REGULAR ARTICLE

Defining Disease Modification in Pulmonary Arterial Hypertension

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With the advent of novel therapeutic agents for pulmonary arterial hypertension (PAH), the debate surrounding disease modification has gained attention. While distinguishing therapies with disease-modifying potential is of interest to patients, clinicians, and industry partners, the ultimate authority for such designations rests with regulatory agencies like the U.S. Food and Drug Administration and European Medical Agency. In this review, we explore the challenges in defining and establishing a therapy as disease-modifying in PAH. Additionally, we examine whether this distinction truly matters from the perspectives of both patients and clinicians.

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a relentlessly progressive disease marked by increasing resistance of the pulmonary vasculature.[1] The increasing resistance leads to uncoupling of the pulmonary vasculature from the right ventricle (RV), gradual reduction in the RV cardiac output (CO), and end-organ failure of the right heart and death.[1] The mechanisms leading to the development of increasing resistance in the pulmonary vasculature are multifactorial and have led to the development of therapies that target mainly vasoconstriction.[1] Further investigation has led to the identification of other pathways that are involved in a more fundamental manner in the pathogenesis of PAH. One such signaling mechanism is the activin pathway, which was found to be closely tied to proliferative effects within the pulmonary vasculature and ultimately laid the groundwork for the development of the activin receptor antagonist sotatercept.[2] By opposing the activin 2a receptor, sotatercept acts to balances 2 opposing mechanisms, the proproliferative transforming growth factor-beta (TGF-beta) pathway and its antiproliferative counterpart, the bone morphogenic protein receptor-2 (BMPR-2) pathway.[2] This was subsequently tested in PAH patients, with both trials meeting their primary endpoints of a robust drop in pulmonary vascular resistance (PVR) in the Phase 2 trial[3] as well as a significant increase in 6-minute walk distance (6MWD) in the Phase 3 trial.[4] The identification of a therapy that appears to target more fundamental pathways of disease has spurred a growing interest in the concept of disease modification and disease-modifying therapies (DMTs). While the exercise of defining what a DMT is (and perhaps just as importantly, what it is not) retains great value, its translation to trials and clinical medicine is still fraught with challenges. These challenges range across the spectrum of health care, encompassing trial design that must be able to demonstrate disease modification, interactions with industry and regulatory bodies, and most importantly, the patients seeking to understand the mechanisms of their therapies. The benefits of this exercise are far reaching, spurring us to the development of new treatment paradigms for PAH.

We must note at the outset of our discussion that, while the term *disease modification* has been variously used in the literature as a general catch-all phrase for any molecule that could potentially target original pathophysiologic pathways, the use of the DMT designation for specific medications is generally avoided since none of our current therapies have been approved as disease-modifying agents by regulatory authorities.

DEFINITIONS AND IMPLICATIONS

The definition of DMT found its origins in the annals of neurological disease, eventually spreading to multiple other specialties. Whether in clinical practice or by Food and Drug Administration (FDA) guidelines, a common theme to many of these definitions is the focus on a drug that acts directly on the underlying pathophysiologic mechanisms, fundamentally altering disease course and resulting in improved clinical outcomes. We will discuss these commonalities, their variants, and the resulting implications of their use within the context of PAH.

The indication for disease modification originated with interferon-beta (IFN-B) in 1993, which was labeled as a DMT for relapsing-remitting multiple sclerosis (MS).[5] Investigators of an earlier trial had shown that IFN-B was able to decrease relapses; however, it was not until the pivotal Multiple

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Sclerosis Collaborative Research Group Phase 3 trial in 1996 that researchers demonstrated that IFN-B could alter disease course by decreasing patient disability over time.[6] The FDA continued to furnish more direction on attainment of the disease-modification designation in guidance documents published in 1999 and then 2013.[7] The DMT definition would be further bolstered by the advent of rheumatologic disease-modifying agents (DMARDs), ultimately followed by multiple other chronic diseases including systemic sclerosis, Alzheimer's, epilepsy, MS, Parkinson's disease, chronic obstructive pulmonary disease, and emphysema (see Table 1).[8] A review of these demonstrates the breadth of varying definitions, with some focusing on prevention of end-organ failure and others on prevention of disease relapse.[8] The majority, however, focus on the alteration of disease course by targeting underlying disease mechanisms.[8]

While this emphasis on alteration of disease course is readily acknowledged, 2 other key concepts have been variably described in DMT, which the PAH community will need to define for itself: that of durability of effect and end-organ dysfunction.

