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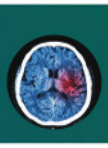

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SHORT COMMUNICATION

Real-life experience with inotersen in hereditary transthyretin amyloidosis with late-onset phenotype: Data from an early-access program in Italy

Marco Luigetti[1,2] | Giovanni Antonini[3] | Andrea Di Paolantonio[2] | Luca Gentile[4] | Marina Grandis[5,6] | Luca Leonardi[3] | Alessandro Lozza[7] | Fiore Manganelli[8] | Anna Mazzeo[4] | Roberta Mussinelli[7] | Filomena My[9] | Laura Obici[7] | Elena Maria Pennisi[10] | Marina Romozzi[1,2] | Massimo Russo[4] | Mario Sabatelli[11] | Alessandro Salvalaggio[12] | Matteo Tagliapietra[13] | Stefano Tozza[8]

[1]Fondazione Policlinico Universitario Agostino Gemelli IRCCS UOC Neurologia, Rome, Italy

[2]Department of Neuroscience, Catholic University of the Sacred Heart, Rome, Italy

[3]Department of Neurosciences, Mental Health and Sensory Organs, Faculty of Medicine and Psychology, Sant'Andrea Hospital, Sapienza University of Rome, Rome, Italy

[4]Unit of Neurology and Neuromuscular Diseases, Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy

[5]Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics and Maternal Infantile Sciences, University of Genova, Genoa, Italy

[6]San Martino Polyclinic Hospital, Scientific Institute for Research and Health Care, Genoa, Italy

[7]Amyloidosis Research and Treatment Center, San Matteo Polyclinic Foundation, Scientific Institute for Research and Health Care, Pavia, Italy

[8]Department of Neuroscience, Reproductive and Odontostomatological Science, University of Naples "Federico II", Naples, Italy

[9]UOC Neurologia Vito Fazzi Hospital, Lecce, Italy

[10]Neuromuscular and Rare Neurological Diseases–Neurology Unit, San Filippo Neri Hospital, Rome, Italy

[11]Centro Clinico NEMO Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy

[12]Department of Neurosciences, University of Padova, Padua, Italy

[13]Department of Neurosciences, Biomedicine, and Movement Sciences, University of Verona, Verona, Italy

Correspondence
Marco Luigetti, Fondazione Policlinico Universitario A. Gemelli IRCCS, UOC Neurologia, Largo A Gemelli 8, 00168 Rome, Italy.
Email: mluigetti@gmail.com

Funding information
Universita Cattolica del Sacro Cuore

Abstract

Background and purpose: Hereditary transthyretin (TTR) amyloidosis (ATTRv) is a dominantly inherited, adult-onset, progressive, and fatal disease caused by mutations in the *transthyretin* gene. Therapeutic agents approved for this disease include the TTR stabilizer tafamidis and the gene-silencing drugs patisiran and inotersen. Inotersen is an antisense oligonucleotide that suppresses the hepatic production of transthyretin. After European Medical Agency approval in 2018, an early-access program was opened in Italy, and in this article, we present the long-term outcome of a cohort of Italian ATTRv patients who received inotersen within this program.

Methods: This is a multicenter, observational, retrospective study of patients affected by ATTRv that started inotersen during the early-access program. The primary end point was safety. Secondary end points included change from baseline in familial amyloid

All the authors, after the first one, are listed in alphabetical order and contributed equally to the study.

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polyneuropathy (FAP) stage, Polyneuropathy Disability, Neuropathy Impairment Scale, Compound Autonomic Dysfunction Test, Norfolk Quality of Life–Diabetic Neuropathy, troponin, N-terminal pro–brain natriuretic peptide, interventricular septum thickness, and body mass index.

Results: In total, 23 patients were enrolled. No patient permanently discontinued the treatment because of thrombocytopenia, and no cases of severe thrombocytopenia were observed. Five patients discontinued the treatment permanently because of voluntary withdrawal (two patients), renal failure after infective pyelonephritis, not related to inotersen, drug-related hypotension, and amyloid-negative crescentic glomerulonephritis. In seven patients, dosing frequency was reduced to every 2 weeks due to recurrent thrombocytopenia. Considering the FAP stage, only two patients worsened, whereas the other 21 patients remained stable until the last follow-up available.

