https://doi.org/10.31925/farmacia.2019.1.2 **REVIEW**

UNMET THERAPEUTIC NEEDS IN PSORIATIC ARTHRITIS: DATA FROM THE ROMANIAN REGISTRY OF RHEUMATIC DISEASES – NEW THERAPIES AND TARGETS

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Abstract

The objectives of this article were to identify the potential Romanian psoriatic arthritis patients (PsA) subpopulation in need for new therapeutic principles, currently unavailable in our country. Data were retrieved electronically from the Romanian Registry for Rheumatic Diseases (RRBR) database between January 1st and December 31st 2017. In order to define remission and low disease activity, patients were assessed with the Disease Activity in Psoriatic Arthritis (DAPSA) and Simplified Disease Activity Index scores. Of the 804 PsA patients enrolled in RRBR in 2017, 721 (89.7%) patients were treated with biologics for more than 6 months. Of these, 86 patients (11.9%) were in moderate and high disease activity according to DAPSA and 196 patients (27.2%) according to SDAI, respectively. Compared to patients in DAPSA remission or low disease activity, these patients had a higher toll of inflammation and a higher prevalence of sacroiliitis. Up to 30% of Romanian PsA patients registered in RRBR would be candidates for new and locally unavailable biologic and synthetic disease-modifying anti-rheumatic drugs, such as abatacept, apremilast, certolizumab, ixekizumab, tofacitinib and ustekinumab.

Rezumat

Obiectivele studiului au fost identificarea sub-populației pacienților cu artrită psoriazică (APs) potențial candidați pentru noi principii terapeutice indisponibile în prezent în țara noastră. Datele au fost preluate electronic din baza de date a Registrului Român de Boli Reumatice (RRBR) în perioada 1 ianuarie - 31 decembrie 2017. Pentru a defini remisiunea și activitatea scăzută a bolii, pacienții au fost evaluați cu scorurile testelor specifice DAPSA și SDAI. Dintre cei 804 pacienți cu APs înscriși în RRBR în 2017, 721 (89,7%) pacienți au fost tratați cu medicamente biologice mai mult de 6 luni. Dintre aceștia, 86 de pacienți (11,9%) aveau o activitate moderată și ridicată a bolii, conform DAPSA și respectiv 196 de pacienți (27,2%) conform SDAI. În comparație cu pacienții cu remisiune sau activitate scăzută a bolii conform DAPSA, acești pacienți au avut un grad mai ridicat al inflamației sistemice și o prevalență mai mare a sacroiliitei. Până la 30% din pacienții români cu APs înregistrați în RRBR ar fi candidați pentru medicamente anti-reumatice biologice și sintetice țintite care nu sunt disponibile la nivel local, cum ar fi abatacept, apremilast, certolizumab, ixekizumab, tofacitinib și ustekinumab.

Keywords: psoriatic arthritis, disease activity, biologic therapy

Introduction

Psoriasis arthritis (PsA) is a chronic inflammatory disease that involves peripheral joints (synovitis in several articular joint patterns, dactylitis) and/or the axial skeleton (spondylitis, either isolated or in combination with peripheral involvement). PsA and psoriasis are highly associated: in 85% of PsA patients the disease started with the appearance of psoriasis; as much as 40% of patients with psoriasis can develop PsA; undiagnosed PsA has a prevalence of around 30% among patients with psoriasis [1]. In Europe, PsA has a prevalence ranging from 0.05-0.21% [2]. PsA is recognized to have erosive and destructive potential in approximately 40-60% of patients, with progressive radiographic changes from the first year of diagnosis. Similar to rheumatoid arthritis (RA) or even worse, PsA can cause chronic joint damage, functional deficit, a very high impact on quality of life [3] and ultimately excess mortality [4], with significant medical and social costs [5]. Despite these facts, there is a very large population of PsA patients who don't receive any treatment, or just receive topical treatment (e.g. 59% [6]), even though joint manifestations do not respond to any form of topical drugs. Even when correctly applied, conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs; e.g. methotrexate, leflunomide, sulfasalazine, cyclosporine) have a very limited efficacy on enthesitis, dactylitis and axial manifestations of PsA.

