The interleukin 1 receptor antagonist anakinra to reduce disease severity of palmoplantar pustulosis in adults: APRICOT RCT and PLUM mechanistic study

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Scientific summary

APRICOT RCT and PLUM mechanistic study

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Scientific summary

Background

Palmoplantar pustulosis (PPP) is characterised by painful, intensely inflamed red skin studded by sheets of monomorphic, sterile, neutrophilic pustules on the hands and/or feet. There are very few treatment options currently available for this rare and debilitating chronic skin disease.

Interleukin (IL) 1 antagonists have proven therapeutic benefit in IL-1-mediated diseases. Preliminary data indicate a potential pathogenic role for IL-1/IL-36 axis in pustular psoriasis.

Anakinra [Sobi (Swedish Orphan Biovitrum AB), Stockholm, Sweden] is an IL-1 receptor antagonist that is currently licensed to treat rheumatoid arthritis and periodic fever syndromes. There are early (but limited) proof-of-concept data that show that anakinra may have some therapeutic improvement in some pustular forms of psoriasis.

We therefore hypothesised that anakinra would deliver therapeutic benefit for PPP.

Objectives

The primary objective was to determine whether or not anakinra improves disease severity in the treatment of adults with PPP, as assessed by the Palmoplantar Pustulosis Psoriasis Area Severity Index (PP-PASI).

Secondary objectives were to evaluate whether or not anakinra improves disease severity, as assessed by other investigator-assessed efficacy outcomes, participant-reported measures of efficacy and quality of life and safety measures.

Methods

Trial design

This was a Phase IV, two-stage, adaptive, double-blind, randomised, placebo-controlled trial followed by an open-label extension (OLE), which aimed to recruit 64 participants (24 to stage 1 and 40 to stage 2). An analysis at the end of stage 1 was used to compare treatment groups to ensure sufficient efficacy and safety to progress to stage 2. The primary outcome for stage 2 was also selected out of two prespecified candidate outcomes (PP-PASI score or fresh pustule count) based on assessments of reliability and discriminatory ability using stage 1 data.

Participants

Recruitment, investigational medical product (IMP) delivery and collection of data took place in 16 hospitals across England, Scotland and Wales. Participants were adults (aged $\geq$ 18 years) with a diagnosis of PPP made by a trained dermatologist, with a disease duration of $>$ 6 months and disease of sufficient impact and severity to require systemic therapy. Disease activity that rated at least moderate disease on the Palmoplantar Pustulosis – Investigator's Global Assessment (PPP-IGA) with evidence of active pustulation on palms and/or soles had to be present at baseline for each participant to be randomised into the study.

Randomisation

Participants were randomised (1 : 1) to receive either anakinra or the placebo for 8 weeks via a secure online randomisation system. The randomisation sequence was stratified by centre and prepared using blocked randomisation.

Blinding

Throughout the study, participants, research nurses, treating physicians and independent outcome assessors were blinded to treatment assignment. Analysis was conducted subgroup blind (i.e. as group A vs. group B).

Interventions

Once randomised into the study, participants self-administered a daily, subcutaneous 100-mg injection of IMP (either anakinra or placebo) for 8 weeks and were followed up for 12 weeks.

Participants who completed the 12-week trial were invited to take part in the OLE study (which involved a daily, subcutaneous 100-mg injection of anakinra) for a maximum of 8 weeks. The OLE was added to the study in July 2019 (as part of substantial amendment 11).

All participants were followed up for safety for 90 days after the last dose of IMP/open-label anakinra.

Primary outcome

The primary outcome was selected to be the PP-PASI score measured at 0, 1, 4, 8 and 12 weeks, with the primary end point at week 8. Assessments were carried out by an independent assessor (who was blind to study treatment).

Secondary outcomes

Secondary investigator-assessed outcomes included fresh pustule counts (palms and soles) at week 8, total pustule counts (palms and soles) at week 8, PPP-IGA at week 8, time to response of PPP (75% reduction in fresh pustule count compared with baseline), relapse rate (return to baseline fresh pustule count), clear on PPP-IGA at week 8, development of a disease flare (> 50% deterioration in PP-PASI scores) at week 8, pustular psoriasis at non-acral sites measured by change in percentage area at week 8 and Psoriasis Area and Severity Index (PASI scores) to assess plaque psoriasis if present at week 8. Secondary participant-reported efficacy outcomes included Participants Global Assessment at week 8, Palmoplantar Quality of Life instrument at week 8, Dermatology Life Quality Index (DLQI) at week 8, EuroQoL-5 Dimensions, three-level version (EQ-5D-3L), at week 8, and treatment acceptability and adherence at week 8. Safety measures included serious infection, neutropenia, serious adverse events and reactions, and adverse events and reactions.

Statistical methods

The overall sample size was established using a standardised effect size as calculated prior to the completion of stage 1 of the study, when the primary outcome of the main trial analysis was unknown. A large effect size of 0.9 standard deviation (SD) was selected to be the minimum important difference to detect because of the cost of the drug and the high patient burden of daily self-administered subcutaneous injection treatment. To detect a difference of 0.9 SD with a power of 90% and a 5% significance level, with a conservative allowance for a 15% withdrawal rate, a sample size of 32 participants per group ($n = 64$ in total) was required. The observed SD for the baseline PP-PASI score in APRICOT (Anakinra for Pustular Psoriasis: Response in a Controlled Trial) ($n = 64$) was 10.5; therefore, 0.9 SD was approximately a change of 9.5 in the PP-PASI score.

