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REVIEW

Immunotherapy of Rheumatoid Arthritis Targeting Inflammatory Cytokines and Autoreactive T Cells

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Abstract Rheumatoid arthritis is a chronic disorder for which there is no known cure. Concentrating on specific elements of the abnormal immune response that characterizes the disease, scientists are reaching into biotechnology's bag of tricks to develop immunotherapeutic techniques. This paper will present some advances in the immunotherapy of rheumatoid arthritis targeting inflammatory cytokines and autoreactive T cells.

Keywords Rheumatoid arthritis · Immunotherapy · Inflammatory cytokines · Autoreactive T cells · Regulatory T cells · Th17 cells

Abbreviations

CD	Cluster of differentiation
CIA	Collagen-induced arthritis
CTLA-4	Cytotoxic T lymphocyte antigen 4
DMARDs	Disease-modifying antirheumatic drugs
FLS	Fibroblast-like synovial cells
GM-CSF	Granulocyte–macrophage colony-stimulating factor
IFN	Interferon
IL	Interleukin
IL-1ra	IL-1 receptor antagonist
IL-6R	α-Chain of IL-6 receptor
MMPs	Matrix metalloproteinases
OPG	Osteoprotegerin
RA	Rheumatoid arthritis
RANKL	Receptor activator of NF-κB ligand
TGF	Transforming growth factor
TNF	Tumor necrosis factor
Treg	Regulatory T cells
SF	Synovial fluid
VLA-1	Integrin $\alpha 1\beta 1$

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Introduction

Rheumatoid arthritis (RA) is characterized by chronic inflammation of the synovium of the peripheral joints the etiology and pathogenesis of which remain elusive despite the efforts of many investigators over the past 40 years, but it shows several of the clinical and laboratory features of an autoimmune process (Feldmann et al. 1996). It comprises a syndrome of pain, stiffness, and symmetrical synovitis of diarthrodial joints that leads to articular destruction, functional decline, and substantial comorbidity in the cardiovascular, neurologic, and metabolic systems. It is estimated to affect 0.5–1% of the world's population. In spite of its low prevalence, RA has a significant impact on patients' physical, emotional, and social functioning that often occurs very early in the disease with the onset of symptoms and extends to almost every area of life. One half to two-thirds of patients report lost social relationships, disrupted leisure activities, and limitations in employment (Yelin et al. 1987a, b).

Although the etiology and pathogenesis of RA remain unknown, it is generally considered an autoimmune pathology in which autoreactive T cells of pathogenic potential, such as Th1 cells, are thought to play an important role (Afzali et al. 2007; Chen et al. 2007b; Furuzawa-Carballeda et al. 2007; Gaston 2008; Gutcher and Becher 2007; Pfeffer 2003). Also, cytokines known to

be produced primarily by "effector" cells (macrophages) and connective tissue cells (fibroblasts) are expressed in abundance in RA synovium and synovial fluid (SF). These cytokines, including tumor necrosis factor (TNF), interleukin (IL)-1, IL-6, IL-8, and granulocyte–macrophage colony-stimulating factor (GM-CSF), regulate a broad range of inflammatory processes in the pathogenesis of RA (O' Gradaigh et al. 2004). In rheumatoid joints, it is well known that an imbalance between pro- and anti-inflammatory cytokine activities favors the induction of autoimmunity, chronic inflammation, and, thereby, joint damage (Ahlen et al. 2002; Blair and Athanasou 2004; Firestein et al. 1988; Maini and Taylor 2000).

