Inflammatory Bowel Disease (IBD) Pharmacotherapy – Advanced Therapies in Focus and Context

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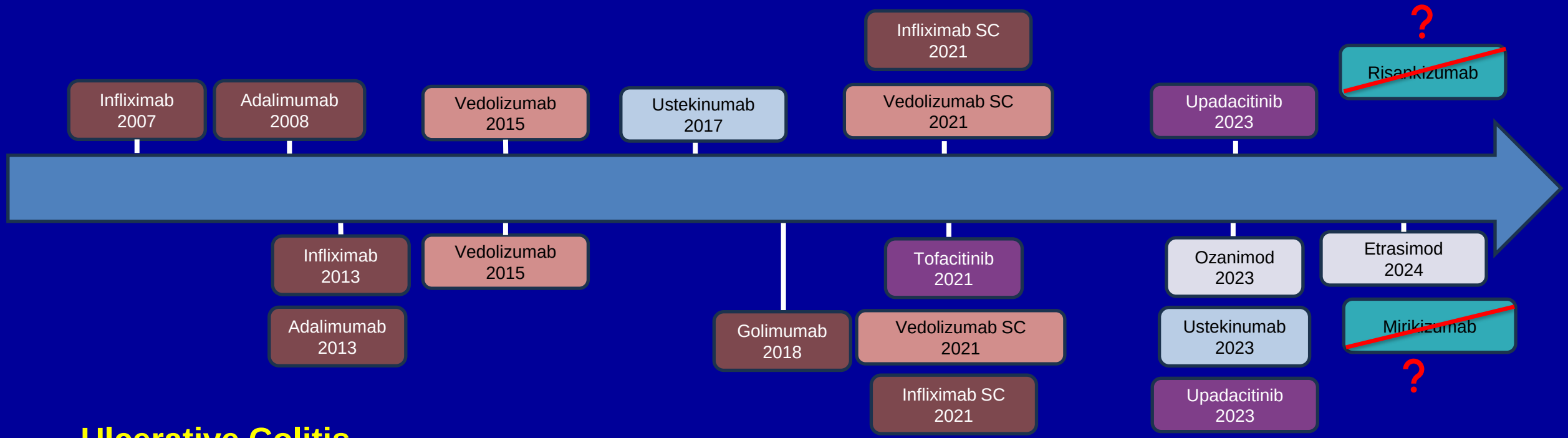
Overview

- The IBDologists therapeutic armamentarium in 2024
- Important differences between biologics and newer small molecules
- The need to understand comparative effectiveness research (CER)
- Choosing the right medical therapy
- Using the right treatment strategy
- Managing treatment failure – principles and emerging algorithms
- Conclusions and take home messages

Registration Timeline of Inflammatory Bowel Disease Advanced Therapies

Crohn's Disease



Ulcerative Colitis

*Biosimilars for adalimumab, infliximab now available (ustekinumab soon)

**Adapted from slide courtesy of Dr. David Rubin*

The IBD Therapeutic Armamentarium in 2024

Small molecules

Corticosteroids
Prednisolone
Budesonide

5-ASAs
Sulfasalazine
Mesalazine

Immuno modulators
Thiopurines
Methotrexate
Calcineurin inhibitors

JAK inhibitors
Tofacitinib - UC
Upadacitinib – UC and CD

S1P modulators
Ozanimod – UC
Etrasimod – UC (soon)

Biologics

Anti-TNFs
Infliximab
Adalimumab
Golimumab - UC

Anti-Integrin
Vedolizumab

Anti-IL12/23
Ustekinumab

Important Differences Between Small Molecules and Biologics

	Small Molecules	Biologics
Molecular Weight (Da)	< 1000	>> 1000
Chemical structure	Small organic compounds	Proteins
Location of target	Intracellular	Extracellular
Mechanism of action	Receptor or enzyme inhibition	Cytokine Depletion
Route of administration	Oral	Parenteral
Distribution	Variable	Plasma and extracellular fluids only
Serum half-life	Short	Long
Immunogenicity	No	Yes
Drug-drug interactions	Possible	Infrequent
Toxicity	Due to parent compound or metabolites, including “off-target” effects	Receptor-mediated
Production	Chemical synthesis	Biological production
Cost of production	Variable	High
Generics	Identical	Biosimilar

Olivera P et al, Gut 2017 Feb; 66(2): 199-209

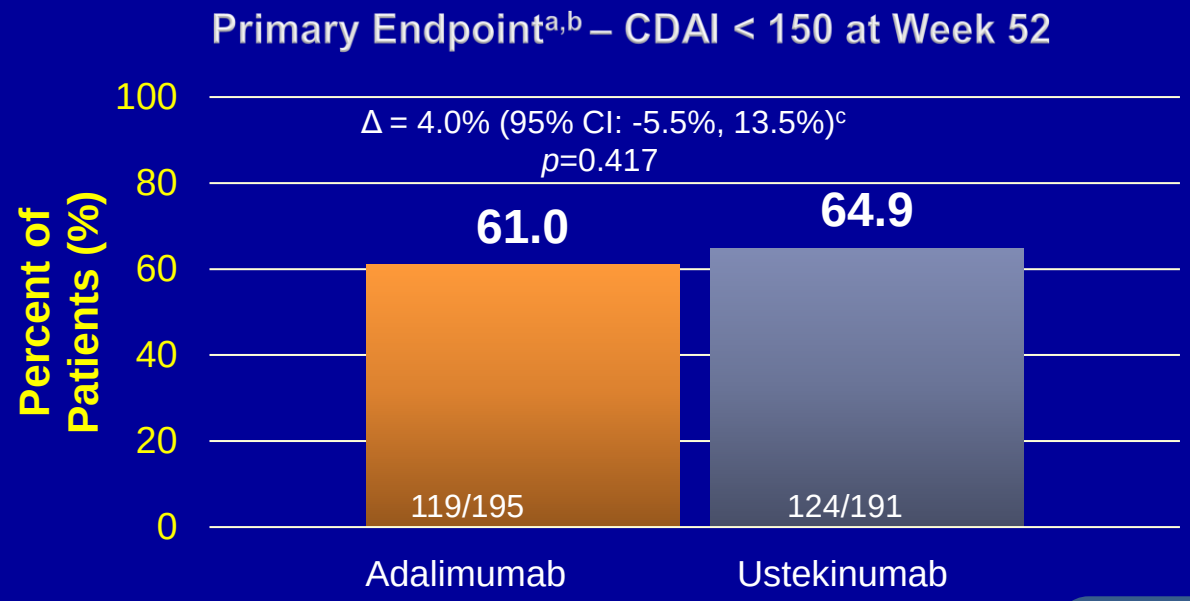
Understanding Comparative Effectiveness Research is Important in Positioning Therapies

	Pros	Cons
Head-to-Head Trials	• Highest level of CER • No placebo	• Hard to perform • Clinical trials may not reflect clinical practice
Network Meta-Analyses	• Comparison between therapies, using placebo as indirect comparator • Allows for ranking of therapies (SUCRA – Surface Under Cumulate RAnking Curve)	• Only as good as data in included studies • Heterogenous trial designs of included studies • Publication bias
Observational Studies	• Includes real-world data and patients that may have been excluded from clinical trials • Can include large numbers (eg. population-based or insurance claims analyses) • Propensity Score Matching helps minimize confounding	• Potential for bias, confounding and missing data

Ahuja D et al, Curr Opinion Gastroenterol. 2022 Jul 1; 38(4):337-346

SEAVUE - Ustekinumab Versus Adalimumab for Induction and Maintenance Therapy in Moderate-to-Severe Crohn's Disease

- Randomised, double-blind study comparing adalimumab and ustekinumab monotherapy in biologic-naïve Crohn's disease patients

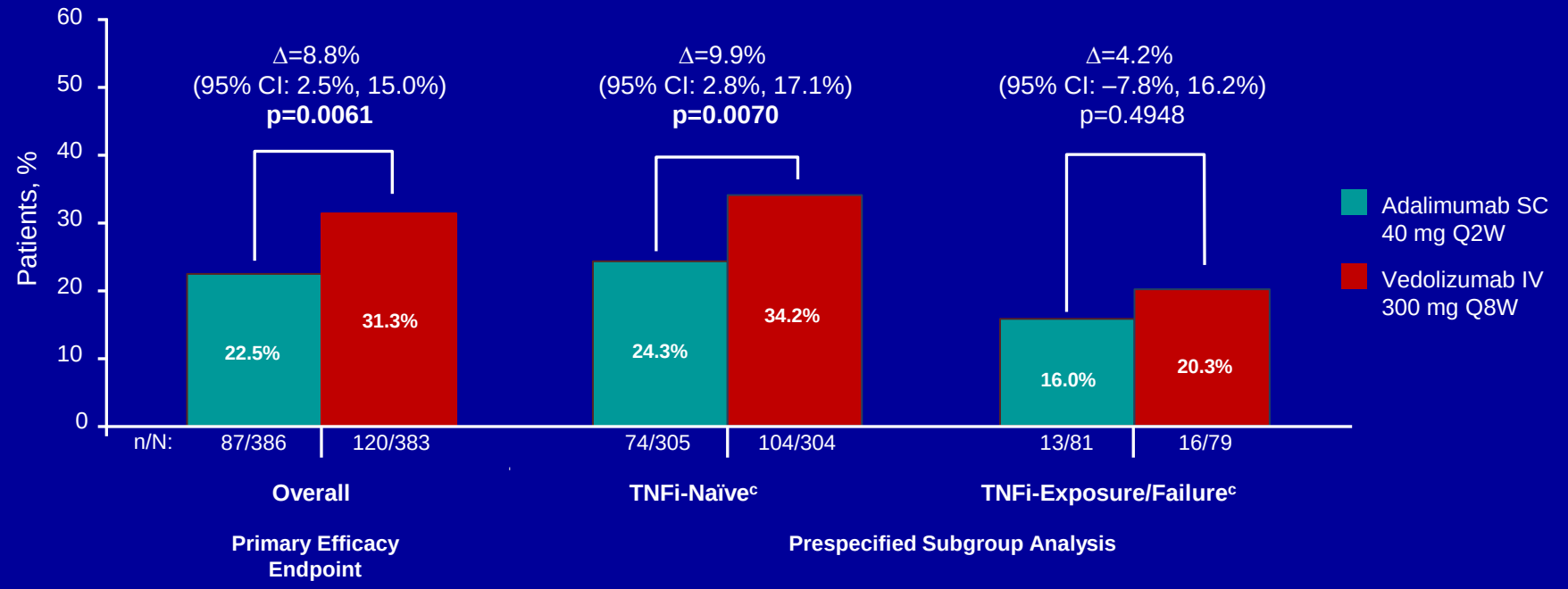


Because primary endpoint was not met, formal testing of major secondary endpoints was not performed

