Anakinra for palmoplantar pustulosis: results from a randomized, double-blind, multicentre, two staged, adaptive placebo controlled trial (APRICOT)

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Authors (initial(s), surname):

S Cro[1], VR Cornelius[1], AE Pink[2], R Wilson[3], A Pushpa-Rajah[3], P Patel[3], A Abdul-Wahab[4], S August[5], J Azad[6], G Becher[7], A Chapman[8], G Dunnil[9], A D Ferguson[10], A Fogo[11], S A Ghaffar[12], J R Ingram[13], S Kavakleiva[14], E Ladoyanni[15], J A Leman[16], A E Macbeth[17], A Makrygeoegou[18], R Parslew[19], A J Ryan[20], A Sharma[21], A R Shipman[22], C Sinclair[23], R Wachsmuth[24], RT Woolf[2], A Wright[25], H McAteer[26] , JNWN Barker[27], DA Burden[28], CEM Griffiths[29], NJ Reynolds[30], RB Warren[29], HJ Lachmann[31], F Capon[32] , Smith CH[3] and the APRICOT Study Group

Institutions:

[1]Imperial Clinical Trials Unit, Imperial College London. London, W12 7RH, UK
[2]St. John's Institute of Dermatology, 1st Floor - Counting House, Guy's Hospital, Guy's and St Thomas' NHS Foundation Trust, London, SE1 9RT, UK.
[3]St. John's Institute of Dermatology, 9th Floor - Tower Wing, Guy's Hospital, Guy's and St Thomas' NHS Foundation Trust, London, SE1 9RT, UK.
[4]St George's University Hospitals NHS Foundation Trust, Blackshaw Rd, Tooting, London SW17 0QT, UK.
[5]Poole Hospital NHS Foundation Trust University Hospitals Dorset, Longfleet Rd, Poole BH15 2JB, UK.
[6]South Tees Hospitals NHS Foundation Trust, Middlesbrough, TS4 3BW, UK.
[7]West Glasgow Ambulatory Care Hospital, Dalnair St, Yorkhill, Glasgow, G3 8SJ, UK.
[8] Homerton University Hospital, Homerton Row, London, E9 6SR, UK.
[9]Bristol Royal Infirmary, Upper Maudlin St, Bristol, BS2 8HW, UK.
[10]University Hospitals of Derby and Burton NHS Foundation Trust, Uttoxeter Road, DERBY, DE22 3NE, UK.
[11]Kingston Hospital, Galsworthy Rd, Kingston upon Thames KT2 7QB, UK.
[12]Ninewells Hospital & Medical School, Dundee, DD1 9SY, UK.
[13] Division of Infection & Immunity, School of Medicine, Cardiff University, University Hospital of Wales, Heath Park, Cardiff, CF14 4XN, UK
[14]Royal Lancaster Infirmary, Ashton Rd, Lancaster LA1 4RP, UK.
[15]Russells Hall Hospital, Pensnett Rd, Dudley DY1 2HQ, UK.
[16] Kings Park Hospital, Stirling, FK7 9JH.
[17]Norfolk and Norwich University Hospitals NHS Foundation Trust, Colney Ln, Norwich, NR4 7UY, UK.
[18]West Glasgow Ambulatory Care Hospital, Dalnair St, Yorkhill, Glasgow, G3 8SJ, UK.
[19]Liverpool University Hospitals NHS Foundation Trust, Lower Ln, Liverpool L9 7AL, UK.
[20] Kings College Hospital, Denmark Hill, Brixton, London, SE5 9RS.
[21] Nottingham University Hospitals NHS Trust, Nottingham, NG7 2UH, UK
[22] Portsmouth Hospitals Universities NHS Trust, St Mary's Community Health Campus, Milton Road, Portsmouth, PO3 6AD, UK
[23]Broomfield Hospital, Court Rd, Broomfield, Chelmsford CM1 7ET, UK.
[24] Royal Devon and Exeter NHS Foundation Trust, Barrack Road, Exeter, Devon, EX2 5DW, UK.
[25]Bradford Teaching Hospitals NHS Foundation Trust, Duckworth Ln, Bradford BD9 6RJ, UK.
[26] The Psoriasis Association, Northampton, NN4 7BF, UK.

[27]St. John's Institute of Dermatology, School of Basic & Medical Biosciences, Faculty of Life Sciences & Medicine, King's College London, London, SE1 9RT, UK.
[28]Institute of Infection, Immunity and Inflammation, University of Glasgow, Glasgow, G12 8TA, UK.
[29]Dermatology Centre, Salford Royal NHS Foundation Trust, University of Manchester, NIHR Manchester Biomedical Research Centre, Manchester, M6 8HD, UK.
[30]Institute of Translational and Clinical Medicine, Medical School, University of Newcastle, Department of Dermatology, Royal Victoria Infirmary and NIHR Newcastle Biomedical Research Centre, Newcastle Hospitals NHS Foundation Trust, Newcastle upon Tyne, NE2 4HH, UK.
[31] National Amyloidosis Centre, University College London, London, NW3 2PF, UK.
[32]Department of Medical & Molecular Genetics, King's College London, London, SE1 9RT, UK.

