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Topic: Psoriasis

Beyond skin deep: Baseline systemic immune-inflammatory index as predictor of treatment response of HRO350 in mild-to-moderate psoriasis. Results from the HeROPA study

Ingeborg Bachmann*[1], Thomas Ringheim-Bakka[2], Nils Meland[3], Knut Smerud[3], Brian Kirby[4], Runhild Gammelsæter[2]

[1]Haukeland University Hospital, Bergen, Norway
[2]Arctic Bioscience, Ørsta, Norway
[3]Smerud Medical Research, Oslo, Norway
[4]Saint Vincents University Hospital, Dublin, Ireland

Introduction

Psoriasis affects roughly 2-4% of the Western population, of which >80% have mild to moderate disease. The HeROPA trial was a multicountry, randomized, placebo-controlled phase 2b trial (N = 521) evaluating the investigational product HRO350 in patients with mild-to-moderate psoriasis.

Severity assessments of psoriasis are predominantly evaluated using PASI and sPGA, including in the HeROPA trial. These tools lack precision for assessing changes over time in milder psoriasis populations and thus complicate efficacy assessments.

There has been an increased interest in biomarkers to complement skin assessments in psoriasis. However, the mild to moderate population has been largely understudied - a population where classic cytokines are not consistently systematically elevated.

Here we present the main outcome from the HeROPA phase 2b trial along with a *post hoc* stratification strategy utilizing the systemic immune-inflammation index (SII; neutrophils x platelets / lymphocytes) to increase sensitivity and filter placebo response in efficacy assessments.

Materials and Methods

The HeROPA phase 2b trial (NCT06125808) was conducted in five European countries. Patients (N = 521) were randomized (1:1:1) to receive oral HRO350 (API: Phospholipid esters from herring roe), IRIS Substance ID: 300000046327) 1050 mg daily, 2100 mg daily, or matching placebo b.i.d. for 52 weeks.

Patients eligible for recruitment were adults (≥18 years) with chronic and active mild-to-moderate plaque psoriasis (PASI 3-10, BSA ≥3, sPGA 2-4). SII stratification and response analysis is herein presented for patients in the high dose arm (2100 mg) vs placebo.

Results

The primary endpoint of PASI50 at week 26 was not met due to unexpectedly high placebo response in the 2100 mg arm (ITT: 22% vs 25%, p = 0.56). The key secondary sPGA 0/1 indicated a nonsignificant trend in the 2100 mg arm at week 52 (PP: 47% vs 34%, p = 0.07). The safety data showed a favourable safety profile, and the absence of HRO350-related SAEs supports the conclusion that HRO350 is safe and well tolerated.

The unexpectedly high placebo rate was investigated, and intriguing efficacy results were found when the patients were stratified *post hoc* based on their baseline SII being above or below the median SII (506, IQR: 368-707). After

stratification, response rates after week 52 were assessed for PASI50, sPGA 0/1, sPGAxBSA75, BSA < 3, and DLQI 0/1.

Patients with a SII baseline ≤506 showed clearly improved response rates in the active treatment arm after week 52 compared to those >506, with proportion differences reaching >20 pp for 3/5 endpoints. The opposite was observed in the placebo arm, where responder proportions were higher in the high SII group.

This response improvement led to statistically significant proportions of patients with baseline SII ≤506 achieving sPGA 0/1 (25/48; ARD 21.3 pp; 95% CI 2.4 - 40.2 pp, $p < 0.05$), sPGAxBSA75 (21/48; ARD 22.6 pp, 95% CI 4.7 - 40.4 pp; $p < 0.05$), and DLQI 0/1 (20/48; ARD 21.7 pp; 95% CI 3.8 - 39.5 pp; $p < 0.05$) after week 52 in the PP population.

Conclusions

Treatment benefit from HRO350 compared to placebo was found to be statistically significant across multiple endpoints in patients with baseline SII ≤506. High baseline SII was associated with reduced treatment benefit versus placebo and moderately increased placebo response compared to lower baseline SII.

Baseline SII impacting treatment trajectories is a very interesting finding, as mild-to-moderate psoriasis patients are generally acknowledged to have low systemic inflammatory burden associated with their psoriatic disease.

Stratifying patients based on baseline SII enhanced treatment effect detection in a patient population prone to high placebo responses and whose disease severity assessments are limited by insufficiently granular clinical assessment tools.

SII stratification provides an accessible tool for increasing treatment sensitivity and predicting responder trajectories in mild to moderate psoriasis.