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Review

Therapy and clinical trials in frontotemporal dementia: past, present, and future

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Abstract

Frontotemporal dementia (FTD) is a common form of dementia with heterogeneous clinical presentations and distinct clinical syndromes. This article will review currently available therapies for FTD, its related disorders and their clinical evidence. It will also discuss recent advancements in FTD pathophysiology, treatment development, biomarker advancement and their relation to recently completed or currently ongoing clinical trials as well as future implications.

Keywords: frontotemporal dementia, clinical trials, treatment, 10th International Conference on Frontotemporal Dementia, behavioral variant frontotemporal dementia (bvFTD), primary progressive aphasia (PPA), progressive supranuclear palsy (PSP), tau, TDP-43, C9ORF72.


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Frontotemporal dementia (FTD) is a common form of dementia with heterogeneous clinical presentations encompassing dysfunctions in behavioral, language, motor, and cognitive domains. FTD typically comprises of three distinct clinical syndromes; behavioral variant frontotemporal degeneration (bvFTD), and two primary progressive aphasias (PPA): non-fluent variant primary progressive aphasia (nvPPA) and semantic variant primary progressive aphasia (svPPA). FTD also frequently overlaps clinically with three additional neurodegenerative diseases with profound motor deficits: corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), and amyotrophic lateral sclerosis (ALS) (Bang et al. 2015).

Each of the above clinical syndromes have established diagnostic criteria that identify the seminal features including: social dysfunction, executive, and behavioral changes for bvFTD (Rascovsky et al. 2011), agrammatic, effortful speech for nvPPA, and impaired single-word comprehension, naming in svPPA (Gorno-Tempini et al. 2011). CBD, now referred to as corticobasal syndrome (CBS) for the syndromic presentation and CBD for the underlying neuropathology, can present with multiple subtypes encompassing motor, behavioral, or cognitive changes (Armstrong et al. 2013). Ophthalmoplegia and early falls are characteristic for the most common presentation of PSP (Richardson’s) (Litvan et al. 1996), whereas ALS is a motor neuron disease with increasingly recognized cognitive and behavioral features (Ringholz et al. 2005). Despite such a wide range of clinical presentation, the above syndromes are generally recognized under the umbrella term frontotemporal lobar degeneration (FTLD) as the different clinical phenotypes often share underlying neuropathological substrates. The most common underlying forms of FTLD involve

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Abbreviations used: AD, Alzheimer’s disease; ALS, amyotrophic lateral sclerosis; ASO, antisense oligonucleotide; bvFTD, behavioral variant frontotemporal dementia; C9ORF72, chromosome 9 open reading frame 72; CBD, corticobasal degeneration; CBS, corticobasal syndrome; CSF, cerebrospinal fluid; FDA, food and drug administration; FTD, frontotemporal dementia; FTLD, frontotemporal lobar degeneration; GRN, progranulin; HDACi, histone deacetylase inhibitor; MAPT, microtubule-associated protein tau; MRI, magnetic resonance imaging; nvPPA, non-fluent variant primary progressive aphasia; NPI, neuropsychiatric index; PET, positron emission tomography; PiD, Pick’s disease; PPA, primary progressive aphasia; PSP, progressive supranuclear palsy; SSRI, selective serotonin reuptake inhibitor; svPPA, semantic variant primary progressive aphasia; TDP-43, TAR DNA-binding protein 43 KDa.

Currently available symptomatic treatments

Currently available medications commonly used for FTD were developed for use in psychiatric disorders or Alzheimer’s disease (AD) and are not indicated (approved) for treatment of FTD. The majority of these agents work by modulating the levels or downstream effects of various neurotransmitters, strategies that have been effective in AD or Parkinson’s disease. Abnormalities in the cholinergic, serotonergic, dopaminergic, noradrenergic, and glutamatergic systems in FTD provide the rationale for these treatment efforts (Kaye et al. 2010). Unfortunately, the majority of available evidence is limited to small case series or open label trials. In some cases, initially promising agents failed to prove efficacious in further, more rigorous testing under randomized, double-blind, placebo-controlled conditions. The majority of these treatment efforts were aimed at improving behavioral, cognitive, or motor symptoms of FTD.

