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Pyoderma gangrenosum: proposed pathogenesis and current use of biologics with an emphasis on complement C5a inhibitor IFX-1

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Abstract

Introduction: Pyoderma gangrenosum (PG) is a rare neutrophilic dermatosis with no FDA approved treatment. The complement pathway has received renewed attention because it is elevated in inflammatory cutaneous conditions such as hidradenitis suppurativa (HS) and psoriasis. IFX-1 is a complement C5a inhibitor which inhibits neutrophil activation, chemotaxis, and reduces inflammatory signalling and complement driven tissue damage in various diseases.

Areas Covered: The article discusses a proposed pathogenesis of PG, early clinical investigations of IFX-1 for the treatment of HS and PG, its potential as a treatment for PG and those other biologics currently under investigation.

Expert Opinion: Further studies should explore how patients with PG and other neutrophilic conditions may respond to complement inhibitors such as IFX-1. C5a blockade led to a reduction in inflammatory tunnels in HS, and alteration in neutrophil migration and activation supports the role of this pathway in the development of PG. The main challenges to the approval of IFX-1 are the identification of the optimal dose, duration, and stage dependent factors in cutaneous inflammatory disorders. Further studies are required; however, complement inhibitors such as IFX-1 could find a place in clinical practice in years to come for severe, resistant PG that does not respond to conventional therapies.

Article Highlights

- PG is a rare neutrophilic dermatosis that presents as an inflammatory ulcerative disorder.
- We review the current clinical trials and a proposed pathogenesis model for PG.
- There are no FDA approved drugs for the treatment of PG and most biologics under investigation for PG are limited to small case reports or cohort studies
- IFX-1 is a complement C5a inhibitor which has demonstrated complete remission in 2 out of 5 patients with PG in a recent Phase IIa open-label trial, with no reported serious adverse events
- IFX-1 also showed an acceptable safety profile in hidradenitis suppurativa (HS) but did not achieve significant clinical response vs. placebo in a phase IIb study. However, there was a significant reduction in draining fistulas and IHS4 scores.
- Although more studies are required, complement inhibitors such as IFX-1 could find a place in clinical practice in the following years for severe, resistant PG that does not respond to conventional therapies.

1. Introduction

Pyoderma gangrenosum (PG) is a rare neutrophilic dermatosis that presents as an inflammatory ulcerative disorder with a significant burden on patients and health care systems.[1] Despite four existent diagnostic frameworks (von den Driesch,[2] Su et al.,[3] PARACELSUS,[4] Delphi criteria[5]), they lack concordance and PG is commonly misdiagnosed as infections and other ulcerative inflammatory conditions.[6] PG affects individuals of any age with a reported incidence of 3-10 patients per million.[7] It commonly manifests as a painful papule, pustule, or vesicle with red or blue base sloughing which rapidly progresses to a gangrenous ulcer with an undermined border.[7] PG is often associated with inflammatory bowel disease, rheumatoid conditions, leukemia, and monoclonal gammopathies and is a disease of interest for many disciplines other than dermatology.[8, 9] However, due to its rarity, there is a lack of validated outcome measure instruments.[10]

The exact etiology of PG is unknown and multiple inflammatory mediator and defects in chemotaxis and hyperreactivity of neutrophils has been implicated in the pathogenesis of PG.[7] Experimentally, abnormalities in neutrophil trafficking have been described.[7] Consequently, neutrophilic dysfunction has been implicated in the pathogenesis of PG.[11] Defects in neutrophil chemotaxis, migration, phagocytosis, and bactericidal activity have been reported in PG patients.[12-14] More recently, an interleukin (IL)-1β- and IL-α- driven innate immunity dysfunction has been demonstrated, suggesting that autoinflammation plays a critical role in PG pathogenesis,[15, 16] with a contributing role of adaptive immunity.[17, 18] Based on the current literature, the proposed pathogenesis of PG is highlighted in **Figure 1**.

