HSTalks
By leading world experts

TNF / IL-1 & Pipeline Therapeutics

Frew J.W., and Krueger J.G. What's in the pipeline for hidradenitis suppurativa? Emerging and novel therapeutics. *Drugs Fut.* 2021; **46(1):** 43–60

Table I. *Summary of pipeline therapeutics currently in clinical trials in hidradenitis suppurativa (HS). Table of drug classes, mechanism(s) of action and evidence in clinical studies in HS.*

Drug class	Therapeutic molecule		Studies undertaken to date in HS	
	Drug name	Mechanism	Study type	Clinical response rate
TNF-α	Adalimumab	Fully human IgG1 TNF-α binding antibody	Phase II placebo-controlled RCT (NCT00918255)	EW: 54.5% HiSCR week 16 EOW: 33.3% HiSCR week 16 PBO: 25.6% HiSCR week 16
			Phase III placebo-controlled RCT (PIONEER 1, NCT01468207)	EW: 41.8% HiSCR week 12 PBO: 26.0% HiSCR week 12
			Phase III placebo-controlled RCT (PIONEER 2, NCT01468233)	EW: 58.9% HiSCR week 12 PBO: 27.6% HiSCR week 12
	Infliximab	Chimeric monoclonal antibody to free and membrane-bound TNF-α	Retrospective cohort study	Infliximab: 64% HiSCR week 8
	Etanercept	Soluble TNF-α and TNF-β receptor	Placebo-controlled RCT (NCT00949546)	Etanercept: Nil effect as per PGA, DLQI week 12 week 24
	Certolizumab pegol	PEGylated anti-TNF-α humanized antigen binding fragment	Case report	N = 1
IL-1	Anakinra	IL-1R1 competitive antagonist	Open-label nonrandomized trial (N = 6) (NCT01516749)	Δ = −34.8 MSS week 8
			Placebo-controlled RCT (N = 10) (NCT01558375)	N = 7 HiSCR week 12
	Bermekimab	Fully human IgG1 IL-1a binding antibody	Placebo-controlled RCT (NCT02643654)	N = 6 HiSCR week 12
			Phase II open-label (NCT04019041)	61-63% HiSCR week 12
	MEDI-8968	IL-1R1 antagonist	(NCT01838499)	Trial terminated due to lack of efficacy
	Rilonacept	Dimeric fusion protein - binds IL-1A and IL-1B (decoy receptor) and functions as IL-1R1 antagonist	-	-

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Drug class	Therapeutic molecule		Studies undertaken to date in HS	
	Drug name	Mechanism	Study type	Clinical response rate
IL-17	Secukinumab	Fully human IL-17A antibody	(NCT03713632)	Results pending
			Case series (N = 18) (NCT03099980)	N = 8 HiSCR week 24
			(NCT04179175)	Results pending
	CJM-112	Fully human IL-17A antibody	Placebo-controlled RCT (NCT02421172)	NS $P = 0.974$ (PGA)
	Ixekizumab	Fully human IL-17A antibody	Case report	N = 1
	Brodalumab	IL-17RA antagonist	Cohort study (N = 10) (NCT03960268)	100% HiSCR week 12 100% HiSCR week 24
			Cohort study (N = 10) (NCT04249713)	100% HiSCR week 12 100% HiSCR week 24
	Bimekizumab	Humanized antibody binding to IL-17A and IL-17F	(NCT03248531)	Results pending
IL-23	Guselkumab	Human IL-23p19 subunit antibody	(NCT04061395)	Results pending
			(NCT04084665)	Results pending
			(NCT03628924)	Results pending
			Case series (N = 3)	> 50% IHS4 reduction
	Risankizumab	Human IL-23p19 subunit antibody	(NCT03926169)	Results pending
IL-12/23	Ustekinumab	Human IL-12/23p40 subunit antibody	Open-label study (N = 17) (NCT01704534)	N = 8 HiSCR week 40
			Case series (N = 6)	N = 5 improvement
C5a/C5aR1 antagonists	IFX-1	Human C5a antibody	Open-label phase II trial (N = 12) (NCT03001622)	N = 9 HiSCR week 7 N = 10 HiSCR week 19
			Placebo-controlled RCT (N = 175) (NCT03487276)	IFX-1 HiSCR 51.5%; PBO HiSCR 47.1%; $P > 0.05$
	Avacopan	C5aR1 antagonist	(NCT03852472)	Results pending
Bacteria (antibiotics)	Rifampicin-clindamycin	Antimicrobial	(NCT0106327)	No results
	Doxycycline vs. clindamycin	Antimicrobial	RCT	No significant difference
	Clindamycin	Antimicrobial	Placebo-controlled RCT	No significant difference to placebo
	Rifampin–moxifloxacin–metronidazole	Antimicrobial	Retrospective chart review (N = 28)	Complete remission N = 16/28

