


SHORT PAPER

Clinical efficacy, speed of improvement and safety of apremilast for the treatment of adult Psoriasis during COVID-19 pandemic

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Abstract

Time to improvement is a crucial characteristic for effective treatments of chronic inflammatory conditions, such as psoriasis. Apremilast is a recently approved drug, belonging to the small molecule phosphodiesterase 4 inhibitors, whose optimal safety and efficacy profile is somewhat affected by slow activity rate in clinical trials. Real world case series are suggesting a more consistent improvement, and with this additional personal investigation on 48 patients, we signal that 58% of patients achieved Psoriasis Area and Severity Index (PASI) 50, and 19% PASI 75 improvement in the first 8 weeks of treatment. Results at 16-week are remarkable, with overall 55% of patients achieving PASI 75, 21% PASI 90 and 14% PASI 100. Only 8 patients (18, 6%) had slightly improved, although satisfied with the regimen, and determined to continue. Noteworthy, our population was rather problematic in terms of comorbidities (86%), and resistance to other treatments, with only 28% naïve to systemics, including biologics. Moreover, the observation period includes the Italian outbreak of COVID-19 epidemic, and further information on apremilast safety are provided, no one of the patients having stopped treatment. In such a critical period, the apremilast satisfactory speed of therapeutic response in a real-world setting has further strengthens patient's compliance to remain safely at home, which is the best strategy to limit contagion.

KEYWORDS

apremilast, COVID-19, efficacy, psoriasis, safety

Apremilast is an innovative small-molecule phosphodiesterase 4 inhibitor that has been approved for the treatment of moderate-to-severe plaque psoriasis in adult patients; it has a remarkable efficacy and safety profile and does not require particular screening or follow-up blood tests.¹ The main criticism seems to be its slower activity, in terms of the time required for improvement, with a low rate of

Psoriasis Area and Severity Index (PASI) 75 achievement at week 16 in clinical trials: 33.1% of patients in ESTEEM1 and 28% of patients in ESTEEM2.^{2,3} However, in daily practice, the results were much more satisfactory from the first follow-up, even in very difficult patients. Thus, a study was conducted in a real-world setting at the Dermatology Clinic of the University of Cagliari to investigate the short-term clinical rate of response: at 8 and 16 weeks of treatment. The secondary endpoints were efficacy and safety for difficult-to-treat areas and challenging comorbidities. Data collection was initiated in December 2019, and 2 months later, the novel coronavirus disease

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(COVID-19) outbreak emerged, spreading across Italy and raising concerns about the risk of contagion and severity of COVID-19 in immunosuppressed patients.⁴ Thus, enhanced surveillance has been arranged in this cohort of patients, advising them to continue the treatment and contact the psoriasis service on noticing the occurrence of any symptoms.

Forty-eight patients were recruited after they provided informed consent to participate in the study, comprising 25 men and 23 women, with a mean age of 59 years (range, 20-82). Each patient was administered apremilast (30 mg, twice a day) as monotherapy, after initial titration to minimize side effects. A wide range of different subtypes of psoriasis was included, with 56% of patients affected by difficult-to-treat conditions, including palmoplantar psoriasis, scalp psoriasis, and three sub-erythrodermic forms (Table 1). Comorbidities with contraindications to other treatments were present in 86% of patients: hypertension and dysmetabolic syndrome, a history of malignancies

TABLE 1 Baseline patient characteristics concerning type of psoriasis, previous treatments and comorbidities

	No of patients	Percentage
<i>Type of psoriasis</i>		
Chronic plaque psoriasis	20/48	42
Palmoplantar psoriasis	10/48	21
Psoriasis of the scalp	13/48	27
Sub-erythrodermic psoriasis	3/48	6
Facial psoriasis	2/48	4
<i>Previous treatments</i>		
Totally naïve to systemics	14/48	29.1
Cyclosporine	10/48	20.8
Methotrexate	7/48	14.5
Acitretin	2/48	4.1
Etanercept	1/48	2.1
Infliximab	1/48	2.1
Adalimumab	6/48	12.5
Ustekinumab	2/48	4.1
UVB narrow band therapy	4/48	8.3
<i>Comorbidities</i>		
None	7/48	14.5
1-2	23/48	47.9
>2	18/48	37.5
<i>Type of comorbidities</i>		
Hypertension	13/48	27
Hyperlipidemia	11/48	23
Diabetes mellitus	7/48	16
Malignancy in personal history	13/48	27
Psychiatric disorders	6/48	12
Severe infections	7/48	15
Liver disease	3/48	6
Latent tuberculosis	2/48	4
Other	7/48	15

(mammary tumor, bladder cancer, or colorectal cancer), severe viral infections (human immunodeficiency virus, hepatitis C virus, hepatitis B virus), latent tuberculosis, psychiatric disorders, and advanced-stage liver disease. Only 14 (29%) patients were naïve to systemic therapies, while several courses of traditional systemic treatment were used in 19 (39%) patients, and 11 patients (23%) were required to discontinue biologics because of cancer occurrence or hepatic impairment. Four patients were treated with narrow-band ultraviolet B-rays without consistent improvement (Table 2).

At the 8-week follow-up (Table 2), the primary efficacy endpoint of consistent improvement, quantified as at least a 50% reduction (Figure 1) in baseline signs and symptoms (PASI 50), was achieved in 58.3% of patients (28/48), 9 of whom (18.7%) achieved PASI 75 (Figure 2). Four patients discontinued treatment because of the development of gastrointestinal adverse events (AEs). The remaining 17 patients showed a less consistent improvement, although considering the absolute PASI, there was a mean reduction from 9.2 to 6.4, and patients were satisfied with the treatment.

