Overcoming Challenges of Drug Development in Behavioural Variant Frontotemporal Dementia

Background

Frontotemporal lobar degeneration (FTLD) encompasses a variety of clinical and genetic progressive neurodegenerative syndromes, which include the behavioural variant of frontotemporal dementia (bvFTD), primary progressive aphasia (PPA), corticobasal syndrome (CBS), and progressive supranuclear palsy (PSP). Although considered rare, FTLD represents the second most common type of early-onset dementia, predominantly affecting younger populations than Alzheimer's disease (AD), and is thought to have an even greater deleterious effect on the lives of patients and their families.

FTLD is typically diagnosed in middle age, with age 56 being the median age of onset, although it has been reported in patients as early as their third decade,[1] with 13% of cases occurring before age 50.[2] A systematic review of 26 population-based studies on FTLD showed large variation in the estimates of incidence (up to 31 cases per 100,000 person years) and prevalence (up to 461 people per 100,000).[3] Unlike AD which is preferentially seen in females, the overall rates of FTLD among men and women appear to be roughly equal.[3] Importantly, in contrast to AD, an association with genetic mutations has been recognised in 15–20% of all FTLD patients representing a dominantly inherited familial disorder (f-FTLD). The most common mutations associated with FTLD occur in the microtubule-associated protein tau (MAPT),[4] progranulin (GRN),[5] and chromosome 9 open reading frame 72 (C9orf72 or C9ORF72)[6–7] genes. Together, these mutations account for at least 50% of all f-FTLD.[6–7]

FTLD is categorised pathologically by the accumulation of three different protein aggregate inclusions within neurons and glia, which determine pathological subtypes of the disease. These aggregates include tau (FTLD-tau), transactive response DNA-binding protein 43 kDa (FTLD-TDP), and fused in sarcoma protein (FTLD-FUS).[8]

Behavioural Variant FTD (bvFTD)

The most common pheno type of FTLD is bvFTD, which represents over half of all FTLD cases. It is characterised clinically by early changes in behaviour, personality, emotion, and executive control. Episodic memory and visuospatial skills are widely considered to be relatively preserved at the onset of bvFTLD, but more recent evidence has suggested more subtle impairment of memory functions and subjective memory complaints even in early stages of bvFTD.[9] Language impairment frequently emerges later in the course of bvFTD, expressed as anomia and semantic deficits.

These neurocognitive symptoms are thought to reflect dysfunction in the nondominant prefrontal cortex, anterior temporal lobe, paralimbic structures (anterior cingulate, frontal insular, and lateral orbitofrontal cortices), hippocampus, and subcortical structures (ventral striatum and dorsomedial thalamus).[10] Structural brain imaging has consistenly shown atrophy within the non-dominant frontal, anterior temporal, and anterior insular cortices, and atrophy in these brain structures is universally included in the diagnostic criteria of probable bvFTD.[11] Of note, structural brain MRI in bvFTD can initially be inconclusive and serial longitudinal MRI assessments at yearly intervals may be needed to document progressive brain atrophy congruent with a clinical impression of deterioration. Functional neuroimaging (SPECT and FDG-PET) appears to have a limited role in diagnosis but may be useful in distinguishing FTD from AD and other neurodegenerative diseases based on patterns of regional hypometabolism, acknowledging that these functional imaging modalities may not reliably differentiate bvFTD from frontal variants of AD.

Differential Diagnosis of bvFTD

The differential diagnosis of bvFTD can be challenging, particularly in early stages where the predominantly psychopathological phenotype may mislead clinicians and triallists into falsely rendering a primary psychiatric diagnosis[12] including schizophrenia, schizoaffective disorder, and bipolar disorder. Formal diagnostic criteria can distinguish possible bvFTD based on symptomatology alone, whereas probable bvFTD requires both imaging findings and documentation of functional decline. A definitive diagnosis of bvFTD with FTLD pathology requires a histopathological analysis or presence of a known genetic pathological mutation.[11] A lack of specificity is a major disadvantage of the current diagnostic criteria while brain MRI results, provide only moderate sensitivity and specificity.[13] Unfortunately, there are no validated cerebrospinal fluid (CSF) or blood/plasma biomarkers for diagnosis of bvFTD as yet, and there is an urgent need for such biomarkers for use in differential diagnostics, disease monitoring, and the assessment of the effects of potential therapeutic treatments in FTLD patients.

