Safety issues related to emerging therapies for rheumatoid arthritis

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ABSTRACT

Several novel biologic therapies for rheumatoid arthritis (RA) are emerging that target aspects of the immune system other than tumor necrosis factor (TNF). Two such therapies currently in development include CTLA4Ig (Abatacept) and anti-CD20 monoclonal antibody (Rituximab). CTLA4Ig has been demonstrated to be well tolerated with a good short-term safety profile. Rituximab has also been shown to have a good safety profile in a limited number of RA patients. Further safety data with larger numbers of RA patients treated with Rituximab is required.

Introduction

Despite their impressive efficacy, only a portion of the RA population responds well to TNF antagonists and few patients achieve complete remission. Because of the continuing unmet clinical need in RA and other autoimmune diseases, other therapeutic agents targeting different aspects of the immune response are under development. This paper will provide an overview the safety issues related to emerging therapies.

Pathogenic elements thought to be critical in the perpetuation of disease have become key therapeutic targets, and include: 1) adhesion molecules; 2) chemokines; 3) inflammatory cell subsets including T cells, B cells, dendritic cells, macrophages and synovial fibroblasts; 4) co-stimulatory molecules; 5) cytokines, 6) angiogenesis factors; 7) proteolytic enzymes; and 8) the intracellular signal transduction cascade that generates pro-inflammatory molecules (1).

This review will address two new therapeutic targets, co-stimulatory molecules and B cells, in the treatment of rheumatoid arthritis.

Targeting co-stimulatory molecules

T cell activation by antigen requires 2 distinct signals: (i) formation of the T-cell receptor–antigen–MHC, trimolecular complex, and (ii) binding of a co-stimulatory molecule, CD28, on the surface of T cells to CD80/CD86 on antigen presenting cells. Following T cell activation a protein homologous to CD28 – cytotoxic lymphocyte associated antigen-4 (CTLA4) – is upregulated on the T cell surface, which downregulates T cell activation when binding to CD80/86. Agents have been designed to inhibit the interaction of costimulatory molecules on activated cells. One of these is a fusion protein of the Fc portion of IgG1 and soluble CTLA4, and a mAb.

Based on promising pre-clinical studies in the New Zealand Black/New Zealand White (NZB/NZW) mouse model of SLE (2) and collagen II induced rat model of arthritis (3), CTLA-4Ig was evaluated in psoriasis. Phase I data showed a substantial improvement in approximately 50% of patients, without interference in assays of delayed hypersensitivity and proliferation to recall antigens (4). Subsequently, a 6-month placebo randomized, placebo controlled trial of CTLA4-Ig (2 and 10 mg/kg) in combination with methotrexate (MTX) was completed in 339 RA patients with active disease despite MTX treatment for at least 6 months (5). Patients were similar to those in the usual clinical trials in patients with RA, with a mean age of about 55 years of age and a disease duration of about 9.5 years. Patients had severe active disease, with a high number of tender joints, swollen joints, and an elevated CRP. An analysis at 12 months during which the blind was maintained, revealed ACR 20, 50 and 70 responses in the 10 mg/kg group of 63%, 42%, and 21% respectively compared to 36%, 20%, and 8% for the placebo (6).

With regards to safety, both the 10 mg/kg CTLA4-Ig-treated patients and placebo-treated patients had high levels of adverse events, at a similar rate (90.4% vs 94.1% respectively). However, the proportion of patients exhibiting serious adverse events was low, and the

same i.e. 1.7%. The most common side effects at 12 months in the 10 mg/kg CTLA4-Ig (n = 115) and placebo (n = 119) treated patients were upper respiratory tract infection (24.3 vs 18.5%), nausea and vomiting (15.7 vs 16.0%), and headache (14.8 vs 16.0%), respectively. An increase in adverse events in the 10 mg/kg CTLA4-Ig group relative to the placebo group was observed with respect to diarrhea (13.0% vs 6.7%), tracheobronchitis (8.7% vs 4.2%) and dizziness (6.1% vs 2.2%) respectively. No clinically significant antibody response directed against CTLA4-Ig was detected in the CTLA4-Ig treated groups.

