Azathioprine for treating rheumatoid arthritis (Review)

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[Intervention Review]

Azathioprine for treating rheumatoid arthritis

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ABSTRACT

Background

Azathioprine is a purine analogue with immunosuppressive properties. Although several trials have reported a beneficial effect in patients with rheumatoid arthritis (RA), because of concerns over its safety it is generally used only in severe RA.

Objectives

To assess the short-term effects of azathioprine for the treatment of rheumatoid arthritis (RA).

Search methods

We searched the Cochrane Musculoskeletal Group's trials register, the Cochrane Controlled Trials Register (issue 3, 2000), Medline up to and including August 2000 and Embase from 1988 to August 2000. We also conducted a handsearch of the reference lists of the trials retrieved from the electronic search.

Selection criteria

All randomized controlled trials and controlled clinical trials comparing azathioprine against placebo in patients with rheumatoid arthritis.

Data collection and analysis

Data was extracted independently by two reviewers (CS, EB); disagreements were resolved by discussion or third party adjudication (MS). The same reviewers (CS, EB) assessed the methodological quality of the trials using a validated quality assessment tool. Rheumatoid arthritis outcome measures were extracted from the publications for the six-month endpoint. The pooled analysis was performed using standardized mean differences for joint counts, pain and functional status assessments. Weighted mean differences were used for erythrocyte sedimentation rate (ESR). Toxicity was evaluated with pooled odds ratios for withdrawals and for adverse reactions. The 95% confidence intervals (95% CI) are presented. A chi-square test was used to assess heterogeneity among trials. Fixed effects models were used throughout, since no statistical heterogeneity was found.

Main results

Three trials with a total of 81 patients were included in the analysis. Forty patients were randomized to azathioprine and forty-one to placebo. A pooled estimate was calculated for two outcomes. A statistically significant benefit was observed for azathioprine when compared to placebo for tender joint scores. The standardized weighted mean difference between treatment and placebo was -0.98 (95% CI -1.45, -0.50). Withdrawals from adverse reactions were significantly higher in the azathioprine group OR=4.56 (95% CI 1.16, 17.85).

Authors' conclusions

Azathioprine appears to have a statistically significant benefit on the disease activity in joints of patients with RA. This evidence however is based on a small number of patients, included in older trials. Its effects on long-term functional status and radiological progression were not assessed due to lack of data. Toxicity is shown to be higher and more serious than that observed with other disease-modifying anti-rheumatic drugs (DMARDs). Given this high risk to benefit ratio, there is no evidence to recommend the use of azathioprine over other DMARDs.

PLAIN LANGUAGE SUMMARY

Azathioprine for treating rheumatoid arthritis

Azathioprine is a drug that suppresses the immune system. This review includes three trials with a total of 81 patients. Forty patients were given azathioprine and forty-one were given placebo. Patients taking azathioprine had lower tender joint scores when compared to patients taking placebo. Significantly more patients in the azathioprine group withdrew from the studies due to adverse reactions compared to patients in the placebo group.

This evidence is based on a small number of patients in older trials. These findings suggest that several other drugs should be used before considering azathioprine for a patient with rheumatoid arthritis.

BACKGROUND

Azathioprine is a purine analogue with immunosuppressive properties. Although several trials have reported a beneficial effect in patients with rheumatoid arthritis (RA), because of concerns over its safety it is generally used only in severe RA.

OBJECTIVES

To evaluate the short-term effects of azathioprine for the treatment of RA, by conducting a systematic review of randomized controlled trials (RCTs) and controlled clinical trials (CCT) comparing azathioprine and placebo.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials and controlled clinical trials, with a minimum duration of six months.

Types of participants

All Adult patients with a diagnosis of rheumatoid arthritis.

Types of interventions

Azathioprine - minimum dosage 2 mg/kg/day, oral administration versus a placebo.

Types of outcome measures

Efficacy

The entire outcome measures in OMERACT (Outcome Measures for Rheumatoid Arthritis Clinical Trials) (OMERACT 1993, Felson 1993) were included for potential analysis, although only some were consistently reported across trials.