Sadly, early recognition of bvFTD can be especially challenging due to the variability of initial symptoms, which results in an average delay from the onset of symptoms to diagnosis of bvFTD of 3.6 years,[14] which unfortuantely is roughly equivalent to the average survival time after diagnosis calculated to be between three and four years.[15] FTLD is associated with a relatively rapid progression compared to AD with lethal outcome usually occurs within ten years from the onset.[16] However progression with longer survival (ranging 20–30 years) has been infrequently described. The complexity, heterogeneity, large interplay of FTLD phenotypes and neuropathology, rapid progression of clinical course, and delay in accurate diagnosis create unique challenges for drug developers which include the appropriate selection and retention of study populations, as well as selection of optimal outcome measures sensitive to treatment effects.

Lessons Learned from Previous Clinical Trials in bvFTD

To date, there have been relatively few published placebo-controlled trials in bvFTD, recruiting less than approximately 450 patients in total. These have largely been proof-of-concept studies designed to provide early evidence of the likelihood of success in later trials, or were designed to explore initial safety and tolerability of investigational products in subjects with bvFTD. A few clinical trials have included both bvFTD and sematic dementia subjects. Together, this paucity of data and heterogeneity of outcomes measures makes a quantitative assessment of bvFTD via formal meta analytic techniques implausible at this point.

A systematic qualitative literature review of randomised controlled trials (RCT) of pharmacological therapies for bvFTD has suggested significant heterogeneity in design and methodology.[17] Participants with different clinical phenotypes have been enrolled across studies using diverse eligibility criteria based on the clinical diagnosis, age at baseline, and the presence or absence of certain cognitive deficits. Various drugs with different pharmacodynamic and pharmacokinetic properties, as well as numerous tools and scales with different psychometric properties, have been investigated, and most studies reviewed were early-phase clinical trials that were small in size, relatively short in duration and frequently underpowered in terms of both, making it difficult to make comparisons across studies and render statistical inferences.

Nevertheless, the experience gained from the few clinical studies in this rare patient population remains vital in the planning of future clinical trials. It is essential to carefully consider all elements of design potentially affecting the execution, analysis, and interpretation of the potential new study. Domains to be carefully evaluated included the sites' current practice and metrics in the treatment of patients with bvFTD, the impact of protocol-mandated restrictions, and protocol structural elements that might influence IRB/regulatory approval or study execution. In addition, as with other dementia studies, it is critical to apply a targeted and country-specific approach to mobilise these patient volunteers and their study partner/caregiver/informant to participate as randomisation should be thought of in terms of dyads.

As such, the requirement of caregiver participation is crucial to enrolment and retention of bvFTD patients. It is not necessary to demand a minimum number of hours per day or days per week that a caregiver has contact with the patient. Rather, it is important that the patient has a primary caregiver willing to accept responsibility for supervising the treatment and assessing the condition of the subject throughout the study in accordance with all protocol requirements. The accuracy and validity of the information obtained in several clinical assessment scales used in bvFTD trials is highly dependent on the caregiver, who must have access to and observe the patient regularly. The availability of a single caregiver informant throughout the duration of the clinical trial is essential.

