Neurology Research Review™

Making Education Easy

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Abbreviations used in this review:

FTD = frontotemporal dementia; **ICD** = impulse control disorder **MS** = multiple sclerosis; **OR** = odds ratio; **PD** = Parkinson's disease **PegIFN-β-1a** = pegylated interferon beta-1a

Welcome to the latest issue of Neurology Research Review.

The non-dopaminergic class of drugs appear promising in the treatment of patients with advanced Parkinson's disease who develop disabling motor fluctuations when levodopa wears off between doses. A study published recently in *The Lancet Neurology* reports that tozadenant, an adenosine A_{2A} receptor antagonist, reduced "off-time" for patients by at least 1 hour per day compared with placebo. These phase IIb study results are promising; they should be worth pursuing in phase III trials.

This issue covers a variety of topics, including evidence in support of the role of calcitonin gene-related peptide in the pathogenesis of migraine, an investigation into the degree of mental incapacity present in brain tumour patients, and an investigation into the clinical and pathological diagnostic implications of the new criteria for frontotemporal dementia syndromes.

I hope you find the papers in this issue useful in your practice and I look forward to your comments and feedback throughout the coming year.

Kind Regards,

Dr Stacey Jankelowitz

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Pegylated interferon beta-1a for relapsing-remitting multiple sclerosis (ADVANCE)

Authors: Calabresi PA et al.

Summary: This paper reports 48-week results from the 2-year, phase III ADVANCE trial, in which 1512 patients aged 18–65 years with relapsing-remitting multiple sclerosis (MS) and with an Expanded Disability Status Scale score ≤5 were randomly assigned to placebo (n=500) or subcutaneous peginterferon beta-1a (PegIFN-β-1a) 125 µg once every 2 weeks (n=512) or every 4 weeks (n=500). A total of 1332 patients (88%) completed 48 weeks of treatment. Adjusted annualised relapse rates were 0.397 in the placebo group versus 0.256 in the every 2 weeks group and 0.288 in the every 4 weeks group (rate ratio for every 2 weeks group 0.644, 95% CI 0.500 to 0.831, p=0.0007; rate ratio for the every 4 weeks group 0.725, 95% CI 0.565 to 0.930, p=0.0114). Adverse events, including relapses, were reported by 83% of patients in the placebo group, and by 94% of patients in each PegIFN-β-1a group. The most common adverse events associated with PegIFN-β-1a were injection site reactions, influenza-like symptoms, pyrexia, and headache. Fifteen percent of patients taking placebo, 11% of those receiving PegIFN-β-1a every 2 weeks, and 14% of those receiving PegIFN-β-1a every 4 weeks reported serious adverse events; relapse, pneumonia, and urinary tract infection were the most common.

Comment: This study examines the benefit of PegIFN-β-1a in relapsing-remitting MS. Pegylation is the covalent linkage of polyethylene glycol to bioactive molecules and increases molecular size and hydrodynamic radius and renders the altered protein resistant to proteolytic degradation. This extends the drug's half-life, reducing the frequency of injections and improving compliance. Pegylation also reduces the toxicity and immunogenicity of the drug. This study suggests that the 2-weekly injection of pegylated interferon is effective in reducing relapse rate, although the comparator was placebo and not a routine treatment.

Reference: Lancet Neurol 2014;13(7):657-65

http://www.thelancet.com/journals/laneur/article/PIIS1474-4422(14)70068-7/abstract

Safety and efficacy of LY2951742, a monoclonal antibody to calcitonin gene-related peptide, for the prevention of migraine

Authors: Dodick DW et al.

Summary: Outcomes are reported from a phase II proof-of-concept study involving 218 patients aged 18–65 years reporting 4–14 migraine headache days per month, who were randomised to treatment with a calcitonin gene-related peptide (CGRP) monoclonal antibody, LY2951742 (150 mg; n=108), or placebo (n=110), given as a subcutaneous injection once every 2 weeks for 12 weeks. At 12 weeks, the mean change from baseline in the number of migraine headache days was −4.2 (62.5% decrease) in the LY2951742 group versus −3.0 (42.3% decrease) in the placebo group (p=0.0030). Injection site pain, erythema, or both, upper respiratory tract infections, and abdominal pain each occurred more frequently with LY2951742 than with placebo.

