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EDITORIAL

Pharmacoeconomics and motor neuron disease

We live in an era of cost containment in health care. New therapies for motor neuron disease, just as for other diseases, are therefore properly subject to cost/benefit considerations. A new treatment in a disease may increase costs, as it may be more expensive to cure, or to alleviate suffering, than to do nothing. The cost of care for someone disabled by a disease that has been arrested by a medical intervention may be very large when continued for many years, as in renal dialysis or in many cancers. Healthcare costs are only truly saved when disease is prevented—for example, by immunisation, or when disability is prevented by timely treatment. No prospective evaluation of the cost of care for people with motor neuron disease, the expenses borne by their families and carers, or the opportunity costs consequent on the disease has been performed. Indeed, there is no currently accepted standard of care for people afflicted with this progressive fatal neurodegenerative disease. Thus, the health and social benefits of treatments and interventions in motor neuron disease cannot presently be calculated.

However, cost is not the only criterion to be applied in determining the value of a therapy. The level of benefit to the individual patient should always be the major relevant consideration.[1] In a universal and budget limited system, such as the NHS, this is balanced by the needs of society as a whole. In the United Kingdom each citizen has an equal entitlement to the available NHS resource. The NHS, like other healthcare systems, has little direct control over the future costs of new therapies. The overall NHS resource is determined by a complex combination of largely politically determined factors.[2] These include national and local resource allocation and prioritisation policies in relation to certain conditions and treatments, together with the effects of clinical decisions made by physicians, and by people with disease such as motor neuron disease. Problems arise when there is conflict within this process, as in the "rationing" of scarce resources such as repeated bone marrow transplantation in the management of refractory leukaemias.[3] Consumer choice is difficult to deny when the lobby is powerful.

Motor neuron disease is a progressive disease with a mean life expectancy of about 3 years from diagnosis. People with the disease do not, therefore, have long in which to enunciate their needs. Degenerative neurological diseases pose particular problems for healthcare planners. These diseases cannot, as yet, be cured in the sense that function can be restored. Indeed, progression continues despite current therapies. The burden of disease and disability borne by those affected, their carers, and the wider community is large and will increase as the number of elderly persons in the population increases. A treatment with a modest effect might increase this individual and societal burden. How should the costs and benefits accruing from the care of motor neuron disease, one such progressive neurological disease, be evaluated? What decisions can be made? When is it appropriate to consider these matters in an individual case?

A logical approach to these difficult questions is to make an estimate of the direct and indirect financial costs of care for a patient with motor neuron disease, including in the estimate the lost opportunity costs caused by the disease to the patient, their family, and to society,[4] and to balance this with an estimate of the personal and social benefit resulting from the therapy. Cost-utility analyses however, can only be as good as the data from which they are derived. In motor neuron disease there is no agreement on the data which should be used. In the face of inexorable decline, rather than a series of potentially preventable exacerbations as might occur—for example in multiple sclerosis or even cancer—this process seems insensitive. In reality, no research has been applied to this problem in this disease; for example, the eight point Rosser scale[5] has not been evaluated in the context of motor neuron disease. The European quality of life (EuroQoL) measure, which was derived from existing quality of life instruments, including the Rosser scale, the Nottingham health profile, the sickness impact profile, and the quality of wellbeing scale, is probably a suitable generic instrument for assessment, but must, inevitably, lack specificity to motor neuron disease. A specific quality of life scale for application to this disease is currently under development.[6]

It is not appropriate, given current lack of knowledge on pathogenesis of motor neuron disease,[7] to expect a new treatment to cure or even to totally arrest the disease. The multinational, dose ranging, double blind clinical trial that has led to licensing of riluzole in the United States, Europe, Japan, and China, but not in Australia or Canada, showed a modest reduction in mortality over the 18 month trial period, amounting to about 7%, a result that just reached significance.[8] This was translated by the triallists into a 3 month overall improvement in life expectancy over a 3 year period.[8] Although this result represents an advance this is not an effect of the magnitude that people with motor neuron disease, or their physicians, are looking for; indeed, prevention remains the ideal. Closer analysis of the data using a Cox proportional hazards model to adjust for predictive factors known to influence outcome suggested that the risk of death or tracheostomy (equated to death in this study design) was reduced by 35% in the treated group; the relative risk of death after 1 year in the treated group was

0.57 (95%CI 0.41–0.8), and in the untreated group 0.72 (95%CI 0.52–0.99).[8 9] This result can be viewed as indicating that treating seven patients for 1 year will prevent one death. This is a misleading statistic in the context of a therapy that neither arrests nor cures the disease. Indeed, the effect of riluzole became less pronounced at 18 months in both the smaller first trial,[10] and the larger second trial.[8]

