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Trials of Anti-Diabetic Drugs in Amyotrophic Lateral Sclerosis: Proceed with Caution?

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Abstract

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder with limited therapeutic options. Clinical trials of several drugs which were shown to be effective in the superoxide dismutase (SOD1) model of ALS have shown null or negative effects when tested in humans. Here we discuss the role of pioglitazone, a peroxisome proliferator-activated receptor gamma agonist, which failed to show efficacy in a recently published phase II clinical trial of ALS patients. The anti-oxidant and anti-inflammatory properties of pioglitazone make it an attractive therapeutic candidate for neurodegenerative disorders. However, its anti-diabetic and anti-dyslipidemic effects might be detrimental, as emerging evidence suggests that some features of the metabolic syndrome maybe protective in ALS. A number of clinical studies show that dyslipidemia, and high body mass index are associated with better clinical outcomes in ALS. This is further corroborated by studies on transgenic animal models and immortalized neuronal cell lines. Finally, the intricate interplay between glucose/lipid metabolism and susceptibility to oxidative damage in neurons warrants a judicious approach in further trials of anti-diabetic drugs in ALS.

Amyotrophic Lateral Sclerosis (ALS) is a fatal neurodegenerative disease leading to progressive degeneration of both upper and lower motor neurons. Most ALS cases occur sporadically, but about 10% of individuals with ALS have at least one other affected family member and are said to have familial ALS (fALS). ALS has a well-established clinical overlap with frontotemporal lobar degeneration (FTLD) [1]. Furthermore, the occurrence of TAR-DNA binding protein 43 kDa (TDP-43) aggregates in patients with ALS, FTLD and ALS-FTLD suggest a pathophysiological continuum between these disorders [1]. In addition to TDP-43, FTLD is also characterized by pathological aggregation of other RNA-binding proteins: Fused in Sarcoma (FUS), TATA-binding protein-associated factor 15 (TAF15) and Ewing's Sarcoma (EWS) [2].

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The field of ALS research was revolutionized by the discovery of super oxide dismutase (SOD1) mutations in familial ALS patients roughly two decades ago [3]. Subsequently, transgenic mouse models of ALS-related SOD1 mutations were successfully developed which recapitulated the motor phenotype representative of human pathology [4]. These animals have been used extensively for the pre-clinical screening of potential novel therapeutic agents. However, only about 20% of familial cases of ALS in humans, and almost none of the sporadic cases, are associated with SOD1 mutations. None of the SOD1 mutant cases show a clinical over-lap with FTLD [5]. Additionally, SOD1-related ALS does not show the hall-mark aggregation of TDP-43/FUS/TAF15/EWS [2]. These discrepancies might explain, at least in part, why positive results in SOD1 transgenic animals have consistently failed to predict therapeutic efficacy in humans [5].

In the July, 2012 issue of the journal *PLOS One*, Dupuis et al. reported a Phase II, multi-centric, placebo-controlled trial of the oral anti-diabetic pioglitazone in patients with ALS as an add-on therapy to riluzole [6]. The rationale for the trial was based on positive pre-clinical data obtained in SOD1 transgenic mice by at least three independent groups [7-9]. Contrary to their hypothesis and to the pre-clinical data, Dupuis et al. did not observe a survival benefit in the pioglitazone group. Instead, pioglitazone was associated with a 21% increased hazard ratio for mortality, which was not statistically significant (p=0.48) [6].

Pioglitazone is a peroxisome proliferator-activated receptor gamma (PPAR-Y) agonist, which has known anti-hyperglycemic, anti-dyslipidemic, anti-oxidant, and anti-inflammatory properties [10-11]. While pioglitazone is used in clinical practice as an anti-diabetic agent, its anti-oxidant and anti-inflammatory roles make it an attractive candidate drug for ALS since oxidative stress and inflammation are implicated in ALS pathophysiology [6].

