

Prospective Study of Risk Factors of Relapse after Treatment of Acne with Oral Isotretinoin

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Key Words

Acne relapse · Isotretinoin stop

Abstract

Background: The effectiveness of oral isotretinoin against acne is undeniable. However, few data on the maintenance of effect after treatment termination have been published. **Objective:** The purpose of the study was to identify the risk factors of relapse after stopping isotretinoin. **Method:** This prospective open study examined 52 patients with moderate to severe acne at the Dermatological Clinic of the Nantes University Hospital (France). Variables likely to influence relapse were studied using the Cox model. **Results:** 27 patients (52%) relapsed after stopping treatment. In multivariate analysis, severe seborrhoea and a high score of inflammatory lesions at the end of the treatment, an early age, a family history of acne, prepubertal acne and acne extended to the trunk were the factors increasing significantly the risk of relapse. **Conclusion:** Our data allow to define more precisely the profile of acne patients for whom the risk of relapse is highest and who should therefore be followed up quite regularly after treatment termination.

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Introduction

For about 20 years, oral isotretinoin has been part and parcel of our therapeutic outfit against acne. It holds a selected position as the only really curative treatment currently available. Thus, it is often used after a combination treatment with oral antibiotic therapy and local treatment has failed or as first-line treatment for severe nodulocystic acne or acne conglobata. Its effectiveness against acne is undeniable and is well documented in the literature [1, 2]. Secondary effects necessitate of course a close follow-up of patients [3, 4]. However, despite its high efficacy, isotretinoin may lead to relapse within a variable time after treatment termination. The frequency of relapse remains much discussed, especially due to the absence of well-defined criteria for relapse and because most studies are retrospective [1, 5–12].

This prospective study was performed in a cohort of acne ambulatory patients to assess the efficacy and the clinical and biological tolerability of oral isotretinoin in the treatment of acne as well as the frequency of relapse, by performing a count of lesions at each visit and defining quantitative criteria for relapse. In addition, this study attempted to determine prognostic factors for the occurrence of a possible relapse.

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Table 1. ECLA scale (clinical assessment scale for acne lesions)**a** Factor 1: type and intensity of acne on the face (count on the whole face)

	Absent = 0	Rare = 1	Slight = 2	Moderate = 3	Important = 4	Very Important = 5	Factor 1
R Open or closed comedones (microcysts)	none	<5	5–9	10–19	20–40	>40	
Is Papules and pustules	none	<5	5–9	10–19	20–40	>40	
Ip Nodules and inflammatory cysts	none	1	2	3	4	≥5	

b Factor 2: extension and intensity of acne outside the face

	Absent = 0	Slight = 1	Moderate = 2	Important = 3	Factor 2
Neck high cervical area low cervical area					
Chest					
Back above bottom of shoulder blade below bottom of shoulder blade					
Arm					

c Factor 3: scars

	Absent = 0	Present = 1	Factor 3
Inflammatory			
Non-inflammatory			
Excoriations			

Patients and Methods*Patients*

This prospective study was performed at the Dermatological Clinic of the Nantes University Hospital (France). The patients were included between January 1999 and December 2000. All patients for whom a treatment with oral isotretinoin was indicated, i.e. who presented either with severe (nodulocystic or conglobate) acne or for whom an at least 3-month combination therapy with oral antibiotics and local treatment had failed, were included. Patients with a previous treatment with systemic isotretinoin were excluded. Patients were followed up during isotretinoin treatment and after treatment termination. If a relapse occurred that necessitated a repeated local or general treatment, the patient had to be withdrawn. Patients whose former dermatological history could not be known precisely or for whom follow-up after treatment termination was not possible were excluded from the study.

