

# Amyotrophic lateral sclerosis: clinical perspectives

Verena C Haringer  
Summer B Gibson

Clinical Neurosciences Center,  
Department of Neurology,  
University of Utah School of  
Medicine, Salt Lake City, UT, USA

**Abstract:** Amyotrophic lateral sclerosis (ALS) is the most common motor neuron disease in adults. It is a rapidly advancing neurodegenerative disease leading to progressive paralysis and death, with a mean time of survival from onset of symptoms to death of 2–5 years. The pathophysiology of ALS remains poorly understood. The only US Food and Drug Administration–approved therapy for ALS is riluzole, a glutamatergic neurotransmission inhibitor, with modest benefits on survival. Many other agents have shown promising results in preclinical trials, but have yet to show benefit in human clinical trials. This review gives an overview of drugs that have been studied in clinical trials and their reported outcomes. This also includes more recent treatment strategies, including antisense oligonucleotides (ASOs) and stem cells. ASOs have the potential to target genes known to cause ALS by silencing their function. Many clinical trials are under way using these therapies. Different kinds of stem cells have been used in an attempt to either replace the lost motor neurons or to improve their metabolic supply and thus prolong their death. Given the limited therapeutic treatment options to date, the most important approach to improve the patient’s quality of life remains symptom-based management. Additionally, we give an overview of the current treatment offered in multidisciplinary clinics.

**Keywords:** motor neuron disease, symptom management, treatment and experimental therapies, stem cells, antisense oligonucleotides, clinical trials

## Introduction

Amyotrophic lateral sclerosis (ALS) is a fatal disease in which the upper and lower motor neurons degenerate, leading to progressive muscle weakness and eventual respiratory failure. The incidence of ALS is about 2 in 100,000.<sup>1</sup> It generally progresses rapidly, with a mean survival time of 2–5 years following symptom onset.<sup>2,3</sup> The clinical hallmark of the disease is death of the motor neurons leading to muscular atrophy, muscular weakness, dysarthria, and fasciculations as well as clinical findings of hyperreflexia and spasticity. The symptoms typically manifest as focal weakness in one limb; however, one-third of the cases have a bulbar presentation resulting in dysarthria, dysphagia, and respiratory dysfunction.<sup>4</sup> About half the affected patient population will develop frontotemporal lobe dysfunction with cognitive and behavioral abnormalities and pseudobulbar affect; a subgroup of these will go on and fulfill diagnostic criteria for frontotemporal dementia (FTD).<sup>5</sup> As there is significant overlap in the pathogenesis and genetics of FTD and ALS,<sup>6</sup> there is growing belief that these two diseases are different phenotypes of an ALS–FTD spectrum disorder.<sup>7</sup>

It is known that the pathogenesis of ALS has a genetic component.<sup>3</sup> While most cases of ALS are sporadic, approximately 10% of cases report a family history

Correspondence: Summer B Gibson  
Clinical Neurosciences Center,  
Department of Neurology, University  
of Utah, 175 N Medical Drive East,  
Salt Lake City, UT 84132, USA  
Tel +1 801 585 7575  
Fax +1 801 582 4192  
Email summer.gibson@hsc.utah.edu

of ALS.<sup>8</sup> Currently, about 68% of ALS patients with a family history of ALS (aka familial ALS) and 11% of ALS patients without a known family history of ALS (aka sporadic ALS) have an identifiable genetic cause.<sup>3</sup> The first ALS mutation, Superoxide dismutase-1 (*SOD1*), was discovered in 1993,<sup>9</sup> and since then, many additional genes have been found. Mutations in *SOD1* account for 10%–20% of familial ALS cases, and to date, >155 mutations have been identified.<sup>10</sup> Two genes that play a role in the pathological findings of ALS are TAR DNA binding protein (*TARDBP*)<sup>11</sup> and fused in sarcoma (*FUS*),<sup>12</sup> which account for ~5% of familial ALS cases. The GGGGCC hexanucleotide expansion of *C9orf72* is a common cause of FTD and ALS.<sup>13</sup> This mutation is the most common known cause of both sporadic and familial ALS, responsible for about 7% of all ALS cases in the Caucasian population.<sup>14</sup> Mutations of many other genes have been reported, but the genetic cause of about 32% cases of familial ALS and the majority of sporadic ALS continue to be unknown.<sup>3</sup>

