Common Denominators of Inflammatory Joint Diseases

HANI EL-GABALAWY

ABSTRACT. Inflammatory joint diseases (IJD) are a heterogeneous group of disorders whose primary pathologic target is articular and periarticular tissue. Although each form of IJD is clinically distinct, these disorders share a number of common clinical, epidemiological, and pathogenetic elements. In all cases, there is a complex interaction between genetic and environmental factors that serves to initiate the process, and likely, there is a different set of interactions to perpetuate the arthritis, as well as determine the destructiveness of the process. There are a number of intervention checkpoints common to all forms of IJD. These include pri-mary prevention by identifying populations at risk and environmental triggers; prevention of persistent syn-ovitis, articular damage, and functional disability; and restoration of function. Research and innovation directed at each of these key intervention checkpoints will improve the care of these disorders, and ulti-mately save valuable health care resources. (J Rheumatol 2005;32 Suppl 72:3-6)

Key Indexing Terms:
ARTICULAR INFLAMMATION
PATHOLOGIC PROCESSES
EPIDEMIOLOGY

Inflammatory joint diseases (IJD) are a group of idiopathic systemic disorders that feature articular inflammation as the primary clinical and pathologic process. These include rheumatoid arthritis (RA), several forms of juvenile idiopathic arthritis (JIA), and the spondyloarthropathies, the latter group including psoriatic arthritis (PsA), ankylosing spondylitis (AS), reactive arthritis (ReA), and enteropathic arthritis (EA). Each of these disorders is characterized by typical clinical features that are used in clinical practice to place patients into diagnostic categories, and in turn to develop a management program. Classification criteria sets have been developed for the most common of these disorders[1,2]. These criteria sets are of more value for clinical studies than for establishing clinical diagnosis. It is important to note that patients presenting to early arthritis clinics with symptoms of joint inflammation often cannot be classified into any of these criteria sets, and are typically labeled as having undifferentiated arthritis[3,4]. Despite the clinical differences between the various forms of IJD, there are also a number of common characteristics, as summarized in Table 1.

The etiology of most forms of IJD is not known, and the pathogenesis is incompletely understood. Notwithstanding this incomplete understanding, the pathogenesis of all forms of IJD incorporates 3 interrelated processes: an immune response, an inflammatory response, and an articular response (Figure 1). The degree to which each of these processes contributes to the clinical phenomenology continues to be defined, and differs at different stages of the diseases. For example, the immune response plays a key role in the initiation and early stages of ReA, while the mesenchymal response of the synovial tissue plays a key role in the destructive phase of RA.

Table 1. Common clinical characteristics of inflammatory joint diseases.

- Onset difficult to predict
- Genetic and environmental factors
- Typical patterns of articular involvement
- Persistent synovitis
- Damage to cartilage, bone, soft tissues
- Variable functional loss and disability
- Systemic and extraarticular inflammation

Regulation of the immune, inflammatory, and articular responses involves a complex interaction between genetic predisposition and environmental factors. Moreover, this interaction differs somewhat with each type of IJD. It is now well established that the strongest genetic predisposition for most forms of IJD resides in the HLA locus of the MHC, attesting to the importance of the immune system in the pathogenesis of these disorders. In the case of the spondyloarthropathies, genetic susceptibility is associated with the HLA-B27 allele found in the class I region of the MHC, while in the case of RA, the susceptibility lies in the class II region, with certain alleles of the HLA-DRB1 locus conferring the risk. Other MHC loci that confer additional risk are currently being sought[5], and a host of non-MHC loci have also been identified in whole-genome scans in RA and AS[6,7].

Although equally important, the environmental susceptibility factors have been more difficult to define for each form of IJD. In the case of ReA, the role of specific microbial agents in triggering articular inflammation is now well established. In contrast, a role for microbial agents in RA has been difficult to demonstrate repro-

From the University of Manitoba, Winnipeg, Manitoba, Canada.

H. El-Gabalawy, MD, FRCPC, Professor of Medicine and Immunology, Rheumatology Research Chair, Director, Arthritis Centre.

