Medical Briefs

An abridged look at current events in and around the health-care industry

This Month:

First Therapy for Severe Sepsis

The Biologics and Genetic Therapies Directorate of Health Canada approved the first and only therapy in Canada for the treatment of severe sepsis. Xigris™ [drotrecogin alfa (activated)] was approved for the reduction of mortality in adult patients with severe sepsis (*i.e.*,sepsis associated with acute organ dysfunction) who have a high risk of death.

Health Canada based its approval on the results of an international Phase III clinical trial known as the Recombinant Human Activated PROtein C Worldwide Evaluation in Severe Sepsis (PROWESS), which was published in the *New England Journal of Medicine* in March 2001. The trial, which included 1,690 patients, demonstrated that Xigris reduced the absolute risk of death from severe sepsis by 6.1% and the relative risk of death from severe sepsis by nearly 20%. One in five patients who would have died from severe sepsis survived because of Xigris use.

Severe sepsis is a complex syndrome that affects an estimated 28,000 Canadians. Among those who get sepsis, a staggering 30% to 50% will die.

First Therapy Approved to Specifically Treat Severe Sepsis in Canada. Press Release, Toronto, Ontario, February 18, 2003.

ACEI Improves Long-Term Outcomes for Hypertensives

A new analysis showed that first-line treatment with angiotensin-converting enzymes inhibitors (ACEI), including Vasotec® (enalapril), improved long-term outcomes in hypertensive patients and that ACEI therapy led to significant reductions in cardiovascular mortality, as well as cardiovascular events. The review of the United Kingdom General Practice Research Database (GPRD) showed that first-line treatment with ACEI was associated with a significant 37% reduction in coronary heart disease and 13% reduction in cerebrovascular events. Of the 11,249 ACEI-treated patients, 8.4% developed coronary heart disease (which included angina), compared to 15.2% of patients in the calcium channel blocker-treated group.

Patients treated with ACEI also had a significantly lower incidence of cerebrovascular events (4.4%) compared to patients treated with calcium channel blockers (6.9%). The incidence of left ventricular failure in patients treated with ACEI was 5.3%, while it was 8.1% for patients treated with calcium channel blockers.

A majority of patients on ACEI were taking enalapril (40%), with smaller proportions of patients taking captopril (28%), lisinopril (28%), or ramipril (7%).

New Data from the GPRD Study: Comparative Analysis of ACE Inhibitors and Calcium Channel Blockers for the Treatment of Hypertension in Reducing Cardiovascular Mortality and Cerebrovascular Events. Press Release, Montreal, Quebec,December 17, 2002.

Medical Briefs

Largest Study on Seizure Freedom

New long-term data published in *Epilepsy Research*, shows that Keppra® (levetiracetam) offers sustained efficacy as an add-on over the long term (54 months or 4.5 years) in reducing seizure frequency in adult patients with difficult-to-treat, partial seizures.

This was the first and largest published study to collect data on patient retention and seizure freedom rates for adults with refractory epilepsy over a long-term treatment period. Data was taken from 1,422 patients and analysed for changes in seizure frequency per week, seizure freedom, and adverse events. Patients included in the study suffered from a very refractory epilepsy, with a median seizure frequency of 2.17 per week.

The study revealed that Keppra was well tolerated and, overall, 38.6% and 20.1% of patients experienced a decrease in the numbers of seizures by at least 50% to 75% respectively. Also, 4.6% of the patients were completely seizure free from the first day of treatment until their last day, with the median duration of seizure freedom at 385 days. During the last six months of followup, 11.6% of patients were seizure-free and during the last 12 months, 8.9% were seizure-free. There was also a tendency towards a reduction in the number of additional antiepileptic drugs (AEDs) taken by patients, with 14.4% of patients taking fewer AEDs at the end of the treatment. The incidence of adverse events in this trial were similar to the incidence described in previous clinical studies.

New Data Demonstrate Keppra® Offers Sustained Efficacy, Reduction in Seizure Frequency and in Concomitant Medication. Press Release, Brussels, February 7, 2003.

A Breath of Relief: COPD Treatment

New international data shows that Advair® (salmeterol 50 µg/ fluticasone propionate 500 µg twice daily combination) is significantly more effective, when compared to the established long-acting bronchodilator, Serevent® (salmeterol), in patients with chronic obstructive pulmonary disease (COPD).

An estimated 750,000 Canadians suffer from COPD. It is the leading cause of death, second to lung cancer, and it continues to rise at a significant rate. The placebo-controlled, clinical TRial of Inhaled STeroids ANd long-acting beta$_2$ agonists (TRISTAN) conducted in 1,465 patients with moderate to severe COPD already taking treatment, compared Advair to its individual components. Results showed improvements in lung function (FEV_1) almost twice as great for Advair as for Serevent. Advair also provided significantly better control of breathlessness and a reduction in the number of night-time awakenings per week compared with Serevent.

Moderate to severe exacerbations, considered a cause for hospitalisation, were reduced by 25% compared to placebo. Acute episodes of symptom exacerbations requiring oral corticosteroids were reduced by 39%. Advair also produced a significant improvement in health status as defined by the St. George's Respiratory Questionnaire.

