Integrating Biologic Therapy into the Comprehensive Care of Patients with Rheumatoid Arthritis

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ABSTRACT. The advent of biologic therapy has not only provided the opportunity for better care of patients with rheumatoid arthritis (RA), but also has permitted a better understanding of the pathogenesis of this autoimmune/inflammatory disease. The capacity of these agents to suppress signs and symptoms as well as radiographic progression of RA strongly indicates that they can alter the course of the disease. Appropriate analysis of the effect of biologics should provide new insight into the role of the specific targeted molecules in rheumatoid inflammation, and provide information about means to optimize therapy with these highly potent therapeutics. (J Rheumatol 2005;32 Suppl 72:54-57)

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Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disorder whose etiology is unknown. Because of its persistent course and the damaging potential of the chronic inflammation, RA can cause considerable damage to articular structures and progressive disability[1,2]. Previously, treatment was aimed at nonspecific suppression of inflammation and control of pain, but afforded little opportunity to alter the course of the disease and prevent disability[3,4]. Recently, biologic agents targeting specific inflammatory cytokines, such as tumor necrosis factor (TNF) and interleukin 1 (IL-1), have been approved for the treatment of RA and specific other inflammatory conditions[5-11]. Blockers of TNF have proven to be extremely effective in controlling signs and symptoms of RA and also inhibiting progressive damage to articular structures[5-8]. The availability of these agents has profoundly affected the treatment of RA and also our understanding of disease pathogenesis.

THE PATHOGENESIS OF RA: NORMAL GENES OPERATING IN A CHANGED ENVIRONMENT

There is a strong genetic basis for RA[12,13]. However, unlike single-gene diseases, multiple genes play a role in RA and can influence different stages of the disease. It is important to remember that the genes that predispose to RA are not abnormal genes, but rather perfectly normal ones that serve to alter the reactivity of the individual (Figure 1). Some genes control the responsiveness of the individual's innate or adaptive immune system and others likely control the intensity or the organ manifestations of RA. Indeed, the genes operative in RA susceptibility were probably selected because they provided ancestral populations with a survival advantage before there was sanitation, hygiene, vaccination, or antibiotics. It was probably advantageous to have a very robust immune system and inflammatory response to survive in ancient times. Now hygiene, antibiotics, and vaccination have made many of these infectious agents less threatening, but we still have the genes in the population and they likely encode for robust responses to environmental stimuli. Nowadays these previously beneficial genes are probably what are conveying risks for autoimmune and inflammatory diseases, such as RA. The environmental triggers for these diseases remain unclear, and after all the years of investigation, the only stimulus we know is cigarette smoking[14]. It could be argued that one program that would have a major impact on RA is education about the danger of cigarette smoking.

LESSONS LEARNED FROM TARGETED BIOLOGIC THERAPIES

Despite knowing a great deal about the pathogenesis of RA, the precise mechanism of action of most of the classic disease modifying antirheumatic drugs (DMARD) remains elusive. Although these agents are useful to treat patients with RA, since their mechanism of action is not understood, little can be learned about the disease pathogenesis by analyzing the response to DMARD. Previously, clinicians empirically tried to modify DMARD regimens so as to affect the patients in the best possible way, without actually knowing the pathologic pathways that were being influenced.

With the development of biologics, things have changed. Biologics are very important conceptually as well as therapeutically because each of them selectively targets a specific inflammatory molecule. Because of this, use of biologics permits the clinical researcher to ask

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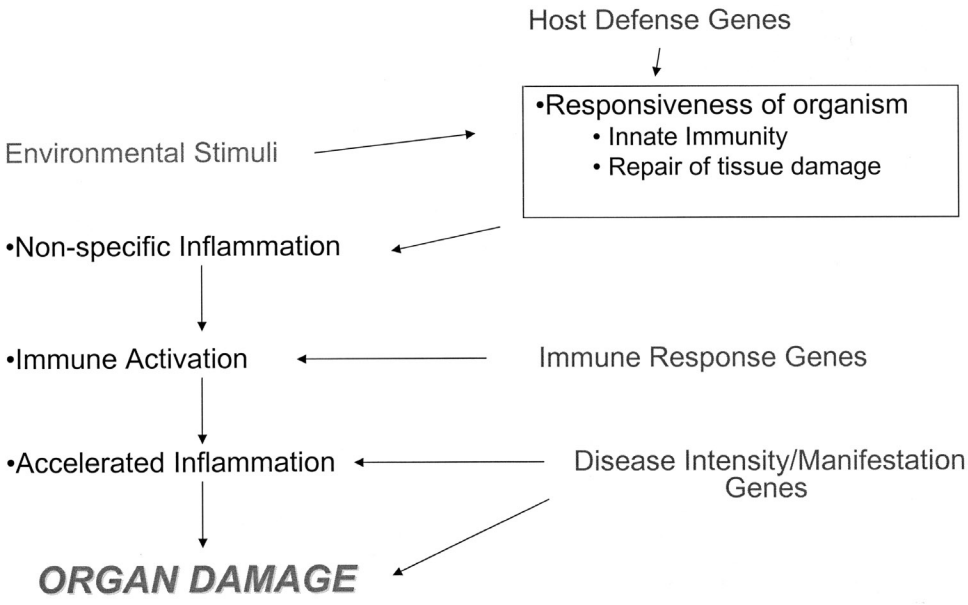

Figure 1. Pathogenic mechanisms in RA.

whether the individual targeted molecule plays a role in rheumatoid inflammation or psoriatic inflammation or ankylosing spondylitis. The use of biologics in these diseases, therefore, permits assessment of the role of the specific targeted molecule in the pathologic and clinical manifestation of these conditions.

