Optimal Management of Mild to Moderate Ulcerative Colitis

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Disclosure

- Procter & Gamble Phar. Research Grant

Agenda

- Controversial aggravating Factors
- Distal ulcerative Colitis
- Extensive Ulcerative Colitis

Ulcerative Colitis
Controversial Factors

- Acne medications
- Infections

Isotretinoin and Ulcerative Colitis

Isotretinoin and Ulcerative Colitis Controversy

(-)	(+)
Univ. of Manitoba Pop. Based, Case-control	Univ of North Carolina Case-Control
Isotretinoin Use IBD 1.2% No difference in CD & UC Controls 1.1%	Isotretinoin Use UC Odds Ratio 4.36 Highest risk with > 2 mo use CD Odds Ratio 0.68

Bernstein CN Amer J Gastro 2009; 104: 2774-78
Crockett SD Am J Gastro 2010; 105: 1986-93

Oral Tetracycline and IBD

- UK Health Improvement Database
- 94,487 people with acne
- 406,294 person years follow-up

Risks for IBD

	UC / CD Hazard Ratios
– Minocycline	1.10 / 1.28
– Tetracycline	1.27 / 1.61
– Doxycycline	1.06 / 2.25

Margolis DJ Amer J Gastro 2010. August. epub

Refractory UC Controversial Causes?

- C. difficile
  - Frequency of toxigenic C. difficile [1]
    - Asymptomatic IBD 8.2%
    - Healthy volunteers 1.0%
- CMV
  - Prevalence, active UC 10%
    - A marker of disease severity? [2]
  - No relation of IBD activity and viral load [3]

[1] Clayton EM Am J Gastro 2009; 104: 1162-9
[2] Kim JJ Dig Dis Sci 2010: 55:1059-65
[3] Leveque N J Med Vir 2010; 82: 1694-00

Ulcerative Colitis Practice Guidelines in Adults: American College of Gastroenterology, Practice Parameters Committee

Am J Gastroenterol 2010; 105: 501-23

Left-sided Ulcerative Colitis Proximal Extension

- Population-based, retrospective study
  - Olmsted County, MN
- 146/368 pt with left-sided disease
- 5 year cumulative extension rate
  - 44%

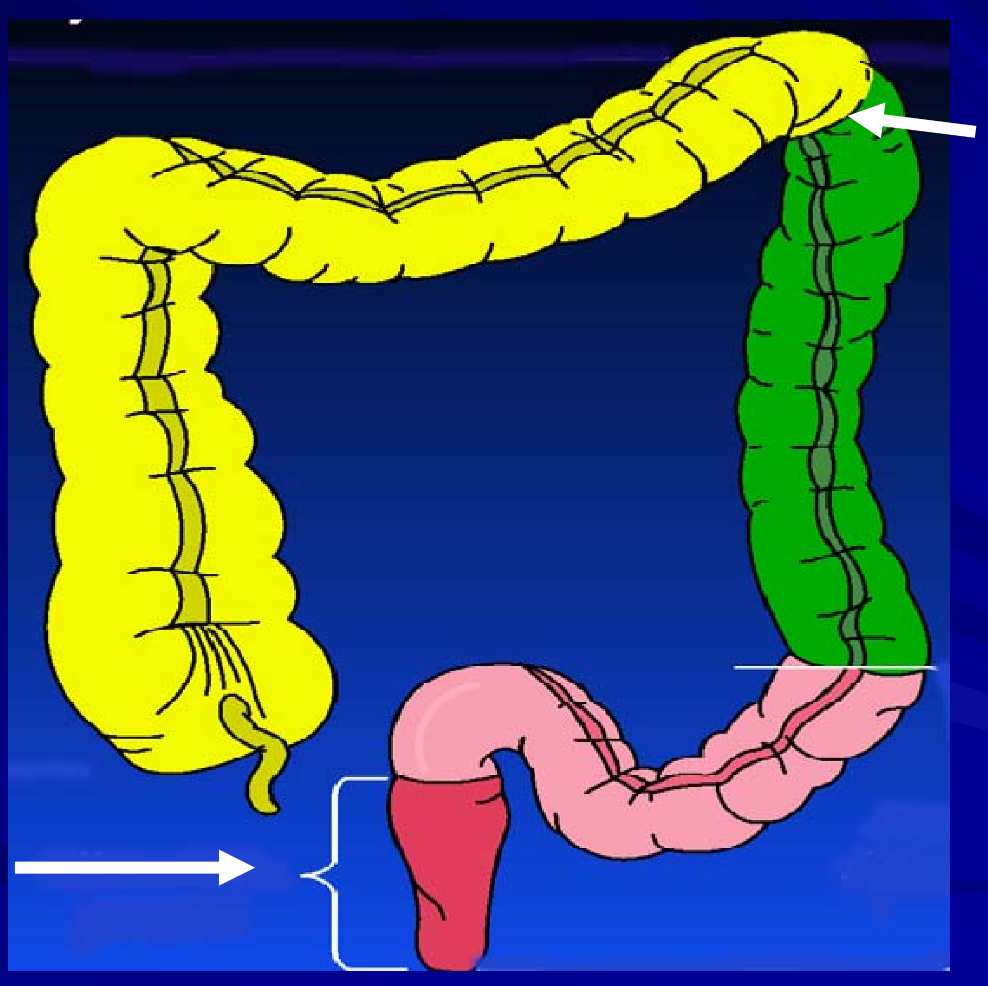
Tremaine W Gastroenterology 2008: Abstract

