

EDITORIAL

Antiinflammatory Therapy for Rheumatoid Arthritis?

Irun R. Cohen¹ and Lars Klareskog²

Glucocorticoids, since their spectacular introduction into clinical medicine in 1948 (1), remain a classically efficient treatment for arthritis and other inflammatory conditions (2). Indeed, the discoverers of this therapy were awarded an immediate Nobel Prize. Since then, glucocorticoids have remained a cornerstone in the treatment of chronic inflammation, and despite the introduction of novel therapies such as tumor necrosis factor–blocking agents (3), we have lately witnessed the increased use of glucocorticoids in arthritis. Recent studies confirm the capacity of glucocorticoids both to diminish inflammation and to reduce the pace of joint destruction (4–8), particularly when these agents are used at high doses and in the early phases of arthritis (6–8).

Unfortunately, glucocorticoids are equally well known for their undesirable side effects, particularly with long-term use and systemic administration (2). A major problem has been achieving effective concentrations of active drug at the site of chronic inflammation and while avoiding too-high concentrations systemically and in uninflamed sites. The first attempt to reduce the undesirable effects of glucocorticoids on the rest of the body involved injecting them directly into the inflamed joints (9,10). This route of administration is still frequently used in practice, and it offers an efficient complement to other currently used therapies, despite the obvious drawbacks of repeated joint needling and the problem of polyarthritis involving small and inaccessible joints. Nevertheless, there is convincing evidence

that glucocorticoids delivered in sufficiently high concentrations to an inflamed joint are beneficial.

An attractive way to guide glucocorticoid treatment selectively to affected joints is to attach them to molecular delivery vehicles that, following systemic administration, accumulate in inflamed tissues to a relatively greater degree than they do in healthy tissues. Because of increased blood flow and vascular permeability at inflamed sites, liposomes could theoretically carry glucocorticoid drugs to arthritic joints (11). Despite efforts over the years, and some reports of success (12), liposome delivery of glucocorticoids has not been developed into a clinically useful therapy; this may be due, at least in part, to insufficient encapsulation of the drug into the liposomes and to lack of controlled release at the diseased joints.

In this issue of *Arthritis & Rheumatism*, Avnir and colleagues report the engineering of a novel glucocorticoid-loaded liposome preparation, with promising results (13). The authors devised stabilized liposomes of ~80 nm that could be loaded with relatively large amounts of an amphipathic weak acid glucocorticoid. This preparation manifested controlled release of the glucocorticoid in the circulation and especially in the swollen paws of rats with adjuvant-induced arthritis. This special liposome–glucocorticoid preparation produced a clinical effect on the rat arthritis much superior to that obtained with free glucocorticoid drug (13). The hope is that such glucocorticoid-loaded liposomes will safely work in humans to release sufficient amounts of drug into inflamed joints without exposing other body tissues to the hazards of too-high levels of the glucocorticoid. In view of the evidence that timely systemic administration of glucocorticoids can both ameliorate inflammation and prevent joint destruction (14), it is of great interest to explore the liposome formulation used by Avnir and colleagues in controlled clinical trials.

Antiinflammatory cure?

Antiinflammatory agents such as glucocorticoids clearly ameliorate joint inflammation. Is this effect only

¹Irun R. Cohen, MD: The Weizmann Institute of Science, Rehovot, Israel; ²Lars Klareskog, MD, PhD: Karolinska Institute at Karolinska University Hospital, Stockholm, Sweden.

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Address correspondence and reprint requests to Irun R. Cohen, MD, Department of Immunology, The Weizmann Institute of Science, Rehovot 76100, Israel. E-mail: Irun.cohen@weizmann.ac.il.

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symptomatic, or could antiinflammatory agents be expected to cure or prevent the disease?

The answer depends, of course, on the role of inflammation in the etiology of rheumatoid arthritis. Arthritis, by definition, denotes an inflamed joint; the question is whether rheumatoid arthritis requires a specific immune response to a self antigen (or an antigen cross-reactive with self) expressed in the joints. Alternatively, one might consider the possibility that rheumatoid arthritis develops by way of innate immune mechanisms independent of antigen-specific autoimmunity. Obviously, these alternatives are not mutually exclusive. Indeed, recent evidence is compatible with the hypothesis that a significant proportion of rheumatoid arthritis might arise through an interaction between preexisting antigen-specific autoimmunity and primary joint inflammation. If primary joint inflammation is a necessary factor in the etiology of rheumatoid arthritis, then the right antiinflammatory treatment at the right time could be curative. Let us briefly discuss the evidence for antigen-specific autoimmunity in pathogenesis and then consider primary joint inflammation.

