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What are the therapeutic advances in neurology? Opinions from world experts

Gordon Mallarkey

Introduction

Clinical neurology is an exciting area of therapeutics. There have been profound drug advances in each of its diverse areas; however, there are still concerns about the best treatment strategies and their relative safety, outcomes, quality-of-life impact and costs. For this inaugural issue of *Therapeutic Advances in Neurological Disorders*, we asked our international editorial board to give us their opinion on significant therapeutic advances in their area of neurology, what the future holds, and what needs to be addressed. This snapshot provides a clinical picture of where we are and where we should head in the years to come. Of course, there is some overlap in opinion, but there is also diversity – the point being that collectively, there will be progress in the drug treatment of neurological disorders. Not all of the areas we cover in the journal are presented, and they may form the basis of a future editorial.

Frank Mastaglia, University of Western Australia, Perth, WA, Australia

Neuromuscular disorders *Therapeutic advances*

- The use of intravenous immunoglobulin (IVIg) for the treatment of immune-mediated peripheral neuropathies (Guillain-Barre syndrome; chronic inflammatory demyelinating polyneuropathy; multifocal motor neuropathy), myasthenia gravis and inflammatory myopathies.

This has largely replaced plasma exchange and has made a major impact on the management and clinical outcomes in these conditions. The downside is that IVIg therapy is very expensive and is not as freely available in less well-developed countries.

- Cytokine-based therapies such as tumor necrosis factor α (TNF α) inhibitors for the treatment of immune-mediated inflammatory myopathies – this is still an emerging therapy which is undergoing evaluation in clinical trials.
- Monoclonal antibodies: rituximab which induces B-cell depletion – for the treatment of certain types of immune-mediated inflammatory neuropathies and myopathies; alemtuzumab which induces T-cell depletion and is currently being evaluated for the treatment of certain T-cell mediated disorders such as inclusion body myositis and polymyositis.
- Enzyme replacement therapy with alglucosidase alfa (Myozyme) for Pompe's disease (adult acid maltase deficiency).

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Future therapeutic developments

- Exon-skipping approaches using antisense oligonucleotides in Duchenne muscular dystrophy (DMD), and possibly other hereditary neuromuscular disorders.
- Stem-cell therapy for inherited neuromuscular disorders.
- Gene therapy for inherited neuromuscular disorders.
- Up-regulation of fetal isoforms in hereditary disorders (e.g., myophosphorylase deficiency).

Current issues that need to be resolved

- Better understanding of the pathogenesis of hereditary and acquired neuromuscular disorders which should allow identification of novel therapeutic targets.
- Identification of protein and lipid autoantigens targeted by the immune response in immune-mediated inflammatory myopathies and neuropathies which is a prerequisite for the development of more specific forms of immunotherapy.

Parkinson's disease

Therapeutic advances

- The development of non-ergoline dopamine agonists and their complementary use with levodopa.
- Recognition that pulsatile oral therapy is likely to be a major contributor to the development of motor fluctuations and dyskinesias and the importance of achieving in-so-far as possible 'continuous dopaminergic stimulation'. Although, this ideal has yet to be fully achieved, there has been major advances; for example, transdermal administration of dopamine agonists (e.g., rotigotine); continuous apomorphine infusion by subcutaneous pump; intraduodenal levodopa infusion (Duodopa).
- Deep-brain stimulation of subthalamic nucleus and globus pallidus internus for the treatment of Parkinson's disease (PD) and dystonia.

Future therapeutic developments

- Development of more effective forms of drug therapy particularly suitable for transdermal delivery.
- New and better targets for deep brain stimulation.
- Cellular therapies to restore the population of dopaminergic neurons in basal ganglia.
- Gene therapy.
- Other forms of neuromodulation (e.g., transcranial magnetic stimulation, transcranial DC stimulation).

Current issues that need to be resolved

- The greatest challenge is to better understand the pathogenesis of the disease and to develop effective forms of neuroprotective therapy to prevent or arrest the abnormal protein aggregation and neuronal degeneration in the brain.
- To develop formulations of levodopa (which is the most effective drug currently available for the symptomatic treatment of PD) which

can be administered on a continuous basis using a transdermal delivery system.

- The development of new therapeutic agents with the same efficacy as levodopa but with a more sustained duration of action compatible with single-dose daily administration.

