Dermatology Practical & Conceptual

Supplementary File

Table S1. Adherence to the STROBE checklist for observational studies.

	Item No	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 2	The study's design as a retrospective cohort is indicated in the title and abstract.
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2	The abstract provides a summary of the study's objectives, methods, results, and conclusions.
Introduction				
Background /rationale	2	Explain the scientific background and rationale for the investigation being reported	3	[…] the available evidence on isotretinoin photosensitivity is outdated and often contradictory. Only a few cases, a long-time ago, reported phototoxic or photoallergic mechanisms. Immediate-type hypersensitivity with IgE involvement has been suggested. Attempts to confirm the allergic mechanism through phototesting have not demonstrated sunlight as the primary cause of erythema in patients taking oral isotretinoin. Moreover, studies have shown no significant changes in the ultraviolet A and B minimal erythema dose (MED) in patients using the drug. 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	3	State specific objectives, including any prespecified hypotheses	4	The aim of this study was to evaluate the safety of using oral isotretinoin, at a reduced daily dosage, during the sunny season in a real-world clinical setting.
Methods				
Study design	4	Present key elements of study design early in the paper	4	This study was designed as a single-center, retrospective cohort study.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5	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 north-east of Italy) were retrospectively considered for inclusion.

Table S1 continues

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Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5	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 north-east of Italy) were retrospectively considered for inclusion. Patients were eligible if they had received oral isotretinoin for at least 4 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 patients who underwent multiple cycles of oral isotretinoin, among those that met the inclusion and exclusion criteria, only the first in chronological order was taken into consideration. The only exclusion criteria were refusal to participate or incomplete demographic or clinical data.
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6	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. Regarding side effects, all adverse events which occurred during therapy were taken into account, except for lip xerosis, which was excluded as it is an expected effect.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5	The severity of acne is assessed using the Leeds Revised Acne Grading System, both at baseline and at subsequent control visits, which are scheduled at 12-week intervals.
Bias	9	Describe any efforts to address potential sources of bias	6	See: Sample size and Statistical analysis
Study size	10	Explain how the study size was arrived at	6	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.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6, 7	See: Sample size and Statistical analysis

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Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6, 7	See: Sample size and Statistical analysis
		(*b*) Describe any methods used to examine subgroups and interactions	6, 7	See: Sample size and Statistical analysis
		(*c*) Explain how missing data were addressed	7, 8, 9	Discussed in "Results"
		(*d*) If applicable, explain how loss to follow-up was addressed	7, 8, 9	Discussed in "Results"
		(*e*) Describe any sensitivity analyses	NA	NA
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7	A total of 359 patients were included in the study. […] A total of 352 patients were evaluated for facial acne severity, 219 for back acne, and 118 for chest acne.
		(b) Give reasons for non-participation at each stage	NA	NA
		(c) Consider use of a flow diagram	NA	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7	See: Baseline study population features
		(b) Indicate number of participants with missing data for each variable of interest	7, 8	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 S1). 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.
		(c) Summarise follow-up time (eg, average and total amount)	7	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 S1 continues

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Outcome data	15*	Report numbers of outcome events or summary measures over time	7, 8	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 […] 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).
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8	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). […] 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). […]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).
		(*b*) Report category boundaries when continuous variables were categorized	NA	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9	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.
Discussion				
Key results	18	Summarise key results with reference to study objectives	9, 10	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.

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Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10, 11	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.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11	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.
Generalizability	21	Discuss the generalizability (external validity) of the study results	10, 11	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.
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1	This was an observational study conducted without external funding.