Expert consensus exploring the definition of a disease-modifying therapy, and the data required to establish a therapy as disease-modifying in PAH

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Background

- Pulmonary arterial hypertension (PAH) is a progressive and incurable disease.[1] As the understanding of PAH mechanisms improves, the landscape is evolving with treatments targeting the different pathways known to contribute to the pathophysiology.[2]
- Currently, there is no consensus definition on what constitutes a disease modifying agent in PAH.[3] Achieving consensus on the definition and characteristics of disease modification (DM), and the data requirements to establish a therapy as disease-modifying are important as new medications become available.

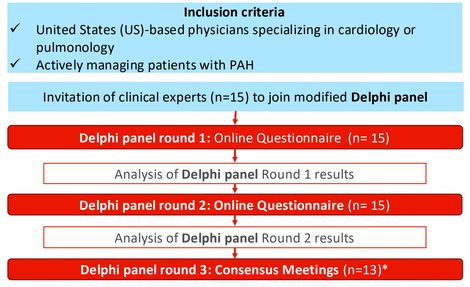
Objective

To collate, clarify, and develop a consensus of expert clinical opinion on the definition and characteristics of DM in PAH, the assessment of the clinical impact of disease-modifying therapies, and the data requirements to establish a therapy as disease modifying.

Methods

- A modified Delphi panel involving two survey rounds followed by two final consensus meetings was conducted with clinical experts.

FIGURE 1: Modified Delphi panel process



*Due to unforeseen changes in panelists' schedules, n=7 panelists were able to join the consensus meeting, therefore a second meeting was held with n=6 panelists. A statement/factor had to be agreed, or disagreed, by all panelists during both meetings to be reported as having achieved consensus.

- A nine-point Likert scale (from 1 [strongly disagree] to 9 [strongly agree]) was used to rate consensus.

Presented at: CHEST 2024 Annual Meeting

Results

Panelist characteristics

Criteria		N
US-based physicians		15
Mean number of patients with PAH in a 3-month period		~191
Specialty area	Cardiology	2
	Pulmonology	13
Type of practice	Center of Comprehensive Care	12
	Academic Medical Center	3
Years in practice	5-10 years	1
	11-30 years	8
	30+ years	6

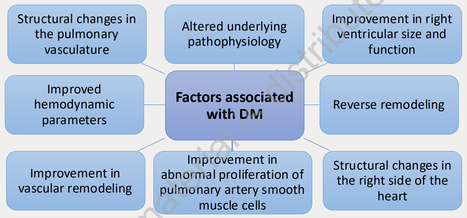
Challenges of defining disease modification in PAH:

The lack of a consistent definition or objective measure

Difficulties in translating outcomes between pre-clinical and clinical studies

Definition of disease modification in PAH

- The panelists did not reach a consensus in agreement on a specific definition of DM using a modified Delphi approach due to the complexity of the underlying pathophysiology of PAH. However, panelists agreed the definition of DM in PAH should be multimodal, incorporating multiple factors.
- Panelists proposed that DM exists as a spectrum/ continuum (i.e., there are levels to DM) wherein some pathophysiological mechanisms may exert a greater effect than others.



Reverse remodeling

- Reverse remodeling is the improvement in the pathological changes in the vasculature. However, there are a lack of direct measurable clinical endpoints to support this.
- DM and reverse remodeling may be linked, but they are separate concepts since DM can occur without reverse remodeling (i.e., a patient's disease course can be altered/improved without reverse remodeling).

"Disease modification can happen if you prolong the patient's life [and] if they feel better. But that can happen without the reverse remodeling".

Clinical outcomes for disease modification in PAH

- Multiple clinical outcomes need to be improved in conjunction with hemodynamic improvements for a therapy to be considered disease modifying.

"You may have an improvement in six-minute walk test without an improvement in [NT pro BNP]. Achieving low risk status may not mean that the patient is going to live longer. This is why I think there is a lack of consensus on these much softer endpoints, which [cannot] be considered independently, but as [part of] a more global picture".

