

Efficacy of ISA247 in plaque psoriasis: a randomised, multicentre, double-blind, placebo-controlled phase III study

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Summary

Background The use of systemic calcineurin inhibitors for the treatment of patients with psoriasis is limited by toxicity, particularly nephrotoxicity. ISA247, a novel inhibitor, was effective and well tolerated in a phase II study of patients with plaque psoriasis. Therefore its efficacy was assessed in this phase III study.

Methods 451 patients aged 18–65 years with plaque psoriasis involving at least 10% of the body surface area were randomly assigned in equal proportions to receive placebo or ISA247 at 0.2 mg/kg, 0.3 mg/kg, or 0.4 mg/kg orally twice a day in dermatology clinics. The primary endpoint was a 75% reduction in the psoriasis area and severity index (PASI 75) score at week 12. Treatment allocation was concealed from patient and physicians doing the assessments by use of sealed envelopes. The method of analysis was by modified intention to treat. The trial is registered at ClinicalTrials.gov, number NCT00244842.

Findings 107, 113, and 116 patients were assigned to the ISA247 0.2 mg/kg, 0.3 mg/kg, and 0.4 mg/kg groups, respectively, and 115 to the placebo group. At week 12, PASI 75 scores were achieved in the ISA247 0.2 mg/kg, 0.3 mg/kg, and 0.4 mg/kg groups by 14 (16%; 95% CI 9–24) of 105, 26 (25%; 17–24) of 111, and 44 (47%; 27–57) of 113 patients, respectively, and in the placebo group by 4 (4%; 0–8) of 113 patients. Efficacy was maintained during 24 weeks. Mild to moderate glomerular filtration rate reductions were noted in seven patients in the ISA247 0.4 mg/kg group and in one in the ISA247 0.3 mg/kg group. ISA247 blood concentrations showed a strong correlation with mean percentage reduction in PASI.

Interpretation ISA247 was safe and effective in the treatment of patients with moderate to severe psoriasis during 24 weeks, with the highest dose providing the best efficacy. The strong correlation between ISA247 concentrations and efficacy might allow for accurate dosing of patients compared with existing calcineurin inhibitors.

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Introduction

One of the most effective treatments for psoriasis is the calcineurin inhibitor ciclosporin.^{1–3} However, the side-effect profile of ciclosporin, in particular nephrotoxicity, restricts its long-term use.^{4–7} Studies have shown that new biological treatments, in particular infliximab,^{8,9} are safe and effective for treatment of plaque psoriasis. However, with their high cost, inconvenience of administration, and few data on long-term safety and effectiveness, their widespread use might not be possible.¹⁰

ISA247 (Isotechnika, Edmonton, AB, Canada) is a novel calcineurin inhibitor intended for the treatment of autoimmune diseases, such as psoriasis and uveitis, and prevention of organ transplant rejection. It differs from ciclosporin by a chemical modification of the functional group at the aminoacid-1 residue (figure 1). This modification has improved the molecule in two ways. First, ISA247 binds more tightly to calcineurin than does ciclosporin, leading to a more complete inhibition of calcineurin. Second, the metabolism of ISA247 has been shifted away from aminoacid-1, which is the major site of metabolism for ciclosporin. This shift leads to a faster elimination of metabolites and a lower drug and metabolite load after the administration of ISA247 than with ciclosporin. In turn, fewer

metabolites lead to improved pharmacokinetic and pharmacodynamic predictability.

In animal models, ISA247 was more potent and had a more favourable side-effect profile than ciclosporin, particularly with regards to renal toxicity.^{11–13} Consistent with these preclinical data, results of a phase II study of patients with stable plaque psoriasis showed that ISA247 was effective and well tolerated, without much change in blood pressure or concentrations of lipids or triglycerides.¹⁴ Therefore the efficacy of a commercial preparation of ISA247 was assessed in this phase III clinical trial.