Named members of the APRICOT Study Group and institutions can be found in supplementary file 1.

Corresponding author:
Name: Professor Catherine Smith
Email: catherine.smith@kcl.ac.uk

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What's already known about this topic? (maximum 70 words)

- Treatment options for palmoplantar pustulosis include super-potent corticosteroids, phototherapy, acitretin, methotrexate and ciclosporin. However these have poor evidence for benefit, and toxicity risk with long-term use.
- Anakinra is a recombinant interleukin (IL)-1 receptor antagonist (IL-1Ra) that blocks the activity of IL-1α and IL-1β, two cytokines repeatedly linked to neutrophil activation and extravasation.
- Therapeutic benefit of anakinra has been shown in neutrophilic dermatoses and conditions that manifest with skin pustulation.

What does this study add? (maximum 70 words)

- Anakinra was not significantly superior to placebo at eight weeks for objective investigator-assessed and patient-reported measures.
- A greater proportion of participants in the anakinra group strongly agreed the treatment was worthwhile.
- The safety profile of anakinra was consistent with previous studies.
- This is one of the largest randomised controlled trials in this rare condition, providing important data on its natural history and change in disease severity over time.

Plain Language Summary:

Palmoplantar pustulosis (PPP) is a rare chronic skin disease characterised by recurrent outbreaks of pustules affecting the hands and feet which can limit mobility and interfere with daily living tasks and work. Few treatment options are currently available for this painful disease. Previous research has shown that anakinra, a drug that blocks an important inflammation pathway, may help in the treatment of PPP. The anakinra for pustular psoriasis: response in a controlled trial (APRICOT) was therefore conducted to address whether anakinra offers benefits for the treatment of PPP. In the trial, 64 patients (adults aged 20 to 76 years, 84% female, 92% white ethnicity) were given either 8 weeks of treatment with anakinra or an inactive placebo, which was decided at random. The patients had clinician-assessments of disease severity, safety measures, and patient assessments of disease severity and impact on quality of life measured to determine whether anakinra was efficacious and safe in PPP. We found that 8 weeks of anakinra use did not offer benefit for the treatment of PPP .

Summary (word count: 243/250)

Background: Palmoplantar pustulosis (PPP) is a rare, debilitating, chronic inflammatory skin disease affecting the hands and feet. Clinical, immunological and genetic findings suggest a pathogenic role for interleukin (IL)-1.

Objective: To determine whether anakinra (an IL-1 receptor antagonist) delivers therapeutic benefit for PPP.

Methods: A randomised (1:1), double-blind, two-staged, adaptive, UK multi-centre, placebo-controlled trial. Participants had a diagnosis of PPP (>6 months) requiring systemic therapy. Treatment was eight weeks of anakinra or placebo via daily self-administered subcutaneous injections. The primary outcome was the Palmoplantar Pustulosis Psoriasis Area and Severity Index (PPPASI) at 8 weeks.

Results: A total of 374 patients were screened and 64 were enrolled (31 anakinra, 33 placebo) with mean baseline PPPASI 17.8 (SD=10.5); PPP investigator's global assessment severe (50%) or moderate (50%). The baseline adjusted mean difference in PPPASI favoured anakinra but did not demonstrate superiority in intention-to-treat analysis, -1.65, 95% CI [-4.77 to 1.47], p=0.300. Secondary objective measures including fresh pustule count (2.94, 95% CI [-26.44 to 32.33] favouring anakinra), total pustule count (-30.08, 95% CI [-83.20 to 23.05] favouring placebo), and patient-reported outcomes, similarly did not show superiority of anakinra. When modelling the impact of adherence, the PPPASI complier average causal effect (CACE) for an individual who receives ≥90% total treatment (48% anakinra group), was -3.80, 95% CI [-10.76 to 3.16], p=0.285. No serious adverse events occurred.

Conclusions: No evidence for superiority of anakinra was found. IL-1 blockade is not a useful intervention for the treatment of PPP.

Trial registration: ISCRTN: ISCRTN13127147 (Registered 1st August 2016). EudraCT Number: 2015-003600-23 (Registered 1st April 2016).

