IBD – Biologicals and Novel therapeutic regimes

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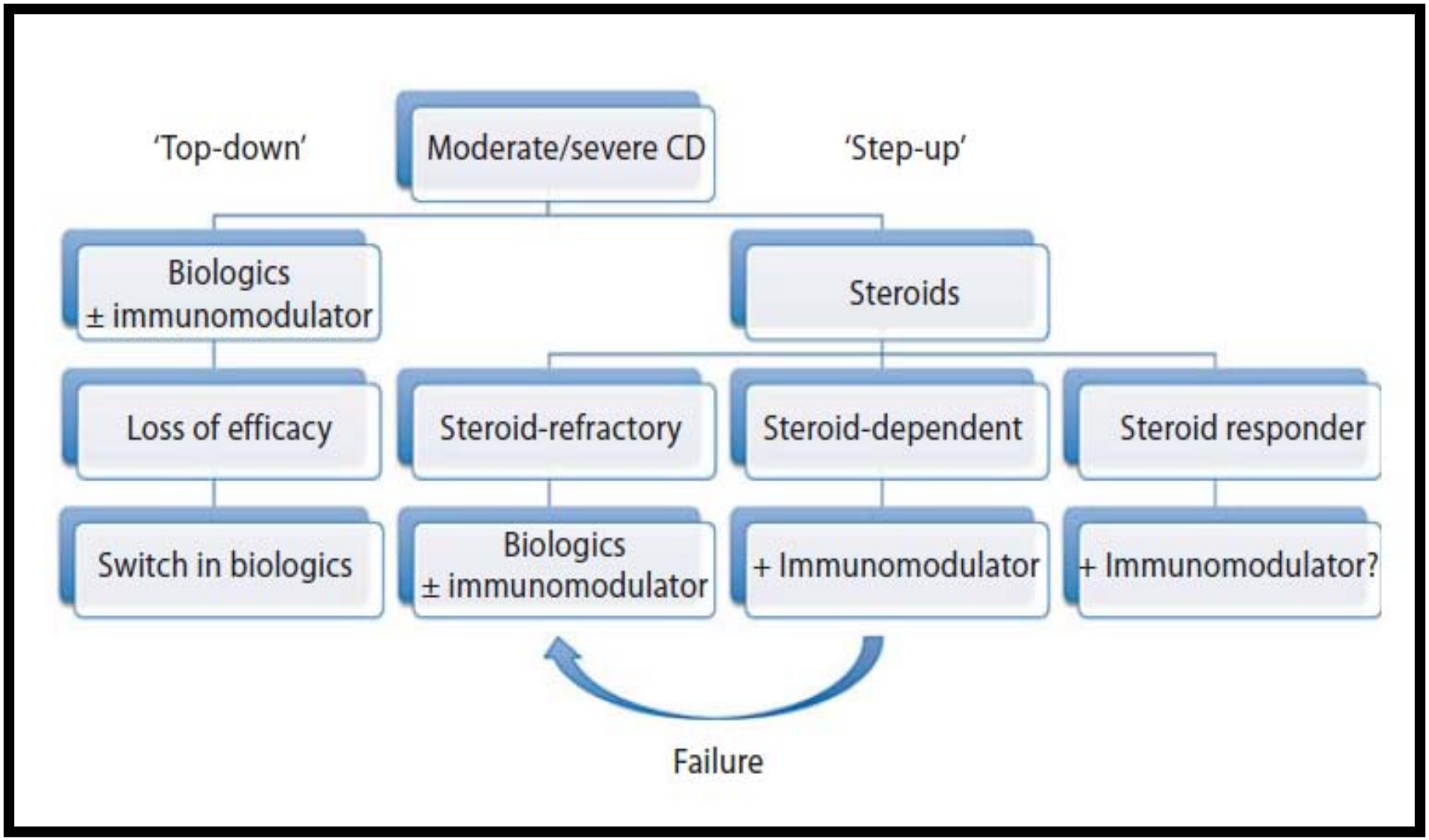
Treatment aims in IBD

- **Traditional treatment goals of IBD**
  - **Control of symptoms**
    - **?Improvement in quality of life**
  - **Induction of remission**
    - **Improvement in quality of life**
    - **? Reduction in complication related to inflammation**

- **Treatment of goals in the era of biologicals & IM**
  - **Mucosal healing: Histological/Endoscopic**
    - **In addition to above, change in course of disease**
  - **Deep remission**
    - **Dream destination – achievable for some**
    - **Reduced risk of all complications**
    - **Change in course of disease – Concept of DMAIDs**

Treatment strategies in IBD- Step up or Top down

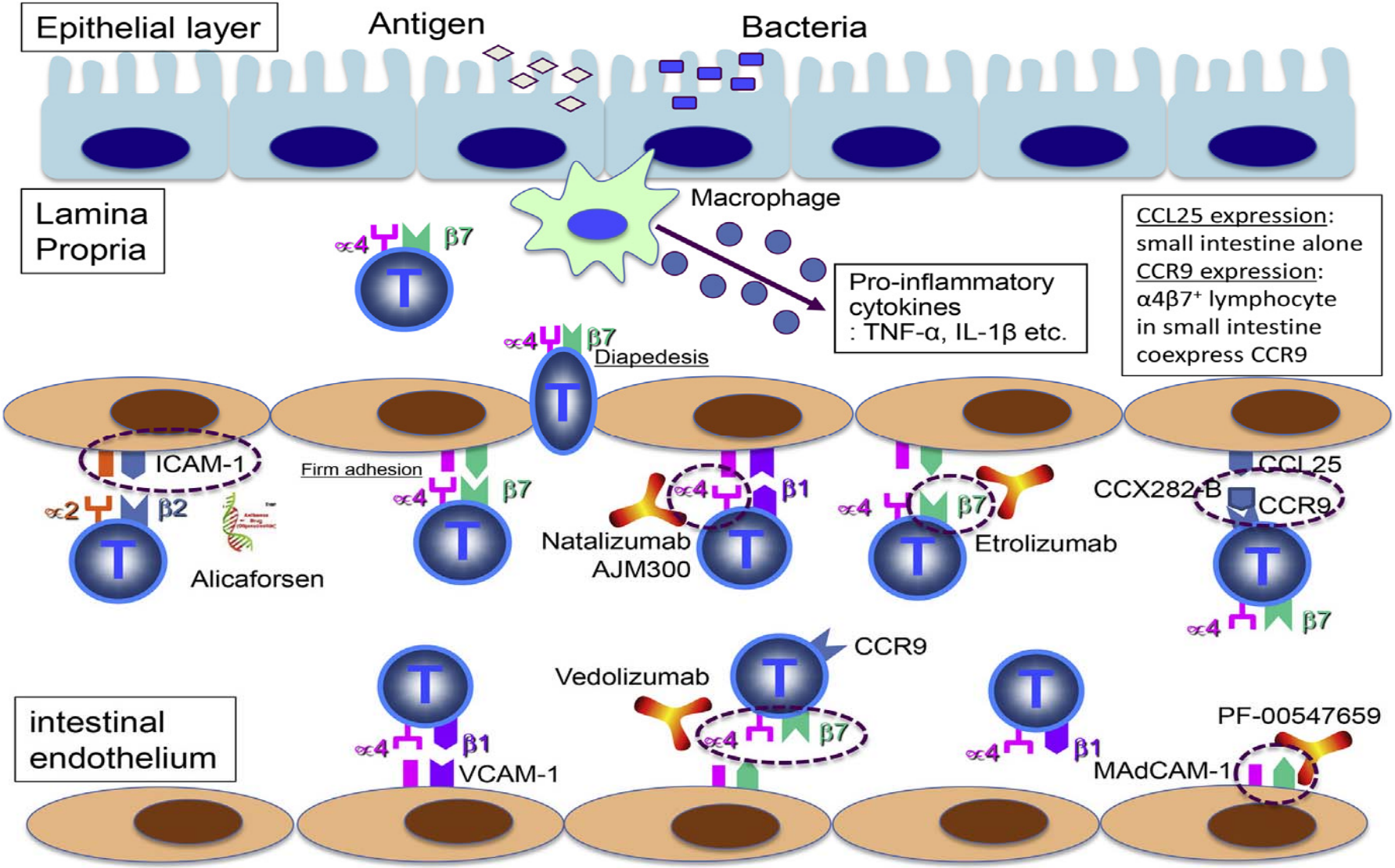


Biological agents for treatment of IBD

Table 1
Some of the key biologic molecules in active use or under study for treatment of IBD

Biologic Target	Antibody/Drug	Mechanism of Action	CD, UC, or Both
TNF-α	Infliximab	Neutralization of TNF-α	Both
	Adalimumab	Neutralization of TNF-α	Both
	Certolizumab pegol	Neutralization of TNF-α	CD
	Golimumab	Neutralization of TNF-α	UC
	Debiaerse	Vaccine against TNF-α consisting of a TNF-α derivative TNF-α kinoid	CD
Effector T cells, B cells	Antigen specific Type 1 regulatory cells (OvaSave)	Autologous ova expanded regulatory T cells injected	CD
α4 integrin	AJM-300	Blockade of α4 integrin	CD
α4 integrin	Natalizumab	Blockade of α4 integrin	Both
α4β7 integrin	Vedolizumab	Blockade of α4β7 integrin	Both
β7 integrin	Etrolizumab (aka rHuMab β7)	Anti-β7 integrin	UC

Lymphocyte Homing Antagonists for IBD

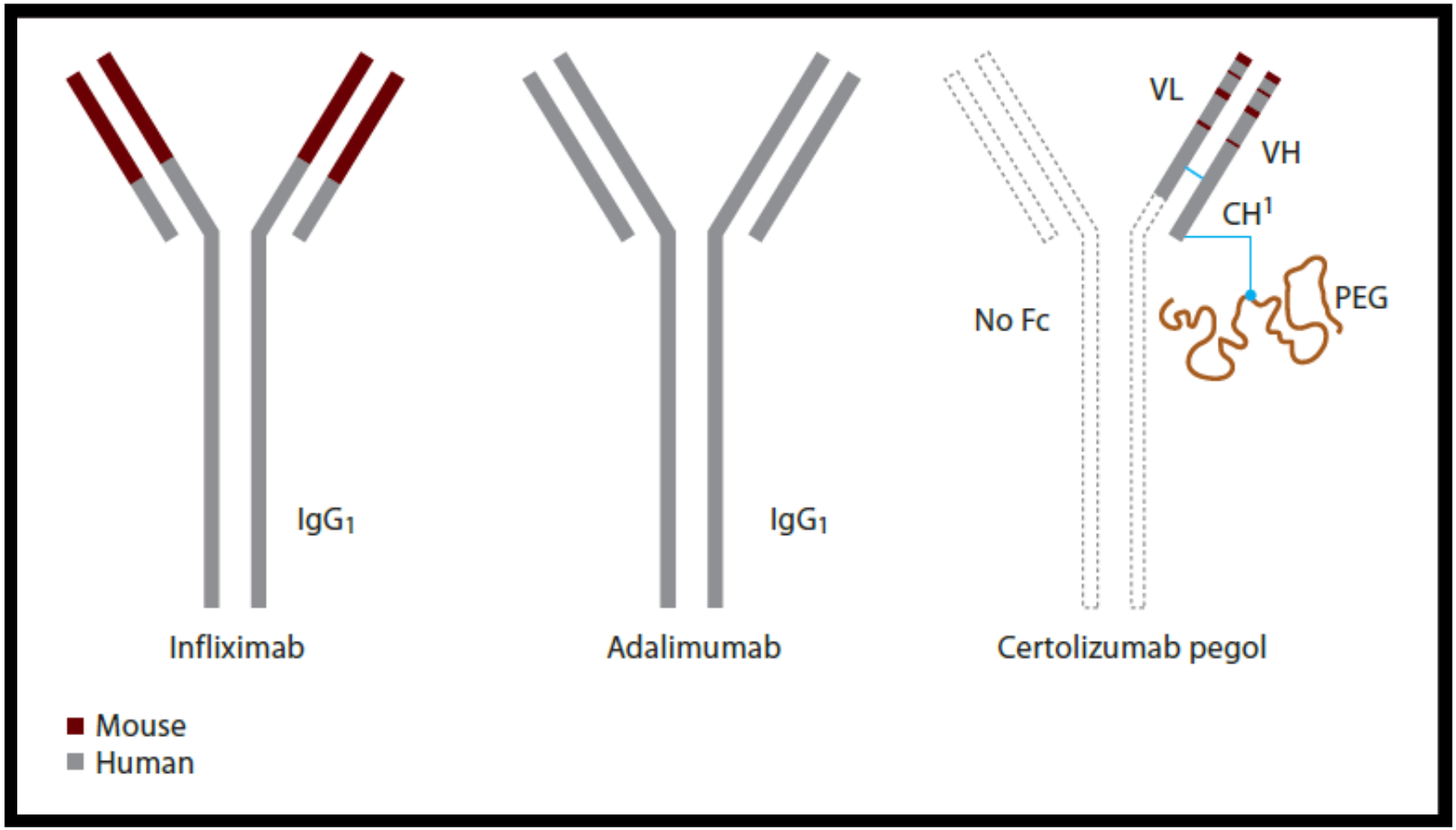


Biologic agents on the horizon

Table 1
Some of the key biologic molecules in active use or under study for treatment of IBD

