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CLINICAL REPORT

Anxiety, Depression, Quality of Life and Patient Satisfaction in Acne Patients Treated with Oral Isotretinoin

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Oral isotretinoin is effective in the clinical control of acne, but the relationship between this treatment and its psychosocial impact on the patient has not been completely clarified. The aim of this study was to determine if the use of oral isotretinoin in total accumulated doses of 120 mg/kg in a sample of 346 patients with moderate acne was useful in controlling symptoms of anxiety and/or depression and improving quality of life. A further objective was to ascertain the level of patient satisfaction with the treatment. After 30 weeks, there was a significant reduction in clinical symptoms ($p < 0.001$). The negative impact on quality of life, measured with the Dermatology Life Quality Index and the Health Survey Short-Form-36 ($p < 0.001$), showed a significant reduction, as did the Hospital Anxiety and Depression Scale scores for anxiety ($p < 0.001$) and depression ($p < 0.005$). At the end of the study, the mean level of patient satisfaction with improvement of symptoms was 84.4%. *Key words: anxiety; depression; quality of life; patient satisfaction; acne; oral isotretinoin.*

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Acne is a multifactorial disorder of the pilosebaceous units. Although the many forms of acne can affect all age groups, it is most common in adolescence, when it can be prevalent in up to 80% of the population (1).

Health professionals are sometimes dismissive of the psychosocial implications of dermatological disorders and lack an empathetic attitude towards the emotional suffering of their patients (2). The psychosocial impact of acne has been particularly well documented in adolescents (3–5). The disease frequently provokes shyness and social isolation. Compared with healthy individuals, patients with acne present symptoms of high levels of anxiety and/or depression (6).

The main goals in the treatment of acne are: the prevention of physical sequelae (scars); limitation of the number and intensity of lesions; reduction in the duration of the disease; and minimization of its psychosocial impact (7, 8). Studies have shown that effective treatment can reduce symptoms of anxiety and depression and significantly improve other physiological parameters (9). Assessment of psychosocial aspects gives the clinician a better understanding of the patient, and allows them to adjust treatment to the specific needs of each individual.

Oral isotretinoin is a potent retinoid that has been shown to be useful in controlling forms of acne that do not respond to the more usual treatment with oral antibiotics and can produce significant physical or emotional scarring (10). Oral isotretinoin reduces sebum by up to 90%, which prevents the proliferation of *Propionibacterium acnes* and normalizes keratinization. Dosage can vary; in general 0.5–1 mg/kg/day is recommended for conventional acne (the European Medicines Agency; EMA), starting at a dose of 0.5 mg/kg/day, titrating up as tolerated and well received. In some patients with persistent acne (especially in the mature age group), and in cases where side-effects are not tolerated at the recommended doses, low doses and/or intermittent treatment have been advocated in the literature. Isotretinoin is used until complete recovery and for a further month of treatment, independent of the total cumulative dose that is reached (11).

A study of cases between 1982 and 2000 reported 37 suicides, 110 hospitalizations due to depression with suicidal tendencies or suicide attempts, and 284 reports of patients with depression (12). A large cohort study that compared isotretinoin users with users of oral antibiotics found no significant differences with regards to the risk of development of depression or psychosis (13).

The objective of this study was to assess the physical and psychosocial evolution, as well as the level of treatment satisfaction in a group of patients treated with oral isotretinoin.

MATERIALS AND METHODS

Patients

The study population comprised 346 consecutive patients who met the inclusion criteria for participation and were treated for acne between June 2005 and September 2011 in the outpatient clinics of the Aragon public health system hospitals in Alcañiz and Calatayud. In the Spanish public health system, the treatment and control of patients with acne is sometimes carried out

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through both primary care and specialist attention, although only the dermatologist is authorised to prescribe isotretinoin. All the participants in this study had previously been seen by their primary care physicians and prescribed systemic antibiotic and topical treatments, which had been unsuccessful.

