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ORIGINAL RESEARCH ARTICLE

Safety and Effectiveness of Upadacitinib in Patients with Moderate-to-Severe Atopic Dermatitis Who Smoke: a 2-Year Real-Life Multicenter Study

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Abstract

Background Atopic dermatitis (AD) is a chronic inflammatory skin condition that significantly impairs the quality of life. Recent advancements in systemic therapies, such as Janus kinase (JAK) inhibitors, offer very effective new treatment options. However, concerns regarding potential adverse events, including cardiovascular and thromboembolic risk, have emerged from clinical studies and call for further real-life investigations. This has highlighted the need to establish specific risk categories, such as tobacco smokers.

Objective This study aims to evaluate the safety and effectiveness of upadacitinib, a JAK1 inhibitor, in patients who smoke with moderate-to-severe AD over a 2-year treatment period, comparing outcomes with patients who do not smoke.

Patients and Methods A retrospective multicenter study was conducted across 12 dermatology departments in Italy, including 375 patients treated with upadacitinib. The presence and intensity of smoking habits as well as effectiveness scores and safety data were collected.

Results Patients who smoke accounted for 36.8% of the sample. Two thromboembolic events in patients who do not smoke were recorded in the 2-year (median follow up of 52.6 weeks) observation period. The most common adverse event was acneiform eruption (12.4% of patients after 104 weeks). No significant differences related to safety emerged regarding the presence or absence of a smoking habit. Drug survival was very high with no differences between the two cohorts (83.5% after 104 weeks for patients who smoke).

Conclusions This study suggests that upadacitinib is a safe and effective treatment for moderate-to-severe AD in presence of tobacco smoke, with no significant differences in safety or effectiveness compared with patients who do not smoke.

1 Introduction

Atopic dermatitis (AD) poses a substantial clinical challenge, marked by its chronic inflammatory nature and diverse symptomatology [1]. Intense itching, skin discomfort, inflammation, and dryness, coupled with sleep disruption, mental health issues, and concurrent atopic conditions collectively impact the quality of life, especially among individuals with moderate-to-severe AD [2, 3]. The therapeutic management of moderate-to-severe AD has changed dramatically since the introduction of drugs blocking selectively Th2 cytokines and Janus kinase (JAK) inhibitors, which provides very effective treatment options [4–8]. However, the enthusiasm surrounding JAK inhibitors has been tempered by concerns over potential adverse effects: clinical trials in rheumatoid arthritis (RA) have identified a potential risk regarding JAK inhibitor-induced venous thromboembolic

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Key Points

This study assessed upadacitinib effectiveness and safety in moderate-to-severe AD in a real-life setting, exploring response differences in relation to smoking habit.

The results from our real-world study demonstrate for the first time the effectiveness and safety profile of upadacitinib in patients who smoke treated with upadacitinib for moderate-to-severe AD, showing no significant differences according to smoking status.

Upadacitinib emerges as a potentially safe and effective treatment for patients who smoke with moderate-to-severe AD, showing no increase in adverse events in patients without other cardiovascular risk factors. Further and more in-depth long-term studies are required to explore our findings.

events (VTEs), including deep vein thrombosis and pulmonary embolism, major cardiovascular events, serious infections, and development/recurrence of malignancies, leading regulatory agencies to issue "black-boxed warnings" [9–12]. The mechanisms supporting these potential risks are intricate and incompletely understood. The inhibition of JAK-STAT signaling, central to immune modulation, may disrupt the delicate equilibrium of cellular processes governing cardiovascular homeostasis and regulation of thrombosis [13, 14]. It is well known that tobacco smoking significantly increases the risk of developing various diseases, including heart disease, thrombotic events, and cancer. Numerous studies have demonstrated that the harmful chemicals in tobacco smoke can damage the heart and blood vessels, increase risk of clotting, and lead to the development of multiple types of cancers [15].

On the basis of the lack of real-life studies aimed at evaluating the effect of tobacco smoking on patients with AD undergoing therapy with a JAK inhibitor, in this retrospective multicenter study we analyze the safety and effectiveness of the JAK1 inhibitor upadacitinib in patients who smoke with moderate-to-severe AD and were treated for up to 2 years.

2 Patients and Methods

This retrospective multicenter chart review study included patients (age > 12 years) affected by moderate-to-severe atopic AD and treated with upadacitinib at 12 hospital-based dermatology departments in Italy for a period of up to 2 years. The main objective was to understand the safety and effectiveness of upadacitinib in patients who smoke and compare outcomes with those without a smoking habit. For each patient, the presence or absence of smoking habit was determined based on information directly provided by the patient, specifying the extent in terms of intensity (number of units smoked per day) and duration (years). Effectiveness was assessed with the Eczema Area and Severity Index (EASI), evaluating its mean value, mean percentage reduction, and improvements from baseline of 75% or more (EASI-75), 90% or more (EASI-90), and 100% (EASI-100) after 28, 52, and 104 weeks of treatment. We also assessed the decrease in the Pruritus-Numerical Rating Scale (P-NRS), Sleep Loss-Numerical Rating Scale (S-NRS), and Dermatology Life Quality Index (DLQI) over the course of the study. Additionally, the safety profile was evaluated by analyzing adverse events (AEs) during the treatment, as well as any treatment interruptions that occurred along with the corresponding reasons. Furthermore, the drug survival was assessed after 104 weeks of treatment. Upadacitinib was used at 15 mg for patients under 18 years of age, as this is the only approved dosage for this age group. For the adult population, the dosage (either 15 mg or 30 mg) was determined by the physician at the time of the visit on the basis of the patient's clinical presentation, medical history, and demographic characteristics.

