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Letter to the Editor

Oral supplementation with bovine whey-derived Ig-rich fraction and lactoferrin improves SCORAD and DLQI in atopic dermatitis



To the Editor

Atopic dermatitis (AD) is a chronic but relapsing skin condition, which has a substantial impact on quality of life [1]. Concerns regarding side effects of medications have led to interest in non-pharmacological interventions [2]. While the cellular and molecular mechanisms of AD continue to be elucidated, the immune – skin microbiota aberrations associated with AD [3] are progressively being utilised as a basis for novel treatments for this inflammatory disease. Bovine-derived immune proteins with immunomodulatory properties, such as lactoferrin and the Ig-rich fraction from whey [4], are being investigated for their effectiveness in AD. Immunoglobulins are key effector molecules produced by plasma cells as part of the adaptive immune response. Lactoferrin is a constitutive component of mucosal secretions and limits bacterial colonisation through iron scavenging. More recently, evidence of a role for lactoferrin in limiting chronic inflammation by linking innate and adaptive immune processes [5] suggests that there may be promise in the use of bovine whey-derived immune proteins in chronic inflammatory diseases.

We examined the effectiveness of bovine whey-derived Ig-rich fraction and lactoferrin in AD in a double-blind phase 2 study utilising a Simon Two-Stage design [6]. Using this design, a sample size of 30 patients would provide 80% power with 95% confidence to exclude a non-interesting clinical rate of 10% (to account for clinical variability in symptoms, such as flares) for a meaningful clinical rate of 30%. Under these assumptions treatment would be considered promising for continued investigation if ≥ 5 patients experienced a clinically beneficial effect. To improve efficiency and reduce selection bias, we used a contemporary control arm in a 2:1 randomisation schedule for this non-comparative randomised study. We therefore recruited 45 patients to the active treatment ($n=30$) or an identical looking and tasting placebo ($n=15$). Inclusion criteria were a physician confirmed diagnosis of AD and score above 20 on the SCORing of Atopic Dermatitis Index

(SCORAD). Patients on topical steroid or immunomodulatory drug therapy, or consuming pro- or prebiotics or antibiotics in the previous 12 weeks were excluded. Patients consumed one tablet daily containing 250 mg bovine whey-derived lactoferrin and 250 mg bovine whey-derived Ig-rich fraction (Probiotec Pharma, Victoria, Australia) or placebo (100 mg calcium phosphate) for 56 days. Patients visited a dermatology clinic at day 0, day 14, 28, day 42, day 56 during the supplementation period for clinician (SCORAD) and patient scoring of AD symptoms (PO-SCORAD and Dermatology Life Quality Index (DLQI) questionnaire). Patients also provided a blood sample for assessment of serum immunoglobulin E (IgE), C reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Patients had a follow up visit 28 days after supplementation ceased. A clinically relevant effect was determined to be a reduction in the SCORAD index from severe (>40) to moderate (<40) or mild (<20), or from moderate to mild. Secondary outcomes included the DLQI score, with clinically relevant changes determined as previously described [7]. Ethical approval was provided by the Griffith University Human Research Ethics Committee and the trial was registered at the Australia New Zealand Clinical Trials Registry (ACTRN12614000635662).

Patient characteristics at baseline are at Table 1. The groups were matched with regard to age and SCORAD index on recruitment. A total of 35 patients completed the trial, with 2 dropping out of the study in the placebo group and 8 withdrawing from the treatment group (Fig. 1), with reasons including protocol variations ($n=2$), difficulty in keeping fortnightly clinic visits ($n=3$) or no reason provided. Data for the clinical response rate are presented in Fig. 2. Of the 22 patients with complete data in the active supplement group, 13 patients were observed to have a clinically beneficial effect, seven patients remained unchanged and two patients worsened between day 0 and day 56 in their SCORAD values. In contrast, four patients in the control group were observed to improve over the course of the study, seven had no change and two patients worsened in the placebo group. When examining the DLQI, five patients in the active supplement group had an improvement in their quality of life while one patient had an improvement in the placebo group, with the remaining patients experiencing minimal change. Serum IgE values were elevated in both cohorts (pre-supplementation treatment group 151 kU/L; 26–10,179 kU/L, median; minimum-maximum versus placebo group 74 kU/L; 9–7135 kU/L and day 56 treatment group 95 kU/L; 30–10,411 kU/L versus placebo group 85 kU/L; 10–8717 kU/L),

Table 1
Participant characteristics at baseline.