Distal UC
Guidelines: Evidence A

- Topical Mesalamine
  - Superior to: topical steroids
    oral 5-ASA
- Combo Oral + Topical
  - Superior to: either alone
- If refractory to oral 5-ASA and top steroids
  - 5-ASA enemas or suppositories may be effective

Am J Gastroenterol 2010; 105: 501-23

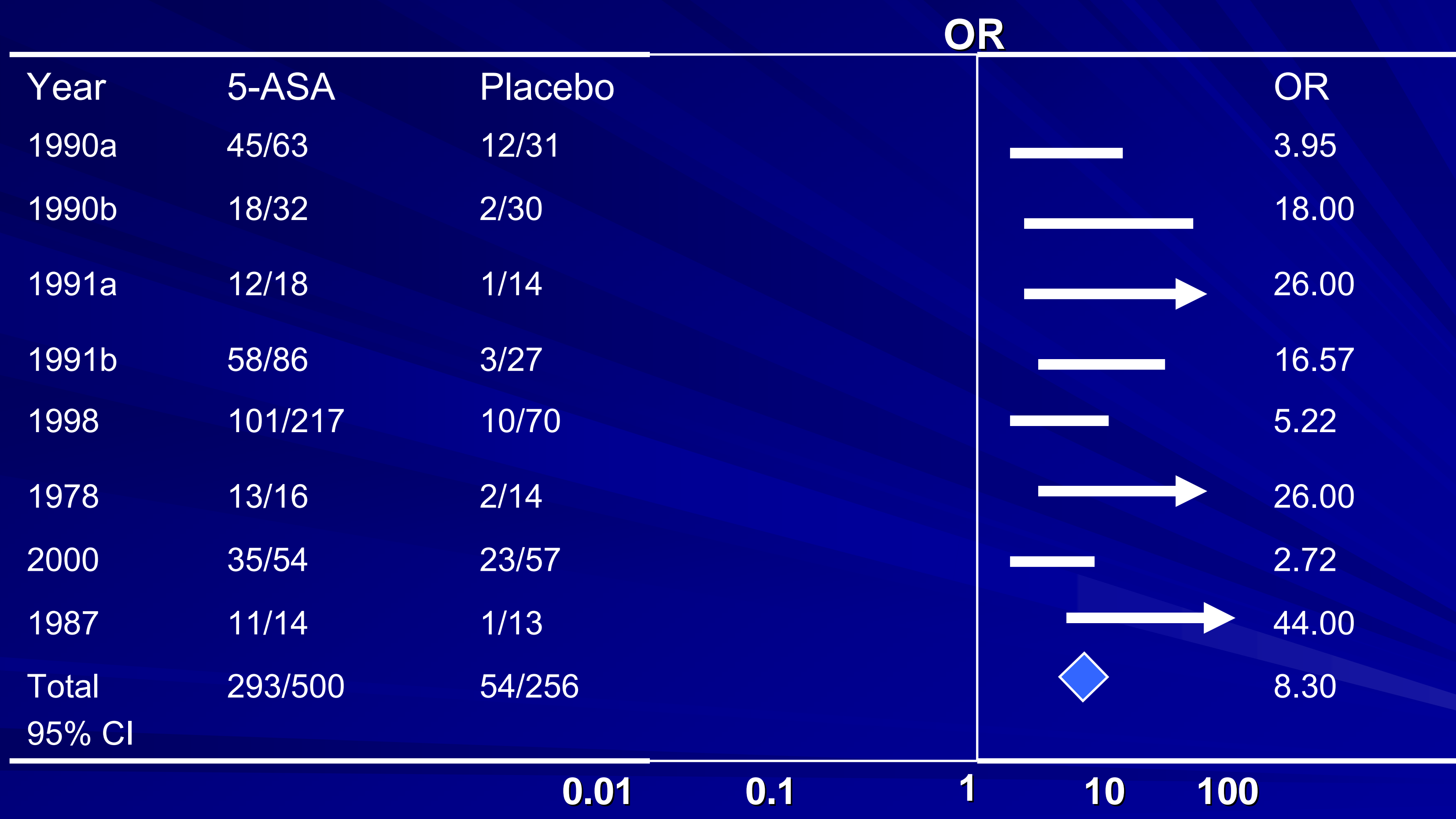
Extent of coverage



Enemas
Splenic Flexure

Suppositories
12 cm

Rectal 5-ASA vs Placebo
Induction of Remission



Year	5-ASA	Placebo	OR
1990a	45/63	12/31	3.95
1990b	18/32	2/30	18.00
1991a	12/18	1/14	26.00
1991b	58/86	3/27	16.57
1998	101/217	10/70	5.22
1978	13/16	2/14	26.00
2000	35/54	23/57	2.72
1987	11/14	1/13	44.00
Total 95% CI	293/500	54/256	8.30

Marshall JK Cochrane Database of Sys Rev 2010; 1

Distal UC
Guidelines: Evidence C

- If refractory to 5-ASA and topical steroids
  - The following may be effective:
    - Prednisone 40-60 mg/d
    - Infliximab 5mg/kg

Am J Gastroenterol 2010; 105: 501-23

Tacrolimus Suppositories

- 7 pt with refractory proctitis
- Suppositories 1 mg BID or Q.D x 28d
- 5 responded
  - Trough levels < 1.5 mcg/L
  - 2 hr and 6 hr peak levels < 4.3 mcg/L

Van Bodegraven, et al. Gastroenterology. 2005. 128(4);Supplemt 2: A-588

Tacrolimus Suppositories

- 47 y/o man. Distal UC for 20 yrs.
- Disease to 50 cm
- Continued proctitis symptoms despite:
  - 5-ASA, Prednisone, Azathioprine
- Tacrolimus suppositories 1mg Q12 HR x 3 wk

  Trough level: 6.8 (therapeutic 5.0-20)
- Tacrolimus suppositories 1 daily for 10 days

  Trough level: <3.0

Distal UC Maintenance of Remission Guidelines: Evidence A