Criteria for participation were as follows: (*i*) patients of both sexes who had been diagnosed with moderate acne in accordance with the grading scales of the American Academy of Dermatology (10); (*ii*) no contraindications to the use of isotretinoin; (*iii*) 16 years of age or older; (*iv*) to have given signed, informed consent of voluntary participation; (*v*) no antecedents of mental illness (personal or family members); (*vi*) no language difficulties that made participation impossible; (*vii*) no prior treatment with oral isotretinoin; (*viii*) unresponsive to other combination therapies, including antibiotics. During the treatment process, patients were excluded from the study for the following reasons: (*i*) if follow-up was impossible (the patient could not be contacted; (*ii*) if the patient decided that they did not wish to continue; (*iii*) if the doctor decided to halt the treatment; (*iv*) if the patient presented adverse effects that impeded participation.

During the study, 12 patients withdrew: 5 because follow-up became impossible; 3 decided against initiating treatment for fear of adverse effects; 3 patients stopped taking the medication due to unspecified side-effects; and 1 was advised to stop the treatment, as the doctor had observed a more despondent mood in the patient after the initiation of medication.

Study design and treatment

The analysis was based on a prospective, observational, longitudinal study, with measurements taken before and after treatment. Oral isotretinoin was administered in weight-dependant doses; a total cumulative dose of 120 mg/kg was given for 30 weeks to patients of both sexes who had moderate acne. Medication was taken twice a day.

Assessment instruments

The Hospital Anxiety and Depression Scale (HADS) (14) is a self-administrated screening scale for symptoms of anxiety and/or depression. There are 14 questions, 7 refer to symptoms of anxiety and 7 refer to depression. The intensity and frequency of symptoms is evaluated on a 4-point Likert scale (range 0–3), with differing response formulations. The range of scores is 0–21 for each subscale and 0–42 for the global result. In previously validated studies different cut-off points have been established in accordance with the study population (15, 16). In this work, an original cut-off point of ≥ 11 was used to identify a clinical case and 8–10 to identify a probable case; the scale was validated and culturally adapted to Spain by Caro & Ibañez (17).

The Health Survey Short-Form–36 (SF-36) (18) is a questionnaire used in mental health and general health research; it offers a global perspective of the state of health of an individual, it is easy and quick to complete and evaluation is relatively simple. The SF-36 has 36 questions that assess the positive and negative aspects of a person's health. The final questionnaire has 8 scales that represent the most habitual concepts used in the evaluation of health, treatment and illness. This study used the Spanish version (19). The 8 scales are hypothesized to form 2 distinct higher-ordered clusters based on the physical and mental health variance that they have in common. The Mental Component Summary (MCS) comprises the Vitality scale (VT), Social Functioning (SF), Emotional Role (ER), and Mental Health (MH). The Physical Component Summary (PCS) is made up of the Physical Functioning scale, Physical Role (PR), Bodily Pain (BP), and General Health (GH).

The Dermatology Life Quality Index (DLQI) (20) is a dermatology-specific HRQoL questionnaire consisting of 10 questions. The total DLQI score ranges between 0 (no impairment of HRQoL) and 30 (maximum impairment of HRQoL). The 10 questions are subdivided into 6 domains: symptoms and feelings, daily activities, leisure, work/school, personal relationships and treatment. The questionnaire is self-administered.

Patient satisfaction assessment

At the end of the treatment process, participants were asked to evaluate the treatment received in relation to the improvement in the symptoms, the complementary psychosocial circumstances and the effects of the treatment on their day-to-day lives and activities. The degree of satisfaction was measured by means of a visual analogue scale (0–100).

Clinical information and procedure

Participants were visited on 4 scheduled occasions during the period of the study (3 times by the dermatologist, and once by the general practitioner). On the baseline visit, sociodemographic data were collected in addition to details on clinical factors concerning the condition: evolution of the disorder, diagnosis; the most recent treatment; previous treatments; concomitant treatments; adverse side-effects. The patients were given information on the treatment and the aims and methodology of the research, and asked to sign informed consent. A blood test was taken for the analysis of liver enzymes and lipids panel and there was a systematic urine analysis. The analyses were undertaken at initiation of treatment, at 1 month and 3-monthly throughout the course of treatment. The oral isotretinoin was monotherapeutic, with the exception of women of childbearing potential, all of whom were given a pregnancy test before treatment commenced. In addition, monthly pregnancy testing took place during the treatment period and a pregnancy prevention programme (PPP) was implanted. The programme involves education, therapy management and control or distribution of the drug (21). The patients were advised to use 2 complementary contraception methods and to always use a condom when having sex.

