Disease-Modification in Neurodegenerative Disorders

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The clinical failure rate for disease-modifying treatments (DMTs) that slow or stop disease progression has been nearly 100% for the major neurodegenerative disorders (NDDs), with many compounds failing in expensive and time-consuming phase 2 and 3 trials for lack of efficacy. However, as our understanding of NDDs is improving, there is a rise in potentially disease-modifying treatments being brought to the clinic. Further increasing the rational use of mechanistic biomarkers in early phase trials for these (targeted) therapies can increase R&D productivity with a quick win/fast fail approach in an area that has seen a nearly 100% failure rate to date.

Keywords: clinical pharmacology ; neurodegenerative disorders ; disease-modification

1. Introduction

While there have been successes in neuropharmacology, most central nervous system (CNS) pharmaceutical approaches treat symptoms rather than disease cause. Such symptomatic treatments can be very successful at suppressing disease symptoms at first, however, the effects eventually diminish over time and do not stop disease progression. Therefore, there is an urgent need for better treatments that can slow or stop disease progression of neurodegenerative disorders (NDDs), especially since the burden of these debilitating diseases on patients and society is on the rise as populations age [1]. Alarmingly, the clinical failure rate for such disease-modifying treatments (DMTs) for NDDs has been nearly 100% to date [2][3][4][5]. Exceptions include the approval of riluzole and edaravone as treatments for amyotrophic lateral sclerosis (ALS); however, both arguably show only marginal effects [6][7]. With the recent approval of nusinersen for the treatment of spinal muscular atrophy (SMA) [8], new hope may be on the horizon.

In fact, our understanding of underlying NDD pathophysiological mechanisms is rapidly expanding [9][10][11][12][13], and this has sparked a new interest in the development of (targeted) disease-modifying treatments. This is reflected for example, by the >100 compounds currently in clinical development for Alzheimer's disease [4] and close to 150 compounds in clinical development for Parkinson's disease [14], many of which can be categorized as DMTs.

Compared to most other fields, the clinical development path of NDD DMTs faces some important additional challenges that contribute to the high failure rate experienced to date. First, preclinical and animal models have historically shown poor translatability to predict drug efficacy in human NDDs because of the complexity of the pathophysiology of neurodegenerative disorders and our incomplete understanding of these processes [2][15][16]. Secondly, in NDDs, it may take a long time from disease onset to the manifestation of clinical symptoms to objectifiable disease progression and clinical trials have struggled to separate out symptomatic effects from disease-modifying effects [2][16][17]. Moreover, by the time of diagnosis, significant (irreversible) damage to the CNS has often already occurred, and it has been challenging to identify robust diagnostic biomarkers to initiate treatment in earlier disease stages [18]. Thirdly, unlike diseases of most other organ systems, CNS disorders are localized to a body compartment that is not easily accessible for obtaining tissue samples in clinical studies to verify molecular pathophysiologic mechanisms and drug effects. Finally, there has been a lack of validated biomarkers as outcome measures for disease progression in disease-modification trials [16].

However, considerable progress is being made in the development of biomarkers for NDDs [19][20] that cannot only help diagnose or track progression of NDDs, but can also be used as tools during clinical development to demonstrate central exposure, (peripheral) target engagement and functional responses to guide dosing-decisions or facilitate patient enrichment in later stage clinical trials [21]. In particular, peripheral biomarkers for their relatively easy clinical accessibility hold a promise to help overcome some of the fundamental challenges in CNS drug development and allow for more efficient screening of drug candidates in early-phase clinical trials [22]. In a field where nearly 100% of investigational drugs fail to make it to market, the use of such biomarkers can offer an indirect yet relatively quick strategy to confirm (peripheral) target and pathway-engagement and provide early proof-of-concept in short-duration mechanistic early-phase trials in both healthy volunteers and patients [23][24]. This quick win/fast fail approach can increase research and development (R&D) productivity and help guide dosing-decisions for maximizing success rates in later stage trials [25].

