INTRODUCTION

Between Charcot’s first description, in 1864, of a rapidly progressive neurodegenerative disease and the early 1990s, physicians’ efforts in the field of amyotrophic lateral sclerosis (ALS) focused mainly on the definition of the diagnostic criteria for this disease, which was for a long time considered fatal.

Only recently, parallel to an improved understanding of the physiopathogenesis of the disease, have we entered the era of pharmacological treatment of ALS.

In 1993, riluzole, a glutamate antagonist first approved in 1980 for the treatment of convulsions, underwent, in the USA, phase II and III trials for the treatment of ALS; it became (in 1994) the first ALS drug approved by the FDA, was registered in the USA in 1995 and is now available in over 21 countries. It is still not clear whether it slows the progression of the disease or not.

Various experimental model systems, both in vivo and in vitro, have been developed to investigate the mechanisms leading to the selective motor neuron degeneration related to ALS; these models have also been used to test the efficacy of various drugs in preventing or arresting the cascade leading to degeneration. Unfortunately, the success of the treatment in these...
models did not translate into equal success in a number of clinical trials performed in the last decade. Therefore, at the beginning of the 21st century, the etiology of ALS remains obscure, and truly effective, causal therapy is not available for the disease.

Understanding the reasons why so many treatments have failed to cure ALS constitutes a major problem, and future developments must be based on discussion of the same.

First of all, human ALS is a complex, multifactorial disease, resulting from the interaction of at least two mechanisms, i.e., excitotoxicity and oxidative stress, which potentiate each other in a sort of “positive feedback” loop. It is thus possible that a polytherapy combining anti-oxidants and anti-glutamate agents will prove to be more effective than single drugs in the treatment of ALS. Furthermore, mice genetic models do not take into account potential environmental factors leading to motoneuron disease, yet these factors might in fact be important in the development of new preventive strategies.

Furthermore, the genetic background might be the source of important risk factors for human ALS and influence its onset, progression and responsiveness to therapy. Experimental studies on animals have raised the hypothesis that oxidative stress from any source might influence disease onset, progression and death in an individual genetically predisposed to develop ALS (1). Evidence for a genetic contribution to sporadic ALS is increasing, as suggested by twin studies; a polymorphism in the gene for apurinic/apyrimidinic exonuclease has been implicated in a study of sporadic ALS (2). In the future, DNA chip technology and single nucleotide polymorphisms (SNPs) might contribute to the identification of subpopulations of responders and non responders to a drug.

Another issue to consider is the adequacy of the experimental models used for the preclinical testing of drugs intended to treat human ALS. The main problem with these models is that they do not closely resemble the human disease. For example, three naturally occurring genetic rodent models show, respectively, a temporal course (nmd mouse), spatial patterns (mnd mouse), and pathology (pmn mouse) that differ markedly from the ones observed in human ALS, generating the suspicion that they may represent disorders distinct from human ALS. In the wobbler model, which exhibits a clinical course and a pathology more closely resembling human motor neuron disease, genetic and molecular mechanisms underlying motoneuron loss are unknown; this implies that the outcome of therapeutic interventions in these mice cannot be used to predict a successful outcome in human ALS trials.

A landmark in pathogenetic and therapeutic research was the development of a transgenic mice model overexpressing mutant Cu-Zn superoxide dismutase (SOD1) as an in vivo model of human FALS. Moreover, many lines of transgenic mice, showing different SOD mutations and different levels of mutant enzyme, have been generated, providing a broad clinical spectrum of the disease with regard to age at onset and rate of progression of the symptoms. Nevertheless, the effectiveness of drugs such as gabapentin and vitamin E in this murine model (3) have not been replicated in human trials (4). It follows that the mutant SOD1 transgenic mouse may be an excellent model of 21q-linked human FALS, but not extendable to ALS in general because, even though it shows a final phenotype similar to the human disorder, critical upstream triggers may be quite different.