- Mesalamine enemas are effective
  - $\leq$ Every third night
- Mesalamine suppositories are effective
- Oral 5-ASA is effective
  - Sulfasalazine
  - Mesalamine
  - Balsalazide
- Combo oral/topical better than either alone

Am J Gastroenterol 2010; 105: 501-23

Distal UC Maintenance of Remission Guidelines: Evidence A continued

- Topical steroids including budesonide ineffective
- Other effective maintenance therapies:
  - Mercaptopurine, Azathioprine
  - Infliximab

Am J Gastroenterol 2010; 105: 501-23

Extensive UC: Mild to Moderate Induction Guidelines: Evidence A

- Sulfasalazine 4-6 g/d
- 5-ASA up to 4.8 g/d
- Prednisone 40-60 mg/day, taper slowly
- Steroid Refractory or Dependent
  - Mercaptopurine, Azathioprine
  - Infliximab

Am J Gastroenterol 2010; 105: 501-23

Which Oral 5-ASA to Use?

Release Mechanism	Generic Name
Azo-Bonded N=N	Sulfasalazine Olsalazine Balsalazide
Delayed-release H_2N	Mesalamine pH sensitive lipophilic, hydrophilic matrices Ethylcellulose granules Sustained release pellets

Which Oral 5-ASA to Use?

- History of 5-ASA use
- Allergies
- Likelihood of Compliance
- Cost

5-ASA Adverse Effects Comments about some

- Paradoxical worsening of colitis
- Pancreatitis
- Renal insufficiency
- Hair loss

Extensive UC: Mild to Moderate Maintenance Guidelines: Evidence A

- Sulfasalazine
- Olsalazine
- Mesalamine
- Balsalazide
- Mercaptopurine, Azathioprine
- Infliximab

Am J Gastroenterol 2010; 105: 501-23

Corticosteroid Side Effects
Treatment of UC

- Indicator of bioavailability?

