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ORIGINAL ARTICLE

Pyoderma gangrenosum and tumour necrosis factor alpha inhibitors: A semi-systematic review

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Pyoderma gangrenosum (PG) is a rare ulcerative skin disease that presents a therapeutic challenge. Tumour necrosis factor alpha (TNFα) inhibitors have been reported to successfully control PG. Our aim was to systematically evaluate and compare the clinical effectiveness of TNFα inhibitors in adults with PG. A literature search including databases such as PubMed, Embase, Scopus, and Web of Science was conducted, using search terms related to PG and TNFα inhibitors. Studies and case reports were included if patients were diagnosed with PG, over the age of 18 and administered TNFα inhibitor. A total of 3212 unique citations were identified resulting in 222 articles describing 356 patients being included in our study. The study we report found an 87% (95% CI: 83%-90%) response rate and a 67% (95% CI: 62%-72%) complete response rate to TNFα inhibitors. No statistically significant differences in the response rates ($P = 0.6159$) or complete response rates ($P = 0.0773$) to infliximab, adalimumab, and etanercept were found. In our study TNFα inhibitors demonstrated significant effectiveness with response and complete response rates supporting the use of TNFα inhibitors to treat PG in adults. Our study suggests that there is no significant difference in effectiveness among infliximab, adalimumab, and etanercept.

KEYWORDS

adalimumab, etanercept, infliximab, pyoderma gangrenosum, TNFα inhibitors

1 | INTRODUCTION

Pyoderma gangrenosum (PG) is a rare ulcerative skin disease with an incidence of 0.3 to 1.0/100.000[1] and is associated with systemic diseases and preceding trauma in 57% and 16% of cases, respectively.[2] PG is a neutrophillic dermatosis characterised by skin infiltrations of polymorphonuclear leukocytes in the absence of vasculitis and infection.[3] Commonly located on lower limbs, lesions typically present as tender pustules or nodules that rapidly progress to ulcers with violaceous undermined borders.[4] With no uniformly accepted diagnostic criteria, PG has been a diagnosis of exclusion.[1,5] However, recent diagnostic criteria have been proposed as a result of a Delphi consensus exercise using the RAND/UCLA Appropriateness Method.[6] The pathophysiology and aetiology are poorly understood, but recent studies have suggested that immune dysregulation with activation of the inflammatory cascade leads to lesions of PG, but triggers of immune dysregulation remain unknown.[7]

The mainstay of treatment is immunosuppression that presents a therapeutic challenge, with no acknowledged standard treatment guidelines, because of incompletely understood pathogenesis and lack of high-quality studies. The literature is characterised by a paucity of controlled clinical trials with only two randomised controlled trials, one comparing infliximab with placebo ($n = 30$)[8] and the other comparing prednisolone with cyclosporine ($n = 112$).[9] Consequently, clinical management relies primarily upon case reports, case series, and local practice. TNFα inhibitors have been reported to successfully control PG. Nevertheless, to the best of our knowledge, no large systematic evaluation has been carried out.

Therefore, the aim of our study was to systematically evaluate and compare the clinical effectiveness of TNFα inhibitors in adults with PG.

2 | METHODS

The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[10] It was not possible to conduct the review in full accordance with the PRISMA statement, hence the name semi-systematic review, because the data were on the individual level as a result of the literature lacking high-quality studies and consisting predominantly of case reports and case series.

2.1 | Search strategy

A literature search of citations from 1998 to 2018 was conducted in larger databases including PubMed, Embase, Web of Science, Scopus, and Cochrane Library. Grey literature was searched in NHS Evidence, OpenGrey, NICE Local Practice Case Studies, The National Technical Information Service, Greylit, Trials Register of Promoting Health Interventions, World Health Organisation International Clinical Trials Registry Platform, ClinicalTrials.gov, and UK Clinical Trials Gateway. The literature search was limited to include citations from 1998 to 2018 because the first TNFα inhibitor, infliximab, was first approved in 1998 by U.S. Food and Drug Administration.[11,12] The search strategy consisted of search terms related to PG and TNFα inhibitors. Search terms were truncated to include all variations and word endings. Complete search history, including search strings, databases, search dates, filters and hits, is available in Supporting Information Table S1. The reference lists of relevant or included studies were manually searched for additional citations.