A total of 52 patients have been included in the study. In addition to demographic data, information was collected for each patient about the first occurrence of acne, the family history of acne and former local as well as general treatments. None of the females included in the study had a clinical or biological hyperandrogenism (free testosterone and dehydroepiandrosterone sulphate concentrations were normal). An initial clinical evaluation was performed on

the day isotretinoin treatment was initiated, after 1 month and then every second month until treatment termination, as it was usual for any patients treated with isotretinoin in the department. Patients were then seen every 4 months, during 2 years on average after treatment termination. Seborrhoea was assessed at each visit (semi-quantitative scale from 0 to 4) and the number of acne lesions was evaluated using the ECLA scale (table 1) [13]. Thus, superficial inflammatory lesions (papules and pustules), retentional lesions (open and closed comedones) and nodules were counted on the face. Lesions on the neck, the trunk [anterior thorax, upper back (to the bottom of the shoulder blades), lower back, shoulders] were assessed with a semi-quantitative scale (from 0 to 4). Adverse events were also recorded at each visit. Complete clinical remission was defined by nil scores for inflammatory and retentional lesions, because we know that in our clinical practice a good result for a patient is no more lesions. Thus, we decided to determine in how many cases isotretinoin is able to obtain this result. Relapse was defined by a re-increase in the number of lesions after isotretinoin withdrawal, with a score of 2 or more for superficial inflammatory lesions (more than 4 papules or pustules), with a score of 3 or more for retentional lesions (more than 9 open or closed comedones) or with the presence of 1 or more nodules, which represents a deterioration in acne sufficient to merit a treatment.

Table 2. Patient characteristics

Age at acne diagnosis, years	
Mean \pm SD	13.8 \pm 2.2
Range	8–20
Age at treatment initiation, years	
Mean \pm SD	18.0 \pm 4.4
Range	13–34
Sex	
Female	29 (56%)
Male	23 (44%)
Family history	
None	26 (50%)
At least 1 parent	26 (50%)
Type of acne	
Non-prepubertal	44 (85%)
Prepubertal	8 (15%)
Former local treatment ¹	
Erythromycin	39 (75%)
Benzoyl peroxide	45 (87%)
Local tretinoin	16 (31%)
Adapalene	15 (29%)
Former systemic treatment ¹	
Cyclines	49 (94%)
Zinc gluconate	36 (69%)
Diane 35 [®]	6 (12%)
Androcur [®]	2 (4%)
Localization of acne	
Face	12 (23%)
Face and body	40 (77%)

¹ One or more by patient.

Treatment Conditions

Any topical or general anti-acne treatment was withdrawn 1 month before initiating isotretinoin administration.

Isotretinoin (Roaccutane[®]) was initiated with a dose ranging from 0.3 to 1 mg/kg/day. The dose was then adapted according to tolerability and clinical outcome.

All women of child-bearing potential used contraception initiated 1 month before treatment start and continued 1 month after treatment termination (oral oestroprogestative contraceptive or intra-uterine device). In addition, a pregnancy test had to be performed no more than 3 days before isotretinoin prescription and repeated every second month, until 1 month after treatment termination (following regulatory recommendations in force at the time the study was performed).

Lipid parameters (cholesterol and triglycerides) and transaminases were assayed before treatment initiation and 1 month after full-dose treatment.

Statistical Methods

The Cox proportional hazard model was used to assess the event relapse. The first step consisted in a univariate analysis for each explicative variable. Then from variables for which the univariate p value was less than 20%, a descending procedure was applied including all these variables. At each step, the variable that was least

significantly associated with the event (i.e. for which the p value was maximal) was excluded from the model. Before excluding a variable from the model, it was checked that it did not play a confusing role. The procedure was stopped when only variables remained that were significantly associated with relapse at the 5% level. Interactions between variables were assessed in the final model.

Adequation of the Final Model

The Cox model is based on the hypothesis of risk proportionality with time. If this hypothesis is not confirmed for a variable, it means that the effect of this variable varies with time; consequently the Cox model is not suitable anymore. The test proposed by Grambsch and Therneau (based on Schoenfeld residuals) was used.

Results

Patient Characteristics

Characteristics of the population are summarized in table 2. A total of 52 patients (23 male and 29 female) with a mean age of 18 years (13–34 years) have been included in the study.