The complement system has a critical role in the modulation of immune response and regulation of cutaneous commensal bacteria. This pathway has recently gained renewed attention in inflammatory cutaneous disorders such as psoriasis, atopic dermatitis, vasculitis, and hidradenitis suppurativa.[19] The complement pathway activates the immune system through the downstream effects of C3 and C5 complement proteins which produces inflammation, opsonization, and bacterial lysis.[20] More importantly, C3a and C5a are complement anaphylatoxins which are potent neutrophil activators and recruiters, suggesting complement inhibition may be warranted in PG. Furthermore, complement inhibition may accelerate wound healing time, as C5a receptor

deficient mice had more effective cutaneous wound healing.[21] Components of the complement system including C5a protein is upregulated in serum proteomics.[19] Evidence from other systemic inflammatory disorders identifies complement receptors as present on neutrophils, dendritic cells and monocytes.[22, 23] The complement pathway serves an important role in the innate immune response, as formation of the membrane attack complex C5b-9 (MAC), offers defense against bacterial infection. Importantly, C5a inhibition does not interfere with MAC formation and the important opsonization and lysis of pathogens, which facilitates removal of immune complexes and damaged cells. In addition, the mechanism of C5a antagonism impacting upon neutrophil migration and activation supports the post-hoc analysis demonstrating a significant reduction in draining dermal tunnels found in hidradenitis suppurativa (HS), a condition also associated with neutrophilic dermatosis.[24] The role of complement in disease pathogenesis has led to the development of novel anticomplement agents and clinical trials investigating the efficacy of such treatments in HS.[24, 25]

2. Overview of the current market in PG

There are currently no FDA-approved drugs for the treatment of PG.[26] As PG represents an immunologic disease, mainstay treatment involves topical or systemic corticosteroids and cyclosporine as first line therapies in conjunction with wound care and analgesia management.[8] A randomized controlled trial from 2015 found no difference in outcomes between PG patients that received prednisolone compared to cyclosporine, suggesting that their use may be dependent on their contraindications and the presence of other comorbidities.[27] A summary of biologics tested for pyoderma gangrenosum in the literature and their effectiveness is illustrated in **Table 1**.

As the role of cytokines and other inflammatory molecules in PG continue to be elucidated, recent investigations into biologics may yield promising results **(Table 2)**. TNF-α inhibitors such as infliximab have shown a strong benefit among PG patients either with or without IBD in a randomized clinical trial.[28] Adalimumab, another TNF-α inhibitor, is limited to case reports and case series, with complete remission in 38/51 patients from a recent review.[26] Etanercept, a

decoy receptor for TNF-α, is also limited to case reports, with 17/28 achieving complete remission **(Table1)**.[26]

IL-1 inhibitors such as anakinra, canakinumab, gevokizumab are also being investigated for the treatment of PG. Anakinra, a homolog of the IL-1 receptor antagonist, provided significant clinical improvement (defined as reduction in ulcer size, depth, pain, or other sequelae) or complete remission in 10/13 patients from 9 case reports.[26] Out of 10 patients treated with canakinumab, a monoclonal antibody (mAb) targeting IL-1β, 6 patients demonstrated complete remission and 1 experienced clinical improvement. Gevokizumab, another mAb targeting IL-1β, underwent a phase II open label trial.[26] Out of 6 patients, 3 patients experienced complete remission, 2 demonstrated significant improvement, and one resulted in treatment failure.[26] However, a phase III trial for gevokizumab (NCT02315417) was terminated in March 2016 and its potential use in PG is unclear. **Tables 1 and 2** provide a summary of current therapeutic targets for PG.

Clinical trials for IL-17 inhibitors (secukinumab and ixekizumab) are currently in progress. For secukinumab, one trial is beginning recruitment (NCT04274166) while another clinical trial is currently active (NCT02733094). One trial is complete for ixekizumab although no results are published (NCT03137160). Interestingly, IFX-1 is the only complement inhibitor being investigated in PG and is currently in the recruitment process (NCT03971643). While there are favourable outcomes to support the use of biologics in PG, more studies with larger sample sizes are required before conclusions can be drawn on their overall effectiveness. A proposed pathogenesis and current drugs being evaluated in PG is highlighted in **Figure 1**.