An important difference between preclinical animal and clinical human trials is that, in the former, treatment precedes the onset of symptoms, while in the latter it necessarily follows clinical diagnosis. Since many studies indicate the existence of a long preclinical phase in human ALS too, early treatment would be expected to produce more beneficial effects.
This observation might partly explain the different effect of various drugs, particularly of riluzole, in mice and in men. This hypothesis is supported by a retrospective study showing a greater effect of riluzole on the mild and moderate stages of ALS than on its late stages (5).

Certainly the most rational and ambitious way to solve this problem would be to discover the early biological markers of the disease, in order to act before the occurrence of irreversible neuronal damage. In fact, the maximum therapeutic effect of a neuroprotective drug should preferably precede decimation of the motor neuron pool.

**TRIAL DESIGN**

Selection of the patients enrolled in a study is a fundamental issue in a trial design, whose goal is to evaluate drug efficacy. Since ALS is a heterogeneous disease, knowledge of factors potentially interfering with its course and prognosis (and thus interfering with this goal) – such as age at disease onset (6), rate of progression of the symptoms, bulbar involvement, respiratory failure – is essential in order to form homogeneous subgroups of subjects and to compare data in and between studies. Unfortunately, most ALS clinical trials do not provide enough information on these characteristics and on the clinical stage of the patients.

Clear end-points and valid, sensitive, reliable measurements of disease progression are other essential requisites for the success of a trial. The most useful and important primary end-point is survival; it is readily measured, but it necessitates trials running over a long period (usually >18 months) and it may be blurred by the different times to respiratory support (particularly invasive ventilatory support) applied in different countries.

Moreover, death may occur at different stages of progression of ALS in different patients, due to the biological variability of the disease and also in relation to the parts of the body initially and more severely involved.

Another problem is the great difference between the procedures used to assess end-points in the various trials, which makes it difficult to compare their results: most of these end-point measures are influenced by a variety of poorly controlled factors, such as patient and physician motivation. Thereafter, large numbers of patients and longer periods of observation are needed to obtain clinical trials with adequate statistical power.

To address the need for standardization of end-points and their measures, the 1995 Airlie House Workshops developed consensus guidelines for the conduct of clinical trials and introduced categorization, as preferred or acceptable, of the evaluation criteria. For example, the preferred method of muscle testing was considered to be maximum voluntary isometric contraction (MVIC) evaluation, while the preferred function test is believed to be the ALS functional rating scale with the use of the Ashworth scale to assess upper motor neuron involvement.

The Airlie House guidelines recommend the development and use of quality of life measures to ascertain the effect of treatment on the activities of daily living (ADL). As in many intractable diseases, quality of life after treatment is an essential criterion to define a “good” therapy.

For a long time, quality of life was assessed using scales that were not specific to ALS and suffered from major “floor effects”. To address this problem, the Swash-Jenkinson ALS-AQ40 scale has recently been validated and published (7). It represents an ALS-specific health status measure in relation to 5 domains: eating and drinking, communication, ADL/independence, physical mobility, emotional functioning.

The scale appears to have high internal reliability and construct validity; its applicability and capacity to measure changes over time in...
patients with ALS are still be demonstrated through further application.

PATHOGENETIC THEORIES TO ADDRESS ALS THERAPY: GLUTAMATE EXCITOTOXICITY AND OXIDATIVE STRESS

Recent advances in knowledge of the pathogenetic mechanisms underlying ALS may constitute a basis on which to address the question of present and future therapies.

ALS is perhaps the best clinical example of a multifactorial disease in which excitotoxicity contributes to selective neurodegeneration.

The putative role of abnormal glutamate metabolism in ALS has been hypothesized since 1987, when glutamate levels were consistently found to be decreased in various brain regions, reflecting a decreased intracellular glutamate pool (8,9). Subsequently, glutamate levels were found increased in plasma (10) and CSF (11) of ALS patients, although conflicting results have been reported (12), due to methodological problems (13). All these studies seemed to indicate a disturbance of the glutamate transport system, which was indeed demonstrated in affected regions of the central nervous system of ALS patients (14).