The mean age of acne diagnosis was 13 years (8–20 years). Eight patients had presented with prepubertal acne; 26 patients out of 52 (50%) had no family history of acne, 11 (21%) reported acne on the mother's side, 11 (21%) on the father's side and 4 (8%) for both parents.

All patients had received other anti-acne treatments before isotretinoin initiation.

Topical Treatments

Only 6% of the patients had received no former local treatment; 13.5% had received 1 local treatment, whereas a combination of 2, 3 or 4 different treatments had been prescribed for 44, 27 and 9.5% of the patients, respectively.

Systemic Treatments

All patients had received at least 1 systemic treatment before isotretinoin initiation; 31% had been prescribed a single treatment (zinc gluconate, Rubozinc, for 19% of them and cyclines for 81%), 59.5% had received 2 different treatments (cyclines and Rubozinc for 94% of them) and 9.5% 3 different systemic treatments.

On the whole, 94% of patients had received a combination of local and general anti-acne treatments.

Evolution of Lesions under Treatment

The cumulative dose of isotretinoin was above 120 mg/kg for all patients but one. The mean cumulative dose was

Fig. 1. Distribution of patients according to the change in the seborrhoea score before and after treatment.

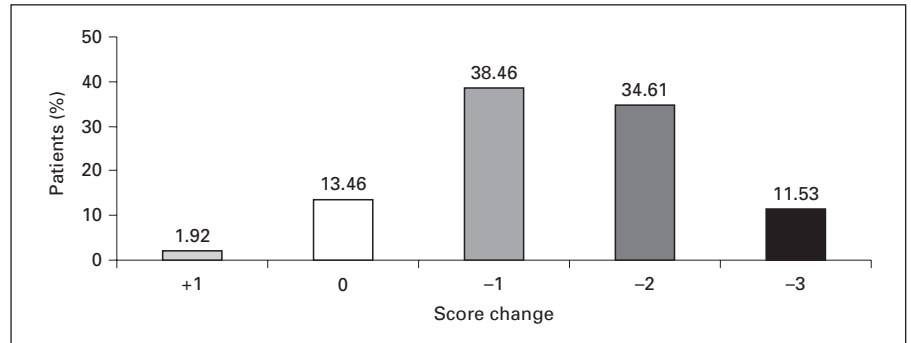


Fig. 2. Distribution of patients according to the change in the retentional lesion score before and after treatment.

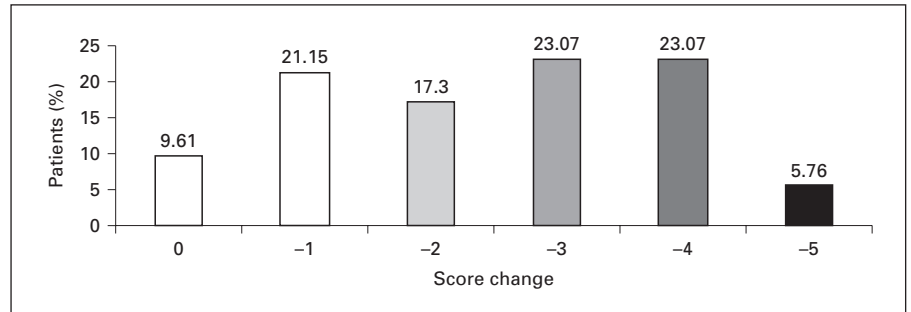


Fig. 3. Distribution of patients according to the change in the superficial inflammatory lesion score before and after treatment.