Conclusions: The long-term safety profile of inotersen is favorable. Neurologic disease severity at baseline is the main factor associated with progression.

KEYWORDS
amyloidosis, ATTRv, inotersen, real life

INTRODUCTION

Hereditary transthyretin amyloidosis (ATTRv; v for variant), is a dominantly inherited, adult onset, progressive, and fatal disease caused by mutations in the *transthyretin* (*TTR*) gene [1,2]. TTR amyloid fibrils deposit in several tissues and organs, leading to a multisystem disorder with prevalent involvement of the peripheral nervous system and the heart [3]. The most typical presentations include a progressive sensory-motor and autonomic axonal polyneuropathy [4], and/or infiltrative cardiomyopathy. Most patients exhibit signs and symptoms of both nerve and heart involvement, but kidneys, eyes, liver, and gastrointestinal tract may also be involved [1,5].

Management therefore requires a multidisciplinary approach [1,2]. In recent years, pharmacological therapies that significantly modify the natural course of this disease have emerged, improving outcomes and prolonging survival [6]. Approved therapeutic agents include the TTR stabilizer tafamidis and the gene-silencing drugs patisiran and inotersen [7–9].

Inotersen is an antisense oligonucleotide, administered at the dosage of 284 mg subcutaneously once weekly, which suppresses the hepatic production of TTR by specifically targeting and degrading the messenger RNA of both mutant and wild-type alleles. Based on the positive results of the NEURO-TTR trial, inotersen was approved by European Medical Agency (EMA) in 2018 for the treatment of ATTRv with familial amyloid polyneuropathy (FAP) Stage 1 and 2 polyneuropathy [7].

After EMA approval, an early-access program was opened in Italy (see Supplementary Material for inclusion/exclusion criteria) to provide treatment in advance of the marketing authorization. Here, we present the long-term outcome of a cohort of patients who received inotersen within this program.

MATERIALS AND METHODS

Study design

This is a multicenter, observational, retrospective study in patients treated with inotersen from February 2019 in an early-access program according to Italian regulations.

We collected and analyzed the main clinical and laboratory parameters useful for assessing neurological and cardiac disease progression as well as safety and tolerability indicators (detailed in the Supplementary Material).

Patients and methods

Patients and outcome measure

Patients treated with inotersen within the compassionate-use program approved by the Italian Medicines Agency in February 2019 were recruited from 11 Italian centers. As routine monitoring, all patients underwent a comprehensive neurological evaluation, a cardiological examination, and laboratory tests. Serum TTR concentrations were obtained in a subgroup of patients. All parameters were evaluated at baseline and every 6 months.

Study end points

The primary end point was the safety that comprised the percentage of patients who discontinued the therapy for drug-related adverse events, including monitoring of platelet count and renal and liver function. [10] Secondary end points included change from baseline

in FAP stage, Polyneuropathy Disability (PND) score, the Neuropathy Impairment Scale (NIS), Compound Autonomic Dysfunction Test (CADT), Norfolk Quality of Life–Diabetic Neuropathy (Norfolk QoL-DN) questionnaire, troponin, serum TTR concentration, N-terminal pro–brain natriuretic peptide (NT-proBNP), interventricular septum (IVS) thickness, and body mass index (BMI).

Statistical analysis

Statistical analysis was performed by SPSS version 24.0 (IBM, Armonk, NY). Data were presented as mean values with standard deviations or percentages, as appropriate. For nonnormally distributed variables, we used the Wilcoxon sign ranked test as a nonparametric significance test. Within-group changes in values over time were assessed by Friedman nonparametric test for repeated measures. A p value of <0.05 was considered statistically significant.

Patients were divided into subgroups according to genotype (V30M vs F64L vs other mutations), phenotype (neuropathic vs. mixed), previous treatment with tafamidis, the severity of disease at baseline (FAP Stage 1 vs. FAP Stage 2), and dose of inotersen (full dose vs. dose reduction). Logistic regression analysis was used to determine significant associations among covariates and dependent variables.

Ethics

The study was approved by the Ethics Committee of Fondazione Policlinico A. Gemelli IRCSS (Prot. ID 3846) as the coordinating center and then by ethics committees of other institutions.

