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## Treatment of chronic inflammatory diseases with biologic agents: Opportunities and risks for the elderly

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### Abstract

The treatment armamentarium in rheumatic inflammatory diseases has drastically increased in the last years. Earlier uses of conventional disease-modifying antirheumatic drugs (DMARDs), along with the arrival of newer therapies including the so-called “biologic” agents, have provided better long-term outcomes for patients suffering from these illnesses. Biologic agents have shown efficacy for several diseases and failed in others. Due to a high prevalence of some of these diseases in the elderly population, this age group may also benefit, although treatment will have to be tailored to its special needs. In this mini review, we will discuss the use of these medications in rheumatic diseases with a significant prevalence in the elderly, their proven and potential uses, and the considerations that need to be taken into account when using them in this population.

### Keywords

Biologic agents; autoimmune rheumatic disease; B cells; T cells; elderly

### Introduction

In the last years, advances in our understanding of the immune system, as well as the advent of the era of biotechnology, have triggered great interest in the development of new therapies for autoimmune rheumatic diseases. Our better understanding of these disorders has also shifted treatment strategy from a more conservative approach to a much more aggressive one, especially in rheumatoid arthritis (RA). Although conventional treatment modalities remain the mainstay and are sufficient and appropriate in many and maybe the majority of patients, we have clearly entered the “biologic” treatment era in the rheumatic diseases. Therapeutic agents are partially or fully humanized proteins that target different pathways of the immune response (Table 1). Most agents can be placed in one of three groups depending on their mechanism of action:

#### 1. cytokine blockade,

Interleukin (IL)-1 receptor antagonist, IL-18 binding protein, soluble TNF receptor, antibodies to TNF- $\alpha$ , IL-6, IL-15, IL-17, and BLyS

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## 2. cell depletion,

Antibodies to CD20 on B cells

## 3. or regulatory cell surface receptor blockade.

Abatacept (CTLA-4 fusion protein), Efalizumab (anti-CD11a antibody), Alefacept (LFA-3 fusion protein)

Compared to conventional treatment, these agents may target the immune system more selectively and therefore have fewer non-specific side effects, although many cytokines are certainly pleiotropic. Biologics are not less potent in their immunosuppressive abilities than conventional immunosuppressive medications and affect general immunocompetence as well as the autoimmune process. Consequentially, their use in an elderly population requires special considerations. This review will focus on recent literature and on the benefits and risks of newer biologic agents, with particular emphasis on diseases that are prevalent in this age group.

## Rheumatoid Arthritis

RA is a chronic systemic inflammatory disease mainly affecting diarthrodial joints. It can present at any age, but it is well known that its incidence and prevalence increases with age. Because of its high incidence, RA (in addition to psoriasis) is the prototype of an autoimmune disease that is being selected in clinical studies using biologics. Interestingly, RA patients have evidence of accelerating immune aging, including short telomeric length in hematopoietic cells, contracted T-cell receptor diversity, and increased prevalence of CD28 loss on T cells (Weyand et al., 2003). Accordingly, treatment studies of this disease may be particularly informative for the use of these agents in the elderly. Early agents that have been introduced in RA therapy are TNF- $\alpha$  and IL-1 $\beta$  inhibitors. Although effective in some forms of juvenile RA, soluble IL-1 receptor antagonist has not lived up to its promise in adults. In contrast, TNF- $\alpha$  inhibitors are commonly used in clinical practice today. Due to their therapeutic and commercial success in treating the disease, it is not surprising that several TNF- $\alpha$  blockers have been developed with similar safety and efficacy profiles (Etanercept, Adalimumab, Infliximab). Most studies show average response rates with 20% improvement in 65% of patients, and 70% improvement in 20% (Breedveld et al., 2006; Lipsky et al., 2000; van der Heijde et al., 2006)