OMERACT measures for efficacy include:
a) Number of tender joints per patient
b) Number of swollen joints per patient
c) Pain
d) Physician global assessment
e) Patient global assessment
f) Functional status
g) Acute phase reactants
h) Radiological damage
Withdrawals and dropouts - these were analyzed as:
a) Total number of withdrawals and dropouts
b) Number of withdrawals from lack of efficacy
c) Number of withdrawals from concurrent illness
d) Number of withdrawals due to adverse reactions
e) Number of withdrawals due to system-specific adverse reactions (e.g. gastrointestinal, renal, etc.)
Adverse reactions - these were analysed as number of system-specific adverse reactions grouped as follows:
a) Gastrointestinal
b) Muco-cutaneous
c) Renal toxicity
d) Liver toxicity
e) Haematological
f) Neurological (headache, dizziness, tingling)
g) Miscellaneous adverse reactions

Search methods for identification of studies

1. Electronic searches
We searched the Cochrane Musculoskeletal Group trials register and the Cochrane Controlled Trials Register (CCTR) (issue 3, 2000), MEDLINE (up to August 2000) and EMBASE (1988 to August 2000), with a strategy similar to the one used for Medline.
2. Hand searches
Reference lists of all the trials selected through the electronic search were manually searched to identify additional trials.

Data collection and analysis

Data extracted from the publications included study characteristics and outcome measures of efficacy and toxicity. Data was extracted independently by two reviewers (CS, EB); disagreements were resolved by discussion or third party adjudication (MS).
Efficacy
The results on efficacy were analysed for the 6-month endpoint when available. This endpoint was reported in two of the trials and was thought to be the minimum required time to adequately assess the efficacy of azathioprine. One trial (Urowitz 1973) reported outcomes at 16 weeks, these are included with the 6-month data. When the standard deviation (SD) was not reported we estimated it from the coefficient of variation (CV = SD/mean) from other included trials and weighted it by sample size. In the case of ESR we used a CV = 0.7 for both treatment and control groups. This value was based on other clinical trials in RA. We thought this procedure would introduce less bias than excluding the trial altogether.
End-of-trial results were pooled using standardized weighted mean differences (SMD) for joint scores. This was necessary because of the variation in the outcome measures included in each study (e.g. joint count, articular index). End of trial results is reported for swollen joint counts and ESR values. Change from baseline scores is reported for pain and functional status. Trial results were entered in RevMan 3.1.1 using the same direction to enable the pooling of results where the lowest value was improvement and the highest value was worsening. Negative values in standardized weighted means indicate a benefit of the active drug over placebo. ESR results were pooled using a weighted mean difference (WMD). Negative values also indicate a benefit for azathioprine.
Withdrawals and dropouts
Withdrawals and dropouts were generally pooled at the end of the study. Toxicity was analysed using a pooled odds ratio for total withdrawals from adverse reactions, and withdrawals for system-specific adverse reactions. Adverse reactions not causing withdrawal were analysed using a pooled odds ratio for system-specific adverse reactions.
Adverse reactions
Adverse reactions were generally reported as number of events in total. Some patients experienced more than one adverse reaction. Each reaction was included in the appropriate system and a pooled odds ratio for total number of events per total number in the treatment group was calculated.
The heterogeneity of the trials for each pooled analysis was estimated using a chi-square test. No heterogeneity was found so fixed effects models were used throughout.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.
Three clinical trials met the inclusion criteria (Levy 1972 (abstract), Urowitz 1973, Woodland 1981). Azathioprine was administered orally at a dose ranging from two to three mg/kg/day. Woodland reported data at six months; Urowitz conducted a 32-week crossover trial. Data was reported for the first period ending at 16 weeks and only this data was included. Levy conducted a six-month crossover trial and reported only combined data from both periods.
All patients were adults with active rheumatoid arthritis. Urowitz reported a mean duration of disease of 13.6 yr. (SD 13.3). The

other two studies did not report disease duration See 'Table of Included Studies' for other study characteristics.

Risk of bias in included studies

The methodological quality of the studies was assessed by two of the investigators (CS, EB) using a quality scale validated and published by Jadad 1996. This scale includes an assessment of randomization, double-blinding procedures and description of withdrawals. The possible range of scores is 0 (worst) to five (best). Two (Urowitz 1973, Woodland 1981) received a score of three and one (Levy 1972) a score of two. The Urowitz trial was assessed to have adequate allocation concealment; the other two were unclear

Effects of interventions

For the most part, trials did not report data for similar outcomes. A pooled estimate of effect could be obtained for two outcomes - tender joint scores and ESR values. Number of swollen joints, pain, and functional status outcomes were each reported by only one trial. No trials reported physician or patient global assessment scores. Woodland reported patient assessments of joint symptoms in a visual analogue scale, which we considered as pain and in an ordinal scale (not included in review).

