Neurological Sciences (2023) 44:1419–1422
https://doi.org/10.1007/s10072-022-06568-w

BRIEF COMMUNICATION

A case of severe increase of liver enzymes in a ATTRv patient after one year of inotersen treatment

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Received: 13 November 2022 / Accepted: 15 December 2022 / Published online: 28 December 2022

Abstract

Background Inotersen is an antisense oligonucleotide used to treat hereditary transthyretin amyloidosis (ATTRv). The most common drug-related adverse effects (AEs) include thrombocytopenia and glomerulonephritis. Hepatic damage is rare, but liver enzyme monitoring is mandatory.

Case report A 70-year-old man with ATTRv (Val30Met) treated with inotersen developed a severe increase of transaminases, with normal bilirubin and cholinesterase levels, that forced us to stop therapy. At the same time, other causes of acquired hepatitis were excluded, and the hypothesis of an inotersen-related hepatic toxicity was supported by the normalization of liver enzymes after 40 days from the drug interruption.

Discussion Our case showed that 1-year inotersen treatment can stabilize neurological impairment and even improve quality of life and suggests to carefully monitor liver enzymes in order to avoid an inotersen-related hepatic dysfunction.

Keywords Hereditary TTR amyloidosis · Inotersen · Adverse event · Liver toxicity

Background

Hereditary transthyretin amyloidosis (ATTRv) is a progressive and life-threatening disease due to deposition of amyloid fibrils of mutated transthyretin (TTR). Amyloid deposits occur above all in the peripheral nervous system (PNS) and heart [1, 2].

In the last years, TTR gene-silencer molecules drastically changed ATTRv natural history [3]. Inotersen, an antisense oligonucleotide (ASO) inhibitor of the hepatic production of transthyretin protein, is effective in halting the progressive disability [4]. The most common drug-related adverse effects (AEs) include thrombocytopenia and glomerulonephritis, which require monitoring platelet count every 2 weeks and renal function every 3 months. Other frequently reported adverse effects are represented by nausea, urinary tract infection, vomiting, diarrhea, fatigue, chills, fall, peripheral edema, injection site–related pain, and reactions [5]. As other ASOs, inotersen accumulates in hepatic tissue, so liver damage, although uncommon, is possible and makes liver enzyme monitoring mandatory 4 months after the start of treatment and then every year. We reported a case of severe increase of liver enzymes in a ATTRv patient treated with inotersen.

Case report

A 71-year-old man complained of 1-year history of progressive imbalance during walking associated with unintentional weight loss. No comorbidity was present with the exception of a duodenal ulcer several years before. Nerve conduction study showed a sensory-motor axonal polyneuropathy and TTR genetic test resulted positive for Val30Met mutation. Multidisciplinary evaluation showed hypertrophic cardiomyopathy with positive bone scintigraphy (Perugini score 3), and no laboratory findings of kidney involvement were present.

His baseline evaluation showed familial amyloid polyneuropathy (FAP) stage I, Polyneuropathy Disability

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(PND) score II, total Neuropathy Impairment Score (NIS) equal to 50.75, and Norfolk quality of life questionnaire (Norfolk QOL-DN) equal to 70 points. Before starting therapy with inotersen, blood and urinary examinations were performed in order to exclude any possible contraindication to treatment. Basal platelet count was 201,000/μL (required value > 100,000/μL). Urinary protein to creatinine ratio (UPCR) and estimated glomerular filtration rate (eGFR), the most important renal function tests to perform according to current recommendations, were respectively 95 mL/min/m^2 (required value > 45 mL/min/m^2) and 0.18 g/g (required value < 1 g/g). Liver enzymes (AST = 12 U/L; ALT = 58 U/L; GGT = 27 U/L) were normal, and a severe hepatic impairment was excluded. The patient started treatment with inotersen in November 2020, and a follow-up was performed with neurological evaluations every 6 months, laboratory examinations consisting of platelet count every 2 weeks, UPCR and eGFR every month, and liver enzymes 4 months after the start of therapy and then every 6 months. At neurological evaluation, NIS score appeared unchanged at 12-month visit (50.7). FAP stage and PND remained unchanged. Norfolk QOL-DN showed a significant improvement of quality of life after 12 months of treatment (Fig. 1A). Nerve conduction studies showed unremarkable changes at follow-up. Concerning laboratory analyses, serum transthyretin level become soon suppressed (0.08 g/L) with respect to the baseline (0.39 g/L; normal value > 0.20 g/L) (Fig. 1B). A non-significant (> 100,000/μL) reduction of platelet count occurred during treatment that did not necessitate any drug reduction/discontinuation (Fig. 1C) and renal function (UPCR and eGFR) remained stable over time. Liver enzymes slightly increased at 6-month follow-up during therapy (AST = 35 U/L; ALT = 65 U/L; GGT = 49 U/L), without any sign or symptoms of hepatic damage; however, at 12 months, a severe increase of liver enzyme (AST = 833 U/L; ALT = 665 U/L; GGT = 135 U/L) was observed (Fig. 1D). Bilirubin level and cholinesterase were both normal. Therefore, since the patient denied the assumption of other liver-harming substances (e.g., alcohol), inotersen therapy was immediately stopped considering a possible drug-related adverse effect. Moreover, according to the gastroenterologist consultant, *N*-acetylcysteine was administered.