According to the recommendations of the Romanian Society of Rheumatology and in line with the current European League against Rheumatism (EULAR) recommendations [7], the therapeutic goal in PsA is to achieve and maintain

remission or low disease activity (LDA) where remission is not possible, and to monitor disease activity using the Disease Activity in Psoriatic Arthritis (DAPSA) score [8, 9]. Several remission criteria applied to RA (Disease Activity Score using 28 joints [DAS28][10]; Simplified Disease Activity Index [SDAI] [11]; Clinical Disease Activity Index [CDAI] [12]; Boolean definition [13]) have been tested and used over time in PsA to define remission.

Current therapeutic options in PsA focus primarily on csDMARDs and biologic DMARDs (bDMARDs). Tumor necrosis factor alpha (TNFα) blockers are the world's most widely used drugs for this condition, but other agents (e.g. anti-interleukin 17, JAK inhibitors etc.) are also becoming increasingly used. Currently, in Romania, the National Insurance House reimburses treatment for PsA with adalimumab, etanercept (original and biosimilar), golimumab, infliximab (original and biosimilar) and secukinumab. In spite of these options, there is a significantly numerous category of patients for whom the therapeutic goal cannot be achieved using the current available strategy in our country.

In this context, the objectives of this study are to identify the potential Romanian PsA subpopulation in need for new therapeutic principles currently unavailable in our country, and to briefly review the characteristics of these therapeutic molecules.

Materials and Methods

The Romanian Registry for Rheumatic Diseases

The Romanian Registry for Rheumatic Diseases (RRBR) is an online database that includes all patients with rheumatic diseases in Romania treated with bDMARDs. The application belongs to the Romanian Registry of Rheumatic Disease Association, a non-governmental association, initiated by the Romanian Society of Rheumatology, which was launched in February 2013. RRBR is designed as a prospective observational study. The purpose of the study is to generate a database representative of the population of patients with rheumatic diseases undergoing bDMARD treatment in Romania. The data are introduced by approximately 350 physicians, distributed throughout the entire country, using personalized and secure access. For each patient, RRBR contains information regarding demographics, comorbidities, disease history, joint surgery, pulmonary (tuberculosis) and hepatitis B and C status, disease activity scores and their components, usual biochemical parameters, current and previous medication (including DMARDs), imaging, using radiology and ultrasonography (optional), quality of life assessment (Health Assessment Questionnaire) and costs (hospitalization, medical visit, labor productivity, absenteeism), adverse events. The frequency of data collection is of 6 months, except for adverse events that are reported at any time during the course of the disease.

Any patient that fulfills the national criteria for accessing bDMARD treatment is included in RRBR, after the patient has signed an informed consent. In order to be considered for bDMARD therapy, Romanian PsA patients must simultaneously fulfill 4 criteria outlined in Table I.

Table I

Inclusion criteria in RRBR for PsA patients.

a patient is included in RRBR and begins biologic treatment if all 4 criteria are fulfilled	
criterion	*definition*
1. diagnosis of PsA	fulfillment of CASPAR criteria [42].
2. high disease activity	DAPSA > 28 and ≥ 5 painful and swollen joints* and CRP > 3 x ULN#.
3. failure of conventional therapy	3.1. without unfavorable prognostic factors&: unresponsive† to ≥ 2 csDMARDs for ≥ 12 weeks each; 3.2. with unfavorable prognostic factors&: unresponsive† to ≥ 1 csDMARD for ≥ 12 weeks; 3.3. if axial disease¶: BASDAI > 6 and unresponsive to ≥ 2 NSAIDs for ≥ 6 weeks each; 3.4. if active enthesitis and/or dactylitis: unresponsive to ≥ 2 NSAIDs for ≥ 6 weeks each and/or local GC injections.
4. no contraindications	according to product summary characteristics and physician evaluation