The pathophysiology of this devastating disease remains unclear. The pathological finding of ubiquitinated TDP-43 aggregates is found in patients who carry a mutation in the *TDP-43* gene (*TARDBP*), as well as in ALS patients without this mutation,<sup>11,15</sup> except in cases caused by *SOD1* or *FUS* mutations. Similar TDP-43 aggregates are also found in FTD, leading to speculation that both diseases are variations of a spectrum of TDP-43-associated disorders.<sup>16</sup> Although TDP-43 pathology is common to most ALS cases, the pathomechanism causing this disease is unknown. Potential contributing factors include mitochondrial dysfunction, neuroinflammation, and oxidative stress. Additionally, glutamate toxicity is thought to play a role, because ALS patients have higher levels of glutamate in serum and cerebral spinal fluid (CSF) compared to healthy controls.<sup>17</sup>

## Disease-modifying treatment

### US Food and Drug

#### Administration—approved treatment

Riluzole has several targets, although its proposed mechanism is as a glutamergic neurotransmission inhibitor. It remains the only US Food and Drug Administration (FDA)—approved therapy for ALS that affects survival. Randomized trials show modest improvement in survival, possibly greater in patients with bulbar onset.<sup>18</sup> It is likely that riluzole has less effect in advanced stage disease.<sup>19</sup> A recent meta-analysis of all randomized controlled trials confirmed the modest increase in median survival of 2–3 months and a modest impact on functional measures.<sup>20</sup> Given the relatively short duration of

these randomized studies ( $\leq 18$  months), an analysis of ALS databases over a 5- to 10-year period was initiated, for which data are suggestive of a greater long-term improvement in survival, ranging from 6 up to over 21 months.<sup>20</sup> Given these longer studies were not randomized, these results must be interpreted with caution.

## Drugs in clinical trials

Over the past decades, a multitude of experimental pharmaceutical therapies were shown to delay disease progression in ALS animal models but failed to show efficacy in clinical trials or are still in Phase I–III trials. The mechanisms of these agents include antioxidants, neuroprotection, promotion of growth factors, antiglutamate, induction of heat shock proteins, anti-inflammatory, mitochondrial-protective agents, maintenance of muscle, and reduction of SOD1. Several drugs that have been FDA-approved for other indications are currently in clinical trials for ALS, including rasagiline, fingolimod, anakinra, and tamoxifen (<http://www.clinicaltrials.gov>). Of the agents that have completed clinical trials, none have been able to significantly modify disease progression or increase survival in humans with ALS (Table 1). The failure to translate from animals to humans is at least in part due to inherent limitations when using animal models to study human diseases. There are metabolic, anatomic, and cellular differences between humans and other organisms, laboratory animals are often heavily inbred, and negative study results are often not published leading to bias. Additionally, animal models often do not accurately mimic human disease.<sup>21</sup> The most frequently used animal model to study ALS has been transgenic *SOD1*<sup>G93A</sup> rodents, which have multiple copies of the human coding sequence for *SOD1* with the G93A mutation.<sup>22</sup> While this model appears to be a mimic of human ALS due to *SOD1* mutations, it is unclear if the results from these rodents can be applied to non-*SOD1* cases of ALS. Additional rodent models of ALS are currently being studied including *TDP-43* mediated,<sup>23</sup> which have the potential to be relevant for the majority of ALS cases.

## Antisense oligonucleotides

Mutations in *SOD1*, associated with 10%–20% of familial ALS cases, cause the protein to misfold, leading to toxic effects on the cellular degradation machinery and formation and accumulation of SOD1 protein aggregates.<sup>10</sup> This results in a cellular stress response and eventual cell death, although the exact mechanism is unknown.<sup>10,24</sup> Reduction of toxic SOD1 proteins has been proposed using antisense oligonucleotides (ASOs).<sup>25</sup> ASOs are short, synthetic

