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*Correspondence to: Andrea Murina, MD, Associate Professor of Dermatology, Dermatology Department, Tulane University School of Medicine, 1430 Tulane Avenue, Suite 8036, New Orleans, LA 70112*

*E-mail: amurina@tulane.edu*

**Conflicts of interest**

Dr Murina is a speaker for AbbVie, Amgen, Eli Lilly and Company, Janssen, Ortho-Dermatologics and a consultant for Janssen, Novartis, and UCB.

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## Telemedicine management of systemic therapy with isotretinoin of patients with moderate-to-severe acne during the COVID-19 pandemic: A longitudinal prospective feasibility study

*To the Editor:* Moderate-to-severe acne bears a high risk of scarring, which makes timely therapy a mainstay for successful management. A prospective longitudinal study was conducted at the Dermatology Digital Center of the University Hospital Virgen Macarena (Seville, Spain), an academic public hospital covering an area of 550,000 inhabitants, between September 1, 2020, and December 31, 2020, to assess the feasibility of store-and-forward teledermatology to manage patients with acne suitable for treatment with oral isotretinoin.[1] Family physicians captured clinical pictures using mobile phones (Fig 1).[1] The Dermatology Digital Center responded with a report with the diagnosis and recommended treatment (oral isotretinoin), additional information sheets, and instructions. Acne severity was assessed using the Global Acne Grading System (GAGS) and the Investigator Global Assessment of acne.[2]

During the study period, the Dermatology Digital Center received 4394 teleconsultations with an average response time of 33.03 hours (range, 0.7-164.00 hours) and 284 of those (6.46%) involving patients with acne. Oral isotretinoin was offered to 60 patients (21.13%) with moderate-to-severe acne. Six of them (9.38%) refused isotretinoin. Fifty-three patients composed the intention-to-treat sample, and 46 (86.79%) patients completed the treatment as per protocol (Table I). Oral corticosteroids were prescribed before isotretinoin for 8 patients (15.09%), and 11 women (52.38%) started receiving oral contraceptives.

In the intention-to-treat analysis, 42 patients (79.25%) achieved an 80% reduction in the basal GAGS score, with 31 patients (58.49%) achieving a 100% reduction in the basal GAGS score (Investigator Global Assessment score, 0). At the end of the study, the GAGS score showed an 87.94% reduction (Table I). The per-protocol analysis yielded GAGS80 and GAGS100 rates of 91.30% ($n = 42$) and 67.39% ($n = 31$), respectively (Table I).

After exclusion of mucocutaneous effects, the most common adverse effects were hyperlipidemia (13.04%), myalgia (10.87%), and hypertransaminasemia (6.52%), followed by creatine-phosphokinase increase (6.52%), headache (4.30%), arthralgia (4.30%), effluvium (4.30%), keloids (2.17%), and hand eczema (2.17%). All these toxic events were mild and led to isotretinoin discontinuation in only 1 patient, who showed a 3-fold increase in liver enzyme levels.

This study was conducted during the second wave of the COVID-19 pandemic in Spain. Primary care services had still not been restored to normal, and hospital services were avoiding in-person care as much as possible. In these settings, teledermatology-based acne management has yielded remarkable therapeutic response, with a refusal rate (9.38%) similar to the rate reported with face-to-face visits (13.3%)[3] and an early termination percentage (13.21%) much lower than that reported by the iPLEDGE REMS (Risk Evaluation and Mitigation Strategy) program (36.8%).[4]

Limitations of this study are related to the sample size, consequence of the innovative approach, GAGS score underestimation due to the lack of pictures from some anatomic areas in 15.43% of teleconsultations, and the more difficult assessment of nodules (score, 4).