Methods

Patients

Male and female patients aged 18–65 years with stable chronic plaque psoriasis involving at least 10% of the body surface area (BSA) for at least 6 months before screening were enrolled. These patients had a psoriasis area and severity index (PASI) score of 10 or more, a glomerular filtration rate (GFR) greater than 60 mL/min, and less than 30% change in the GFR between screening and randomisation. Use of nephrotoxic medications or medications known to interact with ciclosporin or ISA247 was not allowed. Patients with erythrodermic, guttate, or pustular psoriasis, or other dermatoses that would

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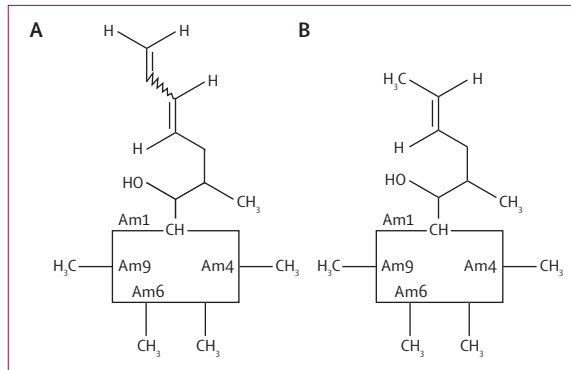


Figure 1: Comparison of the structures of ISA247 (A) and ciclosporin (B)

interfere with the assessment of psoriasis were excluded. Additionally, patients were excluded if they had malignant disease (present or history); past or present serious bacterial, viral, or fungal infections; history of tuberculosis; were positive for HIV, or hepatitis B or hepatitis C virus; had uncontrolled hypertension (systolic blood pressure ≥ 150 mm Hg or diastolic blood pressure ≥ 90 mm Hg); alanine transaminase, aspartate transaminase, or gamma-glutamyl transferase concentrations that were at least three times the upper limit of normal; a white blood cell count of less than or equal to 2.8×10^9 per L; and concentrations of triglycerides at least three times the upper limit of normal. Women who were pregnant or nursing were also excluded.

Patients were screened 28 days before the start of the study to ensure washout of prohibited medications. Non-medicated, non-lanolin-based emollients were not applied to the target site at any time or to any psoriatic area within 24 h before any study visit.

An institutional review board or ethics committee approved the study protocol at every site. Written informed consent was obtained from patients before the start of any study related procedure.

Procedures

In a double-blind, placebo-controlled, multicentre, four arm, phase III study, patients with stable plaque psoriasis who qualified at the screening and baseline visits were randomly assigned in equal proportions to treatment with ISA247 at 0.2 mg/kg, 0.3 mg/kg, or 0.4 mg/kg orally twice a day or placebo twice a day for 12 weeks in dermatology clinics. At the end of this period, the primary endpoint was assessed and all patients in the ISA247 groups remained in their treatment groups for a further 12 weeks. Those in the placebo group received ISA247 0.3 mg/kg twice a day for the second 12 weeks. Randomisation was done with computer-generated pseudorandom number sequences that were generated by PharmaNet. Physicians doing the assessments and patients were unaware of the treatment arm through the use of sealed envelopes. The placebo and active drug were identical in appearance.

The primary endpoint was an improvement in PASI score¹⁵ of 75% (PASI 75) at 12 weeks. The PASI 75 score was calculated with the area-weighted sum of the subtotal scores of erythema, infiltration, and desquamation. The weighted sum was multiplied by the appropriate body area of psoriatic involvement (head [weight of body area relative to total body surface area, 0.1], trunk [0.3], upper extremities [0.2], and lower extremities [0.4]). Secondary endpoints included a two-point reduction in the static global assessment (SGA-2) score from baseline to the end of treatment; the proportion of patients with a 70% reduction in BSA (BSA 70) score; target-site lesion assessment; proportion of individuals with a 50% improvement in PASI (PASI 50) score; and proportion of patients with a 90% improvement in PASI (PASI 90) score.