RESULTS

Patient disposal, baseline clinical characteristics, and demographics

Twenty-three out of 31 ATTRv patients receiving inotersen in the Italian early-access program were enrolled (Figure 1). Demographic and baseline clinical characteristics are summarized in Table 1. Eleven patients (47.8%) were previously on treatment with tafamidis meglumine 20 mg/day. Serum TTR concentration at baseline was available in 12 patients (24.75 ± 5.05 mg/dl).

The mean disease duration at treatment start was 3.68 ± 2.37 years. The mean follow-up on inotersen treatment was 14.6 ± 5.9 months (range, 6–24 months).

Safety and tolerability

A significant decrease in platelet count ($p = 0.001$, Friedman test) was observed from baseline to month 6 (M6), but no patient permanently discontinued the treatment because of this reason and no severe thrombocytopenia (<50.000 per cubic millimeter) occurred. Pairwise comparisons highlighted that there was a significant difference between basal and M6 in mean platelet count ($p = 0.017$), whereas it remained stable from M6 to M24 (Supplementary Figure S1).

Five patients (21.7%) permanently discontinued the treatment due to voluntary withdrawal (two patients); renal failure after infective pyelonephritis, not drug related; drug-related hypotension; and amyloid-negative crescentic glomerulonephritis (proved by kidney biopsy), respectively. Hypotension and crescentic glomerulonephritis improved after treatment discontinuation. Mean time from the beginning of therapy to discontinuation was 305.0 ± 231.9 days (range, 92–672).

Four patients temporarily skipped the treatment for a decrease in platelet count (<75.000 per cubic millimeter) with prompt resolution of thrombocytopenia.

In nine patients (39.1%), dosing frequency was reduced according to the summary of product characteristics to 284 mg every 2 weeks for thrombocytopenia (<100.000 per cubic millimeter) and platelet count returned to baseline or near-baseline levels after dose reduction. The mean time from the beginning of the therapy to dose reduction was 343.125 ± 208.13 days (range, 34–627).

In seven cases (30.4%), this treatment schedule was maintained due to recurrent mild thrombocytopenia on weekly administration. Mean time from the beginning of therapy to reduction to 284 mg every 2 weeks was 382.4 ± 219.6 days (range, 34–627).

Except for the two patients who suspended therapy for renal changes, we did not observe a decline in renal function, measured by estimated glomerular filtration rate and urine protein/creatinine ratio. No abnormalities in liver function tests occurred.

No cardiac-related events occurred, and we did not report any deaths in our cohort.

Efficacy end points

All secondary end point values are summarized in Table 2.

Neurologic evaluation

Considering FAP stage, two out of 23 patients (8.7%) worsened, both at M6 from Stage 2 to 3 (Figure 1).

Considering PND stage, four out of 23 patients (17.4%) worsened at M6 (two from class 3b to 4 and two from class 3a to 3b), whereas one out of 23 (4.3%) patients improved (Figure 1).

Mean NIS was 77.0 ± 37.9 at baseline and 133.2 ± 43.1 at M24. We observed an average monthly progression of 0.83 ± 1.16 on the NIS scale. We found an almost significant worsening of NIS values ($p = 0.053$) from baseline to M24 (Supplementary Figure S2); however, we should consider that only four patients (two FAP 2 and two FAP 3) reached this follow-up.

Mean CADT score was 14.65 ± 3.25 at baseline and 11.66 ± 0.58 at M24. We did not find a significant worsening of CADT values from baseline to M24 (Supplementary Figure S3).

