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Alimentary Tract

Identification and management of gastrointestinal manifestations of hereditary transthyretin amyloidosis: Recommendations from an Italian group of experts

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ABSTRACT

Gastrointestinal manifestations are common across all hereditary transthyretin amyloidosis (ATTRv) genotypes. However, they are poorly specific, and their recognition as part of ATTRv is difficult, resulting in misdiagnosis with more common conditions. Moreover, delays in diagnosis occur because of fragmented knowledge, a shortage of centers of excellence and specialists dedicated to ATTRv management, and the scarce involvement of gastroenterologists in multidisciplinary teams. A group of Italian gastroenterologists with experience in the management of ATTRv took part in a project aimed at assessing the awareness of ATTRv among the community of Italian gastroenterologists through an online survey and providing education about practical aspects of ATTRv management. Survey results reported low participation, and very few patients with ATTRv were cared for by gastroenterologists. This highlights the need for greater attention to rare diseases in gastroenterology and emphasizes increasing awareness of ATTRv and diagnostic suspicion. Based on the experts' recommendations, a diagnosis of ATTRv should be suspected when at least one of the 'red flags' is detected. Subsequently, it is suggested to promptly ask for genetic testing and exclude a serum and urinary monoclonal protein, even before the detection of amyloid in biopsy samples, particularly in non-endemic areas.

1. Introduction

Hereditary transthyretin amyloidosis (ATTRv, variant) is a rare, rapidly progressive and fatal disease caused by pathogenic variants in the *TTR* gene, which are transmitted in an autosomal dominant manner [1,2]. ATTRv is characterized by the accumulation of amyloid fibrils in the extracellular milieu of different organs, mainly peripheral nerves, heart, kidney, eye and gastrointestinal (GI) tract, which progressively undergo impairment of functionality [3,4]. ATTRv has been increasingly reported worldwide, with a cumulative estimated number of patients of 10,186 (range: 5526-38,468) updated in 2018 [5]. The prevalence of ATTRv in Europe is 0.052

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per 10,000, with an incidence of 0.003 cases per 10,000/year [6]. Italy represents a non-endemic area for ATTRv with a prevalence of 4.3 per million, with quite variable regional differences [7,8]. The mean age of ATTRv onset in Italy is relatively high (59 years), with only 20 % of patients showing an early onset [7].

Although ATTRv has long been defined as an untreatable disease, in recent years, the therapeutic scenario has changed significantly due to the availability of drugs able to target key molecular events in the process of amyloidogenesis [9–13]. In light of these developments, the correct and timely diagnosis of ATTRv plays a central role in setting up effective therapy, increasing the patient's survival and quality of life, and offering adequate genetic counseling to family members at risk [14,15].

Phenotypes associated with ATTRv can be extremely heterogeneous since the presentation can be predominantly neurologic, predominantly cardiac, or a mix of both depending on the *TTR* variant and other, yet unknown, factors [16]. In most cases, the involvement is often multisystemic [17–20]. In this context, GI manifestations are quite common across all ATTRv genotypes and are most common in patients with neuropathic amyloidosis, in particular those with Val30Met, Glu89Gln, Glu54Gln and Gly47Glu *TTR* mutations [6,21]. In a cross-sectional study from the Transthyretin Amyloidosis Outcomes Survey (THAOS) registry, between 56 and 69 % of patients reported GI disturbances, depending on *TTR* mutation [22]. More recently, results from one single-center Italian study involving patients with ATTRv reported that the prevalence of GI symptoms was 82 % [23].

GI disturbances can present even before the onset of polyneuropathy and are associated with significantly reducing the quality of life [22]. The GI disease course is highly variable, and clinical signs and symptoms are not necessarily related to genotypes and geographic area of origin [24,25].

GI manifestations are poorly specific, and their recognition as part of ATTRv may be difficult, resulting in misdiagnosis with more common conditions with higher epidemiological relevance, such as irritable bowel syndrome (IBS) and functional dyspepsia [26,27]. Moreover, delays in diagnosis may occur because of fragmented knowledge, a shortage of centers of excellence and specialists dedicated to ATTRv disease management, and the scarce involvement of gastroenterologists in multidisciplinary teams [28].

Identification of systemic red flags along with GI disturbances might alert the gastroenterologist to start a diagnostic work-up to confirm or rule out ATTRv. Consequently, promoting awareness among gastroenterologists represents an unmet need to improve patient management, especially in non-endemic areas.

