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Short communication

Prevalence of transthyretin-related amyloidosis in Tuscany: Data from the regional population-based registry

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ABSTRACT

The limited available data regarding the prevalence of transthyretin amyloidosis, both for wild-type (ATTRwt) and hereditary form (ATTRv), is inferred from highly selected patients and subsequent extrapolations that limit the comprehension of the clinical disease impact. The Tuscan healthcare system in 2006 developed a web-based rare disease registry, to monitor and profile patients affected by rare diseases.

Clinicians belonging to regional validated healthcare data centres can register patients at the diagnosis, with a rigorous approach and distinguishing the types of amyloidosis, i.e., ATTRwt versus ATTRv. Thanks to this data collection method, available from July 2006 and extended with electronic therapy plans related to a diagnosis since May 2017, we analysed prevalence and incidence of ATTR and its subtypes. On November 30th 2022, ATTRwt prevalence in Tuscany is 90.3 per 1,000,000 persons and ATTRv prevalence is 9.5 per 1,000,000 persons, whereas the annual incidence ranges from 14.4 to 26.7 per 1,000,000 persons and from 0.8 to 2.7 per 1,000,000 persons, respectively. The male gender is predominant in both forms. All except one patient showed evidence of cardiomyopathy. This epidemiological data requires attention, not only to increase the effort for the clinical management and earlier diagnosis, but also to underline the need for the disease-specific treatments.

Transthyretin amyloidosis (ATTR) foresees in its natural history a high prevalence of cardiac involvement due to the extracellular myocardial deposition of insoluble transthyretin (TTR) amyloid fibrils (variant or wild-type) [1]. The belief that cardiac injury in ATTR is progressive and life-threatening has pushed to achieve an early diagnosis [2], refining the non-invasive diagnostic techniques, and studying

Abbreviations: AL, light-chain; ATTR, transthyretin cardiac amyloidosis; TTR, transthyretin; ATTRv, variant ATTR; ATTRwt, wild-type ATTR.

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specific disease-modifying therapies. The incidence of wild-type ATTR (ATTRwt) has increased over the years, due to progressive aging of the population, improvement of diagnostic capabilities and increased disease awareness. As a result, it is no longer perceived as a rare entity in the general population [3]. Variant ATTR (ATTRv), inherited in an autosomal-dominant manner, can be caused by more than 130 different mutations in the TTR gene, and its incidence/prevalence and tissue expression are largely variable among different countries and even in different regions of non-endemic areas [4], such as Italy. Available data is mostly drawn from insurance claims or registries and present relevant limitations. For example, patients are usually tagged using generic codes, which do not differentiate between ATTRwt, ATTRv and AL amyloidosis. Thus, while the epidemiology of AL amyloidosis in the general population is established and comparable in cohorts across different countries [5,6], the actual incidence and overall prevalence of ATTRwt and ATTRv is still unknown [3,7].

In the present work, we report data from the Tuscany registry of rare diseases, a web-based registry created and supervised by the regional healthcare service, in which clinicians in different hospitals across the Tuscany region are requested to insert data regarding patients diagnosed with ATTR.

Methods

Since July 2006 the Tuscan health care system has developed a web-based rare disease registry, to monitor and profile patients affected by rare diseases (https://malattierare.toscana.it/dati-statistici/registro-toscano-malattie-rare/), for all rare diseases (RDs) in Italian ministerial decree attachments since 2001 until 2017, including amyloidosis; the registry is managed by FTGM (Fondazione Toscana Gabriele Monasterio for medical and public health research in Pisa). This web-based registration by selected and trained regional validated healthcare data centres is mandatory to: 1) certify to the National health care system that a patient is affected by a rare condition (after a conclusive diagnosis of ATTR achieved according to the current shared diagnostic flow-chart [8], 2) obtain a co-payment exemption for health care expenses, and 3) generate a therapeutic plan for prescription of available disease-modifying drugs. This registry is only accessible based on specific areas of expertise; specifically, for amyloidosis, only specialized Centres are authorized to enter patients. Therefore, the registry represents an ideal platform to obtain data on the prevalence of amyloidosis in the Tuscany region, which had a population of 3,676,000 inhabitants (of whom 1,903,000 women), at last census in 2021.

