Pustular Psoriasis and the Potential Therapeutic Usage of an IL-36 Receptor Monoclonal Antibody

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ABSTRACT

Pustular psoriasis is an uncommon subtype of psoriasis that dramatically affects the quality of life of affected patients. Pustules can emerge anywhere along the trunk, limbs, soles, palms, and fingers, which debilitates the functionality of these appendages. Currently, there are no approved treatments for pustular psoriasis in the US; off-label usage of psoriasis vulgaris medications is usually prescribed. These treatments are insufficient for patients with difficult to manage and/or severe forms of pustular psoriasis. Psoriasis vulgaris biologic medications mainly target the IL-17 and IL-23 axis. However, novel clinical findings have demonstrated that pustular psoriasis's central inflammatory axis depends on the dysregulation of the IL-36 family of cytokines. The lack of inhibition of IL-36α, IL-36β, IL-36γ, as well as the absence of insufficiency of an IL-36 receptor antagonist (IL-36RA), is involved in the upregulation of proinflammatory cytokines and neutrophil chemotaxis necessary for pustular lesion formation. An IL-36 receptor monoclonal antibody has the potential to disrupt the IL-36 inflammatory loop and inhibit the pathogenesis of pustular psoriasis. Spesolimab is an IL-36 receptor (IL-36R) monoclonal antibody undergoing clinical trials for the treatment of pustular psoriasis that has exhibited promising results.

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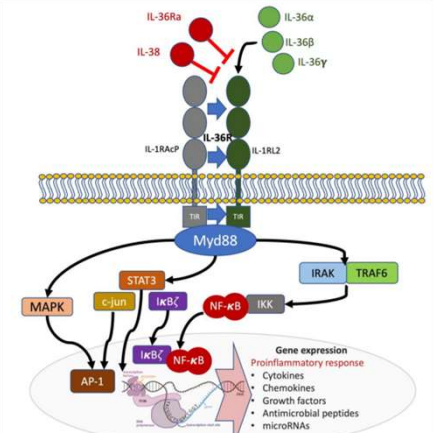
INTRODUCTION

Pustular psoriasis is a rare subtype of psoriasis that makes up approximately 1% of all psoriasis cases.[1,2] It is characterized by recurrent neutrophilic skin inflammation with the presence of large erythematous non-infectious pustules. [2,3] These pustules may initially be between 2-3 millimeters in diameter, but they can coalesce and become large lakes of purulent material. [2] The enlarged lesions can be quite painful and last days to weeks. [2] Pustular psoriasis can be subdivided into 3 distinct phenotypes:

- Generalized Pustular Psoriasis (GPP)
  - Widespread lesions on large areas of the body
  - Fever, chills, and loss of appetite may occur
  - Potential for life-threatening complications in need of emergency treatment
- Palmoplantar Pustular Psoriasis (PPP)
  - Localized on the palms of hands and soles of the feet
  - Recurrent flares with severe pain and itching
  - Considered to be the most debilitating subtype
- Acrodermatitis Continua of Hallopeau (ACH)
  - Localized on fingers, toes, and nail beds
  - Progressive condition
  - Lead to permanent nail damage and underlying bone erosion

Homeostatic Function of IL-36

- IL-36α, IL-36β, IL-36γ
  - Proinflammatory
  - Repair damaged epithelium by stimulating keratinocyte proliferation and differentiation
  - Broad sensor of pathogenic infection
- IL-36 receptor antagonist (IL-36RA)
  - Inhibits of IL-36α, IL-36β, IL-36γ
  - Limits intensity of immune response in the skin
  - Limits the intensity of systemic innate immune responses



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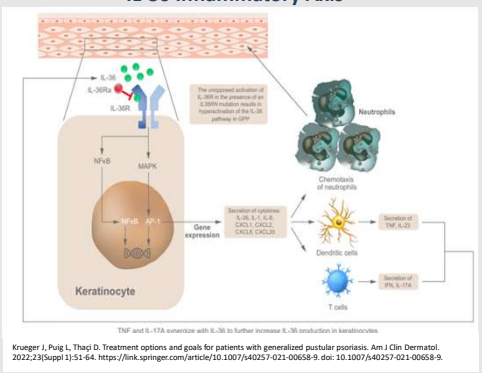
Pathogenesis

Triggers for the development of Pustular Psoriasis
- Trauma to the skin
- Localized or systemic infection
- Drug use
- Pregnancy
- Smoking
- Medication withdrawal

Resulting in a proinflammatory IL-36 autoamplifying loop

IL-36 Inflammatory Axis



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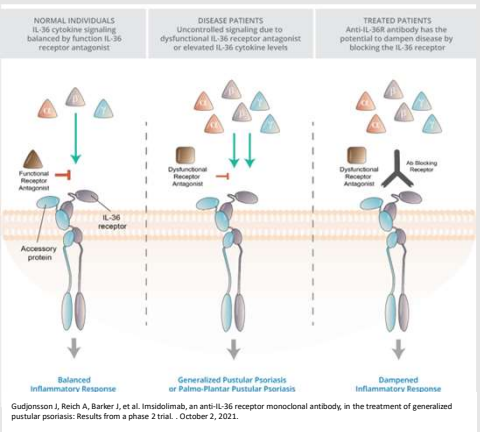
Function of IL-36R Antagonist



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Phase I: Spesolimab Proof of Concept

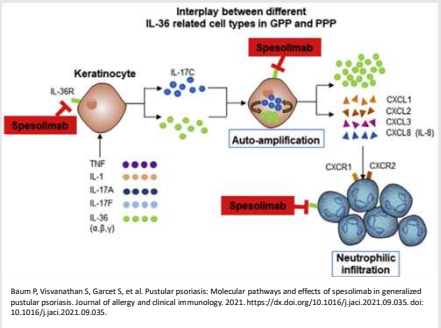
- All participants (n=7) had significant improvement by week 4 and the effects lasted up to week 20[4]
- Decrease in
  - Differentially expressed genes to non-lesional levels[5]
  - Keratinocyte activation, differentiation, and mediated inflammatory pathways[5]
  - Proinflammatory mediators and neutrophil recruitment[5]

Phase II: Efficacy of Spesolimab

Phase IIA: Efficacy in PPP (n=59)
- Patients with a baseline PPPASI above the median had more improvement in response to spesolimab[4]
- Dose-dependent attenuation of symptoms[5]
- Well tolerated by all patients[5]
- 27.1% experienced a mild to moderate adverse event(s) while taking Spesolimab[5]

Phase IIB: Efficacy in GPP (n=53)
- Reached secondary Endpoint of GPPASI75
  - 16 patients with 1 dose of 900 mg Spesolimab (n=23)[6]
  - 2 patients with 2 doses of 900 mg spesolimab (n=12)[6]
  - 6 from the placebo group with 1 dose of 900 mg Spesolimab as rescue treatment (n=15)[6]

Mechanism of Action



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CONCLUSIONS

The dysregulation of the IL-36 family of cytokines is crucial for the pathogenesis of pustular psoriasis. The increase of IL-36α, IL-36β, and IL-36γ levels along with the inadequate levels of IL-36Ra, results in the production and recruitment of other proinflammatory cytokines and chemotaxis of granulocytes. An IL-36 receptor antagonist monoclonal antibody can interrupt these pathways and attenuate disease progression. Spesolimab, an IL-36R monoclonal antibody, has displayed promising results in GPP and PPP patients. Spesolimab is one of the first pharmaceutical treatment authorized in the USA and Japan to treat pustular psoriasis by regulating the IL-36 axis and finally fulfilling an unmet need in the pustular psoriasis patient population.

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