CLINICAL VIGNETTE

Allopurinol: Risk Stratification and Safe Prescription

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Brief Summary

A 52-year old Asian male presents to the clinic with fever, chills, body aches, and rash.

He has history of acute lymphoblastic leukemia (ALL), gout, MI, thyroid disease and chronic kidney disease (CKD) presents to the clinic with fever, chills, body aches, and rash.

His primary care physician (PCP) noted right sided neck pain and a new rash. Patient reports temperature of 99°F for the previous two days with neck pain associated with swallowing. His PCP ordered labs and neck ultrasound after finding new lymphadenopathy.

The patient's rash worsens, and disseminates over his entire body over the following week. He was concerned about possible infectious disease exposure and lab testing for measles was ordered. The patient was recently started on allopurinol three weeks prior. Patient was asked to stop allopurinol and a dermatology e-consult was obtained. Initial labs showed an elevated ESR/CRP, normal WBC without eosinophilia, creatinine of 1.48 (baseline) and GFR 57.

Dermatology promptly responds and notes the new onset of morbilliform rash, fever, and lymphadenopathy with recent allopurinol initiation concerning for a drug reaction with eosinophilia and systemic symptoms (DRESS). Patient was advised to go to the emergency room for an in-person evaluation.

He was evaluated at the emergency room later and started on IV steroids with additional labs to evaluate for organ damage and HLA screening. ER labs were remarkable for a suppressed white blood cell count of 3.12 without eosinophilia, stable renal function and no elevation of liver enzymes. Blood cultures were negative. The HLA-B*58:01 was negative.

Once stable, he was discharged on a prednisone taper with outpatient follow up.

Follow up with Dermatology 1 week later showed improvement of the rash, lymphadenopathy and resolution of fevers. The patient was recommended to taper prednisone to 10mg daily for 4 days and to restart if rash, lymphadenopathy, or fever recur. Follow-up thyroid testing was recommended in 3 months for sequelae of DRESS syndrome, in addition to indefinite avoidance of allopurinol.

Discussion

Allopurinol has been associated with severe cutaneous adverse reactions (SCAR), including drug reaction with eosinophilia and systemic symptoms (DRESS), toxic epidermal necrolysis (TEN), Stevens–Johnson syndrome (SJS) and allopurinol hypersensitivity syndrome (AHS). These syndromes have similar clinical features, including rash, fever, eosinophilia, hepatic and renal dysfunction.[1]

A number of risk factors for drug reaction have been identified and can be grouped into three broad categories: time/onset of medication, genetic factors/HLA and drug concentration factors (dose/renal function/concomitant use of diuretics).[1] The only current mechanism to predict and minimize risk of severe allopurinol-related adverse reactions is by screening for and modifying known risk factors.

Allopurinol related adverse effects typically occurs within the first few weeks to months after starting allopurinol.[2] In a review of 901 published cases of AHS, the median time to onset of AHS was 3 weeks, with onset of 90% of cases within the first 2 months.[2] Our patient's allopurinol was initiated 3 weeks prior to onset of symptoms.

The American College of Rheumatology guidelines recommend screening East Asian patients for the *HLA-B*58:01* genotype prior to prescribing allopurinol, to eliminate the risk of SCARs in this population.[3] American Association of Family Physicians (AAFP) recommends screening high risk patients as category B, indicating that the benefit of screening outweighs any potential harm/risk.

The frequency of HLA-B*5801 allele varies across different ethnic populations. The allele is most common in East Asian populations, including those of Han Chinese,[4,5] Korean and Thai[6] descent and much less frequently in Japanese (0.6%)[7] and European descent.[8] Although genetic factors are not modifiable, rapid tests to identify the presence of HLA-B*5801 are available. This makes screening before initiation of therapy with allopurinol practical. Our patient was screened for HLA-B*5801 with negative result. His ALL was treated with an allogenic transplant from an unrelated donor. As such, the results showed the HLA type of the donor rather than the patient.

Lastly, dose of allopurinol, renal function and diuretic therapy also increase risk of allopurinol related adverse reactions. CKD is one of the most common comorbidities in patients with gout.[9]

Risk of an adverse reaction is highest risk in those homozygous for HLA-B*5801 with eGFR <30 ml/min/1.73 m2.[10] Due to coexisting medical conditions such as cardiovascular disease, it is not uncommon for individuals requiring allopurinol to also be on diuretics. Diuretics can increase serum urate levels and also interfere with allopurinol by enhancing the renal clearance of its active metabolite oxypurinol.[10] Both these mechanisms result in needing higher doses of allopurinol to ensure effectiveness.[10]

Conclusion

Allopurinol has been associated with multiple potentially severe reactions. It is commonly used to treat gout. Risk of adverse reactions increases with 3 risk categories including: 1. Dose and time of onset 2. Underlying medical conditions such as cardiovascular disease and CKD and 3. Genetic susceptibility. While no strategy exists to predict all patients who will develop an adverse reaction, we are able to risk stratify and more safely prescribe allopurinol. We can identify high risk individuals by using genetic markers such as HLA-B*5801 testing in individuals of East Asian descent, utilizing caution with those who have CKD especially if GFR <30 by initiating with the lowest dose and slow titration. We can also identify patients who are on diuretics and use alternatives when possible. Lastly, it is important to counsel patients on the potential risks and monitor for symptoms during the window where adverse effects are most likely. By following these strategies, we may be able to more safely prescribe and avoid major complications from an otherwise important tool for gout therapy.

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