The Biologic Treatments for Inflammatory Arthritis: Is There a Role in the Elderly?

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The inflammatory polyarthritides take a huge toll on the well-being of an individual. The ability to specifically target inflammatory molecules with the new "biologic" treatments has been an outstanding laboratory development that has rapidly entered the clinical domain. Early experience in the use of these costly agents has shown an excellent clinical response with both alleviation of symptoms and slowing of disease progression. There is, however, concern regarding the emergence of adverse effects. The side effect of both chronic and bacterial infections, likely more prevalent in the elderly, requires caution and meticulous patient care. Until more is known about the long-term use regarding both continued efficacy and side effects, these treatments currently should be offered to patients with the most severe and poorly responsive disease.

Key words: *inflammatory arthritis, disease modifiers, biologics, infectious complications.*

Background

Inflammatory arthritic diseases encompass a wide spectrum of disease processes that manifest usually in the middle years of life. There are two scenarios whereby an older patient will present with inflammatory joint disease. In the first instance, the disease may have been present for many years and will accompany the patient into the later years of life. Alternatively, the disease may develop as a new event in the geriatric patient. Although older texts refer to "burned out" rheumatoid arthritis, referring to quiescence of disease after many years of active disease, this is not commonly seen. Many older patients spend their senior years struggling with ongoing joint pain and the consequences of a debilitating inflammatory process.

There is currently no cure for inflammatory arthritis in general, nor for rheumatoid arthritis (RA) in particular. The best aim of treatment is to slow the disease process, avoid deformity and disability and improve quality of life. Traditionally, the disease modifying antirheumatic drugs (DMARDs) have given some degree of control, although imperfect. Clinical experience has shown that all treatments, including non-steroidal anti-inflammatory drugs (NSAIDs) as well as the DMARDs, hold greater risks for the elderly.

The introduction of strategies targeting specific pathophysiologic processes with biologic agents has heralded a new era in the management of RA.[1-3] These agents influence the disease process by specifically targeting inflammatory molecules or their reciprocal receptor sites. The excellent response reported in clinical trials for these agents has been encouraging. The initial enthusiasm, however, has been tempered with reports of adverse events when these agents are used in normal clinical practice, thus emphasizing the need for prudence and informed use. No studies to date have specifically addressed the use of the biologic treatments in the elderly. However, careful reading of published studies and reports does suggest that the older patient is likely at greater risk for complications of biologic treatment.

Although RA is the most readily recognized of the inflammatory arthritides, the other arthritic conditions are of equal importance and are usually categorized as the seronegative arthritides, including psoriatic arthritis, inflammatory spondyloarthropathy and reactive arthritis. It should be remembered that any new treatment innovation directed towards RA eventually will likely be applied to at least some of the other inflammatory arthritides.

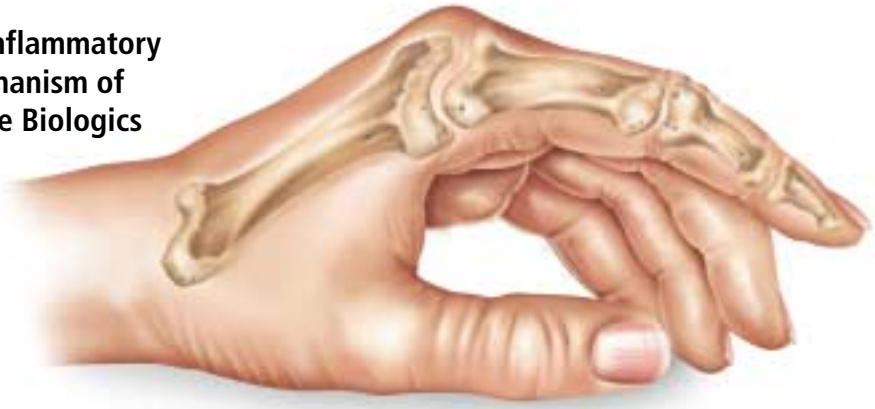
Pathogenesis of Inflammatory Arthritis

The rationale for the use of the "biologics" in treating inflammatory joint disease is better appreciated if the pathogenesis of the disease process at the cellular and molecular levels is understood (Figure). The inflammation of RA is triggered by some factor—as yet unknown—in a susceptible individual and which induces cell activation. The hallmark of disease is thickened synovium infiltrated with inflammatory cells lining the joint cavity.[4] Once cells are activated, a communication process between cells is initiated via proteins, called cytokines, interacting with receptors. In RA, the proinflammatory component of the cycle is dominant and therefore sets in motion the destructive effects of RA. Some of the important proinflammatory cytokines are tumour necrosis factor-α (TNF) and interleukin-1 (IL-1). Damage is caused when the synovial tissue erodes into bone, cartilage and the ligamentous tissue of the joint.

