Comments on "Short-term reasons for withdrawal and adverse events associated with apremilast therapy for psoriasis in real-world practice compared with in clinical trials: A multicenter retrospective study"

To the Editor: The effect of apremilast in the treatment of psoriatic arthritis (PsA) has been assessed in the Psoriatic Arthritis Long-term Assessment of Clinical Efficacy (PALACE) phase III clinical trial program,[1-3] but observational data are still lacking. We read with great interest the article by Ighani et al,[4] who compared the safety profile of apremilast observed in a real-life cohort of psoriasis patients with that in the main randomized controlled trials. They found worse apremilast tolerability in real-life patients, with a significantly greater number of withdrawals because of adverse events (AEs).

To confirm these findings in patients with PsA, we performed a retrospective analysis of data from the Real-Life Apremilast for Psoriatic Arthritis Evaluation Registry (RAPPER), which is a multicentric observational cohort of patients with PsA (the compilation of which has been approved by local ethics committees) that includes all patients with PsA who are at least 18 years of age and have been treated with apremilast in 12 Italian tertiary rheumatology centers. Treatments were administered according to the licensed regimen, and concomitant therapies were prescribed if ordered by the referring rheumatologist. Reported AEs and tolerability (AEs leading to discontinuation) were assessed over a 6-month follow-up period. Withdrawals were considered definitive when indicated in the registry or when no consecutive reintroduction of treatment was reported. A chi-square test was used to compare safety outcomes

Table I. Baseline characteristics and safety profile of apremilast population included in RCTs and in the RAPPER cohort

	Cohort					
Indicator	**RAPPER (N = 131)**	**PALACE I[1] (N = 168)**	**PALACE II[2] (N = 162)**	**PALACE III[3] (N = 167)**	**Pooled RCTs (N = 497)**	***P* value vs pooled**
Baseline characteristics						
Female, n (%)	83 (63.3)	92 (54.8)	95 (58.6)	88 (53)	275 (55.3)	.11
Mean age, y (SD)	57.5 (12)	51.4 (11.7)	50.5 (11.2)	49.9 (11.4)	50.6 (11.4)	
Mean duration of PsA, y (SD)	10.8 (12.4)	8.1 (8.1)	6.8 (7.6)	7.5 (7.6)	7.5 (7.7)	
Mean weight, kg (SD)	73.3 (18.7)	87.1 (19.6)	82.7 (18.9)	83.7 (20.1)	84.5 (19.5)	
Mean body mass index, kg/m^2 (SD)	27.8 (16.3)	30.6 (5.9)	29.2 (6.2)	29.2 (6.4)	29.6 (6.2)	
Prior use of biologics, n (%)	62 (47.7)	41 (24.4)	23 (14.2)	43 (26)	107 (21.5)	<.0001
Concomitant csDMARD use, n (%)	47 (35.9)	106 (63.1)	113 (69.8)	101 (61)	320 (64.3)	<.0001
Overall AEs						
Diarrhea	19 (14.5)	32 (19)	24 (14.8)	26 (16)	82 (16.4)	.68
Headache	12 (9.1)	18 (10.7)	19 (11.7)	20 (12)	57 (11.4)	.53
Nausea/vomiting	10 (7.6)	31 (18.5)	26 (16.0)	31 (19)	88 (17.7)	.004
Depression	1 (0.7)					
UC relapse	1 (0.7)					
Weight loss	2 (1.4)					
Upper respiratory tract infection	6 (4.5)	7 (4.2)	11 (6.8)	12 (7)	30 (6)	.67
Rash	1 (0.7)					
Abdominal pain	7 (5.3)					
Herpes zoster infection	1 (0.7)					
AEs leading to discontinuation						
Overall	23 (17.5)	12 (7.1)	12 (7.4)	12 (7)	36 (7.2)	.001
Diarrhea	10 (7.6)	4 (2.4)				.05*
Headache	7 (5.3)	1 (0.6)				.023*
Nausea/vomiting	3 (2.3)	2 (1.2)				.65*
Depression	1 (0.7)					
UC relapse	1 (0.7)					
Anemia	1 (0.7)					

AE, Adverse events; *csDMARD*, conventional synthetic disease-modifying antirheumatic drug; *PALACE*, Psoriatic Arthritis Long-term Assessment of Clinical Efficacy; *PsA*, psoriatic arthritis; *RAPPER*, Real-Life Apremilast for Psoriatic Arthritis Evaluation Registry; *RCT*, randomized controlled trial; *SD*, standard deviation; *UC*, ulcerative colitis.
**P* value versus PALACE I.

between the RAPPER cohort and the pooled population from the PALACE I, II, and III clinical trials. *P* values of .05 or lower were considered statistically significant.

The study population of the RAPPER cohort included 131 patients with long-standing PsA (mean disease duration, 10.8 years) presenting with oligoarticular (58%), entheseal (26.7%), polyarticular (22%), axial (12.2%), skin (48%), and nail (40.4%) involvement. About two-thirds of patients (64.1%) had at least 1 comorbidity, in particular, a history of malignancies (25.9%) and a positive screening result for latent tuberculosis (16.3%).

Diarrhea (14.5%), headache (9.1%), and nausea/vomiting (7.6%) were the most commonly reported AEs (Table I). We observed no cases of malignancy, opportunistic infection, or tuberculosis reactivation. Apremilast withdrawal because of AEs was reported in 23 patients after a mean period of 82.3 plus or minus 47.4 days. The most frequent AEs leading to discontinuation were diarrhea (n = 10), nausea/vomiting (n = 3), and headache (n = 7). No difference in the incidence of AEs between the RAPPER and PALACE pooled populations was found, the only exception being the incidence of nausea/vomiting (17.7% [$P = .004$]); however, the rate of discontinuation due to AEs was significantly higher in the RAPPER cohort ($P = .001$). On the basis of the available data, withdrawals because of diarrhea ($P = .05$) and headache ($P = .023$) were each more common in our experience than in the PALACE I study. These findings can be partially explained by the differences in population characteristics between RAPPER and PALACE cohorts, in particular, regarding the proportions of enrolled patients with failure of biologics (47.7% versus 21.5%, respectively [$P < .0001$]) and the inclusion in the RAPPER cohort of patients carrying comorbidities excluded by the PALACE enrollment criteria.

In conclusion, our data confirmed the lower real-life tolerability of apremilast in a cohort of patients with PsA than in the randomized controlled trials previously reported by Ighani et al[4] in patients with psoriasis, with gastrointestinal complaints and headache as the most frequent reasons for drug discontinuation.

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