Overall, when pooling the studies, 40 patients received azathioprine and 41 placebo. The pooled result for tender joint scores indicated that azathioprine was statistically significantly superior to placebo: SMD -0.98 [95% CI -1.45, -0.50]. Urowitz reported a statistically significant improvement in swollen joints: SMD -2.44 [95% CI -3.79, -1.10] and Woodland reported statistically significant improvement in pain assessments using change from baseline values: SMD -1.05 [95% CI -1.85, -0.25]. The difference in ESR favoured azathioprine but did not reach statistical significance: WMD -12.94 [95% CI -33.94, 8.05].

Analysis of withdrawals and dropouts was available for two trials (Urowitz 1973, Woodland 1981), and adverse reactions not leading to withdrawal was available for one (Urowitz 1973). Overall, patients on azathioprine were 4.6 times more likely to withdraw than those receiving placebo [95% CI 1.16, 17.85]. All withdrawals were due to adverse reactions. Gastrointestinal (5/34 = 15%) and muco-cutaneous symptoms (4/15 = 26%) and hematological disturbances (3/34 = 9%) were the most frequent reactions responsible for azathioprine discontinuation.

Leukopenia was reported in five patients but it was corrected by lowering the dose of azathioprine. Because of the small numbers of patients, only gastrointestinal adverse reactions reached statistical significance, OR=7.81 [95% CI 1.24, 49.19]. Statistically significant heterogeneity was not observed,

DISCUSSION

Azathioprine is a DMARD with immunosuppressive properties, which has been used in RA mostly after failure with other DMARDs. It has been used both alone and in combination with other second line agents.

The purpose of this systematic review was to evaluate the efficacy and toxicity of azathioprine for the treatment of patients with RA, when compared to placebo. We only included in this review placebo-controlled RCTs and CCTs, reporting results at approximately six months. The dosage of azathioprine in these trials was the usually accepted, 2.0 - 3.0 mg/kg/day. Woodland 1981, tested 1.25 mg/kg/day dose but the results were not included as this dose was thought to be subclinical. Only three trials complied with our selection criteria, all of them published before OMERACT and the American College of Rheumatology (ACR) agreed on a core set of measures for RA (OMERACT 1993, Felson 1993). Only two outcomes were reported by two or more studies and could be pooled (tender joints and ESR). A few other outcomes were measured and reported by just one trial. Overall, the review included 40 patients receiving azathioprine and 41 placebo. Statistically significant differences between placebo and azathioprine were observed for tender joints in the pooled results (all three trials), swollen joint scores (one trial), and patient's assessment of joint symptoms (one trial; we considered this measure as overall pain). No differences were observed for ESR. None of the studies examined function with comprehensive functional scales and therefore, this outcome could not be adequately assessed in our meta-analysis. No studies examined radiological progression.

The effect size for tender joint counts was -0.98, and for swollen joint counts -2.44 which can be considered as large and clinically significant effects. These effect sizes are larger than those observed for other DMARDs, which are usually around 0.5 (Clark 1998, Suarez-Almazor 1998a, Wells 1998). Nevertheless, the sample sizes were very small, with large confidence intervals, overlapping with the pooled results of the other placebo-controlled meta-analyses, for example, methotrexate. Head to head comparisons between azathioprine and gold, chloroquine, methotrexate, cyclophosphamide and D-penicillamine have not shown an efficacy advantage for azathioprine (Dwosh 1977, Paulus 1984, Halberg 1984, and Jeurissen 1991).

Overall, patients receiving azathioprine were more likely to withdraw from the study, and were five times more likely to discontinue the drug because of adverse effects. There are additional concerns from longer-term observational studies about serious toxicity including liver function abnormalities, increased cancer rates and infection (Whisnant 1982, Singh 1989).

The results of our review do not support increased efficacy from the use of azathioprine when compared to other DMARDs, with lower toxicity profiles. The evidence for efficacy is based on a very small number of patients, and it is possible that publication

bias may have occurred with only large positive findings being published, since trials of this size showing a result comparable to other DMARDs would not have reached statistical significance.

AUTHORS' CONCLUSIONS

Implications for practice

Azathioprine appears to have beneficial effects in the short-term treatment of patients with RA (six months). Nevertheless, its efficacy cannot be considered to be larger than that observed for other DMARDs, and its toxicity profile is significantly more severe. These findings suggest that several other DMARDs should be used before considering azathioprine for a patient with rheumatoid arthritis.