Introduction

Palmoplantar pustulosis (PPP) is a rare, chronic, inflammatory skin disease characterised by sterile neutrophilic pustules on the palms and soles (1, 2). It is associated with plaque psoriasis in about 20% of cases (3). Often accompanied by fissures, pruritus and a burning sensation, the disease is painful and disabling and can severely impact quality of life (4-6). Management options are profoundly limited. Commonly used treatments include super-potent corticosteroids, phototherapy, acitretin, methotrexate and ciclosporin for which there is poor evidence for benefit, and risk of significant toxicity with long term use (7). Equally, the biologic therapies, particularly those targeting the canonical interleukin (IL)-23/IL-17 pathway, that deliver such impressive clearance rates in plaque psoriasis only show modest benefit with two recent randomised controlled trials (RCTs) reporting data for secukinumab and guselkumab, respectively (8, 9).

Anakinra is a recombinant IL-1 receptor antagonist (IL-1Ra) that is currently licensed for the treatment of rheumatoid arthritis and cryopyrin associated periodic syndromes. It blocks the activity of IL-1α and IL-1β, two cytokines that have been repeatedly linked to neutrophil activation and extravasation. In keeping with these observations, anakinra has shown therapeutic benefit in neutrophilic dermatoses and in conditions charcterised by skin pustulation (10). The latter include deficiency of IL-1Ra(11), generalised pustular psoriasis caused by *IL36RN* mutations (12, 13), acrodermatitis continua of Hallopeau (14) and amicrobial pustulosis of the folds (15). Anakinra also showed efficacy in patients that present with PPP in the context of SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, osteitis) (16).

We therefore designed this randomised, double-blind, multicentre, two-staged adaptive placebo-controlled trial to determine the efficacy of anakinra for the treatment of adults with PPP.

Patients and methods

Study design and participants

Enrolment to APRICOT was conducted across 16 sites in England, Scotland and Wales between October 2016 and January 2020. Participants were randomly allocated to 8 weeks of treatment with anakinra or placebo. Study visits for outcome assessments occured at weeks 1, 4, 8 and 12. The trial included two stages and an adaptive element. Stage one (the first 24 participants) compared treatment groups to ensure proof-of-concept and select the primary outcome for stage two (see suplemetary file 1 for stage 1 details). Full details on the trials methods have been previously published in the study protocol (17). Ethical approval was granted by London Dulwich Research Ethics Committee (REC Number: 16/LO/0436).

In brief, eligible participants were aged ≥18 years with a diagnosis of PPP with disease of a sufficient severity to require systemic therapy, duration > 6months not responding to topical therapy including potent corticosteroids, active pustules on palms and/or soles, at least moderate on the Palmoplantar Pustulosis Investigators Global Assessment (PPP-IGA), women of child bearing potential on adequate contraception and not pregnant or breastfeeding and able to give written informed consent to participate. The list of exclusions can be found in the trial protocol and included use of therapies

with potential or known efficacy in PPP during or within stipulated time frames before treatment initiation (see supplementary file 1, Table S1) (17). After the trial commenced two exclusions were added as a precaution following new information in the Summary of Product Characteristics (18); (i) with thrombocytopenia and (ii) diagnosis (or historic diagnosis) of childhood or adult onset Still's disease. Part way through the trial an open label extension was added and offered to all who had completed the treatment period primarily to enhance recruitment and are reported elsewhere (19)

Patient involvement

A patient and public involvement group including people with pustular psoriasis and representation from the UK's main psoriasis patient organisation (Psoriasis Association) provided input and support into study design (prioritising the study question, use of placebo and 8 week treatment duration), delivery (patient information and recruitment communications), results interpretation and communication of outcomes.

Randomisation and blinding

To ensure allocation concealment, participants were randomised (1:1) to anakinra or placebo using a secure web-based randomisation system hosted by King's College London Clinical Trials Unit. The allocation sequence was generated using blocked randomisation stratified by centre. Throughout the trial participants, research nurses, treating physicians and independent outcome assessors were blind to treatment assignment. To avoid inadvertent unblinding (injection site reactions are common and can be severe with anakinra), independent assessors performed outcome assessment in silence, and with only the trial participant's hands and feet exposed.

Interventions

Participants allocated to the active group received anakinra (Kineret; SOBI, Stockholm, Sweden) 100 mg/0.67 ml daily through self-administered subcutaneous injection. The placebo group received identical matched syringes containing 0.67 ml of vehicle solution only. Participants self-administered a daily subcutaneous injection of the product for 8 weeks.

Adherence was measured using a daily text message reminder which required participants to confirm treatment had been taken. Participants were also instructed to complete an injection diary card and asked at each visit for a record of their daily usage.

Emollient therapy was permitted throughout the trial. Potent corticosteroid dispensed as 'rescue' therapy was recorded by the study team. Prohibited therapies included ultra potent topical corticosteroids, phototherapy and systematic therapies (see supplementary file 1, Table S2). Mild-moderate corticosteroid were permitted for plaque psoriasis at sites other than hands and feet. Mild topical corticosteroids and/or anti-histamines could be used to treat injection site reactions.

