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Has azathioprine still a place in the treatment of IBD?

Gerhard Rogler, Department of Gastroenterology and Hepatology, University Hospital Zürich

UniversitätsSpital Zürich

Universität Zürich[UZH]

Thiopurines for IBD: Conflicting findings

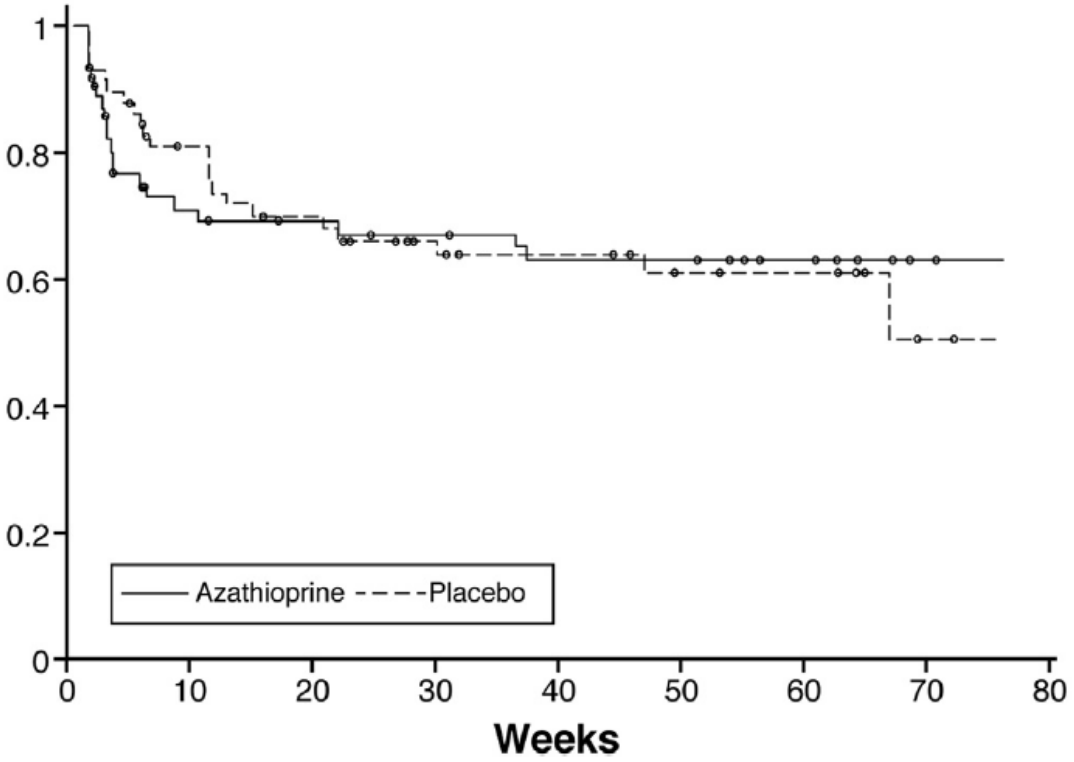
- ✓ Reduced rates of surgery in cohort studies[1,2]
- x No convincing benefit for thiopurines in large population-based studies[3]
- ✓ Improved long-term remission by early treatment with 6-MP in children with CD[4]
- x No benefit of early azathioprine in adults[5,6]
- ✓ 50% mucosal healing by azathioprine in ileitis and 70% in colonic involvement[7]
- x Rare mucosal healing in SONIC[8]

[1] Ramadas AV et al. Gut 2010; [2] Vernier-Massouille G et al. Gastroenterology 2008;
[3] Rungoe C et al. Gut 2014; [4] Markowitz J et al. Gastroenterology 2000;
[5] Cosnes J et al. Gastroenterology 2013; [6] Panés J et al. Gastroenterology 2013;
[7] Mantzaris G et al. Inflamm Bowel Dis 2009; [8] Colombel JF et al. N Engl J Med 2010

Early use of azathioprine for ALL newly diagnosed patients with CD is not better than conventional therapy

prospective double-blind study in patients with newly (<8 weeks) diagnosed CD (n = 65 per group)

“survival free of relapse” CDAI <175



“In a study of adults with Crohn’s disease, early azathioprine therapy was no more effective than placebo to achieve sustained corticosteroid free remission but was more effective in preventing moderate to severe relapse in a post hoc analysis.»

Early use of azathioprine for ALL newly diagnosed patients with CD is not better than conventional therapy

"A post hoc analysis of relapse, defined as a Crohn's Disease Activity Index score >220, showed lower relapse rates in the azathioprine group than in the placebo group (11.8% vs 30.2%; P < 0.01)."

