If My IBD Patient Is Well on Combination Therapy What Should I Do? Be Happy or De-Escalate?

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Disclosure Statement

In the past 12 months, I have had **no** relevant financial relationships with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services discussed in this CME activity.

Objectives

- Outline rationale for and against de-escalation
- Explore de-escalation options
- Evaluate factors that may help predict success of de-escalation
- Suggest future directions

Why De-Escalate?

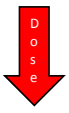
- Risk of adverse events
  - Infection
  - Malignancy

- Side effects
- High cost of medications
- Patient and family satisfaction

Common Arguments Against De-Escalation

- Goals reached → Be happy
- Immunogenicity
- Lower response rates after re-initiation of biologic
- Limited additional options
- Complete puberty to promote growth
- Paucity of data, particularly pediatric

De-Escalation Options



- Immunomodulator
- Anti-TNF

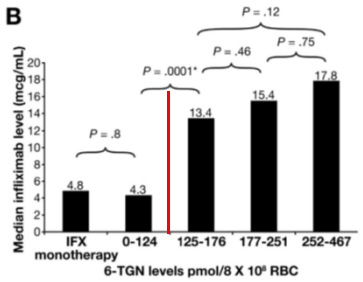
- Immunomodulator
- Anti-TNF
- Both

Combination Therapy → Immunomodulator Dose De-Escalation

Immunomodulator Dose De-Escalation

- No interventional studies re: IM dose de-escalation for combination therapy

6-TGN Concentration Correlates with IFX Trough in Combination Therapy



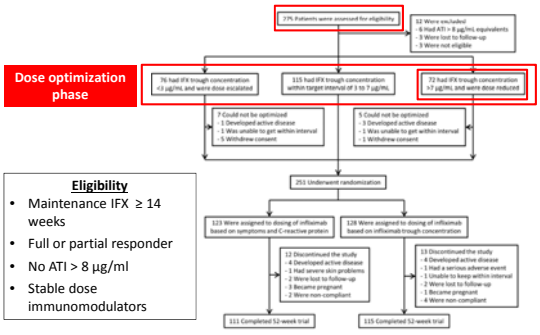
"Therapeutic levels" of 6-TGN were not necessary to achieve higher IFX troughs

Yarur AJ et al. *Clin Gastroenterol Hepatol* 2015;13:1118-1124

Combination Therapy → Biologic Dose De-Escalation

TAXIT

Trough Concentration Adapted InfliXImab Treatment (TAXIT)

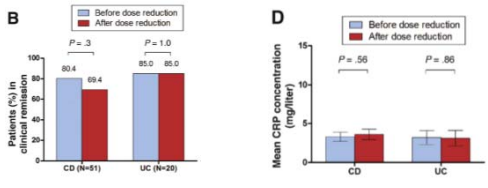


Vande Casteele N et al. *Gastroenterology* 2015;148:1320-1329

TAXIT

Dose Optimization Phase

72/263 (27.4%) required dose reduction due to high trough



Dose optimization for high trough
1. Reduce dose to 5 mg/kg (if applicable)
2. Prolong interval by two weeks (up to 12 weeks)

Vande Casteele N et al. *Gastroenterology* 2015;148:1320-1329

Combination Therapy → Withdrawal of Immunomodulator

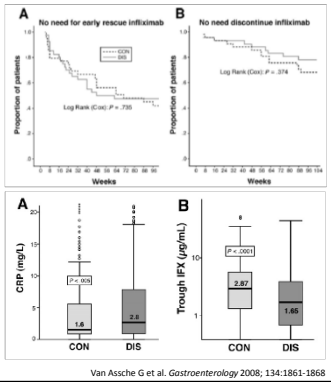
Dual Therapy – Withdrawal of Immunomodulator

- 80 patients w/ inactive disease on ≥ 6 mo dual therapy, randomized to continue or stop IM
  - Continued IFX at 5 mg/kg q8
- Primary endpoint: Discontinue or escalate IFX
- Discontinuation group: Median 24 mo dual therapy

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

Dual Therapy – Withdrawal of Immunomodulator

- No difference between groups
  - Primary endpoints
  - Mucosal healing
- Laboratory differences between groups