Behavioral symptoms management

Disinhibition, apathy, lack of empathy, compulsive behavior, and altered eating habits are cardinal features for bvFTD (Rascovsky et al. 2011). These behavioral symptoms are also prominent in PSP (Kobylecki et al. 2015), right temporal variant of svPPA (Seeley et al. 2005), have been described in nfvPPA (Gómez-Tortosa et al. 2015) and as a possible clinical presentation of CBD (Murray et al. 2007; Ling et al. 2010; Lee et al. 2011). Furthermore, depression is a commonly seen symptom in all neurodegenerative dementias. Neuropathological analyses have shown dysfunctional serotonergic systems with reduced 5HT1, 5HT2A receptors in orbital frontal, cingulate, frontal medial, temporal regions, and 40% loss of neurons in the serotonergic raphe nuclei (Procter et al. 1999; Yang and Schmitt 2001; Franceschi et al. 2005). As selective serotonin reuptake inhibitors have historically been successful in managing mood symptoms in psychiatric and AD patients, a variety of serotonergic medications have seen use in FTD patients with mixed results.

In a case series and a 14-month open label trial without placebo, paroxetine was shown to improve repetitive behavior and neuropsychiatric index (NPI) respectively (Chow and Mendez 2002; Moretti et al. 2003a). However, the same drug failed to demonstrate significant differences in NPI or the Cambridge Behavioral Inventory in a randomized, double-blind, placebo-controlled crossover trial (Deakin et al. 2004). Sertraline has been shown to improve behavior in several open label trials in FTD patients (Swartz et al. 1997; Mendez et al. 2005) and improved the NPI in four svPPA subjects in another trial (Prodan et al. 2009). Citalopram has been shown in a 15 FTD patients open label trial to improve the NPI and frontal behavioral index (Herrmann et al. 2012), and a 12 week randomized, placebo-controlled, double-blind crossover trial demonstrated efficacy of trazodone in 26 FTD patients via improved NPI (Lebert et al. 2004). It is generally accepted that antidepressants may help manage behavioral symptoms in FTD patients and are well tolerated.

While antipsychotics have long been used to control difficult behavior, evidence for their use in FTD comes mainly from case reports and uncontrolled series. Furthermore, all antipsychotic use carry the risk of extrapyramidal side effects, to which FTD patients are particularly...
vulnerable (Pijnenburg et al. 2003). In the US, there is also a FDA black box warning (drugs marketed in the US with special problems that lead to serious injury or death have warning information displayed within a box in the prescribing information) for all antipsychotics as use of atypical antipsychotics for dementia is associated with higher mortality than placebo, because of a higher cardiaco-infection-related mortality. Quetiapine was shown in a case series to improve agitation (Chow and Mendez 2002) but failed to show significant changes in NPI in an eight FTD subject, double-blinded crossover trial (Huey et al. 2008). Risperidone and apriprazole have been described to improve agitation, inappropriate behavior in a series of case reports (Curtis and Resch 2000; Chow and Mendez 2002; Fellgiebel et al. 2007; Reeves and Perry 2013), whereas olanzapine was reported to improve NPI scores in 17 FTD patients in an open-label study (Moretti et al. 2003b). Other approaches to controlling behavioral symptoms in FTD involve use of antiepileptics with mood stabilizing effects such as valproic acid, topiramate, carbamazepine, but evidence is mostly limited to case reports (Chow and Mendez 2002; Cruz et al. 2008; Nestor 2012; Poetter and Stewart 2012; Shinagawa et al. 2013; Singam et al. 2013).

Of note, other novel approaches to managing behavioral symptoms for FTD are currently being studied in placebo-controlled trials. The neuropeptide oxytocin, an important mediator of social behavior, was administered intranasally to 20 bvFTD and three svPPA patients in a double-blind, randomized, placebo-controlled, crossover trial over 1 week and demonstrated possible trend toward improved apathy and empathy (Finger et al. 2015).