There are, however, a number of issues of concern regarding the pre-clinical potential of pioglitazone as a therapeutic agent for ALS. Despite the established disease-modifying effect of gender in ALS, one pre-clinical study used only male mice [7], the animal cohorts were small (n<8) in size [7-8] and the observers were not blinded [9]. In addition, pioglitazone has not shown a beneficial effect in any non-SOD1 models of ALS or FTLD. This becomes crucial considering the drawbacks of the SOD1 model of ALS as mentioned previously.

While there may be multiple reasons underlying the failure of the Phase II trial of pioglitazone in humans, here we propose the hypothesis that its effects on whole body metabolism, including its anti-diabetic and anti-dyslipidemic effects, might play a significant role. A growing body of evidence suggests that ALS is associated with systemic metabolic changes and abnormal energy metabolism Impaired lipid metabolism, in particular, is receiving increasing attention since it was found that, in SOD1-ALS mouse models, increasing the fat content of the diet prolongs lifespan and maintains motor neuron numbers [12], whereas restricting fat intake hastens disease onset and death [13]. In humans, several studies have reported an association between dyslipidemia and improved survival in ALS [14-15]. We observed that change in body mass index (BMI) after ALS onset correlated inversely with rate of ALS motor disease progression [16], i.e. weight loss was

associated with faster rates of progression. Also, in two independent studies we showed that there is a “U-shaped” association between mortality and BMI in ALS with people with mild obesity or stable BMI having the least mortality [16-17]. Data about glucose metabolism in ALS is more limited, but is the subject of active research efforts suggesting that pre-morbid diabetes mellitus type 2 (DM2) might affect disease onset and progression [18]. Taken together, our findings and those of several others have lead to an emerging hypothesis that some features of the “metabolic syndrome” are associated with reduced risk and/or slower disease progression in ALS (Table 1). Several molecular as well as prospective studies are now under-way to corroborate this hypothesis.

It is important to consider that there is plausible biological rationale for the protective effect of the metabolic syndrome in ALS. There is evidence to suggest that the proteins whose mutated forms are associated with ALS and FTLD might have a physiological role in lipid metabolism. It was shown that conditional knock-down of TDP-43 leads to down-regulation of Tbc1d1, a gene linked to obesity. These mice exhibited a lean phenotype and features of features of hyper-metabolism, besides reduced survival [19]. Progranulin which is mutated in some cases of FTLD has been shown to play a role in high-fat mediated insulin resistance and obesity [20].

Similarly, alterations in glucose metabolism may lead to altered susceptibility to oxidative stress-one of the postulated pathways leading to neurodegeneration in ALS/FTLD. Of particular interest here is glycolysis, which is regulated by insulin-glucagon signaling and has important implications for survival of cells. Cancer cells are known to enhance their glycolysis under aerobic conditions, which is associated with decreased production of reactive oxygen species (ROS) and confers a survival advantage to the cancer cells under hostile conditions [21]. There is evidence to suggest that resistance to amyloid-beta (Aβ) toxity in neuronal lines is also related to enhanced glycolysis and subsequent decrease in the production of ROS [22]. Hyperglycemia in DM2/metabolic syndrome provides increased substrate for glycolysis, and also replenishes the active reduced form of the anti-oxidant enzyme glutathione through stimulation of the pentose phosphate pathway, hence countering oxidative stress through different pathways. Thus, in the pioglitazone trial, the anti-oxidant effect of the medication through stabilization of SOD1 could be counter balanced by its concomitant anti-hyperglycemic effects.

The relationship between hypoxia and glucose metabolism is also complicated by complex and sometimes disparate regulation of the two at the molecular level. A notably relevant study would be that of Mergenthaller et al., which showed that the glycolytic enzyme Hexokinase 2 (HK2) acts as a molecular switch and controls the fate of neurons depending on the ongoing metabolic state. Hypoxia leads to activation of hypoxia induced factor 1 (HIF1), which up regulates HK2. HK2 in turn protects primary neurons from hypoxia through its interaction with phophoprotein enriched in astrocytes (PEA15). Alternatively, HK2 also acts as a sensor for glucose starvation and initiates a cascade leading to apoptotic neuronal death in reaction to prolonged glucose starvation [23]. There is evidence to suggest that pioglitazone is associated with up regulation of HK2 [24]. Hence, pioglitazone may confer increased sensitivity of neurons to glucose starvation. There are a number of reasons for which patients with ALS may be glucose starved, including dysphagia,

hypermetabolism, physical disability, or riluzole-associated nausea and fatigue. The hypoglycemic action of anti-diabetics itself may further aggravate the glucose starvation.

