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Unmet needs in psoriatic arthritis patients receiving immunomodulatory therapy: results from a large multinational real-world study

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Abstract

Objective There are limited data on therapy selection and switching in psoriatic arthritis (PsA). This 18 country, real-world study assessed use and switching of immunomodulatory therapy (biologic/apremilast), the extent of treatment failure and its association with reduced physical functioning, health-related quality of life (HRQoL), and work productivity and activity impairment (WPAI).

Methods PsA patients under routine care and their treating physicians provided demographics, current therapy, reasons for switching, duration of first therapy, HRQoL, HAQ-DI, and WPAI. Current immunomodulatory therapy was determined as "failing" if, after ≥ 3 months, physician-rated disease severity had worsened, remained severe, was "unstable/deteriorating," or they were dissatisfied with disease control and/or did not consider treatment a "success."

Results Included were 3714 PsA patients; 1455 (40.6%) had never received immunomodulatory therapy; 1796 (50.1%) had ever received 1 immunomodulatory therapy and 331 (9.2%) ≥ 1. Lack of efficacy with first immunomodulatory therapy was the most common reason for switching; patients whose physicians indicated "primary lack of efficacy" as the reason, switched after a mean of 9.4 months. Patients currently failing immunomodulator therapies ($n = 246$) had poorer HRQoL compared with treatment success ($n = 1472$) measured by EQ-5D-3L (0.60 vs 0.77%; $P < 0.0001$); SF-36 PCS (40.8% vs 46.1%; $P < 0.0001$) MCS (41.1% vs 45.3%; $P < 0.0001$). Physical functioning, activity, and work productivity were also more impaired (HAQ-DI: 0.88 vs 0.56; activity impairment: 46.7% vs 29.7%; overall work impairment: 35.4% vs 26.1%; all $P < 0.0001$).

Conclusions Poor treatment response in PsA is associated with substantial negative patient impact. In cases of primary treatment failure, timely switching is needed.

Keywords Health-related quality of life · Psoriatic arthritis · TNFi · Treatment · Work

Introduction

Psoriatic arthritis (PsA) is a multifaceted systemic chronic inflammatory disease with diverse features, varied outcomes, and disease course, which affects skin and joints simultaneously [1–4]. The prevalence of psoriatic arthritis (PsA) varies by country, from 0.001% adults in Japan to 0.42% in Italy, and 0.16% in the USA, and is seen in up to 40% of

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psoriasis patients [1–4]. Patients with PsA experience pain, stiffness, enthesitis, swelling, and tenderness of the joints, with 40–60% of patients developing erosive joint disease leading to impaired articular functioning and higher mortality [1, 2]. These symptoms have a detrimental effect on social relationships, quality of life, and mortality as well as burdening the patient and society with impaired ability to work and substantial healthcare costs [1, 5].

Conventional disease modifying anti-rheumatic drugs (cDMARDs) including sulfasalazine and methotrexate are widely used in the treatment of PsA [6]. However, advances in understanding PsA pathogenesis, especially the role of T cells and cytokines, have led to a range of immunomodulatory treatments for PsA. The therapeutic armamentarium now also includes biologic DMARDs (bDMARDs) such as tumor necrosis factor inhibitors (TNFis), anti-interleukin (IL)-12/23 ustekinumab, anti-IL-17A secukinumab and ixekizumab, and abatacept. Targeted synthetic DMARDs (tsDMARD) include phosphodiesterase-4 (PDE-4) inhibitor apremilast and janus kinase inhibitor (JAKi) tofacitinib [7–11].

The choice of first-line therapy, and which treatment to switch to in the event of first-line treatment failure, is well described in several recent treatment guidelines. The American College of Rheumatology (ACR) and the National Psoriasis Foundation (NPF) most recent guideline for treating PsA recommends TNFi as first-line treatment for active PsA [12]. If a TNFi is not an option, conventional DMARDs (cDMARDs) are preferable to other biologics. Methotrexate is preferable to NSAID, and anti-IL17 is preferable to an IL-12/23 [12]. If PsA is still active after the change, switching to anti-IL-17 should be the next step rather than a cDMARD or other biologic. If PsA continues to be active, switching to an anti-IL12/23 rather than cDMARD, abatacept, or tofacitinib is recommended [12]. The most recent GRAPPA and EULAR recommendations also prefer switching to a bDMARD for patients with active PsA despite cDMARD treatment, usually TNFi, anti-12/23 or anti-IL17 if TNFi is not appropriate, or apremilast if a bDMARD is inappropriate [13, 14]. EULAR recommends switching TNFi if target is not achieved within 3–6 months [14].

The aim of this large multi-national study was to describe the use of immunomodulatory therapy in PsA patients using real-world data, and assess treatment switching and failure rates, as well as the association between treatment failure and reduced physical functioning, quality of life, and work capability.

Materials and methods

Data source

This was an analysis of data drawn from the Adelphi PsA Disease Specific Program (DSP) conducted between 2015 and 2016 in 18 countries: North America (USA, Canada), Latin America, (LatAm, covering Brazil, Mexico), EU5 (Europe, covering France, Germany, Italy, Spain, UK), Asia Pacific, (APAC, covering Japan, Malaysia, South Korea, Taiwan, Australia), and Turkey & Middle East, (T&ME, covering Egypt, Saudi Arabia, United Arab Emirates) regions [15]. DSPs are large, point-in-time surveys collecting evidence of real-world clinical practice, designed to identify current disease management and patient and physician reported disease impact.

Physicians included in the survey were instructed to complete a pre-specified questionnaire for the next 1–8 (variable by country) consecutive patients with active PsA who visited for routine care. Physician-reported questionnaires included detailed questions on patient demographics, clinical assessments, medication use and treatment history. Each patient with a physician-completed questionnaire was invited to fill out a patient-reported form after providing informed consent. Patients completed their forms independently from physicians, returning them in sealed envelopes to ensure confidentiality.

The Rheumatology DSPs were conducted in accordance with the relevant legislation at time of data collection, including US Health Insurance Portability and Accountability Act 1996 (HIPAA; www.hhs.gov/ocr/privacy/) [16], and Health Information Technology for Economic and Clinical Health Act legislation [17]. The DSP is a market research project and complies with all relevant market research guidelines and legal obligations. Data were collected according to European Pharmaceutical Marketing Research Association guidelines and thus did not require ethics committee approvals [18]. Namely, the DSP is non-interventional and employs solely retrospective data collection, and no identifiable protected health information was extracted during the course of the study.

