Disease Modifying Therapy for Motor Neurone Disease – A Realistic Aspiration?

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121

INTRODUCTION

Despite much research and effort no clear insights into a unifying hypothesis for the pathogenesis of motor neurone disease (MND) have so far emerged. Nonetheless our knowledge of MND is punctuated by many threads and aetiological hypotheses. These have ranged from heavy metal intoxication through environmental exposures, genetic influences and autoimmunity to excitotoxicity. The number of putative disease modifying drug therapies has been similarly diverse. The purpose of this paper is to review some of the better known putative therapies in the context of these aetiological hypotheses alongside theories of the neurobiology of the degenerative process in MND.

HEAVY METALS AND CHELATING AGENTS

Early recognition of MND as a specific clinical entity came out of the familiarity of early neurologists with the neurological sequelae of heavy metal poisoning, particularly lead. This lead to early clinical trials of chelating therapy. The results, along with outcomes of other research have been such that heavy metal toxicity is not thought to be implicated in the pathogenesis of MND.[1]

NEUROMODULATORY APPROACHES

Thyrotrophin releasing hormone (TRH)

During the 1980's a suggestion emerged from clinical observation that the administration of TRH to people with MND might be associated with at least a short-lived improvement in muscle strength. TRH was known to be a potential chemical neuromodulator and it was thought that any improvement in muscle strength in MND associated with the administration of TRH would be likely to relate to this physiological function. It was necessary to give the TRH parenterally and a number of studies were done encompassing subcutaneous, intramuscular, intravenous and even intrathecal administration through an implanted constant infusion pump. Although TRH is thought to penetrate the blood-brain barrier poorly, CSF levels were shown to increase 29-fold following a single injection. The eventual conclusion after a number of acute and chronic studies was that TRH does not show any beneficial effect in MND.[2-6]

EXCITOTOXICITY

The principle of excitotoxicity depends on a concept in which chemical neurotransmitters which are required for normal function can become toxic at supraphysiological concentration. Supraphysiological concentrations of excitotoxic amino acids are thought to influence the transfer of substances across the neuronal membrane. This is thought to result in an excessive intracellular influx of calcium and initiate an intraneuronal cascade mechanism which eventually results in cell death. The most important putative excitotoxin is the neurotransmitter glutamate. One of the most important glutamate receptors is the N-methyl-D-aspartate (NMDA) receptor. Others include the kainate and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors.

Early attempts to approach this hypothesis from a therapeutic perspective addressed the possible use of NMDA receptor antagonists such as dextromethorphan and MK801; a range of other categories of intervention have however also been studied in this context including riluzole, the first licensed disease modifying drug for MND which is now approved for use in many countries.

NMDA antagonists

Dextromethorphan

Assuming the presence of glutamate-induced neurotoxicity in MND at least three trials with dextromethorphan, an N-methyl-D-aspartate receptor antagonist in MND have been undertaken. These trials involved a total of 53 MND patients in all receiving dextromethorphan. All were randomised placebo-controlled studies but two were parallel design and the third, crossover. Doses ranged from 100-300mg assuming a "standard" 70 kg body weight. None of these studies however yielded any results to suggest that dextromethorphan might have a useful disease modifying effect in MND.[7-9]

Calcium channel antagonists

Nimodipine

Calcium channel blocking drugs inhibit the activation of excitatory amino acid receptors and decrease calcium entry into damaged neurons. In the light of these actions it has been thought that these drugs might potentially have a disease modifying effect in

MND. A randomised, placebo-controlled, prospective, double-blind crossover study of nimodipine was undertaken in 87 MND patients. There was no significant difference in the rate of decline of pulmonary function or limb strength during treatment with drug or placebo and nimodipine was thus considered ineffective in slowing the progress of MND.[10]

Branch chain amino acids (BCAAs)

During the late 1980s a hypothesis gained some support suggesting that the neurotransmitter amino acid glutamate accumulated to toxic levels in motor neurones in MND. Further work identified a possible MND-specific impairment of glutamate removal from the central nervous system (CNS). A laboratory model was subsequently developed in which glutamate apparently induced the selective death of motor neurons. A reduction of glutamate transporter protein has also been reported in MND. Despite these pieces of evidence however, these findings remain unconfirmed and indeed some other groups have been unable to reproduce them.

