Title: Use of Azathioprine in Adults: Safety

Date: 29 August 2014

Research Question

What is the clinical evidence regarding the adverse events associated with the use of azathioprine for any indication?

Key Findings

Nine systematic reviews, one randomized controlled trial, and six non-randomized studies included clinical evidence regarding adverse events associated with the use of azathioprine.

Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2014, Issue 8), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. A methodological filter was applied to a focused search (main concept appearing in the title or major subject heading) to limit retrieval to health technology assessments, systematic reviews and meta-analyses. An adverse events filter was applied to a broader search (main concept appearing in the title, abstract or subject heading) to limit retrieval to articles containing safety data. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2009 and August 26, 2014. Internet links were provided, where available.

The summary of findings was prepared from the abstracts of the relevant information. Please note that data contained in abstracts may not always be an accurate reflection of the data contained within the full article.

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SELECTION CRITERIA

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RESULTS

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials and non-randomized studies.

Nine systematic reviews (SR), one randomized controlled trial (RCT), and six non-randomized studies (NRS) included clinical evidence regarding adverse events associated with the use of azathioprine. No health technology assessments were identified.

Additional references of potential interest are provided in the appendix.

OVERALL SUMMARY OF FINDINGS

The summary of adverse events reported in the included studies is grouped below according to disease or procedure.

**Crohn’s disease**
Three SRs\(^1\,5\,9\) reported adverse events in patients receiving azathioprine or 6-mercaptopurine (both purine analogues) for Crohn’s disease. All reviews reported adverse events common to treatment with both azathioprine and 6-mercaptopurine:

- leukopenia\(^1\,5\,9\)
- arthralgia\(^1\)
- abdominal pain or severe epigastric intolerance\(^1\)
- elevated liver enzymes\(^1\)
- nausea and vomiting\(^1\,5\,9\)
- pancreatitis\(^1\,5\,9\)
- anemia\(^1\)
- exacerbation of Crohn’s disease\(^1\)
- nasopharyngitis\(^1\)
- flatulence\(^1\)
- allergic reactions\(^5\,9\)
Inflammatory bowel disease
Two SRs\textsuperscript{2,8} reported adverse events in patients receiving azathioprine or 6-mercaptopurine for inflammatory bowel disease (IBD). One NRS\textsuperscript{16} reported adverse events in patients receiving only azathioprine. Adverse events reported by the studies were:

- lymphoma\textsuperscript{2}
- myelotoxicity\textsuperscript{8}
- hepatotoxicity\textsuperscript{8}
- pancreatitis\textsuperscript{6}
- gastrointestinal intolerance\textsuperscript{8}
- herpes flares\textsuperscript{16}
- appearance or worsening of viral warts\textsuperscript{16}

One SR\textsuperscript{4} and one NRS\textsuperscript{13} focused on adverse pregnancy outcomes in patients receiving purine analogues for IBD. The SR\textsuperscript{4} reported that exposure to either of the drugs in women was associated with preterm birth, but not with low birth weight or congenital abnormalities; and that exposure to the drugs in men at the time of conception was not associated with congenital abnormalities. The NRS\textsuperscript{13} found that the risk of pregnancy complications was not increased and the drugs seemed to be safe for the newborn.

Azathioprine combined with anti-TNF agents for rheumatologic and non-rheumatologic diseases
One SR\textsuperscript{3} reported an increased risk of tuberculosis reactivation when azathioprine was combined with anti-TNF (anti-tumour necrosis factor) agents.

Systemic lupus erythematosus (SLE)
One SR\textsuperscript{6} reported that there was an increased rate of hematological cytopenias with azathioprine in patients with SLE.

Ulcerative colitis
One SR\textsuperscript{7} and one NRS\textsuperscript{14} reported adverse events in patients receiving azathioprine or 6-mercaptopurine for ulcerative colitis; one RCT\textsuperscript{10} reported on adverse events with axothioprine only. Reported adverse events in the studies were:

- acute pancreatitis\textsuperscript{7}
- significant bone marrow supression\textsuperscript{7}
- lymphoma\textsuperscript{14}
- serious infection\textsuperscript{10}

Organ transplantation
Three non-randomized studies\textsuperscript{11,12,15} reported adverse events in patients receiving azathioprine following organ transplantation:

- increased risk for myelodysplastic syndromes\textsuperscript{11}
- alternaria infection\textsuperscript{12}
- fungal skin infection\textsuperscript{12}
- lymphoproliferative disorder\textsuperscript{12}
- infectious viral warts\textsuperscript{15}
REFERENCES SUMMARIZED

Health Technology Assessments
No literature identified.

Systematic Reviews and Meta-analyses


Randomized Controlled Trials


Non-Randomized Studies


PREPARED BY:
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APPENDIX – FURTHER INFORMATION:

Non-Randomized Studies – Non-North American populations


Review Articles


Government Safety Advisories/Alerts