Cognitive symptoms management

Cognitive symptoms are present in FTD and all its related disorders in varying degrees. Acetylcholinesterase inhibitors have been the mainstay of Alzheimer’s treatment, and perhaps because of their success, acetylcholinesterase inhibitors have been studied extensively in the treatment of FTD, though all have produced disappointing results. Donepezil was studied in a 6 month, open label study of 24 FTD patients, with the treatment group resulting in worsening on the FTD inventory and four had worsening behavior. Discontinuation of donepezil resulted in abatement of behavioral symptoms, which was replicated in other recent studies (Mendez et al. 2007; Arciniegas and Anderson 2013; Kimura and Takamatsu 2013). In PSP, donepezil was tested with positive effects on memory but with more impaired motor function in a five patient series and a randomized, placebo-controlled, double-blind crossover trial of 21 PSP patients (Fabbrini et al. 2001; Litvan et al. 2001). Rivastigmine was studied in a 12-month open label study in FTD and showed some improvements in NPI but did not prevent cognitive deterioration (Moretti et al. 2004). In PSP, rivastigmine produced similar results compared to donepezil, where a five PSP case series resulted in positive effects on memory but decreased motor function (Liepelt et al. 2010). The third most commonly used acetylcholinesterase inhibitor, galantamine, was studied in 36 bvFTD and PPA patients. No significant differences were found in the bvFTD group, whereas the language function remained stable in the treated PPA group compared to placebo, although it is likely these subjects had the logopenic form of PPA which is typically caused by underlying Alzheimer’s pathology and not FTLD (Kertesz et al. 2008). Currently, the evidence suggest cholinesterase inhibitors are not effective in FTD or PSP patients, and may worsen behavior or motor function respectively. Routine use is not recommended.

Memantine is a N-methyl-d-aspartate receptor antagonist with an indication for treatment in moderate to severe AD, with beneficial effects on activities of daily living and cognition (Reisberg et al. 2003; Tariot et al. 2004). Although AD and FTD differ in underlying pathology, excitotoxicity via over activation of N-methyl-d-aspartate receptors may be a final common pathway for neuronal death. With this rationale in mind, memantine was studied in a small case series and open label study that suggested some improvements in NPI (Swanberg 2007; Boxer et al. 2009). Memantine was then tested in two rigorous, randomized, placebo controlled trials over 52 weeks and 26 weeks. Although both trials did not enroll the originally planned number of patients, both failed to demonstrate significant benefits on NPI or clinical global impression of change. Furthermore, the memantine group was associated with worsening cognitive function (Vercelletto et al. 2011; Boxer et al. 2013a). Experience with memantine in FTD stresses the limitations of extrapolating AD therapy to FTD and importance of randomized, placebo-controlled, double-blind trials to truly demonstrate efficacy.

Motor symptoms management

A substantial portion of FTD patients also present with parkinsonism. Frontotemporal dementia with parkinsonism (FTDP-17), an autosomal dominant form of FTD associated with mutations in the MAPT or PRG gene, is frequently characterized by progressive movement difficulties, including tremors, rigidity and bradykinesia. Furthermore, the FTD-related disorders PSP and CBD are defined by atypical parkinsonism, typically with substantial rigidity and infrequent tremors. Unfortunately, FTD, PSP, and CBD patients generally do not respond to dopaminergic therapy such as levodopa/carbidopa. A few cases of FTD with benefits from levodopa/carbidopa have been reported (Chow and Mendez 2002). In PSP, despite prominent parkinsonism, dopamine replacement therapy has seen limited benefit. This may be because of more widespread pathology involving additional basal ganglia, brainstem and cerebellar structures in PSP as opposed to limited involvement in dopaminergic output via the substantia nigra pars reticulata in Parkinson’s disease.

Clinical studies with levodopa in PSP were limited to open label case series without placebo control, and true benefits were difficult to determine (Klawans and Ringel 1971; Kompoliti et al. 1998; Birdi et al. 2002).

**Non-pharmacological interventions**

Non-pharmacological interventions in FTD and its related disorders remain an important cornerstone of FTD management and should not be ignored. FTD patients with behavioral and cognitive difficulties often cause significant caregiver stress and may place the patient or caregiver in harm as well. Strategies to intervene in troublesome symptoms involving environmental, behavioral, and physical interventions have been discussed in a detailed review (Merrilees 2007). Physical therapy for gait, balance training, and home safety evaluation by occupational therapy is critical for FTD patients with movement dysfunction, PSP patients with high fall risk and CBD patients with limb, fine motor difficulties. Moreover, exercise has been shown to benefit cognition, mood, and overall health in dementia and should be recommended to all patients capable of performing exercise in a safe manner (Cheng et al. 2014). Speech therapy by speech pathologists experienced with neurodegenerative aphasias may be especially helpful in the primary progressive aphasias. (Kortte and Rogalski 2013; Tippett et al. 2015).

