Clinical and Genetic Registries in Psoriatic Disease

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ABSTRACT. Clinical and genetic registries are an important tool in studying psoriasis and psoriatic arthritis (PsA). They assist in delineating disease features and are crucial in defining phenotype and identifying genetic and other markers of disease expression. At the 2007 Annual Meeting of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), members of the clinical registries and genetics committees described several ongoing registries, including their construction, protocols, and some results from their analyses. In breakout groups, members discussed data issues, including identification of core datasets, ownership, and how to share data; and ethical issues and possible sources of funding for registries. Proceedings of these meetings are summarized. (J Rheumatol 2008;35:1458–63)

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At the 2007 Annual Meeting of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), members of the clinical registries and genetics committees described several ongoing registries, including their construction, protocols, and some results from their analyses. This article summarizes those proceedings.

Disease registries have been developed with a number of objectives:

- Administrative registries track patients with a particular condition (but provide little clinical information)
- Clinical trials registries record events in patients participating in a particular drug trial
- Observational cohort registries collect information on a large number of variables and outcomes over time
- Genetic registries track patients participating in genetic studies[1].

The ideal registry would combine several purposes, for example, integrate genetic and clinical information with treatment outcome.

GRAPPA Registries Committee Survey

A survey of the members of the clinical registries and genetics committees identified a number of current registries (Table 1). The number of patients varied from 200 to 2000 per registry, and information collected was variable. While observational cohort studies collect most detailed information, genetic registries generally require only enough information to identify the phenotype. More detailed information is necessary if pharmacogenomic information is sought, or if the relationship between a genetic marker and disease expression is being probed.

The preferred type of registry was surveyed among the GRAPPA 2007 attendees. Of the 38 responders, 29 were rheumatologists, 7 were dermatologists, and 2 were scientists. Twenty-eight (74%) were associated with a registry: none in a psoriasis-only registry, 18 in PsA registries, and 10 in a registry for both PsA and psoriasis. Twenty-eight of the 38 respondents (74%) preferred a combined registry (observational, genetics, and biologics), while 4 preferred observational and biologics, 3 observational and genetics, 2

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Table 1. Current registries in psoriasis and psoriatic arthritis and the number of patients registered.

Investigator	Site	Psoriasis, no.	PsA, no.
Gladman	Toronto, Canada	228	850
McHugh	Bath, UK	NA	450
CORRONA	US multicenter	NA	2000
Fernandez	Spain	NA	100
Ujfalussy/Koo	Hungary	NA	700
Lindqvist	Sweden	NA	350
Helliwell	Leeds, UK	NA	300 + 500
Kruger/Callis	Utah, USA	900	25%
Carneiro	Brazil	250	30%
Qureshi	Boston, USA	600	40%

NA: not available.

biologics and genetics, and 1 genetics only. Thirty-seven of 38 (97%) favored a common database, including both skin and joint information. All 38 agreed that a minimal database should include demographic, clinical, and therapeutic information; and most (92%) agreed it should include enough information to clearly define the phenotype for analysis.

Current Registries

Single-Center Registry (D. Gladman)

The University of Toronto PsA Program, where patients have been followed prospectively for 30 years, is directed by Dr. Dafna Gladman and includes Drs. Vernon Farewell (Cambridge, England) and Richard Cook (Waterloo, Canada), biostatisticians; Dr. Janice Husted (Waterloo, Canada), an epidemiologist; and Dr. Proton Rahman (Newfoundland, Canada), a genetic epidemiologist. The longitudinal observational cohort was established in 1978, is located at Toronto Western Hospital, Toronto, and is affiliated with HLA and genetics laboratories. Patients are assessed at 6–12 month intervals, according to a standard protocol comprising clinical, laboratory, and imaging information. All information is entered and tracked in an ORACLE data base. The reliability of the measures collected in the clinic has been proven[2].

Analyses from this registry have shown that PsA is much more serious than previously thought. On entry into the clinic, 20% of patients had clinical deformities and damage, resulting in functional disability. After 10 years of followup, 55% of patients had at least 5 deformed joints. Baseline predictors for progression of clinical damage were 5 or more swollen joints and high medication levels. Actively inflamed joint counts at each visit predicted progression, and low baseline erythrocyte sedimentation rates (ESR) were "protective" for progression. Genetic markers for disease progression included HLA-B27 in the presence of DR7, HLA-B39, and HLA-DQw3 in the absence of DR7. HLA-B22 was associated with protection from progression. In an analysis of 628 patients, predictors for radiological damage included the number of tender, swollen, and deformed joints, and a high ESR. Remission, defined as no tender or swollen joints for at least 3 clinic visits (representing at least 1 year), occurred in 17.6% of all patients and lasted 2.6 years on average. Male gender, less active disease, and less severe disease at baseline were associated with remission. An increased risk of death, which was related to active and severe disease in the first 428 PsA patients, was demonstrated by a mortality risk of 1.62 compared with the general (Ontario, Canada) population, although the causes of death in PsA patients were similar to those in the general population. In a more recent analysis (including 700 patients), the overall risk of death decreased to 1.36[3]. Analyses of quality of life (QOL) confirmed the validity of several instruments in PsA and demonstrated a reduction in QOL in patients with PsA compared with the healthy population.