The above two sets of pathogenic factors play important roles in the pathogenesis of RA. The T cell, through its interaction with an as yet unidentified antigen, is the primary cell responsible for initiating the disease as well as for driving the chronic inflammatory process. This is based upon the known association of RA with class II major histocompatibility antigens, the large number of $CD4^+$ T cells, and skewed T cell-receptor gene usage in the RA synovium. There is evidence that these T cells are activated during the disease process and accumulate in the inflamed synovium, leading to perpetuation of the joint inflammation and tissue destruction (Furuzawa-Carballeda et al. 2007; Gaston 2008; Scott and Kingsley 2006; Smolen et al. 2008). A significant contributor to the demise of the T cell model of RA was the paucity of Th1-type cytokines in the rheumatoid synovium. The discovery of T cell subsets led to immunopathological paradigms characterized by "immune deviation" away from a healthy balance of T cell-derived cytokines. Th2 excess (IL-4, IL-5, IL-10) underpinned allergic or "humoral" diseases such as atopic eczema and asthma, whereas Th1 excess was implicated in cellular pathologies such as diabetes, multiple sclerosis, and RA. However, levels of T cell cytokines such as interferon (IFN)-γ and IL-2 were low in RA synovium, in contrast to monokines such as TNF-α and M-CSF (Firestein et al. 1988). It was subsequently demonstrated that synovial T cells activated macrophages via membrane interactions. A link between the immune system and bone resorption is supported by the finding that several cytokines with regulatory effects on immune function, such as TNF-α, IL-1β, IFN-γ, IL-6, IL-11, and IL-17, also contribute to bone homeostasis by enhancing bone resorption (Blair and Athanasou 2004). These cytokines have been identified in the rheumatoid synovium and could promote synovial membrane inflammation and osteocartilaginous resorption via the stimulation of osteoclastic mediators (Ahlen et al. 2002; Maini and Taylor 2000; Nishimoto et al. 2007; Park et al. 2005).

IL-17, produced by the imaginatively named Th17 T cells, has recently been implicated in human autoimmune inflammation (Lubberts et al. 2003; Sato 2008; Yamada et al. 2008). Although discovered some 10 years ago, a potentially key role in diseases such as RA has only recently been attributed to IL-17 (Miossec 2007). Th17 T cells mature from naive T cells, and survive, in an environment characterized by IL-6, transforming growth factor (TGF)-β, and IL-23 (Bettelli et al. 2006). IL-17 is a highly pleiotropic cytokine with effects on a variety of cell types, including monocytes, fibroblast-like synovial cells (FLS), chondrocytes, and osteoclasts. Direct or indirect effects include inflammation, angiogenesis, osteoclastogenesis, and breakdown of bone and cartilage. A number of studies have demonstrated elevated levels in blood and synovium of RA patients, with correlations between synovial levels and joint damage (Chabaud et al. 1999; Kirkham et al. 2006; Zeltser et al. 2001). Nonetheless, the biology of Th17 cells differs in important ways between mouse and human, and the relative contributions of Th1 and Th17 T cells to RA pathogenesis remain to be formally established (Acosta-Rodriguez et al. 2007; Chen et al. 2007b; Dolhain et al. 1996; Yamada et al. 2008).

On the other hand, regulatory T cells (Treg), which normally keep pathogenic Th1 and Th17 cells in check, are deficient in patients with RA, further tilting the immune system toward a pro-inflammatory state (Anderton et al. 1995; Van der Aa et al. 2003). Importantly, the cytokine milieu built progressively in inflamed synovium over the course of RA is particularly critical to the self-perpetuation of the inflammatory process in the joint. The cytokine milieu carries the inflammatory signature of RA and is crucial to the differentiation and maintenance of pathogenic T cells, such as Th1 and Th17, and to the dysfunction of Treg (Van der Aa et al. 2003). Studies over the past several years have identified a number of key players that are drivers in the induction and maintenance of the cytokine milieu characteristic of RA joint inflammation, which has led to effective therapy for RA.