Participating physicians and patients

Rheumatologists (and orthopedists and internists in Japan) and dermatologists were eligible to participate if they had worked ≥3 years' as a physician, had qualified between 1979 and 2012, and were responsible for treatment decisions. Rheumatologists were responsible for treatment decisions of axial SpA and PsA patients and dermatologists were responsible for treatment decisions of PsA patients.

Patients were eligible for inclusion if aged ≥ 18 years, with a physician-confirmed diagnosis of PsA, not currently involved in a clinical trial. There were no restrictions according to treatments, clinical features such as disease activity/severity or demographics.

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Defining "treatment switching"

"Treatment switching" was defined as progressing from a first immunomodulator therapy to a second therapy of the same or different class. Physicians reported reasons for switching from a list of choices. Reasons for switch included factors associated with lack of initial or ongoing efficacy, failure to control (specific) symptoms, patient change (improvement, worsening), intolerability, issues associated with treatment administration, patient preference, administrative reasons including formulary requirements and physician preference for an alternative therapy. The full list is shown in Supplementary Fig. 1.

Defining "failing" and "success" treatment groups

Patients were categorized as "failing to respond" on current immunomodulatory treatment if, > 3 months after initiating therapy with TNFi, apremilast, or ustekinumab, ≥ 1 of the following criteria, assessed by the treating physician, were met: disease severity (reported as mild, moderate, severe PsA) had worsened or remained severe; disease activity (reported as improving, stable, unstable, deteriorating) was unstable or deteriorating; physicians reported dissatisfaction with current control of PsA; or reported they did not consider the patient's current treatment regimen a "success". Any patient not considered in the "failing to respond" group was included as a "treatment success".

Patient-reported outcomes

Patient-reported forms included validated instruments including the Health Assessment Questionnaire-Disability Index (HAQ-DI) [19], 5-dimension EuroQoL (EQ-5D-3L) [20], Medical Outcomes Study Short-Form Health Survey version 2 (SF-36v2) [21], and the Work Productivity and Activity Impairment (WPAI-GH) [22] questionnaire.

Statistical analyses

Patient characteristics were descriptively analyzed for the total study sample at global and regional levels (North America, LatAm, EU5, APAC, T&ME) by demographics and underlying patient condition (including age, gender, BMI, and BSA affected by psoriasis), number of immunomodulators received, reasons for switching from first to second agent, duration patients remained on first therapy and overall rates of patients failing to respond to immunomodulator therapy and according to line of therapy.

Categorical variables were described by counts and proportions of respondents and continuous numerical variables were described by their medians, means, and standard deviations. Pearson's χ^2 test assessed differences in failure rates by lines of therapy.

Linear regression analyses were performed for EQ 5D, SF-36 PCS and MCS, and WPAI. The independent variable was treatment response (failing to respond or success), and differences in age, gender, BMI, smoking status, time since symptom onset and region were controlled for. Predicted values for all outcomes were subsequently stratified by failure or success while all other variables were fixed at their means.

All analyses used Stata Statistical Software: Release 15 (StataCorp LP, College Station, TX).

Results

Patients and physicians

A total of 949 physicians from 18 countries (North America, $n = 155$; LatAm, $n = 85$; EU5, $n = 450$; APAC, $n = 127$; T&ME, $n = 132$) and 3714 PsA patients (North America, $n = 707$; LatAm, $n = 281$; EU5, $n = 1820$; APAC, $n = 543$; T&ME, $n = 363$) from the DSP were eligible for inclusion in this analysis; in total 48.2% provided by rheumatologists (including Orthopedic Internal Medicine in Japan), 51.8% by dermatologists.

Key patient demographic and disease characteristics are summarized in Table 1. Patient characteristics including mean age, BMI, time since diagnosis and HAQ-DI were comparable for most regions with some exceptions. In T&ME, median time since diagnosis and symptom onset was less than other regions at 0.5 year and 1 year compared to 2–3 years and 4–5 years respectively. HAQ-DI was higher for T&ME than for other regions. In addition, there were less patients with mild disease severity and more with moderate disease severity as reported by the treating physician than for other regions. Among patients with psoriasis, those in APAC had the highest proportion of psoriasis affected BSA, with a mean of 13.6% compared to 8.5%–11.3% in other regions.

Of 3714 patients with PsA, 1856 patients completed the voluntary questionnaires, including EQ-5D ($n = 1809$), SF-36 ($n = 1699$), and WPAI ($n = 1779$). Patient reported outcomes were comparable across most regions, other than T&ME where they were notably poorer than other regions.

Use of immunomodulators

Of 3582 patients with complete treatment data, 1455 (40.6%) had never received immunomodulators, 1796 (50.1%) were receiving the first immunomodulator, 243 (6.8%) the second immunomodulator, and 88 (2.5%) the third or later immunomodulator (Table 2). Of 2221 globally treated patients (including 94 with incomplete data as to total number of immunomodulators used), the majority received TNFi (84.5%); true across all regions included in this study (Table 2).

