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Real-World Safety of Oral Isotretinoin in Patients During Sunny Months: Retrospective Cohort Study

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ABSTRACT

Introduction: There is a widespread clinical practice of avoiding oral isotretinoin administration during the sunny season due to its purported photosensitizing effect. However, this approach is not supported by solid evidence.

Objective: The aim of this study was to assess the safety and effectiveness of administering oral isotretinoin at a reduced daily dosage during the sunny period in a real-world clinical setting.

Methods: This retrospective cohort study included all acne patients treated with oral isotretinoin at our Acne Clinic (January 2014 - December 2023) who had received the drug between June and September, when UV index exceeds a threshold of 6. Conventionally, oral isotretinoin daily dosage is reduced by approximately half during these four sunny months and then increased again. We compared the occurrence of side effects or treatment discontinuation between sunny and non-sunny periods. The therapeutic response was explored in relation to the daily dosage.

Results: 359 patients (61.3% males, with a mean age of 19.0 years, standard deviation (SD) 6.7) were included. Adverse events were reported by 39.2% and 28.3% of patients during the non-sunny and sunny months, respectively. The incidence of treatment discontinuation was negligible. The reduction in acne severity was independent of the daily dosage of oral isotretinoin.

Conclusions: The study results support the lack of any necessity to suspend or refrain from administering oral isotretinoin during sunny seasons. The preventive reduction of its daily dosage during sunny periods does not negatively affect the drug's effectiveness. Oral isotretinoin can be taken, at a slightly reduced dosage, during sunny months.

Introduction

Oral isotretinoin is the most effective therapeutic option for acne by virtue of its broad spectrum of action [1,2]. According to European guidelines, it is typically reserved for severe papulopustular or moderate nodular acne as well as for acne that has not responded to oral antibiotics and topical treatments [3].

Despite its efficacy, dermatologists are often hesitant to prescribe oral isotretinoin due to its well-documented side effects. The most significant, and not dose-dependent, extracutaneous side effect is teratogenicity, necessitating the use of effective contraception in females of childbearing age, along with monthly pregnancy tests [4]. Common and dose-dependent cutaneous side effects include dryness of the skin, lips, and eyes, which may cause discomfort and require the use of moisturizers or eye drops [5].

Photosensitivity is listed as a potential side effect in the technical data sheets, recommending limited exposure to ultraviolet (UV) radiation and the use of protective measures such as long clothing, hats, and high SPF sunscreen along with the personalization of the dosage. However, the available evidence on isotretinoin photosensitivity is outdated and often contradictory. Only a few cases, a long-time ago, reported phototoxic [6,7] or photoallergic [8] mechanisms. Immediate-type hypersensitivity with IgE involvement has been suggested [9]. Attempts to confirm the allergic mechanism through phototesting have not demonstrated sunlight as the primary cause of erythema in patients taking oral isotretinoin [10]. Moreover, studies have shown no significant changes in the ultraviolet A and B minimal erythema dose (MED) in patients using the drug [11].

Despite that, there is a widespread clinical practice of avoiding its administration during the sunny season or temporarily suspending treatment during ongoing therapy. This approach lacks solid evidence to support it, as no study has addressed the use of oral isotretinoin in the summer or in seasons with high UV indices. Therefore, there is no concrete evidence to suggest that more frequent or severe side effects occur during the sunny season compared to other times of the year.

Objectives

In our clinical practice, we do not suspend or delay the initiation of oral isotretinoin treatment during the sunny months. However, we have found that reducing its daily dosage can be beneficial. This precaution is based on oral isotretinoin's effect on the skin, including the reduction of the lipid film and thinning of the stratum corneum, which may increase its vulnerability to external factors, including solar radiation.

The aim of this study was to assess the safety of using oral isotretinoin, at a reduced daily dosage, during the sunny season in a real-world clinical setting.

Methods

Study Design and Objectives

This study was designed as a single-center, retrospective cohort study to analyze the use of oral isotretinoin in acne patients during the sunny months of the year, when administered at a reduced daily dosage. The study was conducted in a geographic region where the UV index typically exceeds a threshold of 6 during June, July, August, and September. Specifically, the objectives of the study were to assess the safety of oral isotretinoin administration during the aforementioned four sunny months and to evaluate the effectiveness of a reduced daily dosage regimen of oral isotretinoin, tailored to the sunny season.