The second visit was in week 8 and the third visit was in week 19. Treatment progress was checked for any adverse side-effects that required withdrawal from the programme or any other difficulties that needed attention.

The fourth and final visit was at 30 weeks. Clinical evolution was evaluated and the patient's satisfaction with the treatment was assessed. The HADS, SF-36 and the DLQI questionnaires were completed before starting the treatment and when the programme was finished.

Statistical analyses

An intent-to-treat analysis (ITT) was performed with the total initial sample of 346 subjects. The ITT analysis (22) is aimed at achieving the most equal initial conditions as practicable and conditions that are the most similar to clinical daily practice. A sensitivity analysis was employed and the subjects who withdrew from the study were assigned the most negative outcomes.

Data were analysed with SPSS 11.0. A descriptive and differential examination of the sample was carried out through the study of the frequencies and percentages for the qualitative variables and summary measures (mean, median, maximum and minimum typical deviation). Prior to the inferential analysis, the Kolmogorov-Smirnov/Shapiro–Wilk test was applied to the dependent quantitative variables to check the normal distribution adjustment for the values of the evaluation scales. A parametric study of the data was chosen due to the goodness of

fit to the normal distribution and the sufficient sample size. A multivariate analysis using the Student's *t*-test was implemented for the 2 related samples in order to determine the influence of the treatment on the study variables.

Contingency tables were used to consider the possible dependent relationships of the qualitative scores before and after treatment. An independence test, based on Pearson's χ^2 statistic was undertaken. The significance level was 5% when the *p*-value was < 0.05.

RESULTS

Clinical characteristics

The age range of the participants was 17–33 years, mean ± standard deviation (SD) age was 20.7 ± 2.1 years. Of the 346 patients, 203 (58.6%) were women and 143 (41.4%) were men. The main sociodemographic characteristics are shown in Table SI (available from http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1638).

In accordance with the classification criteria of Pochi et al. (10) all the patients ($n = 346$) had moderate acne. Evolution time was between 9 and 138 months (mean ± SD 46.8 ± 18.8). Diagnosis time ranged between 0 and 129 months (19.6 ± 8.2). Before inclusion in the study 107 patients (31%) had received more habitual topical treatments (benzoyl peroxide, tretinoin, adapalene, tazarotene, erythromycin, clindamycin, azelaic acid), 69 (20%) had received oral medication (erythromycin, tetracycline, doxycycline or minocycline), 83 (24%) had received mixed treatment (oral and topical) and 87 (25%) had received no treatment prior to their first visit to the dermatologist.

We agree with Faure et al. (23) on the importance of a global assessment of acne severity, taking into account 4 main factors with prognostic significance: the time since acne onset, involvement of the trunk, previous treatment and family history. After 30 weeks of isotretinoin therapy, 333 patients (96.2%) had no visible lesions, which implied a significant reduction in clinical symptoms ($p < 0.001$). The most important results are shown in Table SII (available from http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1638).

Quality of life, general health and psychological data

The mean ± SD score for DLQI at baseline was 13.2 ± 3.7. At the end of the study this score was 4.2 ± 2.4, which implies a significant reduction in the negative impact of the patient's acne condition on their quality of life (QoL) ($p < 0.001$).

