Influenza: the story continues…

Once again microbiologists, and the public, are focused on a potential pandemic influenza.

As the number of cases of H1N1 influenza A virus continues to increase, and the story dominates the news media, all new research relating to influenza is seen in a new light and takes on an ever-increasing importance and relevance.

In a recent paper in *PLoS Medicine*, a team led by Joseph Wu of the University of Hong Kong, China, reported the results of a mathematical model that tested the effectiveness of different antiviral intervention strategies in the event of an influenza pandemic.

The group constructed a stochastic model in which a small stockpile of secondary drug (1%) was made available during the early phase of an influenza pandemic. They then modeled to potential treatment strategies for administration of the second antiviral: early combination chemotherapy, in which both drugs are administered at the same time; or sequential multidrug chemotherapy, where the secondary drug is administered alone, until its supply is exhausted, then the primary drug is used.

Our ability to combat an influenza pandemic will be extremely hampered by the emergence of antiviral resistance. Therefore, uncovering an antiviral strategy that makes the risk of resistance as low as possible is a vital endeavor, especially as the majority of global pandemic planning relies on stockpiling only one drug, namely, oseltamivir.

The group found that, provided that the large populations that produce resistant strains implement one of the two strategies, augmentation of existing one-drug stockpiles with a secondary drug could provide a useful, and potentially cheap, method by which to limit the emergence of untreatable, drug-resistant strains of the virus.

However, the authors do urge caution in the interpretation of these results, which is especially important given the current climate of heightened concern. While the results are interesting, real-life experimental studies are needed to test the applicability of these strategies, especially studies to determine the safety and effectiveness of various drug–drug combinations.

A separate study, published in the *Journal of Leukocyte Biology*, explores another aspect of pandemic influenza, the relationship between viral infection and subsequent bacterial complications. A number of epidemiological studies have suggested that morbidity and mortality during previous large-scale influenza pandemics, such as the 1918 Spanish Flu, may have, in fact, been a result of secondary bacterial infection as opposed to the initial influenza infection.

The latest paper, by researchers led by Kathleen Sullivan of the Children's Hospital of Philadelphia, explores the pathological mechanisms behind this. They found that influenza infection can reduce the responsiveness of Toll-like receptors, one of the primary means that the immune system uses to detect bacterial infection. Therefore, this work shows that influenza may lay the body susceptible to bacterial infection by dampening the body's ability to respond to pathogenic bacteria that it would ordinarily clear.

US President Barack Obama was recently quoted as saying that the H1N1 influenza outbreak "reminded us of our shared stake in science and research". The continued good work of those studying influenza around the world, and the promise that new discoveries hold, continue to justify his view.

Sources: http://news.yahoo.com/s/politico/20090427/pl_politico/21745; http://www.eurekalert.org/pub_releases/2009–04/plos-uas043009.php.

Wu JT, Leung GM, Lipsitch M, Cooper BS, Riley S: Hedging against antiviral resistance during the next influenza pandemic using small stockpiles of an alternative chemotherapy. PLoS Med. *(2009) (Epub ahead of print).*

http://www.eurekalert.org/pub_releases/2009–05/foas-slw050409.php.

Heltzer ML, Coffin SE, Maurer K et al.*: Immune dysregulation in severe influenza.* J. Leukoc. Biol. *DOI: jlb.1108710v1 (2009) (Epub ahead of print).*

in the news...

future medicine part of fsg

New drug for the treatment of multidrug-resistant TB shows promising results in Phase II clinical trial

Promising results to be published in the June issue of the *New England Journal of Medicine* were reported for the treatment of multidrug-resistant (MDR) TB with a new compound, TMC207, developed by Tibotec, a subsidiary of Johnson & Johnson. On addition of TMC207 to a drug cocktail to treat the life-threatening infection with MDR TB, the treatment was shown to be five-times more efficient.

MDR TB is a threat to life in many populations, and is extensively associated with long treatment regimes (up to 18 months) and high treatment costs.

