Externally Led Patient Focused Drug Development (EL-PFDD) Meeting Identifies Urgent Care Needs in Adults with X-linked Adrenoleukodystrophy

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Abstract/Purpose

Introduction
X-linked adrenoleukodystrophy (ALD) is a rare disorder caused by ABCD1 gene variants. ABCD1 encodes a peroxisomal half-transporter and the resulting faulty protein leads to accumulation of very long-chain fatty acids. This leads to progressive inflammatory demyelination of the brain in some patients but more commonly affects the adrenal gland, spinal cord and peripheral nerves. Phenotypes include adrenal insufficiency, childhood or adult cerebral ALD (cALD), and adrenomyeloneuropathy in men and women (AMN). The EL-PFDD meeting, led by ALD Connect, aimed to educate the U.S. FDA on the perspective of adults with ALD on the disease burden and unmet needs.
Method
The 254 attendees included people with ALD, caregivers, family members, clinicians, scientists and representatives from the FDA, industry and non-profit entities. Patients and caregivers contributed responses via online polling, phone calls, and email (N=40-60 per poll question).
Results
Respondents included adults with ALD (57%), caregivers (28%), and those representing both groups (15%). Most were from the US, Europe and Canada. Their ages ranged from 19-71 years or older, and 50% were female.
Adults with ALD struggle to obtain an accurate diagnosis. Until recently, women with ALD were mistakenly believed to be asymptomatic; they report feeling excluded from drug trials. ALD increasingly impacts the lives of patients and caregivers, resulting in psychosocial impacts and burnout.
Top ALD-related health concerns were those impacting walking, including balance (81%), gait (67%) and spasticity (67%) issues, followed by bowel and bladder incontinence (65%). Top worries were symptoms worsening (88%), losing the ability to walk (61%), developing cerebral ALD (39%), and falling (29%). Most reported that treatments are ineffective (69%).
Conclusion
We now have a deeper understanding of the unmet needs and severe disease burden impacting men and women with ALD and their families. Dissemination of these findings can promote future research and new product development for people living with ALD.

Background

- Adrenoleukodystrophy is a very heterogeneous disease
- There is an urgent need for U.S. FDA or EMA approved therapies for adult ALD (AMN and cALD)
- *It is critical to 1) understand the current unmet needs and disease burden of adult ALD patients and 2) continue efforts to capture outcomes that are sensitive to change and clinically meaningful to these patients*
- **Aim**: Revisit *the* Voice of the Patient Report from the Adult ALD Externally Led – Patient Focused Drug Development (EL-PFDD) Meeting held in 2022
  - Organized by ALD Connect
  - Adults with ALD (AMN and cALD) and caregivers shared their experiences with FDA staff and other stakeholders on challenges and treatment needs

Method

Session 1 - Living with ALD

Pre-recorded patient conversations representing a range of individuals living with different adult manifestations of ALD

Online polling, dial-in calls, online portal

Session 2 - Approaches to Treatments for ALD/AMN

Pre-recorded patient panel describing medical therapies and approaches used to address ALD symptoms and hopes for future therapies

Online polling, dial-in calls, online portal

Who Responded to the Polls?

Figure 1. Participants living with ALD or caregivers

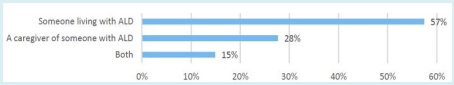


Figure 2. Participant or caregiver gender

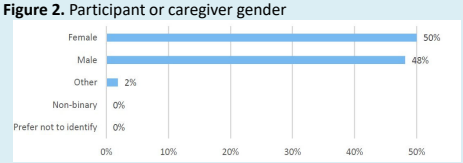
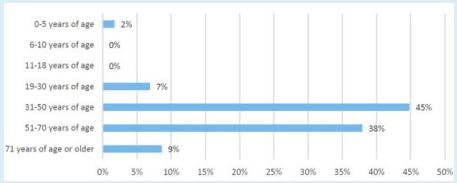


Figure 3. Participant or caregiver age



Session 1: Living with ALD

Figure 4. Lifetime ALD Health Concerns

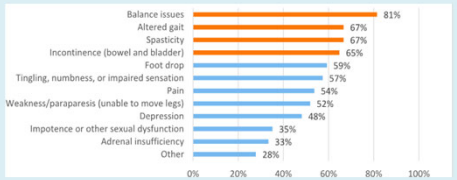


Figure 5. Daily Activities Not Able To Do Due to ALD

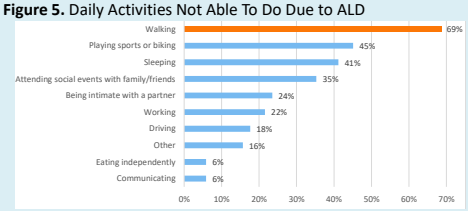
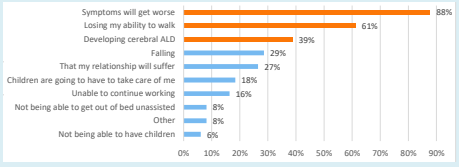