The safety analysis was done for all patients who had received at least one dose of the study drug. Standard clinical and laboratory tests were done every 4 weeks. Renal function was assessed with calculated GFR¹⁶ to

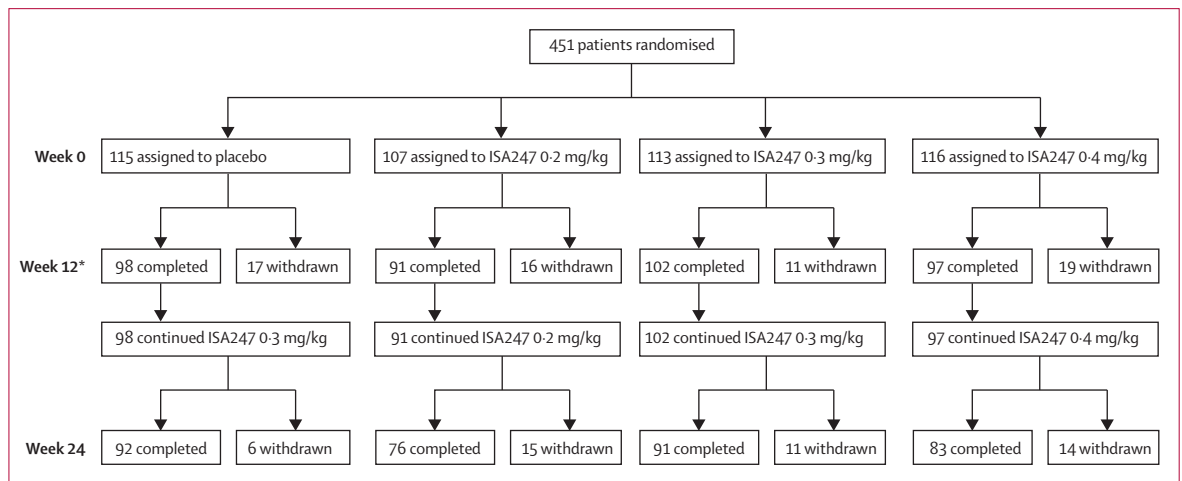


Figure 2: Trial profile

*Primary endpoint assessed.

identify any potential nephrotoxicity. If a patient had a 30% or more (defined as mild to moderate) reduction in baseline GFR, a second GFR was obtained. If the second GFR was reduced by at least 30% compared with baseline, the patient was withdrawn from the trial.

To assess the concentration-effect association, whole blood concentration of the drug (C_0) data were correlated with PASI scores by use of a simple maximum drug effect (E_{max}) model because one molecule of ISA247 binds with one molecule of cyclophilin:

$$E = \frac{E_{max} C}{EC_{50} + C}$$

where C is the drug concentration and EC_{50} is the effect at 50% of the E_{max} . The percentage change from baseline PASI was used to normalise the differences from baseline. Goodness of fit was assessed by visual inspection of the residuals, SE, 95% CIs, and correlation between the recorded data and fitted line.

Statistical analysis

The study was designed to enrol up to 480 patients with stable plaque psoriasis from about 32 centres in Canada and a 10% dropout rate was assumed. The sample size was estimated with the clinical results from previous studies of oral ciclosporin at doses of 2.5 mg/kg per day and 5.0 mg/kg per day¹⁷ and from the phase II psoriasis study of ISA247.¹⁴ An assumption was made that ISA247 at 0.2 mg/kg orally twice a day would result in a PASI 75 response rate of 13% and that the placebo group would have a response rate of 1%.

The modified intention-to-treat population was defined as randomly assigned patients who received at least one dose of study drug, and for whom one baseline measurement and at least one postbaseline efficacy measurement were available. The overall similarity of the treatment group success rates at 12 weeks was assessed with the Cochran-Mantel-Haenszel general association test, stratified by pooled centre. Additionally, 95% CIs were calculated. Continuous data were summarised as the mean (SD or SE) or median (range), and the number of patients. Categorical data were summarised by the frequency and percentage of patients in every treatment group.

All statistical analyses were done with the SAS statistical software package (version 8.2). Statistical tests were all two-sided ($\alpha \leq 0.05$).

The trial is registered at ClinicalTrials.gov, number NCT00244842.

Role of the funding source

The sponsor of the study was responsible for data collection. PharmaNet did the data analysis. All authors contributed to the data interpretation and writing of this report. The corresponding author had full access to the data and had final responsibility for the decision to submit for publication.

Results

Between November, 2004, and September, 2005, 451 patients were enrolled in the study across 32 centres in Canada. Figure 2 shows the trial profile. Table 1 summarises the patient demographics. A total of 109 (24%) patients discontinued the study before completion (table 2). The most frequent reasons for this were abnormal laboratory results (3%), lost to follow-up (3%), adverse events (3%), and other reasons (10%), including withdrawal for absence of efficacy.

