Updated Therapeutic Options for Vitiligo patients Using Azathioprine

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Abstract

Background: Vitiligo negatively influences patient's quality of life by decreasing self-esteem and causing significant psychological distress. Its prevalence is approximately 0.1% to 2% of people including adults and children worldwide and it affects all races equally. Vitiligo is commonly known as multifactorial polygenic disorder, various theories have been found, but the exact etiology is still unknown. There are numerous treatment modalities aimed at repigmentation. The medical modalities of therapy include corticosteroids (both topical and systemic), immunomodulatory agents, phototherapy (narrow band ultraviolet B and PUVA). Azathioprine is an immunosuppressive medication. It is used in rheumatoid arthritis, granulomatosis with polyangiitis. It works via 6-thioguanine to disrupt the making of RNA and DNA by cells.

Keywords: Vitiligo, Azathioprine.

Vitiligo

Vitiligo is an acquired pigmentary skin disorder characterized by absence of pigmentary cells from the epidermis that results in well-demarcated white macules and patches that can present on any part of the body (1). Vitiligo is classified based on clinical presentation into two major forms, segmental vitiligo (SV) and NSV. NSV include acrofacial (affects the distal extremities and face), generalized (has more widespread distribution and more areas of involvement), mucosal, and universal (involves complete or nearly complete depigmentation of skin). Rare clinical variants of vitiligo such as focal, inflammatory, confetti-like or "punctate," and trichrome have been reported. (2).

Azathioprine

Azathioprine is an immunosuppressant that inhibits DNA synthesis in immune effector cells. (3). It is used in the treatment of inflammatory bowel disease (4), Churg-Strauss syndrome, autoimmune hepatitis (for maintenance treatment along with steroids) (5), chronic ITP (second-line agent), lupus nephritis, connective tissue disease, multiple sclerosis, severe myasthenia gravis, recurrent pericarditis psoriasis, non-infectious uveitis (6), relapsing polychondritis, dermatomyositis/polymyositis, erythema multiforme, severe and refractory atopic dermatitis, chronic actinic dermatitis, pyoderma gangrenosum, Behcet disease, cutaneous vasculitis, pityriasis rubra pilaris, lichen planus, bullous pemphigoid, and pemphigus vulgaris. It is also used as a maintenance treatment option for Crohn disease in children (7).
Azathioprine is a purine analogue that converts to its active metabolites, 6-mercaptopurine (6-MP) and 6-thioguanine (6-TGN), by the action of hypoxanthine-guanine phosphoribosyltransferase (HPRT) and thiopurine methyltransferase (TPMT) enzymes. It then inhibits purine synthesis. (8).

Its metabolites are incorporated into the replicating DNA and halt division. Azathioprine (AZA) metabolites may also mediate most of its immunosuppressive and toxic effects. AZA is absorbed rapidly through the GIT system and does not penetrate the blood-brain barrier. It undergoes metabolism in the liver, and excretion is via the kidneys, which increases its toxicity in renal failure (9).

The starting dose for AZA is 2 to 2.5 mg/kg/day, except for patients with TPMT or NUDT15 (Nudix Hydrolase15) gene mutation, in which the starting dose is lower than normal (10).

Dose adjustments are necessary for hepatic and kidney disease. AZA tablets may be administered after meals to decrease adverse GI effects. (11).

**Side Effects**
Frequent side effects include nausea which is dose dependent (Early-onset nausea usually resolves without dose alteration), fever, fatigue, arthralgias/myalgia and Bone marrow suppression causing pancytopenia, thrombocytopenia, leukopenia which is dose-dependent, life-threatening. This complication correlates with the 6-TGN level. There is a higher risk of myelosuppression in patients who take allopurinol or ACEI and in renal insufficiency (12).

