Current Advances in Rheumatoid Arthritis Therapy

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INTRODUCTION

Exciting advances in the understanding of rheumatoid arthritis (RA) and its pathogenesis are providing new hope for those suffering from this debilitating disease. A currently incurable autoimmune disorder, RA is one of the most common forms of inflammatory arthritis, causing suffering, disability (90% within 20 years will become clinically disabled), and even premature death. Many of the past and current therapies offer little more than symptomatic relief. Even the so-called disease modifying antirheumatic drugs (DMARDs) do not halt the progression of this disease, but rather decrease the onset of disability by 30%. Recent research into the complex and varied components of this disease is leading to the development of more effective targets for pharmacological approach than ever before.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)

Current treatment of RA frequently includes the use of nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen and diclofenac. As first line drugs, these offer little protection against tissue degeneration. They do, however, reduce the levels of prostaglandins, bradykinins, and oxygen radicals; thereby contributing to pain relief. NSAIDs work by inhibiting cycloxygenase (COX), decreasing prostanoid production. Two types of this enzyme exist in the body. Type I is “constitutive” and helps maintain mucosal blood flow and platelet function. Type II is “inducible” and is generated at sites of inflammation. Most available NSAIDs inhibit both COX-I and COX-II, reducing pain and inflammation, but also leading to side effects such as peptic ulceration, impairment of renal blood flow, renal papillary necrosis, nephrotic syndrome, and hepatic injury. Despite these complications, NSAIDs remain a first-line treatment for pain and inflammation, although not all patients respond favorably to treatment with these agents.

An encouraging new development is the discovery of agents that selectively target COX-II, such as rofecoxib and celecoxib. COX-II inhibitors have proven to reverse oedema and cellular infiltrate, reduce joint inflammation, and return PGE, levels to normal. They also decrease COX-II mRNA levels to normal without affecting COX-I, and they modulate local and systemic cytokine production (including IL-6), thereby reducing inflammation in affected joints and diminishing subsequent erosion of bone and cartilage. It is hoped that COX-II selective inhibitors will allow for the same therapeutic benefits of non-selective COX inhibitors, without the typical NSAID side effects.

CORTICOSTEROIDS

For many years, corticosteroids have been used extensively as another modality for treatment of RA. These drugs have been shown to decrease circulating monocytes and reduce macrophage phagocytosis and IL-1 secretion, resulting in inhibition of collagenase and lysosomal enzyme release (as well as reducing prostaglandin and leukotriene synthesis). Their anti-inflammatory and immunosuppressive effects provide relief for many patients and are especially useful for those patients refractory to treatment with NSAIDs. Unfortunately, corticosteroid therapy is often accompanied by numerous side effects, including bone loss, increased susceptibility to infection, osteoporosis, and peptic ulcers. Additionally, weaning patients from corticosteroids can be difficult and relapses of articular degeneration are frequent once the steroid is discontinued. Intra-articular application of these drugs has been implemented (in order to diminish the complications of oral administration) and has proven effective in reducing symptomatic joint inflammation.

DISEASE-MODIFYING ANTI-RHEUMATIC DRUGS (DMARDs)

In addition to the drugs mentioned previously, current therapy also involves the DMARDs, which are often given simultaneously with NSAIDs. DMARDs include gold, hydroxychloroquine, methotrexate, auranofin, sulfasalazine, d-penicillamine, cyclosporin, azathioprine, and cyclophosphamide. There is little evidence to suggest that DMARDs affect the underlying disease in the long run. They do improve physical function and retard radiographically apparent joint degeneration, and improvements in clinical condition are observed in as many as two-thirds of the patients. Like corticosteroids, DMARDS act to decrease inflammation. Sulphasalazine, for example, inhibits translocation of NF-kappa B into the nucleus by inhibiting I-kappa-B-
alpha kinase. This in turn inhibits transcription of various inflammatory cytokines, adhesion molecules, and chemokines. Methotrexate (an immunosuppressive agent) has become the dominant second line agent for treatment of RA. One study has shown that it induces apoptosis and clonal deletion of activated T-cells (which play a pivotal role in initiating and modulating humoral and cellular immune responses in RA). A comparison study using a combination of prednisone, sulphasalazine, and methotrexate versus sulphasalazine alone found that combination therapy induced immediate and highly significant improvement (including remission) of disease activity in patients with severe, early RA. Furthermore, withdrawal rates and lack of efficacy were also lower with this combined therapy.