Graeme Sills, Liverpool University, Liverpool, UK

Therapeutic advances

After a period of stagnation in drug development for epilepsy throughout the 1970s and 1980s, eleven new antiepileptic drugs (AEDs) have been licensed around the world since 1989. Most have been introduced as add-on treatment for difficult-to-control adult epilepsy, with some becoming available as monotherapy for newly diagnosed patients. Increased choice represents a significant advance in itself, but these drugs are also associated with less severe side effects than their more established counterparts (with one or two notable exceptions) and possess simpler pharmacokinetics and fewer drug interactions. Unfortunately, there is as yet no evidence that these novel compounds have better efficacy than traditional AEDs and this is perhaps the single biggest disappointment in what has otherwise been a period of unprecedented optimism.

Future therapeutic developments

Epilepsy treatment has traditionally relied on the control of symptoms (i.e., seizures), with little or no consideration of the underlying disease process. This is partly because we had, until recently, no real understanding of what causes epilepsy at the cellular or molecular level. That understanding is now improving and it is hoped that, in the future, novel AED development can be targeted to known neurochemical or physiological defects in the epileptic brain. Another area for potential pharmacological exploitation is epileptogenesis, or the process of developing epilepsy itself. Identifying the biomarkers that indicate a predisposition to developing seizure disorders following a specific insult (i.e., febrile seizure, head injury) can form the basis for the assessment of possible prophylactic treatments in 'at risk' individuals.

Current issues that need to be resolved

The single biggest issue in the treatment of epilepsy today is that of pharmacoresistance.

Up to 40% of people with epilepsy are unresponsive to current medications and continue to experience regular seizures that impact significantly on their quality of life (QOL). A number of plausible hypotheses have been proposed to explain this phenomenon including inadequate penetration of AEDs across the blood–brain barrier, alterations to the functionality of ion channels and neurotransmitter receptors that represent the targets of AEDs, an inherent resistance governed by genetic variants of proteins involved in AED action, and the pharmacological inadequacy of current treatments. Each of these concepts and their relative contribution to the pharmacoresistant phenotype is currently under intense scrutiny as investigators attempt to find novel approaches to overcoming or circumventing the problem of drug resistance.

Hurdles in drug therapy

Arguably, one of the biggest hurdles to the successful development of novel drugs for neurological disorders in general has been the appropriateness (or otherwise) of the animal models that are used in the initial characterization of candidate compounds. Identifying novel models that more accurately mirror the clinical condition and which allow direct extrapolation of efficacy, tolerability, and essential pharmacokinetic data would represent a major advance in this area.

**Ichizo Nishino, National Center of
Neurology and Psychiatry, Tokyo, Japan**

Therapeutic advances

The most important therapeutic advances include the development of enzyme replacement therapy (Myozyme) for Pompe's disease and exon-skipping therapy for DMD using Morpholino. Myozyme is now commercially available in many countries and works dramatically for infantile cases and less remarkably but still significantly for late-onset cases. Exon-skipping therapy by Morpholino seems to be the most promising therapy for DMD at the moment. We are currently developing therapy for distal myopathy with rimmed vacuoles (DMRV)/hereditary inclusion body myopathy (HIBM) and are planning to submit our manuscript soon. I think that, once our therapy paper is published, this will also be one of the most important advances in our field. This topic will be covered in a future review article we are planning to submit to this journal.

Future therapeutic developments

The use of inducible pluripotent stem (iPS) cells to muscular dystrophy and other muscle diseases will draw much attention in the myology field, just as in other areas, although we do not know if iPS cells will be truly helpful for muscle diseases.

Current issues that need to be resolved

As in DMRV/HIBM, theoretical solutions will become available for many muscle diseases in the future as research progresses. However, because of the rarity of muscle diseases – in fact, all muscle diseases satisfy the definition of 'rare disease' – the development of drugs is extremely difficult.

Hurdles in drug therapy

Because of the availability of enzyme replacement therapy for Pompe's disease, clinicians have greater responsibility than before to correctly identify patients. This is not so difficult for infantile cases; however, the diagnosis of adult-onset cases may sometimes be tricky. Clinically, the phenotype is similar to limb girdle muscular dystrophy. Pathologically, typical vacuoles may be subtle and can even be not included in the specimen. Therefore, clinicians and pathologists now have to always bear in mind the possibility of Pompe's disease for a wide variety of nonspecific myopathic cases.