Other side effects include rash, hepatotoxicity, hepatic injury correlates with a 6-MP level of more than 5700 pmol/, infections (7.4%) with concomitant use of AZA and steroids will increase the risk of pneumocystis carinii pneumonia in leukopenic patients, Hypersensitivity erythema nodosum and kidney damage are other side effects of azathioprine (13).

**Rare side effects** include Diarrhea Carcinogenesis, cutaneous hyperkeratosis nonmelanoma skin cancer (SCC) and Pancreatitis (3.3%): more in females with Crohn disease. Pancreatitis is dose-dependent and usually happens in the first six weeks. In the case of pancreatitis, discontinue AZA (14).

Other rare side effects are alopecia including telogen effluvium, anagen effluvium, and plica neuropathic, Macrocytic anemia, Sweet syndrome (acute febrile neutrophilic dermatosis) Pneumonitis and Tremor (15).

**Contraindications**
Hypersensitivity and Pregnancy or plan for pregnancy (Contraception recommended) as AZA can increase the risk of spontaneous miscarriage, low birth weight, and preterm delivery. Although data in systemic lupus erythematosus (SLE) and renal transplant patients showed safety in pregnancy. In some specific conditions like SLE and antiphospholipid antibody syndrome, the benefits of taking immunosuppressive medications are more than harms in keeping the mother safe (16).
It is also contraindicated in breastfeeding as 6-MP was present in breast milk of women who take azathioprine (17).

Relative Contraindications
Allopurinol intake concomitantly with AZA due to severe myelosuppression and Cyclophosphamide or chlorambucil treatment in the past (18).

Monitoring
It usually requires 6 to 8 weeks for AZA to work. The recommendation is to consider stopping the medication if there is no improvement in 3 months. Checking TPMT activity is suggested before starting the medication (7). Test the patient for hepatitis B and C and PPD. A pregnancy test before treatment initiation is also a recommendation (18).

Complete blood count (CBC) and liver function test (LFT) monitoring weekly are recommended initially for the first 4 to 8 weeks. CBC and LFT should get checked every three months for the rest of the treatment once the maintenance dose is achieved. However, it is advisable to check CBC and LFT more frequently in patients with kidney or renal diseases or elderly patients on high dosages of AZA or low TPMT activity. If labs show leukopenia (WBC less than 3 x 10^9/L), thrombocytopenia (platelet less than 120 x 10^9/L), or transaminitis (liver biochemistry more than half of the normal upper limit), the medication should be stopped (19).

If patients have abdominal pain or severe nausea/vomiting, serum amylase requires checking to rule out pancreatitis. Lymph node and skin examination should be done. If a generalized wart occurs, the AZA dose should be reduced or switched to another agent (18).

Some studies suggested monitoring the level of AZA metabolites (e.g., 6-TGN and 6-MP) to avoid specific complications (20).

Toxicity
Toxicity symptoms include gastrointestinal symptoms, bradycardia, hepatotoxicity, myelosuppression. Acute toxicity usually happens when more than 1.5 times of daily dose is taken by the patient (21). No specific antidote is known for AZA. In severe cases of toxicity, dialysis is permissible as AZA is dialyzable. If severely leukopenic, thrombocytopenic, or infection, treatment should stop (22).

Radmanesh and Saedi performed a study on 60 patients randomized into two groups. The first group received azathioprine calculated at 0.60-0.75 mg/kg per day (maximum dosage 50 mg) combined with twice-weekly oral psoralen (methoxypsoralen 0.3-0.4 mg/kg) plus UVA. The second group only received oral psoralen plus UVA (PUVA). Both groups were followed for 4 months. The results exhibited earlier repigmentation at fifth session with greater repigmentation (58.4%) in the combination group compared with the oral PUVA monotherapy group at eighth session with 24.8% repigmentation. (23).
There is another study of its use in vitiligo comparing azathioprine 50 mg twice daily to betamethasone 5 mg on 2 consecutive days every week for 6 months. Remarkable improvements were observed in both groups, and the authors suggest that both therapies are equally effective in vitiligo (24).

References