Sands BE et al, Lancet. 2022 Jun 11;399(10342):2200-2211

VARSITY – Vedolizumab vs Adalimumab in Ulcerative Colitis – Primary Efficacy Endpoint: Overall Clinical Remission at Week 52

- Randomised, double-blind study, comparing vedolizumab and adalimumab in anti-TNF naïve and exposed ulcerative colitis patients



Sands BE et al, N Engl J Med. 2019 Sep 26;381(13):1215-1226

Newer Head to Heads Favour IL-23 Antagonists over Ustekinumab in Crohn's Disease (CD)

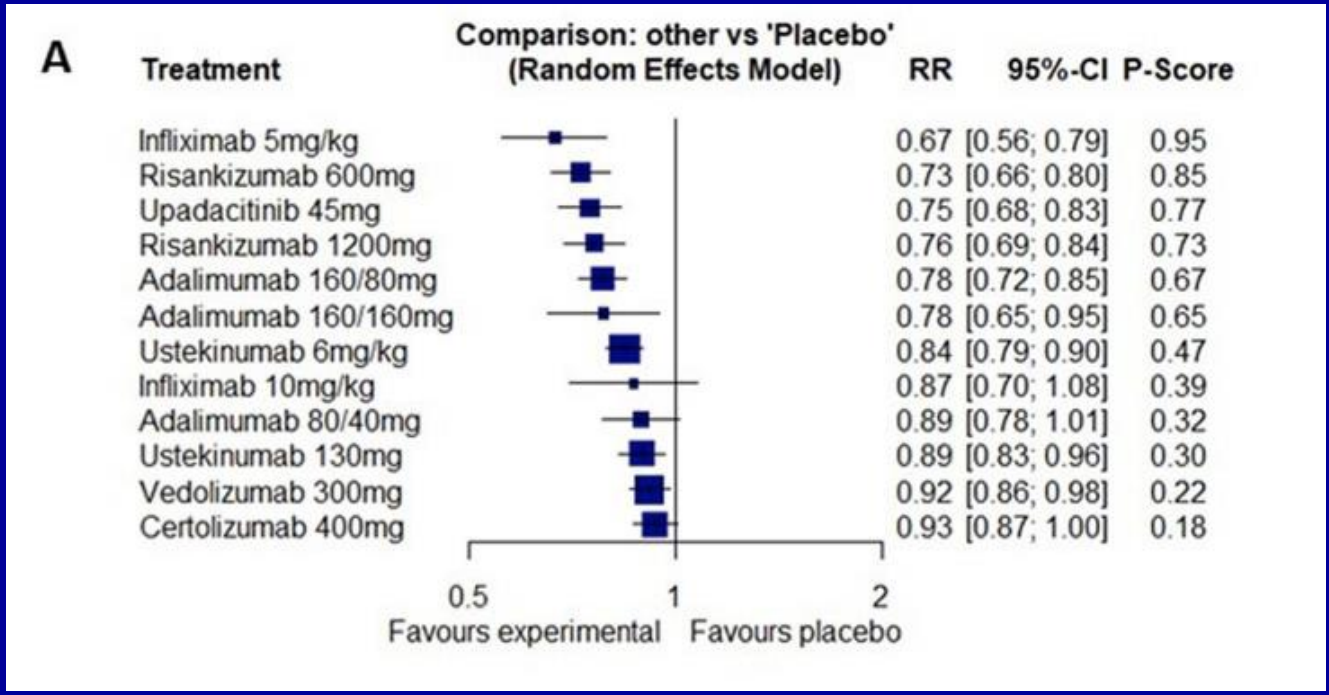
Trial	Comparison	Key Outcomes
SEQUENCE*	Risankizumab vs ustekinumab in CD patients failing anti-TNFs	Risankizumab superior to ustekinumab for endoscopic remission at week 48
GALAXI**	Guselkumab vs ustekinumab in biologic naïve and experienced CD patients	Guselkumab superior to ustekinumab for endoscopic remission at week 48
VIVID-1***	Mirikizumab vs ustekinumab in biologic naïve and experienced CD patients	Mirikizumab non-inferior to ustekinumab for clinical remission and endoscopic response at week 52

*Peyrin-Biroulet L et al, N Engl J Med. 2024 Jul 18;391(3):213-223 **Panaccione R, et al. Presented at DDW. May 2024. 1057b ***Jairath V et al, DOP 35, ECCO 2024

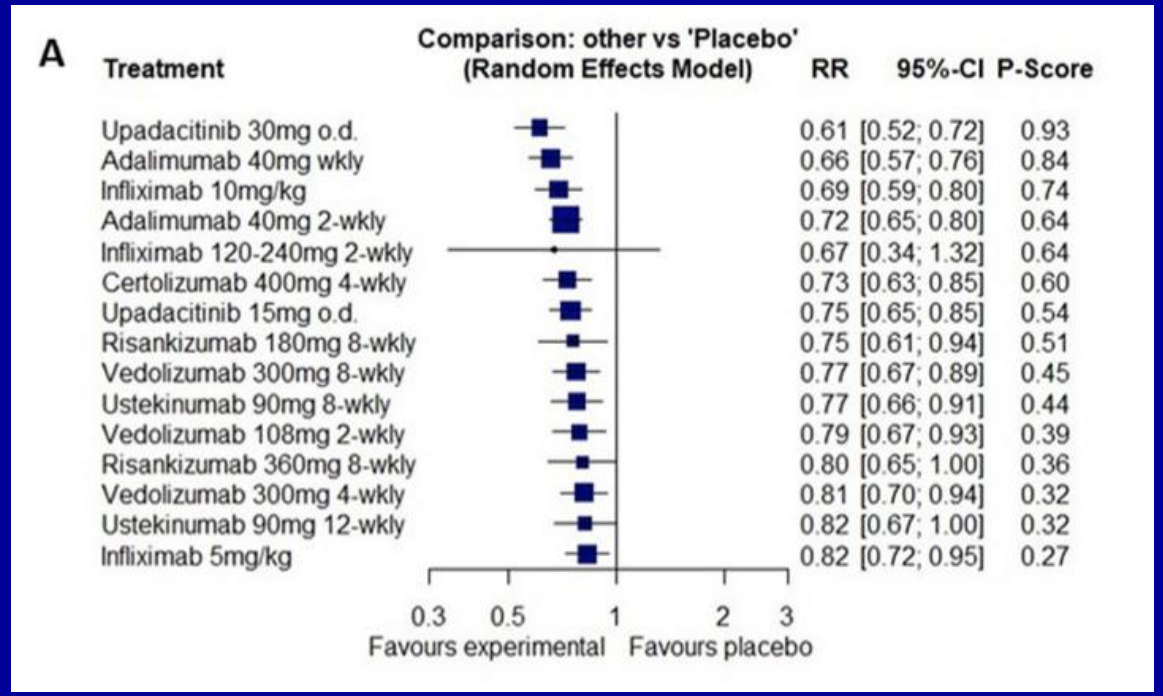
Network Meta-Analyses (NMA) in Crohn's Disease Favour Anti-TNFs, JAK Inhibitors and IL-23 Antagonists in Bio-Naïve and Bio-Experienced Patients

- NMA of 25 RCTs of induction and maintenance therapy with advanced therapies in luminal CD, n= 8720
- Bio-naïve and bio-experienced patients

