



## **Artropatia Psoriasica e malattie reumatiche sistemiche**

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# **Psoriatic arthritis**

- Psoriatic arthritis (PsA) has been defined as an inflammatory arthritis associated with psoriasis,
- Usually seronegative for rheumatoid factor

Presence of certain clinical features:

- Distal interphalangeal (DIP) joint involvement
- Asymmetric distribution
- Dactylitis (inflammation of the whole digit)
- Enthesitis (inflammation at the site of tendon insertion in to bone)
- Presence of spinal involvement
- Association with the HLA-B\*27 allele.

*Gladman DD, Rahman P. Psoriatic arthritis. In: Harris ED, Sledge CB, Budd RC, Sergent JS, eds. Textbook of Rheumatology, 6th edn. Philadelphia: W.B. Saunders Co, 2001:1071–1079.*

## Epidemiology of PsA

- The exact prevalence of PsA is unknown
- Estimates of PsA in the general population vary from 0.04% in the Faroe Islands, to 1.2% in Sweden.
- The prevalence of PsA among patients with psoriasis has varied from 6% in the Mayo Clinic study, to 42% in an outpatient clinic in South Africa
- The true estimate is likely between 25% and 34%, based on a study from Italy, where patients are followed by both dermatologists and rheumatologists, as well as a recent study from Sweden.
- If psoriasis occurs in 1– 3% of the population, and about a third of those patients have PsA, than PsA may occur in 0.3– 1% of the population, a frequency similar to that of rheumatoid arthritis.

*Scarpa R, Oriente P, Pulino A, et al. Psoriatic arthritis in psoriatic patients. Br J Rheumatol 1984; 23:246–250.  
Zachariae H. Prevalence of joint disease in patients with psoriasis: implications for therapy. Am J Clin Dermatol 2003; 4: 441–447.*

## Clinical features of PsA

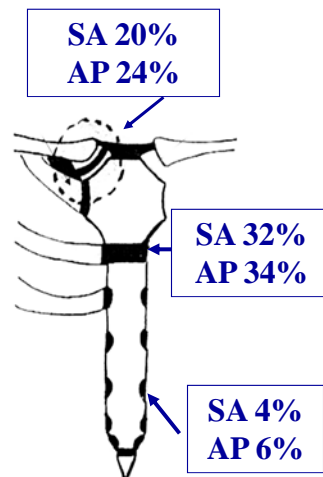
- PsA affects men and women almost equally
- The average age at onset in most studies is 36–40 years although it may occur in childhood
- The classic description of PsA includes five clinical patterns first described by Wright in 1956:
  1. DIP joint disease pattern
  2. Oligoarticular (less than five joints involved), which is usually asymmetric in distribution
  3. Polyarticular pattern (five or more joints involved), which is only symmetric in about half the patients
  4. Arthritis mutilans, which is a very destructive form of arthritis
  5. Spondyloarthritis, affecting the sacroiliac joints and the apophyseal joints of the spine.
- Change in pattern in the course of the disease

*Wright V, Moll JMH. Psoriatic arthritis. In seronegative polyarthritis. North Holland Publishing Co 1976: pp. 169–223.*

- **Morning stiffness** is only detected in 50% of patients with PsA
- **Dactylitis**, may occur in about half the patients  
Dactylitis is associated with higher rate of erosions in the affected digits (14).
- **Tendonitis**, which may affect the finger joints, as well as the Achilles tendon and the plantar fascia
- **Tenosynovitis** may also affect the flexor tendons of the fingers, as well as the tendons around the wrist
- **Enthesitis**, or inflammation at the site of tendon insertion, at these latter sites is also common
- **Spondylitis**, which includes sacroiliac and apophyseal joint involvement, may present with inflammatory back pain, which usually occurs at rest and immobility and improves with activity  
It is associated with prolonged morning stiffness. However, spondylitis in PsA may be totally asymptomatic  
Both the sacroiliac changes and the spinal changes may be asymmetrical in PsA  
The spondyloarthritis of PsA is less severe than that seen in ankylosing spondylitis