In 1995, the same authors showed reduced expression of the excitatory amino acid transporter (EAAT)2-protein in the motor cortex of more than 60 percent of ALS patients (15), subsequently linked to abnormal splicing of EAAT2 mRNA (16). However, other authors reported the presence of alternative splicing of EAAT2 both in ALS patients and in normal subjects (17-19) and, more recently, in Alzheimer patients (20, 21), indicating that the presence of these abnormal EAAT2 splice variants does not appear to be ALS-specific.

After the demonstration that about 20 percent of FALS subjects carry mutations in the SOD1 gene (22), oxidative stress damage was shown in proteins from the spinal cord of sporadic ALS patients (23). Among the damaged proteins, glutamate transporters appear to be particularly vulnerable: oxygen free radicals and arachidonic acid, in fact, inhibit glutamate uptake in animal and in vitro models (24-26), and 4-hydroxynonenal, a product of membrane lipid peroxidation, alters EAAT2-protein in the lumbar spinal cord of sporadic ALS patients (27), which is a selective target of the oxidation mediated by SOD1 mutants (28).

Taken together, current evidence indicates that cell death in ALS reflects a complex interplay between genetic factors, oxidative stress, excitotoxicity and damage to critical target proteins and organelles; the relative importance of these factors may vary in different subgroups of patients.

Following the hypothesis that oxidative stress might be systemic in ALS, the search for possible peripheral markers of these phenomena in ALS patients might represent an important adjunctive diagnostic or prognostic tool.

Human platelets are a peripheral model for the glutamatergic neuron: platelets possess a high-affinity and energy-dependent glutamate uptake, similar to that described in brain synaptosomes (29), and express the three major glutamate transporter subtypes, including EAAT2 (30).

Our group demonstrated a significant reduction of platelet glutamate uptake in patients with sporadic ALS compared to normal controls and chronic neurological disorder patients, suggesting a systemic impairment of glutamate uptake in ALS; we also found increased glutamate plasma levels in ALS patients, but with no correlation emerging between platelet glutamate uptake and plasma concentration of glutamate (31). No correlation between these biochemical changes and disease severity was found. These neurochemical abnormalities may be interpreted as the hallmark of a generic susceptibility to development of an impairment of motor neurons and might be useful as early markers of disease, to target
antiexcitotoxic therapies. To confirm this hypothesis, a longitudinal study of glutamate uptake in a larger population of ALS patients, followed-up for 1 year, is in progress and preliminary data indicate stable uptake values over time in individual patients, suggesting that decreased uptake is a marker of disease trait rather than disease state (31). Since it is known that the levels of lipid peroxidation products are increased in the plasma of ALS patients (32,33), we are investigating the expression and the oxidative status of platelet glutamate transporters, in order to verify possible glutamate transporter damage linked to systemic oxidative stress.

Identifying patients who “biologically” respond to the treatment might also serve to plan and optimize future more targeted trials. This is a critical issue, especially if we consider that trials of neuroprotective drugs in neurodegenerative diseases such as ALS are extremely expensive, time-consuming and, last but not least, generate great expectations in patients and their caregivers.

ANTIEXCITOTOXIC THERAPY

There are several different approaches to reduce excitatory tone:

– modulation of presynaptic glutamatergic production;
– enhancing glutamate transport;
– modifying glutamate receptor activity;
– protecting neurons from glutamate induced intracellular processes.

Riluzole

There have been two prospective, randomized, double-blind, placebo-controlled, clinical trials with riluzole in ALS (34,35). The first enrolled 155 patients from seven French and Belgian hospitals, with definite or probable ALS; they received either 100 mg riluzole per day or placebo for 12 months as from the enrollment of the final patient.

In the second, phase III, dose-finding trial, 959 patients from 31 centers in Europe and North America were included; they were given riluzole at three different dosages (50 mg, 100 mg, 150 mg daily) or placebo for 18 months.

Both studies demonstrated a statistically significant 35% decrease in risk of death or tracheostomy over an 18-month period in patients given 100 mg/day riluzole compared with placebo. The greatest effect of riluzole was detected after 12 months of treatment. In the second trial, the 100 mg dosage presented the best benefit/risk ratio. There are two interesting differences between these trials: site of onset appeared to condition treatment efficacy in the first study, but not in the second; the first study indicated some slowing of deterioration of muscle strength but this finding was not confirmed by the second study. This latter discrepancy was explained by the drug-related side-effect of asthenia on functional scores. Nevertheless this symptom was fairly equally distributed in the four treatment groups, thus including the placebo one, as a consequence of the disorder.