Induction of Remission



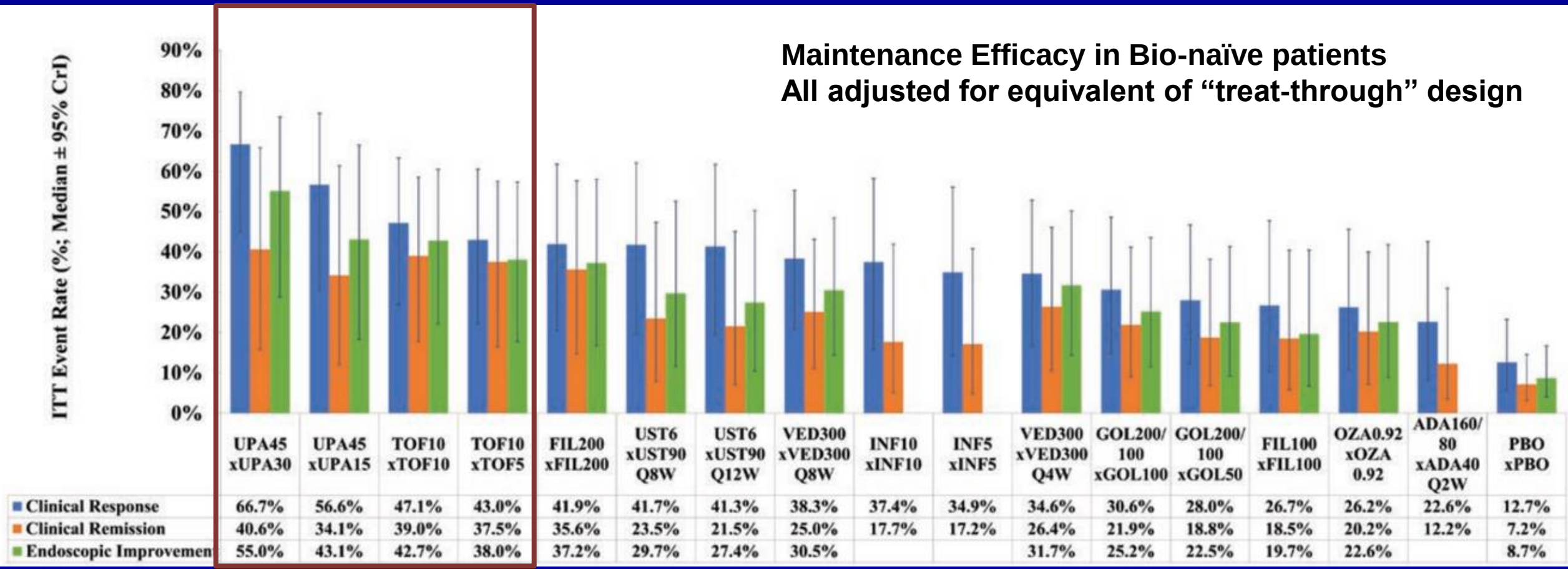
Maintenance of Remission



Barberio B et al, Gut 2023 Feb;72(2):264-274

Network Meta-Analyses (NMA) in Ulcerative Colitis are Favourable for JAK Inhibitors in Bio-Naïve and Bio-Experienced Patients

- NMA of 23 RCTs of induction and maintenance therapy with advanced therapies in UC



	UPA45 xUPA30	UPA45 xUPA15	TOF10 xTOF10	TOF10 xTOF5	FIL200 xFIL200	UST6 xUST90 Q8W	UST6 xUST90 Q12W	VED300 xVED300 Q8W	INF10 xINF10	INF5 xINF5	VED300 xVED300 Q4W	GOL200/ 100 xGOL100	GOL200/ 100 xGOL50	FIL100 xFIL100	OZA0.92 xOZA 0.92	ADA160/ 80 xADA40 Q2W	PBO xPBO
Clinical Response	66.7%	56.6%	47.1%	43.0%	41.9%	41.7%	41.3%	38.3%	37.4%	34.9%	34.6%	30.6%	28.0%	26.7%	26.2%	22.6%	12.7%
Clinical Remission	40.6%	34.1%	39.0%	37.5%	35.6%	23.5%	21.5%	25.0%	17.7%	17.2%	26.4%	21.9%	18.8%	18.5%	20.2%	12.2%	7.2%
Endoscopic Improvemen	55.0%	43.1%	42.7%	38.0%	37.2%	29.7%	27.4%	30.5%			31.7%	25.2%	22.5%	19.7%	22.6%		8.7%

Panaccione R, et al. Crohns Colitis 360. 2023;5(2)

Choosing a First Advanced Therapy in IBD

- Choosing an advanced therapy involves consideration of multiple factors:
  - Patient-related factors, including safety considerations
  - Disease-related factors, including EIMs
  - Current and previous-treatments – monotherapy versus combination therapy
  - Specific scenarios for Crohn’s disease and ulcerative colitis
  - Pregnancy considerations
  - Practical considerations and patient preferences

Choosing an Advanced Therapy in Either CD or UC – Patient-Related Factors

	Anti-TNFs		Vedolizumab	Ustekinumab	JAK Inhibitors	S1P Modulators (UC)
	Infliximab	Adalimumab/ Golimumab (UC)				
Age - children	+++	+++	++	+	?/+	?
Age - elderly	+/- -	+/- -	+++	++	+/--	++/-
Co-Morbidities	+/- -	+/- -	+++	++/-	+/--	++/-
Serious infections	+/- -	+/- -	+++	++/ -	+/--	++/-
Increased BMI	++ / -	+ / - -	+/-	+/-	+/-	+/-
Multiple IMIDs	+++	+++	--	++	++	--

+++ = highly favourable*
- - - = highly unfavourable
++/ - = favourable but some limitations
+/- - = favourable but significant limitations
+/- = equivocal
? = no data

*Personal opinion

Choosing a First Advanced Therapy in Crohn's Disease - Disease-Related Factors

	Anti-TNFs		Vedolizumab	Ustekinumab	JAK Inhibitors (Upadacitinib)
	Infliximab	**Adalimumab**			
Disease Location – • Colonic or ileocolonic Disease	**++**	**++**	**+++**	**++**	**++**
• Upper GI Disease	**++**	**++**	**+/ - -**	**+/?**	**+/?**
• Perianal Disease	**+++**	**++**	**+**	**+**	**++**
Disease Severity	**+++**	**++**	**+/-**	**++**	**+++**
Disease Duration	**+ / - -**	**+ / - -**	**+/-**	**+/-**	**+/-**
EIMs	**+++**	**+++**	**+/- -**	**++**	**+++**

**Personal opinion*

Choosing a First Advanced Therapy in Ulcerative Colitis - Disease-Related Factors

	Anti-TNFs			Vedolizumab	Ustekinumab	JAK Inhibitors	S1P Modulators
	Infliximab	Adalimumab	Golimumab				
Disease extent	+/ -	+ / -	+ / -	+ / -	+/-	+/-	+/-
Disease severity	+++	++	++	++	++	+++	++
Disease duration	+ / -	+ / -	+ / -	+ / -	+/-	+/-	+/-
EIMs	+ + +	+ + +	+ + +	+ / - -	++	+++	?

**Personal opinion*

Extra-Intestinal Manifestations are an Important Variable in the Choice of Advanced Therapy in Both CD and UC

	Anti-TNFs			Vedolizumab	Ustekinumab	JAK Inhibitors	S1P Modulators
	IFX	ADA	GOL				
Peripheral Arthritis							
Spondyloarthritis							
Pyoderma Gangrenosum							
Uveitis							
Erythema Nodosum							

Adapted from Greuter T et al, Gut 2021 Apr;70(4):796-802

Choosing a First Advanced Therapy in Either CD or UC – Previous and Current (Immunomodulator) Treatments

	Anti-TNFs			Vedolizumab	Ustekinumab	JAK Inhibitors	S1P Modulators
	Infliximab	Adalimumab	Golimumab (UC)				
Monotherapy preferred	- - -	- -	- -	+++	+++	N/A	N/A
Combination therapy with IM preferred	+ + +	+ + / -	++/-	+ / -	+ / -	N/A	N/A

*Personal opinion

Choosing a First Advanced Therapy in Crohn's Disease – Specific Scenarios

	Anti-TNFs		Vedolizumab	Ustekinumab	JAK Inhibitors (Upadacitinib)
	Infliximab	**Adalimumab**			
Post-Operative CD	**+ + +**	**+ + +**	**+ +**	**+**	**?**
Anti-TNF induced psoriaform lesions (CD and UC)	**- - -**	**- - -**	**-**	**+ + +**	**+**

**Personal opinion*

Choosing a First Advanced Therapy in Ulcerative Colitis - Specific Scenarios

	Anti-TNFs			Vedolizumab	Ustekinumab	JAK Inhibitors	S1P Modulators
	Infliximab	Adalimumab	Golimumab				
Acute Severe UC	+ + +	+	?	-	?	++	-
Pouchitis	+ +	+ +	?	+++	+	++	?

*Personal opinion

Pregnancy Plans are an Important Variable in the Choice of Advanced Therapy in Both CD and UC

Contraindicated Medications	Medications to Avoid	Medications to Continue
Methotrexate	Prednisolone in 1st Trimester	Budesonide
	S1P modulators • Ozanimod* • Etrasimod	Mesalazine/Sulfasalazine
Thalidomide	JAK Inhibitors • Tofacitinib* • Upadacitinib	Thiopurines
		Anti-TNFs
		Ustekinumab (And Risankizumab and Mirikizumab)
		Vedolizumab

* Recent case series of successful use when agent stopped at time of pregnancy confirmation

***Adapted from slide courtesy of Uma Mahadevan*

Choosing a First Advanced Therapy in Either CD or UC – Practical Considerations and Patient Preferences

	Anti-TNFs			Vedolizumab	Ustekinumab	JAK Inhibitors	S1P Modulators (UC)
	Infliximab	**Adalimumab**	**Golimumab**				
IV administration preferred	**+**	**-**	**-**	**+**	**-**	**-**	**-**
S/C administration preferred	**+**	**+**	**+**	**+**	**+**	**-**	**-**
Oral therapy preferred	**-**	**-**	**-**	**-**	**-**	**+**	**+**
Availability of TDM	**+++**	**++**	**+**	**+/-**	**+/-**	**-**	**-**
Cost (biosimilars)	**+**	**+**	**-**	**-**	**- (soon)**	**-**	**-**

**Personal opinion*

Patient-related Factors
- Age
- Co-morbidities/PHx adverse events
- BMI
- Multiple IMIDs