At the 16-week follow-up, 43 patients were assumed to be taking apremilast, and another patient had discontinued taking apremilast because of treatment failure. The improvement was remarkable, with an additional 6 patients achieving PASI 50. Overall, 55% of patients achieved PASI 75, 21% achieved PASI 90, and 14% achieved PASI 100 (Figure 3), with a mean absolute PASI score of 3.29 (Table 2). Only 8 patients (18.6%) showed slight improvements in symptoms, although they were satisfied with the regimen and were determined to continue.

Few real-world studies have investigated the profile of apremilast⁵⁻⁹; there have been no reports of efficacy after 8 weeks of treatment, which we valued as a PASI 50 achievement in 58% of patients and PASI 75 in 19%. Outcomes at 16 weeks were comparable with those of previous case series, even with respect to AEs and the rate of discontinuation.⁹ Notably, our population was problematic in terms of comorbidities (86%), and only 28% of the patients were naïve to systemic treatments, including biologics. Overall, only 1

TABLE 2 Clinical response to apremilast

	No of patients	Percentage	
<i>Primary endpoints at 8 wk</i>			
PASI 50	28/48	58.3	
PASI 75	9/48	18.7	
Drug discontinuation for AE	4/48	8.3	
Mild AEs	16/48	33.3	
<i>Primary endpoints at 16 wk</i>			
PASI 50	34/43	79	
PASI 75	24/43	55	
PASI 90	9/43	20.9	
PASI 100	6/43	13.9	
Treatment failure	1/48	2	
Mean PASI	T0	T8	T16
PASI	10.44	5	3.3

Abbreviation: PASI, Psoriasis Area and Severity Index.



FIGURE 1 Improvement on infiltrated plaque psoriasis of the legs, the patient overall achieving PASI 50 after 8 weeks of apremilast monotherapy. PASI, Psoriasis Area and Severity Index

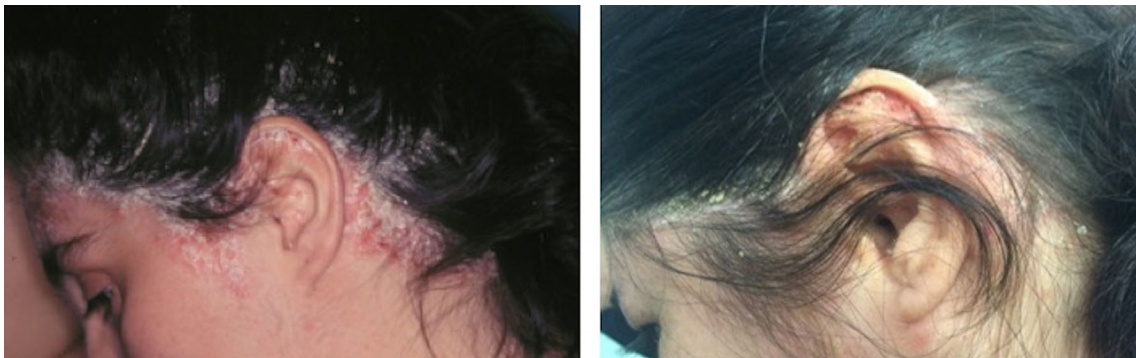


FIGURE 2 Improvement on severe scalp psoriasis, the patient overall achieving PASI 75 after 8 weeks of apremilast monotherapy. PASI, Psoriasis Area and Severity Index

patient was considered a non-responder, and 8 patients experienced a less remarkable but progressive improvement. The latter might represent a subset of slow responders. The achievements of PASI 90 and PASI 100 were unexpected after only 4 months of treatment. The main limitation to apremilast adherence was the intensity of AEs during the first weeks (41.6%), leading to discontinuation in 4 patients (8.3%), and reports of mild, bearable, and healed with treatment prosecution in the remaining 16 patients. As expected, diarrhea was the most frequent AE (28%), followed by abdominal discomfort, nausea, vomiting, and headache. Unlike other reports, no weight loss or worsened psychiatric disease was observed.^{5,6} None of the patients developed symptoms requiring assessment for COVID-19.

During the observation period, the Italian outpatients' services were required to suspend all visits because of the COVID-19

pandemic outbreak in Italy and the recommendation to prevent patient access to hospitals (Decree of the President of the Council of Ministers, 03/09/2020). Thus, an extraordinary effort was made to implement monitoring of and support for this cohort of patients by distance. Regular telephone recalls were performed to assess whether patients had discontinued taking the drug or had contracted COVID-19. We followed current experts' opinion⁹ that apremilast is one of the safer options for moderate-to-severe psoriasis management due to its very specific, non-immunosuppressive mechanism of action. Recent experience in a COVID-19 disease affected patient, who maintained apremilast treatment during the bilateral pneumonia course and recovered completely, confirms safety and compatibility with critical patient's management.¹⁰ Exacerbation of psoriasis might have



FIGURE 3 PASI 100 achievement in two different patients, at week-16 of apremilast monotherapy. PASI, Psoriasis Area and Severity Index

occurred as a consequence of stress burden, with the COVID-19 pandemic conferring severely limited wellness and opportunities to relieve anxiety and mood disorders through social activities. Of course, COVID-19, as well as certain medications currently used to control the disease, might exacerbate psoriasis, as recently reported.¹¹

In this very critical period, the satisfactory speed of the therapeutic response to apremilast in a real-world setting has further strengthened patient compliance to remain safe at home and led to patients eventually enduring the initial side effects, although further studies are warranted to explore this topic.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

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