Outcomes

The primary outcome was the week 8 Palmoplantar Pustulosis Psoriasis Area and Severity Index (PPPASI) (20), adjusted for baseline PPPASI (i.e. change PPPASI at week 8). Investigator assessed secondary outcomes at 8 weeks included baseline adjusted: fresh pustule count on palms and soles, total pustule count on palms and soles, PPP-IGA, clear on PPP-IGA, disease flare (>50% deterioration in PPPASI). Time to response of PPP (≥75% reduction in fresh pustule count) and time to relapse (return to baseline of fresh pustule count) were assessed over 12 weeks. Participant assessed secondary outcomes at 8 weeks adjusted for baseline include the Dermatology Life Quality Index (DLQI), Palmoplantar Quality of Life instrument score (PPQoL), Patient's Global Assessment (PGA),

treatment acceptability evaluated using a five-point response scale as to whether the treatment was worthwhile (strongly disagree/disagree/neither agree nor disagree/agree/strongly agree) at week 12 and adherence. Safety outcomes included serious infection, neutropenia, clinically significant changes in other haematological parameters, renal or liver function. The incidence of adverse events (AE) was recorded and coded according to MedDRA. Outcomes assessed *post-hoc* were PPPASI-50, PPPASI-75 and the PPPASI pustule subscale at 8 weeks.

Statistical analysis

Sample size was calculated by reference to a standardised effect size as determined prior to the end of stage 1 when the primary outcome was unknown. A large effect size of 0.9 Standard Deviations (SDs) was selected to be the minimum important difference to detect as described in the protocol (17). To detect 0.9 SD with 90% power, 5% significance level and allowing for 15% withdrawal, a sample size of 64 (32 per arm) was required.

Analysis was conducted subgroup blind (i.e. group A versus group B) in accordance with the APRICOT SAP (21). The main analysis was based on the Intention-to-treat principle to estimate the effect of the 8 week treatment policy (see supplementary file 1 for description of estimands) (22). For the primary outcome, a linear mixed-effect model estimated the mean between-group difference in PPPASI at 8 weeks. Missing responses were assumed to be missing-at-random (MAR). Sensitivity analysis explored missing-not-at-random (MNAR) assumptions (23). Supplementary analysis, using methods described in supplementary file 1, explored the treatment effect (i) if rescue therapy was not available, (ii) if rescue and prohibited therapy was not available (iii) if all topical therapy was not available and (iv) the complier average casual effect (CACE) were calculated. The CACE analysis retains the initial randomisation and provides an estimate of the treatment effect for individuals who would be able to comply with ≥50%-90% of the prescribed daily injections by comparing the compliers in the anakinra group with the comparable group of compliers in the placebo group. Estimates are presented with 95% confidence and p-values. A p-value < 0.05 was interpreted as statistically significant for the primary outcome. Additional statistical methods are described in supplementary file 1.

Results

Participant flow

From October 2016 to January 2020, 374 patients were screened and 64 eligible participants were enrolled; 33 randomised to placebo and 31 to anakinra (Figure 1). Trial participants had a mean age of 50.8 years (SD=12.7), were predominantly female, white and current or ex-smokers. Baseline characteristics, including disease characteristics, were well balanced across treatment groups with a mean baseline PPPASI of 17.8 (SD 10.5) (Table 1).

Withdrawals, adherence and use of non-trial treatment

Over the eight-week treatment period, six (18%) placebo and five (16%) anakinra participants permanently withdrew from treatment. Retention in the study was high, 97% at week eight and 95% at week twelve (Figure 1). However, overall, adherence to treatment fell over time in both arms from a mean number of injections over week one of 6.1 (SD=1.9) for placebo and 6.7 (SD=0.6) for anakinra, to 4.8 (SD=3.1) and 5.3 (SD=2.7) respectively over week 8; 81% of the anakinra group took ≥50% of daily injections but only 48% took>90% of daily injections (see supplementary file 1, Table S6-S7).

There was no clinically significant difference between treatment arms with respect to use of rescue therapy or prohibited therapy (3 in each group) (see Supplementary file 1 Tables S8-S11). Other topical treatments used at sites other than areas affected by PPP were used more in the anakinra group (n=13, 42%) compared to placebo (n= 7, 21%) reflecting use for anakinra-related injection site reactions (see supplementary file Tables S12-S13).

Primary outcome

In intention-to-treat analysis the mean difference in PPPASI at week 8 was in favour of anakinra but did not demonstrate superiority, -1.65 95% CI [-4.77 to 1.47], p=0.300 (Figure 2 and Table 2). Sensitivity analyses under alternative missing data assumptions supported the primary result (supplementary file Table S14). The mean difference in PPPASI at week 12, for anakinra versus placebo was -2.42 95% CI [-5.97 to 1.13], p value = 0.182.