Approaches to Immunotherapy for RA

The goal of treatment is twofold: alleviating current symptoms and preventing future destruction of the joints with resulting handicap if the disease is left unchecked. These two goals may not always coincide; while pain relievers may achieve the first goal, they do not have any impact on long-term consequences. For these reasons, most authorities believe that most RA should be treated by at least one specific anti-rheumatic medication [disease-modifying antirheumatic drugs (DMARD)] to which other medications and nonmedical interventions can be added as needed. Many rheumatologists consider methotrexate to be the most important and useful DMARD, largely for several

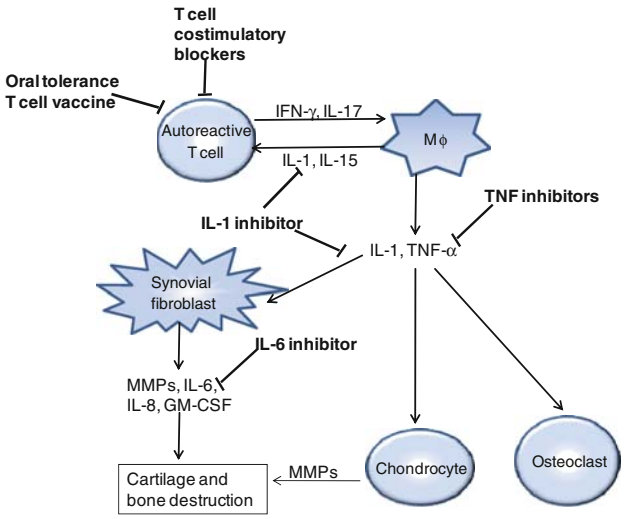

Fig. 1 Basic mechanisms of action of biological agents in the pathogenesis of RA

reasons: a good benefit/toxicity ratio, low cost, easy administration, particularly by the oral route, and subsequent lower drop-out rates. All these advantages over classic DMARDs make MTX suitable to work in combination with other drugs, especially biological agents.

Several approaches to immunotherapy are being developed and tested to prevent and/or treat RA. Because of the key role of inflammatory cytokines and autoreactive T cells in the pathogenesis of RA, for the purpose of this review we will focus on two kinds of biological agents, those which target inflammatory cytokines and those which target autoreactive T cells, for which both clinical and experimental findings are available (Fig. 1).

Targeting Inflammatory Cytokines

The current inflammatory cytokine inhibitors used for RA therapy (Table 1) are discussed below.

TNF Inhibitors

TNF is found in large quantities in the rheumatoid joint and is produced locally in the joint by synovial macrophages and lymphocytes infiltrating the joint synovium. TNF has been recognized as a key pathogenic cytokine that drives a pathogenic cytokine milieu leading to tissue damage (Choy and Panayi 2001; Harriman et al. 1999). Anti-TNF treatment has achieved important therapeutic goals in RA (Bazzoni and Beutler 1996; Harriman et al. 1999; Klinkhoff 2004; Mohler et al. 1993; Pfeffer 2003; Scott and Kingsley 2006; Ziolkowska et al. 2000). TNF antagonists were the first of the biological DMARDs to be approved for the treatment of RA and have also been referred to as biological response modifiers or "biologics" to differentiate them from other DMARDs such as methotrexate, leflunomide, and sulfasalazine. Three TNF antagonists are approved for the treatment of RA and additional agents are under investigation (Chabaud et al. 1999). These drugs are similar in their efficacy in decreasing signs and symptoms of RA, slowing or halting radiographic damage, and improving function and quality of life. These agents are also now approved for the treatment of other forms of inflammatory arthritis, including psoriatic arthritis and ankylosing spondylitis. These drugs began to enter the market for RA in 1999 and are now considered a routine part of the armamentarium available to treat patients. Early concerns about the toxicity of these agents are now being answered with data on substantial numbers of patients treated worldwide using these drugs and for longer periods of time. Cost and insurance reimbursement issues have limited the use of these agents for some patients.