3. IFX-1

IFX-1 (InflaRx GmbH, Jena, Germany) is a chimeric monoclonal IgG4 antibody which inhibits C5a, a key activation product of the complement system. The complement pathway is a complex network of proteins (which converge into downstream C3 and C5 proteins) to produce inflammation, lysis, and opsonization of foreign pathogens.[29] However, C5a has been shown to act as a potent activator of neutrophils and other inflammatory cells through mechanisms

associated with inflammatory tissue damage.[29] Accelerated wound healing time was observed in C5a receptor deficient mice.[21]

Chemistry, pharmacokinetics, pharmacodynamics, and metabolism

Specifically, IFX-1 binds to the soluble human complement split product C5a, thereby leaving formation of MAC (C5b-9) intact, which is an important function of the complement system relevant for bacterial defense. IFX-1 has a molecular weight of approximately 148,472 Daltons.[30] The molecular structure is currently unavailable.

In vitro analysis of IFX-1 has shown a strong binding capacity to soluble human C5a.[30] IFX-1 activity results in high blocking activity of C5a-induced biological effects (ex. lysosome release from neutrophils or CD11b up-regulation in neutrophils in human whole blood). In one study, human whole blood model was used to assess blocking activity of IFX-1 to recombinant human C5a (rhC5a).[30] CD11b levels on neutrophils were measured as markers of neutrophil activation. This study showed that rhC5a strongly stimulated the CD11b upregulation on human neutrophils. In the presence of IFX-1, this effect could be completely blocked. IFX-1 is highly specific and the irrelevant human IgG4 antibody did not show any blocking activity.[30]

When experiments were performed to use zymosan-activated plasma (ZAP) to upregulate CD11b and thus stimulate neutrophilic activity, it was shown that the CD11b expression on neutrophils via flow cytometry was significantly decreased by 82-100% following administration of IFX-1, even at an Ab:Ag molar ratio of 0.5:1.[30] After Zymosan A, a fungus cell wall component known to induce inflammatory response, was administered to human blood neutrophils, IFX-1 was able to decrease the CD11b upregulation by 79-93%, depending on the IFX-1 concentration used. With respect to the inflammatory response in this experiment, the generation of IL-8 was reduced by up to 54% relative to IL-8 concentrations after zymosan A stimulation.[30]

The only available data for pharmacokinetics was conducted in a monkey model of H7N9 virus infection.[31] Four monkeys received an intravenous dose of 5 mg/kg of IFX-1 and the levels were then measured and followed by a pharmacokinetic assay. After one day of treatment, the assay

showed 40 µg/ml of IFX-1 in the four monkeys. On day 7, the level of IFX-1 dropped to 10 µg/ml in the two monkeys.[32] Additional pharmacokinetic data and metabolism data is not yet published.

4. Clinical efficacy

The clinical utility of IFX-1 has been studied in phase I and II studies in healthy male subjects and patients with hidradenitis suppurative, respectively.[24, 32] A phase I study evaluating the pharmacokinetics, pharmacodynamics, safety, and tolerability of CaCP29 (the initial experimental name for IFX-1) was completed in October 2011.[32] This was a double-blind, randomized interventional study involving 26 healthy participants. Primary outcomes included the number and extent of changes in safety after injection of CaCP29. Secondary outcomes included assessment of pharmacokinetic parameters of CaCP29 over time, number of patients developing ant-drug antibodies to CaCP29, and bioactivity of CaCP29 in human whole blood over time after injection. Unfortunately, there are no reported or published reports on the results of this study.[32]

