Mellen Center Approaches: Azathioprine and Multiple Sclerosis

Is Azathioprine effective in relapsing MS?

There are multiple randomized trials of azathioprine vs placebo in the literature with variable study methodology robustness. However there are some trials with high quality information (ie blinding, concealment allocation, patient tracking, outcome measures) showing that there are reductions in attack frequency, EDSS measures, and MRI measures. In general efficacy is comparable to presently Disease Modify Agents though there are no head to head trials. Most of the trials of azathioprine predated the availability of DMA.

BEST RESOURCE: Casetta, I., Iuliano, G., Filippini, G. Azathioprine for multiple sclerosis. Cochrane Database of Systematic Reviews. 2008;2

Massacesi L, et al. Efficacy of azathioprine on multiple sclerosis new brain lesins evaluated using magnetic resonance imaging. Arch Neurol. 2005;62:1843-1847

Who would we use azathioprine in?

In general due to side effect profile and lack of FDA approval in MS, azathioprine is used in relapsing MS patients who either are unable to take disease modifying agents or are unwilling to use injectables or who lack financial resources to pay for injectable agents. Add on use of azathioprine has been studied in the literature but outcome data is less robust for this use.

RESOURCE:

Mellen Center Consensus

What are the side effects of azathioprine in MS?

Overall adverse reactions in trials of azathioprine were acceptable. 9% of azathioprine patients and 2% of controls had gastrointestinal disturbances in a pooled analysis of trials (Casetti 2008).Other side effects seen in excess of placebo rates were cutaneous rash (5 vs 3%), leucopenia <3000wbc/mm3 (2%), Macrocytic anemia (3 vs 0.4%), abnormal liver function tests (8 vs 1%). Deaths in two trials were reported and were due to various causes including pneumonia, urinary tract infection, carcinoma, suicidal overdose, aortic aneurysm rupture, and accidental causes. In one study there were 9 deaths in the azathioprine group and 2 in placebo, in another there were 1 in the azathioprine group and 2 in placebo.

There is a potential lifetime risk of increased rates of malignancy with long term use of azathioprine. Studies of long term use indicate that use over 10 years of continuous therapy or total lifetime dosages exceeding 600 grams raise this risk and probably should be avoided.

BEST RESOURCE: Casetti, 2008

Confavreux C, et al. Risk of Cancer from azathioprine therapy in multiple sclerosis: a case-control study. Neurology 1996;46:1607-1612

What is the dose of azathioprine and how should it be titrated?

In trials in MS the maintenance dose of azathioprine was between 2.0 and 3.0 mg/kg/day in divided doses. Dose titration protocols varied among studies. There is no consensus statement in the literature about dosing. Most trials targeted a dose that did not lower total white blood count below 3,000 wbc/mm3.

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The Mellen Center approach is to calculate a target dose based on 2.5 mg/kg per day if there are no concurrent immunosuppressing agents, and 1.5 mg/kg/day if on other agents concurrently. The medication dose is rounded down to the nearest 50 mg increment. Medication is begun with 50 mg orally daily, and titrated as tolerated by 50 milligrams every 2 weeks up to the target dosing. Dosage may be lowered for leucopenia, elevated liver function tests, MCV elevations above 110 or anemia, or due to dose related side effects of fatigue or nausea.

BEST RESOURCE: Casetti, 2008

Gauthier SA, Weiner HL Use of cyclophosphamide and other immunosuppressants to treat multiple sclerosis. In Cohen JA, Rudick RA Multiple sclerosis therapeutics. United Kingdom, Informa. 2007

What contraindications to azathioprine are there?

Azathioprine is contraindicated in pregnancy or with breast feeding, with prior azathioprine hypersensitivity. There is a higher risk of toxicity in patients with low or absent TPMT (thiopurine transferase) concentrations due to lowered metabolism of azathioprine and higher circulating levels.

Patient on ACE inhibitors should not concurrently use azathioprine due to altered metabolism of azathioprine.

BEST RESOURCE: Micromedex

What initial blood work and follow up blood work is needed?

The Mellen Center Consensus is to do a baseline CBC, renal and liver functions. It was recommended to also test for TPMT status and avoid or significantly reduce dosing and slow dose titration in patients with a low or absent TPMT status. Thereafter monthly CBC and CMP x 3 months then every 3 months thereafter. Dose adjustments should be made for WBC <3,000 mm3, MCV >110 or anemia with Hgb <10.5, or for 2.5 or greater increase in baseline SGOT or SGPT.

REFERENCE:

Mellen Consensus

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