BMJ Open  Randomised controlled trial of topical kanuka honey for the treatment of rosacea

Irene Braithwaite,1 Anna Hunt,1 Judith Riley,1 James Fingleton,1 Janwillem Kocks,1 Andrew Corin,2 Colin Helm,2 Davitt Sheahan,3 Christopher Tofield,4 Barney Montgomery,5 Mark Holliday,1 Mark Weatherall,6 Richard Beasley1

ABSTRACT

Objective: To investigate the efficacy of topical 90% medical-grade kanuka honey and 10% glycerine (Honevo) as a treatment for rosacea.

Design: Randomised controlled trial with blinded assessment of primary outcome variable.

Setting: Outpatient primary healthcare population from 5 New Zealand sites.

Participants: 138 adults aged ≥16, with a diagnosis of rosacea, and a baseline blinded Investigator Global Assessment of Rosacea Severity Score (IGA-RSS) of ≥2. 69 participants were randomised to each treatment arm. 1 participant was excluded from the Honevo group, and 7 and 15 participants withdrew from the Honevo and control groups, respectively.

Interventions: Participants were randomly allocated 1:1 to Honevo or control cream (Cetomacrogol), applied twice daily for 8 weeks.

Main outcome measures: The primary outcome measure was the proportion of participants who had a ≥2 improvement in the 7-point IGA-RSS at week 8 compared to baseline. Secondary outcomes included change in IGA-RSS and subject-rated visual analogue score of change in severity (VAS-CS) on a 100 mm scale (0 mm ‘much worse’, 100 mm ‘much improved’) at weeks 2 and 8.

Results: 24/68 (34.3%) in the Honevo group and 12/69 (17.4%) in the control group had a ≥2 improvement in IGA-RSS at week 8 compared to baseline (relative risk 2.03; 95% CI 1.11 to 3.72, p=0.020). The change in IGA-RSS for Honevo compared to control at week 2 minus baseline was −1 (Hodges-Lehman estimate, 95% CI −1 to 0, p=0.03), and at week 8 minus baseline was −1 (Hodges-Lehman estimate, 95% CI −1 to 0, p=0.005). The VAS-CS at week 2 was 9.1 (95% CI 3.5 to 14.7), p=0.002, and at week 8 was 12.3 (95% CI 5.7 to 18.9), p=0.001 for Honevo compared to control.

Conclusions: Honevo is an effective treatment for rosacea.

Trial registration number: This trial was registered in the Australian and New Zealand Clinical Trials Registry ACTRN12614000004662.

INTRODUCTION

Rosacea is a common chronic inflammatory skin condition which primarily affects the face, and occurs in up to 10% of the adult population.1–4 There is no cure, and affected individuals may experience substantial morbidity. There is a range of treatment options, including several topical and oral antibiotics, however, these are only partially effective and side effects may limit their use4–7 Also, there are global concerns about the increasing rates of resistance to antibiotics resulting from their widespread use, particularly with long-term use in chronic conditions.8–9 For example, the United Kingdom Standing Medical Advisory Committee now recommends the fewest number of antibiotic courses should be prescribed for the shortest period possible.10

Among the alternative therapies to antibiotics, medical-grade kanuka honey is of interest due to its potent antibacterial and anti-inflammatory activities.11–15 The pathophysiological rationale underlying its use is that rosacea is an inflammatory disorder, and that antigenic proteins related to the bacterium Bacillus oleronius isolated from the Demodex folliculorum mite, which infests the skin in rosacea, exacerbates this inflammatory response.16–17 Furthermore, people with rosacea express abnormally high levels of the antimicrobial peptide cathelicidin, which promotes the inflammatory response in rosacea.18
A recent pilot study of topical medical-grade kanuka honey as a treatment for rosacea found it to be an acceptable and potentially effective treatment.\(^1\) The addition of 10% glycerine to the honey has resulted in a product that is easier to apply to the skin. In this randomised controlled trial, we have investigated the efficacy of kanuka honey in the treatment of rosacea. We designed the trial to overcome the recognised limitations of previous studies, in particular to ensure that there was blinded investigator assessment of rosacea severity.\(^2\)

**METHODS**

This parallel group, randomised, controlled trial with assessor blinding was undertaken at a hospital-based research facility and four community-based research and/or primary care sites in New Zealand. Ethics approval was obtained from the Central Health and Disability Ethics Committee (13/CEN/118). Adults aged 16 or over with a doctor’s diagnosis of rosacea on the face, and a baseline blinded Investigator Global Assessment of Rosacea Severity Score (IGA-RSS) of facial rosacea of ≥2 were recruited. The IGA-RSS is a 7-point scale (from 0: ‘clear’, to 6: ‘severe’) that provides an integrated assessment of rosacea severity based on the principal facial signs of papules/pustules, inflammatory lesions, erythema and telangiectasia\(^5\) (see online supplementary table S1). Participants were identified at the time of first presentation or, with their primary care practitioner’s consent, from pre-existing databases, or by public advertisement.