Implications for research

The evidence for the efficacy of azathioprine is poor. No new placebo-controlled trials are recommended. Drug-to drug comparisons trials may be appropriate in a population of severe RA patients unresponsive to other DMARDs with milder toxicity profiles.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Levy 1972

Methods	Allocation: randomized Blinding: double blind Design: crossover trial, two 6 month periods Sample size at entry: 18. AZA n=9, placebo n=9 Intention to treat analysis
Participants	Country: USA Patients with active RA Age: not reported Duration of disease: not reported Females: not reported Rheumatoid Factor: not reported Concomitant use of steroid or DMARD: not reported Previous use of DMARDS: not reported
Interventions	Azathioprine 3 mg/kg/day vs placebo Treatment duration: two 6 month periods
Outcomes	Joint count was entered as tender joint count
Notes	Quality score: 2 Allocation concealment: B Results: end of trial, combined both periods. sd calculated from SE using n=18

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Urowitz 1973

Methods	Allocation: randomized Blinding: double blind Design: crossover trial, two 16 wk periods Sample size at entry 19: AZA n = 9, placebo n = 10 Analysis of completers
Participants	Country: Canada Patients with active RA Age: mean=53.6 yr (sd 12.3) Duration of disease: mean=13.6 yrs (sd 13.3) Female: 73.7%

Urowitz 1973 (*Continued*)

	RF: not reported Concomitant steroid use: intra-articular only Concomitant use of DMARD: one on myochrysine Previous use of DMARDS: all
Interventions	Azathioprine 2.0 -2.5 mg/kg/day (100-150 mg/day in PM) Duration of trial: period 1 = 16 wks, period 2 = 16 wks
Outcomes	Articular index Active joint count was reported as swollen joint count ESR New erosions
Notes	Quality score: 3 Allocation concealment: A Reported: first period results for joint count (swollen joints) and articular index (tender joints) Reported ESR results on 17 patients end of trial only. sd was imputed using a coefficient of variation = 0.70 derived from other trials

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Woodland 1981

Methods	Allocation: minimisation. stratified by severity and duration Blinding: double blind Design: parallel study, two doses AZA vs placebo Sample size at entry 42. AZA 1.25 mg/kg/day n = 14 (not included), AZA 2.50 mg/kg/day n = 15, placebo n=13 Intention to treat analysis
Participants	Country: UK Patients with active RA. Age: > 20 yrs Duration of disease: not reported. Female: 66.7% RF: 100% Concomitant use of steroids: not reported Concomitant use of DMARDS: none Previous use of DMARDS : none in past 3 months
Interventions	AZA 1.25 mg/kg/day (not included) AZA 2.50 mg/kg/day Placebo Duration of treatment: 24 weeks

Woodland 1981 (*Continued*)

Outcomes	Joint score = tender joints: max score 16 Patient assessment: only VAS results included Function: Steinbrocker ESR
Notes	Quality score: 3 Allocation concealment: B Computed end of trial results from change scores for tender joints. sd imputed: weighted average of coefficients of variation (CV=sd/mean) from other included trials. Change scores and sd reported for pain and functional status

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Barnes 1969	No OMERACT outcomes reported.
Cade 1976	No placebo results.
De Silva 1981	Studied effect of withdrawal of AZA.
Dixon 1971	No OMERACT outcomes reported.
Goebel 1976	Crossover trial: no first period data, reported % change at end of trial
Heurkens 1991	No placebo group results.
Levy 1975	Drug A/drug B/placebo crossover trial. No first period results, all placebo group results combined into one. No dose reported
Mason 1969	No OMERACT outcomes reported.
Nicholls 1973	Outcomes for vasculitis only.
Pedersen 1984	No OMERACT results reported.

DATA AND ANALYSES

Comparison 1. Azathioprine vs. placebo - Efficacy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Joint scores and pain	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Tender joints	3	81	Mean Difference (IV, Fixed, 95% CI)	-3.08 [-5.24, -0.93]
1.2 Swollen joints	1	17	Mean Difference (IV, Fixed, 95% CI)	-18.0 [-24.76, -11.24]
1.3 Pain (change scores)	1	28	Mean Difference (IV, Fixed, 95% CI)	-25.09 [-42.11, -8.07]
2 Global assessment of efficacy and function	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 Functional status (change scores)	1	28	Mean Difference (IV, Fixed, 95% CI)	-0.24 [-0.79, 0.31]
3 ESR	2	62	Mean Difference (IV, Fixed, 95% CI)	-12.94 [-33.94, 8.05]