Notes: * out of 68 possible painful joints and 66 possible swollen joints; # for the local laboratory; & unfavorable prognostic factors: swollen joints count > 5; CRP > 5 x ULN and/or ESR > 50 mm/h; radiologic joint erosions; extra-articular manifestations; † unresponsiveness defined at the failure to achieve DAPSA remission or low disease activity; ¶ axial disease is defined as sacroiliitis and/or vertebral syndesmophytes.
Abbreviations: BASDAI – Bath Ankylosing Spondylitis Disease Activity Index [43]; CRP – C-reactive protein; csDMARDs – conventional synthetic disease-modifying anti-rheumatic drugs; DAPSA – Disease Activity in Psoriatic Arthritis [9]; ESR – erythrocyte sedimentation rate; GC – glucocorticoids; PsA – psoriatic arthritis; RRBR – Romanian Registry for Rheumatic Diseases; ULN – upper limit of normal.

Disease activity assessment

According to current practice, bDMARD treatment of PsA is monitored in Romania using DAPSA [9] every 6 months, using the usual cut-offs: remission (DAPSA ≤ 4); LDA (4 < DAPSA ≤ 14); moderate disease activity (MDA; 4 < DAPSA ≤ 28) and high disease activity (HDA; DAPSA> 28). A patient is considered to be a responder if DAPSA remission or LDA are achieved. Compared to the baseline assessment (before initiating bDMARD), a good or

moderate response to treatment (≥ 75% decrease in DAPSA) is also accepted until remission of LDA is achieved. A patient is considered to be a non-responder if DAPSA remains above 14 and if it decreases by less than 50% compared to the baseline assessment. In this case, the current practice is to switch the initial bDMARD with any other bDMARD. Literature data suggest that in PsA, DAS28 has a lower stringency compared to the other scores [14], while SDAI revealed a very high correlation with DAPSA [15]. Therefore, we also used SDAI to define the therapeutic target of remission in PsA, using the following cut-offs [16]: remission (SDAI ≤ 3.3); LDA (3.3 < SDAI ≤ 11); MDA (11 < SDAI ≤ 26) and HDA (SDAI > 26).

Statistics

Data recorded between January 1st and December 31st 2017 were retrieved electronically from the RRBR database. Nominal variables are reported as "absolute frequency (percent fraction of group or subgroup)". Continuous variables are reported as "mean (standard deviation)" if normally distributed or as "median (inter-quartile range)" if non-normally distributed. Body mass index (BMI) was computed by dividing weight in kilograms to square height in meters. Differences between patients who attained DAPSA target and those who did not were tested using 2-tailed independent samples t-test for continuous variables and χ^2 tests for dichotomous variables. The statistical tests were considered significant if $p < 0.05$. All the statistical analysis was performed using IBM SPSS Statistics version 22.0 for Windows (Armonk, NY, IBM Corp.)

Results and Discussion

In 2017, a total of 804 PsA patients were enrolled in RRBR on active bDMARD therapy. Table II summarizes their main demographic characteristics, indicating equal proportions of genders and low prevalence of reported cigarette smoking.

Table II

Demographics of PsA patients from RRBR in 2017 (n = 804)

average age (y; SD)	55.6 (11.7)
BMI (kg/m^2; SD)	28.6 (5.2)
women (n; %)	402 (50.0%)
urban dwelling (n; %)	571 (71.0%)
smoking (n; %)	60 (7.5%)
employed (n; %)	341 (42.4%)
PsA retired (n; %)	282 (35.1%)

Notes: continuous variables are reported as "mean (SD)"; nominal variables are reported as "absolute frequency (percent fraction of group)".
Abbreviations: BMI – body mass index; PsA – psoriatic arthritis; RRBR – Romanian Registry for Rheumatic Diseases; SD – standard deviation; y - years.

On average, the RRBR PsA patients had established disease, with long disease duration and high prevalence of comorbidities (Table III). Of note, a fifth of the sample had latent TB (defined by a positive QuantiFERON TB Gold test anytime reported in RRBR) and another fifth of the sample had serological markers of contact with hepatitis B virus.