Conducted in South Africa, this recent study is the first part of a randomized, placebo-controlled Phase II trial, including 47 hospitalized patients that were recently diagnosed with MDR-TB. The patients were randomized into two groups, one receiving TMC207 (23 patients) within a background regimen of five second-line anti-TB drugs, while the other group (24 patients) received placebo in the background regimen. TMC207 was administered at a dose of 400 mg/day for 2 weeks and subsequently at 200 mg three-times weekly for 6 weeks. Every day, patients gave a sputum sample, which was analyzed for TB bacteria. After 8 weeks, a total of 46.6% of patients were sputum culture-negative in the TMC207 group, while only 8.7% of patients achieved this result in the placebo group. Furthermore, TMC207 significantly reduced the time to culture conversion (positive to negative); the probability of a culture becoming negative was 11.8-times higher in the TMC207 group at any given day during the 8 weeks than in the placebo group. In addition, the mean colony-forming units count in sputum cultures reduced significantly faster in the TMC207 group. Adverse effects were reported to be mild-to-moderate, and only nausea was reported more frequently in the TMC207 group (26%) than in the placebo group (4%).

Peter Donald from Stellenbosch University in Capetown, South Africa, commented: "The results of this study are highly encouraging news for the treatment of tuberculosis. Not only is this an agent with a radically different means of action, but it shows potential to shorten the treatment of tuberculosis in the foreseeable future, something the tuberculosis community has been hoping for years."

The second part of the trial will prolong treatment with TMC207 to 24 weeks, and will be enrolled at sites in South Africa, Peru, Latvia and Russia. Results are expected later this year.

Source: Diacon AH, Pym A, Grobusch M et al. *The diarylquinoline TMC207 for multidrug-resistant tuberculosis.* N. Engl. J. Med. *360, 2397–2405 (2009).*

Promising trial results for maraviroc

Phase III clinical trials have demonstrated the efficacy of maraviroc, a member of a new class of antiretroviral agent, as a HIV treatment in patients with resistance to currently used antiretroviral medication.

Results from the double-blind, placebo-controlled, Maraviroc versus Optimized Therapy in Viremic Antiretroviral Treatment-Experienced Patients (MOTIVATE) 1 and 2 studies (of patients in Canada/USA, and Australia/Europe/USA, respectively) were published in the October issue of the *New England Journal of Medicine*. The study examined 1049 patients with R5 HIV-1 who had previously been treated with, or had already developed resistance to, three antiretroviral drug classes and who also had HIV RNA levels of more than 5000 copies per mm. Safety and efficacy were tested following 48 weeks of treatment. The mean change in HIV-1 RNA levels was significantly greater in maraviroc-treated patients, compared with placebo in both trials; -1.66 and -1.82 log10 copies per ml with the once-daily and twice-daily regimens of maraviroc, respectively, versus -0.80 with placebo in MOTIVATE 1, and -1.72 and -1.87 log10 copies per ml, respectively, versus -0.76 with placebo in MOTIVATE 2. CD4 counts were also significantly better in maraviroc-treated patients compared with controls in both studies. Furthermore, side effects were similar in both arms, suggesting that the use of maraviroc does not cause an increase in adverse effects.

These findings are of immense importance to the field of HIV therapy, as maraviroc is a member of a novel class of HIV drugs. Mararvoric is a CCR5 receptor antagonist. CCR5 is found on the surface of immune cells and is used by HIV as a coreceptor to enter and infect these cells. By blocking this interaction the drug inhibits viral entry and so prevents HIV replication. Due to the mutability of HIV, patients who take antiretrovirals for many years eventually develop resistance to the drugs. However, the demonstration that this novel class of drugs can be effective gives such patients renewed hope, as the virus has not had time to develop resistance.

Roy Gulick, of Weill Cornell Medical University (NY, USA) and lead author on the study, explains the significance of the results, "It is now possible to expect that a majority of treatment-experienced patients who experience failure on their current HIV drugs will regain control of their HIV infection with maraviroc combined with other newer antiretroviral drugs. This is an important step forward".