**Michael K. Racke, The Ohio State
University Medical Center, Columbus,
OH, USA**

Therapeutic advances

In multiple sclerosis (MS), the major advance in the last decade has been the use of immunomodulatory agents (interferon-beta and glatiramer acetate) to treat MS. While only having modest effects on the reduction of the number of relapses in the initial clinical trials, more recent use earlier in disease has had more significant effects on outcome measures such as relapse rate. In addition, the severity of relapses also has been reduced, resulting in fewer patients requiring hospitalization for relapses (although it is also recognized that clinical practice has changed in terms of administration of steroids on an outpatient basis).

Future therapeutic developments

This is going to be interesting depending on whether taking the short or long view. I suspect that we will get an oral agent approved for MS in the near future. Whether that is going to be something like FTY720, a statin, laquinimod, a PPAR agonist remains to be determined. I also think that areas such as the development of gene therapy and the use of small interfering RNA (siRNA) may become a viable therapeutic strategy further down the line as we gain a better understanding of MS and develop tools which will allow better control of these molecular medicines.

Current issues that need to be resolved

I think the development of monoclonal antibodies for use in MS has brought us some potentially very potent therapeutic strategies; however, there are also issues with regard to toxicity. Whether natalizumab will have any complications when used as a single agent remains to be seen. Rituximab and alemtuzumab also have produced exciting clinical results, but both also will likely have more significant toxicities when compared to the current immunomodulatory therapies.

Hurdles in drug therapy

I think that developments in terms of biomarkers will also have profound effects on how we look at therapeutics in MS. While MRI has given us a unique view into the pathogenesis of MS, higher field strength magnets and new imaging techniques are providing incredible new insights into a number of pathophysiologic processes in MS ranging from axonal damage to remyelination. Whether laboratory markers will be developed to identify which patients will be the best responders for specific drugs will likely also be a useful by-product of pharmacogenomics as the promise of a molecular era of medicine continues to be realized.

**Eugen Trinka, University Hospital
Innsbruck, Innsbruck, Austria**

Therapeutic advances

With regard to epilepsy, the development of best-evidence criteria by the international league against epilepsy (ILAE) about what class I studies actually mean is a significant advance [Glauer *et al.* 2006]. This will contribute to a

major improvement of (pivotal) studies. In future, the regulatory authorities will keep in line with these quality criteria set by the ILAE. It is a pity that the regulatory authorities (EMA, FDA) still do not take part in the process of improving the drug trials, but rather remain in a passive role. Levetiracetam seems to be the first drug that is not inferior to carbamazepine or valproic acid (see KOMET trial, which is going to be published this year). In other areas, immunomodulation in MS and neurooncology seems to be promising, but is associated with high cost, and a health economic evaluation in this area is necessary.

Future therapeutic developments

Immunomodulation in MS and related fields may turn out to be too expensive (How much is the cost of a quality-adjusted life year?). Neurostimulation in PD and other movement disorders will shed light into mechanisms, but the technical devices are a major drawback and drugs acting on these targets may be developed. Neurostimulation in epilepsy (rather disappointing) and psychiatry (quite promising) are other interesting fields. Stem cell approaches in neurodegenerative diseases are a challenge for the future.

Current issues that need to be resolved

The high cost in the health system has to be addressed at the outset of research: health economic evaluation in diagnosis and treatment has to be performed. In areas where the pharmaceutical industry has no interest, governmental or non-governmental organizations will have to take over the sponsorship.

Hurdles in drug therapy

As previously mentioned, the relative efficacy in some areas is very small but the costs are extremely high. This has to be adequately addressed without impeding research in these fields (e.g., immunology/oncology).

**Felix Rosenow, University of Marburg,
Marburg, Germany**

Therapeutic advances

A significant drug advance has been levetiracetam (oral and IV), which is a broad spectrum AED with good safety profile (except for irritability) and high efficacy. With regard to studies that

have advanced our therapeutic approaches, the SANAD-trials [Marson *et al.* 2007a,b] established for the first time a newer AED, lamotrigine, as first-line treatment in focal epilepsy and provided evidence that valproic acid is still the most efficacious drug for generalized epilepsies. The only problem with the study was that levetiracetam was not included. The EURAP pregnancy registry should also be mentioned as it provides reliable data on the teratogenic potential of AEDs. To date, the best designed comparator trial of slow-release carbamazepine with levetiracetam provided sound evidence that both drugs are equally effective in the initial therapy of focal epilepsy and that 80% of those becoming seizure free for 6 months will do so under the lowest doses given (400 mg carbamazepine or 1000 mg levetiracetam/d) [Brodie *et al.* 2007].