A prospective, open-label, single-arm observational study evaluating the safety and efficacy of IFX-1 in patients with hidradenitis suppurativa was conducted from December 2016-July 2017.[24] Twelve patients were enrolled and received 800mg of IFX-1 at 30 minute intravenous infusions on days 1, 4, 8, 15, 22, 29, 36, 43 and 50. The proportion of patients achieving a positive Hidradenitis Suppurativa Clinical Response Score (>50 % improvement) following IFX-1 was 75% (n=9/12) at the end of the treatment period and 83.3% (n=10/12) after 3 months.[24] The International HS4 Score as well as draining fistula count was significantly decreased over time following administration of IFX-1. The Dermatology Life Quality Index score decreased from a mean of 19.4 ± 7.5 at baseline to 15.3 ± 6.9 at day 50 and 13.4 ± 8.3 at day 134.[24] The follow-up Phase IIb SHINE study did not show a significant effect on HS using HiSCR as the end point due to high placebo response.[25] However, the HiSCR does not account for reduction in draining fistulas and the company reported a statistically significant reduction of draining fistula (45.2%, p = 0.04) and IHS4 score (31.7%, p=0.02) in the high dose group when compared to placebo by week 16.[33]

An ongoing phase IIa open-label study investigating the efficacy and safety of IFX-1 on patients with PG is currently being conducted (NCT03971643). From a recent press release, patients are treated with 800mg of IFX-1 biweekly for 12 weeks after an initial phase with three doses of 800 mg on day 1, 4 and 8 of the study, with a three-month observational period.[34] The Physician Global Assessment (PGA) scale is being used to evaluate efficacy. Primary efficacy endpoints include the PGA score is ≤3 of the target ulcer at various timepoints and the time to complete closure (remission) of the target ulcer. A total of 5 patients have been enrolled thus far and 2 patients have achieved complete remission of PG despite previously failing traditional therapy. One patient achieved complete healing at all affected sites and remained disease free two months after cessation of IFX-1 therapy. The second patient remained symptom free except for one minimal area and is close to completion of therapy. The remaining patients still have severe disease and did not show a healing response but are eligible for dose escalation.

5. Safety and tolerability

No drug-related severe adverse events (SAEs) have been recorded to date for IFX-1 in five PG patients.[34] In a phase IIa study evaluating safety and efficacy of IFX-1 in twelve patients with HS, six patients reported nine AEs, with five patients experiencing SAEs; however, none were considered to be drug-related.[24] The most common AE was HS exacerbation while other AEs were furuncle development, respiratory tract infection, soft tissue *infection*, increase of aspartate aminotransferase and depression (during follow-up period).[24]

6. Regulatory affairs

As of August 2020, IFX-1 is currently under the recruiting phase for a clinical trial (NCT03971643) and is not approved by the U.S. Food and Drug Administration for the treatment of PG.

7. Conclusion

IFX-1 may represent a promising treatment strategy for PG. It showed an acceptable safety profile in HS but did not achieve significant clinical response vs. placebo in a phase IIb study by using HiSCR as the endpoint.[25] However, there was a significant benefit on the reduction of draining fistulas and IHS4 scores.[33] IFX-1 is the only complement inhibitor being investigated in

clinical trials for PG. Due to the neutrophilic involvement and pathogenesis of PG and the role of the complement system in neutrophil recruitment, continued research and development of therapies of PG is warranted. Furthermore, with several biologics under investigation for PG, the landscape of PG therapy will most likely be dynamic over the coming years.

8. Expert opinion

Although there are currently no approved FDA drugs for PG, IFX-1 appears to be a promising therapy for neutrophilic conditions such as PG. Neutrophilic infiltration is a hallmark of PG and PG is also associated with congenital complement deficiencies of C2, C4, C7, suggesting that dysregulation of this pathway is involved in PG. In addition, deficiencies of C7 is associated with decreased neutrophil chemotaxis, opsonization, and phagocytosis similar to the immunologic abnormalities described in patients with PG.[35] Complement anaphylatoxins such as C3a and C5a are important neutrophil recruiters and activators and have found to be upregulated in the serum of patients with hidradenitis suppurativa,[24] a condition associated with neutrophilic dermatosis. When administered to patients with hidradenitis suppurativa, IFX-1 was shown to have a good safety profile in both HS studies and the Phase II clinical trial of IFX-1 for PG will help determine its safety and efficacy.

