Clinical and cost-effectiveness of spironolactone in treating persistent facial acne in women: SAFA double-blinded RCT

Miriam Santer,[1*] Megan Lawrence,[2] Sarah Pyne,[3] Susanne Renz,[2] Beth L Stuart,[4] Tracey Sach,[1] Matthew Ridd,[5] Kim S Thomas,[6] Jacqueline Nuttall,[2] Natalia Permyakova,[2] Zina Eminton,[2] Nick Francis,[1] Paul Little,[1] Ingrid Muller,[1] Irene Soulsby,[7] Karen Thomas,[7] Gareth Griffiths[2] and Alison M Layton[8]

[1]Primary Care Research Centre, School of Primary Care, Population Sciences and Medical Education, University of Southampton, Southampton, UK
[2]Southampton Clinical Trials Unit, University of Southampton, Southampton, UK
[3]Health Economics Group, Norwich Medical School, University of East Anglia, Norwich, UK
[4]Pragmatic Trials Unit, Wolfson Institute of Population Health, Queen Mary University of London, London, UK
[5]Population Health Sciences, University of Bristol, Bristol, UK
[6]Centre of Evidence Based Dermatology, School of Medicine, University of Nottingham, Nottingham, UK
[7]Public Contributor, Northeast England, UK
[8]Skin Research Centre, Hull York Medical School, University of York, York, UK

[*]Corresponding author m.santer@soton.ac.uk

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Scientific summary

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Scientific summary

Background

Acne vulgaris (hereon 'acne') is common, can cause significant psychosocial impact and risks permanent scarring. Topical treatments are first line, but people commonly receive long courses of oral antibiotics, raising concerns regarding antimicrobial resistance. Spironolactone, a potassium-sparing diuretic, is widely used for other conditions, such as hypertension. Spironolactone has anti-androgenic properties and is prescribed by dermatologists to treat acne in women, but robust evidence of effectiveness is lacking.

Objective

To evaluate whether spironolactone is clinically effective and cost-effective in treating persistent facial acne in women.

Methods

Design

This was a pragmatic, multicentre, participant-blinded and clinician-blinded, placebo-controlled randomised trial. Participants were recruited through primary care (search and mail-out or opportunistic recruitment), secondary care (opportunistic recruitment) and advertising, including community and social media advertising.

Trial participants were randomised to receive either 50 mg spironolactone or matched placebo one tablet daily for the first 6 weeks and then two tablets daily (total 100 mg spironolactone or matched placebo) at (or after) week 6, providing the participant was tolerating any side effects. Treatment continued for 24 weeks in both groups.

Participants in both groups could continue to use usual topical treatments throughout the trial but adherence to topicals was not promoted beyond usual care. Between baseline and week 12, participants were asked not to change their topical treatments and not to take oral treatments for acne such as oral antibiotics, hormonal treatments or isotretinoin. After week 12, participants could change usual acne care, including oral treatments, if needed.

In both groups, spironolactone or placebo was stopped at week 24, participants were informed of their treatment allocation and entered an unblinded follow-up period up to week 52. After week 24, participants could seek any treatment from their usual clinical team, including spironolactone.

Baseline assessment was carried out in secondary care to ensure standardisation of clinical assessments, as the Investigator's Global Assessment (IGA) for acne is not commonly used in primary care and was an important secondary outcome. The baseline appointment included pregnancy test, blood test (to exclude renal impairment or raised serum potassium), participant photo to aid recall about changes in acne, and contraceptive counselling. Baseline visits were conducted by research nurses and/or dermatologists.

Participants were followed up face-to-face (or by video call or telephone due to the COVID-19 pandemic) in secondary care at week 6 and week 12, with primary outcome assessment at week 12, and longer-term follow-up by questionnaires at week 24 and up to week 52.

Participants

Participants eligible for inclusion were women aged 18 years or over:

- with facial acne vulgaris for at least 6 months
- acne of sufficient severity to warrant oral antibiotics, as judged by trial clinician; and with IGA ≥ 2 (mild or worse)
- women of childbearing potential at risk of pregnancy had to be willing to use their usual hormonal or barrier method of contraception for the first 6 months of the trial and for at least 4 weeks afterwards
- willing to be randomised
- sufficient English to self-complete acne-specific quality of life (Acne-QoL).