Future therapeutic developments

Major developments will include the approval of lacosamide (oral and IV) for focal epilepsy in late 2008 and the approval of brivaracetam for focal (and perhaps generalised) epilepsy in 2009 or 2010. A study comparing lamotrigine (current standard) and levetiracetam as initial monotherapy in epilepsy is required in order to help define the new standard drug for the first monotherapy in (focal) epilepsy. This could be done in a SANAD-like design over the next years. Shorter studies comparing the two substances are already underway (e.g., the LaLiMo study to be presented at the European Epilepsy Congress in Berlin 2008).

Current issues that need to be resolved

The EU directive (2001/20/EC, 4.4.2001, Article 5) regarding clinical trials on incapacitated adults not able to give informed legal consent renders it virtually impossible to perform prospective trials in diseases treated in neurology intensive care units. One example is in status epilepticus. There is an urgent need to perform regulatory trials in this major neurological emergency associated with about 10–20% case fatality. We do have new medical options (IV valproic acid and IV levetiracetam) and others may become available in the near future (IV lacosamide). However, we cannot include patients with status epilepticus because they need immediate treatment and, according to the EU-directive, a ‘representative’ of the patient (transformed

into German national law, this means a judge) must approve trial participation before a patient can be randomized. This ill-directed directive, based on lack of knowledge of medical emergency situations, needs to be changed rapidly in order to allow the generation of evidence regarding possible progress in the treatment of neurological emergencies such as status epilepticus.

Hurdles in drug therapy

There are still no AEDs surpassing the efficacy of carbamazepine and valproic acid in the treatment of focal and generalized epilepsy, respectively; however, most of the newer drugs have fewer interactions and some show better tolerability and safety. We need more studies in children and in emergency situations in order to decrease the amount of unavoidable off-label drug use. IV lorazepam should be approved for the use as first-line drug in status epilepticus worldwide, based on already available evidence [Prasad *et al.* 2005; Alldredge *et al.* 2001; Treiman *et al.* 1998].

A bright future for migraine therapeutics

In a recent review, Peter Goadsby (Institute of Neurology, London, UK) commented that there are insufficient studies in migraine and that there needs to be more options for its effective management [Goadsby, 2007]. The triptans transformed the treatment of acute migraine; however, they are not effective in all patients and are associated with cardiovascular and cerebrovascular complications. Other treatments for acute migraine (e.g., simple analgesics, NSAIDs, opiates and ergotamine) have some utility but have their own disadvantages. Newer therapies for migraine will better target the disease mechanisms of migraine, and significant advances have been made in elucidating the neural mechanisms that lead to migraine.

Investigational preventive drugs include tonabersat, a gap-junction blocker that is undergoing a large dose-finding study, and botulinum toxin A. Other approaches include neurostimulation of the occipital nerve, which shows promise – whereas an initial study of patent foramen ovale closure was disappointing. Several studies have shown a role for calcitonin gene-related peptide receptor (CGRP) in migraine, and several investigational CGRP antagonists are being studied for their effects in acute migraine attacks. In an

accompanying editorial to a study on the CGRP antagonist, MK-0974, Prof Goadsby commented that the future of migraine therapeutics is bright [Goadsby, 2008]. Other nonvasoconstrictive approaches being investigated are vanilloid TRPV1-receptor antagonists and nitric oxide synthase inhibitors, as well as serotonin 5-HT_{1F} receptor agonists (e.g., CO-144), which Prof. Goadsby believes will almost certainly show good efficacy once phase II studies are completed. GM

Corrado Angelini, University of Padova, Italy

The most significant therapeutic advances in my area of interest, neuromuscular diseases, has been in the field of neuroimmune and metabolic

disorders (e.g., the use of IVIg, L-carnitine, Coenzyme Q10 and new immunosuppressors, alglucosidase alfa [Myozyme]). In the future, antisense oligonucleotides appear promising as well as exon-skipping drugs (e.g., PTC 124) for muscular dystrophies. Controversies surround the use of expensive treatments (such as Myozyme) and proteasome inhibitors that have possible side effects. A new treatment that needs to be fully proven is lithium in motor neuron disease, where large trials with definite outcomes are needed (i.e., patient survival). Outcomes are in general a difficult issue in such patients, because of their heterogeneous clinical presentation and the relative rarity of the neuromuscular disorders and the difficulty to standardize diet and physical exercise of the individual patient.

