The Comparative Efficacy for Novel Treatments of Moderate to Severe Plaque Psoriasis

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• A. W. Armstrong serves as investigator and/or consultant to AbbVie, Amgen, Janssen, Merck, Lilly, Novartis, Pfizer, and Modernizing Medicine.
• L. Puig has served as investigator and/or consultant or paid speaker to AbbVie, Almirall, Amgen, Biogen, Boehringer Ingelheim, Celgene, Janssen, Leo, Lilly, Merck, Novartis, Pfizer, and UCB.
• A. Joshi, M. Skup, S. Kalabina and D. Williams are employees of AbbVie and may own AbbVie stock or stock options.
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Background, Objective and Methods

**Background:** The clinical benefits of novel treatments for moderate to severe psoriasis have been well-established, but wide variations exist in patient response across different therapies. In the absence of head-to-head randomized trials across the entire set of comparators, meta-analyses combining data from multiple studies to assess comparative efficacy are needed.

**Objective:** This study estimated the relative rates of response over the primary response period and the maintenance period, assessed as 90% and 100% reductions from baseline in the Psoriasis Area and Severity Index (PASI 90/100), among novel psoriasis treatments.

**Methods:**
- A systematic literature review to identify phase II or III randomized controlled trials of treatments and dosages licensed by the European Medicines Agency (EMA) for adult patients with moderate to severe psoriasis.
- Treatments assessed included:
  - **Anti-TNF agents:** adalimumab, certolizumab pegol, etanercept, and infliximab.
  - **Anti-IL agents:** brodalumab, guselkumab, ixekizumab, risankizumab, secukinumab, tildrakizumab, and ustekinumab.
  - **Anti-PDE4:** apremilast.
  - **Fumaric acid esters:** dimethyl fumarate.
- Outcomes compared were probabilities of achieving PASI 90/100 at the end of the primary response period of included trials (10-16 weeks from baseline) and at the end of the maintenance period (44-60 weeks from baseline).
- At weeks 10-16, PASI 90/100 rates for each randomized treatment were estimated in a Bayesian random effects network meta-analysis (NMA). To account for variation across trials, an ordinal model which adjusted for reference arm response was implemented.
- At weeks 44-60, the PASI rates were estimated using data from trial arms in which baseline treatment assignment was maintained during the maintenance period. In the absence of a common reference arm over the maintenance period, a direct random effects meta-analysis was conducted to estimate the response rates and pairwise comparisons were conducted among treatments.
Network Meta-Analysis Results at Weeks 10-16

• A total of 60 trials meeting all inclusion criteria were included in the NMA

• Risankizumab, ixekizumab, brodalumab, and guselkumab had the among the highest PASI 90/100 rates at weeks 10-16 among assessed treatments; there were no statistically significant differences among these four treatments

• Risankizumab, ixekizumab, brodalumab, and guselkumab had significantly higher PASI 90/100 rates compared to etanercept, adalimumab, ustekinumab, certolizumab pegol, tildrakizumab, dimethyl fumarate, and apremilast; risankizumab, ixekizumab and brodalumab also had significantly higher rates than secukinumab and infliximab (p-value < 0.05)


Note: Error bars "I" denotes a 95% credible interval. Difference between treatments was tested at a significant level of 0.05.
Meta-Analysis Results at Weeks 44-60

- A total of 23 trials on 10 treatments meeting all inclusion criteria were included in the meta-analysis. Long-term data were only reported for the 50mg BIW dose for etanercept; PASI 100 were not reported for apremilast, etanercept, and infliximab.

- Risankizumab, brodalumab, ixekizumab, guselkumab, and secukinumab had among the highest estimated PASI 90/100 response rates at weeks 44-60, whose rates were significantly higher than etanercept, infliximab, adalimumab, ustekinumab and apremilast.

- Among those five biologics, risankizumab had a significantly higher PASI 90 rate than ixekizumab and secukinumab; in addition, risankizumab, brodalumab, and ixekizumab had significantly higher PASI 100 rates than secukinumab, while risankizumab and ixekizumab also had significantly higher PASI 100 rates than guselkumab (p-value < 0.05).

- A sensitivity analysis including only trials that reported non-response imputed (NRI) data had similar results.
Strengths:
• The NMA approach allows for estimation of comparative effects among treatments that have not been investigated in head-to-head, randomized clinical trials and provides useful evidence for judiciously selecting the best choice(s) of treatment; adjusting for reference arm response can reduce the effects of cross-trial heterogeneity, as the reference arm response rate integrates the effects of other observed and unobserved trial-level factors likely to affect treatment arm outcomes
• Direct meta-analysis allows for the amalgamation of scientific evidence and offers an objective appraisal of the available evidence; by combining data from multiple independent trials, the meta-analysis increases the effective sample size and improves statistical precision for the estimation of long-term PASI responses

Limitations:
• Cross-trial differences and patient characteristics that may modify the treatment effect and can introduce bias in the comparisons. Adjusting for reference arm response in the NMA can reduce the effects of cross-trial heterogeneity; however, the adjustment is not guaranteed to eliminate these effects
• Results presented were derived based on data from clinical trials, which may not be generalizable to real world settings

Conclusion:
• This study provides the most up-to-date data on comparative efficacy among treatments for moderate to severe plaque psoriasis.
  ▪ Over the primary response period, risankizumab, ixekizumab, brodalumab, and guselkumab were associated with the highest estimated PASI response rates.
  ▪ Over the long-term maintenance period, there were some notable differences with risankizumab having significantly higher PASI 90 rates than secukinumab and ixekizumab and significantly higher PASI 100 rates than guselkumab
• Future research:
  ▪ Comparing safety outcomes would provide a complete benefit-risk assessment of novel psoriasis therapies
  ▪ Analyses using real-world data would be warranted to better understand the use of these treatments in practice