Comment: This is a promising study of a humanised monoclonal antibody against CGRP. The patients received 2-weekly subcutaneous injections of the drug and had reduced rates of migraine. CGRP levels are known to increase in the blood during migraine and cluster headache. It is interesting that this peripherally-acting drug had a significant effect for what is a central nervous system disease (the drug does not cross the blood brain barrier). Nevertheless, this is a promising new drug for which the long-term safety and efficacy still needs to be determined.

Reference: Lancet Neurol 2014;13(9):885-92

http://www.thelancet.com/journals/laneur/article/PIIS1474-4422(14)70128-0/abstract

Tozadenant (SYN115) in patients with Parkinson's disease who have motor fluctuations on levodopa

Authors: Hauser RA et al.

Summary: This phase IIb, dose-finding clinical trial of tozadenant recruited 420 levodopa-treated patients (mean age 63.3 years) with Parkinson's disease (PD; mean duration of PD 8.7 years) who were experiencing motor fluctuations with at least 2.5 h off-time during their daily waking hours. They were randomised to receive oral tozadenant 60, 120, 180, or 240 mg or matching placebo twice daily for 12 weeks. The primary outcome was change from baseline to week 12 in hours per day spent in the off-state (assessed from daily symptom diaries completed by patients). A total of 403 patients provided post-baseline diary data and 337 completed study treatment. Off-time was reduced by at least one hour per day, compared with placebo, in 55% of those receiving tozadenant 60 mg twice daily, 65% of those on 120 mg twice daily, 72% of those on 180 mg twice daily, and 68% of those on 240 mg twice daily. The between-group comparisons were significant with placebo for tozadenant 120 mg twice daily (–1.1 h; p=0.0039) and tozadenant 180 mg twice daily (–1.2 h; p=0.0039). The most common adverse events were dyskinesia (8% of the placebo group, 16% of the 120 mg twice-daily group, and 20% of the 180 mg twice-daily group), nausea (4%, 11%, and 12%, respectively), and dizziness (1%, 5%, and 13%, respectively). Tozadenant 60 mg twice daily was not associated with a significant reduction in off-time, and tozadenant 240 mg twice daily was associated with the highest dropout rate due to adverse events (20% of patients).

Comment: This novel drug is a selective adenosine A_{2A} receptor antagonist and has been shown to be effective in animal models of Parkinson's disease. Adenosine A_{2A} receptors are highly expressed on striatal spiny neurons and modulate dopaminergic neurotransmission. In animal models, blockade of A_{2A} receptors extends the efficacy of levodopa and prevents the onset of dyskinesias. A drug from this class has been approved for use in Japan but was not approved in the USA because phase III trials did not replicate the results of phase 2 trials. This study shows a clinical effect for the 120 mg and 180 mg doses of tozadenant, which should set the way for a phase III trial of the drug.

Reference: Lancet Neurol 2014;13(8):767-76
http://tinyurl.com/p672pkl

Mental incapacity in patients undergoing neuro-oncologic treatment

Authors: Kerrigan S et al.

Summary: These researchers evaluated the preoperative mental capacity to give valid consent to neurosurgery in a cohort of 100 patients with radiologically suspected intracranial tumours. Study participants underwent formal assessment of mental capacity with the MacArthur Competence Assessment Tool for Treatment (MACCAT-T) conducted by a dual-qualified physician and lawyer. Cognitive function was assessed after the MACCAT-T interview using the Addenbrooke's Cognitive Examination-revised (ACE-R). According to the assessor, 25 patients lacked the necessary mental capacity to give valid consent to neurosurgery; 13 of these patients were also judged as lacking capacity by the neurosurgical team and were treated under the provisions of the Adults with Incapacity (Scotland) Act 2000. Mental incapacity was most common among patients with World Health Organisation grade IV tumours (38%) and was more common in men (36%) than in women (14%). Patients lacking mental capacity were significantly more cognitively impaired than those with capacity (median total ACE-R scores were 44 and 88, respectively). A score of <4/7 in the semantic verbal fluency subset of the ACE-R (naming up to 10 animals in 1 minute) was predictive of incapacity.

