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Alzheimer's and Parkinson's Diseases Face Common Challenges in Therapeutic Development: Role of the Precompetitive Consortium, Coalition Against Major Diseases

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Abstract

Alzheimer's disease (AD) and Parkinson's disease (PD) pose significant challenges for successful development of new therapies, with anextremely high drug trial failure rate and yet no approved disease modifying drugs available. Given the magnitude of the challenges, it has become clear that larger collaborations and multi-partner joint efforts, pooling resources and expertise,are required for the advancement of methods and tools that are critically needed to support drug development studies. Critical Path Institute's Coalition against Major Diseases was formed in 2008, at a time prior to the era of public private partnerships, with the mission of streamlining and de-risking drug development for AD and PD. Since its origin, the consortium has achieved several milestones including development of consensus data standards for AD and PD, a unified clinical trial database comprised of placebo data from AD therapeutic trials and regulatory endorsement of drug development tools. In addition, the consortium is progressing strongly on other initiatives, with ongoing regulatory interactions. The coalition held its annual conference at the U.S. Food and Drug Administration, where diverse stakeholders including industry, academic experts, government agency representatives, patient advocacy organizations and regulators gathered together to share their accomplishments and focus on the needs of the future. The current landscape was emphasized with focus on the need to expand the precompetitive space and enhance data sharing globally.

Keywords: Alzheimer's disease; Parkinson's disease; Therapy development; Precompetitive consortium; Regulatory science

Introduction

CAMD and FDA: A decade after the critical path initiative

It has been a decade since the U.S. Food and Drug Administration (FDA)published the Critical Path Initiative, articulating the need for cross-disciplinary collaboration to move science forward and expedite drug development [1]. Despite much progress, major challenges remain. Today, the Critical Path Institute (C-Path), founded in 2005, comprises eight consortia aimed at providing the resources, tools and infrastructure to increase the efficiency of the drug development process by focusing on indication-specific areas [Alzheimer's disease, (AD), Parkinson's disease, (PD), multiple sclerosis, tuberculosis, polycystic kidney disease] or on broad areas like translational drug safety or patient-reported outcome measures. C-Path consortia bring academic, advocacy and industry partners together with regulatory agencies to identify areas of common interest and projects that can be executed collaboratively in the pre-competitive space.

Neurodegenerative disease is among the most challenging of these disease areas. Thus, the Coalition against Major Diseases (CAMD) was established in 2008 to develop tools applicable to drug development for AD and PD. At the CAMD-FDA Annual Scientific Meeting in October 2014, members from the pharmaceutical industry, academic key opinion leaders, and representatives of the FDA, the European Medicines Agency (EMA), Japan's Pharmaceutical and Medical Devices Agency (PMDA), the National Institute Neurological Disorders and Stroke (NINDS) and advocacy groups came together to discuss progress made and plans for the future.

CAMD is organized into sub-teams active in specific projects focusing on developing and achieving regulatory endorsement of drug developing tools (DDTs) for evaluating treatment efficacy and improving the efficiency of clinical trials. These tools are intended to de-risk and accelerate the drug development process, as well as to streamline the regulatory review process for new drug entities to treat AD and PD. At the annual meeting, these teams outlined progress made, ongoing work, and proposed next steps to advance the CAMD teams goals. CAMD teams include AD imaging and cerebrospinal fluid (CSF) biomarkers, modeling and simulation tools for mild to moderate AD and PD, a clinical outcome assessment tool for prodromal AD, and a PD imaging biomarker for prognostic use.

Unmet needs in Alzheimer's disease and Parkinson's disease

New treatments are desperately needed for both AD and PD across their prolonged trajectories, beginning in the earliest stages before symptoms are apparent and continuing through all stages of the disease. For AD, the cholinesterase inhibitors, such as donepezil, galantamine and rivastigmine, as well as the N-methyl-d-aspartate (NMDA) receptor channel blocker memantine, have been marketed for years for symptomatic improvement in patients at the dementia stage of the disease. Unlike these drugs, which address neurotransmitter deficits presumed to underlie cognitive and behavioral symptoms of AD, most compounds that are currently in clinical development for patients with AD are putative "disease-modifying" agents that target the amyloid pathway [2] in hopes of slowing disease progression. So far, none of these compounds has met the primary endpoints in pivotal trials, and questions about the validity of the amyloid hypothesis are gaining visiability [3].