Plaitakis suggested that some disorders that could present as atypical MND were associated with a deficiency of glutamate dehydrogenase (GDH). Three BCAAs, L-leucine, L-valine and L-isoleucine, were thought to up-regulate GDH activity and were thus explored as a potential disease modifying therapy in MND. Reports were subsequently published of an alternative glutamate-modifying therapy, the amino acid L-threonine: it was suggested that this increased concentrations of the inhibitory amino acid glycine.

Several trials of BCAA and L-threonine followed. All originated before the development of accepted diagnostic criteria and guidelines on clinical trials for MND. These included a large scale RCT, the results of which have unfortunately not yet been published in definitive form in a peer reviewed journal. A Cochrane Systematic Review has however been undertaken. This concluded that no benefit could be demonstrated for either branch-chain amino acids or L-threonine in improving survival in MND. Neither could any evidence of an effect of either treatment be discerned on muscle strength or disability as measured by functional rating scales. None of the studies addressed quality of life issues.[11]

Glutamate release inhibitors

Lamotrigine

A possible anti-excitotoxic effect of the anticonvulsant drug lamotrigine prompted interest in this drug as a potential disease modifying drug in MND. The anti-excitotoxic effect was thought to be associated with the drug's action as a glutamate release inhibitor. An initial double-blind, placebo-controlled trial of oral lamotrigine, 100 mg daily in 67 patients over 18 months did not show any differences between the placebo and lamotrigine groups and the authors concluded that lamotrigine 100mg daily does not alter the course of MND.[12]

Following the publication of the results of this trial discussion ensued regarding the dose of lamotrigine used. It was suggested by some that this was relatively low in the context of doses used in the treatment of epilepsy. In view of this, as well as the evidence on the use of riluzole which has a similar pharmacological action to lamotrigine, a further RCT was undertaken.[13] A group of MND patients were entered into a double-blind, placebo-controlled, crossover study of lamotrigine 300mg daily. No evidence of a beneficial effect for lamotrigine on the clinical progression of MND could be found. The results of these two studies taken together do not suggest a significant disease modifying effect for lamotrigine in MND.

Riluzole

Evidence that chronic glutamate excitotoxicity may contribute to neuronal death in MND provided a rational basis for undertaking clinical trials of riluzole, a drug which blocks the presynaptic release of glutamate. The first trial demonstrated a modest increase in survival in treated patients compared to placebo controls. However, many questions were raised by this study, especially in view of the disproportionate benefit observed in patients with bulbar onset as opposed to limb-onset disease.

To address these concerns, a second much larger dose-ranging study was carried out. Again there was a small but statistically significant prolongation of survival in patients receiving the 100mg and 200mg/day doses of riluzole. A third study was also carried out in France and Belgium involving patients with more advanced MND who did not qualify for main study. In this trial there was no significant survival advantage from riluzole. A fourth trial was carried out in Japan with multiple outcome measures that differed from the other three trials. This study involved small numbers of patients, had confusing end-points and lacked survival-specific data.

A Cochrane systematic review concluded that riluzole 100 mg daily is safe and probably prolongs survival by about two months in MND patients but suggested that further studies were needed to clarify its effect in older patients (over 75 years), and those with more advanced disease. In the meantime however more recent studies using large databases spanning five to 10 years have focussed on the use of riluzole in the earlier stages of MND and suggested that treatment with riluzole might be associated with a median survival prolongation of six months, 12 months, or even 21 months. It is not clear to what extent the greater reported efficacy of riluzole in these uncontrolled studies was influenced by other factors, such as riluzole users having less advanced disease than non-users, or differential use of interventions such as gastrostomy and non-invasive respiratory support. These studies had the advantage of longer follow up than the RCTs and included patients treated earlier in the course of MND which may approximate routine clinical practice more closely, but the effects of uncontrolled potential confounders on survival could have biased the survival results.[14]

NEUROTROPHIC FACTORS

There has been a clear realisation or the role of neurotrophic factors in maintaining neuronal viability. From this has emanated suggestion that the therapeutic administration of neurotrophic factors might halt or even slow the degenerative process in MND.