Ulcerative Colitis
Nicotine

- Induction of Remission
  - Nicotine superior to placebo
  - No advantage over 5-ASA

Cochrane Reviews
Probiotics

Ulcerative Colitis Induction of remission	"…not enough evidence to recommend the use.." 2007
Crohn's Disease Induction of remission	"…insufficient evidence to make any conclusions about the effectiveness…" 2009
Crohn's Disease Maintenance of remission	"..there is no evidence to support the use of probiotics…" 2009

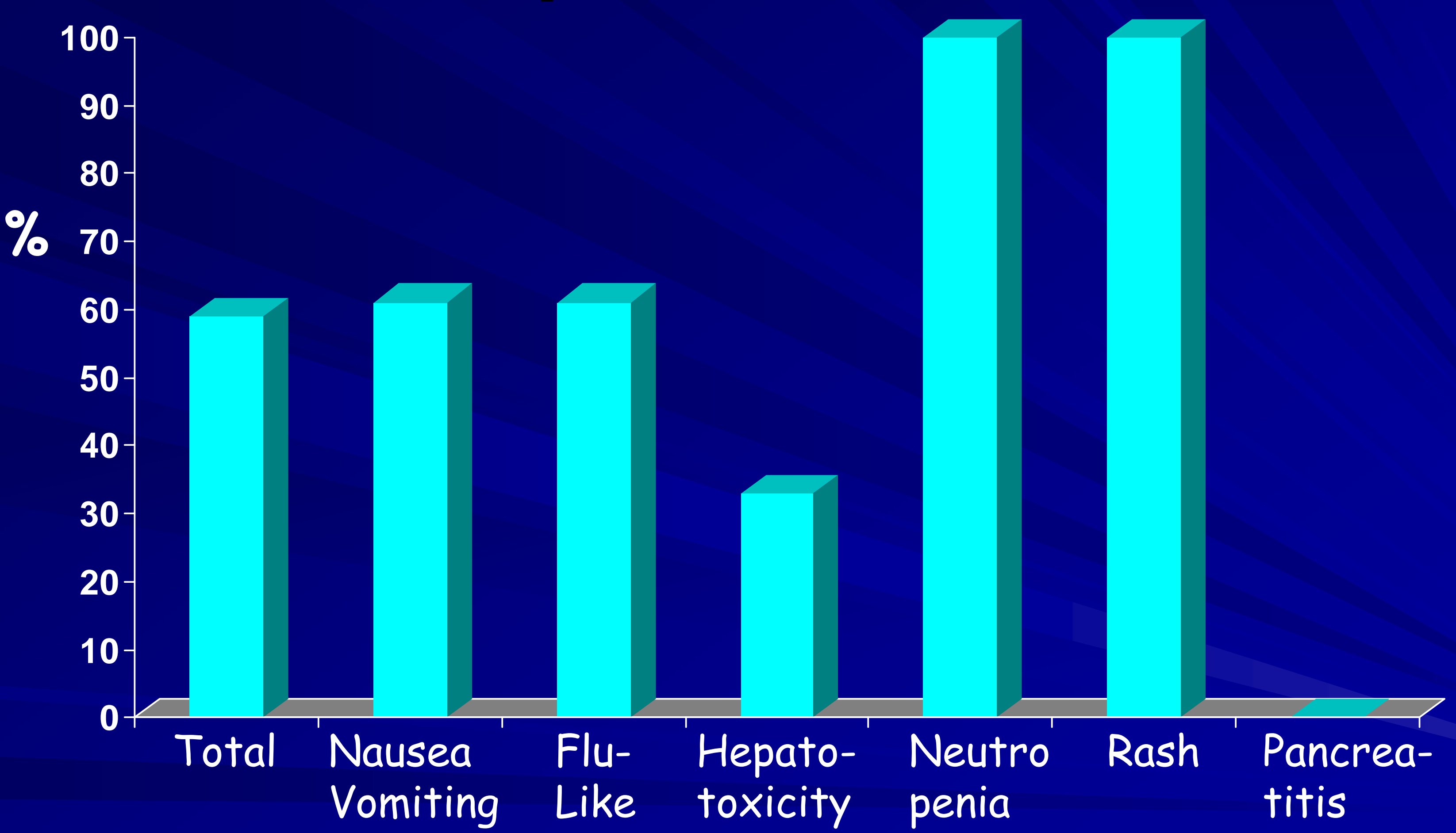
Aza / 6-MP
Which one to use?