In summary, of primary importance in this longitudinal registry were active patient participation in the study (to assure their attendance in the clinic), teamwork among investigators, and adequate and stable financial support.

Single-Center Multidisciplinary Registry (A. Qureshi)

The Center for Skin and Related Musculoskeletal Diseases of the Department of Dermatology at Brigham and Women's Hospital, Harvard Medical School, initiated the Psoriatic Arthritis and Psoriasis Follow-up Study (PAFS) in September 2005. This ongoing longitudinal study has recruited more than 500 participants thus far. PAFS is a multidisciplinary, disease-based registry that captures epidemiologic data from patient interviews, data from medical records, and high quality biological specimens from patients with both psoriasis and PsA. The biological specimen repository includes blood and lesional skin specimens, which provide DNA, RNA, peripheral blood mononuclear cells, and plasma. A dermatologist and a rheumatologist jointly evaluate each participant who enrolls in PAFS, which allows objective documentation of disease severity. Overall strengths of PAFS include dense phenotype information on both skin and musculoskeletal disease (if applicable), followup data on outcomes, and inhouse processing and storage of biological specimens.

Multicenter Registry (P. Mease)

The Consortium of Rheumatology Researchers of North America (CORRONA) was founded in 2002 by Dr. Joel Kremer, initially for rheumatoid arthritis (RA) and more recently, for PsA. Currently, CORRONA includes about 14,000 RA patients and about 2,000 patients with PsA at approximately 90 clinical sites throughout the US, involving about 350 physicians. A large biostatistical support team and a steering committee include several members of GRAPPA. CORRONA is funded by pharmaceutical support. Data collection includes detailed medical information: patient demographics, disease activity/severity status (Disease Activity Score-28), Health Assessment Questionnaire (HAQ), skin

assessments, laboratory evaluations (complete blood cell count, lung function tests, C-reactive protein, ESR, rheumatoid factor, cyclic citrullinated peptide), joint radiography and dual-energy x-ray absorptiometry (with radiologist reports), and adverse event reporting. Followup data are recorded at least every 6 months and each time treatment changes occur. Recently, the steering committee approved a plan for an in-depth PsA-specific database within CORRONA, which will include full Psoriasis Area and Severity Index (PASI) scores, enthesis, dactylitis, and spine examinations, as well as Medical Outcome Study Short Form-36 (SF-36) data.

The database may be queried by both investigators and pharmaceutical sponsors. Several abstracts and manuscripts report preliminary results of analyses of the registry[4-7]. This multicenter registry is likely to be one of the largest for PsA, with longterm data that can provide insight into disease natural history, responses of various disease domains to multiple therapeutic interventions, and comorbidities; genetics data may be collected in the future.

Genetic Registries

Canadian Registry (P. Rahman)

Three important points to consider in registries for genetic studies and in particular genetic association studies are the sample size, the detailed phenotypic assessment, and appropriate selection of controls.

Recent identification of the IL-23R gene in psoriasis and PsA provides a valuable lesson regarding the design of future genetic association studies. A recent genome-wide pooling study by Cargill, *et al* noted a significant association with a two-SNP (single-nucleotide polymorphism) haplotype in the IL-23 receptor (IL-23R) on chromosome 1p31[8]. One of these variants, a non-synonymous SNP (Arg381Gln; rs11209026), is also associated with Crohn's disease[9]. Rahman, *et al* recently identified single-marker association with the coding SNP Arg381Gln in PsA[10]. The 2-marker haplotype (comprising rs7530511 and rs11209026), reported to be associated with psoriasis, was also protective in the Newfoundland population, with a trend noted in the Toronto population. Functional studies have noted overexpression of interleukin 23 (IL-23) in psoriatic skin lesions, and IL-23 has been shown to induce marked epidermal proliferation[11]. Despite the apparent importance of this genetic association, the minor allele frequency for the coding SNP was less than 5% in most populations. When the minor allele frequency is below 10%, the sample size increases exponentially as the minor allele frequency falls. The odds ratios in the genome-wide scans of IL-23R in Crohn's disease, psoriasis, and ankylosing spondylitis are modest (between 1.2 and 1.6). The lower the odds ratio, the greater the sample size required. For these reasons, large cohorts are required to adequately power genetic association studies and are best met via a large multicenter collaborative group. For complex genetic diseases, inflammatory bowel disease (IBD) researchers have led the world in successful genetic analysis, in part because they have large international consortia. A survey of the GRAPPA genetics committee members revealed populations of about 5,000 psoriasis patients and about 3,100 PsA patients. While these are impressive numbers, they may not be sufficient for discovery and replications samples.