Exclusion criteria included current requirement for systemic corticosteroids, or systemic corticosteroid treatment in the 4 weeks prior to visit 1, current requirement for oral or topical antibiotic therapy for rosacea, current requirement for topical corticosteroid treatment for rosacea, known or suspected allergy to honey, or Cetomacrogol control cream, or any other condition which, at the investigators discretion, it was believed may present a safety risk or impact the feasibility of the study or the study results.

Participants attended for 3 visits (see online supplementary table S2). Visit 1 (week 0) consisted of consent, baseline assessments (the IGA-RSS), a participant-rated dermatology quality of life index (DLQI), and white soft paraffin topical emollient.\(^21\)\(^22\) The participants were instructed to apply an appropriate amount of cream to the affected area twice daily for 30–60 min per application, for 8 weeks, and to remove the treatment with warm water as desired. Participants were asked not to use any additional treatment for their rosacea for the duration of the study, as per the exclusion criteria.

**Randomisation and blinding**

Treatment allocation was randomised using a computer generated sequence concealed to investigators by enclosing the proposed treatment arm in an opaque envelope that was opened only by primary investigators after informed consent was obtained from each participant. Participants were randomised in a 1:1 ratio to the topical application of Honevo or control cream. Owing to the nature of Honevo, it was not possible to blind the participants and primary investigators to the treatment allocation. An independent investigator at each site remained blinded to the treatment allocation throughout the study to perform the blinded IGA. The blinded investigator undertook only the IGA-RSS assessment for this study, and was not involved in any other study procedures. Participants were instructed not to communicate with the blinded investigator during the assessments.

**Randomised treatments**

The Investigational Product was topical medical-grade kanuka honey with 10% glycerine content (Honevo). The control cream was Cetomacrogol, a liquid paraffin and white soft paraffin topical emollient.\(^21\)\(^22\) The participants were instructed to apply an appropriate amount of cream to the affected area twice daily for 30–60 min per application, for 8 weeks, and to remove the treatment with warm water as desired. Participants were asked not to use any additional treatment for their rosacea for the duration of the study, as per the exclusion criteria.

**Outcome measures**

The primary outcome measure was the proportion of participants who had a ≥2 improvement (reduction) in the IGA-RSS at week 8 (designated ‘responders’). This measure represents a clinically meaningful improvement in severity of rosacea. The secondary outcome measures included the change from baseline in IGA-RSS at weeks 2 and 8; the participant-rated VAS-CS at weeks 2 and 8; the change from baseline in participant-rated VAS-S at weeks 2 and 8; the weekly diary-documented Rosacea severity VAS-S from participant diaries; the change from baseline in the participant-rated DLQI\(^20\) at weeks 2 and 8; withdrawals due to worsening of Rosacea; adverse events; and the daily self-reported use of Honevo (applications per day). Data for all participants was included for analysis up until the time the participant withdrew from the study or became ineligible due to the use of prohibited medications.

**Sample size and study power**

We anticipated the proportion of participants in the control group who respond with a ≥2 reduction in blinded IGA would be between 25% and 50%.\(^6\) A total of 124 participants (62 in each group) has 80% power at 5% significance to detect a 25% response rate in the control group, and a 50% response rate in the Honevo...
group. We recruited 138 participants to allow for a 10% drop-out rate.

**Statistical methods**
The study was analysed by an intention to treat, with the participants who withdrew considered to be non-responders. The prespecified statistical analysis was logistic regression for the difference in proportions with response.

Relative risks for a ≥2 point change in IGA-RSS at week 8 from baseline and for total study withdrawal were calculated, with p values using Fisher’s exact test. ORs were also calculated from logistic regression.

For the Likert-scaled variables, the Wilcoxon test, and Hodges-Lehman estimator of location shift for the difference between treatments were used. DLQI and VAS variables were analysed by analysis of covariance (ANCOVA) with the baseline value as a continuous covariate and the randomisation as the main predictor variable. The estimates for these analyses are interpreted as the difference between randomised groups adjusted for baseline.

