Risk Factors for Toxicity to Allopurinol

Allopurinol is a drug used to decrease the production of uric acid in the body. It's used in Gout, kidney stones and in hyperuricemia caused by chemotherapy in cancer patients.

Skin rash is one of the most common adverse effects of Allopurinol in toxicity; it's also the most feared, because Allopurinol has been associated with life threatening severe cutaneous adverse reactions (SCAR), including drug rash with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS) and toxic epidermal necrosis (TEN). Allopurinol should be discontinued at first sign of rash. Allpurinol toxicity may also include significant hepatic disease.

Prognostic factors for these severe adverse reactions remain unclear. Many studies have been done to find risk factors for this toxicity.

In Aug 2014, a cohort study was done to investigate the relationship of dosing, renal function, plasma levels of oxypurinol (active metabolite of Allopurinol) and granulysin (cytotoxic proinflammatory molecule), the disease severity and mortality in allopurinol-SCAR. They enrolled 48 patients with allopurinol-SCAR and 138 Allopurinol tolerant controls from 2007 to 2012. The result of this study is that impaired kidney function and increased serum concentrations of oxypurinol and Granulysin were all associated with increased Allopurinol toxicity. Also, the presence of genotype HLA B*5801 was strongly associated with Allopurinol SCAR. However, the dose had no association with the disease.
Systematic review and meta-analysis in 2011 was done by Ratchadaporn Somkrua and his colleagues, after comprehensive search in databases from their inceptions to june 2011, a total of 4 studies were identified with 55 SCAR cases and 678 matched allopurinol tolerant controls. This study established a strong and significant relationship between HLA-B*5801 allele and Allopurinol-related SCAR.

Also, a retrospective review had been done in 2012 by Ágnes Kinyó and his colleagues for all patients who were referred with allopurinol induced hypersensitivity syndrome in the previous four years. During four years, 11 patients were identified with this syndrome. Their average age was 70.3 years. Before the initiation of allopurinol therapy: 36% of them had already suffered from various degrees of renal impairment, and 72% had been taking thiazide diuretics. So as a conclusion, Old age, impaired kidney function and concomitant thiazide therapy should be considered as potential risk factors for developing hypersensitivity syndrome.

As a conclusion, risk factors for Allopurinol toxicity are: renal insufficiency, old age, genetic predisposition (HLA-B*5 allele), concomitant therapy with Thiazides

References:

1. http://online.lexi.com.lib.just.edu.jo/lco/action/doc/retrieve/docid/multinat_f/4668912

2. Chung WH, Chang WC, Stocker SL, et al. Insights into the poor prognosis of allopurinol-induced severe cutaneous adverse reactions: the impact of renal insufficiency, high plasma levels of oxypurinol and granulysin. *Annals of the rheumatic diseases*. 2014; annrheumdis-2014-205577. doi: 10.1136/annrheumdis-2014-205577

3. Ratchadaporn S, Elizabeth EE, Surasak S, et al. Association of *HLA-B*5801* allele and allopurinol-induced stevens johnson syndrome and toxic epidermal necrolysis: a systematic review and meta-analysis. *BMC medical genetics*. 2011; 12: 118

4. Kinyó A, Lakatos A, Varga A, et al. allopurinol induced hypersensitivity syndrome. 2012; 153(15): 586-591

Prepared by: Roa Jaradat, Wala Shloul and Ayham Naji.