Moving forward, due to its neutrophilic and inflammatory pathogenesis, biological treatments will continue to be investigated and considered for approval for the treatment of PG. Due to the low incidence of PG, the vast majority of data is reported from small case series and case reports with varying doses, methods for assessing severity, and differences in time periods which makes comparison difficult. There is also a lack of long-term data with respect to adverse events and maintain disease remission. Furthermore, multiple other cytokines have been reported being involved in the pathogenesis of PG, and combinational therapies may also need to be explored soon. The main challenges to IFX-1 being approved is identifying the optimal dose, duration, and stage dependent factors in cutaneous inflammatory disorders such as PG. Although more studies are required, complement inhibitors such as IFX-1 could find a place in clinical practice in the following years for severe, resistant PG that does not respond to conventional therapies.

Declarations of interest

A Alavi has received honoraria as a consultant, speaker, or advisory board participant from AbbVie, Galderma, Janssen, LEO, Novartis, Sanofi, and Valeant; received grants from AbbVie; and was a research investigator with AbbVie, Aristea, Asana, Boehringer-Ingelheim, Bristol-Myers Squibb, Dermavant, Eli Lilly, Genetech, Glenmark, Incyte, Infla Rx, Janssen, Kyowa, LEO, Novartis, Pfizer, Regeneron, and UCB. A Ortega-Loayza was part of the advisory board for Janssen Inc. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

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**Double-blind, randomized interventional, phase I study evaluating the pharmacokinetics, pharmacodynamics and tolerability of CaCP29 (the initial experimenttal name for IFX-1) in healthy patients.

Drug summary box:

Drug name (generic): IFX-1
Phase: Phase IIa
Dermatologic Indication: Pyoderma gangrenosum, hidradenitis suppurativa
Pharmacology description/mechanism of action: Inhibitor of the soluble human complement split product C5a.
Route of administration: IV infusion diluted in sodium chloride
Chemical structure: IFX-1 is a chimeric monoclonal IgG4 antibody
Pivotal trials: NCT03971643, NCT01319903, NCT03001622, NCT03487276

