

The No Man's Land of Undifferentiated Inflammatory Polyarthritis



No Man's Land was the term used by soldiers to describe the dangerous, unoccupied strip of ground between the 2 opposing trenches along the Western Front during World War I. It has come to mean areas of indefinite or ambiguous character, a fitting concept to describe undifferentiated inflammatory polyarthritis, a patient's clinical state falling between an ill-defined joint inflammation, spontaneous remission, and the development of the dreaded "R" word, rheumatoid arthritis (RA)¹⁻⁷. It refers to that "territory" where the initial stirrings in the evolution of arthritis yearn for a diagnostic or therapeutic solidity, possessed by its elder cousin RA.

In this early, evolutionary stage of joint inflammation, a search continues for clarity as the patient and physician look through an opaque therapeutic "window of opportunity" that oftentimes remains poorly defined^{8,9}. It is an embryonic period that represents a critical branch point in the history of that person's arthritis. Yet, how to best predict future outcome remains an enigma, as does how to choose the safest, and most effective, treatment options that will achieve an optimal joint and functional outcome. Early disease remains the poor stepchild of RA, seeking to find its rightful name, destiny, and therapeutic algorithms.

When does arthritis begin and when does it reach its critical, cumulative inflammatory burden, beyond which joint damage and other attendant problems such as premature atherosclerosis occur? This is a key question whose answer should define how early and aggressively we institute therapy in the setting of any persistent inflammatory joint disease. The fact is, we really cannot even be sure when it does begin, let alone when it takes on a destructive phenotype and begins to damage joints and internal organs. In this issue of *The Journal* Amjadi-Begvand, *et al* have brought into question even the accuracy of a patient's reporting of disease onset and duration. They demonstrate, employing information from their consortium's excellent longterm observational study of 186 patients with RA, that the accuracy of recall of RA symptom duration by patients tends to decline over a period of 5

years, and the proportion underestimating it even at 13 months after disease onset is as high as 23%¹⁰. Given these facts and the reality that the earlier the treatment of RA, the better the outcome, we should, for our patients' sake, probably err on the side of employing a longer likelihood of disease rather than a shorter one in our therapeutic equation. This insecurity about when the "window of opportunity" opens and closes in a given patient needs to be placed into the context of the following facts about the "embryology" of arthritis.

Studies have demonstrated that as long as 13 years before a patient is recognized as having RA, the serum may contain rheumatoid factor (RF) and antibodies to cyclic citrullinated peptide (anti-CCP). In one study, about half of RA patients had serologic abnormalities a median of 4.5 years before onset of joint symptoms^{11,12}. Of interest is that normally proteins are not citrullinated unless they are damaged. Does this mean that smoldering, subclinical joint damage is occurring before it reaches a critical mass and may take years to become clinically evident to the patient, let alone the doctor? In a cohort of patients with early arthritis seen initially within a mean of 4 months' duration of arthritis onset and followed for 2 years, patients who eventually developed more radiologic progression and functional limitation were anti-CCP positive 55% of the time and RF positive 55% of the time at baseline. Thus, there is a clear connection between the presence of these antibodies and a worse clinical outcome.

Importantly, synovial inflammation is present and can be characterized histologically and via magnetic resonance and ultrasound imaging, even in the asymptomatic joints of patients with early arthritis and established RA¹³⁻¹⁵. One biopsy study of asymptomatic joints in early arthritis patients revealed evidence of synovitis in 11 of 20 patients with lining cell hypertrophy and an inflammatory cell infiltrate consisting of predominantly macrophages/monocytes and T lymphocytes. Of note, there are no well defined differences between this early histologic snapshot and those that are

See Dating the "window of therapeutic opportunity" in early rheumatoid arthritis, page 1686

found in damaged joints of RA patients with chronic disease. Clinically relevant progression of joint damage may occur even during prolonged remission. Thus, who is to say, in a given patient, that early synovial infiltrates have less aggressive joint-damaging tendencies than those found in a joint subject to years of RA? And if we cannot say this, mustn't we assume that all inflammation is intrinsically bad and demands optimal control? Some have even hypothesized that early disease may very well be more amenable to suppression, or even remission-inducing with the disease modifying antirheumatic drugs (DMARD) or biologic agents that are amazingly effective in as many as 70% of RA patients with longstanding severe disease¹⁶.

More facts: At the Hospital for Special Surgery we employed ultrasound to define the presence of atherosclerosis in the carotid arteries, a proxy for the coronary arteries, in patients with systemic lupus erythematosus and RA. We found an equally high prevalence (45%) in both systemic inflammatory disorders. Our study results supported our hypothesis that the unopposed inflammatory states themselves were the cause of atherosclerosis. It is important to note that all our patients were treated at an academic, tertiary care center according to modern aggressive treatment paradigms, with 58% of those RA patients with plaque presently being treated with anti-tumor necrosis factor (TNF) agents¹⁷. These data, along with the clinical trials that show early treatment of RA leads to a better overall outcome, do support the use of earlier aggressive DMARD therapy in patients with any persistent inflammatory joint disease¹⁸.