Frequency of Inflammatory Arthritis in the Elderly

Epidemiological studies report that 1% of the population will be afflicted with RA at some point in their lifetime.[5] It is estimated that 300,000 Canadians have a diagnosis of RA, with a peak incidence between the fourth and sixth decades of life.[6] Females are affected 2.5 times more frequently than males, and about 10% of patients have onset of disease after the age of 60.[7] The prevalence of RA increases with age, with 0.8% of men and 2.5% of women being affected in the eighth decade.[7]

Pathogenesis of Inflammatory Arthritis and Mechanism of Action of Available Biologics

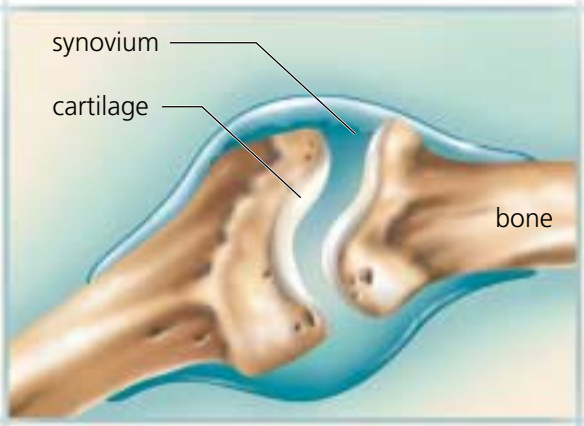


TNF and IL-1

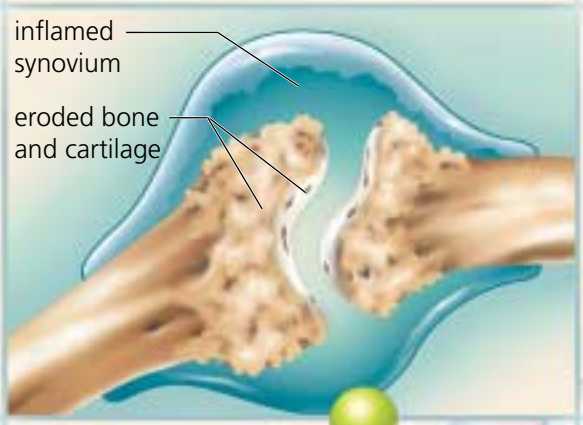
Osteoclasts
stimulate bone resorption and bone erosion

Synoviocytes
induce joint inflammation, pain and swelling

Chondrocytes
stimulate cartilage degradation and joint space narrowing



Healthy Joint



Arthritic Joint

Treatment of Inflammatory Arthritis in the Elderly

Treatment needs to be rapid, aggressive and efficient because damage occurs early in the disease. The objective is to slow the disease process, reduce the rate of erosions and improve quality of life. RA is seldom controlled simply with the use of NSAIDs; therefore, DMARD treatment either singly or in combination usually is required. No single DMARD is universally recommended, and treatment choices depend upon individual patient characteristics, lifetime needs and severity of disease. Taking into account current understanding of treatment with biologic agents, including the limited knowledge of possible complications, it is prudent to recommend this form of therapy to patients with disease poorly responsive to standard DMARD treatment and with ongoing moderate to severe disease.

Currently Available Biologic Treatments

Currently, the three biologic agents available in Canada are etanercept and infliximab, both TNF antagonists, and anakinra, an IL-1 receptor antagonist (Table). Another TNF antagonist, adalimumab, is expected to be available within the next year. The care of patients treated with biologic agents requires rigorous surveillance regarding arthritic treatment adjustments and attention to adverse events. The response following initiation of treatment with the biologics is usually fairly rapid, with measurable improvement occurring within a few weeks in up to 60–70% of patients. The absence of a clinically meaningful response within a few months indicates that the biologic treatment is unlikely to be effective.

