

Original Article

Acne recurrence after treatment with oral isotretinoin: 5-year follow-up

Recidiva de acne após tratamento com isotretinoína oral: seguimento de cinco anos

Authors:

Carolina Ribas do Nascimento¹
 Ana Luíza Grizzo Peres Martins²
 Simone de Padua Milagres³
 Ivander Bastazini Jr⁴

¹ Masters in Dermatologic Internal Medicine, Universidade Federal do Rio Grande do Sul (UFRGS) – Porto Alegre (RS), Brazil

² Dermatology Resident Physician, Instituto Lauro de Souza Lima (ILSL) – São Paulo (SP), Brazil

³ Masters in Dermatology, Universidade de São Paulo (USP) – São Paulo (SP), Brazil

⁴ Preceptor and Head of Dermatologic Surgery, Instituto Lauro de Souza Lima

Correspondence:

Carolina Ribas
 Rodovia Comandante João Ribeiro de Barros, Km 225/226
 17034-971 – Bauru - SP, Brazil
 Fone: (14) 3103-5900
 E-mail: dra.carolribas@gmail.com

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ABSTRACT

Introduction: Isotretinoin was initially used to treat severe inflammatory acne and is now widely recognized as an effective therapy for acne vulgaris. Many factors are associated with the recurrence of this condition, which ranges from 5.6–65.4%. There is much controversy regarding the importance and contribution of each factor.

Objectives: To determine the recurrence rate in patients who underwent full treatment with oral isotretinoin (dose between 120 and 150 mg/kg) and risk factors.

Methods: Retrospective study of data from 276 patients treated with isotretinoin. The analysis was carried out after a minimum of 30 months after the end of the treatment. Recurrence was defined as the appearance of new active lesions that required retreatment.

Results: While the recurrence rate in patients who underwent the full dose was 25.53%, it reached 81.03% in those who received an incomplete dose. The other studied factors presented no statistical significance.

Conclusion: Oral isotretinoin therapy is effective in producing a significant and long-term reduction of acne. Nevertheless, it is important to note that recurrence can occur, especially when recommended doses are not reached.

Keywords: acne vulgaris; isotretinoin; recurrence.

RESUMO

Introdução: A isotretinoína foi inicialmente utilizada no tratamento da acne inflamatória grave, sendo atualmente bem reconhecida como tratamento de sucesso para acne vulgar. Muitos são os fatores associados com a recorrência da doença, que varia entre 5,6% e 65,4%. Há muita controvérsia sobre a importância e a contribuição de cada um desses fatores. **Objetivos:** Determinar a taxa de recidiva dos pacientes que receberam tratamento completo com isotretinoína oral (dose entre 120 e 150mg/kg) e fatores associados ao risco.

Métodos: Estudo retrospectivo a partir de dados de 276 pacientes tratados com isotretinoína. Após período mínimo de 30 meses a contar do término do tratamento realizou-se a análise. Considerou-se recidiva o surgimento de lesões ativas que necessitassem de retratamento.

Resultados: Houve 25,53% de recidiva nos pacientes que fizeram dose completa, e 81,03% nos que receberam dose incompleta. Os demais fatores estudados não demonstraram significância estatística.

Conclusão: A isotretinoína oral é tratamento efetivo em produzir redução significativa e de longa duração da acne. No entanto, deve ser reforçado o fato de que recidivas ocorrem com frequência significativa principalmente quando não se atingem as doses preconizadas.

Palavras-chave: acne vulgar; isotretinoína; recidiva.

INTRODUCTION

Acne, one of the most prevalent dermatologic disorders¹, can affect patients' quality of life and cause relevant psychosocial impacts. Isotretinoin (13-cis-retinoic acid) was first used to treat serious inflammatory acne in Europe in 1976 and in the US in 1982. Its use transformed the therapeutics of serious and resistant acne, and it is now widely recognized as an effective treatment for acne vulgaris^{2,4}.

