Risankizumab versus ustekinumab for plaque psoriasis

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DR ALI AL-JANABI (Orcid ID : 0000-0002-2094-0556)

DR ZENAS ZEE NGAI YIU (Orcid ID : 0000-0002-1831-074X)

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Title: Risankizumab versus ustekinumab for plaque psoriasis: a critical appraisal

Authors: A. Al-Janabi¹, Z. K. Jabbar-Lopez², C.E.M. Griffiths¹, Z.Z.N. Yiu¹

1. Dermatology Centre, Salford Royal Hospital, University of Manchester and the Academic Health Science Centre, Manchester, United Kingdom.
2. Unit for Population-Based Dermatology Research, St John's Institute of Dermatology, King's College London & Guy's and St Thomas' NHS Foundation Trust, London, U.K.

Corresponding author:

Ali Al-Janabi, ali.al-janabi@nhs.net

Dermatology Centre, Salford Royal NHS Foundation Trust, Stott Lane, Salford, M6 8HD

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What is already known about this topic?

- Interleukin(IL)-23 is important in the pathogenesis of plaque psoriasis.
- Ustekinumab, which targets the p40 subunit common to IL-12 and IL-23, is an effective biologic treatment for chronic plaque psoriasis.
- More recently, biologics targeting the p19 subunit specific to IL-23 have been shown to be very effective in the treatment of moderate-to-severe plaque psoriasis.

What does this study add?

- This is a critical appraisal of the study by Gordon *et al*, a parallel group randomized controlled trial comparing risankizumab, a p19 inhibitor, with ustekinumab and placebo.
- This is a well-conducted study with high internal validity.
- External validity of the trial is less clear and further information regarding the participants' prior medical history and psoriasis treatments could help the reader apply the results to real-world populations.

Summary

Aim Gordon *et al* investigated the efficacy and safety of risankizumab (an anti-interleukin[IL]23p19 biologic) compared with ustekinumab (anti-IL12/23p40) and placebo in patients with moderate-to-severe chronic plaque psoriasis. This is a parallel group controlled study up to 16 weeks with a planned switch of the placebo group to risankizumab at 16 weeks.

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Setting and design This study consisted of two replicate phase 3, double-blinded randomised-controlled trials (UltIMMa-1 and UltIMMa-2) conducted across 139 centres in Australia, Austria, Belgium, Canada, Czech Republic, France, Germany, Japan, Mexico, Poland, Portugal, South Korea, Spain and the USA.

Study exposure Patients with a minimum 6 month history of chronic plaque psoriasis were randomly assigned to receive either 150 mg risankizumab, 45 mg or 90 mg ustekinumab or placebo. Prior to this, each group was also stratified by weight (either more than or less than 100kg) and previous exposure to tumour necrosis factor inhibitor. Those assigned to receive placebo were transitioned onto risankizumab at week 16. The study drugs were given at weeks 0, 4, 16, 28 and 40.

Outcomes The severity of psoriasis was measured using the Psoriasis Area and Severity Index (PASI) and a static Physician's Global Assessment (sPGA). The authors additionally recorded the number of adverse events in each treatment arm, and a measure of quality of life.

Primary outcome measures

The co-primary outcomes were the proportion of patients achieving a 90% reduction in their baseline PASI (PASI 90) and a sPGA score of 0 or 1 (clear or almost clear) at week 16.

Results

A total of 506 patients were included in UltIMMa-1 and 491 patients in UltIMMa-2. In UltIMMa-1, PASI-90 by week 16 was achieved by 75.3% of patients receiving risankizumab compared with 42.0% receiving ustekinumab and 4.9% receiving placebo ($p < 0.0001$ vs placebo and ustekinumab). sPGA of 0 or 1 by week 16 was achieved by 87.6% of patients receiving risankizumab compared with 63.0% receiving ustekinumab and 7.8% receiving placebo ($p < 0.0001$ vs placebo and ustekinumab). The results for UltIMMa-2 are similar. The frequency of adverse events in the risankizumab, ustekinumab and placebo groups was similar in both studies.