Selection of Patients

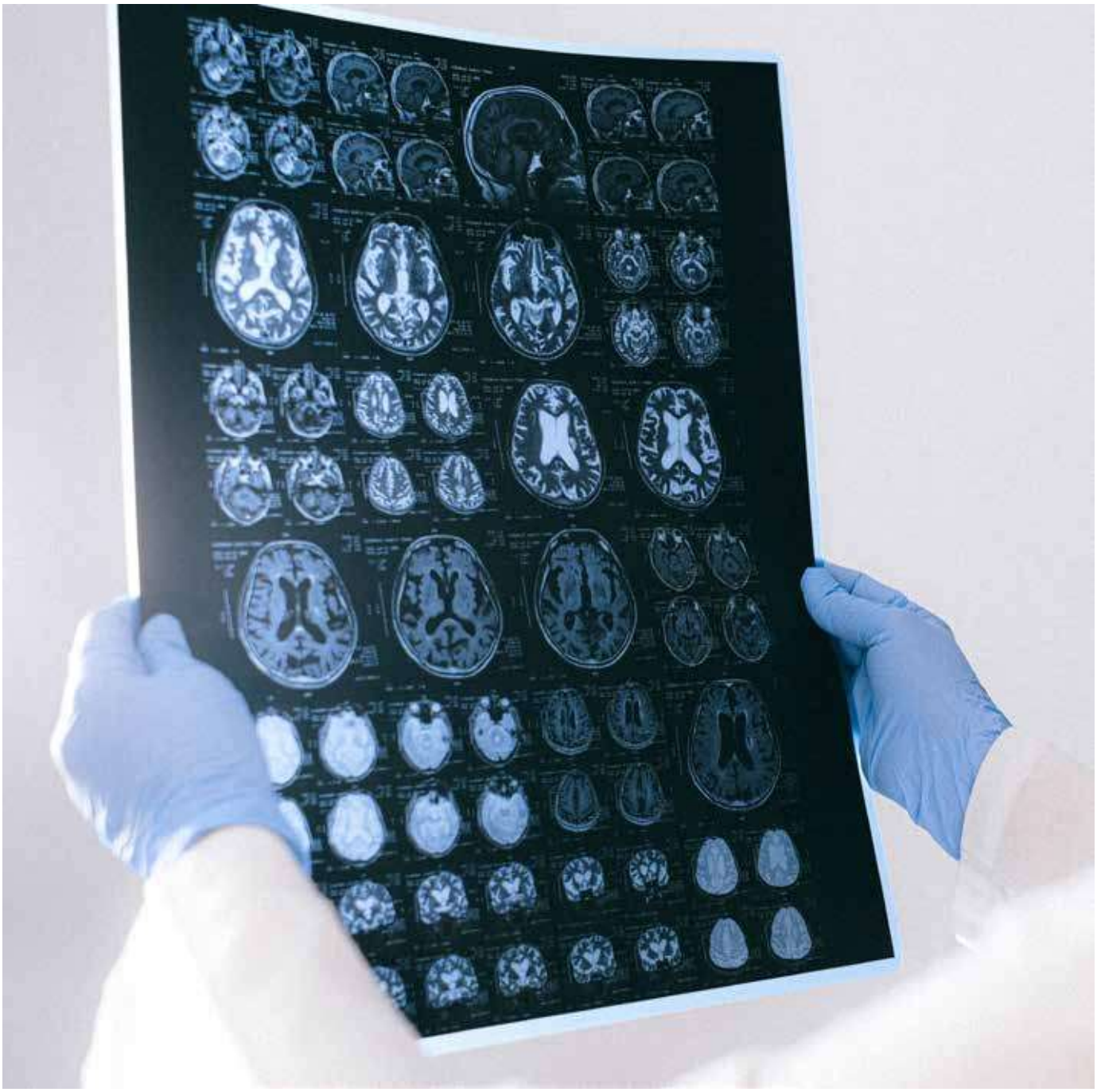
As stated, one major challenge in bvFTD studies is that the disease is rare and patients often have symptoms that overlap with other neurological/psychiatric disorders, making the selection of appropriate patients problematic. Due to this, there has been a real lack of standardised and broadly used criteria used to enrol bvFTD patients. For example, barely 60% of bvFTD published trials required lower and upper age limits for inclusion purposes, with a minimum age ranging from 30 to 60 years and the maximum age 65 to 80 years. The presence of significant cognitive impairment was an important exclusion criterion in nearly 70% of bvFTD trials. Several trials have used neuropsychiatric inventory (NPI) sub scores (aggression and/or disinhibition >4) as an inclusion criterion, whereas others selected patients based only on diagnostic criteria for possible bvFTD and mini-mental state examination (MMSE) or clinical dementia rating (CDR) scales.. Researchers have recently developed a new behavioural disturbance scale adapted from diagnostic criteria,[11] which explores six domains: disinhibition, apathy, perseverations, hyperorality, personal neglect, and loss of empathy (DAPHNE),[18] which has shown excellent reliability, reproducibility, and external validity and should be considered for use as a quick tool for both screening and diagnostic purposes in bvFTD.[18] Several ongoing studies in subjects with bvFTD have also utilized a recently modified version of the clinical dementia rating (CDR-FTLD) scale for inclusion purposes recruiting subjects with global score "2" or lower. The CDR-FTLD is an extended version of the CDR, which includes two additional domains – language and behaviour – that reportedly has higher sensitivity in tracking bvFTD-associated decline over 12 months than the standard CDR score.[19]

The presence of brain imaging abnormalities, mainly fronto-temporal atrophy, has been used as an entry criterion in approximately 60% of bvFTD trials, although the methodology to assess severity of brain atrophy was provided in only one trial[20] (published as an abstract only), which enrolled participants with evidence of frontal and/or temporal lobe atrophy on brain MRI a Kipps level "2" or greater.[21] Kipps et al devised a method for the systematic assessment of structural MR images in FTD that is very easy and applicable in a wide range of clinical and research settings. This frontotemporal atrophy scale is based on postmortem staging which has been shown to be both reliable and to correlate with disease duration and disease severity. This *in vivo* method involves the assessment of frontal and temporal lobe atrophy at two coronal levels on MRI which correspond to those utilised in postmortem ratings. Kipps devised a five-point scale (ranging from zero to four, with zero describing a normal MRI and four being the most severely abnormal) with specific criteria formulated for each level. For enrolment into research studies, it is best if subjects have a Kipps frontotemporal atrophy score of two or greater, irrespective of whether they have pre-existing structural or functional imaging evidence supporting a diagnosis of bvFTD; as ratings of two or greater have been shown to predict cognitive decline in bvFTD subjects. Thus, utilising simple imaging criteria such as this may help to enrol subjects who expected to decline sufficiently on the outcome measures such as the Addenbrooke's Cognitive Examination-Revised (ACE-R).