2. Neurodegenerative Disease Mechanisms

Neurodegenerative disorders, including as Alzheimer's disease (AD), frontotemporal- (FTD) and Lewy body dementia (LBD), amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), Parkinson's disease (PD), and spinocerebellar ataxias (SCAs), are characterized by a progressive degeneration of neurons in various regions of the brain and result in losses in cognitive and/or motor function [26][27]. As it appears, these NDDs share multiple overlapping pathological mechanisms including misfolding, aggregation, and accumulation of proteins, dysfunctional mitochondrial homeostasis, formation of stress granules, and maladaptive innate immune responses, eventually leading to cellular dysfunction, loss of synaptic connections, and brain damage [28][29]. In AD, amyloid-β protein fragments that cluster together and form amyloid plaques, as well as tau proteins forming neurofibrillary tangles, disrupt neurological functioning and contribute to neurotoxicity leading to inflammation and neuronal cell death. In PD, clumping of α-synuclein into so-called Lewy bodies in dopaminergic neurons is believed to play an important role in neuroinflammation and eventually neurodegeneration, while in ALS, the aggregation of TAR DNA-binding protein 43 (TDP-43) in cell stress granules may contribute to disease pathology, neuroinflammation, and motor neuron death. Because of an overlap in the underlying pathological mechanisms, as well as involvement of the same cell types, it is not surprising that many DMT mechanisms under development often target multiple NDDs. For example, inhibition of receptor-interacting serine/threonine-protein kinase 1 (RIPK1), a regulator of inflammation, cytokine release, and necroptotic cell death, is being investigated as treatment for AD, ALS, and multiple sclerosis (MS) [30], while tau protein is being targeted with antibodies for both progressive supranuclear palsy (PSP) and AD [31]. In addition to the more general mechanisms of neurodegeneration, genetic studies have begun identifying risk-associated alleles and disease-causing rare mutations in NDDs [13][32]. These genetic studies may pave the way for targeted therapies in selected subpopulations, such as an antisense oligonucleotide targeting the mutated superoxide dismutase (SOD1) enzyme in ALS [33], or glucocerebrosidase (GBA)-activators or leucine-rich repeat kinase 2 (LRRK2)-inhibitors targeting disease-causing mutations in GBA or LRRK2 respectively in Parkinson's disease [34].

3. Innovative Drug Development of Disease Modifying Treatments

The development of innovative disease modifying treatments for these NDDs with novel mechanisms of action is radically different from the development of a generic version of an existing effective drug from a well-established class [25]. For innovative compounds, the uncertainty about the different aspects of the drug is far greater, which is also reflected in the high clinical failure rate in the field of DMTs for NDDs. This uncertainty requires a high level of flexibility in the drug development program, the use of innovative methods, and a high level of integration of information rather than the purely operational requirements of a generic development program [25]. Innovative drug development in essence starts with the preclinical development of assays to identify and validate a novel pharmacological target, subsequently demonstrating safety and efficacy in a (relatively standardized) battery of laboratory and animal studies. Hereafter, the clinical development trajectory starts in humans and revolves around answering a set of six basic scientific questions in a series of what are traditionally called phase 1–3 clinical trials: (1) what is the safety and pharmacokinetic behavior of the drug, (2) does the drug occupy the intended pharmacological target, (3) is the drug capable of activating the target, (4) does this target activation lead to the intended physiological response, (5) and subsequently to the intended pathophysiological response, and (6) does the drug result in a sufficient clinical response [25]? Traditionally these questions are addressed in a chronological order, starting with small-scale phase 1 clinical studies focusing on safety and pharmacokinetics in healthy volunteers or patients and ending with large-scale, often global and multi-center, phase 3 studies to demonstrate safety and efficacy versus placebo or an active comparator in the intended drug label target population. However, as stated above, drug development does not need to take this linear approach. Especially if one considers that development becomes more and more expensive the further a compound progresses into later stage trails. In fact, for truly innovative compounds such as the development of DMTs in NDDs, there is a strong scientific and financial argument to be made to demonstrate proof-of-concept for a new compound in humans as early as possible [35]. From a scientific perspective, an early demonstration of proof-of-concept helps focus future efforts to the most promising leads. From a financial perspective, early proof-of-concept contributes to a quick win/fast fail development approach, thereby increasing R&D productivity and preventing investments in compounds only to fail in the most expensive later stages of drug development.

Demonstrating proof-of-concept of DMTs in early-stage trials is challenging, however. Considering the definition of a neurodegenerative DMT: "an intervention that produces an enduring change in the clinical progression of the NDD by interfering in the underlying pathophysiological mechanisms of the disease process leading to cell death" [36], proof-of-concept for the first part of this definition is difficult to demonstrate because of the short-duration of early phase clinical trials. Moreover, traditional clinical outcomes—such as disease progression scales or patient-reported outcomes (PROs)—are not suitable for demonstrating effects of DMTs in NDDs in healthy subjects for a lack of disease, nor in patients because of the general short duration and small group sizes in phase 1 trials and large placebo-effects in PROs often

seen in these patient populations. The ability of an investigational compound to “interfere in the underlying pathophysiological mechanisms leading to cell death” on the other hand, is something that could be demonstrated with the use of pharmacodynamic biomarkers in short-duration early phase trials, even in healthy subjects.