In PD, the situation is somewhat different. Symptomatic treatments for the motor aspects of the disease have been available since the late 1960s and have dramatically improved the lives of people who live with PD, despite the debilitating adverse effects of these drugs. Unfortunately, neuroprotective or disease-modifying approaches have been unsuccessful so far, and current candidates remain in the early stages of development. Even if promising treatments were available, the trials that would evaluate their efficacy and safety would be lengthy, large, and expensive. Thus, there is an urgent need to find scientific means, resources, and financial incentives to evaluate treatments more efficiently in terms of both resources and time.

At the basic science level, resources are required for both AD and PD to support further research into disease mechanisms as well to expand our insights into genetic and environmental risk factors. New tools are needed for drug development that will enable accurate and early patient selection, as well as accurate measurement and prediction of disease progression. The AD field has made tremendous progress in this regard, through observational studies, such as the Alzheimer's Disease Neuroimaging Initiative (ADNI). The PD field is now replicating that approach through the Parkinson's Progression Markers Initiative (PPMI). Both of these programs focus primarily on efforts to clinically characterize candidate disease biomarkers and standardize the use of such biomarkers. Expanding this critical knowledge may allow impactful application of biomarkers, for more refined patient characterization or selection in clinical trials, as well as possibly provide supportive outcome measures better linked to underlying pathology. However, essential data are still lacking regarding how biomarkers progress through the continuum of the disease, how they change in response to treatment, their ability to detect and monitor the biochemical effects of a drug (i.e., their theragnostic value), and the clinical meaningfulness of a biomarker change. There is a need to embed biomarkers, including exploratory biomarkers, into clinical trials whenever feasible, and to share the data generated from such trials. Improved cognitive, behavioral and functional endpoints are also needed, which need be well anchored to clinically meaningful aspects of the diseases. As an example, in the AD field the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) represents the most commonly used cognitive assessment scale in trials to date, yet ADAS-Cog shows limited sensitivity in the early stages of the disease [4].

Modeling and simulation

CAMD's disease modeling team achieved a key milestone in 2013 with regulatory endorsement from the FDA and EMA, of its clinical trial simulation tool for mild and moderate AD. This is the first example of enabling model-based drug development by regulatory decision making [5]. The CAMD consortium has plans to develop a similar modeling tool for PD. The development of treatments for PD faces many of the same challenges as for AD: slow progression of the disease across multiple domains; declining efficacy of symptomatic therapies as the disease progresses; insensitive outcome measures impacted by factors other than treatment effects; high clinical failure rate for novel therapeutics; and the need for lengthy and costly clinical trials to investigate effects on disease modification.

To begin to address these issues, CAMD has developed a three-stage, multi-year plan to develop a quantitative PD progression model and clinical trial simulation tool with three primary tracks: science, data, and regulatory. The science track will develop models that will lead to an improved understanding of the disease and its progression as well as how to select the proper population for clinical trials, track placebo and drug effects, and model the effect of patient drop outs. The data track will focus on developing data standards and an integrated database to support model development. The regulatory track will work with the FDA and EMA to align in the model-development strategy and to formally review these quantitative platforms for potential regulatory endorsement.

Recognizing that large amounts of data will be needed in standardized form to support the development of the modeling tool, CAMD met with Parkinson's UK, and diverse influential stakeholders in London in May 2014, to map out a strategy for outlining the rationale and impact of precompetitive data sharing for PD. Existing datasets were identified that could be captured in a large, global database to support the development of the tool. These datasets represent clinical and observational studies as well as clinical trials data held by pharmaceutical companies. Also discussed were strategies to integrate and provide access to these data to qualified researchers, as has been successful in CAMD's AD database [6].

AD Biomarkers – CSF and imaging

Regulatory qualification of biomarkers holds broad impact for drug

development through the issuance of guidance that has applicability for diverse drug targets, independent of mechanism of action. For prognostic biomarker-specific enrichment, choice of the appropriate subjects to enroll in trials serves to de-risk the costly studies with regard to the proper enrollment of patients. The EMA has qualified CSF $A\beta_{1-42}$ and t-tau, and/or amyloid PET imaging for enrichment in AD trials [7] as well as low hippocampal volume (HV) by MRI for enrichment in prodromal AD trials [8]. CAMD represented the consortium that achieved successful EMA qualification of low hippocampal volume for the enrichment of clinical trials in pre-dementia stages of the AD [9]. Qualification of AD biomarkers by FDA is at the consultation and advice stage with an identified key success factor being data sharing of biomarker data from prodromal AD clinical trials.

