

RGH Pharmacy E-Bulletin

Volume 41 (12): April 18, 2011

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.

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Pegloticase

There have been relatively few recent advances in pharmacotherapy for the treatment of gout. Current standard therapy includes the use of corticosteroids, colchicine and NSAIDs for acute flares and primarily allopurinol and probenecid as urate-lowering therapy to prevent gout flares. Uricase (urate oxidase) is an enzyme that converts urate (uric acid) to allantoin, a more water soluble metabolite and therefore more easily excreted by the kidneys. Rasburicase (Fasturtec[®]), a recombinant aspergillus-derived version of this enzyme, is used as urate-lowering therapy in the setting of tumour lysis syndrome. However, this agent has a relatively brief biological half-life and is highly immunogenic and is therefore unsuitable as maintenance therapy in chronic gout. Pegloticase (Krystexxa[®]) is a novel urate-lowering agent approved in October 2010 by the US FDA for use in treatment-failure gout. It is a modified version of uricase (conjugated with PEG), which significantly increases its active half-life and decreases immunogenicity compared with rasburicase. Pegloticase is administered as an intravenous infusion and given at a dose of 8 mg every two weeks.

Gout is a disease of monosodium urate deposition, occurring when uric acid levels are sufficiently elevated (>0.46mmol/L) for long enough that the solubility coefficient of sodium urate is exceeded and crystals form in tissues. In theory, long term use of pegloticase will enable both soluble and insoluble (crystalline) deposits of uric acid to decrease as a result of the induced concentration gradient between tissue stores and circulating urate.

One study published in 2008 by Sundy *et al* enrolled 41 patients who were hyperuricaemic (urate \geq 8mg/dl or 0.44mmol/L), and who had established and symptomatic gout (tophus, flare in previous 6 months or chronic gouty arthropathy). In addition, patients were required to have been treated unsuccessfully (treatment-failure gout) with other urate-lowering therapy (defined as failure to reduce urate to < 6mg/dl or 0.33 mmol/L with at least three months of treatment), or have intolerance or contraindication to these existing therapies. 15 patients withdrew, and only 26 completed all courses of pegloticase. This phase 2 study was randomised but open-label, and included multiple dose regimens for a total of 12 weeks. All treatment groups experienced a rapid reduction (within 6 hours) of plasma urate to \leq 6 mg/dl, sustained throughout the 12 weeks of the trial except at the lowest dose (4 mg every 2 weeks). The most responders were seen in the group given 8 mg every two weeks, however this was not statistically significant as the sample size was inadequate. Across all groups, mean time without hyperuricaemia was 75%. Of note, however, 93% of patients reported an adverse effect ranging from nausea and headache to kidney stones and muscle spasms, and infusion reactions occurred in 44% of cases. 88% of patients had an acute gout flare during the study, however these seemed to decrease with time and continued treatment. Medication for gout flare prophylaxis was allowed in the study at the discretion of the investigator. The high rates of gout flare may not be surprising given the chronic nature of the disease and prerequisite uncontrolled hyperuricaemia in the study population. Gout flare is commonly seen to occur after initiation of existing urate-lowering therapy such as allopurinol.

One significant advantage of pegloticase is that no dosage adjustment is required in renal failure. However, given the small sample size used in the study and significant safety concerns raised in the Phase 2 trial, as well as remaining unanswered questions regarding the clinical significance of potential immunogenicity and the high rates of infusion reactions and gout flare, extreme caution should be exercised in the prescribing of pegloticase. Though not available in Australia at this stage, it is anticipated that this agent will be reserved as a last-line option for treatment-failure gout where all other therapies have been conclusively unsuccessful or are absolutely contraindicated. A Phase 3 double-blinded, randomised controlled trial is currently underway but the results are not yet published.

Acknowledgment – This E-Bulletin is based on work by Stephanie Vaughan, Senior Clinical Pharmacist, RGH

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