*Brockbank JE, Stein M, Schentag CT, Gladman DD. Dactylitis in psoriatic arthritis: a marker for disease severity? Ann Rheum Dis. 2005;64:188-90.*

## DISTRIBUZIONE DELLE LESIONI DELLA PARETE TORACICA ANTERIORE NELLA SA E NELL'AP



Fournié et al, Rev Rhum, 1997

## Extra-articular features in PsA

- The major extra-articular feature in PsA is psoriasis
- Psoriasis vulgaris is the main form of psoriasis associated with PsA, but pustular psoriasis, and guttate lesions have also been recognized
- Nail lesions occur in much higher frequency among patients with PsA than those with uncomplicated psoriasis
- No direct relationship between the extent and severity of psoriasis and joint manifestations
- Other extra-articular manifestations include ocular involvement, either conjunctivitis or iritis, occurs in 7–33% of patients. Aortic incompetence was reported in less than 4% of patients with PsA and usually develops late in the course of the disease.

Jones SM, Armas JB, Cohen MG, et al. Psoriatic arthritis: outcome of disease subsets and relationship of joint disease to nail and skin disease. *Br J Rheumatol* 1994; 33: 834–839.

Queiro R, Torre JC, Belzunegui J, et al. Clinical features and predictive factors in psoriatic arthritis-related uveitis. *Semin Arthritis Rheum* 2002; 31: 264–270.

Gladman DD, Rahman P. Psoriatic arthritis. In: Harris ED, Sledge CB, Budd RC, Sargent JS, eds. *Textbook of Rheumatology*, 6th edn. Philadelphia: W.B. Saunders Co, 2001:1071–1079.

## Course and prognosis of PsA

- **Progression of joint damage**
- 20% of patients with PsA have a severe and debilitating form of arthritis
- the number of actively inflamed joints at each clinic visit, as well as the degree of damage accrued, are predictive of future damage
- HLA antigens sustained their predictive value even when added to the clinical model
- The HLA-DR\*0401 was associated with more erosive disease among patients with PsA
- Polyarticular disease was predictive of progression of clinical and radiological damage

Gladman DD, Shuckett R, Russell ML, Thorne JC, Schachter RK. Psoriatic Arthritis – an analysis of 220 patients. *Q J Med* 1987;62: 127–141

Queiro-Silva R, Torre-Alonso JC, Tinture-Eguren T, Lopez-Lagunas I. A polyarticular onset predicts erosive and deforming disease in psoriatic arthritis. *Ann Rheum Dis* 2003;62: 68–70.

Gladman DD, Farewell VT. Progression in psoriatic arthritis: role of time varying clinical indicators. *J Rheumatol* 1999;26: 2409–2413.

### Remission in PsA

- Remission was defined as the absence of actively inflamed joints for 12 months, and was achieved by 69 of 391 (17.6%) patients followed longitudinally for over 20 years.  
52% of the patients who achieved remission went on to flare after that period of remission  
Male patients with a lower number of actively inflamed joints at presentation were more likely to achieve remission

### Quality of life and function in PsA

- Patients with PsA demonstrate reduced quality of life, manifested by lower scores on the SF-36  
Patients with PsA demonstrate reduced function, as measured by higher HAQ scores, which may be as high as those of patients with RA

### Mortality

- Increased mortality
- The standardized mortality ratio (SMR) was 1.62 in one clinic where patients had been followed prospectively for over 15 years. Causes of death were similar to those seen in the general population
- Previously active and severe disease, as manifested by a high ESR, high medication level and a high radiological damage score at first visit, were predictive of this early mortality

Gladman DD, Ng Tung Hing E, Schentag CT, Cook R. Remission in psoriatic arthritis. *J Rheumatol* 2001;28:1045–1048.

Sokoll KB, Hellmell PS. Comparison of disability and quality of life in rheumatoid and psoriatic arthritis. *J Rheumatol* 2001;28: 1842–1846.

Wong K, Gladman DD, Husted J, Long J, Farewell VT. Mortality studies in psoriatic arthritis. Results from a single center.

