Use of Concomitant Immunomodulators and Anti-TNFs: Emerging Insights

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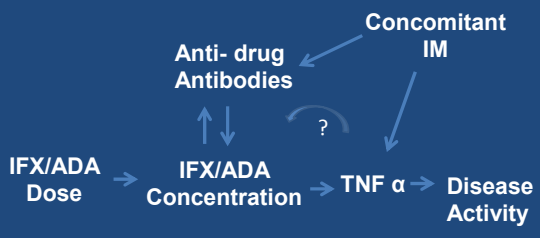
Objectives

- Discuss evidence behind use of concomitant therapy
- To discuss effects of concomitant therapy on immunogenicity and drug levels
- Discuss safety concerns regarding use of concomitant therapy

Pharmacokinetic Variability



Synergistic/additive benefit

MTX, 6MP, AZA

- Inhibit purine synthesis
- Apoptosis of activated B and T cells

Anti-TNFs

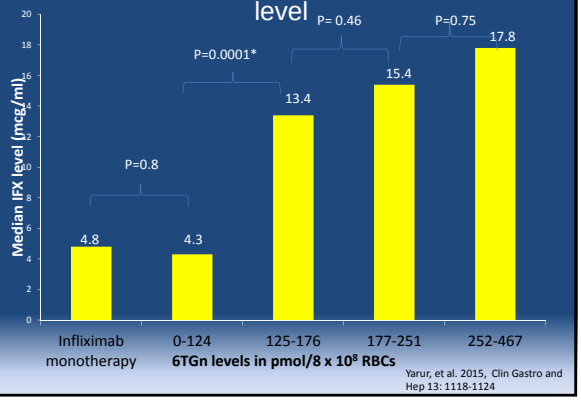
- Bind to TNFα receptors
- Inhibit secretion of pro-inflammatory cytokines
- Inhibit leukocyte infiltration
- Directly reduce osteoclast activity

How is anti-TNF metabolism impacted

Drug	Concurrent IM	Effect on PK	Effect on ADA incidence	
			IM-	IM +
Adalimumab	AZA, 6MP, MTX	No effect	4%	0%
Infliximab	AZA,6MP, MTX	14% decrease in clearance	15%	1%

Adapted from Xu, et al. (2014) J of Clinical Pharmacology 55; S60-74

Correlation of infliximab trough level with 6TGn level



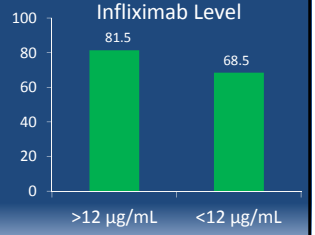
Yarur, et al. 2015, Clin Gastro and Hep 13: 1118-1124

Infliximab trough level correlates with duration of response to anti-TNF

Prospective design
- N=125, 30% Rx for fistula
- Median follow-up: 36 months

- Infliximab concentrations ≥12 µg/mL associated with greater median duration of response
- Immunomodulator use associated with IFX concentrations ≥12 µg/mL

Duration of Response (days) Based on Infliximab Level



Baert F, et al. N Engl J Med. 2003;348:601

Two situations

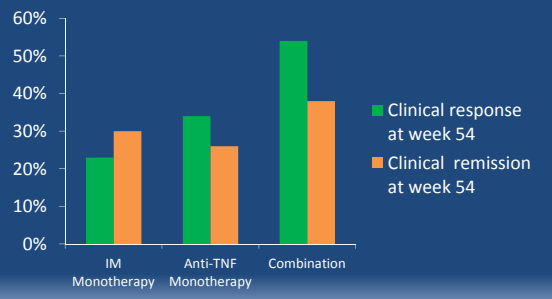
Inadequate response or failure of IM "step-up"	IM-Naïve "top-down"
Later stage of disease	Earlier stage of disease
More structural bowel damage?	Earlier mucosal healing?