2.1 Statistical Analysis

For this analysis, epidemiological data (i.e., demographic and disease characteristics and medical history) were summarized using descriptive statistics. Descriptive statistics were used to evaluate the data set according to the number of patients and their percentage proportion in the groups related to the categorical variables; mean and standard deviation (SD) were used for continuous variables. Categorical variables were analyzed using a chi-squared test and Fisher's exact test as appropriate, while continuous variables were tested using the Shapiro-Wilk test to investigate the normality of the distribution. Dichotomous normal distributions were compared using Student's *t*-test, and non-normal distributions were tested using the Mann–Whitney *U* test. Imputation of nonresponders was not conducted, and only observed cases were evaluated. Survival curves were approximated through the Kaplan–Meier estimator and compared using the long-rank test. Differences between groups were considered statistically significant for p-values < 0.05. All statistical analyses were performed with STATA 17 software.

3 Results

Table 1 lists the demographic data of the entire population and the two subgroups on the basis of smoking habit, including distribution by sex, age, comorbidities, age of onset,

Table 1 Baseline demographics, comorbidities and previous therapies

	Total ($N = 375$)	Patients who smoke ($N = 138$)	Patients who do not smoke ($N = 237$)
Sex, *N* (%)			
Female	149 (39.1)	48 (34.8)	101 (42.1)
Male	226 (60.9)	90 (65.2)	136 (57.9)
Age at upadacitinib start, years			
Mean (SD)	37.1 (14.4)	36.7 (13.9)	37.3 (14.7)
Median	34.0	32.0	34.0
Range	16–83	16–70	16–83
Duration of atopic dermatitis (SD)	25.7 (14.2)	25.5 (13.4)	25.8 (14.6)
Age at onset of AD, years			
Mean (SD)	12.6 (16.9)	12.8 (16.2)	12.5 (17.4)
Median	5.0	5.0	5.0
Range	0–70	0–60	0–70
Atopic comorbidities, *N* (%)			
Allergic conjunctivitis	76 (20.3)	19 (13.8)	57 (24.1)
Food allergies	24 (6.4)	4 (2.9)	20 (8.4)
Asthma	80 (21.3)	20 (14.5)	60 (25.3)
Allergic rhinitis	103 (27.5)	24 (17.4)	79 (33.3)
Family history of AD	110 (29.3)	37 (26.8)	73 (30.1)
Comorbidities, *N* (%)			
Atopic comorbidities	169 (45.0)	42 (30.4)	127 (53.6)
Arterial hypertension	33 (8.8)	9 (6.5)	24 (10.1)
Dyslipidemia	14 (3.7)	5 (3.6)	9 (3.8)
Alopecia areata	11 (2.9)	7 (5.1)	4 (1.7)
Diabetes	5 (1.3)	2 (1.4)	3 (1.3)
Others	66 (17.6)	23 (16.7)	43 (18.1)
Previous therapies, *N* (%)			
Topical steroid	367 (97.9)	137 (99.2)	230 (97.2)
Topical calcineurin inhibitors	242 (65.4)	85 (61.5)	161 (67.9)
Systemic steroid	83 (22.1)	31 (22.5)	52 (21.7)
Cyclosporine	196 (52.3)	75 (54.3)	121 (50.4)
Narrowband UVB phototherapy	4 (1.1)	2 (1.4)	2 (0.8)
Dupilumab	219 (58.4)	80 (58.0)	139 (57.9)
Tralokinumab	11 (2.9)	3 (2.2)	8 (3.3)
Abrocitinib	2 (0.5)	1 (0.7)	1 (0.4)
Baricitinib	2 (0.5)	0 (0.0)	2 (0.8)
Concomitant therapies, *N* (%)			
Topical steroid	134 (35.7)	47 (34.0)	87 (36.7)
Topical calcineurin inhibitors	13 (3.5)	5 (3.6)	8 (3.4)
Systemic steroid	16 (4.3)	5 (3.6)	11 (4.5)
Cyclosporine	3 (0.8)	0 (0.0)	3 (1.2)

AD atopic dermatitis, *SD* standard deviation

family history of AD, and previous and concomitant therapies. Within the cohort of 375 patients, those who smoke accounted for 138 (36.8%), with an average duration of smoking habit of 15.3 years and a mean daily consumption of 9.2 cigarettes (8.5 pack-years). At baseline, the dosage was 30 mg per day for 163 patients and 15 mg per day for the remaining 212 patients. Among the latter group, 143 patients had no smoking habit (67.5%) and 69 did smoke (32.5%) ($p = 0.04$). No statistically significant differences were observed at subsequent timepoints regarding dosage between the two cohorts.