New Advair® Data Shows Significant Advance in COPD Treatment, Bringing hope to Canadians Suffering From This Lung Disease. Press Release, Mississauga, Ontario, February 7, 2003.

Medical Briefs

New Anemia Drug Covered by Provinces

Ontario and Quebec have joined other provinces including Alberta, Saskatchewan, British Columbia, Nova Scotia, Prince Edward Island, and Newfoundland/Labrador in reimbursing the cost of the biologic Aranesp™ (darbepoetin alfa) for patients with chronic renal failure (CRF) who also suffer from anemia.

Patients with CRF and anemia are left feeling tired and exhausted, making the simplest of tasks difficult. Securing full reimbursement in Quebec and the Special Drugs Program in Ontario represents a major advance and convenience for these patients. Aranesp can be given by subcutaneous injection or intravenous administration. Clinical studies showed patients with CRF receiving Aranesp consistently reached target hemoglobin (red blood cell) levels and required less frequent administration. Aranesp treatment can be given to patients on or off dialysis.

New Anemia Drug Now Covered by Provincial Programs in Canada. Press Release, Toronto, Ontario, February 20, 2003.

Kidney Failure Mounting in People With Diabetes

Kidney disease has increased by 150% in the past decade, mostly in people with diabetes. While controlling insulin levels in the body is the mainstay of keeping people with diabetes healthy and prolonging their lives, another vital area of their health maintenance lies in maintaining a healthy blood pressure and preventing kidney disease.

Optimal control of blood pressure often requires additional agents, such as calcium channel blockers (CCB), that cause the blood vessels to widen and relax. Although two classes of CCBs exist, many doctors remain unaware that one class can actually exacerbate and contribute to progressive kidney decline, while the other may provide benefits that are additive with angiotensin-converting enzyme inhibitors.

In a recent review article in the *New England Journal of Medicine*, it was suggested that "renal benefits from CCBs for diabetic hypertensives may only exist with treatment using a non-dihydropyridine (non-DHP) CCB, such as diltiazem and verpamil." The author, Dr. Giuseppe Remuzzi, commented that patients with diabetes who were treated with DHP CCBs, "had more severe proteinuria and more rapid decline in the glomerular filtration rate (a measure of kidney function) than those treated with other antihypertensive agents."

Confronting an Emerging Epidemic in Kidney Disease: Treating to Target or Aiming Beyond? Press Release, Toronto, Ontario, February 24, 2003.

Finding the Optimal Low-cost Therapy for ARD

Clinical trials examining the diagnosis and management of dyspepsia and acid-related diseases (ARDs) confirmed the efficacy of both Nexium® (esomeprazole magnesium trihydrate) and Losec® (omeprazole magnesium) as optimal low-cost therapies for ARDs, and showed further evidence supporting the empirical treatment approach to the primary-care management of ARDs currently affecting 8 million Canadian adults.

The Practice Audit Program study underscored the role of practice audits in improving disease managment and supports the concept that accurate pre-test assessments may warrant initiation of treatment before endoscopy or even without any need for endoscopy. The Confirmatory Acid Suppression Test (CAST) study showed that, out of 388 patients with heartburn-dominant uninvestigated dyspepsia symptoms, approximately 70% responded to once or twice-daily Nexium as early as the first week, with 80% of patients responding at four weeks. The Canadian Adult Dyspepsia Empirical Treatment study program showed that in 512 *Helicobacter pylori* negative non-heartburn dominant patients with moderate to severe dyspepsia, the success rate after four weeks of treatment was considerably greater for patients taking Losec (51%), compared to patients taking ranitidine (36%) or cisapride (31%).

The CAST study showed that treating patients with Nexium in primary-care based on symptom presentation can successfully identify patients who may respond to proton pump inhibitors without endoscopy.

Practice Audit and Clinical Trials Support Empirical Test Approach to ARDs. Press Release, Banff, Alberta, February 25, 2003.

Favourable National Report Card on Antibiotic Resistance

Canada remains a world leader in the fight against antibiotic resistance according to the National Information Program on Antibiotics (NIPA).

Data compiled by the Canadian Bacterial Surveillance Network (CBSN) showed that, in 2002, the rate of penicillin-resistant *Streptococcus pneumoniae* was only slightly up from 2001 (15.5% versus 14.4%). Rates of high-level resistance remain unchanged.

Streptococcus pneumoniae is the leading infectious cause of morbidity and mortality worldwide and is the most common bacterial cause of community-acquired infections, such as bronchitis, sinusitis, middle ear infections, and pneumonia.

Rates of penicillin-resistant *Streptococcus pneumoniae* are significantly lower in Canada than in many other parts of the world, where they range from more than 30% in parts of South America to as high as 80% in Hong Kong and South Africa. In the U.S., the latest figures show resistance at 41%, more than triple that of Canada.

Antibiotic Awareness Week Marks 75th Anniversary of the Discovery of Penicillin with Favourable National Report Card on Antibiotic Resistance. Press Release, February 25, 2003.