On November 30th 2022, all living patients diagnosed with ATTRwt and ATTRv were extracted from the Tuscan rare diseases registry. After excluding patients with a residence outside the Tuscany region, prevalence data were calculated according to the Tuscany population certified by the National Institute of statistics (Istituto Nazionale di Statistica; ISTAT, http://dati.istat.it/index.aspx?queryid=18561). Incidence data were extracted for the last 5 years. The following parameters were recorded: gender, age at diagnosis, mutation of ATTRv, ongoing therapy with disease-modifying drug. In addition, for the extracted list of patients, medical records were checked to assess their cardiac manifestations.

Results

From July 2006 to November 2022, 367 alive patients with ATTR had been registered in Tuscany, including 332 with ATTRwt and 35 patients with ATTRv. This translates into an estimated prevalence of 90.3 per 1,000,000 for ATTRwt and 9.5 per 1,000,000 for ATTRv. The annual incidence ranged from 14.4 to 26.7 per 1,000,000 for ATTRwt and from 0.8 to 2.7 per 1,000,000 for ATTRv. Mean age at diagnosis of the 367 patients was 74 years. Two-thirds of patients with ATTRwt were in the 80–99 year age-range, while the other third was in the 60–79 range. Conversely, age of patients with ATTRv ranged from 40 to 87 years. There was a clear male preponderance for both types of ATTR (293 of 332, 88%, among ATTRwt patients, and 25 of 35, 71%, among ATTRv). The prevalence of ATTR was higher among men compared with women (ATTRwt: 172.3 vs 20.5 per 1,000,000; ATTRv: 11.1 vs 7.9 per 1,000,000).

In ATTRv patients, different mutations have been identified: 23 Ile68Leu, 4 Val122Ile, 1 Glu89Gln, 1 Glu74Gln, 1 Val30Met, 1 Glu54lys, 2 Phe64Ile, 2 Phe64Leu.

All patients with ATTRwt achieved a conclusive diagnosis based on cardiac manifestations; among the 35 patients with ATTRv, 27 had evidence of isolated cardiomyopathy, 7 had a mixed phenotype with both neuropathy and cardiomyopathy, and only one had isolated neuropathy (Glu54Lys). Fig. 1 shows the geographical distribution of the Tuscan cities involved in the management of patients with ATTR. Notably, there was a progressive increase in the number of diagnoses over the years (Fig. 2), and a corresponding increase in the prescription of dedicated therapies. Overall, 93 of the 332 ATTRwt (28%) patients were on tafamidis 61 mg, while among the 35 ATTRv patients 13 (37%) were on tafamidis 61 mg, 1 (2.8%) was on tafamidis 20 mg and 7 (20%) were on patisiran.

Discussion

The prevalence of ATTRwt and ATTRv in Tuscany is 90.3 and 9.5 per million respectively, with an annual incidence ranging from 14.4 to 26.7 and from 0.8 to 2.7 per million respectively, an increasing trend in diagnoses during the recent years. This data likely results from a greater awareness in the clinical community, an organized regional network with 2 Referral Centres in Florence and Pisa, favouring early and comprehensive diagnostic process, allowing rapid ATTR diagnoses, as well as an increased availability of advanced imaging techniques and genetic testing which are increasingly prescribed in the older strata of the population. Notably, two-thirds of patients with ATTRwt were in the 80–99 years as age-range.

