ORIGINAL ARTICLE

Isotretinoin 5 mg daily for low-grade adult acne vulgaris – a placebo-controlled, randomized double-blind study

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Abstract

Background Despite acne persisting into adulthood in up to 50% of the population, very few therapeutic studies have been performed in this age group.

Objectives To assess the efficacy of 5 mg/day isotretinoin in adult acne.

Methods An investigator initiated, industry-sponsored, randomized, double-blind, placebo-controlled, parallel-group clinical study of isotretinoin 5 mg/day in the treatment of low-grade adult acne for 16 weeks followed by an open-label phase of 16 weeks. Group 1 received 32 weeks of 5 mg isotretinoin/day; Group 2 first received 16 weeks of placebo, followed by 16 weeks open-label 5 mg isotretinoin/day. Patients were followed for a further 10 weeks off treatment. The primary end-point was the difference in acne lesion count and disability score after 16 weeks isotretinoin compared to placebo. Secondary end-points included differences in these counts/scores after 32 weeks of isotretinoin compared to baseline, and after 10 weeks off treatment, compared to end of treatment (week 32).

Results There were highly significant differences ($P < 0.0001$) in acne lesion count, Dermatology Life Quality Index and self-assessment after 16 weeks of isotretinoin, compared to placebo (both per protocol and intention to treat). Acne lesions fell significantly, within 4 weeks of 5 mg isotretinoin/day (Group 1) and continued to fall during 32 weeks of treatment [acne lesion count (mean ± SD): 11.3 ± 8.1 (baseline), 3.6 ± 5.5 (week 16), 1.3 ± 3.1 (week 32), $P < 0.0001$)]. There was a similar significant reduction in acne lesion count in Group 2, but only from week 20, 4 weeks after starting open-label 5 mg isotretinoin. Adverse effects were minimal.

Conclusions Isotretinoin 5 mg/day is effective in reducing the number of acne lesions, and improving patients dermatologic quality of life, with minimal adverse effects.

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Conflict of interest

MR is on the speaker bureau for Douglas Pharmaceuticals Ltd., Auckland, New Zealand, but has no financial or other conflicts of interest. JMW and NMB declare no conflicts of interest.

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Introduction

Acne vulgaris is generally regarded as a self-limiting disorder affecting predominantly adolescents. However, a significant and growing body of literature suggests that acne is a chronic disease that continues to afflict adults.[1–11] Post-adolescent acne, particularly in women can be divided into 'persistent acne', which represents a continuation of acne from adolescence into adult life, and 'late-onset' acne, which describes significant acne occurring sometimes for the first time after the age of 25 years.

In a community-based study, 54% of women and 40% of men aged over 25 years continued to have some degree of acne vulgaris. This acne was principally physiological in nature, but clinical facial acne (grade > 0.75) was recorded in 3% of men and in 12% of women. The prevalence of acne did not substantially decrease until after the age of 44 years.[1] In an earlier Brit-

ish study, 6% of men and 8% of women still had definite, albeit mild, clinical acne at 50–59 years of age.[2]

In a study of acne across a woman's life span, Perkins *et al.*[3] showed that among 2895 women aged 10–70 years, 55% had some form of acne, of which 27% was considered clinically significant. As expected acne peaked in the teenage years, but 45% of women aged 21–30 years, 26% aged 31–40 and 12% aged 41–50 still complained of clinical acne.[3]

This is similar to a French study, which showed persistence of acne in 41% of older women (24% physiological acne, 17% clinical acne). In addition, 49% of the acne patients had acne sequelae, including scars and/or pigmented macules.[4]

In a further study of 540 women over the age of 20, Collier *et al.*[5] demonstrated self-reported acne in 50.9% of women aged 20–29 years; 35.2% aged 30–39 years; 26.3% aged 40–49 years; and 15.3% of women aged 50 years and older.[5]

The acne described is predominantly inflammatory, mild-to-moderate in severity, and characterized by papules and pustules located mainly on the lower third of the face, jaw line and neck.[6] However, a study of 296 older women with acne, showed a very high prevalence of predominantly comedonal pattern acne, which was strongly correlated with smoking.[7]

