Rheumatoid Arthritis: The future is not yet now

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Rheumatoid arthritis is a relatively common (0.5–1%) chronic inflammatory systemic disease that primarily affects peripheral joints. Its clinical course is characterized by insidious progression and destruction of the affected joints, resulting in significant morbidity and mortality. Despite considerable efforts to ascertain its cause, the etiology of RA remains an enigma. Extensive investigation of metabolic, endocrine, nutritional, as well as psychosocial, geographic, ethnic and occupational factors suggests that some or all may influence the course of the disease but there is very little evidence that they are involved in its cause.

In recent years, research in this area has concentrated on the interplay between genetic susceptibility and environmental exposure [1]. Family and twin studies indicate that RA probably involves many genes as attested to by only 15–30% concordance for RA in monozygotic twins and its incomplete penetrance. RA-associated HLA molecules that stem from the HLA-DR4 locus have been considered to be genetic markers for disease evolution. In patients with RA, certain HLA-DR4 subtypes, i.e., Dw4, Dw10, Dw13, Dw14 and Dw15, predominate. In HLA-DR4-negative RA patients other HLA-DR molecules – DR1, DR6 and DR10 – share structural homology with the above-mentioned subtypes [2]. The shared epitope (HLA-DRB1) theory generated considerable promise that individuals at risk would be identified relatively easily. However, population-based studies have not shown an association between HLA-DR and RA [3]. The HLA genes probably modify disease expression, as HLA-DRB1-negative patients tend to have a milder, less aggressive form of the disease [4]. While the HLA system has been the focus of most of the genetic studies, the polygenic nature of RA mandates that candidate genes other than HLA-DR alleles be considered and that these, independently or in combination with HLA-DR alleles, may significantly influence disease initiation and expression [5,6].

While some progress has been made in the genetic characterization of patients at risk for developing progressive destructive RA, the search for putative environmental mechanisms that initiate tissue injury in RA has been unsuccessful. An attractive avenue of study has been the pursuit of an infectious etiology for RA [7]. Bacterial and viral infectious agents have been shown to produce polyarthritis, often resembling RA, in animals and humans. Extensive investigation into the possible role of viruses (HTLV-1, parvovirus B19, herpesviruses, papillomavirus, adenovirus) has largely revealed data that support an attenuated immune response, systemically and in the synovium, to these viruses rather than a causative role in RA. For example, parvovirus has been isolated from the joints of a small percentage of patients with inflammatory arthritis. However, the disease is often mild and rarely destructive [8]. By and large, microorganisms have not been cultured from the synovium, and a direct relationship between a putative infectious agent and chronic arthritis has eluded investigators. The identification in the synovium of breakdown products derived from the cell walls of dead bacteria as well as bacterial antigens that can induce synovitis are indirect lines of evidence that lend credence to the postulate that RA may have an infectious etiology. Alteration of the intestinal flora in patients with RA, examples of therapeutic response to antimicrobial agents, the detection of cellular and humoral immune responses to some bacteria, and the localization of bacterial DNA or RNA in the joints of RA patients have received and continue to receive unabated attention.

In this issue of the Journal, Rashid et al. [9] review the evidence supporting the causative link between *Proteus mirabilis* and RA. They summarize immunological, biochemical, bacteriological, structural and genetic data suggesting a cause and effect relationship. Isolation of *P. mirabilis* from the urine of some patients with rheumatoid arthritis and/or identification of serum anti-*Proteus* antibodies with cytotoxic capability are not conclusive evidence for the role of this species in the etiology or pathogenesis of RA. These authors advocate the implementation of specific antimicrobial measures directed against *P. mirabilis* as a possible "curative" treatment for RA. They propose antibacterial therapy, with or without traditional anti-inflammatory and disease-modifying drugs, in the early stages of RA before structural damage has begun. The authors agree that studies reporting antibiotic use in the treatment of RA have shown marginal efficacy. Minocycline, for example, probably exerts its anti-rheumatic effects via metalloproteinase inhibition, an action shown to be independent of antimicrobial activity. Extensive investigation is necessary before "well-controlled prospective studies" can be performed with more potent agents. Which antibiotics? Who are the appropriate patients? For how long should they be treated? It is proposed that the most suitable candidates for this intervention would be those individuals who carry disease-susceptibility markers. As

RA = rheumatoid arthritis

mentioned above, present-day understanding of the genes that can accurately identify potential RA patients is lacking and, consequently, administration of broad-spectrum antibiotics on an empiric basis is probably premature.