2.2 | Study selection

All citations from the search were merged, duplicates were removed and followed by a 2-step process consisting of (a) examination of titles and abstracts to find relevant citations (b) that were full-text read to assess their eligibility for inclusion. Articles written in other languages than English, French, and Scandinavian languages were translated.

Studies and case reports were included if patients were diagnosed with PG, over the age of 18 and administered TNFα inhibitor, and if the response of PG to the TNFα inhibitor was reported. Articles were excluded if patients had been previously reported in another publication to avoid duplication or if patients developed PG during anti-TNFα treatment because it was not possible to distinguish whether the treatment led to a partial response, no response, or triggered PG.

Key Messages

- pyoderma gangrenosum is an ulcerative skin disease that presents a therapeutic challenge with no acknowledged standard treatment guidelines
- TNFα inhibitors have shown to successfully treat pyoderma gangrenosum. However, the evidence regarding the use of TNFα inhibitors relies primarily upon case reports and series, and has yet to be systematically summarised
- this systematic review included 222 studies describing 356 patients
- TNFα inhibitors demonstrated significant effectiveness with an 87% (95% CI: 83%-90%) response rate and a 67% (95% CI: 62%-72%) complete response rate
- this study suggests that there is no significant difference in effectiveness among infliximab, adalimumab, and etanercept

A large fraction of articles were assessed by a full-text read to find eligible patients, especially to find the patients that responded poorly to the TNFα inhibitor without the TNFα inhibitor administration being reported in the title or abstract.

2.3 | Data extraction

The data extraction process was a 2-step process with (a) an extraction of data and (b) a control to find potential errors. For each patient included, following data items were collected: age, gender, location and number of PG lesions, duration of PG, comorbidities, and treatment and response. Furthermore, we extracted data regarding previous treatment, response to previous systemic corticosteroid treatment, TNFα inhibitor regimen, time to response, time to complete healing, and reoccurrence and adverse events.

The primary outcome measure was reported as complete response (complete healing of PG ulcers or major improvement, within weeks or with almost complete healing, and without a later known response), partial response (significant improvement of lesions and symptoms), and no response (minimal improvement, no change or worsening of lesions and symptoms).

Patients administered different or multiple courses of TNFα inhibitors were reported based on the first TNFα inhibitor administration to have homogenous and TNFα inhibitor-naive patients, as the TNFα inhibitor experienced patients may respond differently to anti-TNFα treatment. Patients administered TNFα inhibitors resulting in no or partial response followed by an addition of immunosuppressive drugs were reported based on the initial treatment attempt because the response would best reflect the effect of TNFα inhibitors when minimising effects from other concomitant drugs.

To avoid duplicates, included articles were compared based on author names, title, date, and publisher, and patients were compared based on age, gender, comorbidity, and response to treatment.

2.4 | Statistical analysis

Categorical variables were compared using Fisher's exact test and means were compared using one-way ANOVA. Only available data were used. A $P < 0.05$ was considered statistically significant. The statistical analyses were generated with SAS Studio software.

3 | RESULTS

A total of 3212 unique citations were found. 1286 and 1704 citations were excluded by abstract and full-text read, respectively, yielding 222 articles[4,8,13–232] with 356 patients that fulfilled the eligible criteria and none of the exclusion criteria. The selection process is depicted in Supporting Information Figure S1, data of the included patients are available in Table S2 and the excluded articles with reasons for exclusion are available in Table S3.