With the exception of the variable "Bodily Pain" all the results for the 8 scales of the SF-36 were statistically significant for both mental and general health. There was a significant improvement ($p < 0.001$) in the following dimensions: Physical Function, Role Physical, Vitality,

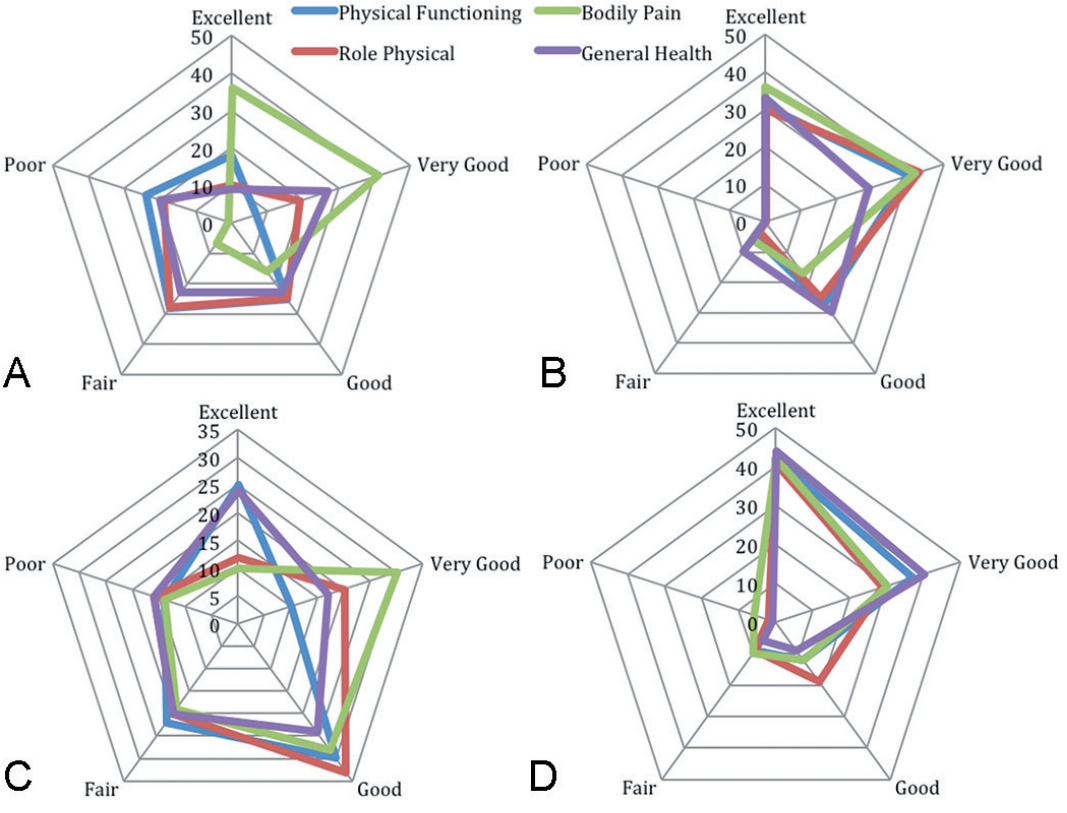

Fig. 1. Health Survey Short Form-36 (SF-36) ($n = 346$). (A) Baseline: physical health. (B) End of treatment: physical health (C) Baseline: mental health. (D) End of the treatment: mental health.

Table I. *Health Survey Short Form-36: Physical Component Summary (PCS) and Mental Component Summary (MCS). Significant improvement after treatment (*n = *346)*

Summary measures	Baseline (%)	End of treatment (%)	*p*-value
PCS	51.7	72.4	<0.001
MCS	50.8	73.6	<0.001

Social Function, and Mental Health. There was also a significant improvement ($p < 0.005$) in General Health and Emotional Role Function (Fig. 1). The Mental Component Summary (MCS) and the Physical Component Summary (PCS) revealed statistically significant results ($p < 0.001$), as shown in Table I.

At baseline, the results of the HADS classified 90 patients (26.0%) as clinical cases on the Anxiety subscale and 12 (3.5%) on the Depression subscale. At the end of treatment these figures had fallen to 12 (3.5%) and 6 (1.7%), respectively. There was a significant decrease in both the Anxiety ($p < 0.001$) and Depression ($p < 0.005$) scores. The results are shown in Table II.

