Introduction and reprise of prior ISCTM work

From Challenges to Opportunities in Disease Progression / Modification

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Apart from my Academic roles, I am the Chief Scientific Officer of EDRA-LSWR Publishing Company and of Inpeco SA Total Lab Automation Company. In the last year I have been a scientific consultant to Acadia USA, Ferrer Spain, Johnson & Johnson USA, VeraSci USA, Otsuka USA, Pfizer Global USA, PharmaMar Spain. **I do not bear any direct or indirect financial interest in concepts and products of this talk.**

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Introduction and reprise of prior ISCTM work

Expectations: Disease modifying treatments must impact on how patients feel, function, survive. Must they impact the biological process as well?

Proposed Definitions:

1. Gold Standard: Improves all aspects of the disease/disorder (Biological, Clinical symptoms / signs, Functioning)
2. Targets fundamental pathogenic mechanisms; ideally at the initiating processes & events (right place, right time)
3. Based on clinical benefits – changing course of the illness (MS)
4. Slowing disease progression (AD)
5. Delay in reaching predefined disease milestones (*e.g.* conversion from MCI to AD; prodromal/APS to Schizophrenia)
6. Reduction in progression of a biomarker: halting neurodegeneration or neuropathology (neuritic plaque), amyloid, cortical atrophy, hippocampal atrophy, metabolism-PET)

Clinical trials possible Designs:

1. Delayed Start
2. Withdrawal (randomized or not)
3. Enrichment of subgroups based on: clinical, cognitive, functional, duration and/or course of illness, digital?
4. Any combination of the above?

(Modified from Levine R., 2014)

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Disease Modification is only a regulatory concept?

The case of disease-modifying osteoarthritis drugs (D-M OA Ds) structural vs. clinical endpoints

1999-FDA. Clinical Development Programs for Drugs, Devices and Biological Products Intended for the Treatment of OA: Approvals for OA have been based on patient-reported outcome measures that assess pain and functional impairment.

2011 The Osteoarthritis Research Society International initiated a number of working groups to address a call from the FDA on updating draft guidance on conduct of OA clinical trials. The Assessment of Structural Change (ASC) Working Group recommended various structural endpoints (Conaghan et al., 2011).

2018 FDA: There is a **recognized discordance between structural changes and signs/symptoms/function**, the lack of standard definitions of disease progression, and, correspondingly, the absence of endpoints to reliably assess the ability of a product to alter OA disease progression. At this time it is unclear what magnitude of change in **structural endpoints would translate to a clinically meaningful benefit** to patients. To accept structural endpoints as valid outcome measures for accelerated approval, there should be **substantial confidence**, either based on empirical evidence from **randomized, controlled** comparisons clinical trials and/or based on a **comprehensive understanding of the disease process and product mechanism of action** that an effect on the candidate structural endpoint will reliably predict an effect on the clinical outcomes of interest.

At this time, the ability of treatment effects on common measures of structural progression to reliably predict treatment effects on direct measures of how patients function and feel, **has not been established**.

Disease Modification and efficacy measures in Diabetes

Rates of **severe hypoglycemia** and **diabetic complications** ultimately will be improved by therapies that are effective at **preserving beta-cell function** (Lord S, 2015)

American Diabetes Association (Palmer et al., 2004)

Measurement of C-peptide under standardized conditions provides a sensitive, well accepted, and clinically validated assessment of beta-cell function. C-peptide measurement is the most suitable primary outcome for clinical trials of therapies aimed at preserving or improving endogenous insulin secretion in type 1 diabetes patients.

EMA Guidelines:

The primary outcome should preferably consist of co-primary endpoints:

- Change from baseline in C-peptide (*e.g.* C-peptide AUC)

AND

- HbA1c;
- Frequency of hypoglycemic episodes, particularly severe events
- Percentage of patients not requiring insulin therapy or with a relevant reduction in insulin requirements.