Reactive arthritis encompasses a group of diseases clinically distinct from RA in which a sterile synovitis develops after infection in a site remote from the affected joint(s). Clinically, ReA is characterized by asymmetric oligoarthritis, enthesitis, sacroiliitis, uveitis and skin lesions. Serum rheumatoid factor is absent, but sometimes symmetric involvement of the small joints of the hands and feet may resemble RA. The course may vary from a mild episodic non-destructive arthritis to a chronic debilitating disease. Also in this issue of *IMAJ* [10], Auli and Paavo Toivanen review the current understanding of ReA and underscore a number of questions. Firstly, within days to weeks, primary infections of the gastrointestinal, urogenital and respiratory tracts can trigger an inflammatory arthropathy in previously healthy but genetically susceptible individuals. Secondly, although the HLA–B27 antigen is a marker for disease susceptibility, not all B27-positive individuals will contract the disease following appropriate infectious exposure, and ReA may develop after streptococcal (rheumatic fever) or spirochetal (Lyme disease) infection, an association that is unrelated to the presence of B27 [11]. Thirdly, following proven chlamydial urogenital infection, bacterial degradation products as well as chlamydial RNA and DNA can be demonstrated in the synovial fluid and synovium of those patients who have developed ReA. Finally, despite the definite antecedent infectious etiology of ReA, the value of antibiotic therapy either at the time of infection or upon the onset of joint inflammation is essentially unproven [12].

These two papers [9,10] taken together beg the following question. Apart from the ostensibly different clinical phenotypes seen in RA and ReA, are they really separate entities? In RA, where an infectious etiology cannot be readily shown, and ReA, which is triggered by ubiquitous gastrointestinal and urogenital pathogens, microbial breakdown products and antigens stimulate synovial immune responses and thereby perpetuate joint inflammation [13]. Currently, research in all facets of both diseases originates from collecting relevant specimens (DNA, blood samples, synovial fluid, etc.) only from patients who meet pre-defined clinical criteria for inclusion. Such an approach, forced upon investigators for pragmatic reasons, sets boundaries that limit conceptual thinking. Conceivably, the differences in disease expression are genetically mediated. Some individuals with certain gene(s) respond, in a limited clinical pattern, following exposure to an infectious pathogen, e.g., *Proteus mirabilis* or a myriad of other possible agents. In others, a specific gene(s) may dictate different clinical responses to the same pathogen. Hopefully, population-based genetic studies testing large numbers of candidate genes will provide the missing link between genotypes and clinical disease.

While the etiology and genetic influence on disease expression continue to elude us, over the last 10 to 15 years tremendous strides have been made in our understanding of the pathogenesis of RA and, in particular, the mediators of the inflammatory response [14]. Moreland [15], in this issue of *IMAJ*, reviews the physiological functions of tumor necrosis factor-alpha, the major pro-inflammatory cytokine that promotes tissue inflammation and damage in RA and other chronic inflammatory disorders. He describes the development of two biologic agents (Etanercept and Infliximab) that block TNF activity, and highlights the controlled clinical studies that have demonstrated their efficacy in active refractory RA [16,17]. The data are impressive! Both agents, alone and in combination with methotrexate, significantly ameliorate disease activity, improve function, and retard radiographic progression. This was true not only for established disease. Etanercept given early (within 3 years of onset) was superior to methotrexate in terms of clinical response and in preventing erosive changes in the joints. Efficacy has been maintained for more than 3 years and side effects have been generally mild. In addition, TNF is also prominent in the pathogenesis of ReA and the spondyloarthropathies, and TNF blockade has been shown to be most efficacious [18].

For those patients inflicted with this devastating illness and the physicians involved in their care, advances like these are most welcome. Some have proclaimed, "in rheumatoid arthritis the future is now"! However, before we pat ourselves on the back and tout that RA has been conquered, a few words of caution are appropriate. Post-marketing surveillance studies have shown an increased incidence of infections, particularly tuberculosis, and isolated cases of aplastic anemia and a demyelinating neurological condition resembling multiple sclerosis have been reported. Physiologically, TNF plays a role in immune surveillance (especially during infection), and inhibition of its action for prolonged periods may compromise the immune system and expose patients to infection or neoplasms. Anti-DNA autoantibodies have been observed but their significance is presently unknown [19]. For many patients, the hope generated by the availability of these agents is illusory. At $13,000–16,000 a year, cost alone places it out of the reach of most patients. While many health plans and insurance companies in the United States cover patients for anti-TNF treatment, in Europe and other parts of the world the onus is placed squarely on the patient and their families. Notwithstanding these remarks, sophisticated biological drugs – tailor made to interfere with molecules relevant to specific disease-promoting processes – are here to stay [20]. Hopefully, with the development of new agents, cost will be contained and they will be made available to all patients with chronic inflammatory joint disease.

ReA = reactive arthritis

TNF = tumor necrosis factor

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