As before, who is to say at what duration and intensity systemic inflammation overflows to and has an influence upon vascular and other tissues? Figure 1 speaks to the possible cumulative effects the inflammatory burden might have on an individual patient. An international consortium is addressing these important issues by considering a randomized con-

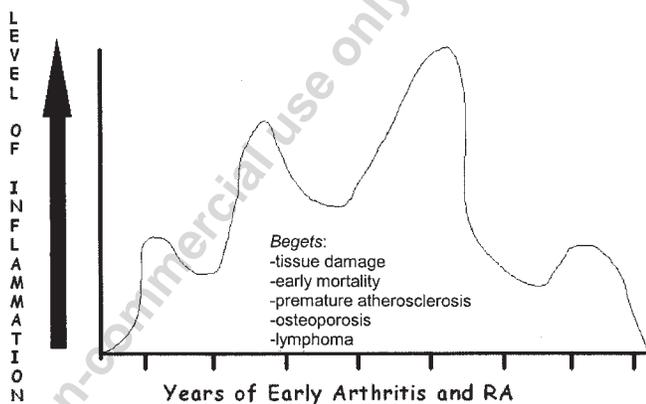


Figure 1. The cumulative impact of an unoppressed inflammatory burden of arthritis can lead to tissue damage and a shortened lifespan. Where the therapeutic window of opportunity should be placed on any person's timeline continues to be a guessing game.

trolled trial that includes anti-TNF agents and methotrexate (MTX) to abort disease and induce remission in patients with persistent arthritis in 2 or more joints for less than 4 months. Haven't we come a long way?

What's in a name? Whether it is called early arthritis, early undifferentiated inflammatory arthritis, or the undifferentiated polyarthritis syndrome (UPS), it is a very real entity — and this is not early RA, a term that probably should be avoided because it has no real diagnostic or therapeutic meaning. RA is RA, whether it has existed for one month or 3 years, and needs to be treated as such.

UPS also reflects a major perturbation of the immune system that has not spontaneously reset itself for weeks or months; a new and potentially chronic immunologic and inflammatory assault; a disorder that may lead to irretrievable tissue damage and functional limitation in a timeframe that is unpredictable; a process that, to that specific individual and her balance between immune damage and healing set points, may lead to irreversible damage and a missed therapeutic opportunity. Regardless of what we call it, these patients need to be treated with the intensity demanded to bring about a “no evidence of disease” state in an attempt to alter the natural course of the illness as much as we can. It must be appreciated that cases of early inflammatory arthritis are indeed undifferentiated, and are likely a symptom of a spectrum of different diseases, with a heterogeneous outcome. RA is one possible outcome. Many of these patients will either go into remission or develop a less destructive, seronegative disease.

Diagnosis is less important in UPS than risk prediction in an attempt to sort out who is more or less likely to evolve to full-blown American College of Rheumatology (ACR) criteria-fulfilling RA that demands early, aggressive DMARD use. The use of standard ACR criteria, which were developed based on patients with about 7 years of established disease, is inappropriate in these patients because, as Symmons has so well stated, “by the time the criteria are fulfilled, the opportunity for early treatment will have passed”¹⁻⁷.

What do we know about these entities? Thanks to the superb investigative work of a large number of thoughtful scientists that have instituted early arthritis centers, mostly in Europe¹⁻⁷, the following facts are known about these disorders:

1. Undifferentiated inflammatory polyarthritis is common, with an estimated prevalence of between 30% and 50% of patients presenting to a rheumatologist.
2. The diagnosis is usually one of exclusion, with the patient failing to satisfy criteria for disorders such as psoriatic arthritis, RA, or parvovirus B19 infection.
3. As few as 13%⁶ and as many as 60%² of patients with UPS have a self-limited inflammatory joint disorder.
4. However, as defined recently by Emery and his Leeds group, UPS is not a totally benign disorder: remission rates are low, and 30% of patients with hand UPS need treatment with DMARD at the one-year point (sulfasalazine in 66% of

patients, MTX in 14%, and hydroxychloroquine in 10%). The other key finding from their study: if synovitis resolved by 12 weeks, with or without therapy, the likelihood of persistence of the illness was nil. Thus, evolution and resolution tend to occur early and the illness defines itself, one way or the other. This allows for reasonable management decisions to be made both before and after 12 weeks of followup⁶.