Table 1 Patient characteristics

Characteristic	All ($n = 3714$)	North America ($n = 707$)	LatAm ($n = 281$)	EU5 ($n = 1820$)	APAC ($n = 543$)	T & ME ($n = 363$)
Age, years	($n = 3710$)	($n = 707$)	($n = 281$)	($n = 1820$)	($n = 539$)	($n = 363$)
Median	47.0	49.0	48.0	48.0	51.0	40.0
IQR	39.0, 57.0	39.0, 57.0	40.0, 58.0	40.0, 58.0	41.0, 61.0	35.0, 43.0
Mean (SD)	48.2 (12.5)	48.1 (12.6)	49.1 (12.1)	48.9 (12.4)	51.5 (13.5)	39.7 (7.3)
Male, n (%)	1916 (51.6)	345 (48.8)	141 (50.2)	956 (52.5)	320 (59.0)	154 (42.4)
BMI, kg/m^2	($n = 3708$)	($n = 707$)	($n = 281$)	($n = 1820$)	($n = 539$)	($n = 361$)
Median	25.7	26.7	26.0	25.4	23.9	26.1
IQR	23.3, 28.4	24.3, 30.4	23.9, 28.4	23.3, 28.0	21.7, 27.0	24.6, 28.4
Mean (SD)	26.4 (4.7)	28.0 (5.6)	26.4 (4.0)	26.1 (4.3)	25.0 (4.9)	26.8 (3.7)
Time since symptom onset (years)	($n = 2943$)	($n = 542$)	($n = 262$)	($n = 1405$)	($n = 390$)	($n = 344$)
Median	4.0	4.0	4.0	5.0	5.0	1.0
IQR	2.0, 8.0	2.0, 10.0	1.8, 8.0	2.0, 9.0	2.0, 10.0	1.0, 2.0
Mean (SD)	6.3 (7.4)	6.8 (7.1)	6.3 (6.7)	7.0 (7.9)	7.2 (7.7)	1.9 (2.0)
Time since diagnosis (years)	($n = 3210$)	($n = 583$)	($n = 267$)	($n = 1597$)	($n = 412$)	($n = 351$)
Median	3.0	3.0	2.0	3.0	3.0	0.5
IQR	1.0, 6.0	1.0, 6.0	0.8, 5.0	1.4, 7.0	1.0, 7.0	0.1, 1.0
Mean (SD)	4.7 (6.0)	4.9 (5.7)	4.4 (6.0)	5.5 (6.5)	5.1 (5.5)	1.0 (1.5)
Current severity (physician reported), n (%)						
Mild	2378 (64.1)	478 (67.6)	183 (65.1)	1159 (63.7)	379 (70.1)	179 (49.6)
Moderate	1162 (31.3)	208 (29.4)	80 (28.5)	568 (31.2)	149 (27.5)	157 (43.5)
Severe	170 (4.6)	21 (3.0)	18 (6.4)	93 (5.1)	13 (2.4)	25 (6.9)
PsA with psoriasis, n %	3512 (94.6)	677 (95.8)	261 (92.9)	1727 (94.9)	497 (91.9)	350 (96.4)
% BSA currently affected by psoriasis	($n = 2731$)	($n = 562$)	($n = 259$)	($n = 1172$)	($n = 400$)	($n = 338$)
Median	5.0	5.0	1.8	7.0	8.0	6.0
IQR	2.0, 15.0	2.0, 15.0	0.0, 11.8	3.0, 15.0	2.0, 20.0	3.0, 12.0
Mean (SD)	11.1 (13.4)	11.3 (14.2)	8.5 (14.2)	11.2 (12.5)	13.6 (15.9)	9.5 (9.9)
EQ-5D utility score	($n = 1809$)	($n = 371$)	($n = 217$)	($n = 742$)	($n = 265$)	($n = 214$)
Median	0.8	0.83	0.77	0.84	0.85	0.08
IQR	0.59, 1.00	0.77, 1.00	0.59, 1.00	0.68, 1.00	0.73, 1.00	−0.02, 0.52
Mean (SD)	0.72 (0.32)	0.84 (0.17)	0.73 (0.29)	0.76 (0.28)	0.84 (0.19)	0.18 (0.32)
SF36 PCS	($n = 1657$)	($n = 382$)	($n = 69$)	($n = 728$)	($n = 263$)	($n = 215$)
Median	44.3	48.9	39.6	44.7	47.8	37.4
IQR	37.0, 52.0	40.2, 54.2	34.1, 44.1	36.9, 52.1	41.9, 52.8	33.6, 42.2
Mean (SD)	44.1 (9.2)	46.9 (9.2)	40.0 (7.3)	43.9 (9.6)	46.6 (8.2)	37.9 (6.0)
SF36 MCS	($n = 1657$)	($n = 382$)	($n = 69$)	($n = 728$)	($n = 263$)	($n = 215$)
Median	44.5	53.2	36.5	45.6	44.8	38.0
IQR	37.0, 53.0	42.9, 58.0	35.0, 41.6	37.0, 51.7	37.4, 52.2	34.2, 41.3
Mean (SD)	44.4 (10.4)	50.1 (9.9)	38.1 (8.0)	44 (10.7)	44.6 (9.4)	37.5 (5.7)
HAQ-DI	($n = 1668$)	($n = 383$)	($n = 69$)	($n = 735$)	($n = 266$)	($n = 215$)
Median	0.5	0.13	0.88	0.5	0.19	1.5
IQR	0.00, 1.13	0.00, 0.50	0.38, 1.13	0.00, 1.14	0.00, 0.63	1.13, 1.63
Mean (SD)	0.67 (0.70)	0.36 (0.48)	0.89 (0.64)	0.70 (0.76)	0.40 (0.52)	1.37 (0.45)
WPAI, overall work impairment	($n = 886$)	($n = 235$)	($n = 98$)	($n = 300$)	($n = 135$)	($n = 118$)
Median	20	10	20	20	20	67.6
IQR	10.0, 50.9	0.0, 30.0	0.0, 52.6	10.0, 40.0	10.0, 30.0	63.5, 78.3
Mean (SD)	29.2 (27.5)	17.1 (19.9)	30 (30.3)	25.2 (24.4)	24.2 (20.6)	68.7 (15.2)

APAC, Asia Pacific region; BMI, body mass index; BSA, body surface area; EQ-5D, EuroQol 5-dimensions questionnaire; EU5, European Union 5; HAQ-DI, health assessment questionnaire disability index; MCS, mental component score; LatAm, Latin America; PsA, psoriatic arthritis; T & ME, Turkey & Middle East; PCS, physical component score; SD, standard deviation; SF-36, Medical Outcomes Study Short-Form (36-item) Health Survey; WPAI, work productivity and activity impairment questionnaire

Immunomodulator treatment switching

Supplementary Fig. 1 presents the data for reasons for switching from first to second immunomodulatory therapy. Physicians selected reasons for switching from a pre-specified list for 304 PsA patients who had received > 1 immunomodulator and reason for switch was known. Responses that explicitly indicated lack of efficacy were selected for more than two thirds of patients who switched therapy;