Unfortunately adult acne is very indolent, so conventional management of acne with topical medications, or standard courses of systemic antibiotics, is often not particularly effective.[8] Isotretinoin is acknowledged as the most effective treatment for nodulocystic acne. While conventional dosing recommends 0.5–1.0 mg/kg/day for 4–6 months,[9] it is becoming clear that lower dosages are equally as effective,[10–15] with a significantly more favourable adverse effect profile.[16] We therefore undertook a 42-week study to determine the effectiveness of very low-dose (5 mg once daily) isotretinoin in adult low-grade acne vulgaris.

Patient and methods

This investigator initiated, industry-sponsored study was designed, as a randomized, double-blind, placebo-controlled, parallel-group clinical study of isotretinoin 5 mg capsules (once daily) in the treatment of low-grade adult acne for 16 weeks followed by an open-label phase of 16 weeks. Patients, both male and female, aged 25–55 years of age, with low-grade adult acne, were recruited from three private dermatological practices in metropolitan New Zealand.

Low-grade acne was defined as three or more acne lesions/month on the face, for at least the last 3 months; any patients with acne greater than grade 2, by the Modified Leeds Acne Assessment scale,[17] were excluded. Other exclusions included pregnancy (or unwilling to adopt contraception), breast-feeding, any significant systemic illness, BMI over 35, or any systemic agent likely to influence the patient's acne (including systemic glucocorticoids or antibiotics). Patients were not allowed any topical or systemic anti-acne products in the preceding 4 weeks, or during the study period. Oestrogen and/or progesterone therapy (including levonorgestrel-releasing intrauterine device) was acceptable, but only if on a stable dose for at least 6 months preceding the start of the study. Patients were excluded if they had been on a systemic retinoid in the preceding 6 months.

Following written informed consent, patients were randomized to receive either isotretinoin for 32 weeks, (Group 1) or placebo for the first 16 weeks, followed by open-label isotretinoin for 16 weeks (Group 2). Both groups were then followed, off treatment, for a further 10 weeks to determine the rate and speed of early relapse (if any). Participants were instructed to take the daily dose in the morning during or directly after breakfast. The placebo capsules were developed to be indistinguishable in smell, taste and appearance from the 5 mg isotretinoin test product.

Patients were seen at baseline and then four weekly (±1 day) intervals to week 36, and then for a final visit at week 42 (±1 day). The following assessments were made at each visit: facial acne lesion count (both inflammatory and non-inflammatory lesions); assessment of facial erythema using a 0–3 scale (0 – no erythema, 1 – slight centrofacial erythema, 2 – pronounced erythema, centrofacial and/or generalized on the face, 3 – severe purple-coloured erythema, centrofacial and/or generalized on the face); self-assessment of the severity of acne using a linear visual 10 cm scale with the extremities graded 0 and 10, with 0 'none' and 10 'very bad acne'; and completion of the Dermatology Life Quality Index (DLQI) questionnaire.[18] Safety evaluations consisted of monitoring and recording all spontaneous adverse events (AE) (using a daily diary) and any serious adverse events. The participants' vital signs and pregnancy tests (females only) were conducted at every visit, with laboratory (blood count, liver function and lipids) testing conducted at the beginning, middle and end of the study. To keep the assessor blinded to adverse events (e.g. dry lips), the DLQI, patient diary and safety assessments were performed by a study nurse separately to the acne lesion count and erythema scoring.

There were two per protocol (PP) populations, based on two time periods: week 16 (baseline to week 16) and week 32 (week 16–32). This required at least 90% compliance with study medication over the preceding 16 weeks, had not used any excluded medications, had a complete data set and had no other relevant protocol deviations/violations during the time period. The intention to treat (ITT) population consisted of all participants who had at least one valid post-treatment acne lesion count. Missing data were imputed using the Last Observation Carried Forward technique when the ITT population was the analysis population. No imputation of data occurred for any safety data or for the PP population.