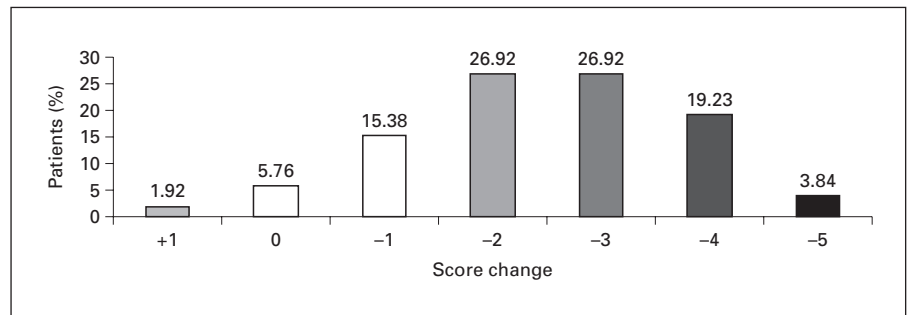
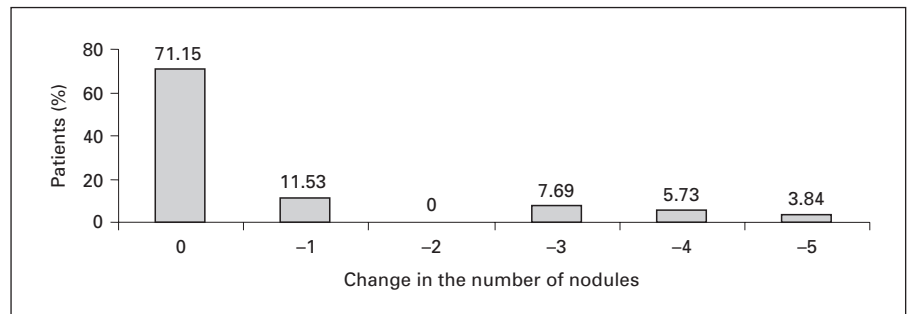


Fig. 4. Distribution of patients according to the change in the number of nodules before and after treatment.



137 mg/kg (108–180 mg/kg). The mean daily dose was 0.73 mg/kg (0.36–1 mg/kg).

A clinical response to treatment was achieved for all patients (decrease in retentional or inflammatory lesions), but only 24 patients out of 52 (46%) presented with complete remission at the end of treatment, following the

agreed definition, i.e. disappearance of all retentional or inflammatory lesions. Among the 28 patients with a partial remission there were 15 females and 13 males.

Figures 1–4 display the repartition of patients according to the evolution of the score for seborrhoea and for each type of lesion before and after treatment. A decrease

Table 3. Incidence of adverse events during isotretinoin treatment (n = 52)

Adverse events	Incidence
Cheilitis	52 (100%)
Dry skin	19 (37%)
Ocular irritation	9 (19%)
Hypertriglyceridaemia	7 (13%)
Epistaxis	5 (10%)
Hypercholesterolaemia	5 (10%)
Inflammatory outbreak	3 (6%)
Myalgia	3 (6%)
Erythema	3 (6%)
Eczema	2 (4%)
Arthralgia	2 (4%)
Gastritis	1 (2%)
Pruritus	1 (2%)
Phototoxicity	1 (2%)
Headache	1 (2%)
Increased transaminases	1 (2%)

in seborrhoea was achieved under treatment for 84% of patients (44/52; fig. 1), and seborrhoea was absent for 58% of patients at the end of treatment. The score for seborrhoea remained unchanged under treatment for 13% of patients (7/52).

As well, retentional lesions decreased significantly under treatment. Indeed, 67% of patients presented with a score of 3 or more at baseline versus only 6% of patients at the end of treatment. The score for retentional lesions decreased for 90% of patients (47/52), but the extent of this decrease was very variable: the score decreased by 1 unit for 21% of patients, and by 2, 3, 4 and 5 units for 17, 23, 23 and 5% of patients, respectively (fig. 2).

A marked decrease in the number of inflammatory lesions was also shown. The score for inflammatory lesions decreased under treatment by 2 units or more for 77% of patients (40/52). The score was 1 or nil for 12% of patients at baseline versus 88% at the end of treatment.

All nodules on the face disappeared under treatment.

Treatment-Related Adverse Events

All patients presented with treatment-related adverse events, which are summarized in table 3. The most frequent were cheilitis (100% of patients), cutaneous xerosis (37%) and ocular irritation (19%). Biological adverse events included an increased triglyceride level for 13% of patients and an increased cholesterol level for 10%. Only 1 patient presented with an increase in transaminases.