Any of these endpoints not included as co-primary should be evaluated as important secondary endpoint.

Disease modification in CNS: the Case of Multiple Sclerosis

Modification of the natural course of the disease includes:

- Preventing or delaying the accumulation of disability.
- Preventing or modifying relapses.

The **primary efficacy parameter** in confirmatory trials in SPMS and in PPMS should be a clinically measured prevention or delay of the disability progression (EDSS)

In patients with RRMS or SPMS with superimposed relapses (RMS), the primary efficacy parameter may be based on relapses, and both the annual relapse rate (ARR) and the time to relapse are considered acceptable as primary endpoints. **A relapse-based primary endpoint though cannot be taken as a surrogate for disability progression and this would be expressed accordingly in the SmPC.**

Trial design for disease modification is parallel double blind however:

Confirmatory studies should be of an enough large scale and of sufficient duration to allow for the evaluation of an effect on relapses and disability

EMA Guidelines

Disease Progression Concept Development in MS

- Established disease progression;
- Understand the pathophysiology (some of): inflammatory/immune; white matter degeneration;
- Subgroup/Enrichment/Indication: Relapsing MS, specific disability scale score, failed on interferon;
- Clinically meaningful endpoints (symptoms, function, MRI findings);
- Primary endpoints:
  - Time to onset of sustained increase in disability.
  - Defined event.
  - Survival analysis.
  - Endpoint at 2 Years
- Kurtz Expanded Disability Status Scale (EDSS)

Modified from Levine R., ISCTM, 2014

Challenges in the Definition of Disease Modification in AD

Disease Modification Therapies (DMT) are defined as interventions that produce an enduring change in clinical progression of AD by interfering with the underlying pathophysiological mechanism(s).

Efficacy for DMTs **must (should?)** be demonstrated through clinical trial designs **and** biomarkers (Cummings 2017), however:

1. Does the word "Disease" include the prodromal phase when clinical symptoms are not present?
2. A "Modification" is defined as an enduring change in the disease process, but:
   a) does it involve biomarkers evidence of a change in the pathophysiological process or an enduring modification in the clinical course of symptoms is sufficient?
   b) biomarkers are not a direct evidence of a change in the process that leads to neuronal death, they could be used, at best, as an inferential concept and agnostic approach o gain a comprehensive view (as such, the more, the better)
3. Therapy is referred to a pharmacological intervention, however non pharmacological factors impacting biology cannot be disregarded.

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Conclusions

- Disease progression/modification could be considered a regulatory concepts, possibly translatable into a label.
- In most, if not all cases, disease modification must consist in an improvement of significant clinical symptoms.
- Improvement in clinical symptoms is such that the outcome, course and eventually compliances of the disease process are stably altered.
- Proving disease modification is challenging when the natural history of the disease is not completely known or significant heterogeneity is observed in large groups such as those in trial populations.
- Disease modification is also challenging when the biological process underlying the disease are not completely clear/univocal resulting in discordance between biological (biomarkers) and clinical evidence (PROs or functional endpoints).

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Future Perspectives for Discussion

- To label claims for disease progression/modification, knowledge of the natural history, years of observation and large samples are needed. In order to speed up the process, worldwide clinical trial networks should be built and in the very near future digital medicine products (*e.g.* sensors, pattern analysis, human-machine interactions, deep learning and predictive analytics by A.I. should be included and used in the trials).
- To narrow down heterogeneity in complex disease populations biomarkers could be useful if they allow for sub-samples definition with specific and sensitive molecular characteristics.
- If biomarkers fail or are not sufficient to address heterogeneity, behavioral or clinical parameters could be monitored with digital endpoints trying to define new subgroups based on patients profiling.
- In order to link biological and clinical evidence, large sets of reproducible data are needed. Virtual data platforms to collate worldwide clinical populations cohorts (biomarker positive or negative) would also be very useful.

Thank you