Ciliary neurotrophic factor (CNTF)

While the hypothesis that neuronal degeneration might be caused by a lack of neurotrophic factors is well established it has

only become testable more recently. CNTF and brain-derived neurotrophic factor (BDNF) have emerged as prominent motor neurotrophic factors, because both show remarkable survival-promoting effects on motor neurons in cell cultures, embryos, and adult animals. In particular, CNTF has been shown to retard the disease progression and improve muscle strength in the wobbler mouse model of MND. Investigations of neurotrophic factors in animal models of MND were thus rapidly progressed to clinical studies in man. Phase I-II trials indicated that in human MND subcutaneous doses of CNTF up to 5 μg/kg were generally well tolerated, whereas higher concentrations were not. Delivery of human CNTF directly to motor neurons has been achieved by transplanting immunoprotected xenogeneic cell lines genetically engineered to release human CNTF.

A Cochrane review of studies of CNTF in MND has been undertaken.[15] Only two trials were found which fulfilled the inclusion criteria. They were both multicentre studies including a total of 1100 patients. Each study included different CNTF doses (0.5 μg/kg, 2 μg/kg or 5 μg/kg CNTF in the first and 15 μg/kg or 30 μg/kg CNTF in the second). The data showed that subcutaneous administration of CNTF at these different doses did not alter the progression of MND, compared with placebo. The outcomes published in the two trials were very similar, eventhough CNTF doses were different. Administration of CNTF was however associated with several adverse events that were more frequent at higher doses. Moreover, in the group treated with 5 μg/kg CNTF there was a significant increase in the number of deaths.[15]

Recombinant human insulin-like growth factor I

Recombinant human insulin-like growth factor I (rhIGF-I) is a naturally occurring peptide with multi-target neurotrophic potential on motor neurons as well as the neuromuscular junction and muscle. Recombinant human insulin-like growth factor I has promoted the survival of spinal and facial motor neurons in experimental models of peripheral nerve transection and excitatory amino-acid-induced cell death and has also promoted peripheral nerve regeneration in motor nerve axotomy models. Receptors for rhIGF-I have been reported to be up-regulated in the spinal cord of patients who have died of MND. These studies provided the background for randomised placebo-controlled trials of rhIGF-I in MND. Two randomised controlled trials of rhIGF-I in MND have so far been published.

A Cochrane review of these studies has been undertaken.[16] These were the only trials from which results were available for inclusion in the review. The reviewers were not able to gain access to the results of a further RCT which is thought to have been conducted in Japan. A fourth trial is currently ongoing in North America. The efficacy of IGF-I in MND remains unproven. There is a clear suggestion that the drug might be modestly effective but the results of randomised placebo-controlled trials as currently available do not permit a definitive assessment. These opportunities to evaluate the efficacy of IGF-I in MND were seriously compromised by details of trial design. It is hoped that the current trial in North America will provide new insights into the potential role of IGF-I as a treatment for MND.

Brain-derived neurotrophic factor (BDNF)

In an initial phase I/II study, BDNF appeared to increase survival and retard loss of pulmonary function in MND patients. Patients were randomised to placebo, 25 or 100 mug/kg BDNF for 9 months in a subsequent study. This failed to show benefit of BDNF treatment for the primary end points. Survival in patients treated with 25 mug/kg BDNF was identical to placebo, but there was a trend toward increased survival in the 100 mug/kg group.[17]

Studies have also been undertaken evaluating the potential place of intrathecal administration of BDNF in MND. This route of administration was found to be associated with mild sensory symptoms, including paraesthesiae or a sense of warmth, which were usually confined to the lower limbs and were frequently exacerbated by neck flexion. This could have clear implications concerning blinding in any future RCTs. The small number of patients and the design of the study did not permit conclusions to be drawn about the efficacy of the treatment.[18]