Etanercept is a fusion protein that combines two extracellular binding domains of the p75 form of the TNF receptor with the Fc portion of a human IgG1 antibody molecule and which is used either as monotherapy or in combination with methotrexate. The components of the protein are entirely human and anti-etanercept antibodies are relatively uncommon. Etanercept binds TNF in the circulation and in the joint, preventing interaction with cell-surface TNF receptors, thereby reducing TNF activity (Catrina et al. 2006; Moreland et al. 1999; Ziolkowska et al. 2000). Etanercept continued to be safe and well tolerated and its clinical benefit was sustained for a median of 25 months and for as long as 43 months in patients with RA (Moreland et al. 2001). Another long-term open-label trial of the safety and efficacy of etanercept in patients reported that sustained improvement was also found in Health Assessment Questionnaire scores throughout the 3-year trial period (Klareskog et al. 2006).

Infliximab is a chimeric monoclonal antibody (mAb) that binds TNF with high affinity and specificity. The antibody binding site for TNF is of mouse origin, with the remaining 75% of the infliximab antibody derived from a human IgG1 antibody sequence. Infliximab is effective as monotherapy in reducing the signs and symptoms of RA, but anti-infliximab antibodies can develop which can, in turn, reduce the durability of the response. Co-treatment with methotrexate reduces the frequency of these antibodies and is therefore recommended along with infliximab. The combination of infliximab and methotrexate is very effective in reducing clinical manifestations of disease. Infliximab binds TNF in the joint and in the circulation, preventing its interaction with TNF receptors on the surface of inflammatory cells and eventually clearing TNF from the circulation. Monoclonal antibodies also bind to cell-bound TNF. Through its actions,

Table 1 Biological therapeutics that target inflammatory cytokines in RA

Target	Name of therapeutic	Product of description	Stage of development
Current			
TNF-α	Etanercept	Soluble p75 TNFR–human IgG1Fc fusion protein	Licensed
	Infliximab	Chimeric mAb specific to TNF-α	Licensed
	Adalimumab	Humanized mAb specific to TNF-α	Licensed
IL-1	Anakinra	IL-1ra	Licensed
IL-6	Tocilizumab	Humanized mAb specific to IL-6R	Phase III clinical trials
Prospective			
IL-1	AMG 108	Humanized mAb specific to IL-1β	Phase II clinical trials
IL-15	HuMaxIL-15 (AMG 714)	HuMax IL-15 (AMG 714) Baslund et al. (2005)	Phase II clinical trials
IL-17	Lubberts (2008)		
IL-21	Andersson et al. (2008)		

infliximab inhibits the activity of TNF (Harriman et al. 1999; Hlavaty et al. 2005; Maini et al. 1999; Maini and Feldmann 2002). Long-term results of infliximab therapy in RA showed that infliximab was safe and was continued for more than 2 years in more than two-thirds of the patients and remained effective (Ducoulombier et al. 2007; Zintzaras et al. 2008).

Adalimumab is a fully human anti-TNF mAb with high specificity for TNF. Like the other TNF antagonists, it is effective as monotherapy and in combination with methotrexate. It is administered by subcutaneous injection every 2 weeks, but can be increased to weekly administration if needed. Adalimumab binds specifically to TNF and blocks its interaction with the p55 and p75 cell-surface TNF receptors, thereby interfering with endogenous TNF activity. Adalimumab binds to both soluble as well as cell-bound TNF (Capsoni et al. 2005). Adalimumab is generally well tolerated as both concomitant therapy and monotherapy. Adalimumab has a rapid onset of action and sustained efficacy. It retards the progression of structural joint damage and improves HR-QOL (Bang and Keating 2004; van de Putte et al. 2004).

The actions of TNF-α perceived to be important in the pathogenesis of RA include its ability to induce the production of other (equally) proinflammatory cytokines, including IL-1 and IL-6, together with its ability to induce the production and release of chemokines that attract leukocytes from the blood into the inflamed tissue. Reduced IL-1 levels result in reduced synthesis of matrix metalloproteinase (MMP) and other degradative enzymes (Catrina et al. 2002; Charles et al. 1999; Ulfgren et al. 2000). These are all recognized components of the RA disease spectrum and explain the broad effects of TNF blockade in patients.