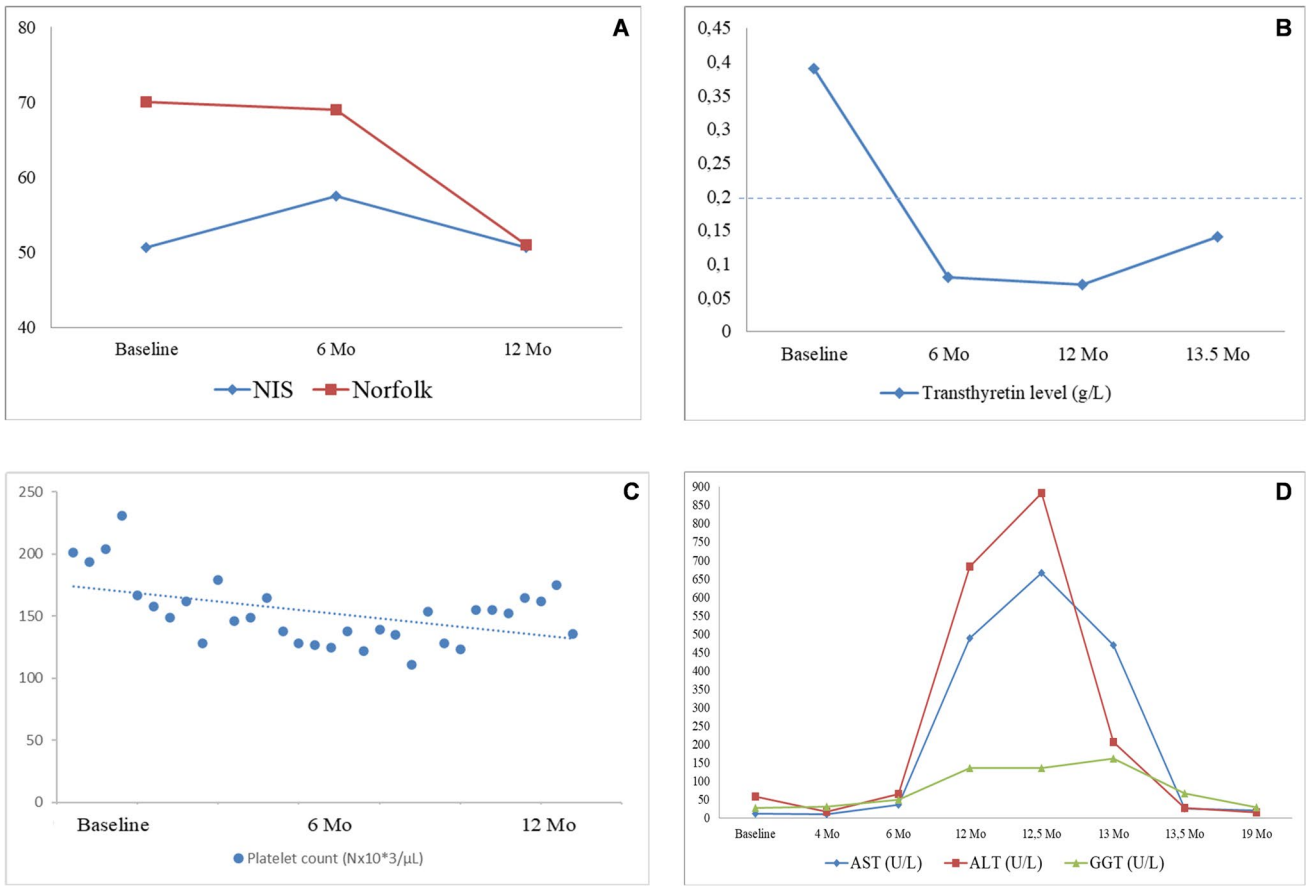

Fig. 1 Clinical and laboratorial findings. Figure shows the neurological impairment (NIS) and quality of life (Norfolk) (**A**), serum transthyretin level (**B**), platelet count (**C**), and liver enzymes (**D**) of the patient during the 12-month period of inotersen treatment