**Table 1** Summary of human clinical trial results of agents delaying disease progression in ALS animal models

Compound	Proposed mechanism	Results from preclinical studies	Results from human clinical trials	Improvement in human survival
Anakinra	Interleukin-1 receptor antagonist	Prolongs survival of <i>SOD</i> <sup>G37R</sup> mice <sup>117</sup>	Phase II trial of anakinra in combination with riluzole is currently under way (NCT01277315)	To be determined
Arimoclomol (BRX-345)	Amplifies heat shock protein expression under cell stress	Delayed denervation and nerve sprouting, reversed muscle fiber transformation, and increased Hsp70 expression in <i>SOD</i> <sup>G37R</sup> mice in early <sup>118</sup> and late stages of the disease <sup>119</sup>	Well tolerated in Phase I study, <sup>120</sup> Phase II/III study under way (NCT00706147)	To be determined
Brain-derived neurotrophic factor	Growth factor	Promotes survival in spinal motoneurons after axotomy <sup>121</sup> or ventral root avulsion <sup>122</sup> ; improves motor dysfunction in wobbler mouse motor neuron disease; <sup>123</sup> protects neuron from <i>in vivo</i> excitotoxicity <sup>124</sup>	No survival benefit <sup>125</sup>	No benefit
Ciliary growth factor	Growth factor	Prevents degeneration of motoneurons after axotomy; <sup>126</sup> prevents degeneration of motor neurons in the pmn/pmn mouse model (model of progressive motor neuropathy)	No survival benefit and side effects at higher doses <sup>127</sup>	No benefit
Ceftriaxone	Direct decrease of glutamate production and indirect increase of glutamate breakdown (upregulates mRNA for glutamate transporter on astrocytes)	Delays loss of neurons and muscle strength, increased survival in <i>SOD</i> <sup>G37R</sup> mouse model <sup>128</sup>	No change in decline of ALSFRS-R <sup>129</sup>	No benefit
Celecoxib	Reduction of astrocytic glutamate release, reduced production of free radicals, anti-inflammatory	Delays onset of weakness and weight loss and increases survival in <i>SOD</i> <sup>G37R</sup> mice <sup>130</sup>	No change in the rate of upper extremity motor function decline <sup>131</sup>	No benefit
Coenzyme Q Creatine	Mitochondrial cofactor, free radical scavenger Antioxidation	Improves survival in <i>SOD</i> <sup>G37R</sup> mice <sup>132</sup> Dose-dependent improvement in motor performance and extended survival in <i>SOD</i> <sup>G37R</sup> mice <sup>134</sup>	No change in decline of ALSFRS-R <sup>133</sup> No change in decline of ALSFRS-R or on quality of life <sup>135</sup>	No benefit No benefit
Cyclosporine	Inhibits mitochondrial permeability transition pore	Reduces neuronal death and prolongs survival of late-stage <i>SOD</i> <sup>G37R</sup> mice after intrathecal administration <sup>136</sup>	No change in the rate of disease progression <sup>137</sup>	No benefit
Dexrampipexole	Preservation of mitochondria function by reducing apoptosis	No published ALS animal data prior to clinical studies, later found to have no effect in <i>SOD</i> <sup>G37R</sup> mice <sup>138</sup>	No change in the decline of ALSFRS-R <sup>139</sup>	No benefit
Edaravone	Antioxidant, scavenger of free radicals	Slows motor decline and decreases SOD1 deposits in <i>SOD</i> <sup>G37R</sup> mice <sup>140</sup>	No effect on disease progression <sup>141</sup>	No benefit
Fingolimod	Sphingosine-1-phosphate receptor modulator, which leads to sequestration of lymphocytes in lymph nodes, thus preventing them from contributing to an autoimmune reaction	No data from animal studies in motor neuron disease available	Phase II trial is currently under way (NCT01786174)	To be determined
Gabapentin	Reduces glutamate synthesis at high doses	Prevents neuronal death <sup>142</sup> and prolongs survival in <i>SOD</i> <sup>G37R</sup> mice <sup>134</sup>	No change in the rate of decline of the arm muscle strength and more rapid decline of forced vital capacity <sup>144</sup>	No benefit
Glaciramer acetate	T-cell modifier	Initial studies showed delayed disease progression in low-copy but not high-copy <i>SOD</i> <sup>G37R</sup> mice, <sup>145</sup> follow-up studies showed no effect in <i>SOD</i> <sup>G37R</sup> or <i>SOD</i> <sup>G37R</sup> mice <sup>146</sup>	No change in decline of ALSFRS-R <sup>147</sup>	No benefit
Insulin-like growth factor I (IGF-1)	Growth factor	Increases motor performance, delays onset of disease, and increases survival in <i>SOD</i> <sup>G37R</sup> mice <sup>148</sup>	Initial study showed reduction in functional impairment, <sup>149</sup> but two large follow-up studies did not show benefit <sup>150,151</sup>	No benefit

