



**Psoriatic Arthritis
Program Directors**

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University of Toronto Psoriatic Arthritis Program



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The **Psoriatic Arthritis Clinic** has been at The Centre for Prognosis Studies in the Rheumatic Diseases (**CPSRD**) at the Toronto Western Hospital since October 1995. The Centre has provided a very comfortable environment for our patients, with easy approachability, a large waiting area, in close proximity to the food court, the laboratory for routine blood tests within the facility, and the X-ray department just down the corridor.

The Centre provides an improved research facility for studies in psoriatic arthritis. The physicians working at the Centre are in close proximity to the “laboratory” which includes trainees, research assistants, biostatisticians and programmers, as well as computer equipment. This has helped us in understanding the disease better and trying to develop a cure. The centre also has a clinical trials area as part of our program.

The purpose of this Newsletter is to update our patients on advances in research and treatment for patients with psoriatic arthritis. We also provide some basic information about the disease for new patients entering the Clinic.

What is Psoriatic Arthritis?

Psoriasis is a common skin disease, affecting 3% of the population. Psoriatic arthritis is an inflammatory arthritis associated with psoriasis. The arthritis presents with pain, swelling and stiffness of the affected joints. It may also affect the neck and the back, causing pain, stiffness and limitation of movement. Other common features include swelling of the whole digit (finger or toe) so called “sausage digit” or dactylitis, and inflammation at the site of tendons inserting into bones, called enthesitis.

Psoriatic arthritis may develop in as many as one third of the patients with psoriasis; thus, it is a relatively common condition. Psoriatic arthritis was considered a mild form of arthritis and physicians have tended not to treat it very aggressively. The cause of the disease and the reason for its persistence are still not well understood.

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Why is the Psoriatic Arthritis Clinic special?

The paucity of knowledge regarding psoriatic arthritis prompted Dr. Dafna Gladman to start the Psoriatic Arthritis Clinic at the University of Toronto in 1978 and we have learned a great deal since its inception. Dr. Vinod Chandran who trained with Dr. Gladman for a number of years joined the Clinic when he was appointed to the staff of the University of Toronto in October 2010. The Clinic generally takes place on Monday morning between 9 am and 12:30 pm, and Wednesday afternoons, between 1:00 and 5:00 p.m. Patients are initially evaluated by rheumatology fellows having a special interest in this disease. All patients are then reviewed by either Dr. Gladman or Dr. Chandran, in order to provide expert advice regarding management and continuity of care.

All patients are evaluated in a standard way, according to a specially designed format, which includes a complete history, physical examination, blood and urine tests and x-rays at regular intervals. This information is entered into a computer database. In this way, patients can be compared, and knowledge about the disease enhanced.

The Clinic includes about 1000 patients who have been closely followed over the years and thus constitutes the largest and the most comprehensively studied group of psoriatic arthritis patients in the world. The Clinic has close ties with biostatistics departments at the University of Waterloo, Canada and the MRC Biostatistics Unit, Cambridge, England, where biostatisticians participate in analysis of the extensive data generated in the Clinic. The biostatisticians use the data from our database to develop new statistical methods to help analyze information from other studies.

Various centers around the world have invited Dr. Gladman and Dr. Chandran, to speak and share their knowledge about this disease. Similar clinics are now being established around the world.

Research - From Bedside to Bench and Back Again

In addition to clinical research, our program also includes the HLA Laboratory directed by Dr. Gladman. This “wet lab” is located on the 14th floor of the Toronto Western Research Institute. A generous donation enabled the laboratory to become a fully functional independent molecular lab carrying out a multitude of genetic studies supporting our local research as well as other multicentre projects. In addition, we have a strong collaboration with colleagues in Newfoundland, Ann Arbor, Michigan and Rochester, New York who help with laboratory investigations not provided in our own laboratory.

Translational research is the detailed study of clinical disease combined with cellular or molecular information leading to the development of specific patient-centered therapies, which brings us back to the “bedside” for treatment. Thus, the strength of our clinic lies in the linkage of the extensive clinical information collected at the “bedside” with genetic and molecular data generated in the “wet-bench lab” allowing for “translational research”.