In 2014, a candidate mass spectrometry-based reference method for $A\beta_{1-42}$ and a surrogate matrix for calibrators and quality control samples were developed under the auspices of the Global Biomarkers Standardization Consortium [10]. This represents important progress toward the qualification of CSF biomarkers because it provides, by direct measure of an analyte, a reproducible reference method against which the various immunoassay platforms can be compared. Importantly, the team is presently aligning with regulatory colleagues to determine how to support incorporation of CSF biomarker tests into treatment trials and how to integrate the data from CSF studies with other forms of data obtained in these trials.

Efforts by CAMD's AD Hippocampal Volume (HV) Biomarker Team to meet the FDA's request for more data have been supported by the European Alzheimer's Disease Consortium and ADNI (EADC-ADNI) Hippocampal Harmonization project, which this year achieved consensus on a protocol for manual segmentation of hippocampal MRI scans [11]. This provides a standard method for the qualification of human tracers and automated segmentation algorithms. In addition, the team has been preparing data for the FDA that addresses their concerns about instrument variability. Furthermore, data modeling carried out by CAMD experts has successfully demonstrated the practical benefit of hippocampal volume enrichment on protocol design [12].

Another issue that the HV Biomarker Team has been addressing is the transferability of enrichment cutpoints among different datasets. Analysis of three different datasets produced encouraging results [13-15], suggesting that the variability of cutpoints among different studies is low; however, it has been difficult to obtain data from published analyses that could be reanalyzed to confirm this finding.

Numerous additional new biomarkers have been discovered that show promise for AD and PD and there is a need to identify when novel candidate biomarkers are deemed ready for formal regulatory engagement. Although out-of-scope for this meeting, CAMD is presently actively engaging in identification of novel biomarkers and evidentiary standards for biomarker qualification.

AD clinical outcome assessments

The FDA published a draft guidance on developing drugs for early stage AD in 2013, which called for outcome measures that assess both cognitive and functional domains that are clinically meaningful to patients and caregivers [16]. The predementia Clinical Outcome Assessments (pCOA) Team, in alliance with the Clinical Outcomes Working Group in ADNI Private Partners Scientific Board (PPSB), has thus worked over the past few years to harmonize industry efforts to develop composite outcome measures that would provide more sensitive clinical measures in the earlier, mild cognitive impairment, stages of the disease.

After consideration of the various composites in development, the team selected the AD COMposite Score (ADCOMS) as the prototype clinical composite outcome assessment tool to be advanced through the regulatory qualification process. ADCOMS consists of a weighted combination of items from commonly used outcome scales, ADAS-Cog, MMSE, and CDR-SB, which have been identified through an un-biased statistical approach to be most sensitive in patients with amnestic mild cognitive impairment (aMCI) and prodromal AD. In 2013, CAMD submitted formal letters of intent (LOI) to both FDA and EMA. Both agencies accepted the pCOA project into their qualification procedures, however, both stressed the need to demonstrate the clinical meaningfulness of the composite. The FDA suggested leveraging qualitative research from Critical Path Institute's Patient-Reported Outcome (PRO) Consortium as one way of demonstrating clinical meaningfulness. Therefore, a sub-team consisting of members of the pCOA team and the PRO Consortium conducted a study designed to identify the cognitive symptoms that patients and informants endorse in early disease stages, and compare the results of this analysis to the subcomponents of ADCOMS. This study showed that the most frequently cited concerns of patients and informants mapped to one cognitive domain – episodic memory; while secondary concerns mapped to the domains of language, orientation, and executive functioning. Each of these concerns corresponds to one or more items represented in ADCOMS[17]. Regulatory briefing packages were submitted by the pCOA Team to both FDA and EMA in mid-2014, which were discussed in an EMA scientific advice meeting, with FDA present, in November 2014.

PD imaging biomarkers

The evaluation of biomarkers for PD lags behind that for AD, despite the prevalence of the disease and the lack of disease-modifying therapies. The joint meeting between CAMD and Parkinson's UK, mentioned earlier, signified CAMD's efforts to tackle this challenge through data integration across the globe. CAMD has successfully acquired key data in support of the development and qualification of dopamine transporter imaging as a prognostic biomarker for PD trials, targeting patients at the early motor stage of the disease.