Response to current and prior therapies
- Monotherapy preferred
- Combination therapy preferred/acceptable

Patient preferences and practical considerations
- Subcut. route preferred
- IV route preferred
- Oral preferred
- Availability of biosimilars
- Availability of TDM

Disease-Related Factors
- Disease location
- Disease severity
- Disease duration
- EIMs

Choosing a First Advanced Therapy in CD or UC – Anti-TNF

Specific scenarios
- Post-operative CD
- ASUC
- Pregnancy

Favouring Anti-TNF CD or UC
- Severe disease activity
- Children, young patients
- EIMs or multiple IMIDs
- Combination therapy preferred/acceptable
- Pregnancy
- Cost (biosimilars)

Favouring Anti-TNF CD
- Short disease duration
- Perianal disease
- Post-operative CD

Favouring Anti-TNF UC
- Severe disease activity including ASUC (infliximab)

**Personal opinion*

Patient-related Factors
- Age
- Co-morbidities/PHx adverse events
- BMI
- Multiple IMIDs

Response to current and prior therapies
- Monotherapy preferred
- Combination therapy preferred/acceptable

Patient preferences and practical considerations
- Subcut. route preferred
- IV route preferred
- Oral preferred
- Availability of biosimilars
- Availability of TDM

Disease-Related Factors
- Disease location
- Disease severity
- Disease duration
- EIMs

Choosing a First Advanced Therapy in CD or UC - Vedolizumab

Specific scenarios
- Post-operative CD
- ASUC
- Pregnancy

Favouring Vedolizumab in CD or UC
- Moderate disease activity
- Elderly/co-morbidities/PHx infections
- Monotherapy preferred
- No EIMs / IMIDs

Favouring Vedolizumab in CD
- Colonic or ileocolonic disease

**Personal opinion*

Patient-related Factors
- Age
- Co-morbidities/PHx adverse events
- BMI
- Multiple IMIDs

Response to current and prior therapies
- Monotherapy preferred
- Combination therapy preferred/acceptable

Patient preferences and practical considerations
- Subcut. route preferred
- IV route preferred
- Oral preferred
- Availability of biosimilars
- Availability of TDM

Disease-Related Factors
- Disease location
- Disease severity
- Disease duration
- EIMs

Choosing a First Advanced Therapy in CD or UC - Ustekinumab

Specific scenarios
- Post-operative CD
- ASUC
- Pregnancy

Favouring Ustekinumab in CD or UC
- Moderate disease activity
- Elderly/co-morbidities/PHx infections
- Monotherapy preferred
- Subcutaneous route preferred
- Anti-TNF-induced psoriaform lesions

**Personal opinion*

Patient-related Factors
- Age
- Co-morbidities/PHx adverse events
- BMI
- Multiple IMIDs

Response to current and prior therapies
- Monotherapy preferred
- Combination therapy preferred/acceptable

Patient preferences and practical considerations
- Subcut. route preferred
- IV route preferred
- Oral preferred
- Availability of biosimilars
- Availability of TDM

Disease-Related Factors
- Disease location
- Disease severity
- Disease duration
- EIMs

Choosing a First Advanced Therapy in CD or UC – JAK Inhibitor

Specific scenarios
- Post-operative CD
- ASUC
- Pregnancy

Favouring JAK Inhibitor in UC or CD
- Moderate-severe disease activity
- EIMs
- Younger patients
- No PHx thromboembolism
- Few cardiovascular risk factors
- No recent malignancy
- Oral therapy preferred
- No imminent pregnancy plans

Favouring JAK Inhibitor in CD (Upadacitinib)
- Perianal disease?

Favouring JAK Inhibitor in UC
- ASUC?

**Personal opinion*

Patient-related Factors
- Age
- Co-morbidities/PHx adverse events
- BMI
- Multiple IMIDs

Response to current and prior therapies
- Monotherapy preferred
- Combination therapy preferred/acceptable

Patient preferences and practical considerations
- Subcut. route preferred
- IV route preferred
- Oral preferred
- Availability of biosimilars
- Availability of TDM

Disease-Related Factors
- Disease location
- Disease severity
- Disease duration
- EIMs

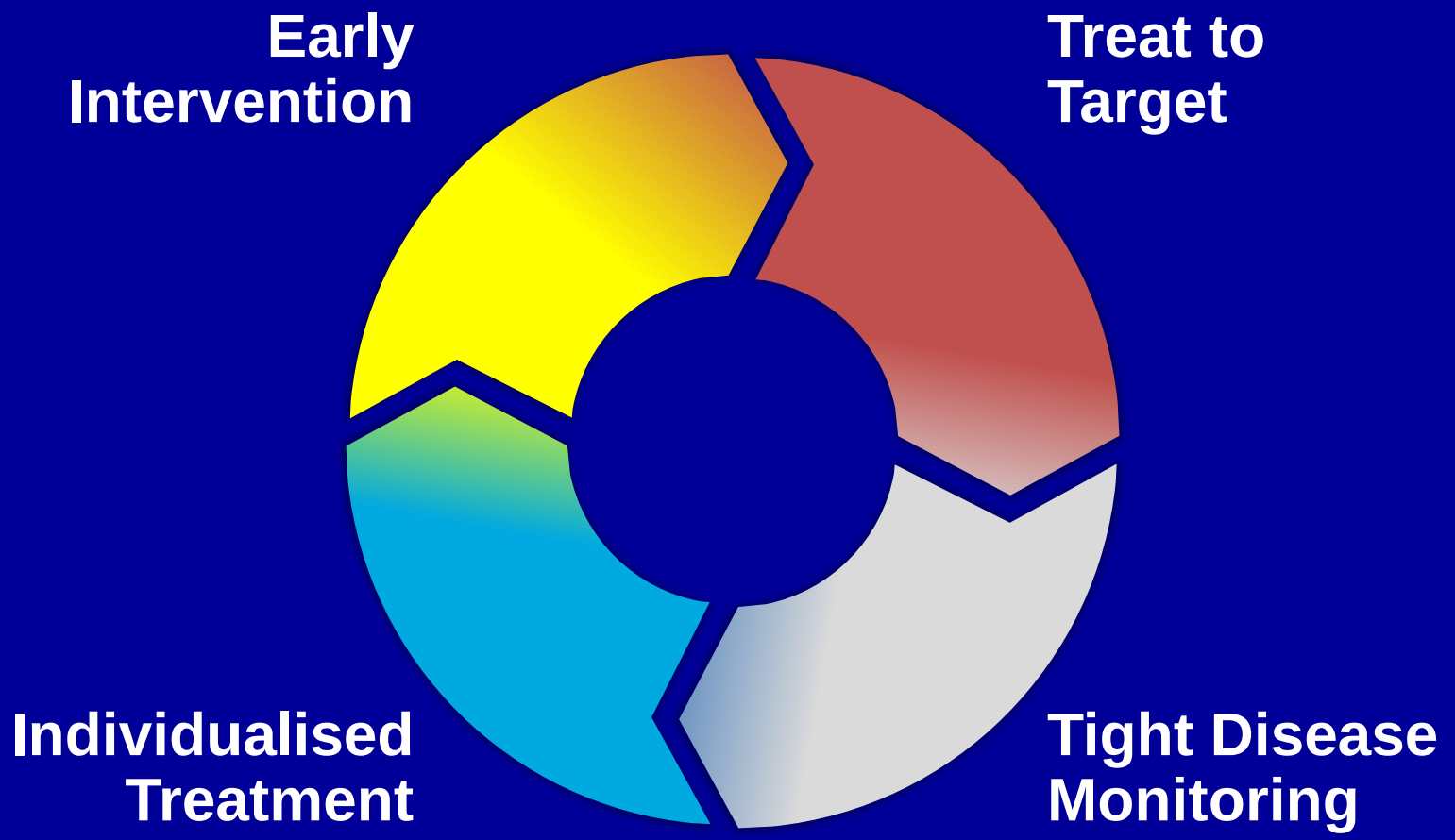
Choosing a First Advanced Therapy in UC – S1P Modulator

Specific scenarios
- Post-operative CD
- ASUC
- Pregnancy

Favouring S1P Modulators
- Moderate disease activity
- No cardiac conduction delays
- No (diabetic) retinopathy
- Oral therapy preferred
- No imminent pregnancy plans
- UC patients flaring after elective cessation of thiopurines