4. Biomarkers

A biomarker (biological marker) is defined as “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention” [37]. When the level of a biomarker changes in response to exposure to a medical product, it can be called a *response or pharmacodynamic biomarker* [38]. Other types of biomarkers can include *diagnostic biomarkers* (detecting or confirming the presence of a disease), *predictive biomarkers* (presence or change in the biomarker predicts an individual or group to experience a favorable or unfavorable effect from the exposure to a medical product), *prognostic biomarkers* (identify the likelihood of a clinical event, disease recurrence, or disease progression in untreated patients), and *safety biomarkers* (indicates the likelihood, presence, or extent of a toxicity as an adverse event) [38][39]—see Table 1. In some cases, a biomarker can be used as surrogate to substitute for a clinical endpoint, but to qualify as a surrogate, a biomarker must correlate with the clinical outcome and the change in the biomarker must also explain the change in the clinical outcome [38]; evidence that is currently lacking for the majority of biomarkers.

Table 1. Biomarker categories and examples of use in NND DMT drug development (adapted from Cummings and Amur et al. [39][40]).

Biomarker Category	Use in Drug Development	Examples from NND DMT Drug Development
Response	Pharmacodynamic biomarker as indicator of intended drug activity • *Proximal* (molecular target occupancy and activation) • *Distal* ([patho]physiological response)	CSF total amyloid-β and fragments in response to amyloid-β antibody treatments
	Efficacy response marker as a surrogate for a clinical endpoint	Braak staging with tau PET as a surrogate biomarker for clinical AD (though no validated surrogate biomarkers are available yet for NDDs).
Diagnostic	Patient selection	GBA1 gene mutation in PD patients SOD1 gene mutation in ALS patients
Predictive	Patient stratification Trial enrichment via inclusion criteria	Tau PET to identify AD patients more likely to respond to anti-tau therapies
Prognostic	Patient stratification Trial enrichment with patients likely to have disease	Percentage of weight loss at baseline for life expectancy and disease progression in ALS patients
Safety	Detect AEs and off-target drug responses	MRI for structural changes (including tumor or syrinx formation) within the brain after stem cell transplantation for ALS

Recent reviews have described the current status of biomarkers in ALS [41], Alzheimer's disease [42], Parkinson's disease [43], Huntington's disease [44], and spinocerebellar ataxias [45], although for most of these indications, reliable indicators of disease severity, progression, and phenotype are still lacking.

5. Early Phase Proof-of-Concept with Mechanistic Biomarkers

Even without a proven correlation with clinical outcome, biomarkers are useful in early phase trials of DMTs for NDDs. At this stage of development, it is more important and feasible to demonstrate that the investigational drug engages its molecular pathway in humans as envisioned (mechanistic proof-of-concept). This can be accomplished with mechanistic biomarkers, by demonstrating pharmacologic activity of the compound both in healthy subjects as well as patients, allow for the application of mechanism-based pharmacokinetic/pharmacodynamic (PK/PD) modelling [40], and help define the optimal dose for phase 2/3 efficacy trials. This maximizes the eventual chance of clinical development success, or can save valuable resources by supporting an early "no-go" decision in case the compound fails to reach or appropriately modulate its target [46]. In fact, disease specific regulatory guidance for drug development in NDDs also recommends the use of biomarkers in the early phases of the clinical development to: (1) establish the pharmacological mechanism(s) on which the drug may be thought to have therapeutic activity, (2) demonstrate target engagement and proof-of-concept, and (3) determine the PK/PD relationship and the dose-response curve [47][48][49].

Additionally, by including a pharmacological effect or target engagement biomarker in a first-in-human (FIH) study, the dose-response curve in humans can be linked to the non-clinical experience, thereby supporting more informed dose escalation decisions. This is especially true for innovative drugs with a novel mode of action, where the relationship between the minimally pharmacologically active dose and a safe therapeutic dose in humans is not yet known [50]. Inclusion of a pharmacodynamic measure in FIH trials is now also recommended by the regulatory bodies for safety reasons [51].

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