Impaired function of a subset of T cells called regulatory T (Treg) cells has been implicated in the pathogenesis of RA. Indeed, Treg cells from patients with active RA are defective in their ability to suppress proinflammatory cytokine production by activated T cells and monocytes in vitro. Anti-TNF-α antibody treatment significantly boosts the numbers of circulating Treg cells; the increase in Treg cells correlated with a reduction in C-reactive protein (Ehrenstein et al. 2004). Furthermore, TNF-α blockade inhibits the expansion of human $CD4^{+}VLA\text{-}1^{+}$ effector T cells in vitro while augmenting the percentage of Treg cells in cultures (Goldstein et al. 2007). These data suggest modulation of Treg cells as a potential mechanism of action of TNF blockers in RA.

The formation and activation of osteoclasts at the cartilage-pannus junction is an essential component of RA-associated bone loss. TNF-α promotes osteoclast differentiation and activates osteoclasts to resorb bone, leading to joint erosions (Goldring and Gravallese 2002). These processes involve an interaction between receptor activator of NF-κB ligand (RANKL) and its decoy receptor osteoprotegerin (OPG) (Goldring and Gravallese 2002). Anti-TNF-α therapy can modulate the OPG/RANKL system by reducing the RANKL/OPG ratio (Catrina et al. 2006). This might be a potential mechanism by which anti-TNF-α therapy retards radiographic damage in patients with RA.

IL-1 Inhibitors

IL-1 is produced by a variety of cells that are part of the innate immune system. There is increasing evidence that constant activation of the innate immune system occurs in several chronic inflammatory processes, including RA. Experiments have found that the administration of IL-1 stresses host defenses and mediates the response to disease. In animal and human studies, overproduction or continued production of IL-1 compromises host defenses in autoimmune disorders such as RA. IL-1 has effects on cartilage degradation leading to damage as well as inhibiting repair and is a potent stimulus to osteoclasts, leading to bone erosion.

The IL-1b–NF-κB axis is a key pathway in the pathogenesis of RA and is central in the production of proinflammatory mediators in the inflamed synovium. NF-κB activation in FLS contributes to the pathogenesis of RA by activating the transcription of a family of MMPs (Lee et al. 2009; Vincenti et al. 1998). These MMPs are major products of cytokine-stimulated FLS and efficiently degrade the collagenous components of cartilage and bone, which leads to joint deformity and a great deal of pain in RA patients. Thus, reducing the synthesis of IL-1 or blocking the effects of an overabundance of IL-1 may offer a therapeutic option for RA. IL-1 receptor antagonist (IL-1ra) is an endogenous blocker of the cytokine. Evidence supporting an anti-inflammatory role of IL-1ra in vivo is demonstrated by the observation that IL-1ra-deficient mice spontaneously develop autoimmune diseases similar to RA as well as vasculitis.

Anakinra, a human recombinant IL-1ra, is approved for the treatment of RA. Anakinra can be used alone or in combination with DMARDs other than TNF-blocking agents. Anakinra is not recommended for use in combination with TNF inhibitors because studies have shown increased infections without additive clinical benefit. Anakinra differs from native IL-1ra by the addition of an N-terminal methionine. Anakinra blocks the biologic activity of IL-1 by binding to IL-1R type I with the same affinity as IL-1β. A randomized double-blind placebo-controlled trial showed long-term safety and maintenance of clinical improvement following treatment with anakinra in patients with RA. Anakinra was well tolerated for 76 weeks. The only side effects that appeared to be treatment related were skin reactions at the injection site. There was no evidence of decreased tolerance, an increased number of withdrawals, or an increased incidence of clinical complications associated with extended anakinra therapy (Nuki et al. 2002).