The planned primary outcome was the acne lesion count and DLQI score at week 16 in those patients who were compliant with study protocol (PP week 16 – PP16), compared to placebo. Secondary efficacy variables included the following: comparison

of acne lesion count and DLQI scores at 32 and 42 weeks between Group 1 and 2, as well as change in counts/scores in Group 2 patients between week 16 and 32. In addition, erythema scores and self-assessment of acne were assessed at weeks 16, 32 and 42. The safety of isotretinoin was also determined at weeks 16, 32 and 42.

A sample size of 60 patients (allowing for a 20% dropout) was determined to be able to detect a change in acne lesion count of three lesions with an 80% power at the 5% significance level. Each of the three centres was randomized independently, in groups of 10 participants, using a computer-generated randomization schedule.

Statistical methods

Poisson regression was used for acne lesion count, as this data were not normally distributed: the outcome of interest was the acne lesion count, the predictor variable in the model was the treatment group and the acne lesion count at baseline was added as a covariate. The rest of the data was normally distributed, and therefore analysis of covariance (ANCOVA) was employed for erythema scores, DLQI and self-assessment of acne from baseline to the period of interest. The outcome of interest in the models was the individual's score, the independent variable of interest was the treatment group, and score at baseline was included as a covariate. Paired *t*-tests were used to examine change in erythema scores, DLQI and self-assessment of acne within Group 2 between weeks 16 and 32. All statistical programming was done in SAS version 9.2 with significance defined as $P < 0.05$.

The study was approved by the Northern Y Regional Ethics Committee and registered with the Australia/New Zealand Clinical Trials Registry (Reg no. ACTRN12612000062820), albeit after the study had been completed (due to an administrative error).

Results

Sixty participants were initially enrolled in the study (Fig. 1), one patient failed to return for their baseline assessment and a second patient failed to attend for the first follow-up and were therefore excluded from the ITT population ($n = 58$) as no follow-up data were available. Protocol deviations required exclusion of 12 patients from the PP evaluation at week 16 (PP16): use of restricted concomitant medications ($n = 2$), average compliance <90% ($n = 4$) and withdrawn before week 16 ($n = 6$). Similarly, 12 patients were excluded from the PP evaluation at week 32 (PP32): restricted medication ($n = 3$), withdrawn prior to week 32 ($n = 9$). Therefore, the PP population was 46 at both week 16 and 32.

Forty-five patients completed 42 weeks of the study. There were a total of 13 withdrawals from the ITT population over the 42-week period, seven from group 1 and six from group 2. Reasons for withdrawal were adverse events ($n = 3$), failed to attend ($n = 5$), restricted concomitant medication ($n = 3$) and other ($n = 2$).

The mean age was similar in both Group 1 and Group 2 (37.6 vs. 38.5 years) with over 80% in both groups being females of European origin (Table 1). All other characteristics measured at baseline were similar between groups. There was no statistical difference between treatment groups for acne lesion count (or range) at baseline. Compliance was similar in both treatment groups.

Acne lesion counts fell significantly within 4 weeks of starting isotretinoin (i.e. by week 4 in Group 1, and by week 20 in Group 2) (Fig. 2). The acne lesion count continued to fall through the entire treatment period, reaching its nadir at 32 week. The primary efficacy measure was the acne lesion count at week 16 in the PP patients (PP16 population), for which a significant difference was demonstrated against placebo (3.6 vs. 7.2 acne lesions, $P < 0.0001$) (Table 2). Analysis of the ITT population yielded similarly significant results. When the participants in Group 2 went on to receive open-label active treatment, the mean (±SD) acne lesion count was also significantly reduced after 4 weeks of treatment (week 20) and continued to fall to week 32, compared to baseline.

At week 32, the acne lesion count was lower in patients who had received 32 weeks of isotretinoin (Group 1) compared to just 16 weeks (Group 2). Analysis of both PP populations and ITT yielded the same results at each time point. After 32 weeks of isotretinoin, 62.5% of patients were completely clear of acne (i.e. had no acne lesions), with a further 21% having only 1 acne lesion present. At week 42, after 10 weeks off treatment, both groups continued to have acne lesion counts reduced from baseline ($P < 0.0001$ for Group 1, $P = 0.007$ for Group 2).