**Potential disease-modifying treatments**

**Targets**

Recent advancements in the understanding of the genetics, pathophysiology, and neuropathology of FTD and its related disorders have led to a new generation of therapeutics targeted towards potential underlying mechanisms in hopes of a disease-modifying effect. Table 1 displays available

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Examples</th>
<th>Effect</th>
<th>Types of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panel (A)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Treatments for behavioral symptoms</td>
<td></td>
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<tr>
<td>Anti-depressants</td>
<td>Citalopram, paroxetine, sertraline, trazodone</td>
<td>May improve behavioral symptoms</td>
<td>Case reports &amp; series, open label trials, randomized double-blind placebo-controlled trial</td>
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<tr>
<td>Anti-psychotics</td>
<td>Quetiapine, risperidone, aripiprazole, olanzapine</td>
<td>May improve behavioral symptoms</td>
<td>Case reports &amp; series</td>
</tr>
<tr>
<td>Anti-epileptics</td>
<td>Carbamazepine, topiramate, valproic acid</td>
<td>May improve behavioral symptoms</td>
<td>Case reports &amp; series</td>
</tr>
<tr>
<td>Treatment for cognitive symptoms</td>
<td></td>
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<tr>
<td>Acetylcholinesterase inhibitors</td>
<td>Donepezil, galantamine, rivastigmine</td>
<td>No improvements, may worsen behavioral symptoms</td>
<td>Open label trials, randomized, double-blind placebo-controlled trials</td>
</tr>
<tr>
<td>NMDA-antagonist</td>
<td>Memantine</td>
<td>No improvements, may worsen cognition</td>
<td>Case series, open label trials, randomized double-blind placebo-controlled trials</td>
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<tr>
<td>Treatment for movement symptoms</td>
<td></td>
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<tr>
<td>Dopamine replacement</td>
<td>Carbipopa-levadop</td>
<td>Modest to no benefits</td>
<td>Case series</td>
</tr>
<tr>
<td>Panel (B)</td>
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<tr>
<td>TRx0237 (LMTx)</td>
<td>Tau aggregation inhibitor bvFTD</td>
<td>III</td>
<td>NCT01626378</td>
</tr>
<tr>
<td>TPI-287</td>
<td>Microtubule stabilizer CBS, PSP</td>
<td>I</td>
<td>NCT02133846</td>
</tr>
<tr>
<td>C2N-8E12</td>
<td>Anti-tau antibody</td>
<td>I</td>
<td>NCT02494024</td>
</tr>
<tr>
<td>Davunetide</td>
<td>Microtubule stabilizer</td>
<td>II/III</td>
<td>NCT01110720</td>
</tr>
<tr>
<td>Tideglusib</td>
<td>Glycogen synthase kinase-3 inhibitor</td>
<td>II</td>
<td>NCT01049399</td>
</tr>
<tr>
<td>BMS-986168</td>
<td>Anti-tau antibody</td>
<td>I</td>
<td>NCT02460094</td>
</tr>
<tr>
<td>Salsalate</td>
<td>Tau acetylation inhibitor</td>
<td>I</td>
<td>NCT02422485</td>
</tr>
<tr>
<td>FRM-0334</td>
<td>Increase progranulin expression GRN carrier</td>
<td>II</td>
<td>NCT02149160</td>
</tr>
<tr>
<td>Nimodipine</td>
<td>Increase progranulin release GRN carrier</td>
<td>I</td>
<td>NCT01835665</td>
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CBS, corticobasal syndrome; FTD, frontotemporal dementia; LMTx, Leuco-methylthioninium; PSP, progressive supranuclear palsy.
Therapeutics and currently ongoing or recently completed clinical trials with potentially disease-modifying agents in FTD and its related disorders.

Tau

Tau is a microtubule-associated protein localized to neuronal axons that regulate the stability of microtubules by promoting tubulin polymerization and is a major component of axonal transport (Drechsel et al. 1992). In the human brain, alternative mRNA splicing of the MAPT gene produces six tau isoforms, either with three or four repeat domains in the C-terminal part (3R and 4R tau)(Andreadis et al. 1992). Tau is also subject to various post-translational modifications such as acetylation, phosphorylation that may affect its function. Mutations in the gene MAPT has been identified in familial FTD and encompass a wide range of clinical presentation and tau pathology (Ghetti et al. 2015). Abnormal tau, sporadic or familial, and whether it is because of loss of function, or gain of toxicity, has been implicated in many FTD-related neurodegenerative syndromes as well as AD.