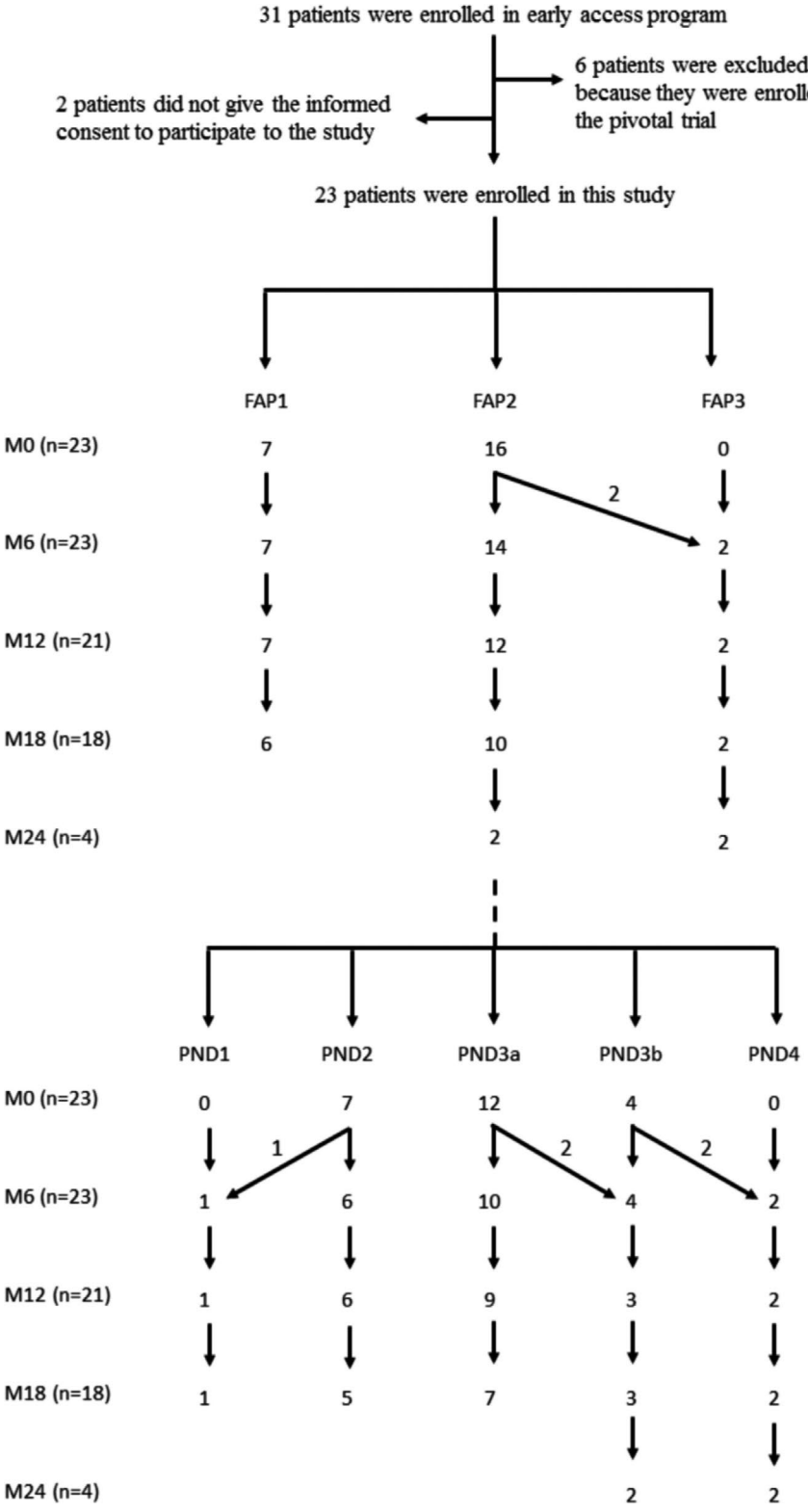

FIGURE 1 Patients' enrollment and familial amyloid polyneuropathy (FAP) stage and Polyneuropathy Disability (PND) score changes across the study. M, month

Subgroups analysis

We found no significant differences in disease progression among the following subgroups: genotype, phenotype, previous treatment with tafamidis, and dose of inotersen.

Considering disease severity at baseline, FAP 1 patients progressed slower than FAP 2. NIS changes from baseline differed significantly between patients with FAP 1 stage and patients with FAP 2 stage at M6 ($p = 0.003$), M12 ($p < 0.0005$), and M18 ($p = 0.001$). Moreover, mean NIS score did not change significantly ($p = 0.984$) in FAP 1 patients along the treatment period, whereas it showed a progressive significant increase along the 24 months in FAP 2 group ($p < 0.0005$) (Figure S4). CADT was significantly higher in FAP 1 versus FAP 2 patients at baseline ($p = 0.004$), at M6 ($p = 0.044$), M12