Applications per day were analysed by analysis of variance (ANOVA) with the response variable as the mean average number of applications per day, predictor variable randomisation group, and using the number of days in the trial as a weight, to account for variations in the number of days of application.

In a post hoc analysis, the proportion of participants in whom the IGA-RSS was zero (clear of rosacea) at week 8 was calculated.

SAS V9.3 was used.

**RESULTS**
The flow of participants in the study is shown in figure 1. There were 69 participants randomised to control and 69 to Honevo. One Honevo participant was subsequently excluded due to the use of a prohibited medication on enrolment, and their data was not used in the consequent analysis. The characteristics of the participants are shown in table 1. Participants were predominantly aged between 50 and 70 years, and had had rosacea for a mean of 15 years. Nineteen per cent of participants in each group had previously used oral antibiotics for rosacea, while 44% and 38% had previously used any topical treatments for rosacea in the Honevo and control groups, respectively. There were 7/68 (10.3%) withdrawals in the Honevo group (3 worsening rosacea, 2 took prohibited medications, 2 for other reasons unrelated to the study) and 15/69 (21.7%) withdrawals in the control group (8 worsening rosacea, 2 took prohibited medications, 1 did not want to take the control medication, 1 found the study inconvenient, and 3 for reasons unrelated to the study).

**Primary outcome**
There were 24/68 (34.3%) in the Honevo group and 12/69 (17.4%) in the control group who had a ≥2 improvement in IGA-RSS at week 8 compared to baseline (relative risk 2.03 (95% CI 1.11 to 3.72), p=0.020. The corresponding OR was 2.59 (1.17 to 5.74).

**Secondary outcomes**
The change from baseline in IGA-RSS for participants who did not withdraw is shown in table 2, online supplementary table S3 and figure 2. The change in IGA-RSS for Honevo compared to control at week 2 minus baseline was −1 (Hodges-Lehman estimate, 95% CI −1 to 0, p=0.03), and at week 8 minus baseline was −1 (Hodges-Lehman estimate, 95% CI −1 to 0, p=0.005; table 3). The subject-rated VAS-CS at week 2 was 9.1 (CI 3.5 to 14.7), p=0.002, and at week 8 was 12.3 (CI 5.7 to 18.9), p<0.001 for Honevo compared to control, representing greater improvement with Honevo. There was no significant difference in diary-captured VAS-S, adjusted for baseline, at any of the time points between weeks 2 and 8 (see online supplementary table S4). There was no significant difference in the participant-rated DLQI adjusted for baseline at week 2 (−0.3, CI −1.1 to 0.6, p=0.51) or week 8 (−0.01, CI −0.7 to 0.7, p=0.97).

The number of applications per day between the randomised treatments was similar (mean (SD) 1.84 (0.23) vs 1.86 (0.20) for the Honevo and control groups, respectively, difference: −0.02 (95% CI −0.10 to 0.05), p=0.55).

In a post hoc analysis, the proportion of participants in whom the IGA-RSS score at week 8 was zero, (ie, full resolution of rosacea) was 9/68 (13.2%) and 2/69 (2.9%) in the Honevo and control groups, respectively, relative risk 4.6 (95% CI 1.0 to 20.4, p=0.031).

In the Honevo group, 23 participants reported 31 adverse events; 17 rosacea related, (3 of which resulted in withdrawal of the participants), and 14 unrelated to rosacea (see online supplementary table S5). In the control group, 27 participants reported 36 adverse events; 22 rosacea related, (8 of which resulted in withdrawal of participants), and 14 unrelated to rosacea.

**DISCUSSION**
This randomised controlled trial has demonstrated that topical 90% medical-grade kanuka honey and 10% glycerine (Honevo) is an effective and well tolerated treatment for rosacea. About one-third of participants had a clinically significant improvement in the IGA-RSS after 8 weeks of Honevo treatment, twofold greater than that observed with the control treatment. We recommend consideration of the use of kanuka honey as a treatment for rosacea.

There are a number of methodological issues that are important in the consideration of the study findings. There are no standard validated tools for assessing the severity of rosacea, which is inherently difficult due to its varied clinical characteristics. The priority with this study of a honey product was to reduce potential bias by blinded clinical assessments where possible, as the
Figure 1  Flow of participants through trial.

