

Paradoxical increases in serum IgM and viscosity levels following rituximab in Waldenstrom's macroglobulinemia

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Background: The anti-CD20 monoclonal antibody rituximab is an important therapeutic in Waldenstrom's macroglobulinemia (WM), producing response rates of 50–70%. Responses, which are based on serum IgM levels, have typically been evaluated at 12 weeks. Paradoxically, we have observed that serum IgM levels can abruptly rise following rituximab therapy in patients with WM, and can often lead to morbidity on the basis of hyperviscosity.

Patients and methods: Eleven WM patients with CD20+ tumor cells who received rituximab at our Institution and had serum IgM levels measured within a 12-week period following start of therapy were evaluated. Therapy consisted of four weekly infusions of rituximab at 375 mg/m². Pre- and post-therapy serum IgM levels were determined by nephelometry and corresponding serum viscosity levels were determined by viscometry.

Results: Ten of the 11 patients demonstrated an abrupt rise in serum IgM levels, with a >25% increase occurring in eight (73%) patients. Mean serum IgM levels for all 10 spiking patients rose from 4370 (range, 655–7940) to a peak of 5865 (range, 872–11 800) mg/dl ($P=0.004$), which occurred at a mean of 4 (range, 1–8) weeks following initiation of therapy. Mean serum viscosity levels also increased from 3.5 to 5.6 centipoise (CP) ($P=0.09$) in eight patients for whom pre- and post-therapy studies were obtained. A subdural hemorrhage occurred in one patient when serum IgM levels rose from 7530 to 11 800 mg/dl, and serum viscosity increased from 3.9 to 10.1 CP. Two other spiking patients with pre-therapy IgM levels of >5000 mg/dl experienced worsening headaches and/or epistaxis attributed to increasing serum viscosity.

Conclusions: Abrupt increases in serum IgM levels commonly occur following rituximab therapy in WM. Careful clinical and laboratory monitoring is warranted, particularly if patients have pre-therapy serum IgM levels of >5000 mg/dl. The mechanism of this effect is under active investigation, and may be related to CD20 signaling triggered by rituximab.

Key words: hyperviscosity, Rituximab, serum IgM, Waldenstrom's macroglobulinemia

Introduction

Waldenstrom's macroglobulinemia (WM) is an indolent B-cell disorder characterized by excess secretion of an IgM monoclonal protein and involvement of the bone marrow by lymphoplasmacytic cells [1]. Elevated serum viscosity (SV) levels commonly occur in patients with WM as a result of excess serum IgM production and can result in morbidity, particularly when SV levels rise above 4.0 centipoise (CP) [2]. Rituximab, a chimeric IgG₁ monoclonal antibody, has been extensively evaluated by us and others in the treatment of WM since its target, CD20, is widely expressed in WM [3]. The successful use of rituximab in WM was first noted by us

in a patient who had a marked reversal in his anemia and a response that lasted over 19 months following treatment with standard rituximab therapy (i.e. four weekly infusions at 375 mg/m²/week) [4]. Subsequent studies employing standard dose rituximab therapy demonstrated major response rates of 30%, and durations of response of 6.6+ to 27+ months [5–8]. More recently, the use of extended schedule rituximab has been evaluated by us and others, wherein patients have received eight infusions of rituximab at 375 mg/m²/week at weeks 1–4 and 12–16. Major response rates of 44–48% were observed in these studies, with durations of response of 16+ to 29+ months [9, (S. P. Treon, C. A. Emmanouilides, E. Kimby et al., submitted for publication)]. Studies combining rituximab with chemotherapy or with immunomodulators are also being explored in patients with WM, with encouraging preliminary findings [10–12]. In view of the above study data, a consensus panel of experts recently recommended use of

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rituximab in the primary, as well as the salvage therapy for WM [13].

With most of the above trials, responses which are based on serum IgM levels have typically been evaluated at 12 weeks following treatment with rituximab. Paradoxically, we have observed that serum IgM and viscosity levels can abruptly rise following initiation of rituximab therapy. In this report, we describe the outcome of 11 WM patients receiving rituximab who had serial IgM levels measured within a 12-week period following start of therapy.

Patients and methods

Patients and treatment

Eleven patients who had serum IgM levels measured within a 12-week period following start of rituximab therapy were evaluated. All patients had an established clinicopathological diagnosis of WM using consensus panel criteria [1], and tumor cells for all these patients were expressive of CD20 as determined by flow cytometric analysis and/or immunohistochemistry. Therapy consisted of four weekly infusions of rituximab at 375 mg/m². Pre- and post-therapy serum IgM levels were determined by nephelometry, and were available for all patients. Corresponding serum viscosity levels pre- and post-therapy were obtained for eight of the 11 patients, and were determined by viscometry.

Statistical analysis

Comparison of pre- and post-rituximab parameters was performed using a two-tailed Student's *t*-test on Microsoft Excel™ software. A *P* value ≤0.05 was deemed to be significant.