3.1 | Clinical characteristics

Patients were categorised into three groups based on infliximab, adalimumab, or etanercept administration. The groups were compared with find any differences in the distribution of clinical characteristics (Table 1). The adalimumab group was statistically significantly ($P = 0.0480$) younger with a mean age of 39.78 years compared with 46.10 years for the infliximab group and 47.94 years for the etanercept group. There was a statistically significant ($P = 0.0001$) difference of associated diseases (inflammatory bowel disease [IBD], haematological diseases, other inflammatory disorders, and no associated diseases) among the etanercept, adalimumab, and infliximab groups. Noticeably, the etanercept group had fewer patients with IBD, 19% compared with 62% for infliximab, and 56% for adalimumab, and more patients with other inflammatory diseases, 47% compared with 20% for infliximab and 28% for adalimumab.

In total, 60% were females and 40% were males, the location was predominantly on lower limbs (49%), the number of PG lesions was single in 33% of the patients and multiple (>1) in 67% of the patients and the duration of PG was more than 12 weeks in 60% of the patients and less than 12 weeks in 40% of the patients. No statistically significant differences of gender, duration of PG, location, or number of lesions were found among the infliximab, adalimumab, and etanercept groups.

3.2 | Treatment and response

Of the 356 patients, 275 were treated with infliximab, 43 were treated with adalimumab, 36 were treated with etanercept, and 2 were treated with certolizumab. An 87% (95% CI: 83%-90%) response rate and a 67% (95% CI: 62%-72%) complete response rate to TNFα inhibitors were found (Table 2). There were no statistically significant differences in response rates ($P = 0.6159$) or complete response rates ($P = 0.0773$) to infliximab, adalimumab, and etanercept. Subgroup analyses according to the TNFα inhibitor agent, type of PG, and associated disease found no statistically significant differences in response or complete response rates.

The 69% complete response rate for patients with PG duration more than 12 weeks was, unlike the response rate, statistically significantly ($P = 0.0124$) lower than the 87% complete response rate for patients with PG duration less than 12 weeks.

3.3 | Additional clinical characteristics

35 of 324 (10.8%) patients had an adverse effect including four patients with fatal outcome because of sepsis or endocarditis (Table 3). Thirty-three of the 35 adverse events occurred with infliximab. Thirty-five of 200 (17.5%) patients with complete response had a reoccurrence including 17 patients while off TNFα inhibitor treatment and 11 patients while on TNFα inhibitor treatment. Time to complete healing was on average 20.37 weeks.

4 | DISCUSSION

4.1 | Key findings

The study we report found response (87%, 95% CI: 83%-90%) and complete response rates (67%, 95% CI: 62%-72%) to TNFα inhibitors that may be considered as clinically significant. In addition, the results showed that infliximab, adalimumab, and etanercept did not statistically significantly differ in response and complete response rates.

Although not statistically significant, it is noteworthy that patients treated with etanercept had a less-favourable response. The response rate for etanercept was 83% compared with 91% for adalimumab and 87% for infliximab. And the complete response rate was 53% for etanercept compared with 77% for adalimumab and 68% for infliximab (Figure 1).

4.2 | Findings in relation to other studies

A randomised controlled trial by Brooklyn et al[8] demonstrated a response after 2 weeks in 46% (6/13) of subjects who received a single infusion of infliximab versus 6% (1/17) of subjects who received placebo ($P = 0.025$). Subsequently, subjects with no response at week 2 received an