Conclusions

Gordon *et al* conclude that risankizumab has a higher efficacy than placebo and ustekinumab in the treatment of moderate-to-severe chronic plaque psoriasis, and that the adverse event profiles were similar across all treatment groups.

Comment

What is already known?

Interleukin-23 (IL-23) is a key mediator in the pathogenesis of psoriasis. It is implicated in driving and maintaining the differentiation of T-helper (Th) 17 cells¹; increased expression of IL-23 has been noted in plaques of psoriasis.² Additionally, biologics targeting IL-23 have been shown to be effective in the treatment of psoriasis. Ustekinumab was licensed in 2009 for the treatment of chronic plaque psoriasis and targets the p40 subunit common to both IL-12 and IL-23.³ It has been shown to be more effective in the treatment of moderate-to-severe psoriasis than etanercept, a tumour necrosis factor (TNF) inhibitor.⁴ More recently, biologics which target the p19 subunit which is specific for IL-23, such as guselkumab have been shown to be highly effective.^{5,6} To date, there have been no phase 3 randomised controlled trials studying p19 versus p40 inhibitors in comparable populations of patients with moderate-to-severe psoriasis.⁷

Strengths

This is the first head to head study comparing risankizumab, an inhibitor of IL-23p19, with a dual IL-12 and IL-23 inhibitor (ustekinumab). These are well-conducted randomised controlled trials which fulfil most aspects of the CONSORT statement.⁸ The primary outcomes are clear, and a number of clinically important secondary endpoints up to 52 weeks are recorded, evaluating risankizumab and

ustekinumab over a longer period of time. The authors have helpfully provided a full list of the inclusion and exclusion criteria in the supplementary materials. The pre-stratification by weight and previous anti-TNF exposure ensures that these factors are balanced between treatment arms. With regards to data analysis, the non-responder imputation methodology provides a more conservative estimate of treatment effect. Additionally, the authors reported a Cochran-Mantel-Haenszel risk difference estimate with a 95% confidence interval for each treatment arm, which demonstrates the degree of difference and the precision of these estimates.

Assessment of validity

Internal validity

Randomisation

Computer randomisation was used to assign study participants in a 3:1:1 ratio to receive risankizumab, ustekinumab and placebo respectively. Randomisation was stratified by weight and previous exposure to anti-TNF agents, and all groups in both studies were similar in terms of demographics, weight, prior use of anti-TNF agent, prior use of biologics and diagnosis of psoriatic arthritis. There was a slight imbalance in the UltIMMa-1 study whereby a higher proportion of participants in the placebo group (24%) had prior non-TNF inhibitor biologic therapy compared to those in the risankizumab (18%) or ustekinumab (17%) treatment arms. In theory, this could lead to bias in favour of intervention though this is unlikely. The nature of prior exposure to an anti-TNF agent, such as whether treatment had failed or was stopped due to adverse events, was not specified. While the study does comment that interactive response technology was used for randomisation, it is unclear whether an allocation concealment mechanism was used to reduce the risk of selection bias, as recommended by the CONSORT statement.⁸

Blinding

The entire study was conducted in a double-blind fashion. Patients, investigators, and study personnel both involved in the conduct of the trial and the analyses of the data were blinded to treatment assignment until the end of the study. Those administering the treatments were also blinded as the treatments or placebo appeared identical.

Intention to treat

The authors have used an intention-to-treat analysis to interpret their data, and have also included a separate sensitivity analysis for patients that did not deviate significantly from the protocol. The dropout rates were low, with 94.8% of enrolled participants completing UltIMMa-1 and 93.4% completing UltIMMa-2.

Power

The authors have indicated the use of power calculations based on both primary endpoints, and have exceeded the sample sizes required to provide over 90% power for both of these endpoints.

External validity

The average baseline Psoriasis Area Severity Index (PASI) in both studies was approximately 20, and combined with the primary outcomes of achieving a 90% reduction in PASI (PASI 90) or static Physician's Global Assessment (sPGA) score of 0 or 1 (clear or almost clear), this study focussed on assessing significant improvement in severe disease. These primary endpoints are consistent with those used in other head to head trials for biologic drugs in psoriasis.^{9, 10}

Both trials were conducted across 139 sites in 14 countries, although the number of sites in each type of clinical or academic setting and in each country have not been specified, which could affect the study's external validity.

