

## Waldenstrom Macroglobulinemia an Auto-inflammatory Syndrome? Efficacy of Tocilizumab: A Case Report

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### Abstract

Waldenström macroglobulinemia is a lymphoplasmocytic lymphoma involving bone marrow and characterized by the production of a monoclonal IgM gammopathy. Despite conventional chemotherapies it is an incurable disease. The recent discovery of the pro-inflammatory transcription factor *MYD88* L265P mutation as a molecular signature of the disease could represent a new therapeutic target. We report here, a case of Waldenström macroglobulinemia associated with a high biological inflammatory syndrome, resistant to conventional therapies and improved by tocilizumab, an anti-interleukin-6 Receptor inhibitor.

**Keywords:** Waldenström macroglobulinemia; *MYD88* L265P mutation; Inflammation; Interleukin-6; Tocilizumab

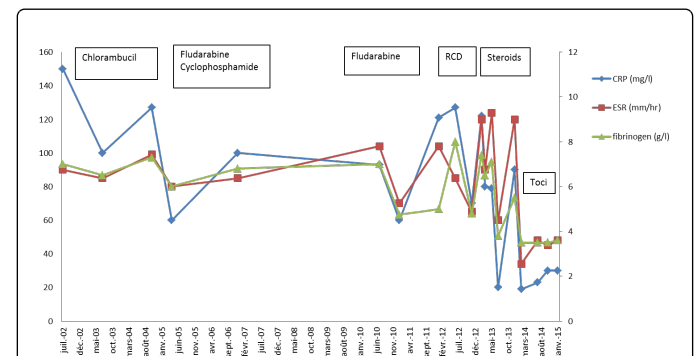
### Introduction

Waldenström macroglobulinemia (WM) is a low-grade B-cell malignancy, also known as lymphoplasmocytic lymphoma, characterized by an infiltration of predominantly small B lymphocytes with variable plasmacytoid differentiation in the bone marrow. It is accompanied by a high circulating monoclonal IgM protein [1]. Clinically, symptoms can be attributed either to tissue infiltration with malignant B cells or IgM-dependent changes in serum (hyperviscosity syndrome) and/or various tissue sites (immunoglobulin deposition disease, autoimmunity) [2]. Treatment usually consists of chemotherapy agents: alkylating agents (chlorambucil, cyclophosphamide, and melphalan), nucleoside analogues (cladribine and fludarabine), proteasome inhibitors (bortezomib), dexamethasone, and monoclonal antibody targeting CD20 (rituximab) [3]. New therapeutic approach could emerge from a better understanding in WM pathophysiology, as for the recent discovery of the recurrent mutation of *MYD88* L265P in WM patients [4]. Here, we report a case of WM associated with biological high levels of systemic inflammatory parameters improved by tocilizumab, an anti-interleukin-6 Receptor (IL-6R) biotherapy.

### Case Report

We report the case of a 65 years old man diagnosed with WM since 2002. Initially he was anemic (Hb 9 g/dl), IgM kappa spike was at 22 g/l. Bone marrow biopsy showed a lymphoplasmocytic infiltrate at 44% and the CT scan revealed a homogenous moderate hepatomegaly without significant lymph nodes. At the time of diagnosis C Reactive protein was at 150 mg/l, Erythrocyte Sedimentation Rate (ESR) at 140 mm/hr and fibrinogen at 12 g/L. We explored this systemic inflammatory syndrome and ruled out infectious causes (Quantiferon TB Gold® was negative as for bacterial and viral serologies and culture samples). There was neither auto-immune disorder nor clue for a neoplasia since endoscopic digestive explorations and TEP scan were

normal. Temporal artery biopsy was also normal. He received successively three lines of chemotherapies: chlorambucil, fludarabine and cyclophosphamide, and at last fludarabine alone with no evidence of efficacy on anemia and inflammatory parameters while the IgM spike decreased around 10 g/dl (Figure 1).



**Figure 1:** Evolution of systemic inflammation parameters under successive lines of treatment, under conventional chemotherapies (chlorambucil, fludarabine and cyclophosphamide, RCD: rituximab, cyclophosphamide, dexamethasone), systemic inflammation persisted. Steroids (prednisone) are very effective but stopped because of poor tolerance. Tocilizumab (Toci) introduced since the end of 2013 is still effective with CRP around 20 mg/L, fibrinogen under 4 g/l and ESR around 40 mm/hr.