Impact of adherence and non-trial treatments on primary outcome

The estimated mean treatment difference using CACE analysis, for a complier defined as an individual taking ≥50% of daily injections (81% anakinra group) was -2.30 95% CI[-6.54 to 1.93], p=0.287. The CACE was similar for ≥60%-≥80% adherence (data not shown). For ≥90% adherence (48% anakinra group) the CACE was -3.80 95% CI[-10.76 to 3.16], p=0.285.

The treatment effect, in the absence of rescue and prohibited therapy was similar, -2.09, 95% CI [-8.47 to 4.29], p=0.518. Additional supplementary analyses similarly demonstrated no benefit (supplementary file 1 Tables S15 – S17).

Secondary outcomes

Anakinra did not demonstrate superiority versus placebo in any of the secondary outcomes including objective disease severity assessments, patient assessed disease severity (PGA) or impact (DLQI, PPQoL) (see Table 2, Figure 2). A total of 12 participants (41%) strongly agreed that the treatment was worthwhile in the anakinra group versus 4 (14%) in the placebo group (see Table S18).

Safety

In accordance with the known profile of anakinra, neutrophil counts, total white cell counts and platelets were lower in the anakinra group but did not reach clinical significance with mean difference in week 8 change -0.9 95%CI [-1.7 to 0.0], -1.0 95%CI [-2.0 to 0.0], and -25.3 95%CI [-39.6 to -11.1] respectively (supporting information, Table S19). Across treatment groups, no participants experienced a serious infection, neutropenia or other serious adverse event. A total of 84 non-serious AEs in 26 participants were reported in the placebo group versus 114 events in 29 anakinra participants. Figure 4 summarises AEs by MedDRA system organ class. There was a higher number of injection site reactions in the anakinra group (20 events, 19 participants) relative to placebo (1 event, 1 participant) explaining the higher number of MedDRA events termed 'general disorders and administration site conditions' in the anakinra group (Figure 3). A full listing of AEs is in supplementary file 1, Table S20.

Discussion

Summary of findings

This novel, two stage adaptive trial aimed to address the hypothesis that IL-1 blockade benefits PPP. We compared the IL1Ra anakinra with placebo in a double-blind randomised trial, and comprehensively evaluated efficacy and safety after eight weeks of treatment using objective investigator- assessed and patient-reported measures. We found no evidence for superiority with anakinra. There were more injection site reactions in the anakinra group, but otherwise the frequency of AEs was comparable to placebo.

Interpretation and context

Some of the findings in this trial raise the possibility that anakinra could have a treatment effect in PPP. Firstly, a greater proportion of participants in the anakinra group strongly agreed the treatment was worthwhile (41%) in comparison to the placebo group (14%). This perceived benefit could be due to an effect on disease severity or an impact that we did not identify despite comprehensivly assessing objective and patient reported measures. Alternatively, it could be that anakinra is exerting some systemic anti-inflammatory effect that improved well-being or reducing neuroinflammation and positively impacting upon fatigue (24) (although there was no difference in CRP between the two arms). Second, the CACE analysis estimate suggests that poor adherence may have contributed to lack of observed benefit. This is perhaps not unexpected given the daily injection schedule. Amongst all randomised participants the PPPASI treatment effect was -1.65, whereas those that had at least 90% of prescribed treatment (approximately half) had just over

double the effect size (-3.80); this corresponds to a 21% reduction in baseline PPPASI and is just outside the calculated minimally important clinical difference in PPPASI (estimated between 4 and 5.25, see supplementary file 1). Third, although not significant, the treatment effect in PPPASI was maintained and marginally increased at 12 weeks (four weeks post treatment cessation). Recent trials with other interventions in PPP are consistent with the notion that longer treatment duration may be necessary to deliver clinical benefit(25, 26). A phase II RCT of guselkumab that showed no significant change in PPPASI after eight weeks, reported benefit at week 16 that improved consistently through to week 52 (8) and a phase 3b RCT of secukinumab showed no difference in the primary PPPASI-75 outcome at 16 weeks but a trend towards benefit up to week 52 (9).