Sources: www.sciencedaily.com/releases/2008/10/081001181314.htm;
Gulick RM, Lalezari J, Goodrich J et al.*: Maraviroc for previously treated patients with R5 HIV-1 infection.* N. Engl. J. Med. *359, 1429–1441 (2008).*

Less is more: analysis shows that lower doses of an Alzheimer's drug may reduce the incidence of adverse events

It is often thought that administering higher doses of a drug results in more effective treatment of a disease. However, recent analysis has demonstrated that, relative to high doses, lower doses of an Alzheimer's drug, rivastigmine, can improve cognition while significantly reducing side effects. Rivastigmine is an acetylcholinesterase inhibitor manufactured by Novartis (Basel, Switzerland). It has been approved for use in 60 countries including all member states of the EU and the USA. Administration of rivastigmine between 6 and 12 mg improves cognitive functions, although a number of side effects are associated with it, including nausea, vomiting, diarrhea, abdominal pain and lack of appetite. Patients have also reported dizziness, fainting and weakness.

> "*This review has confirmed what we knew about the drug – that it provides cognitive improvements similar to other Alzheimer's medications.*"

Previous studies have suggested that lower doses of the drug administered more frequently may lead to a reduction in the number of adverse events. This preliminary evidence formed the basis of a new study that investigated the efficacy and safety of two doses of rivastigmine patch: 9.6 mg/day and 17.4 mg/day. The analyses included nine trials involving a total of 4775 patients. It appeared that patients receiving the 17.4 mg/day dose scored similarly on cognitive function tests compared with those taking the 9.6 mg/day dose. However, two thirds of patients taking the higher dose reported at least one adverse event compared with half of patients taking the lower dose. In addition, patients who were receiving the lower dose of rivastigmine patch had a reduced incidence of adverse events compared with those taking a 6–12 mg/day dose of rivastigmine capsules.

"This review has confirmed what we knew about the drug – that it provides cognitive improvements similar to other Alzheimer's medications", remarked Piero Antuono, a professor of neurology, pharmacology and toxicology at the Medical College of Wisconsin, WI, USA.

Source: Birks J, Grimley Evans J, Iakovidou V, Tsolaki M, Holt FE: Rivastigmine for Alzheimer's disease. Cochrane Database Syst. Rev. *(2009) (Epub ahead of print).*

Anakinra demonstrates a modest benefit for treating RA

The drug anakinra has a moderate beneficial effect for patients suffering from rheumatoid arthritis (RA), according to a recent *Cochrane Systematic Review*. However, the study warns of the possible risks of serious infections and discourages the use of anakinra with other biologic drugs.

The recent review sought to evaluate the clinical efficacy and safety of the drug for treating RA in adults. Data was compiled from five trials of anakinra, involving 2876 patients in total, and the study concluded that the drug is a relatively safe and moderately efficacious biologic therapy for RA.

Nevertheless, the improvements observed were notably less than those demonstrated for other biologics, and the authors recommend caution with the use of anakinra for RA, not least due to the increased rate of serious infections.

Moreover, one study in the review explored the combination of anakinra with etanercept – another biologic used for the treatment of RA – and found a significant increase in the number of serious adverse events. "On the basis of these results, we recommend that doctors avoid combining biologic medications with anakinra when treating patients with rheumatoid arthritis,' said lead researcher Marty Mertens.

Source: Mertens M, Singh JA: Anakinra for rheumatoid arthritis. Cochrane Database Syst. Rev. *1, CD005121 (2009).*

About the Bulletin Board

The Bulletin Board highlights some of the most important events and research in medicine. If you have newsworthy information, please contact:

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Clinical trials show Seroquel® to be effective in treating bipolar depression

Promising results of Seroquel® (quetiapine fumarate) in bipolar depression were recently presented at the 162nd American Psychiatric Association Congress in San Francisco, CA, USA. The data presented were the combined analyses from four large clinical trials evaluating the efficacy and tolerability of Seroquel in treating depressive episodes associated with bipolar I and II disorders.