3.1 Adverse Events

A total of 118 (31.5%) out of 375 patients experienced one or more AEs after starting upadacitinib therapy. All AEs were of mild to moderate severity, with the exception of two VTEs, which are described in detail below. The most frequent AE at each timepoint turned was new onset of acneiform eruption. Table 2 reports the incidence of any AE, acneiform eruption, conjunctivitis, herpes simplex, herpes zoster, cutaneous infections (folliculitis or abscesses), and VTEs for each of the three timepoints, the overall incidence across all timepoints reached, and the number of patients treated for up to 2 years who experienced the cited events, divided according to smoking habit. No significant differences emerged regarding the presence or absence of smoking habit in the development of specific AEs or in their overall incidence. In addition, a sub-analysis conducted exclusively on the population of patients who smoke did not find significant differences regarding the duration of smoking habit or the number of cigarettes smoked daily in relation to the development of AEs (Table 2). Furthermore, the statistical analysis conducted on the subpopulation receiving a dosage of 30 mg per day did not reveal significant differences in the safety of the treatment between patients who smoke and patients who do not (Table 3).

Two patients reported thromboembolic events (VTEs): one episode of deep vein thrombosis (DVT) after 12 weeks of treatment, and one provoked pulmonary embolism (PE) following trauma at 52 weeks from the start of upadacitinib therapy, leading to discontinuation of treatment in both cases. The two patients with VTEs did not belong to the population of patients who smoke.

3.2 Effectiveness

The mean values of EASI, P-NRS, S-NRS, and DLQI at baseline and at each of the three timepoints for both cohorts based on smoking habit are presented in Table 4. The only parameter showing a significant difference between the two subpopulations at baseline was the EASI score, with a mean value of 20.27 in patients who smoke and 22.54 in patients who do not smoke ($p = 0.04$). The mean EASI scores progressively decreased, reaching their lowest values after 2 years of treatment (1.54 for patients who smoke and 1.95 for patients who do not), with no significant differences at any timepoint (Table 4).

The percentages of patients who achieved EASI-75, EASI-90, and EASI-100 after 28, 52, and 104 weeks of treatment progressively increased at each timepoint (Table 4). Two statistically significant differences based on smoking status were observed. The first was that, at the first timepoint (28 weeks), EASI-100 was achieved by 61.3% of patients who smoke compared with 27.1% of the ones without smoking habit ($p = 0.031$). Furthermore, at 2 years of treatment, EASI-100 was reached by 68.6% of patients who smoke and 44.4% of patients who do not smoke ($p = 0.016$). Mean values of P-NRS and S-NRS decreased significantly after 28 weeks and reached their lowest levels after 2 years in both subpopulations. Statistically significant differences were noted only at the initial time point, with a lower mean P-NRS value (1.66) for patients who smoke ($p = 0.046$) as well as lower mean S-NRS value (0.81) ($p = 0.017$).

Regarding mean DLQI values between the two subgroups, significant differences with better results for patients who smoke were observed at 28 weeks (2.17 versus 3.81; $p = 0.004$) and 104 weeks (0.77 versus 1.85; $p = 0.043$).

3.3 Drug Survival

In total, 61 patients (18.7%) discontinued treatment. Among these, 42 (12.9%) were permanent, while 19 (5.8%) were temporary and the therapy was subsequently resumed (median duration of interruption: 30 days). Among the permanent discontinuations, 22 (52.4%) were attributed to AEs, 16 (38.1%) to lack of effectiveness, 2 (4.8%) to either occurring or planned pregnancy, and 2 (4.8%) to sustained complete remission. No significant differences emerged regarding drug discontinuation and the presence or absence of smoking habit ($p = 0.193$). The statistical analysis on the subpopulation of patients who smoke did not reveal significant differences associated with the duration and intensity of smoking in relation to discontinuation of therapy; only one statistical difference emerged, related to the intensity of smoking habit and discontinuation due to lack of effectiveness (Table 5).

The drug survival rate of upadacitinib in the entire population after 104 weeks of treatment was 80.8%. No significant differences were observed between patients who smoke (83.5%) and patients who do not smoke (79.8%) ($p = 0.236$) or among the first group in relation to the duration and intensity of smoking habit (Fig. 1).

4 Discussion

The therapeutic landscape for moderate-to-severe atopic AD has undergone a significant transformation in recent years and continues to expand with the approval of several new treatments and numerous others under investigation [6]. Two key classes of drugs, anti-IL monoclonal antibodies and JAK inhibitors, have emerged as highly effective options in the management of this complex disease. The most notable difference between the two classes of new systemic therapies lies in their safety profiles. Significant regulatory warnings have been issued for JAK inhibitors regarding potential severe side effects, particularly from

Table 2 Upadacitinib safety in patients who smoke and patients who do not with moderate-to-severe AD at week 28, 52, and 104 and overall adverse events