Tau can exist as monomers, oligomers, filaments, and aggregated inclusions. Pathological tau inclusions, often hyperphosphorylated, contain predominantly 3R tau in Pick’s disease (PiD), and 4R tau in PSP and CBD. Tau inclusions present with distinct pathological substrates; as dense, round inclusion bodies (Pick bodies) in ballooned neurons in Pick’s disease, as globose neurofibrillary tangles in neurons, astrocytes (tafited astrocytes), oligodendrocytes (coiled bodies) in PSP, and as threadlike neurofibrillary tangles, astrocytic plaques in CBD (Feany et al. 1996; Takahashi et al. 2002; Zhukareva et al. 2002). Further differences in tau structure reveals that PiD present with coiled, straight filaments, PSP has predominantly straight filaments, whereas CBD has twisted filaments (Buée and Delacourte 1999).

Over the past years, accumulating evidence has pointed to intercellular spread of tau aggregates and its ability to propagate further aggregation via conformational change in a prion like manner (Holmes and Diamond 2014). In addition, intracerebral injection of brain homogenates from pathologically confirmed tauopathies PSP, CBD, and PiD into tau transgenic and non-transgenic mice hippocampus and neocortex was able to recapitulate specific lesions resembling PSP and CBD, respectively, while forming inclusions in PiD. With the exception of PiD, filamentous tau pathology also propagated to neighboring or regions connected to the injection site (Clavaguera et al. 2013). The above suggests that for each FTLD syndrome, tau isoforms with 3R and 4R may be differentially expressed or post-translationally modified, distinct tau species may be responsible for each syndrome and abnormal tau may propagate and spread via a prion-like mechanism along disease-specific networks of vulnerable cells, causing further pathologic aggregates. It is with these recent discoveries in mind that many tau directed therapies have entered clinical trials recently.

Therapies targeting tau aggregates

Experience from reducing amyloid burden in AD with immunotherapy has led to substantial efforts to develop immune therapies aimed at reducing endogenous tau levels. Active immunization in transgenic mouse models with human tau pathology have been shown to have reduced tau pathology and improved performance on sensorimotor testing (Asuni et al. 2007; Theunis et al. 2013). Two active tau vaccines have entered early stage clinical trials for AD. Passive immunization via antibodies has the advantage of high specificity and potentially fewer immune side effects. Over the past 4 years, multiple studies have demonstrated that injection of anti-tau antibodies to various tau epitopes in tau transgenic mouse models resulted in reduction in tau pathology, with three studies reporting cognitive or functional improvement (Boutajangout et al. 2011; Choi et al. 2011; d’Abramo et al. 2013; Yanamandra et al. 2013; Castillo-Carranza et al. 2014a,b; Collin et al. 2014). However, it is currently unclear whether certain tau conformations are better targets for immune clearance and whether there is a differential effect on neurotoxicity with the various tau conformations. Currently there are two ongoing phase I clinical trials utilizing anti-tau antibodies for patients with PSP as shown in Table 1.

Leuko-methylthionium (LMTx) is a reformulated methylene blue compound that is thought to inhibit tau aggregation via selective blocking of a process required of tau to form filaments (Wischik et al. 1996). LMTx has recently published phase II clinical trials results in AD, showing improvements in cognition and the median dose but not the highest dose cohort, where it was argued the drug suffered from impaired absorption (Wischik et al. 2015). LMTx is currently undergoing clinical trials for bvFTD as well, with results expected in 2016.

Therapies targeting tau aggregate formation

Modulation of post-translational tau modifications has been theorized to affect tau aggregation as well. As abnormal tau is hyper-phosphorylated, protein kinase inhibition may prevent phosphorylation, and glycogen synthase kinase (GSK-3) has been an early target of therapies meant to prevent phosphorylation, and glycogen synthase kinase (GSK-3) has been an early target of therapies meant to block tau phosphorylation. Clinical trials using lithium chloride for PSP was unsuccessful because of toxicity, and another GSK-3 inhibitor, tideglusib, recently completed trials for PSP without significant differences in primary outcomes (Tolosa et al. 2014). The tideglusib trial did report reduced brain atrophy in a treatment group subpopulation of uncertain clinical significance (Höglinger et al. 2014). Modulation of tau phosphorylation via enhancing phosphatase activity remains an interesting therapeutic possibility. In addition, other post-translational modifications such as acetylation may be an important step in tau aggregation (Min et al. 2010). Recently a non-steroidal anti-inflammatory drug salsalate was found to inhibit tau acetylation, and when
given to transgenic mouse models of FTD, resulted in lowered levels of total tau, preserved hippocampal atrophy and improved memory deficits (Min et al. 2015). Salsalate is currently being tested in PSP patients in a small clinical trial (Table 1).