For psoriasis, the Icelandic group has a genome-wide association scan well under way. A similar effort is under way by GAIN (Genetics Association Information Network) investigators in the US. Because these groups have already begun these large-scale efforts, it may be prudent to design studies complementary to them. If the phenotypes and the genetic markers are similar, such a registry could greatly facilitate metaanalysis of the genome-wide scans and add power by pooling.

Identifying the phenotype is particularly important in genetic association studies for disease expression. The IL-4 gene has been associated with susceptibility to immune mediated disorders characterized by imbalance in the ratio of Th1 to Th2, such as atopy and Type 1 diabetes mellitus[12,13]. Data from the University of Toronto PsA cohort suggest that the AA genotype of the IL4R-I50V SNP is associated with joint erosions in PsA. For that study, all probands had a plain radiograph of the hands and feet available after at least 2 years of disease onset, and the availability of this radiographic phenotype in longitudinal cohorts allowed us to study the genetics of radiographic disease progression. If replicated, the IL4R-I50V SNP may have potential predictive value for rapid bone erosion in PsA. Thus, the detailed phenotype is most important for association of genetic factors and disease phenotype. A recent metaanalysis by Ioannidis, *et al* of 3 genome-wide association studies in Type 2 diabetes highlights another point[14]. When markers with moderate to large heterogeneity between studies were assessed, some of the markers had an association to a phenotype (obesity), emphasizing the importance of phenotype for clarification of genetic associations.

An important difference between genetic and clinical registries is that the former requires unaffected controls. It is well known that population substructure can provide spurious results for case-control association studies. Ideally, the controls should also have detailed clinical assessment. More important, the controls should be ethnically and if possible geographically matched. For a genome-wide scan, the ethnicity may be matched using selected markers; however, for smaller genetic association studies, matched controls are essential.

Thus, the key steps for an ideal genetic association study are to ensure adequate sample size for the cases and controls; this is particularly important for variants of low minor-allele frequency and low odds ratio, to reduce the risk of false-positive associations. Second, examinations and

records should capture all relevant phenotypic information, not just the affected status. Finally, it is important to use matched controls; ideally, matched for ethnicity and geographical differences.

The Utah Registry (G. Krueger)

The fact that psoriasis is a heritable condition that presents with protean manifestations (e.g., early-age onset vs late-age onset; onset of PsA about 10 years after the onset of psoriasis in about one-fourth of patients vs no PsA) has given rise to the concept that psoriasis is a complex multigenic disorder. Because two-thirds of patients with psoriasis have a family history of psoriasis, it follows that genes/gene sets drive these protean manifestations. This theory gave rise to the Utah Psoriasis Initiative (UPI) in 2002. The UPI is a strategy, or a tool, to phenotype a cohort of psoriasis patients in order to identify genes/gene sets that associate with specific phenotypes. For enrollment into the UPI, patients provide informed consent and complete a detailed questionnaire covering pertinent medical history of their psoriasis. Patients are then interviewed and examined using a structured questionnaire and examination; DNA, serum, and plasma are collected. As of November 2007, nearly 900 patients have been enrolled, including over 96% of patients in the dermatology clinics at the University of Utah. The descriptive demographics demonstrate that patients enrolled in the UPI are very similar to those in other databases. The instrument used for phenotyping has been modified from Alison Ehrlich and Andy Blauvelt[15].

Highlights that have emerged from analysis of patients in the UPI include insights into the association of obesity with psoriasis; the prevalence of obesity in psoriasis patients is much higher than in the general population and generally develops after the onset of psoriasis[16]. Another discovery is that psoriasis in the untreated state reverts to thin, thick, or intermediate thickness (induration) and is associated with response to treatment; thin plaque is responsive to topical and ultraviolet light-based treatments, while thick plaque is resistant to these treatments. All are equally responsive to systemic treatments[17,18].

Two genes, IL-12B(p40P) and IL-23R, have polymorphisms that associate with psoriasis. This discovery was in collaboration with Celera Diagnostics (Alameda, CA, USA), using their orthogonal pooling strategy with about 25,000 SNP gene-centric approach to determine the allele frequency of the various SNP, followed by focused genotyping of all individuals. The first 500 patients in the UPI were the discovery cohort[8]. Shortly after the discovery of this association, the same polymorphism was reported for IBD, which has a well recognized association with psoriasis.