Biologic Target	Antibody/Drug	Mechanism of Action	CD, UC, or Both
CCR9	CCX282-B	Inhibition of CCR9	CD
	CCX 025	Inhibition of CCR9	CD
IL-21	PF 05230900	IL-21 receptor antagonist	CD
IL-13	QAX576	IL-13 antagonist	CD
	Anrukinzumab	IL-13 antagonist	UC
	Tralokinumab	IL-13 antagonist	UC
IL-17	Vidofludimus	Inhibitor of IL-17 A and IL-17F	Both
IL-12/23	Ustekinumab	Blockade of IL-12/23	CD
IL-18	GSK1070806	Blockade of soluble IL-18	CD
IL-6 and IL-6R	Tocilizumab	Inhibitor of IL -6	CD
	PF04236921	Inhibitor of IL -6	CD
IP-10	MDX 1100	Blockade of interferon-γ inducible protein (IP-10 or CXCL10)	UC
IRAK4/TRAF6/ MyD88	RDP58	Disrupts IRAK4/TRAF6/MyD88 signaling and reduces production of proinflammatory cytokines	Both
JAK3	Tofacitinib	Inhibition of JAK3	Both
MAdCAM-1	PF-547659	Blocks MAdCAM-1	Both
NF-κB	HE3286	Synthetic steroid that modulates NF-κB activity	UC
NKG2D	NN8555	Anti-NKG2D receptor monoclonal antibody	CD
PKC	AEB071/Sotrastaurin	PKC inhibitor	UC
T Cell	Laquinimod	Reduces IL-17 level and interferes with migration of T cells	CD
TLR	DIMS0150	Blockade of Toll-like receptor	UC
	BL-7040	Blockade of Toll-like receptor	UC

Anti TNF drugs for IBD



Dose of commonly used biologicals

Table 1. **Biological Agents for Treatment of Moderately to Severely Active Ulcerative Colitis in Adult Patients***

Biological Agent	Dose
ADA	160 mg SC at 0 wk, followed by 80 mg at 2 wk and then 40 mg every other wk
GLM	200 mg SC at 0 wk, followed by 100 mg at 2 wk and then 100 mg every 4 wk
IFX	5 mg/kg IV at 0 wk, followed by 5 mg/kg at 2 and 6 wk and every 8 wk thereafter
VDZ	300 mg IV at 0 and 2 wk and every 8 wk or every 4 wk thereafter

ADA = adalimumab; GLM = golimumab; IFX = infliximab; IV = intravenous; SC = subcutaneous; VDZ = vedolizumab.

Pharmacokinetic properties of common biologicals

Table 1. Pharmacokinetic properties of anti-TNF antibodies used in inflammatory bowel disease [8]

	Infliximab	Adalimumab	Certolizumab pegol
Route of administration	i.v. infusion	s.c.	s.c.
Half-life (days)	7 to 12	10 to 20	14
Distribution volume (liters)	4.5–6.0	4.7–6.0	8.0
Clearance	15.8 ml/h	12 ml/h	17 ml/h

A Eser et al. Curr Opin Gastroenterol 2013, 29:391–396

Goals of therapy with biologicals in IBD

- Induction of remission
- Maintenance of steroid-free remission
- Closure of fistulizing disease
- Minimization of complications and surgery
- Prevention of disease-related mortality
- Preservation of intestinal function
- Improvement of the quality of life of patients
- Minimization of the adverse effects of treatment

Infliximab in IUC – ACT 1 & ACT trials

Outcome	ACT 1		ACT 2	
	Placebo (n = 121)	IFX 5 mg/kg (n = 121)	Placebo (n = 123)	IFX 5 mg/kg (n = 121)
Week 30	8/79 (10.1)	17/70 (24.3)‡	2/60 (3.3)	11/60 (18.3)§
Week 54	7/79 (8.9)	18/70 (25.7)¶	–	–
Mucosal healing††, n (%)				
Week 30	30 (24.8)	61 (50.4)*	37 (30.1)	56 (46.3)**
Week 54	22 (18.2)	55 (45.5)*	–	–

- **Infliximab is effective in induction and maintenance of remission of IUC**

Rutgeerts P et al. N Engl J Med 2005; 353: 2462–76.

Infliximab in IUC – Belgian experience

Table 2 | Long-term outcomes with infliximab from the Belgian cohort ($n = 121$ unless otherwise stated)[8]

- **Infliximab is useful in long term management of IUC**

† $n = 81$; those who achieved clinical response at a certain time.

Ferrante M et al. J Crohn's Colitis 2008; 2: 219–25..

Infliximab in IUC – Italian experience

Table 4 | Outcomes with infliximab from the Italian cohort (n = 126)[10]

Outcome	6 months	12 months
Steroid-free clinical remission	53.2%	46.8%
Steroid-free clinical remission + mucosal healing	N/A	32.5%
Colectomy	N/A	9.5%

Armuzzi A et al. Inflamm Bowel Dis 2013

Infliximab in IUC – French experience

Table 3 | Outcomes with infliximab from the French cohort (n = 191 unless otherwise stated)[9]

Outcome	Proportion of patients
6 years	27.1% (±7.7%)
Colectomy	18%
Probability of maintaining colectomy-free survival	
1 year	83.5% (±2.96%)
2 years	77.8% (±3.6%)
3 years	75.7% (±4.1%)
6 years	61.4% (±10.6%)
Need for UC-related hospitalisations	36.1%

- **Infliximab is useful in long term management of IUC**

Oussalah A et al. Am J Gastroenterology 2010; 105: 2617–25

Adalimumab in IUC – ULTRA 1 & ULTRA 2 trials

Outcome	ULTRA 1			ULTRA 2	
	Placebo ($n = 130$)	ADA 80/40 ($n = 130$)	ADA 160/80 ($n = 130$)	Placebo ($n = 246$)	ADA 160/80 ($n = 248$)
Week 8	66.2%	70.0%	77.7%§	58.1%	70.2%¶
PGA subscore ≤ 1					
Week 8	46.9%	53.8%	60.0%**	37.4%	46.0%
Stool frequency subscore ≤ 1					
Week 8	37.7%	36.2%	48.5%	28.5%	37.9%††

- Adalimumab is effective in induction and maintenance of remission of IUC

Reinisch W et al. Gut 2011; 60: 780–7.
Sandborn WJ et al. Gastroenterology 2012; 142: 257–65

Golimumab in IUC

Table 7 | PURSUIT SC: Summary of results at week 6 (among patients randomised after dose selection)[27]

Outcome	Placebo (n = 256)	Golimumab 200 mg/100 mg (n = 257)	Golimumab 400 mg/200 mg (n = 258)
Clinical response	29.7%	51.8%*	55.0%*
Clinical remission	6.3%	18.7%*	17.8%*
Mucosal healing	28.5%	43.2%†	45.3%*

* $P < 0.0001$.

† $P = 0.0005$.

Comparative efficacy of different anti TNF drugs

Table 2. **Comparative Efficacy of Biological Agents as Induction Therapy for Moderately to Severely Active Ulcerative Colitis in Adult Patients***

Network Comparator Treatment	OR (95% CrI)
Clinical response	
ADA (160/80/40 mg SC) vs. placebo	1.76 (1.19–2.56)
GLM (200/100 mg SC) vs. placebo	2.11 (1.18–3.28)
IFX (5 mg/kg IV) vs. placebo	4.13 (2.39–7.16)
VDZ (300 mg IV) vs. placebo	3.23 (1.42–7.42)
Clinical remission	
ADA (160/80/40 mg SC) vs. placebo	1.91 (0.98–3.72)
GLM (200/100 mg SC) vs. placebo	2.90 (1.19–6.54)
IFX (5 mg/kg IV) vs. placebo	5.33 (2.28–13.63)
VDZ (300 mg IV) vs. placebo	4.51 (1.13–20.76)
Mucosal healing	
ADA (160/80/40 mg SC) vs. placebo	1.64 (1.18–2.31)
GLM (200/100 mg SC) vs. placebo	1.84 (1.18–2.81)
IFX (5 mg/kg IV) vs. placebo	3.31 (2.07–5.32)
VDZ (300 mg IV) vs. placebo	–

S Danese et al. Annals of Int Medicine 2014:120, 706

Combination of Infliximab & Azathioprine

Table 6 | UC SUCCESS: Preliminary results[20]

- **Combination of Infliximab and azathiorprine is more effective than either drug alone for induction of remission and mucosal healing in IUC**

AZA, azathioprine.

* $P < 0.05$ compared to infliximab.

† $P < 0.05$ compared to AZA.

Sandborn WJ et al

Combination of biological and Immunomodulators

Table 2

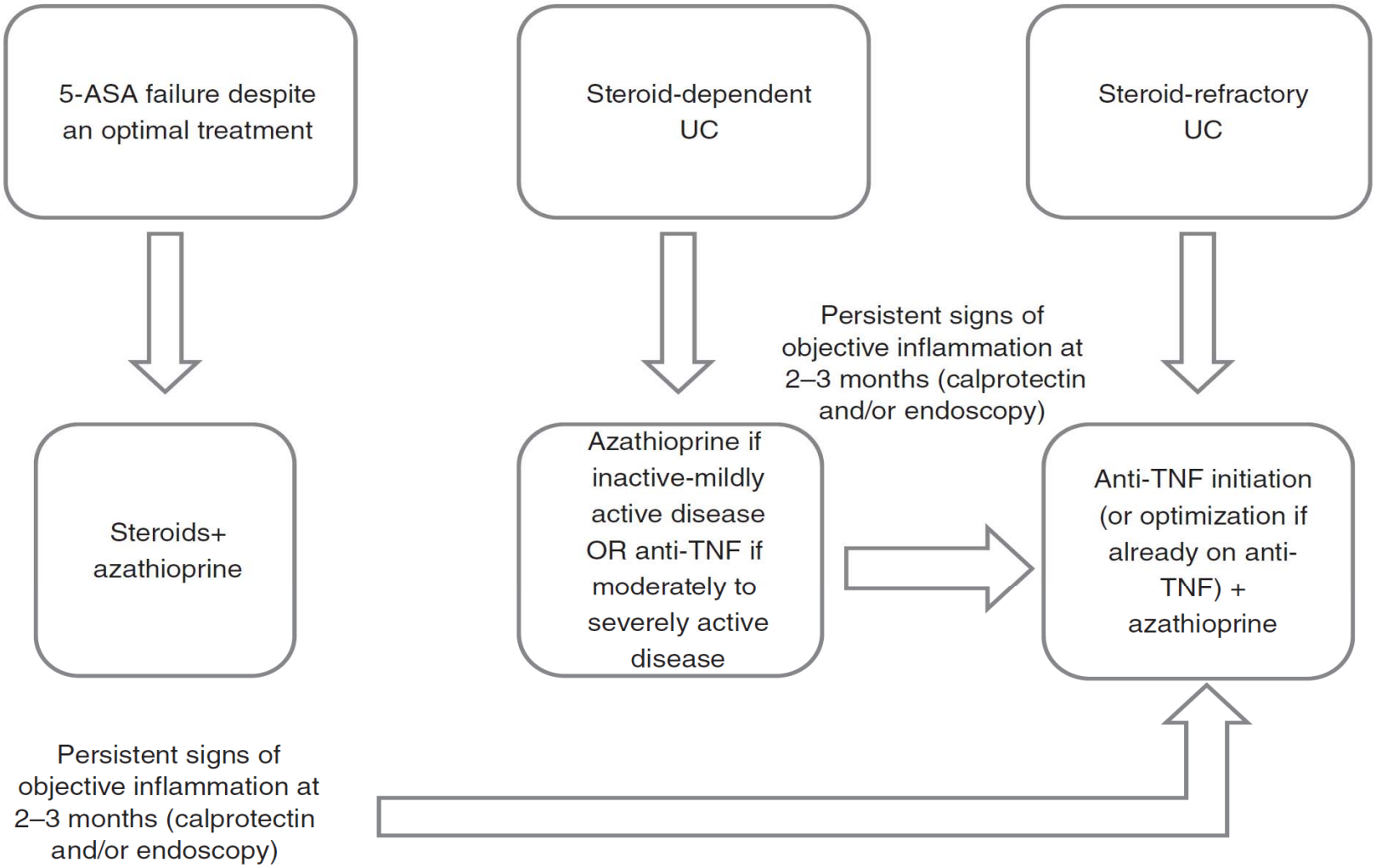
- Combination of anti TNF and immunomodulator is more effective than monotherapy
- Immunomodulator drugs improve the efficacy of anti TNF drug by reducing antibody level and increasing the drug level