FIGURES AND TABLES

Figure 1. Biological treatment use in PG studies

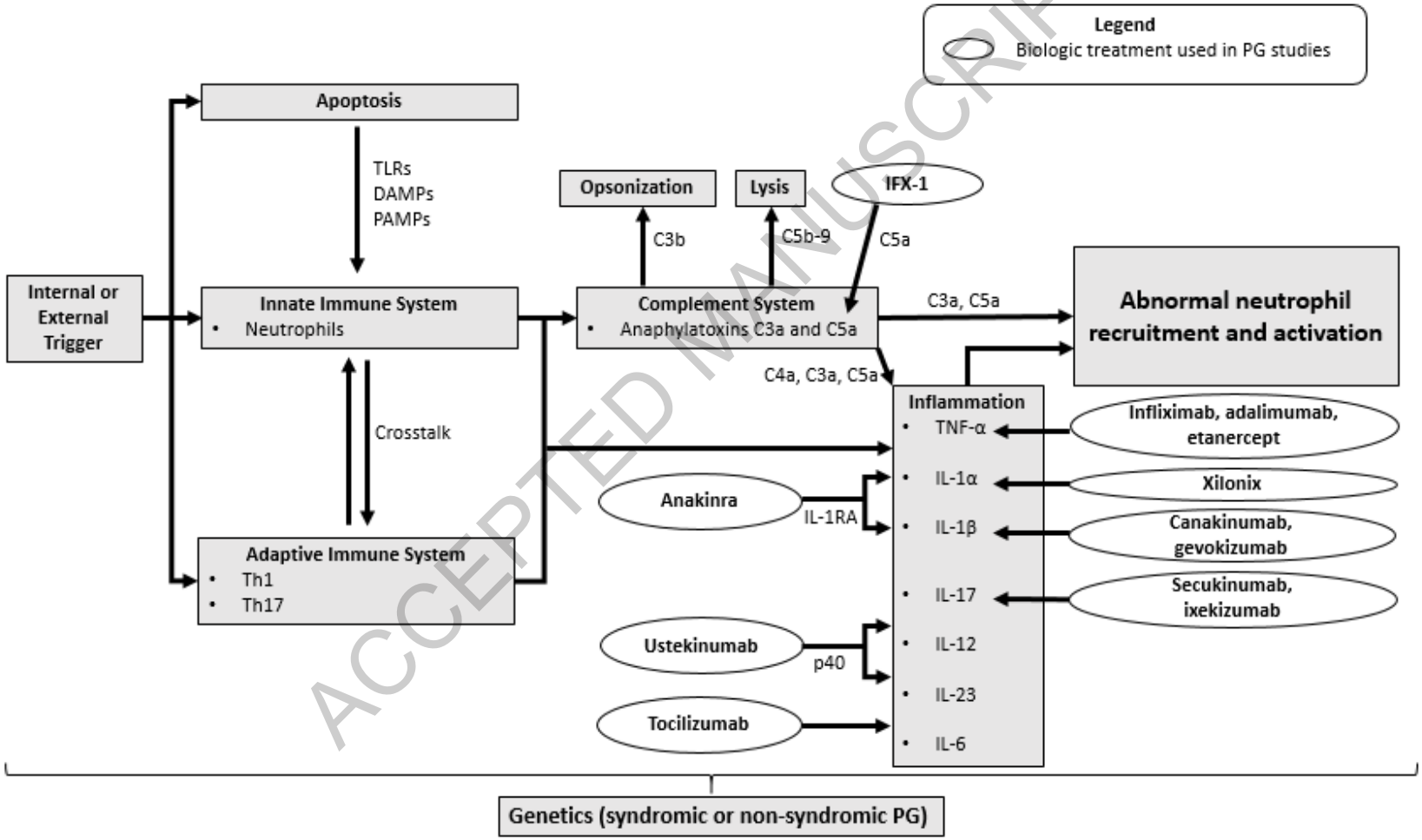

Figure 1. Simplified pathogenesis of pyoderma gangrenosum with current drugs under investigation. PG, pyoderma gangrenosum; TLR, toll-like receptor; DAMP, damage-associated molecular pattern; PAMP, pathogen-associated molecular pattern; Th, T-helper; IL, interleukin; RA, receptor antagonist.

Table 1. Summary of biologics tested for pyoderma gangrenosum in the literature and their effectiveness. Adapted from McKenzie et al.[26] Clinical improvement is defined as reduction in ulcer size, depth, pain, or other sequelae. *High uncertainty due to low number of studies and patients.

Therapeutic Target	Biologic	Number of studies	Total number of patients	Complete remission (n, %)	Clinical improvement (n, %)	Failure (n, %)	Overall Success (n, %)
TNF-α	Infliximab	107 (1 RCT, 3 cohort, 103 case reports and series)	215	134 (63%)	46 (21.4%)	35 (16.3%)	180 (83.7%)
	Adalimumab	32 case reports and series	51	38 (74.5%)	8 (15.7%)	5 (9.8%)	46 (90.2%)
	Etanercept	20 case reports and series	28	17 (60.7%)	4 (14.3%)	7 (25%)	21 (75%)
IL-1	Anakinra	9 case reports and series	13	2 (15.4%)*	8 (61.5%)*	2 (15.4%)*	10 (76.9%)*
	Canakinumab	5 (1 prospective, 4 case reports and series)	10	6 (60.0%)*	1 (10.0%)*	3 (30.0%)*	7 (70.0%)*
	Gevokizumab	1 prospective	6	3 (50.0%)*	2 (33.3%)*	1 (16.7%)*	5 (83.3%)*
	Xilonix	1 prospective (no results published)	N/A	N/A	N/A	N/A	N/A
IL-17	Secukinumab	N/A	1	0	1	0	1
	Ixekizumab	N/A	N/A	N/A	N/A	N/A	N/A

IL-12/23	Ustekinumab	7 case reports and series	9	6 (66.7%)*	3 (33.3%)*	0	9 (100.0%)*
IL-6	Tocilizumab	1 case report	1	1	0	0	1
C5a	IFX-1	1 prospective (no results published)	N/A	N/A	N/A	N/A	N/A

Table 2. Summary of targets, therapeutics, evidence for disease modifying mechanisms, clinical response, and safety for biologics tested in clinical trials for pyoderma gangrenosum. Ongoing studies and some recently completed studies have not yet published their findings.