Etanercept

This soluble TNF receptor fusion protein is self administered by subcutaneous injection of 25mg given twice weekly. The clinical response regarding both joint inflammation and functional status is excellent.[3] A minor problem related to treatment with etanercept is immediate injection site reactions, whereas the more serious adverse events during prolonged use include the occurrence of infections and possible development of malignancies.

Infliximab

This mouse and human chimeric antibody is administered by intravenous infusion at a recommended dose of 3mg/kg body weight. Studies and clinical experience indicate an excellent response to treatment in more than one-half of patients.[2] Similar to etanercept, adverse events include reactions at the time of the infusion and an increased rate of infections that are commonly upper respiratory and viral in type, as well as bacterial infections requiring treatment with antibiotics. The emergence of chronic infections, such as tuberculosis and histoplasmosis, was not anticipated when clinical studies began, but has become apparent with clinical use.

Anakinra

Anakinra is a recombinant version of the human IL-1 receptor antagonist and is similar to the naturally occurring protein except for the addition of a single methionine residue at its amino terminus. Clinical study of RA patients treated with anakinra has shown good symptomatic improvement as well as slowing of radiographic progression of RA.[1] In a recent safety study of this agent, bacterial infections were more frequent in patients treated with anakinra than placebo, but opportunistic infections such as tuberculosis and histoplasmosis were not observed.[8]

Which Patients Might be Considered for Biologic Treatment?

In light of recent enthusiastic response to the advent of biologic agents, various professional bodies have issued guidelines regarding the appropriate use of the biologics in arthritic disease.[6,9,10] In essence, most guidelines recommend that these agents should be used in patients with RA who have failed treatment with at least two DMARDs given in adequate dose and in whom the disease remains clinically active. The need for these guidelines has been driven by both the immediate costs for these agents and the unknown long-term side effects.

It is estimated that 50% of RA patients will experience moderate to severe disease and will require continuous treatment with DMARDs. Up to 10% of these patients are expected to be poor responders and would likely be suitable for biologic therapy.[11] In a recent audit of clinical use of biologic agents in inflammatory arthritis, up to one-quarter of patients were older than 60 years.[12]

A Summary Comparison of Currently Available Biologic Agents

	Mechanism	Administration	Frequency	Dosage	Drug combinations	Side effects
Infliximab	antibody to TNF	intravenous	8 weekly (maintenance)	3mg/kg	with methotrexate	bacterial/opportunistic infections
Etanercept	TNF receptor fusion protein	subcutaneous	2 times/week	25mg	± methotrexate	bacterial/opportunistic infections
Anakinra	IL-1 receptor antagonist	subcutaneous	daily	100mg	± methotrexate	bacterial infections

It is notable that although these agents are currently licensed for use in RA and juvenile arthritis, off-label prescription for other rheumatic disease indications is likely prevalent. There are reports of a favourable response in patients with inflammatory spondyloarthropathy as well as in those with psoriatic arthritis.[13,14] For this reason, it is likely that the use of the biologic agents will become more common in mainstream rheumatology practice.

Risks Associated with the Use of the Biologic Treatments

While the biologics are seen as a major advance for patients with severe inflammatory arthritic disease, there is limited reported experience of open-label and long-term clinical practice. The development of tuberculosis in the initial clinical trials was an unexpected side effect, but is clearly a risk in clinical practice. The possible reactivation of tuberculosis in an older patient requires pretreatment screening for past infection. Patients treated with anti-TNF agents also may be prone to other chronic infections, such as histoplasmosis, as has been reported in a post-marketing FDA report.[15] To date, audit reports indicate that between 5% and 15% of patients treated with an anti-TNF agent develop severe adverse events requiring discontinuation of treatment and most commonly of an infectious nature.[12,16-18]

Although chronic infectious complications of biologic treatments are of concern, recent reports indicate that more common bacterial infections may be of equal or even greater importance, especially in the elderly. In a study by Kroesen and colleagues, common bacterial infections rather than the chronic infections such as tuberculosis or histoplasmosis were prevalent.[19] One-third of patients presenting with serious bacterial infections were older than 65 years.[19] Sites of infection were varied and included lungs, skin and joint, bowel and bladder. In an audit of clinical practice by Phillips *et al.*, it was noted that the overall frequency of serious infectious complications did not increase during treatment with etanercept; however, death due to sepsis occurred in two of three patients who were older than 65 years.[18]

