transplant related mortality (TRM) of 9% overall was observed, with inter disease differences (12.5% in SSc and only one TRM in RA). Around 2/3 of patients responded with improvement or stabilisation. In SSc, 69% achieved a 25% or greater improvement in skin score, and in secondary progressive MS, 78% a 3 year progression free survival. Relapse was more common with RA and JIA, mostly being a synovitis easy to control with agents which were ineffective pre transplant. Randomised, controlled prospective trials are underway in SSc (ASTIS Trial: HSCT versus monthly pulse cyclophosphamide)), and planned for RA and MS. Trials in JIA are being discussed and further phase I/II data are required for SLE and vasculitis. These will be presented, together with immune reconstitution data, sometimes predicting relapse, and new developments in HSCT, especially non myeloablative "mini" allograft techniques. This may be applicable to full sibling matched selected patients.

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Ankylosing Spondylitis – Thursday 14 June, 14.00-15.30/Congress Hall

SP0031 GENETIC STUDIES IN FAMILIAL ANKYLOSING SPONDYLITIS: THE NORTH AMERICAN SPONDYLITIS CONSORTIUM EXPERIENCE

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Recent genome-wide screens of English families multiplex for ankylosing spondylitis (AS) have suggested genes additional to HLA-B27 to be involved in disease susceptibility, particularly on chromosome 2q and 16q. Another recent study has suggested an association of AS with an allele of the IL-1 receptor antagonist gene (IL-1RA) on chromosome 2q. In order to confirm these findings in an independent group of families, 92 sib pairs concordant for AS by modified New York criteria from 74 North American families from the were examined with eight polymorphic microsatellite markers within the major histocompatibility complex (MHC) and HLA-DRB1, DQA1, DQB1 alleles; four markers on chromosome 2q and three on 16q near the regions previously implicated. Results for the MHC markers were as follows:

Abstract SP0031 Table 1

Marker	Map position (cM) ^a	NPL Statistic	p-value
D6S461	40.14	2.6	0.005

D6S276	44.41	3.09	0.001
D6S105	44.41	2.17	0.015
D6S273	44.96	3.17	0.001
D6S1014	45.5	1.56	0.023
D6S1666	45.5	3.03	0.001
D6S1583	47.71	5.38	8×10^{-6}
DRB1	49.87	3.17	9×10^{-7}
D6S1019	53.81	2.09	0.018

No evidence of linkage was found for the markers on chromosome 2q and 16q. In addition, analysis of 29 single nucleotide polymorphisms (SNP's) from the IL-1 RA gene in 30 AS patients and 48 controls found no evidence of disease association. These data strongly suggest the presence of a second MHC gene operative in predisposition to AS at or near the HLA-DRB1 locus. Additional families are currently being studied and fine mapping studies in progress to confirm and extend these findings.

SP0033 UPDATE ON PSORIASIS AS IT RELATES TO SPONDYLOARTHROPATHIES

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Psoriasis is a common disease (affects ~ 2% whites); and up to 10% of these patients have associated inflammatory arthritis [psoriatic arthritis (PsA), including spondyloarthropathy (SpA)], which may, in up to 15% of patients, precede the onset or diagnosis of psoriasis. There are no internationally agreed criteria for the diagnosis of (PsA); it has been broadly defined by Moll and Wright as an "inflammatory arthritis associated with psoriasis, which is usually negative for rheumatoid factor". More precise criteria and a large case-control study comparing patients with PsA with controls without arthritis (despite having had psoriasis for >10 years), properly matched for age, race, gender, geographical area, and for the subtypes of psoriasis/arthritis are needed. It would be advisable to have another control group with inflammatory arthritis without psoriasis.

The sibling recurrence risk (lambda s value) is estimated to be roughly 4 for psoriasis. Self-reported positive family histories for psoriasis among PsA patients have been observed in up to 40% and for PsA in 10%, but the familial aggregation does not follow a simple Mendelian trait. Psoriasis and PsA have not only clinical but also genetic heterogeneity, and multiple susceptibility alleles at different loci may produce the same phenotype, resulting in clinical misclassification of the disease type. There are, as yet unknown, genetic and environmental interactions, and also different combinations of susceptibility genes may predispose to different patterns of psoriasis and PsA (variable disease expression), and not everyone with such genes will develop the disease (variable penetrance). Psoriasis is associated with HLA allele Cw*0602, MICA allele 5.1, corneodesmosin allele 5 (CD*5), OTF3 beta, and HCR (pg8); they are all located on chromosome at the 6p21 region. Associations with chromosomes 17q25, 4q32-35 and 1q (S100A7) have also been reported. Similar studies of affected sib-pair families with PsA are also needed.