ANTIOXIDANT DRUGS

Vitamin E

Increasing evidence suggests that oxidative stress may be involved in the pathogenesis of MND. The anti-oxidant vitamin E ([alpha]-tocopherol) has been shown to slow down the onset and progression of paralysis in transgenic mice expressing a mutation in superoxide dismutase found in certain forms of familial MND. The current study was designed to determine whether [alpha]-tocopherol (500 mg b.i.d.) may be efficacious in the treatment of MND. Two hundred and eighty-nine patients with MND of less than 5 years duration, treated with riluzole, were enrolled in this study, and were randomly assigned to receive either [alpha]-tocopherol or placebo daily for one year. After 12 months of treatment, [alpha]-tocopherol had no effect on the primary outcome measure. Survival was not influenced by treatment.[19]

Selegiline

Based on the hypothesis that free radicals play a general role in the neurodegenerative process in motor neuron disease, selegiline was given to a group of MND patients to examine whether it might modify the progression of the disease. Fifty-three patients were randomly assigned to receive the drug (selegiline 10 mg/day orally for 6 months) and the remaining 58 constituted a control group. The data did not show any significant effect of selegiline in modifying the progression of MND.[20] A further double-blind crossover trial of selegiline was undertaken in 10 MND patients. In the preliminary analysis reported so far, no obvious retardation in the progress of the disease could be observed with selegiline treatment.[21] Another double-blind crossover trial of selegiline in 52 MND patients was coupled with serial evaluations of antioxidant and free radical activity. This study also failed to show any significant effect of selegiline in modifying the progression of MND but subsequent analysis of the results suggested that erythrocyte glutathione peroxidase activity may decline with disease progression in MND.[22] A six-month, double-blind, placebo-controlled study of selegiline in 133 MND patients was subsequently carried out. The results of this further study again

suggested that selegiline had no significant effect on the rate of clinical progression or outcome in MND.[23]

N-acetyl cysteine

On the basis that free radicals may play a role in the pathogenesis of MND a trial to investigate the potential efficacy of the free radical scavenging agent acetylcysteine. A randomised, double-blind, placebo-controlled clinical trial in 110 MND patients was undertaken. In this trial however, treatment with acetylcysteine did not result in a major increase in 12-month survival or a reduction in disease progression in patients with MND.[24]

NEUROTROPHIN ANALOGUES

Following on experience with attempts to assess the potential efficacy of neurotrophins in MND, major trials of a non-neurotrophin with neurotrophin-like effects have been undertaken.

Xaliproden

Two randomised, double-blind, placebo-controlled, RCTs with xaliproden (a drug with neurotrophic effect) were undertaken to assess drug efficacy and safety at two doses. Patients with clinically probable or definite MND of more than 6 months and less than 5 years duration were randomly assigned to placebo, 1 mg or 2 mg xaliproden orally once daily as monotherapy in Study 1 (n=867); or to the same regimen with addition of riluzole 50 mg bid background therapy in Study 2 (n=1210 patients). Although this effect did not reach statistical significance at the 5% level, adjusted RR ratios were consistently more favourable for the xaliproden groups. Tolerability was good, and dose-dependent side effects were largely associated with the serotonergic properties of xaliproden.[25]

PROSPECTS FOR THE FUTURE

Minocycline

CSF from patients with MND has been reported to be toxic to cultured primary neurons. Antagonists of N-methyl-D-aspartate (NMDA) and alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid/kainate receptors prevented the toxic CSF-induced neuronal death but not microglial activation, whereas minocycline, a tetracycline derivative with anti-inflammatory potential independent of antimicrobial activity, reduced both the apoptotic neuronal death and microglial activation. We conclude that the cytotoxic action of CSF is prevalent in all MND cases and that microglia may mediate the toxicity of CSF by releasing excitotoxicity-enhancing factors.[26]

Two double-blind, randomised, placebo-controlled feasibility trials of minocycline in ALS have followed. In Trial 1, 19 subjects received 200 mg/day or placebo for 6 months. In Trial 2, 23 subjects received up to 400 mg/day in an 8-month crossover trial. The mean tolerated dose was 387 mg/day, there was a trend toward more gastrointestinal AE ($p = 0.057$), and blood urea nitrogen and liver enzymes became elevated ($p < 0.05$). Using these data, the authors have designed and launched a phase III trial.[27]