In the last decades, the role of B lymphocytes in the pathogenesis of RA was all but ignored until the arrival of Rituximab, a successful B-cell depletion therapy for certain lymphomas, triggered an interest in using this treatment modality. Rituximab is a chimeric anti-CD20 monoclonal antibody that produces B-cell depletion by cell-mediated cytotoxicity, complement-dependent cytotoxicity, or apoptosis. Due to the lack of the CD20 molecule on other cells, including plasma cells, the effect is specific for B cells and does not alter hematopoiesis. Several open-label trials and randomized, double-blind, placebo-controlled trials have shown significant improvement in American College of Rheumatology scores for patients treated with Rituximab. Effectiveness has been also confirmed in patients with disease that was active on methotrexate (MTX) therapy (Emery et al., 2006). Treatment with Rituximab is given by IV infusion in two doses separated by fifteen days. Premedication with high-dose corticosteroids is recommended to avoid hypersensitivity reactions. The FDA approved Rituximab for RA treatment in 2006.

As a treatment strategy targeting regulatory molecules on immune cells, particularly T cells, CTLA4-Ig, also known as Abatacept, has shown significant efficaciousness, documenting that T cells play crucial roles in the initiation and persistent inflammation characteristic of RA. Activated T cells induce proinflammatory cytokine (TNF- $\alpha$ , IL-1, IL-6) production by other cells including macrophages, monocytes and synovial fibroblasts; B-cell immunoglobulin production; osteoclast differentiation; and matrix metalloproteinase production, which

contribute to the joint destruction seen in RA. T-cell activation requires at least two signals to occur. T-cell receptors need to recognize antigen presented by antigen presenting cells (APCs); however, in the absence of a second costimulatory signal, T cell receptor triggering is insufficient to induce activation and may induce anergy. Arguably, the most important costimulation pathway is the recognition of CD80 and/or CD86 on APCs by CD28 on T cells. Abatacept is a human fusion protein consisting of a modified IgG1 Fc portion and the extracellular domain of CTLA-4, which binds to CD28 with high affinity. This medication has been effective as either monotherapy or in combination with other disease-modifying antirheumatic drugs (DMARDs). A recent phase III study evaluating Abatacept plus MTX vs. placebo plus MTX in patients who showed inadequate response to MTX therapy revealed significant efficacy and good tolerability over one year. Incidence of serious side effects, specifically infections, was slightly higher in the Abatacept group. Still, discontinuation of therapy due to serious adverse effects was similar in both groups (Kremer et al., 2006). In 2005, this drug received FDA approval for its use in RA.

IL-6 has strong proinflammatory properties, including the induction of acute phase reactants. It has synergistic effects with IL-1 and TNF- $\alpha$ ; activates T cells and B cells; augments antibody production; and promotes hematopoiesis. Nevertheless, it also has significant anti-inflammatory properties by promoting glucocorticoid synthesis as well as IL-1ra and soluble TNF- $\alpha$  receptor expression, and inhibiting granulocyte-macrophage colony-stimulating factor and interferon (IFN)- $\gamma$ . IL-6 serum levels correlate with rheumatoid factor titers and play important roles in synovial fibroblast proliferation, periarticular osteopenia, and bone resorption. Tocilizumab is a humanized IgG1 directed against the IL-6 receptor that competes with IL-6 and inhibits signal transduction. Several placebo-controlled trials, including one using tocilizumab as monotherapy versus conventional DMARDs, have shown effectiveness in suppressing clinical symptoms and delaying radiographic progression. Clinical trials showed that the incidence range of adverse effects was wide (10–75%), although most were not considered serious and included diarrhea, fever, skin rash, headache and stomatitis; laboratory abnormalities like increased cholesterol, triglycerides and transaminases; and transient leukopenia (Nishimoto, 2006). Tocilizumab is administered as an IV infusion given every four weeks. This medication is still being studied to evaluate its long-term benefits and side effects. It has yet to achieve FDA approval for the treatment of rheumatic diseases.

