STUDY RESULTS

Potential biomarkers could help identify high-risk acute kidney injury patients

Newly identified biomarkers found in the urine could help emergency department doctors to determine the severity of kidney damage and so lead to higher-risk patients being treated more quickly.

A large multicenter study carried out by clinicians of the Experimental and Clinical Research Center (ECRC), a joint cooperation between the Max Delbruck Center for Molecular Medicine (MDC) Berlin-Buch and the Charité – Universitatsmedizin Berlin, the Helios Hospital Berlin, and two hospitals in the USA have demonstrated that two potential biomarkers, NGAL and KIM-1, may be useful in providing an early risk assessment for patients presenting with kidney disorders. The study found that high levels of NGAL and KIM-1 indicate an increased risk of acute kidney damage, which in turn increases the risk of patients dying in the hospital or requiring dialysis treatment.

"In the initial stage of acute kidney injury, we may have most room for improvement of our current clinical practice," suggests Kai Schmidt-Ott from the ECRC (Berlin, Germany). He recommends that clinicians should base their diagnoses on the NGAL and KIM-1 biomarker readings as well as the serum creatinine levels to give a more exact assessment of the individual patient's risk.

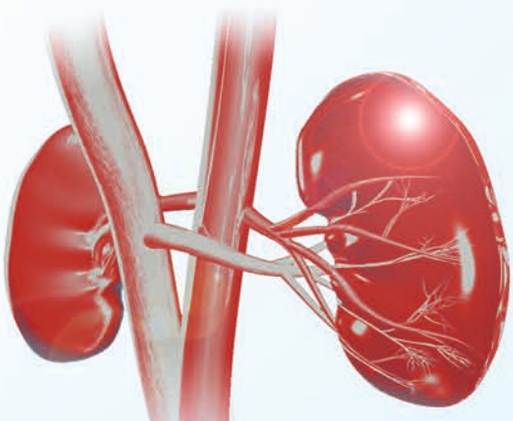
Jonathan Barasch (Columbia University, NY, USA), the senior author of the paper explained that, "When a patient presents to the emergency department and a blood test identifies an abnormal creatinine value, it is difficult to know whether the patient needs to be hospitalized because of ongoing intrinsic acute kidney injury (a potentially fatal disease) or whether the patient needs to be sent home after intravenous or oral fluids and later examined at an outpatient clinic."

At present, the serum creatinine level alone is used for the diagnosis of acute kidney injury. Because creatinine is a molecule that is normally excreted via the kidney, it accumulates in the blood when kidney function is impaired. However, high levels of serum creatinine are not immediately indicative of acute kidney injury; the level could have built up over a longer period of time, and therefore may not indicate tissue damage. Measuring serum creatinine levels alone is not particularly helpful to doctors in deciding how to proceed with treatment.

Damaged kidneys synthesize several other specific proteins. This large-scale study involved taking a single measure of five of these proteins, used as urinary biomarkers, from almost 1635 emergency room patients at the time of hospital admission, in order to determine which could be used to evaluate patient risk.

The findings are hoped to help tackle a real problem; in the USA alone, 1 million patients are diagnosed every year with severe acute kidney injury.

Further research is needed to determine whether or not all patients admitted to an emergency room should be tested for the biomarkers. It also remains to be seen whether or not these biomarkers will actually influence the individual treatment outcome.



– Written by Laura McGuinness

Source: Nickolas TL, Schmidt-Ott KM, Canetta Pietro *et al.* Diagnostic and prognostic stratification in the emergency department using urinary biomarkers of nephron damage: a multicenter prospective study. *J. Am. Coll. Cardiol.* 59, 246–255 (2012).

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TRIAL OUTCOMES

FDA approves exenatide extended-release for the treatment of Type 2 diabetes

Amylin Pharmaceuticals have announced the US FDA approval of exenatide extended-release (BYDUREON™), its once-weekly treatment for Type 2 diabetes. The approval was supported by the safety and efficacy data obtained from the DURATION clinical trial program as well as clinical experience gathered to date with exenatide injection (BYETTA®) – a twice-weekly form of exenatide that has been available in the USA since June 2005 and used in 80 countries worldwide.

Exenatide, a glucagon-like peptide 1 receptor agonist, is indicated as an adjunct to diet and exercise to improve glycemic control in adults with Type 2 diabetes in multiple clinical settings.

"With BYDUREON, US physicians and patients can now choose a therapy that offers continuous blood sugar control in just one dose per week," explained John Buse, University of North Carolina School of Medicine in Chapel Hill. "New treatment options are essential for the millions of adults with Type 2 diabetes who continue to struggle to achieve optimal blood sugar control."

