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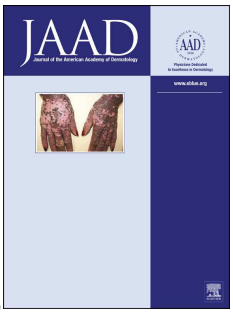

A comparison of apremilast monotherapy and combination therapy for psoriatic arthritis in a real life setting: data from the Leeds Combined Psoriatic Service

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To the Editor: Randomized controlled trials have shown that the phosphodiesterase-4 inhibitor Apremilast is an effective and safe option in the treatment of psoriasis and psoriatic arthritis (PsA) (1) with real-world data now emerging from the dermatology and rheumatology settings (2-5). The Canadian multicenter retrospective study showed no increased reported AEs when Apremilast was used in monotherapy (MT) or in combination therapy (CT) with systemic drugs in patients with plaque psoriasis and that the CT group did not have superior efficacy, likely reflecting more resistant disease (2). Such data is still sparse from the real-world experience in PsA patients.

In the first real-life report of Apremilast 30mg BD in active PsA, data were retrospectively reviewed in seventy-one patients with active PsA at the tertiary Leeds Psoriatic Service (4). Herein we report a sub-analysis of the safety and response to therapy data according to the treatment regimen.The proportions and means were compared using Fisher's exact test and two-tailed unpaired-t-test respectively. Statistical analysis was performed with GraphPad Prism 7 with $p \leq 0.05$ considered significant.

Clinical characteristics and AEs are reported in table 1 and table 2 respectively. Of 71 PsA patients, 39 (54.9%) were on MT, 32 (45.1%) on CT (Table 1). Sub-analysis of the two groups showed no increased number of the reported AEs when Apremilast was used in MT or in CT with conventional and/or biological disease modifying antirheumatic drugs (DMARDS) (table 2), confirming Ighani et al. results (2). We did not perform a statistical analysis due to the small number of AEs. Unlike RCTs (1) and the retrospective study of Ighani et al (2), unwanted weight loss and upper respiratory tract infections were not reported in our experience (table 2) (4). Of the 51 patients with a mean follow-up ≥6 months, in which we could assess the response to therapy (4), 28 were on MT and 23 were taking Apremilast in combination with conventional (n=16) or biologic (n=5) DMARDs, or with both (n=2).

According to the response criteria (4), a slightly greater proportion of MT patients achieved response (18/28 vs 13/23, 64.3% vs 56.5%), with not significant difference. As in the plaque psoriasis real-world experience (2), this may be explained by more difficult-to-treat PsA cases requiring additional drugs in order to control disease activity. When comparing number of previous DMARDs and disease duration, there was no difference between MT and CT groups ($p>0.05$).

In conclusion, the favourable safety profile of Apremilast either in MT or CT makes it highly desirable in some clinical scenarios. While MT could serve to control chronically active disease not responsive to previous conventional/biologic DMARDS or to treat earlier on patients with less severe joint/skin manifestations who may not yet require a biologic DMARD (4), the CT may reduce disease activity not adequately controlled with other treatments without increasing risk of AEs. In clinical practice use of CT, particularly with biologics, is currently limited by costs. Larger observational data are needed to define cases who may benefit of MT and/or CT and characterise specific AEs .

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References

1. Keating GM. Apremilast: A Review in Psoriasis and Psoriatic Arthritis. Drugs. 2017;77:459-472.
2. Ighani A, Georgakopoulos JR, Walsh S, et al. A comparison of apremilast monotherapy and combination therapy for plaque psoriasis in clinical practice: A Canadian multicenter retrospective study. J Am Acad Dermatol 2018;78:623-26
3. Ighani A, Georgakopoulos JR, Shear NH, et al. 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. J Am Acad Dermatol 2018;78:801-3
4. Abignano G, Fadl N, Merashli M, et al. Apremilast for the treatment of active psoriatic arthritis: a single-centre real-life experience. Rheumatology (Oxford) 2018;57:578-80.
5. Abignano G, Laws P, Del Galdo F, et al. Three-dimensional nail imaging by optical coherence tomography: a novel biomarker of response to therapy for nail disease in psoriasis and psoriatic arthritis. Clin Exp Dermatol. 2018 Sep 23. doi: 10.1111/ced.13786.

Table Legend

Table 1. Proportions were compared by using the Fisher's exact test. Means were compared using a two-tailed unpaired t test. SD, Standard deviation.

Table 1. "Clinical characteristics and treatment regimen of the 71 PsA patients on Apremilast "

Table 2. Mean numbers of reported AEs per subject were compared by using a two-tailed unpaired t test. AE, Adverse event; SD, standard deviation.