Subsequent analysis of these trial data, a methodology that risks taking the analysis beyond the limits imposed by the study design, was undertaken using a Markov health state transformation paradigm.[11] In this analysis four health states were arbitrarily defined, based on a retrospective analysis of the clinical data. In state 1 there was functional independence for all activities, and a mild functional deficit in only one of three bodily regions (speech, arm, leg). In state 2 there was a moderate deficit in only one of the three regions, with mild deficits in the other two, and in state 3 assistance was needed in two or three regions. In state 4 there was non-functional use of at least two regions. Relative lack of effectiveness of riluzole in the later stages of the disease was suggested in this modelling study.[11] Clearly, the results of this analysis should not be trusted until tested by direct prospective evaluation, an evaluation that should also include testing of the Markov models for sensitivity and reliability in the context of motor neuron disease.

This Markov model has been applied to a study of the economic burden of motor neuron disease in the United Kingdom.[12] A Delphic analysis of health care in the disease by neurologists in the United Kingdom was used to generate estimates of the healthcare costs in the four stages. Both in the early diagnostic phase, and in the later stages of the disease when disability was greater, admission to hospital was the main cost driver. Indirect cost data were not estimated, but direct medical costs reached £3127 in state 4, £1185 in state 1, and £1698 in state 3. Resource usage, including wheelchair provision, and consultations with other specialists were included in these estimates. Ventilation costs, which amounted to more than US$100 000/year in an American study,[13] were not considered in this British assessment.[10]

Ginsberg and Lev[14] conducted a cost-benefit analysis of the use of riluzole in Israel, assuming a 3 month delay in admission to hospital at the end stage of the illness, and a 3 month increase in longevity. They considered the costs of the drug and the costs of toxicity monitoring—for example, liver function tests—together with the costs of additional drugs used because of increased longevity, and the costs of extra outpatient visits. They calculated that the extra health service costs of treatment with riluzole were US$12 013 for each life-year gained, but found that there was a net benefit to society of US$2884, largely made up of delay in leaving work due to illness, because of the slower course of the treated disease. If a financial assessment of the value of life itself was made, as a way of quantifying the benefit to the individual of life-years gained, then there was a further societal benefit. Ginsberg and Lev noted that the absence of QoL data in the riluzole clinical trials precluded the use of quality adjusted life-year measures in their analysis, although they speculated that these indices might seem less favourable than survival itself. Clearly, this omission was a failure in trial design, although it is difficult to define, even in retrospect, what instrument should have been selected.

The attitudes of Health Authorities in the United Kingdom to the possible use of riluzole in the NHS, as in the case of the introduction of other partially effective, expensive therapies, are evolving. The role of statutory agencies, such as the National Institute of Clinical Effectiveness will become crucial in decision making. There are additional pressures. The introduction of a new treatment in the management of motor neuron disease represents a major shift in clinical attitude, likely to cause changes in the pattern of diagnosis and patient care. It is likely that people with motor neuron disease will be more carefully assessed through the duration of their illness by neurologists than in the past, and that interventions, such as physiotherapy, antispasticity medication, gastrostomy, communication aids, and the use of nocturnal ventilation, as well as pressure on social services to provide help in the home, will be more commonly considered than in the past. The standard and scope of care are likely, therefore, to improve. This should generally benefit people with motor neuron disease and their families, although it will raise costs. The annual cost of riluzole is £3730 per patient plus monitoring costs. In the United Kingdom the cost of treating everybody with motor neuron disease with riluzole is estimated at a minimum of £2.5 million/year, and possibly as much as £15 million/year, depending on the level of acceptance among those eligible and the duration of treatment. Unfortunately, we simply do not know what these figures mean in relation to the quality of the lives of people with motor neuron disease, a state of ignorance that reflects the very recent imperative for this category of research in neurological practice.