CLASSIC II	ADA	45	48	3.8	0
PURSUIT[a]	GOL	50	44	3.8	1.1

Anti TNF therapy in IBD

- **Predictors of good response to Infliximab**
  - Significant short-term C-reactive protein drop
  - Extensive colitis at baseline
  - Concomitant use of immunosuppressive agents
  - Thiopurine- naïve status
  - A detectable trough serum infliximab level
  - Genetic factors
- **Predictors of poor response to Infliximab**
  - Absence of short-term clinical response
  - Baseline CRP level > 5 mg/L
  - Previous IV treatment with corticosteroids and/or cyclosporin

Place of anti TNF therapy in IUC



S Danese et al. Aliment Pharmacol Ther 2013; 37: 855-866

Infliximab for induction of remission in CD

Table 1
Key RCT on the efficacy of anti-TNF therapy for induction of remission in luminal CD

Study, Year of Publication	Location, Time Period	Participants	Intervention (and Comparator)	Outcomes of Interest	Key Results
(SONIC),[6] 2010	2005–2008	severe CD (CDAI 220–450), all patients were immunomodulator-naïve; 36% ileal, 42% ileocolonic, 22% colonic; 508 patients	2, and 6, and then every 8 wk; azathioprine 2.5 mg/kg/d; IFX + azathioprine (combination)	(steroid-free), week 10 Response: 100-point decrease in CDAI, week 10 Mucosal healing: absence of mucosal ulceration at week 26 in patients who had confirmed mucosal ulceration at baseline	sion: IFX vs AZA (vs combination): 37% vs 24% (vs 47%) 2. Response: IFX vs AZA (vs combination): 56% vs 39% (vs 69%) 3. Mucosal healing: IFX vs AZA (vs combination): 30% vs 16% (vs 44%)

- **Infliximab, alone or in combination with the immunomodulators, is effective in inducing remission in moderate to severe CD**

Adalimumab for induction of remission in CD

Study, Year of Publication	Location, Time Period	Participants	Intervention (and Comparator)	Outcomes of Interest	Key Results
ADALIMUMAB					
Hanauer et al	Multinational, 55 sites;	Luminal, moderate-	ADA 40/20 mg, 80/40 mg,	Remission: CDAI <150,	1. Remission: ADA
				decrease in CDAI, week 4; analysis stratified by previous anti-TNF exposure	160/80 vs placebo: 26% vs 8% 2. Response: ADA 160/80 vs placebo: 42% vs 15% In anti-TNF naïve patients: 3. Remission: ADA 160/80 vs placebo: 43% vs 20% 4. Response: ADA 160/80 vs placebo: 50% vs 20%

- **Adalimumab is effective in inducing remission in moderate to severe CD**

Certolizumab for induction of remission in CD

CERTOLIZUMAB PEGOL					
Schreiber et al,[14] 2005	Multinational, 58 centers; 2001–2002	Luminal, moderate-severe CD (CDAI	CZP 100 mg, 200 mg, or 400 mg at weeks 0, 4,	Remission: CDAI <150, week 12	1. Remission: CZP (all doses) vs placebo: placebo: 24% vs 20% In anti-TNF naïve patients: 4. Response: CZP vs placebo: 40% vs 29%
Sandborn et al,[84] 2011	Multinational, 120 sites; 2008–2009	Luminal, moderate-severe CD (CDAI 220–450); 27% ileal, 41% ileocolonic, 29% colonic; 421 patients	Certolizumab 400 mg at weeks 0, 2, and 4; placebo (excluded patients with previous anti-TNF therapy)	Remission: CDAI <150, week 6 Response: 100-point decrease in CDAI, week 6	1. Remission: CZP vs placebo: 32% vs 25% 2. Response: CZP vs placebo: 40% vs 34%

- **Certolizumab pegol is effective in inducing remission in moderate to severe CD**

Biologicals for maintenance of remission in CD

Table 2
Key RCT on the efficacy of anti-TNF therapy for maintenance of remission in patients with luminal CD

Study, Year of Publication	Location, Time Period	Participants	Intervention (and Comparator)	Outcomes of Interest	Key Results
INFLIXIMAB					
Rutgeerts et al[31]	North America and	Luminal, moderate-severe	Initial response to placebo	Relapse: CDAI >150, or	1. Relapse: IFX vs
			then 5 mg/kg or 10 mg/kg at 8-weekly intervals thereafter; placebo		
ADALIMUMAB					
Colombel et al (CHARM),[18] 2007	Multinational, 92 sites; 2003–2005	Luminal and penetrating, moderate-severe CD (CDAI 220–450); 499 patients	Initial open-label ADA 80/40, then randomized (stratified by responder status) at week 4 to ADA 40 mg weekly or 40 mg every other week thereafter; placebo	Relapse: CDAI ≥150, week 56 Maintenance of remission in week 4-responders: CDAI <150, week 56 in patients with 70-point decrease in CDAI at week 4	1. Relapse: ADA vs placebo: 62% vs 88% 2. Remission, in week 4 responders: ADA vs placebo: 38% vs 12%

- **Infliximab and adalimumab are effective in maintenance of remission in CD**

Biologicals for maintenance of remission in CD

Sandborn et al (CLASSIC-II),[19] 2007	North America and Europe, 53 sites; 2002–2005	Luminal, moderate-severe CD (CDAI 220–450), enrolled in CLASSIC-I trial; included only	Initial ADA or placebo as part of CLASSIC-I, then patients with remission (CDAI <150 at week 4 and	Relapse: CDAI ≥150, week 56 Maintenance of remission: CDAI <150, week 56	1. Relapse: ADA vs placebo: 19% vs 56% 2. Remission: ADA vs placebo: 81% vs 44%
(PRECISE 2),[20] 2007	2004–2005	moderate-severe CD (CDAI 220–450); 428 patients	400 mg at weeks 0, 2, 4, then patients with response (CR100) at week 6, randomized to CZP 400 mg every 4 wk; placebo	week 26 Maintenance of remission: CDAI <150, week 26	placebo: 52% vs 72% 2. Remission: CZP vs placebo: 29% vs 48%

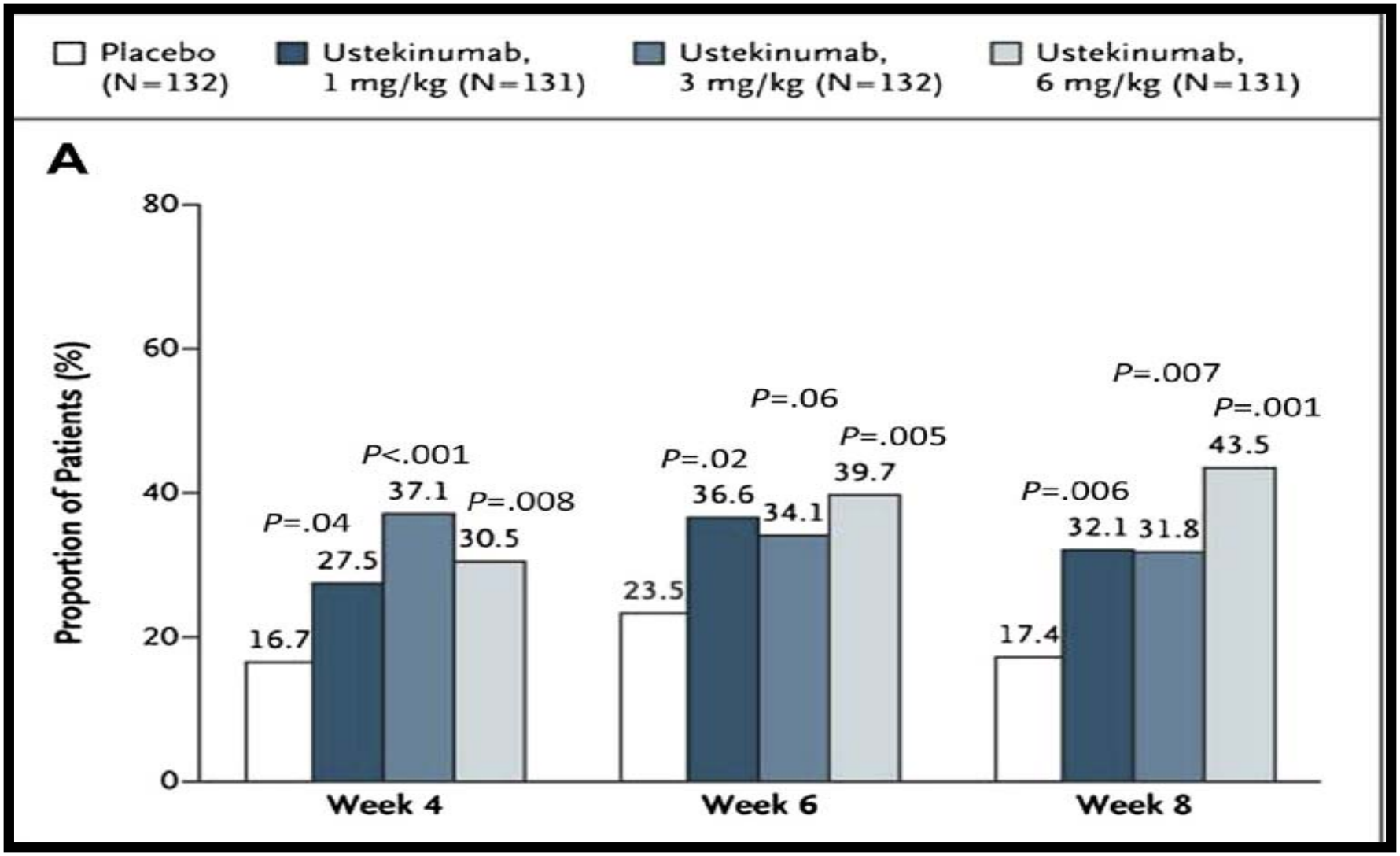
- **Adalimumab and Certozumab pegol are effective in maintenance of remission in CD**

Leukocyte trafficking modulators for IBD

Table 1
Selected leukocyte trafficking modulators for inflammatory bowel disease

Drug	Description	Developer	Target	Indication	Clinical Status
Tysabri	Humanized IgG4 mAb	Biogen Idec (Cambridge, MA)	α4β1 integrin, α4β7 integrin	Multiple sclerosis, Crohn disease	Approved (FDA)
Entyvio	Humanized IgG1 mAb	Takeda Pharmaceuticals (Deerfield, IL)	α4β7 integrin	Crohn disease	Registration (in USA)
AMG-181	Fully human IgG2 mAb	AstraZeneca (London, UK)/Amgen (Thousand Oaks, CA)	α4β7 integrin	Crohn disease, ulcerative colitis	Phase 2
Etrolizumab (rhuMAb β7, RG7413)	Humanized IgG1 mAb	Genentech (South San Francisco, CA)	α4β7 integrin, αEβ7 integrin	Ulcerative colitis	Phase 2
PF-00547659	Fully human IgG2k mAb	Pfizer (New York, NY, USA)	MAdCAM-1	Crohn disease, ulcerative colitis	Phase 2
AJM300	Oral small-molecule prodrug	Ajinomoto Pharmaceuticals (Tokyo, Japan)	α4 integrin	Ulcerative colitis, Crohn disease	Phase 2
Vercirnon (CCX282-B)	Oral small molecule	ChemoCentryx (Mountain View, CA)/GSK (Brentwood, Middlesex, UK)	CCR9	Crohn disease	Phase 3 (on hold)

IL-12 / IL23 inhibitor Ustekinumab for CD



IL-12/IL23 inhibitor Ustekinumab for CD

- **Safety**
  - **Negligible increase in risk of infection**
  - **Drug reactions minimal**
  - **Issue major adverse cardiac event**
  - **One case report of demyelination**

When to start biological therapy

- **IUC and CD**
  - **steroid-refractory,**
  - **Steroid dependent**
  - **immunomodulator-refractory**
  - **patients intolerant to conventional therapies**

- **CD**
  - **A complex fistula in CD is an indication for biological therapy in conjunction with surgical drainage**
    - **Combining anti-TNF therapy with ciprofloxacin may improve results, with 73% " fistula response " after 18 weeks ' combination treatmentvs. 39 % on IFX alone**
  - **Efficacy of IFX for induction of fistula closure is better documented than for ADA or CZP**

Consensus guideline on use of biological in IBD

The London Position Statement of the World Congress of Gastroenterology on Biological Therapy for IBD With the European Crohn's and Colitis Organization: When to Start, When to Stop, Which Drug to Choose, and How to Predict Response?