TABLE 1 Clinical characteristics of patients

Characteristics	All	Infliximab	Adalimumab	Etanercept	*P*-value
Age (y)					
Mean ± SD	45.41 ± 16.39	46.10 ± 16.72	39.78 ± 12.55	47.94 ± 17.32	0.0480
No. of missing values	58	55	2	1	
Gender					
Female	60% (181)	60% (135)	49% (20)	69% (24)	0.2100
Male	40% (123)	40% (91)	51% (21)	31% (11)	
No. of missing values	52	49	2	1	
Location of PG					
Lower limb(s)	49% (133)	45% (94)	48% (16)	68% (23)	0.1357
Torso	25% (69)	28% (59)	21% (7)	9% (3)	
Other body parts[a]	6% (17)	7% (14)	3% (1)	3% (1)	
Multiple body parts[b]	21% (59)	20% (42)	27% (9)	21% (7)	
No. of missing values	78	66	10	2	
Number of PG lesions					
Single	33% (83)	34% (62)	25% (8)	34% (12)	0.6254
Multiple (>1)	67% (167)	66% (119)	75% (24)	66% (23)	
No. of missing values	106	94	11	1	
Associated diseases					
IBD[c]	57% (179)	62% (146)	56% (24)	19% (7)	0.0001
Haematological diseases[d]	4% (14)	4% (10)	2% (1)	8% (3)	
Other inflammatory disorders[e]	24% (75)	20% (46)	28% (12)	47% (17)	
No associated diseases	15% (48)	14% (33)	14% (6)	25% (9)	
No. of missing values	40	40	0	0	
Duration of PG					
<12 weeks	40% (61)	45% (49)	28% (5)	27% (7)	0.1579
>12 weeks	60% (93)	55% (61)	72% (13)	73% (19)	
No. of missing values	201	165	25	10	

Data are given as percentage (number) of patients, unless otherwise specified. Only available data were included in the statistical analyses.
[a] Body parts including upper limb(s), anogenital region, face and neck.
[b] PG located at least on two of the following body parts: upper limb(s), lower limb(s), torso, anogenital area, and extracutaneous area or head/neck.
[c] Patients with IBD were categorised as IBD despite other concomitant diseases.
[d] Patients with haematological diseases and no IBD were categorised as haematological diseases despite other concomitant diseases.
[e] Including primarily rheumatologic diseases.

open-label infliximab infusion regardless of the allocation to infliximab or placebo group. At week 6, the response rate was 69% (20/29) and the complete response rate was 21% (6/29).

The 46% response rate to infliximab found at week 2 is substantially lower than the 87% response rate found in our study, but 2-week observation time and a single infusion might have led to underestimation of the former response rate. The low 21% complete response rate at week 6, compared with the 68% complete response rate from our study, might also be underestimated because of inadequate dosage and observation time when considering that our study found a mean of 20.37 weeks to complete healing.

Brooklyn et al found a difference ($P = 0.014$) in response rates according to the duration of PG. Patients with more than 12-week duration had a less-favourable response than those with less than 12-week duration (47% [7/15] versus 93% [13/14]). This might be a consequence of more cases with recalcitrant PG in the group of patients with more than 12-week duration of PG. Yet, in the present study, we did not find a statistically significant ($P = 0.5678$) difference in response rates according to the duration of PG, but a statistically significant ($P = 0.0124$) difference in complete response rates was found, which supports Brooklyn et al's findings. Consistent with the results of our study, Brooklyn et al found no difference in response rates according to IBD status. Infliximab and adalimumab are licensed for treatment of IBD that may explain why our study found statistically significantly ($P = 0.0001$) fewer patients with associated IBD treated with etanercept (19%) than infliximab (62%) and adalimumab (56%).

The response and complete response rates to TNFα inhibitors in our study were slightly lower, but overall broadly similar to those found in case series or retrospective analyses with PG. Response rates ranged from 87.5% to 100% and complete response rates ranged from 37.5% to 100%.[189,211,219,225,230,233] Most patients from the randomised controlled trial by Brooklyn et al, case series, and retrospective analyses were included in this systematic review.

