

hyperkalemia, and urticarial allergic reaction; however, these affected less than 2% of participants across all studies. Oral spironolactone was generally recommended in nonpregnant women older than 18 years of age at an initial dose of 50 mg daily titrated up to a therapeutic range of 100 mg to 200 mg daily taken for at least 6 months to 1 year to achieve optimal results.

This study is limited by the narrow range of data in the literature, which comprises mostly case series and observational studies. Further randomized studies are needed to validate the efficacy of spironolactone as a monotherapy in the treatment of AGA, although the available data support its use in combination with topical minoxidil. Given the positive outcomes, minimal side effects, and economical cost, spironolactone should be regarded as a safe, effective treatment option in women with AGA.

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Funding sources: None.

IRB approval status: Not applicable.

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Conflicts of interest

None disclosed.

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<https://doi.org/10.1016/j.jaad.2021.07.048>

How safe is prescribing oral minoxidil in patients allergic to topical minoxidil?



To the Editor: We present 9 female patients (Table 1) who became allergic to topical minoxidil and were able to tolerate low-dose oral minoxidil without adverse effects.

Topical minoxidil is the only approved treatment for female pattern hair loss.¹ It has a safe profile, and the most common adverse effects include irritant and allergic contact dermatitis and hypertrichosis. Contact dermatitis to commercial minoxidil is often caused by propylene glycol that is present in the 2% and 5% solutions. Patients with contact allergy or irritation to propylene glycol can use the 5% minoxidil foam, which is free of this ingredient. Contact allergy to minoxidil itself is uncommon and requires discontinuation.

Our patients had been using topical minoxidil for an average of 4.8 years (range, 1-14 years) (Table 1) when an acute contact dermatitis developed. All were patch tested with propylene glycol 30% in water (Chemotechnique Diagnostics, Vellinge, Sweden), 5% commercial minoxidil solution, and 5% commercial minoxidil foam. Patches were removed after 48 hours and the reading was performed at 72 and 96 hours. All 9 patients had a positive patch test result to the 5% minoxidil solution and the foam and a negative patch test result to propylene glycol, indicating that the cause of contact dermatitis was minoxidil itself (Fig 1).

Oral minoxidil has been used in the last few years as an off-label treatment both in male and in female pattern hair loss with good clinical efficacy.^{2,3} Proposed doses are different in men than in women, with a range from 0.25 to 1 mg daily.⁴ Lower doses are used in women because hypertrichosis is a common adverse effect.⁵ Our experience with more than 200 patients on oral minoxidil indicates that 0.5 mg daily is effective and very well tolerated.

The possibility that patients with contact allergy to topical minoxidil could safely tolerate oral minoxidil was suggested by the fact that systemic skin reactions to topical or oral minoxidil have never been described. Systemic contact dermatitis refers to a rare diffuse reaction that individuals sensitized to a contact allergen might develop after exposure to the same allergen via a different route. The exact pathophysiology is unknown; however, it appears to be mediated by a type 4 and possibly type 3 hypersensitivity reaction. Cases of systemic contact dermatitis have been reported for propylene glycol⁵ but not for minoxidil, so treatment with oral minoxidil was

Table 1. List of patients

Patient	Age, y*	Sex	Topical minoxidil use, y	Adverse effects from topical minoxidil	Oral minoxidil use, 0.25 mg twice daily, mo [†]	Adverse effects from oral minoxidil
1	48	Female	8	Scalp pruritus	15	None
2	47	Female	12	Scalp pruritus, scaling	20	None
3	72	Female	14	Scalp pruritus, scaling	33	Mild hypertrichosis on temples
4	49	Female	3	Scalp pruritus, eczematous rash on ears	10	None
5	54	Female	1.5	Scalp pruritus	7	None
6	55	Female	0	Scalp pruritus	18	None
7	31	Female	0	Scalp pruritus, eczematous rash on ears	8	None
8	47	Female	4	Scalp pruritus, scaling	24	Mild hypertrichosis on cheeks
9	22	Female	1	Scalp pruritus, eczematous rash on ears	18	None

*Mean age of 47.2 years (range, 22-72 years).

[†]All patients currently on treatment.**Fig 1.** Patch test results positive to topical minoxidil: *top*, 5% minoxidil solution; *middle*, propylene glycol; *bottom*, 5% minoxidil foam.

started at the dose of 0.25 mg twice daily. The 0.25-mg capsules were compounded by pharmacies.

All of our patients have been using the same dose to date, for an average of 17 months (range, 7-33 months) without any adverse effects. All of them were satisfied with results of treatment. Cardiac adverse effects of oral minoxidil, such as edema, pericarditis, or pericardial effusion, are dose-dependent and have never been reported with low doses. Our experience therefore suggests that oral minoxidil is reasonably safe in patients allergic to topical minoxidil, even if it is advisable to warn patients to stop the medications in case of cutaneous adverse effects.

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Funding sources: None.

Conflicts of interest: Dr Tosti discloses relationships with P&G, DS Laboratories, Monat, Thirty Madison, and Almirall as a consultant; advisory board for LEO Pharma; and primary investigator for Lilly and Nutrafol. Drs Therianou and Vincenzi have no conflicts of interest to disclose.