Geert R. D'Haens, MD, PhD[1], Remo Panaccione, MD[2], Peter D.R. Higgins, MD[3], Severine Vermeire, MD, PhD[4], Miquel Gassull, MD, PhD[5], Yehuda Chowers, MD[6], Stephen B. Hanauer, MD[7], Hans Herfarth, MD[8], Daan W. Hommes, MD, PhD[9], Michael Kamm, MD[10,11], Robert Löfberg, MD[12], A. Quary[13], Bruce Sands, MD[14], A. Sood, MD[15], G. Watermayer[16], Bret Lashner, MD[17], Marc Lémann, MD[18], Scott Plevy[19], Walter Reinisch, MD[20], Stefan Schreiber, MD, PhD[21], Corey Siegel, MD[22], Stephen Targan, MD[23], M. Watanabe, MD[24], Brian Feagan, MD[25], William J. Sandborn, MD[26], Jean Frédéric Colombel, MD, PhD[27] and Simon Travis, MD[28]

GV Assche et al. Am J Gastroenterol 2011; 106:1594–1602;

Guideline: Indications for use of biological

- **Clinical characteristics which define need for biological therapy**
  - **Factors which define "disabling disease"**
    - **Presenting at a young age,**
    - **Stricturing disease,**
    - **Needing initial treatment with steroids,**
    - **Perianal disease at diagnosis**
  - **Prevalence of disabling disease : 37-54%**

- **Complex fistula in (in conjunction with surgical drainage)**
- **Patients with fibrostenotic CD rarely benefit from biologic therapy**
  - **If the stricture is inflammatory, it may respond**

Guideline: Biologicals for IUC

- **Infliximab is effective for treatment-refractory, moderate or severe UC**
  - **IFX can induce or maintain remission and mucosal healing**
    - **IFX appears to halve the risk of colectomy during a year of treatment**
- **For patients admitted to the hospital with severe UC colitis that is then refractory to intravenous steroids, IFX halves the need for colectomy on that admission (29% vs 67%)**
  - **The efficacy of IFX relative to cyclosporine remains to be determined.**
  - **Continued treatment with IFX or AZA to reduce the risk of relapse appears sensible, but it is unclear which approach is superior.**

Guideline: Biological in IBD

- Patients with UC refractory to conventional therapy which has responded to infliximab should best be considered for continuing therapy, since scheduled re-treatment is effective for maintaining response and reducing the risk of colectomy.

- Combined treatment with an immunosuppressant and infliximab for patients with moderate-severe CD is more effective than monotherapy

- Natalizumab should not be combined with an immunosuppressant or prolonged corticosteroids - risk of progressive multifocal leucoencephalopathy.

Guideline: Biological in IBD

- For CD naïve to thiopurines, the combination of IFX and AZA is better for induction of remission and mucosal healing over 1 year
  - Optimal maintenance strategy after this induction regimen unknown.
    - Applicability to other agents ???
    - ? Monotherapy preferable after one year – lower risk of infection / malignancy
- Patients with moderate to severe luminal CD or fistulizing CD who have responded to an induction regimen with anti-TNF therapy should be considered for scheduled re-treatment with or without concomitant immunomodulators.
  - This strategy is more effective than episodic therapy for maintaining response.
  - NAT & other agents are also effective at maintaining response.

Guideline: Biological in IBD

- **Predictors of response to anti TNF therapy**
  - **Early luminal CD vs longstanding disease**
  - **High CRP level**
  - **High trough concentrations of IFX**
  - **Concomitant therapy with immunosuppressive drugs**
  - **Genetic factors**

Guideline: Strategies of treatment with biological

- **Bridge therapy to an oral immunomodulator has been shown to be associated with a higher rate of clinical relapse than scheduled re-treatment for patients with moderate-severe luminal CD who have responded to induction biological therapy**

- **Hospitalized patients with UC refractory to intravenous steroids who have responded to IFX can have a prolonged response to an oral immunomodulator without scheduled re-treatment**

Guideline: Strategies of treatment with biological

- **A diminished or suboptimal response to IFX /other agents can be managed by:**
  - **Shortening the interval between dosing**
  - **Increasing the dose**

- **Suboptimal response even to increased dose –**
  - **Another agent of different class**
  - **Low probability of response with another agent of same class**

- **Patients with CD who have intolerance to one anti-TNF therapy may achieve a therapeutic response to a different anti-TNF agent**

End points for biological therapy

- **When to stop biologicals**
  - **Withdrawal of therapy is possible after one year in patients with CD who have both complete mucosal healing and no biological evidence of inflammation**
  - **Paucity of data for UC.**

Contraindications of anti TNF therapy

- **Patients with a history of malignancy (excluding non-melanoma skin cancer)**
- **Active infection**
- **Lymphoproliferative disorder**
  - ► **“ Boxed Warnings ” alerting prescribers to an increased risk of lymphomaand malignancies in children or adolescents treated with anti-TNF therapy**
- **Severe congestive heart failure,**
- **Demyelinating neurologic disease**

Choice of biological therapy

- **First-line biologic for luminal CD should be tailored to the individual patient, practice and country setting.**
  - **IV – Infliximab, Natalizumab**
    - **Longer time of administration, risk of serum sickness**
  - **SC – Adalimumab, Certolizumab**
    - **Pain and local site reactions**

- **Infliximab has the longest and most extensive history of published clinical trial data and clinical experience in CD.**

- **Studies with other biologic agents (adalimumab, certolizumab pegol and natalizumab) suggest that they produce generally similar benefi ts in CD**

Practical issues with biological therapy

- Primary non-response : about one third
- Secondary non-response or loss of response – 10-30 %

- High cost
- Adverse drug reactions

- Need for monitoring and optimization of therapy
  - ► Significantly inferior results if treatment not optimized
  - ► Cost involved with optimization

- Risk of infections

- ? Risk of malignancy
- Lack of direct comparative trials

Adverse drug reaction to biological in IBD trials

Appendix Table. AE Rates in RCTs of Biological Agents for Moderately to Severely Active Ulcerative Colitis*

Outcome	Event Rates, %							
	ADA Biological Group†	ADA Placebo Group†	IFX Biological Group‡	IFX Placebo Group‡	GLM Biological Group§	GLM Placebo Group§	VDZ Biological Group‖	VDZ Placebo Group‖
Any AE	70.1	67.9	84.7	79.1	48.9	47.1	61.7	63.6
SAEs	8.8	10.5	16.1	22.5	6.4	6.6	5.5	10.9
AEs leading to discontinuation of study drug	8.2	8.8	5.0	9.4	3.1	2.7	–	–
Infectious AEs	32.7	28.8	35.5	31.1	20.4	17.3	44.1	40.4
Serious infection	1.6	1.7	2.1	2.5	1.2	1.9	1.3	2.5
TB	0.2	0.0	0.0	0.0	0.6	0.2	–	–
CHF	0.2	0.0	–	–	–	–	–	–

S Danese et al. Annals of Int Medicine 2014:120, 706

Infections with Biological therapy - TB

- **Look for latent TB**
  - **A TST is considered to be positive when the induration is at least 5 mm in diameter.**
  - **Interferon gamma g release assays (IGRA) (QuantiFERON Gold In-Tube, and T-SPOT.TB)**
    - **No repeat visit**
    - **Better specificity than TST**
    - **Immunomodulator or anti-TNF-a treatments do not seem to significantly interfere with results**
    - **prednisone of 10 mg/d or greater, severely depress the accuracy of both IGRA and TST**
- **Suspicious radiologic findings should also be considered suggestive of TB**
- **INH should precede the biological treatment by at least 3 weeks**

Screening for infection before biological therapy

- Patients with HBV infection should not receive anti-TNF treatment
- There is no evidence of HCV reactivation with anti- TNF
- HIV infection : relative contraindication
- Immunizations
  - ► HBV vaccination, diphtheria, (DTP) vaccination,
  - ► HPV, influenza vaccination, pneumococcal vaccine
- Live vaccines are contraindicated during anti TNF therapy
- Any abscess needs effective drainage first.

Vaccination in IBD patients

Table 4
Recommended routine vaccinations for patients with IBD

Vaccine	Live/ Inactive	Serology Before Vaccination?	Timing	Need for Revaccination	Strategy During Active Immunosuppressive Treatment
MMR	Live	Yes	Once, if never vaccinated	No	Avoid
Varicella	Live	Yes	If no clear history of disease/ vaccination, negative VZV IgG	No	Avoid
Zoster	Live	—	>60 y	No	Avoid
Td/Tdap	Inactive	No	Administer vaccine if not given over the past 10 y or give Tdap if Td ≥2 y	See timing	Allowed
HPV	Inactive	No	Females 9–26 y old	3 Doses (0, 2, 6 mo)	Allowed
Influenza	Inactive	No	Annual	Annual	Allowed Live vaccine (Flumist) should be avoided (including household)
Pneumococcal	Inactive	No	Every 5 y	Every 5 y	Allowed
Hepatitis A	Inactive	Yes	2 doses at 0, 6–12 mo; or 0, 6–18 mo	Booster >10 y	Allowed
Hepatitis B	Inactive	Yes	3 doses at 1, 1–2, 4–6 mo	Check postvaccine titers 1 mo after finishing last dose. If no response, then revaccinate with double dose. If low-titer anti-HBs, administer booster	Allowed
Meningococcal vaccine	Inactive	No	Persons at risk,[a] if not previously vaccinated	Every 5 y	Allowed

Infections in IBD

Table 2
Frequent infections in patients with IBD

Bacterial	*Clostridium difficile* *Legionella pneumophila* *Nocardia* species *Salmonella* species *Streptococcus pneumoniae* TB
Viral	CMV Epstein-Barr virus Hepatitis B (reactivation) Herpes simplex virus Human papillomavirus Influenza JC virus reactivation with natalizumab
Fungal and parasitic infections	Aspergillosis *Candida* species Coccidiomycosis Cryptococcosis Cryptosporidiosis Histoplasmosis

Risk factors for malignancy with biological therapy

- **Non-modifiable risk factors**
  - **Males**
  - **Older age**
  - **Disease duration and subtype**
  - **Extraintestinal manifestations**

- **Modifiable risk factors**
  - **Smoking**
  - **Photoprotection**
  - **Vitamin D deficiency**
  - **Immunomodulators**

Risk of malignancy with biological therapy

Table 3
Overall rate of lymphoma and skin cancer with biologics

	Lymphoma	NMSC	Melanoma
Expected rate (general population)[a]	20/100,000 PYF	NR	21/100,000 PYF
Anti-TNF therapy (infliximab, adalimumab, certolizumab, golimumab)	6.1/10,000 PYF	5/10,000 PYF[b]	n/a
Anti-integrins (vedolizumab, natalizumab)	3.2/10,000 PYF	9.7/10,000 PYF[c]	6.5/10,000 PYF
Anti-IL-12/23 (ustekinumab)[d]	2.2/10,000 PYF	52/10,000 PYF[e]	6.7/10,000 PYF
Janus kinase inhibitors (tofacitinib)[d]	6.6/10,000 PYE	45/10,000 PYE	2.9/10,000 PYE