In a head-to-head study between exenatide extended-release and exenatide injection, known as DURATION-5, patients taking exenatide extended-release experienced a statistically superior reduction in A1C of 1.6% from baseline, compared with 0.9% for patients taking exenatide injection, after 24 weeks of treatment. In addition, the investigators found that both treatment groups achieved statistically significant weight loss by the end of the study, with an average loss of 5.1 lb for patients taking exenatide extended-release and 3.0 lb for patients taking exenatide injection. Weight loss was defined as the secondary end point of the trial.

Nausea was the most frequently reported adverse event in both treatment groups, but was reported less frequently by exenatide extended-release users (14%) than by exenatide injection users (35%).

It is hoped that exenatide extended-release will provide a straightforward single-dose tray so that sufferers of Type 2 diabetes are able to self-administer the once weekly subcutaneous injection.

– Written by Paolo Reveglia

Source: Amylin Pharmaceuticals press release: http://investors.amylin.com/phoenix.zhtml?c=101911&p=irol-newsArticle&ID=1653756&highlight=

STUDY RESULTS

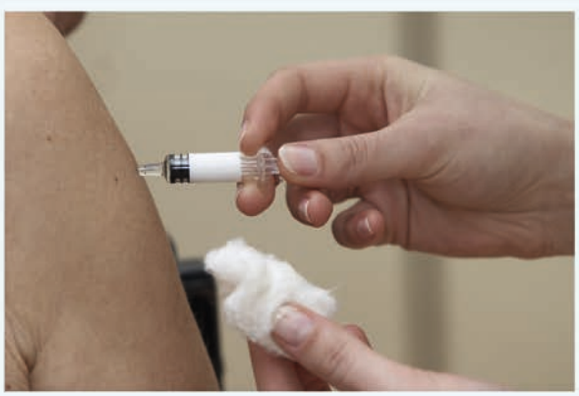
New study highlights improvements needed to promote adult vaccination

Improvements in communication are needed to help increase disappointingly low adult vaccination rates.

A new study has recently been published in an online eBook from the RAND Corporation (Arlington, VA, USA) suggesting that promotion of immunizations as part of a routine office-based medical practice is urgently needed to improve adult vaccination rates; a method previously shown to be highly effective as a means of curbing the spread of diseases across communities.

The RAND study, led by Katherine Harris, a senior economist at RAND (a US-based nonprofit institution), outlines the improvements that are needed to strengthen the role of office-based medical providers to promote vaccination to adult patients. Among these recommendations are the suggestions to create tools to improve communications between patients and providers concering vaccinations and for stronger incentives to encourage health providers to refer patients to community sites that administer vaccinations if they do not offer them.

The study consisted of a comprehensive literature review of published studies



concerning adult vaccinations, a stakeholder workshop (including members of the US Department of Health and Human Services), interviews with experts and meeting participants and a short telephone survey of 1278 adults to learn about the relationship between influenza vaccination, public beliefs and misperceptions about its safety.

"...an estimated 1 million cases of shingles each year, approximately half of which occur in men and women 60 years or older, highlighting the potential benefit of increased vaccination rates to help reduce this prevalence."

Adult vaccination rates, in contrast to childhood vaccination rates, remain disappointingly low. Influenza, which has seen a huge drive in efforts to increase inoculation rates for those at the highest risk of death, do not exceed 70% in the USA. Other vaccines recommended for adults can protect against a variety of pathogens and diseases including pneumococcal sepsis, shingles, hepatitis A and B, pertussis (whooping cough) and the human papillomavirus. The CDC reports an estimated 1 million cases of shingles each year, approximately half of which occur in men and women 60 years or older, highlighting the potential benefit of increased vaccination rates to help reduce this prevalence.

Previous research has estimated that health and productivity costs of influenza alone could be as high as US$87 billion per year in the USA, but the RAND researchers say that recent changes in both the practice environments and policy, have provided a unique window of opportunity to improve the delivery of a variety of vaccinations to adults.

– Written by Patrick Coyne

Sources: RAND press release: www.rand.org/news/press/2012/01/11.html; RAND Corporation; A Blueprint for improving the promotion and delivery of adult vaccination in the United States: www.rand.org/pubs/technical_reports/TR1169.html

Study indicates promising results for new meningitis vaccine

Results of a recent Chilean study suggest that the new 4CMenB vaccine may be effective against meningitis strain B.

While there are meningitis vaccination programs already available in many parts of the world, current vaccinations only provide protection against *Neisseria meningitidis* serogroups A, C, W-135 and Y. Meningitis B is one of the most common forms of childhood meningitis, but since it is caused by a group of thousands of subtly different strains of bacteria, finding a vaccination that is able to target them all has, for a long time, remained elusive.

Scientists produced the 4CMenB vaccine by analyzing the genetic structure of thousands of B strains, looking for shared features that could be targeted.

