Common denominators of inflammatory joint diseases.

Hani El-Gabalawy

J Rheumatol 2005;72;3-6
http://www.jrheum.org/content/72/3

1. Sign up for TOCs and other alerts
   http://www.jrheum.org/alerts

2. Information on Subscriptions
   http://jrheum.com/faq

3. Information on permissions/orders of reprints
   http://jrheum.com/reprints_permissions

The Journal of Rheumatology is a monthly international serial edited by Earl D. Silverman featuring research articles on clinical subjects from scientists working in rheumatology and related fields.
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. 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 differ-
consistent 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).

Arguably the most important common pathogenetic element in all forms of IJD is the development of persistently 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 1. Common pathogenetic elements of inflammatory joint diseases.](image1)

![Figure 2. Histological sample showing progression of synovitis in inflammatory joint diseases.](image2)
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. 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. 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

3. El-Gabalawy HS. The challenge of early synovitis: multiple path...