To address these issues, a group of Italian gastroenterologists coordinated by two clinicians with experience in the management of ATTRv took part in a project aimed at assessing the awareness of ATTRv among the community of Italian gastroenterologists and providing education about practical aspects of ATTRv management. This paper discusses the results of this activity, providing practical recommendations on the correct pathway for patient identification, diagnosis and management of GI involvement to improve clinical practice from the gastroenterologist perspective.

2. Methods

A working group composed of two Coordinators with proven expertise in the management of patients with ATTRv and seven Italian gastroenterologists uniformly distributed throughout the Italian territory (Lombardy, Piedmont, Veneto, Emilia Romagna, Tuscany, Lazio, Campania, Puglia, Sicily) took part in this project. All involved gastroenterologists had ≥5 years' clinical experience, relevant scientific publications in this field and were regularly involved in speaking activity at national/international congresses. In the first phase, an online survey was addressed to the Italian gastroenterologist community to assess the global and specific experience in ATTRv patient management. The survey was composed of 26 questions (Appendix I). It was shared through the AIGO (Italian Association of Gastroenterologists and Hospital Digestive Endoscopists) website, newsletter and dedicated emails between November 2022 and April 2023, accounting for about 1300 recipients.

In the second part of the project, the working group analyzed the survey results to define critical clues and provide possible recommendations to fill the emerging gaps. The discussion on key critical topics and practical recommendations was developed based on available literature and consensus among experts to provide educational support to gastroenterologists and healthcare providers operating in this setting.

3. Results

3.1. Awareness on ATTRv among Italian gastroenterologists: survey results

A total of 44 Italian gastroenterologists participated in the survey, most affiliated with university centers (n=26; 60%) and working in gastroenterology departments (n=37; 84%). Approximately half of these departments (n=24) manage about 100–500 patients per month, including patients with IBS, chronic inflammatory bowel diseases (a mean of 100 patients for both conditions), gastroesophageal reflux disease (GERD, a mean of 80 patients) and dyspepsia (a mean of 60 patients). Eleven departments reported to manage more than 500 patients per month.

57% of gastroenterologists (n=26) have experience in managing gastroparesis (<40 patients in 92% of cases), mostly patients with diabetic gastroparesis (reported by 36% of participants). 66% (n=29) of participants reported experience with chronic idiopathic constipation (<100 patients in 90% of cases) and 84% in managing patients with chronic idiopathic diarrhea (≤100 patients in 92% of cases). In the case of patients with unclear etiology related to the above-mentioned conditions, participants were asked if they investigated some systemic symptoms identified based on the literature as related to ATTRv. Among them, the clinical features investigated further were paresthesia/neuropathic pain in most cases (58%), followed by orthostatic hypotension/syncope (47%), asthenia (41%), balance and/or gait disturbances (36%) and dyspnea (25%).

The vast majority of participants were inexperienced in the management of patients with amyloidosis (n=35; 81%). Two Departments reported managing 10 patients with amyloidosis without further specification and two patients with wild-type ATTR amyloidosis; other departments reported managing at least one patient with localized gastrointestinal or secondary amyloidosis or light-chain (AL) amyloidosis, respectively.

In 57% of cases, patients were referred to the gastroenterologist by a neurologist and 15% by a cardiologist or a rheumatologist. In 15% of cases, the diagnosis was made directly in the gastroenterology Department.

Five participants (11%) reported experience in the management of ATTRv patients. The main gastroenterological symptoms reported by these participants and their frequency rates are shown in Table 1.

Diagnostic tests most frequently suggested to patients included colonoscopy and esophagogastroduodenoscopy in 80% of cases, blood chemistry and anorectal manometry in 40% of cases, gastric scintigraphy, defecography and CT colonoscopy in 20% of cases. The main prescribed treatments were prokinetics, antidiarrheals, probiotics (80% of cases for each treatment), antibiotics (60%) and laxatives (20%).

Table 1
Gastroenterological symptoms reported by participants with experience in managing patients with ATTRv ($n = 5$).

Symptoms	%
Chronic diarrhea	80
Unintentional weight loss	60
Early satiety	40
Vomiting	40
Chronic constipation	40
Alternation of constipation and diarrhea	20
Dysphagia	20

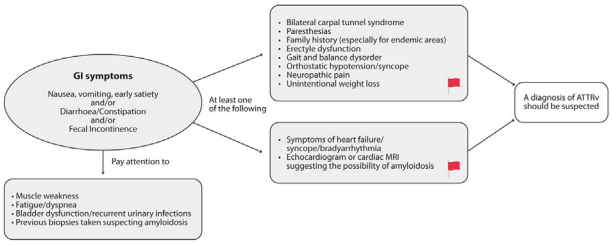

Fig. 1. Red flag symptom clusters suggestive of the diagnosis of ATTRv.

