Latest Highlights on Biologic Treatments for Psoriatic Arthritis from EULAR 2020

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Summary

Psoriatic arthritis (PsA) is a chronic, heterogeneous, immune-mediated arthritis characterised by joint inflammation and diverse clinical manifestations including psoriasis, peripheral and/or axial joint disease, enthesitis, and dactylitis. In recent years, several effective biologic treatments for PsA, including TNF inhibitors, IL-12/23 inhibitors, and IL-17 inhibitors, have been introduced. Several ongoing studies are examining the potential efficacy and safety of PsA treatments, including the monoclonal antibodies guselkumab, which specifically binds to the p19-subunit of IL-23, and ustekinumab, which binds to IL-12/23. The results of the Phase III DISCOVER-1 and -2 trials with guselkumab and the

PsABIO trials with ustekinumab show that these treatments result in sustained improvements in skin, joint, and soft-tissue manifestations of PsA, with no new safety signals, in adult patients with active PsA.

Summary of the DISCOVER-1 and -2 Trial Designs

The DISCOVER-1 trial was a Phase III, randomised, double-blind, placebo-controlled study that aimed to examine the efficacy of guselkumab 100 mg, given subcutaneously every 4 or 8 weeks (q4w or q8w, respectively) on PsA outcomes, including joint and skin symptoms, physical function, and quality of life, through 52 weeks of treatment.[1] The study included adults with active PsA (at least three swollen and three tender joints; C-reactive protein: ≥0.3 mg/dL) who had not responded to earlier treatment; approximately 30% of patients had received up to two TNFα inhibitor (TNFi) agents. A total of 381 patients were randomised 1:1:1 to guselkumab 100 mg q4w; guselkumab 100 mg at Week 0 and Week 4, and then q8w; or placebo. Placebo patients crossed over to guselkumab q4w at Week 24.[2] The DISCOVER-2 trial design was similar to that of DISCOVER-1,[3] and examined treatment efficacy and safety through Week 52, but in 739 patients with active PsA who were biologic-naïve.[4]

The Efficacy and Safety of Guselkumab, an Anti-IL-23p19 Monoclonal Antibody, in Patients with Active Psoriatic Arthritis

Doctor Christopher Ritchlin, Professor Iain B. McInnes, and Professor Philip Helliwell

In the DISCOVER-1 trial, patients receiving guselkumab 100 mg q4w and q8w showed improved American College of Rheumatology (ACR) 20% improvement criteria (ACR20) response rates, which were maintained at Week 52 in 73.4% (q4w) and 59.8% (q8w) of patients. Similar response patterns were also seen for the more rigorous ACR50 and 70 criteria.[2] Response rates were comparable in patients who had received prior TNFi treatment, and in patients who crossed over to guselkumab treatment at Week 24. Treatment with both doses of guselkumab maintained improvements in joint and skin symptoms, dactylitis, enthesitis, and quality of life components through 52 weeks in patients with active PsA who were biologic-naïve or had previous TNFi experience. Treatment was safe and well tolerated, and consistent with previous studies regarding guselkumab safety in psoriasis.[5]

In the DISCOVER-2 trial, outcome measurements included ACR response rates and a PsA-modified van der Heijde–Sharp (vdH-S) score measuring joint damage progression. ACR20 response rates at Week 52 were 70.6% (q4w) and 74.6% (q8w), with similar response patterns for the ACR50 and 70 criteria. Changes in vdH-S scores in Weeks 0–24 (0.62) and Weeks 24–52 (0.46) were comparable in patients receiving the q4w dose; less radiographic progression occurred in Weeks 24–52, compared with Weeks 0–24, for patients receiving the q8w dose (0.23 versus 0.73) and for patients receiving the q4w dose compared with placebo (1.00 versus 0.25). Guselkumab treatment resulted in prolonged improvements in joint and skin symptoms, as well as inhibition of radiographic progression, through Week 52.[4]

A study examining the efficacy and safety of guselkumab in patients with PsA with imaging-confirmed axial involvement consistent with sacroiliitis in the DISCOVER-1 and -2 trials, found that treatment was associated with a reduction of axial symptoms after 24 weeks of treatment. Both guselkumab doses resulted in significant differences in mean least squares changes from baseline to Week 24 in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores (-2.67 [q8w] and -2.68 [q4w] versus -1.35 [placebo]; $p<0.001$) and spinal pain (-2.73

[q8w] and -2.48 [q4w] versus -1.30 [placebo]; p<0.001). A significantly greater proportion of guselkumab-treated patients also achieved BASDAI 50 responses (40.5% [q8w] and 37.9% [q4w]), compared with placebo (19.1%; p<0.01 for both doses) at Week 24.[6]

A network meta-analysis of 26 Phase III studies comparing guselkumab treatment with other targeted therapies for PsA showed that guselkumab treatment is comparable to most treatments regarding improvements in arthritis, soft-tissue damage, physical function, and safety outcomes. For the ACR20 response, the q4w and q8w guselkumab doses ranked fifth and eighth, respectively, out of 20 interventions, and were comparable to IL-17A inhibitors and most TNFi agents, with similar findings for ACR50 and 70 responses. For Psoriasis Area Severity Index (PASI) 90 responses, both guselkumab doses ranked first and second out of 15 interventions and were highly likely to provide a greater benefit for patients, compared with most other agents. Findings for the PASI 75 and 100 responses were similar to those of PASI 90. Both guselkumab doses ranked in the top five out of 19 interventions regarding adverse events and severe adverse events, comparable to IL-17A inhibitors and TNFi agents.[7]