## Giant Cell Arteritis

Giant cell arteritis (GCA) is a large vessel vasculitis that almost exclusively affects individuals over age 50. It mainly affects extracranial blood vessels and although blindness is the most well-known sequela, it can also have other severe complications such as stroke or aortic dissection. GCA responds exceptionally well to glucocorticoid therapy, but it has to be given over an extended time, which is particularly worrisome in the elderly population where this disease is most prevalent. For this reason, therapies with fewer adverse effects have been sought. The granulomatous nature of the disease suggested a role for TNF- $\alpha$ , but this was not supported in pathogenetic studies (Weyand and Goronzy, 2003). Hoffman et al performed a placebo-controlled study using the TNF- $\alpha$  inhibitor Infliximab plus conventional glucocorticoid therapy to maintain remission in GCA patients (Hoffman et al., In press). The study failed to show any difference between the treatment and placebo groups, the latter of which received glucocorticoids alone, emphasizing that treatment with biologics targeting specific pathways cannot always replace the broader actions of steroids. A study by Salvarani and colleagues assessed the efficacy of the same medication in polymyalgia rheumatica (PMR). PMR is closely related to GCA and shares the systemic manifestations, but only infrequently develops vasculitic complications. The study could not show any benefit of TNF blockade in PMR, but had two serious side effects out of only 21 patients treated (Salvarani et al., 2005).

## Wegener's Granulomatosis

Wegener's Granulomatosis (WG) is a small vessel necrotizing vasculitis that usually occurs during adulthood but presents in other age groups including the elderly population. Survival has dramatically increased in patients with this disease over the last 3 decades. Accordingly, it is not unusual to see elderly individuals with WG in rheumatology practice. WG is characterized by the development of non-caseating granulomas, most commonly in the lungs, kidneys and paranasal sinuses, although many other organs can be affected. Granuloma formation requires the presence of TNF- $\alpha$ , and for this reason TNF- $\alpha$  inhibition has been seen as potential therapy in WG. Unfortunately, a recent multicenter placebo-controlled trial showed no benefit of the TNF- $\alpha$  inhibitor etanercept in maintaining remission when added to conventional therapy (2005).

## Cryoglobulinemic Vasculitis

Cryoglobulinemic vasculitis (CV) results from immune complex deposits in small and occasionally medium-sized vessel walls with secondary complement activation. Cryoglobulins are antibodies that precipitate at cold temperatures (4°C) and may be the result of autoimmune disease or malignancies; most frequently, CV is associated with hepatitis C infection (>80% of cases). CV treatment is challenging, especially when associated with hepatitis C. When clinical features do not involve major organs or are life-threatening (purpura, skin ulcerations, arthralgias), most authorities recommend using only antiviral therapy (interferon plus ribavirin). Aggressive disease (glomerulonephritis, mononeuritis multiplex) may require transient immunosuppressive therapy with glucocorticoids and cyclophosphamide. The involvement of antibodies in the pathogenesis of CV has triggered the enthusiasm of using B-cell depletion therapy in this disease. Several reports have shown promising results using Rituximab with or without concomitant corticosteroid therapy (Basse et al., 2005; Cai et al., 2006; Zaja et al., 2003). A recent open study of 5 patients with active glomerulonephritis due to hepatitis C virus-associated CV demonstrated rapid decreases in proteinuria and improvements in urinary sediment when treated with four weekly infusions of Rituximab. All patients achieved a significant response: One continued in remission after 21 months (last follow-up); three others suffered relapses, two of which received and responded to retreatment with Rituximab; and the fifth received maintenance treatment while still in remission. Overall the medication was well tolerated (Quartuccio et al., 2006), but more data is needed to confirm the potential for Rituximab as monotherapy or as an adjuvant for treating CV.

## Inflammatory Myopathies

The two most common forms of idiopathic inflammatory myopathies in the adult, dermatomyositis (DM) and polymyositis (PM), share similarities in their main clinical manifestation, muscle weakness due to immune-mediated muscle destruction; however, their pathogenesis seems significantly different. In DM, there are perivascular infiltrates of B lymphocytes and CD4 T cells, whereas PM is characterized by perifascicular CD8 cytotoxic T-cell infiltration. Despite these differences, high level of inflammatory mediators like IL-1, IL-2, TNF- $\alpha$  and - $\beta$  and IFN- $\gamma$  have been found in PM and DM patient muscle biopsies. Treatment of both conditions has been with glucocorticoids, usually in combination with MTX or azathioprine. Still, some patients are refractory to this conventional management. In such individuals, the use of intravenous immunoglobulin, one of the first "biologic" agents, appears to be useful, although the exact mechanism of action remains unclear. For the past few years, several cases and series reports have shown promising results with the use of TNF- $\alpha$  blockers in patients with refractory disease, showing improvement in creatine kinase levels and muscle strength. A recent retrospective study of eight patients with DM/PM showed benefit in six; two failed to respond. Interestingly, both of the non-responders were older than 60 and had