At week 12, significantly higher proportions of patients in the ISA247 0.3 mg/kg ($p=0.0085$) and 0.4 mg/kg twice a day ($p<0.0001$) groups achieved PASI 75 (table 3) than in the placebo group. Improvement was dose related and evident at 4 weeks for patients given ISA247 at 0.4 mg/kg twice a day and at 8 weeks for patients given ISA247 at 0.3 mg/kg twice a day. The Cochran-Mantel-Haenszel test showed a significant ($p<0.0001$) association between ISA247 treatment and PASI 75 scores at 12 weeks.

| | Placebo (n=115) | ISA247 0.2 mg/kg* (n=107) | ISA247 0.3 mg/kg* (n=113) | ISA247 0.4 mg/kg* (n=116) |
|------------------------------|--------------------|------------------------------|------------------------------|------------------------------|
| Age (years) | 41 (19–63) | 42 (18–62) | 40 (18–65) | 41 (18–65) |
| Men | 70 (61%) | 63 (59%) | 88 (78%) | 81 (70%) |
| Women | 45 (39%) | 44 (41%) | 25 (22%) | 35 (30%) |
| Weight (kg) | 89 (50–138) | 89 (49–138) | 89 (51–139) | 88 (49–140) |
| Previous phototherapy† | 63 (56%) | 60 (57%) | 56 (52%) | 52 (45%) |
| Previous systemic treatment‡ | 60 (54%) | 52 (50%) | 59 (55%) | 54 (47%) |

Data are median (range) or number (%). *Twice a day. †Percentages based on non-missing values.

Table 1: Patient demographics

| | Placebo (n=115) | ISA247 0.2 mg/kg* (n=107) | ISA247 0.3 mg/kg* (n=113) | ISA247 0.4 mg/kg* (n=116) |
|--|--------------------|------------------------------|------------------------------|------------------------------|
| Total discontinued† | 23 (20%) | 31 (29%) | 22 (19%) | 33 (28%) |
| Reason for discontinuation | | | | |
| Abnormality in laboratory tests | 0 | 0 | 2 (2%) | 11 (9%) |
| Adverse event | 0 | 8 (7%) | 1 (<1%) | 3 (3%) |
| Inappropriate enrolment | 0 | 0 | 0 | 2 (2%) |
| Lost to follow-up | 3 (3%) | 5 (5%) | 3 (3%) | 2 (2%) |
| Need for prohibited medication | 3 (3%) | 1 (<1%) | 2 (2%) | 1 (<1%) |
| Non-compliance | 0 | 2 (2%) | 2 (2%) | 3 (3%) |
| Other‡ | 14 (12%) | 13 (12%) | 11 (10%) | 9 (8%) |
| Pregnancy | 1 (<1%) | 1 (<1%) | 0 | 0 |
| Request for termination by the sponsor or regulatory authorities | 0 | 0 | 0 | 1 (<1%) |
| Serious adverse event | 2 (2%) | 1 (<1%) | 1 (<1%) | 1 (<1%) |

Data are number (%). *Twice daily. †Includes all patients who were enrolled at the start but not present at completion of study. ‡Refers to non-specified prospective reasons.

Table 2: Reasons for patient discontinuation from studies

| | Placebo* (n=113) | ISA247 0.2 mg/kg† (n=105) | ISA247 0.3 mg/kg† (n=111) | ISA247 0.4 mg/kg† (n=113) | p value | | |
|----------|------------------|---------------------------|---------------------------|---------------------------|---------|--------|---------|
| | | | | | p0.2‡ | p0.3‡ | p0.4‡ |
| Week 2§ | 0 | 0 | 0 | 0 | NC | NC | NC |
| Week 4§ | 0 | 3 (3%; 0-7) | 3 (3%; 0-6) | 6 (5%; 1-10) | NS | NS | 0.0069 |
| Week 8§ | 1 (1%; 0-3) | 13 (14%; 7-21) | 16 (15%; 8-22) | 35 (34%; 25-43) | 0.0094 | 0.0322 | <0.0001 |
| Week 12§ | 4 (4%; 0-8) | 14 (16%; 9-24) | 26 (25%; 17-24) | 44 (47%; 27-57) | 0.1054 | 0.0085 | <0.0001 |
| Week 24§ | 35 (32%; 24-41) | 16 (16%; 9-24) | 28 (26%; 18-35) | 54 (49%; 40-58) | NC | NC | NC |

Data are number (%; 95% CI). NC=could not be calculated. NS=not significant. *Placebo patients changed to ISA247 0.3 mg/kg twice a day at 12 weeks. †Twice a day. ‡Dunnett's adjusted p values for comparison of each treatment with placebo. §Percentages based on non-missing values.