The treatment hierarchy in psoriasis varies by country and depends on health economics as well as treatment efficacy. For example in the UK, one National Institute for Health and Care Excellence criterion that must be met before commencing biologic treatment is that methotrexate and ciclosporin are either contraindicated or have failed.¹¹ While this study did include patients who had received non-biologic systemic treatments previously, it is not clear how this particular subgroup would respond to risankizumab when compared with those who had no prior exposure to systemic treatment. In addition, the trial report does not state whether these biologic-experienced participants had previous biologic treatment failure, or whether there were other reasons that the biologic therapy was stopped, e.g. financial reasons.

One of the exclusion criterion noted within the supplemental materials is patients with comorbidities deemed by the investigator to compromise patient safety or data quality. It would have been helpful to present the number of each type of comorbidity in the baseline table for the reader to evaluate, as it is not uncommon for patients with multiple comorbidities to have moderate-to-severe psoriasis requiring biologic treatment.

Other issues

As ustekinumab has established efficacy in the treatment of psoriasis,³ the use of a placebo arm was not necessary and arguably not ethically appropriate. However, as this is the first published report of a phase III placebo-controlled trial for risankizumab in the treatment of psoriasis, it is likely that the placebo arm was included to allow approval from the relevant drug regulatory agencies. Regulatory agency requirements may also be the reason that two replicate phase 3 trials, rather than a single trial, were completed. Both trials recruited more participants than required from the sample size calculation; this raises the concern that the trial was also used to increase familiarity with and use of risankizumab in centres internationally.

While the study did record the PASI and sPGA up to 52 weeks to determine some secondary endpoints, the Dermatology Life Quality Index and Psoriasis Symptom Scale were only reported up to week 16. It would have been interesting to see the longer-term effects on the patients' quality of life.

The study was sponsored by two biopharmaceutical companies, Boehringer Ingelheim (originator of risankizumab) and AbbVie (organisation marketing risankizumab), who contributed to study design, analysis, data interpretation and writing. This increases the risk of a biased study.

Overall assessment

This is a very well conducted study with large sample sizes, double-blinding through the duration of the study and an intention-to-treat analysis. The authors have been clear in their reporting of the methodology, for example by outlining the complete list of inclusion and exclusion criteria. The results are well-presented, and the inclusion of the confidence intervals helps in quantifying the certainty (or precision) of the difference between the treatment arms.

Both trials demonstrate a significant improvement in both primary outcomes with risankizumab when compared with ustekinumab and placebo ($p < 0.0001$). The 16-week period of assessment for the primary outcome measures is consistent with the time-frame used in clinical practice. The secondary endpoints up to 52 weeks are helpful in supporting the results of the primary outcomes; these indeed do show a sustained response in PASI-90 outcome at 52 weeks.

This is the first direct comparison of an IL-23 inhibitor versus a combined IL-12/IL-23 inhibitor in a population that has not received either class of treatment before; it is intriguing that a more selective agent has been shown to be more effective. This may suggest that targeting IL-12 is redundant or detrimental in the treatment of psoriasis, and it would be of great interest to understand the mechanism underlying this. This trial was not powered to investigate safety outcomes, and large observational studies will be important to compare IL-23 inhibitors against IL-12/23 inhibitors, and elucidate whether more specific targeting of p19 may result in fewer adverse events. It would be useful to see how risankizumab compares with the other p19 inhibitors, guselkumab and tildrakizumab. One potential advantage of risankizumab over guselkumab is the longer 12-weekly dosing interval, compared with 8-weekly for guselkumab. Though there is no head-to-head comparison yet, tildrakizumab appears to have a lower efficacy in the reSURFACE trials¹² than has been for risankizumab. More research is needed to further elucidate the role of IL-23-selective inhibitors relative to other biologic agents. Anti-IL-17 biologics have also been shown to be highly effective in the treatment of psoriasis,^{13,14} and it will be interesting to see how risankizumab compares when tested against an anti-IL-17,¹⁵ particularly as its downstream effect is to inhibit the differentiation of Th17 cells.

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