IL-6 Inhibitors

IL-6 was identified in 1986 as a B cell regulatory factor and is now recognized as mediating pleiotropic functions; these include effects on the maturation and activation of B and T cells, macrophages, osteoclasts, chondrocytes, and endothelial cells and broad effects on hematopoiesis in the bone marrow. It is likely the primary driver of the hepatic acute-phase response in RA and is implicated directly in the anemia of chronic disease. IL-6 deletion protects DBA/1 mice from collagen-induced arthritis (CIA) (Kishimoto 2005), and neutralization of IL-6 using antibodies specific to either the cytokine or the α-chain of its receptor (IL-6R) ameliorates disease (Alonzi et al. 1998). IL-6 signals via both chains of its heterodimeric receptor, which is composed of gp130 and IL-6R, and the signaling pathways initiated by both receptor components offer therapeutic utility (Richards et al. 2006). Pioneering studies targeting IL-6R were conducted by Nishimoto et al. (2004) and demonstrated significant suppression of inflammation and clinical disease activity (Choy et al. 2002; Nishimoto et al. 2004).

The pivotal proof of concept for a critical role for IL-6 in the pathogenesis of RA is provided by clinical trials, now at phase III, in which tocilizumab, a humanized mAb specific to IL-6R, has been shown to suppress disease activity and erosive progression in patients with RA that is resistant to traditional DMARDs (Smolen et al. 2008). This mAb is also useful in the treatment of systemic juvenile RA (Yokota et al. 2008) and Castleman disease (Nishimoto et al. 2005) and is likely to offer broader utility as clinical trials expand to other diseases (Nishimoto and Kishimoto 2006). Tocilizumab was mostly well tolerated, with a safety profile similar to that of other biological and immunosuppressive therapies (Maini et al. 2006). The toxic effects of this strategic approach remain under investigation, particularly with respect to cardiovascular safety. Efficacy in individuals with RA who fail to respond to drugs that block TNF-α has been demonstrated, and thus drugs blocking IL-6 will likely provide a useful adjunct to the pharmacologic armamentarium. The treatment of RA patients with tocilizumab prevents joint destruction and improves symptoms (Hashizume et al. 2008; Nishimoto et al. 2009). Tocilizumab blocks IL-6 trans-signaling, so the mechanism by which it inhibits joint destruction may be that by blocking IL-6 trans-signaling, it inhibits osteoclast formation in synovia by down-regulating RANKL expression on synovial cells (Nishimoto et al. 2007). Moreover, in a CIA model, Naka's group found that the protective effect of IL-6 blockade, but not TNF blockade, correlates with the inhibition of Th17 differentiation (Fujimoto et al. 2008; Hashizume et al. 2008).

Targeting Autoreactive T Cells

Induction of Oral Tolerance

Oral tolerance is a state of absent or minimal immune responsiveness to protein antigens that were repeatedly administered by oral feeding (Weiner et al. 1994). Although much of RA's pathogenesis remains to be elucidated, it has been reported that joint proteins, probably type II collagen (CII), play a key role in the instigation of T cell-mediated immune responses. The strategies for treatment of RA have undergone a dramatic evolution over the past decade, although the exact origin and pathogenesis of this disease remain unknown. A major challenge in the development of effective therapies for RA is finding a