As systemic inflammatory syndrome persisted over the time, we introduced steroids. CRP decreased under 20 mg/l but prednisone was stopped because of side effects (osteoporosis, weight gain, etc.). Systemic inflammatory syndrome reappeared. We repeated bone marrow biopsy that found, using molecular analysis, the *MYD88* L265P mutation. As *MyD88* is involved in IL6 production downstream of several signals and as this mutation is known as a gain-of-function mutation, we started at the end of 2013 tocilizumab (anti IL-6R biotherapy) at the dose of 8 mg/kg every 4 weeks, in order to prevent

amyloidosis. After only 2 injections, CRP decreased from 100 mg/l to 20 mg/l, fibrinogen from 6 g/l to 3 g/l and ESR normalized at 40 mm/hr vs 120 mm/hr. Besides, general status improved until now.

## Discussion

In the case reported here the presentation of WM is unusual because of systemic inflammatory syndrome evolving since the beginning of the disease and independently of the tumor burden. It can be considered as paraneoplastic syndrome, on which conventional chemotherapies were not very effective. Steroids alone were very effective at high dose but with poor tolerance, so we needed a steroid-sparing treatment. We used anti-IL-6 biotherapy, as for inflammatory diseases like Still's disease [5] that dramatically decreased inflammatory parameters.

IL-6 is a pleiotropic cytokine that plays roles in the immune response, inflammation and hematopoiesis [6]. IL-6 induces the differentiation of B-cells to antibody-producing plasma cells, acute-phase protein synthesis in hepatocytes (like CRP) and the growth of the hematopoietic stem cells. Serum IL-6 levels have been reported to reflect disease severity and high tumor burden in multiple myeloma patients and to correlate with several other laboratory parameters, such as bone marrow plasmacytosis, serum LDH, b2M and CRP [7,8]. It has also been shown that clonal blood B-cells from patients with macroglobulinemia spontaneously differentiate in vitro to plasma cells via an IL-6 pathway [9]. Gene expression profiling studies in WM revealed that among the up-regulated genes, IL6 was the most significant [10]. Two previous studies demonstrated high serum levels of IL-6 in WM [11,12]. These levels significantly decreased under effective chemotherapies. This therefore suggests that IL-6 levels may reflect tumor burden, disease severity and response to therapy. A decrease in IL-6 after prednisone therapy is to be expected, since corticosteroids down-regulate IL-6 [12]. For some authors, genetic background of the IL-6 pathway in WM could be a prognosis factor after treatment initiation [13]. Nevertheless, to our knowledge, our case is the first one to report anti-IL6 therapy effectiveness in a pro-inflammatory form of WM.

Actually, WM is still an incurable disease. Therefore, lots of studies focus on new therapeutic targets. A flurry of recent studies identified the *MYD88* L265P somatic mutation with high frequency in WM patients [14–17]. This mutation promotes the growth and survival of WM cells and could be useful for diagnosis and treatment. *MyD88* is an adaptor molecule in Toll-like receptor (TLR) and interleukin-1 receptor (IL-1R) signaling. Following TLR or IL-1R stimulation, *MyD88* is recruited to the activated receptor complex as a homodimer, which complexes with IL-1R-associated kinase (IRAK) 4 to activate IRAK1. Tumor necrosis factor receptor-associated factor 6 is then activated leading to nuclear factor  $\kappa$ B (NF- $\kappa$ B) activation [18]. The latter is a protein complex that controls inflammation, hematopoiesis, and normal lymphocyte and plasma-cell development. The *MYD88* L265P gain of function mutation is related to NF- $\kappa$ B gene abnormalities [14]. Moreover, *MYD88* L265P mutation promotes JAK-STAT3 signaling, which mediates IL-6 and IL-10 production [19]. One study [14] showed there was no significant difference in IL-6 expression according to *MYD88* mutation status in their WM series, although a significantly higher expression of IL-6 was observed in WM as compared with chronic lymphocytic leukemia. One might thus consider the increase of IL-6 expression through JAK-STAT3 signaling in patients with *MYD88* mutation, whereas other mechanisms of IL-6 expression should be suspected in patients with *MYD88* wildtype.

The potential for *MYD88* L265P to be exploited therapeutically in WM is suggested by studies showing that inhibition of *MyD88* and downstream targets can suppress downstream NF- $\kappa$ B signaling and/or induce WM cell killing. No therapeutic targeting directly *MyD88* is available by now. In our case, we blocked a target downstream its signaling pathway, that is to say the pro-inflammatory cytokine induced by NF- $\kappa$ B, IL-6.

## Conclusion

Interleukin-6 is a cytokine of notably importance in WM that can be overexpressed consecutively to *MYD88* mutation. Targeting this cytokine with tocilizumab should be considered in unusual pro-inflammatory forms of WM, resistant to conventional chemotherapies.

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