Summary of the PsABIO Study Design

The PsABIO study evaluated the effectiveness, tolerability, and persistence of first-, second-, or third-line treatment with ustekinumab or TNFi in PsA, and included outcome data for patients achieving minimal disease activity (MDA) or very low disease activity (VLDA), as well as clinical Disease Activity in PSoriatic Arthritis (cDAPSA) low disease activity and remission.[8-10] The 12-month follow-up study included 929 eligible patients, of whom 438 received ustekinumab and 455 received a TNFi.[10]

Efficacy and Persistence of Ustekinumab, an IL-12/23 Inhibitor, in Patients with Psoriatic Arthritis

Professor Josef F. Smolen, Professor Laure Gossec, and Mister Kirk Geale

The introduction of IL-12/23 inhibition with ustekinumab heralded the first new biologic mode of action after TNFi, though there is a current lack of real-world data comparing these therapies in patients with PsA. In the PsABIO cohort comparing ustekinumab with TNFi treatment effectiveness at 12-month follow-up, the observed data showed differences in the proportion of patients achieving MDA, VLDA, cDAPSA low disease activity, and remission in favour of TNFi. However, after propensity score (PS) adjustment for baseline differences, there were no significant differences in odds ratios between the groups for achieving these targets at 12 months. Comparisons of 6- and 12-month unadjusted data showed sustained MDA and VLDA responses with both ustekinumab (21.8%) and TNFi (29.5%) treatment, with similar proportions of patients achieving these targets between Months 6 and 12 (17.0% and 20.3%, respectively).[10]

A comparative analysis of 1-year persistence of ustekinumab and TNFi within the PsABIO cohort showed a promising persistence profile for ustekinumab. Treatment persistence (up to 15 months of follow-up) was defined as time between start of first biologic disease-modifying antirheumatic drug (bDMARD) treatment in PsABIO, stopping or switching to another bDMARD, or withdrawal from treatment. Persistence was compared using a Cox regression analysis, with PS adjustments for baseline imbalances in demographics and disease-related covariates. Concomitant methotrexate use and skin involvement (body surface area: <3%, 3–10%, and >10%) were added to the Cox model to observe their possible influence on the PS-adjusted treatment effect. The results showed that 121 out of 438 (28%) and 134 out of 455

(29%) patients who began ustekinumab and TNFi treatment, respectively, stopped or switched treatment prior to Month 15, with the probability of treatment persistence decreasing with each subsequent treatment line.[11]

No statistically significant differences between ustekinumab and TNFi persistence were seen in the PS-adjusted Cox analysis for stopping or switching treatment (ustekinumab versus TNFi) (hazard ratio [HR]: 0.82; 95% confidence interval [CI]: 0.60–1.13). However, patients who were receiving bDMARD monotherapy (without methotrexate) and had widespread skin involvement (body surface area: >10%) showed improved drug persistence with ustekinumab, compared with TNFi (HR: 0.61; 95% CI: 0.42–0.90, and HR: 0.41; 95% CI: 0.19–0.89, respectively).[11]

Efficacy and Persistence of Ustekinumab in Sweden

Further evidence for ustekinumab's favourable treatment persistence profile comes from a population-based study in Sweden comparing time to discontinuation of a TNFi (adalimumab), an IL-17 inhibitor (secukinumab), and an IL-12/23 inhibitor (ustekinumab).[12] Data were collected from population-based health data from the Swedish National Patient Register, Swedish Prescribed Drug Register, and Swedish Cause of Death Registry. Discontinuation was defined as a treatment switch to any other PsA-indicated biologic, or failure to redispense treatment within a grace period following end of drug supply.

A total of 3,620 discontinuation events across 4,649 treatment exposures (adalimumab: 3,255; secukinumab: 887; ustekinumab: 507) were found in the main analysis. The results of the multivariate main analysis showed that patients receiving ustekinumab had significantly lower discontinuation rates, compared with adalimumab (HR: 0.56; 95% CI: 0.49–0.64). In the multivariate sensitivity analysis, both ustekinumab (HR: 0.81; 95% CI: 0.70–0.94) and secukinumab (HR: 0.82; 95% CI: 0.70–0.95) treatment resulted in significantly lower discontinuation rates, compared with adalimumab. Previous biologic experience also had a significant ($p<0.05$) impact on discontinuation risk. The results show that ustekinumab treatment results in an improved treatment persistency profile, compared with adalimumab.[12]

Conclusions

In the DISCOVER-1 and -2 trials, treatment with the IL-23p19 inhibitor guselkumab resulted in the improvements of several PsA-related joint and skin symptoms, dactylitis, enthesitis, and quality-of-life outcomes through 52 weeks, compared with placebo, in patients with active PsA, with no new safety signals. In patients with PsA and axial involvement, guselkumab was associated with a reduction in axial symptoms after 24 weeks of treatment. A comparative analysis of guselkumab showed that it ranks consistently equally with other PsA treatments in terms of PsA-related measurements, including improvements in arthritis, soft-tissue damage, physical function, and safety outcomes. Treatment with the IL-12/23 inhibitor ustekinumab resulted in comparable MDA, VLDA, and cDAPSA outcomes and favourable persistence profiles, compared with TNFi, in patients with PsA.

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