	Week 28 (%)	Week 52 (%)	Week 104 (%)	Overall (%)	Overall after 104 weeks (%)
Number of patients					
Total patients	326	246	89	326	89
Tobacco smoking: yes	119	86	35	119	35
Tobacco smoking: no	207	160	54	207	54
Total adverse events (AEs)					
All patients	85 (26.1)	57 (23.2)	13 (14.6)	118 (31.5)	35 (39.3)
Tobacco smoking: yes	33 (27.7)	16 (18.6)	6 (17.1)	43 (36.1)	16 (45.7)
Tobacco smoking: no	52 (25.1)	41 (25.6)	7 (13.0)	75 (36.2)	19 (35.2)
Specific AEs					
Acne					
All patients	35 (10.7)	20 (8.1)	4 (4.5)	44 (13.5)	11 (12.4)
Tobacco smoking: yes	15 (12.6)	6 (7.0)	3 (8.6)	16 (13.4)	5 (14.3)
Tobacco smoking: no	20 (9.7)	14 (8.8)	1 (1.9)	28 (13.5)	6 (11.1)
Conjunctivitis					
All patients	5 (1.5)	1 (0.4)	0 (0.0)	5 (1.3)	2 (2.2)
Tobacco smoking: yes	2 (1.7)	1 (1.2)	0 (0.0)	2 (1.7)	1 (2.9)
Tobacco smoking: no	3 (1.4)	0 (0.0)	0 (0.0)	3 (1.4)	1 (1.9)
Herpes simplex					
All patients	10 (3.0)	12 (4.9)	3 (3.4)	20 (5.3)	8 (8.9)
Tobacco smoking: yes	2 (1.7)	4 (4.8)	1 (2.9)	6 (5.0)	2 (5.8)
Tobacco smoking: no	8 (3.9)	8 (5.0)	2 (3.7)	14 (6.8)	6 (11.1)
Herpes zoster					
All patients	7 (2.1)	4 (1.6)	2 (2.2)	10 (2.6)	6 (6.7)
Tobacco smoking: yes	4 (3.4)	1 (1.2)	1 (2.9)	5 (4.2)	3 (8.6)
Tobacco smoking: no	3 (1.4)	3 (1.9)	1 (1.9)	5 (2.4)	3 (5.6)
Cutaneous infections					
All patients	9 (2.8)	9 (3.7)	2 (2.2)	15 (3.9)	5 (5.6)
Tobacco smoking: yes	3 (2.5)	2 (2.4)	1 (2.9)	3 (2.5)	2 (5.7)
Tobacco smoking: no	6 (2.8)	7 (4.4)	1 (1.9)	12 (5.8)	3 (5.6)
Venous thromboembolism					
All patients	1 (0.3)	1 (0.4)	0 (0.0)	2 (0.6)	0 (0.0)
Tobacco smoking: yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Tobacco smoking: no	1 (0.5)	1 (0.6)	0 (0.0)	2 (0.8)	0 (0.0)
Sub-analysis on smoking habit					
Years of smoking					
≥ 20 years (total patients)	35	27	10	35	10
10–19 years (total patients)	36	27	13	36	13
0–9 years (total patients)	41	26	11	41	11
Total AEs ≥ 20 years	9 (25.7)	5 (18.5)	0 (0.0)	12 (34.3)	4 (40.0)
Total AEs 10–19 years	11 (30.6)	6 (22.2)	3 (23.1)	14 (38.9)	6 (46.2)
Total AEs 0–9 years	11 (26.8)	4 (15.4)	3 (27.3)	14 (34.1)	5 (45.5)
Cigarettes per day (CPD)					
≥ 20 CPD (total patients)	9	9	2	9	2
10–19 CPD (total patients)	33	25	11	33	11
5–9 CPD (total patients)	46	32	14	46	14
< 5 CPD (total patients)	14	9	4	14	4
Total AEs ≥ 20 CPD	3 (33.3)	1 (11.1)	0 (0.0)	4 (44.4)	1 (50.0)
Total AEs 10–19 CPD	8 (24.2)	4 (16.0)	2 (18.2)	14 (42.4)	5 (45.5)
Total AEs 5–9 CPD	15 (32.6)	8 (25.0)	2 (14.3)	25 (54.3)	6 (42.9)
Total AEs < 5 CPD	5 (35.7)	2 (22.2)	2 (50.0)	9 (64.3)	3 (75.0)

AD atopic dermatitis, *W* week, *AE* adverse event, *MACE* major adverse cardiovascular events, *VTE* venous thromboembolism

$^{*}p < 0.05$

Table 3 Upadacitinib 30 mg safety in patients who smoke and patients who do not with moderate-to-severe AD at week 28, 52, and 104

