Future Trends in Research in Psoriatic Arthritis

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ABSTRACT. Major advances have taken place in the study of psoriatic arthritis (PsA) in the past several decades. Future trends in research will likely be based on these advances and will span a wide spectrum of activities including further refinement of disease definition and particularly disease pattern. More precise definitions for axial and peripheral disease and in particular arthritis mutilans will be necessary for further genetic and biomarker studies. Early definition of PsA is crucial. Future research will concentrate on identifying genetic and other biomarkers for early diagnosis, disease expression, disease progression, and comorbidities. Newer therapies will be developed as well. (J Rheumatol 2012;39 Suppl 89:106–10; doi:10.3899/jrheum.120259)

Key Indexing Terms:

PSORIATIC ARTHRITIS	POLYARTHRITIS	AXIAL DISEASE
ARTHRITIS MUTILANS	GENETIC MARKERS	BIOMARKERS

Major advances in the study of psoriatic arthritis (PsA) have occurred over the past several decades. PsA has evolved from a rheumatoid arthritis (RA) variant to a unique disease entity. This has occurred primarily because of the efforts of Verna Wright and John Moll in the 1960s and 1970s[1]. By the early 1970s, Moll and Wright's definition of PsA as an inflammatory arthritis associated with psoriasis, usually seronegative for rheumatoid factor, was widely recognized, together with the disease patterns they identified[2]. For the next several decades PsA would be classified according to "Moll and Wright".

However, based on Moll and Wright's original descriptions, it was thought that PsA was a milder disease than RA. Over the past 2-3 decades, however, it has become clear that the disease was more severe than originally thought, with significant progression of joint damage and a mortality risk[3]. More and more investigators have become interested in PsA, especially in the past decade as anti-tumor necrosis factor (TNF) agents have proven so effective for patients with PsA. This is clearly demonstrated in the number of publications per year over the last 3 decades (Figure 1).

The development of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) in 2003 has served to increase recognition and knowledge of the disease[4]. Although the Classification of Psoriatic Arthritis (CASPAR) group predated GRAPPA, once GRAPPA was established it adopted the CASPAR work and the resulting criteria[5]. Although major strides have been made, there is still a lot to be learned about PsA and a lot to do for our patients to improve their symptoms, quality of life and function, and overall outcome.

Future research must address several outstanding issues related to PsA.

DISEASE DEFINITION

The CASPAR criteria were a tremendous step forward in case definition of PsA for clinical trials, longitudinal observational cohorts, and genetic studies. However, the CASPAR criteria must be applied to patients with inflammatory musculoskeletal conditions, including at least 1 of peripheral arthritis, spondylitis, or enthesitis. This definition must be uniformly accepted so that nonexpert clinicians can apply the criteria.

The proposed definition for inflammatory musculoskeletal disease includes the cardinal signs of inflammation: pain, erythema, swelling, warmth, and limitation of function. Inflammatory pain is characterized by the presence of prolonged stiffness, particularly in the morning, lasting at least 45 min. There is improvement with activity and worsening with rest and inactivity. There is often night pain, which improves if the patient gets up and walks around. Although in practice most rheumatologists use these features to identify inflammatory type conditions, the definition has never been put to a test. GRAPPA is currently working on validating this definition[6].

DEFINITION OF DISEASE PATTERN

Moll and Wright described 5 different patterns of PsA, including distal joint disease, oligoarthritis, symmetric polyarthritis indistinguishable from RA, spondylitis, and arthritis mutilans[1,2]. However, these are not mutually exclusive, and there is evidence that these patterns change over time[7,8]. Should we describe only peripheral versus axial, as has been suggested by Helliwell[9]? If so, do patients with peripheral arthritis and spondylitis fit into the spondylitis group or the peripheral arthritis group? Is arthritis mutilans a separate entity, or just a reflection of more severe disease? Clearly, further study is required to answer these questions.