The treatment satisfaction assessment, completed at the end of the programme, revealed a significant improvement in clinical symptoms (88.4 ± 12.2), satisfaction regarding the treatment (86.2 ± 11.9) and social life (87.6 ± 15.1). The results are shown in Table III.

DISCUSSION

This study has focused on assessing the effectiveness of oral isotretinoin treatment and its impact on the general health, QoL and psychological functioning of patients with acne. Whilst the issues have been dealt with in previously published works (24–27), this study was prospective and based on a relative large number of subjects ($n = 346$). Furthermore, an intention-to-treat (ITT) analysis was undertaken and this aided decisions on prescription or modification of isotretinoin use and its dosage with groups of patients with moderate acne.

With regards to the sociodemographic factors, 58.6% of the participants were women, which is coincident with some studies (28–32). The mean age (20.7 years) was similar to that of other studies (28, 30), and the age range (17–33 years) was also in line with other published research (30, 32). The educational level was lower than the sample used by Al Robaee (33); this may be due to the inclusion of patients up to the age of 44 years. The statistics in relation to employment status are broadly similar to other studies, such as that of Abdel-Hafez et al. (28)

Table II. *Hospital Anxiety and Depression Scale Scores (*n = *346)*

	Baseline *n* (%)	End of treatment *n* (%)	*p*-value
Anxiety sub-scale			<0.001
Clinical case[a]	90 (26.0)	12 (3.5)	
Probable case[b]	53 (15.3)	30 (8.7)	
No case	203 (58.7)	304 (87.8)	
Depression sub-scale			<0.005
Clinical case	12 (3.5)	6 (1.7)	
Probable case	41 (11.9)	19 (5.5)	
No case	293 (84.6)	321 (92.8)	

[a]Cut-off point ≥11. [b]Cut-off point ≥8 and <11.

One-hundred percent of the sample had moderate acne; this contrasts with the work of Abdel-Hafez et al. (28), which included patients with severe and mild acne. The evolution time (mean ± SD: 46.8 ± 18.8 months) is similar to Kaymak et al. (29), but considerably less than the 90 months of Hahm et al. (30). The total cumulative dose of 120 mg/kg was administered for 30 weeks, which contrasts with other studies that used 0.5–0.8 mg/kg/day for 20 weeks (29) or 0.5–1 mg/kg/day for 8 weeks (30). The effect of the oral isotretinoin treatment was clearly positive: After 30 weeks, 333 patients (96.2%) were asymptomatic with no visible lesions. There was a significant reduction in clinical symptoms ($p < 0.001$). Our results are similar to those of McGrath et al. (25).

The baseline mean ± SD DLQI measurements prior to treatment showed that the patients had a poor QoL (13.2 ± 3.7), similar to the results of some studies (28), but higher than others (29). There was a significant improvement in the post-treatment scores ($p < 0.001$), comparable to the results obtained by Kaymak et al. (29). These results must be seen as important in consideration of the negative impact that acne vulgaris can have on an individual's QoL (34) and its association with psychological morbidity (35). It is worth noting that the QoL of acne patients is statistically worse than patients who have illnesses such as epilepsy, diabetes, asthma or arterial coronary disease.

The patient's age or the duration of the acne are not always related to the perceived QoL, which may be affected by factors that have no connection to the severity of the condition (e.g. social, emotional, personality type, the presence of scars or school/work problems). Given the potential interaction and influence of other factors it is not possible to conclude that clinical severity alone explains the patients' perceived QoL evaluation. It should be emphasized that emotional stress can exacerbate acne, but also that acne patients can develop

Table III. *Treatment satisfaction (*n = *346). Visual analogue scale 0–100*

	Mean ± SD	Median	Min–Max
Improvement of symptoms: clinical lesions and greasy skin	88.4 ± 12.2	89.6	43.9–100
Treatment: information: efficacy, secondary effects and administration of medication	86.2 ± 11.9	85.9	19.0–100
Improvement in social life: carrying out daily activities and emotional state	87.6 ± 15.1	90.8	18.0–100

emotional and psychological problems as a result of the condition (36).