	N	AE (%)	Acne (%)	Conjunctivitis (%)	Herpes simplex (%)	Herpes zoster (%)	Cutaneous infections (%)	VTE (%)
W28								
All patients	119	38 (31.9)	35 (29.4)	5 (4.2)	6 (5.0)	4 (3.4)	4 (3.4)	1 (0.8)
Tobacco smoking								
Yes	44	18 (40.9)	16 (36.4)	2 (4.5)	2 (4.5)	3 (6.8)	2 (4.5)	0 (0.0)
No	75	20 (26.7)	19 (25.3)	3 (4.0)	4 (5.3)	1 (1.3)	2 (2.7)	1 (1.3)
W52								
All patients	105	24 (22.3)	20 (19.0)	1 (1.0)	4 (3.8)	3 (2.9)	5 (4.8)	0 (0.0)
Tobacco smoking								
Yes	37	7 (18.9)	6 (16.2)	0 (0.0)	3 (8.1)	1 (2.7)	1 (2.7)	0 (0.0)
No	68	17 (25.0)	14 (20.6)	1 (1.5)	1 (1.5)	2 (2.9)	4 (5.8)	0 (0.0)
W104								
All patients	48	3 (6.3)	4 (8.3)	0 (0.0)	0 (0.0)	2 (4.2)	2 (4.2)	0 (0.0)
Tobacco smoking								
Yes	13	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No	35	3 (8.6)	1 (2.9)	0 (0.0)	0 (0.0)	1 (2.9)	1 (2.9)	0 (0.0)

AD atopic dermatitis, *W* week, *AE* adverse event, *MACE* major adverse cardiovascular events, *VTE* venous thromboembolism

*$p < 0.05$

Table 4 Upadacitinib effectiveness in patients who smoke and patients who do not with moderate-to-severe AD at week 28, 52, and 104

Timepoint	Parameters	N	EASI-75 (%)	EASI-90 (%)	EASI-100 (%)	EASI	P-NRS	S-NRS	DLQI
Baseline	All patients	375	–	–	–	21.70	7.77	6.24	14.98
	Tobacco smoking: yes	138	–	–	–	20.27	7.72	5.96	14.33
	Tobacco smoking: no	237	–	–	–	22.54*	7.80	6.41	15.36
Week 28	All patients	326	79.14	61.66	39.57	3.07	1.98	1.15	3.21
	Tobacco smoking: yes	119	93 (78.15)	79 (66.39)	73 (61.34)	2.59	1.66	0.81	2.17
	Tobacco smoking: no	207	165 (79.71)	122 (58.94)	56 (27.05)*	3.34	2.17*	1.34*	3.81*
Week 52	All patients	246	85.37	69.51	44.71	2.40	1.84	0.90	3.02
	Tobacco smoking: yes	86	73 (84.89)	62 (72.09)	44 (51.16)	2.04	1.66	0.59	2.38
	Tobacco smoking: no	160	137 (85.63)	109 (68.13)	66 (41.25)	2.60	1.93	1.07*	3.36
Week 104	All patients	89	88.76	77.53	53.93	1.79	1.49	0.50	1.43
	Tobacco smoking: yes	35	31 (88.57)	28 (80.00)	24 (68.57)	1.54	1.11	0.49	0.77
	Tobacco smoking: no	54	48 (88.89)	41 (75.93)	24 (44.44)*	1.95	1.73	0.51	1.85*

AD atopic dermatitis, *EASI* Eczema Area and Severity Index, *P-NRS* Pruritus Numerical Rating Scale, *S-NRS* Sleep Loss Numerical Rating Scale, *DLQI* Dermatology Life Quality Index

*$p < 0.05$

a cardiovascular standpoint. Consequently, it has become necessary to identify a broad population of patients for whom JAK inhibitor therapy is contraindicated or strongly discouraged [8].

To more comprehensively understand the safety scenario described above, it is essential to describe the studies that led to the definition of the specified cardioembolic and cardiovascular risk. Indeed, these safety concerns are based on data from clinical trials investigating the use of tofacitinib in rheumatoid arthritis (RA) [9–12]. RA, owing to systemic inflammation, can itself induce thromboembolic and cardiovascular events. Furthermore, most patients with RA are diagnosed after reaching an age of 50 years, often presenting higher rates of obesity and an increased incidence of VTEs and major adverse cardiovascular events (MACE). This makes the correlation between RA, JAK inhibitors, and thromboembolic/cardiovascular risk particularly complex to characterize [18]. Conversely, adults treated for moderate-to-severe AD do not exhibit an elevated thromboembolic and cardiovascular risk and are generally younger than patients

Table 5 Upadacitinib therapy discontinuation in relation to smoking habit

Parameters	*N*	Discontinuation due to lack of efficacy (%)	Temporary discontinuation (%)	Permanent discontinuation (%)
All discontinuations	61	16 (26.2)	19 (31.1)	42 (68.9)
Tobacco smoking				
Yes	18	3 (16.7)	6 (33.3)	12 (66.7)
No	43	11 (25.6)	13 (30.2)	30 (69.8)
Patients who smoke (total)	118	3 (2.5)	6 (5.1)	12 (10.2)
Duration of smoking habit (years)				
Discontinuation:				
Yes	18	23.3	18.2	19.6
No	100	17.1	14.8	14.9
Intensity of smoking habit (cigarettes per day)				
Discontinuation:				
Yes	18	20.0	8.8	9.1
No	100	7.4*	9.2	9.2

*$p < 0.05$

with RA, resulting in a lower baseline risk of VTEs and MACE [16, 17].