Based on these observations, and the shape of treatment response graph, it is thus conceivable that a larger trial of longer duration, higher anakinra dose and/or improved adherence may have identified a significant effect of anakinra. The treatment duration in our trial was limited to eight weeks to balance (uncertain) patient benefit and the importance of the research question, against known harms (patients receiving placebo have no opportunity for clinical benefit and all patients run risk of poorly controlled disease for the duration of the study, plus the burden of self-administered, daily subcutaneous injections commonly associated with injection site reactions, study visits and blood investigations). Early proof of concept data in GPP (n=4) and localised forms of pustular psoriasis (acrodermatitis of Halopeau as well as PPP, n=3) available at the time of the study design indicated rapid resolution of pustules within days (12-14, 27, 28). We therefore hypothesised that we would expect to see an effect on the pustular element of the disease by 8 weeks. We also sought input from our PPI group, and the collective opinion was that 8 weeks was the maximum reasonable duration of treatment given the daily injections and study design. We used the dose of anakinra approved for use in licensed indications to minimise safety concerns. Adherence was perhaps lower than expected given our pro-active text reminder strategy but is likely to be even lower in clinical practice. Thus overall, in the context of our robust primary endpoint and lack of observed benefit detected with any of the secondary outcomes, if anakinra is exerting some effect in PPP, we are confident that this is unlikely to be clinically relevant. We have answered the question for an 8-week treatment policy, but whether there is a benefit for those that adhere to the treatment for a longer duration remains unanswered.

Given the absence of benefit with anakinra, these findings also suggest that the pustular phenotype observed in PPP may not be driven by the same IL-1 family cytokines (IL-1α/β, IL-36α/β/γ) that are abnormally active in clinically related conditions. In fact, we have recently shown that the demographic and genetic features of PPP are entirely distinct from those underlying generalised pustular psoriasis (29). Likewise, Liang et al (30)have reported a very limited overlap between the genes that are over-expressed in acral and generalised forms of pustular psoriasis. Finally, clinical trials have shown that IL-36 blockade ameliorates the symptoms of generalised pustular psoriasis (31), but shows limited efficacy in PPP (32, 33). In this context, further studies of the genetic and immunological basis of PPP may be required to identify disease-specific therapeutic targets.

The PPP clinical phenotype does vary between individuals in terms of sites involved, extent, size and number of pustules, variation that is reflected to some degree in the wide range of fresh pustules and PPPASI subscores reported in our trial, and as also discussed during the development of the European consensus statement on pustular phenotypes (1). Better understanding of the molecular subtypes and roles of environmental triggers that presumably contribute to this variation may offer opportunity for more targeted, and therefore effective, interventions.

Strengths and Limitations

This is one of the largest RCTs in PPP, providing robust evidence, and our follow-up rates were high. We have established a large study population recallable for future trials, and provide important data on the natural history of PPP and change in disease severity over time using various disease severity scores .

To facilitate retention and reflect clinical practice, rescue therapy with potent corticosteroids was allowed. However, this had minimal impact on trial results, only increasing the size of the treatment effect in favour of anakinra by a small amount.

Improvements in outcomes were seen in both treatment groups over time, consistent with trends seen in other recent placebo-controlled trials of biologics in PPP (8, 9). It cannot be ruled out that there was some selection towards less severe or unstable patients entering the trial given the study was placebo controlled and the reuired washout period. Other limitations included the sample size which was calculated to detect a large effect size due to being calculated prior to the conformation of the primary outcome for stage 2. The small sample size meant that estimates for some of the uncommon secondary outcomes lacked precision. We selected anakinra as our preferred IL-1 blocker because uniquely, it blocks both IL-1α and ß, it has a rapid onset of action and established safety profile (>70,000 patient-years exposure), there was early evidence of benefit in pustular psoriasis and the lowest drug acquisition costs. However, the requirement for daily injections along with the injection site reactions may have negatively influenced compliance and use of IL-1 blockers such as rilanocept or canakinumab, which require less frequent administration (weekly and 8 weekly respectively) may have been associated with better compliance.

Conclusion

An eight-week treatment policy of anakinra was not superior to placebo meaning that IL-1 blockade, using anakinra, is unlikely to deliver important clinical utility. These findings also suggest that the IL-1 family cytokines are not the major disease mediators in PPP. This condition remains an area of high unmet need and further research is required to identify new drug targets.

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Contributor statement

CHS is the chief investigator, obtained grant funding, conceived of and designed the study and drafted the manuscript. SC designed the statistical analysis plan, carried out the statistical analyses, and wrote the original draft of the manuscript. VC obtained grant funding, designed the study, designed the statistical analysis plan and drafted the manuscript. RWil, APR, PP were trial managers responsible for the acquisition of data. HM, JNWNB, DB, CEMG, NJR, RBW, HL, and FC contributed to the design and obtained grant funding. FC was responsible for design, delivery and interpretation with mechanistic studies. AEP, AA, SA, JA, GB, AC, GD, ADF, AF, SAG, JRI, SK, EL, JAL, AEM, AM, RP, AJR, AS, ARS, CS, NJR, CHS, RWach, RTW, RBW and AW were Principle site investigators or PIC site investigators and contributed to recruitment and data acquisition. All authors provided critical review of the manuscript and final approval of the manuscript.

Data statement

The Data that support the findings of this study are available from the corresponding author, CHS, upon reasonable request.