"secondary lack of efficacy (loss of response over time)" was selected for 134 (44.1%) and "primary lack of efficacy (initial non-response)" for 69 (22.7%). Other selected reasons included "condition worsened" in 114 (37.5%), "lack of pain relief" in 58 (19.1%), "remission not maintained" in 57 (18.8%) and "remission was not induced" in 50 (16.4%).
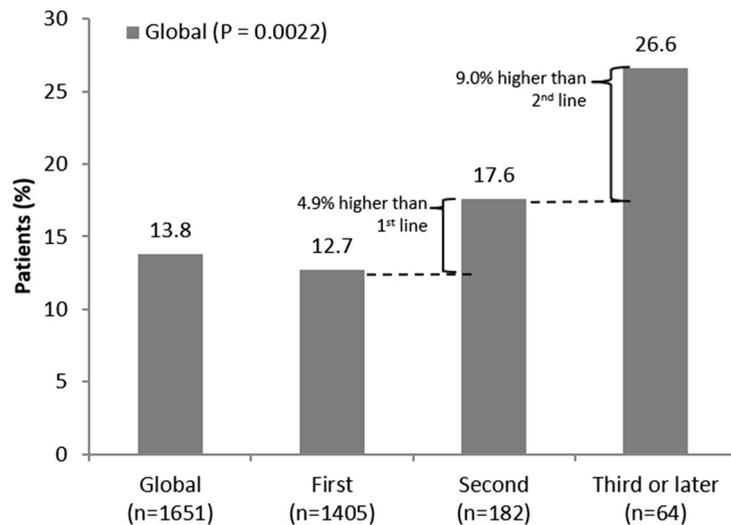
For the 58 whose physicians reported that primary lack of efficacy was the reason for immunomodulator switch, mean duration of initial therapy was 9.4 months (standard deviation

Table 2 Treatment with immunomodulating therapies

	All	North America	LatAm	EU5	APAC	T & ME
Number of immunomodulating therapy ever received, n (%)	(n = 3582)	(n = 680)	(n = 276)	(n = 1780)	(n = 491)	(n = 355)
0	1455 (40.6)	203 (29.9)	24 (8.7)	761 (42.8)	230 (46.8)	237 (66.8)
1	1796 (50.1)	380 (55.9)	229 (83.0)	848 (47.6)	229 (46.6)	110 (31.0)
2	243 (6.8)	64 (9.4)	19 (6.9)	130 (7.3)	23 (4.7)	7 (2.0)
3+	88 (2.5)	33 (4.9)	4 (1.4)	41 (2.3)	9 (1.8)	1 (0.3)
Current class of immunomodulator therapy, n (%)	(n = 2221)	(n = 504)	(n = 257)	(n = 1059)	(n = 276)	(n = 125)
TNFi	1877 (84.5)	355 (70.4)	254 (98.8)	924 (87.3)	238 (86.2)	106 (84.8)
Non-TNFi bDMARD	239 (10.8)	80 (15.9)	3 (1.2)	106 (10.0)	31 (11.2)	19 (15.2)
tsDMARD (oral)	105 (4.7)	69 (13.7)	0 (0.0)	29 (2.7)	7 (2.5)	0 (0.0)
Time on 1st immunomodulatory therapy when physician recorded "primary lack of efficacy," months	(n = 58)	(n = 20)	(n = 2)	(n = 29)	(n = 4)	(n = 3)
Mean (SD)	9.4 (11.9)	12.8 (18.8)	3.5 (3.5)	7.7 (5.7)	7.0 (3.5)	10.7 (1.2)
Median	6.0	6.0	3.5	6.0	6.0	10.0
Min, max	1.0, 84.0	2.0, 84.0	1.0, 6.0	1.0, 24.0	4.0, 12.0	10.0, 12.0
IQR	4.0, 12.0	4.5, 11.0	1.0, 6.0	3.0, 12.0	5.0, 9.0	10.0, 12.0

Patient immunomodulator therapy exposure and switching. APAC, Asia Pacific region; BMI, body mass index; bDMARD: biologic disease modifying anti-rheumatic drug; EU5, European Union 5; LatAm, Latin America; SD, standard deviation; T & ME, Turkey & Middle East; TNFi, tumor necrosis factor inhibitor; tsDMARD, targeted synthetic disease modifying anti-rheumatic drug

Fig. 1 Patients currently "failing" first, second, third, or later immunomodulator therapy rates of failure on successive lines of immunomodulator therapy. APAC, Asia Pacific region; EU5, European Union 5; LatAm, Latin America, T & ME, Turkey & Middle East

Global	(n=1718)	(n=1405)	(n=182)	(n=64)	
% Failing	14.3	12.7	17.6	26.6	P = 0.0022
North America	(n=381)	(n=288)	(n=50)	(n=24)	
% Failing	12.9	11.8	8.0	16.7	P = 0.5368
LatAm	(n=190)	(n=174)	(n=9)	(n=4)	
% Failing	16.3	14.9	33.3	50.0	P = 0.0674
EU5	(n=877)	(n=702)	(n=109)	(n=30)	
% Failing	14.8	12.8	18.3	33.3	P = 0.0030
APAC	(n=197)	(n=174)	(n=12)	(n=5)	
% Failing	12.7	12.1	25.0	20.0	P = 0.3934
T&ME	(n=73)	(n=67)	(n=2)	(n=1)	
% Failing	15.1	11.9	100.0	0.0	P = 0.002

Table 3 Patient characteristics of "immunomodulator therapy success" and "immunomodulator therapy failing" cohorts