(Continued)

Table 1 (Continued)

Compound	Proposed mechanism	Results from preclinical studies	Results from human clinical trials	Improvement in human survival
Intravenous immunoglobulin	Anti-inflammatory	No data from animal studies in motor neuron disease available	No change in decline of muscle strength or bulbar function <sup>152</sup>	No benefit
Lamotrigine	Inhibition of glutamate release	Rescues motor neurons from death from cell death induced by axotomy, <sup>153</sup> not tested in animal models of ALS	No improvement in ALSFRS-R or other clinical scales <sup>154,155</sup>	No benefit
Lithium	Mechanism incompletely understood, may include reduction in glutamate and increase in serotonin	Delays disease onset and prolongs life span of <i>SOD1</i> <sup>G93A</sup> mice <sup>156</sup>	A nonplacebo control study showed delay of disease progression, <sup>63</sup> but controlled follow-up trials showed no change <sup>157,158</sup>	No benefit
Methionine	Antioxidation	Delays disease onset and prevents loss of motor neurons in <i>SOD1</i> <sup>G93A</sup> mice <sup>159</sup>	No change in rate of disease progression <sup>160</sup>	No benefit
Minocycline	Inhibition of microglial activation	Delays disease onset and prolongs survival in a dose-dependent manner in <i>SOD1</i> <sup>G93A</sup> mice <sup>161</sup>	Accelerated decline in ALSFRS-R <sup>162</sup>	No benefit
N-acetylcysteine	Anti-oxidation	Improves survival and preserves motor function in <i>SOD1</i> <sup>G93A</sup> mice <sup>163</sup>	No change in rate of disease progression <sup>160</sup>	No benefit
NP001	Reduction in macrophage activation	Prolongs survival in most accepted animal models of ALS (unpublished data) <sup>164</sup>	Reduction in expression of monocyte CD16 in Phase I study. <sup>165</sup> Phase II study ongoing (NCT01281631)	To be determined
Olesoxime (TRO19622)	Inhibits release of apoptotic factors	Delays muscle denervation and motor neuron death in <i>SOD1</i> <sup>G93A</sup> mice <sup>166</sup>	No effect on survival <sup>167</sup>	No benefit
Plasmapheresis	Anti-inflammatory	Not tested in animal models of ALS	No change in decline of muscle strength or functional ability <sup>168</sup>	No benefit
Pyrimethamine	Reduction of SOD1	Reduced SOD1 in cell culture and <i>SOD1</i> <sup>G93A</sup> mice <sup>169</sup>	Reduction of SOD1 in CSF (Phase I study) <sup>170</sup>	Undetermined
Rasagiline	Irreversible inhibitor of monoamine oxidase	Dose-dependent therapeutic effect on motor function and survival alone and in combination with riluzole in <i>SOD1</i> <sup>G93A</sup> mice <sup>171</sup>	Phase II trial is currently under way (NCT01879241)	To be determined
Talampanel (LY300164)	AMPA receptor	Other AMPA antagonists (NBQX, <sup>172</sup> ZK 187638 <sup>173</sup> ) were shown to preserve motor function and prolong survival in <i>SOD1</i> <sup>G93A</sup> mice. Talampanel itself increases intracellular calcium in motor neurons of <i>SOD1</i> <sup>G93A</sup> mice but does not preserve motor function or prolong survival <sup>174</sup>	Slows decline in muscular strength and in ALSFRS-R but not statistically significant <sup>175</sup>	No benefit
Tamoxifen	Decreases glutamate binding to alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (NMDA) receptors	Extends survival in a virally induced mouse model of ALS <sup>176</sup>	Phase I trial shows safety and tolerability (unpublished data), two Phase II trials completed (NCT01257581; NCT00214110), awaiting final results; one Phase I/II trial is still ongoing (NCT02166944)	To be determined
Tirasemtiv (CK-2017357)	Activation of musculature by increasing its calcium sensitivity	Improves muscle function in <i>SOD1</i> <sup>G93A</sup> mice <sup>177</sup>	Dose-dependent improvement in strength and endurance, <sup>178</sup> Phase II trial completed (NCT01709149), awaiting final results	To be determined
Topiramate	Antagonism of glutamate receptors	Protects against motor neuron degeneration in organotypic spinal cord cultures but not in the <i>SOD1</i> <sup>G93A</sup> mouse model <sup>179</sup>	No survival benefit, additionally high-dose treatment was associated with a faster rate of decline in muscle strength and with an increased risk for adverse events <sup>180</sup>	No benefit