The four trials included in the combined analysis were the Bipolar Depression (BOLDER) I and II studies and the Efficacy of Quetiapine Monotherapy in Bipolar Depression (EMBOLDEN) I and II studies. All four studies had a similarly designed 8-week, randomized, double-blind, placebo-controlled phase to evaluate the efficacy and safety of Seroquel monotherapy (fixed-dose 300 or 600 mg daily) in comparison with placebo in adult patients with bipolar I or II disorder. The combined analysis demonstrated that Seroquel monotherapy was significantly more effective at treating depressive episodes in all patients with bipolar I or II disorder (n = 2593) in comparison to placebo. The Montgomery-Åsberg Depression Rating Scale (MADRS) was used to measure improvement. In addition, improvements were seen as early as the first week of treatment and continued until week 8.

The combined data also suggested that Seroquel was generally well-tolerated and any observed adverse events were consistent with those of quetiapine. The most common adverse events in patients with bipolar disorder were dry mouth, somnolence, sedation and dizziness. The same adverse events were reported among patients with bipolar II disorder, with the addition of headache.

Alan Young, of the University of British Columbia, Canada, summarized, "these important findings confirm that SEROQUEL is an effective agent for the treatment of bipolar depression, and particularly encouraging are the results in bipolar II patients who have historically not responded well to treatment."

Sources: Calabrese JR, Young A, Gustafsson U et al.: *The efficacy of quetiapine monotherapy in bipolar depression: combined data from the BOLDER and EMBOLDEN studies. Presented at:* The American Psychiatric Association, *San Francisco, CA, USA, 16–21 May (2009).*

Young AH, Calabrese J, Gustafsson U et al.: *The efficacy of quetiapine monotherapy in bipolar II depression: combined data from the BOLDER and EMBOLDEN studies. Presented at:* The American Psychiatric Association, *San Francisco, CA, USA, 16–21 May (2009).*

Suppes T, Datto C, Minkwitz M et al.: *Effectiveness of the new extended release formulation of quetiapine as monotherapy for the treatment of acute bipolar depression (trial D144CC00002). Presented at:* The Eighth International Review of Bipolar Disorder Conference, *Copenhagen, Denmark, 14–16 April (2008).*

Oral immunotherapy offers hope for peanut allergy sufferers

Results published in a recent issue of *Allergy* demonstrated the successful utilization of immunotherapy in reducing peanut sensitivity in children with severe peanut allergy.

A group of researchers from the Wellcome Trust Clinical Research Facility Addenbrooke's Hospital in Cambridge (UK) examined the efficacy of oral immunotherapy (OIT), which has been developed for other allergies, in inducing clinical tolerance to peanut protein. The researchers used a case series sample of four boys, aged 9–13 years, all with suspected peanut allergies, two of whom had previously experienced reactions following accidental exposure to peanuts. In the first stage, researchers confirmed the presence of a peanut allergy using a skin prick test and analyzed serum for peanut-specific IgE. Researchers then exposed subjects to a peanut flour and placebo substance in a double-blind food challenge to determine dose threshold; these ranged from 5 to 50 mg, the equivalent of 1/40 to 1/4 of a whole peanut. Participants were then given daily doses to take at home for 2 weeks; starting doses were selected based on individual subjects' pre-OIT threshold and perceived clinical severity. Doses were approximately doubled on a biweekly basis, up to a maximum of 800 mg of peanut protein, equivalent to five peanuts, at which the daily dose was maintained.

A second food challenge was performed 6 weeks following the final dosage increase. All subjects demonstrated substantial increase in dose threshold, between 48–478 times their initial tolerance, following OIT.

