

Promoting Diagnosis and management of AL in Italy.

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AL amyloidosis (AL) is a rare, severe protein conformational disease caused by misfolding and extracellular deposition of patients-specific monoclonal immunoglobulin light chains in form of amyloid fibrils. This process can target all tissues and lead to potentially fatal organ dysfunction.

In most cases, AL amyloidosis is diagnosed late, when advanced organ involvement limits therapeutic options and is associated with poor prognosis. Thus, efforts to promote early diagnosis are urgently needed. A clinically silent monoclonal gammopathy invariably precedes the onset of symptomatic AL by several years. Yet, AL is often diagnosed late also in patients with known monoclonal gammopathy under hematologic follow-up. A screening of at-risk patients with biomarkers of early amyloid organ involvement has been advocated, but not largely implemented. Also, the diagnosis and management of AL patients requires access to sophisticated technologies and expertise available at large tertiary Amyloid Centers. Yet, new models of patients' care are required to intercept those patients who cannot travel to distant, tertiary centers, to provide state-of-the-art care to all and to be able to analyze and describe the natural history of the disease in a contemporary, real-world setting.

New molecular features associated with the propensity of a light chain to form amyloid are emerging, but their potential clinical utility is unknown.

Building on the >30yrs-experience of the Italian Referral Center for Systemic Amyloidoses and leveraging on an already existing disease registry and on a one-of-a kind biorepository of clinically annotated biological samples, we plan to extend the activity of the Italian Amyloidosis Network, through the involvement different Italian Hematology Departments and implement the connection with European collaborators, that already participated in previous joint projects. We aim to establish a structured program of patients' referral (from the Italian Units) and sample/data transfer (from the whole international network).

In the frame of this project, the PhD student will collaborate directly in the management of the national and international networks and will be directly involved in the subsequent data-analysis.

In particular, we plan to:

- 1) Verify the feasibility and efficacy of an active surveillance of early signs of amyloid organ involvement in patients with monoclonal gammopathy of undetermined significance using biomarkers;
- 2) improve patients' referral and increment the inclusion of real-world cases of AL amyloidosis in the Pavia disease registry and linked biobank, as well as accelerate patients' enrollment in other already approved and funded pre-clinical and clinical studies on AL, covering basic disease mechanisms, as well as new diagnostic/therapeutic approaches;
- 3) exploit the large prospective real-life registry in order to establish validated progression criteria for AL amyloidosis and evaluate new possible molecular tools for response assessment.

Promising preliminary data support the rationale of the study, including:

- the implementation of the biomarker-based screening of at-risk subject at the local Hematology Dpt. in Pavia, which enabled the identification of early-stage AL cases with excellent outcomes;
- the establishment of a high-throughput methodology to sequence clonal light chains from large numbers of cases in parallel, facilitating light chain profiling studies;
- prospectively collect data regarding the applicability of minimal residual disease assessment by next generation flow cytometry.

References:

1. Merlini G et al. Hematology ASH Educ Program. 2012;
2. Palladini G et al. Blood 2020;
3. Palladini G et al. Blood Cancer Journal 2021.