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Psoriasis, a Systemic Disease Beyond the Skin, as Evidenced by Psoriatic Arthritis and Many Comorbities – Clinical Remission with a Leishmania Amastigotes Vaccine, a Serendipity Finding

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1. Introduction

Psoriasis is a systemic chronic, relapsing inflammatory skin disorder, with worldwide distribution, affects 1–3% of the world population, prevalence varies according to race, geographic location, and environmental factors (Chandran & Raychaudhuri, 2010; Christophers & Mrowietz, 2003; Farber & Nall, 1974). In Germany, 33,981 from 1,344,071 continuously insured persons in 2005 were diagnosed with psoriasis; thus the one year prevalence was 2.53% in the study group. Up to the age of 80 years the prevalence rate (range: 3.99-4.18%) was increasing with increasing age and highest for the age groups from 50 to 79 years The total rate of psoriasis in children younger than 18 years was 0.71%. The prevalence rates increased in an approximately linear manner from 0.12% at the age of 1 year to 1.2% at the age of 18 years (Schäfer et al., 2011). In France, a case-control study in 6,887 persons, 356 cases were identified (5.16%), who declared having had psoriasis during the previous 12 months (Wolkenstein et al., 2009). The prevalence of psoriasis analyzed across Italy showed that 2.9% of Italians declared suffering from psoriasis (regional range: 0.8-4.5%) in a total of 4109 individuals (Saraceno et al., 2008). The overall rate of comorbidity in subjects with psoriasis aged less than 20 years was twice as high as in subjects without psoriasis. Juvenile psoriasis was associated with increased rates of hyperlipidaemia, obesity, hypertension, diabetes mellitus, Crohn disease and rheumatoid arthritis. The best-known noncutaneous condition associated with psoriasis is joint disease, mostly expressed as Psoriatic arthritis (PsA), (Mrowietz et al., 2007). Palmoplantar psoriasis is associated with significant quality-of-life issues. In 150 patients with palmoplantar psoriasis, 78 (52%) patients displayed predominantly hyperkeratotic palmoplantar lesions, 24 (16%) pustular, 18 (12%) combination, and 30 (20%) had an indeterminate phenotype. In 27 (18%) patients, lesions were confined to the palms and soles. In all, 27 (18%) had mild, 72 (48%) moderate, and 51 (34%) severe disease involvement (Farley et al., 2009).

2. Psoriasis in the clinic

The disease has wide clinical spectra that range from epidermal (scaly) and vascular (thickened, erythematous) involvements of the skin, to the malignant form known as

generalized erythrodermia. Skin involvement is characterized by symmetrically distributed, well-demarcated plaques, its most common form named psoriasis vulgaris or plaque-type psoriasis. Two forms of psoriasis can be recognized: Type I psoriasis, characterized by been hereditary, dominant autosomic (60% penetration), onset: 16 years females, 22 years males; HLA-Cw6 positive (73.8% vs. 20.4 % in normal subjects). Type II psoriasis, characterized by been sporadic, major incidence 57-60 years, poor correlation with HLA-CW6 (27.3% vs. 10.1% in controls). Psoriasis plaques with silvery scales present the Auspitz sign a pinpoint capillary bleeding when the scales are gently scraped away with a spatula or fingernail (Mrowietz, et al., 2007, 2009; Naldi & Mercuri, 2010). Psoriasis may also attack nails, (Augustin et al., 2010b; Farber, & Nall , 1974), tendons, ligaments, fascia, and spinal or peripheral joints as the clinical form, inflammatory PsA similar to rheumatoid arthritis, but no rheumatoid factor present in the blood. PsA can be severely disabling, occurring in up to 10–30% of patients with psoriasis, and is associated with HLA-B27 MHC Class I marker (Mrowietz et al., 2007). Psoriatic plaques induce pain and pruritus, generating discomfort and persistent insomnia. Quality of life decreases considerably because it is a physically disfiguring illness that disrupts social life, induces constant psychological stress, lowered self-esteem, and feelings of being socially ostracized. Common among many patients are the use of tranquilizers, sleeping pills, antidepressants, consumption of alcohol, and cigarette smoking (Choi & Koo 2003, Zeljko-Penavi´c et al. 2010, Wu et al., 2009, Van Voorhees & Fried 2009). Pruritus is an important symptom in psoriasis vulgaris may be severe and seriously affect the quality of life. 85% of psoriatic patients suffered from itching; the frequency of pruritus was daily and mean intensity was moderate. The results confirmed the need for a global study of psoriasis with regard to both the cutaneous manifestations and the itch symptom (Prignano et al., 2009). Ophthalmic complications of psoriasis are numerous and affect almost any part of the eye; however, they may be easily missed. Complications include direct cutaneous effects such as eyelid involvement and blepharitis, and immune mediated conditions such as uveitis (Rehal et al., 2011). In Spain, between January 2007 and December 2009 of a total of 661 patients included, 47.4% were diagnosed with nail psoriasis, which was 13.5% more prevalent in men. The group of patients with nail disease had more severe psoriasis (12.82 vs 8.22 points on PASI) and a longer disease duration (20.30 vs 13.94 years), and included a larger percentage of patients with psoriatic arthritis (29.7% vs 11.5%), a positive family history of the disease (53.7% vs 42.8%), and a body mass index greater than 30 (31.6% vs 23.9%). A larger percentage of the patients with nail disease had early-onset psoriasis (74.1% vs 65.5%) and fewer were carriers of the human lymphocyte antigen Cw0602 allele (33% vs 50.3%). Nail disease is frequent in psoriasis and is associated with greater severity of psoriasis and a larger number of comorbidities (Armesto et al., 2011).

3. Psoriasis pathogenesis

3.1 General concepts

The introduction of the new concept of psoriatic disease represents a novel opportunity to better understand the pathogenesis of psoriasis and comorbidities (Scarpa et al., 2010). The disease is genetically determined with the involvement of multiple genes that interact with each other and with environmental factors (Elder, 2009). Analysis of patients demonstrated a strong association between psoriasis and all components of metabolic syndrome, which also explains comorbidities (Boehncke & Sterry, 2009). In early lesions, macrophages are present in the epidermis followed by monocytes, lymphocytes, and granulocytes with

formation of spongiform micro abscesses (Munro abscesses), more pronounced with disease activity, a hallmark of psoriasis. Physical trauma to the skin, results in a psoriatic lesion (Koebner phenomenon), which increases when the disease is active (Farber & Nall, 1974). The inflammatory process is immune mediated by unknown antigens through binding and specific activation and costimulation of T cells by antigen-presenting cells (APC), dendritic cells (DC), and macrophages in epidermis and dermis. A multimolecular complex is formed between APC and T cells: the immunological synapse, structured by major histocompatibility complex (MHC) receptors and T-cell receptors (TCR), with the following costimulatory molecules: lymphocyte functional antigen (LFA-1 and LFA-3), intercellular adhesion molecule (ICAM- 1), cluster of differentiation CD2, CD28, CD80, (Mrowietz, & Reich, 2009). Epidermal keratinocytes are highly active immunological cells, controlling the acute and the chronic phase of skin inflammation by cytokine/chemokine production and surface molecule expression, which lead to inflammatory infiltrate in the whole skin including the upper layers of the epidermis, perpetuating the skin disorder (Albanesi & Pastore, 2010). Dendritic cells and effector T-cells are central in the development of the psoriastic lesion, and cytokines produced by these cells stimulate keratinocytes to proliferate and increase the migration of inflammatory cells into the skin, promoting epidermal hyperplasia and inflammation (Monteleone et al., 2011). Psoriasis is a common chronic inflammatory disease of the skin and joints. Autoantibodies have been reported in psoriasis patients. Anti-nuclear antibody and antibody to double-stranded deoxyribonucleic acid, rheumatoid factor, anti-thyroid microsomal antibody (anti-TMA) were studied. About 28.8% of psoriasis cases were positive for at least one autoantibody. Age of onset and types of psoriasis had significant association with gender. Anti-double-stranded deoxyribonucleic acid and anti-thyroid microsomal antibody had significant association with types of psoriasis. Gender wise distribution of psoriasis in age group had significant association with anti-TMA. Autoantibodies are found to be present in psoriasis patients or latent autoimmune diseases develop in psoriasis patients without any clinical symptoms (Singh et al., 2010).

3.2 Blood vessels in psoriasis pathogenesis

Angiogenesis is essential for embryo development as well as for wound healing and progression of a number of diseases such as cancer, inflammatory conditions, eye diseases, psoriasis, and rheumatoid arthritis (RA) in the adult. Current paradigms explain blood vessel growth entirely by sprouting angiogenesis or by vessel splitting through so called intussusceptive angiogenesis. However, these mechanisms are mainly derived from experiments on the developing embryo while less is known about angiogenesis in the adult during, e.g., wound healing, tumor growth, and inflammation. Blood vessel growth in the adult can be induced and directed by mechanical forces that naturally develop during healing or remodeling of tissues (Kilarski & Gerwins, 2009). It is regulated by pro- and anti-angiogenic molecules, and was only implicated in few diseases, such as, cancer, arthritis, and psoriasis, now its research offers a potential to cure a variety of diseases such as Alzheimer's and AIDS. Angiogenesis may have an impact similar to that of antibiotics had in the twentieth century (Bisht et al., 2010). Angiogenic factors, such as vascular endothelial growth factor (VEGF), may dominate the activity of anti-angiogenic factors and accelerate angiogenesis in psoriatic skin. Small peptides with homologies to pigment epithelium derived factor (PEDF) show anti-angiogenic potential for the topical treatment for psoriasis. The specific low-molecular weight peptides (MW<850 Da) penetrated the skin and showed significant anti-angiogenic activity in vitro. Topical application of these peptides in a severe

combined immunodeficient mouse model of psoriatic disease led to reduced angiogenesis and epidermal thickness (Abe et al., 2010). VEGF is overexpressed in lesional psoriatic skin and its serum levels are significantly elevated in patients with moderate to severe disease. Thirty patients with moderate to severe psoriasis and 10 healthy controls were subjected to baseline evaluation of VEGF. Patients were divided into three groups according to the received treatment: psoralen plus ultraviolet A (PUVA) thrice weekly (group 1), acitretin 50 mg daily (group 2), and combined PUVA twice weekly and acitretin 25 mg daily (group 3). Treatment continued for 16 weeks or up to clinical cure. Every patient was subjected to severity evaluation by PASI and measurement of serum VEGF before and after treatment. Mean serum levels of VEGF were significantly elevated in patients (327 ± 66.2 pg/mL) than control subjects (178 ± 83.4 pg/mL). A highly significant correlation was found between VEGF and PASI score. VEGF is important in the pathogenesis of psoriasis, and could serve as a good indicator of disease severity and control (Nofal et al., 2009).

3.3 T cells and cytokines in psoriasis

The chemokine/chemokine receptor network is an integral element of the complex system of homeostasis and immunosurveillance. Initially studied because of their role in coordinating tissue-specific migration and activation of leucocytes, chemokines have been implicated in the pathogenesis of various malignancies and diseases with strong inflammatory components. There is a critical involvement of chemokine receptor interactions in the immunopathogenesis of classical inflammatory skin disorders such as psoriasis and atopic dermatitis, as well as neoplastic diseases with a T-cell origin, such as mycosis fungoides (Lonsdorf et al., 2009). In psoriasis, leukocytes that infiltrate skin lesions have been shown to be involved in the pathogenesis of this disease. The presence of CXCR3+ T lymphocytes in psoriatic lesional skin, have suggested a role of this receptor in the recruitment of T cells into the lesion. The mRNA levels of CXCR3 and its ligands, CXCL9-11, were significantly elevated by real-time reverse transcriptase-polymerase chain reaction in psoriatic lesions, as compared to non-lesional samples. The number of CXCR3+ cells was low in non-lesional tissues, wile the number of both epidermal and dermal CXCR3+ cells increased in lesional compared with non-lesional tissues. The majority of CXCR3+ cells were located in the dermis of the lesional skin and 74% were CD3+ T lymphocytes. A small number of CXCR3+ cells were CD68+ myeloid cells and all BDCA-2+ plasmacytoid dendritic cells were CXCR3+ (Chen et al., 2010).

Psoriasis is associated with chronic inflammation and it often coexists with inflammatory arthritis (Nestle et al., 2009) in which IL-33 has been implicated (Xu et al., 2008). IL-33 is one of the newest members of the IL-1 family of inflammatory cytokines (Castellani et al., 2009) and can mediate IgE-induced anaphylaxis in mice (Pushparaj et al., 2009). IL-33 also induces release of IL-6 from mouse bone marrow-derived cultured mast cells (Moulin et al., 2007) and IL-8 (Iikura et al., 2007). IL-33 augments SP-stimulated VEGF release from human mast cells and IL-33 gene expression is increased in lesional skin from patients with psoriasis (Theoharides et al., 2010b). Mast cells may, therefore, be involved in the pathogenesis of psoriasis and other inflammatory skin diseases. Macrophage migration inhibitory factor (MIF) is implicated in a range of pathological conditions, including asthma, rheumatoid arthritis, atherosclerosis, inflammatory bowel disease and cancer. In the field of dermatology, MIF is believed to be a detrimental factor in diseases such as systemic sclerosis, atopic dermatitis, psoriasis, eczema and UV radiation damage (Gilliver et al., 2011).

CD4+ effector cells have been categorized into four types: 1)- T helper1 cells produce IFN-γ, TNF-β, lymphotoxin and IL-10; 2)- T helper2 cells produce IL-4, IL-5, IL-10, IL-13, IL-21, IL-31; 3)- T helper3, or regulatory T-cells, produce IL-10, TGF-β and IL-35; 4)- T helper-17 cell produces IL-17, IL-17A, IL-17F, IL-21, IL-26 and CCL20. By producing IL-17 and other molecules, Th17 contributes to the pathogenesis of multiple autoimmune diseases including psoriasis, allergic inflammation, rheumatoid arthritis, autoimmune gastritis, inflammatory bowel disease and multiple sclerosis. IL-17-producing CD4+ T lymphocytes (Th17) are currently considered relevant participants in the pathogenesis of psoriasis skin lesions, together with IL-17-producing CD8+ T cells, which are also present at the psoriatic plaque, and produce TNFα and IFNγ as well as IL-17, IL-21, and IL-22. These cells are refractory to Tregs but show a proliferative response to anti-CD3/CD28 stimulation that is enhanced by IL-12 and IL-15. Blocking of TNF-α activity inhibits TCR-mediated activation and IL-17 production. CD8+IL-17+ T cells are cytotoxic cells that display TCR/CD3-mediated cytotoxic abilities to kill target cells (Ortega et al., 2009). Human Th17 cells and IL-23 play an important role, in the context of Th17 cell dependent chronic inflammation in psoriasis (Di Cesare et al., 2009). Th17 cells, is now into the centre of psoriasis pathogenesis. These cells secrete interleukin (IL)-17, IL-21 and IL-22, the latter of which appears to significantly contribute to the epidermal changes observed in this disease. Differentiation and maintenance of Th17 cells depends on IL-23 and transforming growth factor (TGFβ) secreted by activated monocytes or macrophages within the dermal compartment (Kunz, 2009). Factors such as climate, physical trauma, drug, stress and infections (Streptococcus, human immunodeficiency virus) are known to trigger psoriasis. T helper (Th) 17 mechanisms of how these cells traffic into inflamed skin are unknown. By immunostaining for interleukin (IL)-17A and IL-22, it has been shown numerous cells present in psoriasis lesions that produce these cytokines. Th17 cytokines (IL-17A, IL-22, and tumor necrosis factor (TNFα) markedly increased the expression of CC chemokine ligand (CCL)-20, a CC chemokine receptor (CCR)6 ligand, in human keratinocyte monolayer and raft cultures in a dose- and time-dependent manner. In mice that subcutaneous injection with recombinant IL-17A, IL-22, or TNF-α led to the upregulation of both CCL20 and CCR6 expression in skin as well as cutaneous T-cell infiltration. Taken together, these data show that Th17 cytokines stimulate CCL20 production in vitro and in vivo, and thus provide a potential explanation of how CCR6-positive Th17 cells maintain their continual presence in psoriasis through a positive chemotactic feedback loop (Harper et al., 2009).

The skin harbors a complex and unique immune system that protects against various pathologies, such as infection and cancer. Several cell populations are involved in this immune regulatory function, including CD4+ T cells that coexpress the transcription factor Foxp3, known as Tregs, and cells with immune-regulatory function known as myeloid-derived suppressor cells (MDSCs). Although their depletion may serve to augment immunity, expansion of these cells may be used to suppress excessive immune reactions (Ilkovitch, 2011).

Production and uptake of inducible HSP70 by keratinocytes may critically influence the chronic course of inflammatory skin diseases. Human keratinocytes release high levels of inducible heat shock protein (HSP)-70 that enhances peptide uptake. The stress-inducible chaperone HSP70 is considered a 'danger signal' if released into the extracellular environment. It has been proposed to play a role in the pathogenesis of skin diseases such as

psoriasis and lupus erythematosus (LE). Living keratinocytes are an important source of HSP70 in the skin and release more HSP70 than fibroblasts, macrophages or lymphocytes. Keratinocytes also bind and internalize HSP70 / HSP70–peptide complexes a process enhanced by TNFα and IL-27. No difference with regard to HSP70 release or uptake was observable between keratinocytes from healthy donors or patients with cutaneous LE. Keratinocytes pulsed with HSP70–peptide complexes significantly increased IFNγ production by autologous T cells which influence the chronic course of inflammatory skin diseases (Wang et al., 2011).