Overall, the authors found that OIT was well tolerated, as none of the participants required an adrenaline injection during the OIT phase of the study, although one subject experienced anaphylaxis during the initial challenge. In addition, some participants experienced abdominal pain upon dosage increase.

Following the completion of the study, all subjects were instructed to ingest 800 mg of peanut protein per day, either as 1.6 g of peanut flour, 2.5 ml of smooth peanut butter or five whole roasted peanuts as maintenance. The authors warned that "tolerance may be lost if subjects were to stop OIT at this stage, and it is likely that long-term maintenance is required, as for other forms of immunotherapy."

Source: Clark AT, Islam S, King Y, Deighton J, Anagnostou K, Ewan PW: Successful oral tolerance induction in severe peanut allergy. Allergy *DOI: 10.1111/j.1398–9995.2009.01982.x (2009) (Epub ahead of print).*

Drug approvals April to June 2009.

Trade name	Generic name	Indication	Region	Manufacturer	Date approved
Cardiology					
Adcirca™	Tadalafil	For the improvement of exercise ability in patients with pulmonary arterial hypertension	USA	Eli Lilly	May 2009
Azor®	Amlodipine and olmesartan medoxomil	As initial or 'first-line' therapy in patients likely to need multiple antihypertensive agents to achieve their blood pressure goals	USA	Daiichi Sankyo	May 2009
Exforge HCT®	Exforge (amlodipine and valsartan) and hydrochlorothiazide	Hypertension	USA	Novartis	April 2009
Dermatology					
Dysport®	Abobotulinumtoxin A	The temporary improvement in the appearance of moderate to severe glabellar lines (vertical lines between the eyebrows)	USA	Ipsen and partner Medicis Pharmaceutical Corp.	April 2009
Endocrinology & metabolism					
ACTOplus met® XR	Pioglitazone HCl and metformin HCl	For adults with Type 2 diabetes who are already treated with ACTOS® (pioglitazone HCl) and metformin or who have inadequate glycemic control on ACTOS or metformin. alone	USA	Takeda	May 2009
Cycloset™	Bromocriptine mesylate	An adjunct to diet and exercise to improve glycemic control in adults with Type 2 diabetes mellitus	USA	VeroScience	May 2009
Gastroenterology & hepatology					
Prevacid®	Lansoprazole	To treat frequent heartburn	USA	Novartis	May 2009
Nexium®	Esomeprazole	For prevention of re-bleeding following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers	Sweden	AstraZeneca	May 2009
Infectious disease					
Besivance™	Besifloxacin ophthalmic suspension 0.6%	Bacterial conjunctivitis	USA	Bausch & Lomb	May 2009
Cetraxal®	Ciprofloxacin otic solution 0.2%	For the treatment of acute otitis externa due to susceptible isolates of *Pseudomonas aerugenosa* or *Staphylococcus aureus*	USA	Laboratorios Salvat	May 2009

Drug approvals April to June 2009.