Table 3: Number of patients in the modified intention-to-treat population with 75% reduction in psoriasis area and severity index (PASI 75) scores at different timepoints

At 12 weeks, treatment with ISA247 at 0.3 mg/kg twice a day and 0.4 mg/kg twice a day resulted in significantly ($p=0.0016$ and $p<0.0001$, respectively) greater success rates with respect to the SGA-2 scores than in the placebo group; the Cochran-Mantel-Haenszel test showed a significant ($p<0.0001$) association between ISA247 treatment and SGA-2 scores. The ISA247 0.3 mg/kg twice a day and ISA247 0.4 mg/kg twice a day groups also showed greater success rates than placebo after 12 weeks of treatment with other secondary endpoints (data not shown), including BSA 70, PASI 50, PASI 90, and most of the quality-of-life scores, including target-site lesion assessment scores (specifically erythema, plaque elevation, scaling, and pruritus, and general improvement), dermatology life quality index scores (specifically itchiness, embarrassment, clothing, social or leisure activities, work or study, and treatment), and psoriasis disability index scores (specifically daily activities, work or school, relationships, and leisure activities).

From 12–24 weeks, patients in the ISA247 0.3 mg/kg twice a day and 0.4 mg/kg twice a day groups maintained their PASI 75, SGA-2, PASI 50, and BSA 70 scores, and most of the target-site lesion assessment scores. Patients in the ISA247 0.4 mg/kg group also maintained their PASI 90 scores from 12 to 24 weeks.

Patients in the placebo group who were given ISA247 0.3 mg/kg twice a day at the end of 12 weeks had a clinically significant improvement in their efficacy scores (PASI 75, SGA-2, and BSA-70) through to 24 weeks. This improvement was similar to or better than that seen in the ISA247 0.3 mg/kg group.

Adverse events were reported by 368 (82%) of 451 patients. About half of ISA247-treated patients (58 [54%] of 107 patients in the 0.2 mg/kg group, 50 [44%] of 113 in the 0.3 mg/kg group, and 64 [55%] of 116 in the 0.4 mg/kg group) had adverse events that were thought to be treatment-related, compared with 45 (39%) of 115 placebo-treated patients. Headache, nasopharyngitis, and upper-respiratory-tract infections were the most frequently reported adverse events (table 4). In all treatment groups, most of the adverse events were mild or moderate in intensity. Overall, 30 patients discontinued because of adverse events—8% in the ISA247 0.2 mg/kg group, 4% in the ISA247 0.3 mg/kg group, 13% in the ISA247 0.4 mg/kg group, and 2% in the placebo group. Of these, 75% occurred at or before 12 weeks (data not shown).

Two patients died during the clinical trial—one as a result of bile duct cancer (remotely related to treatment), which was diagnosed during the study after several years of treatment with other systemic agents, and another as a result of a motor vehicle accident (unrelated).

Mild to moderate GFR reductions were seen in eight (2%) patients during the study, two of which had marginal GFRs at the start of the study. Reductions in GFR in patients in the ISA247 0.3 mg/kg ($n=1$) and ISA247 0.4 mg/kg groups (5) occurred during the first 12 weeks; reductions in the other patients (2) in the ISA247 0.4 mg/kg group occurred after 12 weeks. Although most reductions were transient and resolved by the end of the study, reduced GFR—as defined by the protocol—was