TABLE 1 Demographic and baseline clinical characteristics

Patient	Mutation	Age at baseline, years	Age at diagnosis, years	Phenotype	FAP stage	PND	NIS	CADT	Norflolk-QoL	IVS, mm	Serum TTR, mg/dl
1	T59K	59	48	Mixed	2	3a	82.5	8	113	25	N/A
2	V30M	62	57	Neuropathy	2	3b	124.5	14	130	15	N/A
3	V30M	76	72	Neuropathy	2	3b	147	14	90	N/A	N/A
4	V30M	73	68	Mixed	2	3a	148	13	70	13	N/A
5	F64L	63	60	Neuropathy	1	2	19	19	20	N/A	24
6	F64L	71	66	Neuropathy	2	3b	105	16	79	N/A	20
7	V30M	60	58	Mixed	2	3a	56	16	90	15	20
8	F64L	62	65	Neuropathy	2	3b	93	11	92	N/A	33
9	A120S	78	77	Mixed	1	2	40	15	68	18	N/A
10	F64L	82	76	Neuropathy	2	3a	128	14	128	14	25
11	F64L	80	72	Neuropathy	2	3a	128	12	128	13	24
12	F64L	87	83	Neuropathy	2	3a	88	14	88	14	23
13	V30M	85	84	Neuropathy	2	3a	33	16	49	N/A	N/A
14	V30M	78	76	Mixed	2	3a	46.5	16	58	16	N/A
15	V30M	69	67	Mixed	2	3a	34	15	43	17	N/A
16	F64L	68	66	Mixed	1	2	48	17	55	14	21
17	Y78F	78	75	Neuropathy	2	3a	63	18	36	11	N/A
18	F64L	73	71	Mixed	2	3a	79	13	65	16	N/A
19	V30M	67	63	Neuropathy	1	2	48	19	56	10.8	35
20	F64L	73	70	Neuropathy	1	2	75	15	61	12.5	19
21	F64L	71	67	Neuropathy	1	2	63	19	64	13.5	28
22	F64L	58	56	Neuropathy	1	2	44	17	60	10.2	25
23	F64L	71	69	Neuropathy	2	3a	79	6	62	14	N/A

Abbreviations: CADT, Compound Autonomic Dysfunction Test; FAP, familial amyloid polyneuropathy; IVS, interventricular septum; N/A, not available; NIS, Neuropathy Impairment Scale; Norfolk QoL-DN, Norfolk Quality of Life–Diabetic Neuropathy questionnaire; PND, Polyneuropathy Disability score; TTR, transthyretin.

TABLE 2 Secondary end points values (mean ± SD)

End points	Baseline, $n = 23$	M6, $n = 23$	M12, $n = 21$	M18, $n = 18$	M24, $n = 4$
NIS, 0–244	77.0 ± 37.9	85.9 ± 39.0	91.8 ± 42.4	90.8 ± 39.9	133.2 ± 43.1
CADT, 0–20	14.65 ± 3.25	14.31 ± 2.83	13.70 ± 2.97	13.81 ± 3.39	11.66 ± 0.58
Norfolk QoL-DN, −4 to 136	74.1 ± 29.5	77.3 ± 27.9	77.6 ± 29.2	72.8 ± 25.7	94.5 ± 16.0
Troponin, ng/ml	0.03 ± 0.03	0.02 ± 0.02	0.01± 0.1	0.05 ± 0.06	0.3 ± 0.2
NT-proBNP, pg/ml	596.4 ± 1073.5	642.0 ± 1140.6	630.4 ± 1535.0	727.9.7 ± 1729.3	365.0 ± 192.7
IVS, mm	15.4 ± 1.8	16.9 ± 4.3	16.3 ± 1.3	16.3 ± 1.4	12.55 ± 2.0
eGFR	91.2 ± 17.5	95.6 ± 15.5	90.6 ± 17.4	100.0 ± 26.0	90.0 ± 13.8
UPCR, mg/mmol	0.02 ± 0.05	0.02 ± 0.05	0.3 ± 0.9	0.02 ± 0.08	0.1 ± 0.1
Platelet count, $\times 10^3/\mu l$	192.2 ± 53.9	175.2 ± 81.1	163.6 ± 53.6	148.7 ± 41.7	147.0 ± 34.7
BMI	25.1 ± 3.4	24.0 ± 2.5	24.9 ± 3.6	24.2 ± 2.9	23.4 ± 0.6
TTR, mg/dl	24.75 ± 5.05	6.07 ± 4.88	6.17 ± 2.23	4.33 ± 1.53	5.5 ± 2.12

Abbreviations: BMI, body mass index; CADT, Compound Autonomic Dysfunction Test; eGFR, estimated glomerular filtration rate; IVS, interventricular septum; NIS, Neuropathy Impairment Scale; Norfolk QoL-DN, Norfolk Quality of Life–Diabetic Neuropathy; NT-proBNP, N-terminal pro–brain natriuretic peptide; TTR, transthyretin; UPCR, urine protein/creatinine ratio; M, month.