3.4 Mast cells and natural killer cells in plaque psoriasis

Psoriasis is a common inflammatory skin disease triggered by dysregulated immune response and characterized by hyperproliferation and altered differentiation of keratinocytes, as well as mast cell accumulation and activation (Harvima et al., 2008). Mast cells are increased in lesional psoriatic skin (Özdamar et al., 1996), and have important functions as sensors of environmental and emotional stress (Paus et al., 2006; Harvima et al., 1993) possibly due to direct activation by corticotrophin release hormone (CRH) and related peptides secreted under stress (Theoharides et al., 2004; Katsarou-Katsari et al., 1999; Church & Clough 1999; Theoharides et al., 2010; Harvima et al., 1993; Fortune et al., 2005; Harvima et al., 1996). Psoriasis is associated with increased serum CRH and decreased lesional skin CRHR-1 gene expression (Tagen et al., 2007). Formation of psoriatic lesions is elicited by the complex cellular and cytokine network arising from the pathogenic interactions between keratinocytes and components of innate and acquired immune system. Natural killer T (NKT) cells are a heterogenous T-cell lineage that has been implicated in the pathogenesis of various autoimmune diseases including psoriasis. Due to the numerous functions of NKT cells that link innate and adaptive immunity, their role in psoriasis is still elusive (Peternel & Kastelan, 2009). NKT cells are best known for their ability to recognize and kill tumor cells and virally infected cells and by production of large amounts of some cytokines, such as IFNγ. In addition to the functions in cancer and autoimmunity, contributions from NK cells to allergies and various skin diseases have emerged. In patients with allergic diseases, the production of TH2 cytokines by NKT cells contributes to the known immune deviation. In patients with psoriasis, their pathophysiologic role seems to be especially the production of IFNγ. NK cell overactivation can be found in patients with alopecia areata and pemphigus vulgaris (von Bubnoff et al., 2010).

3.5 Psychosomatics, neuropeptides, central and peripheral nervous system, nerve growth factor, and skin

In the central nervous system (CNS), neuroinflammation is due to local production of IL-17 in the brain. Inflammation in various tissues is achieved by secreted IL-17, IL-17A, and IL-17 F due to their proinflammatory effects on cellular targets, which include endothelial cells, epithelial cells, fibroblasts, keratinocytes, monocytes/macrophages and osteoclasts. Under CNS inflammatory conditions, microglia, which act as antigen presenting cells, produce IL-1b and IL-23. Acting in an autocrine manner, these cytokines may further induce IL-17 expression in microglia, contributing to neuroimmune disorders. Another inflammatory pathway involving IL-17 is the IL-17-induced activation of MMP-3, which recruits neutrophils to the site of inflammation (Vojdani &, Lambert, 2009).

Outpatients experiencing exacerbation of psoriasis in the last 6 months (n = 110) were compared with outpatients affected by skin conditions in which psychosomatic factors are believed to play a minor role (n = 200). In comparison with controls the patients with psoriasis reported more stressful life events. Also, patients with psoriasis were more likely to score higher on both anxiety and avoidance attachment scale and perceived less support from their social network than did the comparison subjects (Janković et al., 2009). 32 consecutive outpatients (9 males and 23 females), age M = 43.9 with psoriasis were examined by a team of dermatologists, psychiatrists and a psychologist using a standard set of methods. In addition, 32 patients with other chronically occurring skin diseases, including 11 males and 21 females, age M = 31.6, were also examined and formed the control group. The point prevalence of mental disorders was significantly higher in the psoriatic group: 20 (62.5%) versus 5 (15.62%) in the control group. In all of the cases, affective disorders were diagnosed. Mild anxiety disorders were additionally found in 10 psoriatic patients (31.25%) and in 2 controls (6.25%). The level of depression was much higher in the study group than in the control group. Neurotic symptoms were also significantly more intense in the psoriatic group (54.37± 40.99) than in the control group (35.28±23.96). The results imply the need for the careful examination of the mental state of patients with psoriasis in order to offer and provide treatment of any concomitant psychiatric conditions (Parafianowicz et al., 2010).

Neuropeptides (Saraceno et al., 2006) especially substance P (SP) (Remröd et al., 2007) are involved in the pathogenesis of psoriasis. In particular, SP reactive fibers are localized close to mast cells (Naukkarinen et al., 1996). SP can stimulate mast cells (Kawana et al., 2006; Kandere-Grzybowska et al., 2003) and contributes to inflammation (Leeman & Ferguson, 2000; O'Connor et al., 2004). SP-positive nerve fibers are denser in psoriatic lesions and have an increased number of mast cell contacts compared to normal skin (Chan et al., 1997; Al'Abadie et al., 1995). The nervous system contributes to inflammatory skin diseases. The neuronal contribution to psoriasis at the remission and exacerbation phases were analyzed by the expression of the neuronal markers protein gene product 9.5 (PGP 9.5), growth-associatedprotein-43 (GAP-43) and substance P, in addition to its receptor (R), neurokinin-1R (NK-1R) in psoriatic skin from seven female patients at remission and exacerbation, using immunohistochemistry. The number of epidermal PGP 9.5 immunoreactive nerve fibres in the involved skin during exacerbation was decreased compared to involved skin at remission and non-involved skin at the exacerbation phase. GAP-43-positive nerve fibres were decreased in the involved skin in contrast to non-involved skin, during exacerbation. Substance P expression was seen on both immunoreactive nerve fibres and cells with a down-regulation in the number of positive nerve fibres in the involved skin compared to non-involved skin, at the exacerbation phase. The number of substance P-positive cells was slightly lower in the involved skin at exacerbation than at remission. The number of NK-1R immunoreactive cells was increased in the involved skin in contrast to non-involved skin, at the exacerbation phase. These findings suggest a crosstalk between the nervous system and inflammation during psoriasis exacerbation in the form of an altered expression of nerve fibres, substance P and its NK-1R(El-Nouretal.,2009). A contributing role of nerve growth factor (NGF) mediated neuroimmunologic mechanisms has provided a new dimension in the understanding of various cutaneous and systemic inflammatory diseases and comorbidities. Recent evidence implicates NGF as a key mediator of inflammation and pain.

NGF influences an inflammatory reaction by regulating neuropeptides, angiogenesis, cell trafficking molecules, and T cell activation. The recognition of a pathologic role of NGF and its receptor system has provided an attractive opportunity to develop a novel class of therapeutics for inflammatory diseases and chronic pain syndromes (Raychaudhuri SK, & Raychaudhuri SP , 2009). Psoriasis is characterized by keratinocyte hyperproliferation and reduced apoptosis, leading to an increased epidermal turnover. Interestingly, NGF that is both a mitogen and a survival factor for keratinocytes, is overexpressed in psoriatic lesions as well as in psoriatic keratinocytes, (Fantini et al., 1995; Raychaudhuri et al., 1998) and its high-affinity receptor TrkA, that is located only in basal keratinocytes in healthy skin, is expressed throughout all epidermal layers in psoriasis (Pincelli, 2000). On the other hand, P75NTR that plays a proapoptotic role in keratinocytes, is absent in psoriatic keratinocytes. The rate of apoptosis in psoriatic transit amplifying (TA) cells is significantly lower as compared to TA cells from normal epidermis. On the contrary, in psoriasis, NGF and Trk upregulation associated with reduced P75NTR expression result in increased keratinocyte proliferation and reduced apoptosis, thus favoring epidermal thickness, a typical feature of this dermatosis (Truzzi et al., 2011). The question of lymphocyte being an initiator of psoriatic events remains open. Plaque symmetry, stress-induced onset or exacerbations, pruritus, and possibility of generalization, suggest a role of the nervous system and neurogenic inflammation in pathogenesis. A key to understanding the role of melanocyte in psoriasis is their ability to act as regulatory cell in maintaining epidermal homeostasis. It has been suggested melanocyte, acting as a local ‘‘stress sensor”, provide communicatory link between CNS and skin. The disease probably begins with so far unknown signal directed through neuronal network to the melanocyte, placed in the center of epidermal unit. That signal governs keratinocyte cellular activities and lead to reactive abnormal epidermal differentiation and hyperproliferation. Increased proliferation of basal keratinocytes and high metabolic demands creates angiogenesis in papillary dermis and elongation of dermal papillae. Stimulated melanocytes and basal keratinocytes become an important source of proinflammatory cytokines that attract lymphocytes into the dermis (Brajac et al., 2009). Pruritus involves skin surface receptors, peripheral and central nerves and specific brain regions. Peripheral unmyelinated C nerve fibres are stimulated. These nerves relay the itch signal to an ipsilateral spinal nucleus. At the same spinal level, involved nerve fibres carry the signal to the thalamus while giving off fibres to the cerebral aqueduct; the thalamus relays the signal to the somatosensory cortex. Psoriasis, has been named as the itch that scales; its importance is shown by the observation that sensory denervation leads to plaque resolution. Characteristic areas of psoriatic itch are the buttocks, extensor surfaces of the knees and elbows, and the ears and scalp. In psoriasis, 41–80% of patients have daily itch. Neuropeptide Y is inhibitory with respect to itch and decreased levels are seen in patients with psoriasis, which may explain the increased pruritus in psoriasis. Itch description varies in patients with psoriasis, ranging from stinging to burning to itch that affects sleep (Langner & Maibach, 2009)

3.5.1 Oxidative stress in skin disorders

The involvement of oxidative stress in the pathogenesis of various skin disorders has been suggested for decades. However, few clinical studies have assessed oxidative stress in skin diseases. The easiest and least invasive method to assess oxidative stress in patients may be

the measurement of oxidation products in urine. Nitrate as a metabolite of nitric oxide, malondialdehyde as a major lipid oxidation product, and 8-hydroxydeoxyguanosine (8-OHdG) as a DNAoxidation marker. Urinary nitrate and 8-OHdG levels, but not malondialdehyde, were significantly higher in psoriasis patients than those in healthy controls. The severity and extent of both psoriasis and atopic dermatitis significantly correlated with urinary nitrate level and malondialdehyde level, but it did not correlate with urinary 8-OHdG level (Nakai et al., 2009). Psoriatic keratinocytes are poorly differentiated and hyperproliferative. Low concentrations of nitric oxide (NO) induce keratinocyte proliferation, while high concentrations induce differentiation. The NO-producing enzyme inducible NO synthase is overexpressed in psoriatic skin, but so is arginase. The overexpressed arginase competes for arginine, the common substrate for both enzymes, and may reduce NO production. Arginase is overactive in psoriatic skin, leading to a relative increase in the consumption of arginine (Abeyakirthi et al., 2010). Oxidative stress (OS) and increased free-radical generation have been linked to skin inflammation in psoriasis (Rashmi et al., 2009). Skin is a major target of oxidative stress mainly due to reactive oxygen species (ROS) originating from the environment and skin metabolism itself. Although endogenous antioxidants attenuate the harmful effects of ROS, increased or prolonged presence of free radicals can override ROS defense mechanisms and mediate numerous cellular responses that contribute to the development of a variety of skin disorders, including psoriasis. The cellular signaling pathways such as mitogen-activated protein kinase/activator protein 1, nuclear factor κB, and Janus kinase–signal transducers and activators of transcription are known to be redox sensitive and proven to be involved in the progress of psoriasis (Zhou et al., 2009). The skin is permanently exposed to physical, chemical, and biological aggression by the environment, and chronic inflammatory events taking place in the skin are accompanied by abnormal release of pro-oxidative mediators. Homeostatic systems are active in the skin to maintain the redox balance and also to counteract abnormal oxidative stress. There is evidence that a local and systemic redox dysregulation accompanies the chronic inflammatory disorder events associated to psoriasis, contact dermatitis, and atopic dermatitis. Several treatments for the therapy of chronic inflammatory skin disorders are based on the application of strong physical or chemical oxidants onto the skin, indicating that, in selected conditions, a further increase of the oxidative imbalance may lead to a beneficial outcome (Pastore & Korkina, 2010).

3.6 Genetics in skin psoriasis

Psoriasis is a complex inflammatory skin pathology probably of autoimmune origin. Several cell types are perturbed in this pathology, and underlying signaling events are complex and still poorly understood. Network-based analysis revealed similarities in regulation at both proteomics and transcriptomics level. A group of transcription factors are responsible for overexpression of psoriasis genes and a number of previously unknown signaling pathways may play a role in this process. Investigation of proteomics and transcriptomics data sets on psoriasis revealed versatility in regulatory machinery underlying pathology and showed complementarities between two levels of cellular organization (Piruzian et al., 2010). The linkage analysis has been used to identify multiple loci and alleles that confer risk of the disease. Some other studies have focused upon single nucleotide polymorphisms (SNPs) for mapping of probable causal variants. Other studies, using genome-wide analytical techniques, tried to link the disease to copy number variants (CNVs) that are segments of

DNA ranging in size from kilobases to megabases that vary in copy number, an important element of genomic polymorphism, predisposing to a variety of human genetic diseases. Genotyping of single nucleotide polymorphisms, copy number variations and statistical tools have become extremely important to researchers for understanding the pathogenesis and molecular mechanism of psoriasis. Microarray analysis of psoriasis patients highlights the variability in gene expression occurring between individual patients, probably on the basis of their age, ethnicity, sex, genetics, skin types and environmental influences. The gene expression data and their analyses have suggested that psoriasis is a chronic interferon-γ and T cell mediated immune disease of the skin with imbalances in epidermal cellular structures (Al Robaee, 2010). Psoriasis is a systemic disease of the skin, nails, and joints, with an acknowledged but complex genetic basis. Early genome-wide linkage studies of psoriasis focused on segregation of microsatellite markers in families; however, the only locus consistently identified resided in the MHC. Subsequently, several groups mapped this locus to the vicinity of HLA-C, and two groups have reported HLA-Cw6 itself to be the major susceptibility allele. The development of millions of SNP, coupled with the development of high-throughput genotyping platforms and a comprehensive map of human haplotypes, has made possible a genome-wide association approach using cases and controls rather than families. A collaborative genome-wide association study of psoriasis involving thousands of cases and controls revealed association between psoriasis and seven genetic loci: HLA-C, IL12B, IL23R, IL23A, IL4/IL13, TNFAIP3, and TNIP1 (Elder et al., 2010).

3.7 Infections and psoriasis

Invasive streptococcal infections may have been a factor in psoriasis becoming a common skin disease in some parts of the world. Many of the candidate genes linked to psoriasis are associated with the acquired or innate immune system, which are also important in host defence to invasive streptococcal infections. High rates of positive streptococcal throat swabs among patients with chronic plaque psoriasis suggest that they are efficient at internalizing/carrying beta-haemolytic streptococci. Internalization of streptococci in the throat is dependent upon the transforming growth factor (TGF)-β/fibronectin/α-5 β-1 integrin pathway that also appear to be operative in psoriasis. It has been postulated that some of the genotypic/phenotypic changes in different immunological pathways in psoriasis, including the acquired T-cell response, the innate immune response, the TGF-β/fibronectin/α-5 β-1 integrin pathway and the Th17 cell system, confer protection against mortality during epidemics of invasive streptococcal infections, heightened efficiency in internalizing and allowing carriage of streptococci as well as predisposition to the development of psoriasis (McFadden et al., 2009).

4. Psoriatic comorbidities

Psoriasis has been associated with a number of behavioral and systemic comorbidities, including psoriatic arthritis, anxiety, depression, obesity, hypertension, diabetes mellitus, hyperlipidemia, metabolic syndrome, smoking, cardiovascular disease, alcoholism, Crohn's disease, lymphoma, and multiple sclerosis. Many of these conditions have a similar immunologic pathogeneses. Canadian and international studies have not only confirmed the presence of these comorbidities but also have demonstrated that patients with psoriasis have a significantly reduced life span. Given that patients with psoriasis are often unaware

of their comorbidities, they should be screened for these conditions and treated if required by their dermatologist and/or primary care physician. It is important to keep in mind that the comorbidities and drugs used to treat them have an impact on the choice of antipsoriatic treatment. In addition, comorbidities often preclude the use of traditional systemic agents. Recent studies have demonstrated that patients with preexisting comorbidities can be safely and effectively treated with biologic therapy. Furthermore, literature is evolving to suggest that better control of psoriasis might decrease cardiovascular mortality and prolong life (Guenther & Gulliver, 2009). In Taiwan, 51,800 psoriasis cases were identified (prevalence: 0.235%) and 17.5% of cases were severe psoriasis type. Psoriasis was associated with a significantly increased prevalence ratio (RR) for hypertension (1.51), diabetes (1.64), hyperglyceridaemia (1.61), heart disease (1.32), hepatitis B viral infection (1.73), hepatitis C viral infection (2.02), rheumatoid arthritis (3.02), systemic lupus erythematosus (6.16), vitiligo (5.94), pemphigoid (14.75), pemphigus (41.81), alopecia areata (4.71), lip, oral cavity and pharynx cancer (1.49), digestive organs and peritoneum cancer (1.57), depression (1.50), fatty liver (2.27), chronic airways obstruction (1.47), sleep disorder (3.89), asthma (1.29), and allergic rhinitis (1.25). Conversely, psoriasis was not associated with an increased risk of Crohn's disease. Psoriasis was associated with a significantly increased risk of comorbidities, especially for those patients with moderate to severe disease (Tsai et al., 2011).

Epidemiological studies have shown that, in patients with psoriasis, associated disorders may occur more frequently than expected. Such comorbidities include PsA, inflammatory bowel disease, obesity, diabetes, and cardiovascular disease (CVD), several cancer types, and depression. Comorbidities often become clinically manifest years after onset of psoriasis and tend to be more frequently seen in severe disease (Naldi & Mercuri, 2010). In particular, nonalcoholic fatty liver disease affects about 50%, Crohn's disease 0.5% and celiac disease 0.2 to 4.3% of patients with psoriasis. The presence of comorbidities has important implications in the global approach to patients. In particular, traditional systemic antipsoriatic agents could negatively affect cardio-metabolic comorbidities as well as nonalcoholic fatty liver disease and may have important interactions with drugs commonly used by psoriasis patients. Moreover, patients with psoriasis should be encouraged to drastically correct their modifiable cardiovascular and liver risk factors, in particular obesity, alcohol consumption, and smoking habit, because this could positively affect psoriasis, PsA and their life expectance (Gisondi et al., 2010). Clinical measures of disease activity were related to fatigue over time; however, these relationships disappeared in the context of patient reported physical disability and pain. Patient reported measures of physical disability, pain, and psychological distress were most closely related to higher "Modified Fatigue Severity Scale" (mFSS) scores (greater fatigue) across clinic assessments. Fatigue was found to vary over time, at least when assessed at yearly intervals. In general, measures of clinical and functional status at the current visit were more predictive of change in mFSS scores in between previous and current visits than change scores between visits. Comorbid fibromyalgia and hypertension were also associated with greater fatigue across multiple visits and with change in fatigue between visits. A combination of factors is associated with fatigue in PsA (Husted et al., 2010) .