| | Placebo (n=115) | ISA247 0.2 mg/kg* (n=107) | ISA247 0.3 mg/kg* (n=113) | ISA247 0.4 mg/kg* (n=116) |
|------------------------------------|-----------------|---------------------------|---------------------------|---------------------------|
| Any adverse event | 91 (79%) | 91 (85%) | 90 (80%) | 96 (83%) |
| Diarrhoea | 3 (3%) | 2 (2%) | 4 (4%) | 12 (10%) |
| Vomiting | 4 (3%) | 3 (3%) | 2 (2%) | 7 (6%) |
| Increased blood pressure | 5 (4%) | 4 (4%) | 5 (4%) | 7 (6%) |
| Increased diastolic blood pressure | 0 | 1 (<1%) | 1 (<1%) | 3 (3%) |
| Increased systolic blood pressure | 0 | 0 | 0 | 1 (<1%) |
| Reduced GFR | 0 | 0 | 1 (<1%) | 7 (6%) |
| Arthralgia | 6 (5%) | 2 (2%) | 3 (3%) | 11 (10%) |
| Back pain | 2 (2%) | 5 (5%) | 6 (5%) | 7 (6%) |
| Headache | 12 (10%) | 18 (17%) | 12 (11%) | 26 (22%) |
| Nasopharyngitis | 27 (23%) | 27 (25%) | 34 (30%) | 26 (22%) |
| Upper-respiratory-tract infections | 9 (8%) | 12 (11%) | 13 (12%) | 12 (10%) |
| Hypertension | 7 (6%) | 8 (7%) | 8 (7%) | 12 (10%) |

Data are number (%). If a patient had more than one adverse event for a particular adverse event, the patient was counted once for that event. GFR=glomerular filtration rate. *Twice a day.

Table 4: Summary of all adverse events occurring in 5% or more of the patients in each group

the most frequently reported adverse event that resulted in discontinuation (table 4).

No significant changes in mean systolic or diastolic blood pressures were noted in any of the groups. Overall, 8% of patients developed hypertension (table 4). No differences in the mean lipid concentrations were noted between the ISA247-treated and placebo-treated patients.

Individual drug concentration timepoints were compared directly with all PASI scores and 91% of the reduction in PASI scores could be attributed to the trough concentrations of ISA247 taken at any timepoint in this study. Reduction in PASI scores and ISA247 whole blood concentration correlated at an r value of 0.9473 (figure 3).

Discussion

At 12 weeks, ISA247 treatment improved plaque psoriasis in patients as shown by the achievement of the primary efficacy endpoint. Improvement in efficacy scores was maintained during weeks 12–24. In particular, treatment with ISA247 at doses 0.3 mg/kg and 0.4 mg/kg twice a day resulted in a greater success rate than treatment with placebo or ISA247 0.2 mg/kg; the highest dose provided the best efficacy.

No changes in renal function were noted in any of the groups at 12 or 24 weeks compared with baseline; no increases in serum creatinine concentration or decreases in the GFRs from 12–24 weeks were noted. Overall, only eight of 451 patients (one in the ISA247 0.3 mg/kg group and seven in the ISA247 0.4 mg/kg group) had a mild to moderate reduction in GFR at 24 weeks compared with baseline. This low rate contrasts with the 10–27% of patients who developed 30% or more reductions in renal function when given ciclosporin in a previous study.¹¹ Similarly, in the PISCES (Psoriasis Intermittent Short Courses Efficacy of Sandimmun neoral) study,^{2,3} in which patients were given intermittent 12 week courses of titrated ciclosporin, renal function (measured by serum creatinine concentrations) decreased in 17% of patients. Furthermore, functional renal changes seen with ciclosporin treatment have been associated with histopathological changes in the kidney; renal biopsy samples from patients given ciclosporin 1.8–6 mg/kg per day for 6–18 months showed increased interstitial fibrosis that was inversely related to creatinine clearance.⁷

No significant changes in mean systolic or diastolic blood pressure were noted in any of the ISA247 or placebo groups. Importantly, less than 8% of patients developed hypertension, which in this study was defined as a systolic blood pressure of at least 150 mm Hg or diastolic blood pressure of at least 90 mm Hg. This low rate contrasts with 18 (24%) of 76 ciclosporin-treated patients who developed hypertension (systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 95 mm Hg) during the 2-year follow-up in another study,³ and with 45 (12%) of 365 ciclosporin-treated patients in the PISCES study.² The difference in hypertension rates might be due