This was an observational study conducted without external funding. All patients treated at our outpatient clinic adhered to the ethical principles outlined in the Declaration of Helsinki (1975, revised 2013). The study was approved by the Comitato Etico Area Vasta Centro della Regione Emilia-Romagna (CE-AVEC) (protocol number 395/2024/Oss/AOUFe, approval date: 18/07/2024) and by the ethics committees at all participating sites. Written informed consent was obtained from all patients. A waiver of informed consent was granted for patients who could not be traced and for whom obtaining consent was not feasible. Adherence to the STROBE checklist for observational studies is summarized in Table S1.

Study Patients

In our clinical practice, acne patients are offered treatment with oral isotretinoin when they fail to respond to prior conventional combined therapies, which typically include a systemic antibiotic and a topical agent, or in cases of acne relapse after discontinuation of first-line treatments.

All acne patients treated with oral isotretinoin between January 2014 and December 2023 at the Acne Clinic of the Dermatology Unit at the University Hospital of Ferrara (located in northeastern Italy) were retrospectively considered for inclusion. Patients were eligible if they had received oral isotretinoin for at least four weeks between June and September, regardless of when the treatment was initiated or its overall duration. Age, acne severity, and whether the treatment was the first or a subsequent course were not used as inclusion criteria. For recruitable patients who underwent multiple cycles of oral isotretinoin, only the first in chronological order was taken into consideration. The only exclusion criteria were refusal to participate or incomplete demographic or clinical data.

Study Procedures and Assessments

At our Acne Clinic, the mean daily dosage of oral isotretinoin is between 0.2 and 0.3 mg/kg [12]. Initially, a daily dose of <0.2 mg/kg is administered to reduce the potential for acne flare-ups [13,14], and this is gradually increased over the first four weeks of treatment. Conventionally, the daily dosage is reduced by approximately half during the four sunny months, then increased again in October and the following months.

Oral isotretinoin is never suspended a priori during the sunny season.

The severity of acne is assessed using the Leeds Revised Acne Grading System [15], both at baseline and at subsequent control visits, which are scheduled at 12-week intervals. Liver function tests and lipid profile are evaluated for all patients prior to treatment initiation and again at six weeks after treatment begins. These tests are repeated as needed throughout the treatment course. For female patients of childbearing potential, a pregnancy test is performed before starting treatment and monthly thereafter, prior to each prescription. Oral contraception is required to be initiated before starting treatment and continued throughout the entire treatment period as well as for four weeks after therapy ends.

All patients receive both verbal and written information on the need to use emollients for their lips and moisturizing products for their skin and to adhere to rigorous photoprotection during the sunny months. Patients can contact the Acne Clinic at any time to report side effects, with a follow-up visit scheduled as necessary.

The following data were collected from the patients' clinical records: i) age and sex; ii) acne severity at baseline, using the Leeds Revised Acne Grading System; iii) acne severity at each control visit; iv) daily dosage of oral isotretinoin for each month of therapy; v) occurrence of clinical side effects or laboratory anomalies, specifying the month of onset or diagnosis; vi) treatment discontinuation for any reason; vii) treatment duration in months. All adverse events which occurred during therapy were taken into account, except for lip xerosis, which was excluded as it is an expected effect.

Sample Size and Statistical Analysis

In the literature, there is no scientific evidence of the seasonal proportion of adverse events in patients receiving oral isotretinoin. For the sample size calculation, historical data of our Acne Clinic were employed: a "seasonal" adverse events proportion (sunny period from June to September and not-sunny period from October to May) of 13.4% and 5.2%, respectively, was registered. A power estimation, based on the comparison of the two proportions, given a level $\alpha = 0.05$ and $1-\beta = 0.8$, allowed a sample size of 182 patients. Despite the fact that 182 is the minimum number of patients to be considered in order to identify a statistically significant difference in terms of seasonal proportion of adverse events, we considered the entire historical cohort of patients treated at our Acne Clinic in the time frame considered.

The Shapiro-Wilk test was used to check the normality assumption of continuous variables. In the presence of symmetry, variables were represented with mean and standard deviation (SD) or, in case of asymmetry with median and quartiles [Q1 Q3]; categorical data are expressed as absolute values and percentages (%).