Comparison 2. Azathioprine vs. placebo - Withdrawals and dropouts

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Withdrawals: global reasons	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 Withdrawals: total	2	64	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.56 [1.16, 17.85]
1.2 Withdrawals: lack of effect	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
1.3 Withdrawals: concurrent illness	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
1.4 Withdrawals: adverse reactions	2	64	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.56 [1.16, 17.85]
2 Withdrawals: specific adverse reactions	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
2.1 Withdrawals: Gastrointestinal adverse reactions	2	64	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.81 [1.24, 49.19]
2.2 Withdrawals: Mucosal / cutaneous adverse reactions	1	28	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.48 [0.52, 23.37]
2.3 Withdrawals: Hematological abnormalities	2	64	Peto Odds Ratio (Peto, Fixed, 95% CI)	6.84 [0.69, 68.05]
2.4 Withdrawals: Neurological adverse reactions (headache, dizziness)	1	28	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.77 [0.17, 18.66]
2.5 Withdrawals: Miscellaneous adverse reactions	1	28	Peto Odds Ratio (Peto, Fixed, 95% CI)	6.47 [0.13, 329.19]

Comparison 3. Adverse reactions not requiring withdrawal

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adverse reaction by specific system	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 Adverse reactions: Gastro intestional	1	36	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.44 [0.04, 4.51]
1.2 Adverse reactions: Mucosal / cutaneous	1	36	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.46 [0.72, 77.01]
1.3 Adverse reactions: Hematological	1	36	Peto Odds Ratio (Peto, Fixed, 95% CI)	8.49 [1.31, 54.86]

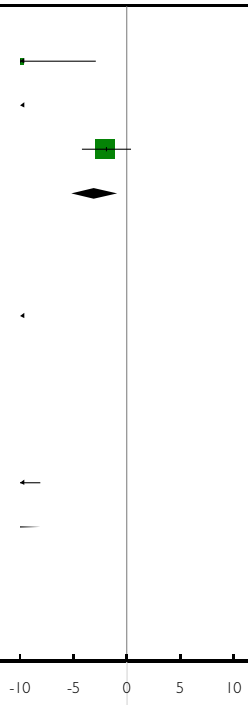
Analysis 1.1. Comparison 1 Azathioprine vs. placebo - Efficacy, Outcome 1 Joint scores and pain.

Review: Azathioprine for treating rheumatoid arthritis

Comparison: 1 Azathioprine vs. placebo - Efficacy

Outcome: 1 Joint scores and pain

Study or subgroup	AZA N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Tender joints							
Levy 1972	18	6 (8.49)	18	16 (12.73)		9.3 %	-10.00 [-17.07, -2.93]
Urowitz 1973	7	72 (17)	10	168 (48)		0.4 %	-96.00 [-128.31, -63.69]
Woodland 1981	15	2.91 (3.16)	13	4.82 (2.96)		90.3 %	-1.91 [-4.18, 0.36]
Subtotal (95% CI)	**40**		**41**			**100.0 %**	**-3.08 [-5.24, -0.93]**
Heterogeneity: Chi² = 36.48, df = 2 (P<0.00001); I² =95%							
Test for overall effect: Z = 2.80 (P = 0.0051)							
2 Swollen joints							
Urowitz 1973	7	19 (7)	10	37 (7)		100.0 %	-18.00 [-24.76, -11.24]
Subtotal (95% CI)	**7**		**10**			**100.0 %**	**-18.00 [-24.76, -11.24]**
Heterogeneity: not applicable							
Test for overall effect: Z = 5.22 (P < 0.00001)							
3 Pain (change scores)							
Woodland 1981	15	-38.74 (25.59)	13	-13.65 (20.31)		100.0 %	-25.09 [-42.11, -8.07]
Subtotal (95% CI)	**15**		**13**			**100.0 %**	**-25.09 [-42.11, -8.07]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.89 (P = 0.0039)							
Test for subgroup differences: Chi² = 22.55, df = 2 (P = 0.00), I² =91%							

