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Obinutuzumab is Effective in Chronic Lymphocytic Leukemia and Rheumatoid Arthritis After Rituximab Failure: A Case Report

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Patient: Male, 68
Final Diagnosis: Chronic lymphocytic leukemia
Symptoms: Arthritis
Medication: —
Clinical Procedure: —
Specialty: Oncology

Objective: Rare co-existance of disease or pathology

Background: Chronic lymphocytic leukemia (CLL) is the most common leukemia affecting older adults. As such, many of these patients suffer from co-existing disease states, and the provider must take these comorbidities into account when determining a treatment regimen. The widespread use of monoclonal antibodies (mAbs) has drastically changed the treatment landscape of multiple diseases, ranging from leukemia to autoimmune conditions such as rheumatoid arthritis.

Case Report: We present the case of a patient who had progression of his CLL and rheumatoid symptoms on rituximab therapy, and was subsequently treated with the second-generation anti-CD20 antibody obinutuzumab. Obinutuzumab therapy was associated with simultaneous sustained remission of both disease states, allowing for discontinuation of all other disease-modifying anti-rheumatic drugs (DMARDs), and prolonged remission of his CLL.

Conclusions: While anti-CD20 antibodies have a clear role in the treatment of leukemia and inflammatory conditions, the success of obinutuzumab in RA has not been fully evaluated. We present this case as further evidence of the strong role of anti-CD 20 therapy in multiple conditions, and the unique opportunity for control of simultaneous disease states through targeted inhibition of shared common pathways.

MeSH Keywords: Arthritis, Rheumatoid • Leukemia, Lymphocytic, Chronic, B-Cell • Medical Oncology

Abbreviations: **CLL** – Chronic lymphocytic leukemia; **RA** – rheumatoid arthritis; **RAPID3** – routine assessment of patient index data 3; **ALC** – absolute lymphocyte count

Full-text PDF: http://www.amjcaserep.com/abstract/index/idArt/903747

Background

Chronic lymphocytic leukemia (CLL) is the most common leukemia in the Western world and mainly affects the elderly, with a median age at diagnosis of 71 years [1]. As such, CLL patients commonly have multiple comorbid conditions that influence the clinical approach to therapy. The widespread use of monoclonal antibodies (mAbs) has significantly improved the outcomes in CLL, especially when combined with chemotherapy [2–6]. Furthermore, the broader use of mAbs in autoimmune and inflammatory diseases, including vasculitis, neurologic conditions, and rheumatoid arthritis (RA), has improved management of these conditions [7–9]. Incorporation of rituximab, a first-generation monoclonal antibody directed against CD-20 on B lymphocytes, into the CLL treatment paradigm has become a treatment standard, resulting in significantly higher response rates, durable remissions, and improved survival, while its use in RA results in symptom relief and reduced structural damage in patients who continue to have active disease despite prior therapy [3–5,7–9]. The success and tolerability of anti-CD20 therapy has led to the development of a number of second-generation agents such as the FDA-approved agents obinutuzumab and ofatumumab, as well as mAbs in development, including ocrelizumab, ublituximab, and veltuzumab, which to date have shown enhanced activity via improved specificity of CD-20 targeting, receptor binding, and antibody-mediated cell cytotoxicity for use in the treatment of various autoimmune diseases and malignancies [10,11]. Obinutuzumab is FDA-approved for the initial treatment of CLL, where, in combination with the alkylating agent chlorambucil, it has shown superior efficacy compared to rituximab plus chlorambucil. However, little is known about its efficacy in RA or in CLL that has progressed after rituximab [6,12]. Here, we present a patient with CLL and RA who demonstrated progression of RA and CLL within 4 months of completing rituximab therapy and was subsequently successfully treated with the second-generation anti-CD20 mAb obinutuzumab.

Case Report

A 68-year-old male patient was followed by our Rheumatology Department for a diagnosis of seropositive RA (+ RF, + anti-CCP) diagnosed in 2006. Prior treatments included methotrexate, sulfasalazine, hydroxychloroquine, leflunomide, and the anti-tumor necrosis factor alpha (TNF-alpha) agents etanercept and adalimumab. In the fall of 2009, he was found to have leukocytosis (WBC of 13×10^3 cells/μL, SI: 13×10^9/L) with a lymphocyte predominance. Peripheral flow cytometry demonstrated a monoclonal population of CD5+, CD20+, CD19+, CD23+, CD38+, and Zap 70+ lymphocytes, consistent with CLL. Fluorescent *in situ* hybridization (FISH) studies demonstrated deletion of 11q and 13q. Further testing showed the CLL cells harbored an unmutated immunoglobulin heavy-chain gene (IGHV), which is associated with more aggressive disease and shorter survival. On exam, he did not have any adenopathy or splenomegaly and his hemoglobin and platelets were within normal limits, consistent with Rai stage 0 disease. He did not have any indications for CLL-directed therapy, and observation was recommended [13–16]. Adalimumab was discontinued due to the concerning development of CLL while on anti-TNF-alpha therapy, and the patient was restarted on methotrexate monotherapy. However, due to progressive arthritis, hydroxychloroquine and sulfasalazine were added.