TABLE 2 Response and complete response rates to TNFα inhibitors according to TNFα inhibitor agent, associated disease, type of PG, and duration of PG

	Response rate	Complete response rate	No response rate	*P*-value[a]	*P*-value[b]
No stratification	87% (309) (95% CI: 83%-90%)	67% (240) (95% CI: 62%-72%)	13% (47) (95% CI: 10%-17%)		
TNFα inhibitor agent					
Infliximab	87% (239)	68% (187)	13% (36)	0.6159	0.0773
Adalimumab	91% (39)	77% (33)	9% (4)		
Etanercept	83% (30)	53% (19)	17% (6)		
No. of missing values	0	0	0		
Type of PG					
NPPSPG	87% (183)	71% (149)	13% (27)	0.7061	0.2970
PPG	83% (45)	61% (33)	17% (9)		
PSPG	93% (13)	79% (11)	7% (1)		
No. of missing values	68	47	10		
Associated diseases[c]					
IBD	91% (162)	74% (132)	10% (17)	0.2136	0.6667
Haematological diseases	93% (13)	64% (9)	7% (1)		
Other inflammatory disorders	81% (61)	68% (51)	19% (14)		
No associated diseases	90% (43)	69% (33)	10% (5)		
No. of missing values	30	15	10		
Duration of PG					
<12 weeks	93% (57)	87% (53)	7% (4)	0.5678	0.0124
>12 weeks	89% (84)	69% (65)	11% (10)		
No. of missing values	168	122	33		

Abbreviations: NPPSPG, non-peristomal or non-post surgery pyoderma gangrenosum; PPG, peristomal pyoderma gangrenosum; PSPG, postsurgery pyoderma gangrenosum.
Data are given as percentage (number) of patients, unless otherwise specified. Only available data were included in the statistical analyses.
[a] *P*-values for response rates. Calculated using Fisher's exact test. The response rate is the percentage of patients with partial and complete response.
[b] *P*-values for complete response rates. Calculated using Fisher's exact test. The complete response rate is the percentage of patients with complete response.
[c] Same as Table 1.

TABLE 3 Additional clinical characteristics

Clinical characteristics	Numbers
Adverse effects	10.8% (35/324)
No. of missing values	32
Reoccurrence	17.5% (35/200)
No. of missing values	40
Time (weeks) to complete	20.37 (mean)
Healing	1 to 156 (range)
No. of missing values	117

Another randomised controlled trial ($n = 112$) by Ormerod et al[9] found approximately 90% response rates and 47% complete response rates to oral corticosteroid or cyclosporine after 6 months. The response rates were found in fig. 3 and the complete response rates were found in Table 3.[9] This is inferior to the rates to TNFα inhibitors, suggesting that TNFα inhibitors may be more efficacious. The rates to oral corticosteroid or cyclosporine may be overestimated compared with the response and complete response rates to TNFα inhibitors from our study because patients treated with TNFα inhibitors are usually more therapy resistant and have failed multiple treatments. In our study, 60% (84/141) of the patients had a duration of PG more than 12 weeks indicating that a significant fraction of patients treated with TNFα inhibitors might have been resistant to previous therapy.

In the study, we report 4 of 356 (1.12%) patients died of infection after administration of infliximab. By comparison, 5 of 23 (21.7%) patients died of infection in a retrospective analysis of 23 patients requiring inpatient management of PG.[84] These five patients were receiving immunosuppressive drugs but no TNFα inhibitors. Therefore, suggesting that a high risk of death by infectious causes is not limited to administration of TNFα inhibitors. Rather, it may be related to immunosuppression along with PG lesions being portal of entry for pathogens. Our study suggests that infliximab may be associated with more adverse events than etanercept and adalimumab, as 33 of 35 adverse events occurred with infliximab administration. However, it should be taken into consideration that more patients were treated with infliximab and not solely rely on the number of adverse events reported.