Training Clinicians and Researchers of the Future

The **University of Toronto Psoriatic Arthritis Program** hosts trainees from many levels of medicine and related fields. In particular, Clinical Research Fellows (qualified physicians who have completed their training in rheumatology), come to our Centre to gain expertise in the management of these patients and learn clinical research methodology. Many of them also pursue advanced degrees in epidemiology or genetics through the Institute of Medical Science, University of Toronto, as part of this training.

These trainees come from across Canada and around the world and go on to set up their institutional clinics modeled on the Psoriatic Arthritis Program. They continue to collaborate in research through our multi-centre research programs. With the help of donations from some of our patients as well as other funding agencies, we have been able to fund fellows specifically to train in our Clinic and help carry out this research.

The clinic also hosts medical students and undergraduate science students through summer research scholarships. These students work in the clinic and laboratory and have carried out many important projects.

What have we learned from these assessments of patients in the Psoriatic Arthritis Clinic?

A great deal of knowledge has been gained. The recognition that the disease may result in a destructive form of arthritis in some patients has changed the approach of rheumatologists all over the world. The availability of the computer database and sophisticated statistical analyses allows us to study the patterns of the disease and its progression, which cannot be identified when a physician looks after a small number of patients in his/her own office.

We have confirmed that the methods we use to assess patients clinically, in terms of active inflammation and joint deformities, as well as the interpretation of the x-ray changes, are reliable. Indeed, since we published the results of our initial study in 1987, several other centers have started using our definitions and methods to study their patient populations.

Most recently, we have shown that the methods used in our Clinic are also reproducible by physicians from different centers around the world. The assessment of joint tenderness, sausage digits, and spinal disease has been proven to be reliable in two international studies carried out in our Centre – the INternational SPondyloarthritis Interobserver Reliability Exercise (INSPIRE) and the International Multi-centre Psoriasis and psoriatic Arthritis Reliability Trial (IMPART).



In addition to joint inflammation and the development of joint deformity and damage, patients' perception of their health status and quality of life is an important outcome measure. Our patients have helped us evaluate the quality of life in psoriatic arthritis as it provides additional information about the patients that is not reflected in our clinical measures of activity and damage. We have now incorporated these measures into our regular assessments. These measures have also been incorporated into clinical trials for new medications. More recently we have begun studying the frequency of depression among our patients and its relationship to the disease process.

A major investigation into the prognostic factors for this disease is being carried out in our clinic, supported initially by the Ontario Ministry of Health, the Medical Research Council of Canada and the Canadian Institute for Health Research (CIHR), and more recently by the Krembil Foundation. The results have taught us that joint inflammation predicts progression of both clinical and radiological damage and suggests that **we need to be more aggressive with therapy earlier in the course of the disease.**

This is particularly important since we have also found that patients with psoriatic arthritis have an increased death rate compared to the general population. An important risk factor for death is disease severity at presentation, the causes of death remaining same as in the general population. Therefore it appears that if we treat our patients earlier we may prevent some of these problems.

We have determined that in addition to the information collected at first visit to the clinic, the degree of joint inflammation over time is predictive of subsequent damage. Thus, patients with psoriatic arthritis need to be followed serially over time so that appropriate intervention is provided in a timely manner. Importantly, inflammation in a particular joint is predictive of damage to that joint, suggesting that joint inflammation must be controlled to prevent damage. We recently found that patients who present to our clinic earlier in the course of their disease do better than those who present later in their course.

We have also identified a group of patients who have a better course, and achieve clinical remission (absence of clinical evidence of inflammation for at least a year). Seventeen percent of our patients achieved clinical remission, but only a few achieved what we call complete remission. However, half of the patients who achieved clinical remission went on to flare after a period of about two and a half years. **This confirms that we must continue to be vigilant in our follow-up of our patients.** Since remission may not be achieved by all patients, the concept of minimal disease activity was developed. A measure for minimal disease activity was produced by colleagues in Leeds, England, and was tested in our database. We demonstrated that about a third of the patients achieve a state of minimal disease activity lasting at least 12 months. These patients do better than those who do not achieve this state, again demonstrating that disease control prevents progression of damage.

Involvement of the spine is known to occur in 30-50% of patients with psoriatic arthritis. Spinal involvement is slowly progressive, and gradually there is increasing difficulty in turning the neck and bending sideways. We have shown that patients with severe peripheral arthritis are more likely to have spinal involvement.