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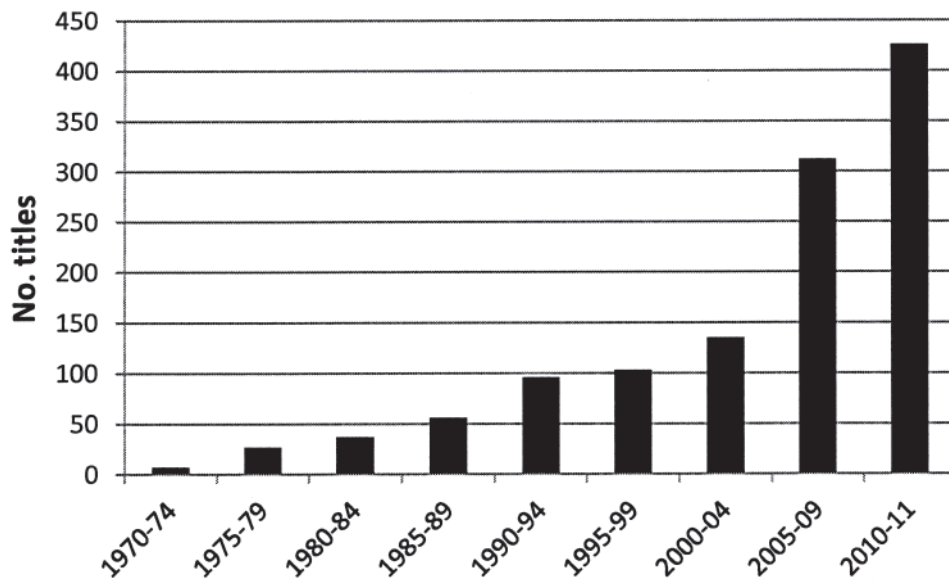
Figure 1. Average number of articles per year about psoriatic arthritis in each 5-year period since 1970.

DEFINITION OF AXIAL DISEASE

It has been difficult to define axial disease in PsA[10]. It has been shown that axial PsA is not as severe as ankylosing spondylitis. Patients with axial PsA complain less of pain and have less limitation of movement. With this background, should we include only the modified New York criteria as the definition of axial disease? The recent Assessment of Spondyloarthritis International Society (ASAS) classification criteria for axial disease in spondyloarthritis (axSpA) high-light some of the problems[11]. According to the ASAS criteria, a person may be classified as having axSpA if they have sacroiliitis on imaging and 1 other SpA feature (Figure 2). To qualify for PsA, that feature has to be psoriasis, which is reasonable. However, a person may have axSpA if they have a positive HLA-B27 and 2 clinical features. That might mean that a person with psoriasis, positive HLA-B27, and arthritis, might be labeled as having axial PsA. However, that may not necessarily be the case, because patients with PsA have a higher prevalence of HLA-B27 than the general population, whether or not they have axial involvement. Therefore, the ASAS definition is not helpful for investigators wishing to properly define axial PsA. Whether the definition should include only clinical features is another question that arises. That would raise difficulties because the majority of patients do not have any clinical complaints. The use of radiology only may be reasonable, as may be the clinical plus radiological assessment. Genetic markers such as HLA-B27 and HLA-B39 may help, as was recently shown by Eder, *et al*[12].

DEFINITION OF ARTHRITIS MUTILANS

The definition of arthritis mutilans remains unclear. A recent discussion with John Moll revealed that in their original paper, he and Wright cons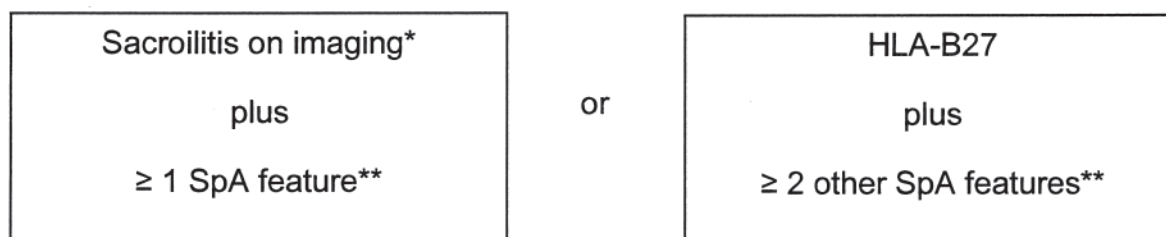idered any patient who had a flail joint (which generally reflects a pencil-in-cup change) as having arthritis mutilans. Does that mean that 1 joint is enough or should there be 5 or more joints involved to declare that a patient has arthritis mutilans? What about the severity of the destruction? What about patients who do not have flail joints, but instead have fused joints? Do they not have very severe disease? Should arthritis mutilans be defined solely on radio-logical appearance or would the clinical picture of flail and/or fused joints be appropriate to identify such patients? These questions must be included in future research in PsA.

Recently it has been suggested that there are genetic markers for arthritis mutilans[13]. This needs to be confirmed, and other genetic markers might be sought to identify patients with arthritis mutilans, which, regardless of the exact definition, remains the most severe form of PsA.