Activated T lymphocytes and dendritic cells mediate the disease, but the antigen (s) responsible are not known. Although

CD4⁺ T cells may help initiate the skin lesions, CD8⁺ T cells that produce type 1 cytokines (IFN-gamma) are responsible for the persistence of the lesions. This may explain the paradox observed in HIV infected patients in whom psoriasis (and PsA/reactive arthritis) can worsen dramatically even as CD4⁺ T-cell counts fall. In PsA patients a predominantly TH1 cytokine response is observed (increased IL2, TNF-beta, and IFN-gamma), but there is also an increased IL-10 response. It has recently been proposed, based on MRI studies, that PsA is enthesitis based disease, and that it is distinct from RA, where synovitis is the primary pathological feature. Local treatment of psoriasis with psoralens plus ultraviolet A radiation (PUVA) often results in long-standing remissions by greatly reducing the number of activated T cells in psoriatic skin due to induction of T-cell apoptosis. Methotrexate, and DAB389-interleukin-2 preferentially induce apoptosis of activated T cells in skin and other sites. On the other hand, cyclosporine A and topical corticosteroids only inhibits the production of cytokines; and psoriasis often recurs soon after the cessation of this treatment. Likewise, TNF-alpha blockade therapy has been found to be very effective in treating patients with severe psoriasis and PsA (including SpA), but the benefit is relatively short-lived after the therapy is discontinued. Administration of CTLA4Ig fusion protein (that blockades the B7-CD28/CD152 pathway of T cell costimulation) has produced a marked improvement of psoriasis in a phase I trial.

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Pain and memory of pain – Thursday 14 June, 14.00-15.30/Forum Hall

SP0034 PLASTICITY OF PAIN MODULATION DUE TO CHRONIC PAIN

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Descending, propriospinal, and segmental modulatory systems, tonically or phasically inhibit or facilitate the spinal transmission of nociceptive signals. Although it is widely accepted that these endogenous modulatory systems affect sensations of pain, the way in which they are brought into play and their consequences on nociceptive behaviour have rarely been addressed in the context of tissue injury. An increase of tonic descending modulation has been demonstrated during the acute stage of inflammation in both electrophysiological and behavioural experiments suggesting that this enhanced descending inhibition may limit hyperalgesia during acute inflammation.¹

To analyse further the changes of pain modulatory systems under pathological conditions and determine their potential role in the pathophysiology of pain syndromes, we investigated in a recent series of electrophysiological studies in the rat the modulation of the spinal transmission of nociceptive information during the course of inflammation.

In a first series of experiments,² diffuse noxious inhibitory controls (DNIC), which are supraspinally mediated inhibitory

controls triggered by the application of noxious stimuli, were investigated at different stages during the development of adjuvant-induced monoarthritis in the rat. In the acute stage of monoarthritis (i.e., 24-48 h), the DNIC-induced inhibitions of nociceptive neurons produced by mechanical or thermal stimulation of the arthritic joint were significantly increased at all intensities by comparison with the normal joint. In contrast, in the animals with a chronic monoarthritis (i.e., 3-4 weeks), the DNIC-induced inhibitions were not different from those observed in control animals. These data suggested that chronic inflammatory processes might have induced a reorganisation of the spinal transmission of nociceptive signals and/or modulatory systems, which could modify the recruitment of DNIC.

To test these hypotheses, other experiments were designed to analyse the changes of tonic modulation acting on the spinal transmission of nociceptive information in rats with acute or chronic monoarthritis.³ Tonic descending inhibitions were analysed by comparing the electrophysiological properties of spinal convergent neurons with ankle input before and after spinalization. Tonic descending inhibition of convergent neurons with input from the inflamed ankle was enhanced during the acute stage and then decreased during the chronic stage of monoarthritis. In addition, changes in the spinal transmission of nociceptive signals were unmasked by removing descending modulation in animals with monoarthritis: sensitisation of spinal neurons with input from the inflamed ankle was demonstrated during the acute stage of monoarthritis, while a crossed transmission between inflamed and normal sides was observed during the chronic stage of the disease.

In conclusion, these studies showed dynamic and stage-dependent modifications of the spinal transmission and modulation of nociceptive information during the course of inflammation. During both acute and chronic stages of inflammation, descending controls tended to dampen central changes at the spinal level. Such a functional plasticity might play a significant role in the pathophysiology of some acute or chronic pain syndromes observed in humans: an imbalance of descending controls could exacerbate the consequences of the central changes induced by the inflammatory processes and could result in increased and persistent pain.

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SP0035 SUPRA-SPINAL MECHANISMS OF PAIN AND NON-INVASIVE IMAGING IN THE STUDY OF CHRONIC PAIN IN HUMANS

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Pain is a complex experience that includes sensory, emotional, autonomic and motoric components, and each of these components can differ among various pain states. Despite the many qualitative differences of clinical and experimental pain states, they all share a common aversive nature, leading us to characterise each as "pain." This talk will present evidence showing a