Store-and-forward teledermatology is feasible for the management of patients with moderate-to-severe acne who need oral isotretinoin in situations of health care delivery restrictions, such as those stemming from the COVID-19 pandemic. This pilot

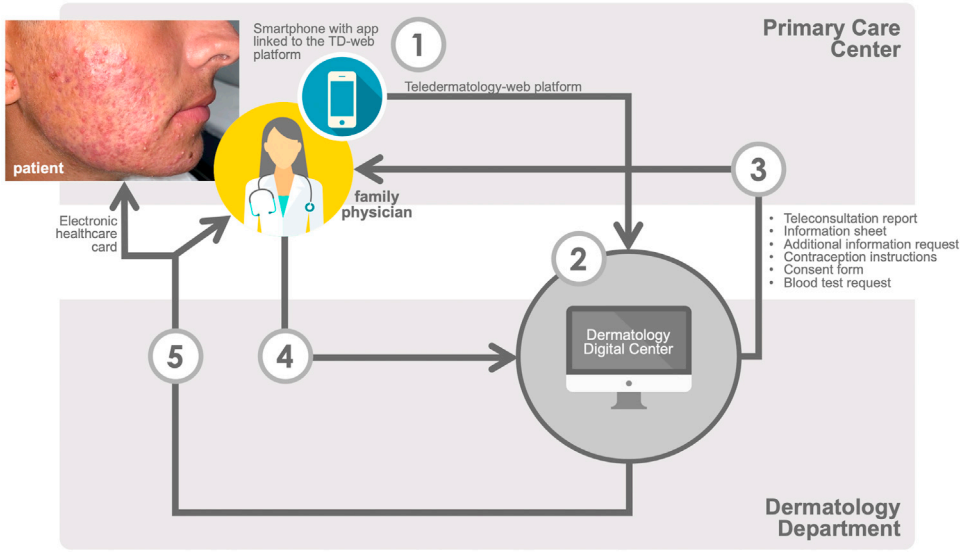


**Fig 1.** Teledermatology-based acne management procedure: (*1*) the family physician captures pictures using a smartphone and a specific app that uploads the pictures to the teledermatology web platform of the Andalusian Health Service; (*2*) the teleconsultation is assessed by the dermatologist of the Dermatology Digital Center; (*3*) in patients suitable for treatment with oral isotretinoin, a teleconsultation report is submitted to the family physician with the following attached documents: an information sheet about expected benefits and potential adverse effects of isotretinoin, instructions about isotretinoin intake, a template to collect additional information (eg, weight, current medication intake, major medical conditions), instructions about oral contraception according to local protocols, a consent form to be signed in case they agree to participate, and basal blood tests request (eg, complete blood cell count, serum lipid profile, liver function tests, and a pregnancy test); (*4*) if the patient agrees to start treatment with isotretinoin, blood tests are taken at the primary care center and are available for the dermatologist through the electronic records; (*5*) isotretinoin is then prescribed by the dermatologist through the electronic prescription platform and is available to be picked up by the patients at their community pharmacy using their health care electronic card. A further teleconsultation report with treatment and follow-up instructions is also submitted to the family physician. Follow-up of these patients is supported by the dermatologist at the digital center through teleconsultations as scheduled in the report or on request in case of any drug reaction or other events. Follow-up teleconsultations and blood tests are scheduled, if no unexpected event occurs, for 2 months after the start and after the end of the treatment. *TD,* Teledermatology.

experience may also support the use of this procedure beyond the pandemic, particularly in health care services not capable of offering timely care to patients with moderate-to-severe acne.

This study has been possible thanks to the efforts and interest of the family physicians and staff nurses of the North Seville and Seville Primary Care Areas who have cared for patients with acne jointly with the dermatologists of the Dermatology Digital Center of the University Hospital Virgen Macarena.

