Brief Report

Doxycycline and Ursodiol for ATTR Amyloidosis: Not Ready for Prime Time

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In this issue of *Journal of Cardiac Failure*, Karlstedt et al describe a study of 53 patients with ATTR cardiac amyloidosis (ATTR-CM) who were treated with a regimen of doxycycline and ursodiol.[1] The authors should be congratulated on reporting a relatively large single-institution experience, and their study represents an important addition to our current knowledge.

What can we conclude from this analysis? The clearest data—relatively consistent with previous reports—are on the tolerability of this combination therapy, demonstrating a dropout rate of 11% due to dermatologic and gastrointestinal side-effects. This is important information for counseling patients who are considering starting such therapy.

On the other hand, tremendous caution should be exercised in interpreting the efficacy data. The lack of a control arm in such a study is understandable, but it means that interpreting results, particularly for a disease with a great degree of heterogeneity in patient course to begin with, is almost hopelessly confounded in the absence of observing an overwhelming signal. Such a signal was not present in this study, with nonsignificant results across New York Heart Association class, troponin-T, N-terminal pro−B-type natriuretic peptide, and 16 different echocardiographic measures. Even parameters that trended toward benefit are confounded by the fact that 11% of patients died during the study; those patients could not have contributed to end-of-study follow-up data, which would likely have been negatively affected by their inclusion.

It is particularly statistically imprecise to retrospectively pick out the group who had improvements in LV global longitudinal strain (GLS), list a P value of $<.01$ for change in GLS in that group (which would almost have to be the case because only patients who had improvements were included), and note that biomarker improvement *almost* reached statistical significance ($P = .06$). Virtually by definition, in following a cohort of patients over time, outcomes will vary among the cohort; it stands to reason that if one picks only the group who happened to do better, other disease parameters will mirror those findings.

Fortunately, there is much reason for hope in the field of ATTR-CM independently from doxycycline and ursodiol (Table 1). In the rigorous phase 3 ATTR-ACT clinical trial, the transthyretin stabilizer tafamidis demonstrated a large treatment effect in patients with ATTR amyloid cardiomyopathy: improving survival, cardiovascular hospitalization rate, quality of life, and 6-minute walk time versus placebo, and with a completely benign safety profile.[2] Diflunisal slows ATTR polyneuropathy (PN) progression, although its use in ATTR-CM is limited because it is a nonsteroidal antiinflammatory drug.[3] Another stabilizer, AG-10, is even more potent than tafamidis in vitro and will likely enter a phase 3 trial later this year.[4] Patisiran and inotersen—which work by knocking down production of transthyretin—dramatically affect the course of ATTR-PN, with patisiran also showing promise in prespecified cardiac end points.[5−7] It is likely that both agents (or next-generation forms of both agents) will enter phase 3 trials for ATTR-CM in the coming year. Notably, given the high cost of patisiran and inotersen and the expected high cost of tafamidis pending its approval, cheaper agents such as doxycycline and ursodiol would be welcome additions to the therapeutic armamentarium if rigorous clinical trial evidence ultimately support their use.

So where does this leave us with doxycycline and ursodiol for ATTR-CM? We know from this and previous studies that the combination is not tolerated in ∼10% of patients. Major adverse events do not seem to be a large problem, though the effects of taking these 2 agents long term are not truly known, and therapy would presumably

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Table 1. Current Status of Transthyretin (TTR) Stabilizers and Knockdown Agents

Drug	Mechanism	Status
Tafamidis	TTR stabilizer	Positive phase 3 trial for ATTR-CM.[2] FDA approval likely in 2019.*
AG-10[4]	TTR stabilizer	Phase 2 trial completed for ATTR-CM. Phase 3 ATTR-CM trial likely in 2019.
Diflunisal	TTR stabilizer/NSAID	FDA-approved for arthritis pain (not ATTR amyloidosis). Randomized trial demonstrating efficacy for ATTR-PN.[3]
Patisiran	TTR knockdown	FDA-approved for ATTR-PN.[5] Promising cardiac subgroup data.[7] Phase 3 trial ATTR-CM likely in 2019.
Inotersen	TTR knockdown	FDA-approved for ATTR-PN.[6] Phase 3 ATTR-CM trial likely in 2019.

*PDUFA date scheduled for July 2019.

end up being lifelong. Some nonrandomized data for doxycycline show promise in light chain (AL) amyloidosis,[8] and a phase III randomized (but not placebo-controlled) study in ATTR-CM is currently being conducted and will likely ultimately tell the tale of the effectiveness of this regimen (NCT03481972).

Until then, abundant caution is urged; another agent affecting amyloid fibril formation and breakdown before (that arguably showed more promise than doxycycline and ursodiol in earlier after studies) failed when subjected to more rigorous clinical trial testing.[9,10] At the Stanford Amyloid Center, we do not regularly recommend doxycycline and ursodiol for amyloidosis unless a patient is enrolled in a study evaluating their use, though given the fairly benign safety profile, we do not strongly urge patients to come off of these agents if they have been previously started.

For ATTR-CM, though it may change if and when rigorous data support their use, doxycycline and ursodiol are simply not yet ready for prime time.

Disclosures

None.

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