*I. Risk and Causes of Death. Arthritis Rheum* 1997;40: 1868–1872.

## Pathogenesis of PsA

- Genetic factors
- Additional different genetic factors in PsA. (HLA-Cw\*0602, CARD15, genes in the HLA region on chromosome 6 including TNF-alpha and its promoter)
- Environmental factors:infectious agent
- Trauma: substance P and vasoactive intestinal peptide are over expressed in psoriatic skin lesions and in psoriatic synovium and may mediate the role of trauma in PsA

Gladman DD, Cheung C, Michener G, Wade JA. HLA Clocus alleles in psoriatic arthritis. *Human Immunol* 1999; 60: 259–261.

Al-Haresh AM, Prtector J, Jones SM, et al. Tumour necrosisfactor- $\alpha$  polymorphisms and the HLA-Cw\*602 allele in psoriatic arthritis. *Rheumatology* 2002;41: 525–530.

Hohler T, Grossmann S, Stradmann-Bellinghausen B, et al. Differential association of polymorphisms in the TNF- $\alpha$  region with psoriatic arthritis but not psoriasis. *Ann Rheum Dis* 2002;61: 213–218

### Immunological meccanisms

- T lymphocytes, particularly CD8+ cells, are thought to play an important role in the pathogenesis of both the skin and joint manifestations of PsA

These activated T cells likely contribute to the enhanced production of cytokines noted both in the synovial fluid and synovial cultures from patients with PsA

These cytokines, including IL-1 $\beta$ , IL-2, IL-10, IFN- $\gamma$  and TNF- $\alpha$  induce proliferation and activation of synovial and epidermal fibroblasts, leading to the fibrosis reported in patients with longstanding psoriatic arthritis

- The pro-inflammatory cytokines IL-1 and TNF- $\alpha$  are regulators of not only the inflammatory response, but also play an important role in bone metabolism by enhancing osteoclastogenesis via the up-regulation of osteoprotegerin ligand (OPGL)
- Monocytes are responsible for the production of metalloproteinases (MMPs). MMPs are thought to mediate cartilage erosion in inflammatory arthritis. MMPs are regulated by IL-1 and TNF- $\alpha$

Panayi G. Immunology of psoriasis and psoriatic arthritis. *Baillières Clin Rheumatol* 1994;8: 419–427.

Costello P, Bresnihan B, O'Farrell C, Fitzgerald O. Predominance of CD8+ T lymphocytes in psoriatic arthritis. *J Rheumatol* 1999; 26: 1117–1124.

Lacey DL, Timms E, Tan HL, et al. Osteoprotegerin ligand is a cytokine that regulates osteoclast differentiation and activation. *Cell* 1998; 93: 165–176.

Ritchlin CT, Haas-Smith SA, Li P, Hicks DG, Schwarz EM. Mechanisms of TNF-alpha- and RANKL-mediated osteoclastogenesis and bone resorption in psoriatic arthritis. *J Clin Invest* 2003; 111: 821–831.

