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Structural Insights: What Makes Some IL-23 Biologics More Effective in Psoriasis

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INTRODUCTION

Psoriasis is a chronic inflammatory skin disease affecting over 7.5 million adults in the United States, and over 41 million people worldwide.[1,2] Among the key players in its pathogenesis is the cytokine Interleukin (IL)-23, making it a prime target for biologic therapies. IL-23 is a heterodimer composed of the p19 and p40 subunits.[3,4] The biologics that target IL-23, such as risankizumab, tildrakizumab, and guselkumab, focus on the p19 subunit, while ustekinumab targets the p40 subunit. In this brief review, we discuss the findings of a study by Daniele SG et al, published in *JID Innovations* in 2024, which analyzes the structural properties of these IL-23 biologics and thereby provides a molecular rationale as to why risankizumab stands out as highly efficacious in psoriasis.[5]

Understanding IL-23 Biologics

IL-23 biologics are designed to bind to specific regions (epitopes) on the p19 or p40 subunits, preventing IL-23 from activating its receptor and triggering the inflammatory cascade responsible for psoriasis. The study compared the binding characteristics of four IL-23 inhibitors:

1. *Risankizumab*
2. *Tildrakizumab*
3. *Guselkumab*
4. *Ustekinumab*

Key Structural Findings

The study focused on several structural properties of these inhibitors, including:

- *Epitope Location:* Each inhibitor binds to a unique epitope on the IL-23 molecule, which does not have to be in the IL-23R binding site region for clinical efficacy.
- *Epitope Chemistry:* Each epitope is made up of a unique composition of polar, basic, acidic, and hydrophobic amino acid residues, all of which do not correlate with clinical efficacy.
- *Epitope Surface Area:* Larger surface areas correlate with stronger and more stable binding, as well as greater clinical efficacy.
- *Binding Affinity (K_D):* This measures how strongly the inhibitor binds to IL-23 and is indirectly correlated with epitope surface area and clinical efficacy.
- *Dissociation Rate (k_{off}):* This measures how quickly the inhibitor-IL-23 complex falls apart and is indirectly related to epitope surface area and clinical efficacy.

Why Some IL-23 Biologics Are Better

1. *Epitope Surface Area and Binding Affinity:*
   - Risankizumab has the largest epitope surface area (2400 Å^2), allowing it to bind more tightly and stably to IL-23.
   - Larger surface areas correlate with lower K_D values, indicating stronger binding affinity.
2. *Dissociation Rate:*
   - Risankizumab has the slowest dissociation rate (k_{off}), meaning it remains bound to IL-23 for a longer duration, enhancing its therapeutic effect.
3. *Clinical Efficacy:*
   - These structural properties translate into higher clinical efficacy, measured by the PASI-90 response rate (a 90% improvement in the Psoriasis Area and Severity Index).
   - Short-term (10-16 weeks) and long-term (44-60 weeks) clinical efficacy, measured by PASI-90 response rates, were highest for risankizumab, followed by guselkumab, based on network meta-analysis.[6] Tildrakizumab exhibited the lowest efficacy, which aligns with its smallest epitope surface area (1290 Å^2).

Clinical Implications

1. *Drug Selection:*
   - Clinicians can use these insights to guide clinical management, selecting the most effective biologic for their patients. Given its binding properties, less frequent dosing schedule, and clinical outcomes, risankizumab may be preferred for patients with moderate and severe plaque psoriasis.

2. *Biologic Switching:*
   - If a patient does not respond to one IL-23 inhibitor, switching to another within the same class may still be effective. The distinct structural characteristics of each biologic mean that a lack of response to one agent does not preclude success with another.
   - A real-world study on switching rates among psoriasis patients initiating biologics over a 24-month period shows that risankizumab had the lowest switch rate at 8.5% followed by guselkumab at 15.7%.[7]
3. *Mechanistic Insights:*
   - Understanding the molecular basis of how these drugs work can help clinicians anticipate their effectiveness and tailor treatments more precisely.

CONCLUSION

Structural properties of IL-23 inhibitors, such as epitope size, binding affinity, and dissociation rate, are important determinants of their clinical efficacy. As such, the highest efficacy outcomes of risankizumab in treating moderate and severe plaque psoriasis may be explained by its larger epitope surface area and slower dissociation rate. These insights empower clinicians to make more informed decisions, optimizing treatment strategies to achieve better patient outcomes.

DISCLOSURES

FG has served as a consultant and/or speaker for AbbVie, Almirall, Arcutis, BMS, Galderma, Janssen, Leo, Novartis, Pfizer, Sanofi, Sunpharma, and UCB.

CGB has served as an investigator for AbbVie and Sun Pharma, and a consultant for AbbVie, Arcutis, Novartis, Takeda, and UCB.

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