Antigen-specific joint autoimmunity

Anti-citrullinated protein antibodies, often accompanied by rheumatoid factor, characterize the major subset of rheumatoid arthritis patients; these autoantibodies show linkage to major histocompatibility complex alleles (15,16). Thus, there is clear evidence for antigen-specific autoimmunity linked to immune response genes in the major subset of patients with rheumatoid arthritis. However, the existence of this autoimmunity alone may not be sufficient to explain the onset of arthritis; it now appears that autoantibodies to citrullinated antigens may be present for a long time without causing disease (17). Additional factors are required to activate this latent, subclinical autoimmunity into a joint-damaging immune effector response. Primary inflammation that up-regulates the local expression in affected joints of stress proteins and citrullinated peptides may be the missing factor in pathogenesis (18). How might primary joint inflammation arise?

Physiology and pathophysiology of inflammation

Inflammation now has a bad name; we blame inflammation for causing disease and we seek antiinflammatory agents to suppress it. Actually, however, most inflammation does not cause disease, it cures disease. Classically, inflammation has been defined as a

dynamic process induced by injury that leads to healing (19). Today, we have discovered that “inflammatory” cytokines, chemokines, growth molecules, and apoptosis molecules mediate wound healing, repair broken bones, remodel connective tissues, activate angiogenesis, and trigger cell movement, proliferation, and differentiation. These processes are essential to regular body maintenance (20). Inflammation, in short, is a key factor in maintaining and renewing the body in the face of the wear and tear of postnatal existence. Inflammation at the molecular level proceeds continuously, and most of the time it goes unnoticed. Inflammation causes disease only when it becomes unregulated, chronic, recurrent, or inappropriate in time, place, or magnitude. Physiology then becomes pathology.

Inflamed joints

Joints are very special structures. The joints devised by biologic evolution outperform by far the best attempts of human engineering and material science. Joints bear enormous amounts of weight, stress, and tension while maintaining an exquisitely engineered dynamic architecture and performing exacting functions for a lifetime of service. The constant stress on joints requires them to have a special relationship with the healing processes of inflammation; joints are constantly in need of maintenance and repair. We would suggest that such medicinal joint inflammation occurs at the molecular scale and is subconscious and subclinical. This molecular inflammation is probably managed by fine regulatory interactions between Toll-like receptors, cytokine receptors, and other innate immune system receptors and their various ligands (19–21). These complex interactions need tight feedback control.

Unfortunately, control systems can falter, and ongoing subclinical medicinal inflammation can, on occasion, become dysregulated and surface clinically as overt arthritis. Once gone awry, the inflammatory process could become recurrent or chronic, leading to the up-regulation of stress proteins (21) and the appearance of citrullinated or glycosylated tissue proteins. These modified joint molecules could activate latent antigen-specific autoimmune B cells and T cells to generate pathogenic autoantibodies and autoreactive effector T cells (18). The combination of primary joint inflammation and autoimmune activation can become a positive feedback loop in which more active autoimmunity generates more active inflammation that generates even more autoimmunity and even more inflammation . . . leading to the in-

involvement of additional joints and what we would call rheumatoid arthritis.

These speculations need experimental testing, but several observations are compatible with the idea that arthritis may be connected to joint stress and innate immune system ligands. The fact that a rheumatoid arthritic knee can respond remarkably well to immobilization suggests that the arthritis could indeed reflect an exaggerated, dysregulated inflammatory response to joint stress (22,23). Moreover, the rat model of adjuvant-induced arthritis, used in the study by Avnir and colleagues (13), demonstrates that an experimental arthritis with some features reminiscent of rheumatoid arthritis (24) can be induced by adjuvants—ligands for receptors that activate (and overactivate) innate inflammation (21). If, indeed, primary inflammation is a necessary feature in the pathogenesis of much rheumatoid arthritis, then antiinflammatory agents that restore well-regulated inflammation might be sufficient to abort or reverse the emerging disease process. From this point of view, it will be important to investigate the potential of the glucocorticoid-charged liposome preparation described by Avnir and colleagues, both in patients in whom arthritis has already developed and in individuals with high-risk genetic and autoimmune markers for future disease development. Time will tell.

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