A newer drug, which acts at the level of T-cells, is lefunamid (LFM). LFM is an anti-inflammatory and immunomodulatory drug that has been used to treat RA and to prevent organ rejection following transplant. In addition to suppressing the effects of IL-2 (and other cytokines) and inhibiting adhesion and migration of inflammatory cells, LFM also retards the proliferation of activated T-cells, which are known to play a significant role in RA. The mechanism of LFM has been disputed for some time, but recent findings suggest that LFM exerts its antiproliferative effects on activated T-cells by blocking biosynthesis of pyrimidines at the level of dihydroorotic acid dehydrogenase. Pyrimidine ribonucleotide availability is crucial for DNA synthesis and lymphoblast transformation. Pyrimidine availability is also important for regulating the magnitude and duration of the T-cell response and for modulating the nucleotide-related cascade following T-cell activation. LFM clearly has a unique role to play in current RA treatment and has been documented to bring about clinical improvement in RA patients.

Traditional therapies no doubt reduce the discomfort and improve the functionality of many patients who suffer from RA, but they do not offer a cure for the underlying disease processes. RA is currently being addressed earlier and with more aggressive treatment than ever before. This approach may further improve the outcome of the long-term disease process. Unfortunately, this aggressive approach cannot yet be unreservedly advocated due to lack of long-term studies. Some researchers suggest that early treatment of this nature is only appropriate in specific cases and may otherwise pose extra problems for the RA patient, including unnecessary drug-induced toxicity. Paving the road for newer intervention strategies is increased understanding of the roles of cells, mediator molecules, and cytokines involved in the initiation and perpetuation of joint disease in RA. These new approaches, directed at removing or impairing the function of lymphocytes, or by blocking the pro-inflammatory cytokines, may further improve the outcome of RA treatment (if not offer long-term remission or cure).

### IMMUNOMODULATION

T-lymphocytes play an important initiating and modulating role in humoral and cellular immune responses in RA. In fact, RA is characterized by accumulation of T-cells in the synovial compartment. For this reason, targets for therapeutic research in RA are beginning to include vaccinations, immunizations, monoclonal antibodies targeting surface receptors of T-cells, and induction of apoptosis in specific T-cells. T-cell receptors (TCR) are thought to share a limited number of variable region determinants, which are important in inciting auto-antigens. Most T-cells express the á and â forms of TCR on their surfaces. TCR peptide vaccination (with IR501) has been shown to promote improvement in the disease after only a short period of time. TCR vaccination is presumed to induce inactivation, tolerance, suppression, or deletion of the autoreactive TCR. In animal models, immunization with TCR Vâ chain peptides has proven to block the development of inflammation, synovial hyperplasia, and erosion of cartilage and bone. This is thought to result from development of antibodies that recognize self-reactive TCR; the exact mechanism remains elusive. Future human studies may prove this to be effective in providing protective immunity against RA by blocking joint infiltration by inflammatory cells and subsequent joint destruction.

Another approach to slow the autoimmune process may be through genetically engineered monoclonal antibodies. Antibodies that target the CD4 surface receptors of helper T-cells may help to dampen T-cell activity without affecting the normal immune functions of the patient. The accumulation of T-cells may be due in part to an anti-apoptotic environment as well as recruitment of these cells to the area. Apoptosis of T-cells in rheumatoid synovia may be inhibited due to the micro-environment that exists in RA. Fibroblasts allow for prolonged T-cell survival in the synovium and may be important therapeutic targets for the resolution of inflammation at the joint site rather than (or in addition to) inhibiting T-cells themselves.

