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## Successful Desensitization to Brentuximab After Anaphylactic Shock

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J Investig Allergol Clin Immunol 2018; Vol. 28(5): 352-354  
doi: 10.18176/jiaci.0288

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**Key words:** Brentuximab vedotin. Hodgkin lymphoma. Anaphylaxis. Hypersensitivity reactions. Drug desensitization.

**Palabras clave:** Brentuximab vedotin. Linfoma Hodgkin. Anafilaxia. Reacciones de hipersensibilidad. Desensibilización medicamentosos.

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Monoclonal antibodies target specific proteins associated with pathogenesis. Brentuximab vedotin (BV) is a CD30-directed antibody-drug conjugate. It has significantly improved the management of patients who have experienced relapses after autologous stem cell transplantation (AUTO-SCT) and can induce durable remission in a subset of patients with relapsed/refractory Hodgkin lymphoma (R/R HL) [1].

As BV is an intravenous chimeric monoclonal antibody, acute infusion reactions to it are not surprising. However, few immediate-type hypersensitivity reactions (HSRs) and desensitization attempts for such reactions have been reported [2-6].

Rapid drug desensitization (RDD) was developed for the delivery of biologic agents that cause immediate-type HSRs by inducing temporary tolerance. However, desensitization protocols for monoclonal agents are seldom used [7]. We have been using RDD, as developed at the Brigham and Women's Hospital, for patients who experience immediate-type HSRs [7,8]. We report the case of a patient with relapsed HL who was successfully desensitized to BV with RDD despite having a history of BV-related grade 3 anaphylaxis.

A 34-year-old man was admitted to the hematology clinic with cervical, paratracheal, subcarinal, and preaortic lymphadenopathy in 2011. Analysis of a biopsy specimen from the cervical lymph node revealed classic HL, and 6 doses of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) were administered. The patient remained in remission until 2016, when he developed generalized itching and multiple lymphadenopathies; recurrence of classic HL was detected. Two cycles of cisplatin, cytarabine, and dexamethasone were given, and AUTO-SCT was planned. Four cycles of BV, etoposide, methylprednisolone, cytarabine, and cisplatin were administered without problems. AUTO-SCT was subsequently performed after high-dose conditioning treatment (BCNU/Etoposid/ARA-C/Melfelan). Unexpected early disease progression was observed at the first post-AUTO-SCT follow-up examination, prompting an immediate decision for allogeneic stem cell transplantation. BV was given again

before allogeneic stem cell transplantation in January 2018. The patient experienced itching on his feet and hands, blurred vision, throat swelling, breathlessness, back pain, nausea, and low blood pressure (90/50 mmHg) within 5 minutes of administration of BV (180 mg/h). The infusion was stopped immediately, and intramuscular pheniramine (45.5 mg) and intravenous dexamethasone (8 mg) were administered. Symptoms resolved after 3 hours, and the BV infusion was completed at a slower rate (60 mg/h). Unfortunately, a blood sample for tryptase levels was not taken. The patient developed the same symptoms during a subsequent infusion 3 weeks later, and the infusion was stopped. He was referred to the allergy department. Skin prick tests with inhalant allergens showed him to be nonatopic. The full-strength prick test with BV was negative, although the results of intradermal tests (IDTs) were positive at concentrations of 1:100 (0.05 mg/mL) and 1:10 (0.5 mg/mL) of (5 mg/mL BV per vial) (Figure).