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

Withdrawal of Immunomodulator Does Not Decrease IFX Trough

- Retrospective review of adult CD patients on maintenance IFX (n=223)
  - 71% also on IM
- 74% (158) on combo therapy withdrew IM
  - Based on durable clinical response (median 13 mo)
  - IFX levels prospectively drawn but not available to clinicians

Drobne D et al. *Clin Gastroenterol Hepatol* 2015;13:514-521

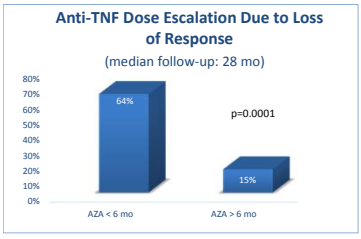
Withdrawal of Immunomodulator Does Not Decrease IFX Trough

- Median follow-up 29 months
  - 38% flared requiring IFX dose escalation (20% prior)
  - 18% discontinued IFX at mean time 67 months
- Infliximab trough levels remained stable
  - Median: 3.2 µg/mL before withdrawal
  - Median: 3.7 µg/mL after withdrawal
- At time of IM withdrawal
  - IFX trough >5 → No patients lost response (n=27)
  - Undetectable IFX trough → 6/7 lost response

Drobne D et al. *Clin Gastroenterol Hepatol* 2015;13:514-521

Is 6 Months a Good Target for Dual Therapy?

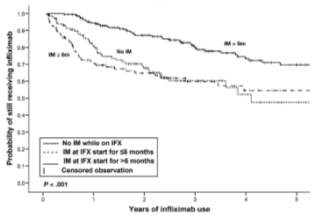
- Prospective adult CD cohort study of anti-TNF induction responders on dual therapy with AZA x 6 mo
  - 22/132 stopped AZA < 6 mo due to intolerance



Viazis N et al. *Eur J Gastroenterol Hepatol* 2015;27:436-441

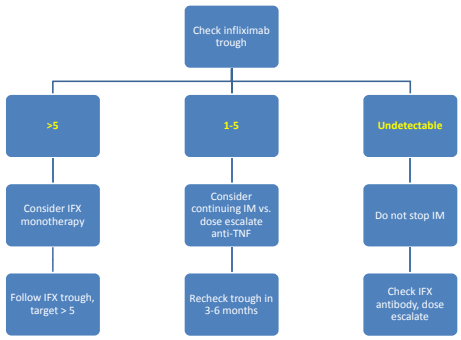
Is 6 Months a Good Target for Dual Therapy?

- Pediatric IBD registry
  - 502 pediatric CD patients starting anti-TNF
- IM > 6 mo:
  - Longer duration of anti-TNF
  - Shorter time to anti-TNF dose escalation
- Thiopurine and MTX
- Did not account for therapeutic monitoring



Grossi V et al. *Clin Gastroenterol Hepatol* 2015;epub ahead of press

Proposed Algorithm for IM Discontinuation After 6 Mo Durable Response on Combination Therapy

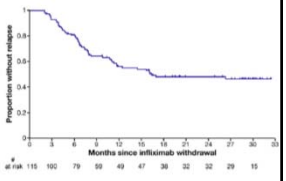


Combination Therapy → Withdrawal of Anti-TNF

STORI

Maintenance of Remission After IFX Stopped

- Prospective study of 115 adult CD patients
  - Steroid free remission x 6 months (CDAI < 150)
- 44% relapse rate in first year (based on CDAI)
- Relapse → restarted IFX
  - 88% clinical remission by 3rd IFX dose
  - No infusion reactions over first 3 doses (w/ steroid pre-treatment)



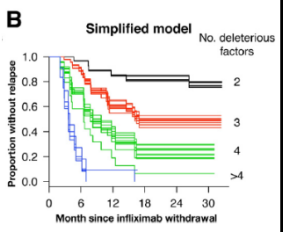
Louis E et al. *Gastroenterology* 2012;142: 63-70