"...4CMenB has the potential to provide significant protection when administered to infants..."

Myron Christodoulides, from the University of Southampton, UK, independently commented that, "Previous studies have shown that 4CMenB has the potential to provide significant protection when administered to infants – this new study shows it could also be highly protective in the adolescent age group."

This randomized, observer-blind, placebo-controlled study, investigated the vaccine's effectiveness in 1631 adolescents aged between 11 and 17 years. The participants received either one, two or three doses of the 4CMenB vaccine at 1-, 2- or 6-month intervals. After two or three doses of the vaccine, 99–100% of recipients had hSBA titres of 4 or more against test strains, compared with 92–97% after one dose ($p < 0{\cdot}0145$) and 29–50% after placebo. Immunogenicity was measured again at 6 months, when 91–100% of participants who had received two or three doses still had titers of 4 or more for each strain, but only 73–76% of participants remained immune after one dose. Seroresponse rates were found to reach 99–100% for each strain if a second or third dose was given at 6 months. No vaccine-related serious adverse events were reported in the study.

Christodoulides did caution that "There are still a number of important questions to be answered such as how many strains it will protect against, how long the protection will last and whether it will stop the bacteria from being passed on to others, providing indirect protection to those not vaccinated."

– Written by Laura McGuinness

Source: Santalaya ME, O'Ryan ML, Valenzuela MT *et al.* Immunogenicity and tolerability of a multicomponent meningococcal serogroup B (4CMenB) vaccine in healthy adolescents in Chile: a Phase 2b/3 randomised, observer-blind, placebo-controlled study. *Lancet* 379(9816), 617–624 (2012).

About the News

The News highlights some of the most important events and research.
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Axitinib for the treatment of renal cell carcinoma receives US FDA approval

Axitinib (Inlyta®, Pzifer Inc.) has recently been approved by the US FDA for the treatment of advanced renal cell carcinoma (ARCC) in patients with whom other pharmaceutical agents have been ineffective.

Renal cell carcinoma is responsible for upwards of 80% of renal cancer in adults, making it the most common renal cancer. It is also known to have the highest fatality rates of all the genitourinary cancers. Traditional treatment usually comprises of a partial or radical nephrectomy. However, in recent years several novel drugs have been approved for the treatment of ARCC. Axitinib, a selective second-generation VEGF inhibitor, is the seventh drug to be approved for this indication since 2005.

The FDA approval was made on data taken from a Phase III comparative trial published in the *Lancet*. Of 723 patients enrolled, 361 patients received axitinib with the remaining 362 patients receiving sorafenib, the standard treatment for ARCC. The primary end point was progression-free survival. The median progression-free survival for patients treated with axitinib was 6.7 months, significantly longer than the 4.7 months recorded for sorafenib.

Richard Pazdur, Director of the Office of Hematology and Oncology Products, Center for Drug Evaluation and Research, FDA commented on high levels of drug development for RCC, "[axitinib] is the seventh drug that has been approved for the treatment of metastatic or advanced kidney cell cancer since 2005. Collectively, this unprecedented level of drug development within this time period has significantly altered the treatment paradigm of metastatic kidney cancer, and offers patients multiple treatment options."

– Written by Caroline Purslow

Sources: www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm289423.htm; Rini BI, Escudier B, Tomczak P *et al.* Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised Phase 3 trial. *Lancet* 378, 1931–1939 (2011).

US FDA has approved vismodegib for the treatment of advanced basal cell carcinoma

Vismodegib (Erivedge™) is the first drug indicated for the treatment of basal cell carcinoma (BCC) – the most common type of skin cancer in the EU, USA and Australia – to gain US FDA approval. It has first-in-class specificity to the hedgehog pathway – abnormal hedgehog signaling is implicated in more than 90% of BCC cases and vismodegib is a ligand-specific inhibitor of this pathway. It suppresses hedgehog signaling by binding to and interfering with the smoothened transmembrane receptor preventing abnormal signaling.

The approval came after a new drug application was submitted to the FDA in September 2011 based on Phase II data from the ERIVANCE BCC trial. The drug then underwent a subsequent priority review by the FDA, which led to its approval. The drug is indicated for patients with BCC that has metastasized to other parts of the body, relapsed after surgery or is unable to be treated with radiation or surgery.

The Phase II study was an international, single-arm, multicenter, two-cohort, open-label trial of 96 patients. The drug was shown to achieve its primary end point of overall response rate assessed by independent review. In patients with locally advanced BCC it was shown to shrink lesions in 27 out of 63 cases and in patients with metastatic BCC, lesions were reduced in ten out of 33 cases. The mean duration of response was 7.6 months. The drug has been shown to have relatively low toxicity, however, adverse events such as muscle spasms, hair and weight loss, diarrhea, fatigue, reduced appetite, constipation, vomiting and loss of taste in the tongue were observed.