Group	All		North America		LatAm		EU5		APAC		T & ME	
	Success (n = 1472)	Failing (n = 246)	Success (n = 332)	Failing (n = 49)	Success (n = 159)	Failing (n = 31)	Success (n = 747)	Failing (n = 130)	Success (n = 172)	Failing (n = 25)	Success (n = 62)	Failing (n = 11)
Age, years												
Median	49.0	49.0	50.5	51.0	49.0	45.0	49.0	49.0	51.0	49.0	40.0	39.0
IQR	41.0, 57.0	41.0, 57.0	42.0, 58.0	46.0, 59.0	41.0, 58.0	42.0, 57.0	41.0, 56.0	41.0, 58.0	41.0, 61.0	45.0, 56.0	35.0, 43.0	35.0, 44.0
Mean (SD)	48.8 (11.6)	49.3 (12.0)	49.1 (11.8)	51.4 (12.6)	49.2 (11.6)	48.5 (11.5)	48.7 (11.3)	49.3 (12.1)	51.1 (12.8)	50.6 (10.8)	39.5 (5.9)	38.6 (5.4)
P	0.6918		0.2225		0.7465		0.7560		0.7142		0.7452	
Male, n (%)	819 (55.6)	131 (53.3)	182 (54.8)	21 (42.9)	89 (56.0)	15 (48.4)	407 (54.5)	73 (56.2)	112 (65.1)	14 (56.0)	29 (46.8)	8 (72.7)
P	0.4894		0.1271		0.5546		0.7748		0.3813		0.1898	
BMI, kg/m²												
Median	25.8	26.4	27.2	27.3	26.4	25.0	25.5	26.3	23.5	25.7	26.0	26.5
IQR	23.4, 28.8	24.1, 29.4	24.8, 30.8	24.4, 34.6	24.2, 29.1	23.4, 28.1	23.3, 28.3	23.9, 29.4	21.6, 26.3	23.6, 29.1	24.9, 28.5	25.8, 27.7
Mean (SD)	26.6 (4.8)	27.2 (5.1)	28.4 (5.8)	29.2 (6.0)	27.0 (4.2)	25.9 (4.0)	26.2 (4.3)	27.1 (5.2)	24.7 (4.7)	26.1 (4.8)	26.9 (2.5)	26.6 (1.3)
P	0.0600		0.4942		0.1627		0.0578		0.0309		0.7402	
Time since symptom onset (years)												
n	1177	190	252	38	152	31	585	91	126	20	62	10
Median	5.0	5.0	5.0	7.0	5.0	4.0	6.0	7.0	5.0	3.0	2.0	3.0
IQR	3.0, 10.0	2.2, 10.0	3.0, 10.0	3.0, 12.0	3.0, 10.0	1.3, 7.0	3.0, 10.0	4.0, 15.0	2.0, 10.0	2.0, 7.5	2.0, 2.0	1.0, 4.0
Mean (SD)	7.6 (7.2)	8.6 (8.7)	8.0 (7.4)	8.7 (6.9)	7.4 (6.9)	6.3 (8.2)	8.3 (7.6)	10.3 (9.3)	6.5 (5.4)	7.0 (9.9)	2.4 (1.6)	2.6 (1.5)
P	0.7789		0.4084		0.1040		0.1140		0.4063		0.7294	
Time since diagnosis (years)												
n	1282	205	277	40	151	31	659	103	134	21	61	10
Median	4.0	4.0	4.0	5.0	3.0	2.0	5.0	6.0	3.0	2.0	1.0	1.5
IQR	2.0, 8.0	2.0, 8.0	2.0, 8.0	2.8, 10.0	2.0, 7.0	0.8, 5.0	2.5, 9.0	3.0, 10.0	2.0, 7.0	1.2, 3.0	0.8, 2.0	0.7, 3.0
Mean (SD)	6.0 (6.1)	6.3 (6.8)	6.0 (5.8)	6.8 (5.5)	5.5 (6.2)	4.9 (8.1)	6.8 (6.4)	7.6 (7.2)	5.1 (4.9)	3.1 (3.3)	1.6 (1.6)	1.7 (1.1)
P	0.6836		0.2577		0.1052		0.4101		0.0406		0.7275	
% BSA affected by psoriasis currently												
n	1143	179	280	38	155	30	509	80	138	20	61	11
Median	4.0	10.0	5.0	9.0	0.2	12.0	5.0	10.0	5.0	9.5	3.0	6.0
IQR	1.0, 10.0	5.0, 20.0	1.0, 10.0	5.0, 24.0	0.0, 7.3	1.8, 15.4	1.0, 10.0	5.0, 22.5	1.0, 10.0	5.0, 16.5	2.0, 5.0	5.0, 10.0
Mean (SD)	7.4 (10.4)	14.5 (14.4)	7.5 (10.1)	15.3 (16.9)	5.9 (11.7)	14.2 (16.3)	6.9 (8.5)	15.1 (13.0)	11.1 (15.4)	13.2 (13.9)	6.2 (7.6)	10.5 (10.9)
P	<0.0001		0.0004		<0.0001		<0.0001		0.0832		0.0072	
ESR, mm/h (within 3 months)												
n	547	85	95	15	10	0	324	51	63	10	55	9
Median	12.0	23.0	16.0	23.0	11.5	—	11.0	22.0	10.0	22.0	15.0	25.0
IQR	7.0, 20.0	15.0, 34.0	10.0, 24.0	18.0, 43.0	10.0, 13.0	—	5.0, 19.0	15.0, 34.0	6.0, 16.0	8.0, 38.0	12.0, 19.0	19.0, 32.0
Mean (SD)	14.4 (10.4)	27.7 (20.9)	17.4 (9.7)	29.5 (20.3)	11.6 (4.5)	—	13.6 (10.4)	26.9 (20.6)	13.0 (13.0)	30.4 (31.0)	16.1 (6.6)	25.7 (9.9)
P	<0.0001		0.0276		—		<0.0001		0.0426		0.0050	
CRP, mg/l (within 3 months)												

Table 3 (continued)

Group	All		North America		LatAm		EU5		APAC		T & ME	
	Success (n = 1472)	Failing (n = 246)	Success (n = 332)	Failing (n = 49)	Success (n = 159)	Failing (n = 31)	Success (n = 747)	Failing (n = 130)	Success (n = 172)	Failing (n = 25)	Success (n = 62)	Failing (n = 11)
n	506	82	74	12	11	0	307	52	62	10	52	8
Median	2.6	5.0	1.8	4.3	0.7	—	4.0	6.0	0.6	1.1	1.8	5.0
IQR	1.0, 5.4	2.4, 10.0	0.9, 3.4	2.7, 7.6	10.0, 13.0	—	2.0, 7.0	3.0, 10.5	0.2, 2.9	0.3, 3.0	1.3, 2.5	2.9, 6.5
Mean (SD)	4.5 (5.9)	8.9 (12.9)	4.7 (8.3)	5.5 (3.7)	0.8 (1.1)	—	5.4 (5.6)	9.9 (12.6)	2.5 (5.6)	5.0 (11.5)	2.3 (1.8)	12.4 (22.5)
P	< 0.0001		0.0073		—		0.0004		0.8005		0.0003	

Patients were deemed to be failing immunomodulator therapy after at least 3 months if disease severity had worsened or remained severe, disease activity was unstable or deteriorating, disease was not considered by physician to be controlled, nor treatment a success. Patients not considered to be failing immunomodulator therapy were considered to be "immunomodulator therapy success." APAC, Asia Pacific region; BMI, body mass index; BSA, body surface area; CRP, c-reactive protein; ESR, erythrocyte sedimentation rate; EU5, European Union 5; LatAm, Latin America; T & ME, Turkey & Middle East; SD, standard deviation

11.9 months) before switching with a maximum time to switch of 84 months (Table 2).

