

Seronegative Spondyloarthropathy – Studies from the Asia Pacific Region

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Abstract

Recent therapeutic advances, in particular the use of anti-tumour necrosis factor (anti-TNF) agents, have revived interest in the seronegative spondyloarthropathies (SpA), a group of arthritides characterised by axial skeletal involvement and the absence of rheumatoid factor. The purpose of this article is to review the studies that have been done in the Asia Pacific region, as a broad understanding of the scope and severity of this group of diseases would enable rheumatologists and physicians in this part of the world to better manage their patients. The majority of genetic studies have focused on the associations of HLA-B27 with ankylosing spondylitis (AS) and SpA, while a few studies examined the associations of the CARD, IL-1, LMP2, TAP and TGF with AS. There are a handful of studies on the immunological responses to bacteria and cytokine levels in AS. The onset and clinical features of SpA have been reported from most countries in the region, but no data on patient outcomes, using current measurement tools such as the Bath Ankylosing Spondylitis Disease Activity index (BASDAI), is available. Validation of these instruments of measurement as well as classification criteria in different ethnic populations is necessary where no prior data exist. Future studies will likely be focused on better clinical characterisation of patient cohorts, particularly with regard to the use of currently used measurement tools for disease activity and spinal function and mobility, and the identification of the need for biologic therapy in each country.

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Introduction

Seronegative spondyloarthropathies (SpA), a group of arthritides characterised by axial skeletal involvement and the absence of rheumatoid factor, are now enjoying a resurgence of research interest due to recent therapeutic advances. With the availability of anti-tumour necrosis factor (anti-TNF) agents, the short-term improvement in patient outcome in terms of symptom relief, reduction of inflammation and retardation of radiological deterioration has been impressive. However, their cost prohibits their use in many patients in the Asia Pacific region. Thus, it is important to have a broad understanding of the scope and severity of this group of diseases in this region, so as to enable rheumatologists and physicians to better manage

their patients. The purpose of this article is therefore to review the studies that have been performed on this group of diseases in the Asia Pacific region.

Genetic Studies

The prevalence of HLA-B27 in ankylosing spondylitis (AS) and SpA patients has been reported in studies from Australia and New Zealand,¹ China and Taiwan,²⁻¹⁵ India,¹⁶⁻²⁵ Indonesia,²⁶⁻²⁸ Japan,²⁹⁻³² the Middle East,³³⁻³⁸ Singapore^{39,40} and Thailand.⁴¹ The prevalence of HLA-B27 subtypes has been summarised in the article by Khan⁴² in a survey of HLA-B27 subtypes in world populations, in which the 5 subtypes B*2701, B*2702, B*2704, B*2705 and B*2707 are those documented to be associated with AS and SpA.

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The negative associations of B*2706 with AS have been reported in some^{8,39,43} but not all²⁶ studies.

Other HLA Class I associations reported are with HLA-B60 and -B61 in Taiwan⁴⁴ and -B39 in Japan⁴⁵ in B27 negative AS patients. HLA-A11 has been associated with SpA in Thai patients.⁴¹ More recently, an extended 6 locus haplotype B*2705-Cw*02-STR-MICA (A4)-C1_4_1 (213 bp)-C1_2_5 (178 bp)-MIB (340 bp) was found to be significantly associated with SpA in South Indian patients.¹⁶ As for HLA Class II, -DR8 has been associated with acute anterior uveitis in AS in Japan.⁴⁶

LMP2 gene polymorphism was associated with extraspinal disease in both Chinese and Caucasian HLA-B27 positive AS patients.⁴⁷ Negative associations include TAP²⁹ and transforming growth factor beta-1 gene polymorphisms.⁴⁸ IL-1 and NF-kappaB gene SNP polymorphisms were found not to play a major role in AS susceptibility in patients from Seoul and Toronto.⁴⁹ In contrast, a study of Taiwanese Chinese found an association between the IL-1 gene cluster and AS, particularly the marker IL1RN.4, and the 2-marker haplotype IL1RN.4-IL1RN.VNTR.⁵⁰ The CARD15 gene was found to be not a major contributor to AS susceptibility in the Korean population.⁵¹

HLA-A3, -B13, -B38, -DRB0101, and -DRB0301 have been found to be associated with psoriatic arthritis (PsA) in Israeli patients, while the same study found that HLA-B27 was not a marker of PsA in this cohort of patients, including those with spondyloarthritis.⁵² In Taiwan, cytochrome p450 1A1 gene polymorphisms CYP1A1 4887A and 4889G have been reported to be associated with PsA,⁵³ whereas CYP1A1 4887A appears to be a protective factor for AS.⁵⁴ The promoter polymorphisms of the TNF α gene were not associated with PsA in Japanese patients.⁵⁵

Serological and Laboratory Immunological Studies

There are few such studies from the Asia Pacific region. Immunoglobulin responses to enterobacteria in AS have been reported from Taiwan,⁵⁶ India^{57,58} and Japan.^{59,60} In the study from India, significantly elevated levels of IgG to outer membrane proteins of *Klebsiella pneumoniae* were demonstrated in AS patients. Japanese AS patients had significantly elevated IgA antibodies to *K. pneumoniae* LPS, *Salmonella enteritidis* LPS and *Salmonella typhimurium* LPS, but levels were not correlated with acute phase reactants.