Vascular endothelial growth factor	Growth factor	Improves motor performance and prolongs survival of <i>SOD1<sup>G93A</sup></i> mice and rats, when administered via intrathecal <sup>181</sup> or intraperitoneal <sup>182</sup> injection or viral <sup>183</sup> delivery	A Phase I trial showed safety and tolerability of intracerebroventricular administration (NCT00800501), a second Phase I trial to assess the safety of a continuous intracerebroventricular infusion is under way (NCT01999803). A Phase II trial is also currently under way (NCT01384162) <sup>184</sup>	To be determined
Vitamin E	Antioxidation	Delays onset of disease and slows progression but does not improve survival in <i>SOD1<sup>G93A</sup></i> mice <sup>143</sup>	No change in rate of deterioration of function (Norris limb scale) at low <sup>185</sup> or high <sup>186</sup> dose when taken in addition to riluzole. Possible protective benefit, as long-term users have lower risk of developing ALS <sup>187</sup>	No benefit

**Notes:** Phase I clinical trial: Screening for safety in a small group of patients. Phase II clinical trial: Establishing the efficacy of the drug, usually against a placebo in a larger group of patients. Phase III clinical trial: Final confirmation of safety and efficacy in comparison to commonly used treatment.

**Abbreviations:** ALS, amyotrophic lateral sclerosis; ALSFRS-R, ALS functioning rating scale-revised; AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor; SOD1, superoxide dismutase-1.

oligonucleotide sequences that bind to target mRNA in a sequence-specific manner through Watson–Crick base pairing; they are degraded by endogenous RNase.<sup>25,26</sup> ASOs cannot cross the blood–brain barrier and must be infused intrathecally.<sup>27</sup> Continuous intrathecal infusion of ASOs via osmotic pumps reduced SOD1 protein and mRNA levels throughout the brain and spinal cord and prolonged survival in both a rodent (*SOD1* rat) and a primate (rhesus monkey) model.<sup>28</sup> Initial human clinical trial results suggest that intrathecal infusion of ASOs via lumbar puncture is safe and tolerable.<sup>27</sup>

Similar strategies have been employed to target other toxic gain of function ALS genes. Sustained ASO-mediated lowering of *C9orf72* RNA throughout the central nervous system of mice following an intrathecal (lateral ventricle) injection was found to be well tolerated.<sup>29</sup> As it is currently unclear whether haploinsufficiency of *C9orf72* is relevant to the disease process in ALS, it remains unclear if using ASOs to lower *C9orf72* RNA is a viable treatment strategy. Currently, the only human ALS trial with ASOs is in *SOD1*, though this strategy might become an important and individually targeted approach, particularly as more ALS genes are discovered.

## Cell-based treatments

In addition to pharmacological treatments, several clinical trials use stem cell transplantation, with two main therapeutic concepts behind this approach.<sup>30</sup> These concepts include the potential replacement of motor neurons lost during the disease process and neural protection by improving metabolic support of the diseased motor neurons.

## Neural stem cells

During development, pluripotent embryonic stem cells (ESCs) give rise to specific multipotent progenitor cell populations<sup>31</sup> including neural stem cells (NSCs), which differentiate into neurons, astrocytes, and oligodendrocytes.<sup>32</sup> Human NSCs can be derived from human ESCs<sup>33</sup> or isolated from fetal neurologic tissue.<sup>34</sup> When grafted into rat spinal cord, they retain their ability to differentiate into motor neurons, which integrate into spinal circuits.<sup>35</sup>

NSCs may be useful for ALS treatment. Human motor neuron administration delayed disease onset and prolonged survival in mouse<sup>36</sup> and rat<sup>37</sup> *SOD1<sup>G93A</sup>* ALS models. In a Phase I clinical trial, human NSCs (NSI-455-RSC cells)<sup>38</sup> were injected into the lumbar and/or cervical spinal cord without major adverse events or accelerated disease progression.<sup>39</sup> A Phase II trial is in progress (NCT01730716).

