Successful Treatment of a Patient with Rheumatoid Arthritis and IgA-Kappa Multiple Myeloma with Tocilizumab

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Abstract

A 63-year-old woman receiving tumor necrosis factor (TNF) inhibitors for rheumatoid arthritis (RA) was found to have smoldering IgA-kappa type multiple myeloma (MM). Retrospective examination of stored serum samples revealed a steady increase of serum IgA levels after the start of TNF inhibitor therapy. The patient’s articular symptoms showed marked exacerbation when TNF inhibitors were discontinued because of fear of worsening the MM. Tocilizumab improved RA symptoms dramatically and stabilized serum IgA levels for 13 months after a transient steep rise. This case suggests that tocilizumab can be used safely in patients with inflammatory disorders with coexisting MM.

Key words: tocilizumab, interleukin-6, rheumatoid arthritis, multiple myeloma


Introduction

Biological agents that block the action of pro-inflammatory cytokines have emerged as a new therapeutic modality for chronic inflammatory disorders. In patients with rheumatoid arthritis (RA), which is a chronic inflammatory disorder of the joints, inhibitors of tumor necrosis factor (TNF)-α, such as anti-TNF-α monoclonal antibodies (infliximab [INF] and adalimumab) and a soluble TNF receptor fusion protein (etanercept [ETN]), have shown clinical efficacy and can prevent joint damage (1, 2). Since TNF plays an important role in tumor surveillance, there has been concern that TNF inhibitors might also accelerate the growth of malignancy when used in patients with tumors (3). In patients with multiple myeloma (MM) and monoclonal gammopathy of undetermined significance (MGUS), a plasma cell malignancy and a pre-malignant state, respectively, serum levels of monoclonal gamma-globulin have been reported to increase during treatment with ETN (4, 5). Here, we report a patient with RA and smoldering MM, in whom a humanized monoclonal anti-IL-6 receptor antibody (tocilizumab [TCZ]) improved RA symptoms and also stabilized the serum levels of monoclonal IgA.

Case Report

A 63-year-old Japanese woman had a 17-year history of RA that was well controlled by treatment with methotrexate (MTX) and TNF inhibitors; INF was used first but was replaced by ETN due to secondary failure. In February 2009, an elevated serum IgA level (1,771 mg/dL, normal [110-410]) was found incidentally. Serum electrophoresis revealed monoclonal IgA-kappa gammopathy, and examination of the bone marrow showed 10% plasma cells. Since there were no symptoms related to MM, a diagnosis of smoldering IgA-kappa type MM was made. ETN and MTX were discontinued for fear of adverse effects on MM, with low-dose oral prednisolone (5-7.5 mg/day) and sulfasalazine (1-3 g/day) being substituted. Subsequently, her articular symptoms worsened and she required hospitalization in June 2009. On admission, there were 20 tender and 18 swollen joints...
according to the DAS28 scoring system (6). Laboratory findings were as follows: erythrocyte sedimentation rate, 139 mm/hr; hemoglobin, 8.8 g/dL; serum IgA, 1,735 mg/dL; IgG, 346 mg/dL (normal: 870-1,700); and IgM, 31 mg/dL (46-260). The serum calcium level was within normal limits. Serum C-reactive protein (CRP) was 9.0 mg/dL (<0.06) and matrix metalloproteinase-3 was 380 ng/mL (<59). Rheumatoid factor was negative. Anti-cyclic citrullinated peptide antibody was positive at 81 U/mL (<4.5). Urinary Bence-Jones protein was negative. Radiographs of the hands and feet showed typical RA erosions. Lytic bone lesions suggesting MM were not observed in the spine or skull. Retrospective examination of stored serum samples revealed a steady increase of serum IgA levels after the start of TNF inhibitors (Fig. 1). Serum IL-6 levels also increased gradually during treatment with ETN and INF with some fluctuation.

In July 2009, monthly administration of TCZ (8 mg/kg) was started and her articular symptoms improved dramatically. Levels of CRP and matrix metalloproteinase 3 in sera
improved and the hemoglobin level also improved. Shortly after the start of TCZ therapy, the serum IgA level showed a transient increase to reach 3.070 mg/dL. At its maximum and the serum IL-6 level was also elevated to 38.4 pg/mL. However, serum IgA levels decreased spontaneously and stabilized after the second administration of TCZ while the surge in IL-6 levels was observed. Adverse events were not observed except for transient neutropenia (nadir of 1,300/µL) and one episode of bronchitis that responded to oral antibiotics. Consequently, at 13 months after the start of TCZ, both her RA and MM are under good control.

Discussion

MM is a plasma cell malignancy that classically presents with lytic bone lesions and high levels of monoclonal protein in the blood and/or urine. Smoldering MM is a subset of this disease that fulfills the diagnostic criteria for MM (i.e., serum monoclonal protein >3.0 g/dL and bone marrow plasmacytosis ≥10%), but occurs without lytic lesions or symptoms (7). Patients with smoldering MM do not require chemotherapy. However, about 60% of patients with smoldering disease eventually develop symptomatic MM, and the IgA-type generally progresses most swiftly (8, 9). In the present case, the increase of monoclonal protein levels during TNF inhibitor therapy discouraged continued treatment with ETN and MTX.

An earlier pilot study revealed that ETN did not show anti-myeloma activity and that four out of 10 patients with refractory MM experienced significant deterioration during ETN administration (4). In addition, an increase of monoclonal protein levels after the start of ETN therapy was reported in an RA patient with MGUS (5). Similar to observations in these reports, a gradual increase of monoclonal protein levels was observed during treatment with ETN or INF in the patient reported here. An increase in serum IL-6 levels during TNF blockade suggests that up-regulation of IL-6 after TNF blockade might have resulted in a higher production of monoclonal protein from myeloma cells. IL-6 plays a major role in the growth and survival of myeloma cells, suggesting that anti-IL-6 therapy may have potential for the treatment of MM. TCZ was reported to inhibit in vitro proliferation of cloned and freshly isolated myeloma cells from 20 patients with advanced MM (10). In addition, Nishimoto et al reported the first 2 cases of refractory MM treated with TCZ, noting that it improved fever and systemic edema, and also stabilized the monoclonal protein levels (11). The serum levels of monoclonal protein stabilized in the patient reported here, similar to that reported in the cases of Nishimoto et al.

This is the first case in which TCZ was used to treat a patient with RA and MM following TNF inhibitors, which were discontinued due to a potential risk of aggravating MM. A sudden increase in the serum IgA level shortly after the start of TCZ therapy was unexpected and the mechanism is unknown. However, the effect of TCZ on her articular symptoms and serum CRP levels was very favorable. The amount of TCZ required for IL-6 receptor blockade may be different between myeloma cells and hepatocytes/synovium. During the steep increase in serum IgA levels, serum levels of IL-6 gradually increased. At this point, IL-6 receptor blockade was sufficient against hepatocytes/synovium but insufficient against myeloma cells. After the second administration of TCZ, serum IgA levels remained stable independent of serum IL-6 levels.

Levels of serum IgA and IL-6 returned to the pre-TCZ range. Articular symptoms and anemia stabilized and serious clinical manifestations associated with MM have not been observed. Judging from the response of serum monoclonal protein levels along with symptoms/signs over a 13-month observation period in the present case, TCZ might be safer than TNF inhibitors for RA patients with coexisting MM. Although more clinical experience is definitely needed, this case suggests that TCZ can be used safely in patients who have inflammatory diseases complicated by MM.

Author’s disclosure of potential Conflicts of Interest (COI).


References