Table 1  Baseline characteristics of participants

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
<th>Median (IQR)</th>
<th>Minimum–maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at enrolment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Honevo N=68</td>
<td>57.7 (13.7)</td>
<td>58.2 (46.7–68.3)</td>
<td>23.4–86.5</td>
</tr>
<tr>
<td>Control N=69</td>
<td>58.9 (15.9)</td>
<td>60.1 (49.0–68.6)</td>
<td>18.2–90.1</td>
</tr>
<tr>
<td>All N=137</td>
<td>58.3 (14.8)</td>
<td>58.9 (48.1–68.6)</td>
<td>18.2–90.1</td>
</tr>
<tr>
<td><strong>Age at diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Honevo N=64</td>
<td>42.2 (15.4)</td>
<td>40 (30–51.5)</td>
<td>19–80</td>
</tr>
<tr>
<td>Control N=67</td>
<td>43.6 (15.4)</td>
<td>43 (35–55)</td>
<td>10–79</td>
</tr>
<tr>
<td>All N=131</td>
<td>42.9 (15.4)</td>
<td>41 (32–54)</td>
<td>10–80</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Honevo N (%)</th>
<th>Control N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>N=68</td>
<td>N=69</td>
</tr>
<tr>
<td></td>
<td>32 (47.1)</td>
<td>36 (52.2)</td>
</tr>
<tr>
<td>History of oral antibiotics</td>
<td>13 (19.1)</td>
<td>13 (18.8)</td>
</tr>
<tr>
<td>History of topical therapy</td>
<td>24 (35.3)</td>
<td>20 (29.0)</td>
</tr>
<tr>
<td>History of topical steroid</td>
<td>6 (8.8)</td>
<td>6 (8.7)</td>
</tr>
<tr>
<td>European</td>
<td>64 (94.1)</td>
<td>68 (98.6)</td>
</tr>
<tr>
<td>Maori</td>
<td>4 (5.9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Asian</td>
<td>0 (0)</td>
<td>1 (1.5)</td>
</tr>
</tbody>
</table>
A participant could not be blinded due to the appearance and smell of Honevo. It was for this reason we chose to use the seven-point IGA-RSS representing a global assessment of severity of rosacea that was undertaken by an investigator who was blinded to treatment.

The primary outcome variable identified the proportion in each treatment arm who had a two-point reduction or more in IGA-RSS, representing a clinically meaningful improvement in severity of rosacea, for example, a change from ‘severe’ to ‘moderate’, or from ‘moderate’ to ‘mild’. Thirty-four per cent of those who were randomised to Honevo had an IGA-RSS improvement of two or more at 8 weeks compared to 17% of the placebo group, and 13% achieved full resolution of rosacea compared to 3% in the placebo group. Although these point estimates are consistent with effectiveness, the CIs are wide which could be consistent with a small effect or quite large effect. This is especially the case for the post hoc analysis of IGA-RSS for the proportion of participants with complete resolution, which although it favours the active treatment, could be consistent with quite a small effect. The estimate of the location shift for the difference between the treatments was $-1$, $(95\% \ CI -1$ to $0)$ at both weeks 2 and 8 and the estimated change in IGA-RSS at week 8 adjusted for baseline was $-0.6$ $(95\% \ CI -1.1$ to $-0.2)$. These findings reflect the variability in response to Honevo, perhaps dependent on subtypes of rosacea which were not assessed in this study.

In addition, we assessed patient-reported outcomes, based on participant’s assessment of current severity of symptoms (VAS-S), participant’s perceived change in severity (VAS-CS), and the DLQI questionnaire, to provide a comprehensive assessment of efficacy. The VAS-CS at the 2-week and 8-week clinic visits was significantly better with Honevo. However, there was no difference with the 2-week and 8-week DLQI assessments or the weekly diary VAS-S measures. Thus, the patient assessments were not completely consistent with the other assessments of efficacy. This could mean that the variability in these led to insufficient statistical power to detect a difference, or in the context of rosacea, that an ideal measurement related to efficacy that is sensitive to change needs further development. The rosacea quality-of-life instrument has been recently reviewed in addition to the DLQI and a generic health-related quality-of-life instrument, the SF-36, in rosacea, and may be a suitable instrument for future research.21 In the absence of a validated VAS for rosacea severity, it is difficult to comment on the clinical relevance of a reduction of 11 points from baseline in the VAS-S or the 12.3 improvement in VAS-CS in the Honevo group compared to the control group after 8 weeks. As these outcomes were participant assessed and participants could not be blinded to the interventions, there is a risk of detection