CTLA 4Ig was also evaluated in a 6-month randomized, placebo-controlled trial compared to placebo in combination with etanercept (25 mg subcutaneous, twice per week) in patients with an inadequate response to etanercept alone (7). Combination therapy resulted in ACR 20, 50, and 70 responses of 48%, 26%, 11% respectively compared with 28%, 19%, 0% in patients receiving placebo + etanercept, differences which were statistically significant for ACR20 and ACR70. The combination was well tolerated with a safety profile comparable to etanercept alone, without detection of anti-CTLA4-Ig. antibodies.

Targeting B cells

Until recently, antibody producing B cells were thought to play a secondary role in RA by the production of IgM, IgG and IgA rheumatoid factors. Recent data support the role of B cells as antigen presenting cells, specifically capturing antigen via cell surface immunoglobulin and presenting it to T cells. A recent study indicated that B cells provide a critical function in T cell activation and may harbor a relevant antigen in RA. Depletion of CD20 +vB cells in RA synovium – SCID mouse chimeras was associated with a reduction of proinflammatory cytokines in the synovial tissue, suggesting a critical role for mature B cells in perpetuating the inflammatory process (8). Rituximab is a chimeric anti-CD20 IgG1 monoclonal antibody which is effective as monotherapy in treating relapsed or refractory indolent lymphomas when given in combination with chemotherapy. In non-Hodgkins lymphomas (NHL), Rituximab (RTX) is used as initial therapy and with re-treatment and maintenance regimens. Approximately 250,000 NHL patients have received Rituximab.

An initial open label study in RA was conducted in 5 patients who received RTX, cyclophosphamide (CTX) and prednisolone (9). At 26 weeks, 3 of 5 patients had ACR70% responses, and 2 of 5 ACR50% responses. These were maintained or improved to ACR70% responses in 3 of 5 and to ACR50% responses in 2 of 5 at 12 months, and to ACR 70% in all patients at 19 months with retreatment in 2 patients. Peripheral B cell counts fell to undetectable levels after treatment and remained decreased for 6-12 months. In 2 patients, increases in CD19+ cells were correlated with relapses. No infusion reactions were reported.

A subsequent report extended these results to a series of 22 patients (10). A total of 29 treatments using 5 different regimens of RTX in combination with CTX and/or high dose prednisolone were administered. The authors concluded that RTX should be administered in doses not less than 600 mg/m^2, and be combined with CTX as well as prednisolone. They reported afmean duration of responses to a single treatment of 14.4 months, ranging from 6–33.5 months. Again peripheral B cell depletion was observed of 5.5 to 11 months' duration.

More recently, a 24-week randomized, placebo-controlled trial involving 161 patients with DMARD-refractory RA and an inadequate response to methotrexate demonstrated substantial clinical benefit after 1 course of therapy with RTX in combination with methotrexate and corticosteroids – comparable to the responses of RTX in combination with MTX (11). Patients had longstanding disease of about 11 years' duration and were refractory to about 2.5 prior DMARDS. Patients had quite active disease as evidenced by high swollen and tender joint counts, and elevated ESR, CRP, and DAS levels. The methotrexate dose ranged between 12.5 – 15 mg/week. In an exploratory analysis at 48 weeks, during which the sites had remained blinded, ACR 20, 50 and 70 responses were met in 65%, 35% and 15% of RTX-treated patients compared to 20%, 5%, and 0% respectively in methotrexate monotherapy treated patients (12, 13).