### ANGIOGENESIS INHIBITORS

Another important feature in the development and maintenance of the disease state of RA includes neovascularization. Angiogenesis aids in the delivery of inflammatory cells to the synovium and delivers blood borne elements to the pannus (interdigitating folds of tissue resulting from synovial proliferation over articular surfaces). Pannus blood vessels demonstrate increased expression of the integrin v3. A cyclic peptide antagonist of v3, which can be administered intra-articularly, has targeted this in animal models. Upon introduction to the joint capsule, the cyclic peptide induces vascular apoptosis and decreased pannus formation, synovial infiltrate, and joint swelling. This agent also appears to serve as a protector against the erosive damage characteristic
of RA. With further development and clinical trials on human subjects, this discovery may provide for another novel approach to the treatment of RA.

**GENE THERAPY**

Recent animal studies have also suggested that gene therapy attenuation of hyperactive synovial cells (characteristic of RA) may present a possible route for treating RA. When hyperactive synovial cells and arthrogenic lymphocytes are eliminated, cytokines and degradation enzymes are no longer introduced into the joint and inflammation ceases. Through adenovirus-mediated gene transfer, the death factor Fas/Apo-1 and its ligand (FasL) confer high levels of FasL expression (Fas is normally up-regulated at sites of inflammation). FasL induces apoptosis of synovial cells (normally playing a role in self-tolerance) and effectively reduces inflammation and prevents the progression of the disease in mice. Another approach (also through adenovirus-mediated gene transfer) is to induce expression of anti-inflammatory molecules such as IL-1Ra (a natural inhibitor of TNF-á and IL-1), found in synovial tissue. In the future, transgenic expression of specific proteins in arthritic joints may prove to be yet another valuable therapy for RA.

**CYTOKINES**

Because of the emerging acceptance of RA as an autoimmune disorder, much of the current therapeutic research has naturally focused on the immune mediators associated with the development and persistence of RA. One such mediator is tumor necrosis factor (TNF), a cytokine produced by many cell types (especially macrophages) which is known to be one of the pivotal factors initiating and maintaining the inflammatory cascade. TNF-alpha is thought to stimulate production (by RA synovial cells) of IL-1, IL-6, and granulocyte-macrophage colony stimulating factor. TNF-alpha is also known to induce release of tissue degradative enzymes (such as matrix metalloproteinases) from neutrophils and various synoviocytes. TNF-alpha exerts its effects through binding with two types of membrane-bound receptors (TNFRs), type I (p55 and p60) and type II (p75 and p80). The extracellular portions of these receptors can be cleaved to become soluble TNFRs (sTNFRs) in sera and synovial fluid and have been shown to suppress the pro-inflammatory actions of TNF-alpha. Based on these findings, it was thought that RA treatment might involve infusion of sTNFRs into RA affected joints to suppress the actions of TNF-alpha. To increase the half-life and affinity of the sTNFRs for TNF-alpha, researchers developed recombinant sTNFR fusion proteins (rsTNFR:Fc), composed of monomeric sTNFR and the Fc portion of IgG. These compounds are currently undergoing clinical trials. One such agent, rhu sTNFR:Fc (p75), or **etanercept**, has already shown significant efficacy in decreasing joint pain and reducing clinical signs of inflammation and joint destruction. It is currently being evaluated in selected patients. A related strategy for diminishing the actions of TNF-alpha involves treatment of patients with anti-TNF-alpha monoclonal antibodies derived from murine anti-TNF-alpha mAb and human IgG (**infliximab**). This complex (which binds TNF-alpha and appears to reduce its activity) has been shown to significantly reduce joint pain and swelling. Both sTNFRs and anti-TNF-alpha mAbs are currently receiving a great deal of attention and present much promise as therapies for RA.