The main analysis followed the intention-to-treat (ITT) principle and included all participants with at least one follow-up as randomised, regardless of subsequent adherence, to estimate the effect of the treatment policy. The primary analysis model was a linear (Gaussian) mixed-effects model, using PP-PASI data from the 1-, 4- and 8-week follow-up assessments, with random subject and centre effects and fixed effects for baseline PP-PASI scores, study visit, treatment group and study visit by treatment group interaction to obtain the treatment effect estimate at 8 weeks. The estimated treatment effect at 8 weeks was reported with 95% confidence intervals (CIs) and corresponding *p*-value. The main conclusion of the trial was based on this analysis time point.

Results

Recruitment took place between October 2016 and January 2020. A total of 64 participants were randomised, and all initially received treatment with anakinra ($n = 31$) or placebo ($n = 33$). Baseline characteristics, including disease characteristics, were generally well balanced across the treatment groups. Participants had a mean age of 50.8 years (SD 12.7 years), 84% were female, 92% were of white ethnicity and the mean baseline PP-PASI score was 17.8 (SD 10.5).

A total of six (18%) placebo and five (16%) anakinra participants permanently withdrew from the study treatment over the 8-week treatment period. Of these, only three participants withdrew entirely from the study: two (7%) in the placebo group prior to week 8 and one (3%) in the anakinra group after week 8 but prior to week 12. Temporary treatment discontinuations were reported for three (9%) placebo group and six (19%) anakinra group participants.

In the primary ITT analysis, which estimated the effect of the treatment policy, the mean treatment group difference at week 8, after adjustment for the baseline PP-PASI scores, was −1.65 points (95% CI −4.77 to 1.47 points; $p = 0.300$), in favour of anakinra, but was not high enough to demonstrate superiority. In the planned exploratory analysis (ITT), the mean difference in PP-PASI scores at week 12, adjusted for baseline PP-PASI scores, was −2.42 points (95% CI −5.97 to 1.13 points; *p*-value = 0.182). Sensitivity analyses that explored alternative missing data assumptions supported the result of the primary analysis. In the supplementary compliance-adjusted analysis that estimated the complier-average causal effect (CACE), the mean treatment group difference at 8 weeks among those who received ≥ 50% of injections, after adjustment for the baseline PP-PASI scores, was −2.30 points (95% CI −6.54 to 1.93 points; $p = 0.287$) and among those who received ≥ 90% of injections was −3.80 points (95% CI −10.76 to 3.16 points; $p = 0.285$), in favour of anakinra.

Secondary investigator-assessed outcome measures did not show statistical superiority of anakinra: the baseline-adjusted mean difference in fresh pustule count across the palms and soles between the anakinra group and the placebo group was 2.94 (95% CI −26.44 to 32.33) pustules, with the point estimate in favour of placebo. For the total pustule count, the mean difference was −30.08 pustules (95% CI −83.20 to 23.05 pustules) and for PASI this was −0.41 points (95% CI −0.96 to 0.15 points), for which the point estimates were in favour of anakinra. For those in the anakinra group compared with those in the placebo group, the odds of a higher PPP-IGA score were 0.54 (95% CI 0.13 to 2.19) and the odds of disease flare were 0.55 (95% CI 0.08 to 3.71). There was no evidence for a difference in the time to relapse (hazard ratio 0.58, 95% CI 0.22 to 1.50) or time to response (hazard ratio 0.94, 95% CI 0.50 to 1.78) between treatment groups.

Participant-assessed outcome measures did not show statistical superiority of anakinra: the baseline-adjusted mean difference in score between the anakinra group and the placebo group was 0.52 points (95% CI −2.04 to 3.07 points) for the DLQI, 1.27 points (95% CI −3.04 to 5.57 points) for the Palmoplantar Quality of Life and−0.09 points (95% CI −0.23 to 0.06 points) for the EQ-5D-3L. The odds of the PGA score being higher in the anakinra group than in the placebo group was 1.39 (95% CI 0.41 to 4.70). However, the proportion of participants who strongly agreed that the treatment was worthwhile was

greater in the anakinra group (12/29, 41%) than in the placebo group (4/28, 14%). No serious infections, cases of neutropenia or other serious adverse events occurred in either treatment group. Injection site reactions were more frequent for participants in the anakinra group (19/31, 61%) than for those in the placebo group (1/33, 3%).

Conclusions

An 8-week treatment policy of anakinra was not demonstrated to be superior to placebo.

Recommendations for research

An effective, safe treatment is still required for this very high-need and hard-to-treat disease.

Future randomised controlled trials should capitalise on the now-established network of UK investigators with precisely phenotyped participants willing to participate in clinical trials and should consider the novel two-stage, adaptive design, which worked well in this rare disease setting.

Data from this and other studies in PPP judged to be clinically similar could be pooled, using appropriate meta-analysis techniques, to explore whether or not the level of drug bioavailability may explain poor response to targeted therapies and to inform future dosing strategies when testing therapeutic interventions in PPP. Planned mechanistic studies from this study will explore the expression of IL-1 signature genes in skin samples at week 1 and investigate differences in response, taking into account patient-level adherence data.

Samples and data from this study will be made available to the scientific community to enable identification and validation of future therapeutic targets, as well as validating outcome measures to be used in PPP, which are currently lacking.

Implications for health care

Clinicians treating PPP could be encouraged to enter participants into clinical trials evaluating disease mechanisms, and efficacy and safety of therapeutic interventions.

Anakinra, or drugs mediating IL-1 blockade, should be used only in the context of a clinical trial.

Trial registration

This trial is registered as ISCRTN13127147 and EudraCT 2015-003600-23.

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