To our knowledge, this study is one of the first real-world investigations exploring the correlation between the use of a JAK inhibitor (upadacitinib) in patients with moderate-to-severe AD and the presence of an important and very common cardiovascular and thromboembolic risk factor, namely, smoking. Tobacco smoking significantly elevates the risk of cardiovascular and VTEs, making it a critical factor in the management of patients undergoing JAK inhibitor therapy [6]. Owing to these heightened risks, JAK inhibitors must be prescribed with caution in patients who smoke to mitigate potential adverse cardiovascular outcomes [9]. However, in some instances, the risk–benefit assessment for patients who smoke still leads to the decision to initiate a JAK inhibitor, especially in patients who are nonresponsive to currently available anti-IL biological drugs [18].

The data presented in our study suggest that, over up to 2 years of treatment with upadacitinib, there are no significant differences in the occurrence of major AEs related to smoking habit in patients with moderate-to-severe AD. The overall incidence of these events was very low within the entire population, with no cases of MACE or neoplastic disease and two VTEs (among these, one provoked PE). It is important to highlight that the patient who experienced DVT after 12 weeks of treatment was 73 years old, an age that constitutes a risk factor for thromboembolic events. Additional comorbidities included hypothyroidism and arterial hypertension, which are not directly significant risk factors for thromboembolic events. Therefore, a causal relationship between the use of upadacitinib and the described adverse event cannot be definitively established or excluded.

Our results confirm the data on safety observed in both clinical trials and real-life studies regarding the risk of VTEs during therapy with JAK inhibitors for moderate-to-severe AD: a recent systematic review and meta-analysis reported no significant differences between patients with AD receiving dupilumab or placebo and those on JAK inhibitor therapy, with the latter showing an overall incidence of 0.15 events per 100 patient-years [19]. Recent evidence on the safety profile related to the development of malignancies and MACE in patients with AD receiving JAK inhibitor therapy indicates a low incidence, suggesting a lower risk compared with patients with RA [20]. However, the possibility of long-term risk cannot be excluded. The risk of malignancies and MACE may increase with prolonged exposure to the drug, particularly as this treatment is often required over a lifetime. As patients age, they may also accumulate additional risk factors, particularly those associated with smoking-related comorbidities, further contributing to their overall risk burden.

Overall, this evidence underscores that, compared with patients with RA, those with AD appear to have lower baseline cardiovascular and thromboembolic risk; this may allow for JAK inhibitor therapy in the presence of smoking habit, when it represents the sole cardiovascular risk factor.

Moreover, although the patients in this study who smoke tended to experience more adverse events, such as acneiform reactions and herpetic infections, and those who smoke a higher number of cigarettes per day and for a longer period show a greater frequency of these events, our analysis does not reveal statistically significant differences between the two subpopulations, nor in relation to the duration and intensity of the smoking habit when considering only the