Supporting Information

Supplementary File 1.doc

Protocol.pdf

CONSORT Checklist.doc

Figure Legends

Figure 1: CONSORT flow chart

Figure 2: a) Palmoplantar Pustulosis Psoriasis Area and Severity Index (PPPASI), b) fresh pustule count, c) total pustule count and d) Dermatology Life Quality Index (DLQI) over 12 week follow-up period. Error bars represent 95% Confidence Intervals.

Figure 3: Adverse events by MedDRA system organ class

Tables

Table 1 – Baseline characteristics of participants in APRICOT by treatment group

Baseline demographic		Placebo		Anakinra		Total	
Age	Mean, SD	51.7	13.6	49.9	11.9	50.8	12.7
Sex (n, %)	Male	6	18%	4	13%	10	16%
	Female	27	82%	27	87%	54	84%
Ethnicity (n, %)	White	31	94%	28	90%	59	92%
	Asian/Asian British	1	3%	1	3%	2	3%
	Black/Black British	0	0%	1	3%	1	2%
	Chinese/Japanese/ Korean/ Indochinese	0	0%	1	3%	1	2%
	Other	1	3%	0	0%	1	2%
Smoker (n, %)	Current smoker	19	58%	16	52%	35	55%
	Ex-smoker	9	27%	12	39%	21	33%
	Non-smoker	5	15%	3	10%	8	13%
PPPASI	Mean, SD	18.0†	10.4	17.5	10.8	17.8	10.5
	Median, IQR	15.9	(10.4, 21.3)	15.4	(11.7, 20.7)	15.6	(10.6, 21.0)
Fresh pustule count (palms and soles)	Mean, SD	36.1	33.1	39.8†	46.3	37.9	39.6
	Median, IQR	28.0	(18.0, 45.0)	25.5	(11.0, 58.0)	27.0	(15.0, 49.0)
Fresh pustule count (soles)	Mean, SD	25.9	23.4	29.6†	43.2	27.7	34.1
	Median, IQR	23.0	(4.0, 36.0)	15.0	(5.0, 37.0)	19.0	(4.0, 37.0)
Fresh pustule count (palms)	Mean, SD	10.2	19.2	10.2†	16.5	10.2	17.8
	Median, IQR	2.0	(0.0, 13.0)	2.5	(0.0, 13.0)	2.0	(0.0, 13.0)
Total pustule count (palms and soles)	Mean, SD	116.9	96.4	154.3†	198.7	134.7	153.7
	Median, IQR	97.0	(45.0, 169.0)	89.0	(45.0, 157.0)	95.0	(45.0, 169.0)
PPP-IGA[1]	Moderate	16	48%	16	52%	32	50%
	Severe	17	52%	15	48%	32	50%
Participant global assessment	Almost clear	0	0%	2	6%	2	3%
	Mild	3	9%	3	10%	6	9%
	Moderate	14	42%	14	45%	28	44%
	Severe	13	39%	7	23%	20	31%
	Very severe	3	9%	5	16%	8	13%
DLQI	Mean, SD	13.9	7.2	15.1	7.0	14.5	7.1
PASI‡	Mean, SD	2.1	5.4	1.1	1.6	1.6	4.1
	Median, IQR	0.0	(0.0, 1.8)	0.2	(0.0, 1.6)	0.0	(0.0, 1.6)
PPQoL	Mean, SD	46.4	13.8	45.5	14.8	46.0	14.2
EQ5D utility score	Mean, SD	0.37	0.43	0.47	0.35	0.42	0.40
	Median, IQR	0.62	(0.09, 0.73)	0.62	(0.16, 0.73)	0.62	(0.09, 0.73)
EQ5D VAS	Mean, SD	57.7	27.7	68.4§	18.3	62.5	24.4
	Median, IQR	65.0	(45.0, 80.0)	75.0	(55.0, 80.0)	70.0	(50.0, 80.0)

Palmoplantar pustulosis Psoriasis Area and Severity Index (PPPASI). Palmoplantar pustulosis investigators global assessment (PPP-IGA). Dermatology Life Quality Index (DLQI). Psoriasis Area and Severity Index (PPPASI). Palmoplantar Quality of Life instrument score (PPQoL). †One participant was missing this outcome in the indicated treatment group. ‡PASI measurements were available for 19 in the placebo group and 16 in the anakinra group. §Four participants in the anakinra group were missing baseline EQ5D VAS. [1]Worse PPP-IGA rating from two independent assessors.