## Mesenchymal stem cells

Multipotent mesenchymal stem cells (MSCs) differentiate into osteoblasts, adipocytes, chondrocytes, and myocytes. They do not naturally differentiate into neural lineages but can be induced to do so.<sup>40</sup> They can be isolated from bone marrow, cord, or peripheral blood and are thus more easily available than ESCs and, depending on the source, may not require immunosuppression.

MSCs may be useful for ALS treatment as a delivery vehicle to the central nervous system. Intraventricular injection of MSCs overexpressing glucagon-like peptide 1, an antioxidant with neuroprotective property, improved survival in the *SOD1* mouse model.<sup>41</sup> Injection of human MSCs overexpressing growth factors into the musculature of *SOD1* rats reduced neuromuscular junction denervation and delayed disease progression.<sup>42</sup> A synergistic effect was observed in overexpression of both vascular endothelial growth factor and glial cell line-derived neurotrophic factor.<sup>43</sup> Injections of unmodified MSCs have also shown benefits on survival and disease progression in the *SOD1* mouse model,<sup>44</sup> possibly due to endogenous production of neuroprotective factors, which improves motor neuron metabolic support. Human autologous MSCs can be differentiated into neurotrophic factor secreting cells. A recent study showed that injection of these cells intrathecally and intramuscularly in an ALS patient treated on a compassionate basis was safe and clinically beneficial.<sup>45</sup> A Phase I/II study in Israel was completed but no study results have been published (NCT01777646).

Several ALS clinical trials assessed the safety of MSC transplantations into the spinal cord<sup>46,47</sup> or brain of ALS patients.<sup>48,49</sup> These injections were safe without a clear clinical benefit. Postmortem pathological analysis of patients' spinal cords showed more motor neurons and fewer degenerative ubiquitin deposits, suggesting neurotrophic activity in the grafted cells.<sup>49</sup> Intrathecal MSC application has been shown to be safe via lumbar puncture<sup>50</sup> as well as Ommaya reservoir.<sup>51</sup>

Another approach utilizing MSCs is subcutaneous injection of granulocyte colony-stimulating factor to mobilize endogenous MSCs, with<sup>52</sup> or without<sup>53</sup> collection and reinfusion of peripheral blood stem cells. Long-term administration of granulocyte colony-stimulating factor is safe<sup>54</sup> and leads to persistent mobilization of hematopoietic stem cells<sup>55</sup> but has no effect on the disease course.<sup>56</sup>

## Olfactory ensheathing cells

Mammalian olfactory neurons regenerate throughout life from a stem cell layer at the base of the epithelium<sup>57</sup> and are

enfolded and guided by olfactory ensheathing cells (OECs) in the olfactory bulb.<sup>58</sup>

Based on findings in rodent spinal cord injury models<sup>59</sup> and spinal cord injury clinical trials,<sup>60</sup> OECs were applied for ALS treatment. Spinal grafts showed increased survival of *SOD1* rats and slowing of motor neuron loss.<sup>61</sup> Before there was clear evidence of benefit in an animal model, a laboratory in People's Republic of China grafted OECs in ALS patients based on spinal cord injury clinical trials.<sup>62</sup> OECs extracted from human fetal olfactory bulbs were injected into the bilateral corona radiata in 15 patients who were compared to 20 untreated controls. Over a 4-month follow-up period, a five-point difference in the ALS functioning rating scale–revised (ALSFRS-R) was detected. The study was halted as the authors felt there was “conclusive proof of positive and beneficial results”.<sup>63</sup> Simultaneously, this group enrolled 327 patients in a noncontrolled trial that compared injection of OECs into the spinal cord, the bilateral corona radiata, or both. They reported improved ALS functioning rating scale and normalized electromyographical findings 4 weeks after transplantation, with no differences between the three groups.<sup>64</sup> These results are largely contested and no further follow-ups were conducted. Despite this, hundreds of additional patients underwent OEC grafting in People's Republic of China based on these results, some with multiple injections. The authors reported improved ALS functioning rating scale after each injection but diminished response after repeated injections.<sup>65</sup> Independent follow-up studies on patients who received OEC transplants in People's Republic of China could not confirm the reported observations.<sup>66</sup> Postmortem studies did not suggest neuroprotection or axonal regeneration.<sup>67</sup>