4. Experts recommendations

Based on the survey results, five topics were identified and further investigated through bibliographic research with an educational intent. Topics were: 1) 'red flags' from the gastroenterologist's perspective; 2) the gastroenterological work-up; 3) accuracy in diagnosis; 4) disease-modifying therapies for ATTRv management; and 5) ATTRv monitoring from the gastroenterologist's perspective.

4.1. "Red flags" from the gastroenterologist's perspective

GI symptoms of ATTRv can involve the upper and/or lower GI tract. Upper GI symptoms of gastroparesis, such as early satiety, postprandial fullness, nausea, and vomiting, are common in ATTRv patients due to delayed emptying of contents from the stomach into the small bowel [6]. Gastroparesis in ATTRv is generally attributed to autonomic dysfunction, but the efferent sympathetic and parasympathetic autonomic system's actual role is unclear [21]. Esophageal involvement in ATTRv can rarely lead to dysphagia, even though the prevalence ranges of esophageal involvement from 13% in a radiology study to 22% in an autopsy series, while isolated dysphagia is reported in a few case reports [29]. Indeed, amyloid deposition within the muscularis propria and submucosa could directly impact the Auerbach's and Meissner's plexuses throughout the GI tract, leading to various neurological presentations, such as a dilated and atonic esophagus with diminished peristalsis and narrowing, presenting as a clinical picture similar to achalasia.

Early manifestations of ATTRv may also involve the lower GI tract, presenting as either constipation, alternating constipation/diarrhea or diarrhea, particularly in patients with the early-onset V30M variant [6,22,30]. Diarrhea is the most frequently reported symptom, followed by unintentional weight loss and nausea; fecal incontinence is less frequently reported and mainly occurs in later stages [2,6,31,32]. Other GI disorders that may cause diarrhea, including celiac disease, microscopic colitis or exocrine pancreatic insufficiency, have never been associated with ATTRv to date [21].

Unintentional weight loss, malabsorption of fat and bile acids, and small bowel bacterial overgrowth (SIBO) have also been described in patients with ATTRv, as well as abdominal pain and bloating [31,33,34].

The wide spectrum of GI symptoms in ATTRv patients requires that all gastroenterologists be aware of this potential presentation alone or in combination with signs and symptoms of other organ involvement. Accordingly, some 'red flags' symptoms clusters suggestive for the diagnosis of ATTRv were defined by the working group (Fig. 1), namely: 1) the presence of chronic diarrhea/constipation and/or nausea, vomiting, early satiety (GI symptoms) in concomitance with at least one among bilateral carpal tunnel syndrome, paresthesia, erectile dysfunction, gait and balance disorder, orthostatic hypotension/syncope, neuropathic pain; 2) GI symptoms in concomitance with unintentional weight loss, also to distinguish a functional versus organic pathology; 3) GI complaints and symptoms of heart failure/syncope/bradyarrhythmia and an echocardiogram (i.e., increased left ventricular wall thickness, restrictive filling pattern, abnormal left and right ventricular longitudinal strain, and atrial septal thickening) or cardiac magnetic resonance (restrictive morphology, abnormal gadolinium kinetics, and extracellular volume expansion based on T1 mapping) imaging suggesting the possibility of amyloidosis; 4) GI symptoms and a familial history of ATTRv (especially if patient origin from an endemic area). In addition, in the presence of GI symptoms, gastroenterologists must pay attention to muscle weakness, fatigue/dyspnea, bladder dysfunction/recurrent urinary infections and previous biopsies suspecting amyloidosis.

4.2. The gastroenterological work-up

Investigations of upper and lower GI symptoms are recommended to provide diagnosis and to exclude other treatable and reversible diseases (differential diagnosis, further details in the next paragraphs). Examinations may include endoscopy with esophageal biopsies, and if gastroparesis is suspected, a scintigraphy study of gastric emptying can be performed. However, evidence on the role of these examinations in the context of ATTRv is limited [21]. In particular, macroscopic endoscopic findings are usually non-specific for ATTRv, including a fine granular appearance of the mucosa, which may appear as white/yellow elevated/depressed circular areas, and therefore not useful for a definitive diagnosis [35,36]. Anorectal functional disorders must be diagnosed with anorectal manometry, which has not been evaluated in ATTRv patients; thus, abnormal findings are not useful for ATTRv diagnosis [6].

