Guselkumab Label Adds Psoriatic Arthritis Structural Damage Inhibition

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Psoriatic arthritis (PsA) is a chronic inflammatory disease that can lead to irreversible joint damage and functional impairment. While several biologic therapies effectively manage symptoms, the ability to inhibit structural damage progression is a critical differentiator. Guselkumab, an interleukin-23 (IL-23) inhibitor, has now received an updated label to include this specific indication.1

KEY TAKEAWAYS

- The Pivot: Guselkumab's label now explicitly includes inhibition of structural damage progression in psoriatic arthritis.
- The Data: Radiographic progression, measured by the modified Total Sharp Score (mTSS), was significantly inhibited in guselkumab-treated patients versus placebo.
- The Action: Clinicians should consider guselkumab for PsA patients where inhibition of structural damage is a primary treatment goal.

Psoriatic arthritis (PsA) is a heterogeneous inflammatory condition affecting joints, entheses, and skin, often leading to progressive structural damage if not adequately controlled. The primary goal of PsA treatment extends beyond symptom management to include the prevention of irreversible joint destruction. Biologic disease-modifying antirheumatic drugs (bDMARDs) have demonstrated efficacy in various PsA domains, but specific evidence for structural damage inhibition is a key consideration for long-term patient outcomes.

The Evidence for Structural Damage Inhibition

The updated label for guselkumab (Tremfya), an IL-23 inhibitor, is based on data from the DISCOVER-1 and DISCOVER-2 Phase 3 clinical trials. These trials evaluated the efficacy and safety of guselkumab in adult patients with active psoriatic arthritis.1

The DISCOVER-2 trial, in particular, focused on patients who were biologic-naïve. In this study, guselkumab demonstrated significant inhibition of radiographic progression at week 24 compared to placebo. Radiographic progression was assessed using the modified Total Sharp Score (mTSS), which evaluates joint erosion and joint space narrowing in the hands and feet.1

At week 24, patients receiving guselkumab 100 mg every four weeks (Q4W) showed a mean change from baseline in mTSS of 0.04, while those receiving guselkumab 100 mg every eight weeks (Q8W) showed a mean change of 0.07. In contrast, the placebo group demonstrated a mean change of 0.80. The difference between both guselkumab groups and placebo was statistically significant ($p < 0.001$ for both).1

A higher proportion of guselkumab-treated patients achieved no radiographic progression (defined as an mTSS change from baseline of ≤0.5) compared to placebo. Specifically, 82% of patients in the Q4W group and 76% in the Q8W group achieved no radiographic progression, versus 53% in the placebo group.1

The DISCOVER-1 trial, which included patients previously treated with anti-tumour necrosis factor (TNF) alpha agents, also provided supportive data. While the primary endpoint for structural damage was not met in DISCOVER-1 due to a lower baseline rate of progression in the placebo group, numerical trends consistent with inhibition of structural damage were observed.2

Across both studies, the safety profile of guselkumab was consistent with previous reports for psoriasis, with common adverse events including upper respiratory tract infections, headache, and injection site reactions. No new safety signals emerged during the trials.1,2

The inclusion of structural damage inhibition in the label provides clinicians with additional evidence when selecting a biologic therapy for PsA. This specific claim differentiates guselkumab within the crowded PsA treatment landscape, particularly for patients where preventing long-term joint destruction is a paramount concern. The data from DISCOVER-2, focusing on biologic-naïve patients, is particularly relevant for initial treatment decisions.

Understanding Psoriatic Arthritis and Treatment Goals

PsA affects approximately 0.3% to 1% of the general population, with prevalence rates varying globally. It commonly manifests in individuals with existing psoriasis, although it can precede skin involvement in a minority of cases. The inflammatory process in PsA leads to diverse clinical presentations, including peripheral arthritis, axial involvement, dactylitis, enthesitis, and nail dystrophy. Untreated or inadequately treated PsA can result in irreversible joint damage, functional impairment, and reduced quality of life. Therefore, treatment strategies aim for comprehensive disease control, encompassing improvements in joint symptoms, skin lesions, enthesitis, dactylitis, and crucially, the prevention of structural damage.