The DLQI analysis yielded significant differences between treatment groups at week 16 ($P < 0.0001$), but there was no difference between treatment groups by week 32 ($P = 0.08$) or week 42 ($P = 0.10$) (Table 3). However, the DLQI was significantly reduced at weeks 32 and 42 compared to baseline in both groups. Erythema scores were not statistically different at any time point. Self-assessment of acne scores was significantly different between treatment groups at week 16 ($P < 0.0001$) and at week 32 ($P = 0.03$), but not at week 42 ($P = 0.13$), demonstrating early efficacy in Group 1 that persisted to week 42. Analysis of both PP populations and ITT yielded the same results at each time point.

There was no correlation in the improvement in acne lesion count, using either dose relative to bodyweight or the cumulative dose relative to bodyweight. The lack of a significant covariate effect demonstrates that the effect of the treatment is independent of dose relative to bodyweight or cumulative dose.

During the blinded phase of the study adverse events occurred more frequently in the active treatment group (Group 1) than in the placebo group (Group 2) (Table 4), whereas during the open-label treatment phase from week 16 to 32, after Group 2 had commenced isotretinoin, this group experienced more adverse events than Group 1 who had already received 16 weeks of isotretinoin. Adverse events were generally mild in both treat-

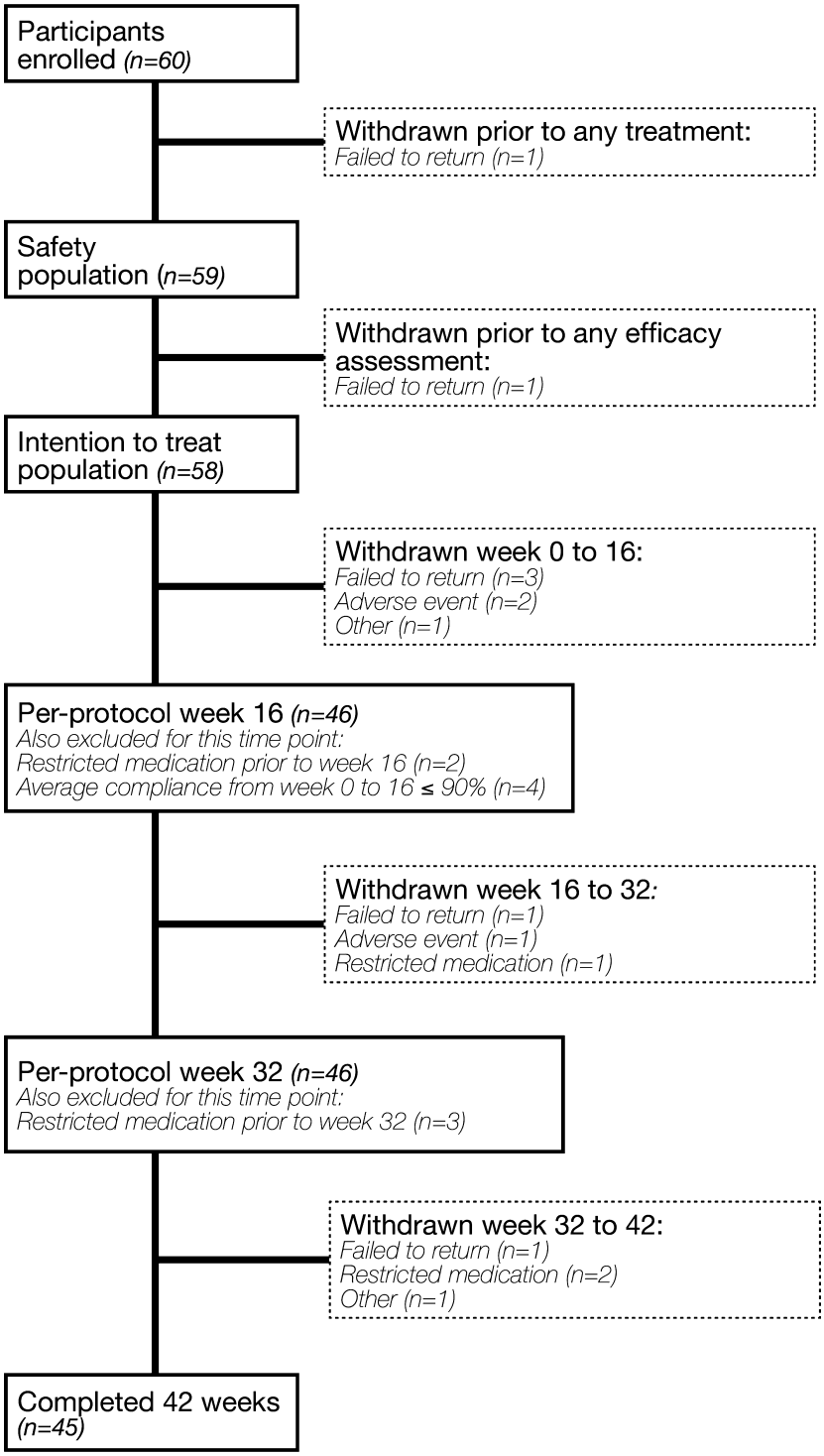

Figure 1 Participant disposition (n = 60). Week 16 per-protocol analysis: 46 patients (8 withdrawals and a further 6 temporarily excluded for minor protocol violations, but available for the week 32 analysis). Week 32 per-protocol analysis: 46 patients (11 withdrawals and 3 temporarily excluded for minor protocol violations, but available for the week 42 analysis). Week 42 per-protocol analysis: 45 patients (15 withdrawals).

Table 1 Patient characteristics

Characteristic	Group 1 (n = 29)	Group 2 (n = 29)