	Treatment	Placebo
N (F/M)	30 (14/16)	15 (7/8)
Age (mean $\pm$ SD)	32 $\pm$ 11	35 $\pm$ 10
SCORAD	38 $\pm$ 18	39 $\pm$ 18
DQL	19 $\pm$ 6	19 $\pm$ 5

SCORAD – scoring of atopic dermatitis, DQL – dermatology quality of life, SD – standard deviation, F – female, M – male.

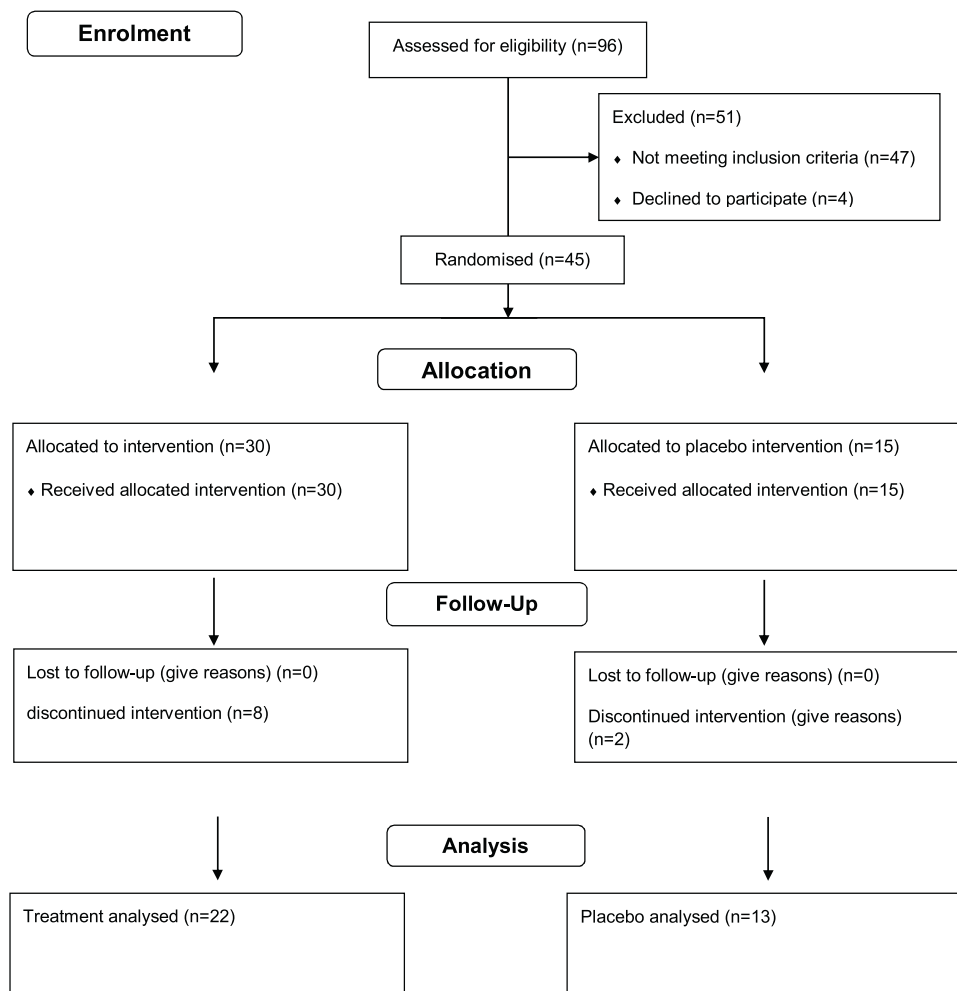


Fig. 1. “CONSORT diagram of participant flow through the study”.

consistent with those of an atopic cohort. There were no significant changes in the serum CRP and ESR (data not shown) in either active supplement or placebo group over the course of the supplementation period.