In conclusion, the progression of MND may be retarded during treatment with riluzole; no supporting evidence relating to other factors, such as quality of life, was presented to add weight to the trend towards better survival.

The success of riluzole in slowing down the rate of ALS evolution in two clinical trials has strengthened belief in the glutamate hypothesis and prompted excitotoxicity studies; at the same time it has paved the way for further testing of drugs potentially interfering with this mechanism. Indeed, a clear link between riluzole’s mechanism of action and the glutamate hypothesis in ALS remains to be demonstrated.

Riluzole has several potential mechanisms of action (36):
– inhibition of glutamate release;
– non competitive antagonism of excitatory aminoacid receptors at NMDA channel sites, NMDA glycine sites, -AMPA or kainate receptors;
– prevention of neuronal depolarization through blocking of the voltage dependent sodium channel;
– link to unidentified receptors coupled to G-proteins, possibly leading to a neuroprotective effect;
– interaction with potassium, calcium, chloride channels;
– interference with transporters of neurotransmitters such as GABA, dopamine, acetylcholine, serotonin and D-aspartate.

Recently, it was reported that riluzole also has neurotrophic, antioxidant and antiapoptotic effects. The limited effect of riluzole might be explained by the fact that acts at the end of the cascade, when motoneuron damage is practically irreversible. The prolonged survival of transgenic mutant SOD mice treated with riluzole early in the preclinical period and the lack of efficacy after the onset of clinical disease (3) seem to support this hypothesis.

An important stimulus for industrial research is riluzole’s possible application in other neurodegenerative diseases, such as Parkinson’s disease (it is currently in Phase III trials at over 120 centers), Alzheimer’s disease (Phase II trials), Huntington’s disease (Phase I trials) and HIV-associated dementia.

**Branched-chain amino acids (BCAAs)**

The branched-chain amino acids L-leucine and, to a lesser extent, L-isoleucine and L-valine, have proved to activate in vitro the enzyme glutamate dehydrogenase (GHD), which interconverts glutamate and α-ketoglutarate. In the first 12 months of a double-blind trial (37), BCAAs seemed to slow the rate of decline of some spinal scores compared with placebo, but this data was not confirmed by subsequent studies. In 1993, the Italian Subgroup of the European Study Group, reported a possible increase in the risk of death in the treated group, based on a double-blind, placebo-controlled trial.

**Gabapentin**

Gabapentin is a BCAA homolog and is stereosimilar to L-leucine. Its mechanism of action is unknown, although experimental evidence seems to suggest that it could decrease the synthesis of glutamate (38). Gabapentin was first tested in a double-blind, phase II placebo-controlled trial (39) in 152 patients at doses ranging from 800 mg/day to 2,000-2,400 mg/day (adjusted on the basis of adverse reactions), for six months. The primary end-point, i.e., the mean arm megascore slope of the intention-to-treat population (39), was not achieved. No treatment effect was observed on secondary end-point results (rates of decline of forced vital capacity and of arm megascore slope of the completers).

A phase III longer (nine months), larger (204 patients), higher dose (3,600 mg/day) study with gabapentin performed in North America, failed to confirm the encouraging preliminary findings provided by the previous phase II trial. It showed no significant difference between patients treated with gabapentin and placebo in the mean rate of decline of arm strength (primary outcome) or in the other secondary outcome measures.

**Dextromethorphan (DMP)**

This is a non-competitive antagonist of the NMDA glutamate receptors. The results of four trials using DMP at dosages ranging from 100 to 150 mg/die gave no significant results. Phase II and III trials at higher dosages (about 7 mg/kg/day), shown to be tolerable in phase I safety and pharmacokinetic studies (40), are under way.
ANTIOXIDANT AGENTS

Acetylcysteine

A double-blind placebo-controlled trial with acetylcysteine sc 50 mg/kg/day for 12 months was conducted by Louwerse et al. in 111 patients (41). The primary end-point, i.e., survival at 1 year, was not achieved. No differences in the rate of progression of the various parameters measured were observed.