Age (mean ± SD) (range in years)	37.6 ± 7.95 (25–55)	38.5 ± 7.12 (26–52)
Female gender [number (%)]	25 (86.2)	26 (89.7)
Height (mean ± SD in cm)	168.4 ± 7.65	166.7 ± 7.46
Weight (mean ± SD in kg)	69.1 ± 11.03	70.6 ± 9.16
BMI (mean ± SD in kg/m^2)	24.23 ± 3.09	25.43 ± 3.23
Acne lesion count at baseline, mean ± SD (range)	10.6 ± 7.7 (3–32 lesions)	9.7 ± 6.8 (3–37 lesions)

ment periods. During the first 16 weeks, the most common adverse events were at least one episode of dryness of the skin and/or mucous membranes, with 62% of Group 1 complaining of dry lips compared to only 10% of Group 2; during the next 16 weeks, only 8% of Group 1 complained of dry lips despite continuing on isotretinoin, compared to 56% of Group 2. In all but one patient, the dry lips were mild and managed with topical emollients/lip balms. In most instances, the dryness only lasted a few days.

There were no serious treatment-related adverse events reported during any phase of the study. One participant from Group 1 developed moderately elevated ALT and GGT values requiring PP withdrawal from the study; he had a previous history of elevated liver function tests (normal liver biopsy), and his baseline gamma GT had been elevated, although considered not clinically significant at the time. Two further subjects were withdrawn from the study due to adverse events; one from Group 1 was withdrawn due to dry lips (probably actinic cheilitis) during the blinded phase, the other from Group 2 was withdrawn due to variable symptoms of mood change during the open-label phase. Both were considered possible drug-related events, but neither was considered serious. There were no significant changes in haematological or biochemical indices including lipids, during the study period. There were no pregnancies.

Acne flare, which is frequently reported to occur for several weeks at the start of treatment with higher doses of isotretinoin, was only reported in one out of fifty-eight (1.7%) participants, which was short lived and minimal.