Creatine

Creatine showed a promising increase in survival in a transgenic mouse model of MND. A double-blind, placebo-controlled RCT was therefore undertaken to assess the effect of creatine on survival and disease progression in patients with MND. One hundred seventy-five patients with probable, probable-laboratory supported, or definite MND were randomly assigned to receive either creatine 10 gm or placebo daily. Creatine did not affect survival or the rate of decline of functional measurements.[28]

Gabapentin

Gabapentin has been postulated as having neuroprotective properties. A phase II trial was undertaken to evaluate the efficacy of gabapentin in slowing the rate of decline in muscle strength of patients with MND and to assess safety and tolerability. Gabapentin (2.4g/day) or placebo was administered in a randomised, double-blind, placebo-controlled, trial for 6 months. One hundred fifty-two MND patients were included. A non-statistically significant trend ($p = 0.057$-0.08) toward slower decline of arm strength was found in patients taking gabapentin compared with those taking placebo. No treatment effect on forced vital capacity was observed and it was considered that further studies of gabapentin in MND are warranted.[29]

A phase III randomised clinical trial was therefore undertaken. Patients were randomly assigned to oral gabapentin 3.6 g or placebo daily for 9 months. Two hundred and four patients enrolled, and 128 patients completed the study. The mean rate of decline of the arm muscle strength was not significantly different between the groups. The results of the trial provided no evidence of a beneficial effect of gabapentin on disease progression or symptoms in patients with MND.[30]

Stem cell therapy

Stem cells were initially restricted to neurobiology studies on the principles of embryonic development. This situation has changed rapidly in recent years since neuronal stems and precursors were isolated in vitro, thus allowing expansion and controlled differentiation of selective populations of neuronal cells. This theoretically unlimited reserve would then supply specific cells for transplantation in diseases characterized by widespread degeneration of selective cell populations as motor neurons in MND. Although stem cell technology is at an early stage the desperate need for a therapy in MND patients may legitimise clinical trials in absence of conclusive scientific evidence.[31] These theoretical possibilities were progressed by the comment that attraction of cell implantation or transplantation is that it might help to overcome the inability of the CNS to replace lost neurons. The point that neural implantation would yield little benefit if the donor cells fail to integrate functionally into the recipient CNS circuitry was stressed.[32] It was subsequently shown in animal models of MND that stem cells could significantly slow the progression of the disease and prolong survival. The feasibility and safety of intraspinal cord implantation of autologous mesenchymal stem cells was thus considered in some MND patients. The results were thought to demonstrate that the procedures of ex vivo expansion of autologous mesenchymal stem cells and of transplantation into the spinal cord of humans are safe and well tolerated by MND patients.[33] The advent of

stem-cell research has highlighted MND as a candidate for stem-cell treatment. Stem-cell transplantation is an attractive strategy for neurological diseases and early successes in animal models of neurodegenerative disease generated optimism about restoring function or delaying degeneration in human beings. The success of cell-replacement therapy in MND will depend heavily on preclinical evidence, because of the complexity and precision of the pattern of connectivity that needs to be restored in degenerating motor neurons. If found to be useful in MND, stem-cell therapy may need to be used with other drugs or treatments, such as antioxidants and/or infusion of neurotrophins in order to secure maximal efficacy.[34]

GENERAL COMMENT

The crucial unknown at this stage is the question of whether the achievement of a truly effective disease modifying drug therapy in MND is a realistic aspiration. In common with other neurodegenerative disorders such as Parkinson's disease significant neuronal loss is thought to have occurred before the disease becomes clinically manifest. Has the neurodegenerative process in MND thus become irreversible by the time the disease becomes clinically apparent? This paper has attempted to provide an overview of the evidence so far. Are we at an analogous stage in MND as we were in the early days of anti-tuberculous and cancer chemotherapy in which the crucial advances came from the discovery of synergistic drugs? It is the hope of all concerned with MND research that if answers to these questions are forthcoming, these further insights will come as soon as possible.

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