Continuation of IM beyond 6 months offered no benefit

- Followed for 104 weeks: > half needed "rescue" IFX, regardless of IM
- No difference in CDAI or endoscopic healing at 2 years
- Concomitant group showed higher median IFX trough and decreased CRPs

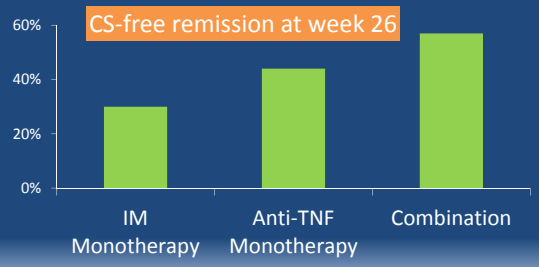
Van Assche, et al. 2008. Gastroenterology; 134: 1861-1868

ACCENT 1 and 2 (luminal and fistulizing CD) ACT 1 and 2 (ulcerative colitis)



Lichtenstein, et al. (2009) Aliment Pharmcol Ther 30:210-226

Study of Biologic and Immunomodulator Naïve Patients in Crohn's Disease (SONIC)



Colombel, et al., 2010. NEJM, 362: 1383-1395

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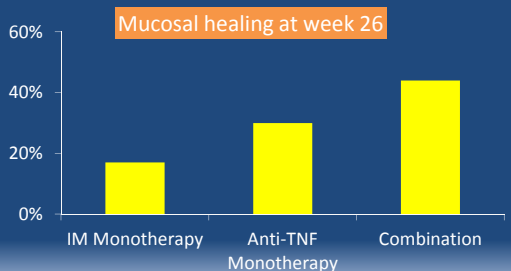

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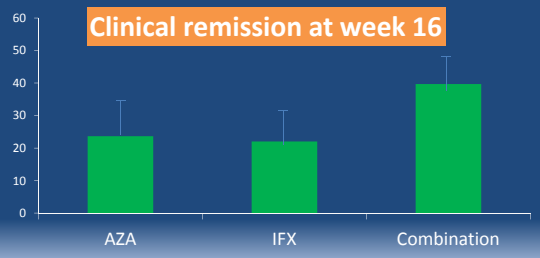
Combination of Maintenance Methotrexate-Infliximab Trial (COMMIT)

- 50 week, double-blind RCT
- 126 patients received either infliximab or infliximab plus MTX
- On steroid taper during trial
- No difference in treatment failure over time, or prednisone-free remission

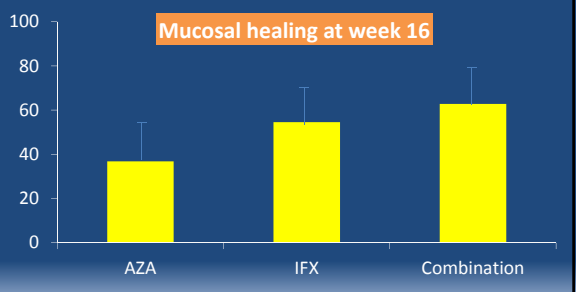
Feagen, et al. 2014. Gastroenterology, 146: 681-688

Infliximab, azathioprine, or infliximab + azathioprine for treatment of moderate to severe ulcerative colitis: the UC SUCCESS trial



Pannacione, et al. 2014, Gastroenterology;146:392-400

UC SUCCESS



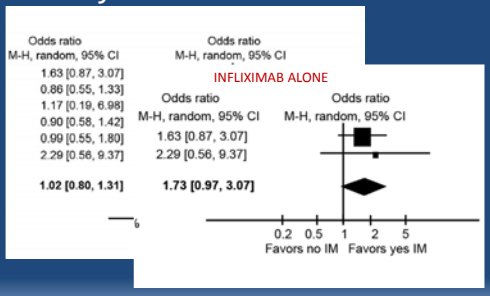
Pannacione, et al. 2014, Gastroenterology;146:392-400

Continuing IM after stepping up may not add to effectiveness

			No. of patients	
	Year	Agent	Yes IM	No IM
Hanuer, et al (CLASSIC 1)	2006	Adalimumab	22	54
Colombel, et al. (CHARM)	2007	Adalimumab	156	173
Sandborn, et al (GAIN)	2007	Adalimumab	73	86
Sandborn, et al. (CLASSIC II)	2007	Adalimumab	9	28
Sandborn, et al. (PRECISE 1)	2007	Certolizumab Pegol	126	205
Schreiber, et al. (PRECISE 2)	2007	Certolizumab Pegol	87	128
Targan, et al.	1997	Infliximab	27	48
Present, et al.	1999	Infliximab	26	31
Rugeerts, et al	1999	Infliximab	18	15
Hanauer, et al. (ACCENT 1)	2002	Infliximab	53	150
Sands, et al. (ACCENT 2)	2004	Infliximab	28	58
Total			**625**	**976**