Address reprint requests to Dr. H. El-Gabalawy, University of Manitoba, Health Sciences Centre, RR149, 800 Sherbrook Street, Winnipeg, Manitoba R3A 1M4. E-mail: elgabal@cc.umanitoba.ca

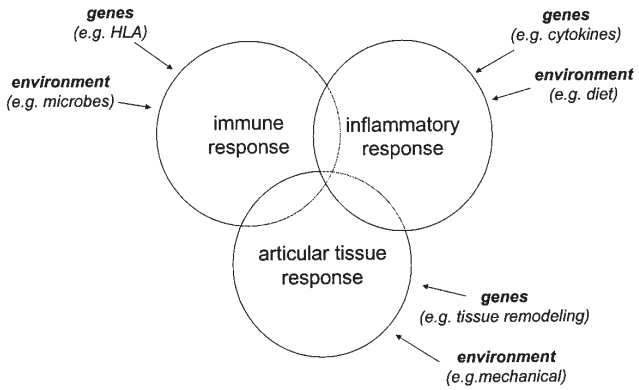

Figure 1. Common pathogenetic elements of inflammatory joint diseases.

ducibly. Interestingly, it would appear that one of the strongest environmental factors involved in RA is smoking[8]. The mechanisms involved in this predisposition are presently unknown. A role for diet in modulating the inflammatory response has also been described, with omega-3 fatty acids having modest but definite antiinflammatory effects[9]. Finally, a role for mechanical factors in modulating the cellular and molecular responses of articular cartilage is currently an area of active investigation.

Arguably the most important common pathogenetic element in all forms of IJD is the development of persistent synovitis. In clinical practice, the presence of synovitis in one or more joints as evidenced by pain, swelling, and stiffness is the earliest clinical manifestation of IJD. In the case of spondyloarthropathies, axial inflammation is typically present, along with a predilection for enthesitis. For the most part, the early synovitis is nonspecific in these disorders, and detailed histopathologic studies have generally not discriminated between the various forms of IJD (reviewed in[10]).

It has long been proposed that the initiation of RA and other forms of IJD likely involves presentation of an arthritogenic antigen to T cells. Despite extensive investigation, to date, such an antigen has not been identified in any form of IJD, with the possible exception of some cases of ReA. An alternative hypothesis based on the currently available data suggests that the early events in most forms of IJD involve a nonspecific inflammatory response mediated primarily by elements of the innate immune system. An important role for adjuvants in this process has been established in animal models. Although it remains challenging to explain the localization of such nonspecific inflammatory responses to the synovium, animal models such as adjuvant arthritis suggest that this can easily be achieved in genetically susceptible strains (individuals).

A key event in the pathogenesis of IJD is the transition from early, nonspecific synovitis to persistent, chronic synovitis that in many individuals lasts a lifetime. A study