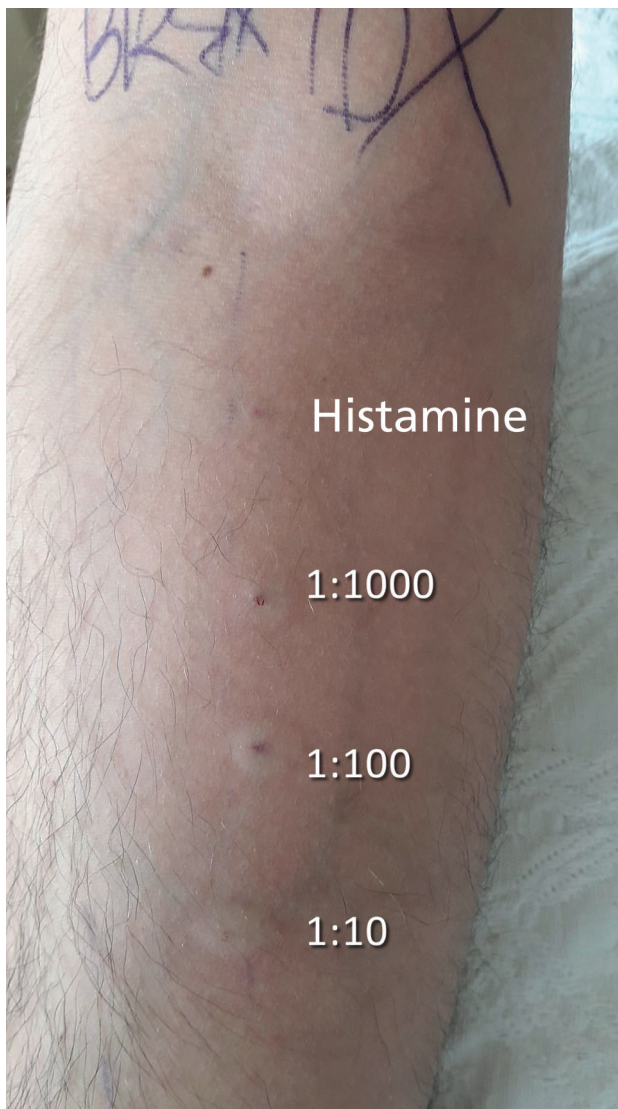


Figure. Intradermal skin tests with brentuximab vedotin.

The reaction was defined as Brown Classification grade 3, which indicates severe HSR [9]. A 12-step rapid RDD protocol was developed for 180-mg final doses of BV. The patient was premedicated with H1 and H2 blockers and systemic corticosteroids and was desensitized by an experienced allergist using established protocols (Supplementary Table). He received 4 RDDs with no breakthrough reactions; the desensitization protocol is ongoing.

Acute infusion reactions to BV occur following initial or repeated intravenous administration of the agent, thus limiting its use [10]. Most reactions are consistent with immediate-type HSRs including anaphylaxis. If a patient develops hypersensitivity to a first-line drug, RDD is a valid alternative.

Few cases of immediate HSRs and desensitization efforts to BV have been reported. In 2014, 3 cases of BV-induced anaphylaxis and successful RDD were reported [2-4]. In the first, DeVita et al [2] reported the case of a patient who experienced 3 episodes of severe anaphylaxis to BV before being successfully desensitized. O'Connell et al [3] described a 12-step RDD to BV in a patient with relapsed anaplastic large cell lymphoma who had anaphylaxis during a second infusion. Similarly, successful RDD in a patient with non-HL who had anaphylaxis during her second infusion was reported by Story et al [4]. Arora et al [5] presented the case of a patient with refractory HL who developed anaphylaxis during the second dose of BV, with successful desensitization in 2015. However, none of these patients underwent skin or in vitro tests with BV. Isabwe et al [10] recently reported the case of a patient with a positive IDT result to 0.0018 mg/mL of BV. Noguero-Mellado et al [6] demonstrated an IgE-mediated mechanism through positive results in IDT and immunoblotting tests in a patient with classic HL who experienced an anaphylactic reaction to BV after 7 previous cycles. However, desensitization was not completed. Similarly, a reaction occurred in the case we report after 5 previous cycles and IDTs with positive results to BV in the immediate reading, thus supporting a type 1, IgE-mediated phenotype [10]. We use the same concentrations of BV for skin tests as Noguero-Mellado et al. These concentrations were negative in 3 patients who tolerated BV in the case report of these authors.

A specific in vitro test for the measurement of IgE to BV is not available in Turkey. To our knowledge, our case is the third with a positive IDT result to BV [6,10]. Unlike DeVita et al [2], we managed successful RDD with BV despite skin test positivity. Although the premedication protocols used in both cases were quite similar, the patient reported by Noguero-Mellado et al [6] experienced hives and then anaphylaxis, with the result that desensitization was not achieved. The authors stated that this failure of desensitization was presumably related to marked sensitization to the drug. It might also be associated with the infusion rate, because breakthrough reactions occurred first at 120 mL/h and then at 80 mL/h. In our protocol, the final infusion rate was slower, 60 mL/h, and we achieved almost 2-times higher total doses of BV than the total dose of the first case (180 mg vs 93.6 mg), with no breakthrough reaction. In the other patients in whom desensitizations were completed successfully, reactions mostly occurred during the first infusion of the first or second cycle and none had positive IDT results to BV or positive in vitro test results suggesting an infusion reaction.

### Funding

The authors declare that no funding was received for the present study.

### Conflicts of Interest

The authors declare that they have no conflicts of interest.

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■ *Manuscript received April 9, 2018; accepted for publication June 14, 2018.*

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