



News and Stories - Summer 2023

Striving for Full Reabsorption in AL By: Giada Bianchi, MD

Patients with AL amyloidosis are faced with the challenge of having to endure treatment to achieve not one, but ultimately two remissions. The first goal in the care of the patients with AL amyloidosis is successful treatment of underlying hematologic disease driving the production of immunoglobulin free light chains (FLC). This is most commonly a form of plasma cell disorder. Complete or near complete eradication of the driving plasma cell disorder is necessary to: 1- mitigate organ damage directly mediated by freely circulating, amyloidogenic FLC; 2- stop progressive deposition of amyloid fibrils in target organs; and 3- maximize the chances that amyloid is reabsorbed, and tissue damage repaired. To our knowledge, plasma-cell targeting treatments exert no direct effect on the removal of deposited light chain amyloid fibrils. In fact, while it is indispensable for organ response, achievement of a hematologic remission is not sufficient to guarantee regain of organ function. In patients with advanced cardiac amyloidosis, lack of rapid and adequate cardiac response is the leading cause of mortality early in the phase of disease therapy, representing a major unmet need. There are currently no biomarkers to predict to what extent and how rapidly amyloid fibrils reabsorption will occur in patients in a hematologic remission from their AL amyloidosis. This notion is a source of significant distress as, our patients with advanced organ involvement cannot be assured that successful chemo-immunotherapy treatment will certainly translate in significant improvement in organ function and return to a quality of life comparable to prior to their diagnosis.



Studies have shown that neutrophils and macrophages (types of white blood cells) are capable of engulfing and degrading amyloid fibrils from target organs, confirming that the process of amyloid deposition is in fact reversible. However several factors contribute to the inefficient removal of AL amyloidosis: 1- continuous production of new amyloidogenic FLC pushes the equilibrium towards the ongoing formation of amyloid; 2- deposited fibrils facilitate rapid deposition of more amyloid fibrils by acting as a seed; 3- extracellular matrix macromolecules such as collagen and proteoglycans may

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What is a Recurring Donation?

Did you know? The Amyloidosis Foundation offers our donors the option to choose recurring donations (monthly, quarterly, semi-annually, and annually). Recurring giving feels more palatable than dropping a large sum all at once.

If you're the type of person who wants to donate but forgets to revisit the Amyloidosis Foundation semi-regularly, this is a convenient way to donate. It may also take the pressure off of your end-of-year giving. Small recurring donations can have just as much impact as a large, one-time donation!

Why Should I Do A Recurring Donation to Amyloidosis Foundation?

- Donations are tax-deductible
- It's easy and convenient
- Give the amount you want
- You can stay within your budget
- You can adjust your contribution or cancel at any time
- You provide a steady flow of income that we can count on



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Patient Resources

The foundation has several programs that benefit patients and their families. All of these are provided free of charge.

- Webinar recordings posted on our website
- Updated informational pamphlets
- Listing of experienced physicians that specialize in amyloidosis. Email us anytime with questions: info@amyloidosis.org
- Treatment Centers (US / International)
- Support Groups
- Newsletters
- Webinars
- Caregiver/Patient Binder
- Fundraising Toolkits

Our comprehensive website has information for patients, caregivers and physicians featuring:

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Support Group Meeting

On June 3, 2023, the Amyloidosis Foundation Support Group meeting was held in Nashville, TN. There were 29 amyloidosis patients, caregivers, and family members in attendance.

Gene from Prothena Biosciences presented on breaking down drug mechanics, clinical trials, and the process of drug development.

Drs Goodman and Hung helped to clarify the benefit of clinical trials in that they offer vital information in drug efficacy, safety, and dosing. Clinical trials also give the patients (that are randomized to receive the drug), the advantage of starting treatment before FDA approval.

The next meeting will be held on **Saturday, August 26, 2023 from 12:00 PM - 02:00 PM** at Connor's Steak & Seafood at Cool Springs Galleria (1916 Galleria Blvd Franklin, TN 37067).

Contact Adrienne Molteni to register:
adrienne.e.molteni@vumc.org

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Our newsletter is published quarterly (Spring, Summer, Fall and Winter) by the **Amyloidosis Foundation**. We welcome letters, articles and suggestions.

Please contact us anytime at: **info@amyloidosis.org**, **(248) 922-9610**
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Striving...