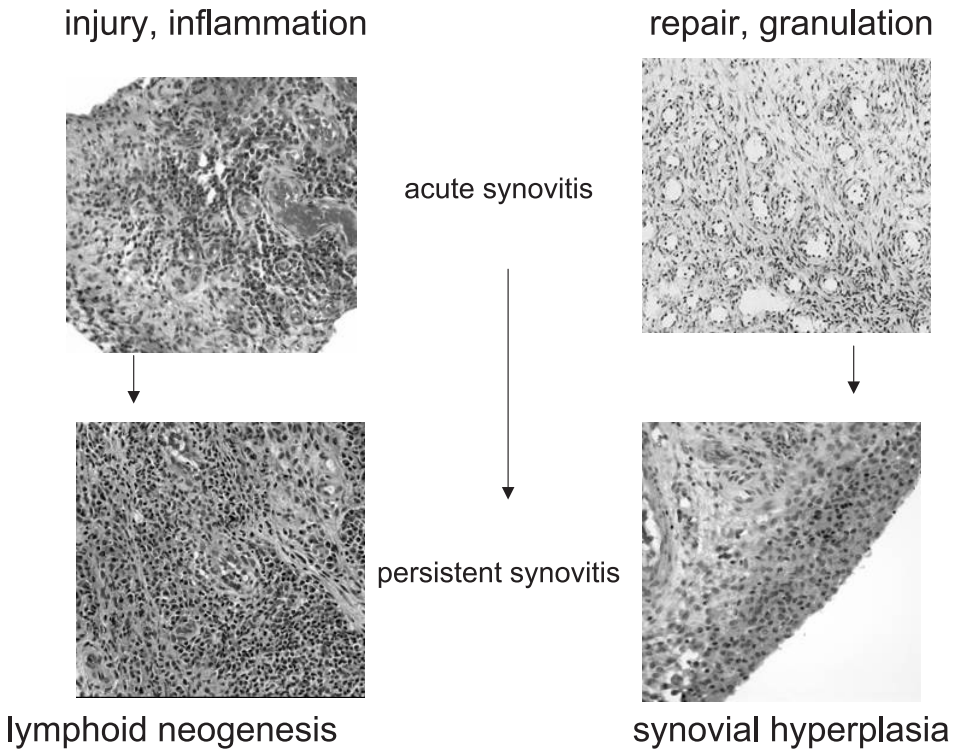

Figure 2. Histological sample showing progression of synovitis in inflammatory joint diseases.

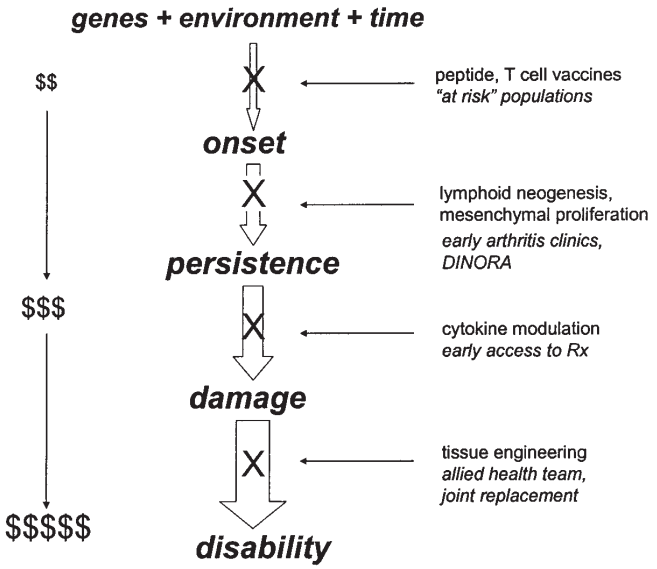

Figure 3. Points of intervention in inflammatory joint diseases.

of synovial histopathology in a US National Institutes of Health cohort of early synovitis patients examining predictors of persistence and remission showed that lymphoid neogenesis and proliferation of mesenchymal/stromal elements in the synovium were the most predictive of persistent synovitis[5] (Figure 2). Interestingly, the presence of lymphoid neogenesis in the synovium was highly associated with the presence of RA autoantibodies in the serum, including rheumatoid factor (RF), anticyclic citrullinated peptides (CCP), and anti-Sa.

INTERVENTION CHECKPOINT IN INFLAMMATORY JOINT DISEASES

As shown in Figure 3, there are a number of intervention checkpoints that are common to all forms of IJD. The first, and certainly the most ideal from an epidemiologic and healthcare delivery point of view, is primary prevention. This strategy has recently gained momentum with the report that RA associated autoantibodies such as RF and anti-CCP can in some cases be detected in the serum of patients years before the onset of clinical symptoms[11]. Thus, it is at least theoretically possible to identify "at-risk" cohorts of individuals in whom to test novel prophylactic strategies such as peptide or T cell vaccination.

The next checkpoint is the prevention of persistence, once early synovitis has been detected. This strategy is critically dependent on very early detection of synovitis, likely within a number of weeks from the onset of clinical symptoms. The establishment of national and international networks of early arthritis clinics would provide the best basis for undertaking such an initiative. Currently, a large international protocol, DINORA (Definitive Intervention in New-Onset Rheumatoid Arthritis), has been proposed to test the hypothesis that very early intervention can indeed produce long-lasting remissions or even cure.