STORI

Stratifying Risk for Relapse After IFX Stopped

Risk factors for relapse
- Male
- Absence of surgical resection
- WBC > 6.0
- Hb ≤ 14.5
- CRP ≥ 5.0 mg/L
- Calprotectin ≥ 300 µg/g

- CDEIS > 0
- IFX trough ≥ 2 mg/L
- Steroids 6-12 mo before trial

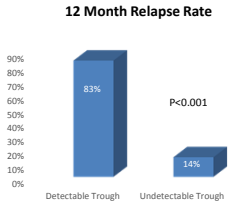


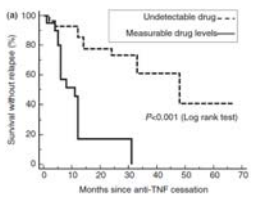
≤2 risk factors → 15% risk of relapse at 1 yr

Louis E et al. *Gastroenterology* 2012;142: 63-70

Anti-TNF Trough and Drug Withdrawal

Retrospective cohort (n=48): Deep remission, discontinued anti-TNF

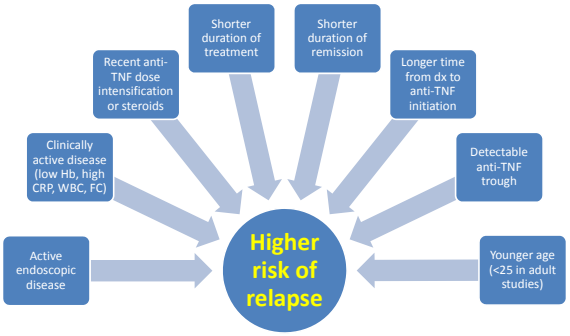




Deep Remission → Undetectable trough may suggest ability to de-escalate

Ben-Horin S et al. *Aliment Pharmacol Ther* 2015; epub ahead of press

Risk Factors for Relapse After Anti-TNF Withdrawal



Stratifying Risk for Relapse with Treatment De-Escalation

Table 4 | Risk level of relapse in case of treatment de-escalation according to disease and therapeutic factors

Low risk	Intermediate risk	High risk
Deep remission: clinical remission with biomarker normalisation and complete mucosal healing	Clinical remission and biomarker normalisation or low elevated inflammation parameters and nonsevere endoscopic lesions	Complicated disease: stenosis and/or fistula (in case of CD)
Long duration of combination therapy (immunosupressant and anti-TNF agent)	Short treatment duration	Perianal disease (in case of CD)
		Extensive disease
		Clinical symptoms
		Elevated biomarkers
		Severe endoscopic lesions
		Treatment with monotherapy

Pariente B et al. *Aliment Pharmacol Ther* 2014;40:338-353

Anti-TNF Withdrawal with Deep Remission

- Prospective, 52 adult IBD patients
  - Endoscopic remission, calprotectin < 100 µg/g
  - 84% also on IM
- **67% clinical remission** at median 13 months
  - 85% were also in endoscopic remission
- No specific risk factors associated with relapse
- Infliximab reinitiation successful & well tolerated

Molander P et al. *Inflamm Bowel Dis* 2014;20:1021-1028

Studies of Anti-TNF Withdrawal for IBD

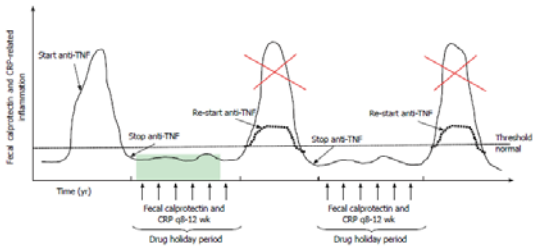
Table 1 Studies on the discontinuation of anti-tumor necrosis factor α therapy in inflammatory bowel disease

IBD type	Anti-TNFα therapy	*n*	Median follow up, mo	SCR at the end of follow up, %	Clinical benefit after re-introduction of anti-TNFα therapy for relapse, %	Ref.
CD	IFX	115	28	55	88	[3]
CD	IFX	48	49	35	ND	[4]
CD	IFX	53	16	12	96	[7]
UC	IFX	28	29	40	71	[7]
CD	IFX or ADM	121	12	55	55	[11]
UC	IFX	51	12	65	94	[13]
CD	IFX or ADM	37	1-44 (range)	26 (1 yr)	ND	[10]
CD	IFX or ADM	17	13	71	100	[9]
UC	IFX	34	13	65	90	[9]
CD	IFX	100	120	52	ND	[6]
CD	IFX or ADM	86	17	64 (1 yr)	93	[12]
CD	IFX	92	47	28	89	[5]

Successful reintroduction of anti-TNF therapy is possible

Papamichael K et al. *World J Gastroenterol* 2015;21:4773-4778

Novel Approach – Intermittent Anti-TNF Therapy?



