Editorial

HLA Studies in Psoriatic Arthritis: Current Situation and Future Needs

Psoriatic Arthritis (PsA) has been defined as an inflammatory arthritis associated with psoriasis, usually seronegative for rheumatoid factor (RF)[1]. Since psoriasis affects 1–3% of the population and up to one-third of the patients with psoriasis may develop an inflammatory form of arthritis, the prevalence of PsA may be as high as 1%[2-4]. PsA has been identified as a clinical entity distinct from rheumatoid arthritis (RA) because of several distinguishing features, including the equal sex distribution, the frequency of distal joint involvement, the asymmetric distribution at presentation, the presence of spondyloarthropathy in 40–50% of the patients, the absence of RF, the association with HLA-B27 antigen, and the presence of extraarticular features of seronegative spondyloarthropathies, none of which are typical features of RA.

Although Moll and Wright[1] recognized a subset of patients with a mutilating form of arthritis among patients with PsA, PsA was considered a mild disease until the mid-1980s, when it was documented that some 20% of the patients had a severe progressive and destructive arthritis[5]. Subsequent studies confirmed the notion that PsA may lead to joint destruction[2], and that patients with PsA may fare as poorly as patients with RA[6]. Indeed, because of the inflammatory peripheral arthritis, which in some patients may be indistinguishable from RA, the identity of a unique form of arthritis associated with psoriasis has been questioned[7].

Genetic factors have been considered important in studies of both the susceptibility and severity of PsA. An investigation of 100 families revealed that relatives of patients with PsA were 48 times more likely to have PsA than the general population[8]. Several genome scans performed in psoriasis have shown linkage with genes on chromosomes 1p, 4q, 6p, and 17q, and the strongest association is with a locus on chromosome 6p[9,10].

HLA association studies have identified that class 1 HLA antigens are associated with both psoriasis and PsA[11]. HLA-B13, B16 and its splits HLA-B38 and HLA-B39, B17, and Cw6 have been associated with psoriasis, while HLA-B7 and B27 have been associated with PsA. The association of class 2 antigens has been more controversial. While HLA-DR7 has been associated with psoriasis in most studies, HLA-DR4 has been variably associated with PsA. One study suggested the association with HLA-DR4 is noted only among patients with the PsA pattern that is indistinguishable from RA[12].

Since the HLA-DR4 was noted to be associated with the RA-like pattern of PsA, the question arose of the role of the shared epitope, the RA motif of the third variable region of the class 2 molecule at position 74–86, in PsA. We addressed this issue by comparing the HLA-DRB1*04 alleles among patients with PsA and RA and healthy controls, all of whom carried at least one HLA-DRB1*04 allele[13]. The study indicated that patients with PsA had a lower frequency of HLA-DRB1*0401, but a higher frequency of the HLA-DRB1*0402 allele. Patients with RA were more likely to have more than one shared epitope allele than either patients with PsA or the healthy controls. However, this study did not include patients who did not carry at least one HLA-DRB1*04 allele.

The association studies clearly show a role for HLA antigens in the susceptibility to PsA. Recent studies have also implicated HLA antigens in disease progression. HLA-B27 in the presence of HLA-DR7, HLA-B39, and HLA-DQw3 in the absence of HLA-DR7 are associated with disease progression, whereas HLA-B22 is "protective"[14]. It has also been reported that the HLA-C*0602 is associated with PsA and with the early onset of psoriasis[15,16].

Korendowych, *et al*[17] recently compared HLA-DRB1 alleles in 158 patients with PsA with 250 healthy controls. They found an increased frequency of HLA-DRB1*07 among the patients with PsA compared to controls. They confirm previous serological studies showing no increased

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frequency of HLA-DRB1*04 in patients with PsA compared to controls, and demonstrate no difference in the frequency of the shared epitope between patients and controls. However, they did find that patients with the shared epitope were more likely to develop erosions. Unfortunately, the study did not include class 1 alleles and this limits comparisons with other disease susceptibility and expression studies.

The comparison of HLA studies in PsA usually raises the question of why there are differences between the studies. With respect to actual frequencies, one obvious answer is that populations differ. The frequency of certain alleles in a patient cohort will be dependent on the frequency of the alleles in the control population. With respect to relative frequencies in patient and control populations, some quantitative differences might also be expected across populations, but qualitative differences should be less common.

Apparent qualitative differences sometimes arise because of a reliance on statistical significance in the reporting of results. If multiplicity considerations are ignored, Korendowych, *et al* (elsewhere in this issue) report a p value of 0.03 for the comparison of HLA-DR2 (HLA-DRB1*15 or HLA-DRB1*16) frequencies in patients (19%) and controls (28%)[17]. In our Toronto database, 23% of 473 patients and 26% of 641 controls have HLA-DR2. This leads to a comparison p value of 0.29, suggesting a conflict with the results of Korendowych, *et al*. However, based on the data of Korendowych, *et al*, the estimated odds ratio (OR) that compares the probability of having HLA-DR2 in patients versus controls is 0.59 with an associated 95% confidence interval (CI) of (0.36, 0.96). Based on the Toronto data, the estimated OR is 0.86, with a CI of (0.65, 1.14). The overlapping CI indicate that there is no demonstrable conflict between the 2 data sources.