Immunomodulator treatment response

Based on the definition provided, 246 (14.3%) of patients receiving immunomodulator were currently failing to respond. Rates of current treatment failure increased significantly with successive immunomodulators. Globally, 12.7% of patients currently receiving first therapy were failing current treatment; this doubled to 26.6% for patients currently receiving their third or later therapy ($P = 0.0022$) (Fig. 1). In North America and LatAm, rates of failure followed this trend, 11.8% and 14.9% of patients currently failing first therapy increased to 16.7% and 50.0% at third respectively (both $P = $ NS). In Europe and APAC 12.8% and 12.1% of patients on first therapy were reportedly failing which increased to 33.3% ($P = 0.0030$) and 20.0% ($P = $ NS) failing third respectively. In T&ME, 11.9% patients on first therapy were failing; data are only available for 2 patients who had switched to a second therapy both of whom were failing (Fig. 1).

Patient demographics by therapy success and failure

Patient characteristics were similar between success and failing groups across all regions with some exceptions in the APAC region; mean BMI was significantly higher (26.1 vs 24.7, $P = 0.0309$), and time since diagnosis significantly shorter (3.1 vs 5.1, $P = 0.0406$) for those who were failing therapy (Table 3). Globally, BSA affected by psoriasis was significantly higher in patients failing therapy (14.5 vs 7.4, $P < 0.0001$). This pattern was observed for every region apart from APAC (Table 3). Globally, ESR and CRP levels were significantly higher in patients failing treatment: ESR in North America, EU5, APAC and T&ME; CRP in North America, EU5 and T&ME and numerically higher in the APAC region. ESR and CRP data were too limited in LatAm to be meaningful (Table 3).

Association of failing treatment with HRQoL and WPAI

Linear regression analysis, controlling for age, gender, smoking status, BMI, time since onset of symptoms and region, confirmed that failing treatment was significantly associated across all regions with lower EQ-5D and HAQ-DI scores (Fig. 2a and b); and worse SF-36 PCS and MCS scores (Fig. 2c). We also observed that patients who were failing treatment reported significantly worse outcomes on all the individual SF-36 domains (Fig. 3).

Adjusted WPAI scores were higher in patients failing treatment indicating more work impairment, time missed at work,
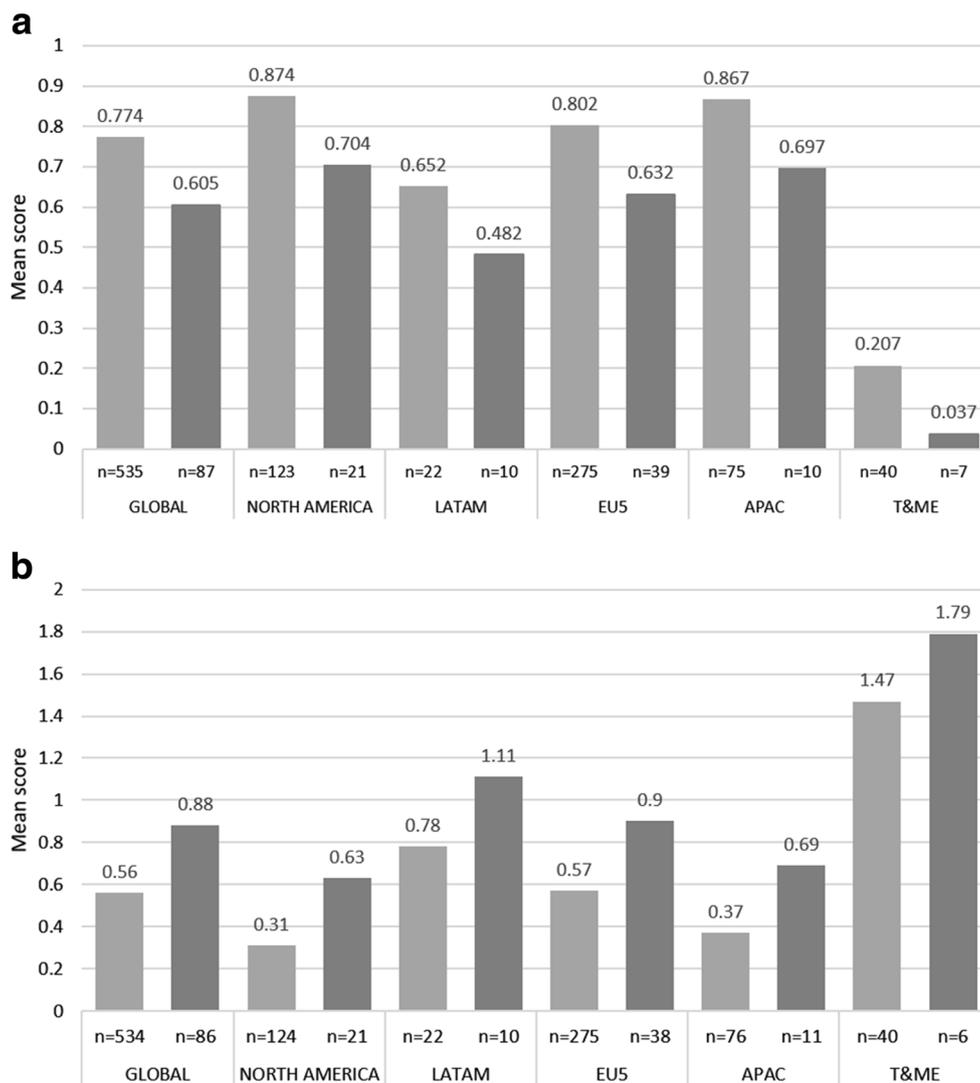
a

b

Fig. 2 EQ-5D scores (**A**), HAQ-DI scores (**B**), SF-36 scores (**C**), and WPAI (**D**) for patients failing immunomodulator therapy vs. immunomodulator therapy success. Results are adjusted for age, gender, smoking status, BMI, time since onset of symptoms, and region. ABS, absenteeism; ACT, activity impairment; APAC, Asia Pacific region; EU5, European Union 5; LatAm, Latin America; O, overall work impairment; PRES, presenteeism; SD, standard deviation; T & ME, Turkey & Middle East. SF-PCS, $P < 0.0001$; SF-MCS, $P = 0.0010$; overall work impairment, $P = 0.0727$; presenteeism, $P = 0.0212$; absenteeism, $P = 0.3932$; activity impairment, $P < 0.0001$

impairment while working and impairment in daily activities than in patients for whom therapy was not failing (Fig. 2d).