Overall, our results are in line with previous reports, despite the different time frame of evaluation and study methodology [4,9], and are consistent with the emerging perception of ATTR as less uncommon than previously believed. Although the research on Scandinavian population revealed a comparable prevalence of ATTR with a steep increase over time [9], it did not distinguish between ATTRwt and ATTRv, and considered only patients with cardiomyopathy identified using a combination of diagnosis codes. Instead, the Tuscany Registry was established to gather epidemiological information discriminating between ATTRwt and ATTRv, enabling the display of data that is consistent with the growing perspective of ATTR that appears to be less rare than previously thought. Despite that, it must be considered that, even with the most accurate reporting, epidemiological evaluations still underestimate the likely true prevalence of the disease, given its subtle onset and peculiar age range of patients. Indeed, the main limitation of this study is the potential for underreporting due to a lack of definitive diagnosis in very old and/or fragile patients, missed referral or incomplete diagnosis. With these biases overcome, and with the expected ascending trend in diagnoses, the present estimates may need to be revised, with potential impact of the allocation of resources for treatment of ATTR. In our population, only one-third of our ATTRwt patients received tafamidis according to our Registry. The substantial proportion of untreated patients reflects several factors: 1) tafamidis 61 mg is reimbursable in Italy only for subjects in NYHA class I-II, while, according to the ATTRACT study, one-third are already in NYHA class III at initial diagnosis [10], 2) the exclusion of multi-comorbid patients with reduced life expectancy (conflicting with the late onset of tafamidis-related benefit), and 3) the enrolment of patients in ongoing trials with other disease-modifying drugs for ATTR.

In conclusion, by exploiting systematic reporting in a regional healthcare registry, we observed an increasing trend in the reporting of ATTR in the community during the recent years, with an overall