In conclusion, we hypothesize that the potential protective anti-oxidant and anti-inflammatory properties of pioglitazone might be countered in ALS by its effects against the metabolic syndrome. This hypothesis is also consistent with the finding that another widely used anti-diabetic drug, metformin, was associated with worse neurological scores and faster symptom progression in female SOD1 mice in a dose-dependent manner [25]. However, another class of anti-diabetics, glucagon-like peptide 1 (GLP-1) analogs, has demonstrated neuroprotection against Kainate-induced excitotoxicity and trophic-factor withdrawal in SOD-1 *in vitro* and *in vivo* models [26-27]. The generalizability of this data is currently limited because of lack of reproducibility in ALS-TDP model, besides the fact that there was no viability/survival assessment under the oxidative stress induced by SOD-1 mutation itself. Nevertheless, these studies do raise a possibility that some anti-diabetics may be beneficial in particular forms of ALS and future studies should judiciously account for this.

It would be extremely interesting to further analyze the data from the pioglitazone study to test whether changes in weight, glycemia and/or lipid levels were associated with worse survival. It is urged that the disease-modifying effect of dyslipidemia, BMI, DM2 and other metabolic perturbations should be accounted for in future trials of ALS. This might lead to valuable clues about the pathophysiology of ALS, and would help to delineate which patients might benefit from one therapy versus another.

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Table 1

Studies that support the hypothesis that metabolic syndrome is associated with reduced risk of ALS or improved ALS survival.

Dupuis et al. 2008 (France)	ALS patients with high LDL/HDL ratio had a 12 month longer survival when compared to ALS patients with low LDL/HDL ratio
Jawaid et al. 2010 (USA)	ALS patients with pre-morbid DM2 had a four year later onset of motor symptoms as compared to patients without DM2
Jawaid et al. 2010 (USA)	Loss of BMI>1 unit over two years after ALS diagnosis was associated with significantly shorter survival and faster progression of motor symptoms
Sutedja et al. 2011 (Netherlands)	ALS patients more likely to have lower BMI and favorable lipid profile as compared to healthy age matched controls
Marin et al. 2011 (France)	36% increased risk of death per unit decrease in BMI Malnourished patients at diagnosis had an increased (RR 2.15) risk of death, whereas over-weight and obese patients had a decreased (RR 0.71) risk of death
Dorst et al. 2011 (Germany)	ALS patients with higher Triglycerides and TC had longer survival
Huisman et al. 2011 (Netherlands)	Reduced prevalence of vascular disease in ALS patients and their relatives as compared to age-matched controls
Paganoni et al. 2011 (USA)	U-shaped relationship between BMI and survival in ALS patients, with the maximum survival at BMI 30-34.9
Shimizu et al. 2012 (Japan)	Faster reduction in BMI post onset was associated with significantly shorter survival
Ikeda et al. 2012 (Japan)	Elevated TC and LDL levels were associated with worsened ALS-FRS and FVC
Gallo et al. 2013 (UK)	Increased pre-diagnostic body fat was associated with decreased risk of ALS mortality
Reich-Slotky et al. 2013 (USA)	For ALS patient with BMI less than 30, higher initial BMI predicts slower functional decline
O'Reilly et al. 2013 (USA)	For each 5-unit increase in BMI, ALS rates were 21% lower

LDL: low density lipoproteins, HDL: high density lipoproteins, DM2: diabetes mellitus type 2, BMI: body mass index, RR: relative risk, TC: total cholesterol, ALS-FRS: ALS functional rating scale, FVC: forced vital capacity