In 2013 the patient developed progression of his CLL with increasing lymphocytosis (absolute lymphocyte count (ALC) of 62.78×10^3 cells/μL; reference $1.0–4.8\times10^3$ cells/μL), fatigue, and lymphadenopathy. At that time his arthritis also worsened despite the aforementioned therapy. He was treated with 4 consecutive doses of weekly single-agent rituximab (375 mg/m^2), resulting in decreased lymphadenopathy, normalization of his lymphocytosis (ALC following therapy of 1.72×10^3 cells/μL), and symptomatic improvement of his rheumatoid symptoms based on a clinical disease activity index score (CDAI score) of 2 (<2.8 indicative of remission) [17]. He had a sustained response to rituximab therapy until August of 2013, when he again developed worsening arthritis with a RAPID 3 score (Routine Assessment of Patient Index Data 3) of 2.1, indicating moderately active disease [17,18]. A total of 4 additional doses of rituximab therapy were administered (1000 mg, every other week for a total of 2 doses in the fall and repeated again in the spring for his RA); however, the clinical benefit was fleeting, with clinical activation of his RA (7 swollen and tender joints, RAPID3 score 1.5) despite being in remission from his CLL within 4 months of therapy. Additionally, 1 month after his last dose of rituximab, he developed worsening symptomatic submandibular lymphadenopathy and recurrence of his lymphocytosis (ALC: 11.2×10^3 cells/μL).

Given his progressive symptoms, obinutuzumab (100 mg on day 1, 900 mg on day 2, and 1 g on days 8 and 15 of cycle 1 and then on day 1 of each subsequent 28-day cycle) was initiated. Following cycle 1 of obinutuzumab, the patient had a dramatic response in RA symptoms and CLL disease burden, as evidenced by normalization of lymphocyte count, complete resolution of adenopathy, lack of painful, tender, or swollen joints, and discontinuation of triple therapy and PRN non-steroidal anti-inflammatories for his RA. After a total of 6 cycles of obinutuzumab, his RAPID3 score was 0.17, indicative of complete remission of his RA. Peripheral blood eight-color flow cytometry evaluating for CLL minimal residual disease (sensitivity 10^{-4}) 6 months following completion of treatment was negative, and demonstrated a sustained lymphopenia (ALC: 640×10^3 cells/μL). After a follow-up period of 24 months after initiation of obinutuzumab, the patient remained in remission

from his CLL and remained off all DMARD, with ongoing remission of his RA.

Discussion

This case demonstrates the superior efficacy of obinutuzumab compared to type 1 anti-CD20 mAbs in the treatment of CLL and inflammatory conditions such as RA. While anti-CD20 monoclonal antibodies are traditionally combined with a chemotherapy backbone in the treatment of CLL, we provide evidence of durable remission obtained with anti-CD20 monotherapy in RA and CLL refractory to rituximab. Rituximab, a first-generation type 1 monoclonal anti-CD-20 antibody, has been shown to be effective in RA refractory to disease-modifying anti-rheumatic drugs and TNF-alpha inhibitors, and more recently has shown modest efficacy as monotherapy [7–9,19]. Rituximab also has demonstrated efficacy in CLL, a disease characterized by a clonal population of B cells with a low level of CD-20 expression [20]. Rituximab is typically administered in combination with a chemotherapy backbone, such as bendamustine plus rituximab (BR), fludarabine plus rituximab (FR), and fludarabine, cyclophosphamide, and rituximab (FCR), all of which have shown efficacy in the treatment of CLL [2–5]. However, rituximab has limited efficacy as a single agent [21].

It has been proposed that type 1 anti-CD-20 antibodies may have less single-agent activity because they operate mainly via complement-mediated cytotoxicity, antibody consumption, and, to a lesser degree, antibody-mediated cell death [20,22]. Additionally, the effectiveness of rituximab therapy may be limited by the quantity of CD20-expressing B lymphocytes in diseases such as CLL, which have a low level of CD20 surface expression. Obinutuzumab and other type 2 anti-CD 20 antibodies appear to be more potent and effective than type 1 anti-CD20 mAbs. These agents invoke higher levels of direct cell death, have Fc regions with higher affinity for Fcγ-receptors, have a longer duration of binding, and higher affinity and alternative conformation for the target epitope, leading to a more profound, effective, and prolonged immune response compared to first-generation anti-CD20 mAbs [10,18,22]. This improved activity was highlighted in a recent randomized control trial in which obinutuzumab plus chlorambucil showed superiority to rituximab plus chlorambucil in the treatment of CLL [12]. In our patient, clinical evidence for increased activity of obinutuzumab is not only supported by the resolution of his CLL-related symptoms, but also by the magnitude of lymphopenia after obinutuzumab treatment (obinutuzumab ALC nadir 600×10^3 cells/μL, rituximab ALC nadir 1.57×10^3 cells/μL). The effectiveness of obinutuzumab as a B cell-depleting therapy in the treatment of RA is likewise demonstrated by our patient's prolonged remission of RA based on RAPID3 scores of less than 1.

Conclusions

While the efficacy of obinutuzumab has mainly been demonstrated in CLL, our case provides clinical evidence of an additional agent for the treatment of severe rheumatoid arthritis. What is even more interesting is the long-lasting durable remission achieved in this patient even in the setting of rituximab refractoriness. While the time to new antileukemic treatment has been established to be longer with obinutuzumab than with rituximab in CLL, this has yet to be fully investigated in rheumatoid arthritis [6], despite a clear role for B cell-depleting therapies in the management of rheumatic disease [7–9]. Thus, further studies are warranted to evaluate the use of obinutuzumab as monotherapy in patients with CLL who may not be able to tolerate a more robust chemotherapy backbone, as well as in patients with RA, including patients who have relapsed or progressed after initial rituximab treatment.

Conflicts of interest

None.

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