**Tau loss of function therapies**

Compromise of tau binding to microtubules leads to microtubule instability and may impair their function in transporting cellular constituents (Higuchi et al. 2002). Stabilization of microtubules has been proposed as a way to make up for tau’s loss of function. Davunetide, a peptide derived from a growth factor activity dependent neurotrophic protein, was theorized to promote microtubule stability and studied in an international, multi-center clinical trial with 313 PSP subjects. Despite no differences in all outcomes, the davunetide trial has shown that large, multicenter, international clinical trials in FTD are feasible (Boxer et al. 2014). Paclitaxel, from the taxane family of chemotherapy agents, works by interfering with the disassembly of microtubules, and the blood brain barrier permeable microtubule stabilizing agent, Epothilone D, has been shown to be efficacious in transgenic mouse models, but was abandoned after a small clinical trial in AD (Brunden et al. 2013). Paclitaxel itself has poor blood–brain barrier permeability but currently TPI-287, a synthetic, taxol-derived compound with good blood–brain barrier permeability developed for neuro-oncology has been repurposed for study in FTD and a phase I clinical trial for PSP and CBS is currently ongoing (Table 1).

**Progranulin**

Mutations in the GRN gene accounts for up to 5–10% of FTD cases with European ancestry (van Swieten and Heutink 2008). GRN mutations are associated with an underlying TDP-43 pathology. GRN mutation results in haploinsufficiency of GRN mRNA expression, resulting in readily measurable decreased levels of progranulin (PGRN) protein in serum and CSF (Ghidoni et al. 2008; Finch et al. 2009; Sleegers et al. 2009). In the CNS, PGRN may have neurotrophic and synaptic effects, though the exact function of PGRN remain an area of continued investigation. In addition, it has been demonstrated that patients with GRN mutation often have co-existing autoimmune disorders (Miller et al. 2013a). PGRN may also have a role in inflammation regulation, as it appears to antagonize the inflammatory effects of tumor necrosis factor alpha (TNF-alpha) (Tang et al. 2011). Despite incomplete understanding of the pathophysiological mechanism of GRN mutations, a readily measurable CSF and serum PGRN level can serve as not only a useful biomarker for diagnosis but also for target engagement and treatment response.

Because of the presence of haploinsufficiency in GRN mutation patients, it has been theorized that raising or restoring PGRN levels may be an effective therapy. Alkalizing drugs such as chloroquine, bepridil, and amiodarone that affect endosomal sorting may stimulate PGRN production (Capell et al. 2011). Unfortunately, a recent pilot study using amiodarone in 5 FTD patients with GRN mutation failed to demonstrate any elevated granulin levels or change in disease course (Alberici et al. 2014). A recent phase I clinical trial utilizing the CNS-penetrant calcium channel blocker nimodipine in GRN mutation carriers was recently completed and results of its effects on serum and CSF PGRN levels should be available soon. A high throughput screen identified suberoylanilide hydroxamic acid, a histone deacetylase inhibitor, was also shown to enhance PGRN expression, but this drug does not cross the blood brain barrier (Cenik et al. 2011). A phase 2 clinical trial utilizing FRM-0334, a proprietary histone deacetylase inhibitor that crosses the blood–brain barrier and enhances PGRN expression in preclinical models, is currently underway in GRN mutation carriers (Table 1).

As described above, patients with GRN mutation have a higher prevalence of systemic autoimmune conditions when compared when AD controls, normal controls, and the general population. Elevated TNF-alpha levels have been demonstrated in FTD, but without clear differentiation as to which pathological subtype (Sjögren et al. 2004). In addition, GRN knockout mice has been shown to develop inflammatory arthritis alleviated by PGRN, which shows antagonistic effects to TNF-alpha signaling (Tang et al. 2011). The above suggest a role for inflammation in the pathogenesis of FTD, especially in TDP-43 pathology subtypes or GRN mutations. A number of anti-TNF-alpha agents are already approved for systemic autoimmune disease, such as infliximab, adalimumab, etc. Clinical trials of such agents could potentially be pursued in FTD.