We have found that certain **genetic markers** present on the membranes of white blood cells also serve as indicators of progression, and these may be more important than the clinical features. These markers are known as **HLA antigens** and are important in the immune response, the ability of our bodies to fight off infections. Some of these markers are more likely to occur among patients with psoriasis and psoriatic arthritis than in the general population, and thus are thought to play a role in the development of disease. Moreover, we recently demonstrated that there are specific HLA alleles associated with psoriatic arthritis when compared to patients with psoriasis without arthritis.

Through collaborations with colleagues in Newfoundland and the National Institutes of Health, we have also identified other genes that predispose to the development of psoriatic arthritis and its progression. This information is crucial, since these markers may identify those individuals destined to develop a more severe form of arthritis and provide for a more rational approach to the treatment of individual patients. We have been funded by the Canadian Institute of Health Research (CIHR) to study these genetic factors in collaboration with 6 centers in Canada, 2 in the USA and one in Argentina.

Even though patients may have certain genes which predispose to a certain disease, these genes may not be expressed. **Microarrays** are a cutting-edge technique used to determine which genes are actually expressed. Some very informative and exciting results were obtained from our pilot study and work is in progress to further investigate these findings. Identifying genes specific for psoriatic arthritis will be useful in identifying new drug targets as well as identify not only those individuals who are at risk of development of psoriatic arthritis, but also those destined to develop severe disease.

Are hereditary factors important in Psoriatic Arthritis?

About 40% of patients with psoriatic arthritis have relatives with either psoriasis or psoriatic arthritis, suggesting some hereditary contribution. We have also shown that close blood relatives of patients with psoriatic arthritis have about 30 times the risk of developing psoriatic arthritis compared to the general population. Our studies and those of other investigators have shown that there are certain HLA antigens that identify those patients with psoriasis more likely to develop psoriatic arthritis.

We are currently looking for the role of other genes as well. In collaboration with centers in Newfoundland, Vancouver, Rochester and Ann Arbor through the International Psoriasis and Arthritis Research Team (**IPART**), we are conducting large scale studies to identify these genes, which have been partially funded by the Canadian Institute of Health Research (CIHR) and The Arthritis Society. *We hope the patients and their families will continue to support our efforts.*



Are we any wiser in the understanding of the cause of Psoriatic Arthritis?

There is now evidence to support a role for genetic, immunological and environmental factors in the development of psoriatic arthritis. We have also identified several patients, whose psoriasis and arthritis were precipitated by injury, suggesting that this may be a factor in the development of the disease. Dr. Lihi Eder, one of our foreign trainees recently received her PhD degree in clinical epidemiology, in which she demonstrated that infection and heavy lifting predispose patients with psoriasis to develop psoriatic arthritis. While smoking predisposes people to develop psoriasis, once patients with psoriasis smoke, they are less likely to have psoriatic arthritis. Current investigations are focused on the relationship between genetic and environmental factors.

Are there new therapies available for patients with Psoriatic Arthritis?

A number of medications have been tested in our Clinic. These include the retinoic acid analogue, Tegison; an anti-inflammatory drug called Meclomen; Gold, Methotrexate, Sulfasalazine (Salazopyrine), Imuran and Fish Oil. While these medications may work for some of our patients, they do not work for all of them.

The turn of the millennium has brought with it new hope. Several new medications, which were originally developed for rheumatoid arthritis, including leflunomide (ARAVA) and several anti-tumour necrosis factor (anti-TNF) agents (Infliximab, Etanercept, Adalimumab, Golimumab) have now been tested for efficacy in psoriatic arthritis.

We participated in an international study that tested the efficacy of ARAVA for both skin and joint disease in psoriatic arthritis (TOPAS trial). The results revealed that the drug was effective in controlling both skin and joint manifestations in psoriatic arthritis; however, only about 40% of the patients responded.

We have tested the role of **Infliximab** (Remicade) in severe psoriatic arthritis, and found that while it works for both skin and joints, there are infectious complications in some patients. We also participated in two international trials of Infliximab in Psoriatic arthritis (IMPACT and IMPACT II). Infliximab proved effective for psoriatic arthritis in both these trials and we have been using it in our patients. It has now been approved in Canada for the treatment of psoriatic arthritis, but is not available on the Ontario Drug Benefit (ODB) program.