Biologics are highly potent therapies[5-11]. They suppress inflammatory arthritis, including signs and symptoms, and radiographic progression, and they improve physical function and quality of life. We know biologics are associated with adverse events; most of these relate to infectious complications. We know that in established disease, they are suppressive of inflammation but not curative, although there is emerging information to suggest that the effect in early arthritis may be more profound.

One factor influencing the use of biologics is their cost. These therapies are quite expensive. An important principle, however, is that cost, while an important element in decision-making, should not be the only driver, because the biologics are fundamentally important new advances in treating patients.

LESSONS LEARNED FROM BIOLOGICS REGARDING DISEASE PATHOGENESIS

It is clear from the application of biologics that TNF is a central player in rheumatoid inflammation[5-8]. However, it is also clear that inhibition of TNF is not curative in established disease, but that may be different in early disease. We have learned that there may be a lesser role for IL-1 in most patients with RA[9-11]. It should be noted that there are persons with a mutation in the *CIAS-I* gene who manifest a spectrum of spontaneous inflammatory syndromes, and persistently produce large amounts of IL-I[15,16]. Those children are very effectively treated with anakinra[17,18]. So it is clear that anakinra can be an effective drug in individuals whose disease is driven prominently by IL-l. Therefore, the less impressive results with anakinra in RA suggest that IL-I is not a major inflammatory mediator in this disease.

In addition, we have learned that there is a major role for TNF in radiographic progression in RA. Even more striking is the observation that this effect is not necessarily linked to the role of TNF in inflammation. The 2 year data from the ATTRACT trial show that in the individuals treated with methotrexate alone there is a significant progression over 2 years in the radiographic scores, whereas there is basically no mean change in the anti-TNF plus methotrexate treated groups over a 2 year period[19]. Interestingly, not only did the clinical responders to anti-TNF have inhibition of radiographic progression, but there was inhibition of radiographic progression in the patients who did not appear to respond to TNF blockade on clinical grounds. Therefore, radiographic damage and inflammation appear to be independent outcomes in the context of TNF blockade.

There is currently an unresolved question about whether radiographic damage in RA can heal. The radiographic data from the ATTRACT trial did suggest that this healing phenomenon may occur, in that some patients actually had improvement in their radiographic scores over 2 years. We have some evidence to support these observations in studies using a combination of magnetic resonance imaging and computerized tomography to analyze individual erosions in patients with RA. These data suggest that when TNF is blocked, inflammation assessed as "bone edema" often improves, and in

some cases the erosions appear to decrease in volume. Although these preliminary data are tantalizing, further application of sensitive imaging techniques to this question will be important in order to obtain a more definite answer.

LESSONS REGARDING CLINICAL TRIALS IN RA

The impact of biologics on clinical care has been profound. Biologic therapies have altered what physicians and what patients expect. Previously, patients expected to be as free of pain as possible, but still were resigned to have chronic symptomatic disease and progressive disability. Now patients expect to lead normal lives. One important question, therefore, is whether the outcome measures used in RA clinical trials really help in predicting responses of this magnitude. It is a challenge for clinical researchers to develop outcome measures that both predict anticipated real-world outcomes and can be used in clinical trials. It is essential to have outcome measures that can discriminate the effects of the various biologics with precision. In addition, it would be advantageous to develop clinical trial designs that can evaluate agents that may have radiographic but not clinical benefit.

Another important question relates to how to do clinical trials in the post-anti-TNF era. The effectiveness and popularity of these agents in the United States has limited the availability of patients for clinical trials. The rapid acceptance of these agents into the clinician's armamentarium raises the question of whether these agents are now the gold standard, against which newer agents should be measured. If this is the case, will it make trials of new agents prohibitively expensive? Finally, are we at the stage where combinations of new biologic agents should be considered? Traditionally, after new agents are approved, clinical trials designed by the rheumatology community have helped to "fine tune" the use of these agents in clinical practice. However, the high cost of biologic agents makes this an unlikely scenario. The mechanism is not clear with respect to addressing a number of important questions on the use of these agents in practice. Moreover, whether a group of "thought leaders" with experience and expertise but no ties to pharmaceutical companies will emerge is not obvious.

THE FUTURE OF BIOLOGIC THERAPY

The challenge is to learn to use this generation of biologics and the next wisely, in particular biologics in late stages of development that will become available in the very near future. Because these unique agents target a specific molecular entity, their introduction affords the opportunity to address the role of specific molecules in individual patients with RA. For this information to be mined optimally and not lost as anecdotal, every person treated with biologics should ideally be enrolled in a clinical study. This can take place in a doctor's office or in a more formal setting, but we have the opportunity to gather objective data on every subject providing fundamental information about RA from good observation.

Canada, for example, is particularly well poised to do this because of its organized, single-payer healthcare system. However, such an endeavor requires an organized approach: informed discussion between bench investigators, outcomes researchers, pharmacoeconomists, clinical trialists, and the clinical care team. Importantly, health administration cannot be omitted from this activity.

The first goal of this coordinated clinical approach is to learn to use biologics appropriately in patients with established RA to identify those who require a biologic agent to control inflammation or prevent articular damage, and to avoid depriving patients who require biologics strictly for economic reasons. An additional goal is to assess the longterm risk-benefit ratio without penalizing individuals who currently have disease. Eventually, these lessons may be applied to patients with very early disease with the goal of preventing articular damage and progression to disability. With the availability of targeted biologic therapy, it might not be unreasonable to think in terms of primary prevention of RA in individuals with inflammatory arthritis who do not yet meet classification criteria for established RA, or secondary prevention in those with a diagnosis of RA with minimal articular damage or disability. Novel clinical trials are currently testing these possibilities. The suggestion from studies in very early disease is that immediate intervention with biologics may indeed alter the course of inflammatory arthritis.

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