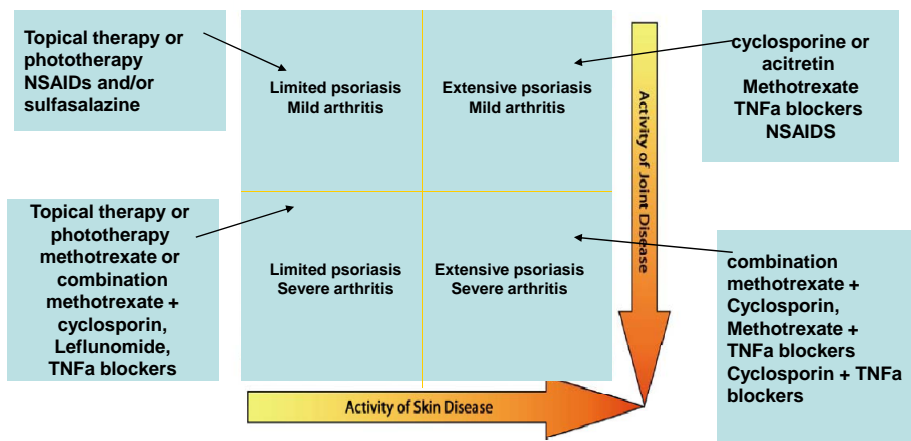
## Treatments for psoriatic arthritis

Treatment	Strength of evidence	Efficacy
Sulfasalazine <sup>15,16</sup>	Several placebo-controlled trials	Modestly effective for peripheral arthritis (PsARC 58% vs placebo 45%)
Methotrexate <sup>18</sup>	Single, small, placebo-controlled trial, uncontrolled observations	In controlled trial, improvement only in physician assessment. Effective in multiple uncontrolled reports
Azathioprine <sup>29</sup>	Uncontrolled trial	Modestly effective
Cyclosporine <sup>20,21</sup>	Open, active comparator trials	Modestly effective
Etretinate <sup>11</sup>	Blinded, active comparator trial	Modestly effective
Leflunomide <sup>22</sup>	Placebo-controlled trial	PsARC 59% vs placebo 30%
Etanercept <sup>7,24</sup>	Placebo-controlled trials	ACR20 59% vs placebo 15%. Halted radiographic progression
Infliximab <sup>25,26</sup>	Placebo-controlled trials	ACR20 58% vs placebo 11%
Adalimumab <sup>9</sup>	Placebo-controlled trial	ACR20 58% vs placebo 15%
Alefacept <sup>23</sup>	Uncontrolled trial	DAS response in 5 of 11 patients

ACR20, American College of Rheumatology 20% response; DAS, Disease Activity Score; PsARC, Psoriatic Arthritis Response Criteria.

Gordon KB, Ruderman EM. The treatment of psoriasis and psoriatic arthritis: an interdisciplinary approach. *J Am Acad Dermatol.* 2006 ;54:S85-91.

## APPROACH FOR THE TREATMENT OF PSORIATIC ARTHRITIS



From Gordon KB, Ruderman EM. The treatment of psoriasis and psoriatic arthritis: an interdisciplinary approach. *J Am Acad Dermatol.* 2006;54(3 Suppl 2):S85-91. (personal modified)

## Cyclosporine A in PsA

- *Mazzanti G, Coloni L, De Sabbata G, Paladini G. Methotrexate and cyclosporine combined therapy in severe psoriatic arthritis. A pilot study. Acta Derm Venereol (Stockh) 1994; (Suppl.) 186: 116–117.*
- *Spadaro A, Riccieri V, Sili-Scavalli A, Sensi F, Taccari E, Zoppini A. Comparison of cyclosporine A and methotrexate in the treatment of psoriatic arthritis: a 1-year prospective study. Clin Exp Rheumatol 1995; 13: 589–593.*
- *Fraser AD, van Karyk A, Westhoven R, et al. A randomized double-blind, placebo-controlled, multi-centre trial of combination therapy with methotrexate plus cyclosporine versus methotrexate plus placebo in patients with active psoriatic arthritis (PsA). Arthritis Rheum 2003; 48 (Suppl.9): S170.*
- *Salvarani C, Macchioni P, Olivieri I, et al. A comparison of cyclosporine, sulfasalazine, and symptomatic therapy in the treatment of psoriatic arthritis. J Rheumatol 2001; 28: 2274–2282*
- Combination therapy with Cyclosporine A and methotrexate has been shown effective in controlling PsA
- side effects, mainly renal impairment and hypertension were mild and reversible and responded to a reduction in CSA dosage.

## Take home message

- Patients with psoriasis who manifest joint involvement should consult a rheumatologist, who will oversee their joint disease.
- Patients who present with joint disease and have suspected psoriasis to consult a dermatologist who should supervise their skin treatment.
- Ideally, the dermatologist and rheumatologist would work as a team to supervise all aspects of the patient's disease.
- It is important that patients with PsA are diagnosed early and treated more aggressively at the onset of the disease to control the inflammatory process and prevent joint destruction and disability.