## Induced pluripotent stem cells

The discovery of induced pluripotent stem cells (iPSCs) showed that pluripotency can be induced in adult somatic mouse cells via introduction of transcription factors.<sup>68</sup> Similarly, human iPSCs can be generated from human fibroblasts.<sup>69</sup> iPSCs differ from human ESCs in gene expression and DNA methylation patterns but are germline-competent,<sup>70</sup> generate all three germ layer cell types,<sup>71</sup> and form active motor neurons.<sup>72</sup> The potential for iPSC technology is enormous as it allows for a limitless supply of autologous pluripotent cells that can be reintroduced into the patient without immunosuppression. However, the current knowledge about these cells and ability for clinical application is limited.<sup>73</sup>

iPSCs have several important potential applications in ALS. Neural progenitor cells derived from human iPSCs

survived and showed neuronal phenotypes when grafted into the spinal cord of *SOD1* rats.<sup>74</sup> Intrathecal or tail vein cell injection in *SOD1* mice significantly improved survival and neurological function.<sup>75</sup> Transplantation of glial-restricted precursor cells derived from human iPSCs targets astrocytic dysfunction observed in ALS and prolongs the lifespan of *SOD1* mice.<sup>76</sup>

Besides possible clinical applications, it is important to emphasize the role that iPSCs play in modeling diseases in vitro. Several groups used either iPSCs derived from ALS patients<sup>77,78</sup> or motor neurons derived from these iPSCs<sup>79,80</sup> to further study ALS pathophysiology.

## Symptomatic treatment

As the treatment options for ALS continue to be limited, symptomatic treatment is very important in the care of ALS patients. Specialized clinics provide multidisciplinary care by neurologists, specialty nurses, physical, occupational, respiratory, and speech therapists, dieticians, and social workers. The benefits of multidisciplinary clinics have been demonstrated in several studies, including survival<sup>81–83</sup> and quality of life<sup>84</sup> when compared to patients seen in general neurology clinics. Both American<sup>85</sup> and European guidelines<sup>86</sup> recommend multidisciplinary care.

## Dyspnea

Dyspnea and respiratory compromise are common progressive symptoms, with several possible interventions. Respiratory muscle training is often recommended, but the evidence to support its benefit is limited.<sup>87</sup> Noninvasive positive pressure ventilation (NIV) has been shown to not only improve quality of life<sup>88</sup> but also prolong life, especially in patients without significant bulbar dysfunction and in those who are able to tolerate daily use of at least 4 hours.<sup>89,90</sup> A potential additive to NIV is diaphragmatic pacing, especially in patients with bulbar symptoms, as the effectiveness of NIV correlates inversely with the severity of bulbar symptoms.<sup>91</sup> In diaphragmatic pacing, electrodes are implanted in each hemidiaphragm, helping to provide maximal contraction of the diaphragm. In an open-label pilot study, 16 patients were implanted and showed benefits on survival (when compared to historical controls) and quality of life (as sleep dysfunction was reduced).<sup>92</sup> Results of small follow-up studies have been mixed.<sup>93,94</sup> Large, randomized controlled trials comparing NIV and diaphragmatic pacing are ongoing in the United States and Europe.<sup>95</sup> Invasive ventilation remains another option to prolong survival.<sup>96</sup> This is generally well tolerated<sup>97</sup> but is rarely selected for a

variety of reasons, including patient's wishes and difficulties in home care.

Medications including opiates and benzodiazepines can be helpful in symptomatic treatment of dyspnea and dyspnea-related anxiety.<sup>98</sup>

## Sialorrhea

About 25% of patients with motor neuron disease suffer from sialorrhea due to pseudohypersalivation.<sup>99</sup> The majority of the treatments used for sialorrhea in ALS patients have not been studied in randomized controlled trials so there are no clear guidelines. Anticholinergic medications are generally recommended first.<sup>85</sup> There are several oral agents, including atropine, glycopyrrolate, and amitriptyline. Transdermal application of hyoscyamine or scopolamine has the advantage of a constant concentration of drug in the circulation.<sup>100</sup> For patients with sialorrhea refractory to medical therapy, salivatory gland botulinum toxin injections are an option, which lead to a significant decrease in saliva volume<sup>101</sup> and have been shown to improve quality of life.<sup>102</sup> Another alternative for treatment of refractory sialorrhea is radiation therapy of salivary glands.<sup>103</sup>

