The scientific and regulatory approaches to facilitating disease-modifying drug development and registration in a global environment

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Declaration of conflict of interest

Thomas Blaettler is employee of F. Hoffmann-La Roche

Key considerations

- Consideration 1 – What do patients want?
- Consideration 2 – The Challenge:
  Disease Modification Claim requires correlation between Clinical Outcome and Biomarkers
- Consideration 3 – Alternatives to Disease Modification – Delay of disability

What do patients want?

Prevention Of Disease

- Identify individuals at risk and prevent disease
- Very Aspirational!

Cure

- Cure patients who have developed disease
- Very Aspirational!

If one cannot prevent or cure disease:

Delay of Clinical Decline/ Progression

- Aim at delaying clinical decline or disease progression
- Direct impact on patient and care-givers: Delay disability, maintain independence, allow to live normal live for longer

Relief of Symptoms

- Relieve symptoms to best degree possible
- (Incrementally) Improve cognition, function and behavioral symptoms and mood
- Where we are today?

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Definition of disease-modifying vs. symptomatic effect

Disease-modifying effect:

- "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." (EMA guideline on medicinal products for the treatment of Alzheimer's disease and other dementias)

Symptomatic improvement

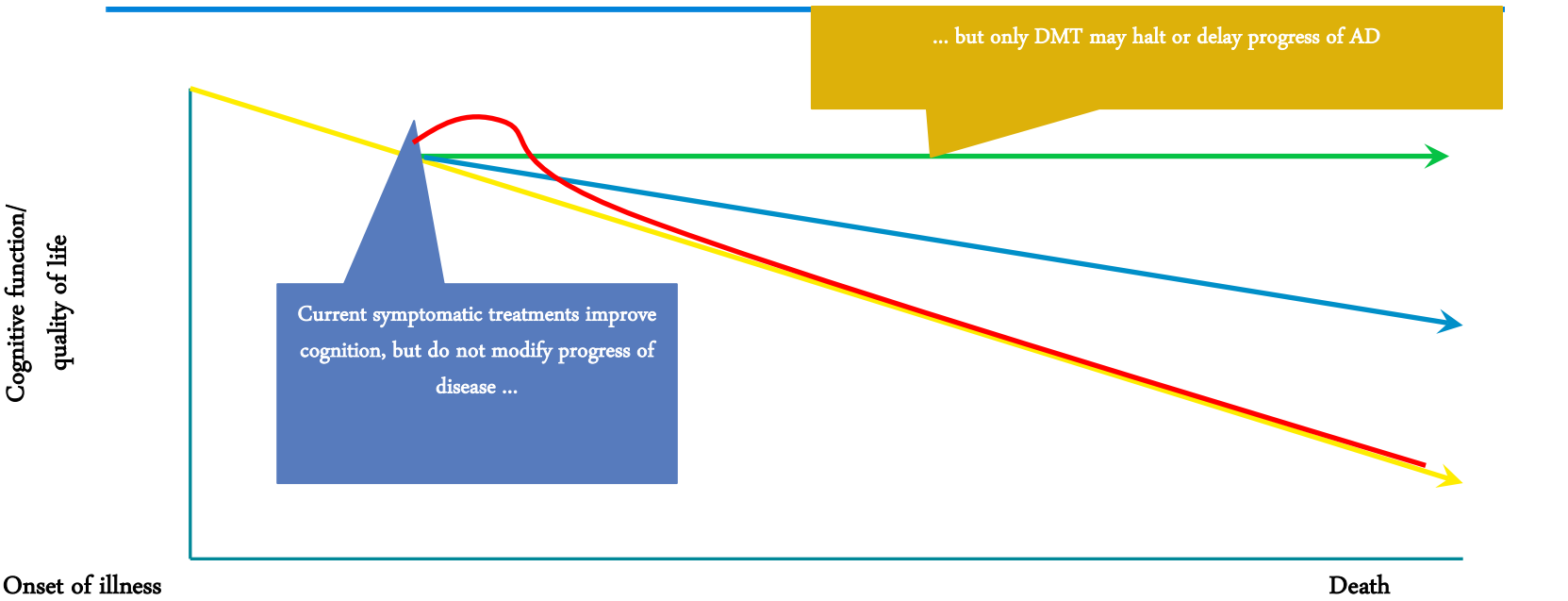
- May consist of enhanced cognition, more autonomy and/or improvement in neuropsychiatric and behavioral dysfunction (EMA guideline), likely for a limited duration

Therapies approved to date

- Last Approval in 2002 (memantine) – symptomatic treatment only
- Limited improvement: may delay or prevent symptoms from becoming worse for a limited time
  - cholinesterase inhibitors: mild to moderate Alzheimer's Disease
  - memantine: moderate to severe Alzheimer's Disease
- No new therapies for more than 10 years
- Although many development programs ongoing targeting underlying pathology, no DM therapies approved to date!