method for the specific inhibition of the inflammatory disease processes without the induction of generalized immunosuppression (Maini and Taylor 2000; Ruderman 2005; Trentham et al. 1993). Of note, the effective oral treatment of RA with native chicken or bovine type II collagen to induce immune tolerance is a good example of this (Choy and Panayi 2001; Trentham et al. 1993). This is because CII has been confirmed as a critical autoantigen in RA, CII-specific antibodies are frequently found in RA patients, and an RA-like disease can be induced by CII in certain susceptible mice, rat, and primate strains. Studies conducted in animal models have suggested that the possible mechanism may involve secretion of anti-inflammatory cytokines, including IL-4, IL-10, and TGF-β, by mucosal T lymphocytes that have differentiated into Th2 or Th3 cells after encountering the antigen (Fishman-Lobell et al. 1994; Tsuji et al. 2001; Weiner 1997). A greater proportion of IL-10-producing $CD4^+CD25^+$ T cells in mice that have undergone repeated oral administration of CII has been observed (Min et al. 2004). Together with increased production of IL-10 and TGF-β in peripheral lymphoid organs, the induction of this suppressor population is believed to block the induction of IFN-γ from CII-stimulated $CD4^+$ cells. However, individual studies often report conflicting findings, depending on the route, dose, and timing of antigen administration. Since 1993, oral administration of heterogeneous CII has proven to be beneficial against RA in some of clinical trials, although a lot of conflicting results have also been reported (Ausar et al. 2001; Barnett et al. 1996; Barnett et al. 1998; McKown et al. 1999; Sieper et al. 1996; Trentham et al. 1993). With one major problem being the identification of appropriate antigens for administration in individual diseases, particularly little is known of the individual epitopes on collagen which might be the most potent tolerogens. However, the majority of clinical trials of oral tolerance in human diseases, including RA, in recent years have been disappointing.

T Cell Costimulatory Blockers

Accumulating evidence suggests that RA is a T cell-mediated autoimmune disease. Early attempts at disease modulation using strategies such as CD4 mAbs and Campath were severely hampered by a lack of biomarkers of autoreactivity (Strand et al. 2007). Recently, however, co-stimulation blockade has emerged as an effective treatment for RA. Alongside a greatly improved mechanistic understanding of immune regulation, this has rekindled hopes for authentic and robust immune programming.

Abatacept is the first of a class of agents known as T cell costimulatory blockers. These agents interfere with the interactions between antigen-presenting cells and T lymphocytes and affect early stages in the pathogenic cascade of events in RA. T lymphocytes become activated due to an unknown stimulus, likely involving the interaction between antigen presented in the context of class II major histocompatibility complex molecule on the surface of antigen-presenting cells. T cells recognize antigens as foreign, and if they receive a second stimulus they will become active, proliferate, traffic to inflamed sites, and secrete proinflammatory cytokines, including TNF-α. One of the important second signals for T cell activation is mediated by the molecules CD80 and CD86 found on antigen-presenting cells and the CD28 molecule on the T cell surface. Abatacept is a fusion protein that combines the extracellular domain of the molecule cytotoxic T lymphocyte antigen 4 (CTLA-4; CD154) with the Fc portion of a human immunoglobulin molecule. CTLA-4 has very high affinity to CD28. When abatacept binds to CD28 on the T cell surface, it prevents the second signal from being delivered, thus turning down the T cell response. Additional effects are decreasing the production of T cell-derived cytokines, including TNF-α (Emery 2003; Kremer et al. 2003; Kremer et al. 2005; Kremer et al. 2006; Moreland et al. 2002). Abatacept was generally safe and well tolerated (Moreland et al. 2002). The results of a 2-year follow-up study of patients with RA who received a combination of abatacept and methotrexate showed that the improvements in signs and symptoms, physical function, and HR-QOL observed after 1 year of abatacept treatment were maintained through 2 years of treatment. This durability was accompanied by a safety profile consistent with that in the double-blind portion of the study. Radiographic progression was further inhibited in year 2 compared with year 1, suggesting an increasing effect of abatacept on the inhibition of structural damage in year 2 (Kremer et al. 2008).