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protect fibrils from phagocytosis; 4- FLC is expected to behave as a self-antigen and therefore does not elicit an immune response. Altogether, these factors make amyloid reabsorption an incredibly inefficient process during the active phase of the hematologic disease. Normalization of circulating FLC ratio and suppression of production of new amyloidogenic FLC addresses the first issue, pushing the chemical balance towards reabsorption and there is growing interest in the targeting matrix proteins that protect amyloid fibrils from reabsorption.

Direct targeting of the amyloid fibril by agents that facilitate reabsorption has been long sought after. In preclinical studies, doxycycline was shown to exert anti-fibrillary activity across a spectrum of amyloid subtype, particularly transthyretin amyloidosis (ATTR), presumably by inhibiting unidentified molecules in the extracellular matrix. This led to the off-label use of doxycycline alongside plasma cell-directed therapy to aid in amyloid reabsorption. Recently, a phase III study showed lack of significant clinical benefit from doxycycline use in AL amyloidosis with cardiac involvement.

An increasing body of knowledge stemming from fundamental, basic science discoveries in the fields of amyloid chemistry, biophysics and biochemistry has fueled the development of monoclonal antibodies directed against amyloid components, so called anti-fibrillary antibodies. These agents recognize portion of amyloid fibrils either shared across distinct types of amyloidoses or instead specific to only certain subtypes. Once bound to the amyloid fibrils, the antifibrillary antibodies “flag” it for reabsorption by body scavenger cells (typically macrophages and neutrophils).

Seminal work from Pepys and colleagues resulted in the development of an IgG1 antibody binding serum amyloid P component (SAP), a normally folded plasma glycoprotein. SAP derives its name by its identification as a common constituent of amyloid, binding amyloid fibrils with high avidity independently on the nature of the amyloid precursor protein itself. In preclinical studies, SAP-targeting antibody dezamizumab led to clearance of hepatic and splenic AA amyloid deposits in mouse models. In a phase I study in patients with amyloidosis of any kind affecting liver or spleen, there were no obvious severe adverse events and a signal of potential efficacy emerged with decreased load of amyloid in a subset of patients. These results informed the design of larger studies enrolling patients with cardiac amyloidosis related to either ATTR (hereditary or WT) or AL amyloidosis. Disappointingly, this trial did not show convincing evidence of cardiac reabsorption of amyloid, raising concern about adequate delivery of the antibody in the heart. Instead, several patients experienced treatment-related vessel inflammation (so called vasculitis), presumably related to dezamizumab binding to SAP in the context of the wall of blood vessels. Based on safety concerns and lack of obvious clinical benefit, further development of this therapy was halted. Subsequent efforts have focused on using a similar strategy, but narrowing the target to antigens uniquely found in amyloid fibrils, in an effort to mitigate risk for side effects.

Birtamimimab is a humanized IgG1 antibody initially identified based on its specificity

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against the amyloidogenic component of serum amyloid A protein (SAA), the precursor protein of AA amyloidosis. However, it was later discovered that birtamimab avidly binds to both soluble and insoluble amyloid fibrils derived from both lambda and kappa free light chains. Birtamimab proved effective at clearing AL amyloid deposits in mouse models and entered clinical development as a single agent in a first in human, phase I/II study in AL amyloidosis patients in a hematologic remission but who had not yet achieved an organ remission. The drug was well tolerated and a signal for organ response prompted rapid advancement to randomized, placebo-controlled studies as single agent in patients with previously treated AL amyloidosis, or in combination with anti-plasma cell directed therapy in newly diagnosed AL amyloidosis patients. Unfortunately, these studies did not disclose any signal of enhanced amyloid reabsorption based on pre-set endpoints, leading to discontinuation of birtamimab clinical development. Nevertheless, an analysis suggested a significant improvement in overall survival in patients with advanced stage (Mayo stage IV) AL amyloidosis receiving birtamimab and a large, phase III, randomized, placebo control study is currently ongoing targeting this specific patient population.

The most recent antifibrillary antibody in advanced clinical trial for AL amyloidosis is anselamimab (CAEL-101). Anselamimab binds specifically to a stretch of amino acids exposed only by amyloidogenic, but not normally folded, lambda and kappa FLC. Similar to previously developed anti-fibrillary antibodies, anselamimab successfully cleared amyloid deposits in mouse models, leading to advancement to clinical studies. In a phase I study, single agent anselamimab was well tolerated in AL amyloidosis patients in a hematologic remission post plasma cell-directed therapy. There was a strong signal for cardiac response, although it could not be excluded that this was the result of spontaneous reabsorption of amyloid deposits in patients who had achieved a deep hematologic remission. Phase III, placebo-controlled, double blind studies are currently ongoing in newly diagnosed AL amyloidosis patients with stage IIIA or IIIB cardiac amyloidosis receiving frontline, plasma cell directed therapy with/without anselamimab. The amyloid community is eagerly awaiting the results of randomized clinical trials of anselamimab and birtamimab in newly diagnosed AL amyloidosis as accelerating amyloid reabsorption early in the phase of the disease is critical to maximize the chances of short- and long-term survival for patients.