First, disease modification is intrinsically durable. How *durability* is defined varies across disease state. Mounting evidence has clearly demonstrated that early initiation of therapy alters the course of a disease and its progression in MS.[9] Certain other realms argue that the definition should be taken even farther—that is, because it alters fundamental mechanisms of disease, the drug should be able to induce beneficial effects within the molecular milieu that persist after the drug has been cleared.[8]

Second, and perhaps more controversially, the PAH community must determine whether to include prevention of end-organ failure in our definition of disease modification. In the case of PAH, the most obvious candidate for end-organ failure is the RV. Acknowledging that sotatercept has not been granted the FDA designation of DMT, let us consider it as a corollary for a DMT for the moment, given its effects on fundamental signaling pathways. In this context, we must allow that the relationship of sotatercept to the RV has yet to be fully elucidated. Use of sotatercept did not increase CO in the STELLAR[4] and PULSAR[3] trials, while it did improve multiple other echocardiographic parameters of RV function in a post hoc analysis of STELLAR.[10] By this standard, would sotatercept fail the definition of disease modification in this hypothetical context? We would argue that, while CO did not increase during the trials, it did not decrease, which has been demonstrated to occur in untreated placebo populations linked to trials of similar length. It can be argued that prevention of end-organ failure does not necessitate increase in but rather maintenance of CO, which occurred in the STELLAR[4] and PULSAR[3] trials, and thus, a delay in end-organ failure can be presumed.

Considering these variable descriptions, we propose the following definition of DMT in PAH: It must be able to alter an underlying common pathophysiologic pathway in Group 1 PAH, improving clinical outcomes and delaying end-organ failure in such a fundamental physiological way as to demonstrate durable benefit beyond drug discontinuation and clearance.[11]

Having defined DMT, we must note that there are multiple other characteristics of therapy that this definition excludes; we will discuss the implications these have within the PAH realm. First, disease modification does not imply disease reversal. Disease modification is not equivalent to cure. This would necessitate the identification of a fundamental cause of PAH that is yet unrecognized. We know that PAH is the culmination of multiple processes—genetic, epigenetic, and environmental—which result in disordered regulation. From a genetic perspective, for example, we know that while BMPR-2 mutations are the major cause of heritable PAH, the overall penetrance of the mutation is only 20%.[12] This suggests a strong role for nongenetic factors.[12] Further, we know that many patients with PAH who do not code for the mutation nevertheless have disordered BMP signaling—what we have not identified is the cause of this disruption, in the absence of genetic mutations.[12] Additionally, this represents only 1 of multiple disordered pathways.[12] The concept of disease reversal is further hindered by the advanced state at which PAH presents. The pulmonary vasculature is extremely generous compared with the systemic circulation, with about 10 times the density of the other arterial vasculature.[12] The resultant high compliance and redundancy is adaptive; however, this also means that, by the time the disease is reflected in the proximal vasculature on screening echocardiography, approximately 50%–60% of the vasculature has been destroyed.[12] Reversal in this case would necessitate reformation of a large amount of obliterated, fibrotic pulmonary vasculature to such a degree that the distal pulmonary arterioles would achieve significant recanalization and functionality.

Second, disease modification does not signal a particular level of drug efficacy. It is well established in the rheumatologic world that DMTs have differing potencies, and multiple meta-analyses have been done attempting to quantify comparative efficacy among the various agents.[13] Further, drugs may have variable responses based on yet unrecognized phenotypes. The discussion invites further investigation into subgroups that are nonresponders and superresponders to DMT, using biomarkers, proteomics, and immunologic phenotyping, with the goal of one day being able to predict individual response to therapies. Until then, our ability to identify a patient who would experience particular benefit from DMT is limited.

