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Bulevirtide for the treatment of hepatitis D: a case series

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Introduction

- Infection by the hepatitis D virus (HDV) represents a relatively rare yet significant health concern.[1]
  HDV infection is associated with a rapid onset of cirrhosis and increased risk of hepatocellular carcinoma. While some progress has been made using interferon therapy, outcomes have shown a high variability, often accompanied by a high incidence of relapses.[2]
  A milestone in HDV management occurred with the approval of bulevirtide by the EMA in 2020.[3] This marked a significant advancement in the treatment landscape for patients afflicted by chronic hepatitis delta, particularly those with compensated cirrhosis. The Italian Medicines Agency (AIFA) granted approval for its reimbursement on April 13th, 2023. This decision facilitated its broader dissemination and availability to a wider patient population within the Italian country.[4]

Study Design

- In this case series we collected clinical and virological data regarding patients who accessed our centre (Luigi Sacco Hospital outpatient hepatological clinic, Milan, Italy) since the licensing of bulevirtide by AIFA.
  Patients were followed until 24 weeks from treatment start. All patients underwent treatment with daily, self-administered subcutaneous injections of bulevirtide 2mg in combination with a background treatment for HBV with NUC analogues. The primary end point was a 2log decrease in HDV-RNA viremia.

Results

- Eight patients have met the eligibility criteria for receiving bulevirtide, all of which had stage A cirrhosis according to the Child-Pugh classification. Four out of the 8 patients had previously been treated with IFN without success. Three out of the 8 individuals were people with HIV under stable antiretroviral treatment. Baseline characteristics of the eight patients are summarized in Table 1.
- As of May 2024 five patients have completed the first 24 weeks of treatment, one has completed 12 weeks, one the first 4 weeks, while the last started treatment during April 2024 and are now completing the first 4 weeks of therapy.
- Therapy was well tolerated by all participants, with only one adverse event recorded, namely a self-resolving itch.
- From a virological perspective, after the initial 24 weeks of treatment, every patient met the primary endpoint, demonstrating a decline of over 2 log in HDV viremia, as for the one that has completed the 12 weeks an initial decrease of 0.44 log UI/ml has been described; moreover, the patient who completed the first 4 weeks of treatment already showed a decrease of 1.82 log UI/ml. Additionally, we observed a decline in alanine aminotransferase (ALT) levels in four out of the six patients that completed the first 12 weeks. The remaining two already had liver enzymes within the normal range at baseline.
  Our findings regarding HDV viral load and ALT levels are summarized in Graphic 1 and Graphic 2, respectively.
  No patient lost the hepatitis B surface antigen.

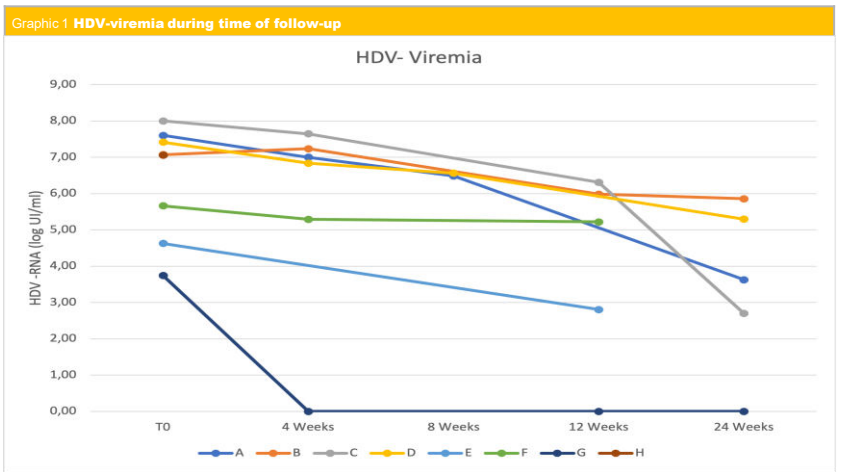
Conclusion

- Our experience underscores the safety, feasibility, and effectiveness of bulevirtide monotherapy in patients with chronic hepatitis delta (CHD) with and without HIV. Nevertheless, further studies are needed to assess the long-term benefits and determine the optimal duration of treatment.

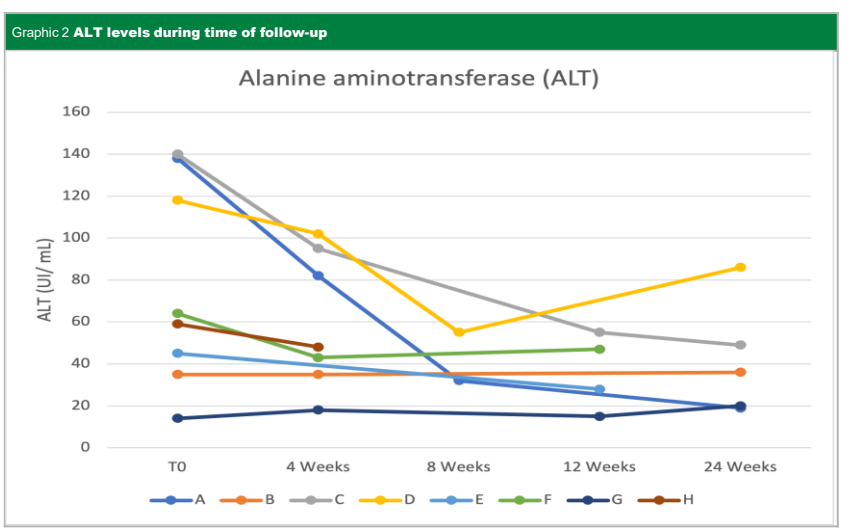
Table 1 **Baseline characteristics of the eight patients**

	A	B	C	D	E	F	G	H
Year of birth	1959	1987	1964	1974	1964	1969	1959	1971
Year of HDV diagnosis	2004	2013	1988	1992	2018	2000	1983	2023
AST (U/L)	183	29	123	86	49	54	33	59
ALT (U/L)	138	35	140	118	45	64	18	53
HBV-DNA (IU/mL)	<20 R	<20 R	<20 R	52	<10 R	<10 R	< 10 R	< 10 NR
HBsAg (IU/mL)	9443	19084	14932	16979	27	12683	1752	21.611
HBeAg (IU/mL)	Negative	16.5	Negative	Negative	Negative	Negative	Negative	Negative
HDV-RNA (IU/mL)	40.277.546	11.839.602	>100.000.000	26.103.445	42.575	461.621	5.529	11.464.276
PLWH	No	No	Yes	No	Yes	No	No	Yes

Graphic 1 **HDV-viremia during time of follow-up**



Graphic 2 **ALT levels during time of follow-up**



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2. *Asselah, T. & Rizzetto, M. Hepatitis D Virus Infection. N Engl J Med 389, 58–70 (2023).*
3. *European Medicines Agency. Hepcludex. August 2020 (https://www.ema .europa.eu/en/medicines/human/EPAR/ hepcludex)*
4. *Determina AIFA n.8/2023 del 13/01/2023 "Riclassificazione del medicinale per uso umano «Hepcludex», ai sensi dell'articolo 8, comma 10, della legge 24 dicembre 1993, n. 537" (GU Serie Generale n.20 del 25-01-2023).*