In a study at Tan Tock Seng Hospital, serum TGF β 1 levels were measured in AS patients and the ability of AS patients' peripheral blood mononuclear cells (PBMCs) to synthesise TGF β 1 and other cytokines was also assessed.⁴⁸ Significantly higher levels of serum TGF β 1 were found in AS patients when compared with controls. Phyto-

haemagglutinin (PHA)-induced TGF β 1 production by PBMC was enhanced in AS patients, whereas production of the proinflammatory cytokines TNF α and IFN γ was reduced. Similar findings of reduced T cell production of TNF α and IFN γ in AS were reported by Rudwaleit.⁶¹ The results of these studies suggest that AS patients may have dysregulation of their cell-mediated immune response.

Clinical and Epidemiological Studies

Descriptive studies of SpA have been reported from China and Taiwan,⁶²⁻⁷² Japan,⁷³⁻⁸⁴ Korea,⁸⁵⁻⁹² the Middle East,⁹³⁻¹⁰¹ South Asia,¹⁰²⁻¹⁰⁹ Indonesia,¹¹⁰ Singapore¹¹¹⁻¹¹³ and Thailand.¹¹⁴⁻¹¹⁷

A study of the prevalence of undifferentiated spondyloarthritis (USpA) among first-degree relatives of AS probands in Taiwanese Chinese found that female gender predisposed one to USpA rather than AS.⁶³ A study of 370 consecutive AS patients seen over a 15-year period from 1983 to 1997 in Shantou, China had 107 patients which were followed for more than 3 years.⁶⁵ Forty-four out of the 57 patients (11.9% of the total 370) treated with slow-acting anti-rheumatic drugs (SAARDs) for more than 3 years appeared to benefit from the treatment. In a small study from Kuwait comparing 29 Arab and 26 South Asian patients with AS and USpA, no significant differences were found in the occurrence of bamboo spine, syndesmophytes and sacroiliitis in both groups.⁹⁹ Adult onset AS patients in Korea with peripheral joint disease (hips and shoulders excluded) had fewer spinal symptoms at presentation compared to those without peripheral joint disease.⁸⁵ The course of spinal disease in Korean juvenile onset AS was less severe than in adult onset AS.⁸⁸ Out of 107 Korean patients fulfilling European Spondyloarthritis Study Group (ESSG) criteria for SpA, joint involvement tended to be monoarticular or pauciarticular, most frequently involving the lower extremities.⁸⁹

Clinical features of SpA did not differ in between Chinese and native Indonesians in a study from Indonesia,¹¹⁰ while another study found that Thai AS patients had similar features to those reported elsewhere in the world.¹¹⁷ Peripheral joint involvement was common in a study of 150 AS patients in Singapore but extraarticular manifestations were rare apart from uveitis (17%).¹¹¹

Acute anterior uveitis (AAU) was found to occur more in patients who develop peripheral arthritis during the course of AS, in a study of 222 Caucasian and 49 Taiwanese patients.⁶⁸ A study of 102 AS patients in South India found that 59 presented with axial involvement, 38 with peripheral arthritis, 18 with heel pain and 11 with AAU.¹⁰⁵

A survey of SpA patients seen at tertiary centres in Seoul, Sydney and Singapore yielded the data shown in Table 1.

Table 1. A Survey of Seronegative Spondyloarthritis in the APLAR (Asia Pacific League of Associations for Rheumatology) Region

	The St. George Hospital University of NSW Sydney, Australia 1999 No. of patients	Seoul National University Hospital Seoul, Korea 1999 No. of patients	Tan Tock Seng Hospital Singapore 2002 No. of patients
AS	21	80	84
Male/Female	18/3	72/7	69/15
Average age of onset (y)	34	29.3	38.3
B27+/No tested	13/14	79	31/35
NSAID	19	77	75
SSZ	15	36	47
MTX	8	16	12
IA steroid	12	2	13
Alt/Trad Rx	0	55	7
Surgery	4	2	3
PsA	50	4	112
Male/Female	15/35	3	58/54
Average age of onset (y)	47.4	36.3	44.6
NSAID	43	4	41
SSZ	24	1	75
MTX	18	2	16
IA steroid	18	0	3
Alt/Trad Rx	0	2	2
Surgery	5	0	4
IBD	6	1	0
NSAID	6	1	
SSZ	5	1	
MTX	3	0	
IA steroid	4	0	
Alt/Trad Rx	2	1	
Surgery	0	0	
SARA	0	0	1
NonSARA	6	0	4
B27+/No tested	4/6		2/4
NSAID	6		3
SSZ	3		1
MTX	2		2
IA steroid	4		1
Alt/trad Rx	1		0
USpA	15	15	19
Male/Female	4/11	12/3	11/8
Average age of onset (y)	38.4	34.7	45.7
B27+/No tested	10/11	9	0
NSAID	13	15	16
SSZ	8	6	8
MTX	5	1	11
IA steroid	12	0	1
Alt/Trad Rx	0	7	1
Surgery	3	1	0
Total	98	100	220