Table III

PsA features and comorbidities of RRBR patients in 2017 (n = 804)

PsA features		*comorbidities*	
disease duration (y; SD)	11.0 (6.7)	osteoporosis* (n; %)	46 (5.7%)
psoriasis (n; %)	749 (93.2%)	CVD*† (n; %)	433 (53.9%)
arthritis (n; %)	804 (100%)	dyslipidemia* (n; %)	144 (17.9%)
spondylitis (n; %)	94 (11.7%)	T2DM* (n; %)	121 (15.1%)
sacroiliitis (n; %)	135 (16.8%)	CKD* (n; %)	40 (5.0%)
Achilles' enthesitis (n; %)	45 (5.6%)	latent TB# (n; %)	169 (21.0%)
dactylitis (n; %)	34 (4.2%)	HBV immunity& (n; %)	153 (19.0%)
uveitis (n; %)	10 (1.3%)	chronic hepatitis B* (n; %)	4 (0.5%)

Notes: continuous variables are reported as "median (IQR)"; nominal variables are reported as "absolute frequency (percent fraction of group)".
* comorbidities reported as such by rheumatologists filling data in RRBR; † category of cardiovascular disease includes arterial hypertension, chronic ischemic heart disease, chronic heart failure, peripheral vascular disease, stroke; # latent TB defined as a positive QuantiFERON TB Gold test at any time reported in RRBR; & HBV immunity defined as negative HBs antigen, positive anti-HBs antibodies and positive anti-HBc antibodies.
Abbreviations: CVD – cardiovascular disease; CKD – chronic kidney disease; IQR – inter-quartile range; HBV – hepatitis B virus; PsA – psoriatic arthritis; RRBR – Romanian Registry for Rheumatic Diseases; T2DM – type 2 diabetes mellitus; TB – tuberculosis; y – years.

From the total sample (n = 804), 725 patients (90.2%) were treated with a bDMARD combined with at least one csDMARD, while 79 patients (9.8%) had bDMARD mono-therapy (Table IV). The most frequently used bDMARD was etanercept (original and biosimilar) with 321 patients (39.9%), followed by original adalimumab with 287 patients (35.7%) and infliximab (original and biosimilar) with 103 patients (12.8%). Throughout 2017, 688 patients (85.6%) continued the treatment with the same bDMARD, while 68 patients (8.5%) switched their bDMARD and 48 patients (6.0%) started their first bDMARD.

Table IV

Treatment of PsA patients from RRBR in 2017 (n = 804)

csDMARDs		*bDMARDs*	
methotrexate (n, %)	477 (59.3%)	original adalimumab (n, %)	287 (35.7%)
leflunomide (n, %)	213 (26.5%)	original etanercept (n, %)	317 (39.4%)
sulfasalazine (n, %)	93 (11.6%)	biosimilar etanercept (n, %)	4 (0.5%)
hydroxychloroquine (n, %)	4 (0.5%)	original infliximab (n, %)	95 (11.8%)
cyclosporine (n, %)	21 (2.6%)	biosimilar infliximab (n, %)	8 (9.9%)
azathioprine (n, %)	1 (0.1%)	golimumab (n, %)	87 (10.8%)
glucocorticoids* (n, %)	20 (2.5%)	secukinumab# (n, %)	6 (0.8%)

Notes: nominal variables are reported as "absolute frequency (percent fraction of group)"; * glucorticoids refer to cases treated for more than 3 months with doses of 7.5 mg/day prednisone equivalent or more; # according to the nation protocol, secukinumab is only available for bDMARD-naïve patients.

Abbreviations: b/csDMARDs – biologic/ conventional synthetic disease-modifying anti-rheumatic drugs; PsA – psoriatic arthritis; RRBR – Romanian Registry for Rheumatic Diseases.

Compared to patients who had achieved the DAPSA therapeutic target (remission and LDA), those who did not (MDA and HDA) had a higher toll of inflammation measured with ESR ($p<0.001$), a higher prevalence of sacroiliitis ($p=0.034$) and a higher prevalence of osteoporosis ($p=0.006$; Table V).