**C9ORF72**

FTD and ALS are both neurodegenerative processes, with up to 22% of ALS patients meeting FTD diagnostic criteria and 48% manifesting cognitive or behavioral abnormalities without meeting full criteria. An estimated 15% of FTD patients display signs of motor neuron disease and both disease have a 10% autosomal dominant pattern as well, suggesting some shared pathophysiology (Sha and Boxer 2012). In 2011, a hexanucleotide repeat expansion in the 5’ non-coding region of the C9ORF72 gene was found to be the cause of FTD and ALS in a strongly chromosome 9p linked family (Boxer et al. 2011; DeJesus-Hernandez et al. 2011; Renton et al. 2011). This expansion is now thought to be the most common genetic cause of FTD-ALS, but also less commonly associated with CBS and nfvPPA presentations (Snowden et al. 2012; Anor et al. 2015). The pathology of C9ORF72 mutation carriers have been overwhelmingly TDP-43, but also with a unique p62 positive, TDP-43 negative polypeptide repeat inclusion in the cerebellum and hippocampus (Ash et al. 2013). Although recent studies have
shown that specific dipeptide products are toxic in animal and cell models via cytoplasmic aggregates or nuclear inclusions and nuclear stress, whether it is a major or exclusive pathogenic mechanism in humans remain to be elucidated (Mackenzie et al. 2015).

Although the precise function of C9ORF72 remains unknown, expanded RNA transcripts may result in both loss of function or toxic gain of function. Recent studies have identified intranuclear RNA foci produced by abnormal localization of expanded C9ORF72 transcription in FTD-ALS patients’ motor cortex, spinal cord tissues (DeJesus-Hernandez et al. 2011). The nuclear RNA aggregation may sequester RNA-binding protein and is thought to disrupt RNA-binding protein function, resulting in abnormal RNA processing and may play a role in C9ORF72 pathophysiology (Echeverria and Cooper 2012).

In light of the above, antisense oligonucleotide (ASO) may be a viable strategy for FTD because of C9ORF72 repeat expansions. ASO are synthetic nucleic acids that can inactive the mRNA of a target gene by direct binding or inducing RNase H mediated cleavage via a DNA/RNA heteroduplex. ASOs have been successfully tested in ALS patients with super-oxide dismutase 1 mutation via intrathecal administration, and may serve as a roadmap for treatment development for FTD (Miller et al. 2013b). Several ASO candidates are in pre-clinical development and demonstrated reduction in RNA aggregation without toxic effects in human C9ORF72 induced pluripotent stem cell neuron and fibroblast (Donnelly et al. 2013; Lagier-Tourenne et al. 2013; Sareen et al. 2013).

**Future clinical trials considerations**

Rapid development of successful FTD therapies will require close collaboration between academic laboratories, clinical research centers, pharmaceutical/biotechnology industry, and the FDA. The cooperation of the pharmaceutical industry will be critical with its large therapeutic compound libraries, clinical trial expertise, funding, and established infrastructure. The recent davunetide trial for PSP, although unsuccessful, has proven that large, multicenter, international trials for rare neurodegenerative disease are feasible. It has also provided a wealth of experience and natural history data that will be crucial for future clinical trial design. As a larger percentage of FTD cases are familial compared to AD, several recently launched treatment initiatives in preclinical and familial Alzheimer’s disease; Dominantly Inherited Alzheimer’s Network (DIAN) treatment unit, Alzheimer’s prevention initiative, and Anti-Amyloid Treatment in Asymptomatic Alzheimer’s disease (A4) may serve as models for patient recruitment, data collection, multicenter collaboration, and clinical trial design. Efforts to develop research networks and biomarkers for FTD are underway via the Longitudinal Evaluation of Familial Frontotemporal Dementia project and Genetic FTD Initiative, focused on familial forms of FTD, and Advancing Research and Treatment for Frontotemporal Lobar Degeneration (ARTFL) project, focusing on all FTLD syndromes. Several additional topics relevant to FTD clinical trials development are discussed below.

**Biomarkers**

Differentiating between the various pathological subtypes of FTD will be important for proper patient selection in clinical trials, and biomarkers may help. Biomarkers can also provide evidence confirmation that a particular therapeutic candidate engages its intended target and exerts the predicted physiological effect (e.g., a pharmacodynamic effect).

The clinical trial environment for AD has undergone dramatic changes as the advent of β-amyloid positron emission tomography (PET) imaging with the ligands 11C-Pittsburgh Compound B and 18F-Flurbetapir. The ability to detect β-amyloid pathology has led to an understanding of the limitations of a clinical diagnosis of dementia, as up to 16% of recruited patients in a previous AD trial did not have amyloid pathology by PET scan (Vellas et al. 2013). Beta-amyloid PET imaging is now a required part of most AD clinical trials to ensure proper patient recruitment, and is also being used for a CBS clinical trial to rule out Alzheimer’s pathology presenting as a FTD-related syndrome.