Deprenyl

Deprenyl, a selective monoamine oxidase B, was tested in a 6-month, open randomized trial involving 111 patients. The results were not significant. In another trial, Jossan et al. performed a double-blind, crossover trial with 10 patients, obtaining negative results (42).

NEUROTROPHIC FACTORS

In the late 1980s and early 1990s, many new neuronal growth factors were discovered. In the adult these factors play a key role in maintaining structural integrity and initiating repair subsequent to injury. Some of these trophic factors modulate the maintenance of cortico-motoneuronal connections. The promoting properties of these molecules were mainly demonstrated using the neonatal axotomy model of induced motor neuron degeneration in animal models. On the basis, primarily, of the success of many trophic factors (including CNTF, BDNF, NT-4/5, GDNF) in this model, ALS clinical trials were instituted with these substances, although there was no demonstration of a specific lack of a neurotrophic factor in patients with MND.

The results of these trials were far from satisfying, probably due to major pharmacokinetic and procedural difficulties, including the route of administration for appropriate delivery of trophic substances to the target organ, achievement of effective concentrations at this site (short half-life), antibody formation and drug inactivation. These problems may perhaps be solved through the use of intrathecal injections or infusion pump.

Brain-derived neurotrophic factor (BDNF)  

Brain-derived neurotrophic factor (BDNF) belongs to the family of neurotrophins, which includes also NGF and neurotrophins 3,4 and 5 (NT-3,4,5). In a phase I-II study, recombinant human methionyl brain-derived neurotrophic factor (r-met HuBDNF) appeared to increase the survival and delay the loss of pulmonary function in ALS patients (43). A following phase III multicentric (1,135 patients), randomized, placebo-controlled trial at 25 and 100 µg/kg r-met HuBDNF, lasting nine months, failed to demonstrate either effect on survival, or effect on respiratory function (44). This failure has been partly explained by a bias of recruitment, as survival in the placebo group was better than expected (85% patients alive at nine months). Indeed a post-hoc analysis demonstrated that ALS patients with early respiratory impairment and those developing altered bowel function showed a statistically significant survival effect with 100 µg/kg BDNF respect to placebo. On these bases, further BDNF trials using either high-dose subcutaneous administration or intrathecal delivery began in 1998, coordinated by Amgen.

On January 2001, Amgen and Regeneron discontinued all clinical development of both intrathecal and subcutaneous BDNF administration in ALS as neither study had demonstrated an improvement in survival (data not published).

Ciliary neurotrophic factor (CNTF)  

Ciliary neurotrophic factor (CNTF) is a cytosolic molecule expressed postnatally in myelinating Schwann cells, from where it may be re-
leased as a result of nerve injury, thereby reducing death of motoneurons. Disruption of the mouse CTNF gene results in progressive muscle atrophy and loss of motoneurons in adult mice (45). Moreover, CNTF immunoreactivity was found to be markedly decreased in the anterior horn of spinal cord from patients with ALS (46).

On these bases, two similarly designed phase II-III, double-blind trials, each involving about 600 patients, were conducted using sc rhCNTF at three – and two – dosage arms (0.5, 2 or 5 µg/kg/day in one study; 15, 30 µg/kg/day in the other) or placebo. No beneficial effect was observed at any of the dosages tested. A statistically significant decrease in strength early on in rhCNTF treated patients and an increased number of deaths at the highest dosage level were observed. Adverse effects included asthenia, weight loss, anorexia, fever (probably due to the drug’s ability to activate receptors for cytokines), untreatable cough and dose-related frequency of aphthous stomatitis.

**Insulin growth factor-1 (IGF1)**

Insulin growth factor-1 (IGF1) can induce sprouting of motoneurons in transgenic mice (47).