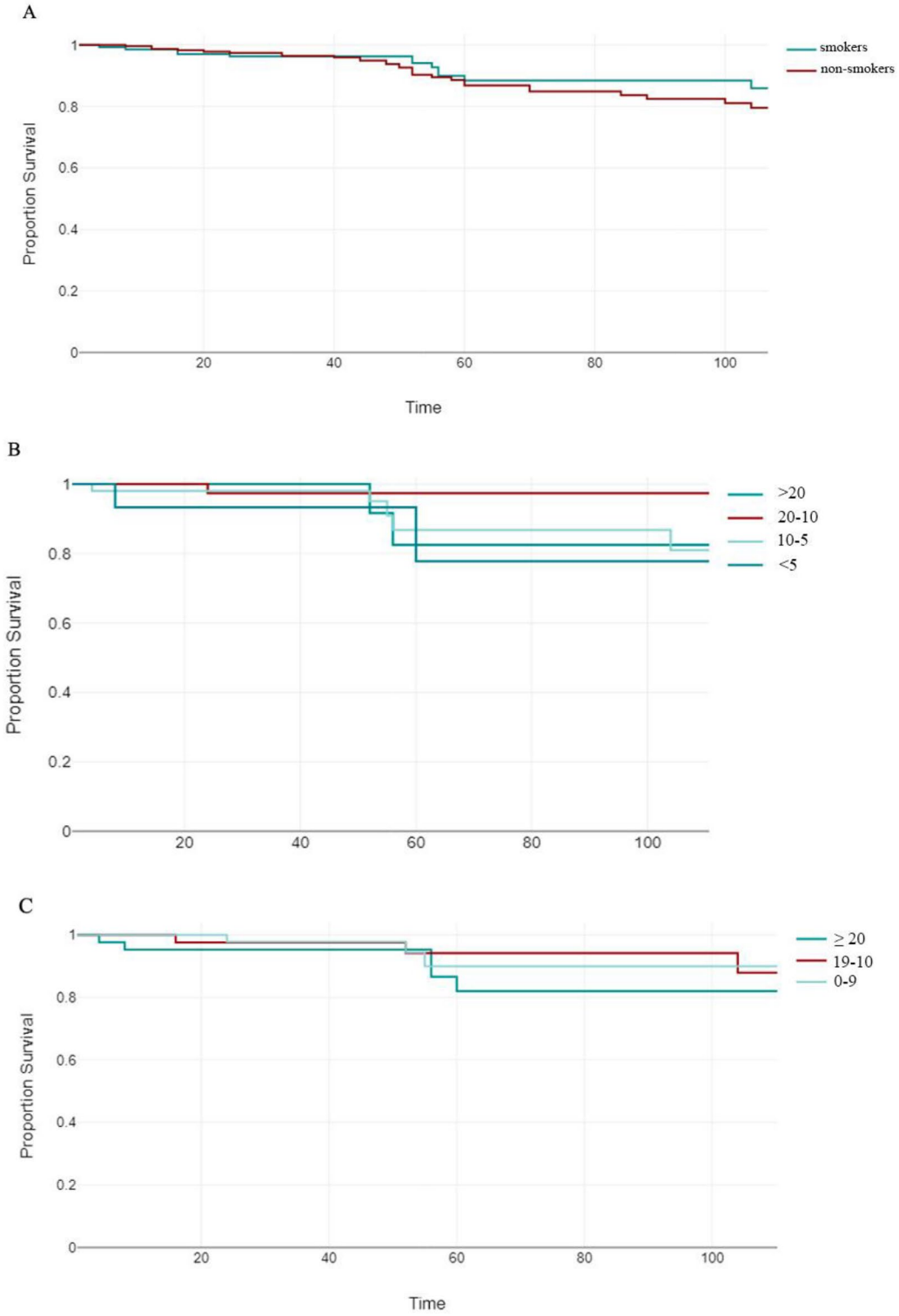

Fig. 1 Drug survival of upadacitinib after 104 weeks of treatment in relation to smoking habit. **A** Drug survival in patients who smoke and patients who do not. **B** Drug survival in relation to intensity of smoking habit (> 20 units per day; 10–20 units per day; 5–10 units per day; or < 5 units per day). (C) Drug survival in relation to duration of smoking habit (≥ 20 years; 10–19 years; 0–9 years)

smoking subpopulation. These results seem to indicate that tobacco smoking does not substantially impact the safety of upadacitinib therapy in patients with moderate-to-severe AD. The most frequently reported side effect for both subpopulations was the development of acneiform reaction, a common effect documented in both clinical trials and real-life studies [21].

The results on the therapy's effectiveness confirm the well-established positive data described in clinical trials and current real-life studies [22–26]. EASI, P-NRS, S-NRS, and DLQI scores decreased significantly from the first time point, not only maintaining the response but also progressively improving it over up to 2 years of treatment. This suggests that longer-term therapy may offer progressively greater benefits, potentially extending beyond just temporary disease control. In this context, it is interesting to consider the possibility that the therapy might have a disease-modifying role. Although this is not yet supported by specific studies, it opens an interesting avenue for future research [27]. Furthermore, our results suggest that tobacco smoking does not significantly negatively impact the effectiveness of the therapy (Table 4). On the contrary, in some cases, patients who smoke appear to achieve a slightly better clinical response. This finding could be explained by lower baseline scores in the smoking population in our cohort compared with nonsmokers, indicating a potentially lower initial disease burden, which may lead to a more favorable response to therapy. Moreover, we could hypothesize that tobacco smoking may reduce stress levels in those patients, potentially affecting itch, sleep disturbances, and, consequently, the overall disease burden, although this remains speculative and unsupported by evidence.

In addition, smoking habit does not appear to affect drug survival, which is slightly higher in this group of patients compared with nonsmokers, without significant differences between the two cohorts or within the smoking population in relation to the duration and intensity of tobacco smoking (Fig. 1).

Research investigating tobacco smoke exposure (TSE) as a risk factor for AD has led to conflicting findings. A systematic review and meta-analysis of 86 studies found that active and passive smoking are associated with an 87% and 18% increased risk of AD, respectively. However, many of the studies had methodological limitations, and there was significant heterogeneity in the results [28]. In contrast, a recent prospective cohort study aimed at examining the relationship between passive and active TSE during childhood and adolescence and the activity and severity of AD appears to challenge the correlation between AD and tobacco smoking [29]. This unclear correlation highlights the need for real-life studies, currently lacking in existing scientific literature, aimed at analyzing not only the safety of these patients undergoing systemic therapies but also the potential impact of smoking on treatment effectiveness.

5 Conclusions

The results of our real-world study seem to demonstrate the effectiveness and safety profile of upadacitinib in patients who smoke treated with upadacitinib for moderate-to-severe AD, showing no significant differences related to tobacco smoking. Additionally, when analyzing the subpopulation of patients who smoke, the duration and intensity of smoking habit does not appear to significantly impact the incidence of AEs or the effectiveness of treatment.

To our knowledge, this study is one of the first investigations assessing the influence of tobacco smoking on patients with AD treated with a JAK inhibitor in a real-life setting. Tobacco use should always be strongly discouraged, and physicians should consistently recommend cessation when initiating therapy with JAK inhibitors. However, the risk–benefit assessment for patients who smoke with moderate-to-severe AD, especially after inadequate response to anti-IL therapies, should not preclude this therapeutic approach (in the absence of other cardiovascular risk factors) given its favorable safety and effectiveness profile, as demonstrated for the first time in this study.