Relapse

Considering relapse as a re-increase in lesional scores after treatment, with a score of 2 or more for superficial inflammatory lesions (more than 4 papules or pustules), with a score of 3 or more for retentional lesions (more than 9 open or closed comedones) or with the presence of 1 or more nodules, 27 patients (52%) relapsed after treatment termination. The relapse occurred both in the subgroup of patients who achieved complete remission (9/24: 37%) and in the patients with partial remission (18/28: 64%). For 92.5% of patients, relapse occurred during the first year (44.5% before 6 months and 48% after 6 months). A second course of isotretinoin was necessary for 44.5% of patients who relapsed.

Each variable likely to influence this risk of relapse was analysed using a Cox model. Table 4 displays the results obtained for each variable assessed separately, and table 5 summarizes the results obtained using a multivariate model.

According to the univariate model, factors likely to increase significantly the risk of relapse were a high number of retentional lesions before and after treatment, a high number of superficial inflammatory lesions and an important seborrhoea after treatment, young age when acne appeared or when isotretinoin was initiated, acne on both the face and the body, prepubertal acne as well as a close family history of acne (father and/or mother; table 4). On the other hand, no significant difference was shown regarding gender, daily dose of isotretinoin, treatment duration, cumulative dose or seborrhoea before treatment (table 4).

According to the multivariate model, 7 factors remained significantly associated with the risk of relapse (table 5): important seborrhoea after treatment, high number of superficial inflammatory lesions after treatment, young age when treatment was initiated or when acne was diagnosed, family history, prepubertal acne and acne on both the face and the body. Two significant interactions were shown for these variables: first between seborrhoea and the score for superficial inflammatory lesions after treatment and second between family history and young age when treatment was initiated.

Results of the comparative analysis of the evolutive profile of lesions during treatment between patients who presented or not with relapse are presented in figures 5–8.

Seborrhoea decreased more slowly in the relapse group compared to the remission group (fig. 5).

The curves illustrating the decrease in retentional lesions are similar in both patient groups (fig. 6).

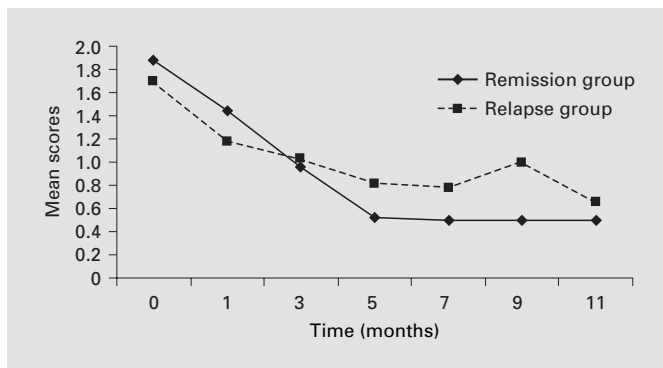


Fig. 5. Evolution of seborrhoea under treatment.

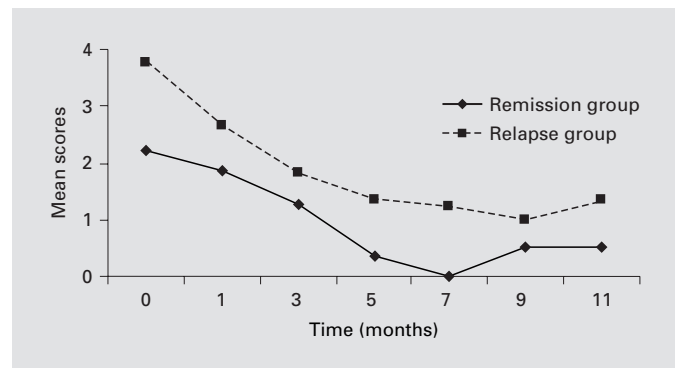


Fig. 6. Evolution of retentional lesions under treatment.