Are there sensitive predictors that can guide the physician and the patient about the future aggressiveness or benignity of the illness? Unfortunately, there are no absolute predictive clinical, imaging, or laboratory criteria, no crystal ball for defining who will or will not develop joint-damaging RA with its attendant collateral damage including premature atherosclerosis, osteoporosis, lymphoma, or amyloidosis. In a 2-year followup study of 524 patients in Leiden, The Netherlands, presenting with undifferentiated arthritis, 60% had a self-limited disease, 16% developed a persistent, seronegative, non-erosive polyarthritis, and 24% an erosive, largely seropositive polyarthritis¹⁹. In that and other studies, the patient characteristics that best predicted the eventual need for DMARD or the development of joint damage were the presence of persistent synovitis at 3 months, along with: RF positivity; anti-CCP positivity; the possession of at least one allele of the shared epitope; elevated erythrocyte sedimentation rate or C-reactive protein level ≥ 10 mg/l; female sex; and the presence of early radiographic erosions. The use of these important but imperfect predictors and the possible use of sensitive imaging tests such as magnetic resonance imaging or ultrasound, which can act as “early warning signs” of disease extent or damage potential can guide the physician and the patient in making balanced treatment decisions¹⁴. However, even in the absence of one or more of these predictors, doctor and patient together will need to make therapeutic judgments that will factor in disease duration, severity, and functional limitation.

So what is one to do regarding treatment of patients with UPS? While in RA early effective management has led to a marked reduction in longterm disability and joint damage, no such accepted management strategies exist for patients with UPS. Clearly, as we discuss with our patients the known “stats” about the potential clinical outcomes of UPS and available predictors, we can still make practical cost-benefit therapeutic decisions. Those patients who have joint inflammation for less than 12 weeks, are seronegative for RF and anti-CCP, have no erosions, and are not functionally limited by their illness can be treated with nonsteroidal antiinflammatory drugs and courses of oral or injected steroids. Seropositivity or any of the above, however, should alert both the patient and the doctor that something is amiss and that more aggressive DMARD treatment may be needed, especially should marked functional limitation and significant constitutional symptoms persist. As implied in Emery’s recent study, those with persistent joint inflammation for more than 3 months have likely entered into a new, more fixed immuno-

logical and inflammatory realm that will likely need to be treated with a DMARD.

While I can certainly understand concern about treating an unknown percentage of patients with DMARD for an illness that may resolve spontaneously, I believe that persistent inflammation (especially of more than 3 months’ duration) reflects a physiologic process that is potentially “out of control” from an immunologic and inflammatory point of view, which, supported by our less than perfect knowledge base, may very well result in a lifelong disorder that damages joints and other tissues and limits function. Here, a “wait and see attitude” that does not consider employing DMARD is avoiding our responsibility to direct our best therapeutic efforts at the earliest phases of disease, before irreparable damage occurs.

Thus I favor “striking while the iron is hot.” Since most erosions do not heal, even with the best therapy available, their development, like that of a bed sore, needs to be avoided in the first place²⁰. In this regard, in one series, as many as 24% of UPS patients develop erosions after one year. The cumulative effect of inadequately suppressed systemic inflammation can be joint damage and major visceral dysfunction. One may fear that if we treat every patient suffering from early, persistent joint inflammation, many will eventually go into remission and they will have unnecessarily been subjected to the potential side effects of the most effective and potentially toxic medications that we now have. However, the question we then have to ask is: Given our present knowledge base and the lack of foolproof predictors, what would be worse — allowing as many as 60% or as few as 13% of remission-bound patients to be treated with DMARD for a period of time, or not treating them and letting them take their chances?

In this context, what are the potential side effects of the DMARD that should give us pause? For MTX it is infection risk, cytopenias, liver toxicity, and lymphoma, all very uncommon side effects. With sulfasalazine and hydroxychloroquine, it is bone marrow toxicity, rash, and retinal problems, again infrequent and easily monitored. Biologic agents do not have as long a track record as the above medications, but their cost-benefit balance has been surprisingly positive, at times profoundly so. Given the likelihood that an unknown proportion of patients who will go into remission will probably not need to be treated for long periods of time, cumulative medication side effects will likely be avoided.

This treatment approach, selected in partnership with informed patients who decide for themselves the personal costs and benefits, is balanced and evidence-based. I believe that persistent inflammation is both inherently and unpredictably damaging to tissues and, with our present inability to define the destiny of early arthritis, the harm that we are avoiding in “first, do no harm” represents the harm from inflammation, not from the drugs that can suppress it. Aiming for remission and no evidence of disease status is no less an

important goal in early arthritis than it is in established RA. As our knowledge expands, as innovative imaging technology becomes better, more standardized and less expensive, and as biomarkers and predictors improve, a greater clarity of the presence and extent of the window of opportunity will allow more refined treatment options. For now, “do no harm.”

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