Third, the designation of disease modification should not apply to all medications that have secondary, less potent effects within a similar biologic pathway. These secondary benefits have been demonstrated in both the phosphodiesterase-5 (PDE-5) inhibitors and the endothelin receptor antagonists (ERAs). For instance, the PDE-5 inhibitor sildenafil, in addition to its vasodilatory effects via the cyclic guanosine monophosphate pathway, has been demonstrated to potentiate BMPR signaling in human pulmonary arterial smooth muscle cells and monocrotaline

Table 1. Prior Definitions of Disease-Modifying Therapy by Disease State

	Definitions
Rheumatologic disease	
Rheumatoid arthritis	"A DMARD is defined as a medicine that interferes with signs and symptoms of rheumatoid arthritis, improves physical function, and inhibits progression of joint damage"[8] EULAR: "The concept of 'disease modification' comprises a combination of relief of signs and symptoms; improvement or normalization of physical function, quality of life and social and work capacity; and most characteristically the inhibition of occurrence of progression of structural damage to cartilage and bone"[8] ACR: "Agents that apparently alter the course and progression of rheumatoid arthritis, as opposed to more rapidly acting substances that suppress inflammation and decrease pain, but do not prevent cartilage or bone erosion or progressive disability"[8]
Multiple sclerosis	"Ideal DMT should halt the progression of the disease and hopefully induce remission, and preferably also reverse some of the major organ complications. . . It is reasonable to expect a DMT to stabilize organ function without any further worsening of other domains"[8]
Neurologic disease	
General neurodegenerative diseases	"A disease-modifying therapy is an intervention that produces an enduring change in the trajectory of clinical decline of a neurodegenerative disorder by impacting the disease processes leading to nerve cell death"[8] EMA: "For regulatory purposes, a disease modifying effect will be considered when a pharmacologic treatment delays the underlying pathological or pathophysiological disease processes and when this is accompanied by improvement in clinical signs and symptoms of the dementing condition"[8]
Alzheimer's disease	"Disease modification can be defined as treatments or interventions that affect the underlying pathophysiology of the disease and have a beneficial outcome on the course of Alzheimer's disease"[8] "A disease-modifying therapy is as an intervention that produces an enduring change in the clinical progression of Alzheimer's disease by interfering in the underlying pathophysiological mechanisms of the disease process that lead to cell death"[8] EMA: "A medicinal product can be considered to be disease modifying when the pharmacologic treatment delays the underlying pathological or pathophysiological disease processes. This can be demonstrated by results that show slowing in the rate of decline of clinical signs and symptoms and when these results are linked to a significant effect on adequately validated biomarkers. Such biomarkers should reflect key pathophysiological aspects of the underlying disease process based on a plausible disease model. The choice of biomarker as well as the type of analysis is left open, although more weight will be given to those biomarkers showing not only target engagement, but also an effect on the downstream disease mechanisms"[8] FDA: "Permanently altering the course of Alzheimer's disease through a direct effect on the underlying disease pathophysiology; the effect persists in the absence of continued exposure to the drug"[8] PMDA: "Medical agents that delay neurodegeneration and neuronal cell death by acting on the pathological mechanism of Alzheimer's disease and, as a result, inhibit the progression of clinical symptoms"[8]
Epilepsy	"According to the definition of epileptogenesis, 'disease modification' refers to every clinically relevant therapeutic outcome which does not necessarily prevent epilepsy onset but significantly improves the disease course by reducing seizure burden and/or decreases concomitant comorbidities"[8]
Multiple sclerosis	Disease-modifying therapies are "drugs targeted to prevent relapses of the disease, and consequently, progression of disability"[8]
Parkinson's disease	"A disease-modifying therapy. . . slows or stops disease progression"[8]
Pulmonary disease	
COPD	"An improvement in, or stabilization of, structural or functional parameters as a result of reduction in the rate of progression of these parameters which occurs whilst an intervention is applied and may persist even if the intervention is withdrawn"[8]
Emphysema	"Disease modification is a sustained improvement in disease state following therapeutic intervention that persists when therapy is discontinued"[8]

Abbreviations: ACR indicates American College or Radiology; COPD, chronic obstructive pulmonary disease; DMARD, rheumatologic disease modifying agents; DMT, disease-modifying therapy; EMA, European Medicine Agency; EULAR, European Alliance of Associations for Rheumatology; FDA, Food and Drug Administration; PMDA, Pharmaceuticals and Medical Devices Agency.