Table 4. Results of univariate Cox models

	β	S(β)	RR	95% CI	p value
Characteristics of acne at treatment initiation					
Seborrhoea	-0.020	0.23	0.98	0.62-1.54	0.93
Retentional lesions	0.51	0.20	1.66	1.13-2.44	0.0093
Superficial inflammatory lesions	0.14	0.19	1.15	0.80-1.65	0.45
Nodules	0.025	0.13	1.03	0.80-1.32	0.84
Characteristics of acne at the end of treatment					
Seborrhoea	0.67	0.32	1.96	1.04-3.68	0.037
Retentional lesions	0.56	0.17	1.75	1.25-2.45	0.0011
Superficial inflammatory lesions	0.82	0.27	2.27	1.35-3.83	0.0021
Nodules	-	-	-	-	-
Treatment duration	-0.059	0.088	0.94	0.79-1.12	0.50
Mean daily dose of isotretinoin	0.21	1.14	1.23	0.13-11.4	0.86
Age at treatment initiation	-0.27	0.09	0.76	0.64-0.91	0.0022
Age at acne diagnosis	-0.36	0.10	0.70	0.57-0.85	0.0004
Sex					
Female	0	-	1	-	-
Male	0.067	0.39	1.07	0.50-2.30	0.86
Family history					
No	0	-	1	-	-
Yes (at least 1 parent)	0.84	0.41	2.32	1.05-5.15	0.039
Type of acne					
Non-prepubertal	0	-	1	-	-
Prepubertal	1.41	0.47	4.10	1.63-10.3	0.0027
Localization of acne					
Face	0	-	1	-	-
Face and body	2.15	1.02	8.55	1.15-63.3	0.036
Former treatment with cyclines = no					
Cyclines = yes	-0.95	1.05	0.39	0.05-3.05	0.37
Former treatment with zinc gluconate = no					
Zinc gluconate = yes	-0.11	0.41	0.90	0.40-2.01	0.79
Former treatment with Diane 35® = no					
Diane 35® = yes	-1.23	1.02	0.29	0.04-2.16	0.23
Former treatment with Androcur® = no					
Androcur® = yes	0.065	1.03	1.07	0.14-7.97	0.95

RR = Relative risk; CI = confidence interval.

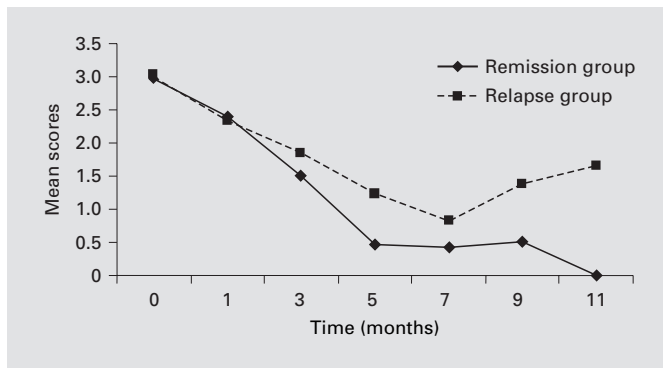


Fig. 7. Evolution of superficial inflammatory lesions under treatment.

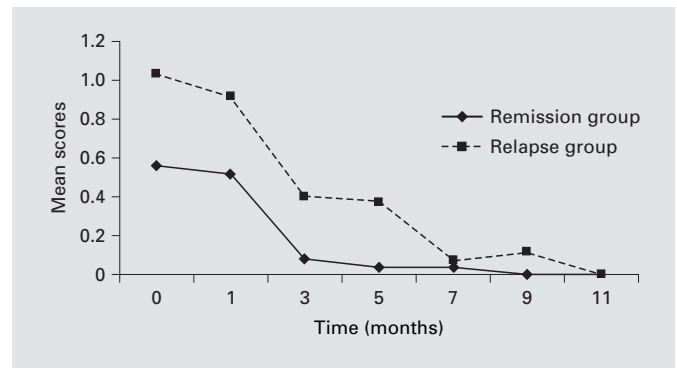


Fig. 8. Evolution of nodules under treatment.