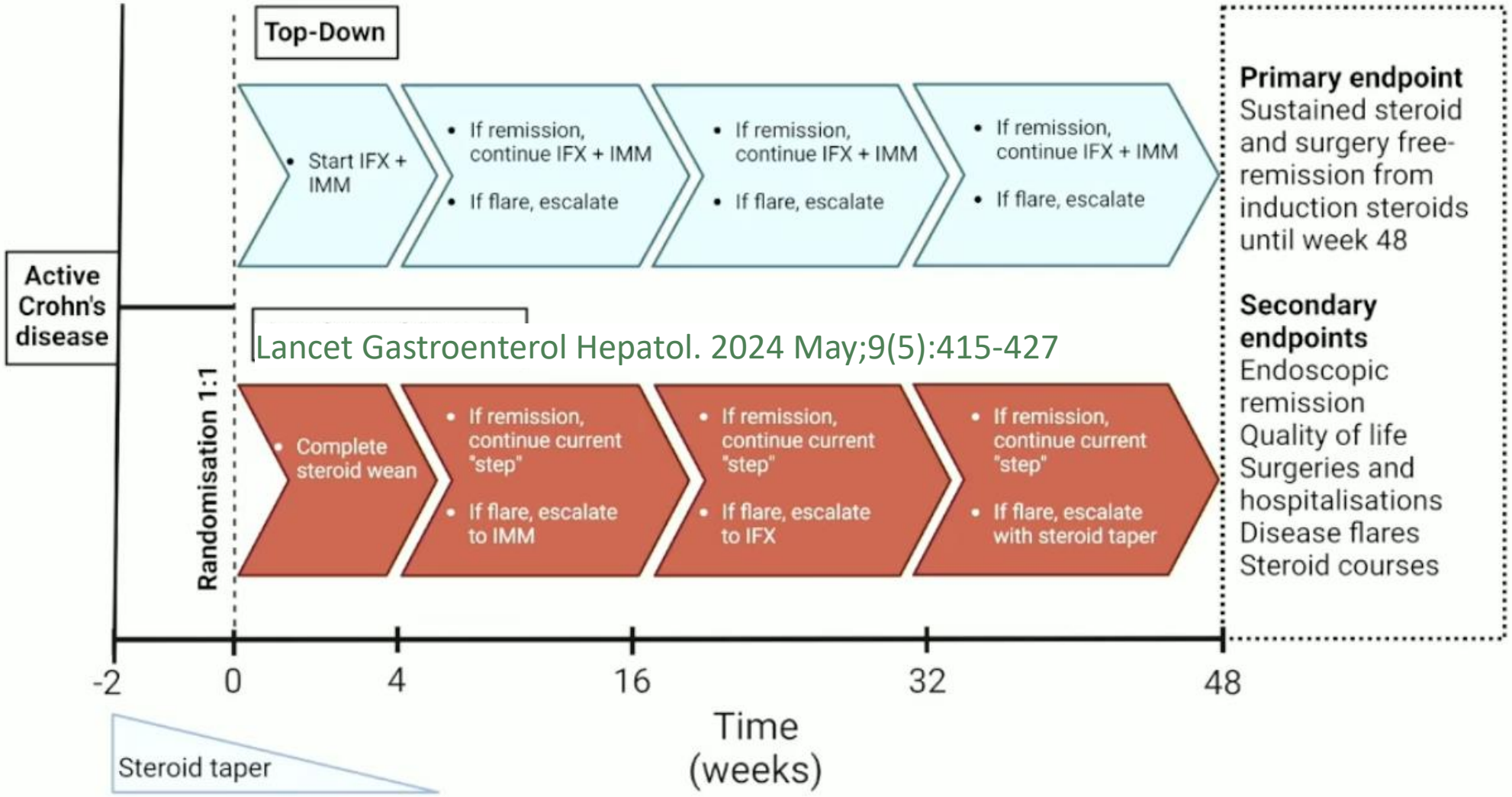
**Personal opinion*

Using The Right Treatment *Strategy* is Equally (or More) Important as the Choice of Medical Therapy



Colombel JF, et al. Gastroenterology 2017;152:351–61

PROFILE outline



Lancet Gastroenterol Hepatol. 2024 May;9(5):415-427

Noor NM et al, Lancet Gastroenterol Hepatol. 2024 May;9(5):415-427

Key baseline demographics (n=386)

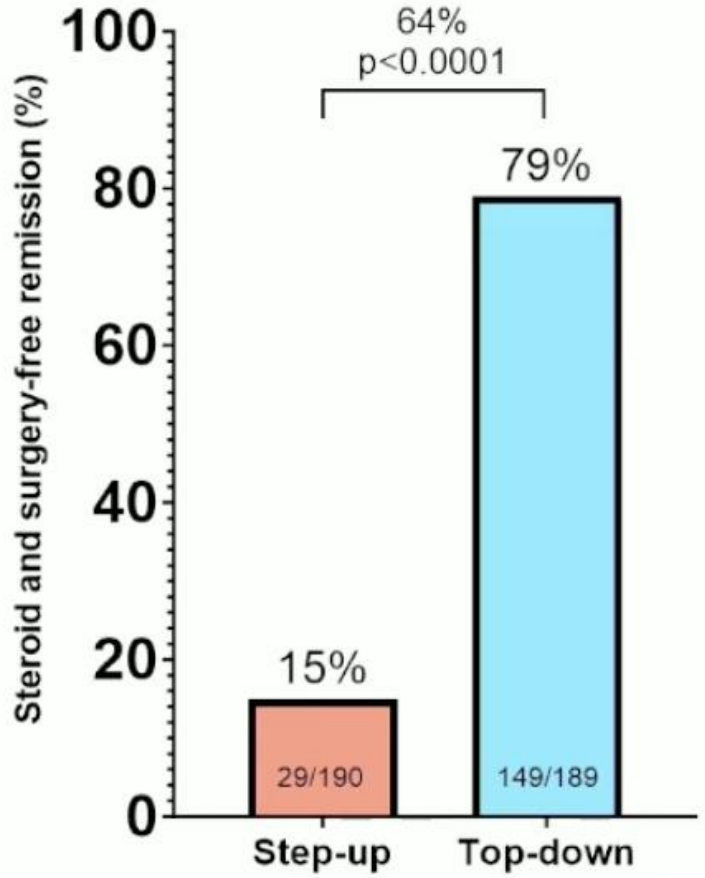
Variable	IBDlo Step up (n=97)	IBDhi Step up (n=96)	IBDlo Top down (n=94)	IBDhi Top down (n=99)
Mean age (years)	34.0 (13.3)	34.0 (13.3)	33.3 (13.2)	33.3 (13.2)
Female	48/97 (49%)	40/96 (42%)	43/94 (46%)	48/99 (48%)
Mean HBI score (SD)	9.6 (3.1)	10.0 (2.8)	9.8 (2.8)	10.2 (3.0)
Median CRP (mg/L; IQR)	10 (4-27)	13 (4-19)	9 (6-23)	13 (7-25)
Median FCAL (ug/g; IQR)	600 (249 - >1800)	905 (396 - >1800)	714 (383 - 1671)	886 (386 - >1800)
Median SES-CD (IQR)	9 (7 - 13)	9 (7 - 14)	10 (6 - 13)	10 (7 - 15)
Median time from diagnosis to enrolment (days; min-max)	13.0 (0 - 138)	17.5 (0 - 191)	10.0 (0 - 168)	8.0 (0 - 165)

Noor NM et al, Lancet Gastroenterol Hepatol. 2024 May;9(5):415-427

Primary endpoint - sustained steroid-free and surgery-free remission through to week 48

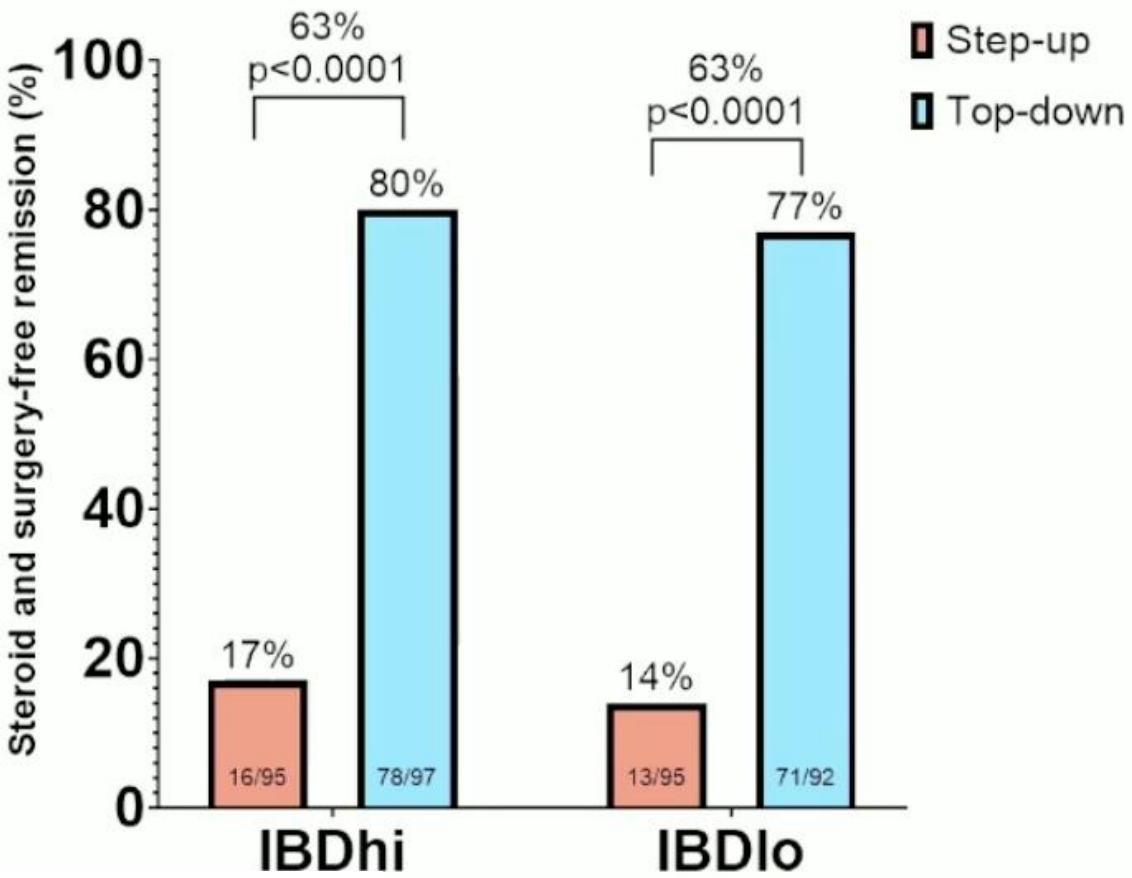
Treatment effect

64% (95% CI=57 to 72%, p<0.0001)