There is a great need for large definitive HLA studies in PsA. This requires the maintenance of large clinical databases and/or collaborative efforts. For example, the data from Korendowych, *et al*[17] lead to an estimated OR of 2.02 with a 95% CI of (1.32, 3.10) for the comparison of HLA-DRB1*07 frequencies in patients and controls. The Toronto data, based on larger sample sizes, lead to an estimate of 1.54, with a narrower 95% CI of (1.17, 2.01). The combination of the 2 data sources, adjusting for differences between institutions, leads to an overall OR estimate of 1.66, with an even narrower CI (1.32, 2.09). There is no evidence of different OR in the 2 clinics (p = 0.29). The value of larger data sets in the provision of more precise information is well illustrated. A further value of larger data sets is the capability they offer for multivariate studies of genetic relationships that can take into account linkage and the possibility of interaction effects.

The role of the shared epitope and disease expression in RA has been controversial. The creation of large data sets with relevant information could greatly reduce the uncertainty surrounding this intriguing question. Minimally, even the careful replication of studies in various populations can help by reduction of the need for multiplicity adjustments. For example, the association between shared epitope and erosions found by Korendowych, *et al*[17] can now be taken as an *a priori* hypothesis for studies in other centers.

The article by Korendowych, *et al* in this issue serves to confirm some previous findings and to raise some new questions. While in no way detracting from this type of contribution, which characterizes much of the work concerning HLA relationships with disease susceptibility and expression, it is perhaps time to call for a concerted effort to produce more definitive data sources.

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REFERENCES

1. Wright V, Moll JMH. Psoriatic arthritis. In: Wright V, Moll JMH. Seronegative polyarthritis. Amsterdam: North Holland Publishing Co.; 1976:169-223.
2. Goodfield M. Skin lesions in psoriasis. Baillieres Clin Rheumatol 1994;8:295-316.
3. Gladman DD, Rahman P. Psoriatic arthritis. In: Ruddy S, Harris ED, Sledge CB, Budd RC, Sergent JS, editors. Kelly's textbook of rheumatology. 6th ed. Philadelphia: W.B. Saunders Co.; 2001:1071-9.
4. Gladman DD, Shuckett R, Russell ML, Thorne JC, Schachter RK. Psoriatic arthritis — clinical and laboratory analysis of 220 patients. QJM 1987;62:127-41.
5. Sokoll KB, Helliwell PS. Comparison of disability and quality of life in rheumatoid and psoriatic arthritis. J Rheumatol 2001;28:1842-6.
6. Cats A. Psoriasis and arthritis. Cutis 1990;46:323-9.
7. Moll JM, Wright V. Familial occurrence of PsA. Ann Rheum Dis 1973;32:181-201.
8. Elder JT, Nair RP, Henseler T, et al. The genetics of psoriasis 2001. The odyssey continues. Arch Dermatol 2001;137:1447-54.
9. Schmitt-Egenolf M, Windemuth C, Hennies HC, et al. Comparative association analysis reveals that corneodesmosin is more closely associated with psoriasis than HLA-Cw*0602-B*5701 in German families. Tissue Antigens 2001;57:440-6.
11. Eastmond CJ. Genetics and HLA antigens. In: Wright V, Helliwell P, editors. Bailliere's clinical rheumatology. Psoriatic arthritis. London: Balliere Tindall; 1994:263-76.
12. Gladman DD, Anhorn KB, Schachter RK, Mervart H. HLA antigens in psoriatic arthritis. J Rheumatol 1986;13:586-92.
13. Gladman DD, Farewell VT, Rahman P, et al. HLA-DRB1*04

alleles in psoriatic arthritis: comparison with rheumatoid arthritis and healthy controls. Hum Immunol 2001;62:1239-44.
14. Gladman DD, Farewell VT, Kopciuk K, Cook RJ. HLA antigens and progression in psoriatic arthritis. J Rheumatol 1998;25:730-3.
15. Gladman DD, Cheung C, Michener G, Wade JA. HLA C-locus alleles in psoriatic arthritis. Hum Immunol 1999;60:259-61.
16. Enerback C, Martinsson T, Inerot A, et al. Evidence that HLA-Cw6 determines early onset of psoriasis, obtained using sequence-specific primers. Acta Dermatol Venereol 1997;77:273-8.
17. Korendowych E, Dixey J, Cox B, Jones S, McHugh N. The influence of the HLA-DRB1 rheumatoid arthritis shared epitope on the clinical characteristics and radiological outcome of psoriatic arthritis. J Rheumatol 2003;30:96-101.