Table 5. Results of the multivariate Cox model

	β	S(β)	RR	95% CI	p value
Seborrhoea at the end of treatment	-0.47	0.75	0.63	0.14–2.73	0.53
Superficial inflammatory lesions at the end of treatment	0.17	0.49	1.18	0.45–3.10	0.74
Age at treatment initiation	0.25	0.22	1.29	0.84–1.97	0.25
Age at acne diagnosis	-0.84	0.23	0.43	0.27–0.68	0.00030
Family history					
No	0	–	1	–	
Yes (at least 1 parent)	22.06	5.97	3.8×10^9	3.15×10^4 – 4.63×10^{14}	0.00022
Type of acne					
Non-prepubertal	0	–	1	–	
Prepubertal	-5.65	1.44	0.0035	2.10×10^{-4} –0.059	0.000086
Localization of acne					
Face	0	–	1	–	
Face and body	7.68	1.96	2170	46.7 – 1.00×10^5	0.000087
Mean daily dose of isotretinoin	-0.01	0.016	0.99	0.96–1.03	0.69
Seborrhoea at the end of treatment \times inflammatory lesions at the end of treatment	2.65	0.89	14.2	2.47–81.9	0.0030
Age at treatment initiation \times family history	-1.05	0.31	0.35	0.19–0.65	0.00084

RR = Relative risk; CI = confidence interval.

Regarding superficial inflammatory lesions, the score decreased more importantly and more rapidly in the remission group, with significantly different scores between groups at the end of treatment (relapse and remission; $p = 0.009$; fig. 7).

Compared to patients who achieved remission, patients in the relapse group presented with more nodules at baseline, though not significantly so (fig. 8). Both curves showed identical profiles during treatment and tended to nil at the end of treatment.

Discussion

This study represents the first prospective study in which a precise count of each type of acneic lesion was performed before, during and after treatment, with a nil score for inflammatory and retentional lesions as criterion for complete clinical remission. This count of lesions allowed to define the kinetics of the evolution of lesions under treatment for patients who experienced a relapse after treatment termination compared to those who did

not. In other studies published in the literature, the assessment of acne was thus far less precise, using the classification of Burke and Cunliffe [10, 11], the technique of Leeds [1, 8, 14] or subjective improvement scales [9, 15].

A response to isotretinoin was observed for all patients; however, only 46% of patients achieved a complete response. This response rate is lower compared to those commonly observed in the literature. Indeed, Falk and Stenvold [9] obtained 70% of complete remission, Lehucher-Ceyrac and Weber-Buisset [10] obtained 95% in 1993 and Lehucher-Ceyrac et al. [11] 92% in 1999. Data are less precise for Layton et al. [1] and Ng and Goh [12], with an improvement for 85 and 97% of patients, respectively, without distinguishing between partial and complete response. The variability of results is mainly linked to the definition of therapeutic response: calculations are indeed different and a global quantification was used, with no precise count of lesions.

It is worth pointing out that only a partial improvement was achieved for the majority of patients (54%) despite a cumulative dose above 120 mg/kg (for all patients but one). The daily dose expressed per unit of weight had no influence on the therapeutic response or on the frequency of relapse. The precise measurement of each type of lesions during treatment allowed to observe that seborrhoea decreased for 84% of patients and was absent for 58% of patients at the end of treatment. Retentional lesions also decreased for 90% of patients, but the extent of this decrease was very variable between patients in our population. In addition, all nodules of the face disappeared under treatment in this study.