IRB approval status: Not applicable.

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<https://doi.org/10.1016/j.jaad.2020.04.027>

Adverse events associated with dupilumab in the World Health Organization pharmacovigilance database



To the Editor: Dupilumab is a monoclonal antibody targeting the interleukin 4/interleukin 13 pathway and is approved to treat atopic dermatitis. Dupilumab has shown a favorable safety profile in randomized controlled trials and observational cohorts but has been associated with a number of adverse events, including exacerbation of atopic dermatitis, eye disorders, or eosinophilia.^{1,2} Nevertheless, data are limited by short time frames. In order to assess adverse events associated with dupilumab, we conducted a pharmacovigilance study using Vigibase, the World Health Organization's global pharmacovigilance database.

We searched Vigibase and included all reports with dupilumab as the suspected cause from January 1, 2016, to October 15, 2020. Adverse events were classified according to the Medical Dictionary for Regulatory Activities classification, grouped into the 27 branches of the System Organ Class.³ To identify adverse events associated with dupilumab, we used

the information component (IC), an indicator for disproportionate reporting, and IC_{025} , the lower limit of its 95% credibility interval. $IC_{025} > 0$ is the statistical significance threshold used in Vigibase (Supplementary Text 1, available via Mendeley at <https://doi.org/10.17632/bf5vnbh33r.1>), meaning that the adverse event is likely associated with dupilumab.⁴ The higher the IC_{025} , the stronger the association. We included physician reports in the primary analysis and overall reports in the sensitivity analysis.

Among the 4894 physician reports, a total of 11,751 events (including 1326 different adverse events) were reported. The median age was 44 years (interquartile range, 28-57 years), and 1884 patients were female (38%) (Supplementary Table I, available via Mendeley at <https://doi.org/10.17632/bf5vnbh33r.1>). IC_{025} was positive for 168 (14%) of the 1326 different adverse events. Skin disorders displayed 53 (32%) associated adverse events, mostly related to atopic dermatitis ($n = 15$, IC_{025} ranging from 0.6 to 6.6), alopecia areata (IC_{025} 4.1), and psoriasis-like eruptions (IC_{025} 2.2). Eye disorders displayed 35 (21%) associated adverse events, mainly related to conjunctivitis and keratitis symptoms (Supplementary Table II, available via Mendeley at <https://doi.org/10.17632/bf5vnbh33r.1>), infections, and infestations; 14 adverse events (8%) were mainly related to herpes infections (Supplementary Table III, available via Mendeley at <https://doi.org/10.17632/bf5vnbh33r.1>). Musculoskeletal disorders displayed 8 adverse events (5%), blood and lymphatic disorders 5 adverse events (3%), and immune disorders 5 adverse events (3%), including serum sickness

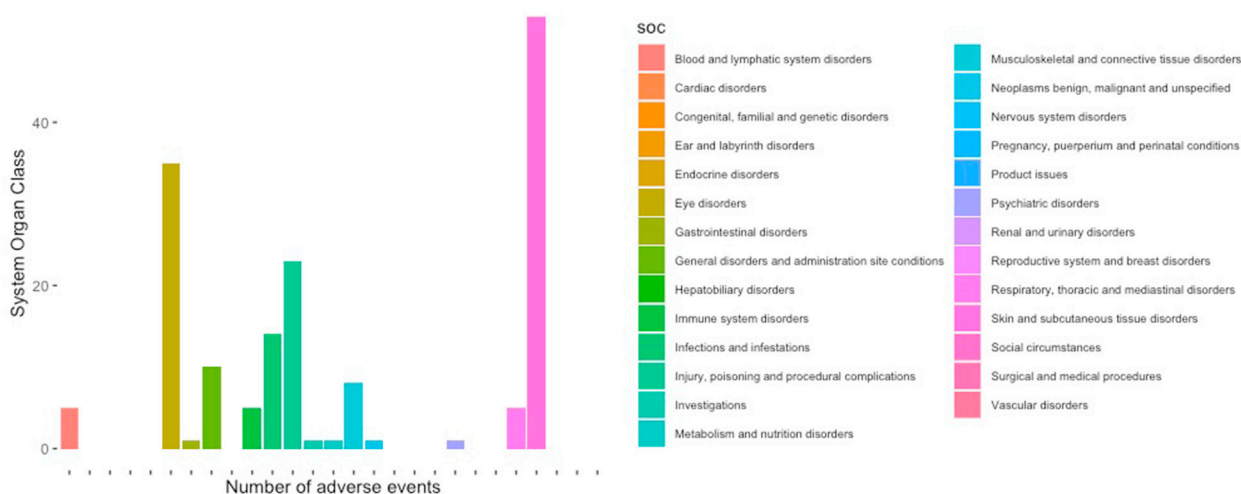


Fig 1. Number of adverse events with positive IC_{025} according to the System Organ Class, in the primary analysis. IC_{025} is the lower limit of the 95% credibility interval of IC. A positive IC_{025} is the statistical threshold used in Vigilyze. IC, Information component; SOC, System Organ Class.