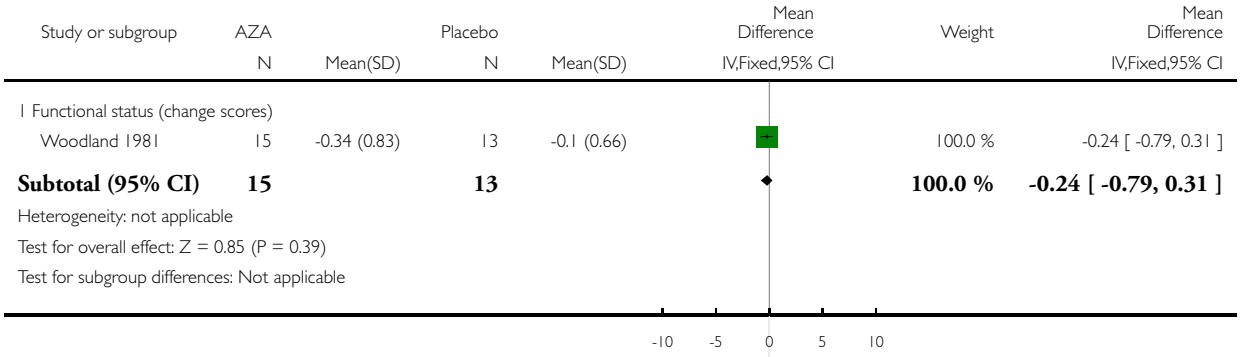


Analysis 1.2. Comparison 1 Azathioprine vs. placebo - Efficacy, Outcome 2 Global assessment of efficacy and function.

Review: Azathioprine for treating rheumatoid arthritis

Comparison: 1 Azathioprine vs. placebo - Efficacy

Outcome: 2 Global assessment of efficacy and function

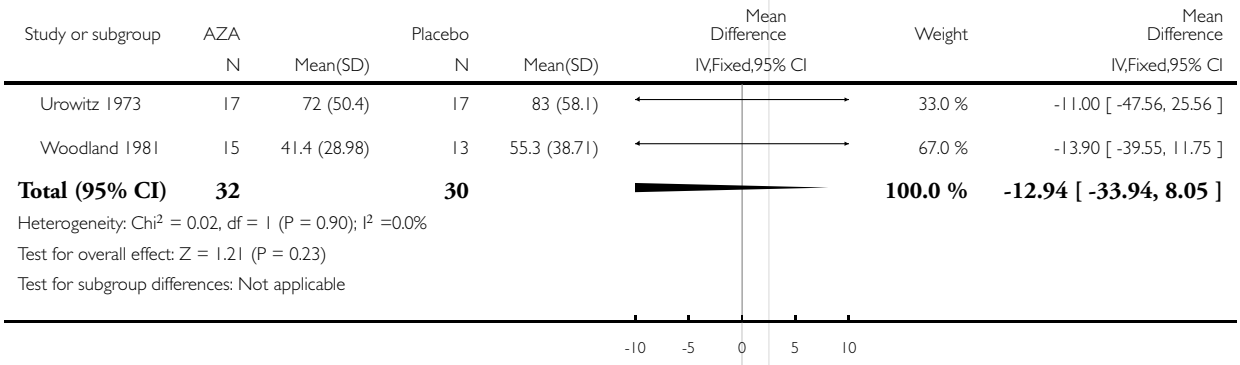


Analysis 1.3. Comparison 1 Azathioprine vs. placebo - Efficacy, Outcome 3 ESR.

Review: Azathioprine for treating rheumatoid arthritis

Comparison: 1 Azathioprine vs. placebo - Efficacy

Outcome: 3 ESR



Analysis 2.1. Comparison 2 Azathioprine vs. placebo - Withdrawals and dropouts, Outcome 1 Withdrawals: global reasons.

