Successful infusion of obinutuzumab by desensitization: A case of anaphylactic shock during desensitization

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.18176/jiaci.0581

Key words: Desensitization, Obinutuzumab, Adverse reaction, Anaphylaxis

Palabras clave: Desensibilización, Obinutuzumab, Reacción adversa, Anafilaxia

Obinutuzumab is a humanized, type II, anti-cluster of differentiation-20 (CD20) monoclonal antibody that binds to CD20 on B cells and causes cell death by activating intracellular apoptosis pathways and the complement system [1]. It recently demonstrated to confer overall survival advantages compared with rituximab for the treatment of chronic lymphoblastic leukemia (CLL), small lymphocytic leukemia with comorbidities, and relapsed or refractory follicular lymphoma [2]. The common adverse reactions of obinutuzumab are infusion reactions, neutropenia, thrombocytopenia, anemia, pyrexia, cough, and musculoskeletal disorders [1]. Infusion reactions occur in approximately 10% of patients receiving obinutuzumab and can be fatal in severe forms, such as anaphylaxis [1]. Herein, we present an 18-step intravenous desensitization protocol for obinutuzumab successfully carried out in a general ward setting.

A 71-year old man with a history of B-cell CLL was admitted for chemotherapy. He had never received chemotherapeutic agents and denied having any underlying disease history, including allergies. His hematologist administered him with obinutuzumab/chlorambucil. A total of 1,000 mg of obinutuzumab was planned to be administered on days 1, 8, and 15 with premedication; obinutuzuamb was planned to be administered as 100 mg on day 1 and 900 mg on day 2 in the cycle 1 in order to prevent an infusion reaction, which commonly occurs

doi: 10.18176/jiaci.0581

during the initial administration of obinutuzumab. Despite co-premedication with per oral (PO) chlorpheniramine (4 mg), PO dexamethasone (20 mg), and PO acetaminophen (650 mg), abrupt development of chest and abdominal discomfort and sore throat occurred one hour after the initiation of obinutuzumab infusion (100 mL of 1 mg/mL solution). The oxygen saturation decreased to 85%. The infusion was immediately discontinued, and the symptoms improved after oxygen supply and intravenous chlorpheniramine administration After symptom resolution, obinutuzumab was resumed on the same day with a 12-step desensitization protocol (Supplementary table) and premedication including chlorpheniramine (4 mg), methylprednisolone (40 mg), and propacetamol (1 g). Infusion was initiated with a solution of 1 mg/mL at a rate of 0.1 mL/h (0.25 mg/15 min), and it was doubled every 15 min using a syringe pump (Injectomat Agilia, France) based on the institutional protocol for chemotherapeutic agents [3]. However, when the rate reached 0.4 mL/h, breakthrough reactions (BTRs) such as high fever, dyspnea, chest discomfort, and stridor developed. Instantly, O_2 saturation decreased to 85% at room air, and pulse was not palpable. The diagnosis of anaphylactic shock was confirmed, and massive intravenous normal saline infusion with an intramuscular epinephrine (0.3 mg) injection reversed the symptoms.

After recovery, a skin test of obinutuzumab was carried out in two weeks with 0.1 mg/mL and 1 mg/mL concentrations of obinutuzumab. but it did not show positivity to histamine as well as obinutuzumab. To resume obinutuzumab in this patient who experienced an anaphylactic shock during desensitization, the desensitization protocol was modified by mitigating the increments of the rate between steps to 1.6 times per 15 minutes and prolonging the total number of steps to 18. One hour before initiating desensitization, premedication consisting of ketotifen (1.38 mg), famotidine (20 mg), montelukast (10 mg),

doi: 10.18176/jiaci.0581

and dexamethasone (20 mg) was administered. For the completion of cycle 1, two bags of obinutuzumab (100 mg in 100 mL of 0.9% normal saline (1 mg/mL) and 900 mg in 250 mL of 0.9% normal saline (3.6 mg/mL) based on the package insert) were serially administered by application of an 18-step desensitization protocol with two bags (Table 1). Desensitization of the first solution was successfully completed without BTRs in 6.3 hours. Subsequently, the remnant 900 mg of obinutuzumab (3.6 mg/mL) was followed by the same incremental rate for the continued desensitization. Following successful initial chemotherapy, desensitization was repeated for obinutuzumab administration without any BTRs.