Discussion

Despite this high prevalence of acne vulgaris in patients over 25 years of age, there are very few studies, which specifically address treatment in this age group. In a survey by Shaw, 80% of older women reviewed had failed to respond to repeated courses of antibiotics, with a mean duration of acne of 20.4 years.[19] There are a few studies of topical retinoids, which include small numbers of older women, but none appear to specifically study this age group.[20,21]

Isotretinoin has, on the other hand, been found to be quite helpful in a number of small studies involving older patients. Seukeran and Cunliffe, in an open-label review, reported nine patients treated with 0.25 mg/kg isotretinoin per day for 6 months, with excellent clinical results.[22] Goulden treated 80 (58 women) consecutive older adults (mean age 35.1 years) with persistent acne with open-label intermittent moderate dose isotretinoin (0.5 mg/kg/day for 1 week in every 4 weeks for a total period of 6 months).[23] The best results were in patients with predominantly facial acne, total acne grade less than 1, and

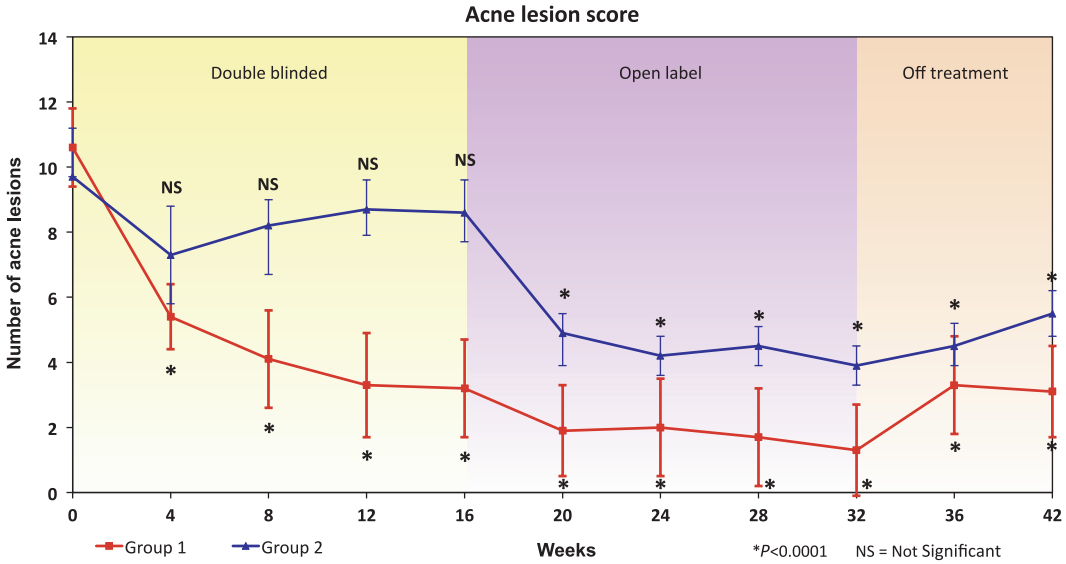

Figure 2 Acne lesion count [Group 1 (red) = 5 mg isotretinoin/day for 32 weeks; Group 2 (blue) = 16 weeks placebo followed by 16 weeks isotretinoin]. * $P < 0.0001$ from baseline; NS = non significant.

Table 2 Acne lesion counts by treatment group at baseline and week 16, 32 and 42 with change from baseline and *between groups (a) per protocol population, $n = 46$, (b) intention to treat population, $n = 58$

Treatment	Visit	Mean	SD	*P*-value
(a)				
Group 1	Screening	11.3	8.1	
	Week 16*	3.6	5.5	<0.0001
	Week 32	1.3	3.1	<0.0001
	Week 42	3.2	4.0	<0.0001
Group 2	Screening	9.0	6.8	
	Week 16*	7.2	6.0	NS
	Week 32	2.0	1.0	<0.0001
	Week 42	3.8	2.0	0.0003
(b)				
Group 1	Screening	10.6	7.7	
	Week 16*	3.2	5.1	<0.0001
	Week 32	1.3	2.9	<0.0001
	Week 42	3.1	3.8	<0.0001
Group 2	Screening	9.7	6.8	
	Week 16*	8.6	8.2	NS
	Week 32	3.9	7.8	0.0005
	Week 42	5.5	7.6	0.0074

*Between group comparison at week 16 – $P < 0.0001$.

