% (95% CI 45–68%) complete response rates and few (4%) mild adverse events, thus supporting the off-label use for the treatment of PG. The therapeutic response is high when considering

that the study population represented recalcitrant PG as indicated by the fact that all patients had tried another treatment, 63% had tried TNF α inhibitors, and 86% had PG lesions for >12 weeks before treatment with interleukin inhibitors.

The response and complete response rates to interleukin inhibitors in our study were marginally lower but broadly similar to those found for TNF α inhibitors [11], cyclosporine, and systemic corticosteroid [10]. Recently, a semi-systematic review ($n = 356$) with the same methodology as this review found an 87% (95% CI 93–90%) response and an 67% (95% CI 62–72%) complete response rate to TNF α inhibitors. Moreover, approximately 90% response and 47% complete response rates to cyclosporine or oral corticosteroid were found in a randomized controlled trial ($n = 112$). However, when comparing these rates to those of interleukin inhibitors, it is important to take into consideration that the patients treated with interleukin inhibitors are recalcitrant cases.

In our review, the complete response rates of 71% to ustekinumab and of 38% to anakinra were, respectively, statistically significantly higher ($p = 0.0420$) and lower ($p = 0.0185$) compared to those of other interleukin inhibitors. A similar trend was found in a cohort study with 66% (6/9) response and 44% (4/9) complete response rates to ustekinumab and 0% (0/4) response and complete rates to anakinra [71], although, based on the low number of patients, these findings show that the effect of anakinra was inferior to that of other interleukin inhibitors. However, this should be interpreted cautiously due to differences in both known (e.g., associated diseases) and unknown factors (e.g., ulcer size) among the treatment groups. In our review, the associated diseases were not evenly distributed among the treatment groups (Table 2) and might have biased the results. Both anakinra and canakinumab exert their effect through IL-1 inhibition. Anakinra is an IL-1 receptor antagonist, while canakinumab is a humanized monoclonal antibody targeting IL-1 β . Canakinumab showed a nonsignificant difference to the other interleukin inhibitors, suggesting that IL-1 inhibition, and thus theoretically anakinra, is effective to treat PG. However, the different mode of action between anakinra and canakinumab may reflect clinical differences. A systematic review found that 64% (9/14) achieved complete response to canakinumab among 14 patients with familial Mediterranean fever who had insufficient response to anakinra [72], though another systematic review ($n = 104$) found no significant difference in treatment response of anakinra and canakinumab in patients with familial Mediterranean fever [73]. Neverthe-

less, future trials with PG are needed before conclusions can be drawn about differences in effectiveness among the different interleukin inhibitors.

Our study suggests that inhibition of IL-1 (anakinra and canakinumab) and IL-12/23 (ustekinumab) may be effective therapeutic options in refractory PG in adults.

In our review, 4 patients treated with either tildrakizumab, tocilizumab, or brodalumab achieved complete response (4/4). Three patients were treated with secukinumab; 1 achieved no response, 1 achieved complete response, and 1 achieved partial response. Due to the small sample size, further studies are needed to evaluate the therapeutic options on inhibition of IL-6 (tocilizumab), IL-17 (secukinumab and brodalumab), and IL-23 (tildrakizumab).

Although most likely underreported due to inconsistent reporting of the included papers and too short follow-up, only 4% (4/78) experienced mild adverse events, suggesting that interleukin inhibitors may be safe to use in PG.

Limitations

Due to the data originating from case reports and series, publication bias might have overestimated efficacy. Likewise, concomitant therapies might have overestimated efficacy. Limitations with the outcome measure instruments include risk of misclassification due to variable follow-up time and lack of uniform and objective assessment of lesions. Given the challenge of diagnosis, patients might have been misdiagnosed with PG in the papers included in our review. Another limitation was that the data were incomplete due to missing values.

Due to the observational nature of the included studies, the treatment groups are incomparable because of uneven distribution of both known (e.g., underlying disease) and unknown potential confounding variables; thus, conclusions of the comparison of the different interleukin inhibitors cannot be drawn due to the heterogeneity of the treatment groups.

Conclusion

Our study suggests that inhibition of IL-1 (anakinra and canakinumab) and IL-12/23 (ustekinumab) may be effective and safe therapeutic options in moderate to severe recalcitrant PG in adults. Further studies are warranted to compare the efficacy of the different interleukin inhibitors with other biologic agents, cyclosporine and corticosteroid, and to investigate the importance of un-

derlying disease to treatment response from different medical therapies. Also, international consensus on diagnostic, severity, and outcome measure instruments would provide better evidence for PG.

Key Message

Our study suggests that inhibition of IL-1 (anakinra and canakinumab) and IL-12/23 (ustekinumab) may be effective and safe therapeutic options in moderate to severe recalcitrant PG in adults.

Conflict of Interest Statement

The authors have no conflict of interest to declare.

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Author Contributions

H. Ben Abdallah, K. Fogh, and R. Bech made substantial contributions to the conception and design of the study. H. Ben Abdallah drafted the manuscript. K. Fogh, C. Vestergaard, and R. Bech revised it critically of important intellectual content. All authors made substantial contributions to the interpretation of data, approved the final version to be published, and agreed to be accountable for all aspects of the work.

Data Availability Statement

All data generated or analyzed during this study are available in the article or online supplementary material. Further enquiries can be directed to the corresponding author.

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