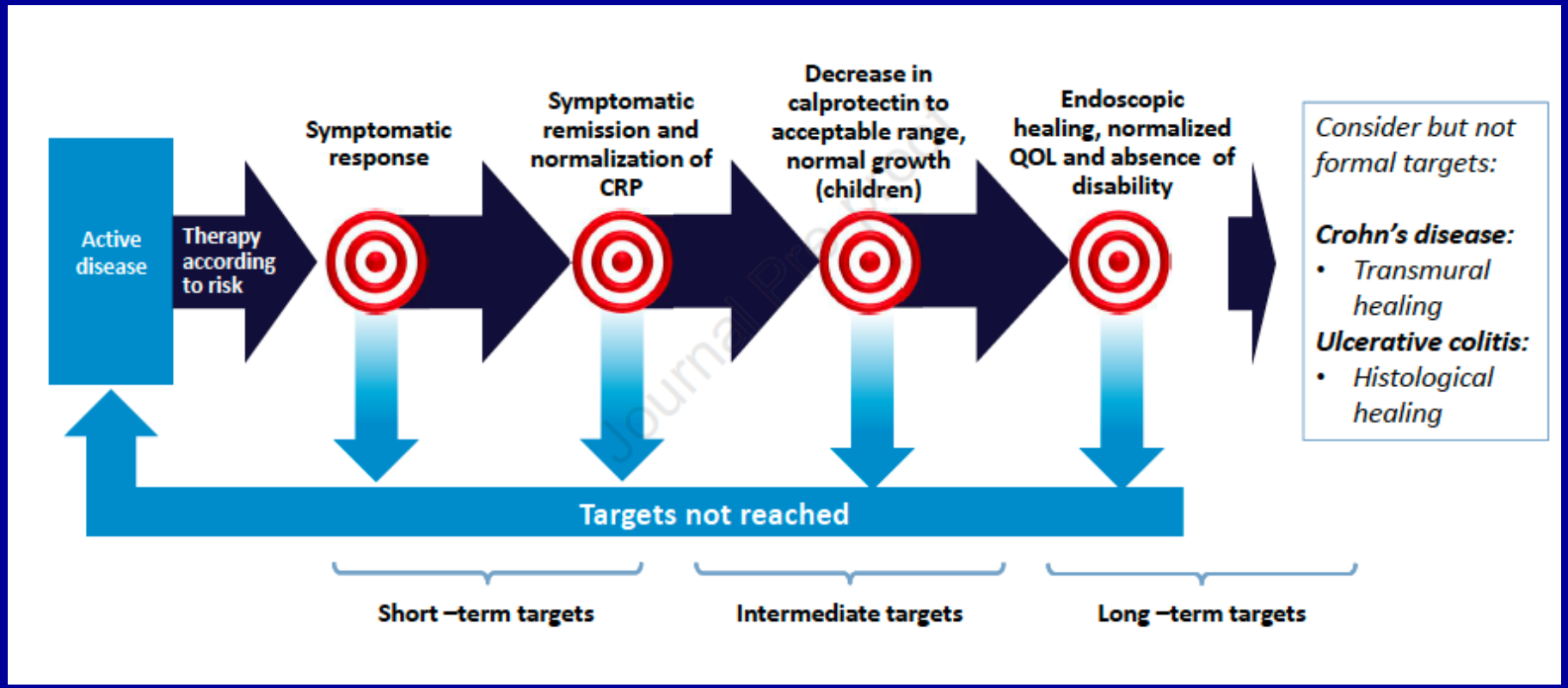
Biomarker effect

1% (95% CI=-15% to +15%, p<0.944)



Noor NM et al, Lancet Gastroenterol Hepatol. 2024 May;9(5):415-427

Treating to Target – The STRIDE II Guidelines Advocate for Timebound Treatment Goals and The Use of Non-Invasive Biomarkers



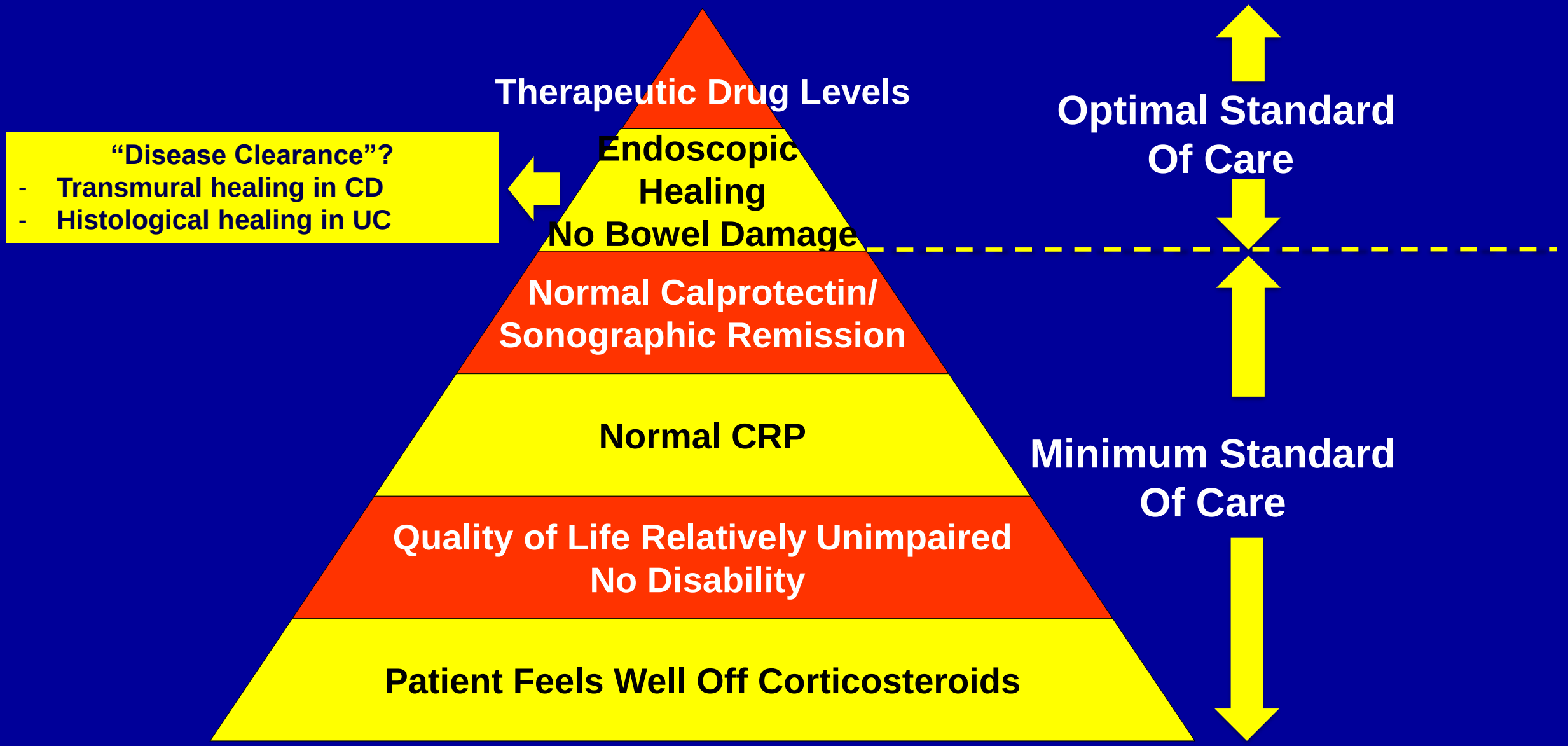
Short-term –
- clinical response

Intermediate-term –
- clinical remission
- normalisation of CRP
- normalisation of calprotectin

Long-term –
- endoscopic healing
- normalization of QOL
- absence of disability
- restoration of growth in children

Turner D et al, Gastroenterology. 2021 Apr;160(5):1570-1583

Practical IBD Treatment Targets in an Individual Patient in 2024



Tight Disease Monitoring Is Essential and Should Preferentially Use Non-Invasive Methods

- The SCOPELESS study compared the total number of endoscopies performed for IBD disease activity evaluation in the pre-defined five year pre-intestinal ultrasound (IUS) (2010-2014) and IUS (2015-2019) time periods