Once persistent synovitis is present, the next checkpoint is the prevention of joint damage. Although a number of strategies have been developed to accomplish this, it is clear that prevention of articular damage occurs predictably only when a state of clinical remission, or as close as possible to it, is achieved. Moreover, a number of lines of evidence suggest that the inhibition of tumor necrosis factor-alpha (TNF-α) may be particularly important in inhibiting the development of erosive damage in RA, and possibly other forms of IJD[12,13]. This may relate to the central role that TNF-α plays in osteoclastogenesis. Taken together, these observations suggest that early access to aggressive therapies is of major importance in preventing articular damage in IJD.

The final intervention checkpoint, once irreversible articular damage has occurred, is to prevent loss of function and disability. The multidisciplinary "rheumatology team," which typically brings together rheumatologists, orthopedic surgeons, physiotherapists, occupational therapists, nurse clinicians, and other professionals, has proven to be an effective approach to the prevention of disability and the maintenance of function in patients with IJD. It should be noted that evidence for the effectiveness of nonpharmacological interventions in improving outcomes of IJD is lacking, and high quality research is needed in this area.

Joint arthroplasty has arguably been the single most important advance in reversing the disability caused by IJD. Canadian health services research has revealed disparities in the access to these procedures, the causes of which are not clear[14]. Further investigation in this area, and in the area of health disparities in general, is also much needed.

CONCLUSIONS

Inflammatory joint diseases pose a challenging problem for healthcare delivery because of their unpredictable onset, variable outcome, and their tendency towards a progressive, disabling course in a substantial number of cases. There are multiple checkpoints for intervention in these disorders. A research agenda focused on early detection and on the development and testing of innovative therapeutic strategies holds the best promise of preventing disability, damage, and persistence.

REFERENCES

1. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24.
2. Dougados M, van der Linden S, Juhlin R, et al. The European Spondylarthropathy Study Group preliminary criteria for the classification of spondylarthropathy. Arthritis Rheum 1991;34:1218-27.
3. El-Gabalawy HS. The challenge of early synovitis: multiple path

ways to a common clinical syndrome. Arthritis Res 1999;1:31-6.
4. El-Gabalawy HS, Duray P, Goldbach-Mansky R. Evaluating patients with arthritis of recent onset: studies in pathogenesis and prognosis. JAMA 2000;284:2368-73.
5. El-Gabalawy HS, Hitchon CA, Schumacher HR, Yarboro C, Duray P, Goldbach-Mansky R. Synovial histopathological features and RA autoantibodies predict persistence in patients with synovitis of recent onset [abstract]. Arthritis Rheum 2003;48 Suppl:1743.
6. Eyre S, Barton A, Shephard N, et al. Investigation of susceptibility loci identified in the UK rheumatoid arthritis whole-genome scan in a further series of 217 UK affected sibling pairs. Arthritis Rheum 2004;50:729-35.
7. Laval SH, Timms A, Edwards S, et al. Whole-genome screening in ankylosing spondylitis: evidence of non-MHC genetic-susceptibility loci. Am J Hum Genet 2001;68:918-26.
8. Silman AJ, Pearson JE. Epidemiology and genetics of rheumatoid arthritis. Arthritis Res 2002;4 Suppl 3:S265-72.
9. Cleland LG, James MJ, Proudman SM. The role of fish oils in the treatment of rheumatoid arthritis. Drugs 2003;63:845-53.
10. Hitchon CA, El Gabalawy HS. The histopathology of early synovitis. Clin Exp Rheumatol 2003;21 Suppl 31:S28-S36.
11. Rantapaa-Dahlqvist S, de Jong BA, Berglin E, et al. Antibodies against cyclic citrullinated peptide and IgA rheumatoid factor predict the development of rheumatoid arthritis. Arthritis Rheum 2003;4:2741-9.
12. Goldring SR. Bone and joint destruction in rheumatoid arthritis: what is really happening? J Rheumatol 2002;29 Suppl 65:44-8.
13. Lipsky PE, van der Heijde DM, St. Clair EW, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. N Engl J Med 2000;343:1594-602.
14. Hawker GA, Wright JG, Coyte PC, et al. Differences between men and women in the rate of use of hip and knee arthroplasty. N Engl J Med 2000;342:1016-22.