IDENTIFYING PSA EARLY

It was recently demonstrated that patients with PsA who present within the first 2 years of disease fare better than those who present later[14]. Thus it is important to identify these patients early.

As highlighted earlier, because it is difficult for nonexperts to use the CASPAR criteria other tools must be considered. Among a number of screening questionnaires developed to identify PsA several specifically screen for PsA among patients with psoriasis; these include the psoriasis and arthritis questionnaire and its Swedish modification[15], the Psoriasis Epidemiology Screening Trial (PEST) questionnaire[16], the PsA screening questionnaire[17], and the Psoriatic Arthritis Screening and Evaluation (PASE) questionnaire[18]. One tool was developed to screen for PsA among individuals with and without psoriasis, the Toronto Psoriatic Arthritis Screen (ToPAS) questionnaire[19]. All these questionnaires have been shown to be sensi-

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│ Sacroilitis on imaging* │   or   │   HLA-B27   │
│   plus   │   │   plus   │
│   ≥ 1 SpA feature**   │   │   ≥ 2 other SpA features**│
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** SpA features:
Inflammatory back pain
Arthritis
Enthesitis (heel)
Uveitis
Dactylitis
Psoriasis
Crohn's disease/ulcerative colitis
Good response to NSAID
Family history of SpA
HLA-B27
Elevated CRP

* Sacroiliitis on imaging:
– Active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with SpA
or
– Definite radiographic sacroiliitis according to modified New York criteria

Figure 2. Assessment of Spondyloarthritis International Society criteria for axial disease in spondyloarthritis (axial SpA). Sensitivity 82.9%, specificity 84.4%; in 649 patients with back pain ≥ 3 months and age at onset < 45 years. Imaging arm (sacroiliitis) alone has a sensitivity of 66.2% and a specificity of 97.3%. ** Note: Elevated CRP is considered an SpA feature in the context of chronic back pain. NSAID: nonsteroidal antiinflammatory drugs; CRP: C-reactive protein; MRI: magnetic resonance imaging. From Rudwaleit, et al. Ann Rheum Dis 2009;68:777-83; adapted with permission.

tive and specific, and should likely be incorporated into clinical practice. A recent study demonstrated that the PEST and the ToPAS were better at identifying patients with PsA than the PASE[20]. There are currently 2 additional studies under way that compare the usefulness of these questionnaires.

Imaging may also provide an opportunity to identify patients with PsA early. Several investigators are working on the use of ultrasound to identify patients with psoriasis who are likely to develop PsA[21,22]. Magnetic resonance imaging (MRI) likewise can detect early lesions, and the development of the PsA MRI score should facilitate the use of MRI to detect early disease[23,24].

Genetic markers, particularly at the major histocompatibility locus on chromosome 6, have been identified as susceptibility factors in both psoriasis and PsA. Recent studies have shown that there are specific HLA alleles that differentiate between PsA and psoriasis without arthritis. These include HLA-B27, which is increased in PsA compared to psoriasis alone, and HLA-C06, which is higher in patients with psoriasis without arthritis than in PsA[12]. Thus patients with psoriasis who carry the HLA-B27 alleles should be followed carefully for the development of PsA. Other genetic markers will likely be identified through the genome-wide association studies (GWAS) currently being completed in PsA when compared to those carried out in psoriasis.

Biomarkers can also identify patients with psoriasis who are destined to develop arthritis. Chandran, et al[25] found that increased serum levels of receptor activator of nuclear factor-κB ligand, tumor necrosis factor receptor superfamily (member 14), matrix metalloprotease 3 (MMP-3), and cartilage oligomeric matrix protein were independently associated with psoriatic disease (PsD). However, high-sensitivity C-reactive protein, osteoprotegerin, MMP-3, and CPII:C2C [ratio of C-propeptide of type II collagen to the Col2-3/4 (long mono) neoepitope] are biomarkers for PsA in patients with psoriasis (Table 1).

Further studies of other biomarkers are planned to identify patients with PsA early.

OUTCOME MEASURES
In defining outcome measures for clinical trials in PsA, the question arises of whether only the joint disease should be assessed or whether a composite measure should be used. At present, most clinical trials use the American College of Rheumatology (ACR) 20, 50, and 70% response criteria, borrowed from RA. Although these have not been specifically validated in PsA, an assessment of clinical trials has demonstrated that they function well in distinguishing drug-treated from placebo-treated patients[26]. Likewise, the Disease Activity Score of 28 joints, also developed for RA, has been

Table 1. Demographic and disease characteristics of patients with AxPsA at study entry. AxPsA-CR was defined by clinical and/or radiographic evidence of AxPsA, and AxPsA-R was defined by the presence of radiographic criteria alone. Data are number (%) of patients or mean (SD), unless specified.