Comment: This study highlights the degree of incapacity present in brain tumour patients, yet surgeons continue to discuss treatments with patients and allow them to make treatment decisions. One of the major obstacles highlighted by the study is the lack of an easily administered sensitive and specific test that could assess capacity to make decisions. Translating this data into practice therefore will be difficult until a quick, validated, appropriate tool is available for the assessment of mental capacity in brain tumour patients.

Reference: Neurology 2014;83(6):537-41
http://www.neurology.org/content/early/2014/07/02/WNL.0000000000000671.abstract

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Independent commentary by Stacey Jankelowitz, who is a staff specialist neurologist and clinical neurophysiologist at Royal Prince Alfred Hospital.

She is a senior lecturer at Sydney Medical School, where her research interests include neurophysiology, peripheral nerve and muscle disease and stroke.

Fulranumab for treatment of diabetic peripheral neuropathic pain

Authors: Wang H et al.

Summary: Results are reported for 77 patients with moderate-to-severe diabetic peripheral neuropathic pain (DPNP) treated with subcutaneous fulranumab (1, 3, or 10 mg) or placebo every 4 weeks. The primary endpoint, the mean reduction of average daily pain at week 12 compared with baseline, showed a positive dose-response relationship (p=0.014); the comparison was significant between the 10-mg group and placebo (p=0.040). In an exploratory responder analysis at week 12, a greater proportion of patients in the 10-mg group reported ≥30% reduction in the average DPNP intensity compared with placebo (p=0.006). Although not statistically significant, results for several secondary endpoints were directionally to those for the primary efficacy dose-response relationship. The most common treatment-emergent adverse events in the combined fulranumab group were arthralgia (11%), oedema peripheral (11%), and diarrhoea (9%). No cases of joint replacement or death were reported.

Comment: This phase II randomised, placebo-controlled trial provides Class I evidence that this fully human monoclonal antibody against nerve growth factor is effective in the treatment of painful diabetic neuropathy. However, the study was stopped prematurely by the FDA due to the concern that the entire class of anti-NGF antibodies may be associated with a condition representing either rapidly progressing osteoarthritis or osteonecrosis.

Reference: Neurology 2014;83(7):628-37
http://www.neurology.org/content/83/7/628

Treatment of relapsing-remitting multiple sclerosis after 24 doses of natalizumab: evidence from an Italian spontaneous, prospective, and observational study (the TY-STOP study)

Authors: Clerico M et al.

Summary: The Italian TY-STOP study evaluated the effect of therapeutic choices on the mean annualised relapse rate and on magnetic resonance imaging MS activity after 24 doses of natalizumab in patients with relapsing-remitting MS. The study enrolled 124 adult patients without any clinical or magnetic resonance imaging MS activity after 24 doses of natalizumab. In the intent-to-treat group (n=124), the decision was made to continue (n=43) or interrupt natalizumab (n=81) after 24 doses; clinical and radiological MS activity was significantly lower in natalizumab continuers than in those who interrupted natalizumab. Natalizumab continuation showed a protective effect for both outcomes (odds ratio [OR] 0.33; 95% CI, 0.15 to 0.70 for clinical activity and OR 0.35; 95% CI, 0.15 to 0.79 for radiological activity). In the as-treated group (n=124), natalizumab continuers received natalizumab, natalizumab switchers changed to different therapies, and natalizumab quitters discontinued natalizumab during the study year. In this cohort, clinical and radiological MS activity was significantly lower in natalizumab continuers than in natalizumab switchers or quitters, confirming a protective effect of natalizumab on the risk of relapse in natalizumab continuers compared with natalizumab quitters (OR 4.40; 95% CI, 1.72 to 11.23) and natalizumab switchers (OR 3.28; 95% CI, 0.99 to 10.79). No disease rebound was observed in natalizumab quitters. After natalizumab discontinuation, 1 patient developed progressive multifocal leukoencephalopathy (PML) during the observation period, with complete recovery.

Comment: The controversy surrounding natalizumab has been when to discontinue treatment and if so what drug to use next. The main reason for discontinuing natalizumab has been the risk of PML. Three factors are associated with the overall risk of PML:

1. a positive serostatus for anti-JCV antibodies;
2. the use of immunosuppressants before initiating natalizumab use; and
3. the duration of natalizumab therapy (alone or in combination).