Higher percentage frequency in PsA than psoriasis patients was found in hypertension, vascular diseases, intestinal diseases, infections, gastritis, cardiac arrhythmia, gallstones in gallbladder, osteoporosis, hyperuricemia and epilepsy. Up to 7-8 comorbidities were found in both psoriasis and PsA patients together in the same subject, thus, psoriasis is a systemic

disease, induced by cytokines in all body organs, being expressed in each tissue according to genetic and environmental factors due to shared inflammatory pathways. Development of psoriasis and PsA is centered in the blood vessels behavior. Both diseases start by proliferation of blood vessels after up-regulation of VEGF, TGFβ and other angiogenic factors. Clinical remission in psoriatic lesions also starts by decrease proliferation of blood vessels, after treatment with leishmania antigens (O'Daly, 2011, manuscript in press).

4.1 Cardiovascular disease

Psoriasis and atherosclerosis are interrelated; pathogenic mechanisms are shared between the two diseases inducing inflammation. Within the lymph nodes, antigen-presenting cells activate naive T-cells to increase expression of LFA-1 following which activated T-cells migrate to blood vessel and adhere to endothelium. Extravasation occurs mediated by LFA-1, LFA-3 and ICAM-1 or CD2. Activated T-cells interact with dendritic cells, macrophages and keratinocytes in psoriasis or with smooth muscle cells in blood vessels, in atherosclerosis. These cells further secrete chemokines and cytokines that contribute to the inflammatory environment, resulting in the formation of psoriatic plaque or atherosclerotic plaque (Ghazizadeh et al., 2010). Patients with psoriasis are at increased risk for severe vascular disease (Shelling *et al.*, 2008). This increased risk is imparted by both a predilection for patients with psoriasis to have traditional vascular disease risk factors like diabetes, hypertension, smoking, dyslipidemia (Federman *et al.*, 2009) and the recognition that psoriasis itself is an independent risk factor for vascular disease (Gelfand *et al.*, 2011). The latter is probably mediated by systemic inflammation associated with psoriasis, similar to that observed in patients with rheumatoid arthritis. Patients whose psoriasis develops at a young age and those with more severe disease are at the greatest risk (Gelfand *et al.*, 2011). Initial psoriasis comorbidity studies focused on cardiovascular disease, but atherosclerosis is a systemic disease (Prodanovich *et al.*, 2009). It is reasonable to postulate that if the likelihood of myocardial infarction is increased in patients with psoriasis, other manifestations of atherosclerosis, such as stroke, might also be more common in these patients. Stroke is a leading cause of mortality, and many who survive experience functional disability, with up to 30% being permanently disabled and 20% requiring institutional care (Rosamond *et al.*, 2008; Rico et al., 2009). A cohort study of patient's ≥18 years from 1987 to 2002, were analyzed. Patients with a psoriasis code and a history of systemic therapy consistent with severe psoriasis (n=3603) were compared with patients with no history of psoriasis (n=14,330). Patients with severe psoriasis were at increased risk of death from cardiovascular disease hazard ratio (HR) (1.57), malignancies (1.41), chronic lower respiratory disease (2.08), diabetes (2.86), dementia (3.64), infection (1.65), kidney disease (4.37), and unknown/missing causes (1.43). The absolute and excess risk of death was highest for cardiovascular disease (61.9 and 3.5 deaths per 1000 patient-years, respectively). Severe psoriasis is associated with an increased risk of death from a variety of causes, with cardiovascular death being the most common aetiology (Abuabara et al., 2010).

Psoriasis patients of a health-maintenance organization were compared with enrollees without psoriasis regarding the prevalence of hypertension in a case-control study. The study included 12,502 psoriasis patients over the age of 20 years and 24,285 age- and sex-frequency-matched controls. The prevalence of hypertension was significantly higher in psoriasis patients than controls (38.8% vs. 29.1%, respectively). In a multivariate analysis, hypertension was associated with psoriasis after controlling for age, sex, smoking status,

obesity, diabetes, non-steroidal anti-inflammatory drugs (NSAIDs) and use of Cox-2 inhibitors (odds ratio: 1.37). The results of this study support the previously noted association between psoriasis and hypertension (Cohen et al., 2010).

Treatment with multiple anti-hypertensives was significantly associated with the presence of psoriasis using univariate and multivariable analysis, after adjusting for diabetes, hyperlipidemia, and race. Compared to hypertensive patients without psoriasis, psoriasis patients with hypertension were 5 times more likely to be on a monotherapy antihypertensive regimen, 9.5 times more likely to be on dual antihypertensive therapy, 16.5 times more likely to be on triple antihypertensive regimen, and 19.9 times more likely to be on quadruple therapy or centrally-acting agent in multivariable analysis, after adjusting for traditional cardiac risk factors. Psoriasis patients appear to have more difficult-to-control hypertension compared to non-psoriatic, hypertensive patients (Armstrong et al., 2011).

The cardiovascular risk factors in patients with psoriasis and the association between psoriasis and coronary artery, cerebrovascular, and peripheral vascular diseases was examined. Similar to previous studies, it was found higher prevalence of diabetes mellitus, hypertension, dyslipidemia, and smoking in patients with psoriasis. After controlling for these variables, a higher prevalence not only of ischemic heart disease but also of cerebrovascular and peripheral vascular diseases in patients with psoriasis compared with controls. Psoriasis was also found to be an independent risk factor for mortality. Psoriasis is associated with atherosclerosis. This association applies to coronary artery, cerebrovascular, and peripheral vascular diseases and results in increased mortality (Prodanovich et al., 2009). Patients with psoriasis (N = 4752) between 1999 and 2001 and patients without a diagnosis of psoriasis (N = 23,760) who were matched by age and sex to the patients with psoriasis were analyzed. Of the total sample, 70 patients (0.2%) had acute myocardial infarct (AMI) during the 5-year follow-up period: 22 (0.5% of the patients with psoriasis) from the study cohort and 48 (0.2%) from the comparison cohort. The hazard of AMI during the 5-year follow-up period was 2.10 times greater for patients with psoriasis than for comparison patients (Lin et al., 2011).The event rates and rate ratios (RRs) of cardiovascular death, myocardial infarct (MI), coronary revascularization, stroke and a composite of MI, stroke and cardiovascular death were increased in patients with psoriasis. The RRs increased with disease severity and decreased with age of onset. The risk was similar in patients with severe skin affection alone and those with PsA (Ahlehoff et al., 2010). Patients with psoriasis have an increased prevalence of major cardiovascular (CV) risk factors and a clinically significant increased risk of myocardial infarction, stroke, and CV death that is independent of conventional risk factors (Gelfand *et al.*, 2011). These epidemiological studies have led to the recognition that psoriasis may be a systemic inflammatory disorder (Davidovici *et al.*, 2010). Two recent studies have added to this previously summarized literature. First, Ahlehoff *et al.* (2010), in a nationwide Danish study of 34,371 people with mild psoriasis and 2,621 with severe psoriasis, demonstrated independent risk ratios (RRs) for CV death of 1.14 and 1.57 respectively, with the greatest increase in young people ages 18–50, RR 2.98, with severe disease. The authors also compared CV risks in patients with severe psoriasis with the risks in patients with diabetes mellitus and found comparable increases in major adverse CV events and CV deaths in these groups, demonstrating the clinical importance of the risk of CV disease attributable to psoriasis. Other recent studies have investigated the clinical

significance of CV risk in patients with severe psoriasis, demonstrating that these patients have about a 6-year reduction in life expectancy and that excess risk of CV death is the largest contributor to this premature mortality (Abuabara *et al.*, 2010; Gelfand et al., 2011)

4.2 Metabolic syndrome

Psoriasis is associated with metabolic syndrome, cardiovascular disease, and osteoporosis and may be considered a systemic disease (Nijsten & Wakkee, 2009). The metabolic syndrome is the constellation of abdominal obesity, dyslipidemia, hypertension and insulin resistance. Presence of the metabolic syndrome significantly increases a patient's risk for cardiovascular disease, stroke and type II diabetes. Recent studies have found that psoriasis patients are at increased risk for metabolic syndrome as well as the individual components of metabolic syndrome, and the two diseases appear linked through a common mechanism of inflammation. Psoriasis treatments have been shown to reduce the risk of developing metabolic syndrome components and comorbidities (Alsufyani et al., 2010). The prevalence of obesity in psoriatic patients within the "Utah Psoriasis Initiative" (UPI) population was higher than that in the general Utah population. Obesity appears to be the consequence of psoriasis and not a risk factor for onset of disease. It was not observed an increased risk for PsA in patients with obesity; furthermore, obesity did not affect the response or adverse effects of topical corticosteroids, light based treatments, and systemic medications. The prevalence of smoking in the UPI population was higher than in the general Utah population and higher than in the non-psoriatic population. It was found a higher prevalence of smokers in the obese population within the UPI than in the obese population within the Utah population (Herron et al., 2005)

5. Psoriasis treatments

Psoriasis is an inflammatory skin disease with a chronic relapsing course. In about 20%–30% of psoriatic patients, disease severity requires systemic treatment, which carries a huge economic and management burden for the healthcare system. The decision to employ systemic treatment, reserved for severe or extensive forms, needs to be weighed carefully and is influenced by factors from the host. Traditional treatments like: photochemotherapy, cyclosporin A, methotrexate, and acitretin, should be evaluated for each specific clinical condition (Altomare et al., 2009). Psoriasis is important to the clinician because it is common and has treatment implications beyond the care of skin lesions. It is important to the physician-scientist because it serves as a model for studies of mechanisms of chronic inflammation. It is important to the clinical-trial investigator because it is increasingly a first-choice disease indication for proof-of-principle studies of new pathogenesis-based therapeutic strategies. In recent years, advances have been made in elucidating the molecular mechanisms of psoriasis. However, major issues remain unresolved, including the primary nature of the disease as an epithelial or immunologic disorder, the autoimmune cause of the inflammatory process, the relevance of cutaneous versus systemic factors, and the role of genetic versus environmental influences on disease initiation, progression, and response to therapy. (Nestle et al., 2009). Psoriasis may lead to disability and significant effects on patients' quality of life. A challenge in psoriasis management is to use an effective therapy early in the disease course in order to achieve a safe and well tolerated maintenance of remission with an improvement of both skin and joint manifestations. Recent advances in

knowledge of the pathogenesis of psoriasis helped develop targeted treatment options that may be effective and well tolerated over long periods of administration, thus improving the patient's quality of life. These biologic agents specifically target tumor necrosis factor-α (infliximab, etanercept, and adalimumab) or T cells (efalizumab) (de Felice et al., 2009).

Immune modulating therapies gain increasing importance in treatment of patients with autoimmune diseases such as psoriasis. None of the currently applied biologics achieves significant clinical improvement in all treated patients. In an open label study, 20 psoriasis patients were treated weekly with Alefacept over 12 wk. Transcription of the tolerance-associated gene (TOAG-1) is significantly up-regulated whereas receptor for hyaluronic acid mediated migration (RHAMM) transcription is down-regulated in PBMCs of responding patients before clinical improvement. TOAG-1 is exclusively localized within mitochondria. Overexpression of TOAG-1 in murine T cells leads to increased susceptibility to apoptosis. Addition of Alefacept to stimulated human T cells in vitro resulted in reduced frequencies of activated CD137+ cells, increased TOAG-1 but reduced RHAMM expression. This was accompanied by reduced proliferation and enhanced apoptosis. Inhibition of proliferation was dependent on enhanced PDL1 expression of APCs. Thus, peripheral changes of TOAG-1 and RHAMM expression can be used to predict clinical response to Alefacept treatment in psoriasis patients. In the presence of APCs Alefacept can inhibit T cell activation and survival by increasing expression of TOAG-1 on T cells and PDL1 on APCs (Keeren et al., 2009).

People with mild to moderate chronic plaque psoriasis after 3 months had no significant difference in the reduction PASI score between classic acupuncture vs. sham acupuncture (Jerner et al., 1997). Significantly more people (64%) having a thermal bath (bicarbonate, calcium, and magnesium rich water) had improvement in PASI score at 3 months compared with people (11%) having tap water bath (Zumiani et al., 2000).

All the data from here on have been referenced in a deep analysis of treatments for psoriasis performed in an excellent review by Naldi & Rzany, 2009, a summary follows: Fish oil and effects of psychotherapy reported inconclusive results with chronic plaque psoriasis. Tazarotene, a topical retinoid, may be more effective in the short term (6–12 weeks) at improving symptoms of mild to moderate chronic plaque psoriasis. Vitamin D derivatives (topical) were more effective at improving psoriasis severity scores at 3–8 weeks. Different types of vitamin D derivatives compared with each other revealed Calcipotriol may be more effective than tacalcitol and calcitriol at reducing psoriasis severity scores at 8 weeks. Calcipotriol may be more effective at prolonging time to relapse in people with stable psoriasis for at least 3 months after prior treatment with methotrexate for 6 months. Dithranol may be more effective at improving psoriasis severity scores at 4–8 weeks. Emollients plus UVB radiation compared with UVB alone and oil-in-water emollient plus UVB radiation may temporarily be more effective at improving psoriasis at 12 weeks. There is consensus that they are effective, and are mostly used initially or as adjunctive treatment in people with chronic plaque psoriasis. Salicylic acid may be no more effective at improving psoriasis severity scores at 3 weeks. There is consensus that keratolytics are a useful adjunct to other treatments for psoriasis Topical corticosteroids applied less frequently may be more effective at maintaining clear or nearly cleared areas at 6 months but they may cause striae and atrophy, which increase with potency and use of occlusive dressings. Continuous use may lead to adrenocortical suppression, and case reports suggest

that severe flares of the disease may occur on withdrawal. Coal tar plus fatty acids is no more effective at 8 weeks at improving composite scores for erythema, desquamation, and infiltration in people with mild to moderate chronic plaque psoriasis. Goeckerman treatment compared with UVB irradiation alone. Goeckerman treatment (daily application of coal tar followed by UVB irradiation) may be no more effective at improving response rates in people with chronic plaque psoriasis. Compared with no intervention Heliotherapy may be more effective at improving symptom severity scores at 1 year in people with all forms of chronic plaque psoriasis severities. There is consensus that heliotherapy is an effective option for most people with chronic plaque psoriasis. Different doses of psoralen in PUVA regimens compared with each other. Higher doses of psoralen are more effective at increasing clearance of lesions in people with severe psoriasis. Maintenance treatment with PUVA is more effective at reducing relapses at 18 months in people whose psoriasis has been cleared with prior PUVA treatment. Long-term adverse effects of PUVA treatment include photoaging and skin cancer, mainly squamous cell carcinoma. Narrowband UVB and broadband UVB may be equally effective at increasing clearance rates. Twice-weekly and three times-weekly administration of ultraviolet light are equally effective at increasing clearance rates, but twice-weekly treatment prolongs the time to reach clearance in people with mild to moderate psoriasis. Compared with placebo UVA sun bed treatment may be more effective than visible light at improving psoriasis severity scores in people with mild to moderate chronic stable plaque psoriasis. Alefacept is more effective at increasing the proportion of people with a reduction in psoriasis severity scores at 12 weeks. The FDA issued a Medical Product Safety Alert to inform people that alefacept reduces CD4+ T lymphocyte counts and should not be given to people with HIV. Efalizumab is more effective at increasing the proportion of people who achieve an improvement in psoriasis severity scores at 12 weeks in moderate to severe psoriasis. The FDA issued a warning about Raptiva (efalizumab) to healthcare professionals and patients about reports of immune mediated haemolytic anaemia, and warnings regarding post-marketing reports of thrombocytopenia and serious infections including necrotising fasciitis, tuberculous pneumonia, bacterial sepsis with seeding of distant sites, severe pneumonia with neutropenia, and worsening of infection (e.g. cellulitis, pneumonia) despite antimicrobial treatment. Raptiva (efalizumab) has a potential risk of developing progressive multifocal leukoencephalopathy. Efalizumab is a humanised monoclonal antibody which targets the CD11a component of lymphocyte function-associated antigen-1. It is a relatively new drug for the treatment of psoriasis. Efalizumab has been associated in some cases with fatal brain infections and has been withdrawn from the market (Major, 2010). Etanercept is more effective at increasing the proportion of people with improved psoriasis severity scores at 12–24 weeks in people with moderate to severe psoriasis. A drug safety alert has been issued on the risk of opportunistic fungal infections of lymphoma and other malignancies in children and adolescents associated with TNF-α blockers, which could be fatal. Etanercept is a recombinant molecule consisting of the human TNF-α p75 receptor fused to the Fc portion of the human immunoglobulin G1 molecule.