As potent mediators of immune response, the interleukins are also being considered as potential targets in RA treatment. In particular, IL-6 (a cytokine with both pro- and anti-inflammatory activities) is released in large amounts by rheumatoid fibroblast-like synoviocytes (FLSs), and is involved in T-cell and B-cell growth among many other activities. Recent clinical studies have shown that anti-IL-6 mAbs are very effective at reducing many of the clinical and biochemical markers of disease activity. Additionally, recent research has shown that transcription of IL-6 genes (specifically in FLSs) may be regulated by IL-1, a finding which shows some potential for very specific local regulation IL-6 production in the RA patient. Other interleukins are also under investigation as therapies for RA. IL-4 and IL-10 appear to be natural anti-inflammatory cytokines that suppress the release and actions of TNF-alpha, IL-1, and IL-6, and increase the release of cytokine inhibitors such as sTNFRs. IL-4 and IL-10 also limit the production of certain compounds, such as matrix metalloproteinases (MMPs), which are collagenases responsible for breakdown of joint tissues. Recombinant IL-10 and IL-4 are currently undergoing clinical trials in RA treatment. IL-11 is also gaining some attention as an anti-inflammatory agent for RA. IL-11 has recently been shown to indirectly decrease production of TNF-alpha, as well as directly reduce the activity of MMP-1 and MMP-3 (thereby reducing destruction of joint tissue). IL-11 also shows other indirect anti-inflammatory effects by enhancing the activity of IL-10. Based on these findings, interleukins clearly present another promising pathway in the fight against RA.

**PHYSICAL TREATMENTS FOR RA**

While this paper concentrates mainly on the pharmacological treatment of rheumatoid arthritis, physical therapy must also be acknowledged as an important adjunctive treatment in managing RA. The main goals of physical therapy are to maintain or increase muscle strength around affected joints and to maintain joint range of motion while taking steps to limit or relieve pain. Physical therapy programs will necessarily be tailored to each individual patient and will involve various physical agents and exercises based upon the desired outcome. Heat, for example, is applied in various forms in order to provide pain relief, increase blood flow, and decrease stiffness in the affected joints. Cryotherapy is also used in RA.
patients to mitigate acute swelling and to directly elevate the pain threshold by reducing the temperature of neural receptors. Joint mobilization exercises are also crucial and serve to overcome joint hypomobility, restore proprioception, and separate adhesions between articular surfaces. Joint mobilization can be passive or active and can involve massage, which is indicated to relieve pain and stiffness and increase blood flow to the area. Physical therapy also plays an important recovery role for those patients undergoing total joint replacement operations. The two most common joint replacements are total hip arthroplasty (THA) and total knee arthroplasty (TKA). The suggested recovery time and recommended physical therapy regimes for THA or TKA will vary based upon the surgeon, the technique employed, the surgical approach, and the condition of the patient. Generally, post-operative rehabilitation routines will involve therapeutic exercise, gait training, and instruction in safe and proper execution of daily living activities. Whether preventative or post-operative, proper adherence to physical therapy guidelines is very important in complete management of the RA patient.31

CONCLUSION

Even based on the superficial overview of rheumatoid arthritis therapy put forth in this paper, it is clear that RA is immensely complex and very likely caused by more than one type of inciting factor in each individual patient. Modern biochemical techniques are allowing researchers to delve deeper into the workings of RA, and each new experimental finding potentially represents another unique avenue of treatment (and perhaps cure) for this disease. Developing ways in which to tailor the various available therapies to the unique circumstances and disease processes of each individual patient will prove very challenging. Fortunately for patients and clinicians, the sheer amount of scientific interest and research in RA guarantee that innovative therapeutic advances will continue to trickle into mainstream medical practice for many years to come. The new immunological treatments currently on trial, promise to go far beyond the symptomatic relief of the NSAIDS and corticosteroids to a refined treatment of the disease mechanisms that drive rheumatoid arthritis.

REFERENCES

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