Characteristics	AxPsA-CR	AxPsA-R
No. patients	297	244
Male/female	169/128	156/88
Age, yrs	42.5	43.8
Duration of psoriasis, yrs	14	16
Duration of PsA, yrs	8	9
Median (range) duration of followup, yrs	10.9 (5.1–32.7)	10.3 (5.0–28.4)
No. of actively inflamed (tender and/or swollen) joints	10.5 (9.8)	9.7 (10.0)
No. of swollen joints	3.3 (4.3)	3.4 (4.3)
No. of clinically damaged joints	4.2 (9.1)	5.1 (9.7)
No. of radiographically damaged joints	5.7 (9.4)	7.3 (9.9)
Axial symptoms	166/297 (56)	110/244 (45)
Inflammatory neck pain	122/297 (41)	92/244 (38)
Inflammatory back pain	114/297 (38)	66/244 (27)
Clinical sacroiliitis	54/282 (19)	27/227 (12)
Syndesmophytes (classical and/or paramarginal)		
Cervical	29/284 (10)	38/239 (16)
Thoracic	36/250 (14)	52/223 (23)
Lumbar	28/250 (11)	36/222 (16)
Radiographic sacroiliitis*		
Grade 2	63/285 (22)	125/240 (52)
Grade 3	47/285 (16)	55/240 (23)
Grade 4	13/285 (5)	14/240 (6)

Chandran V, Barrett J, Schentag CT, Farewell VT, Gladman DD. J Rheumatol 2009; 36:2744-50. * When asymmetric, number indicates the higher grade of sacroiliitis. AxPsA: axial psoriatic arthritis.

shown to be discriminative in PsA clinical trials, as has the European League Against Rheumatism response. A novel outcome measure, the PsA Joint Activity Index, was developed from phase III trials of anti-TNF agents in PsA[27]. It includes joint count, acute-phase reactant, physician and patient global assessment, pain assessment, and the Health Assessment Questionnaire, and requires a 30% reduction. In that study, the addition of the Psoriasis Area Severity Index score did not improve the model, suggesting that skin and joints should be assessed separately.

The Composite Psoriatic Disease Activity Index was developed to include all aspects of PsD in an outcome measure[28]. It identified more responders than the ACR20 using the PRESTA trial data[29], and promises to be an excellent instrument to assess disease activity, as well as to function as a responder index. A further study to identify a composite measure for disease activity is currently being performed by GRAPPA[30]. It is therefore expected that in the near future there will be PsD-specific instruments to be included in clinical trials and observational cohort studies.

Future research will also concentrate on genetic markers for disease expression. These studies will compare GWAS in psoriasis and PsA and identify genetic markers for specific manifestations of PsA[12]. For example, HLA-B39 is associated with axial disease in PsA[12]. Markers for disease progression will be identified. HLA-B27 was found to be a predictor for progression of clinical damage, and IL4RI50V polymor-

phism was associated with erosions within 2 years of disease[31]. Other genetic markers may be identified through the GWAS. It is important to recognize that detailed definition of the phenotype is necessary for such studies to produce meaningful results. Likewise, genetic markers may be identified for response to therapy as well as drug toxicity.

GRAPPA is embarking on a biomarker study for damage among patients with PsA and will also address the development of PsA among patients with psoriasis, and the development of comorbidities. These studies will likely include serum, plasma, cellular, and tissue biomarkers for disease expression and disease progression, and will provide an opportunity to identify new therapeutic targets.

Although the advent of anti-TNF agents for the treatment of psoriasis and PsA has been a major breakthrough, at least 40% of patients still do not achieve an ACR20 response. Thus, new therapies are needed, and future studies will likely identify new therapeutic targets.

Patient-reported outcome measures are also being developed. The concept of participation was introduced at Outcome Measures in Rheumatology Clinical Trials 8 and several studies looking at participation have been carried out[32]. More attention will be paid to work disability and work limitations.

Comorbidities are increasingly recognized among patients with PsD[33]. The presence of PsA is an additional burden. Future studies will need to address these comorbidities and

prevent their development by addressing disease-related features that may be contributing to their occurrence.

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