Infliximab is more effective at increasing the proportion of people who achieve an improvement in psoriasis severity scores at 10 weeks in people with moderate to severe psoriasis. A drug safety alert has been issued on the risk of opportunistic fungal infection of lymphoma and other malignancies in children and adolescents, and the risks of leukaemia and new onset psoriasis. Infliximab is a monoclonal antibody that binds to and inhibits the

activity of TNF-α. Compared with placebo Adalimumab is more effective at increasing the proportion of people with moderate to severe psoriasis who achieve an improvement in severity scores at 12 weeks. Drug safety alerts have been issued on the risk of hepatosplenic T-cell lymphoma associated with adalimumab and the risk of opportunistic fungal infections associated with TNF-α which could be fatal. A drug safety alert has been issued on the increased risk of lymphoma and other malignancies in children and adolescents, and the risks of leukaemia and new onset psoriasis, associated with TNF-α blockers. Ciclosporin may be more effective at 10 weeks at increasing lesion clearance and at reducing psoriasis severity scores in people with severe psoriasis. Conventional oil-based ciclosporin and microemulsion preconcentrate are equally effective at increasing the proportion of people achieving a marked response. Ciclosporin is more effective at increasing the proportion of people who remain in remission. Ciclosporin has been associated with hypertension, renal dysfunction and increased risk of malignancies for up to 5 years. Ciclosporin is an established treatment option for moderate to severe psoriasis. Relapses are often seen on withdrawal, and long-term treatment is limited by adverse effects. Dimethylfumaric acid alone or mixed with monoethyl fumaric acid may be more effective at 16 weeks at reducing psoriasis severity scores in people with severe psoriasis. Oral fumaric acid plus calcipotriol may be more effective at improving psoriasis scores at 13 weeks in people with severe chronic plaque psoriasis. Fumaric acid esters have been associated with flushing and with gastrointestinal symptoms.

Methotrexate may be more effective at reducing the surface area of psoriasis at 12 weeks in people with psoriatic arthritis, but has been associated with acute myelosuppression. Long-term methotrexate carries the risk of hepatic fibrosis and cirrhosis, which is related to the dose regimen employed. People using methotrexate are closely monitored for liver toxicity and are advised to limit their consumption of alcohol. The most reliable test of liver damage remains needle biopsy of the liver. When treatment was stopped, 45% of people experienced a full relapse within 6 months. Acitretin and etretinate are equally effective at increasing the proportion of people who achieve a marked improvement as measured by a reduction in psoriasis severity scores. Teratogenicity renders oral retinoids less acceptable. Etretinate is no longer available in many countries. Leflunomide may be more effective in people with psoriatic arthritis at increasing the proportion of people with a reduction in psoriasis symptom severity scores at 24 weeks. Leflunomide significantly increased the proportion of people with at least a 75% improvement in PASI but had diarrhoea (24% with leflunomide vs. 13% with placebo). More people taking leflunomide had increased liver enzymes and tiredness lethargy (alanine transaminase increase of at least 2 times the upper limit of normal:12% with leflunomide v 5% with placebo; tiredness/lethargy: 6% with leflunomide vs. 1% with placebo). Pimecrolimus significantly improved PASI at 12 weeks, but with higher rates of gastrointestinal disorders, pruritus, and paraesthesia in the pimecrolimus groups compared with the placebo group (Naldi & Rzany, 2009).

5.1 Treatment with drug product Leismania amastigotes vaccine

While treating subjects in Venezuela with a vaccine containing *Leishmania* amastigotes antigens for prevention of cutaneous leishmaniasis (CL), (O'Daly et al., 1995a, 1995b) we observed 100% clinical remission of a psoriatic lesion in one subject, a natural double blind

serendipity finding. A first generation polyvalent vaccine (AS100-1) was manufactured with protein from four cultured *Leishmania* species: *L(L)amazonensis, L(V)brasiliensis, L(L)chagasi and L(L)venezuelensis* (O'Daly et al., 2009a).

5.2 Characterization of the amastigotes drug product

Protein test samples from the amastigote extracts of the four *Leishmania* spp. present in AS100-1 were tested for the presence of Leishmania DNA. PCR reactions for amplification of the variable regions of kDNA minicircles of Leishmania were performed to confirm the absence or presence of parasite DNA in the polyvalent AS100-1 final drug product. DNA isolated from Leishmania amastigote parasites were used as positive controls. No PCR product was detected in the AS100-1 protein samples. As expected, agarose gel electrophoresis of the 610 and 116pb fragments showed presence of DNA in the positive controls. Additional PCR sequencing from the positive controls showed 92% identity with the kinetoplast DNA minicircles. Lipophosphoglycan (LPG) is a glycoconjugate present on metacyclic promastigotes, which functions as a virulence factor in all *Leishmania* spp. The final product of amastigotes extracts after TLCK treatment and NP40 surface antigen extraction, had 10 ng/m or less of LPG. The acceptable endotoxin limit for the drug substance was 700 EU/ml. A sample of the drug substance was screened for endotoxin content with results <50 EU/ml but >25 EU/ml. well below the acceptable limit. BSA was between 12.5 and 25.0 ng/ml, evidence that no fetal bovine serum (FBS) proteins from the culture medium were present. SDS acrylamide gels of AS100-1 drug product under reducing conditions exhibited 23–30 bands from 112.0 to 10.0 kDa molecular weight in the four *Leishmania* spp.; 21 bands (70%) with similar molecular weights (value variations 1% or less) in all lots. The percent homology between lots of the same specie was *L(L)amazonensis* 96.6%; *L(V)brasiliensis* 86.7%; *L(L)chagasi* 95.8%; *L(L)venezuelensis* 91.3% (O'Daly et al., 2009a).

5.3 Clinical trial with amastigote antigens vaccine

A double-blind, placebo-controlled, parallel group study, of multiple doses of AS100-1 was performed on psoriatic subjects, to confirm safety and efficacy. Treatment of plaque psoriasis, was conducted in 2,770 volunteers and included plaque (79%), guttate (10%), plaque and guttate (10%), palm/plantar (0.3%), erythrodermia (1.8%), inverse (0.8%), plaque and arthritis (3.4%) and nail psoriasis (0.3%). Eficacy of AS100-1 was assessed by performing skin examinations and recording psoriasis area and severity index (PASI) parameters at each visit. The primary eficacy parameters were the percentage reduction in PASI score at each visit and the comparative proportions of subjects with 100, 75 and 50% PASI improvement in each treatment group. The lesions and the extent of body surface area involved were measured separately for the head (Ah), trunk (At), upper extremities (Au) and lower extremities (Al). The PASI combines lesion measurements of the skin erythema, (E, redness), skin induration (I, thickness) and skin desquamation (D, scaliness) of the lesions. Each sign in the lesion was quantified as follows: 0 none, 1 slight, 2 mild, 3 moderate and 4 severe. The extent of body surface area affected was evaluated as follows: 1 < 10%, 2 = 10–30%, 3 = 30–50%, 4 = 50–70%, 5 = 70–90%, 6 > 90%. For evaluation purposes, the weighted contribution of each section of the body to the total body surface area is as follows, the head 10%, the thorax 30%, the upper extremities 20% and the lower extremities 40%. To calculate disease severity, the following formula was applied: PASI = 0.1(Eh + Ih + Dh)Ah + 0.3(Et + It +

Dt)At +0.2(Eu + Iu + Du)Au + 0.4(El + Il + Dl)Al. PASI scores rise or fall in units of tenths (0.1) and range from 0.0 to 72.0. A score of 0.0 indicates absence of lesions, while a score of 72.0 represents the malignant form of the disease (erythrodermia). Body surface area involvement of over 10% or a PASI score greater than 10.0–12.0 is used as a criterion for severe disease. Percent PASI reduction was calculated as follows: (PASI at base line—PASI at each visit)/PASI at baseline* 100. Baseline PASI compared with post-treatment values were: PASI 100, 23%; PASI 75, 45%; PASI 50, 13%; PASI 10, 9%; <PASI 10, 3% while 7% quit treatment. Of the 648 subjects (23%) who experienced total remission of lesions, 188 (29%) had relapses of their disease after 15.4 months. The PASI values at the time of the first relapse were 7.7 units, one-third of the PASI value (21.0 units) recorded before any treatment. The new remission occurred with 7.1 doses of AS100 after 5.8 weeks, a shorter time period than initially observed in the first treatment cycle for clinical remission of lesions. In the relapsing group, 161 of the 188 subjects (85.6%) experienced new remission of lesions after six to seven doses of AS100 (O'Daly et al., 2009a).

There were no serious adverse events attributed to the treatment drug. Some patients with PsA benefited after treatment (see below). Of the 2,770 subjects treated in the open label psoriasis study, a random group of 108 subjects was selected for antibody screening. The test group included a positive control group with active CL, a negative control group before treatment and subgroups with one to six doses of the immunotherapeutic agent. All subjects received 500 μg/dose of AS100-1. The concurrent negative control group (n = 36) consisted of psoriatic subjects, prior to any AS100-1 treatment, with no previous history of Leishmania infection, no prior exposure to AS100-1 and with a negative delayed type hypersensitivity (DTH) to Leishmania antigens. All subgroups with one to six doses of AS100-1 in the treatment group had the same results as the negative control group, exhibiting antibody values between 30 and 87 ng/ml; well below 100 ng/ml, the cutoff value to consider a reaction as positive. It is also interesting to note that after four doses of AS100-1, all subjects had undetectable levels of antibodies (ELISA), but a positive DTH cellular response to AS100-1 after intradermic reaction (IDR) ≥10 mm in diameter with Leishmania antigens. These results suggest that the AS100-1 drug product does not induce significant humoral immunity but a strong cellular immunity. Approximately 2,289 subjects (83%) experienced at least one adverse event (AE). The most frequent AE were injection site related, and included the following, pain 43%, nodule formation 23%, heat 21% and erythema 14%. The injection sites were assessed after each administration of the study drug. Injection site related AE, were relatively short lived, lasting between 24 to 72 h. The types of systemic AE and their rates of occurrence were as follows: fever 18%, general discomfort 12%, a flulike syndrome 11%, pruritus 8%, sleepiness 8%, accidental injury 8%, cough 6%, dizziness 6%. AE attributed to the treatment drug were rated mild or moderate in severity, with none being classified as serious. The few severe adverse events that occurred were attributed to other diseases, the subjects were experiencing while participating in the study trial. There were no age or gender diferences observed for AE, and no deaths occurred during the study. All adverse events resolved without intervention, usually within 24–72 h. (O'Daly et al., 2009a).

To determine the effective factor, a single blind trial with four monovalent second generation vaccines (AS100-2) was performed. The AS100-2 trial was a single blind AS100-1 controlled trial with four treatment groups one for each AS1002 vaccine (AS1002-amazonensis, AS1002-brasiliensis, AS1002-chagasi, and AS1002-venezuelensis). The trial included 26 subjects, 58% females, average 43.8±16.4 years old, and age range 8–76 years,

initial PASI 10.2± 6.6 units, time with psoriasis 12.2±13.1 years. The treatment subjects received 500 µg/ dose injections of AS100-2 and control subjects received 500 µg/dose of AS100-1. The results achieved with monovalent AS100-2 produced reductions in psoriatic lesions similar to those induced by polyvalent AS100-1. AS100-2 vaccines were further purified, resulting in seven chromatography fractions (AS200) per species. AS100-2, and AS200 final product, gave the following results for LPG and endotoxin: LPG: 10 ng/ml or less; Endotoxin: <50 EU/ml but >25 EU/ml. Parasitic DNA was absent in all products and BSA was between 12.5 and 25.0 ng/ml, basically within the same range, as previously published AS100-1 values. No carbohydrates were found in AS100-1, AS100-2 or Lb fractions by HPLC analysis or staining of gels with PAS-SCHIFF (O'Daly et al., 2009b).

Subsequently, a single-blind trial in 55 subjects treated with a third generation vaccine AS200 prepared with seven DEAE chromatography fractions from *L(V)brasiliensis* was performed. The AS200 study was a single-blind, AS100-1 controlled trial, with a seven arm treatment group, one for each AS200 (Lb) vaccine. The AS200 trial included 53 subjects, 62% females average 40.6±18.6 years old, age range 7–78 years of age, initial PASI 26.4±19.2, time with psoriasis 15.0±12 years.The treatment subjects received four 200 µg/dose injections of AS200 (Lb) and control subjects received four 500 µg/dose of AS100-1. However, treatment with the vaccine containing fraction 7 was discontinued due to general discomfort and psoriasis flare subsequent to vaccination in one subject. All subjects had PASI scores determined prior to treatment, prior to each injection, and at follow-up for 2 weeks after the last injection. All AS200 (Lb) vaccines induced PASI reductions in the same range as the active control. Protein (DEAE) fractions 2, 3, 4, and 5 had similar values and induced the highest in vitro lymphocyte stimulation index (SI) values in peripheral blood mononuclear cells (PBMC) from post-treatment PASI100% reduction subjects, with no statistical differences among them. The same fractions, from *L(V)brsiliensis* and *L(L)chagasi s*pecies, also yielded the highest IDR diameter in DTH screenings. All leishmania DEAE fractions stimulated lymphocytes from PBMC from patients in vitro, after vaccination wit AS100-1, none were immunosuppressors, contrary to all treatment in the market today (O'Daly et al., 2009b).

Long-term heat shock proteins (Hsp) confrontation of the immune system similar in the host and invaders may convert the immune response against these host antigens and promote and/or decrease autoimmune diseases including psoriasis (Boyman et al., 2005; Rajesh Rajaiah & Moudgil, 2009; Rambukkana et al., 1993). There is evidence that recognition of self-Hsp60 can have beneficial effects in arthritis and may offer new strategies for improved control measures in the inflammatory processes by administration of peptides cross-reactive to self-determinants (Zügel & Kaufmann, 1999). Hsp60, Hsp70, Gp96 function as host-derived ligands for toll like receptors (TLR2), and have been described to play a role in the pathogenesis of RA and psoriasis (Rajesh Rajaiah & Moudgil 2009). Leishmania antigens are produced after a heat shock in promastigotes that become amastigotes in a liquid culture medium (O'Daly & Rodríguez, 1988). The molecular weight of AS200 is similar to the range of most Hsp host ligands (50–70 kDa) and could be inhibiting the symptoms of psoriasis, psoriatic arthritis and CIA by competing with peptides in the respective receptors (O'Daly et al., 2009a, 2009b, 2010a, 2011).

Two male subjects, both HIV+; 36 and 41 years of age, with plaque psoriasis for 4 years in one subject and 7 months in the other were treated with AS100-1. Both subjects had no familial history of psoriasis, and were treated with AS100-1 concurrently with their

previously prescribed retroviral treatments. The AS100-1 treatment consisted of 500 µg/dose, injected in the deltoid area, every 2 weeks. Baseline PASI for one subject was 26.4 units, while the other subject presented with a baseline PASI of 32.4 units. Both subjects showed clinical remission of psoriasis after treatment with AS100-1. The hematologic values with respect to total lymphocytes (CD3, CD4, and CD8 cells) were lower than the values routinely found in healthy subjects. One subject had a relapse after the ninth dose and subsequently received a second course of treatment 3 weeks later. The second course resulted in clinical remission of the psoriatic lesions. Neither of these two subjects presented local adverse events nor did they present any systemic adverse events after vaccination (O'Daly et al., 2009b).

5.4 Cellular immunity in guinea pigs and regression of lesions in experimental Rheumatoid Arthritis model with amastigote antigens vaccine

AS200 *Leishmania* antigenic fractions induced linear DTH reactions in guinea pigs over a 1-40 µg dose range. This finding allowed us to build a potency assay for the drug product. Interestingly, RA, another autoimmune disease, shares several similarities with psoriasis and PsA. While some diseases lack acceptable animal models for adequate study, this is not the case with RA. Collagen induced arthritis (CIA) is an experimental animal model that has been used to dissect the pathogenesis of human RA. The model is dependent on activated T cells, is associated with both cell mediated and humoral immunity to collagen and can be induced upon immunization with heterologous collagen II (CII) or by monoclonal antibodies to CII combined with LPS in DBA/1 mice. When a DBA-1 mouse CIA model was used to compare AS200 treatment against: a polyvalent vaccine (AS100-1), a monovalent vaccine (AS100-2) and placebo, the AS200 treated mice had the least amount of forepaw inflammation and the lowest mean arthritis scores (O'Daly et al., 2010a).

5.5 Lympocyte subsets in peripheral blood monocuclear cells of psoriatic patients, before and after treatment with amastigote polyvalent vaccine

Peripheral blood mononuclear cells (PBMC) collected from subjects prior to treatment and post-treatment with AS100-1 were analyzed by flow cytometry. Lymphocyte subsets (LS) varied with PASI range (1-10, 11-20 and 21-72). Pretreatment absolute values of gated LS were as follows: CD4+CD8-, CD3+CD8-, CD8+CD3+, CD8+CD4- and CD8+HLA- decreased in PBMC as PASI increased, suggesting migration from the blood to the skin. Contrary to the previous finding, the following LS, CD8+HLA+, HLA+CD8-, CD8+CD4+, CD19, and membrane surface immunoglobulin IgA+, IgD+ and IgM+ increased in PBMC as PASI increased, suggesting activation and proliferation by unknown antigens in the skin lesions. After treatment with seven doses of AS100-1, the following LS, CD3+CD8-, CD8+CD3-, HLA+CD8-, CD8+HLA+ and CD4+CD8-, increased as PASI returns to normal values and psoriatic plaques disappeared, while CD8+CD3+, CD8+HLA-, CD19 and CD8+CD4+ decreased in PBMC suggesting lower sensitization in skin. Lymphocyte trafficking from blood to skin decreased significantly, stopping the vicious cycle as psoriasis lesions disappeared (O'Daly et al., 2010b). Previously we demonstrated that leishmania antigens induced T cell proliferation and absence of immunosuppression after stimulating PBMC from psoriatic patients with amastigote fractions. DTH positive reactions were found with isolated amastigote antigens in humans in vivo, after treatment

with AS100-1 polyvalent vaccine. These facts of *in vivo* and *in vitro* T cells stimulation (O'Daly et al., 2009b) suggest that variations in blood LS, before and after treatment in psoriatic subjects, is a function of lymphocyte trafficking from blood to skin and vice versa, as well as T cell activation in skin plaques, not to killing of T cells as has been described with current treatments used in psoriatic patients.