rats.[14] Endothelin-1, in addition to being a potent vasoconstrictor, has a much less potent effect on mitogens that contribute to vascular overproliferation via the rapidly accelerated fibrosarcoma/mitogen-activated protein kinase pathway.[15] Based on these findings, we can reasonably hypothesize that ERAs would exert a weak and indirect antiproliferative effect.[16]

REGULATORY AND CLINICAL CHALLENGES

While the delineation of definitions is helpful in theory, multiple challenges arise to its use. From a regulatory standpoint, the main challenges center on how to demonstrate durability in clinical trials and how to address barriers to FDA approval; within clinical practice, the challenge is to identify the best phenotypes for therapy and the ideal timing of treatment initiation and withdrawal. Finally, the most important challenge is to responsibly communicate the DMT label and incorporate the perspective of our patients.

The most conspicuous difficulty is that of demonstrating durability of benefit in clinical trials. Two study designs that can demonstrate persistence and thus disease-modifying effect include delayed-start and drug discontinuation studies.[11,17] The delayed-start trial design involves 2 study groups, an early and a delayed-start group, who are followed for clinical worsening from the baseline study visit through 2 phases.[17] In Phase 1, the early group is started on therapy, while the delayed group is treated as the placebo; in Phase 2, the placebo group is then also initiated on therapy.[17] Once on the same therapy, the 2 populations are expected to demonstrate a constant rate of clinical worsening over time, with the difference between the 2 groups presumed to be due to disease-modifying effect (Figure 1).[17] The main challenges of these trials involve discerning the best length of time for each phase. Phase 1 requires a duration that is long enough before the delayed group is started, to demonstrate benefit to the first group.[17] Likewise, Phase 2 must be able to avoid an early conclusion that could miss a potential intersection of the slopes.[17] Thus, the delayed-start design exposes the trialist to all the costs and risks of a study that will be at least twice as long as single-phase trials. The second type of trial, the drug discontinuation design, follows the slope of clinical worsening after withdrawal of a treatment.[11] This design introduces multiple inherent difficulties. The first is the obvious safety issues from withdrawal of treatment in a disease characterized by persistent progression (Figure 2). Strict monitoring guidelines for disease worsening would be required.[18] The second would be defining how late in the disease stage one could withdraw and still see results—ie, how far into the disease state will we able to attain enough of a slope differential to demonstrate durable effect? In such a scenario, the ability of a DMT to not only prevent forward progression but to also demonstrate resounding ability to reverse prior processes could help bolster the results of such a trial. Encouragingly, both experimental and genetic studies of a sotatercept analog demonstrate not only prevention of progression but also potential reversal of inflammatory processes and normalization of pulmonary vasculature.[19]