Several studies have reviewed FDA post-marketing adverse event reports for patients treated with anti-TNF agents. Neurologic illness suggesting demyelination has been identified in 19 patients, but none of the cases were older than 65 years.[20] Infection with *Listeria monocytogenes* has been reported in 15 patients.[21] This infection presented either with septicemia or meningitis, and 50% of the patients were older than 65 years. Four of these infections resulted in death and one patient suffered severe neurological damage. In another study, two of 10 cases of *Histoplasma capsulatum* infection were in patients older than age 65 and one resulted in death.[15] Among 26 cases of lymphoproliferative disorder identified in patients treated with either infliximab or etanercept, almost half of the cases were elderly.[22]

Conclusions

Although no report to date has specifically addressed the use of the biologic agents in the elderly, clinical experience suggests that treatment response in the older patient is likely similar to that in younger patients, but the elderly may be more prone to complications of treatment. Long-term studies are still needed to clarify both continued efficacy as well as concerns regarding side effects. Malignancy, if it is a true side effect of the biologic treatments, also may have different connotations in the elderly compared to younger patients with regard to both quality of life and true impact on life expectancy. Bacterial infectious complications are likely to cause most comorbidity and be of greater immediate concern when these agents are used in older people.

At this time, it seems reasonable to adopt a common sense approach regarding the use of the biologics in the older patient. An important consideration in the use of these agents is the very high cost. Long-term outcome studies are needed to determine true cost-effectiveness with regard to improved quality of life, reduced morbidity due to disease and reduction in need for surgery.

Treatment with a biologic agent is not simply the writing of a prescription, but rather careful surveillance of the patient for side effects, adjustment of concomitant medications and fiscal responsibility. Currently, it is prudent that the biologic agents be prescribed by physicians experienced in the care of patients with rheumatic diseases. ◆

No competing financial interests declared.

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Symmetrical inflammatory arthritis (affecting both halves of the body in the same joint groups), especially in the small joints of the hands, associated with morning stiffness in the joints lasting over one half hour. Lab test results. Positive rheumatoid factor.Â What Is the Role of the PCP and PT/OT in Early Inflammatory Arthritis? Primary care physicians and physical therapists should be attuned to the early warning signs of IA and recommend early consultation with a rheumatologist for work-up and possible early intervention. They can also educate the patient about the systemic and destructive nature of inflammatory joint disease and the "window of opportunity" presented by proper diagnosis of early arthritis. Inflammatory arthritis is characterized by damaging inflammation that does not occur as a normal reaction to injury or infection. This type of inflammation is unhelpful and instead causes damage in the affected joints, resulting in pain, stiffness and swelling.Â The main job of the smooth, slippery cartilage is to help the joints glide and move smoothly. This type of arthritis causes the cartilage to become thinner and rougher. To compensate for the loss of cartilage and changes in joint function, the body begins to remodel the bone in an attempt to restore stability. This can cause undesirable bony growths to develop, called osteophytes. The joint can become misshapen. Introduction The role of biologic therapies in the treatment and management of patients with inflammatory joint disease is an evolving area that has significant implications for all practitioners. The number of patients with rheumatoid arthritis eligible to receive the biologic therapies is estimated at 40-50 patients per 100,000 of the population. These calculations are based on a model business case prepared by the British Society for Rheumatology (BSR), and may underestimate the true number of eligible patients. The BSRs work has shown that many patients have not yet gained access to these treatments What Are Medical Treatments for Rheumatoid Arthritis? Follow-up for Rheumatoid Arthritis. Home Remedies. Are There Any Home Remedies for Rheumatoid Arthritis?Â Biologic Response Modifiers and RA. JAK Inhibitors and RA. Glucocorticoids and RA. Nonsteroidal Anti-inflammatory Drugs (NSAIDs) and Analgesics for RA.Â Is There a Cure for Rheumatoid Arthritis? Complications. What Are Complications of Rheumatoid Arthritis?Â Rheumatoid arthritis is the most common form of autoimmune, inflammatory arthritis in adults. It can also affect children. The joint damage is caused by inflammation of the joint lining tissue. Inflammation is normally a response by the body's immune system to "assaults" such as infections, wounds, and foreign objects.