Jones, et al. 2015. Clinical Gastro and Hepatol, ahead of print

Continuing IM after stepping up may not add effectiveness



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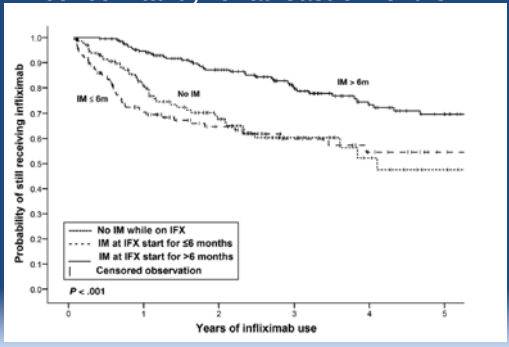
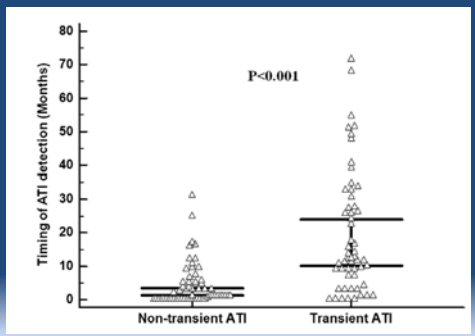
Durability of infliximab improved if IM used concomitantly for at least 6 months

- 

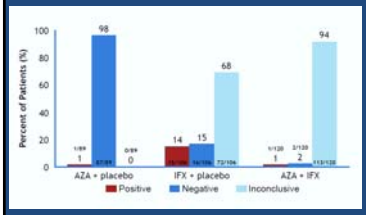
Grossi, et al. Clin Gastro and Hepatol 2015, ahead of print

Most antibodies to infliximab develop in the first year of treatment



Ungar et al., 2014, Gut, 63: 1258-64

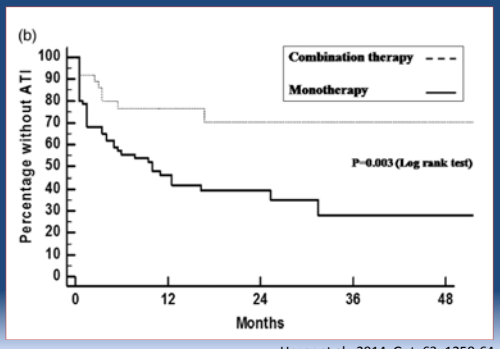
Reduced Immunogenicity in SONIC and COMMIT



COMMIT
Anti-drug antibodies
- 4% in combination group
- 20% in IFX monotherapy group

Colombel, et al., 2010. NEJM, 362: 1383-1395

Use of combination therapy reduces antibodies to infliximab over time



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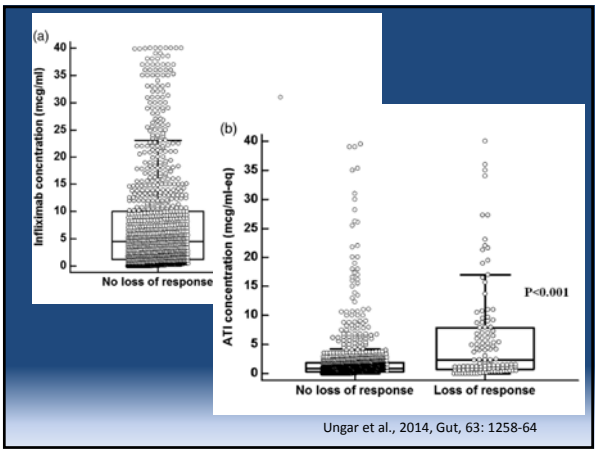


Ungar et al., 2014, Gut, 63: 1258-64

- Lymphoma and other malignancies, some fatal, have been reported inchildren and adolescent patients treate with TNF blockers, including Remicade.
- Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including Remicade. These cases have had a very aggressive disease course and have been fatal. Almost all patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with a TNF-blocker at or prior to diagnosis. The majority of reported Remica cases have occurred in patients with Crohn's disease or ulcerative colitis and most were in adolescent and young adult males.

