RGH Pharmacy E-Bulletin

Volume 48 (2): October 15, 2012

A joint initiative of the Patient Services Section and the Drug and Therapeutics Information Service of the Pharmacy Department, Repatriation General Hospital, Daw Park, South Australia. The RGH Pharmacy E-Bulletin is distributed in electronic format on a weekly basis, and aims to present concise, factual information on issues of current interest in therapeutics, drug safety and cost-effective use of medications.
Editor: Assoc. Prof. Chris Alderman, University of South Australia – Director of Pharmacy, RGH

Farnesyltransferase inhibitors in Hutchinson-Gilford progeria

Farnesyltransferase inhibitors (FTIs) are a new class of biologically active agents originally developed as potential anti-cancer drugs, and are currently unavailable in Australia. FTIs inhibit the enzyme farnesyltransferase, preventing the farnesylation and hence activation of a wide range of target proteins, including Ras (which is mutated in 30 % of all human cancers), ultimately resulting in cell growth arrest. In preclinical models, farnesyl transferase inhibitors showed great potency as a novel anti-cancer agent; yet in clinical studies, the early potential of FTIs were not realised. This was attributed to several reasons: the molecular pharmacology and biology of FTIs had not yet been fully elucidated, an escape mechanism for the inhibition by FTIs was discovered (known as geranylgeranylation) and a well-defined proof of the concept of clinical studies was lacking.

In September 2012, however, Boston Children's Hospital published the results of the trial of a repurposed FTI, lonafarnib, with highly promising findings and evidence of the potential to affect the course of Hutchinson-Gilford progeria syndrome. Hutchinson-Gilford progeria syndrome (HGPS) or progeria is an extremely rare progressive hereditary disorder (estimated to affect one in 4 million newborns worldwide) characterized by signs of premature aging, beginning in the first two years of life. The term progeria is derived from the Greek word *geras*, meaning old age. Average life expectancy is 1-20 years, with significant morbidity and mortality as a result of accelerated, progressive cardiovascular disease. HGPS is considered a segmental aging syndrome (patients do not manifest all the typical features of aging such as neurocognitive decline and increased incidence of cancer). Manifestations include slowed growth, alopecia, scleroderma, thin lips, visible veins, alopecia, arrhythmias, insulin resistance, delayed and abnormal tooth formation, stiff joints, and joint dislocation. A single gene mutation is responsible for HGPS. The mutation changes replaces the nucleotide cytosine with the nucleotide thymine at position 1824 of the gene, known as lamin A (LMNA), which results in an abnormal version of the lamin A protein known as progerin. In order for progerin to be created, a farnesyl group molecule must attach itself to the pre-lamin A protein. This abnormal version of progerin cannot be processed correctly within the cell, and incorporation of the altered protein into the lamina results in a disruption of the shape of the nuclear envelope. Eventually a build-up of this altered protein damages the structure and function of the nucleus, making cells more likely to die prematurely.

There is no known cure for progeria. Current treatment includes pharmacotherapy that may relieve or delay some of the associated signs and symptoms such as low-dose aspirin to help prevent heart attacks and stroke, statins to reduce cholesterol, anticoagulants to prevent blood clots, growth hormones to increase height and weight, and non-pharmacological therapy in the form of physical and occupational therapy. In 2005, however, research by Capell et al. of the National Human Genome Research Institute using FTIs to treat skin cells obtained from progeria patients and grown under laboratory conditions showed promise for treating HGPS. The clinical trial by Boston Children's Hospital enrolled 25 patients with classic HGPS from 16 countries, all treated with oral lonafarnib twice a day for a minimum of two years.

Primary outcome success was defined as a 50 % increase over pre-therapy in estimated annual weight gain rate, or change from pre-therapy weight loss to statistically significant weight gain: 9 patients had an increase of 50 % or more, 6 experienced a decrease of 50 % or more, and 10 remained stable. All patients improved in one or more of the secondary outcomes, which included increases in skeletal rigidity and sensorineural hearing, and decreases in arterial pulse wave velocity and carotid artery echodensity. Side effects, which improved over time for most patients, included mild diarrhoea, nausea, vomiting, anorexia, fatigue, and depressed serum haemoglobin. The results from this clinical treatment trial open up opportunities for research and pharmaceutical intervention using FTIs to reverse the dramatic structural abnormalities of the nucleus, the hallmark of cells from children with HGPS.

Acknowledgment – This E-Bulletin is based on work by Lesley Kong, Intern Pharmacist, RGH.

FOR FURTHER INFORMATION – CONTACT THE PHARMACY DEPARTMENT ON 82751763 or email: chris.alderman@rgh.sa.gov.au