There are various chemotherapy-related hypersensitivity reactions. These mainly include flushing, chest pain, dyspnea, nausea/vomiting, and disorientation, which are observed in each system, and various chemotherapeutic agents can induce these reactions, some of which can be very severe and sometimes fatal [4]. Although more chemotherapeutic options are currently available, the next best option may not guarantee non-inferior survival benefits compared with chemotherapy of high priority. For those patients, physicians can consider desensitization of the culprit agent despite hypersensitivity reactions, instead of switching to other options

Desensitization can be a safe alternative, which is performed by sequentially increasing doses over multiple steps to attain immunologic tolerance [5]. While a 3-bag, 12-step desensitization protocol has been widely used [6], this protocol needs additional labor for serial dilutions of the chemotherapeutic solution. In our institution, a non-dilution rapid desensitization protocol has been successfully adopted for the reintroduction of chemotherapeutics related with hypersensitivity [3]. This protocol is performed with the help of a syringe pump, which enables precise delivery of very small amounts (0.1 mL/h) without

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dilutions. For the current case, desensitization was carried out in two steps since the medication package insert of obinutuzumab recommended two different concentrations for infusion.

Managing BTRs during the desensitization process is important for success. If BTRs occur during the desensitization process, it is recommended to reduce the initial dose, increase the time interval, or add intermediate steps to decrease the increments of rate in order to attain tolerance [7]. In this case, BTRs occurred during the initial desensitization process, but were successfully managed by adding intermediate steps, since lowering the rate of the initial step below 0.1 mL/h was not feasible in our protocol.

Although severe hypersensitivity of obinutuzumab has been reported in cynomolgus monkeys, which demonstrated immune complex deposits in tissue [8], there are currently no reports of preferring true immunologic reactions to infusion reactions in humans. In the current case, a skin test was performed but could not be interpreted due to decreased skin reactivity. Therefore, it was difficult to determine whether an immunoglobulin E-mediated mechanism played a role or not. Isabwe et al. have previously reported the safety and effectiveness of desensitization protocols for 16 monoclonal antibodies including two cases of obinutuzumab hypersensitivity, which presented a remarkable increase in IL-6 during desensitization, thus reflecting cytokine release as the underlying endotype [9]. However, regardless of the mechanism, the general consensus for severe reactions is to discontinue the culprit medicine, and it is not usually recommended to retry desensitization for a case experiencing anaphylactic shock despite desensitization. Desensitization still has the possibility to reduce the chances and severity of BTRs if appropriately individualized and applied with caution in selected cases.

doi: 10.18176/jiaci.0581

In summary, we report a case of successful reintroduction of obinutuzumab in a patient who presented with anaphylaxis to obinutuzumab during initial desensitization, but eventually showed tolerance following a mitigated desensitization protocol with 1.6-time increments between steps.

This Data have been presented in poster form at conference by The Korean Association of Internal Medicine.

This research was supported by a grant from Ministry of Food and Drug Safety to the regional pharmacovigilance center in 2019.

Conflicts of interest

The authors have no conflicts of interest related to this work.

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doi: 10.18176/jiaci.0581

Table. Obinutuzumab desensitization protocol (18-step protocol). The 1.0 mg/mL solution used for step 1-16 was prepared by reconstituting obinutuzumab 100 mg in 100 mL of 0.9% normal saline and the 3.6 mg/mL solution used for step 17-18 step was prepared by reconstituting obinutuzumab 900 mg in 250 mL of 0.9% normal saline

Concentration (mg/mL)	Step	Rate (mL/h)	Time (min)	Administered dose (mg)	Administered volume (mL)	Cumulative dose (mg)
1.0	1	0.1	15	0.024	0.025	0.024
	2	0.2	15	0.0481	0.05	0.0721
	3	0.3	15	0.0721	0.08	0.1442
	4	0.5	15	0.1202	0.13	0.2644
	5	0.8	15	0.1923	0.2	0.4567
	6	1.3	15	0.3125	0.33	0.5048
	7	2.1	15	0.5048	0.5	1.274
	8	3.4	15	0.8173	0.85	2.0913
	9	5.5	15	1.3221	1.38	3.4135
	10	8.9	15	2.1394	2.23	5.5529
	11	14.4	15	3.4615	3.6	9.0144
	12	23.3	15	5.601	5.83	14.6514
	13	37.8	15	9.0865	9.45	23.7019
	14	61	15	14.7356	15.3	38.4375
	15	99	15	23.7981	24.8	62.2356
	16	160	14.7	37.7644	39.3	100
3.6	17	80	15	62.9371	20	162.9371
	18	130	122.8	837.0629	266	1000

doi: 10.18176/jiaci.0581