The rate of relapse in our series (27 patients out of 52, i.e. 52%) is slightly higher compared to other published data. But once again, the definition of relapse was different among teams. We defined relapse as a re-increase in lesional scores after treatment termination, with a score of 2 or more for superficial inflammatory lesions (more than 4 papules or pustules), with a score of 3 or more for retentional lesions (more than 9 open or closed comedones) or with the presence of 1 or more nodules. Ng and Goh [12] and Layton et al. [1], who considered that relapse corresponded to the necessity of resuming a systemic treatment, observed rates of relapse of 47 and 39%, respectively. Stainforth et al. [8], for whom relapse was defined as the necessity of resuming isotretinoin, observed 23% of relapse. In 1993, Lehucher-Ceyrac et al. [11] defined relapse as a grade higher than 2 (classification of Burke and Cunliffe) for a formerly cured patient, and observed a rate of 38%. In addition, it is important to

point out that relapses occur most often rapidly after treatment termination, whatever the features of acne assessment. Indeed in our series, 92.5% occurred within 1 year; as well, 78% of patients who relapsed did so within 18 months for Layton et al. [1] and 85% within 2 years for Stainforth et al. [8]. Thus, it seems essential to follow up patients for at least 1 year after isotretinoin termination.

The other objective of this study was to assess predictive factors of relapse.

This study confirms 3 prognostic criteria that had already been elicited in former studies, namely acne appearing in a young patient [2, 7, 11, 16], initiation of isotretinoin treatment in a young patient [2, 7, 11, 16] and acne located on the trunk [1, 2, 7, 16]. As regards acne located on the trunk, patients with lesions on the face and trunk are particularly at risk of relapse in our study compared to patients presenting with lesions on the face only (relative risk = 2,620).

Both the univariate and multivariate analyses have allowed to identify a new prognostic factor, namely a family history of acne (father or mother). Actually it is well known that a family history of acne is a predisposing factor for severer acne but it has never previously been shown that it is a predictive factor for relapse after oral isotretinoin.

In addition it is classically acknowledged in the literature that the risk of relapse increases with severity [1, 2, 7, 8]; the kinetic study of the evolution of lesions performed in our patients allows to define the link between acne severity before treatment, therapeutic response and frequency of relapse. The risk of relapse after isotretinoin withdrawal is higher when the number of retentional lesions is high, whereas an important seborrhoea and a high number of superficial inflammatory lesions or nodules before treatment do not seem to represent direct prognostic factors of relapse. On the other hand, an obvious interaction exists between an important seborrhoea, a high number of retentional lesions or superficial inflammatory lesions at the end of treatment and an increased risk of relapse. As regards scores for seborrhoea and superficial inflammatory lesions at the end of treatment, a potentialization of risks is shown rather than a simple addition.

Overall, the univariate model shows that early acne, young age at the moment of isotretinoin initiation, family history of acne, prepubertal acne, localization on the trunk, important seborrhoea and a high number of inflammatory lesions at the end of treatment may be considered as independent prognostic factors.

On the other hand, no link was shown between the cumulative isotretinoin dose and the risk of relapse. This is consistent with the hypothesis that beyond a given threshold (100 mg/kg for Harms et al. [16] and Ng and Goh [12], 110 mg/kg for Lehucher-Ceyrac and Weber-Buisset [10] and Lehucher-Ceyrac et al. [11] or 120 mg/kg for Layton et al. [1]) the risk of relapse is not linked anymore with an increased dose; in fact the cumulative dose was above 120 mg/kg for all of our patients but one.

As well we observed no link between the daily dose and the risk of relapse, but the mean daily dose was above 0.5 mg/kg for 90% of our patients. The influence of the daily dose on the risk of relapse is widely discussed in the literature. It is clearly shown that the risk of relapse is increased when the dose is below 0.5 mg/kg/day [17–19],

but on the other hand for doses above 0.5 mg/kg/day, relapse occurs less frequently with 1 mg/kg/day compared to 0.5 mg/kg/day for some authors [1, 2, 5], but not for others [7].

In conclusion, this study shows a high incidence of relapse of acne (52%) after a well-conducted treatment with isotretinoin (with a cumulative dose above 120 mg/kg and a daily dose between 0.5 and 1 mg/kg) if relapse is considered as more than 10 retentional lesions and/or more than 5 superficial inflammatory lesions. In addition, our data allow to define more precisely the profile of acne patients for whom the risk of relapse is highest and who should therefore be followed up quite regularly after treatment termination.

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