Lastly, fluid biomarkers such as plasma and cerebrospinal fluid (CSF) have not been reliably utilised as an entry criterion in many bvFTD trials, mostly due to their insufficient sensitivity and/or specificity. Ideally, biomarkers should be able to differentiate FTLD patients with different underlying pathological processes or genetic underpinnings, leading to focused treatment strategies for a specific group or subgroup of patients. Although significant progress has been made, there is no single fluid biomarker that has shown utility in bvFTD trials to date. However, the combination of biomarkers including increased serum neurofilament level,[22] reduced phospho-tau/tau ratio in CSF,[23] and increased cortical mean diffusivity using diffusion weighted MRI scans[24] may potentially provide greater sensitivity and specificity in differentiating bvFTD from other neurodegenerative and psychiatric disorders and could help potentially define populations more likely to benefit from treatment.[9]

Clinical Outcome Measures

Previous clinical trials have demonstrated the feasibility and practicality of using behavioural questionnaires, cognitive scales, and functional activity ratings as possible outcome measures.[17] Of note, nearly all clinical trials in bvFTD have focused on the treatment of neuropsychiatric symptoms using either neuropsychiatric



inventory (NPI) or the frontal behavioural inventory (FBI). The largest randomised, placebo-controlled study in bvFTD (220 subjects)[20] utilised the Addenbrooke's Cognitive Examination-Revised (ACE-R) as a primary efficacy instrument. The ACE-R has been shown to be useful in the detection, differentiation, and monitoring of cognitive decline longitudinally in dementia syndromes, such as FTD and AD.[25]

The above-mentioned eight-item CDR-FTLD instrument, which is being used in several ongoing studies as the primary efficacy instrument, and a novel 12-item multidomain impairment rating (MIR)[26] scale were both developed to encompass key manifestations of the FTLD spectrum disorders for use in natural history studies and clinical trials. Importantly, the MIR is designed to be more sensitive than standard scales to the earliest signs and symptoms of FTLD in genetic mutation carriers. The MIR encompasses elements of the FTLD-CDR plus a visuospatial domain, as well as domains associated with Parkinsonism, motor neuron disease (MND), and other non-cognitive/non-behavioural aspects of FTLD. The ratings, similar to CDR for each domain, are based on three data sources – the subject, informant, and objective neuropsychological testing. Consensus summary ratings include the MIR neuropsychology score, the global (MIR), and summed score (MIR SS). Although lengthy, the MIR may provide added value to the FTLD-CDR and could be used in natural history studies and clinical trials to more optimally capture the wide spectrum of features in FTLD.[26]

Unfortunately, from an efficacy viewpoint many of these scales have not been able to detect treatment effects for a variety of reasons, as many of these outcome measures do not adequately address the clinical, etiological, and imaging heterogeneity between patients. Additionally, inadequate sample size, short duration of trials, and a mismatch between outcome measures and subjects selection with participants being too early or late in the course of the disease to demonstrate therapeutic benefit may all constitute reasons why changes in outcome measures have been relatively insensitive to treatment.[17]

Conclusion

In summary, despite the widely adopted current diagnostic criteria, timely and accurate diagnoses of the behavioural variant of frontotemporal dementia (bvFTD) have remained challenging for clinicians and triallists. The advent of a novel biomarker or some combination of specific and early sensitive biomarkers should be prioritised by funding agencies. The behavioural variant of frontotemporal dementia is characterised by expression of various cognitive and behavioural manifestations, which may require diverse and targeted pharmacological interventions, and consequently necessitate a variety of assessment tools to measure the effects of these interventions. Clinical tools specifically designed for bvFTD, like DAPHNE or FTLD-CDR, which take into consideration the various manifestations of the clinical phenotype, should be useful in future studies. Clearly, controlled clinical trials in bvFTD can be challenging, but optimising study design through the careful selection of appropriate sites, patients, and outcome measures as described above can dramatically increase the chances of success.

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