WARNINGS

- Tuberculosis - Cases of reactivation of tuberculosis or new tuberculosis infections have been observed in patients receiving REMICADE, including patients who have previously received treatment for latent or active tuberculosis. Cases of active tuberculosis have also occurred in patients being treated with REMICADE duri treatment for latent tuberculosis.
- Malignancies – the incidence of malignancies including lymphoma was greater in REMICADE treated patient than in controls. Due to the risk of HSTCL carefully assess the risk/benefit especially if the patient has Crohn disease or ulcerative colitis, is male, and is receiving azathioprine or 6-mercaptopurine treatment.
- Hepatosplenic T-cell lymphoma (HSTCL)- Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including REMICADE These cases have had a very aggressive disease course and have been fatal. Almost all patients had receiv treatment with the immunosuppressants azathioprine or 6-mercaptopurine concomitantly with a TNF-blocker or prior to diagnosis. The majority of reported REMICADE cases have occurred in patients with Crohn's disea or ulcerative colitis and most were in adolescent and young adult males. It is uncertain whether the occurren

Safety in a Retrospective Cohort Study: Outcomes of Step-up Combination vs. Anti-TNF Monotherapy

	Infliximab		Adalimumab		Adjusted Hazard ratio (95% CI)
	Combination (n=381)	Monotherapy (n=912)	Combination (n=196)	Monotherapy (n=505)	
Surgery	6.1	3.9	4.9	6.1	1.2 (0.73-1.96)
Hospitalization	13.8	13.5	15.3	22	0.83 (0.6-1.14)
Serious infection	6.8	8	9	7.4	0.91 (0.60-1.38)
Opportunistic infection	2.7	1.6	2.6	1.3	2.51 (1.15-5.46)
Herpes Zoster	2.2	1	1.8	0.7	3.16 (1.25-7.97)

Events/Person-Years

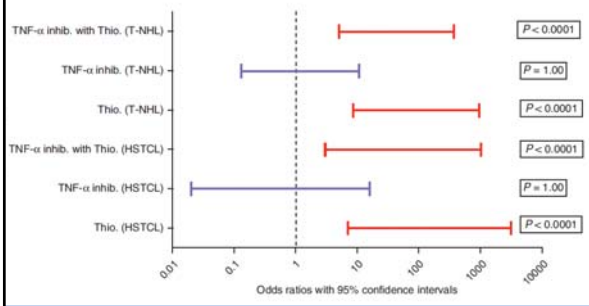
Osterman, et al. 2015, Clin Gastroenterology and Hepatology, 13:1293-2011

Safety in SONIC

	AZA	IFX	Combination
	n=161	n=163	n=179
Total weeks of follow up	45.1	48.3	48.9
AE leading to discontinuation no.(%)	42(26)	29(17.8)	37(20.7)
Serious infection no.(%)	9(5.6)	8(4.9)	7(3.9)
Colon cancer no.(%)	2(1.2)	0	0
Sepsis no.(%)	1(0.6)	0	0
Tuberculosis no.(%)	0	0	1(0.6)
Patients with infusion reactions no(%)	9(5.6)	27(16.6)	9(5.0)

Colombel, et al., 2010. NEJM, 362: 1383-1395

Risk of lymphoma with combination therapy may be similar to risk with thiopurine alone



Deeapak, et al. 2014. Am J Gastroenterology, 108:99-105.

Conclusions

- Concomitant therapy may be more effective when used as top-down therapy
- Use of concomitant therapy may increase risk for infection, especially if used long-term
- Continuing an IM for at least 6 months after stepping-up may not improve efficacy, but may prolong durability of anti-TNF
- Concomitant IM therapy may be best used as initial therapy for patients with severe disease, but may not be worth risk beyond 6 months.
- More data is needed regarding outcomes associated with IM discontinuation in children
- More data needed regarding use of IM with adalimumab