Two examples of Health Authority criticisms of the riluzole trial data illustrate how difficult it is for health purchasers, unused to assessing the role of therapy in motor neuron disease, to consider the information in its neurological context. The Wessex Institute for Health Research and Development evaluated the data on riluzole in motor neuron disease in September 1997. They concluded that there was insufficient evidence on which to base a judgement on riluzole treatment; in particular, they noted no functional improvement. The Trent Institute for Health Services Research conducted a similar analysis in 1997, concluding that there was uncertainty in the interpretation of the trial data, a lack of quality of life data, limited claimed benefit, and a high cost-effectiveness ratio.[15] This judgement failed to take into account the human cost of motor neuron disease, the otherwise total absence of an effective treatment and, perhaps most importantly, the relatively low levels of benefit that are accepted in other medical treatments—for example, chemotherapy for ovarian cancer.[16] Some other health authorities, recognising that riluzole has a limited benefit and that the number of people likely to require the drug is relatively small, fund its use, provided it is prescribed under the supervision of a consultant neurologist. Clearly, these are not easy decisions for health authorities, and they need help in making them.

It is clear that measures of benefit relevant to motor neuron disease treatments, generally acceptable to patients, doctors, and health purchasers, must be developed. In future randomised clinical trials in motor neuron disease QoL measures will certainly be used, although there are major theoretical reasons to cast doubt on their use until data are available from properly conducted analyses of a cohort of patients and their families that will fully assess the sensitivity and specificity of both generic and disease-specific QoL measures in the disease.[17 18] Pharmacoeconomic data collection should form part of the trial protocol in future phase 3 clinical trials. There is a need for closer dialogue between health authorities and neurologists, and this must also include people with motor neuron disease. An ongoing assessment of riluzole as used currently in the United Kingdom might be useful and, perhaps, could foster agreement concerning the data that will prove acceptable in relation to future new drugs applied to the management of this rapidly progressive, lethal disease. The European Medicines Evaluation

Agency is currently addressing this issue. The consensus criteria for clinical trial design in motor neuron disease developed by the World Federation of Neurology Research Committee on Motor Neuron Diseases make a reasonable starting point.[19]

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EDITORIAL COMMENTARIES

Skull fractures and mild head injury

The meta-analysis by Hofman *et al* (this issue pp 416–22)[1] opens again a running argument in both neurosurgery and neuroradiology. The argument is not unimportant: the outcome could affect the outlook for some people with an apparently mild head injury and have a significant impact on costs and workloads. The repercussions of these effects are on different people and it is unsurprising to find the merits of radiography usually being emphasised by surgeons and its demerits by radiologists. Two of Hofman's coauthors are radiologists and the third is an epidemiologist.

Their most valuable contribution is to refute the claim, oft repeated but not concordant with everyday experience, that demonstration of a skull fracture increases the risk of significant intracranial haemorrhage by a factor of 40. Their meta-analysis confirms an increased risk, but only fivefold, more in line with other studies.[2] It has been suggested that radiographs can be used to obviate admission and observation in doubtful cases, but this may be inadvisable for several reasons. Not the least is the substitution of a test of questionable utility for proper evaluation. In 373 patients seen in Los Angeles with minor head injuries (excluded from the analysis of Hofman *et al*, presumably for methodological reasons), Feuerman *et al*[3] noted that, *providing clinical assessment was adequate*, nothing was gained from radiography. Indeed, they suggested that a patient with a Glasgow coma score of 15, shown to have a linear fracture of the skull, could be discharged to the care of a responsible companion. This may seem reasonable but, whereas in California the patient may well have had a detailed examination by at least a junior neurosurgeon, in the United Kingdom he may be seen by a junior non-specialist doctor, who has already been on duty for many hours.

The primacy of clinical assessment was borne out in the study of nine British hospitals by the Royal College of Radiologists.[2] Doctors, from housemen to consultants, asked to assess the likelihood of a skull fracture, were extremely good at correct negative predictions, although this is not surprising, as they formed the majority. However, one in 12 of the patients in whom a fracture was wrongly predicted had significant intracranial complications, suggesting that the predictions more accurately reflected an estimation of the severity of the injury rather than the presence of a fracture.

Guidelines issued by the Royal College of Radiologists[4] unequivocally reject both skull radiography and CT for patients thought to have a "low risk" of intracranial injury (although neither the low risk nor the degree of risk is defined). They also discard the triage value of the skull film, indicating that patients who cannot be placed in the care of a "responsible adult" may be admitted for observation rather than undergoing imaging. That appears to be borne out by the present meta-analysis. The recommendation for patients with a "medium risk" is indecisive, suggesting skull radiography *or* CT. The presence of a skull fracture is said to transform the risk to "high", thereby indicating CT, a recommendation still based on the presumed 40-fold increase in risk. It is to be hoped that the fourth edition of these guidelines, due next year, will omit reference to skull films entirely.

In the United States, even a decade ago, more than half the hospitals in a nationwide survey reported that they rarely used skull radiography for head injuries; CT was preferred, and where it was freely available, requests for