Risk of malignancies with biological therapy

Table 4
Rate of notable extraintestinal malignancies with biologics

	Overall Rate	Lung	Bladder	Breast	Prostate	Leukemia
Expected rate (general population)[a]	463/100,000 PYF	61/100,000 PYF	21/100,000 PYF	124/100,000 PYF	152/100,000 PYF	13/100,000 PYF
Anti-TNF therapy (infliximab, adalimumab, certolizumab, golimumab)	69/10,000 PYF	8.6/10,000 PYF	4.3/10,000 PYF	4.3/10,000 PYF	4.3/10,000 PYF	3.3/10,000 PYE[b]
Anti-integrins (vedolizumab)	58/10,000 PYF	6.5/10,000 PYF	3.3/10,000 PYF	6.5/10,000 PYF	n/a	n/a
Anti-IL-12/23 (ustekinumab)[c]	67/10,000 PYF	1.1/10,000 PYF	2.2/10,000 PYF	4.5/10,000 PYF	15/10,000 PYF	2.2/10,000 PYF
JAK inhibitors (tofacitinib)[c]	94/10,000 PYE	23/10,000 PYE	2.2/10,000 PYE	19/10,000 PYE	2.2/10,000 PYE	n/a

Infusion reactions with biological therapy

Table 1
Classification of acute infusion reactions

Mild	Flushing, dizziness, diaphoresis, nausea, palpitations, hyperemia
Moderate	Chest pain, hypertension (>20 mm Hg increase in systolic blood pressure), hypotension, fever, urticaria, dyspnea, chills, rash
Severe	Hypertension (>40 mm Hg increase in systolic blood pressure), hypotension, significant dyspnea, bronchospasm, stridor, wheezing, rigors

Optimizing the biological therapy

- **Blood level of drug**
  - ► **Value of measurement of trough level**
- **Body weight, age and sex.**
- **Inflammatory burden of disease**
- **Development of anti-drug antibody**
- **Concomitant therapy with immunomodulators (DMAID)**

Factors affecting clearance of Infliximab

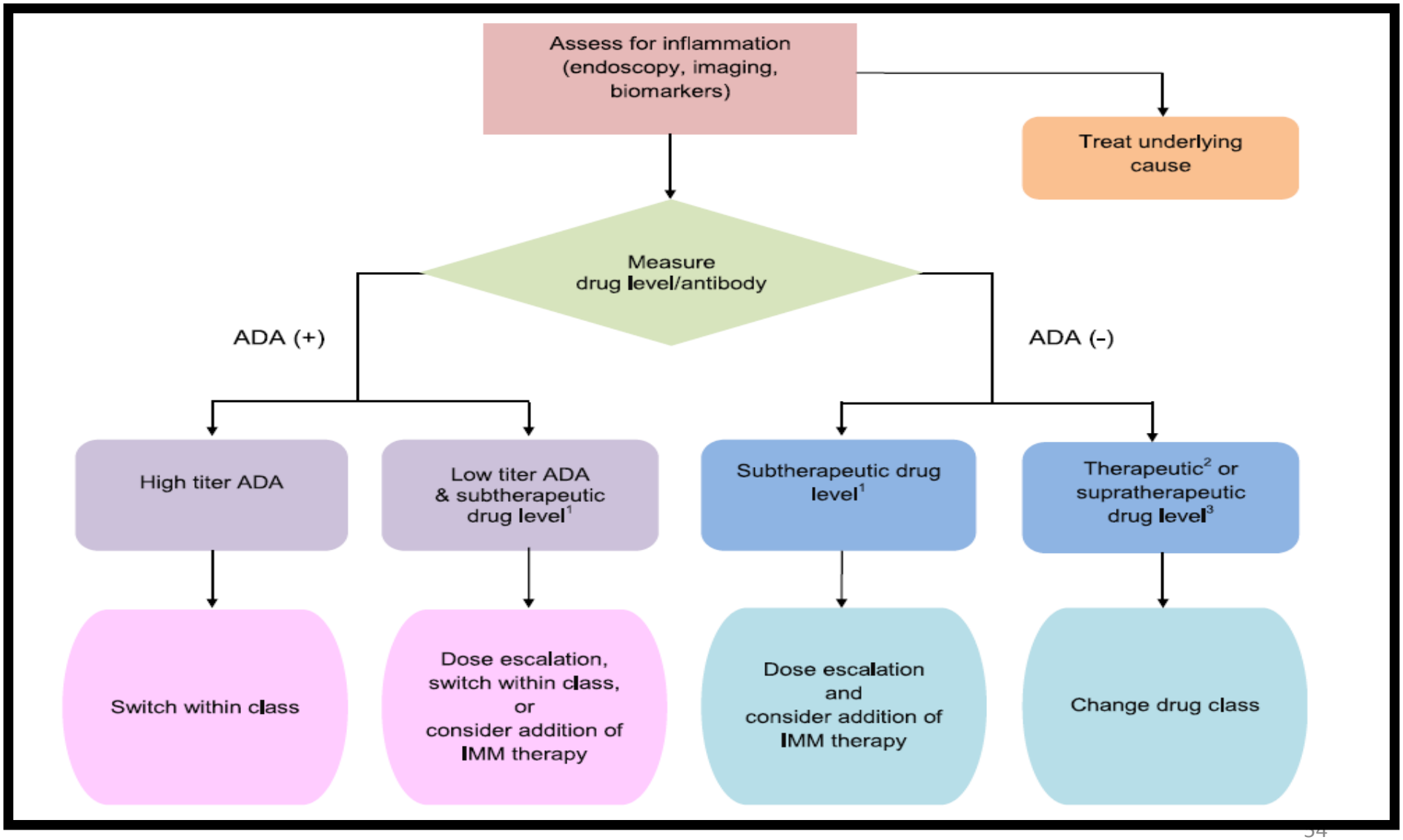
Table 2. Factors influencing the clearance of IFX in a population based PK model (data for ulcerative colitis) [13]

	Higher clearance	Lower clearance
Sex	Male	Female
ADA	Positive	Negative
Albumin levels	Lower	Higher

ADA, antidrug antibodies.

A Eser et al. Curr Opin Gastroenterol 2013, 29:391–396

Strategies for optimization of biological therapy



Non- response to biologicals

- **Primary non-response : 10-30 %**
  - **Change – use of another agent**
    - **Similar mechanism**
    - **Different class**
- **Secondary non-response – 10-30 %**
  - **Dose intensification**
  - **Change of agent**
    - **Similar mechanism**
    - **Different class**
  - **Combination of biological and IS**

Pregnancy and biological therapy

Table 2
Biologic therapy in pregnant patients with inflammatory bowel disease

		FDA Pregnancy		Recommendations for	
	humanized IgG1 monoclonal anti-TNF antibody			newborn infections	
Natalizumab	Recombinant humanized IgG4 monoclonal antibody	C	Limited human data	Low risk: limited human data	Limited human data

- Anti TNF drugs are pregnancy safety class B drugs
- Certolizumab does not cross placental barrier
- Natalizumab is pregnancy safety class C drug

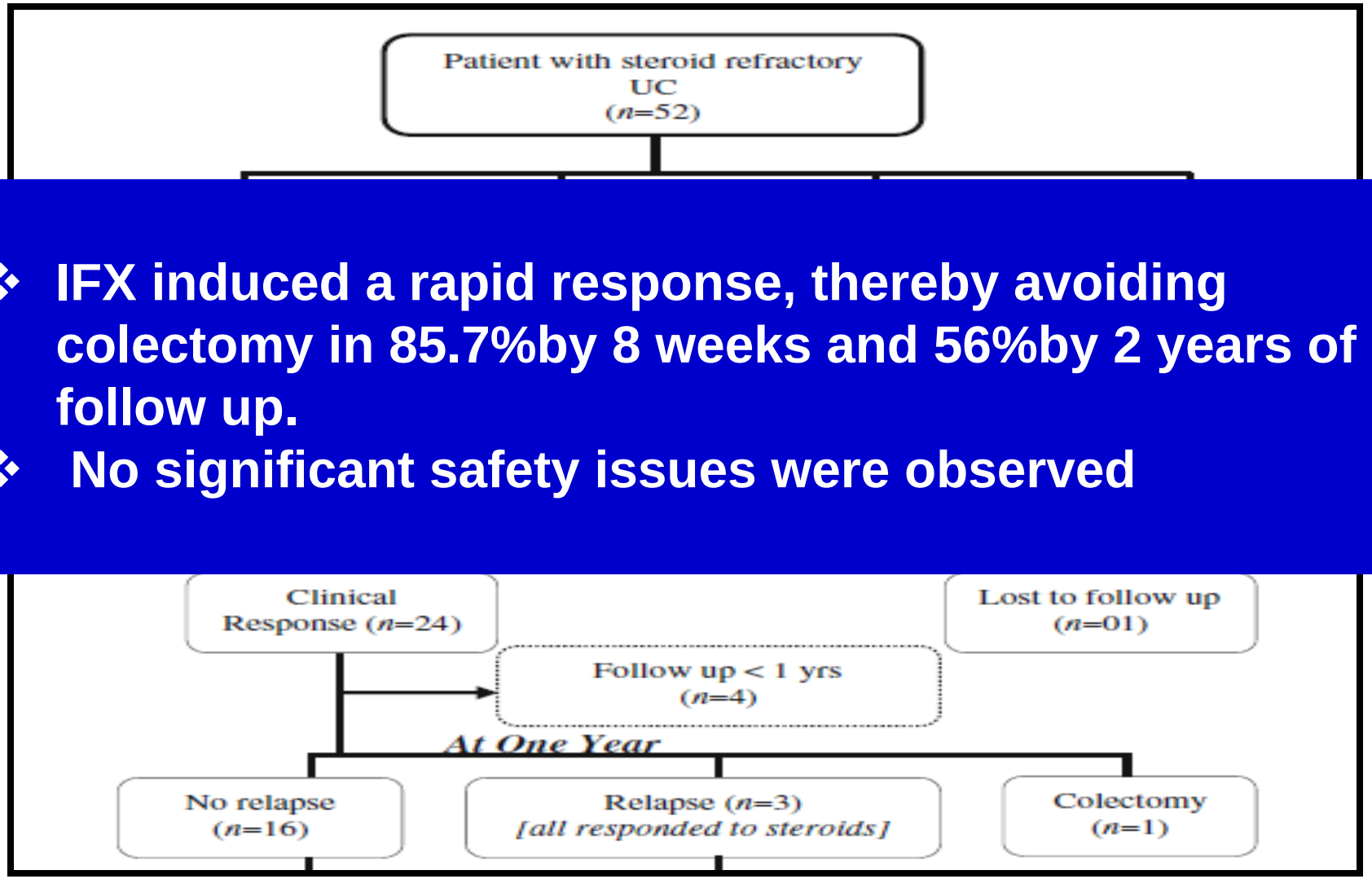
Indian Scenario

Crohn's disease in India – Multicenter study

		UC	CD	*p*-value
Mesalamine	Never	15/510 (2.9)	6/161 (3.7)	<0.001
	Previous	37/510 (7.2)	61/161 (37.9)	
	Current	458/510 (89.7)	94/161 (58.4)	
Other 5-aminosalicylates	Never	145/255 (56.8)	38/59 (64.41)	0.268
	Previous	41/255 (16.1)	4/59 (6.8)	
	Current	69/255 (27.1)	17/59 (28.8)	
Sulfasalazine	Never	186/254 (73.2)	53/80 (66.2)	0.415
	Previous	35/254 (13.8)	15/80 (18.7)	
	Current	33/254 (13)	12/80 (15)	
Corticosteroids	Never	34/444 (7.6)	5/130 (3.8)	0.058
	Previous	281/444 (63.3)	90/130 (69.2)	
	Current	129/444 (29.1)	35/130 (26.9)	
Azathioprine	Never	208/325 (64)	27/116 (23.3)	<0.001
	Previous	20/325 (6.1)	16/116 (13.8)	
	Current	97/325 (29.8)	73/116 (62.9)	
Other immunosuppressant	Never	252/257 (98)	74/77 (96.1)	0.189
	Previous	2/257 (0.8)	0/77 (0)	
	Current	3/257 (1.7)	3/77 (3.9)	
Infliximab	Never	282/283 (99.6)	87/91 (95.6)	0.010
	Previous	1/283 (0.3)	2/91 (2.2)	
	Current	0/283 (0)	2/91 (2.2)	