Data sharing, standardization, and harmonization

Participants at the meeting stressed repeatedly the need for stakeholders to work together to address the unmet needs in AD and PD drug development. Data sharing enables not only integration and pooling of data that can generate new insights and reveal subtle signals, but also reduces redundancies, leading to cost savings. Perhaps, most importantly, data sharing honors the burden on patients and their caregivers when they participate in drug trials, by broadening the use and analysis of data obtained, and by applying the outcome of this work in future drug development programs. While both industry partners and academic researchers commonly have concerns about sharing data and other resources, CAMD members and C-Path have worked to address these concerns. For example, CAMD has successfully developed responsible legal and technical mechanisms that will allow data to be shared while maximizing the value to partners.

Sharing data requires the use of data standardization. The common data elements (CDEs) and Clinical Data Interchange Standards Consortium (CDISC) standards provide such a framework and enablethe use of a common language. NIH has worked with researchers in 17 different disease groups to establish CDEs, and requires their use by investigators receiving NIH funding, although monitoring this has proven to be problematic. One of CAMD's major accomplishments

has been the development of CDISC standards for AD clinical trials. PD CDISC standards have also been successfully developed. Both standards are available at no cost for broad use and application (www.cdisc.org). CAMD used CDISC-AD data standards to build an online data repository currently comprising data on 6500 subjects from 24 AD clinical trials from nine companies [6]. This database was used to create the AD clinical trial simulation tool mentioned earlier [5].

CDISC standards specify how data should be structured, not what should be collected. Both the FDA and EMA have notified the field that, by 2017, data submitted for regulatory review must conform to CDISC standards; a draft guidance, entitled "Providing Regulatory Submissions in Electronic Format – Submissions Under Section 745A(a) of the Federal Food, Drug, and Cosmetic Act," was issued in February 2014. The NIH also requires a data sharing plan in all grant applications, while clinicaltrials.govhas mandated data sharing after a clinical trial has been completed and reported.

Data standards are also a prerequisite for the field to develop "big data" approaches, that provide uniform platforms to enable the collection and utilization of data from a variety of sources; not only from clinical trials but genomics and other -omics studies, electronic medical records and novel sources of data, such as ubiquitous data collected from smartphones and other devices. However, the use of data standards also introduces challenges with regard to the remapping of existing data, and for newly collected data, putting it into a format that is meaningful and sharable. Other concerns related to data integration include harmonizing data collected over long trials where technologies change; obtaining patient consent for data to be shared and addressing issues related to de-identification of data; and addressing restrictions on sharing data across different countries. Having data managed by an independent neutral third party, such as C-Path/CAMD is one potential way of addressing some of these issues.

The consortium approach to qualifying outcome measures

CAMD's pCOA Team has, in particular, demonstrated the value of the consortium approach, while also identifying the challenges. Working in pre-competitive space, the team achieved consensus on an approach to qualification, which enabled them to leverage resources and potentially increase the efficiency of future studies [18]. Regulators noted that qualification is only one pathway to approval of a drug development tool, and in some cases it may be quicker for sponsors to work independently through the Investigational New Drug (IND) review process. However, having individual sponsors progress general drug development methods and tools on their own requires a sponsor to carry all the burden of qualification without, for example, having access to additional samples, data or important information from other sponsors. The standards for achieving qualification can in some ways be viewed as higher than the IND pathway, but it signifies that the endpoints have been adequately validated for a particular context of use and eliminates the need for subsequent sponsors utilizing the qualified tool to validate the tool. Qualification does not, however, indicate that the tool represents a required measurement for use in trials or a 'gold' standard compared to other outcomes. Both pathways are viable options for sponsors and can be advanced to regulators in parallel, suggesting that qualification is not an either/or option for seeking endorsement of a new clinical outcome measure.

Conclusions

Since its inception, CAMD has demonstrated both the feasibility and value of data sharing and collaborative research in the precompetitive space. The CAMD-FDA Annual Scientific Meeting provided an opportunity for industry members, regulators, academic colleagues, and advocacy organizations to revisit the urgent need to collaborate in the development of new treatments for patients suffering from AD and PD. Data sharing is the key to developing precision medicine for addressing the molecular and clinical heterogeneity of both these diseases. Beyond data sharing, big data approaches will enable investigators to access and analyze vast repositories of data from around the globe.

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