The Student's t-test or Mann-Whitney test was used to detect possible mean or median significant differences between the two groups. In case of categorical variables, $\chi 2$ or exact Fisher test was used. A scatter plot with an interpolation line is displayed to represent the joint distribution between the differential daily mean dose (x-axis) and the differential Leeds scores (y-axis), for each site (face, back, and chest). The first and last month of treatment values available were used to calculate the differential in daily mean dose. Moreover, differential values in Leeds scores were computed as the difference between baseline and last available observation. All analyses were performed using the software RStudio Team (2020). RStudio: Integrated Development for R. RStudio, PBC, Boston, MA URL http://www.rstudio.com/. A p-value of <0.05 was considered statistically significant.

Results

Baseline Study Population Features

A total of 359 patients were included, of whom 61.3% were male (N=220) and 38.7% were female (N=139) (Table 1). The median age of all patients was 17 years (range: 16.0–20.0), with a mean age of 19.0 years (±6.7). Male patients were slightly younger (median age: 17.0 years, range: (15.0–19.0)) compared to female patients (median age: 18.0 years, range: (16.0–23.0)), with a difference in the median ages (P=0.009).

Facial acne was highly prevalent, affecting 98.3% of the entire cohort. The difference between males and females was not significant (P=0.086) as 100% of females and 97.3% of males had facial acne. However, significant sex differences were observed in the distribution of truncal acne. Back acne was present in 74.1% of males compared to 40.3% of females (P<0.001). Similarly, chest acne was more common in males (38.6%) than in females (24.5%) (P=0.008).

The severity of acne assessed using the Leeds Revised Acne Grading System showed no significant difference between sexes on the face (P=0.541), back (P=0.666), or chest (P=0.199). The median duration of oral isotretinoin treatment was 10.0 months [8.0 13.0] for the entire cohort, with no significant difference between male and female patients (P=0.233).

Table 1. Baseline Characteristics of the Study Patients.

	All Patients (N= 359)	Female (N= 139)	Male (N= 220)	*p-value*
Age (years), median [Q1 Q3]	17.0 [16.0;20.0]	18.0 [16.0;23.0]	17.0 [15.0;19.0]	0.009
Age (years), mean (SD)	19.0 (6.7)	19.9 (6.2)	18.5 (6.9)	0.056
Sex, N (%)				
Male	220 (61.3%)	0	220 (100%)	
Female	139 (38.7%)	139 (100%)	0	
Face, presence of acne, N (%)	353 (98.3%)	139 (100.0%)	214 (97.3%)	0.086
Back, presence of acne, N (%)	219 (61.0%)	56 (40.3%)	163 (74.1%)	<0.001
Chest, presence of acne, N (%)	119 (33.1%)	34 (24.5%)	85 (38.6%)	0.008
Face Leeds Revised Acne Grading System, median [Q1 Q3]	3 [2;4]	3 [2;4]	3 [2;4]	0.541
Back Leeds Revised Acne Grading System, median [Q1 Q3]	3 [2;4]	3 [2;4]	3 [2;4]	0.666
Chest Leeds Revised Acne Grading System, median [Q1 Q3]	2 [1;3]	1 [1;2]	2 [1;3]	0.199
Treatment duration (months), median [Q1 Q3]	10.0 [8.0;13.0]	10.0 [8.0;12.0]	10.0 [8.0;14.0]	0.233

[Q1 Q3]: first and third quantiles; SD, standard deviation.

Treatment Effectiveness

The effectiveness of oral isotretinoin treatment was assessed by comparing acne severity scores before treatment and at its completion using the Leeds Revised Acne Grading System (Table 2). A total of 352 patients were evaluated for facial acne severity, 219 for back acne, and 118 for chest acne.

There is a minor discrepancy compared to the total number of enrolled patients, as the number of patients with facial acne and truncal cane was 353 and 119, respectively (Table 1). However, one subject did not have a baseline severity score recorded for the face. Similarly, one patient with chest acne lacked follow-up data for this site. They were therefore excluded from the analyses.

For facial acne, the median severity score significantly decreased from 3 (2–4) at baseline to 0 (0–1) after treatment (P<0.001). Similarly, for back acne, the median score dropped from 3 (2–4) to 0 (0–1) (P<0.001). Chest acne also showed substantial improvement, with the median score decreasing from 2 (1–3) to 0 (0–1) following treatment (P<0.001).

These results show a statistically significant reduction in acne severity across all body areas following oral isotretinoin therapy.

Seasonal Safety of Treatment

The seasonal safety profile of oral isotretinoin was assessed by comparing the daily dosage, occurrence of adverse events, and treatment discontinuation rates between the non-sunny months (October to May) and the sunny months (June to September) (Table 3).