The limitations of this study lie in its retrospective nature and the absence of a control group. Moreover, the study is limited to 2 years of therapy. Given the chronic nature of AD, long-term treatment is required, and obtaining real-life safety data over extended periods is one of the most crucial future needs for these emerging systemic therapies.

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Declarations

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Conflicts of Interest Francesca Barei has acted as speaker and/or consultant for LeoPharma and Almirall. Anna Balato has served on scientific boards and/or has received fees for scientific consultations from: Abbvie, Amgen, Boehringer Ingelheim, Janssen, Eli-Lilly, Novartis, and UCB. Andrea Chiricozzi has served as advisory board member and consultant and has received fees and speaker's honoraria or has participated in clinical trials for AbbVie, Almirall, Bristol Myers Squibb, LeoPharma, Lilly, Janssen, Novartis, Pfizer, and Sanofi Genzyme. Silvia Mariel Ferrucci was a principal investigator in clinical trials for AbbVie, Almirall, Galderma, Leo Pharma, Sanofi, Amgen, Novartis, and Bayer and received honoraria for lectures from Novartis and Menarini. Caterina Foti has received personal fees from Abbvie, Sanofi, Eli-Lilly, Novartis, LeoPharma, Amgen, Boehringer-Ingelheim, Incyte, Pfizer, and Almirall. Luigi Gargiulo has been a consultant and/or speaker

and has participated in advisory boards for Abbvie, Almirall, Eli Lilly, Pfizer, Sanofi, and UCB Pharma. Marco Galluzzo has acted as speaker and/or consultant for AbbVie, Almirall, Eli-Lilly, Janssen-Cilag, LeoPharma, Novartis, and Sanofi, outside of the submitted work. Giampiero Girolomoni has received personal fees from AbbVie, Almirall, Amgen, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli-Lilly, Leo Pharma, Merck Serono, Novartis, Pfizer, Pierre Fabre, Samsung bioepis, and Sanofi. Niccolò Gori has served on advisory boards and received honoraria for speaking engagements for AbbVie, Sanofi, Leo-Pharma, Almirall, Pfizer, and Lilly. Mario Bruno Guanti has acted as speaker and/or consultant for AbbVie, Leopharma, Sanofi, Menarini, Lilly, and Almirall. Francesco Leo has no conflicts of interest to declare. Angelo Valerio Marzano reports consultancy/advisory boards disease-relevant honoraria fees from AbbVie, Amgen, Boehringer-Ingelheim, Bristol Myers Squibb, Incyte, Leopharma, Novartis, Pfizer, Sanofi, and UCB. Luca Mastorino has been a consultant and/or speaker and has participated in advisory boards for Accord, Avène, LeoPharma, and Almirall Maddalena Napolitano reports consulting fees from Abbvie, Lilly, LEO Pharma, Almirall, Sanofi; payment/honoraria from Abbvie, Lilly, LEO Pharma, Almirall, and Sanofi; and participation on data safety monitoring boards/advisory boards from Lilly, Sanofi, LEO Pharma, Abbvie, and Almirall; and support for attending meetings/travel from Lilly. Alessandra Narcisi has served on advisory boards or received honoraria for lectures and research grants from Almirall, Abbvie, Leo Pharma, Celgene, Eli-Lilly, Janssen, Novartis, Sanofi-Genzyme, Amgen and Boehringer Ingelheim. Michela Ortoncelli has acted as a speaker and/or consultant for AbbVie, Novartis, Sanofi, LeoPharma, Almirall, and Eli-Lilly. Cataldo Patruno has served as an advisory board member and consultant and has received speaker's honoraria and fees for her participation in clinical trials for Abbvie, Almirall, Eli-Lilly, LeoPharma, and Novartis. Elena Pezzolo has been a consultant and speaker for Sanofi Genzyme, AbbVie, LeoPharma, Novartis, Janssen, Almirall, Pfizer, Galderma, and Boehringer Ingelheim. Simone Ribero has acted as a speaker and/or consultant for AbbVie, Almirall, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli-Lilly, J&J, L'Oreal, LeoPharma, Novartis, Pfizer, Pierre Fabre, and Sanofi. Mariateresa Rossi has been a consultant and/or speaker, has participated in advisory boards, and received honoraria for lectures for Abbvie, Almirall, Eli Lilly, Pfizer, Sanofi, and LeoPharma.

Ethics Approval The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Department of Medicine at the University of Turin, with ethics committee approval number: 0006349 (18 January 2024).

Consent for Participation and Publication Informed consent was provided by all subjects and parents involved in the study, for both participation and publication.

Data Availability: Data will be made available on reasonable request.

Code Availability: Not applicable.

Author Contributions All authors contributed to the study conception and design. Material preparation and data collection were performed by all authors. Data analyses were performed by Luca Mastorino. The first draft of the manuscript was written by Francesco Leo, Luca Mastorino, Michela Ortoncelli, and Simone Ribero, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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