J Surg Res 2021; 4 (2): 284-286 *DOI: 10.26502/jsr.10020136*

Short Communication

Prescribing Azathioprine in Medicine and Surgery

Adel Ekladious*, Abdulrazak Mohamad

Associate professor of medicine, Faculty of health and medical sciences, University of Western Australia, 35/ Stirling Highway, Perth Western Australia 6009

***Corresponding Author:** Dr. Adel Ekladious, Associate professor of medicine, Faculty of health and medical sciences, University of Western Australia, 35/ Stirling Highway, Perth Western Australia 6009, Tel: 61499449905; E-mail: ekladiou@gmail.com

Received: 04 May 2021; **Accepted:** 10 May 2021; **Published:** 14 May 2021

Citation: Adel Ekladious, Abdulrazak Mohamad. Prescribing Azathioprine in Medicine and Surgery- A Review. Journal of Surgery and Research 4 (2021): 284-286.

Introduction

Azathioprine is the most commonly used immunosuppressive and steroid sparing agent, surgeon use it for active ulcerative colitis and pyoderma gangrenosum. The neurologists prescribe it for dermatomyositis, polymyositis and cerebral polyangiitis. The gastroenterologists use it for systemic lupus, renal physicians prescribe it for lupus nephritis, polyangiitis with granulomatosis. immunologists prescribe it for Cogan syndrome, Pemphigus [1-3]. Many heart transplant patients on long term of Azathioprine. It belongs to thiopurine group which are widely used as purine antagonists [5]. It is not an expensive medication over all, it is very short acting medication and the half-life is one hour as it converts to 6- mercaptopurine which is active metabolite and has a half-life of 4-5 hours. 6- mercaptopurine is metabolized by three separate and independent pathways:

6- mercaptopurine is metabolized to 6 thioguanine which is very active immunosuppressant, supratherapeutic level can cause sever bone marrow suppression with severe neutropenia and lymphopenia [5].

second pathway of 6- mercaptopurine is degraded by xanthine oxidase to 6-thiouric acid which cause hepatitis, in supratherapeutic level and idiosyncrancy cholestasis with any dose. It is a culprit of drug-drug interaction specially with Xanthine Oxidase inhibitor (Allopurinol) [6].

Thiopurine Methyl Transferase (TPMT) causes methylation of 6-mercapopurine to 6-methyl mercaptopurine with a process of hypermethylation. 10% of patient they have a variant TPMT genotype

polymorphism which causes Thiopurine toxicity. Asian population has genotype mutation (NUDT15) which causes severe toxicity. Clinicians should advise to check 6- thioguanine and 6-methyl mercaptopurine before starting Azathioprine [7].

Interpretation of blood tests for 6–thioguanine and 6-methylmercatpopurne, 6-Thioguanine above 400pmol correlated with bone marrow depression, Serum level between 235 and 450 is a therapeutic and correlate with clinical efficiency. Hypermethylation of 6 mercaptopurine to 6- methylmercaptourine is a serious risk hepatotoxicity. 6-methylmercaptopurine can cause vascular damage to the liver like veno-occulsive disease of the liver such as portal vein thrombosis, Budd-chairi syndrome, nodular regional hyperplasia. Hypermethylation usually occur with high level of TPMT and the high level of TMPT results in increased level of 6 methyl mercaptopurine with increased liver toxicity. The decreased level of 6-thioguanine reduces myelosuppression [8].

How to apply this in practice

6-mercaptopurine takes a long time before one can decide to stop steroid, usually clinician try to reduce the steroid to the minimum dose and reduce the side effect of steroid. The dose usually is 1 mg/kg for 3 weeks and increased to 2.5-3mg /kg body weight. This does not to apply to people with high BMI and old age. Serum Thiopurine methyltransferase is essential to check before starting Azathioprine. The elevated level of TPMT leads to hypermethylation and patient can be started on small dose of Azathioprine 1mg/kg and recheck in 6 weeks. High MCV and Lymphopenia is a marker of compliance with medication and not a marker of effectiveness of the drug (11). FULL blood count and LFT should be monitored weekly for 6 weeks and then every 6 months, or when change the dose of Azathioprine.

Low level of 6-methylmercaptopurine and 6 thioguanine is a marker of non-compliance or low level. Checking MCV and lymphocytes, low level of 6-thioguanine and high level of 6 methyl mercaptopurine means the dose is high. Therefore, either divide the dose to BD or decrease the dose and add alopurinol and check again. If the level of 6 thioguanine and 6 methyl mercaptopurine are therapeutic, continue on same dose and observe for any drug resistance.

If both level of 6-thioguanine and 6-methyl mercaptopurine are high, reduce the dose and recheck levels again. During pregnancy, if the patient is not naive, continue on the medications and have a discussion with the patient. It is not contraindicated in breast feeding patient as it does not excrete in the milk. We must review any other medication to avoid the drug-drug interaction with Warfarin, angiotensin converting enzyme inhibitors and allopurinol [8].

The risk of malignancy is low, however always encourage photoprotection by using UVA blocker.

References

1. Anstey AV, Wakelines S, Reynolds NJ. Biritish Association of Dermatologists therapy, guidelines and audit subcommittee. Guidelines for prescriping Azathioprine in dermatology. Br J Dermatol 151 (2004): 1123-1132.

2. Donoghue DP, Dawson AM, Powell-Tuck J, et al. Double-Blind withdrawal trial of Azathioprine as maintenance treatment for Crohns disease. Lancet 2 (1978): 955-957.

3. Evans C, Keevil. Effect of allopurinol on the

metabolism of Azathioprine in heart transplant patients. Transplant Proc 30 (1998): 1127-1129.

4. Loftus CG, Loftus EV, Sandbom WJ. The safety profile of Azathioprine (AZA) 6 mercaptopurine in the treatment of inflammatory bowel disease (*ABD), population based study in Olmsted country, Minnesota: AM J Gastroentrol 98 (2003): S242.

5. Chocair P, Duley J, Simmonds HA et al. low dose allopurinol Azathioprine/Cuclosporine/Prednisolne. A novel immune-suppressive regimen. Lancet 342 (1993): 83-84.

6. Sparrow MP, Hande SA, Friedman S et al. Effect of Allopurinol with clinical outcome in inflammatory bowel disease non responders to Azathioprine or 6 mercaptopurine. Clin Gastroenterol Hepatol 5(2007): 209-214.

7. Alvarez LL, Veneg ALerraas MS, Larrondo LM, et al. Quera RPS- methyl transferase gene Polymorphism in children blood doners. Rev Med Chil 137 (2009): 185-192.

8. Anasari A, Hassan C, Du J, et al. Thiopurine methyl transferase activity and use of Azathioprine in inflammatory bowel disease, aliment Pharamacol ther 16 (2002): 17453-1750.