	Azathioprine	Mercaptopurine
Bioavailable 6-MP	47%	100%
Dose	2-2.5 mg/kg	1-1.5 mg/kg
*Generic Cost 50 mg tablet	$0.79	$2.70
Efficacy	Same	Same
Adverse Effects	More	Less

Van Os E. Gut. 1996

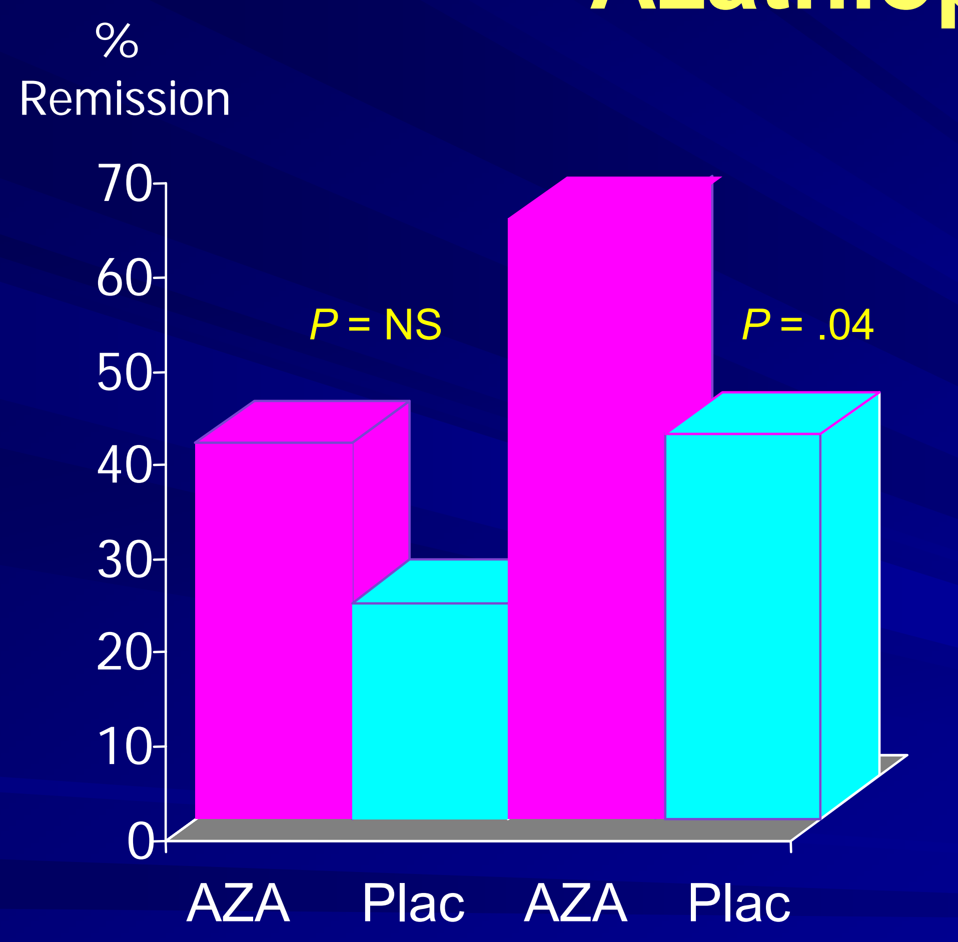
* Internet U.S. prices

6-MP tolerance in 61 pt with Azathioprine Intolerance



Lees CW Alimen Pharm & Ther 2008. 27: 220-27

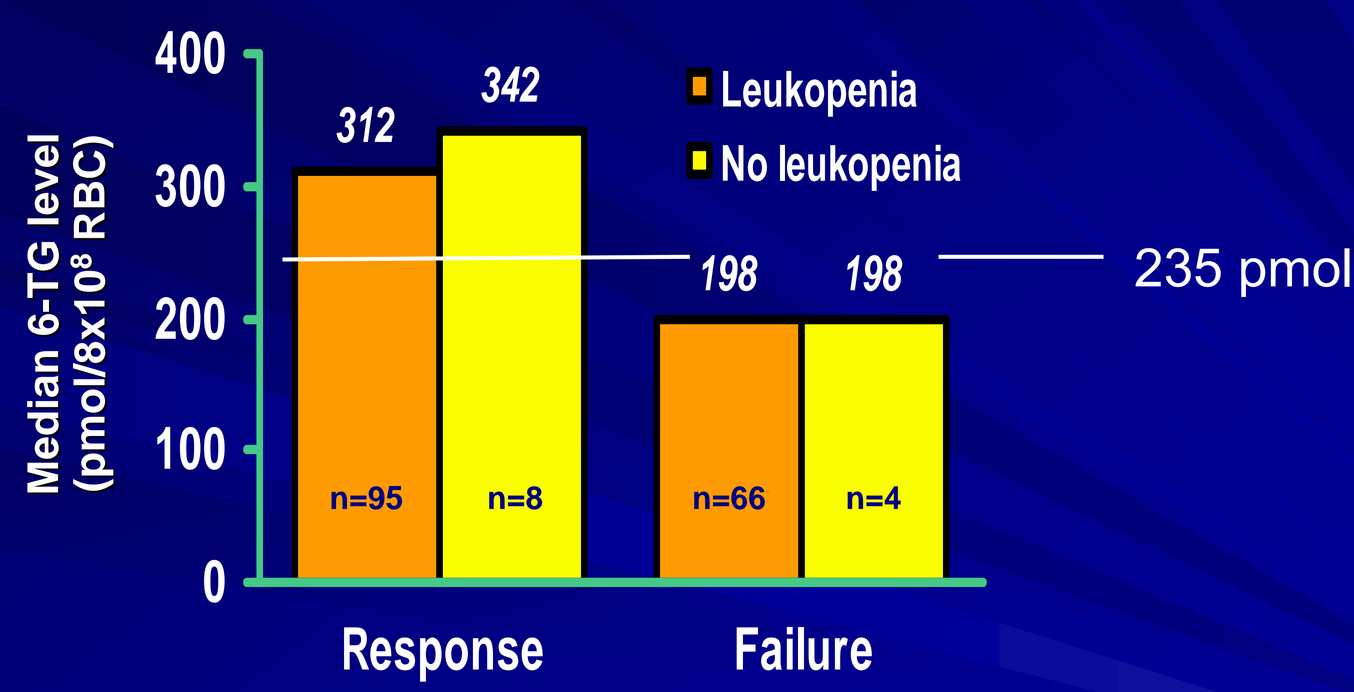
UC Maintenance of Remission Azathioprine



- Jewell and Truelove: AZA 1.5 - 2.5 mg/kg (n = 40) Placebo (n = 40) 11 months
- Hawthorne et al: AZA (x 100 mg) (n = 33) Placebo (n = 34) 12 months [withdrawal trial]

Jewell, Truelove. *BMJ* 1974;4:627-630
Hawthorne, et al. *BMJ* 1992;305:20-22

6-TGN Levels and Efficacy



235 pmol

Dubinsky M, et al. Gastroenterology 2000;118:705-13

MCV as a Surrogate for 6TGN

	Baseline MCV (fL)	Study MCV (fL)	Delta MCV (Study – Baseline) (fL)
n	159	166	159
Mean (SD)	87.2 (7.2)	94.7 (6.6)	7.5 (6.3)
Median	87.4	95.0	7.0
Range	61.1 to 105.0	68.6 to 110.9	–9.6 to 34.9

MCV, mean corpuscular volume.