	Target in PG		**Therapeutic**		**Validation of Disease Modifying Mechanisms**			**Validation of Clinical Response**		**Safety and Tolerability**
	Elevated in Blood	**Elevated in Tissue**	**Name**	**Mechanism**	**Study Type**	**Tissue/ Cell**	**Result**	**Study Type**	**Clinical Response Rate**	

TNF-α	Yes	Yes	Infliximab	TNFα	In Vivo	Human tissue	IL-8 dec IL-6 dec ICAM-1 dec VCAM-1 dec	Open-label study NCT00791557 Completed.	N/A	N/A
								RCT by Brooklyn et al.[28]	Week 6, 20/29 (70.0%) improved, including 6/29 (20.7%) in complete remission, 9/29 did not respond based on PGA, DLQI, EuroQol	N/A
			Adalimumab	TNFα	In Vivo	Human tissue	IL-6 dec MMP-1 dec MMP-3 dec	Open-label study NCT03311464 Completed.	N/A	N/A
			Etanercept	TNFα	In Vivo	Animal model	Modulation of TNFα-dependent responses: E-selectin ICAM-1 IL-6 MMP-3	N/A	N/A	N/A
IL-1	N/A	Yes	Anakinra	IL-1β	Ex Vivo	PBMC	IL-22 inc IFNy dec	N/A	N/A	N/A

			Canakinumab	IL-1β	In vivo	Human tissue	Dec SAA	Open-label study (NCT01302795) Completed.	N=4/5 (80%) with clinical improvement on target-lesion size, PGA and DLQI.[36]	N=2/5 (40%) reported adverse events, including fatigue and presumed infectious scrotal ulcers
			Gevokizumab	IL-1β	N/A	N/A	N/A	Open-label study NCT01882504 Completed.	N=4/6 (67%) of patients achieved complete remission, 1/6 (17%) achieved partial remission, 1/6 (17%) did not respond to therapy.[37]	N/A
								Open-label Study NCT02318914 Terminated.	N/A	N/A
								RCT (NCT02326740) Terminated.	N/A	N/A
								RCT NCT02315417	N/A	N/A

								Terminated.		
			Xilonix	Il-1α	N/A	N/A	N/A	Open-label study NCT01965613. Completed.	N/A	N/A
IL-17	N/A	Yes	Secukinumab	IL-17A	Ex vivo	PBMC	Dec epidermal neutrophils and IL-17A	Open-label study NCT04274166. In progress.	N/A	N/A
								NCT02733094. In progress	N/A	N/A
			Ixekizumab	IL-17A	N/A	N/A	N/A	Open-label study NCT03137160. Completed.	N/A	N/A
IL-12/23	N/A	Yes	Ustekinumab	IL12/23 p40 subunit	Ex vivo	Human skin tissue	Dec mRNA expression of IL-12 and IL-23	N/A	N/A	N/A
IL-6	Yes	Yes	Tocilizumab	sIL-6R and mIL-6R	In vivo	Human tissue	Dec serum amyloid A, increase in hemoglobin, dec in absolute	N/A	N/A	N/A

							neutrophil count			
C5a	Yes	N/A	IFX-1	C5a antagonist	Ex vivo	PBMC	N/A	Open-label study NCT03971643. In progress.	N/A	N/A

PG, pyoderma gangrenosum; PGA, physician's global assessment; DLQI, Dermatology Life Quality Index; PBMC, peripheral blood mononuclear cell; dec, decreased; inc, increased; N/A, not available.