### Table 2

<table>
<thead>
<tr>
<th>Change from baseline</th>
<th>Honevo N/61 (%)</th>
<th>Control N/54 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>−3</td>
<td>11 (18.0)</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>−2</td>
<td>13 (21.3)</td>
<td>11 (20.4)</td>
</tr>
<tr>
<td>−1</td>
<td>20 (32.8)</td>
<td>17 (31.5)</td>
</tr>
<tr>
<td>0</td>
<td>14 (23.0)</td>
<td>15 (27.8)</td>
</tr>
<tr>
<td>1</td>
<td>3 (4.9)</td>
<td>8 (14.8)</td>
</tr>
<tr>
<td>2</td>
<td>0 (0)</td>
<td>2 (3.7)</td>
</tr>
</tbody>
</table>

IGA-RSS: blinded Investigator Global Assessment of Rosacea Severity Score based on a seven-point scale (0 ‘clear’ to 6 ‘severe’).
bias in this methodology. The DLQI is a questionnaire non-specific to rosacea and may not have been sensitive enough to capture changes associated with this condition alone. The drop-out rate for this study was greater than anticipated, which will need to be factored into future research in similar clinical studies. The greater number of withdrawals due to worsening rosacea in the control group (12% vs 4%), and overall withdrawals is likely to have led to an underestimation of the efficacy of Honevo, as these participants did not undergo assessment of the secondary outcome variables following withdrawal.

Cetomacrogol cream was chosen as a comparator as it is a non-ionic moisturising cream, often used as a vehicle for delivery of topical medications. The treatment was administered for 8 weeks to allow both the speed of onset and the duration of effect to be assessed. The mechanism of action was not assessed in this study. Despite this, we have found sufficient evidence of efficacy, albeit with wide CIs, that a reasonable next stage is to conduct randomised controlled trials comparing Honevo with topical metronidazole or azelaic cream.

The mechanism of action was not assessed in this study, however, there are a number of potential mechanisms relevant to the efficacy demonstrated with kanuka honey in this study. First, kanuka honey has a number of anti-inflammatory effects, including inhibition of neutrophil superoxide production, reduction in inflammatory leucocyte infiltration and arachidonic-induced oedema, and stimulation of macrophage release of tumour necrosis factor α, a cytokine with a crucial role in wound healing. These properties may be relevant as rosacea is a chronic inflammatory disorder, characterised by inflammatory cell infiltration, vascular dilation and tissue oedema. In addition, kanuka honey has high antibacterial activities against a...
wide range of bacteria, including *Bacillus subtilis*, *Propionibacterium acne* and *Staphylococcus aureus*, properties which may be beneficial in view of the proposed role of *B. oleronius* in the inflammatory response in rosacea. The effect of honey on *B. oleronius* and the *Demodex folliculorum* mite requires further investigation.

In conclusion, this randomised controlled trial has demonstrated the clinical efficacy and tolerability of 90% medical-grade kanuka honey and 10% glycerine (Honevo) in the treatment of rosacea. Honevo can be recommended for the treatment of rosacea; however, further randomised controlled trials comparing Honevo with topical metronidazole and azelaic acid are now required to determine its relative efficacy and side effect profile compared to these agents.

Guarantor: Dr I Braithwaite had access to all the data on the study and takes responsibility for the integrity of the data and accuracy of the data analysis.

Contributors JF, JK, MH, MW and RB contributed to study concept and design. IB, AH, JR, AC, CH, DS, CT and BM contributed to acquisition of the data. RB, IB and MW drafted the manuscript. All the authors contributed to analysis. IB is the guarantor.

Funding This study was funded by HoneyLab. HoneyLab provided the analysis. IB is the guarantor.

Competing interests None declared.

Patient consent Obtained.

Ethics approval The New Zealand Health and Disability Ethics Committee.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Patient-level data available from the corresponding author.

Open Access This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, See: http://creativecommons.org/licenses/by-nc/4.0/.

REFERENCES

7. Elewski BE. Rosacea trial comparing twice-daily azelaic acid gel 15% with once-daily metronidazole gel 1%. *Cuta* 2007;79:57–8; author reply 8.
10. Wu Q. Antimicrobial effect of Manuka honey and Kanuka honey alone and in combination with the bioactives against the growth of *Propionibacterium* acnes ATCC 6919: a thesis submitted in partial fulfilment of the requirements for the degree Master of Food Technology, Albany, New Zealand, Massey University, 2011.