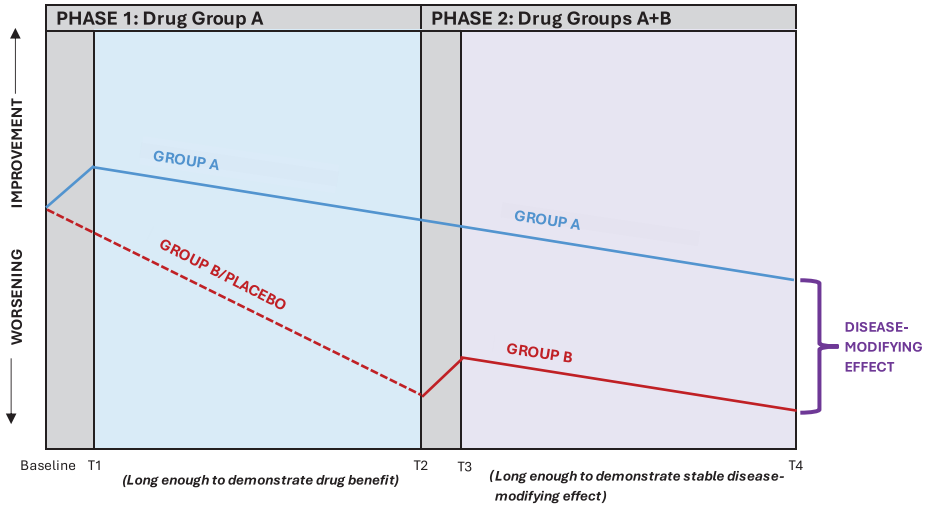

Figure 1: The delayed-start trial. Two groups are started at baseline: Group A (the early-initiation group) and Group B (the placebo/delayed-start group). In Phase 1, Group A is started on therapy. Group B, the delayed start group, is monitored as the placebo group. When sufficient time to allow demonstration of efficacy (and even worsening) in Group A has passed, Phase 2 begins, and Group B is then started on therapy. The difference between the 2 stable rates of worsening is the disease-modifying effect.[17]

Aside from adequate trial design, the issue of FDA approval as a DMT remains. Use of previously accepted trial frameworks does not automatically guarantee FDA designation. As an example, the TRAILBLAZER-ALZ2 was one of the most recent trials in which investigators used a drug withdrawal design in pursuit of DMT designation for its molecule to treat Alzheimer's.[20] Even with a strongly positive endpoint, the FDA delayed approval to convene a panel of experts to discuss the validity of the novel trial design and its results.[20] Only after delays and panel approbation of the study did the FDA move forward with approval[21]—and despite the promising findings of persistence of disease effect demonstrated by drug withdrawal, the disease-modification designation was not given to this therapy.[22] This may be a reflection of the FDA's evolving attitude toward the use of the DMT label. After its initial approval of IFN-B, the FDA continued to provide guidance on DMT designation for the next 20 years.[7] In a 2018 FDA industry guidance document, however, the DMT terminology was removed, and the emphasis was instead placed on a drug's potential to have "persistent effect on disease course."[7] This has led many to conjecture that the FDA was moving away from the DMT designation altogether.[7]

Within clinical practice, several seminal questions persist in the use of DMT. The first is to identify which patients could most likely benefit from DMT. While on first blush this would

appear simple based on previously recognized Group 1 PAH phenotypes, further examination reveals increasing complexity. Subgroups of PAH can be quite heterogeneous, not only in terms of clinical disease but also in terms of molecular pathway modulation. Further, the crosstalk between the 2 of these can be quite variable. This is supported by findings that delineate distinct immune phenotypes in PAH via proteomic analysis, which exist independent of classical Group 1 subtypes.[23] The development of cytological profiles that define immunologic profiles is encouraging and will be part of a broad phenotyping panel that would stratify potential for treatment response.

The next challenge is to identify the ideal time to start DMT along the pathophysiologic continuum. It stands to reason that a DMT should be started early in the course of disease, as pathways are beginning to undergo dysregulation, a phenomenon that has been demonstrated in rheumatology. Indeed, trials in MS and autoimmune disease have consistently shown that earlier initiation of DMT tends to change the course of disease.[9,24] In the HYPERION trial, the use of sotatercept is being examined within the first year of diagnosis, and investigators will hopefully provide further instruction on its use early in the disease course.[25] However, as previously demonstrated, even at the time of diagnosis, the disease has far progressed.[12] It has been shown that patients have a 40% risk of hospitalization within the first year of diagnosis, with hospitalization carrying increasing risks of mortality.[26] Indeed, this almost begs the question of whether there is a point of no return in fundamental disease mechanisms, beyond which disease-modifying pathways can demonstrate lasting benefit and withdrawal would be unwise. In Huntington's disease, this is being defined in terms of genetic mutation rates,[27] while in rheumatoid arthritis, it is defined by functional disability.[28] PAH has yet to assign a descriptor of this point.

The final challenge of disease modification is to responsibly involve the patient perspective. Any use of the term DMT must consider the perceptions of patients who will be interacting with the medication. Certainly, pitfalls to its use exist—as in the case of MS before it, the advent of sotatercept was greeted with much enthusiasm, with some media sources going so far as to proclaim its ability to "stop PAH."[29] Therefore, any discussion using the term must responsibly begin with the absolute distinction between *disease modification* and *cure*—in our speech, writing, and pictorial representation.[11]