Trade name	Generic name	Indication	Region	Manufacturer	Date approved
Neurology					
Axert®	Almotriptan	Acute treatment of migraine headache in adolescents aged 12 to 17 years	USA	Johnson & Johnson/ Almirall	June 2009
Fanapt™	Iloperidone	Acute treatment of adult patients with schizophrenia	USA	Vanda Pharmaceuticals	May 2009
Lamictal™ ODT™ Orally disintegrating tablets	Lamotrigine	For the long-term treatment of bipolar I disorder to lengthen the time between mood episodes in people 18 years or older, who have been treated for mood episodes with other medicine	USA	Eurand/ GlaxoSmithKline	May 2009
Lamictal™ XR™	Lamotrigine	A once-daily add-on therapy for patients with epilepsy aged 13 years or older who experience partial onset seizures	USA	GlaxoSmithKline	May 2009
Risperdal® Consta®	Risperidone	Long-acting treatment as both monotherapy and adjunctive therapy to lithium or valproate in the maintenance treatment of bipolar I disorder	USA	Johnson & Johnson	May 2009
Zebinix®	Eslicarbazepine acetate	An adjunctive therapy in adult patients with partial-onset seizures, with or without secondary generalization	EU	Eisai Europe	April 2009
Seroquel XR®	Quetiapine fumarate	Major depressive disorder	Canada	AstraZeneca	May 2009
Oncology					
Avastin®	Bevacizumab	For patients with glioblastoma, with progressive disease following prior therapy	USA	Genentech Inc.	May 2009
Sprycel®	Dasatinib	For the treatment of adults in all phases of chronic myeloid leukemia (chronic, accelerated, or myeloid or lymphoid blast phase) with resistance or intolerance to prior therapy including Gleevec® (imatinib mesylate)	USA	Bristol-Myers Squibb	May 2009
Glivec®	Imatinib	To reduce the risk of recurrence in adult patients who are at significant risk of relapse following surgery to remove gastrointestinal stromal tumors	EU	Novartis	May 2009
Nexavar®	Sorafenib	Unresectable hepatocellular carcinoma	Japan	Bayer	May 2009
Rheumatology					
Cimzia®	Certolizumab pegol	To treat adults with moderate-to-severe rheumatoid arthritis	USA	UCB	May 2009
Reclast®	Zoledronic acid	To prevent osteoporosis in postmenopausal women	USA	Novartis	June 2009
Simponi™	Golimumab	Once-monthly treatment for moderately to severely active rheumatoid arthritis in combination with methotrexate (MTX); for active psoriatic arthritis alone or in combination with MTX; and as monotherapy for active ankylosing spondylitis	USA	Centocor Ortho Biotech Inc.	April 2009

Drug approvals April to June 2009.

Trade name	Generic name	Indication	Region	Manufacturer	Date approved
Rheumatology (cont.)					
Simponi™	Golimumab	Once-monthly treatment in combination with MTX for reducing the signs and symptoms in adult patients with moderately to severely active rheumatoid arthritis; reducing signs and symptoms in adult patients with moderately to severely active psoriatic arthritis, alone or in combination with MTX; and reducing signs and symptoms in adult patients with active ankylosing spondylitis who have had an inadequate response to conventional therapies	Canada	Centocor Ortho Biotech Inc. and Schering-Plough Corp.	April 2009
Conbriza™	Bazedoxifene	for the treatment of postmenopausal osteoporosis in women at increased risk of fracture	EU	Wyeth Pharmaceuticals	April 2009
Other					
	Benzyl alcohol lotion 5%	Topical treatment of head lice infestation in patients 6 months of age and older	USA	Sciele Pharma, Inc.	April 2009
Creon®	Pancrelipase	Treatment of exocrine pancreatic insufficiency in patients with cystic fibrosis or other diseases	USA	Solvay Pharmaceuticals	May 2009
Dysport®	Abobotulinumtoxin A	Treatment of cervical dystonia to reduce the severity of abnormal head position and neck pain	USA	Ipsen and partner Medicis Pharmaceutical Corp.	April 2009
Nicorette® lozenge	2 mg and 4 mg, nicotine polacrilex	Reduction of withdrawal symptoms, including nicotine craving associated with quitting smoking	USA	GlaxoSmithKline	May 2009
Prograf™	Tacrolimus	Prevention of organ rejection in kidney transplant recipients in conjunction with mycophenolate mofetil	USA	Astellas Pharma US	May 2009
Samsca™	Tolvaptan	Treatment of clinically significant hypervolemic and euvolemic hyponatremia (serum sodium < 125 mEq/l or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction), including patients with syndrome of inappropriate antidiuretic hormone, heart failure and cirrhosis	USA	Otsuka Pharmaceutical Company	May 2009
Renvela®	Sevelamer carbonate	For the control of serum phosphorus in patients with chronic kidney disease, including patients not on dialysis, with serum phosphorous levels > 1.78 mmol/l (5.5 mg/dl)	EU	Genzyme	June 2009