The approval of the drug came with a boxed warning of potential risk of death or severe birth defects to unborn babies. The drug is being marketed by Genetech (USA), part of the Roche group, as a once-daily capsule and costs $7,500 per month. Duration of treatment is expected to be approximately 10 months. A marketing authorization application for vismodegib has been submitted by Roche in the EU in order for European patients to gain access to the drug, while a Phase II safety trial is also underway in order to potentially gain marketing authorization worldwide.

The drug is currently undergoing trials for other indications such as colorectal cancer, small cell lung cancer, advanced stomach cancer and pancreatic cancer.

– Written by Claire Attwood

Source: Genetech newsroom: FDA approves Erivedge (vismodegib) capsule, the first medicine for adults with advanced basal cell carcinoma: www.gene.com/gene/news/press-releases/display.do?method=detail&id=13827

Proton pump inhibitor may not improve symptoms in children with poorly controlled asthma

A recent study conducted by researchers at the American Lung Association's Asthma Clinical Research Center has indicated that addition of the proton pump inhibitor lansoprazole to the treatment of children with poorly controlled asthma may fail to improve clinical symptoms or lung function.

Asymptomatic gastroesophageal reflux is a pervasive condition among children with asthma, and has been implicated as a possible cause of inadequate symptom control in these individuals. Although proton pump inhibitors are commonly used in the treatment of gastroesophageal reflux, it remains unclear whether such treatments will alleviate symptoms in children suffering from poorly controlled asthma.

A randomized, masked, placebo-controlled trial – compared the control of asthma symptoms in children treated with either lansoprazole (n = 149) or placebo (n = 157).

After 24 weeks of follow-up, the researchers observed no statistically significant differences in the control of asthma symptoms, as inferred using the Asthma Control Questionnaire. Significant differences were also absent for several other outcomes, including lung function, asthma-related quality of life and frequency of episodes of poor asthma control.

Notably, adverse events were more frequent among children receiving lansoprazole, who reported more respiratory infections than the placebo group.

Janet Holbrook (Johns Hopkins Bloomberg School of Public Health, MD, USA), an author of the study, commented on the implications of these findings for the treatment of asthma patients: "The data were very clear. Lansoprazole did not improve asthma symptoms in children as compared to a placebo, and there is no evidence to support prescribing these drugs to treat asthma in children."

– Written by Edward Parker

Sources: Writing Committee for the American Lung Association Asthma Clinical Research Centers, Holbrook JT, Wise RA, Gold BD *et al*. Lansoprazole for children with poorly controlled asthma: a randomized controlled trial. *JAMA* 307(4), 373–381 (2012); Johns Hopkins Bloomberg School of Public Health (Baltimore, MD, USA): www.jhsph.edu/publichealthnews/press_releases/2012/holbrook_gerd_asthma.html

Is ICD replacement always the correct approach?

Implantable cardioverter-defibrillators (ICDs) can be life-saving devices. In the USA, more than 100,000 ICDs are implanted annually; at least 25% of these operations are to replace ICD generators owing to a depleted battery. Doctors from Beth Israel Deaconess Medical Center, MA, USA, have written recently in the *New England Journal of Medicine* to suggest that not all of these ICD generator replacements are necessary. Daniel Kramer (Beth Israel Deaconess Medical Center, MA, USA), lead author of the study writes, "Because of the high cost and concern about patient selection, the appropriateness of initial device placement has been closely scrutinized. But there has been little consideration as to what happens in the years after implantation, when ICD batteries drain sufficiently to require replacement, device leads become defective, or systems become infected. Should all these patients receive replacement ICDs?"

In their commentary, the authors identify several key factors relevant to improving decision making surrounding ICD replacement. They indicate that throughout the time that a patient has had an ICD implanted, their health may change significantly, with the potential progression of, or development of entirely new, conditions that could impact the effectiveness of continued ICD therapy. In addition, a patient's cardiovascular health may have improved to the point where it negates the need for an ICD to prevent sudden cardiac death entirely.

The authors continue to highlight that the patient's experience of living with their ICD may influence their views on have a replacement implanted. The authors describe how a patient's own preferences may also have changed during their previous ICD therapy.

In their conclusion, the authors make recommendations for improving ICD replacement decisions and argue that, "From both patient and societal perspectives, the expense and uncertainty of ICD therapy argue for a more considered and nuanced approach to generator replacement. It is time for a change in our approach to this common, costly and complex clinical decision."

– Written by Sean Fitzpatrick

Sources: Kramer DB, Buxton AE, Zimetbaum PJ. Time for a change – a new approach to ICD replacement. *N. Engl. J. Med.* 366(4), 291–293 (2012); Beth Israel Deaconess Medical Center www.bidmc.org/News