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Commentary

DUAL expectations in light chain amyloidosis

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D'Souza and coworkers report their results of the phase II DUAL trial, evaluating the effectiveness of doxycycline combined with chemotherapy for one year in newly diagnosed patients with light chain (AL) amyloidosis [1].

Studies of tetracycline in amyloidosis stemmed from the serendipitous observation of rapid amyloid deposits regression in a patient with AL amyloidosis who received 4′-iodo-4′-deoxy-doxorubicin (IDOX)-based chemotherapy. However, prolonged administration of IDOX was unfeasible and subsequent studies focused on doxycycline, a safe antibiotic, structurally resembling IDOX. Preclinical studies showed that doxycycline reduces amyloid fibrils formation and deposits [2]. This seems associated with reduced metalloproteinase activity [3]. In a *Caenorhabditis elegans* model doxycycline counteracts the toxic effect of light chains (LC) from patients with cardiac AL amyloidosis, alone and synergistically with metal ions chelators [4,5]. A retrospective case-control clinical study showed that patients with cardiac AL amyloidosis receiving doxycycline as antibiotic prophylaxis during chemotherapy have lower early mortality, allowing higher response rates and translating in extended survival [6].

This paper reports the first prospective trial evaluating doxycycline in combination with bortezomib-based chemotherapy in 25 patients with newly diagnosed systemic AL amyloidosis. Heart was involved in 56% of cases (Mayo stage 3 24% and 4 28%). Treatment was well tolerated with few adverse events. The colleagues confirm the low mortality rate with 80% 12-months overall survival. During the study period, almost 2/3 of patients were able to receive high dose melphalan and autologous stem cell transplant after induction therapy. Interestingly, no deaths were observed within 100 days from high dose treatment. Moreover, this study provides a clinical correlation between stage of disease, treatment with doxycycline and metalloproteinase activity.

There is still an urgent need of new therapeutic strategies in AL amyloidosis, that could enhance the effectiveness of standard anti-plasma cell treatment and major efforts have been pushed in development of anti-amyloid drugs. Phase I/II trials of NEOD001, a monoclonal antibody (mAb) that binds misfolded LCs, in previously treated patients with AL amyloidosis gave promising results [7]. However, two clinical trials failed to demonstrate a better outcome. Another study evaluated an anti-serum amyloid P component (SAP) mAb combined with a small molecule, (R)−1− [6− [(R)−2−carboxy−pyrrolidin−1−yl]−6−oxo−hexanoyl]pyrrolidine−2−carboxylic acid (CPHPC), designed to bind SAP in serum, while anti-SAP mAb targeted the deposits, enhancing their clearance. Despite a favorable phase Ia/Ib trial [8], a phase II study was terminated early due to changes in risks/benefits profile [9]. Currently, the only anti-amyloid mAb that is still in evaluation is 11-1F4, which binds a conformational epitope of amyloidogenic proteins and that has shown interesting results in patients with relapsed/refractory AL amyloidosis [10]. This novel antibody will be soon evaluated in a controlled study in newly-diagnosed patients. Failure of randomized trials based on positive phase I/II studies emphasizes the need of caution when evaluating uncontrolled studies such as the present one.

Nevertheless, there are no other confirmed positive results about the use of small molecules in AL amyloidosis, and the presented data open a new perspective on the potential benefit of doxycycline in this rare and dreadful disease. Doxycycline is a marketed, cheap drug, which would make the costs of treatment more affordable. Moreover, being an oral medication, doxycycline is easier to administer than mAbs.

However, as the authors state, their results need a confirmation from a large, controlled and more complex study. Although the reported data are quite promising, the small sample size and absence of a control arm does not allow a clear confirmation of the benefit of doxycycline. Moreover, the primary endpoint was changed from organ response to one-year mortality during the study. Larger, independent randomized clinical trials are not always easy to design in rare diseases as AL amyloidosis. This is even harder when the evaluated drug is a low-priced molecule. However, a further insight of the effectiveness of the combination of bortezomib-based chemotherapy and doxycycline will come from an ongoing prospective, international, randomized trial (NCT03474458). Only patients with newly diagnosed stage II/IIIa cardiac AL amyloidosis are enrolled and primary endpoint is one-year survival. One-hundred-twenty patients will be enrolled to detect an expected 23% improvement in 1-year survival. The exclusion of patients without heart involvement, that is the main prognostic factor and putative target of doxycycline, will

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avoid a potential bias in early-mortality assessment. Hopefully, the results from this large study will further define the role and the benefit of this small molecule in the management of AL amyloidosis.

In the meantime, we are thankful to our colleagues to have shared with the scientific community these important data, that increase our expectations on novel strategies of treatment in AL amyloidosis.

Declaration of Competing Interest

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