If all 3 risk factors are present, the risk of natalizumab-associated PML is approximately 1 in 90, which seems unacceptably high, given that PML is associated with a high morbidity and mortality and that alternative therapies exist. The development of an assay to identify patients who are JCV-positive and the identification of the other known risk factors represent a major plus for initiating therapy, but when a patient becomes positive for JCV or has been on natalizumab for a substantial amount of time and desires to stop therapy, the path is less clear. It would be useful to know if natalizumab has a prolonged effect on disease activity after cessation, but this data is not available. Also, over and above the disease-modifying effect, natalizumab has a positive effect on quality of life in MS patients. This paper unfortunately does not bring us any closer to knowing what drug to choose as ongoing therapy, how to initiate the different drug and when to stop natalizumab.

Reference: JAMA Neurol 2014;71(8):954-60
http://archneur.jamanetwork.com/article.aspx?articleid=1883808

Impulse control disorder in patients with Parkinson's disease under dopamine agonist therapy

Authors: Garcia-Ruiz PJ et al.

Summary: This multicentre study from Spain evaluated the prevalence of impulse control disorders (ICDs) in a cohort of 233 patients with PD on long-term treatment (>6 months) with a single non-ergolinic dopamine agonist (DA; pramipexole, ropinirole, or rotigotine). As assessed by the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's disease, 91 patients (39%) met the clinical criteria for ICD. Patients with ICD symptoms (ICD^+) were younger in age and differed by type of DA intake compared with patients without ICD symptoms (ICD^-). Oral DA treatment (pramipexole and ropinirole) was associated with higher risk of ICDs compared with transdermal DA (rotigotine): 84/197 (42%) patients treated with oral DA developed ICD, versus 7/36 (19%) patients treated with transdermal DA (p<0.01). In univariate analysis, significant associations were observed between ICD and younger age (p<0.01), treatment with rasagiline (p<0.05) and oral DA treatment (p<0.01). In multivariate analysis, oral DA treatment remained significantly associated with ICD (p=0.014; OR 3.14; 95% CI, 1.26 to 7.83).

Comment: This is an interesting study comparing the oral to the transdermal routes of administration of dopamine agonists. The reader, however, needs to note that there were far fewer patients in the rotigotine arm of the study and these patients had less severe disease. It would be good to see if the results hold true in a randomised controlled trial with equal numbers of patients in all 3 arms with similar severity of disease.

Reference: J Neurol Neurosurg Psychiatry 2014;85(8):840-4
http://jnnp.bmj.com/content/85/8/840.abstract

New criteria for frontotemporal dementia syndromes: clinical and pathological diagnostic implications

Authors: Chare L et al.

Summary: This study assessed the new frontotemporal dementia (FTD) clinical diagnostic criteria against the new pathological criteria for these syndromes and for Alzheimer's disease (AD), using data from 178 patients initially diagnosed with a FTD syndrome who were participating in multidisciplinary research programmes investigating neurodegenerative dementias (the Cambridge Brain Bank, UK, and Sydney Brain Bank, Australia). 135 cases were reclassified by the revised diagnostic criteria into a behavioural variant (bvFTD), semantic variant primary progressive aphasia (sv-PPA), a non-fluent/agrammatic variant (nfv-PPA) and a logopenic variant (lv-PPA). Pathological diagnoses included 5 major pathological subtypes of frontotemporal lobar degeneration (FTLD) (FTLD-tau, FTLD-TDP, FTLD-FUS, FTLD-UPS, and FLTD-no inclusions or FTLD-ni) and Alzheimer's disease (AD). For bvFTD and sv-PPA, the majority of cases (90%) did not change diagnosis. The biggest change in FTD diagnoses was observed in previously diagnosed non-fluent PPA cases, with 55% reclassified as being lv-PPA. Previous patterns of pathology were confirmed, although more AD cases occurred in FTD syndromes (10% bvFTD, ~15% sv-PPA and ~30% nfv-PPA) than expected. Under the new lv-PPA diagnosis, AD was the dominant pathology (77%); the remainder were divided between FTLD-tau and FTLD-TDP. Discriminant analyses revealed that object agnosia, phonological errors and neuropsychiatric features differentiated AD from FTLD.