The median isotretinoin dose was significantly lower during the sunny months (10.0 mg; (10.0– 15.0)) compared to the non-sunny months (15.0 mg; (10.0–20.0)) (P<0.001). Adverse events were reported by 39.2% of patients during the non-sunny months, while this figure decreased to 28.3% during the sunny months (P<0.001). The most frequently adverse event recorded was skin xerosis (212 records), followed by epistaxis, and facial dermatitis, reported 136 and 104 times, respectively. Other notable side effects included fatigue (76 records), arthralgia and myalgia (54), conjunctivitis (45), headache (41), and mood disturbances (27). Less common adverse events included xerophthalmia (7), increase in creatine phosphokinase (2), elevated liver enzyme levels (1), and muscle cramps (1).

Treatment discontinuation rates remained consistent across the two periods, with 1.1% of patients discontinuing oral isotretinoin during the non-sunny months and 1.2% during the sunny months (P=0.999). It is worth noting that the treatment was not discontinued due to adverse effects related to the medication but rather due to a temporary suspension for personal reasons and surgical procedures.

Relationship between Daily Dose and Treatment Effectiveness

A further study objective was to assess the therapeutic response based on the daily dosage of oral isotretinoin across the three different skin sites. The relationship between the differential daily dose and the differential Leeds scores, for each site, showed no significant association (Figure 1).

Table 2. Acne Severity Scores by Area, comparing Before and After Treatment. After treatment data have been computed as the median of the last available data for each patient, in each area of interest.

	N	Before treatment	After treatment	*p-value*
Face Leeds Revised Acne Grading System, median [Q1 Q3]	352	3 [2;4]	0 [0;1]	<0.001
Back Leeds Revised Acne Grading System, median [Q1 Q3]	219	3 [2;4]	0 [0;1]	<0.001
Chest Leeds Revised Acne Grading System, median [Q1 Q3]	118	2 [1;3]	0 [0;1]	<0.001

[Q1 Q3]: first and third quantiles

Table 3. Comparison of Oral Isotretinoin Daily Dose, Discontinuation, and Adverse Events Occurrence in Non-Sunny and Sunny Months. Not-sunny period refers to months from October to May while sunny period is between June and September.

	Non-sunny months	Sunny months	*p-value*
Drug daily dose (mg), median [Q1 Q3]	15.0 [10.0 20.0]	10.0 [10.0 15.0]	<0.001
Adverse Events, N (%)			<0.001
none	2,224 (60.8%)	294 (71.7%)	
1 or more	1,434 (39.2%)	116 (28.3%)	
Drug discontinuation, N (%)			0.999
yes	29 (1.1%)	18 (1.2%)	
no	2,488 (98.9%)	1,537 (98.8%)	

[Q1 Q3]: first and third quantiles

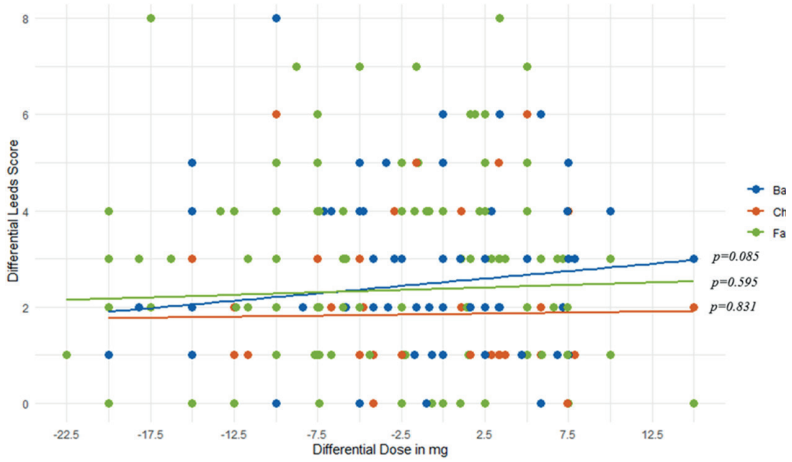

Figure 1. Scatter plot comparing differential values in dose between first versus last month's daily dosage and pre- versus post-treatment Leeds Severity Scoring system by skin site.

Conclusions

The primary objective of this study was to assess the safety of administering oral isotretinoin during sunny seasons. The extensive time frame analyzed retrospectively, along with the high and steady patient attendance at our Acne Clinic, allowed for the inclusion of a greater number of patients than initially estimated through the sample size calculation. The sample included provided a robust opportunity to offer evidence regarding the common belief that oral isotretinoin should be contraindicated during sunny months, either confirming or refuting this assumption.