Table 3 Dermatology Life Quality Index (DLQI) scores by visit and treatment group with change from baseline and *between groups (intention to treat population)

Treatment group	Visit	DLQI value		Change from baseline		
		Mean	SD	Mean	SD	*P*-value
Group 1	Baseline	4.8	2.91			
	Week 16*	1.3	1.92	−3.4	3.09	$P < 0.0001$
	Week 32	1.2	1.96	−3.6	3.68	$P < 0.0001$
	Week 42	1.4	1.55	−3.4	3.12	$P < 0.0001$
Group 2	Baseline	4.9	3.01			
	Week 16*	4.2	3.59	−0.7	2.42	NS
	Week 32	2.3	3.84	−2.5	3.39	$P < 0.0001$
	Week 42	2.6	3.75	−2.3	3.24	$P < 0.0001$

*Between group comparison – $P < 0.0001$.

inflamed lesion count less than 20. The therapy was very well tolerated with mild cheilitis as the only side-effect. At the end of treatment, both total acne grade and lesion counts were significantly reduced ($P < 0.0001$) and the acne had resolved in 68 (88%) patients. Relapse was moderately high though.[23]

However, intermittent treatment was less useful in a younger age group of patients with moderate acne. Lee and colleagues[24] compared several dosaging regimens (0.5–0.7 mg/kg/day, 0.25–0.4 mg/kg/day and 0.5–0.7 mg/kg/day for 1 week in four) in 60 young adults (mean age 22 years, range 16–33) in a 24-week randomized, open label, study with the assessor blinded to treatment. Intermittent isotretinoin was inferior to standard and medium daily dose isotretinoin, with satisfaction being highest with the medium dose regimen.

Palmer used open-label microdoses of isotretinoin (20 mg once or twice a week) very successfully to manage eight adult patients (aged 28–46 years) who relapsed repeatedly after several standard courses of isotretinoin.[25] Adverse events were minimal. A review of persistent acne in women suggested lower dose isotretinoin (initially 0.5 mg/kg/day according to the European Directive for Prescribing Systemic Isotretinoin), intermittent isotretinoin or even very low-dose isotretinoin (10–20 mg/day for 6–8 months).[10] Another review of retinoid therapy in acne suggested that good long-term control of seborrhoea in adult patients could be achieved in an off-label use, with doses as low as 20 mg of isotretinoin twice weekly.[26]

Our current study, one of the very few randomized, placebo-controlled, double-blind studies of isotretinoin, confirms the effectiveness of very low-dose isotretinoin (5 mg/day) in reducing the number of acne lesions, improving the dermatological quality of life and self-assessment of acne in patients with low-grade, persisting acne vulgaris. These improvements were noted within 4 weeks of starting isotretinoin, and continued to improve during the 32 weeks of treatment. Most patients acne cleared completely (i.e. no acne lesions). Perhaps most important of all, nearly all patients requested the option to remain on, or restart low-dose isotretinoin, should their acne happen to re-occur in the future. This reflects the significant un-met need of persistent adult acne, and the relative poor response to conventional treatment.

The improvement in acne lesion count within 4 weeks of starting isotretinoin is faster than one observes with more severe acne in younger teenagers. Although this may reflect the difference in severity of acne, it may also indicate differences in the mode of action of isotretinoin at very low dosages. There is some suggestion that very low-dose isotretinoin may stimulate a different pattern of gene expression than higher dosage perhaps assisting both post-acne scar minimization and wound healing.[27–30]

The adverse events noted during this study using very low-dose isotretinoin were consistent with those previously reported.[16] The majority of adverse events were well tolerated and short term, with most resolving, despite the patients continuing on treatment. Although more patients on isotretinoin complained of dry lips than placebo, in most cases the dryness of the lips persisted for less than 1 week, and was mild. It did potentially challenge the 'double-blindness' of the study, but the assessor was blinded to patients' symptoms.