($p = 0.03$), and M18 ($p = 0.026$) (Figure S5). However, no statistically significant deterioration in CADT values was observed both in FAP 1 and FAP 2 patients.

Serum TTR concentrations did not differ in the FAP1 versus FAP2 group at baseline. Significant reduction was observed in all patients during the treatment period. Furthermore, serum TTR

concentrations did not differ at baseline and during follow-up in patients treated with the full dose of inotersen versus patients with a reduced regimen.

Quality-of-life assessment

Norfolk QoL-DN at baseline was 74.1 ± 29.5. The mean monthly change was 0.26 ± 0.8, with no statistical significance between time points (Figure S6).

Changes in Norfolk QoL-DN score differed significantly between FAP 1 patients and FAP 2 patients at M12 ($p = 0.042$) and M18 ($p = 0.020$). However, no statistically significant increase in Norfolk QoL-DN values was observed both in FAP 1 ($p = 0.392$) and FAP 2 patients ($p = 0.568$).

Other variables

Other variables including IVS thickness, BMI, troponin, and NT-proBNP did not show significant changes during inotersen treatment in the observed period.

DISCUSSION

ATTRv is a highly disabling multisystemic disease characterized by rapidly progressing neurological impairment that irreversibly compromises patients' autonomy in a few years [5].

The annual deterioration rate in NIS significantly exceeds the progression observed in other peripheral neuropathies [11] and is associated with an increasing burden on quality of life [12]. A multicenter, retrospective study in ATTRv patients from different countries estimated an annual NIS change of 14.3 points from a baseline value of 32 [13]. However, progression is expected to occur more rapidly at higher disease stages [13].

In the NEURO-TTR trial, significant improvement in neurological progression and quality of life deterioration was observed in patients treated with inotersen for 15 months compared to placebo [7]. The long-term, sustained impact of this treatment on disease progression was recently confirmed in the open-label extension study [10].

To evaluate the real-world impact of inotersen, we investigated the outcome of a group of patients treated in the setting of a compassionate-use program.

Our study group differs in terms of disease severity at baseline either from the population of the NEURO-TTR trial or from other series reported in the literature. In particular, our patients showed higher NIS baseline values [14].

Despite this significant difference, during the observed follow-up, FAP stage overall remained stable in 91.3% of patients, and PND score, reflecting ability in walking, was unchanged in 78.3% and improved in 4.3% of the patients.

Neurological outcome according to NIS showed moderate worsening over the first 6 months, probably due to the time required to reach an effect [12], and then substantial stabilization was observed up to 18 months. The annual progression of NIS was lower when compared with the natural history of the disease reported in the literature (9.96 vs. 14.3 points) [13].

Quality of life according to the Norfolk QoL-DN score was preserved by inotersen treatment both in FAP 1 and FAP 2 patients. Mean annual change in Norfolk QoL-DN was only 3.2 points, which is significantly lower than the recently published threshold that defines progression [15].

Similarly, the CADT score, indicating autonomic dysfunction, remained stable along the follow-up both in FAP 1 and FAP 2 patients.

Few data are available regarding factors able to influence therapy outcome in ATTRv [12]. Subgroup analysis revealed disease stability in patients starting inotersen in FAP Stage 1 but not in those starting therapy in stage 2. These results are consistent with higher rates of progression in patients with worse baseline disease severity observed in other studies [11]. Hence, our data confirm an increased therapeutic benefit with earlier treatment.

Considering safety, inotersen proved to be safe and well tolerated over 24 months. A drug-related change in renal function was observed only in one patient, in which crescentic glomerulonephritis was shown by biopsy and was promptly reversible after inotersen discontinuation. Moreover, markers of liver and cardiac function did not change significantly during the study. Platelet count relatively decreased after 6 months but then remained stable [7].