Alt/Trad Rx: alternative/traditional treatment; IA: intraarticular; IBD: inflammatory bowel disease; MTX: methotrexate; SARA: sexually acquired reactive arthritis; SSZ: sulphasalazine; USpA: undifferentiated spondyloarthritis

Evaluation of ESSG (European Spondyloarthritis Study Group) Criteria in a Chinese Population

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Although generated in European countries, the ESSG classification criteria for SpA^{118,119} have become a worldwide gold standard for recruiting patients into studies on SpA. But compared to diagnosis by “expert opinion”, the sensitivity and specificity of the European criteria would vary with different ethnicities. Hence, before using these criteria to study patients of a certain ethnicity where no prior data exist, validation of the accuracy of the ESSG criteria for that particular ethnicity is necessary.

We have addressed this problem for a Chinese population in Guangzhou.⁶⁴ In our study, patients were recruited from a rheumatology clinic in a university medical centre irrespective of the diagnosis. Rheumatologists specialising in SpA would then diagnose each patient as having SpA or not based on their own opinion. This approach is called diagnosis by “expert opinion”. Each patient was then reviewed separately by collaborating investigators who had no prior knowledge of the expert opinion. Parameters included in the SpA criteria were assessed. From the results, the degree of concordance between the “expert opinion” and the classification criteria was then calculated.

Two groups of subjects were enrolled consecutively from the rheumatology outpatient clinics of the third affiliated hospital of Sun Yat-Sen University, of which 193 patients were SpA, and 166 were controls with other rheumatic disorders.

The method used to calculate the sensitivity and specificity is shown in Table 2.

Table 2. Calculation of Sensitivity and Specificity of ESSG Criteria

Test result	True diagnosis		
	Disease	No disease	Total
Positive	a	b	a+b
Negative	c	d	c+d
Total	a+c	b+d	a+b+c+d

Sensitivity = $a/(a+c)$: the probability of having a positive test if the patient had disease

Specificity = $d/(b+d)$: the probability of having a negative test if the patient had no disease

Of the 193 patients clinically diagnosed as having SpA, 165 satisfied the ESSG criteria. The sensitivity of the ESSG criteria in these patients was 85.4% (100 x 165/193). Of the 166 control arthritis patients, 6 fulfilled the ESSG criteria, so the specificity of the criteria was 96.4% (100 x 160/166). There was no difference between the 2 genders when the results were calculated separately.

A total of 359 persons were enrolled into the study. The

sensitivity and specificity of ESSG criteria were 85.4% and 96.4%, respectively.

To further characterise the AS patients, 111 consecutive AS patients who fulfilled the modified New York criteria were recruited from outpatient clinics. The mean age was 30 ± 9 years. Of those 111 AS patients, 95 were male (85.6%). There were 104 patients (93.7%) with decreased Schober test (≤ 5 cm), and 48 (43.2%) patients with decreased chest expansion (≤ 2.5 cm). All those 48 patients with limited chest mobility also had limited motion in the lumbar spine (Schober test ≤ 5 cm). These results show that AS patients attending our specialist clinics in China are of a young age group, male gender and already demonstrated limited mobility at the time they sought medical attention.

Therapy

Besides studies on the use of thalidomide in Chinese patients with AS^{119,120} and the use of a traditional Chinese medication^{121,122} there do not seem to be studies on therapy from the Asia Pacific region. Table 1 shows that sulphasalazine was used by half or more of AS patients in the 3 hospitals surveyed in Seoul, Sydney and Singapore, while methotrexate was used in up to a third of AS patients in these countries. More than half of the Korean AS patients also used alternative or traditional therapy while less than a tenth of Singapore patients and none of the Australian patients did so. The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) was not included in the data collection in this survey. It is likely that a survey of the patients at present would find that a significant number would require anti-TNF therapy, as the current recommendation is a BASDAI score exceeding 4 despite optimal NSAID use.¹²³

In conclusion, most studies from the Asia Pacific region over the last 2 decades have focused on the genetic associations and clinical features of AS and SpA patients in hospital-based cohorts. With the advent of biologic therapy, the focus of studies would now be shifted to better clinical characterisation of these cohorts, particularly with current day measurement tools for disease activity and spinal function and mobility, and the identification of the need for biologic therapy in each country.

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