Panes et al. Gastroenterology 2013;145:766–774

Meta-analyses support a role of thiopurines for the maintenance of remission and steroid reduction in IBD

Crohns' disease	studies	N	OR and 95% C.I.	NNT
AZA for induction of remission*	13	1211	1.23 (0.97 – 1.55)	-
AZA for maintenance of remission**	7	462	**2.32 (1.55 – 3.49)**	6
AZA and steroid sparing effect**	7	462	**5.22 (1.06 – 25.68**	3

**Chande N et al. Cochrane Database Syst Rev. 2013 Apr*

***Prefontaine E et al. Cochrane Database Syst Rev 2009 Jan*

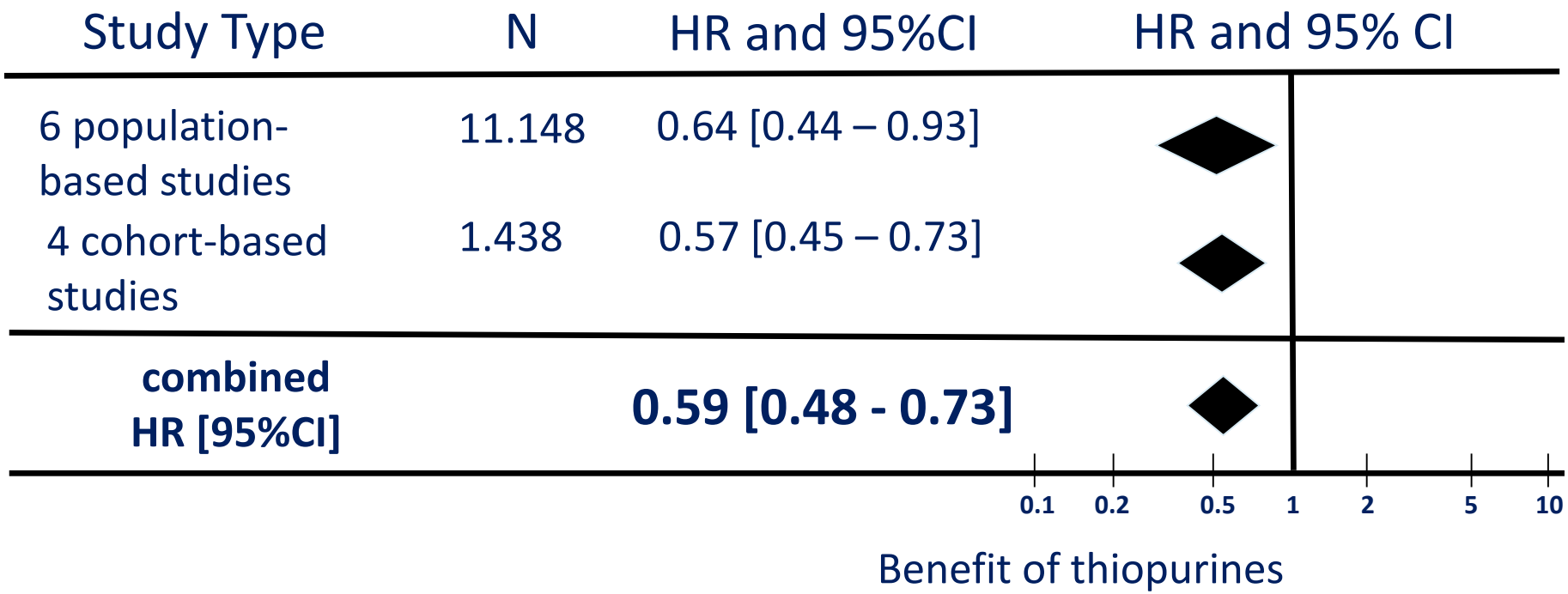
Ulcerative colitis	studies	N	OR and 95% C.I.	NNT
AZA for induction of remission[#]	4	89	1.59 (0.59 – 4.29)	-
AZA for maintenance of remission[##]	4	232	**0.68 (0.54 – 0.86)**	5

[#]Gisbert JP et al. Aliment Pharm Ther 2009; 30(2): 126-37

[##]Timmer A et al. Cochrane Database Syst Rev. 2012 Sep

Thiopurines prevent surgeries in CD patients

- Meta-analysis of 10 trials (12 586 patients)



Thiopurin effect in a population-based cohort

population-based cohort (n=341) Cardiff/UK

	1986-1991 N=99	1992-1997 N=105	1998-2003 N=137
Immunosuppressives	11%	28%	45%*
Median time until start of therapy with thiopurines	77 months	21 months	11 months
Longterm steroid-use	44%	31%	19%*
Cumulative surgery-rate	59%	37%	25% *p=0,001

Ramadas et al. Gut 2010; 59: 1200-06

Summary

- Thiopurines are **not** (very) useful **for the induction of remission** in IBD patients
- thiopurines reduce the number of relapes/flares in patients with CD or UC and can be used for the **maintenance of remission**
- AZA/6-MP therapy is not useful for ALL patients (especially no at disease onset)
- An individualized decision is necessary (age, risk, steroid response)
- 6-MP in more than 50% of AZA intolerance successful
- Therapeutic 6-TGN levels need to be achieved

Thank you for your attention