6. Psoriatic arthritis

The first description of PsA is attributed to Louis Aliberti, who in 1818 first noted the relationship between psoriasis and arthritis (O'Neill & Silman, 1994). Pierre Bazin then described "Psoriasis Arthritique" in 1860, followed by Charles Bourdillon in 1888 with "Psoriasis et Arthropathies". Jeghers and Robinson in 1937, and Vilanova and Piñol in 1951 described PsA as a unique entity (Vilanova & Pinol, 1951). All studies of PsA use the criteria by Moll and Wright in their classic paper published in 1973 (Moll & Wright, 1973) summarized as follows: A- presence of psoriasis, B- inflammatory arthritis and C- negative test for rheumatoid factor. The PsA subgroups described with these criteria were: 1- Distal interphalangeal (DIP) joint disease (5%); 2- Asymmetrical oligoarthritis (70%); 3- Polyarthritis (15%); 4- Spondylitis (5%); 5- Arthritis mutilans (5%), (Wright 1956, 1959a, 1959b). Gladman expanded the five sub-groups to seven: Distal disease (DIP only affected), oligoarthritis (<4 joints), polyarthritis, spondylitis only, distal disease plus spondylitis, oligoarthritis plus spondylitis and polyarthritis plus spondylitis (Gladman et al., 1987).

6.1 Psoriasis artritis epidemiology

Psoriasis is widely diffused in the World. Its average prevalence is about 3-4%. This is probably an underestimate, for it is mostly based on self-reports. In fact, on the one hand minimal psoriasis, e.g. nail disease, could remain undiagnosed; on the other, precise classification criteria for PsA are lacking and the skin disease is often of elusive nature. The frequency of PsA may be higher than commonly believed, as suggested by recent studies reporting a prevalence of up to 0.42%. There are no major differences in the frequency of psoriasis between sexes, or specific time trends (Cimmino, 2007). Prevalence of PsA varies from 5-40% in several trials. A large study conducted in the UK, Italy, France, Spain and Germany in 2006 found 8.1% prevalence of PsA in patients with psoriasis. Survival analysis indicated that the incidence of PsA among plaque psoriasis patients remained constant at 74 per 100 person-years, while the prevalence increased with time since diagnosis of psoriasis, reaching 20.5% after 30 years (Christophers et al., 2010). A population based study in Minnesota USA, reported the annual incidence of PsA per 100,000 to be 7.2. The incidence increased from 3.6 between 1970 and 1979, to 9.8 between 1990 and 2000, providing the first evidence that the incidence of psoriasis increased during recent decades (Wilson et al., 2009). A previous study from 1982-1992 in the same community revealed an incidence rate of 6.59% per 100,000 US population (Shbeeb et al., 2000). The prevalence and incidence estimates of psoriasis and PsA show ethnic and geographic variations, being generally more common in the colder north than in the tropics. In Europe the prevalence of psoriasis varies anywhere from 0.6 to 6.5%. In the USA, the prevalence of diagnosed psoriasis is 3.15%. The prevalence in Africa varies depending on geographic location, being lowest in West Africa. Psoriasis is less prevalent in China (Chang et al., 2009), and Japan than in Europe, and has not been described in natives of the Andean region of South America (Kim et al., 2010;

Gottlieb et al., 2008). The prevalence of PsA also shows similar variation, being highest in people of European descent and lowest in the Japanese. Although, study methodology and case definition may explain some of the variations, genetic and environmental factors are important (Lotti et al., 2010).

People with psoriasis were identified from the computerized morbidity indices of 2 large UK general practices, total population 22,500. Questionnaires were mailed to all 633 patients thus identified. Of the respondents, a 50% sample was assessed clinically and a proportion had blood samples and radiographs taken. Of these 93 people, 12 were thought to have PsA clinically, all fulfilling the CASPAR criteria for PsA. Six of the 93 examined patients did not have psoriasis or a family history of psoriasis and had no historical features or clinical signs of psoriasis on interview and examination. The estimated prevalence of PsA in this population, using the CASPAR criteria, was 13.8% (Ibrahim et al., 2009). Many challenges have made it difficult to determine the prevalence of spondyloarthritis (SpA) in North America. They include the ethnic heterogeneity of the population, the lack of feasibility of applying current criteria as human leukocyte antigen-B27 testing and pelvic radiographs and magnetic resonance imaging scanning, and the transient nature of some SpA symptoms like peripheral arthritis and enthesitis. Current estimates of the prevalence of SpA in the United States range between 0.2% and 0.5% for ankylosing spondylitis, 0.1% for psoriatic arthritis, 0.065% for enteropathic peripheral arthritis, between 0.05% and 0.25% for enteropathic axial arthritis and an overall prevalence of SpA as high as >1% (Reveille, 2011). A population-based study was conducted in two regions of the Czech Republic (with a total population of 186,000 inhabitants), on condition of confirming a definite diagnosis according to existing classification criteria during the study period (1 March 2002 to 1 March 2003). The age-standardized estimates of incidence and prevalence were calculated using the European standard population. The total annual incidence of PsA in adults aged ≥ 16 years was 3.6/100000 and the prevalence of PsA was 49.1/100000. The annual incidence of ankylosing spondylitis (AS) in adults was 6.4/100000 and the prevalence of AS was 94.2/100000. The annual incidence of reactive arthritis (ReA) in adults was 9.3/100000 and the prevalence of ReA was 91.3/100000. The annual incidence and prevalence rates of PsA, AS, and ReA compared well with data reported from other countries (Hanova et al., 2010). SpA includes a group of diseases that share immunogenetic, clinical and radiologic findings, with a particular involvement of the axial skeleton and the entheses. SpA patients attending ambulatory care in 11 rheumatology services located in 6 Argentine provinces were included in a prospective, observational multicentre cohort of SpA. A total of 402 patients were included; 59% were male, with median age of 48.3 years and median disease duration of 8 years. Eighty-six patients were diagnosed with AS, 242 with PsA, 25 with ReA, 10 with SpA associated with inflammatory bowel disease, 33 with undifferentiated SpA and 6 with juvenile AS (Buschiazzo et al., 2011). A cohort of 233 SpA patients, observed in 2 centers in Guatemala City, Guatemala, and in hospitals in San Salvador, El Salvador, and San José, Costa Rica was analyzed. Guatemalan patients were either from the clinic of Guatemalan Association against Rheumatic Diseases (n = 105) or from the private clinic of AGK (n = 78). El Salvador patients (n = 17) were from Hospital Instituto Salvadoreño del Seguro Social, and Costa Rican patients (n = 33) were from Hospital Calderón Guardia, San José, Costa Rica. Except for the Costa Rican data, which were published in 2007, the patients' medical records were analyzed using standardized questionnaires. Prevalence of SpA was slightly higher in females than males (57% versus 43%, respectively). The median age was 47.5 years.

Most of the patients were diagnosed with ReA or undifferentiated arthritis (47% and 33%, respectively); 10% of patients had AS and 9% PsA (García-Kutzbach et al., 2011).

During the period of 2006 to 2007, Twenty eight university centers in Brazil used a standardized protocol of investigation to study the epidemiological, clinical and radiological variables of 1036 consecutive patients with the diagnosis of SpA. Validated translated (Portuguese) versions of the Bath Ankylosing Spondylitis (AS) Disease Activity Index and the Bath AS Functional Index were applied. Patient diagnoses were predominantly AS (72.3%), followed by PsA (13.7%), undifferentiated SpA (6.3%), ReA (3.6%), juvenile SpA (3.1%) and arthritis related to inflammatory bowel disease (1.0%). There was a predominance of male (73.6%) and white (59.5%) patients. Pure axial disease was observed in 36.7% of the patients, whereas the mixed pattern (axial, peripheral and entheseal) was observed in 47.9%. The most common extra-articular involvement was anterior uveitis (20.2%). HLA-B27 was positive in 69.5% of the tested patients (Sampaio-Barros, 2011). The mortality in a cohort of 453 patients with PsA (232 men, 221 women) was analyzed. The sudden mortality rate (SMR) for the men was 67.87%, and for the women, 97.01% and the overall SMR for the PsA cohort was 81.82%.The leading causes of death in this cohort were cardiovascular disease (38%), diseases of the respiratory system (27%), and malignancy (14%).These results suggest that mortality in the single center PsA cohort is not significantly different from the general UK population (Buckley et al., 2010).

A wide variation on the incidence and prevalence of PsA has been reported in different countries. The prevalence in China was similar to the rest of the world, whereas the incidence and prevalence of PsA was much lower in Japan. Among patients with psoriasis, 6-42% of the Caucasians were reported to have PsA, but figures were lower from Asian countries (1-9%). Divergent distribution of HLA in different ethnic groups and other genetic determinants may account for these differences in prevalence. PsA affects men and women almost equally in Chinese, Japanese and Iranians, which is similar to their Caucasian counterparts. Polyarthritis developing in the fourth decade was the commonest pattern of arthritis among Chinese, Indians, Iranians, Kuwaiti Arabs and Malays. Arthritis mutilans and eye lesions have rarely been reported in Asian countries. Chinese patients with nail disease and DIP joints involvement have a significantly higher risk of developing deformed joints. Premature atherosclerosis has been recognized as an important comorbidity in Asian patients with PsA. Increased prevalence of traditional cardiovascular risk factors associated with PsA suggested that the two conditions may share the same inflammatory pathway. Carotid intima-media thickness can identify PsA patients with subclinical atherosclerosis who may benefit from early intervention (Tam et al., 2009)

6.2 Psoriatic arthritis in the clinic

Psoriatic systemic disease encompassing skin, joint and nail involvement is an autoimmune process as evidenced from animal models, the HLA-Cw6 association in man, T cells infiltration in lesional skin and the response to T cell targeted therapies. The nails and joints are associated with inflammation at points of ligament or tendon insertion (i.e., enthesitis). It has been postulated that response to tissue stressing of the integrated nail-joint apparatus, rather than autoimmunity, is driving the inflammatory process with a relative differential involvement of adaptive and innate immunity in the psoriatic disease (McGonagle et al., 2010). Nail fold psoriasis and DIP joint arthritis were associated with nail involvement and

were common in PsA patients. Nail psoriasis has been postulated to be related to the Koebner phenomenon and local inflammatory DIP joint arthritis, and probably indicative of distal phalanx enthesitis in PsA patients (Maejima et al., 2010).

PsA is classified as a SpA and characterized by synovitis, enthesitis, dactylitis, and spondylitis, usually manifesting in a person with skin and nail psoriasis. Our understanding about the PsA disease state, its genetics, pathophysiology, and comorbidities, as well as our ability to assess and treat the disease, has advanced as a result of significant collaborative efforts by rheumatologists and dermatologists (Mease, 2010a). For many years the concept of PsA as a separate disease entity was controversial, its importance has been underestimated. Dermatologists focus on psoriatic skin may overlook PsA due to its clinical heterogeneity or when only minor symptoms are present such as mild enthesitis or arthritis of DIP joints. Because skin lesions occur years before the manifestation of arthritis, however, it is likely that many patients are being seen by a dermatologist when PsA initially develops. A study among 1511 patients found 20% had PsA; in 85% of the cases, PsA was newly diagnosed. Of these patients more than 95% had active arthritis and 53% had five or more joints affected. Polyarthritis (58%) was the most common manifestation pattern, followed by oligoarthritis (31%) and arthritis mutilans (4%). DIP involvement was present in 41% and dactylitis in 23% of the patients. Compared with patients without arthritis, patients with PsA had more severe skin symptoms (mean PASI 14.3 vs. 11.5), a lower quality of life and greater impairment of productivity parameters (Reich et al., 2009). The Classification of Psoriatic Arthritis (CASPAR) study group was established for classification criteria for PsA. The CASPAR criteria comprised: 1- Evidence of psoriasis (a) Current psoriatic skin or scalp disease present today as judged by a rheumatologist or dermatologist (b) Personal history of psoriasis that may be obtained from patient (c) Family history of psoriasis in a first or second degree relative according to patient report, family doctor, dermatologist, rheumatologist or other qualified health-care provider. 2- Psoriatic nail dystrophy including onycholysis, pitting and hyperkeratosis observed on current physical examination. 3- A negative test for rheumatoid factor by any method except latex but preferably by ELISA or nephelometry. 4- Dactylitis: a) current swelling of an entire digit b) history of dactylitis recorded by a rheumatologist. 5- Radiological evidence of juxta-articular new bone formation as ill-defined ossification near joint margins (but excluding osteophyte formation) on plain X-rays of hand or foot. Using the CASPAR criteria, the combination of psoriasis and inflammatory arthritis gave 0.96 for sensitivity and 0.97 for specificity, respectively (Taylor et al., 2006; Chandran et al., 2007; Coates & Helliwell, 2008). The Toronto group evaluated the use of the CASPAR criteria in early disease and found a sensitivity of 99.1% in those patients with disease duration of less than 2.5 years and a sensitivity of 100% for those with disease duration of less than 12 months (Chandran et al., 2007). Both dactylitis and enthesitis are hallmark features of PsA, and dactylitis is a severity marker for the disease. Spinal disease in PsA is qualitatively and quantitatively different from classical AS, and a new scoring system combines elements of the "Bath Ankylosing Spondylitis Radiology Index" (BASRI) and "Modified Stoke AS Spinal Score" (mSASSS) to give a new modified index useful for definition of PsA types (Helliwell, 2009; Coates & Helliwell, 2010). The concept of SpA that comprises a group of interrelated disorders has been recognised since the early 1970s. While the European Spondyloarthropathy Study Group (ESSG) criteria and the Amor criteria have been developed to embrace the entire group of SpAs, new criteria for psoriatic arthritis have been developed recently. The CASPAR study, a large one of more

than 1000 patients, led to a new set of validated classification criteria for psoriatic arthritis. Since their publication in 2006 the CASPAR criteria are widely used in clinical studies. In AS, the 1984 modified New York criteria have been used widely in clinical studies and daily practice but are not applicable in early disease when the characteristic radiographical signs of sacroiliitis are not visible but active sacroiliitis is readily detectable by magnetic resonance imaging (MRI). This led to the concept of axial SpA that includes patients with and without radiographic damage. Candidate criteria for axial SpA were developed based on proposals for a structured diagnostic approach. These criteria were validated in the "Assessment of Spondyloarthritis International Society" (ASAS) study on new classification criteria for axial SpA, a large international prospective study. In these new criteria, sacroiliitis showing up on MRI has been given as much weight as sacroiliitis on radiographs, thereby also identifying patients with early axial SpA. Both the CASPAR and the ASAS criteria for axial SpA are likely to be of use as diagnostic criteria to define PsA types (Rudwaleit & Taylor, 2010). Early PsA is a condition with a consistent risk of clinical progression. Abundant entheseal involvement is a distinctive clinical aspect that helps discriminate early PsA from RA. Today its detection, followed by a rapid therapeutic intervention, predicts a better clinical outcome (Scarpa et al., 2009). Different to RA, the joint distribution in PsA tends to be asymmetrical and oligoarticular (< five joints). Distal joints, particularly the DIP joints of the hands, are more frequently affected; joint tenderness tends to be less; and dactylitis, enthesitis and axial or spinal involvement are more frequent. Unlike seronegative SpA, 40% of patients with PsA suffer from a sacroiliitis that tends to exhibit an asymmetrical rather than a symmetrical distribution. Other features of PsA include the absence of rheumatoid nodules, of rheumatoid factor in the blood and, in some instances, the presence of iritis, mucous membrane lesions, urethritis, bowel inflammation and tendonitis. PsA is often characterized by plain film evidence of juxta-articular new bone formation and magnetic resonance imaging evidence of enthesitis. Eighty per cent of cases are associated with psoriatic nail changes such as pitting, ridging, oil spots and nail plate thickening. Although PsA is preceded by cutaneous psoriasis in 75% of cases, in 10–15% of cases the arthritis precedes the psoriasis, suggesting that the two diseases may be controlled by different mechanisms or that a common etiology, may remains dormant in the synovial compartment. The mean time to onset of arthritis among those with pre-existing cutaneous psoriasis is 10 years, but delays have been reported of up to 20 years. Few instances of PsA without psoriasis have been described because most cases resembling PsA in the absence of personal or family history of skin disease are classified as an undifferentiated SpA (Ciocon & Kimball, 2007; Garg & Gladman, 2010). Patients with clinical symptoms and signs of PsA and a family history of psoriasis can be classified as having PsA *sine* psoriasis. The clinical spectrum of PsA *sine* psoriasis is broad. It is identified by dactylitis and/or DIP arthritis, HLA-Cw6, and a family history of psoriasis following the CASPAR criteria (Olivieri et al., 2009). Outcome measurement is a key part of study design but presents particular challenges in SpA. Enthesitis and dactylitis are typical features of SpA and validated scoring systems for both are available, although the majority of enthesitis outcome measures are validated in AS only. Assessment of axial disease is well researched in AS and composite outcome measures are routinely used. However, assessment of axial disease in predominantly peripheral arthritis, such as PsA, is problematic and under-researched. Extensive research in dermatology has provided multiple outcome measures for skin psoriasis. The PASI remains the most common outcome measure used, despite the fact that significant problems exist

with this scale and that newer scoring methods and modifications of the PASI show better validity. Nail psoriasis is accurately measured by detailed scoring systems but these can be time-consuming (Coates & Helliwell, 2010). The number of actively inflamed joints as measure of disease activity and the number of clinically deformed joints as measure of damage were significantly related to the "Health Assessment Questionnaire" (HAQ) score also useful for defining PsA types. Furthermore, interaction terms for illness duration with the number of actively inflamed joints were statistically significant, with or without inclusion of the erythrocyte sedimentation rate and morning stiffness in the model. The influence of disease activity on HAQ scores declines with increased disease duration (Husted et al., 2007).

Patients with psoriasis from 13 dermatological hospitals and 129 dermatological private practices and outpatient clinics in Germany revealed that nineteen per cent of the patients had PsA, including 14.8% previously confirmed and 4.2% newly diagnosed disease. Another 7.7% had intermittent but clinically unspecific joint symptoms, which could not be clearly attributed to PsA. About half (49.7%) of the patients with PsA had at least 1 swollen joint and 84.9% (n = 287) suffered from joint pain. Patients suffering from pain marked an average of 8.7 joints on a diagram as painful out of a possible 28. The mean number of swollen joints among the affected patients amounted to an average of 6.8. There are still a significant number of patients suspected of having joint involvement without ever having been diagnosed with PsA. Published data indicate that progression of joint damage and functional disability can be prevented if adequate treatment is started promptly (Radtke et al., 2009).