Figure 6. Top Worries About Your/Loved One's Condition in the Future



Session 2: ALD Treatments

Figure 7. Medications Used to Treat ALD Symptoms

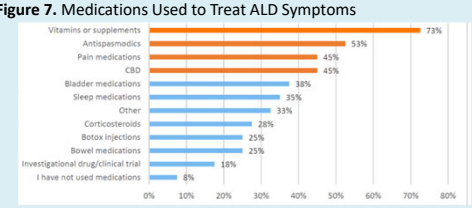


Figure 8. Other Treatments Used to Manage ALD Symptoms

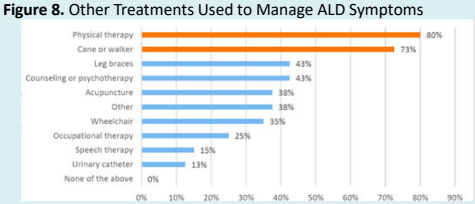


Figure 9. How Well Does Treatment Regimen Address the Most Significant Symptoms of ALD

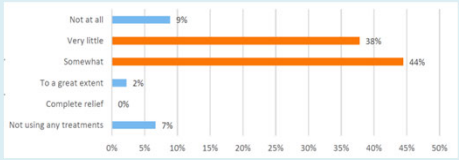


Figure 10. Biggest Drawbacks of Current Treatment Strategy

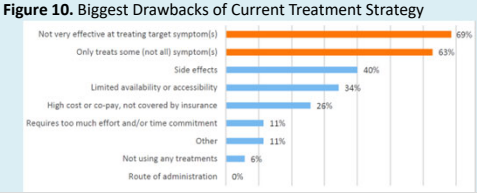
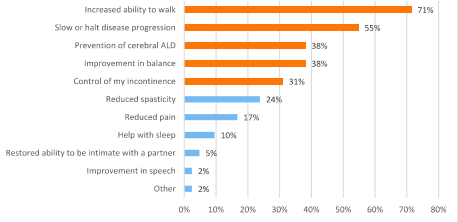


Figure 11. Top 3 Features of an Ideal Treatment for ALD



Insights not Captured by Polls

SESSION 1

Life with ALD is unpredictable and requires a lot of planning	*"With every step that we take and every life event that we want to be a part of, we have to spend so much time strategizing how we can be a part of that without having a life changing accident happen."* - Patrick, man living with AMN
The impact of ALD on families is severe	One family described the disease as *"ALD, the destroyer of life. ALD, the destroyer of families"*. Many patients who are living with symptoms of ALD are also caregivers for children or other family members with the disease. Patients and caregivers often experience psychosocial impacts, including burnout.
ALD can progress very fast after diagnosis	*"Within 2 years I went from doing things as normal to where now I'm using a cane and holding onto walls to get around. I need a wheelchair for anything that requires more than a few steps of walking."* - Alisa, woman living with ALD
Individuals living with cALD will eventually require 24-hour care	*His body was failing and so we tended to his needs, shower, eating, cleaning. All the nurses began to see him decline, breathing, chewing, swallowing difficulty."* – Frank and Cheryl, parents who lost both sons to cerebral ALD

SESSION 2

Treatment should be accessible for everyone	*"I hope that this treatment will halt AMN in its tracks, not just mask symptoms or slow down the pace of the disease. And it must be made available to every affected patient, regardless of age, gender, racial background, or income. ALD does not discriminate, neither can we."* -Miranda, mother of a son with ALD diagnosed through NBS
Treatments targeted specifically for women with ALD are needed	*"The best-case scenario right now as a woman with ALD is to hope that we can get through a trial and that it works for the men with AMN and that maybe, we may be able to find someone willing to write it off script or off label for us later once it's approved."* - Kathleen, founding board member of ALD Connect, caregiver and woman with ALD
A common treatment goal is better quality of life	*"There isn't most likely going to be a wonder pill that will fix all the issues, but even a change to just a few of the symptoms would provide a better quality of life."* - Ken, age 38, man with AMN *"Mine (treatment goals) are pretty much similar to everyone. It's just quality of life."* - Allen, man with AMN

Conclusion

FDA Benefit-Risk Assessment Framework

Analysis of condition

- **ALD has a heavy disease burden.** Mobility challenges, including balance and gait issues and spasticity, as well as bladder and bowel unpredictability have enormous quality of life impacts
- **People living with ALD and their families are burdened by many worries**: that symptoms will get worse, that they will lose the ability to walk, that they will develop cerebral ALD and that they will fall.

Current Treatment Options

- **Individuals living with ALD urgently and desperately need better treatments.** Short of a complete cure, they wish for treatments to help maintain their quality of life. They want a therapy to increase their ability to walk, to slow or halt disease progression and prevent the development of ALD. Women need to be included in research and clinical trials.

These insights can Inform development of *clinically meaningful* trial endpoints and encourage investigation of treatment options

References

1. www.aldconnect.org
2. Report, transcript and videos available at https://aldconnect.org/pfdd/

Acknowledgment

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