In one study patients received placebo or sc rhIGF1 0.05 or 0.1 mg/kg/day for 9 months. Patients receiving the 0.1 mg/kg/day dosage showed approximately 35% less deterioration in the ALS rating scale than the placebo group. Although survival was not the primary endpoint, a significant result (survival time averaging 164 days longer than placebo) was obtained in a subgroup (high rate decliners) of patients who received IGF1 0.1 mg/kg/day (48).

A European phase III trial did not confirm IGF1 efficacy (49).

**SR57746A**

SR57746A is an orally active, 5-HT1a receptor agonist that penetrates the blood brain barrier. Its mechanism of action is not fully understood, but the compound is believed to mimic the activity or stimulate the synthesis of endogenous neurotrophins such as NGF and BDNF (50).

SR57746A increases the innervation of human muscle cells by spinal cord explants and prolongs the survival of mice suffering from progressive motor neuropathy.

In 1997, Sanofi (see www.sanofi-synthelabo/news/2000/20000906-2.htm) initiated two randomized, double-blind, placebo-controlled trials with SR57746A (Xaliproden). In the phase II French trial, 117 healthy volunteers and 110 patients with ALS were given SR57746A in doses of 1 to 4 mg daily for 8 months.

A larger (approximately 2,000 patients) multicenter phase III trial was completed in early 2000. In one arm of the trial, 1,200 patients took 1 and 2 mg of the test drug combined with riluzole 100 mg/day, compared to riluzole 100 mg/day plus placebo. The other 80 patients received SR57746A compared to placebo.

The results of the two clinical trials were not conclusively positive. However, preliminary results demonstrated that the compound is well-tolerated and has a positive effect on pulmonary function, resulting in favorable survival trends (time to permanent assisted ventilation, tracheostomy or death) as well as a positive effect on parameters related to the rate of progression of the disease (unpublished data).

**SYMPTOMATIC TREATMENT**

At present, symptomatic treatment and palliative care are the only interventions that can improve the quality of life of ALS patients.

In order to design clinical trials for the study of new drugs, standardization of the methods employed to treat swallowing and respiratory symptoms is needed. In fact, the dif-
ferent management of these symptoms introduces uncontrolled variables, which may constitute biases in the evaluation of treatment efficacy.

**Dyspnea**

Respiratory failure could be a rare symptom at disease onset, but decline in respiratory function usually occurs with disease progression.

There are multiple causes that contribute to impairment of pulmonary function:

- weakness and fatigue of respiratory muscles leads to reduced lung compliance and atelectasis;
- bulbar dysfunction increases the risk of aspiration pneumonia and also leads to nutritional deficiency, which increases muscular fatigue.

It is important to recognize signs of initial impairment in order to intervene before respiratory failure occurs; to this end, frequent monitoring of respiratory functions is needed [forced vital capacity (FVC) and nocturnal oximetry].

Since hypoventilation depends on a muscular strength defect, the correct way to proceed is to use mechanical ventilation.

Dyspnea is the most fearsome symptom of ALS. Dyspnea causes anxiety and anxiety causes dyspnea, so in cases with a pronounced panic component, it is very important to interrupt this vicious cycle through sublingual lorazepam administration (0.5-1 mg).

Intermittent oxygen administration could also be attempted. It should only be administered during the day, when the patient is awake, because of the risk of respiratory depression in chronic hypercapnic patients receiving oxygen during sleep. In the terminal stage of the disease, the relief of dyspnea can be obtained using opioids.

**Dysphagia**

Multiple factors contribute to impair the nutritional status of ALS patients.

Dysphagia associated with ALS is a result of tongue, soft palate and pharyngeal muscle weakness and of cricopharyngeal spasm.

The timing of nutritional intervention has not been determined yet. It is important to monitor patients frequently and to pay attention to symptoms of dysphagia.

A first step in intervention in these cases is to modify food and fluid consistency and, early on, to involve a nutritionist in the care of the patient. Patients can also be taught special swallowing techniques, such as supraglottic swallowing. If, despite these measures, the caloric intake is still insufficient and the patient continues to lose weight and oral food intake becomes intolerable because of frequent choking, a percutaneous endoscopic gastrostomy (PEG) should be considered.