6.3 Psoriatic arthritis and genetics

The genes involved, in PsA are HLA genes of class I MHC alleles, on the HLA-B and HLA-C loci. Psoriasis is linked to HLA-Cw6 allele. Twenty percent of PsA patients with peripheral joint involvement displayed HLA-B27, a value that climbs to 70% in patients with PsA type spine involvement (Amherd-Hoekstra et al., 2010). The overlap in associated HLA antigens for both diseases (B13, B17, B57, Cw6, and DR7) suggests a shared genetic predisposition (Barton, 2002). Psoriasis and PsA are heritable diseases. Polymorphisms in the genes encoded in the MHC region have consistently been associated with psoriasis and PsA and account for about 30% of the genetic risk. In psoriasis, the association has been primarily with class I antigens: HLA-B13, HLA-B17, HLA-Cw6, and HLA-Cw7, the strongest association being with HLA-Cw6. Typing for HLA-Cw6 may have potential clinical utility, as it is associated with early onset of psoriasis, higher incidence of guttate or streptococcal induced disease flares, and more severe disease. PsA is also associated with multiple HLA antigens, many of which are similar to psoriasis antigens, as the two diseases are interrelated (O'Rielly & Rahman, 2010). However, specific associations do exist for the inflammatory arthritis, as HLA-B27 is associated with greater spinal involvement, and B38 and B39 with peripheral polyarthritis. HLA antigens are also prognostic factors, as HLA-B39 alone, HLA-B27 in the presence of HLA-DR7, and HLA-DQw3 in the absence of HLA-DR7 all confer an increased risk for disease progression. The RA shared epitope was found to be associated with radiologic erosions among patients with PsA. Patients with PsA carrying both HLACw6 and HLA-DRB107 alleles were determined to have a less severe course of arthritis. Recently, the results of multiple well powered genome-wide association studies

have identified several loci outside the MHC region associated with psoriasis risk, including three genes involved in interleukin (IL)-23 signaling (IL-23R, IL-23A, IL-12B), two genes that regulate nuclear factor-κB signaling (TNIP1, TNFAIP3), and two genes involved in the modulation of T-helper type 2 immune responses (IL-4, IL-13) (Bowes & Barton, 2010). Genetic epidemiologic studies have shown that both diseases have a strong genetic component. Environmental risk factors including streptococcal pharyngitis, stressful life events, low humidity, drugs, HIV infection, trauma, smoking and obesity have been associated with psoriasis and PsA (Barton, 2002; Cantini et al., 2010). PsA is even more strongly influenced by genes than is cutaneous psoriasis (Moll & Wright, 1973; Chandran & Raychaudhuri 2010). Family studies continue to suggest a large genetic contribution to PsA. Using a candidate gene approach, genes confirmed to be associated with psoriasis vulgaris have also been found to be associated with PsA: HLA-Cw-0602, IL23R, and IL12B (Castelino & Barton , 2010).

6.4 Psoriatic arthritis interleukins and biomarkers

A key objective of the assessment working group of the "Group for Research and Assessment of Psoriasis and Psoriatic Arthritis" (GRAPPA) was to identify, develop, evaluate, and validate outcome measures for use in clinical trials of PsA and in clinical practice useful in defining PsA types (Mease, 2008) . Biomarkers are helpful in screening patients with psoriasis for PsA types. Patients with psoriasis satisfying CASPAR criteria for PsA were analyzed for IL-12, IL-12p40, IL-17, TNF super family members (TNFSF14), MMP-3, RANK ligand (RANKL), osteoprotegerin (OPG), cartilage oligomeric matrix protein (COMP), C-propeptide of Type II collagen (CPII), collagen fragment neoepitopes Col2-3/4 long mono (C2C), Col2-3/4short (C1-2C) and highly sensitive CRP (hsCRP). Serum levels of RANKL, TNFSF14, MMP-3 and COMP independently associated with psoriatic disease. Twenty six PsA patients (mean swollen and tender joint count: 16, swollen joint count: 5) were then compared with 26 patients who had psoriasis alone. Increased levels of hsCRP, OPG, MMP-3 and the CPII:C2C ratios were independently associated with PsA and are biomarkers for PsA in patients with psoriasis (Chandran et al., 2010).

6.5 Psoriatic arthritis and cardiovascular disease

Immune-mediated inflammatory diseases (IMIDs), including RA and SpA, are associated with increased cardiovascular morbidity and mortality, independent of the established cardiovascular risk factors. The chronic inflammatory state, a hallmark of IMIDs, is considered to be a driving force for accelerated atherogenesis. Consequently, aggressive control of disease activity has been suggested to be instrumental for cardiovascular risk reduction (Bisoendial et al., 2009).

Patients with PsA have an increased incidence of CVD and cardiovascular risk factors such as smoking, hypertension, and metabolic syndrome compared to the normal population as well as nonconventional risk factors such as raised levels of homocysteine and excessive alcohol consumption. In patients with PsA, carotid wave pulse velocity, a measure of arterial stiffness, was significantly higher. Patients with psoriasis were found to have increased coronary artery calcification in direct imaging study compared to controls. Two case control studies also demonstrated that patients with PsA had a higher prevalence of subclinical atherosclerosis as measured by arterial intima-media wall thicknes (IMT) and

endothelial dysfunction without overt CVD. In patients without clinical CVD 35% had increased IMT despite having low cardiovascular risk. One hundred two patients with PsA had a higher prevalence of type II diabetes mellitus and hypertension, and an increased prevalence of HDL cholesterol, apolipoprotein A1 levels, lower total cholesterol and LDL cholesterol levels, and lower total cholesterol to HDL cholesterol ratio. Chronic inflammation has been shown to play a role in the development of atherosclerosis now considered as an inflammatory, autoimmune like disease. Both the innate immune system and T helper-1 lymphocytes appear to be involved in atherogenesis. This is similar to the pattern of immune mediated inflammation in psoriasis and PsA. It is possible that psoriasis and PsA produce chronic, systemic inflammation, with higher levels of inflammatory cells and cytokines invoking endothelial inflammation and plaque formation in the vascular system (Tobin et al., 2010). The increased risk for CVD in RA is well known and inflammation appears to play a pivotal etiological role. There is now substantial interest in whether or not PsA is also associated with an enhanced cardiovascular risk. In all patients CVD was defined as a history of myocardial infarct (MI), stroke and/or transient ischemic attack verified by written documentation of the event. The prevalence of CVD was 10% in patients with PsA compared with 12% in patients with RA (Jamnitski et al., 2010). Flow-mediated dilatation (FMD) was significantly impaired in PsA patients without traditional cardiovascular risk factors or CVD. Another study also showed a higher prevalence of subclinical atherosclerosis, as measured by carotid IMT, among PsA patients. As in RA, CVD and their risk factors including hyperlipidaemia, diabetes mellitus and hypertension were more common in PsA patients. However, mortality in patients with PsA, in a single center cohort was not significantly different from the general population in England. No increased risk of death was observed in this cohort (Buckley et al., 2010). In a population of patients with PsA 23.3% had renal abnormalities as defined by creatinine clearance below the lower cut off of normal distribution and urinary excretion of albumin more than 25 mg/24 hrs. These patients were significantly older at the time of the study, older at joint disease onset, had longer skin disease duration, increased serum levels of beta2-microglobulin, and higher incidence of increased erythrocyte sedimentation rate and C reactive protein levels (Alenius et al., 2001).

6.6 Psoriatic arthritis, metabolic syndrome and malignancies

To evaluate the prevalence of the metabolic syndrome (MetS), patients with RA, AS and PsA were recruited for a study of atherosclerotic risk factors and the MetS, defined according to the 2009 Joint Statements using the Asian criteria for central obesity. The prevalence of MetS was significantly higher in PsA (38%) than RA (20%) or AS (11%). Patients with PsA had significantly higher prevalence of impaired fasting glucose (30%), low HDL-cholesterol (33%), high triglyceride (21%), central obesity (65%) and high blood pressure (56%). Patients with PsA, but not RA or AS, have a significantly higher prevalence of the MetS syndrome compared to the general population. Among the three diseases studied, PsA has the highest prevalence of the MetS and is associated with highest cardiovascular risk (Mok et al., 2010; Papo et al., 2010)

A cohort analysis of SpA patients who were followed up prospectively from 1978 to 2004 at the University of Toronto PsA Clinic was performed. Of the 665 patients included, 68 (10.2%) developed a malignancy at an average age of 62.4 years. The most frequently seen malignancies were breast (20.6%), lung (13.2%), and prostate (8.8%) cancer. However, the

incidence of malignancy in the large PsA cohort did not differ from that in the general population (Rohekar et al., 2008).

6.7 Inflammatory markers C-reactive protein (CRP) and complement 5a (C5a) in patients with psoriatic arthritis, before and after treatment with amastigote antigens

Inflammatory markers C-reactive protein (CRP) and complement 5a (C5a) assayed in two PsA patients decreased significantly in serum after treatment with 6 doses of AS200 DEAE fractions 3 + 4 Leishmania amastigotes antigens at 300 µg/dose (Fig 1). The Leishmania antigens decreased markedly the TNFα concentration in supernatants from PBMC in both patients and controls (Fig 1 to 5 adapted from O'Daly & Gleason, 2010c, by permission of the associate editor)

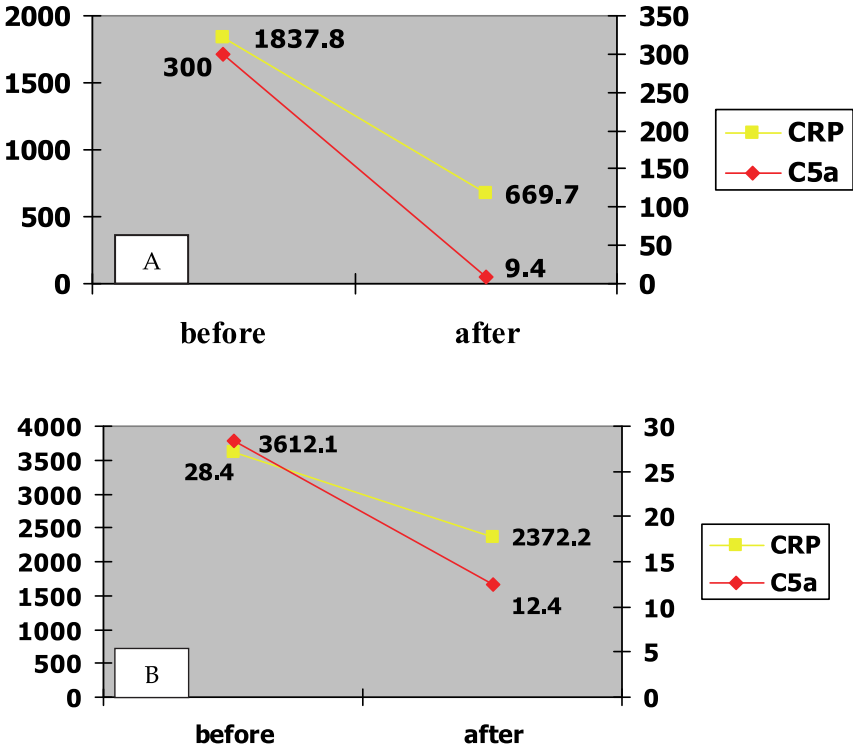

Fig. 1. Psoriatic patients (A and B) with 6 doses of AS200 at 300 µg/dose before and after treatments. Both patients had PASI reduction 61.6% and 66.4% respectively and biopsies with excellent improvement evidenced by decrease of epidermal layer and absence of inflammatory cells in epidermis and dermis in comparison to placebo (Rehydragel).

6.8 TNF-α in psoriatic patients and ConA induced hepatitis in mice

PBMC of patients and controls were stimulated with concanavalin A (ConA); ConA+AS100-2 *L(L)chagasi* antigens and compared to no treatment as control. The *Leishmania* antigens

decreased markedly the TNFα concentration in supernatants from PBMC in both patients and controls (Fig 2). In mice ConA induced hepatitis, injection of 50 µg AS100-2 *L(L)chagasi* antigens subcutaneously (SC) decreased serum TNFα as compared to placebo (PBS) in 8 hours of observation (Fig 3).

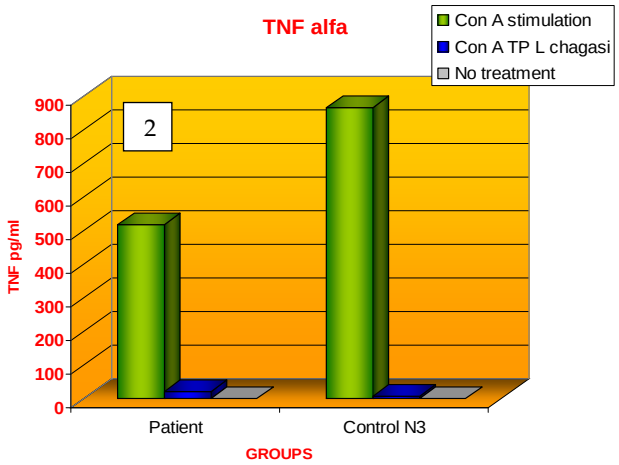

Fig. 2. PBMC of patients and controls after stimulation with concanavalin A (ConA), ConA + AS100-2 *L(L)chagasi* antigens or no treatment 3 patients and controls per group.

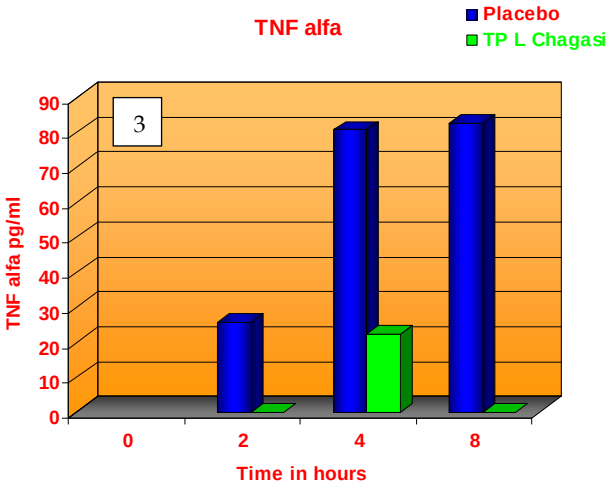

Fig. 3. Serum TNFα in ConA induced hepatitis in mice (n=3 per group). After SC injection of 50 µg AS100-2 *L. chagasi* antigens, TNFα decreased significantly as compared to placebo (PBS) at 2, 4 and 8 hours observation period. STDEV < 5% of average.

Serum IL-1β, 8 hours after SC injection of AS200 L(V)brasiliensis +RH and AS100-1+RH in mice, also decreased significantly as compared to placebo and in a range similar to the

positive control dexamethasone (Fig 4). AS100-2 *L(L)chagasi* antigens decreased proliferation of cutaneous T cell lymphoma in vitro in a dose-response relationship (Fig 5).

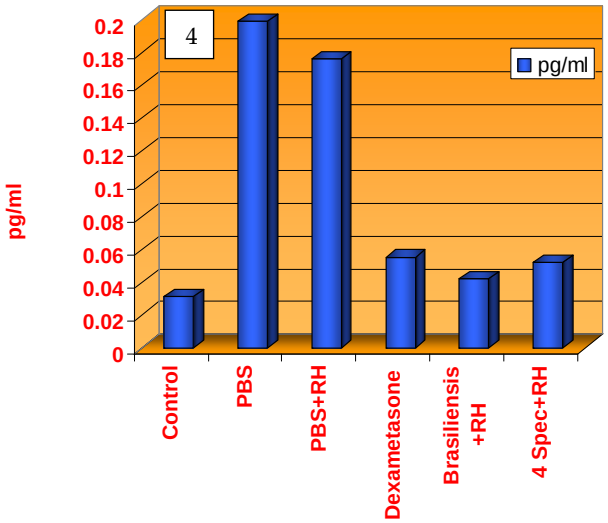

Fig. 4. Serum IL-1β in ConA induced hepatitis in mice (n=3 per group). IL-1β was determined after 8 hours of SC injection of the following products: 1- 50 µL placebo (PBS) 2- 50 µL PBS+Rehydragel (RH), 3- 50 µg/mice *L(V)brasiliensis* AS200 fraction 3 and 4 + RH, 4- AS100-1(4 species)+RH and 5- 1 mg/Kg/mice dexamethasone. Control normal mice, received no treatment. IL-1β decrease significantly after treatment with *L(V)brasiliensis* AS200 antigens 3 and 4, or polyva;ent AS100-1 vaccine, similar to dexamethasone as compared to placebos 1 and 2.

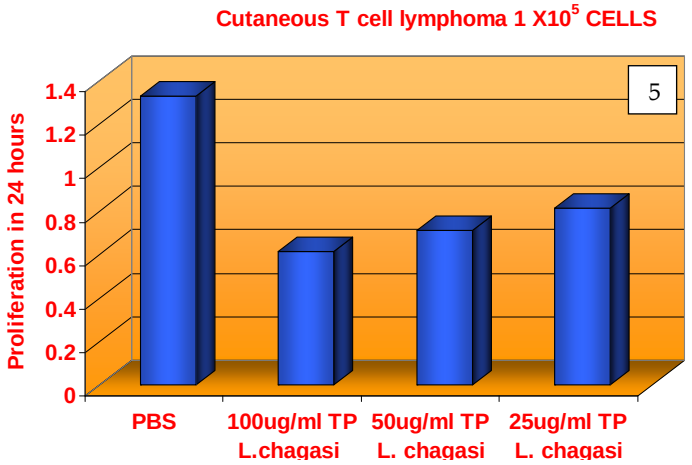

Fig. 5. In vitro proliferation of cutaneous T cell lymphoma cells at different concentrations of AS100-2 *(L) chagasi* leishmania antigens as compared to PBS after 24 hours of culture. Values are average of three different experiments. STDEV < 5% of average.