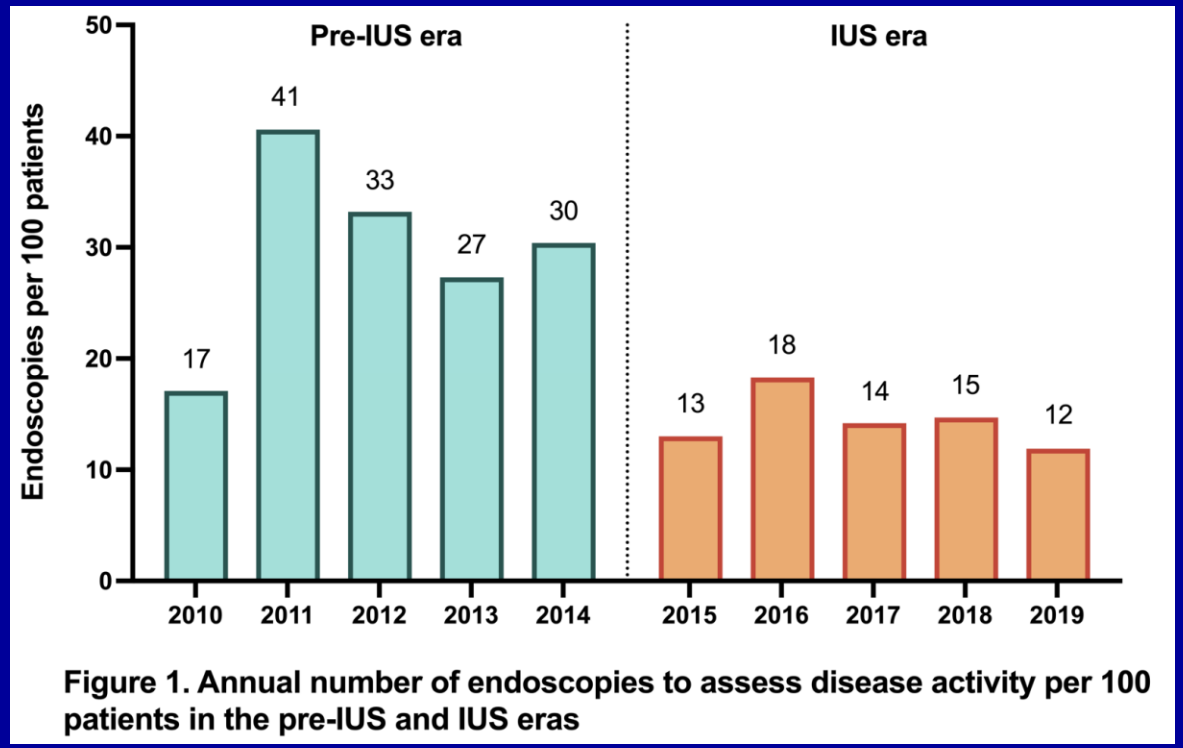
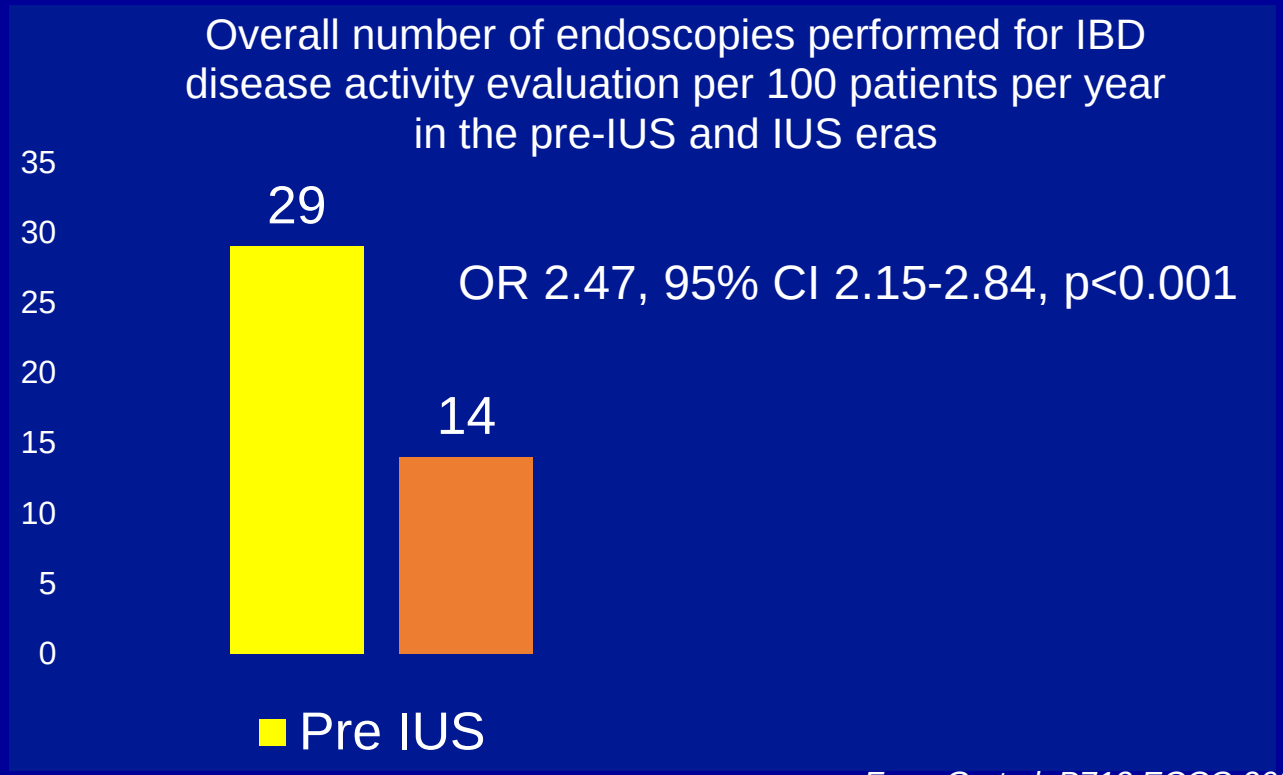
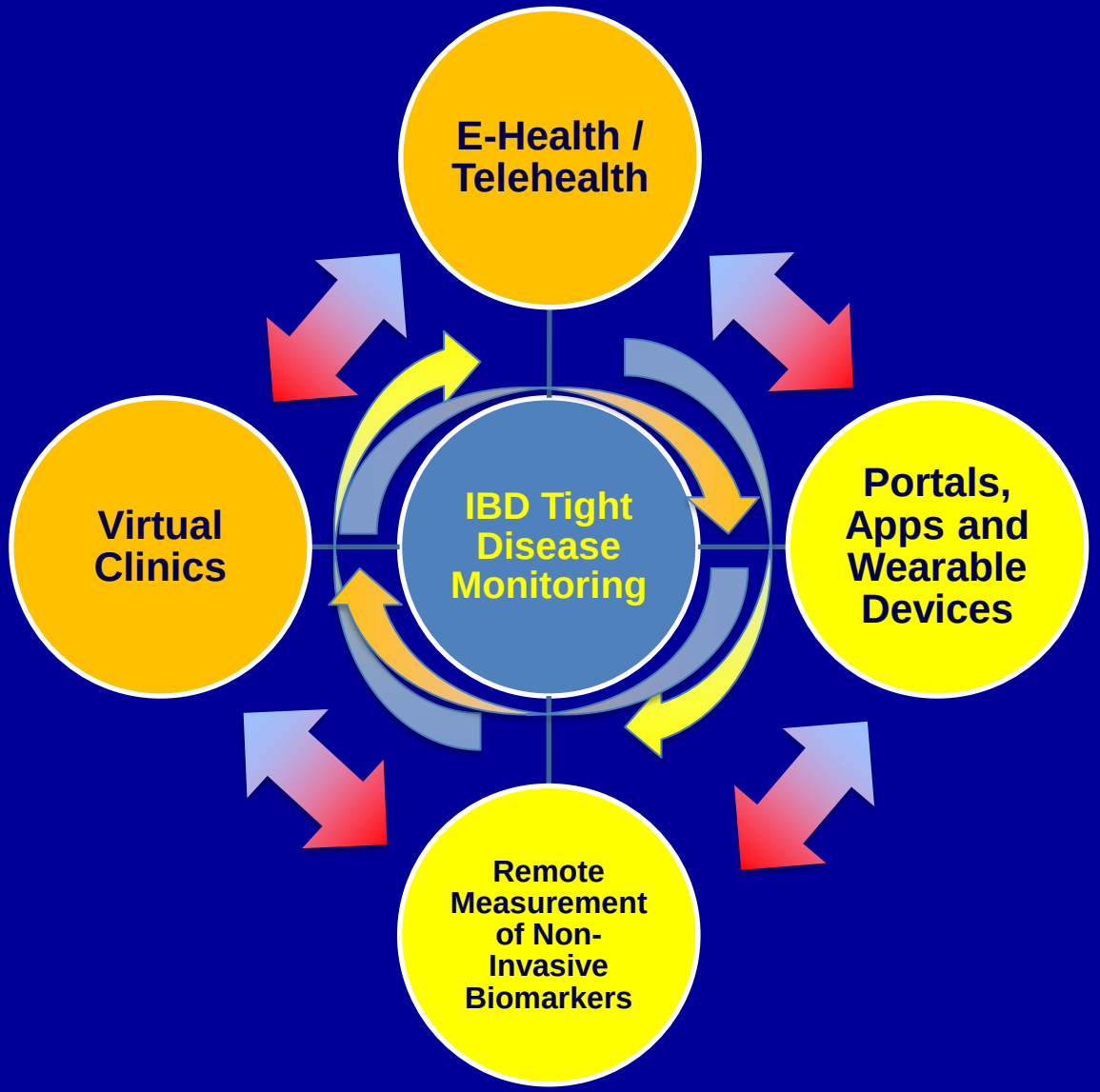


Figure 1. Annual number of endoscopies to assess disease activity per 100 patients in the pre-IUS and IUS eras



Feng G et al, P713 ECCO 2024

Tight Disease Monitoring Should Incorporate Components of E-Health and Remote Disease Monitoring



E-Health in IBD – Summary Principles From Pivotal Studies

Study	QOL	Disease Specific Knowledge	Disease Activity	Health Care Utilisation	Medication Adherence	Patient Satisfaction	Cost
My IBD Coach – de Jong et al, 2017	=	=	=	↓	↑	=	↓
Constant Care – Elkjaer et al, 2010	↑	↑			↑		↓
Tele-IBD – Cross et al, 2019	=	=	=	↑	=		
TECCU – Del Hoyo et al, 2018	↑		↓	↓			
True Colours – Walsh et al						↑	
eIBD – Zand et al, 2021				↓			
Project Sonar – Singh et al, 2018				↓			↓
McCombie et al, 2020	=		=	↓			