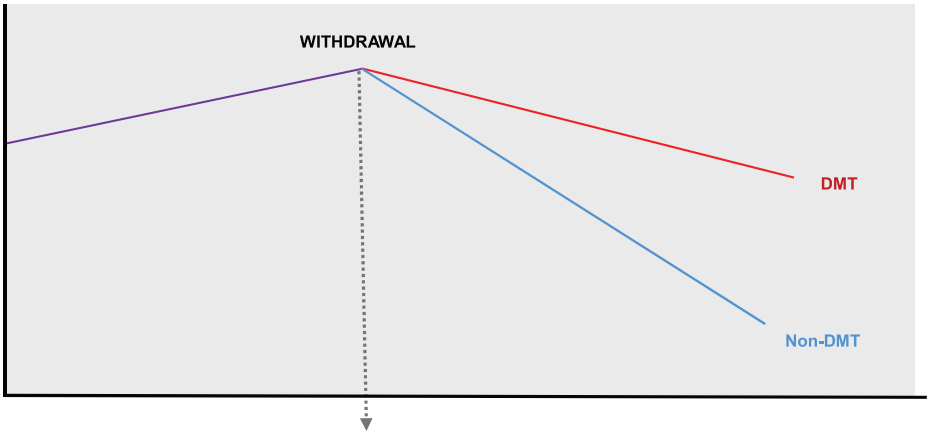

Figure 2: The drug withdrawal trial. Patients are treated with usual therapies, and at a prespecified point, the drug is withdrawn. The rates of clinical worsening are compared between the disease-modifying therapy (DMT) and non-DMT groups.[18]

BENEFITS AND FUTURE DIRECTIONS

Given all the challenges inherent to the use of the DMT designation, the most pressing question is: What is the benefit?

Certainly, the most self-evident benefit of working out the DMT designation is its use within our treatment algorithm. Barring heavy side-effect burdens, one can argue that the ability to modify a course of disease mandates that all patients should have access as early as possible to DMTs. However, this could introduce further issues for all drugs in the same class. Future trials are inevitably affected by the treatment landscape of a recent approval of a DMT.[5] Trial participants would have to balance the risks of forgoing an approved therapy with the potential benefits of a new one.[5] This involves attempting to balance many factors that, in the wake of a newly approved therapy, are often unknown; moreover, not only is the benefit of the trial drug unknown, but the potential risks of the approved therapy outside of the trial in real-world use have also yet to be elucidated.[5] Both noninferiority and superiority trial designs are often introduced at this point as possible alternatives.[5]

Another benefit of the DMT designation is its focus on outcomes that are most important to patients. As previously shown, the Multiple Sclerosis Collaborative Research Group was able to change the focus from disease outcome to the more patient-centered outcome of disability.[6] An FDA report entitled "Voice of the Patient" held specifically for patients with PAH is particularly enlightening on the patient view of current therapies, in which patients described ideal therapies as those that are "less invasive, have fewer side effects, and address the pervasive symptoms of PAH," especially those that are "easier to administer," with "more convenient dosing schedules."[30] The urgency was clearly directed on ease of use and patient quality of life.[30] Taken together, we can presume that the advent of disease modification can only be beneficial to patients if it introduces therapies that balance efficacy with ease of use and improved quality of life.[30] This is in line with the FDA patient-focused outcomes that encourage outcomes assessment based not only on survival but also on how the patient feels and functions.[31]

The final benefit lies in the way in which it forces us to challenge our own current paradigms of therapy. We readily acknowledge that our treatment goals

at this time cannot involve a cure, and thus, our current methodology involves treatment to low risk of progression. This relies upon the tools we have available to profile our patients, which admittedly are not individualized and reliant upon retrospectively derived registry data. The next wave of treatment goals should incorporate a panel of biomarkers, hemodynamics, risk assessment tools, and a focus on patient feeling, function, and survival.[18] Instead of the focus on low risk, the paradigm is instead shifting toward a broader goal of treatment remission that incorporates all these factors.[18]

CONCLUSION

With the increasing focus on fundamental pathways in PAH, we have entered a new realm of therapeutics, one in which we stand at the threshold of being able to not only treat but also fundamentally alter the course of PAH. It is incumbent on our specialty to define DMT for itself, in such a way that we can accurately communicate its promise (and challenges) within clinical trial development and clinical practice to regulators and, most importantly, to those to whom it most affects, our patients.

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