Table V

Differences among patients within and without DAPSA target (n = 804)

	R + LDA (n = 648)	*MDA + HDA (n = 156)*	*p*
age (y)	56.6 (11.0)	57.6 (11.2)	0.466*
BMI (kg/m^2)	28.6 (4.9)	28.4 (4.9)	0.783*
disease duration (y)	11.9 (6.6)	12.3 (6.2)	0.660*
ESR (mm/h)	17.9 (14.3)	33.9 (26.5)	*< 0.001*#
urban dwelling (n; %)	364 (56.2%)	61 (%)	0.703#
high education (n; %)	120 (18.5%)	19 (12.2 %)	0.785#
women (n; %)	246 (37.9%)	44 (28.2 %)	0.772#
smoking (n; %)	37 (5.7%)	5 (3.2%)	0.591#
spondylitis (n; %)	66 (10.2%)	11 (7.1%)	0.904#
sacroiliits (n; %)	71 (10.9%)	20 (12.8%)	*0.034*#
Achilles' enthesitis (n; %)	29 (4.5%)	4 (2.6 %)	0.662#
dactylitis (n; %)	13 (2.0%)	2 (1.3%)	0.876#
psoriasis (n; %)	30 (4.6%)	3 (1.9%)	0.346#
uveitis (n; %)	8 (1.2%)	1 (0.6%)	0.757#
osteoporosis (n; %)	25 (3.8%)	11 (7.1%)	*0.006*#

Notes: continuous variables are reported as "median (SD)"; nominal variables are reported as "absolute frequency (percent fraction of subgroup)"; * t-tests; # $\chi 2$ tests.

Abbreviations: DAPSA = Disease Activity in Psoriatic Arthritis; L/M/HDA = low/medium/high disease activity; PsA = psoriatic arthritis; SD = standard deviation.

Only 721 patients were treated with bDMARDs for more than 6 months, including 33 patients who started their first bDMARD. Of these, 635 patients (88.1%) were in DAPSA remission or LDA and 525 patients (72.8%) were in SDAI remission or LDA (Table VI). Thus, only 86 patients (11.9%) would require changing their bDMARD according to DAPSA categories, but 196 patients (27.2%) would require changing their bDMARD according to SDAI categories. In these cases, widening the therapeutic arsenal by targeting other pathogenic mechanisms or other molecular components is a therapeutic alternative in the management of this condition. Currently the U.S. Food and Drug Administration has approved 6 other molecules for the treatment of PsA: another TNFα inhibitor (certolizumab), bDMARDs targeting other pathogenic mechanisms of PsA (abatacept, ixekizumab and ustekinumab) and targeted synthetic DMARDs (tsDMARDs; apremilast and tofacitinib). Similarly, the European Medicine Agency has approved 4 of these molecules for the treatment of PsA (apremilast, certolizumab, tofacitinib and ustekinumab). The development and use in PsA of these new drugs prompted authors [17] to declare a "therapeutic renaissance" of PsA. TNFα inhibitors are the first big breakthrough in the management of PsA. Even though they target a pivotal cytokine involved in the pathogenesis of the disease [18], studies show that, regardless of the type of TNFα used, only approximately 50% of patients achieve the treatment target after 12 months of therapy [19]. Therefore, one can expect a significant prevalence of primary non-responders which, coupled with other causes of bMDARD switch (e.g. secondary non-responders, adverse events), can result in a significant need for new therapeutic options. The patient profile is also important: for example, etanercept did not prove to be efficacious in patients with inflammatory bowel

disease [20], which can accompany the clinical picture of PsA. One solution, although not optimal (for example cohort studies report inferior response rates of second-time switchers [21]), is to use another TNFα inhibitor. In this regard, certolizumab has been added recently to the treatment scheme of PsA, with the advantage of offering one more switch option. Certolizumab is a recombinant Fab antibody fragment against TNFα which is conjugated to a polyethylene glycol carrier. At the recommended dose of 200 mg every 2 weeks, in combination with methotrexate, certolizumab has proved its efficacy and safety in the treatment of PsA in randomized clinical trials (RCTs) [22], systematic reviews [23] and real-life settings, in which we reported local experience [24].