T Cell Vaccine

Autoantigens that are potentially involved in the pathogenesis and disease process of RA are unknown, although several candidate antigens have been proposed. This has significantly hampered current research efforts in the understanding of the disease mechanism as well as in the development of specific immunotherapy for RA. In 1993, Van Laar et al. 1993 first reported a phase I study of T cell vaccination (attenuated autoimmune T cells) in thirteen RA patients. T cell vaccination has been tested successfully in the prevention and treatment of experimental animal autoimmune disease. All patients received a subcutaneous injection of attenuated autologous T lymphocytes from a CD4-positive clone or line isolated from synovial tissue or SF. No toxic side effects were observed. On average, the patients showed a slight decrease in disease activity which

was most marked 8 weeks after the injection. Specific immune reactivity against the injected T cells was not detected, with the possible exception of one patient who was vaccinated with a clone selected in vitro with antigen and whose disease had begun 1 year earlier. In this patient, a clear decrease in disease activity occurred, which was associated with a decrease in mitogen-induced proliferation of her peripheral blood mononuclear cells and in titers of serum rheumatoid factors. The results of this study show that inoculation of RA patients with autologous T cells is technically feasible and nontoxic and may be associated with clinical and immunological effects. The data suggest that the potential of T cell vaccination should be further explored in diseases with defined antigen reactivity (Van Laar et al. 1993).

Recently, a potentially beneficial immunomodulatory response was obtained by vaccinating RA patients with expanded, activated, and irradiated autologous SF T cells (Chen et al. 2007a). This was an open study of 16 patients. It has been demonstrated that vaccination with irradiated autologous synovial T cells, which are of potential pathological relevance in RA, is technically feasible and is effective in the induction of regulatory immunological mechanisms. Treatment was associated with expansion of $CD4^+$ T and $CD8^+$ T cells, many of which expressed the Vβ2 T cell-receptor chain. Some were anti-idiotypic, responding specifically to vaccine T cells with the production of IL-10 ($CD4^+$ T cells) or granzyme B ($CD8^+$ T cells). A broader regulatory response, however, was directed towards activated T cells in general, specifically against peptides derived from the IL-2R α-chain (so-called anti-ergotypic T cells). The latter response may be critical to harness a disease in which the precise autoantigen and pathogenic T cell clones are not readily identifiable, perhaps explaining why a previous attempt at T cell vaccination using T cell receptor-derived peptides has not been pursued (Moreland et al. 1998).

Conclusions

RA remains a formidable clinical problem despite the remarkable advances of recent years. Progressive articular damage (radiographic progression), functional decline, and risk of comorbidities remain for a substantial proportion of patients. Crucially, there is as yet little evidence that we can reestablish immunological tolerance and hence aim for drug-free remission on a regular basis. Whereas cytokines are now firmly established as therapeutic targets, blockade of TNF-α is beneficial, it is not curative, and its effects are only partial; more than one-third of patients do not benefit clinically. In particular, it will now be essential to recognize that distinct cytokines most likely mediate discrete effects at different disease stages, and thus there may be optimal targets defined by the relative disease stage of intervention. Cytokine patterns will offer rich biomarker opportunities and will play a part in the introduction of personalized medicine strategies. The efficacy of IL-1 and IL-6 inhibitors in RA patients has been demonstrated in recent clinical trials and IL-6 inhibitor can be used in RA patients who fail to respond to TNF-α inhibitors. The increasing number of cytokine inhibitors now available provides an invaluable tool to define disease pathogenesis, in turn leading to the rational design of novel therapeutics in years to come. Therapies targeting autoreactive T cells have also developed, including early clinical trials of CD4 mAbs, induction of oral tolerance, and co-stimulation blockade. More novel approaches, such as T cell vaccine and peptide therapy, will be developed in the future. However, we continue to require better biomarkers of tolerance induction in order to exploit these novel modalities to their full potential. We are also better at recognizing and defining autoantigens, potentially moving us closer to our ultimate goal of inducing antigen-specific tolerance via safe and innocuous treatments. Ultimately established, RA remains a complex disease, and it remains to be seen whether any immunomodulatory therapies will be sufficiently potent to correct many years of cumulative immune dysregulation and pathology. The challenge is significant, but there is well-founded optimism that effective, long-lasting, and safe immunotherapies can indeed be developed.

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