Review: Azathioprine for treating rheumatoid arthritis

Comparison: 2 Azathioprine vs. placebo - Withdrawals and dropouts

Outcome: 1 Withdrawals: global reasons

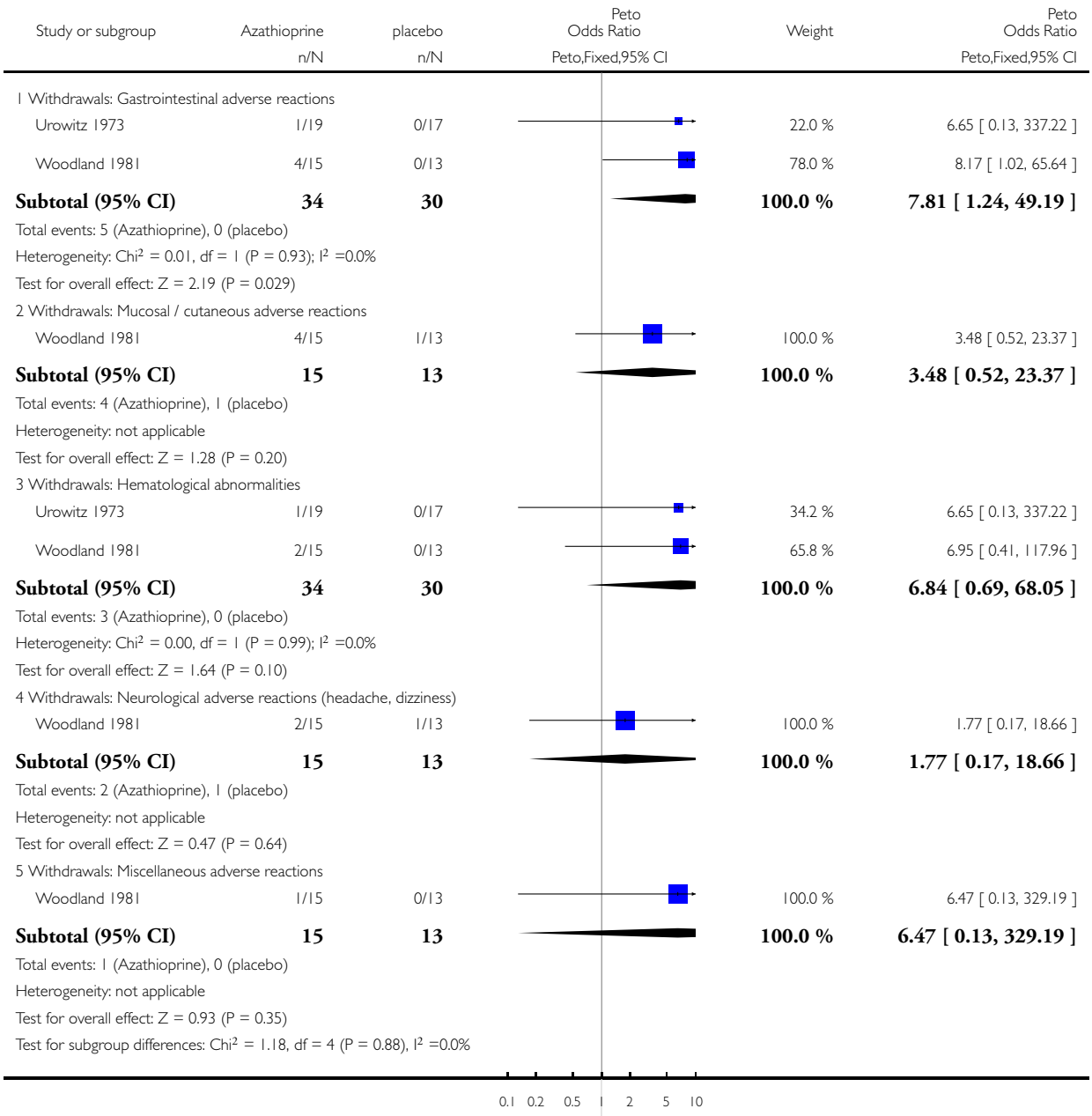
Study or subgroup	Azathioprine n/N	placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Withdrawals: total					
Urowitz 1973	2/19	0/17		23.5 %	7.03 [0.42, 117.58]
Woodland 1981	7/15	2/13		76.5 %	3.99 [0.84, 19.00]
Subtotal (95% CI)	**34**	**30**		**100.0 %**	**4.56 [1.16, 17.85]**
Total events: 9 (Azathioprine), 2 (placebo)					
Heterogeneity: Chi^2 = 0.12, df = 1 (P = 0.73); I^2 =0.0%					
Test for overall effect: Z = 2.18 (P = 0.030)					
2 Withdrawals: lack of effect					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Azathioprine), 0 (placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Withdrawals: concurrent illness					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Azathioprine), 0 (placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
4 Withdrawals: adverse reactions					
Urowitz 1973	2/19	0/17		23.5 %	7.03 [0.42, 117.58]
Woodland 1981	7/15	2/13		76.5 %	3.99 [0.84, 19.00]
Subtotal (95% CI)	**34**	**30**		**100.0 %**	**4.56 [1.16, 17.85]**
Total events: 9 (Azathioprine), 2 (placebo)					
Heterogeneity: Chi^2 = 0.12, df = 1 (P = 0.73); I^2 =0.0%					
Test for overall effect: Z = 2.18 (P = 0.030)					
Test for subgroup differences: Chi^2 = 0.0, df = 1 (P = 1.00), I^2 =0.0%					

Analysis 2.2. Comparison 2 Azathioprine vs. placebo - Withdrawals and dropouts, Outcome 2 Withdrawals: specific adverse reactions.