Discussion

This analysis of real-world data on immunomodulator use in patients with PsA from a large multi-national survey demonstrates that current therapies do not consistently deliver sustained efficacy, evidenced by high rates of primary and secondary lack of efficacy to the first treatment (predominantly TNFi), resulting in patients switching therapies, consistent with previous reports [23, 24].

Time to switch therapy due to lack of efficacy may be longer than recommended by EULAR treatment guidelines

[6]. In cases where physicians reported switching from first to second immunomodulatory therapy was due to primary lack of efficacy, time to switch to an alternative therapy occurred at a mean of 9.4 months. An observational study based on the nationwide DANBIO registry of 1422 patients with PsA initiating TNFis demonstrated that 39% switched to a second TNFi over a median of 2.3 years follow-up and a US study conducted over 4 years reported 22.9% of patients switched biologic therapy [25]. However, in this global analysis of 3582 patients, at the time of data collection 6.8% had received a second and 2.5% a 3rd therapy, with 9.4% and 4.9% receiving a 2nd and 3rd therapy in the US respectively. These differing rates are a result of our analysis being based on a cross-section of patients with differing disease durations, rather than a longitudinal study of patients over time [26, 27].
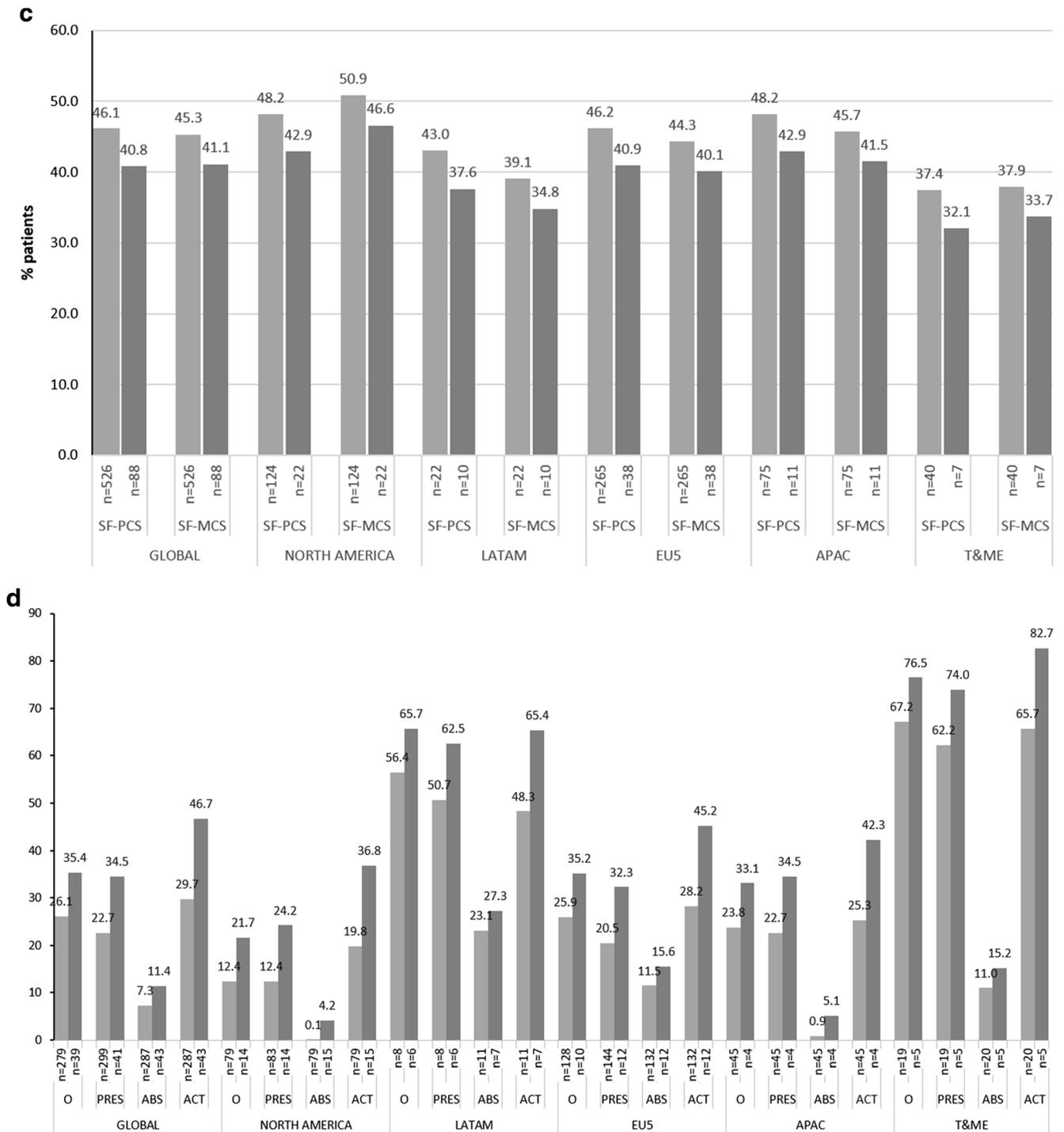
Fig. 2 (continued)

The likelihood of patients failing their current treatment was higher with each successive therapy. These data are consistent with other studies, including a metanalysis of observational studies published between 2007 and 2015 of patients with PsA who have failed at least one prior TNFi. Compared to patients with no TNFi treatment, TNFi in the second-line and subsequent lines demonstrated statistical improvement in PsA outcomes; however, responses to first-line TNFi demonstrated statistically greater improvements than second- and third-line TNFi. No improvement was found at 24 weeks for fourth-line TNFi compared to second-line treatment [28]. In addition, studies reviewed by Merola et al. indicate that treatment responses and length of treatment survival decrease in patients receiving a second or third TNFi [29–32].