Percutaneous endoscopic gastrostomy is indicated when weight loss is more than 5-10 %, the Body Mass Index (BMI) is lower than 20 and before FVC falls below 50% of the expected value. PEG is a relatively safe procedure, while morbidity and mortality rise as FVC falls (51,52); in a recent study, the use of non invasive, positive pressure ventilation for ventilatory support has allowed the placement of PEG in patients with advanced ALS (FVC <50%) (53).

**Sialorrhea**

Sialorrhea is distressing to the patient because it causes significant social unease. Saliva production is usually decreased in ALS patients; the drooling is due to a combination of facial muscle weakness and pseudo-hypersalivation stemming from a reduced swallowing ability.

To decrease saliva production, tricyclic antidepressant and anticholinergic agents can be employed.

**Muscle fasciculations, cramps and spasticity**

Fasciculations and cramps can be treated with the same drugs, even though fascicula-
tions rarely require therapy. Carbamazepine, phenytoin, magnesium, quinine sulfate or diazepam can be helpful.

Spasticity, which is due to upper motor neuron degeneration, can sometimes be clinically severe. Physiotherapy is the most helpful treatment, but some drugs can be used such as: baclofen (10-80 mg), tizanadin (6-25 mg), memantine (10-60 mg) and tetrazepam (100-200 mg).

**Pseudobulbar effect**

A typical symptom of ALS, which needs to be differentiated from a depressed mood state, is the sudden onset of pathologic crying and laughing, which is also referred to as “pseudobulbar effect”. Since this symptom is very disturbing for the patient, pharmacological treatment is helpful. Amitriptyline (10-150 mg), fluoxetine (20-60 mg) and sertraline (50-150 mg) seem to be effective. Positive effects have also been reported following dopamine and lithium administration.

**Dysarthria**

Dysarthria is a common early symptom of bulbar muscle weakness.

Logopedic training is especially helpful in cases with slow progression. Several devices may be employed as communication aids.

**Depression**

Although the occurrence of severe depression is usually rare in ALS patients, reactive depression often follows the diagnosis of ALS (54). Affected patients need supportive psychotherapy. Treatment with antidepressants can be extremely helpful, and may also assist in the management of symptoms such as insomnia, poor appetite, salorrhea, fatigue and emotional lability.

Amitriptyline is often prescribed for its anticholinergic and sedative side effect.

Use of benzodiazepines could be effective when anxiety occurs, whether or not it is associated with depression.

**FUTURE THERAPEUTIC STRATEGIES**

To date, therapeutic efforts in ALS have produced at best modest results, because the treatment strategies were designed to tackle the final stage of disease progression associated with irreversible neurodegeneration.

Nevertheless, combined pharmacological treatments, based on the use of glutamate antagonists, antioxidants and NSAIDs, currently constitute a rational approach.

In the future, therapeutic strategies should be developed to treat aspects of the degeneration cascade in ALS. It is reasonable to speculate that the major therapeutic advances for ALS will result from gene therapy (55); in fact, it might be possible to genetically engineer viral vectors in order to infuse sick neurons with drugs such as growth factors, to replace genes unable efficiently to prevent genomic aging, to modify other genes such as susceptibility genes and to insert protective genes.

These approaches have limitations: only repeated viral vector injections, in fact, produce a significantly increased survival of motor neurons in animal models, making this method unacceptable for the treatment of ALS patients.

In order to obtain a continuous and slow release of neurotrophic factors or other drugs in known concentrations into the central nervous system, a better approach is to use a polymer encapsulation of genetically engineered cells (56).

Since there is strong evidence that apoptosis, rather than necrotic nerve cell death, is a significant factor underlying ALS (57,58), antiapoptosis strategies have been studied and will be developed as a possible therapy for ALS.

The most exciting prospect as regards the future therapy of ALS is probably the injection
of neuronal progenitor or stem-like cells (59,60) which could replace dying and dead neurons and also be used as therapeutic vehicles for gene, trophic factor and drug transfer. Recently, very encouraging results were obtained following stem cell transplantation in rats with ALS-like disease: a partial reversion of paralysis was observed after migration of stem cells from the injection point to brain damaged areas (61).

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