Recently a collaborative effort including the UPI and groups from Washington University (St. Louis, Missouri) and University of Michigan (Ann Arbor, Michigan) through the US National Institutes of Health Foundation completed a genome-wide association scan on 1500 patients with psoriasis and 1500 controls. It is anticipated that information from this scan will lead to the discovery of genes/gene sets that drive not only the protean manifestations of this complex disorder, but also the genes/gene sets that govern response to treatment.

Example of a Web-based Registry (M. Ståhle)

The Swedish psoriasis registry (PsoReg) was launched in 2007 and is a clinical quality register. It is a Web-based national registry where dermatologists enter patients treated with systemic therapies, including biologics. The data are limited as they are entered during clinical practice; however, the technique allows regional development of additional modules. The database is user-friendly, with demographic information (height and weight, alcohol intake, etc.); concurrent diseases; phenotypic description of psoriasis; and a few questions on joint disease. Detailed drug information is collected, including side effects, which can be reported directly to the authorities. In addition to dermatologist assessment of the skin (PASI and PGA), patients complete the DLQI and ESD. Funding for this registry is from the government and the pharmaceutical industry. The pharmaceutical industry will have access to data on their drugs, but only the steering committee can review composite data from the whole country.

Reports from Breakout Groups

Four breakout groups, led by Jan Dutz, Phillip Helliwell, Philip Mease, and Alice Gottlieb, discussed the core datasets of registries, the ethical issues, how registries might be funded, and the ownership of an international registry. The groups' suggestions are summarized below.

Core Datasets

- A longitudinal dataset on psoriasis was suggested as a priority, specifically with the potential of capturing the transition of psoriasis to PsA
- The core demographic dataset should include age or birth date, sex, an ID number, a visit number, ethnicity or race, body mass index (or height and weight), date of onset of arthritis and/or psoriasis; and marital status, work status, smoking, alcohol, trauma, and family history
- Clinical–core items for psoriasis should be listed by site (face, trunk, genitals, extremities) and include type of skin disease (pustular, plaque, inverse, or flexural, erythrodermic) and presence or absence of nail involvement.
- Arthritis data should include counts for tender (68), swollen (66), and damaged joints, presence/absence of dactylitis, enthesitis, and spinal involvement.
- Other required data include comorbodities, medical history (particularly of IBD, cardiovascular disease, liver and metabolic disorders), radiology of peripheral joints and

spine; inflammatory markers; rheumatoid factor; and patient-reported outcomes (HAQ, SF-36).
• Data and tissue samples should be collected according to standard operating procedures to provide quality assurance.

Ethical Issues
• Identity protection requires data to be coded by patient number, with the corresponding name held confidentially at the specific clinic site.
• Administrative maintenance requires regular backups of both local and Web-based database to maintain stability of the database.
• An audit trail is necessary, including the need to know who is accessing the data, when, and how many people would have access (recommended only those individuals who manage the database).
• Differential level of consent; some patients agree to share their clinical information but not their DNA.
• A firewall was recommended between the patient clinical record and the registry, to avoid possible requisition by insurance companies.
• Sharing information between different institutions may be a problem; research boards have different attitudes towards registries.
• Duplication of patients in different registries may lead to amplification of some features in the various datasets.
• Banking of biomaterial without prespecified use.
• Contacting family members.

Funding Suggestions
• Current registries are funded by a mix of pharmaceutical industry, government, and private foundations.
• If possible, funding should be secure for several years at a time.

Ownership of Registries and Sharing of Information
• Data that have already been collected should be uploaded to a new database so that data need not be entered twice.
• The group suggested decentralizing the sample and data collections, having a homepage where data and specimens of interest can be identified, and requesting that the owner of the databanks provide the data needed to address research questions.
• The data collecting process must be agreed upon by all participants, who would all be part of the data analysis and publication process.
• A committee could establish the research question and ask the owners of these decentralized databanks to provide the data for a centralized analysis.
• Concern was raised about the difficulty of transferring materials from one center to another, particularly across national boundaries, unless proper agreements were in place. These agreements also would give ownership to individuals who are building their own databases.
• In the existing multicentered databases, each investigator has access to their own data, but only an administrator has access to all of the data. Access to collective data should be based on directions from the steering committee, which prioritizes the research questions.
• One group suggested that the only way to make an extensive psoriasis database feasible would be through an organization like GRAPPA, potentially with a CORRONA-like model in terms of co-funders. Those who do the work would get the recognition.

Summary

Clinical and genetic registries are considered an important tool in studying psoriasis and PsA. They have helped to delineate disease features in both psoriasis and PsA and are crucial in defining phenotype and analyzing genetic and other markers for disease expression. Investigators agree that detailed information gathered in these registries, with stable financial support and international collaboration, will enhance the study of both psoriasis and PsA.

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