With the broad understanding and experiencing from use of PET tracers in dementia, there is now increasing excitement and research into the possible use of tau PET tracers for FTD. Multiple tau-binding ligands are currently being investigated and was previously reviewed (Dani et al. 2015). 18F THK5351 is one ligand that has been shown to bind to expected tau pathology distribution in AD patients and to tau deposits in postmortem AD tissue (Harada et al. 2016). Another ligand, 18F-T807 appears to readily bind to tau pathology in AD, and regional uptake is correlated with cognitive impairment (Johnson et al. 2015). Its ability to bind to tau pathology in FTD and its related disorders remains an important area of research (Marquie et al. 2015). Such agents could be immensely helpful for tau therapeutic studies in FTD.

Other imaging methods such as volumetric MRI to measure regional gray, white matter atrophy or diffusion tensor imaging for white matter tract integrity may also provide additional support for treatment efficacy. For example, recent work in PSP has demonstrated superior sample size estimates when using neuroimaging measures over standard clinical scales over 6 months (Whitwell et al. 2012).

Fluid biomarkers either from serum or cerebrospinal fluid are other options for FTD clinical trials. Cerebrospinal fluid β-amyloid and tau have been established in clinical use for AD diagnosis, but a similar biomarker for FTD and its related disorder is not yet available. The ratio of phospho-rylate tau to total tau may help identify human cases of FTD with TDP-43 pathology (Hu et al. 2013). Neurofilament light chain is a non-specific marker of central nervous system
injury, but serum levels has been shown to be a prognostic marker in ALS (Lu et al. 2015) and CSF levels reflect disease severity in FTD measured by clinical dementia rating scale, neuropsychology testing, and volumetric MRI (Scherling et al. 2014).

Additional research into biomarkers proven for diagnosis, prognosis or symptom severity in FTD will be crucial for future clinical trials. Diagnostic biomarkers, such as β-amyloid PET imaging in AD, can help to exclude atypical AD cases that may appear to have a FTD clinical syndrome but would not respond to FTD-specific therapies. Biomarkers that may predict disease prognosis can help homogenize the recruited study population to reduce the necessary size to detect treatment effects. Finally, a surrogate biomarker that closely reflects symptom severity, progression or recovery could greatly increase clinical trial efficiency, reducing time and sample size. While no such surrogate outcome biomarkers currently exist, their use could facilitate the design of more efficient clinical trials in this rare disease population.

Outcome measures

Because of the heterogeneous clinical presentation of FTD and its related disorders, encompassing motor, behavioral, language and cognitive symptoms, accurate clinical scales that capture disease progression and are sensitive to change will be crucial for clinical trial outcomes. A number of cognitive, behavior, and motor scales have been studied and validated in longitudinal studies of FTLD syndromes (Boxer et al. 2013b). For example, the Progressive Supranuclear Palsy Rating Scale, a six domain clinical scale encompassing history, mentation, bulbar, limb, gait, oculomotor function has been shown to have excellent sensitivity to disease progression and produces effect size, sample size estimates comparable to imaging outcomes over 12 months (Golbe and Ohman-Strickland 2007; Whitwell et al. 2012). Functional rating scales such as the FTLD-specific version of Clinical Dementia Rating may be more useful over time in bvFTD. A variety of neuropsychological tests are sensitive to change in FTLD (Knopman et al. 2008). The new ARTFL and Longitudinal Evaluation of Familial Frontotemporal Dementia projects (https://www.rarediseasenetwork.org/cms/ARTFL) are using the National Alzheimer’s Coordinating Center Uniform Data Set and FTLD module, including language testing and may provide a wealth of longitudinal data for future clinical trial design. Ultimately rating scales should be sensitive in reflecting change over time, and facilitate translation and transport across sites as future FTD trials will likely be multinational and involve patients from various cultural backgrounds.

Conclusion

FTD and its related disorders are a spectrum of uniformly fatal neurodegenerative diseases with a finite number of pathophysologies that are rapidly being elucidated. Currently there are no FDA approved treatments for FTD, and most treatments are symptomatic therapies for other disorders used off-label. Recent advancements in understanding the molecular and genetic basis of FTD, especially FTD-tau have reached sufficient maturity for new drug targets to be identified, and several clinical trials based on these insights are underway. Development of novel biomarkers that can help with accurate diagnosis of FTD, prognosis and capturing disease progression are also being investigated. With such a road map in place, it may well be a promising decade for therapy for FTD and its related disorders.

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