Adapted from – George LA et al, Curr Gastroenterol Reports 2020; 22: 12 and Spartz EJ et al, Diagnostics 2022 Dec; 13(1): 37

Managing Treatment Failure – Optimise Before Switching

- Your first advanced therapy is usually your best (especially for biologics)……..so choose wisely

- Don’t switch too early - IBD is a marathon not a sprint
  - All advanced therapies should be given at least 3 months, and ideally 6 months, before considering switching where possible
  - Beware of “shiny new advanced therapy syndrome”

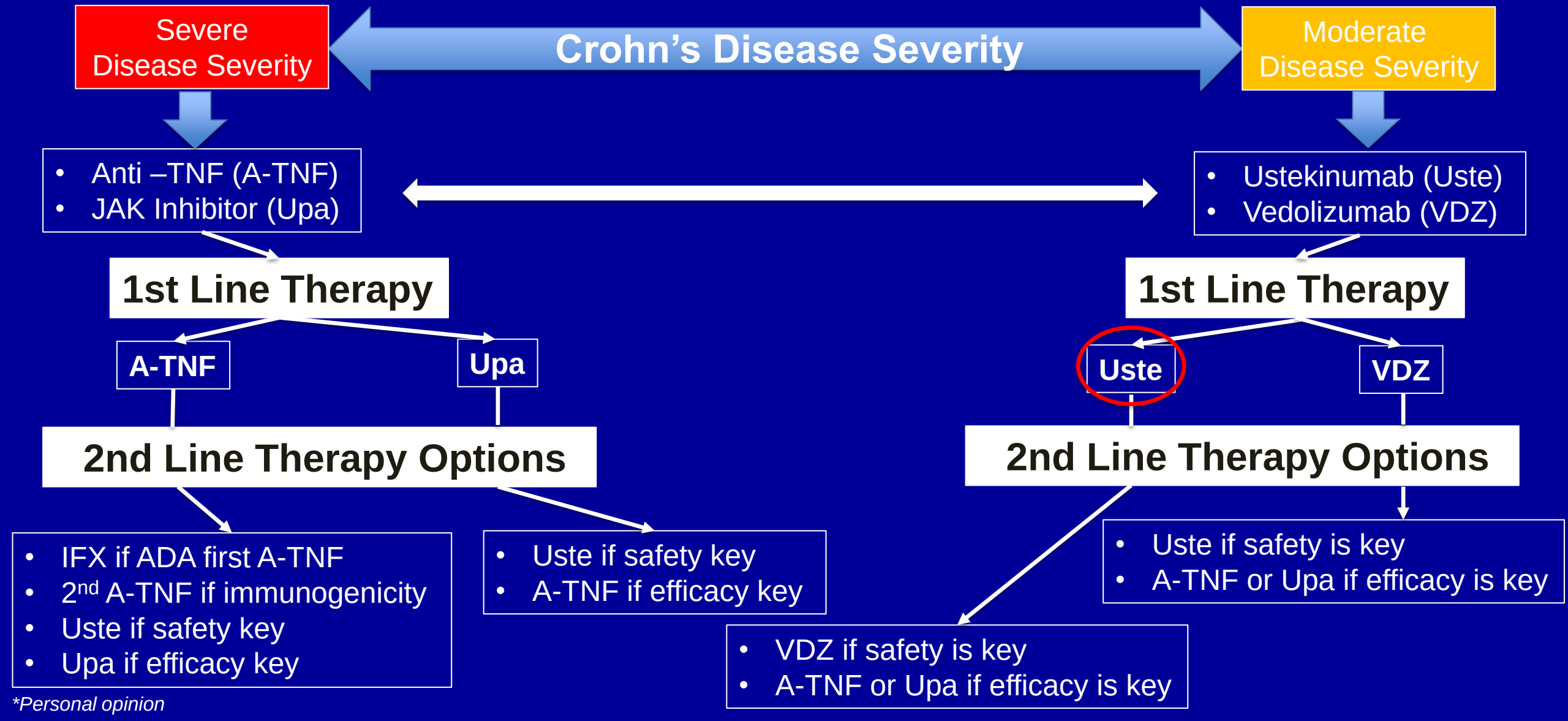
- Always aim to optimize before switching
  - Use objective biomarkers as targets, not just symptoms
  - Use therapeutic drug monitoring if available, especially for anti-TNFs
  - Often more drug is needed, especially for biologics during induction

- Treatment targets need to be individualized - endoscopic healing is not achievable in all patients – sometimes “the enemy of good is perfect”

- Advanced Combination Therapy (ACT) will become increasingly used to manage treatment failure

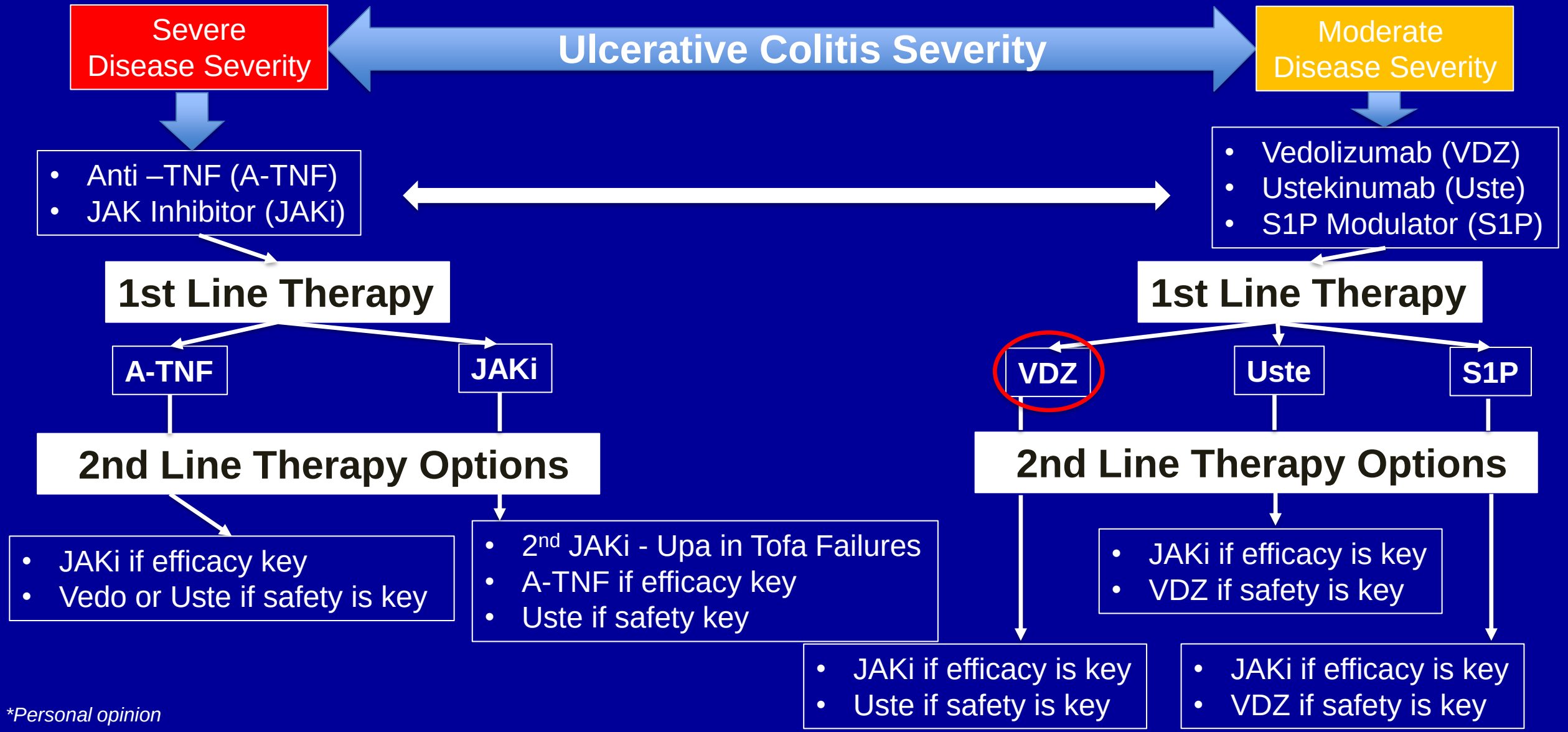
Sparrow MP et al, J Crohns Colitis. 2020 May 21;14(4):542-556

Managing Treatment Failure – Switching Advanced Therapies– Some Emerging (Simplistic) Principles in Crohn's Disease



*Personal opinion

Managing Treatment Failure – Switching Advanced Therapies– Some Emerging (Simplistic) Principles in Ulcerative Colitis



*Personal opinion

Conclusions and Take Home Messages

- Clinical outcomes in IBD continue to improve due to the availability of highly effective medical therapies and, equally or more importantly, better strategies for using them
- IBDologists now need to understand the differences between biologics and newer small molecules and the principles of comparative effectiveness research
- Positioning and sequencing of therapies requires an individualized case by case approach with algorithmic recommendations an evolving science
- Treatment strategy principles include individualisation of treatment choice, early intervention, treating to target and tight disease monitoring
- Patient-centric models of care including telehealth, remote disease monitoring and non-invasive disease monitoring are well suited to IBD care in the treat to target era

Acknowledgements – Alfred Health IBD Unit and Collaborators

theAlfred

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