Brief opinions on multiple sclerosis

‘Natalizumab has been a major recent advance in MS therapy, and other promising agents are in the pipeline. Fingolimod, rituximab, and alemtuzumab are usually regarded as the most promising novel agents currently being tested for MS. One of the most pressing issues is to develop better treatments for progressive forms of MS.’ – *Reinhard Hohlfeld, Institute for Clinical Neuroimmunology, Munich, Germany*

‘The most recent therapeutic advance in MS has been the trials of natalizumab and the approval of natalizumab therapy in the United States and Europe. The use of tailored therapy to the single patient, based on biomarkers would be an important future therapeutic advance. Many new therapies are currently under investigation including other monoclonal antibodies and a prerequisite for a rational use of these therapies would be development of biomarkers for therapeutic response. Today, the best biomarker is MRI, and development of immunological biomarkers is warranted. We need to resolve the issue of disease mechanism regarding the interaction between inflammation and neurodegeneration in progressive MS, and to develop “neuroprotective” therapies. I think that disease control in MS can only be achieved by combination therapy. The experience with natalizumab in combination with interferon beta-1a has delayed clinical trials of combination therapy.’ – *Per Soelberg Sørensen, Copenhagen University Hospital, Copenhagen, Denmark*

‘The development of targeted approaches in immunomodulation, acting on specific molecules involved in the pathogenetic process of MS (e.g., Anti VLA-4/natalizumab or anti CD20/rituximab), has been a significant advance. In the future, the induction and enhancement of repair processes in the CNS of MS patients will be a significant development. Current issues that need to be resolved are the development of new functional scales, which will serve as more meaningful endpoints for the aims of neuroprotection and regeneration. This will initially involve innovative imaging techniques, such as MTR, MWI, DTI, or OCT. It will be critical in the near future to develop escalating treatment strategies. Therefore, we will need more direct head-to-head trials and combination trials focussing on subgroup of diseases.’ – *Peter Rieckmann, University of British Columbia and Vancouver Coastal Health, Vancouver, BC, Canada*

‘The development of disease-modifying drugs, including interferon and glatiramer acetate, has been the most significant advance in MS. In the future, the development of drugs promoting regeneration of myelin and axons that are damaged in MS, and practical use of stem cells for repairing damaged neural tissue will be the most important advances. An issue that needs to be resolved is how to deal with the heterogeneity of MS. Each drug is helpful for only a proportion of patients (perhaps 30% or less), but they are randomly used for

every patient. We need to know more about what type of MS is responsive to one drug but unresponsive to another drug. Personalized medicine is our goal. We also need to look more closely at QOL as it is neglected when analyzing clinical trial data. For example, development of an attack causing total blindness and an attack causing a minor sensory problem is not equivalent but usually counted as one attack, which is wrong. In the case of neuromyelitis optica (NMO, see article in this issue), the therapeutics that would reduce the number of attacks but may cause total blindness should be avoided (nobody wishes to take such medicine, but they rather prefer to have corticosteroid). Thus, the reduction of attacks is not useful for evaluating drugs for treating NMO. Unfortunately, this point is not well understood in the community.’ – *Takashi Yamamura, National Institute of Neuroscience, Tokyo, Japan*

‘Early therapy and the use of antibodies have been the most significant advances in MS. Oral therapies and more individualized therapies will be advances to look forward to in the future. An issue that needs to be resolved is the heterogeneity of MS and therapies for progressive MS,

and we also need to have biomarkers for therapy responders versus nonresponders.’ – *Wolfgang Brück, University of Goettingen, Goettingen, Germany*

‘In MS, the beta interferon and glatiramer acetate trials including the recent comparative trials of Rebif and Copaxone, and Betaferon and Copaxone have advanced therapy in this disease. Future prospects include the recombinant monoclonal antibodies rituximab, alemtuzumab, and fingolimod. There is an urgent need in MS for surrogate markers of possible MS subtypes (biomarkers, MRI markers) and for the development of neuroprotective and repair-promoting strategies. In immune neuropathies, the ICE trial of IVIg in CIDP is significant [Hughes *et al.* 2008]. Further novel immunotherapies are required. In general, many time-honored drugs are used off-label in neurology – many diseases are of little interest to the pharmaceutical industry because of their low incidence and prevalence, which makes it unlikely that randomized controlled trials will be conducted. Finally, we need better and methodologically sound quality of life and health economic investigations.’ – *Hans-Peter Hartung, Heinrich-Heine University, Düsseldorf, Germany*

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Conflict of interest statement

None declared.

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