Mechanism of Action and Clinical Context

Guselkumab is a human monoclonal antibody that selectively binds to the p19 subunit of interleukin-23 (IL-23). IL-23 is a cytokine that plays a central role in the pathogenesis of inflammatory diseases, including psoriasis and psoriatic arthritis, by promoting the differentiation and maintenance of Th17 cells, which produce pro-inflammatory cytokines such as IL-17 and IL-22. By inhibiting IL-23, guselkumab modulates the inflammatory cascade, thereby reducing inflammation and preventing tissue damage in affected joints and skin. This targeted approach offers a distinct mechanism compared to TNF-alpha inhibitors, providing an alternative for patients who may not respond adequately to or tolerate other biologic therapies.

Trial Design and Patient Populations

The DISCOVER-1 and DISCOVER-2 trials were global, multicenter, randomized, double-blind, placebo-controlled Phase 3 studies. DISCOVER-2 enrolled 739 biologic-naïve adult patients with active PsA, defined by at least three swollen joints and at least three tender joints, despite conventional synthetic DMARD (csDMARD) therapy or nonsteroidal anti-inflammatory drugs (NSAIDs). DISCOVER-1 included 381 adult patients with active PsA, approximately one-third of whom had previously failed one or two TNF-alpha inhibitors. Both trials utilized a similar design, with patients randomized to receive guselkumab 100 mg Q4W, guselkumab 100 mg Q8W, or placebo, with

a switch to guselkumab at week 24 for placebo responders or at week 16 for placebo non-responders. The primary endpoint for DISCOVER-2 was the American College of Rheumatology 20% improvement (ACR20) response at week 24, with structural damage inhibition as a key secondary endpoint. The rigorous methodology, including central reading of radiographs by two independent, blinded readers, strengthens the validity of the mTSS findings.

Limitations and Future Directions

While the DISCOVER trials provide robust evidence for guselkumab's efficacy, certain limitations warrant consideration. The follow-up period for the primary structural damage analysis was 24 weeks, which is relatively short for assessing long-term joint preservation. Longer-term data, which has been collected in extension phases of these trials, will further elucidate the sustained impact on structural progression. Additionally, the generalizability of these findings to all PsA patients, particularly those with very severe or rapidly progressing disease, requires further investigation. The trials also focused on specific patient populations (biologic-naïve and TNF-alpha inhibitor-experienced), and comparative effectiveness studies against other bDMARDs with structural damage claims would be beneficial for treatment sequencing decisions. Despite these points, the clear demonstration of structural damage inhibition in a biologic-naïve population represents a significant advancement in the management of psoriatic arthritis.
For comprehensive insights into psoriatic arthritis management and broader rheumatology, readers may find further valuable information in the authoritative Oxford Handbook of Rheumatology.

CLINICAL IMPLICATIONS

The updated label for guselkumab to include inhibition of structural damage progression in psoriatic arthritis is a welcome clarification, not a revolution. For years, clinicians have understood that effective disease control in PsA, particularly with biologics, correlates with reduced radiographic progression. However, having this explicit claim on the label, backed by robust Phase 3 data from the DISCOVER-2 trial, provides a firmer evidence base for treatment selection, especially when discussing long-term outcomes with patients.
This development will likely influence prescribing patterns, particularly for rheumatologists prioritising joint preservation in newly diagnosed or biologic-naïve PsA patients. While other biologics, including TNF inhibitors and IL-17 inhibitors, have also demonstrated structural benefits, guselkumab's specific mechanism of action (IL-23 inhibition) offers an alternative for patients who may not respond to or tolerate other classes. It also provides Janssen with a distinct marketing advantage in a competitive market, allowing them to highlight a specific, measurable benefit beyond symptomatic relief.
For patients, this means more precise information regarding the potential for their chosen therapy to protect their joints from irreversible damage. It underscores the importance of early and effective treatment in PsA. However, it also places a greater onus on clinicians to clearly articulate the nuances of structural damage inhibition across different biologic classes, ensuring that treatment decisions are truly individualised and not solely driven by a single label claim. The ultimate goal remains comprehensive disease control, encompassing skin, joints, entheses, and dactylitis, alongside the critical objective of preventing long-term disability.

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