4.3. Reaching an accurate diagnosis

The diagnosis of ATTRv has been traditionally based on the detection of amyloid in biopsy samples [1,37]. However, even if proof of amyloid in a tissue biopsy and typing of fibrils are still the gold standards for optimal diagnosis, it is well-recognized that sensitivity varies according to different biopsy sites (duodenum and the rectum have the highest diagnostic yield) and staining techniques [38]. Moreover, if biopsies are from the GI tract, submucosa should be reached to ensure the diagnosis of ATTRv, even if this procedure might increase the risk of bleeding. Lastly, the proper number of replicates necessary to validate the exam has not been fully elucidated [38].

Considering that correctly identifying the subtype of amyloidosis has important implications for guiding medical management and proper familial counseling, recent studies reported that genetic testing is key to confirming the presence or absence of a mutation in ATTRv and suggested that this test should not be omitted [39]. Indeed, a negative *TTR* gene test for an amyloidogenic variant eliminates a diagnosis of ATTRv. On these bases, it is now recommended to promptly ask for genetic testing and search for a serum and/or urinary monoclonal protein in parallel with the detection

of amyloid in biopsy samples, particularly in non-endemic areas [1,4] (see Supplementary Figure 1 for the suggested diagnostic algorithm).

Bone tracer scintigraphy is now widely accepted for the non-invasive diagnosis of ATTRv (Supplementary Table 1) [4,40]. Cardiac uptake of bone tracers, such as 99mTc-2,3-dicarboxypropane-1,1-diphosphonate (DPD), 99mTc–hydroxy methylene diphosphonate (HMDP) or technetium 99mTc pyrophosphate (PYP), is considered as a substitute for a positive cardiac biopsy [1]. According to the Gillmore criteria, excluding a monoclonal gammopathy by serum and urinary is mandatory to confirm the diagnosis of ATTRv. If the diagnosis of ATTRv is confirmed, *TTR* genotyping should be performed in all patients to differentiate between wild-type and ATTRv [40].

4.3.1. Differential diagnosis

Upper GI symptoms should be investigated to provide a differential diagnosis with other conditions, such as gastroesophageal reflux and functional and organic dyspepsia. In patients with chronic diarrhea/constipation or alternation of diarrhea and constipation, an accurate dietary and pharmacological history assessment is useful to rule out IBS, constipation or functional diarrhea [41,42]. Some blood chemistry tests (blood count, blood sugar, creatinine PCR, TSH, serological screening for celiac disease, calcemia and fecal calprotectin) are necessary to exclude an organic disease. In the presence of risk factors for organic pathology (age >50 years, family history of colorectal cancer or IBD, weight loss, anemia, etc.), colonoscopy is essential for differentiating ATTRv from colon cancer, colonic obstruction, proctitis and diverticulosis. A fecal calprotectin assessment can be performed if a patient presents with weight loss [43]. In the case of chronic constipation, hypothyroidism should also be taken into account, as well as diabetes mellitus and neurological diseases (e.g., multiple sclerosis, Parkinson's disease). Further, the possible side effects of the patient's medications should be considered [6]. If all those conditions are excluded, ATTRv should be taken into account.

Excluding light-chain (AL) amyloidosis, which is caused by misfolded light chains produced by a small, dangerous B-cell clone, is of fundamental importance since this condition represents a medical emergency and is often clinically indistinguishable from ATTRv on clinical grounds [44]. When a monoclonal protein is identified, amyloid typing by tissue biopsy becomes mandatory.

4.4. ATTRv management

4.4.1. Disease-modifying treatments

Delayed treatment is associated with an accumulating disease burden [45]. Thus, early intervention is fundamental to reducing the risk of developing a significant disability [46]. Increasing knowledge of the molecular mechanisms of the disease has allowed, over the past fifteen years, the progressive development of new targeted therapies [47]. Approved therapeutic strategies presently include gene-silencing agents that suppress hepatic TTR synthesis and TTR stabilizers that prevent the dissociation of circulating TTR tetramers. Moreover, novel therapeutic tools are under investigation to disrupt TTR fibrils [48]. Small interfering RNA (siRNA) or antisense oligonucleotide (ASO) technologies are highly effective in inhibiting liver expression of both mutant and wild-type TTR, significantly suppressing the concentration of the amyloidogenic precursor protein in plasma [47,49]. The siRNA patisiran, vutrisiran and the ASO inotersen have been approved for the treatment of patients with ATTRv polyneuropathy, regardless of the presence and severity of cardiomyopathy [50–52].