Task force of ISG. Indian J Gastroenterol 2012; 31(6):299–306

Infliximab in patients with severe steroid-refractory IUC: Indian experience



- IFX induced a rapid response, thereby avoiding colectomy in 85.7%by 8 weeks and 56%by 2 years of follow up.
- No significant safety issues were observed

Sood A et al. Indian J Gastroenterol 2014; 33(1):31–34

Tofacitinib in IBD

- **A janus kinase inhibitor – predominantly JAK 1 & JAK 3**
  - **A reduction in production of inflammatory cytokines and differentiation into cell lineages associated with autoimmunity**
  - **Disrupted lipopolysaccharide signaling**
- **In IUC – moderate to severe active colitis**
  - **Administered for 8 weeks twice daily**
  - **Clinical response observed in 32%, 48%, 61%, and 78% of patients treated with tofacitinib 0.5 mg, 3 mg, 10 mg, and 15 mg, respectively, compared with 42% of patients on placebo**
  - **Remission rate was 13%, 33%, 48%, 41% (10% with placebo)**

Crohn Disease and Tofacitinib

- **139 pts with with moderate to severe CD**
  - **Clinical response was achieved in 36%, 58%, and 46% of patients in the 1-, 5-, and 15-mg tofacitinib arms (placebo group 47%)**
  - **Clinical remission occurred in 31%, 24%, and 14% (placebo response rate 21%)**
  - **No clinical benefit but improvement in biochemical markers of inflammation**

Adverse effects of Tofacitinib

Table 3
Summary of adverse events with tofacitinib

Major Adverse Effect	Mechanism	Incidence Rate[a]	Dose Dependence	Observed in IBD Trials?
Serious Infection	Blocks cytokine signals via γ-chain	3.00	No	Yes
Malignancy[b]	Blocks IFN-γ signaling and NK cell proliferation	0.94	Yes	No
Lymphoma	Blocks IFN-γ signaling and NK cell proliferation	0.07	Yes	No
Major cardiovascular event[c]	Unclear, possibly related to lipid changes	0.57	No	No

Other Janus kinase & small molecule inhibitors

Table 4
Novel small-molecule inhibitors in clinical trials

Drug	Primary Inhibition	Populations Studied
Tofacitinib	JAK1 & JAK3 > JAK2	RA, UC, CD
Ruxolitinib (Incyte)	JAK 1 & JAK2	RA, Psoriasis
Baricitinib (INCB028050)	JAK1 & JAK2	RA, Psoriasis[a]
GLPG0634	JAK1 > JAK2 & TYK2	RA, CD[a]
GLPG0974	Free fatty acid receptor	UC[a]
VX-509	JAK3	RA
JNJ-54781532	JAK1 & JAK3	UC[a]

Summary

- Wide choice of biologicals are available for treatment of IBD
- They are useful in particularly in disabling disease
- Biologicals are effective in both IUC & CD
  - For induction as well as maintenance of remission
- Multiple practical issues are involved with use of biologicals
  - Primary non-response, loss of response
  - Significant risk of infection and new malignancies
  - Cost issue
- Direct comparative studies with different agents is not available – so initial choice is virtually empirical
- A large number of newer drugs are on horizon

Thank you

Lymphocyte Homing Antagonists for IBD

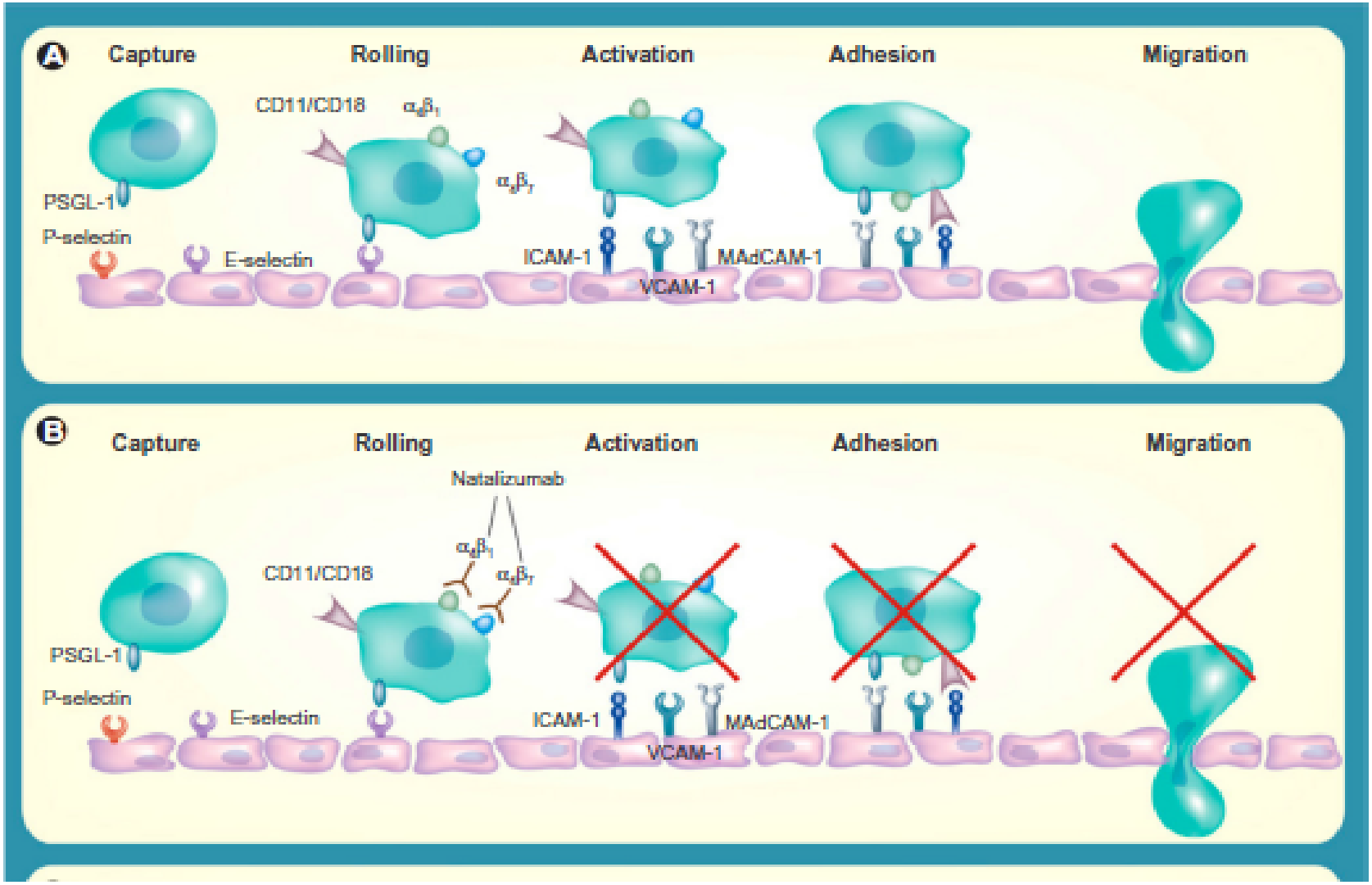


Table 3 Summary of congenital abnormalities reported

Congenital abnormalities (n = 19)	Affected (n)	Anti-TNF exposure
Ventricular septal defect	3	IFX (1), ADA (2)
Chromosomal abnormalities	2	IFX
Congenital hip dysplasia	2	IFX (1), ADA (1)
Intestinal malrotation	1	IFX
Congenital hypothyroidism	1	IFX
Hemangiomas	1	IFX
L hand polydactyly	1	IFX
Tetralogy of Fallot	1	IFX
Patent ductus arteriosus	1	ADA
Atrial septal defect and peripheral pulmonic stenosis	1	ADA
Bicuspid aortic valve and agenesis of corpus callosum	1	ADA
Primary craniosynostosis	1	ADA
Microcephaly	1	ADA
Congenital hydronephrosis	1	ADA
Undescended testes	1	ADA

Table 2 Summary of anti-tumor necrosis factor exposures and birth outcomes *n* (%)

Anti-TNF exposure	Birth outcomes, *n* (with relative percents)						
	Fetal exposures	Live births	SA	SB	PTB/ PMB	LBW/SGA	CA
IFX/ADA/CTZ total	472	405 (85.8)	32 (8.2)	2 (0.6)	41 (19.9)	8 (6.1)	19 (4.1)
IFX[1]	194	155 (79.9)	15 (10.6)	2 (1.1)	21 (26.9)	5 (4.4)	6 (4.0)
IFX in IBD[2]	151	117 (77.5)	11 (8.9)	2 (1.4)	16 (36.4)	5 (4.8)	4 (3.5)
ADA[1]	261	242 (92.7)	16 (6.9)	0 (0.0)	20 (15.9)	2 (28.6)	13 (5.4)
ADA in IBD[2]	224	210 (93.8)	13 (5.8)	0 (0.0)	15 (17.0)	2 (28.6)	12 (5.7)
CTZ[1]	17	8 (47.1)	1 (5.9)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)
CTZ in IBD[2]	17	8 (47.1)	1 (5.9)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)
Outcome percents in general US population[69-73]		64.60%	16.50%	0.60%	12.30%	8.20%	3.00%-5.00%

Table 3
Infectious screening in newly diagnosed patients with IBD (before immunosuppression)

	History	Diagnostic Tests
TB	History of exposure Travel/habitation in endemic areas	Chest radiography (in all patients prebiologic) TST or IGRA (in all patients prebiologic)
Varicella	History of illness or vaccination	Serology (if no clear history of illness/vaccination)
MMR	History of vaccination/illness	Serology (if no clear history of illness/vaccination)
HPV	History of vaccination	None
Hepatitis B	History of vaccination/illness	Anti-HBs, HBsAg, Anti-HBc (in all patients prebiologic) Liver enzymes HBV DNA if there is a history of chronic disease or carrier state
Hepatitis A	History of vaccination	Serology
Diphtheria and pertussis	History of vaccination	None
Meningococcal meningitis	History of vaccination	None
Pneumococcal pneumonia	History of vaccination	None

Infections and drugs therapy for IBD

Medications associated with systemic immunosuppression in patients with IBD	
Corticosteroids	20 mg of prednisone for 2 wk
Immunomodulators	Thiopurines (azathioprine, 6-mercaptopurine) Methotrexate
Biologics	Anti-TNF-a (infliximab, adalimumab, certolizumab pegol, golimumab) Leukocyte adhesion inhibitors (natalizumab, vedolizumab) IL-12/23 receptor antagonist (ustekinumab)

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MMR	History of vaccination/illness	Serology (if no clear history of illness/vaccination)
HPV	History of vaccination	None
Hepatitis B	History of vaccination/illness	Anti-HBs, HBsAg, Anti-HBc (in all patients prebiologic) Liver enzymes HBV DNA if there is a history of chronic disease or carrier state
Hepatitis A	History of vaccination	Serology
Diphtheria and pertussis	History of vaccination	None
Meningococcal meningitis	History of vaccination	None
Pneumococcal pneumonia	History of vaccination	None