Mild-to-moderate elevations of liver enzymes have been reported in 15% of patients taking higher dose isotretinoin, but only occurred in one of 58 (1.7%) participants; his baseline gamma GT had been elevated, although considered not clinically significant at the time. Lipid abnormalities have been reported

Table 4 Emergent adverse events (AE) (%) by severity, and by preferred term for the most common events

	Blinded phase		Open-label phase	
	Group 1 -Isotretinoin	Group 2 -Placebo	Group 1	Group 2
Percentage patients reporting any adverse event				
Any AE	96.6	86.7	58.3	81.5
Possibly related to study	79.3	43.3	29.2	66.7
Mild AE	79.3	80.0	41.7	74.7
Moderate AE	62.1	36.7	20.8	37.0
Severe AE	10.3	10.0	8.3	0.0
Preferred Term				
Dry eyes	17.2	6.7	0.0	3.7
Dry lips	62.1	10.0	8.3	55.6
Dry skin	20.7	13.3	8.3	11.1
Fatigue	10.3	10.0	0.0	7.4
Infections	37.9	50.0	33.3	37.0
Musculoskeletal	20.7	6.7	4.2	3.7
Headache	24.1	46.7	4.2	22.2

with standard-dose isotretinoin, but were not observed in this low-dose study. Controversy continues regarding the association between isotretinoin and mood change, depression, suicidality and suicide. This study does not add to the debate, although one patient did withdraw from the study due to feelings of lower mood. However, from general principals, one would expect a lower risk of these adverse events with the lower dosages of isotretinoin used, particularly in view of the significant improvement in DLQI and patient self-assessment.

There is also ongoing debate as to the importance of cumulative dose in the induction of long-term remission of acne vulgaris, despite the lack of a physiological basis for such an effect.[31] It should be noted that more recent studies of isotretinoin question the validity of cumulative dose. This study does not contribute to this discussion, as it was not designed to do so. We did, however, see no cumulative or weight adjusted dose effect in response to treatment. Isotretinoin does not cure acne, but it is by far the most effective treatment available. As the acne in this patient cohort often persists for many years, it is possible that patients will either request repeated courses, or to stay on the medication for extended periods (e.g. 1–2 years). The safety of such a regimen needs to be examined, but there are numerous reports of patients receiving four or more standard course of isotretinoin (i.e. 1 mg/kg/day for 4/12) with no additional adverse effects.

The European directive for prescribing isotretinoin suggests that it should only be used in severe acne (nodular, conglobata) that has or is not responding to appropriate antibiotics and topical therapy.[32] In New Zealand, we are fortunate to still work in a regulatory framework that allows doctors to prescribe any medication, for any indication, even if that medication is not registered or approved (section 25 and 29, Medicines Act 1981, New Zealand Govt). It is our experience, both from this study and many years of clinical practice, that adult patients with persisting acne do not consider their disease as being mild. Unfortunately, conventional treatment rarely achieves the results these patients expect.

Of concern is the risk of teratogenicity. As we do not know the lower threshold for teratogenicity, we must assume all female patients are at risk. The New Zealand pregnancy prevention plan (PPP) requires that the patient be counselled and understand the risk of teratogenicity; in addition, the prescribing doctor must ensure that the possibility of pregnancy has been excluded prior to the commencement of the treatment. It is interesting to note that the pregnancy rates on isotretinoin in New Zealand appear to be much lower than those reported in countries with more restrictive PPPs.[33]

In summary, 5 mg isotretinoin daily, taken for 16–32 weeks, is a very effective treatment for adult acne, with a tolerable safety profile of mainly mild short-term dryness of mucous membranes. Further studies to confirm the optimum length of treatment, and the safety and efficacy outcomes over a longer term (1–2 years) should be conducted. A similar study in adolescent acne is also warranted. It needs to be noted that the risk of teratogenicity remains even at this very low dose.

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