Fig. 3 Spydergram of adjusted
SF-36 domain scores for patients
failing immunomodulator therapy
vs. immunomodulator therapy
success. Results are adjusted for
age, gender, smoking status, BMI,
time since onset of symptoms,
and region
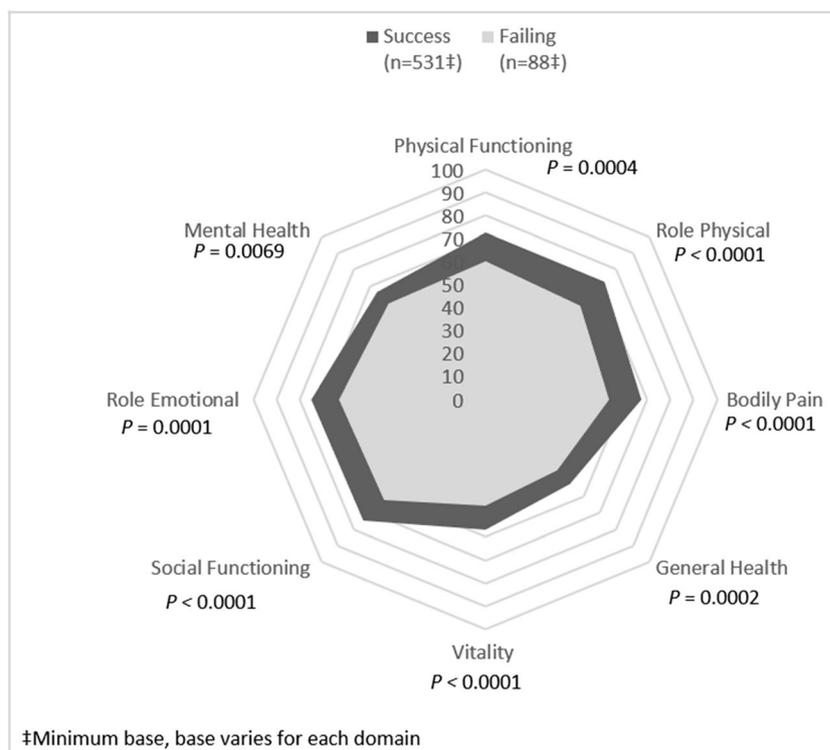
Recently, large-scale randomized controlled trials of bio-
logics and targeted small molecules demonstrated ACR20/50/
70 and PASI-75 responses that were significantly improved
versus placebo in patients who had failed one or more TNFi
[11, 32–34]. As a result, both updated GRAPPA and EULAR
guidelines recommend switching to alternative biologics in-
cluding those with different modes of action after TNFi failure
[13, 14]; ACR-NPF guidelines specify switching to an anti-
IL17 if PsA remains active after failure of a TNFi, followed by
an anti-IL12/23 if PsA continues to be active [12].

The current study was performed before the market autho-
rization of recently approved immunomodulatory agents for
PsA; however, the real-world clinical impact of their availabil-
ity would be expected to impact treatment switching.

Our analyses demonstrate that failure of immunomodulator
therapy is associated with significantly poorer patient reported
HRQoL by EQ-5D and SF-36, physical functioning by HAQ-
DI and performance of daily activities and work by WPAI. We
observed that the T&ME cohort had notably worse disease
activity and patient reported outcomes compared with other
regions. We hypothesize that this may be due to shorter dis-
ease duration and lower use of bDMARDs in this region
which may have led to poorer disease control compared with
other regions.

Although PsA has been reported to negatively impact
HRQOL [35–40], and several studies report increased absen-
teeism and presenteeism in patients with PsA [36, 41–43] to
the best of our knowledge, this is the first real-world study to
compare HRQoL and work productivity in PsA patients fail-
ing treatment, with those whose treatment is considered to
working effectively (i.e., not failing).

A major strength of this study is that it presents real-world
data from a large number of PsA patients around the world,
providing insight into real rates of treatment failure and rea-
sons for treatment switching. Several potential limitations of
this Adelphi PsA DSP should be considered. A primary lim-
itation of the analysis is that the source data is a point-in time
survey and does not capture the exact timepoint at which
patients fail to respond to therapy; therefore, it was necessary
to rely on physician-reported reasons for switching therapy to
identify the sub-set who failed to respond. Other limitations
relate to cross-sectional study design, and selection of patients
based on those who agreed to participate. Physician reported
disease activity/severity can reflect individual physician bias.
Similarly, regional differences in patient characteristics, treat-
ment practices, and physician expertise may have influenced
findings in this cross-sectional study. Recall bias is a common
limitation of surveys; however, as data was collected at the
time of patients' appointments, the likelihood of recall bias is
reduced. Finally, although the level of knowledge and man-
agement strategies for PsA treatment may differ between rheu-
matologists and dermatologists, thereby affecting treatment
satisfaction and clinical outcomes, differences attributable to
physician specialities were not evaluated.

In conclusion, this large multinational real-world survey in
PsA patients demonstrated that lack of efficacy of

immunomodulatory therapy was not uncommon and the predominant reason for treatment switching. Failure to respond was associated with significantly poorer patient reported HRQoL, physical functioning, and work productivity. A significant proportion of patients who switched onto second or third therapy did not respond as expected, albeit the majority were TNFis. More regular monitoring and earlier use of appropriate therapies upon identification of lack of efficacy may lead to improvements in disease control and reduce progression leading to improved HRQoL, physical function, and productivity benefits to society.

Compliance with ethical standards

Conflict of interest RA has received grants or research support from Bristol-Myers Squibb, consulting fees from Bristol-Myers Squibb, Novartis, Pfizer Roche, and Eli Lilly. PGC has received speakers' bureau or consulting fees from Bristol- Myers Squibb, Pfizer, and Novartis. VS has received grants and/or consulting fees from AbbVie, Amgen, AstraZeneca, BMS, Boehringer Ingelheim, Celltrion, Corrona LLC, Crescendo Bioscience, EMD Serono, F. Hoffmann-La Roche Ltd./ Genentech, Inc., GSK, Janssen, Eli Lilly, Merck, Novartis, Pfizer, Regeneron, Samsung, Sandoz, Sanofi, and UCB and has served on advisory boards for AbbVie, Amgen, AstraZeneca, BMS, Celltrion, Crescendo/Myriad Genetics, EMDSerono, Genentech/Roche, GSK, Janssen, Lilly, Novartis, Pfizer, Regeneron, Sandoz, Sanofi, and UCB. AD has received grants or research support from AbbVie, Eli Lilly, GlaxoSmithKline, Janssen, Novartis, Pfizer, and UCB Pharma, and consulting fees from Eli Lilly, Janssen, Novartis, Pfizer, and UCB Pharma. ES and SB are employees of Adelphi Real World; HT and KG are shareholders and employees of Novartis; SJ is a shareholder and employee of Novartis Pharma AG.

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