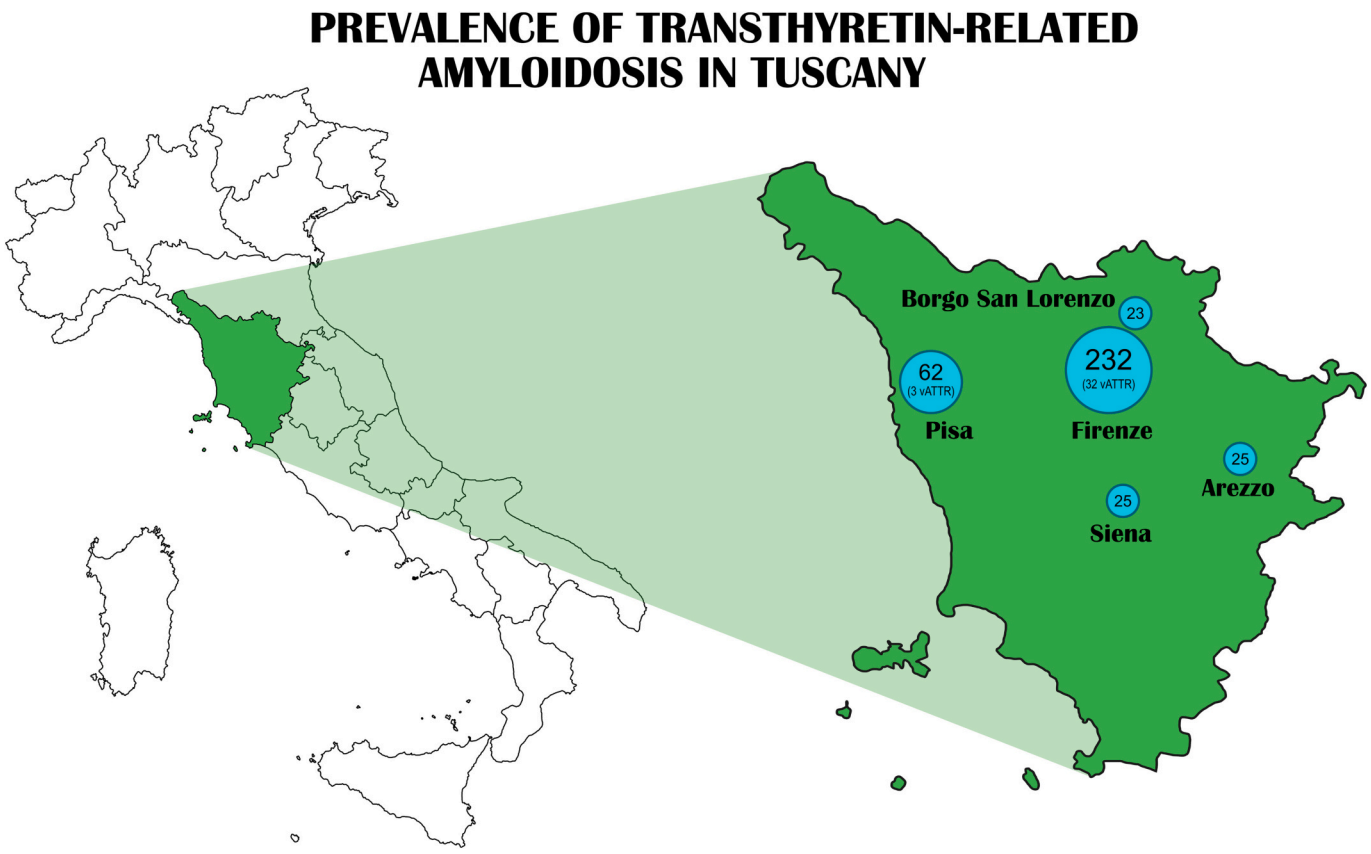

Fig. 1. Geographical distribution in Tuscany region of the centres involved in the management of patients with transthyretin-related amyloidosis and related numbers of alive patients regularly followed. Numbers in brackets indicate the subset of patients with the hereditary form.

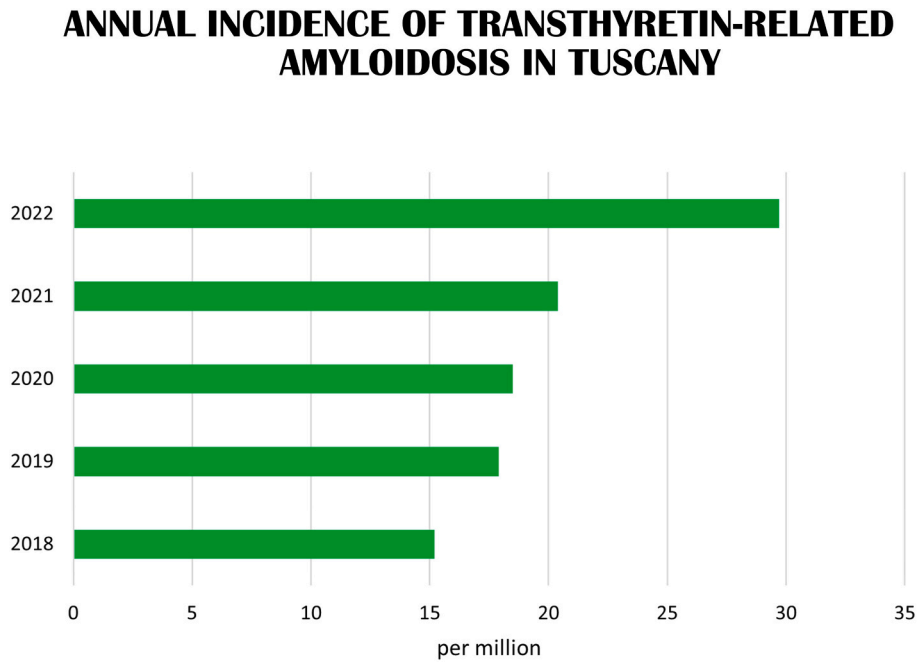

Fig. 2. Annual incidence of transthyretin-related amyloidosis in Tuscany region, for the period from 2018 to 2022.

prevalence of ATTRwt and ATTRv in Tuscany that is 90.3 and 9.5 per million respectively. As previously reported, ATTRv in Tuscany often presents a prevalent cardiac phenotype due to the high prevalence of Ile68leu and val122ile, with a recently proven founder effect for the latter [11–13].

Disclosures

Iacopo Olivotto: Advisory board and research grants from: Bristol Myers Squibb, Cytokinetics, Boston Scientific, Sanofi Genzyme, Amicus, Menarini International, Bayer, Tenaya, Rocket Pharma.

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