No Canadian centres were included in the randomized trials of **Etanercept** (Enbrel) in psoriatic arthritis. These studies were carried out in the US and have proven the drug is effective. Etanercept was the first



anti-TNF agent approved for psoriatic arthritis in Canada, and is available on the ODB program. We led a Canadian study of etanercept in psoriatic arthritis which confirmed its efficacy (for skin and joint manifestations including dactylitis and enthesitis) and safety and demonstrated that the drug allowed people to return to work and work more efficiently.

Adalimumab (Humira) was approved for the treatment of psoriatic arthritis in 2007. We participated in the pivotal international trial with this drug. Data from this trial confirmed our observation from our longitudinal study that inflammation leads to joint damage, and adalimumab was shown to prevent progression of radiological damage. We also conducted a Canadian study with this drug showing not only its effectiveness in controlling signs and symptoms of both skin and joint manifestations, but also an economic benefit. It is also available on the ODB program.

The latest anti-TNF agent to be approved for psoriatic arthritis is **Golimumab** (Simponi). This drug is also effective for both skin and joint manifestations. We have participated in the international trial with this agent, and the long-term follow up is still continuing. As with other agents, Golimumab also reduces progression of joint damage.

Thus, there are currently four anti-TNF agents that are effective for both skin and joint manifestations of psoriatic arthritis. The difficulty is that the drugs are expensive, and physicians are required to use other medications such as methotrexate and leflunomide or sulfasalazine before prescribing these newer medications to patients with severe psoriatic arthritis. Another anti-TNF agent and an agent that blocks interleukin 12 and 23 are currently under investigation in psoriatic arthritis.

There are several other medications which are currently under investigation or will be tested in psoriatic arthritis. This is an exciting time for patients with psoriatic arthritis and the physicians looking after them. *It is most important that the diagnosis be made early and appropriate therapy be offered as soon as the diagnosis is made.* We have therefore, developed a screening tool to identify patients with psoriatic arthritis. The **Toronto Psoriatic Arthritis Screen** (ToPAS) is highly sensitive and specific and should help identify patients in the early stages of their disease.

Multi-centre Collaboration

We are now part of a number of Canadian and International multicentre collaborative groups for psoriasis and psoriatic arthritis. Dr. Gladman recently stepped down from the post of President of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (**GRAPPA** - <http://www.grappanetwork.org>). This is an international group of rheumatologists, dermatologists, radiologists, methodologists and other interested participants who have gathered to study psoriasis and psoriatic arthritis and are involved in both research and education. Both Drs. Gladman and Vinod continue to be actively involved in GRAPPA.



Dr. Gladman is also an executive member of SPondyloArthritis Research Consortium of Canada (SPARCC - <http://www.sparcc.ca>), a group funded by The Arthritis Society, to understand spondyloarthritis. These are a group of diseases affecting the spine and peripheral joints and include psoriatic arthritis. The SPARCC group consists of 7 centers across Canada.

In summary, we have learned a great deal about the disease process in psoriatic arthritis. We now know that the disease may be more serious than previously suspected, at least in certain patients. We appreciate the need to diagnose and treat patients early in order to prevent damage, deformity and mortality. We now have an idea about the type of patient who needs to be treated more aggressively. We are currently developing an approach based on the recently identified markers for disease progression in psoriatic arthritis. We believe that by studying the disease in detail we will be able to find the cause and then the cure for psoriatic arthritis.

Future Plans

- To continue with the efforts identifying prognostic factors for disease progression, damage, poor quality of life, and mortality in psoriatic arthritis.
- To identify genetic factors associated with drug response and sensitivity, particularly with respect to anti-TNF agents and methotrexate.
- To identify biomarkers for disease progression and response to therapy.
- We will continue our ‘family study’ by increasing our multi-case family collection, as well as trios and sibling pairs, so that we have enough data on these families to be able to identify gene(s) responsible for susceptibility to psoriatic arthritis.

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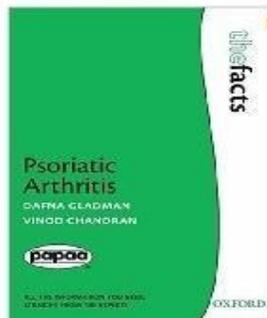


OTHER USEFUL LINKS

<http://www.arthritis.ca>
<http://www.psoriasis.org>
<http://www.rheumatology.org>

We are on the Web!

www.uhnres.utoronto.ca/studies/cpsrd/



BOOKS 2008:

PSORIATIC ARTHRITIS

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ALL THE INFORMATION

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