No Grade 4 thrombocytopenia or deaths occurred in our cohort. In a few cases, a temporary or permanent dose reduction was necessary to maintain platelet count over 100,000 per microliter.

In conclusion, inotersen improves neurological progression and preserves quality of life in patients with a wide range of disease severity at treatment start, and has a good safety profile. In our cohort, worsening of neurologic function was more pronounced in patients with higher disease severity at baseline. On the contrary, health-related quality of life seemed equally preserved during the treatment course. Our data further underscore the importance of early treatment intervention with inotersen. Additional studies with a larger sample size are needed to confirm these results.

CONFLICT OF INTEREST

M.L. received financial grants (honoraria and speaking) from Ackea, Alnylam, and Pfizer, and travel grants from Akcea, Alnylam, Sobi, Pfizer, Kedrion, Csl Behring, and Grifols. G.A. has no potential conflicts of interest to disclose. A.D.P. received travel grants from Pfizer. L.G. acknowledges receiving speaker fees and consulting honoraria from Pfizer. M.G. acknowledges donations from Sanofi Genzyme to support research activities of her Research Unit; financial support from Pfizer, Alnylam, and Sanofi Genzyme for participation in National and International Meetings; participation in Advisory Board of Pfizer; speaker honorarium from Sanofi Genzyme. L.L. has no potential conflicts of interest to be disclosed. A.L. acknowledges

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AUTHOR CONTRIBUTIONS

Marco Luigetti: Conceptualization (lead), data curation (lead), formal analysis (lead), methodology (lead), writing–original draft (lead), writing–review & editing (lead). **Giovanni Antonini:** Conceptualization (equal), data curation (equal), methodology (equal), writing–review & editing (equal). **Andrea Di Paolantonio:** Conceptualization (equal), data curation (equal), methodology (equal), writing–review & editing (equal). **Luca Gentile:** Conceptualization (equal), data curation (equal), methodology (equal), writing–review & editing (equal). **Marina Grandis:** Conceptualization (equal), data curation (equal), methodology (equal), writing–review & editing (equal). **Luca Leonardi:** Conceptualization (equal), data curation (equal), methodology (equal), writing–review & editing (equal). **Alessandro Lozza:** Conceptualization (equal), data curation (equal), methodology (equal), writing–review & editing (equal). **Fiore Manganelli:** Conceptualization (equal), data curation (equal), methodology (equal), writing–review & editing (equal). **Anna Mazzeo:** Conceptualization (equal), data curation (equal), methodology (equal), writing–review & editing (equal). **Roberta Mussinelli:** Conceptualization (equal), data curation (equal), methodology (equal), writing–review & editing (equal). **Filomena My:** Conceptualization (equal), data curation (equal), methodology (equal), writing–review & editing (equal). **Laura Obici:** Conceptualization (equal), data curation (equal), methodology (equal), writing–review & editing (equal). **Elena Maria Pennisi:** Conceptualization (equal), data curation (equal), methodology (equal), writing–review & editing (equal). **Marina Romozzi:** Conceptualization (equal), data curation (equal), formal analysis (equal), methodology (equal), writing–original draft (equal), writing–review & editing (equal). **Massimo Russo:** Conceptualization (equal), data curation (equal), writing–review & editing (equal). **Mario Sabatelli:** Conceptualization (equal), data curation (equal), methodology (equal), writing–review & editing (equal). **Alessandro Salvalaggio:** Conceptualization (equal), data curation (equal), methodology (equal), writing–review & editing (equal). **Matteo Tagliapietra:** Conceptualization (equal), data curation (equal), methodology (equal), writing–review & editing (equal). **Stefano Tozza:** Conceptualization (equal), data curation (equal), methodology (equal), writing–review & editing (equal).

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Marco Luigetti https://orcid.org/0000-0001-7539-505X
Fiore Manganelli https://orcid.org/0000-0001-9478-3744
Marina Romozzi https://orcid.org/0000-0001-6016-3141
Mario Sabatelli https://orcid.org/0000-0001-6635-4985
Alessandro Salvalaggio https://orcid.org/0000-0002-1273-7566
Matteo Tagliapietra https://orcid.org/0000-0002-3048-1453
Stefano Tozza https://orcid.org/0000-0002-9672-4577

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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