Table 2. "Reported adverse events (AEs) in PsA patients treated with Apremilast in real-world setting"

Table 1. Clinical characteristics and treatment regimen of the 71 PsA patients on Apremilast

	Monotherapy 39 (54.9)	**Combination Therapy** 32 (45.1)	**P**
Male, n (%)	16 (41.3)	17 (53.1)	0.3
Age, years, mean (SD)	50.5 (2.3)	51.5 (2)	0.7
Disease duration, years, mean (SD)	7.1 (6.3)	8.5 (6.6)	0.3
Psoriasis, n (%)	33 (84.6)	26 (81.3)	0.8
Time of follow-up, days, mean (SD)	182.5 (114.1)	160.5 (94.3)	0.4
Number of failed cDMARDs prior to Apremilast, mean (SD)	1.6 (1)	1.1 (1.1)	0.2
Number of failed bDMARDs prior to Apremilast, mean (SD)	1.2 (1.4)	1.6 (1.6)	0.4
Failed DMARDs prior to Apremilast, n (%)			
Methotrexate	31 (79.5)	20 (62.5)	0.2
Sulfasalazine	22 (56.4)	3 (9.4)	**<0.0001**
Hydroxychloroquine	7 (18)	5 (15.6)	>0.9
Leflunomide	6 (15.4)	1 (3.1)	0.06
Cyclosporine	5 (12.8)	0 (0)	0.06
Certolizumab	0 (0)	3 (9.4)	0.09
Golimumab	3 (7.7)	6 (18.8)	0.3
Ustekinumab	2 (5.1)	3 (9.4)	0.7
Adalimumab	13 (33.3)	17 (53.1)	0.1
Etanercept	15 (38.5)	11 (34.4)	0.8
Infliximab	5 (12.8)	6 (18.8)	0.5
Secukinumab	0 (0)	0 (0)	-
Tocilizumab	1 (2.6)	0 (0)	-
Prior conventional DMARDs, patients,	38 (97.4)	29 (90.6)	0.3

n (%)			
Prior biological DMARDs, patients, n (%)	20 (51.3)	20 (70.7)	0.1
Combination Therapy (CT), n (%)		**32 (45.1)**	
Dual CT		***28 (39.4)***	
Methotrexate	-	16 (22.5)	-
Sulfasalazine	-	1 (1.4)	-
Hydroxychloroquine	-	2 (2.8)	-
Leflunomide	-	1 (1.4)	-
Certolizumab	-	1 (1.4)	-
Golimumab	-	2 (2.8)	-
Ustekinumab	-	1 (1.4)	-
Adalimumab	-	1 (1.4)	-
Etanercept	-	1 (1.4)	-
Secukinumab	-	1 (1.4)	-
Tocilizumab	-	1 (1.4)	-
Triple CT		***4 (5.6)***	-
Methotrexate + Sulfasalazine	-	1 (1.4)	-
Methotrexate+ Hydroxychloroquine	-	1 (1.4)	-
Methotrexate + Certolizumab	-	1 (1.4)	-
Methotrexate + Ustekinumab	-	1 (1.4)	-

Table 2. Reported adverse events (AEs) in PsA patients treated with Apremilast in real-world setting

Reported AEs, n (%)	Monotherapy (n=39)	Combination therapy (n=32)	All (n=71)	P
Diarrhea	8 (20.5)	5 (15.6)	13 (18.3)	-
Nausea	7 (18)	2 (6.3)	9 (12.7)	-
Headache	6 (15.4)	2 (6.3)	8 (11.3)	-
Vomiting	2 (5.1)	1 (3)	3 (4.2)	-
General malaise	2 (5.1)	0 (0)	2 (2.8)	-
Depression	2 (5.1)	0 (0)	2 (2.8)	-
Suicidal ideation	1 (2.6)	0 (0)	1 (1.4)	-
Abdominal pain and/or loss of appetite	1 (2.6)	0 (0)	1 (1.4)	-
Reported AEs per subject, n (%)				-
0	22 (56.4)	22 (68.8)	44 (62)	-
1	5 (12.8)	5 (15.6)	10 (14.1)	-
2	5 (12.8)	3 (9.4)	8 (11.3)	-
3	4 (10.3)	2 (6.3)	6 (8.5)	-
≥4	3 (7.7)	0 (0)	3 (4.2)	-
Number of reported AEs per subject, mean (SD)	2.3 (1.1)	1.7 (0.8)	2.1 (1)	0.15

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