Review: Azathioprine for treating rheumatoid arthritis

Comparison: 2 Azathioprine vs. placebo - Withdrawals and dropouts

Outcome: 2 Withdrawals: specific adverse reactions

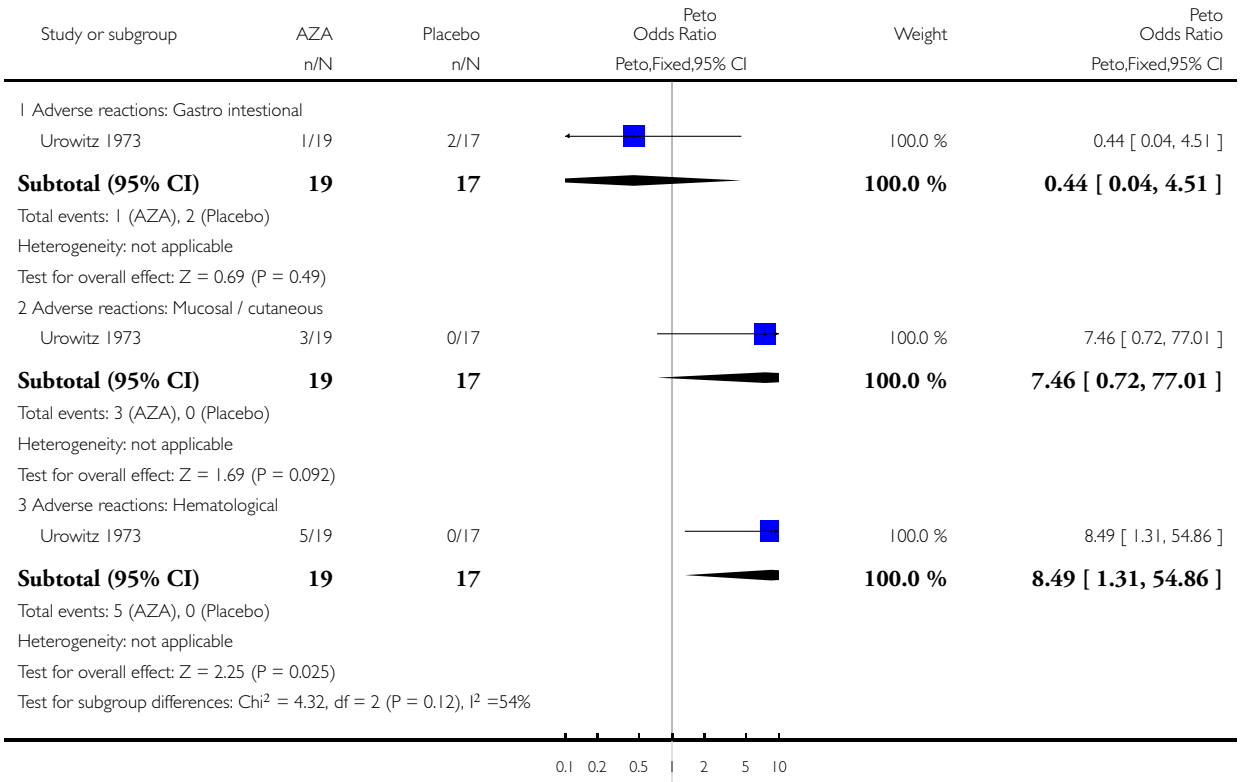


Analysis 3.1. Comparison 3 Adverse reactions not requiring withdrawal, Outcome 1 Adverse reaction by specific system.

Review: Azathioprine for treating rheumatoid arthritis

Comparison: 3 Adverse reactions not requiring withdrawal

Outcome: 1 Adverse reaction by specific system



WHAT'S NEW

Last assessed as up-to-date: 29 August 2000.

Date	Event	Description
22 September 2008	Amended	Converted to new review format. C008-R

HISTORY

Review first published: Issue 2, 1999

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- University of Alberta Hospitals Foundation, Canada.
- The Arthritis Society, Canada.
- Alberta Heritage Foundation for Medical Research, Canada.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Antirheumatic Agents [*therapeutic use]; Arthritis, Rheumatoid [*drug therapy]; Azathioprine [*therapeutic use]; Controlled Clinical Trials as Topic; Randomized Controlled Trials as Topic

MeSH check words

Humans