Peripheral B-cell depletion was rapid and maintained for up to 48 weeks with B-cell recovery beginning as early as 24 weeks (12). By 48 weeks, median peripheral CD 19 B-cell levels for the RTX groups were 20-40% of their baseline values. There were no major differences in the T-cell populations in the RTX-treated groups compared with the MTX group (14). At 48 weeks, rheumatoid factor levels were depressed only in the MTX plus RTX group. Despite this the IgA, IgG and IgM levels remained within normal limits although a slight decrease was observed in the IgM levels relative to the other two isotypes (12). This may be accounted for by the lack of CD20 on mature plasma cells, which therefore will be unaffected by RTX. In a prior study, autoantibody levels decreased more than proportionally: IgA and IgG rheumatoid factor, anti-cyclic citrulinated peptide Abs, and CRP levels, although IgM RF paralleled total Ig levels (15).

The frequency of adverse events over the 48 weeks between MTX and RTX was comparable. The majority of adverse events occurred within the first 4 weeks, mainly as a consequence of infusion-related reactions that occurred within 24 hrs of the infusion. Overall, the number of infusion-related reactions was comparable between the active treatment and placebo groups. Fewer infusion-related reactions were seen during the second infusion. The most frequent infusion reactions in both the RTX and MTX groups were mild to moderate transient hypo- and hypertension, flushing, and pruritis (16). The majority were mild to moderate. The overall number of adverse events in each treatment were comparable The most frequently reported adverse events in the RTX-treated patients included rash, pruritis, pyrexia, bacterial infection pharyngitis and diarrhea (Table I). Few serious adverse events were reported (17) (Table II). There were more events in the patients treated with RTX and cyclophospha-

Table I. Most frequently reported infections (up to week 48).

	MTX (n = 40)	Rituximab (n = 40)	Rituximab plus CTX (n= 41)	Rituximab plus MTX (n = 40)
Infection and infestation *	24 (33%)	14 (30%)	16 (29%)	24 (33%)
Herpes simplex	5%	3%	5%	3%
Herpes zoster	5%	-	2%	5%
URTI viral NOS	3%	-	2%	5%
UTI NOS	5%	3%	2%	-
Bronchitis (bacterial)	5%	-	2%	-
Pharyngitis (viral)	3%	3%	-	3%
UTI (bacterial)	5%	3%	-	-

* Number of events reported by % of patients.

Table II. Summary of serious adverse events over 48 weeks.

	MTX (n = 40)	Rituximab (n = 40)	Rituximab plus CTX (n = 41)	Rituximab plus MTX (n = 40)
All events*	3 (8%)	4 (10%)	8 (17%)	4 (10%)
Corneal abscess	1	-	-	-
Pneumonia (pseudomonal)	-	-	1	-
Bronchopneumonia	-	1	-	-
Septic arthritis	-	1	1	-
Septicaemia	-	-	1	-
Anemia	1	-	-	-
Renal impairment	-	-	-	2
Thrombosis	-	-	-	1
Pericarditis	1	-	-	-
Gastenteriti	-	1	-	-
Arytenoiditis	-	-	-	1

*Number of events reported by % of patients.

mide than in the other groups. One patient receiving RTX alone died of bronchopneumonia. The number of infections was comparable between groups.

An open-label pilot study was carried out with RTX alone, without immunosuppressives or corticosteroids (18). RTX was administered in increasing doses from 100 mg in week 1 to 375 mg/m^2 in week 2 to 500 mg/m^2 in weeks 3 and 4. Of 7 evaluable patients, 3 had ACR20% responses at a median follow up of 5 months. B cell depletion was evident at 8 weeks following treatment; only infusion reactions were reported as adverse events

More information concerning the safety profile of this treatment regimen will require a larger number of patients treated over many months in blinded protocols, in which randomization to comparator therapies is preserved. Prolonged depletion of peripheral B cells has been observed in some patients, and does not appear to closely correlate with the efficacy or lack thereof, or with initial responses followed by flares. Evaluation of tissue B-cell levels in synovium and lymph nodes might be valuable, as peripheral blood findings do not necessarily correlate with those in tissue. Both published reports allude to severe infections, but do not offer sufficient information to analyze the possible correlation of their occurrence with persistent B cell depletion or other potential effects of RTX administration.

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