Immediate-type hypersensitivity reaction to bulevirtide and successful desensitization in a patient with HBV/HDV-associated compensated cirrhosis

To the Editor:

In July 2020, bulevirtide (BLV) – a new HDV hepatocyte entry-inhibitor – was licensed for the treatment of HBV/HDV coinfection in Europe.[1] BLV showed excellent drug tolerability and safety in clinical trials and during the first months of clinical use.[2,3] Notably, no allergic reactions associated with BLV have been recorded so far. We report a case of immediate-type hypersensitivity reaction to BLV and present a clinical approach for desensitization.

A 35-year-old female patient of Romanian descent with HBV/HDV-associated compensated cirrhosis (Child-Pugh A, liver stiffness of 17.5 kPa on transient elastography in October 2020) had been treated with tenofovir (TDF) and pegylated interferon alpha (PEG-IFN) since July 2018 and June 2019, respectively.[4] Due to progressive thrombocytopenia and anemia as well as persisting HDV-viremia (HDV-RNA 10.040 copies/ml) under TDF and PEG-IFN, PEG-IFN was discontinued in exchange for BLV in December 2020. After unremarkable subcutaneous application of the first dose of BLV 2 mg at our outpatient clinic, the patient continued self-administered daily treatment according to current recommendations.[1]

After the sixth dose of BLV, the patient reported progressive pruritus and swelling of the upper extremities, of the face and lips as well as dyspnea starting after the third injection of BLV, indicative of type-1 allergic reaction. BLV was stopped immediately and the patient recovered quickly without any further intervention, therefore no corticosteroids were administered. Concurrent medication at this time included TDF, vitamin D substitution, and on-demand treatment with metamizole for recurrent headaches.

Although the relation between treatment initiation and onset of symptoms (and symptom resolution after treatment cessation) was suggestive of a type-I allergic reaction, potential differential diagnoses were considered: Normal tryptase serum levels after all symptoms had resolved ruled out systemic mastocytosis. No intercurrent infections were reported and symptoms did not persist longer than 6 weeks, thus acute and chronic spontaneous urticaria were ruled out. No atopic predisposition was assumed as both serum IgE and eosinophil counts were within the normal range, and the patient reported an unremarkable family history regarding allergies. Of note, the patient reported a previous anaphylactic reaction to clarithromycin.

Further diagnostic steps were performed at Department of Dermatology at the Vienna General Hospital: (a) prick testing with BLV (1 mg/ml) and (b) intradermal/intracutaneous skin testing with BLV (1:100, 0.01 mg/ml) did not provoke any reaction, however, higher intradermal/intracutaneous BLV concentrations (1:10 0.1 mg/ml; undiluted 1 mg/ml) induced an immediate reaction.[5]

Positive intracutaneous skin testing is typically induced by IgE-mediated mast cell degranulation causing type-I hypersensitivity.[6] Desensitization can be considered for IgE-mediated hypersensitivity under certain preconditions.[5] Due to the strong indication for HDV-active treatment and the previously insufficient response to PEG-IFN, BLV represented the only therapeutic option in this patient. Comedication with corticosteroids was not considered a rationale option due to the long-term treatment indication. Therefore, we decided to perform desensitization to BLV in an in-patient setting with emergency treatment being readily available. Since our patient demonstrated a strong skin reaction at 0.1 mg/ml (1:10 dilution) BLV, the starting dose was cautiously determined as 1/100 (0.03 mg) of the target dose (2 mg).[5] Over the course of 3 days, the patient received consecutive doses of BLV every 30 minutes. Doses were doubled each time until the per-day target dose was reached. Concomitantly, antihistaminergic treatment (levocetirizine 5 mg) was administered once daily (Table 1). Once regular dosing was established, the patient was discharged and self-administered subcutaneous treatment with BLV was continued at the recommended dosage of 2 mg once daily. Concomitant treatment with levocetirizine was discontinued 8 weeks after the re-initiation of BLV. No local or systemic adverse reactions were observed during re-exposure to BLV nor after withdrawal of the antihistaminergic comedication.

Based on this case, the potentially life-threatening consequences of an immediate-type hypersensitivity reaction to BLV have to be considered in clinical application and in patients' counselling, especially since the distinction between common BLV-associated pruritus and incipient allergic reactions may be difficult.[1] Importantly, HDV-related liver disease progression and complications will constitute the major prognostic factor in most HBV/HDV-coinfected individuals.[7–10]

BLV, which is marketed as a soluble powder, does not contain any other potential allergens aside from BLV itself.[1] While several mechanisms have been proposed to cause immediate-type hypersensitivity reactions, IgE-mediated hypersensitivity remains the "typical" pathway for type-I reaction. Positive skin testing confirmatory for IgE-mediated hypersensitivity supported our clinical approach to initiate desensitization, which was originally designed for IgE-mediated reactions.[5,6] Notably, the underlying mechanism of desensitization is currently not fully understood.[5,6] While patients have to be informed about the risk of a recurrent hypersensitivity reaction during re-exposure and its general experimental approach, successful desensitization may enable HDV-active antiviral therapy with BLV in patients with confirmed previous hypersensitivity reactions to BLV.[5]

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Table 1. Bulevirtide desensitization protocol used for our patient.

	Day 1 – 2 mg bulevirtide/2 ml aqua	Day 2 – 2 mg bulevirtide/1 ml aqua	Day 3 – 2 mg bulevirtide/1 ml aqua
Start:	0.03 ml (0.03 mg)	0.50 ml (1 mg)	1.0 ml (2 mg)
30 min:	0.05 ml (0.05 mg)	0.50 ml (1 mg)	
60 min:	0.15 ml (0.15 mg)		
90 min:	0.30 ml (0.30 mg)		
120 min:	0.50 ml (0.50 mg)		
150 min:	0.97 ml (0.97 mg)		

Importantly, adequate safety precautions have to be taken during re-exposure and uninterrupted treatment with BLV must be ensured after successful desensitization to avoid recurrent hypersensitivity reactions.[5]

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Conflict of interest

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Authors' contributions

Caroline Schwarz: Conceptualization, methodology, investigation, data curation, writing - original draft. David Chromy: Conceptualization, methodology, investigation, data curation, writing - review & editing. Christine Bangert: Conceptualization, methodology, investigation, data curation, writing - review & editing. Michael Schwarz: Conceptualization, methodology, investigation, data curation, writing - review & editing. Mathias Jachs: Writing - review & editing. Thomas Reiberger: Supervision, writing - review & editing. Michael Gschwantler: Validation, writing - review & editing.

Supplementary data

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