Alongside efforts to use immunotherapy to accelerate amyloid reabsorption, ongoing work is focused on tackling amyloidogenic proteins before they are aggregated into amyloid deposits. For instance, the Kelly lab (Scripps, San Diego) has spearheaded efforts to identify drugs that can lock the FLC in a stable form, thus avoiding transition to an unstable, amyloid-prone conformation. This strategy is akin to tafamidis, a TTR stabilizer, now approved for the treatment of ATTR cardiomyopathy. Our own lab is instead focusing on earlier events in the FLC lifecycle, specifically the process by which FLC are secreted outside the plasma cells and into the blood stream. We are interested in understanding this fundamental mechanism in order to develop novel drugs that would inhibit FLC release.

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NEURO-TTRansform Phase III Results

The positive results that were presented in an Emerging Science Session at the American Academy of Neurology (AAN) 2023 Annual Meeting in Boston, Massachusetts demonstrate that eplontersen's efficacy, safety and administration profile may provide an important new option in amyloidosis, which has a significant unmet need.



At 66 weeks, patients treated with eplontersen demonstrated consistent and sustained benefit on the three co-primary endpoints of serum transthyretin (TTR) concentration, neuropathy impairment and quality of life (QoL). Eplontersen achieved a least squares (LS) mean reduction of 82% in TTR serum concentration from baseline, compared to an 11% reduction from baseline in the external placebo group ($p < 0.0001$).

Sami Khella, M.D., Chief, Department of Neurology at Penn Presbyterian Medical Center, Professor of Clinical Neurology at the Perelman School of Medicine at the University of Pennsylvania School of Medicine and a Principal Investigator on the NEURO-TTRansform trial, said: "In the past, patients with hereditary transthyretin amyloid polyneuropathy usually deteriorated given the limited available treatments. This new study shows eplontersen can halt progression of neuropathy and improve quality of life at 66 weeks when compared to placebo. Today's important results demonstrate that eplontersen has a consistent and sustained treatment effect and reinforces its potential as an important medicine for the thousands of patients living with this debilitating and fatal disease."

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Striving...

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We are witnessing unprecedented improvement in the quality and length of life of AL amyloidosis patients. As we strive to educate and raise awareness about this disease so that it is diagnosed earlier and earlier, we continue to benefit from therapeutic advancements in multiple myeloma, a plasma cell cancer that share a similar cell of origin to AL amyloidosis. This is an exciting time to think outside the box and focus on innovative therapeutic strategies that build on basic science to hit the Achilles' heel of AL amyloidosis and further improve the lives of our patients.

Dr. Bianchi is the Associate Director, Amyloidosis Program, Brigham and Women's Hospital/Dana Farber Cancer Institute, Boston, MA, Assistant Professor, Harvard Medical School, Boston, MA, and Associate Physician and Principal Investigator, Division of Hematology, Department of Medicine, Brigham and Women's Hospital, Boston, MA

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We Need YOU to Share Your Patient Story

How did it feel when you or a family member were first diagnosed with amyloidosis? What did you most want to hear about from another patient who was going through the same thing?

On our website and in past newsletters, we've shared many patient stories, about various types of amyloidosis.

Now we are asking you to be brave and show how you are managing your disease, what tips you have, how you keep track of symptoms, doctor appointments and more.



Show your support for others who are fighting this rare disease by writing your story, providing hope, encouragement and empathy.

Send your story and a couple of photos to: kathi@amyloidosis.org.

Feel free to call us with any questions—we look forward to hearing from you and know that other patients are waiting to read your story.

Office Phone: (248) 922-9610

Share Your Story

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VIRTUAL Run for Your Life!

Run, Walk, Roll or Bike at your leisure to help raise awareness of amyloidosis, in your local park, or your neighborhood. Encourage your family and friends to register and participate.

You can complete your run/walk/bike/roll anytime from now until July 31, 2023.

Registration is OPEN:
<https://bit.ly/Run23>
Send your pictures to kathi@amyloidosis.org

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may1 - july 31

Run - Walk - Roll - Bike

REGISTER TODAY!

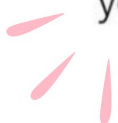


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