The patients enrolled represent a typical acne patient cohort receiving oral isotretinoin, both demographically and clinically. Truncal acne was significantly more prevalent in male patients than in females (Table 1), in accordance with existing epidemiological data [16].

Regarding treatment outcomes, a significant reduction in acne severity was observed across all anatomical areas after oral isotretinoin treatment (Table 2). The Leeds Revised Acne Grading System scores showed marked improvement for facial, back, and chest acne, with the median scores dropping to near-zero values post-treatment (Table 2). These results were expected and are consistent with numerous previous studies that have demonstrated the effectiveness of oral isotretinoin in inducing acne remission, even in severe and recalcitrant cases [3,17–20].

The complete or near-complete resolution of acne in most patients is unsurprising given the unique mechanism of action of oral isotretinoin [4]. The consistency of these outcomes across different body sites further supports its broad-spectrum effectiveness. While facial acne is often the primary focus of treatment, acne on the back and chest can be more challenging due to the thicker skin and larger sebaceous glands in these areas [21]. These results reinforce the role of oral isotretinoin as the gold standard in acne treatment, regardless of the affected body site.

The most noteworthy aspect of this study, which was not specifically addressed in previous research, is its primary objective, i.e., assessing the safety of oral isotretinoin when administered during sunny seasons. The rates of adverse events observed during the sunny months were no higher than those recorded during the non-sunny periods. In fact, our experience indicates that the incidence of side effects was lower during the sunny months compared to the rest of the year. This appears to be attributed to the reduced daily dosage of the drug during the sunniest months, as adverse events are known to be dose-dependent.

The absence of an increased rate of drug discontinuation and severe adverse events during the summer months further supports the notion that oral isotretinoin is neither photoallergic nor phototoxic. While patients on oral isotretinoin may experience heightened skin sensitivity, this vulnerability is not limited to sun exposure; it extends to a variety of exogenous irritants at any time of the year. This underscores the importance of advising patients to adopt protective measures year-round, including emollients for the skin and lips, gentle cleansing, and rigorous photoprotection.

Therefore, our data challenge the common practice of delaying oral isotretinoin administration until after the summer or suspending treatment during the sunny months due to concerns about sun exposure. Given that untreated acne can lead to long-term scarring, postponing treatment for several months could result in permanent skin damage [22]. Instead, initiating oral isotretinoin treatment promptly and advising patients on appropriate skin care can help prevent unnecessary delays in achieving acne remission. This approach also addresses the suffering and emotional burden that acne can cause.

The systematic reduction in the daily dosage of oral isotretinoin before the start of the sunny season raises the question of whether this practice affects the treatment's effectiveness. Figure 1 shows the relationship between mean daily dosages (from the start to the completion of treatment) and changes in acne severity. For the back site, a positive trend was found, albeit not significant (P=0.085). Clinically, this suggests that a temporary reduction in daily dosage does not significantly impact the therapeutic efficacy of oral isotretinoin [23].

The study results have several limitations. As a retrospective study, it did not allow for the collection of detailed information on patients' sun exposure habits, including the use of photoprotection. Given the young age of the participants, it is likely that their ultraviolet exposure was primarily recreational rather than occupational, but specific data on this were not available. Additionally, while comparing the four months with the highest UV radiation to the remaining eight months was a rational approach, it was somewhat arbitrary. The findings of this study are specific to the geographical area in which it was conducted and may not be generalizable to regions with different radiation levels. Furthermore, the subjects included were all Caucasian, while other ethnic groups were not represented.

Despite these limitations, this is the first study to specifically address the use of oral isotretinoin during sunny seasons, with a focus on its safety profile. The study suggests that reducing the daily dose of oral isotretinoin during the sunny months may be a reasonable strategy to minimize the occurrence of adverse events. Based on our findings, there is no evidence to support postponing the start of treatment until the fall or suspending it during the summer months. On the contrary, oral isotretinoin can be safely administered during sunny seasons to reduce acne severity, alleviate its emotional burden, and prevent scarring, which can be worsened by delaying appropriate treatment. While reducing the daily dose may help mitigate side effects during sunny months, it does not appear to compromise the drug's therapeutic effectiveness.

In conclusion, this study's results support the use of oral isotretinoin even during high UV radiation seasons, at a slightly reduced daily dosage.

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