- Panelists agreed that benefits of a disease modifying therapy do not need to be sustained following the withdrawal since DM and curing a disease are separate concepts.
- The panel agreed that DM can be achieved at any disease stage in PAH, and there is no stage beyond which DM is no longer possible in PAH. However, there are potential factors that could prevent administration of disease-modifying therapies first-line, such as:

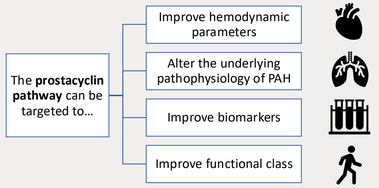
Potential pathways for disease modification in PAH

- Due to the challenge of not having a formal definition of DM in PAH, a consensus in agreement was not reached among the panelists that current PAH therapies could be classified as disease modifying.
- The panel achieved a consensus in agreement that there are multiple therapeutic pathways that are clinically relevant targets for disease modifying therapies in PAH.

"I think our view on this is colored by clinical practice and what we've seen and that has shaped/evolved [our views] that these drugs are more effective when they work together, whether that is synergism between drugs, or we just double our chances of hitting the pathway that is more relevant in that individual patient".

- Consensus in agreement was reached that a combination treatment that impacts the prostacyclin, endothelin, and nitric oxide pathways can be considered disease modifying.

Pathways considered targets for DM in PAH		Pathways where there was a lack of consensus as targets for DM alone	
Prostacyclin	BMP	Endothelin	Nitric Oxide



Testing and imaging modalities to help define and assess disease modification

- A consensus in agreement was not reached that imaging modalities can be used to aid the definition or assessment of DM in PAH. However, improvements in imaging modalities could be useful to assess the underlying pathophysiology of PAH in the future.

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Key takeaway

Disease modification refers to therapies that alter disease course/progression, rather than just treating the symptoms.

Conclusions

- In one of the first systematic approaches to define disease modification in PAH, clinical PAH experts mainly consisting of pulmonologists working in comprehensive care centers, were not able to achieve consensus in agreement on a specific definition using a modified Delphi approach.
- However, the panel suggested that a multicomponent definition of DM that combines the underlying pathophysiological aspects of PAH and associated clinical outcomes may be appropriate.
- Structural changes in the pulmonary vasculature and the right side of the heart, and hemodynamic changes were factors that met consensus as important factors to include in a multimodal definition.
- Both current and future therapies have the potential to be disease modifying in PAH, and combining treatments that target multiple pathways are clinically relevant for DM.
- The findings of this modified Delphi panel can be used to inform future research into the underlying pathophysiology of PAH.
- The characterization of endpoints that demonstrate DM will aid the development of a definition of DM and the requirements of a disease-modifying therapy in PAH.

Disclosures

VML receives grant support from PI-Aerovate, Enzyvant/Altavant, Gossamer-Bio, Keros, Sonovie, Sub-I Janssen, Merck/Aceleron. VML is also a scientific consultant for Aerami, Aerovate, Altavant, Apollo, Bayer, CVS/Caremark, L.L.C., Corvista, Gossamer Bio, Janssen, Keros, Liquidia, Merck, Morphic, Regeneron, Respira, Roivant, United Therapeutics, Vertex. RF receives grant support from PI-Gossamer-Bio, United Therapeutics, Medtronic and is a scientific consultant for Janssen, Merck, Insmed, Liquidia. AH is a stakeholder in Tenax, receives grants from NIH/NHLBI, and is a consultant for Merck, Johnson & Johnson, GossamerBio, UT. SS receives grant support from PI-Gossamer-Bio, Keros, United Therapeutics, Sub I-Merck and is a scientific consultant for Gossamer Bio, Janssen, Keros, Liquidia, Merck, Morphic, Respira, Roivant, United Therapeutics.
MC, GD, JL, DL and PS are employees of Actelion Pharmaceuticals US, Inc, a Johnson & Johnson company, Titusville, New Jersey, USA. DB, AE, RP, LP, HS & MS are employees of Adelphi Values PROVE, who were contracted by Johnson & Johnson Innovative Medicine to conduct this research.

Pulmonary Hypertension

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