With current end-points disease modifying treatments may appear less efficacious in short-term

Symptomatic treatments provide benefit in short-term, but only disease modifying treatment can substantially change course of disease



Longer trials needed to observe statistically significant clinical impact for DMT vs symptomatic Tx

Source: Primary Psychiatry 2013, http://primarypsychiatry.com/from-symptom-palliation-to-disease-modification-implications-for-dementia-care/; Roche

The Challenge: Disease Modification Claim requires correlation between Clinical Outcome and Biomarkers

- BMs available today include:
  - CSF levels of Aβ–42, tau, & p-tau
  - Structural imaging (MRI): measure brain atrophy
  - Amyloid PET: measure amyloid deposition
  - Functional imaging (FDG PET): measure glucose utilization

- Demonstrate differences between patients and normal controls as well as change with progression of disease
- But none of these yet have been correlated with a therapeutic effect on clinical outcome:
  - No positive trial yet…

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What degree of correlation between clinical outcome and BMs is needed to prove disease modification?

Reference in current EU guideline: "*…a disease modifying effect will be considered when the pharmacologic treatment delays the underlying pathological or pathophysiological disease processes and when this is accompanied by an improvement of clinical signs and symptoms….*"

- Thus will a clinical outcome when combined with the appropriate biomarkers support a disease modifying claim?
- If a drug with strong biological plausibility, effect on biomarker and improvement in outcomes (e.g. cognition and/or function), but without strict correlation per se, would totality of data be convincing enough for a DM claim?
- Is replication needed in at least two independent development programs with distinct therapeutic agents?

  - *What are appropriate biomarkers, is a single plausible BM enough or is a combination of BMs needed? (e.g. evidence of target engagement + down stream effect)*

Alternatives to disease modification

- If DM currently presents such a large hurdle, are there alternative intermediate approaches that can be taken?
- If we think back to what the patients want, the Delay in Clinical Progression of Disease would appear to be a valuable aim
- So how we do achieve this..?
  - Reference in current EU guideline: “If in a first step delay in the natural course of progression of the disease based on clinical signs and symptoms of the dementing condition can be established, this may be acceptable for a limited claim, e.g. delay of disability”.

How to demonstrate delay in clinical decline

- Slope analysis
  - Increasing divergence of treatment and placebo groups may indicate disease-modifying effect
  - "We have concerns that a pharmacologically reversible effect that increases over time could also lead to such an outcome" *(EMA and FDA)*
- Randomized start / withdrawal designs
  - Complex trials that have not been successful to date
  - Both EU and US guidelines acknowledge the difficulty with such design
  - While it is important to keep this pathway open, inherent challenges mean it is also important to consider alternatives
- Survival design using appropriate TTE endpoint
  - Commonly used TTE endpoints require long observation periods, may have low inter-rater reliability and may require adjudication
  - Can we define TTE endpoints that have high validity and reliability and that are expected to require a limited observation period
  - Or can correlation between change for BL endpoints and TTE endpoint be established outside the registration trials?

Elephant in the room

- AD trials (especially those to address DM) are large, complex and expensive
- To encourage continued investment in new innovative drugs there has to be a return on that investment
- Return of Investment will be driven by differentiation from current symptomatic treatments
- If hurdle for demonstration of DM is too high, this becomes challenging
- Lack of ability to differentiate will raise challenges to developing high risk programs

Conclusions

- Studies for drugs likely to have an effect on DM are large, complex, long….and expensive
  - Approaches to establish delay in clinical progression are inherently difficult
  - Correlation between clinical outcome and biomarker effect may be too high a hurdle

- To encourage continued investment and to provide physicians and patients with relevant information to help prescribing, it is important to be able to communicate difference of DM drug vs current symptomatic treatments

Key regulatory questions (1/2)

- Question 1 – Disease modification:

EFPIA would contend that a study with positive clinical outcome plus effects on a biologically plausible biomarker could demonstrate disease modification

  - Can EMA allow flexibility around the requirements for validation/qualification?
    - Taking into account variability of clinical progression and biomarker effects does the Agency agree that a study-level correlation between clinical outcome end biomarker effect may support the DM claim in absence of strong patient level correlation?
    - Does the Agency agree that replication across multiple studies and molecules may not be needed for a DM claim?

Key regulatory questions (2/2)

- Question 2 – Delay of Disability as an intermediate step:
  - It is understood that "Delay in Disability" could be an intermediate claim if disease modification could not be demonstrated. This claim does not require additional commitment – Do you agree?
  - The guideline should be flexible to allow multiple different, approaches demonstrating delay in disability / slowing of clinical decline including time to event, slope analysis and randomized start / withdrawal designs – Do you agree?

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