Risk of lymphoma with anti TNF therapy

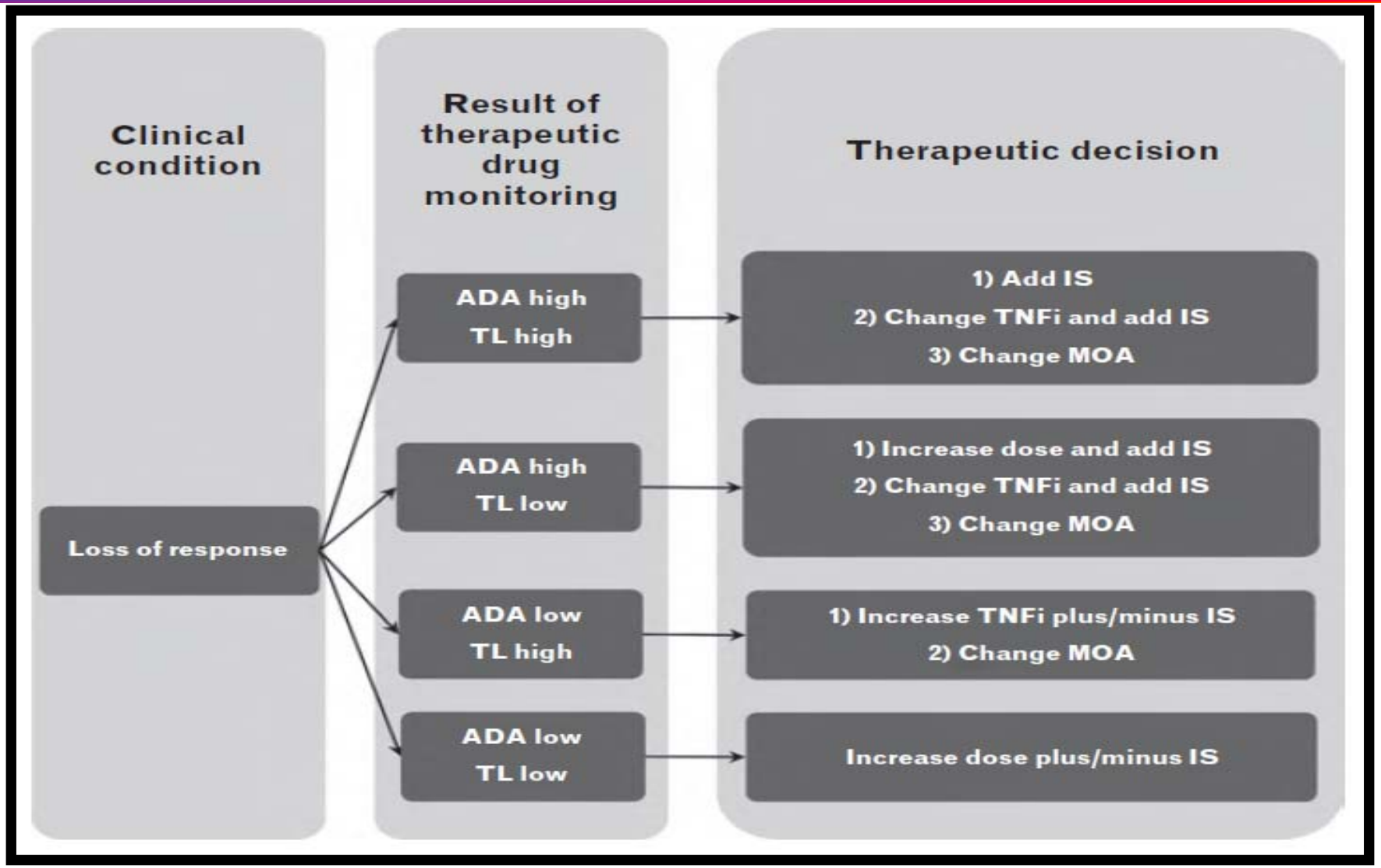
Table 1
Risk of lymphoma with anti-TNF therapy

	Incidence Rate (per 10,000 PYF)	SIR	95% CI
Current Thiopurine Without Anti-TNF Exposure			
Herrinton et al,[16] 2011	4.1	1.4	1.2–1.7
CESAME[20,a]	8.8	6.5	3.5–11.2
Khan et al,[77] 2013	14.6	7.5	4.7–12.0
Current Thiopurine with Previous Anti-TNF Exposure			
CESAME[20,a]	8.8	6.5	3.5–11.2
Herrinton et al,[16] 2011	15.1	5.3	3.5–7.0
Current Anti-TNF Therapy with Current Thiopurine Therapy			
Dulai et al,[10] 2014	2.1	3.5	0.35–19.6
TREAT[29]	4.5	2.0	0.87–3.95
Siegel et al,[26] 2009	6.1	3.2	1.5–6.9
CESAME[20]	10.4	10.2	1.2–36.9
Osterman et al,[25] 2014	14.3	8.0	0.97–29.0
Herrinton et al,[16] 2011	19.1	6.6	4.4–8.8
Current Anti-TNF Therapy with Previous Thiopurine Exposure			
Herrinton et al,[16] 2011	14.9	5.2	3.5–6.8
Current Anti-TNF Therapy Without Thiopurine Exposure			
n/a	—	—	—

Table 2
Risk of NMSC with anti-TNF therapy

	Treatment	OR	95% CI
Long et al,[35] 2010	Recent use (<90 d)		
	Biologics	2.47	1.29–4.73
	Immunomodulators	3.71	2.74–5.02
	Combination therapy	5.85	3.2–10.8
	Persistent use (>365 d)		
	Biologics	3.23	1.24–8.45
	Immunomodulators	4.45	2.94–6.75
	Combination therapy	6.75	2.74–16.65
Long et al,[18] 2012	Overall risk		
	Biologics	1.14	0.95–1.36
	Immunomodulators	1.85	1.66–2.05
	Persistent use (>365 d)		
	Biologics	1.63	1.12–2.36
	Immunomodulators	2.72	2.27–3.26
	Combination therapy	3.89	2.33–6.46
Osterman et al,[25] 2014	Combination therapy	3.46	1.08–11.06

Optimization of biological therapy



A Eser et al. Curr Opin Gastroenterol 2013, 29:391–396

- Visilizumab, an anti-CD3 monoclonal antibody binding to activated T-cells, induces apoptosis
- IL-2 receptor (CD25) inhibitor, basiliximab, has shown potential in open studies for steroid-refractory UC
- another CD25 inhibitor, daclizumab, was ineffective in a controlled trial of 159 patients with moderately active UC
- Abatacept (CTLA4-Ig: a co-stimulatory receptor inhibitor) has not shown benefit in a phase III trial in ulcerative colitis
- Interferon-alpha – trial of 60 pts, not useful

Crohn's disease in India – Multicenter study

Parameter	Definite CD ($n = 141$)	Probable CD ($n = 41$)	
Age at onset (mean ± SD; years)	33.2 ± 13.6	39.0 ± 12.8	$P = 0.013$
Gender (male:female)	97:44	20:21	$P = 0.02$
Age at onset (Montreal) ($n = 179$)			$P = 0.04$
A1 (<16 years)	11 (8%)	0	
A2 (17–40 years)	92 (66%)	22 (56%)	
A3 (>40 years)	37 (26%)	17 (44%)	
Disease behavior (Montreal) ($n = 180$)			$P < 0.001$
B1	57 (40%)	34 (87%)	
B2	40 (28%)	4 (10%)	
B3	44 (31%)	1 (3%)	
Disease location (Montreal) ($n = 179$)			$P < 0.01$
L1	52 (37%)	6 (16%)	
L2	47 (33%)	26 (68%)	
L3	36 (26%)	5 (13%)	
L4	6 (4%)	1 (3%)	
UGI modifier ($n = 179$)	24 (17%)	2 (5%)	$P = 0.07$
Perianal modifier ($n = 179$)	27 (19%)	4 (13%)	$P =$ ns
Both small bowel and colon assessed	110 (78%)	18 (44%)	$P < 0.001$
Symptoms at onset			
Partial intestinal obstruction	46 (33%)	4 (10%)	$P < 0.01$
Bloody diarrhea	49 (35%)	24 (59%)	$P < 0.01$
Fever	42 (30%)	3 (7%)	$P < 0.01$
Disease distribution			
Rectal sparing	82 (62%)	13 (37%)	$P < 0.01$
Skip lesions	39 (32%)	20 (67%)	$P < 0.001$
Terminal ileum	62 (51%)	7 (28%)	$P = 0.04$
Ileum	49 (41%)	3 (13%)	$P < 0.01$
Small bowel stricture	51 (44%)	2 (10%)	$P < 0.01$

Das K. Dig Dis Sci (2009) 54:1099–1107

Site & pattern of involvement in CD in India

Table 1 Demographic characteristics of patients with Crohn's disease and intestinal tuberculosis

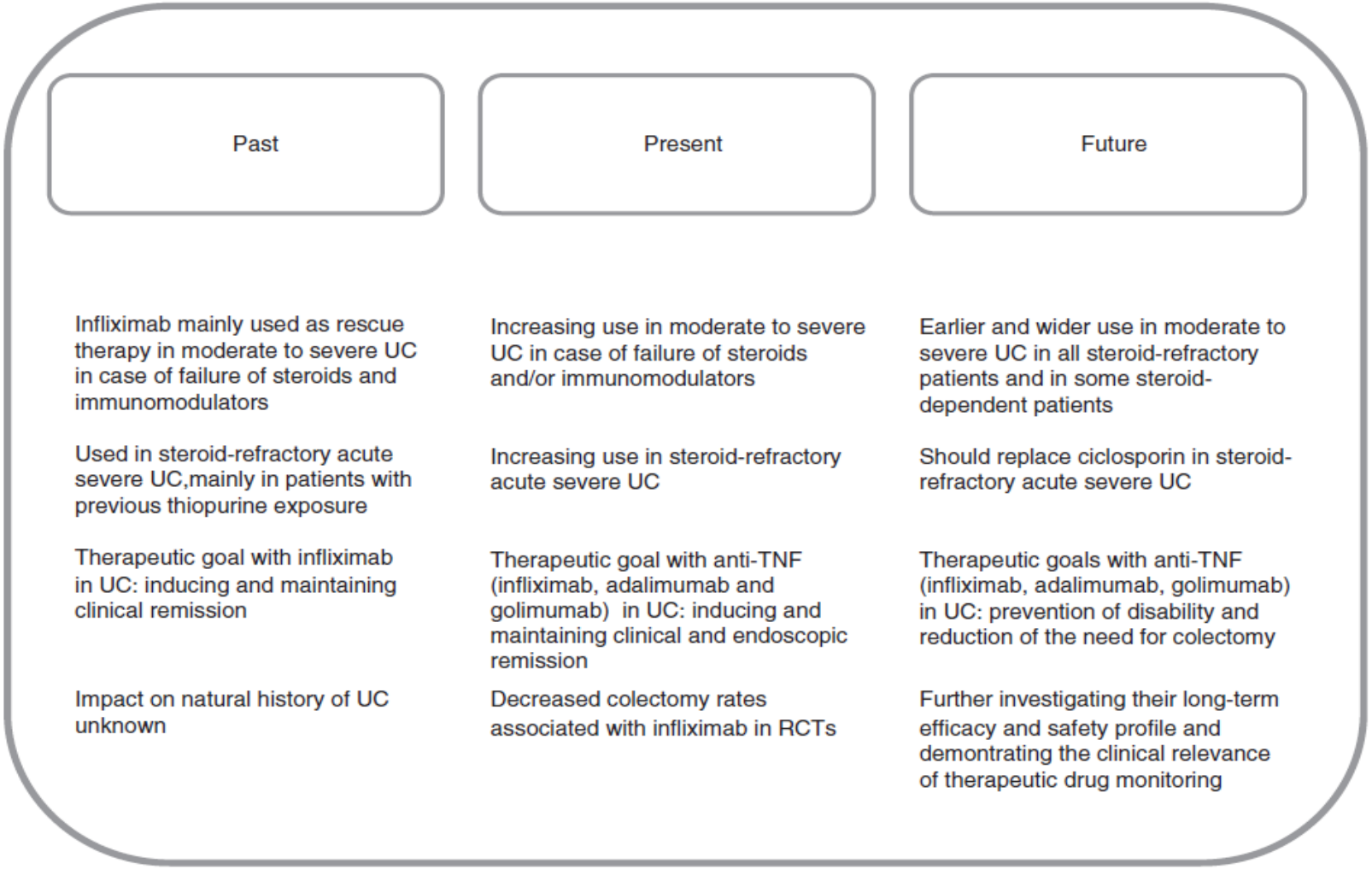
Characteristic	Crohn's disease ($n = 59$)		Intestinal tuberculosis ($n = 30$)	
Mean age ± SD	35.8 ± 12.4		34.6 ± 14.2	
Sex (M:F)	32:27		22:8	
Median (range) duration of the disease (mo)	72 (10–276)		22 (2–120)	
Extent of disease	Terminal ileum (L1):[a]	3 (5.08%)	Ileocolonic:	23 (76.66%)
	Colonic (L2):	21 (35.59%)	Small intestine only:	3 (9.9%)
	Ileocolon (L3):	27 (45.76%)	Colon only:	2 (6.66%)
	Terminal ileum + UGI:	1 (1.69%)		
	Colon + UGI:	3 (5.08%)		
	Ileocolon + UGI:	4 (6.77%)		
Behavior of disease	Nonstricturing, nonfistulizing (B1):	44 (74.57%)		
	Stricturing (B2):	13 (22.03%)		
	Penetrating (B3):	2 (3.38%)		