6.9 Lymphocyte subsets in patients with psoriatic arthritis

As more skin disease is present in PsA patients, more inflammation is found in the joints, suggesting a link between skin and joint inflammatory processes; since both were exacerbated in the PASI 100 and PASI 75 groups and also needed higher number of doses to achieve a lower AS, tender joints and nail changes values (O'Daly et al., 2011). Absolute values of gated LS before treatment decreased in this order: CD8+HLA-, CD8+HLA+, CD4+, CD8+CD3+, CD8+CD3 in PBMC as PASI increased, suggesting migration of CD8+ cells from the blood to the joints and skin. Contrary to the previous finding, LS: CD8+CD4-, CD3+CD8-, HLA+CD8-, CD19+, CD8+CD4+, IgA+, IgD+, IgM+, IgE+, and IgG+ increased in PBMC as PASI increased suggesting activation and proliferation by unknown antigens and subsequent migration to the blood. The LS quantification in this group of PsA patients only (n=508) were different (O'Daly et al., 2011) to the LS quantified in the psoriasis skin disease trial (n=2770, O'Daly et al., 2010b), since in PsA the majority belonged to the CD8+ phenotype, a T cell key in the PsA inflammatory process as described by many authors. In PsA patients there is also evidence of T cell recirculation before treatment and a vicious cycle with T and B cells migrating between blood and skin and joints. After treatment with nine doses of AS100-1 *Leishmania* amastigotes antigens, a dramatic decrease in LS belonging to T and B cells, in PBMC was observed, as PASI, AS, tender joint counts, and nail changes returns to normal values and the vicious cycle disappeared (O'Daly et al., 2011). AS100-1 had a cellular not humoral immune response as supported by the DTH and ELISA results in humans and guinea pigs (O'Daly et al. 2009a; O'Daly et al., 2009b; O'Daly et al., 2010a). All psoriatic patients were DTH positive after the third vaccination with AS100-1, but no ELISA antibodies were detected in serum from these volunteers up to 6 doses of vaccine (O'Daly et al., 2009a). This suggests that the immunological response to AS100-1 after TLCK treatment and NP-40 extraction was mediated by immunization of T-regulatory cells, with no antibody production, a novel mechanism that may play a role in decreasing inflammation in psoriatic skin. Amastigote peptides may induce Th3 regulatory T cells producing IL-10 that inhibits Th1 and Th2 cell cytokine production and induced peripheral cell tolerance.

6.10 Psoriatic arthritis therapies

Psoriasis is one of the most prevalent chronic inflammatory diseases with a high economic impact. The disease persists for life, and the patient has an increased risk of CVD. One out of five patients develops PsA. The clinical picture of psoriasis is highly variable with regard to lesion characteristics and the severity of disease. To improve the management of psoriasis, guidelines must be followed and all appropriate topical and systemic treatment options must be tried, with clearly defined treatment goals. The spectrum of established systemic treatments for psoriasis has been extended by the biologics (Mrowietz & Reich, 2009).

PsA is an inflammatory arthritis occurring in up to 30% of patients with psoriasis. Its clear distinction from RA has been described clinically, genetically, and immunohistologically. Therapies that target cells, such as activated T cells, proinflammatory cytokines, and TNFα, are used extensively today. A variety of items are evaluated including joints, skin, enthesium, dactylitis, spine function, quality of life, and imaging assessment of disease activity and damage (Ceponis & Kavanaugh, 2010). The performance of treatments in these various domains have being evaluated by GRAPPA, and improved measures are being developed and validated specifically for PsA. Traditional therapies for PsA like non

steroidal anti-inflammatory drugs (NSAIDs), oral immunomodulatory drugs, topical creams, and light therapy have been helpful in controlling both musculoskeletal and dermatologic lesions of the disease, but may eventually show diminished benefit, and may produce severe toxicities as side effects (Mease, 2006).

The primary goals in the treatment of PsA are reduction of pain; improvement in the other signs and symptoms of disease, including skin and nail involvement; optimization of functional capacity and quality of life; and inhibition of the progression of joint damage. These goals should be achieved while minimizing potential toxicities from treatment. The management of PsA should simultaneously target arthritis, skin disease, and other manifestations of PsA, including involvement of the axial skeleton dactylitis, enthesitis, and eye inflammation. In this respect targeted biological agents, primarily TNFα inhibitors, have emerged as generally well tolerated and highly effective alternatives to traditional "Disease Modifying Anti Rheumatic Drugs" (DMARDs) (Mease, 2010b)

PsA was considered as a less damaging disease than RA. In early arthritis 50% of patients showed significant joint damage developing erosions in the first 2 years even if DMARDs were used as treatment. The treatment should aim to preserve function, prevent disability and maintain quality of life. The therapeutic approach has employed treatments to benefit both the skin and joints with minimal adverse effects, and to prevent subsequent disability and damage, inflammation i.e. synovitis which must be arrested and controlled early. In this respect combination therapy with conventional DMARDs and biologic drugs, like TNFα inhibitors, has made significant progress in the last 10 years. A remission rate of 58% of patients treated with DMARD and biologic therapy for 12 months has been achieved (Wollina et al., 2010).

Nail involvement in psoriasis is typically overlooked; it can affect up to 50% of patients with psoriasis and cause functional impact as well as psychological stress that affect quality of life. Psoriatic patients with nail disease have more severe skin lesions, and higher rate of unremitting PsA. The current management of nail psoriasis includes topical, intralesional and systemic therapies, although little clinical evidence is available on the effectiveness of conventional treatments. Biologic agents are beginning to emerge as a viable option to treat patients with both cutaneous and nail clinical manifestations of psoriasis and PsA (Vena et al., 2010).

Although they can have some beneficial effect on skin disease and peripheral arthritis, there is lack of evidence for DMARDs, such as methotrexate (MTX), Leflunomide (LEF), cyclosporine (CsA), and sulfasalazine (SSZ) in affecting dactylitis or enthesitis, and they are clearly ineffective in axial disease. Systemic glucocorticoids may cause a flare of psoriasis if treatment is stopped too quickly, and should be used with caution in PsA. In contrast, biologics, particularly TNFα inhibitors seem to be beneficial in skin psoriasis and across of all the manifestations of PsA, including arthritis, skin and nail disease, spinal disease, enthesitis and dactylitis. They also improve quality of life and inhibit joint damage. All the currently used TNFα inhibitors appear to have comparable efficacy and safety profiles in patients with PsA. They can be used as monotherapy or in combination with MTX or other traditional DMARDs. Initiation of anti-TNFα agents is recommended for patients who failed one of the traditional DMARDs or as an initial therapy in patients who have poor prognosis. Other biological agents, including alefacept and abatacept, appear to be less potent than TNFα inhibitors in PsA and their use is likely to be reserved

for patients who failed or cannot be treated with TNFα inhibitors. These agents are usually used in combination with other DMARDs. The Efficacy of ustekinumab in the treatment of PsA has been recently reported and is presently under further investigation (Mease, 2009; Mease, 2010a)

Results from clinical trials of biologic anti-TNFα drugs confirmed the biological relevance of TNFα function in the pathogenesis of chronic noninfectious inflammation of joints, skin and gut. Up to April 2009, more than two million patients worldwide have received the first marketed drugs, namely the monoclonal anti-TNFα antibodies infliximab and adalimumab and the soluble TNF receptor etanercept. All three are equally effective in RA, AS, psoriasis and PsA, and only the monoclonal antibodies are effective in inflammatory bowel disease. The spectrum of efficacy with anti-TNFα therapies includes diseases such as systemic vasculitis and sight-threatening uveitis. New adverse effects are recognized, like development of new onset psoriasis. Reactivation of latent tuberculosis remains the most important safety issue of anti-TNFα therapies (Sfikakis, 2010). RA, AS and PsA are commonly thought of as inflammatory diseases that affect younger individuals. The safety profiles for etanercept, infliximab and adalimumab in patients of 65 years or more, anti-TNFα treatments for an active inflammatory disease such as RA, AS or PsA, or psoriasis were analyzed. Anti TNFα treatment is a safe option possibly leading to better disease outcome (Migliore et al., 2009).

Altogether there is sufficient reason not to dismiss traditional agents for use in PsA because of lack of evidence. Also, due consideration must be given to the considerable cost of biologic treatments versus traditional treatments. The role of combination therapy with TNFα inhibitors is an important one, especially considering that 30%–40% of patients in the TNFα inhibitor trials have been on MTX as concomitant medication (McHugh, 2009). Traditional systemic therapies for psoriasis, such as MTX, CsA, retinoids or psoralen plus ultraviolet light (PUVA) therapy, have a potential for long-term toxicity and may not always provide sufficient improvement of the disease. Biological therapies for the treatment of PsA are defined by their mode of action and can be classified into three categories: the T-cell modulating agents (alefacept and efalizumab), the TNFα blockers, (adalimumab, certolizumab, etanercept, golimumab and infliximab) and the inhibitors of interleukin IL-12 and IL-23 (ustekinumab and briakinumab) (Weger, 2010). DMARDs remain the first choice for the treatment of peripheral arthritis despite scarce evidence of their efficacy or ability to halt radiographic progression. TNFα antagonists have the greatest level of evidence for symptom control and radiographic progression. They are currently used after the failure of DMARDs to effectively treat peripheral arthritis, enthesitis, and dactylitis, and are the first choice when axial disease predominates. Despite the use of these treatments, 30% to 40% of patients will still have active disease. Among new drugs, evidence of efficacy has already been published with regard to anti-IL12/23 monoclonal antibody (ustekimumab) and golimumab (Soriano &, Rosa, 2009)

For a long time, the endothelial covering of the vessels has been considered an inert surface. On the contrary, the endothelial cells are active and dynamic elements in the interaction between blood and tissues. The control of the vessel basal tone is obtained by the complex balance between the relaxing and contracting endothelial factors. Previous clinical studies show that patients suffering from RA and other autoimmune rheumatologic pathologies are at high risk of death being prematurely affected by

atherosclerosis and CVD. Blocking TNFα by biological drugs improves the endothelial function. The effects of two anti-TNFα drugs (infliximab and etanercept) on the endothelial function were evaluated by FMD, which was measured in the brachial artery before and after treatment. 36 patients were enrolled 25 with RA and 11 with PsA. They were divided into three groups: 10 patients were treated with etanercept, 13 with infliximab, and 13 with DMARDs. The carotid IMT was measured and the endothelial function was evaluated by FMD measurement in the brachial artery, before treatment, 1 h after the beginning of treatment and after 8–12 weeks. No statistically significant difference between the three groups before treatment was found for the ultrasonographic evaluation of the carotid IMT. On the contrary, the differences between FMD values before and after the treatment in the patients treated with etanercept and in the patients treated with infliximab were statistically significant. Long-term evaluation for infliximab and etanercept was performed by comparing the FMD values, 8 and 12 weeks after the first treatment. After 8 weeks, FMD value was similar to the value recorded at enrollment in the infliximab group and the FMD values in the etanercept group after 12 weeks showed a not statistically significant reduction of vasodilatating effect. Drugs in patients affected by autoimmune arthritis can modify the endothelial function, as indicated by the induced FMD changes, but the long-term effect tends to be considerably reduced (Mazzoccoli et al., 2010)

Significantly diminished values for swollen and tender joints, patients global and pain assessments, doctor's global assessment of disease activity, erythrocyte sedimentation rate, C-reactive protein, and "Health Assessment Questionnaire" (HAQ) score were observed within 3 months after commencement of both infliximab and etanercept. Values remained significantly lower throughout the 24 months of follow up. ACR20 response at 3 months was 79% (n = 22/28) for infliximab and 76% (n = 34/45) for etanercept. The first biological drug was discontinued in 16% due to lack of effectiveness and in 6% due to adverse events (Virkki et al., 2010). It is unclear if skin cancer risk is affected by the use of immunomodulatory medications in RA, psoriasis, and PsA. RA may potentiate the risk of cutaneous malignancy and therefore dermatologic screening in this population should be considered. The use of immunomodulatory therapy in RA, psoriasis, and PsA may further increase the risk of cutaneous malignancy and therefore dermatologic screening examinations are warranted in these groups. More careful recording of skin cancer development during clinical trials and cohort studies is necessary to further delineate the risks of immunomodulatory therapy (Krathen et al., 2010).

PsA provides an ideal disease model in which to investigate the bioactivities of potentially therapeutic cytokines at multiple sites of tissue inflammation. The effects of subcutaneous rhIL-10, an anti-inflammatory cytokine, was investigated for 28 days in a double-blind, placebo-controlled study in PsA patients. Synovial/skin biopsies, peripheral blood leukocytes, articular magnetic resonance images, and clinical disease activity scores were obtained sequentially. Modest, but significant clinical improvement in skin, but not articular disease activity scores with only minor adverse effects was observed. Type 1, but not Type 2 cytokine production in vitro was suppressed in human rhIL-10 treatment compared with placebo recipients. Similarly, TNFα and IL-1β, production in whole blood stimulated with LPS in vitro was reduced, whereas serum soluble TNFRII levels were elevated, indicating suppression of monocyte function. Decreased T cell and macrophage

infiltration in synovial tissues was accompanied by reduced P-selectin expression. Moreover, suppressed synovial enhancement on magnetic resonance imaging and reduced α(v)β(3) integrin expression on von Willebrand factor(+) vessels were observed. Together these data demonstrate that a short course of IL-10 modulates immune responses in vivo via diverse effects on endothelial activation, leukocyte recruitment and effector functions. Such biological changes may result in clinically meaningful improvement in disease activity (McInnes et al., 2001).

Biologic agents should be considered for use solely in children with psoriasis that is refractory to conventional therapies, including children with severe, widespread, refractory pustular, plaque or PsA. Etanercept appears to have resulted in less severe side effects compared to infliximab in the juvenile RA population. Serious adverse events (including infection), have been reported in the literature and should be taken into account before beginning treatment with any biologic agent (Marji et al., 2010).

The socioeconomic scenario of PsA is similar to RA. Current treatments do not achieve remission of symptoms or prevention of the appearance of damage in the early stage of PsA nor the blocking of PsA progression in old cases. The current management of PsA includes NSAIDs, corticosteroids, DMARDs and anti-TNF-α alpha blocking agents. These biologic drugs are more effective than traditional DMARDs on inflammation, quality of life and function and can inhibit the progression of the structural joint damage. Recent advancement in the immunopathogenesis of PsA has permitted the development of novel drugs including new TNF-α blockers, IL-1, IL-6, IL-12, IL-23 and IL-17 inhibitors, co-stimulator modulation inhibitors, B-cell depleting agents, small molecules and receptor activator of NF-kappaB/receptor activator of NF-kappaB ligand inhibitors (Olivieri et al., 2010).

Baseline clinical characteristics including demographics, previous DMARDs response, tender and swollen joint counts, early morning stiffness, pain visual analogue score, patient global assessment, C reactive protein (CRP) and HAQ were collected. At 12 months remission, defined according to the disease activity score using 28 joint count and CRP (DAS28-CRP), was achieved in 58% of PsA patients compared to 44% of RA patients. DAS28 remission is possible in PsA patients at one year following anti-TNFα therapy, at higher rates than in RA patients and is predicted by baseline HAQ (Saber et al., 2010).

Therapy for inflammatory joint diseases, such as RA, AS and PsA, includes DMARDs. Conventional DMARDs are used as monotherapy or in combination and include MTX, LEF, azathioprine, CsA, hydroxychloroquine, SSZ, gold and minocycline. Biologic therapies are TNFα inhibitors, T-cell modulators and B-cell depleters. They have all been shown to have clinical efficacy and are able to retard structural damage (Vaz et al., 2009).

7. Leishmaniasis, the tropical disease root of the serendipity finding

7.1 What is Leishmaniasis?

Leishmaniasis is a globally distributed zoonosis mostly centered in the tropics and subtropics, with humans serving as accidental hosts. Due to the prevalence of the disease, one-tenth of the world's populations (600 million people) are at risk of infection. Globally, there are approximately 12 million cases and the incidence of new visceral leishmaniasis

(VL) and cutaneous (CL) infections are approximated 0.5 and 1.5 million new cases each year, respectively (World Health Organization, Leishmaniasis Control home page: http://www.who.int/ctd/html/leis.html).

