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Janus Kinase (JAK) Inhibitors: A New Frontier in the Treatment of Vitiligo

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Abstract

Up to 70 million people worldwide suffer from vitiligo, an autoimmune disease characterized by the destruction of melanin. Current treatment options vary in efficacy. The disease manifests clinically as white circular macules of depigmentation seen primarily on the face and appendages.[1] The pathophysiology of vitiligo is multifactorial and still being studied. One proposed mechanism behind the pathophysiology of vitiligo involves the upregulation of interferon gamma (IFN-γ) with downstream effects on JAK/STAT pathways resulting in CXCL10 transcription.[1,2] Here we discuss *Ruxolitinib*, a topical JAK inhibitor, that recently passed its clinical trial phase, and *Ritlecitinib*, an oral JAK inhibitor which is currently undergoing clinical trials.[3,4] These drugs are a reflection of the recent increase in targeted therapies for dermatologic diseases. The promising results of these drugs are widening the possible treatment options for patients that suffer from vitiligo.

Intro

- Chronic autoimmune disease that affects up to 2% of the population worldwide.
- Characterized by the destruction of melanin, leading to areas of the epidermis that are hypopigmented.
- The prevalence varies based on ethnicity, region and inclusion criteria.
- Psychological burden to many individuals with the disease.
- Three classifications of the disease based on the total body surface area affected: generalized, segmental, and localized.

Intro (Continued)

- Mainstay treatment options are not curative. They include topical and oral steroids, calcineurin inhibitors, phototherapy, and surgery.
- Medications that target JAK/STAT cascades are at the forefront of advancements in treatment options. *Ruxolitinib* is the latest FDA approved topical medication that inhibits JAK/STAT. *Ritlecitin* is an oral JAK inhibitor is still undergoing clinical trials.

Pathophysiology

- There are various accepted mechanisms of vitiligo. The autoimmune theory is based on the dysregulation of IFN-γ and the JAK/STAT signaling pathway.[1]
- Patients with vitiligo exhibit high levels of IFN-γ at depigmentation sites. IFN-γ binds to the interferon gamma receptor (IFNgR), which activates the JAK/STAT pathway.
- JAK/STAT upregulates the chemokine ligands 9 and 10 (CXCL9 & CXCL10).
- CXCL9 with cognate receptor CXCR3 promotes the activity of C8+T melanocyte specific cells.
- CXCL10 directs CD8+T cells to the epidermis. [2]
- At the epidermis, CD8+T cells cause a local inflammatory response.
- Inflammation causes dysfunction and destruction of melanocytes, ultimately leading to the pathognomonic depigmentation seen in vitiligo.

JAK Inhibitors

- *Ruxolitinib*: Topical JAK inhibitor formulated for the treatment of myeloproliferative disorders. Subsequently, found to promote repigmentation in vitiligo. Currently, the only repigmentation therapy approved by the FDA.
- The accepted mechanism of action (MOA) of *Ruxolitinib* works by inhibiting JAK which downregulates the cascade ultimately decreasing the CD8+T cells.[2]
- *Ritlecitinib:* Oral JAK3/tyrosine kinase inhibitor. It is approved by the FDA for treatment of alopecia areata.
- *Ritlecitinib* is in phase 3 of clinical trials for the treatment of nonsegmental vitiligo.
- *Ritlecitinib* MOA inhibits JAK/STAT which leads to the inhibition of IL-15 and IFN-γ mitigating the disease process.[3]

Discussion

Vitiligo is a disease that is psychologically devastating for many patients. The exact mechanism of vitiligo is unknown, but hypotheses surrounding the current pathophysiology are becoming clearer. Understanding of the mechanism behind any disease helps guide therapy. One such improvement is the topical JAK inhibitor, *Ruxolitinib*, and the oral JAK inhibitor *Ritlecitinib*. Both work by downregulating IFN-γ signaling by blocking the JAK/STAT cascade.[3,4] Trials have demonstrated promising results. This improvement in patients is critical in reaffirming the hypothesis that high levels of IFN-γ and their downward effects on JAK/STAT pathway critically impair the role of melanocytes leading to dysfunction and depigmentation.[2] Understanding the impact of cascade on the disease, allows for the development of drugs that can target other areas of this pathway leading to more targeted therapies. However, *Ruxolitinib* and *Ritlecitinib* have shown promising starts and will hopefully mitigate the lifelong suffering that these patients endure.

References

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