At the same time, other causes of acquired hepatitis were excluded. Liver echography showed just mild grade steatosis and biliary tract appeared normal. Blood tests for acute hepatic infections (HAV, HBV, HCV, HIV, CMV, EBV, HSV, VZV, toxoplasma, SARS-CoV-2) and autoimmune hepatitis (ANA, ENA, AMA, LKM1) were unremarkable. Eventually, the hypothesis of an inotersen-related hepatic toxicity was supported by the normalization of liver enzymes (AST = 25 U/L; ALT = 26 U/L; GGT = 66 U/L) 45 days after drug discontinuation. At that time, transthyretin concentration remained still suppressed (0.14 g/L), and his neurological conditions were stable.

Therefore, to avoid new events of liver damage, our patient began therapy with patisiran, and 6 months later his clinical condition was still stable (FAP stage I, PND score II, total NIS equal to 50.2) with normal hepatic enzymes.

Discussion

Inotersen is an antisense oligonucleotide, administrable in the first stages (FAP I and II) of ATTRv, which suppresses hepatic production of transthyretin, halts PNS damage progression, and can even improve disease disability and quality of life [4–6]. According to this, our case showed that 1-year lasting treatment with inotersen was able to keep our patient's neurological conditions stable, as demonstrated by stability of NIS and nerve conduction studies, compared to baseline values. Moreover, quality of life appeared to be improved by pharmacological therapy, as documented by the decrease of Norfolk QOL-DN score. Nevertheless, our patient developed a drug-related severe increase of liver enzymes, so that he had to discontinue inotersen. Our patient during inotersen treatment did not experience platelet count reduction and had no laboratory findings of glomerulonephritis, reassuring about the safety profile of inotersen [6].

Inotersen-related hepatitis is rare, but possible, as animal models showed that inotersen dose-dependently accumulates in hypertrophied Kupffer cells of the liver, where, in line with other ASOs, it can elicit an immunological and pro-inflammatory effect and promote histological abnormalities (sinusoidal dilatation, bile duct hyperplasia, individual hepatocellular necrosis, and oval cell hyperplasia) [7]. According to these observations, data from the pivotal phase II/III study (ISIS 420915-CS2) showed an increase of transaminases level in just six subjects. Among them, one subject had a diagnosis of Gilbert's disease, thought to be causal for this, while four subjects showed increases which occurred at single occasions and resolved in a short period of time while inotersen was continued. The last patient had a gradual increase of ALT, AST, and ALP during inotersen treatment, lacking alternative explanations, so it was considered probably drug related [4].

Therefore, inotersen is contraindicated in people suffering from severe hepatic impairment. In conclusion, we confirmed inotersen's efficacy in halting disease disability and improving quality of life, and the good safety profile about thrombocytopenia and glomerulonephritis. Unfortunately, our patient developed a severe drug-related liver enzyme increase, which normalized after therapy discontinuation. Interestingly, serum TTR level appeared still suppressed after 45 days after inotersen interruption. Therefore, we decided to shift to the other TTR gene-silencer therapy, patisiran, since no drug-related liver toxicity was reported, as recently confirmed by the real-life use of patisiran in an Italian cohort of ATTRv patients [8]. Clinical condition after 6-month follow-up was still stable.

Our case highlighted that inotersen-related liver damage, although uncommon as reported in scientific literature, is a possible event and liver function should be carefully monitored, to avoid a drug-related hepatic dysfunction.

Data availability All data generated or analysed during this study are included in this published article (and its supplementary information files).

Declarations

Ethical approval Ethical approval was waived by the local Ethics Committee in view of the retrospective nature of the study and all the procedures being performed were part of the routine care.

Informed consent Informed consent Informed consent for publication was collected from patient.

Conflict of interest D.S. has received a travel grant to attend scientific meetings from SOBI. F.M. received personal fees for scientific events from Alfa-Sigma, Alnylam Pharmaceuticals, and Akcea Therapeutics, and has received a travel grant to attend scientific meetings from CSL Behring. S.T. received personal fees for scientific events from Alnyalm Pharmaceuticals and Amicus Therapeutics, and travel grants to attend scientific meetings from Akcea Therapeutics.

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