Makharia GK. Dig Dis Sci (2007) 52:33–39

- **“Smoking cessation is associated with a 65% reduction in the risk of a relapse compared to continuing to smoke, which is a similar magnitude to that obtained with immunomodulator therapy [22] . So patients with CD who smoke should be strongly advised to stop and also offered help to achieve this “**

- **Smoking has a strong adverse effect on the response to infliximab**

Ole Haagen Nielsen et al. Dig Dis 2012;30(suppl 3):121–133



S Danese et al. Aliment Pharmacol Ther 2013; 37: 855-866

Table 1
Medications associated with systemic immunosuppression in patients with IBD

Corticosteroids	≥20 mg of prednisone for ≥2 wk
Immunomodulators	Thiopurines (azathioprine, 6-mercaptopurine) Methotrexate
Biologics	Anti-TNF-α (infliximab, adalimumab, certolizumab pegol, golimumab) Leukocyte adhesion inhibitors (natalizumab, vedolizumab) IL-12/23 receptor antagonist (ustekinumab)

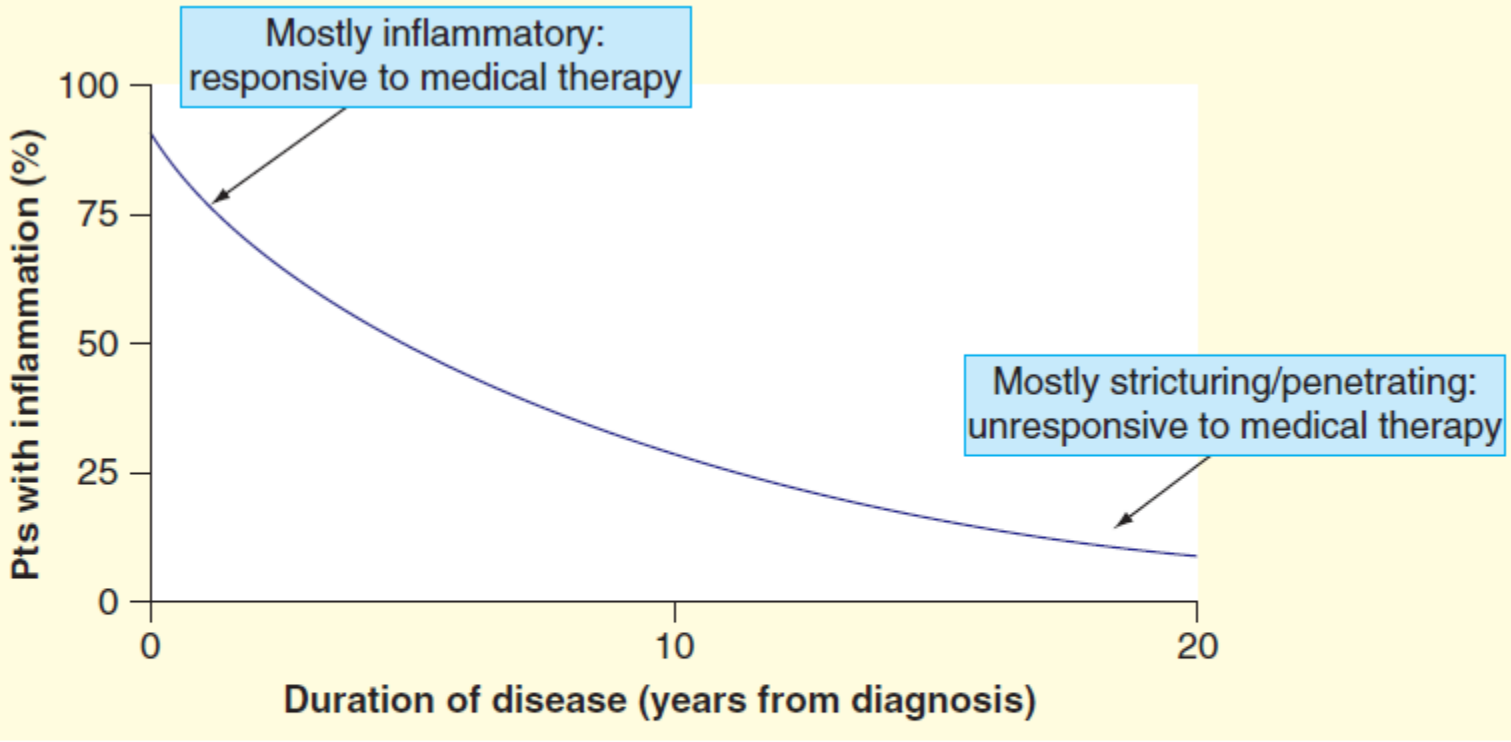
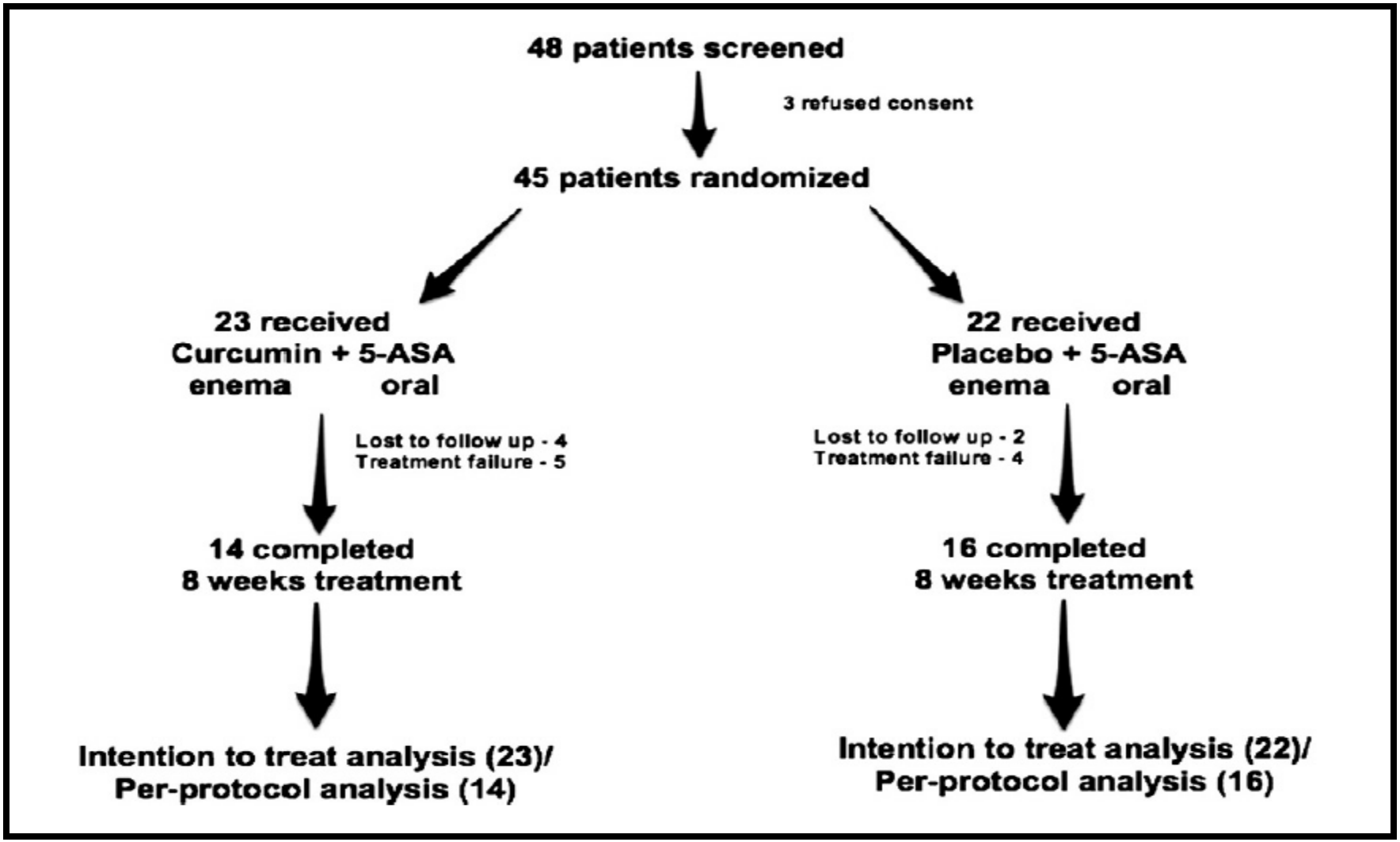


Figure 1. Evolution of Crohn's disease behavior over time. In most patients, Crohn's disease presents at diagnosis as an inflammatory condition, which is amenable, in principle, to medical therapy. Due to scarring and deposition of collagen over the years, Crohn's disease evolves into a stricturing/penetrating disease which is essentially unresponsive to medical therapy and can only be managed by surgery.
Modified with permission from [38].

Curcumin enema for mild-to-moderate distal IUC



Singla V & Ahuja V. Journal of Crohn's and Colitis (2014) 8, 208–214

Curcumin enema for mild-to-moderate distal IUC

Table 2 Results.

Intention to treat analysis	NCB-02 (curcumin) group n = 23	Placebo group n = 22	p value
Response — n (%)	13 (56.5%)	8 (36.4%)	0.18
Remission — n (%)	10 (43.5%)	5 (22.7%)	0.14
Mucosal healing — n (%)	12 (52.2%)	8 (36.4%)	0.29
Per protocol analysis	**NCB-02 (curcumin) group n = 14**	**Placebo group n = 16**	**p value**
Response — n (%)	13 (92.9%)	8 (50%)	0.01
Remission — n (%)	10 (71.4%)	5 (31.3)	0.03
Mucosal healing — n (%)	12 (85.7%)	8 (50%)	0.04

Singla V & Ahuja V. Journal of Crohn's and Colitis (2014) 8, 208–214

Ayurvedic treatment of IUC

- **Medication :** ***Udumbara kvatha basti with oral Ayurveda medicaments including Kutaj ghan vati, Udumbara kvatha, and combination of Musta, Nagakesara, Lodhra, Mukta panchamrut rasa for*** **a one-month period**

Symptoms	Mean score		%	S.D.	S.E.	t *Value*	P *Value*
	B.T.	A.T.					
Bowel frequency	3.06	0.55	81.81	0.827	0.126	19.90	< 0.001
Bleeding in stool	2.48	0.20	91.58	0.908	0.138	16.45	< 0.001
Abdominal pain	2.19	0.29	86.76	0.943	0.169	11.23	< 0.001
Weakness	2.55	0.84	65.97	0.739	0.119	14.04	< 0.001
Body weight (in Kg)	50.55	51.72	02.31	1.181	0.336	3.480	< 0.001

Effects of Ayurved therapy on signs and symptoms of ulcerative colitis

Table 6

Investigations	Mean score		%	S.D.	S.E.	t *Value*	P *Value*
	B.T.	A.T.					
Hemoglobin (g%)	8.40	9.80	16.76	0.765	0.127	11.03	< 0.001
ESR (mm/H)	38.56	21.53	44.16	11.053	2.018	08.44	< 0.001
RBC in stool (/hpf)	2.86	0.2	93.02	1.124	0.205	12.98	< 0.001
Pus cells in stool (/hpf)	2.26	0.43	80.76	0.777	0.162	11.26	< 0.001

Patel MV. Ayu. 2010 Oct-Dec; 31(4): 478–481.

Ayurvedic treatment of IUC: Cordia dichotoma bark

Table 2. Effect of fractions from crude methanol extract of *C. dichotoma* bark on myeloperoxidase (MPO) and malondialdehyde (MDA) activity in blood and tissue.

	Myeloperoxidase		Malonadialdehyde	
Treatment	Blood (U/ml)	Tissue	Blood (nmol/ml)	Tissue
Standard (prednisolon, 5 mg/kg, i.p.)	221 ± 23.0*	+	2.21 ± 1.5*	+
n-Hexane fraction (50 mg/kg, p.o.)	250 ± 32.5	++	6.57 ± 1.5	++
Ethyl acetate fraction (50 mg/kg, p.o.)	237 ± 25.0	++	6.47 ± 2.0*	++
Methanol fraction (50 mg/kg, p.o.)	210 ± 26*	+	2.11 ± 1.0*	+
Crude methanol extract (500 mg/kg, p.o.)	225 ± 35.5*	++	4.88 ± 1.5	++
Control (5% acetic acid)	360 ± 0.2	+++	9.98 ± 1.5*	+++

Ganjare AB et al. Pharmaceutical Biology, 2011; 49(8): 850–855