Potential participants were excluded if:

- IGA acne grade was 0–1 (clear or almost clear)
- ever taken spironolactone
- taken oral isotretinoin within past 6 months
- taken oral antibiotics (lasting longer than 1 week) for acne within previous month
- started, stopped or changed hormonal contraception, co-cyprindiol or other hormonal treatment within past 3 months or planning to start, stop or change within the next 3 months
- intending to become pregnant in next 6 months
- spironolactone contraindicated:
    - currently taking potassium-sparing diuretic, angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker or digoxin
    - hereditary problems of galactose intolerance, lactase deficiency or glucose–galactose malabsorption (as the spironolactone and placebo tablets contain lactose)
    - androgen-secreting adrenal or ovarian tumour
    - Cushing syndrome
    - congenital adrenal hyperplasia
    - estimated glomerular filtration rate below 60 ml/minute/1.73 m^2
    - serum potassium level above upper limit of reference range for laboratory.

Outcomes

Primary outcome was comparison of mean Acne-QoL symptom subscale scores between groups at week 12. Acne-QoL contains 19 questions with seven response categories, each referring to the past week, reported in four domains (acne symptoms, self-perception, role-social, role-emotional).

Secondary outcomes included:

- Acne-QoL symptom subscale score at week 24 and up to week 52
- Acne-QoL other subscales (self-perception, role-emotional and role-social) at week 12, week 24 and up to week 52
- participant self-assessed overall improvement at week 12 recorded on six-point Likert scale (with baseline photo to aid recall)
- IGA change from baseline to week 12
- Participant's Global Assessment (PGA) change at week 12 and week 24
- generic health-related quality of life at week 6, week 12, week 24 and up to week 52 [EuroQol-5 Dimensions, five-level version (EQ-5D-5L)]
- adverse reactions
- use of oral acne treatment during follow-up (e.g. antibiotics, isotretinoin)
- resource use.

Sample size

Sample size calculation was based on Acne-QoL symptom subscale scores as recommended by the questionnaire developer. Based on comparison Acne-QoL symptom subscale scores between groups at week 12, power 90%, alpha 0.05 and seeking a difference of 2 points between groups (effect size 0.35), a target sample size of 346 participants was initially estimated, or 434 participants allowing for 20% loss to follow-up. During the trial, the target sample size was revised to allow for correlation between baseline and follow-up measures, following discussion with trial monitoring committees and funder. Allowing for a correlation with baseline of 0.293 and a deflation factor of $1-\rho^2$, gave a revised target sample size of 398 participants (including allowing for 20% loss to follow-up).

Randomisation and blinding

Participants were randomised in a 1 : 1 ratio to either spironolactone or matched placebo using an independent web-based system (block sizes 2 and 4). Participants were stratified by recruitment centre and baseline acne severity (IGA < 3 vs. IGA ≥ 3). Participants, site staff and investigators were blind to treatment allocation until end of treatment phase (week 24).

Statistical methods

Primary analysis compared mean Acne-QoL symptom subscale between groups at week 12 in a linear regression model, controlling for stratification factors and baseline values [including Acne-QoL symptom subscale score, topical treatment use, hormonal treatment, age and polycystic ovary syndrome (PCOS) status]. Secondary outcomes were analysed on a similar basis for continuous outcomes. Binary outcomes were compared by group using logistic regression, adjusting for the same variables as the primary analysis. All analyses were carried out on an intention to treat basis.

Health economics methods

Within-trial cost–utility analysis assessed value for money of spironolactone used in addition to routine topical treatment versus no active treatment (placebo) in addition to routine topical treatment, for women aged 18 years or over with moderate-severe persistent acne from the perspective of the NHS and Personal Social Services. EQ-5D-5L values were elicited to estimate quality-adjusted life-years (QALYs) for the trial period using linear interpolation and area under the curve with and without baseline adjustment. A secondary cost-effectiveness analysis and a range of sensitivity analyses were undertaken.