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JAK-STAT inhibitors	Tofacitinib	JAK1/JAK3 inhibitor	Cohort study (NCT04246372)	Results pending
	INCB-054707	JAK1 inhibitor	(NCT03569371)	Results pending
	Tofacitinib	JAK1/JAK3 inhibitor	Case report (tofacitinib + cyclosporine)	N = 2 improvement (over 11 months to 3 years of therapy)
PDE4 inhibitors	Apremilast	PDE4A inhibitor	Placebo-controlled trial (NCT03049267)	Apremilast: 58.5% HiSCR Placebo: 0% HiSCR
Retinoids	Isotretinoin	Various - RAR/RXR agonist	Retrospective chart review (N = 209)	Beneficial response N = 14/209
	Acitretin	Various - RAR/RXR agonist CRABP competitive agonist	Prospective cohort study (N = 17) Retrospective cohort study (N = 12)	47% (8/17) HSSI > 50% from baseline Pain reduction in 12/12 (100%)
Hormonal modulators	Drospirenone	Progesterone receptor antagonists	(NCT00722800)	Results pending
	Metformin	Multiple, including indirect antiandrogenic effects	Retrospective chart review (N = 53)	No association with clinical response
Antineutrophilic agents	Dapsone	Inhibits respiratory burst in PMNs	Retrospective chart review (N = 19)	Clinically significant improvement (N = 3)
	Hydroxychloroquine	Inhibits lysosome function and TLR activity	(NCT03275870)	Results pending
Anti-CD40 agents	Iscalimab	Inhibits T-cell signaling	(NCT03827798)	Results pending

DLQI, Dermatology Life Quality Index; EOW, every other week; EW, every week; HiSCR, Hidradenitis Suppurativa Clinical Response; HSSI, Hidradenitis Suppurativa Severity Index; IHS4, International Hidradenitis Suppurativa Severity Score; MSS, modified Sartorius score; NS, not significant; PBO, placebo; PGA, Patient Global Assessment; PMN, polymorphonucleocytes; RCT, randomized controlled trial; TLR, Toll-like receptor.

Novel Targets

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Table II. *Agents with theoretical potential as novel therapeutics for proof-of-concept trials in hidradenitis suppurativa (HS) without documentation of use in HS.*

Drug class	Therapeutic molecule		Theoretical basis for use in HS		
	Name	Mechanism of action	Target identified in HS tissue?	Details	Proof-of-concept use in HS
IL-36 inhibitors	Spesolimab	IL-36R antagonist	Yes	Identified in transcriptomics, IHC	Not reported
IL-6/IL-6R inhibitors	Sarilumab	IL-6 inhibitor	Yes	Identified in transcriptomics/ proteomics/IHC	Not reported
	Tocilizumab	IL-6R antagonist	Yes	Identified in transcriptomics/ proteomics/IHC	Not reported
IRAK-4 inhibitors	-	IRAK-4 degradation	Yes	Identified in transcriptomics/ proteomics	Not reported
5-Lipoxygenase inhibitors	Zileuton	Inhibition of leukotriene formation	Yes	Identified in transcriptomics, proteomics and IHC	Not reported
ILT7 antagonists (plasmacytoid dendritic cell inhibitors)	-	Inhibition of TLR-induced interferon production	Yes	Dendritic cells identified in lesional IHC identified in transcriptomics	Not reported
Bruton tyrosine kinase (BTK) inhibitors	Rilzabrutinib	Inhibition of B-cell activity	Yes	B cells and plasma cell activity identified in transcriptomics, flow cytometry, IHC, proteomics	Not reported
RORγt inhibitors	VTP-43742	Inhibition of IL-17-producing T cells	Yes	Identified via IHC	Not reported
S1P receptor antagonists	Fingolimod	$S1P_{1-5}$ receptors	Yes	Identified in transcriptomics	Not reported
	Ponesimod	$S1P_1$-specific			
	Amiselimod	$S1P_1$-specific			
Neurokinin NK_1 receptor antagonists	Serlopitant	Inhibition of action of substance P	Yes	Identified in transcriptomics	Not reported
Adenosine A_3 receptor antagonists	Piclidenoson/ CF-101	Downregulation of NF-κB	Yes	Identified in transcriptomics	Not reported
Spleen tyrosine kinase (SYK) inhibitors	Fostamatinib	Inhibition of mast cell, macrophage and B-cell signaling and inflammatory propagation	Yes	Identified in transcriptomics	Not reported
PPARγ agonists	Rosiglitazone	Inhibition of fatty acid-induced inflammatory signaling	Yes	Identified in transcriptomics	Not reported