Comment: This study assessed the new clinical criteria for diagnosis of FTD with the new pathological criteria for AD and FTD. The study confirmed that the new logopenic variant FTD showed predominantly AD pathology. The other FTD variants and their pathologies were as shown previously. A third of cases diagnosed as FTD still had AD pathology. The authors highlight the need to determine early features that can be used to discriminate between the types of dementia in an attempt to guide therapy.

Reference: J Neurol Neurosurg Psychiatry 2014;85(8):865-70
http://jnnp.bmj.com/content/85/8/865.abstract

Impact of brain tumour location on emotion and personality: a voxel-based lesion–symptom mapping study on mentalization processes

Authors: Campanella F et al.

Summary: Scant clinical data exist on the changes that are likely to occur following damage from brain surgery at specific sites. These researchers investigated behavioural and emotional regulation deficits in patients undergoing surgery for the removal of cerebral tumours and explored the concept that many of the problems affecting patients after surgery can be ascribed to the onset of difficulties within the process of mentalising (i.e. abstracting and reflecting upon) emotion and intentions, which impacts on everyday behaviour. These were investigated in terms of (i) emotion recognition; (ii) Theory of Mind; (iii) alexithymia; and (iv) self-maturity (personality disorder). Immediately prior to and within a few days after their surgery, 71 patients aged 18–75 years with lesions located in the left or right frontal, temporal and parietal lobes took part in 4 different tasks, Task 1: emotion recognition of Ekman faces; Task 2: the Eyes Test (Theory of Mind); Task 3: Toronto Alexithymia Scale; and Task 4: Temperament and Character Inventory (a personality inventory). Lobe-based and voxel-based analysis confirmed that tasks requiring interpretation of emotions and intentions at more basic (less mentalised) levels (Tasks 1 and 2) were more affected by temporo/insular lesions, with emotion recognition (Task 1) being maximally impaired by anterior temporal and amygdala lesions and Task 2 (found to be a 'basic' Theory of Mind task involving only limited mentalisation) being mostly impaired by posterior temporoparietal lesions. Tasks relying on higher-level mentalisation (Tasks 3 and 4) were maximally affected by prefrontal lesions, with the alexithymia scale (Task 3) being mostly associated with anterior/medial lesions and the self-maturity measure (Task 4) with lateral prefrontal ones.

Comment: This interesting study highlights the importance of considering cognitive as well as functional effects of brain surgery. The authors also highlight the fact that brain tumour patients are a group that can be used to investigate brain function.

Reference: Brain 2014;137(Pt 9):2532-45
http://brain.oxfordjournals.org/content/early/2014/07/09/brain.awu183.abstract

Long-term recovery in critical illness myopathy is complete, contrary to polyneuropathy

Authors: Koch S et al.

Summary: Outcomes are described for 26 patients who underwent conventional nerve conduction studies and direct muscle stimulation in addition to neurological examination during their stay in the intensive care unit (ICU) and at 1 year after ICU discharge. The cohort consisted of 7 ICU controls, 8 patients with critical illness myopathy (CIM) and 11 patients with CIM and critical illness polyneuropathy (CIM/C IP). At the 1-year follow-up, a greater number of patients in the CIM cohort had recovered compared with those in the CIM/CIP cohort (7 [88%] vs 6 [55%]), and 4 CIM/CIP patients (36%) still needed help in their daily routine.

Comment: Critical illness neuropathy and or myopathy are not uncommon in long-term ICU patients, especially those with sepsis and organ failure. These authors followed a cohort of patients seen early in the disease. At one year after discharge, the patients with critical illness myopathy had recovered more than those with critical illness neuropathy. This would suggest that those losing axons in critical illness neuropathy have a poorer prognosis. The authors also highlight the fact that compressive neuropathies add to the impact of the critical illness neuropathy and that nursing care needs to consider sites of nerve compression.

Reference: Muscle Nerve 2014;50(3):431-6
http://onlinelibrary.wiley.com/doi/10.1002/mus.24175/abstract

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