normal creatine kinase levels at baseline (Efthimiou et al., 2006). Studies are needed to confirm these findings and further evaluate other potential therapies being considered, like the use of costimulation blockers and B-cell depletion therapy, the latter of which may be of particular promise in DM.

## Secondary Amyloidosis

Secondary Amyloidosis (SA) usually occurs in individuals with uncontrolled chronic inflammatory conditions which may be infectious (osteomyelitis, tuberculosis) or noninfectious (RA, seronegative spondyloarthropathies, hereditary periodic fever syndromes). SA arises due to fibril deposition known as amyloid A (AA), which is the result of persistent high levels of its circulating precursor serum amyloid A (SSA) produced by the liver in response to the proinflammatory cytokine IL-6. AA may deposit in different tissues like the kidneys, liver, GI tract, and CNS. Clinical manifestations depend on organ-specific deposition and are associated with increased morbidity and mortality. Although some patients may respond to alkylating agents, most therapies have yielded poor results. A recent open-label study evaluated the effectiveness and safety of the TNF- $\alpha$  inhibitors Infliximab and etanercept in the treatment of 25 SA patients. All patients had an active rheumatologic condition (RA or seronegative spondyloarthropathy) and had biopsy-proven SA. All but three patients had renal amyloidosis, and the majority stabilized or improved their renal function; half had significant decreases in proteinuria. The results provide some optimism for treating SA; however, the high incidence of infections (9 subjects), some of which were severe like pulmonary aspergillosis and staphylococcal endocarditis, indicate that more data is needed to corroborate efficacy and safety (Fernandez-Nebro et al., 2005).

## Spondyloarthropathies

All three TNF- $\alpha$  inhibitors have shown significant efficacy in the treatment of ankylosing spondylitis (AS), and although there has been no specific studies in the elder population, at least one clinical trial included individuals aged 65 and over (Davis et al., 2003). AS affects primarily the axial skeleton, causing inflammation of the vertebral and sacroiliac joints, which may fuse after years of activity. It is generally a disease of the young male adult and only infrequently has persistent activity during later adulthood. However, other forms of spondyloarthropathies, such as psoriatic arthritis and seronegative polyarthritis, may resemble reactive arthritis-related diseases that occur in the elderly. Still, although TNF- $\alpha$  inhibitors seem to be well tolerated in the elderly, data is lacking regarding its efficacy in the treatment of spondyloarthropathies in this population.

## Adverse events related to biologic therapy in rheumatic diseases

Most of the serious side effects of biologics are directly related to their immunosuppressive action. Reactivation of chronic infection such as tuberculosis or histoplasmosis is a particular concern with TNF- $\alpha$  blockers. The role of TNF- $\alpha$  in suppressing chronic viral infections is less clear, in particular, zoster reactivation is a concern in this age group. The little data available suggests that TNF- $\alpha$  therapy may be detrimental in hepatitis B but not hepatitis C (Calabrese et al., 2004; Calabrese et al., 2006). Abatacept has been associated with an increased incidence of pneumonias in clinical trials. Data correlating increased infection rates with Tocilizumab are lacking. A second concern with using biologic therapy in rheumatic diseases is the increased likelihood of developing malignancies. Postmarketing surveillance on TNF- $\alpha$  blockers has shown an increased risk for lymphoproliferative malignancies like non-Hodgkin's lymphoma (NHL). It is debated whether confounding variables such as a higher baseline risk for these types of malignancies in patients with RA or the previous and concomitant use of other immunosuppressive therapy are sufficient to explain this finding. Individual clinical studies are usually underpowered to document infrequent events of tumorigenesis or serious infection.