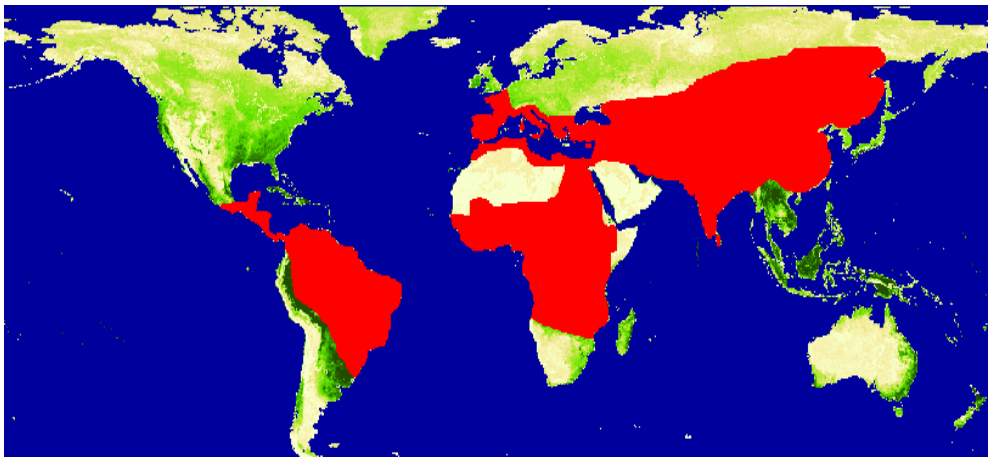

Fig. 6. Cutaneous and Visceral Leishmaniasis in our planet

7.2 Leishmania life cycle and suppression of antigen display

Extracellular procyclic promastigotes in the vector (sandfly) mature to metacyclic promastigotes (motile) that eventually evolve to amastigotes (nonmotile) once they enter cells in the vertebrate host after the insect bite. The amastigote eventually evolves back to the promastigote form in the vector, after a blood meal in infected hosts, closing the cycle. The mature infective metacyclic promastigotes have surface glycoconjugates such as glycosylinositolphopholipid (GIPL) and lipophosphoglycan (LPG), wich is a virulence factor of the mature promastigote and inhibits the action of the complement system (Okwor & Uzonna, 2009). Once inside the host, metacyclic promastigotes are taken up by macrophages through binding to complement receptors 1 and 3 or C reactive protein receptor, without leading to the activation of the macrophage. Approximately 24–72 hours after being taken up by the macrophage, the promastigotes transform into round nonmotile intracellular amastigotes with no surface GIPL or LPG. The amastigotes begin to multiply in the parasitophorous vacuole inside the macrophage (Figure 7), suppressing IFN-γ and the production of nitric oxide (NO) and superoxide (Awasthi et al., 2004; Handman, 2001). The immunological response in humans and experimental animals is induced by the amastigote form (intracellular), and not by extracellular promastigotes form, which enters the host target cell immediately after infection and is not seen by the host immune system. Amastigotes inhibit antigen presentation by repressing the expression of Class I and Class II MHC gene products, both basally and following stimulation with IFNγ (Reiner et al., 1987; Reiner det al., 1988). On the other hand, macrophages infected with *L(L)major* may express

normal levels of MHC class II molecules, but inhibit antigen presentation by interfering with the loading of antigens onto the MHC class II molecule (Fruth et al., 1993). An alternative suppression technique used by several Leishmania species is to sequester the MHC II molecules and antigens within the phagolysosome (Kima et al., 1996).

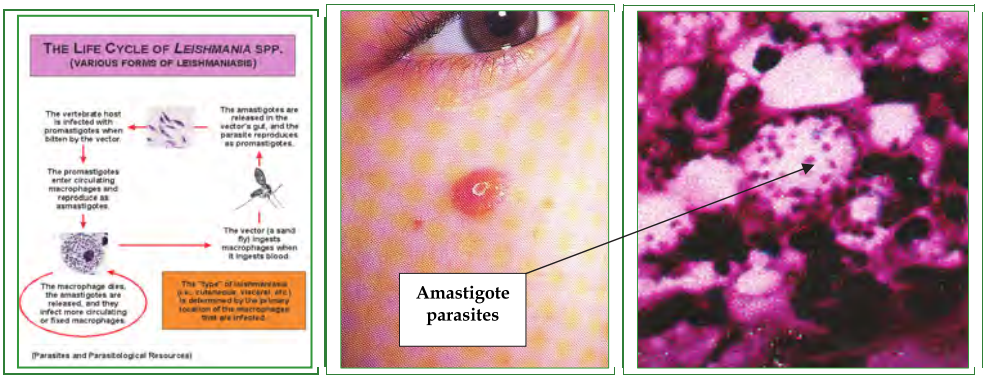

Fig. 7. Life cycle of leismania parasites and initial cutaneous lesion 2-3 weeks after bite

7.3 How do vertebrates defend against Leishmaniasis?

After being bitten, a granuloma composed of granulocytes, lymphocytes, epithelioid cells, monocytes, macrophages, and fibroblasts forms at the site of infection. In addition to killing parasites, activated macrophages produce different cytokines such as TNFα, IL-6, IL-18, IL-12, and IFNγ inducing a protective Th1-type immune response (Awasthi et al., 2004; Handman, 2001). Analyses of immune responses in natural and experimental (healthy human volunteers) infections show that the clear Th1/Th2 T cell responses to *L(L) major* seen in murine studies do not occur. Instead, a typical mixed Th1/Th2 response is observed with PBMC from patients secreting varying amounts of IFNγ, IL-10, and IL-4 depending on the clinical stage of the disease. CD4+ and CD8+ cells contribute to IFNγ and TNFα production in infected patients (Okwor & Uzonna, 2009). Residual parasites remain in the host forever and can be reactivated in the immunocompromised hosts and by AIDS (Fernandez-Guerrero et al., 1987; Rodriguez Coura et al., 1987; Rosenthal et al., 1988; Scaglia et al., 1989; Altges et al. 1991).

TNF plays a central role in the defense against intracellular infections with Leishmania, a disease that ends fatally in TNF–/– mice (Reiner et al., 1987). Resolution of an established infection is mediated by IFN-γ produced by CD4+ T cells in C57BL/6 resistant mouse strains (Reiner et al., 1988). The IFN-γ response allows macrophages to develop leishmanicidal activities as expression of inducible nitric oxide synthase (iNOS) and NO. In contrast, BALB/c susceptible strain develops IL-4- and IL-10-mediated CD4+ T cell response. Rheumatoid arthritis patients treated with TNF antagonists have reoccurrence of leishmaniasis. After blocking TNF, Leishmania donovani-infected mice were unable to

resolve the infection (Körner et al., 2010). VL is characterized by abundant parasites in the spleen, liver, and bone marrow. However, the parasite only establishes chronic infection in the spleen and bone marrow because infection in the liver is self-resolving within 6–8 weeks because of a Th1-dominated granulomatous response, characterized by high IFN-γ production (Stager et al., 2010).

	Endemic area			Hyperendemic area		
Study group	**Infected**	**Noninfected**	**p**	**Infected**	**Noninfected**	**p**
Vaccinated	16	2,000		18	105	
Nonvaccinated	66	1,109	<0.001	52	50	<0.001
Protective efficacy	85.9%			71%		
95% Confidence interval	81.8- 86.1			67.9- 74.3		

Table 1. Cases of leishmaniasis according to vaccination status, protective efficacy

Neutrophils are rapidly recruited to the site of Leishmania inoculation, where they phagocytose the parasites, some of which are able to survive within these first host cells. Neutrophils can thus provide a transient safe shelter for the parasites, prior to their entry into macrophages where they will replicate (Charmoy et al., 2010).

After vaccination with 3 doses of AS100-1 at 500 µg/500 µl , one month apart in the endemic area of "Valle Arriba" and in the hyperendemic area of "La Planta" both in Guatire, Miranda State, Venezuela, (O'Daly et al., 1995a) protective efficacy were 85.9% and 71% respectively (Table 1). In the endemic area we found one person cured from plaque psoriasis one month after the third dose of vaccine. The vaccine also induced regression of leishmania lesions when used as immunotherapeutic agent as seen in Figure 8 (O'Daly et al., 1995b)

7.4 No prior sensitization required to recognize amastigote antigens

Leishmania promastigotes sonicates induced in vitro proliferation and IFNγ production in PBMC from individuals that never had contact with Leishmania parasites. The proliferating T cell population was CD2+ in a frequency <1:10,000 a response that could be abolished after depletion of CD45RO+ memory cells from the PBMC (Kemp et al., 1992). Sera from volunteers vaccinated in the Leishmaniasis trial performed in Caracas, had ELISA negative values and a similar immunoblotting band pattern before vaccination, and 1 month after 3 doses of the polyvalent vaccine using amastigote antigens from the four species present in AS100-1 (O'Daly et al., 1995a). Thus, normal CD2+ T cells (Kemp et al., 1992) and normal immunoglobulin from healthy volunteers that never experienced Leishmania infection reacted with Leishmania antigens in the immunoblotting assay. Interestingly psoriatic patients, DTH negatives to amastigote antigens, also recognized in the blastogenic assay Leishmania antigens and were distributed in two groups, low and high responders to Leishmania amastigote antigens before treatment (O'Daly et al., 2009b).

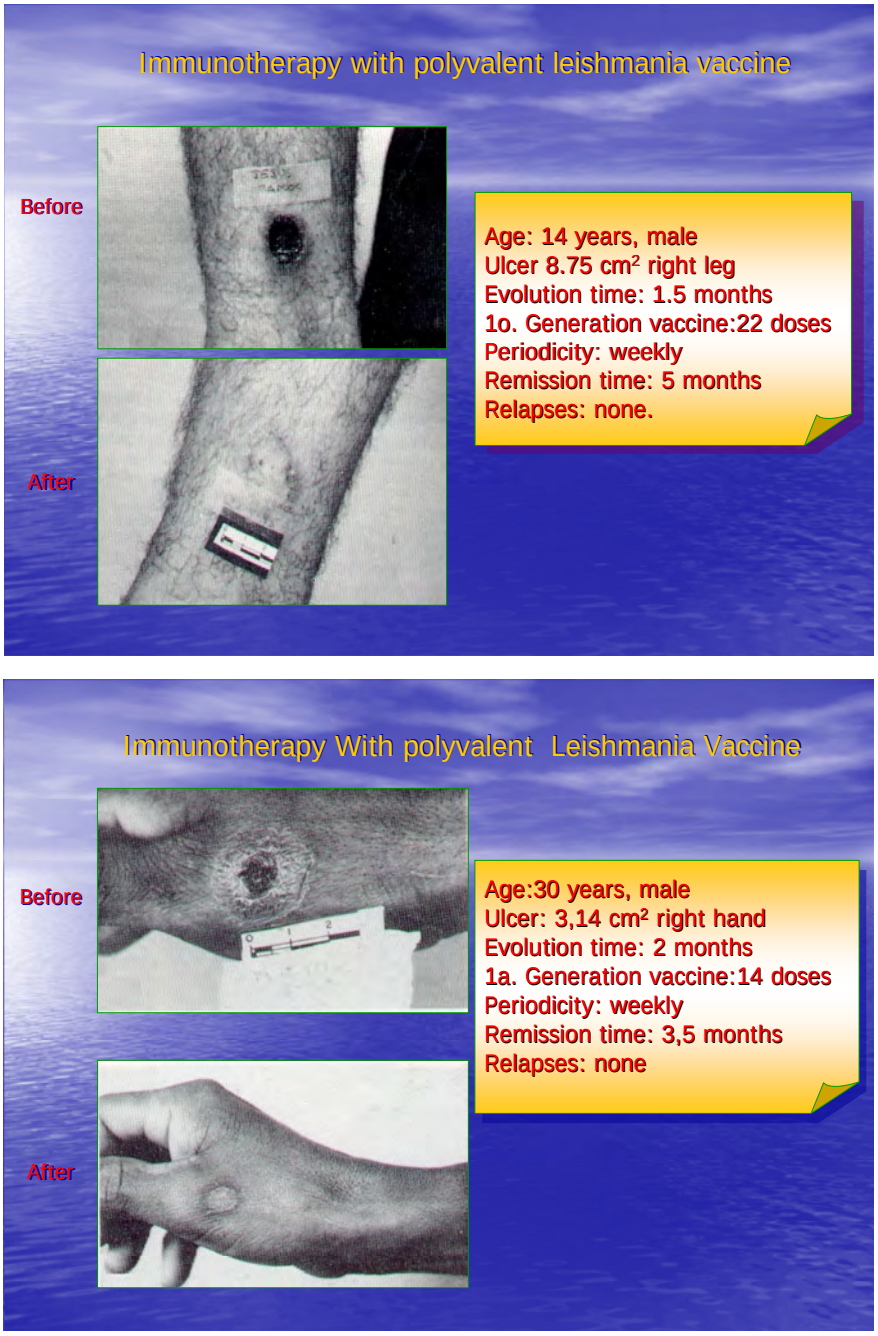

Fig. 8. Treatment with AS100-1 polyvalent vaccine as immunotherapeutic agent in infected volunteers.

Furthermore, we have demonstrated a high DTH response with *L. brasiliensis* and *L. chagasi* protein (DEAE) fractions in vivo after treatment with AS100-1 suggesting a strong T cell response after treatment and confirming the absence of immunosuppression. The SI values obtained by protein (DEAE) fractions were 50–70% lower than the values induced by intact living leishmania parasites and 90% lower than the total stimulation obtained by the T cell mitogen ConA. This suggests their stimulation potential *in vitro* appears to be selectively focus toward a particular subset of lymphocytes which may be regulatory CD8+ T cells as published (O'Daly et al. 2009a; O'Daly et al., 2009b; O'Daly et al., 2010a; O'Daly et al., 2011)

7.5 The role of IL-10 in parasitic defense and autoimmune disease

IL-10 plays an important role in many skin autoimmune diseases, and in certain parasitic infections, in humans as well as in experimental animals (Weiss et al., 2004). IL-10 stimulates NK cells cytotoxicity and IL-2 inducing IFNγ and TNFα production. In addition, IL-10 produced by Th2 cells inhibits IFNγ synthesis by Th1 cells and downregulates cellular immunity. Th3 or regulatory T cells produce IL-10 that inhibits Th1 and Th2 cell cytokine production, mediating peripheral cell tolerance (Seifert et al., 2000). Further underscoring the importance of IL-10 is its role in parasitic infections, in the persistence of *L(L)major* in the skin after healing and the therapeutic potential of anti-IL-10 receptor antibody for sterile cure. (Belkaid et al., 2001) L. donovani-infected BALB/c mice treated with anti-IL-10 receptor had accelerated granuloma formation and rapid parasite killing without excessive tissue inflammation (Murray et al., 2002). A comparison between cells, cytokines, cellular and humoral immunity in bot diseases is presented in Table 2.

7.6 Relationship between leismaniasis and psoriasis

How can we reconcile the finding that treatment with a leishmanial antigen vaccine targeted at leishmaniasis, results in clinical remission of psoriasis in subjects never exposed to Leishmania parasites? Despite some of the obvious differences between the diseases, there are some striking similarities: immunity against both diseases starts with the same cell types, and also both diseases have similar Th1cytokine patterns at least initially, both diseases respond to the Leishmania polyvalent vaccine, AS100-1. It should be noted that both trials showed evidence of cellular immunity not humoral immunity. In psoriasis, initial interaction of antigens between APC and T cells occurs in the lymph nodes. Subsequent psoriatic antigen presentation occurs in psoriatic plaques that structurally resemble a lymph node, but are found in the skin. At this stage of psoriatic disease, the cellular conformation is quite similar to the granuloma found in the skin after Leishmania infection (Table 2).

Finally, many doors have been opened with the serendipity discovery of Leishmania amastigote antigens inducing clinical remission of psoriasis as a systemic disease, which no doubt will provide new roads and answers not solved yet.

Future research and clinical efforts will illuminate many fundamental problems, encountered in those terrible illness affecting human beings in all countries on earth.

PSORIASIS	LEISHMANIASIS
Unknown etiology. Genetically determined disease, multiple genes interacting with environment involved in the inflammatory process manifested as plaques, gutatta, palm/plantar, erythrodermia, nails, and arthritic forms.	Infection by metacyclic promastigotes in vector (sandfly) that transform immediately into intracellular amastigotes in cells of vertebrate host, inducing cutaneous, mucocutaneous, diffuse and visceral clinical forms.
Starting lesions in epidermis with macrophages, monocytes, lymphocytes and neutrophiles at Munro sterile abscesses. Unknown antigen at immunological synapse structured by MHC-TCR receptors between T cells and APC with costimulatory molecules as LFA-1, ICAM-1, CD2, LFA-3 CD28, CD80. Proliferation and migration CD4+ T cells from the lymph nodes to the dermis regulated by cytokines. Dermal CD4+ and epidermal CD8+ cells contribute to plaque formation.	Neutrophiles, lymphocytes, epithelioid cells, monocytes, macrophages and fibroblasts starts at the site of infection. Leishmania antigens at similar immunological synapse MHC-TCR receptors between T cells and APC with same costimulatory molecules. CD4+ and CD8+ cells contribute to IFNγ and TNFα production in infected patients and healing of lesions. Leishmania antigens induce *in vitro* proliferation and IFNγ production in CD2+ T cells from PBMC in individuals that never had contact with parasites.
Cell-cell interactions in skin involve: keratinocytes, melanocytes, Langerhans cells, dendritic cells, mast cells, naive T cells, memory T cells expressing CLA. ICAM-1 and E-Selectin receptors on dermal endothelial cells. In the epidermis neutrophiles and CD8+ T cells with MHCII, IL-2 receptor, modulate inflammation.	Skin immunity delivered by keratinocytes, melanocytes , dendritic Langerhans cells, mast cells, tissue macrophages, neutrophils, dermal dendritic cells and fibroblasts, T cells, memory T cells expressing CLA. Similar receptors on endothelial cells. Epidermal and dermal cells cytokines modulate immune response and inflammation after infection.
TH1 cytokines increase in plaques and serum represented by TNFα, IFNγ, IL-6, IL-8, IL12, and IL-18. High levels of IFNγ, IL12, and IL-18 correlated with disease severity. Relative under expression of TH2 cytokines IL-4 and IL-10. Dilated blood vessels earliest signal within dermal papillae induced by keratinocytes pro-angiogenic cytokines.	Activated macrophages produce: TNFα, IL-6, IL-18, IFNγ and high IL-12, inducing a protective TH1 immune response in resistant mice. TH2 response with IL-4, IL-13, IL-10 and low or absent IL-12 in susceptible mice. Humans with resolving lesions have higher ratios of INFγ/IL4 compared to patients with nonhealing lesions.
Clinical response to IL-10 correlated with decreased cutaneous infiltration and decrease of IFNγ, TNFα, IL-17, IL-8 and CXCR2 in lesions. UV light exerts its therapeutic effects by stimulating keratinocytes or APC to secrete IL-10. Cutaneous IL-10 mRNA is significantly lower in psoriasis.	IL-10 promotes disease progression in cutaneous leishmaniasis. Chronic infections in humans and mice associated with generation of CD4+ T cells expressing IL-10. IL-10 responses and the generation of functionally impaired CD8+ T-cells permit parasites persistence in the host.

Table 2. Comparison of pathogenesis between Psoriasis and leishmaniasis

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