Table VI

PsA disease activity (n = 721)*

	remission (n; %)	*LDA (n; %)*	*MDA (n; %)*	*HDA (n; %)*
DAPSA = 10.2 (8.6)	254 (35.2%)	381 (52.8%)	80 (11.1%)	6 (0.8%)
SDAI = 8.9 (7.2)	142 (19.7%)	383 (53.1%)	141 (19.5%)	55 (7.6%)
CRP (mg/dL; IQR)	6.9 (5.2)			
ESR (mm/h; IQR)	22.0 (20.0)			

Notes: nominal variables are reported as "absolute frequency (percent fraction of group)"; continuous variables are reported as "median (IQR)"; * subpopulation of patients treated with bDMARDs for more than 6 months, including 33 patients who started their first bDMARD. Abbreviations: bDMARD = biologic disease-modifying anti-rheumatic drugs; CRP = C-reactive protein; DAPSA = Disease Activity in Psoriatic Arthritis; ESR = erythrocyte sedimentation rate; IQR = inter-quartile range; L/M/HAD = low/medium/high disease activity; PsA = psoriatic arthritis; SDAI = Simplified Disease Activity Index.

The most common side effects included bacterial (including abscess) and viral infections (including herpes zoster, papillomavirus, influenza), eosinophilic disorders, leukopenia, headaches (including migraine), sensory abnormalities, arterial hypertension, nausea, increased transaminases, rash, pyrexia and injection site reactions. As a particular characteristic of certolizumab, the study of the largest cohort of exposed pregnant women showed no risk increase in fetal death and teratogenic effects [21].

The clinical success obtained with TNFα inhibitors which target pathogenic cytokines lead to the development of new bDMARDs which target other cytokines involved in the pro-inflammatory cascade. These new therapies offer a possible significant advantage of different modes of action which can hopefully lead to achievement of treatment targets in both bDMARD-naïve patients and non-responders to TNFα inhibitors. Following the discovery of interleukins 17 and 12/23 and their role in chronic inflammation and PsA pathogenesis, they became the next therapeutic target, leading to the approval of secukinumab, ixekizumab and ustekinumab. The better clinical outcomes of anti-interleukin 17 agents in terms of psoriasis compared to anti-TNF agents [25] could justify using this class of drugs in PsA patients with extensive and refractory psoriasis. However, in the smaller subpopulation of PsA patients with inflammatory bowel disease, choosing an anti-interleukin 17 agent should not be expected to be effective on the gastrointestinal manifestations [26].

Ixekizumab is an IgG4 monoclonal antibody that binds interleukin 17A and interleukin-17A/F. The recommended maintenance dose in PsA is 80 mg subcutaneous by every 4 weeks, alone or in combination with methotrexate. Extensive RCTs have proved its efficacy for active PsA [27] and a pooled analysis showed it had a good safety profile in PsA patients [28]. Its most common reported side effects were upper respiratory tract infection, *tinea* infection, *herpes simplex*, nausea, oropharyngeal pain and injection site reactions. Unfortunately, brodalumab, a recombinant fully human monoclonal antibody that binds with high affinity to human IL-17RA, indicated and used successfully in moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy, was not approved for use in PsA due to its higher risk of suicidal ideation and behavior [29]. Other 2 new monoclonal antibodies inhibiting interleukin 17, bimekizumab (NCT03347110) and BCD-085 (NCT03598751) are currently under clinical trials in PsA patients.

Ustekinumab is a fully human IgG1κ monoclonal antibody that binds with specificity to the shared p40 protein subunit of human cytokines interleukin 12 and 23. An initial dose of 45 mg is administered subcutaneously, followed by a 45 mg dose 4 weeks later, and then every 12 weeks thereafter, alone or in combination with methotrexate. Its efficacy and safety have been proved by RCTs [30] and meta-analysis [31], and they have been extensively reported in recent real-life studies on different PsA populations [32]. The most common side effects of ustekinumab included upper respiratory tract infections, dizziness, headache, diarrhoea, nausea, vomiting, pruritus, back pain, myalgia, arthralgia, fatigue, injection site reactions. Currently, there are 3 new anti-interleukin 23 monoclonal antibodies being studied in patients with active PsA: guselkumab (NCT03158285; NCT03796858; NCT03162796), which is already approved for plaque-psoriasis, with promising published results from phase 2 trials [33]; risankizumab

(NCT03671148; NCT03675308) and tildrakizumab (NCT03552276; NCT02980692).