A recent meta-analysis of clinical trials studying anti-TNF- $\alpha$  antibody therapy in RA, however, provided clear evidence for a dose-dependent increased risk for solid malignancies and a higher incidence of severe infections (Bongartz et al., 2006). Similarly, the TNF- $\alpha$  inhibitor etanercept was found to be associated with an increased risk for solid malignancies in patients with WG, especially when used in combination with cyclophosphamide (Stone et al., 2006). Based on the extensive use in NHL, Rituximab appears not to carry a significant increase in the incidence of infections. However, antibody recall responses after vaccination were clearly blunted many months after treatment (van der Kolk et al., 2002). Its use in rheumatology is just starting, and further experience and postmarketing surveillance is needed to evaluate possible increases in infection rates as well as long-term side effects especially in patients who undergo repeated treatment. Reactivation of chronic viral infection, defective protection for viral reinfection, and poor vaccine responses remain concerns.

### Special considerations in the elderly population

The immune system in the elderly is already compromised (Goronzy and Weyand, 2005; Grubeck-Loebenstien and Wick, 2002), and the decision for immunosuppressive treatment that confers increased risk of severe infection and of tumor occurrence must be carefully considered. Retrospective data on the use of the TNF- $\alpha$  blocker etanercept did not show an increase in severe adverse events when comparing elderly and younger patients, but this study does not sufficiently assess the impact of age. The risk or history of previous malignancy, which increases with age, also needs to be considered when deciding whether to use biologic agents in the elderly. The effect of biologics on vaccine responses may be particularly evident for those in this age group who are already known to respond poorly to influenza vaccinations (Goodwin et al., 2006). A recent study that compared responses to pneumococcal vaccine in controls and RA patients treated with MTX, prednisolone, or TNF- $\alpha$  blockers showed that only MTX was associated with a decreased response to vaccination (Kapetanovic et al., 2006). As already mentioned, reduced vaccine responses have been found with Rituximab in NHL patients. Data regarding vaccination while using other biologic agents is lacking, but T cell-directed biologics are likely associated with diminished vaccine responses. TNF inhibitors have been shown to reactivate dormant bacterial and fungal infection. It remains to be seen how and whether chronic viral infections like herpes zoster, the reactivation of which is a common problem in the elderly, are influenced by anti-cytokine treatment.

In addition to these concerns common for most of these biologics, there will also be unique considerations to take into account. The use of TNF- $\alpha$  blockers may exacerbate congestive heart failure, which is more prevalent in the elderly population. The effects of IL-6 inhibition in an elderly population where elevated IL-6 has been associated with frailty and increased mortality are impossible to predict. B-cell recovery rates after treatment with Rituximab will be likely protracted or incomplete in the elderly, because these patients have a limited stem cell reserve and impaired B-cell development (Cancro, 2005).

The use of biologics in rheumatic diseases has been exciting. Nevertheless, the examples of GCA and WG have clearly shown that biologics are not always the magic bullet, and their safety profiles will very much depend on the patient populations in which they are used.

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**Table 1**

Biologic agents used in adult rheumatologic autoimmune diseases

Agent	Type	Mechanism of Action	Studied in	FDA approval
Rituximab	Anti-CD20 mAb	B cell depletion	RA, CV, SLE	RA
Abatacept	CTLA4 Ig	Costimulation inhibitor	RA	RA
Tocilizumab	Anti IL-6R	IL-6 inhibition	RA	None
Etanercept	TNF- $\alpha$ R/Fc fusion protein	TNF inhibition	RA, AS, PsA DM/PM, SA, WG (negative results)	RA, AS, PsA
Adalimumab	Anti-TNF- $\alpha$ mAb	TNF inhibition	RA, AS, PsA	RA, AS, PsA
Infliximab	Anti TNF- $\alpha$ mAb	TNF inhibition	RA, AS, PsA DM/PM, SA, GCA (negative results) PMR	RA, AS, PsA
Anakinra	IL-1ra	IL-1 inhibition	RA, AS,	RA