

Synopsis of important papers published in specialty and other general medical journals

Translational medicine: Hypereosinophilia, tyrosine kinase inhibitors and anti-interleukin-5

Hypereosinophilic syndrome (HES), characterised by persistent marked eosinophilia and end-organ damage, is extremely rare but a near perfect example of the way in which molecular diagnostic techniques can lead not only to the identification of a least three variants of the disease but the discovery of highly successful treatments for at least two of them.¹ Historically, the treatment of these patients has involved the rather ineffective non-specific suppression or eradication of eosinophils with corticosteroids, hydroxyurea and interferon α , accompanied by serious adverse effects.

The most frequently encountered genetic change is an alteration in the FLP1-like 1/platelet-derived growth factor receptor α (FIP1L1-PDGFR α) fusion transcript, which results in effect in a myeloproliferative clonal disorder. FIP1L1-PDGFR α -positive patients respond to the tyrosine kinase inhibitor (TKI) imatinib mesylate, making cytotoxic therapy or allogeneic stem cell transplantation unnecessary in the majority of patients.^{1,2} This is a very active area of research and several more potent and more specific TKIs are now reaching the clinic. In a second form a population of aberrant T cells secrete interleukin-5 – a lymphocyte mediated hypereosinophilia. A recent randomised, double-blind, placebo-controlled trial has shown that FIP1L1-PDGFR α -negative patients respond to anti-interleukin therapy with mepolizumab.³ The primary endpoint, a reduction in prednisone dosage to 10 mg, was achieved in 84% of patients on mepolizumab in contrast to 45% in the placebo group. Since, in theory, interleukin-5 primes the eosinophils to release granule proteins that contribute to end-organ damage, it is interesting to note that mepolizumab treatment was associated with a reduction in circulating eosinophil-derived neurotoxins. This proof-of-concept study is only the beginning, and many more studies will be required to determine optimal dosage and minimise the adverse side effects seen in this study.

Hopefully, the current intensive search for molecular abnormalities in a number of myeloproliferative diseases will reveal more potential targets, and new therapies for the patients who do not respond to conventional cytotoxic treatments. However, it should be remembered that successful allo-stem cell transplantation can be curative, and this type of research must also continue.

References

- 1 Kalac M, Quintas-Cardama A, Vrhovac R et al. A critical appraisal of conventional and investigational drug therapy in patients with hypereosinophilic syndrome and clonal eosinophilia. *Cancer* 2007; 110(5):955–64.
- 2 Helbig G, Stella-Holowiecka B, Majewski M et al. A single weekly dose of imatinib is sufficient to induce and maintain remission of chronic eosinophilic leukaemia in FIP1L1-PDGFR α -expressing patients. *Br J Haematol* 2008; 141(2):200–4.

- 3 Rothenberg ME, Klion AD, Roufosse FE et al. Treatment of patients with the hypereosinophilic syndrome with mepolizumab. *N Engl J Med* 2008; 358(12):1215–28.

JS Kelly

Carotid bruits as a prognostic tool

This study analysed 22 of 735 articles found on a literature search. The analysis included 17,295 patients with a median sample size of 273 followed up for four years. Pooled rates, or odds ratios where control groups were available, showed that cardiovascular death or myocardial infarction was twice as likely in those with a carotid bruit than in those without. Carotid auscultation is insensitive but highly specific for carotid atherosclerosis and shows good inter-observer agreement. Finding a bruit may help select those requiring more active treatment of cardiovascular risk factors. An accompanying commentary (p. 1554) points out that physical signs may help to select imaging methods, but that further information from asymptomatic individuals with carotid bruits and comparison with other risk factors are needed to confirm the value of this sign.

Pickett CA, Jackson JL, Hemann BA et al. Carotid bruits as a prognostic indicator of cardiovascular death and myocardial infarction: a meta-analysis. *Lancet* 2008; 371:1587–94.

Transmission of avian flu

This epidemiological, clinical and virological study concerns the close contacts of two patients with H5NI disease. The index case was a 24-year-old man who died of his illness, and the second case was his 52-year-old father who survived and who had had substantial unprotected exposure to his son. Both patients were infected with the H5NI virus. Ninety-one out of 100 close contacts, including the index case's mother and girlfriend who had prolonged unprotected exposure, were followed for ten days. Seventy-eight had received oseltamivir prophylaxis. None showed any evidence of H5NI transmission. Two out of 100 had acute respiratory symptoms within ten days, but both had throat swabs negative for H5NI virus. Transmission from son to father may have occurred in hospital, but transmission to other close contacts was at most limited but not sustained.

Wang H, Feng Z, Shu Y et al. Probable limited person-to-person transmission of highly pathogenic avian influenza A (H5NI) virus in China. *Lancet* 2008; 371:1427–34.

Blood pressure treatment in older patients

This paper analyses 31 trials, including 96,466 patients aged <65 years (mean 57 years) and 94,140 >65 years (mean 72 years). There was no difference in the reduction of relative risk of total cardiovascular events in the different age groups. There was no evidence in eight trials that regimens of β -blockers and diuretics or other drugs varied in risk reduction in younger and older patients. There was no difference in risk reduction per unit blood pressure (BP) reduction in younger or older patients. The authors conclude

that hypertension should be controlled irrespective of age and that the drugs used are less critical. An accompanying editorial (p. 1080) emphasises that the higher risk of cardiovascular risks in older patients supports their treatment and British recommendations for ACE-inhibitors <55 years and diuretics or calcium channel blocker in older patients.

Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different regimens to lower blood pressure on major cardiovascular events in older and younger adults: meta-analysis of randomised trials. *BMJ* 2008; 336:1121–3.

Blood pressure treatment in very old patients

Blood pressure reduction prevents stroke and other vascular events, but the association of BP and stroke falls with age and the value of treating older patients is uncertain. This HYVET study reports a randomised controlled trial of treatment of 3,845 people aged 80 years and over (80–105) with systolic BP >160 mm Hg and diastolic BP 110 mm Hg using indapamide (1.5 mg) with or without perindopril (2 mg or 4 mg) or a placebo over 1.5 years (r. 0–6.5). The results showed a significant reduction in fatal strokes ($p=0.05$) and death from all causes ($p=0.02$). All strokes were reduced but not to statistically significant levels ($p=0.06$), possibly because the trial was stopped early because of the reduction in overall mortality. A BP target of 150/80 is suggested. An accompanying editorial (p. 1958) concludes that hypertension in the very elderly should be treated.

Beckett NS, Peters R, Fletcher AE et al. Treatment of hypertension in patients 80 years of age or older. *N Engl J Med* 2008; 358:1887–98.

Glucose intolerance in pregnancy

Overt diabetes mellitus in pregnancy is associated with increased risks of adverse perinatal events. This multinational study of 23,316 pregnant women aimed to identify the risks of adverse pregnancy outcomes associated with maternal glucose intolerance less than that in overt diabetes mellitus (fasting glucose <5.8 mmol/l; glucose tolerance test at 2-hour glucose <11.1 mmol/g). Primary outcomes were birth weight above 90 percentile, caesarian delivery, clinical neonatal hypoglycaemia and cord blood c-peptide (a surrogate marker for insulin concentrations) above the 90 percentile.

High birth weight and cord blood c-peptide, physiological consequences of maternal glycaemia, were associated strongly with maternal glucose concentrations. Caesarian delivery and clinical neonatal hypoglycaemia were also associated with maternal glycaemia, as were secondary outcomes such as prematurity, pre-eclampsia, birth injury and the need for neonatal intensive care – which are pregnancy complications. An associated editorial (p. 2061–3) considered the need to treat lesser degrees of maternal glycaemia, and concluded this should await further evidence.

The HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med* 2008; 358:1991–2002.

N Finlayson

Depression and ischaemic heart disease mortality

More evidence of the importance of depressive illness in determining mortality from ischaemic heart disease (IHD) comes from the indirect source of a prospective cohort study of cancer. The European Prospective Investigation of Cancer (EPIC) trial includes more than 8,000 men and 11,000 women from Norfolk, UK, who had not had clinically apparent IHD when recruited. Participants had been assessed for depression cross-sectionally between 1996 and 2000. Details of deaths were obtained from national statistics, with a median follow-up of 8.5 years. By August 2006 there had been 274 deaths from IHD (over 162,974 person-years). Participants who had been diagnosed with depression during the year before baseline assessment were 2.7 times more likely to have died from IHD, after accounting for a host of established risk factors and even after excluding the first six years of follow-up data.

Surtees PG, Wainwright NMJ, Luben RN et al. Depression and ischaemic heart disease mortality: evidence from the EPIC-Norfolk UK Prospective Cohort Study. *Am J Psychiatry* 2008; 165:515–23.

Methadone versus naltrexone morbidity

This retrospective, longitudinal study examined data collected by an Australian state hospital's reporting system on 836 heroin-dependent patients who had begun first-time treatment with either oral methadone ($n=522$) or naltrexone implants ($n=314$) in 2001–02. Outcome measures were confined to hospital presentations. While six-months outcomes were similar, the 3.5-year outcomes favoured naltrexone with significant reductions in the rates of admission for opioid overdose (odds ratio [OR]=0.23) and non-overdose reasons (OR=0.64) against no changes among methadone maintenance treatment patients. However, there was an increase in non-opioid drug-related admissions in the naltrexone cohort (OR=1.52), suggesting a switch of abuse to other illicit drugs.

Ngo HTT, Tait RJ, Hulse GK. Comparing drug-related hospital morbidity following heroin dependence treatment with methadone maintenance or naltrexone implantation. *Arch Gen Psychiatry* 2008; 65:457–65.

Suicide after bereavement

Using Swiss mortality statistics covering 1998–2005, the relationship between a death and the subsequent suicide of the widowed person during the ensuing year was investigated. The risk of suicide remained increased in both genders throughout the year apart from latterly among older widows. The risk peaked during the first week when the annualised suicide rates were 941 per 100,000 among men and 207 per 100,000 among women, corresponding to standardised mortality ratios of 34 and 19 respectively. Given this is when the bereaved are most likely to be in contact with their GP and/or clergy, there may be an opportunity to intervene.

Ajdacic-Gross V, Ring M, Gadola E et al. Suicide after bereavement – an overlooked problem. *Psychol Med* 2008; 38:673–6.

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