Results

One thousand two hundred and sixty-seven potential patients were screened for eligibility, of whom 413 were randomised. Three participants were subsequently deemed to be screen failures, leaving 410 randomised participants [201 intervention (spironolactone) and 209 control (placebo)]. A total of 47.6% (195/410) participants were recruited through social media advertising, 19.8% (81/410) secondary care, 15.6% (64/410) primary care, 6.6% (27/410) community advertising, 6.6% (27/410) word of mouth and 3.9% (16/410) participants' online search.

Baseline characteristics

Key participant characteristics were balanced at baseline. Mean age was 29.2 years [standard deviation (SD) 7.2; range 18–59]. Of 356 participants where ethnicity data were available, 92.1% (328/356) were white and 7.9% (28/356) were from non-white background. Mean body mass index (BMI) was 26.1 (SD 5.6).

Approximately half of participants [213/410 (52.0%)] reported having acne for more than 5 years. 77/410 (18.7%) reported they had a diagnosis of PCOS or had baseline characteristics suggestive of PCOS. At baseline, 340/410 (82.9%) participants were using topical treatments, similar in both groups and remaining similar throughout the trial. Types of topical used were also similar across groups. At baseline, 172/410 (42.0%) participants were using hormonal treatments, of whom 123/172 (71.1%)

were taking progesterone-only contraception and 49/172 (28.5%) were taking combined oral contraception or co-cyprindiol.

Mean baseline Acne-QoL symptom subscale was 13.2 (SD 4.9) in the spironolactone group, 12.9 (SD 4.5) in the placebo group and 13.0 (SD 4.7) averaged across both groups. IGA was judged by clinicians to be 3 (mild) for 190/410 (46.3%), 4 (moderate) for 166 (40.5%) and 5 (severe) for 54 (13.2%) of participants. PGA was reported as almost clear by 4/410 (1.0%), mild by 86 (21.0%), moderate by 216 (52.7%), severe by 102 (24.9%) of participants and was not answered by 2 (0.5%) participants. Over 95% of participants in both groups tolerated the treatment and increased their dosage.

Primary outcome

Three hundred and forty-two participants were included in the primary outcome analysis. The completion of primary outcome measure (Acne-QoL at week 12) was 87.6% (176/201) in spironolactone group and 79.4% (166/209) in placebo group. Acne-QoL symptom subscale score at week 12 showed greater improvement at 19.2 (SD 6.1) in the spironolactone group compared with 17.8 (SD 5.6) in the placebo group, a difference of 1.27 points [95% confidence interval (CI) 0.07 to 2.46] after adjusting for baseline variables. The sensitivity analysis on multiply imputed data gave similar results.

Secondary outcomes

The Acne-QoL symptom subscale score at week 24 was 21.2 (SD 5.9) in spironolactone group and 17.4 (SD 5.8) in placebo group, a difference between groups of 3.45 (95% CI 2.16 to 4.75) after adjusting for baseline variables. Other Acne-QoL subscale scores (social, emotional, self-perception) and total scores all showed greater improvement on spironolactone than placebo at both week 12 and week 24.

Secondary outcomes also showed greater improvement at week 12 in the spironolactone group and all outcomes showed significantly greater improvement at week 24 in the spironolactone group. IGA was judged successful at week 12 for 31/168 (18.5%) in the spironolactone group and 9/160 (5.6%) in the placebo group [OR 5.18 (95% CI 2.18 to 12.28)]. PGA was reported 'successful' by participants at week 12 for 36/176 (20.5%) in the spironolactone group and 20/166 (12.1%) placebo [OR 1.69 (95% CI 0.89 to 3.19)]. At week 24, PGA was reported as 'successful' by 53/164 (32.3%) in the spironolactone group and 15/136 (11.0%) in the placebo group [odds ratio (OR) 3.76 (95% CI 1.95 to 7.28)].