Available evidence from clinical trials shows that patients in treatment with patisiran and vutrisiran have a reduced burden of autonomic dysfunction and stabilization of nutritional status, suggesting an effect of these treatments on the gastrointestinal autonomic function [51–53]. In particular, in patients treated with patisiran in the APOLLO phase III trial, the modified body mass index (mBMI) was significantly improved after 18 months compared with placebo-treated patients, with an LS mean difference of + 115.7 (95% CI: −82.4–149.0), as well as GI symptoms within the GI domain of the COMPASS-31 (−0.8) [51].

For instance, a novel ASO formulation, eplontersen, is under investigation in patients with ATTRv polyneuropathy and cardiomyopathy.

Table 2
Symptomatic treatment of gastrointestinal manifestations of transthyretin amyloidosis.

Symptoms	Treatment options
Upper gastrointestinal symptoms	Metoclopramide Domperidone Motilin receptor agonists (e.g., erythromycin, clarithromycin) Proton-pump inhibitors Levosulpiride Clebopride Prucalopride Ondansetron*
Diarrhea	Loperamide Racecadotril Cholestyramine + fat-reduced diet Antibiotics (rifaximine or ciprofloxacin/ norfloxacin or metronidazole/tinidazole) Octreotide Eluxadoline**
Constipation	Increased fiber intake and bulking agents Polyethylene glycol Sodium picosulphate Bisacodyl Lactulose Lubiprostone Linaclotide Prucalopride Enemas
Malabsorption and Weight loss	Vitamin A, D, E, K supplementation Calcium and magnesium supplementation Vitamin B12 supplementation Infusion of human albumin Enteral or parenteral nutrition Guidance from an experienced Dietician

* This drug can be used for the management of diarrhea.
** Not available in Italy.

4.4.2. Supportive measures

Treatment of GI symptoms should aim to relieve the disease burden and slow down the progression of GI dysfunction to preserve nutritional status and quality of life. Overall, GI symptoms can be difficult to control, requiring a personalized therapeutic approach that should involve a gradual intervention. Table 2 summarizes the conventional symptomatic supportive measures for upper and lower GI disturbances that can be suggested for managing GI symptoms in ATTRv patients. Nausea and vomiting can be managed mainly with prokinetics; non-pharmacological agents have no demonstrated efficacy in amyloidosis [54,55]. The initial treatment of diarrhea is generally with the opioid-receptor agonist loperamide or with racecadotril, a peripheral enkephalinase inhibitor. If SIBO is suspected or diagnosed, antibiotics can be used intermittently or continuously. In most cases with constipation, dietary changes with increased fiber intake and bulking agents are first-line interventions; however, this may not be sufficient for patients with ATTRv, and pharmacological interventions should be planned. Supplementation is essential if a patient presents with malabsorption and weight loss, preferably early after the onset of diarrhea.

4.5. ATTRv monitoring from the gastroenterologist's perspective

Periodic assessment of the ATTRv disease course is mandatory to adjust therapy, delay clinical deterioration and preserve the patient's quality of life (QoL). The frequency of assessments needs to be adapted to the disease course and the severity and response to treatment. In general, monitoring should be done every 6–12 months. It should comprise blood chemistry tests, BMI evaluation, questionnaires and instrumental tests, always in the context of a neurological and cardiologic re-evaluation.

Nutritional status and patients' reported symptoms represent useful tools to assess and monitor GI involvement in ATTRv [25,45]. Different questionnaires developed for assessing upper GI symptoms, i.e., the Patient Assessment of Gastrointestinal Disorders Symptom Severity Index (PAGI-SYM) and Gastroparesis Cardinal Symptom Index (GCSI), have not been validated in ATTRv [21]. Thus, the compound autonomic dysfunction test (CADT), which scores upper and lower GI symptoms according to their frequency, has been proposed in ATTRv [33]. The Composite Autonomic Symptom Score (COMPASS)-31, composed of 101 items, proved useful for monitoring longitudinally GI manifestations in combination with other autonomic domains in recent trials, such as the registration trial for the siRNA patisiran [11] and vutrisiran [52].