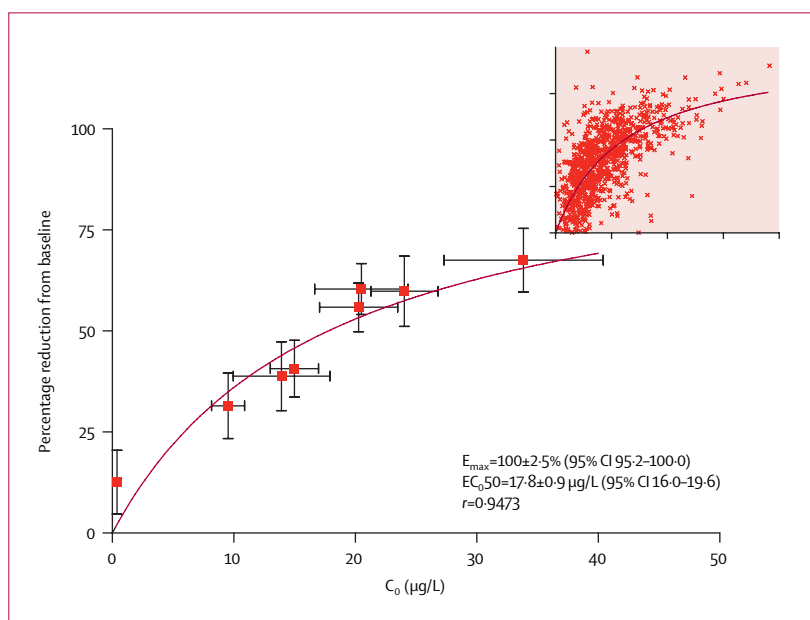


Figure 3: ISA247 whole blood concentration (C_0) correlation with psoriasis area and severity index (PASI) reduction

Raw data (inset) is provided to indicate the fit of the data points, as represented on the main graph. E_{max} =maximum drug effect. EC_{50} =effect at 50% of the E_{max} . r =correlation coefficient.

to length of exposure to the study drug; a longer study of ISA247 is planned to assess this.

Hyperlipidaemia has also been a major concern with the use of calcineurin inhibitors in psoriasis. In this study, no difference in mean lipid concentrations were noted between the ISA247-treated and placebo-treated patients. By contrast, in a meta-analysis of ciclosporin treatment for psoriasis, 2% and 18% of patients given 1.25 mg/kg and 5.0 mg/kg, respectively, had a 10% increase in total cholesterol concentrations. Additionally, 4% and 26% of patients given ciclosporin at 1.25 mg/kg and 5.0 mg/kg, respectively, had a 30% increase in concentrations of triglycerides.¹⁸

As a serine-threonine phosphatase, calcineurin shows classic enzyme pharmacokinetics. Drug-receptor occupancy ultimately shows a sigmoid-shaped association that can be characterised by the Hill equation. The data presented in this study show that a strong correlation exists between ISA247 trough blood concentrations and efficacy as measured by reduction in all PASI scores compared with baseline ($r=0.9473$). The importance of this correlation, which has not been shown with other systemic calcineurin inhibitors, is that it has the potential for easy titration of dose, improved predictability of response, and increased control over toxic effects. Association between ISA247 blood concentrations and efficacy might be related to the chemical modification made to ciclosporin. This modification seems to shift metabolism away from aminoacid-1, resulting in an altered metabolic profile and a reduced metabolite load when compared with ciclosporin.

ISA247 treatment for 24 weeks was efficacious and safe in patients with chronic plaque psoriasis; and pharmacokinetic data show a strong correlation between response and drug concentrations, raising the potential for precise titration of dosing in clinical practice.

Therefore ISA247 could provide effective immunosuppression without many of the dose-limiting side-effects associated with other calcineurin inhibitors. An improved safety profile, coupled with increased potency, could be of benefit to patients with plaque psoriasis.

Contributors

This study was designed by the psoriasis advisory board (KP, RB, CWL, NHS, RBH, and WPM). KP, RB, LR, NW, CWL, GS, and NHS were principal investigators in this study. The report was written by PharmaNet. The initial drafts of the report were written by Isotechnika staff with revisions written by Isotechnika and KP.

Conflict of interest statement

KP and WPM are scientific advisers to Isotechnika. RBH is an employee of Isotechnika. The other authors declare that they have no conflict of interest.

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