This study was designed to obtain an estimate of the treatment efficacy of supplementation with bovine whey-derived Ig rich fraction and lactoferrin for AD. Overall, we observed a clinically beneficial change in the SCORAD index in 13 of 22 patients. Furthermore, changes in the DLQI score in our patient group provide further support that supplementation was associated with

beneficial effects. Importantly, no adverse effects of supplementation were evident. The benefits of supplementing with these immune proteins may lie in their immunomodulatory and protective benefits [8]. Bovine lactoferrin shares high homology to human lactoferrin and has shown benefit for sepsis in human trials [9]. A number of limitations should be taken into account in considering these results, including the nature of the trial as a Phase 2 study, the use of patient rated questionnaires and, while providing greater ecological validity, that this was a community-based study, which have limitations. Inclusion of a placebo arm

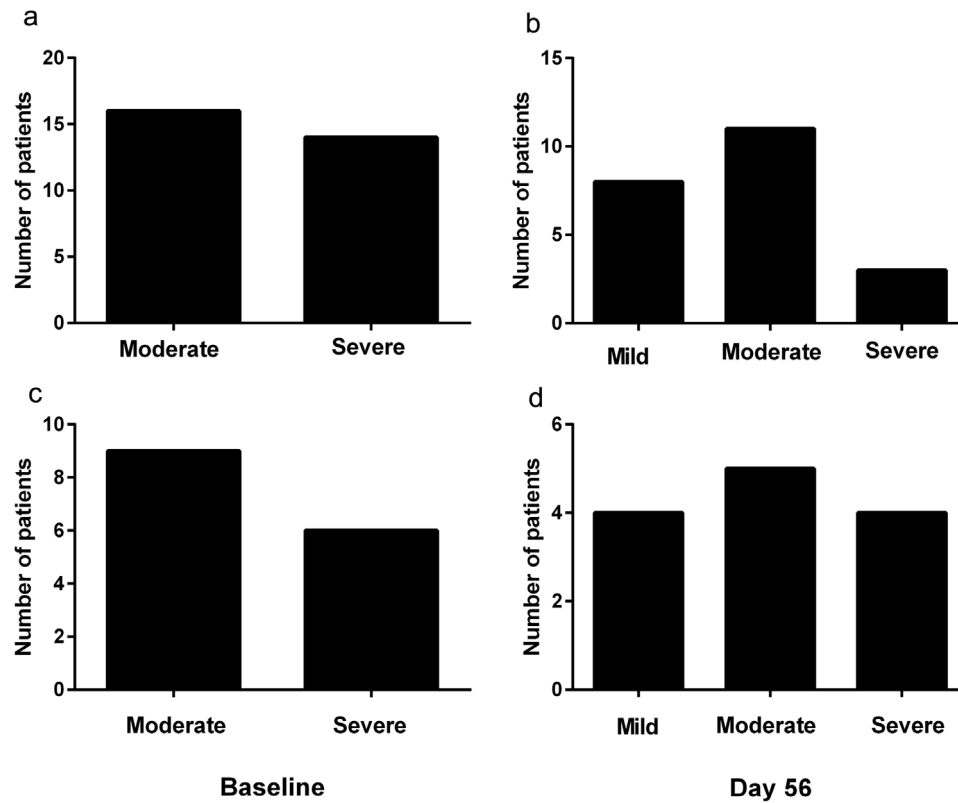


Fig. 2. Changes in the proportions of patients in the active supplement and placebo groups in the SCORAD categories of mild, moderate and severe over the course of the study. In the active supplement group there were 13 patients with a reduction in SCORAD rating compared to four patients in the placebo group over the course of the study. Fig. 2a and b show the number of patients in the active supplement group in the moderate and severe SCORAD categories at baseline and in the mild, moderate and severe categories at day 56. Fig. 2c and d show the number of patients in the placebo group in each category at baseline and day 56.

addresses the lack of a control arm often cited as a weakness in early phase clinical studies. The study team also accounted for compliance to the study protocol. Given the safety profile, ease of administration and cost compared to pharmacological AD interventions, this study provides novel insight into the use of bovine whey-derived Ig-rich fraction and lactoferrin for AD. Overall, the results indicate that further investigation is warranted for the use of bovine whey derived Ig-rich fraction and lactoferrin in AD.

Statement of authorship

The experimental protocol was developed by all authors. The recruitment, experimental work and statistical analysis were undertaken by all authors. All authors contributed to the final manuscript.

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Conflict of interest statement

Allan Cripps, Amanda Cox and Nicholas West are the recipients of research funding from Probiotec Pharma Pty Ltd. There are no other conflicts of interest to declare.

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