*David Moreno-Ramírez, MD, PhD,*[a] *Miguel A. Duarte-Ferreras, MD,*[a] *Teresa Ojeda-Vila, MD, PhD,*[a] *Irene García-Morales, MD, PhD,*[a] *Maria D. Conejo-Mir, MD,*[a] *Almudena Fernández-Orland, MD,*[a] *Ana I. Sánchez-del-Campo, MD,*[a] *Noemí Eiris, MD,*[a] *Ana M. Carrizosa, MD, PhD,*[a] *Andrés Ruiz-de-Casas, MD,*[a] *Jose M. de-la-Torre, MD,*[a] *Juan M. Herrerías-Esteban, MD,*[b] *and Lara Ferrándiz, MD, PhD*[a]

*From the Dermatology Digital Center, Department of Medical and Surgical Dermatology*[a] *and Communication and Technology Department, Hospital Universitario Virgen Macarena, Seville, Spain.*[b]

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**Table I.** Basal and final characteristics of the study patients

| Characteristic | Basal | | End of study |
|---|---|---|---|
| Age (y) | | 18.89<br>95% CI, 11.11-20.66<br>Range, 13-38 | |
| Sex | | | |
| Male | | 60.38% (*n* = 32) | |
| Female | | 39.62% (*n* = 21) | |
| Initial dose | | | |
| 20 mg/d | 5.66% (*n* = 3) | | |
| 30 mg/d | 58.49% (*n* = 31) | | … |
| 40 mg/d | 33.96% (*n* = 18) | | |
| 50 mg/d | 1.89% (*n* = 1) | | |
| Cumulative dose (mg/kg, mean) | … | | 123.1<br>95% CI, 118.18-128.04<br>Range, 160.00-62.07 |
| Treatment time (d) | … | | 240.10<br>95% CI, 229.87-250.33<br>Range, 120-300 |
| Teleconsultations (*n*) | … | | 175 |
| Average number of teleconsultations per patient | … | | 3.57<br>95% CI, 3.31-3.84 |
| IGA 0* | … | | 58.49% *n* = 31 |
| IGA 1† | … | | 22.64% *n* = 12 |
| IGA 2‡ | … | | 5.66% *n* = 3 |
| IGA 3§ | 77.36% *n* = 41 | | 5.66% *n* = 3 |
| IGA 4‖ | 22.64% *n* = 12 | | 0 |
| GAGS | 20.81<br>18.64-22.99 | | 2.51<br>1.17-3.85 |
| | | <0.001 | |
| Mean GAGS reduction | | 87.94% | |

*GAGS*, Global Acne Grading System; *IGA*, Investigator Global Assessment.
*IGA 0: "clear skin"—residual hyperpigmentation and erythema may be present.
†IGA 1: "almost clear"—a few scattered comedones and a few small papules.
‡IGA 2: "mild"—easily recognizable, less than half the face is involved, some comedones and some papules and pustules.
§IGA 3: "moderate"—more than half the face is involved, many comedones, papules and pustules, 1 nodule may be present.
‖IGA 4: "severe"—entire face is involved, covered with comedones, numerous papules and pustules, and few nodules and cysts.

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*Correspondence to: David Moreno-Ramírez, MD, PhD, Dermatology Digital Center, Department of Medical and Surgical Dermatology, Hospital Universitario Virgen Macarena, Avda. Dr. Fedriani 3, Seville 41071, Spain*

*E-mail: david.moreno.ramirez.sspa@juntadeandalucia.es*

**Conflicts of interest**

None disclosed.

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## Safety, tolerability, and efficacy of a novel topical isotretinoin formulation for the treatment of X-linked or lamellar congenital ichthyosis: Results from a phase 2a proof-of-concept study

*To the Editor:* Clinical characteristics of congenital ichthyosis (CI) include hyperkeratosis, scaling, and erythroderma.[1,2] The management of CI typically involves emollients and keratolytics.[2,3] Patients with lamellar or X-linked recessive CI often have considerable hyperkeratosis and scaling, for which systemic retinoids are effective but may cause dose-limiting adverse events (AEs).[2,4,5] PAT-001 is a patented, novel, topical isotretinoin ointment formulation to treat CI. We present the results from a phase 2a study evaluating PAT-001 in patients with lamellar or X-linked recessive CI.