Self-assessed overall acne improvement showed more improvement amongst participants taking spironolactone, with greater differences at week 24 {81.9% vs. 63.3% [OR 2.72 (95% CI 1.50 to 4.93)]} than week 12 {72.2% vs. 67.9% [OR 1.16 (95% CI 0.70 to 1.91)]}. At week 24, 70.6% of participants taking spironolactone were satisfied that the treatment had improved their skin compared with 43.1% placebo (adjusted OR 3.12, 95% CI 1.80 to 5.41).

Subgroup analyses

Pre-specified subgroup analyses suggested that spironolactone may be more effective amongst women aged 25 or over [mean difference in Acne-QoL symptom subscale score 2.42 (95% CI 1.00 to 3.84)], compared with women aged below 25 years [mean difference −0.87 (95% CI −3.67 to 1.92)], although there were only 44 women aged below 25 years in the trial. Other interaction terms were not significant, including BMI, baseline IGA, PCOS status, hormonal treatment use and topical treatment use.

Treatment adherence was similar in both groups. Seventy-four per cent of participants reported taking 80% or more of the prescribed study medication between 12 and 24 weeks. Amongst women who achieved this threshold, the adjusted mean difference in 24-week scores was 5.13 (95% CI 3.17 to 7.08), suggesting greater treatment effect amongst women who took 80% or more of study medication. (There was a lack of data on treatment adherence at week 12.)

Adverse effects

Reported side effects were generally mild and similar in both groups but headaches were more commonly reported in the spironolactone group (20.4% vs. 12.0%, $p = 0.02$). There were no serious adverse reactions reported.

Health economics

We did not find evidence for cost-effectiveness of spironolactone compared to no active treatment (placebo) in women with persistent acne using a complete case analysis (adjusted incremental cost per QALY £67,191; unadjusted £34,770). Taking account of missing data through multiple imputation resulted in an incremental cost per QALY of £27,879 (adjusted). Sensitivity analyses provided a range around these estimates of £2683 per QALY if spironolactone was compared to oral antibiotic control (which would be a common comparator in everyday practice) using multiple imputation, through to £141,955 per QALY in a per protocol analysis where access to spironolactone was via secondary care rather than primary care, and dominated by placebo in the wider perspective complete case analysis (though this reflects the small sample size).

Discussion

This trial provides the strongest evidence to date on the effectiveness and cost-effectiveness of spironolactone for acne, as well as its tolerability at a dose of 100 mg daily. The trial has strong external validity as it was pragmatic in design to reflect normal practice, and participants were broadly reflective of women who could be offered spironolactone in routine care (while acknowledging that women of non-white ethnicity were under-represented in this study).

The trial was run during the COVID-19 pandemic. While recruitment and retention rates are remarkable given the circumstances, some trial procedures were negatively affected. During the pandemic, many week-6 and week-12 visits were conducted remotely and therefore not all IGA assessments were conducted face-to-face and assessment of treatment adherence was mainly by participant report instead of tablet count.

Due to the pragmatic trial design, we used a patient-reported outcome measure for acne as the primary outcome. We chose the symptom subscale of the Acne-QoL, an extensively validated tool. Although no firm conclusions have been published about a minimal clinically important difference in the Acne-QoL, the differences in Acne-QoL were statistically significant in favour of spironolactone at all time points and the 95% confidence interval for the primary outcome at week 12 included the target difference of two points. The larger effect size seen at week 24 on all outcomes would suggest that spironolactone may take several months to achieve maximum response.

Conclusions

Implications for health care

Spironolactone provides a safe low-cost alternative to reduce use of oral antibiotics for women with persistent acne, suitable for use in primary care. Spironolactone treatment of up to 6 months is of greater benefit than shorter treatment duration.

Implications for research

Questions remain around dosing of spironolactone in acne, particularly for women with higher BMI or PCOS, and which women with acne benefit most from spironolactone, for instance age groups and ethnicity. Research into the mechanism of action of spironolactone could inform which treatments should be co-prescribed with spironolactone or develop new treatments.

Trial registration

This trial is registered as ISRCTN12892056 and EudraCT (2018-003630-33).

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