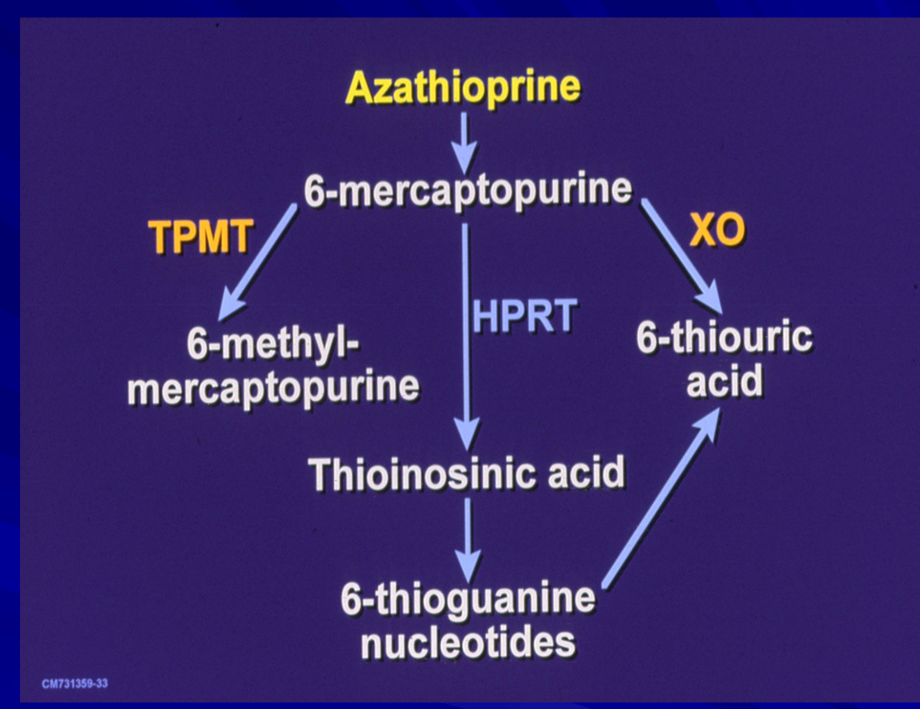
- Correlation between MCV Δ & 6TGN: $r=0.33$ $p<0.001$

Conclusion: MCV Δ = biologic effect

Thomas C. *Inflam Bowel Dis.* 2003;9(4): 237-245

Aza / 6MP Hepatotoxicity Allopurinol

- $\leq$10% of patients
- Reduce AZA /6MP dose by 25%
- Allopurinol 200 mg/d
- 9/11 patients with prior hepatotoxicity
  - Remission
  - Normal LFTs



Ansari A. Aliment Pharm & Ther 2008. 738-41

Methotrexate for UC
Cochrane Review

- Only 1 trial met inclusion criteria
  - 30 pt
  - MTX 12.5 mg p.o. vs. placebo for 9 months
- Cochrane Conclusions
  - Under-powered
  - Dose may have been too low

Chande N, et al. . Cochrane Database Syst Rev. 2007:4

Methotrexate for UC

- Retrospective, Australia
- 23 UC pt
  - AZA failure 91%
  - Infliximab failure 22%
- 15-25 mg S.Q weekly
- 1-37 mo. Median 15 mo.
- Remission 48%
- Response 13%

Adverse Effects 6/23	
Leukopenia	2
Abnormal LFT	2
Diarrhea	1
Dyspnea	1

Nathan D, et al. Journ of Gastro and Hep. 2008. 23:954-58

67 y/o with UC

- Pancolitis, 2 years
- Mesalamine: inadequate response
- Mercaptopurine: fever, nausea
- Comorbidities: CHF, eject fx 44%
Parkinson's
Depression
- Asymptomatic on:
  - Prednisone 30mg/day, Balsalazide 6.75 g/d

67 y/o with UC (cont)

- Declined colectomy
- RX: Methotrexate 25 mg S.Q. weekly
  Folic Acid 1 mg orally daily
- Prednisone tapered and discontinued over 6 months
- Balsalazide stopped after 2 years
- Lab monitoring each 2 months
- Rare symptoms

CyA & Infliximab as Rescue Therapy for Each Other

	Infliximab 1st	Cyclosporine 1st
#	9	10
Remission	33%	40%
Duration	28.5 mo	10.4 mo
SAEs	1 (Bacteremia, pancreatitis, herpes)	1 (sepsis, death)

Maser EA Clin Gastro and Hep 2008. 6: 1112-16

Tacrolimus for UC

- 60 pt
  - Moderate to severe UC
  - Steroid refractory
  - Two wk, double-blind placebo controlled
    - Hi trough tacrolimus (10-15 ng/ml)
    - Lo trough tacrolimus (5-10 mg/ml)
    - Placebo
  - Open label 10 wk extension

Ogata H. Gut. 2006; 55:1255-62

Tacrolimus for UC
Response at 2 wk

	HT	LT	Placebo
# of participants	19	21	20
Complete response	0	0	0
Partial response *p vs placebo*	13 <0.001	8 =.067	2
No response *p vs placebo*	6	13	18

Ogata H. Gut. 2006; 55:1255-62

Management of Mild-Moderate UC Summary

- Multiple treatment options
- Role of intercurrent infections is controversial
- Definitive studies lacking for
  - Methotrexate
  - Tacrolimus
  - Probiotics