A totally different therapeutic approach is to target cells involved in the pathogenesis of the disease. This revolutionary approach has been used successfully in RA with rituximab and abatacept. The latter was also approved for PsA patients. Briefly, abatacept is a fusion protein that consists of the extracellular domain of human cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) linked to a modified Fc portion of human immunoglobulin G1 (IgG1). RCTs proved the efficacy [34] and safety of abatacept for PsA patients, indicated at a subcutaneous dose of 125 mg weekly, alone or in combination with methotrexate. The most common side effects included upper and lower respiratory tract infections, urinary tract infections, herpes infections, headache, dizziness, hypertension, gastrointestinal disorders, increased transaminases, rash, fatigue and asthenia.

The progress in the understanding of intracellular pathways and mediators of inflammation led to the development of tsDMARDs. Interestingly, one of these drugs, apremilast, was used successfully in PsA, but not in RA [35]. Apremilast is an oral small-molecule inhibitor of phosphor-diesterase 4 (PDE4) which modulates the intra-cellular network of pro-inflammatory and anti-inflammatory mediators. It is indicated at an oral dose of 60 mg/day, alone or in combination with csDMARDs. Apremilast has consistently proved its efficacy and safety in RCT [36], pooled analysis of RCTs [37], meta-analyses [38] and in real-life settings [34]. The most common side effects included upper respiratory tract infections, decreased appetite, insomnia, depression, migraine, diarrhea, nausea, vomiting, dyspepsia, abdominal pain, reflux disease, back pain and fatigue. Another class of tsDMARDs which, unlike apremilast, was effective both in RA and PsA, is the JAK inhibitor family. Tofacitinib, selectively inhibits the JAK family (JAK1-3, TyK2). Its recommended dose is 5 mg administered twice daily, in combination with methotrexate, for patients with active PsA. Both RCTs [39] and pooled analysis reports [40] have documented its efficacy and safety in active PsA. Interestingly, tofacitinib showed similar improvement in patient reported outcomes when compared to its active control adalimumab [41]. Its most common reported side effects were *herpes zoster*, upper and lower respiratory tract infections, urinary tract infections, anemia, hypertension, headache, abdominal pain, vomiting, diarrhea, nausea, gastritis, dyspepsia, rash, arthralgia, pyrexia, peripheral edema, fatigue, increased serum creatine phosphokinase. Currently, there are 2 new JAK inhibitors undergoing clinical studies in PsA, namely filgotinib (NCT03320876) and upadacitinib (NCT03104374; NCT03104400).

These diverse options for therapeutic influence on disease pathogenesis offer a good opportunity for PsA patients who remain outside the treatment target despite correct management to attain and maintain biological, clinical, functional and social benefits. As good clinical practice and guidelines recommend, regardless of the specific pharmacological treatment used, the target is to obtain and preserve a state of disease remission whenever possible. In PsA and in practice, this fundamental objective can prove to be particularly difficult because of frequent phenotypes of the disease (skin manifestations, peripheral arthritis, axial involvement, uveitis, inflammatory bowel disease). There are few evidence-based principles, summarized above, to aid the selection of a specific mode of action or a specific therapeutic molecule. One of the most important principles, and maybe the least studied, is patient preference. Any therapeutic choice should involve the patient in order to increase the chance of remission. Compliance on the other hand is a significant issue which should be addressed in routine clinical consults and large scale education programs.

The RRBR data presented above indicate a rather large population of Romanian PsA candidates for treatment with approved drugs. However, these observations may be influenced by study limitations, such as the cross-sectional design of RRBR and its dependence of data input by multiple users.

Conclusions

Depending on the composite score used to define treatment target in active PsA, up to 30% of Romanian PsA patients would be candidates for new and locally unavailable biologic and targeted synthetic DMARDs (potentially abatacept, apremilast, certolizumab, ixekizumab, tofacitinib and ustekinumab). A higher level of inflammatory activity and the presence of axial manifestations of PsA seem to be associated with therapeutic unresponsive cases in our national cohort.

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