Results and discussion

Ten of the 11 patients who had serial IgM levels measured within 12 weeks of receiving rituximab demonstrated a rise in serum IgM levels, with a ≥25% increase occurring in eight (73%) patients (Figure 1). Mean serum IgM levels for all 10 spiking patients rose from 4370 (range 655–7940) to a peak of 5865 (range 872–11 800) mg/dl (*P*=0.004), which

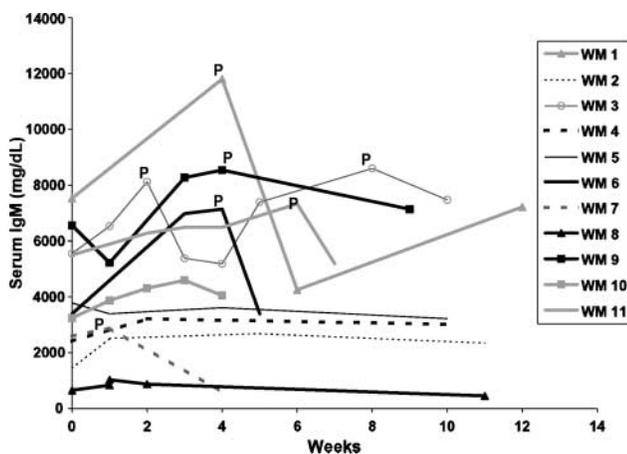


Figure 1. Serial IgM serum levels for 11 patients with Waldenstrom's macroglobulinemia who received treatment with rituximab. P denotes patient required plasmapheresis for hyperviscosity.

occurred at a mean of 4 (range 1–8) weeks following start of rituximab therapy. The mean rise in serum IgM levels to peak levels was 1.34 (range 1.08–1.86)-fold. Interestingly, in one patient (WM 8) for whom serial laboratories were obtained during the first day of therapy, serum IgM levels rose from 655 to 837 (at 3 h) and 1030 mg/dl (at 7 h) following initiation of rituximab therapy.

Coincident with the rise in serum IgM levels, mean SV levels rose from 3.5 to 5.6 CP (*P*=0.09) in eight patients for whom pre- and post-therapy studies were obtained. At least one plasmapheresis was performed for four spiking patients in response to rising SV levels, including three patients who experienced adverse effects attributed to hyperviscosity. A subdural hemorrhage occurred in one patient (WM 1) following four weekly infusions of rituximab when her serum IgM level rose from 7530 to 11 800 mg/dl, and SV increased from 3.9 to 10.1 CP. Another patient (WM 9) experienced worsening epistaxis and headaches following four weekly infusions of rituximab, which coincided with a rise in serum IgM from 6560 to 8540 mg/dl, and SV from 3.0 to 3.8 CP. A third patient (WM 3) after receiving two infusions of rituximab had worsening headaches with a rise in serum IgM from 5790 to 7140 mg/dl, and SV from 3.8 to 5.4 CP.

Transient rises in serum IgM levels were also observed in several patients treated with extended rituximab therapy by Dimopoulos et al. [9]. Serum IgM levels also peaked on or about 30 days following initiation of rituximab treatment in this report. These studies, though, are the first to describe adverse effects coinciding with the abrupt increases in serum IgM and SV levels following rituximab in patients with WM. An important consideration is that these adverse effects occurred among those patients with the highest IgM levels in this study. All three patients had a pre-therapy IgM level of >5000 mg/dl, and a corresponding SV of >3.0 CP. More careful clinical and laboratory monitoring would therefore appear particularly warranted for those WM patients receiving rituximab therapy with pre-therapy IgM levels of >5000 mg/dl.

The mechanism by which rituximab induces IgM levels to rise in WM patients remains to be clarified. While it is tempting to speculate that rituximab-mediated tumor-cell death leads to intracellular IgM release, no appreciable change in disease burden as assessed by bone marrow biopsies and CT scans was observed for two patients who had abrupt increases in their IgM levels following rituximab therapy. These findings suggest that other mechanisms, including rituximab-induced signaling through CD20, may be responsible for the IgM surges observed in WM patients. In support of this hypothesis, modulation of cell surface IgM expression by the anti-CD20 monoclonal antibody B1 has been observed in normal B-lymphocytes and B-cell lines [14]. A signaling mechanism could also account for the abrupt serum IgM surge observed only hours after initiation of rituximab in the patient described above, since elimination of tumor cells in response to rituximab is typically delayed in WM [S. P. Treon, C. A. Emmanouilides, E. Kimby et al., submitted for publication]. Ongoing studies in

our laboratory are addressing such signaling mechanisms by rituximab in WM.

In conclusion, these data suggest that paradoxical spikes in serum IgM levels commonly occur in WM patients following rituximab treatment. Careful clinical and laboratory monitoring is warranted, particularly if patients have pre-therapy IgM levels of >5000 mg/dl prior to initiation of rituximab therapy. The mechanism of this effect is under active investigation, and may be related to CD20 signaling triggered by rituximab.

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