This retinoid is known to have many action mechanisms through connections to specific receptors. It reduces the size of the sebaceous glands and inhibits their activity and lipidic production; modulates epithelium proliferation and differentiation; decreases the proliferation of *Propionibacterium acnes* in the hair follicles; and has other immunological and anti-inflammatory effects^{4,6}.

It is considered to be the most effective treatment for acne due to its capacity to induce complete and prolonged remission in all degrees of severity of the condition; recommended daily doses range between 0.5 and 2.0 mg/kg, with a total recommended dose between 120 and 150 mg/kg^{7,8}. Nevertheless, notwithstanding fully completed treatments, recurrence is frequently seen in the literature and in daily practice. The condition reappears in 5.6% to 65.4% of cases;² this great variation relates to diverse factors and their interaction such as; daily average dose, cumulative dose, treatment duration, variations in patient characteristics (e.g., gender, age, degree and location). There is much controversy over the importance and contribution of each factor in the rates of recurrence⁹.

METHODS

A retrospective study was conducted to determine the recurrence rate and potential risk factors linked to recurrence in patients who completed a treatment regimen of oral isotretinoin (accumulated dose of 120-150 mg/kg) in a public health service in Brazil (Instituto Lauro de Souza Lima/Bauru, SP, Brazil). The medical records of patients (n = 1,167) diagnosed with and treated for acne from 01/01/2005 to 31/12/2006 in a general dermatology outpatient clinic were analyzed. During that period, 276 patients used free isotretinoin supplied by the Brazilian Health Ministry's exceptional medications program. This study was carried out in compliance with the ethical rules of the Declaration of Helsinki.

More than half (n = 188) of the patients completed the treatment regimen, while 58 abandoned the treatment after at least 3 months of use. Patients were excluded from the analysis if they used the medication for less than 3 months or if they could not be contacted after the follow-up period.

Data was available on gender, age, severity, location, total dose of isotretinoin, and treatment duration. A treatment was considered to be complete at accumulated doses between 120 and 150 mg/kg. After a minimum of 30 months after the end of treatment, patients answered a telephone questionnaire about whether or not the acne reappeared and about their use of maintenance treatments and oral contraceptives during that period. Recurrence was defined as the emergence of active

lesions that, in the patient's opinion, needed treatment.

The Chi-square Test and Fisher's Exact Test (5% significance level) were used in the statistical comparison between different factors and the recurrence event.

RESULTS

Of a total of 188 who completed the treatment, 145 (77.12%) were male and 43 were female (22.87%). The average of age at the beginning of the treatment was 18.1 (17.4 for men and 20.2 for women).

Regarding acne severity, 22 patients (11.7%) were diagnosed as Grade 2 (with papules and pustules), 146 (77.65%) as Grade 3 (with nodules and cysts) and 20 (10.63%) as Grade 4 (conglobata). Regarding location, 29 patients (15.42%) had lesions only on the face and 159 on the face and trunk (84.57%). No patients presented lesions only on the trunk. When studying the correlation between location and recurrence, we found that those with acne only on the face had a 13.79% rate of recurrence, while those with lesions on the face and back had a rate of recurrence of 27.67% (Table 1).

The average duration of isotretinoin use was 8.6 months (range 4-15 months). Treatments lasting 4-8 months presented a 23.16% recurrence rate, while treatments lasting longer than 8 months had a recurrence rate of 27.96% (Table 2).

Of the 58 women who used isotretinoin, only 43 completed the treatment regimen and were included in the analysis. Of these, 17 continued using oral contraceptives after the end of the treatment. In this group, the recurrence rate was 29.41%, while among those that didn't use oral contraceptives after treatment the recurrence rate was 15.38% (Table 3). No use

Only 26 patients (13.82%) used topical treatments during the observation period. Of these, 11 presented recurrence (42.31%), while of the 162 who did not use such treatments, 37 experienced a reappearance of lesions (22.8%) (Table 4).