4.3 | Limitations

To minimise publication bias, grey literature was searched, data were controlled for duplications and a large fraction of articles were full-text assessed to find eligible patients without TNFα inhibitor administration being reported in the title or abstract. Nevertheless, the vast majority of data came

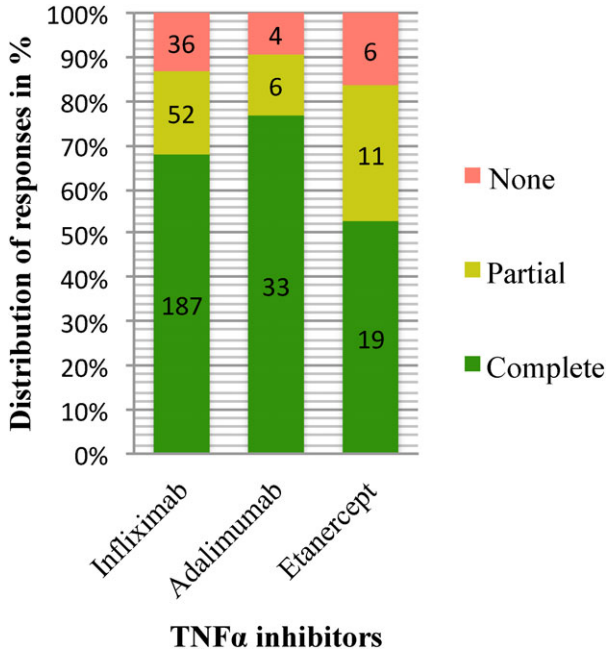

FIGURE 1 Distribution of complete, partial, and no responses to infliximab adalimumab and etanercept. The absolute frequencies of responses are shown within the histograms

from case reports, thus increasing the risk of publication bias that might have overestimated the found response and complete response rates. Patients might have received concomitant drugs that would overestimate the response and complete response rates, while insufficient dosages of TNFα inhibitors might have underestimated the response and complete response rates. Reoccurrences and adverse events may have been underestimated because of inconsistent reporting and too short follow-up time. As there are no diagnostic criteria, patients misdiagnosed with PG might have been included in our semi-systematic review.

Some of the limitations with the outcome measures are that the response rates do not specify the degree of response, and the complete response rates are susceptible to misclassification because of variable follow-up time and no standard objective assessment of lesion response.

It is a limitation that the data were incomplete because of missing values. In addition, extracted data items including previous treatment, response to previous systemic corticosteroid treatment, concomitant drugs, TNFα inhibitor regimen, and time to response were not used in our study because the data were unreliable as a result of inconsistent and low quality of reporting in the included articles.

Infliximab, adalimumab, and etanercept did not differ significantly in response and complete response rates. This should be interpreted cautiously as differences in factors such as severity of PG, concomitant therapy, therapy resistance, TNFα inhibitor regimen, and follow-up time among the three treatment groups could potentially have led to a type II error. The found age difference with the adalimumab group being younger, and therefore possibly had a better response, could have compromised the comparability of the groups. However, etanercept performed worse than infliximab, despite the fact that these two groups had approximately the same mean age, suggesting age might not have been a confounder.

As there was no placebo comparison in our study, it is possible that none of the TNFα inhibitors had a positive effect, but this is unlikely as Brooklyn et al[8] demonstrated that infliximab was superior to placebo in the treatment of PG.

Despite the limitations, this systematic evaluation of TNFα inhibitors provides a significant contribution to the existing scarce literature on treatment options for PG that is characterised by anecdotal evidence.

5 | CONCLUSION

TNFα inhibitors demonstrated significant effectiveness with an 87% response rate and a 67% complete response rate supporting the use of TNFα inhibitors to treat PG in adults. Our study suggests that there is no statistically significant difference in effectiveness among infliximab, adalimumab, and etanercept, but there is a risk of a type II error because the groups of patients treated with these TNFα inhibitors might not have been comparable. Although not statistically significant, patients had a noteworthy less-favourable response to etanercept.

Future controlled trials comparing different TNFα inhibitors with other treatments such as systemic corticosteroid, cyclosporine, or other biologic drugs with objective and meaningful assessment of lesion response, adequate dosage, and at least 6-month follow-up time may validate these findings and further strengthen the evidence for the use of TNFα inhibitors in the treatment of PG.

CONFLICT OF INTEREST

The authors have no conflict of interests to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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