Considering that weight loss is a common symptom of ATTRv amyloidosis, the mBMI, in which the BMI (kg/m^2) is multiplied with serum albumin (g/L) to compensate for edema, can be used to assess the nutritional status and as an indirect evaluation of the GI dysautonomia. mBMI values below 750 $kg/m^2g/L$ are considered underweight, and values below 600 $kg/m^2g/L$ suggest severe malnutrition [22]. The product of serum albumin (g/L) and mBMI has been proven useful in measuring disease progression and as a predictor of survival [6]. The mBMI has been shown to correlate with neurological function, including familial amyloid polyneuropathy (FAP) stages and duration of gastrointestinal manifestations [21]. In clinical trials for ATTRv, preservation of mBMI was closely associated with neurological response and improvement in quality of life [21,52].

5. Concluding remarks

With regard to the Italian scenario, 31 different mutations responsible for ATTRv were recorded in a recent epidemiological study and among them, Ile68Leu, Phe64Leu, Val30Met and Glu89Gln were the most reported [7]. In particular, the Val30Met variant was the most common in northern and central Italy, carried by almost one-quarter of patients [7,56]. Otherwise, in southern Italy, Glu89Gln, Phe64Leu were the most frequently reported variants, manifesting with different characteristics with respect to age of onset, phenotype and severity of the disease [7,57]. This significant genotypic heterogeneity is associated with a great variety of presentations, which made ATTRv diagnosis a real challenge in Italy, as in other non-endemic areas.

In this heterogeneous context, GI manifestations are very common and increase with disease duration, negatively impacting nutritional status and patients' survival [6,58]. Thus, gastroenterologists can play a valuable role in the early identification of at-risk patients and the timely management of gastrointestinal symptoms through specific interventions with approved disease-modifying therapies [11,20]. Despite this evidence, a scarce involvement of gastroenterologists in multidisciplinary teams is reported.

In the first phase of this project, an online survey was addressed to the Italian gastroenterologist community to assess the global and specific experience in ATTRv patient management. Obtained results reported low participation in the survey and a very small number of patients with ATTRv cared for by gastroenterologists. This highlights the need for greater attention to rare diseases in gastroenterology and emphasizes the need to implement training programs in this field by scientific societies to increase awareness of ATTRv and diagnostic suspicion. At the same time, a lack of attention from the specialists traditionally considered as a reference for this pathology (e.g., neurologists and cardiologists) towards gastroenterological problems can be suggested. This further highlights the multidisciplinary team's fundamental role in improving the diagnosis of ATTRv and patient management.

Based on the experts' recommendations, a diagnosis of ATTRv should be suspected when at least one of the 'red flags' is detected (Fig. 1). Subsequently, for a definitive diagnosis of ATTRv, it is suggested to promptly ask for genetic testing and exclude a serum and urinary monoclonal protein, even before the detection of amyloid in biopsy samples, in particular in non-endemic areas. This suggested diagnostic approach may overcome the difficulties of biopsy sampling and other invasive diagnostic tests and represents a new opportunity to increase ATTRv diagnosis, which in turn can provide additional reliable data regarding new diagnostic features and peculiar characteristics of this condition.

Conflict of interest

M.C. has served as an invited speaker and advisory board member for Alnylam, Takeda, Janssen, Biogen, Pfizer, and Galapagos.

L.O. has received consultation and speaker fees from Alnylam, Pfizer, Astra Zeneca, Novo Nordisk, BridgeBio and SOBI; M.B. has served as an invited speaker for Aboca, Alnylam, Alfasigma, Diadema, Agave, GE Healthcare.

Author contribution

Maria Cappello: Conceptualization, Methodology, Validation, Writing – original draft, Writing – review & editing. **Giovanni Barbara:** Validation, Writing – review & editing. **Massimo Bellini:** Validation, Writing – review & editing. **Danilo Consalvo:** Validation, Writing – review & editing. **Antonio Di Sabatino:** Validation, Writing – review & editing. **Giovanni Marasco:** Validation, Writing – review & editing. **Mariabeatrice Principi:** Validation, Writing – review & editing. **Edoardo Vincenzo Savarino:** Validation, Writing – review & editing. **Annalisa Tortora:** Validation, Writing – review & editing. **Laura Obici:** Conceptualization, Methodology, Validation, Writing – original draft, Writing – review & editing.

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Supplementary materials

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