With regards to psychological functioning, the published literature offers contradictory results on the usefulness of effective treatment with acne sufferers; some authors conclude that appropriate treatment alleviates the symptoms of anxiety and/or depression (9, 36), whilst others have noted that they remain unchanged (28). In this present work, the baseline results for the HADS Anxiety subscale classified 90 patients (26.0%) as clinical cases (cut-off point ≥ 11), a result in line with other published studies (37). The mean $\pm$ SD anxiety score was 8.9 ± 3.9), higher than other studies with a mean score of 7.0 ± 3.3) (24). The baseline results of the HADS Depression subscale indicated that 12 patients (3.5%) were clinical cases (cut-off point ≥ 11), lower than other studies (20), which showed 24.2% (SD = 20.9) (cut-off point: ≥ 8). As the cited authors used lower cut-off points than the present study, it was decided to calculate the percentage of patients that would have been classified as clinical cases, using the aforementioned cut-off points; the results were as follows: 17.2% (cut-off point ≥ 8). The differences probably depend on the sample; for example, most of the participants in the present study were from rural areas, and this may partly explain the differences.

The post-treatment results showed significant improvements in the subscales for both Anxiety ($p < 0.001$) and Depression ($p < 0.005$). After finishing the treatment, only 12 patients (3.5%) were classified as clinical cases on the Anxiety subscale, and there were only 6 clinical cases of Depression (1.7%). These results are comparable with those of Kaymak et al. (29)

This study therefore supports the findings of Rubinow et al. (9), Ferahbas et al. (38) and Cohen et al. (39), which suggest that oral isotretinoin is not a risk factor for depression and it produces an improvement in symptoms of anxiety and/or depression in patients with mild to moderate acne (26).

With regards to the Health Survey Short Form-36 (SF-36), when patients were asked to assess their own general health, 42.2% of the sample rated their health as "fair" or "poor", a figure that is considerably lower than the 81.5% of the sample used by Al Robaee (33). This may be due to differences in the seriousness of the patients' conditions prior to treatment. At the end of the treatment period, there were significant reductions ($p < 0.001$) in the following scales: Physical Role Function, Vitality; Social function, and Mental Health; there were also significant reductions ($p < 0.005$) in General Health and Emotional Role Function. These results are similar to those obtained by Al Robaee (33).

Finally, the patient satisfaction questionnaire showed that the participants were very happy with the treatment process; these results are similar to those of Grahame et al. (40), who studied patients diagnosed with acne who had a high degree of emotional discomfort and a poor QoL. Results showed that oral isotretinoin treatment had a positive effect on their condition. This conclusion is coincident with other studies that have reported that the treatment improves psychiatric symptoms (38) and patients' QoL (29). It is clear that acne has an impact on an individual's physical and mental health and is therefore an important factor in their perception of their general health.

However, as other authors have pointed out (25), more research is needed on the relationship between acne, isotretinoin, QoL and psychosocial impact. Before starting oral isotretinoin treatment, acne patients should be tested for symptoms of depression and suicidal tendencies and undergo a detailed psychometric examination. The instruments used in this study, HADS; SF-36 and DLQI, are useful assessment tools as they are reliable and easy to administer.

Oral isotretinoin treatment is not without limitations; it is teratogenic, so great care must be taken if used with women of fertile age. Contraceptives must be recommended to ensure that these women do not become pregnant until at least one month after completion of treatment. Patients must also receive laboratory tests before receiving oral isotretinoin treatment: high levels of triglycerides are common (11) and increased levels of blood cholesterol and liver enzymes are possible. Other possible alterations are leucopoenia, thrombocytopaenia, thrombocytosis, and an increased sedimentation rate. Nevertheless, all these conditions are usually resolved after treatment.

The main limitations of this study are that it was only carried out with subjects from 2 hospitals and there was no control group. However, the results have been systematically compared with other studies.

The authors declare no conflicts of interest.

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