Table 2 – Primary and secondary APRICOT outcomes

Outcome	Placebo		Anakinra		Unadjusted mean difference: Anakinra-Placebo [95% CI]	Adjusted mean difference: Anakinra-Placebo [95% CI]	P value
	Mean (SD)	N	Mean (SD)	N			
Primary outcome							
PPPASI (wk 8)†	15.4 (10.1)	31	13.9 (7.4)	29	-1.4 [-6.0 to 3.2]	-1.65 [-4.77 to 1.47]	0.300
Secondary outcomes							
Fresh pustule count (wk 8) palm + sole	36.9 (79.5)	31	42.4 (65.1)	28	5.5 [-32.6 to 43.6]	2.94 [-26.44 to 32.33]	0.844
Fresh pustule count (wk 8) palm	7.0 (14.7)	31	10.8 (19.2)	29	3.9 [-4.9 to 12.7]	4.07 [-5.78 to 13.92]	0.418
Fresh pustule count (wk 8) sole	29.9 (69.1)	31	31.4 (61.2)	28	1.5 [-32.7 to 35.7]	-1.42 [-27.33 to 24.48]	0.914
Total Pustule count (wk 8)	114.2 (171.8)	31	111.4 (129.3)	28	-2.8 [-82.7 to 77.2]	-30.08 [-83.20 to 23.05]	0.267
PASI	0.8 (1.7)	16	0.9 (1.1)	15	0.0 [-1.0 to 1.1]	-0.41 [-0.96 to 0.15]	0.151
PPQoL	40.2 (16.0)	31	41.4 (13.9)	31	1.2 [-6.4 to 8.8]	1.27[-3.04 to 5.57]	0.564
DLQI	10.5 (6.9)	31	12.5 (8.3)	31	2.0 [-1.9 to 5.9]	0.52 [-2.04 to 3.07]	0.692
EQ5D-3L	0.6 (0.4)	31	0.5 (0.4)	31	0.0 [-0.2 to 0.2]	-0.09 [-0.23 to 0.06]	0.227
	n (%)	N	n (%)	N	Unadjusted difference in proportion: Anakinra-Placebo [95% CI]	Adjusted OR [95% CI]	P value
PPPASI-50‡ (wk 8)	5 (16%)	31	6 (21%)	29	4.6% [-15.1% to 24.2%]	1.68 [0.35 to 8.19]	0.520
PPPASI-75‡ (wk 8)	1 (3%)	31	0 (0)	29	-3.2% [-9.4% to 3.0%]	*unestimable*	
PPPASI pustule subscale palm (wk 8)		31		29			
None	14 (45%)		11 (37%)			2.51 (0.56, 11.28)	0.231
Slight	10 (32%)		9 (30%)				
Moderate	5 (16%)		8 (27%)				
Severe	2 (6%)		2 (7%)				
Very severe	0 (0%)		0 (0%)				
PPPASI pustule subscale soles (wk 8)		31		29			
None	3 (10%)		2 (7%)			1.63 (0.49, 5.46)	0.426
Slight	6 (195)		8 (28%)				
Moderate	11 (35%)		8 (28%)				
Severe	9 (29%)		9 (31%)				
Very severe	2 (6%)		2 (7%)				
PPP-IGA (wk 8)		28		30		0.54 [0.13 to 2.19]	0.384
Almost clear	2 (7%)		1 (3%)				
Mild	4 (14%)		6 (20%)				
Moderate	12 (43%)		17 (57%)				
Severe	10 (36%)		6 (20%)				
Disease flare (>50% deterioration in PPPASI)	4 (13%)	31	2 (7%)	29	-6.0% [-20.98% to 8.97%]	0.55 [0.08 to 3.71]	0.542
PGA (wk 8)		30		31		1.39 [0.41 to 4.70]	0.597
Clear	1 (3%)		0 (0%)				
Nearly clear	3 (10%)		3 (10%)				
Mild	4 (13%)		5 (16%)				
Moderate	11 (37%)		11 (35%)				
Severe	10 (33%)		10 (32%)				
Very severe	1 (3%)		2 (6%)				
						Adjusted HR [95% CI]	P value
Time to response (75% reduction fresh pustule count)	15 (48%)	31	13 (43%)	30		0.58 [0.22 to 1.50]	0.263
Time to relapse (return to baseline fresh pustule count)	19 (61%)	31	20 (67%)	30		0.94 [0.50 to 1.7	0.853

Palmoplantar pustulosis Psoriasis Area and Severity Index (PPPASI). Palmoplantar pustulosis investigators global assessment (PPP-IGA). Dermatology Life Quality Index (DLQI). Psoriasis Area and Severity Index (PPPASI). Palmoplantar Quality of Life instrument score (PPQoL). Patients Global Assessment (PGA). † Complier Average Causal Effect (CACE) for PPPASI: ≥50% Injections -3.37 [-6.98 to 0.23] p=0.066, and ≥90% Injections -5.53 [-11.39 to 0.32], p=0.066. ‡Post-hoc outcome. In both groups, no participants experienced serious infection of neutropenia.

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