This multicenter, double-blind study evaluated the safety and tolerability (primary endpoints) of PAT-001 in patients aged ≥12 years; pharmacokinetics and efficacy were the secondary endpoints. The study was conducted according to the Declaration of Helsinki principles, and all patients provided written informed consent. The patients were randomized 1:1 to PAT-001 0.1% or 0.2% and had 2 comparable contralateral lesional areas—each ≤6% of body surface area and ≥150 $cm^2$—with identical baseline Investigator Global Assessment (IGA) scores of ≥3 (Supplementary Table I, available via Mendeley at https://data.mendeley.com/datasets/b4xj8wmpv9/1). One area was randomly treated with PAT-001 0.1% or 0.2% and the other was treated with vehicle twice daily for 8 weeks (Part 1). Both areas received PAT-001 0.1% or 0.2% twice daily for 4 weeks (Part 2).

Safety measurements included laboratory tests and monitoring for AEs. Optional blood samples measuring isotretinoin/tretinoin levels were collected for pharmacokinetic analyses. Efficacy evaluations included changes in IGA scores and clinical signs/symptoms.

Among the enrolled patients (PAT-001 0.1% [$N = 10$] and 0.2% [$N = 9$]), 10 had lamellar CI, 7 had X-linked recessive CI, and 2 had ichthyosis vulgaris (Supplementary Fig 1, available via Mendeley at https://data.mendeley.com/datasets/b4xj8wmpv9/1). Seven patients discontinued the treatment. In Part 1, 13 and 8 AEs occurred in active- versus vehicle-treated areas, respectively (Supplementary Table II, available via Mendeley at https://data.mendeley.com/datasets/b4xj8wmpv9/1); overall, 28 AEs occurred in 14 patients (Table I). Most AEs were mild; 8 patients experienced AEs that were possibly (25%), probably (3.6%), or definitely (10.7%) active treatment–related and had treatment interruptions or withdrew. Laboratory values were not clinically different from those at baseline. Systemic isotretinoin/tretinoin concentrations remained at baseline levels (Supplementary Table III, available via Mendeley at https://data.mendeley.com/datasets/b4xj8wmpv9/1).

In Part 1, PAT-001 0.1% exhibited greater improvement in ≥1- and ≥2-grade IGA score versus vehicle (100% vs 66.7% and 66.7% vs 33.3%, respectively). PAT-001 0.2% demonstrated similar ≥1- and ≥2-grade IGA improvement versus vehicle (100% vs 87.5% and 50.0% vs 62.5%, respectively). By day 57, IGA score for PAT-001 0.1% and 0.2% treatment areas were ≥1-grade lower versus vehicle (66.7% and 37.5%, respectively; Fig 1). Scaling in all patients for active versus vehicle treatment areas was clear, almost clear, or mild for 0.1% and 0.2% groups (100% vs 55.6% and 100% vs 87.5%, respectively; Supplementary Fig 2, available via Mendeley at https://data.mendeley.com/datasets/b4xj8wmpv9/1).

In Part 2, continued active treatment areas were clear, almost clear, or mild in 85.7% and 60% of patients for PAT-001 0.1% and 0.2%, respectively. In both treatment areas, all patients receiving PAT-001 0.1% had ≥1-grade IGA score reduction versus baseline; 80% and 60% of patients receiving PAT-001 0.2% had 1- and ≥2-grade IGA reductions, respectively.

The results indicate no concerning safety signals or evidence of systemic isotretinoin/tretinoin exposure. PAT-001 0.1% appeared to have a stronger efficacy signal than PAT-001 0.2%; additional characterization is ongoing to better understand this effect. The limitations of the study include small sample size, not being powered for statistical significance, ≤12% body surface area treated, and discontinuations. These findings demonstrate that PAT-001 may be a promising alternative to oral retinoids and support ongoing investigation.

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