## Respiratory secretions

Management of respiratory secretions and thick mucus can additionally become a major issue. Thick mucus production can be a symptom of ALS, medication side effect, or due to dehydration. Following insurance of good hydration and adjustment of medications, specific medication treatments can be added including mucolytics like *N*-acetylcysteine.<sup>85</sup> Cough-assist and suction devices can be used to reduce the difficulty many patients experience with clearing respiratory secretions.<sup>104</sup> Besides improving quality of life, these interventions have the potential to reduce hospitalizations.<sup>105</sup>

## Dysarthria

Dyspnea often coincides with dysarthria. Speech therapy along with assistive devices is recommended.<sup>85</sup> Communication devices greatly improve the patients' mood and quality of life.<sup>106</sup>

## Dysphagia and weight loss

Nutrition management is another important goal in the treatment of ALS, as patients will develop dysphagia due to bulbar muscular weakness. In the early stages, this can be managed by modifying the consistency of food and fluids and teaching swallowing techniques. To ensure adequate nutrition and hydration as well as to stabilize weight loss, placement of a

percutaneous endoscopic gastrostomy (PEG) tube is offered to many ALS patients with dysphagia.<sup>107</sup> Nutritional status is an independent prognostic factor for survival in patients with ALS.<sup>108</sup> However, there is inconclusive data whether placement of a PEG tube actually provides significantly improved nutrition, quality of life, or survival.<sup>109</sup> For patient safety, a PEG tube should be placed before the patient's vital capacity falls below 50% of predicted,<sup>85</sup> even if no significant dysphagia is present at that time, as post-PEG deaths have been associated with reduced vital capacity.<sup>107</sup>

## Muscular symptoms

Muscle issues including progressive weakness, cramps, and spasticity are cardinal features of ALS. Regular exercise of moderate intensity is generally recommended and has been found to improve quality of life, although the long-term benefit is unclear.<sup>110</sup> Muscular cramps are a common complaint of ALS patients in all stages of the disease. Despite a number of medications undergoing trials so far, there has been no evidence supporting any specific intervention for muscle cramps in ALS.<sup>111</sup> In practice, baclofen and gabapentin are frequently used to treat these. Baclofen is also often used to treat spasticity and is equally effective as tizanidine.<sup>112</sup>

## Fatigue

Fatigue can be debilitating and is a common symptom of ALS. It is often associated with malnutrition or early respiratory failure. Fatigue is a potential medication side effect of many medications including riluzole,<sup>85</sup> and medication adjustment should be considered. Multiple factors contribute to poor sleep which should be addressed throughout the disease course, and particularly with new complaints of fatigue. Depression should also be considered, as it is a common cause of fatigue and can benefit from treatment.<sup>113</sup> Modafinil has been shown to have a positive effect on fatigue and sleepiness.<sup>114,115</sup>

## Pseudobulbar affect

Pseudobulbar affect manifests as sudden episodes of uncontrollable laughter or crying without a provoking stimulus and is common in ALS. Dextromethorphan/quinidine has been shown to be effective in reducing the frequency and severity of emotional lability.<sup>116</sup> The combination is necessary as dextromethorphan is rapidly metabolized if administered alone; quinidine reduces the metabolism via CYP2D6 inhibition. This combination has been approved by the FDA for pseudobulbar affect in ALS and represents the second FDA-approved drug specifically for ALS.

## Summary

ALS remains a progressive motor neuron disease with a mean survival of 2–5 years. Symptom-based management of ALS in the setting of multidisciplinary clinics remains the most important current treatment strategy for the individual patient, as no curative therapies exist. Two decades after the first publication on using riluzole for treatment in ALS, this remains the only FDA-approved disease-modifying therapy. A large number of studied drugs showed promising results in animal models but failed translation to the human patient. One of the many difficulties in finding a treatment is the lack of understanding of pathophysiology of ALS. Yet, we remain optimistic about the medication treatments in developmental stages.

Novel therapeutic approaches with ASOs and stem cells have yet to show clear efficacy in humans; however, these remain exciting future directions of the field. Both have promising results in rodent and primate models of ALS. Early human trials have confirmed the safety of several of the potential methods. Preclinical studies showed the most convincing results in studies using NSCs. However, MSCs are more frequently used as they are more readily available and can easily be harvested and reintroduced into the patient without necessary immunosuppression.

## Disclosure

The authors report no conflicts of interest in this work.

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