Among female and male patients, there were 9 (20.93%) and 39 (26.89%) cases of recurrence, respectively. After the

Table 1: Acne location X recurrence

	Recurrence	No recurrence	Total	%
Face	4	25	29	100
Face and back	44	115	159	100
Total	48	140	188	100

Table 2: Treatment duration X recurrence

	Recurrence	No recurrence	Total	%
4 to 8 months	22	73	95	100
More than 8 months	26	67	93	100
total	48	140	188	100

Table 3: Contraceptive use X recurrence

	Recurrence	%	No recurrence	%	Total	%
Use	5	29,41	12	70,59	17	100
No use	4	15,38	22	84,62	26	100
Total	9	20,93	34	79,07	43	100

Table 4: Use of topical treatments X recurrence

	Recurrence	%	No recurrence	%	Total	%
Use	11	42,31	15	57,69	26	100
No use	37	22,84	125	77,16	162	100
Total	48	25,53	140	74,47	188	100

analysis of these variables regarding the presence of recurrence, none showed statistical significance.

On the other hand, when comparing the use of complete and incomplete doses of isotretinoin, there was a statistically significant difference regarding recurrence. Recurrence was verified in 48 patients (25.53%) who received a complete dose. Of the 58 patients who did not use a complete dose but used the medication for more than 3 months, 47 (81.03%) presented recurrence (Table 5).

Table 5: Recurrence with complete dose X recurrence with incomplete dose

	Recurrence	%	No recurrence	%	Total	%
Complete dose	48	25,53	140	74,47	188	100
Incomplete dose	47	81,03	11	18,97	58	100
Total	95	38,62	151	61,38	246	100

DISCUSSION

During more than 30 years of isotretinoin use, many authors have found great variability in recurrence rates. That is due to differences in criteria for including patients in studies, in the definition of recurrence, in daily doses and, in particular, in the cumulative dose and in the duration of the follow-up period. Rates varying from 23.2% to 65.3%^{10,12} illustrate this difficulty. In the present study, the recurrence rate after a complete treatment regimen was 25.53%.

Consistent with findings in the literature, the recurrence rate found in the present study for patients who had a total dose less than 120 mg/kg was 81.03%. This finding demonstrates that reaching the minimum recommended dose is the main factor linked to a long-term maintenance of the treatment effects.

The present study did not succeed in demonstrating significant correlations of individual factors (such as gender, age at the beginning of the treatment, acne severity and location of lesions) with the total risk of recurrence. There is no consensus in the literature regarding the location of the lesions; some authors have found more frequent recurrence in patients who presented lesions only on the face, while others found more frequent recurrence in patients with lesions on the back. Additionally, some authors found greater recurrence in women older than 25, while others found this trend in younger men³. Such findings can be due to differences in the studied populations.

It is inferred that the number of men who used isotretinoin in the study period was much greater than that of women due to the drug's teratogenic risks and the fact that many women can present significant improvement by using oral contraceptives. In addition, the average age at the beginning of treatment was 17.4 for men and 20.2 for women. This difference

might be explained by the fact that the women tried other medications for longer due to the teratogenic risks.

Although the rate of recurrence was slightly greater in patients who took longer to reach the full dose, when they did so this fact was not statistically significant. Therefore, there seems to be no difference between reaching the full dose in a shorter period with higher daily doses and implementing gradual increases of the daily dose until the full dose is reached.

Contrary to the authors' expectations, the use of oral contraceptives following a completed treatment regimen did not reduce recurrence rates. Even when analyzing all female participants (both incomplete and full doses), there was no statistically significant difference regarding the use of oral contraceptives. This might be explained by the small size of the sample of women studied.

The high recurrence rate verified in patients who used topical medications after their treatment was complete (42.31%) compared to participants who did not use such substances (22.84%) suggests the existence of a bias, given that patients who begin to present new lesions are more likely to use topical medications. Furthermore, the number of topical medication users was very small. Even so, the variable for using topical medications after a successful outcome did not significantly affect the rate of recurrence.

CONCLUSION

Oral isotretinoin is an effective treatment that produces a relevant and long-lasting reduction of acne. Nevertheless, it is important to note that the condition frequently recurs, especially when recommended doses are not reached. ●

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