## Cyclosporin A and autoimmune chronic inflammatory diseases

- **T CELLS AS TARGETS OF CYCLOSPORINE A**

Cyclosporine A (CsA) represents the mainstay of immunosuppressive therapy in transplantation. The mechanism of action is the inactivation of the Ca/calmodulin dependent serine–threonine phosphatase calcineurin by the drug-immunophilin complex. This leads to the inactivation of the nuclear factor of activated T cells (NFAT), a transcription factor that is required for the expression of the IL2, IFN $\gamma$ , and GM-CSF genes.

- CsA is capable of activating the gene for TGF $\beta$  1 and of shutting down the expression of CD40L in T cells.
- In addition, CsA inhibits the maturation of dendritic cells from monocytes when stimulated by TNF $\alpha$ .
- All these effects explain the clinical and biological results obtained for SLE, in which an adequate control of nephritis was demonstrated; for UC, in which intravenous infusion, as an induction therapy, has been shown to almost fully control the acute phases of the disease; for RA, for which, in combination with methotrexate, CsA has proved to control the progression of the erosive structural damage much more efficiently than methotrexate alone; and for polydermatomyositis, in which 81% of patients demonstrated reduction of creatine kinase (CK) levels and clinical improvement.
- IL2 and IFN $\gamma$  synthesis by activated T cells is crucial in all autoimmune diseases, whether T or B cell dependent.
- CsA may shut down the autoreactivity through the inhibition of IL2 and IFN $\gamma$  and the down regulation of CD40L on T cells and may reset the immunologic milieu by inducing the synthesis of TGF $\beta$ 1.

GIESE, T., M. ZEIER, P. SCHEMMER, et al. 2004. Monitoring of NFAT-regulated gene expression in the peripheral blood of allograft recipients: a novel perspective toward individually optimized drug doses of cyclosporine A. *Transplantation* 77: 339–344.

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FULEIHAN, R., N. RAMESH, A. HORNER, et al. 1994. Cyclosporin A inhibits CD40L expression in T lymphocytes. *J. Clin. Invest.* 93: 1315–1320.

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MARCHESONI, A., N. BATTAFARANO, M. ARREGHINI, et al. 2003. Radiographic progression in early RA: a 12 month randomized controlled study comparing the combination of cyclosporin and methotrexate with methotrexate alone. *Rheumatology* 42: 1545–1549.

QUSHMAQ, K.A., A. CHALMERS & J.M. ESDAILE. 2000. Cyclosporine A in the treatment of refractory adult polymyositis/dermatomyositis: population based experience in 6 patients and literature review. *J. Rheumatol* 27: 2855–2859.

FERRACCIOLI GF et al. T cell inhibition by Cyclosporin A. *Ann NY Acad Sci* 2005; 1051: 658–665.

## Cyclosporine A and autoimmune disorders in HCV infected patients

- The prevalence of hepatitis C virus (HCV) infection is about 3% in western countries and that there are areas in south Italy where the prevalence rises up to 20% of the population
- All together, autoimmune disorders (AD) have a prevalence of about 10% in western population
- The treatment of AD, especially in systemic severe forms, includes the usage of immunosuppressant agents and/or glucocorticoids that have the potential effect of worsening the outcome of HCV infection
- CsA is an immunosuppressant agent widely used to treat autoimmune disorders and organ transplanted patients.
- Evidences in literature demonstrated that CsA also exerts an inhibitory effect on HCV replication both in vivo and in vitro, through inhibition of cyclophilin B and not by the inhibition on calcineurin, which is responsible of the immunosuppressive effect.
- Preliminary studies suggest that CsA can be safely used in the treatment of patients affected by autoimmune disorders with concomitant chronic HCV infection

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Nakagawa M, Sakamoto N, Tanabe Y, et al. Watanabe M. Suppression of hepatitis C virus replication by cyclosporin A is mediated by blockade of cyclophilins. *Gastroenterology* 2005;129:1031–41.

Galeazzi M, Giannitti C, Manganelli S, et al. Treatment of rheumatic diseases in patients with HCV and HIV infection. *Autoimmun Rev.* 2008;8(2):100-3.