Papamichael K et al. *World J Gastroenterol* 2015;21:4773-4778

Alternative Options for Maintenance Therapy?

Aminosalicylates

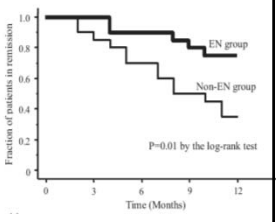
- UC
  - Could be suitable choice for maintenance of remission
  - No data following de-escalation
- Crohn Disease
  - No data

Maintenance Therapy with Enteral Nutrition for Crohn's Disease?

- Prospective, 12 mo study of adult CD patients in remission (CDAI<150)

EN group: 50% calories from elemental diet via overnight NG & low fat diet during day (n=20)

Normal diet (n=20)



Yamamoto T et al. *Inflamm Bowel Dis* 2007;13:1493-1501

Pharmacologic De-Escalation → Dietary Therapies?

Clinical and Mucosal Improvement With Specific Carbohydrate Diet in Pediatric Crohn Disease

*Stanley A. Cohen, *Benjamin D. Gold, †Salvatore Oliva, *Jeffery Lewis, *Angela Stallworth, *Bailey Koch, †Laura Eshee, and §David Mason

(*JPGN* 2014;59: 516–521)

Partial Enteral Nutrition with a Crohn's Disease Exclusion Diet Is Effective for Induction of Remission in Children and Young Adults with Crohn's Disease

Rotem Sigall-Boneh, RD,* Tamar Pfeffer-Gik, RD,* Idit Segal, MD,* Tsili Zangen, MD,* Mona Boaz, RD, PhD,†,‡ and Arie Levine, MD*,‡

(*Inflamm Bowel Dis* 2014;20:1353–1360)

Lifestyle-related disease in Crohn's disease: Relapse prevention by a semi-vegetarian diet

Mitsuro Chiba, Toru Abe, Hidehiko Tsuda, Takeshi Sugawara, Satoko Tsuda, Haruhiko Tozawa, Katsuhiko Fujiwara, Hideo Imai

Newer/Future Therapies

- Vedolizumab
- Ustekinumab
- Tofacitinab (oral JAK inhibitor)
- Mongersen (oral SMAD7 antisense)
- AJM300 (oral α4 integrin antagonist)
- Targeted pathway therapy

Future Questions

- Applicable to patients with more complicated disease behavior?
  - Not represented in most of these studies
- Better predictive factors
  - Biomarkers?
  - Changes in microbiome?
- Which medications more desirable long-term?
  - Risk
  - Cost

Pediatric Considerations

- Paucity of pediatric data
  - Adult data possibly not applicable
  - Need pediatric studies
- Do adult risk factors apply?
  - Age < 25 risk factor for relapse
- Should de-escalation wait until growth completed?

If Considering De-Escalation

- Objectively restage disease → Deep remission
  - Labs/calprotectin
  - Endoscopic
  - Imaging (e.g. bowel ultrasound?)
- Frequent monitoring after de-escalation
  - Consider serial calprotectin*
  - Radiographic/endoscopic when appropriate
  - Therapeutic monitoring
- Aggressive response to relapse

*Molander P et al. *J Crohns Colitis* 2015;9:33-40

Summary

- Goal deep remission before de-escalation
- Evidence supports anti-TNF dose de-escalation
- Combination therapy and durable remission
  - Consider anti-TNF monotherapy
- Data unclear re: de-escalation to IM monotherapy
  - Reinduction possible for relapse
- Pediatric data necessary