Therapeutics for Multiple Immune-Mediated Disorders in IBD

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Disclosures (Jones)

- ***Consultant:*** AbbVie, Janssen, Merck, Shire, Pfizer, Takeda Pharmaceuticals
- ***Speakers' Bureau***: AbbVie, Janssen, Shire, Ferring, Takeda Pharmaceuticals
- ***Advisory Board***: AbbVie, Ferring, Janssen, Merck, Shire, UCB, Pfizer, Takeda Pharmaceuticals
- ***Research/Educational Support***: AbbVie, Janssen, Takeda Pharmaceuticals

Disclosures (Ma)

- ***Consultant:*** Robarts Clinical Trials, Inc.
- ***Speakers' Bureau***: Janssen, AbbVie, Takeda, Pfizer
- ***Advisory Board***: Janssen, AbbVie, Takeda, Pfizer
- ***Research/Educational Support***: None

Objectives

- To gain knowledge of the existing literature relating to the use of combination biologic therapies for the management of multiple immune-mediated conditions
- To understand when it is appropriate to consider combined biologic therapies for the management of multiple immune-mediated disorders
- To learn how to prevent and monitor for relevant adverse clinical safety outcomes

Case Presentation 1

- 29 year-old female you have been following with medically refractory colonic CD previous failure of vedolizumab
- Steroid dependent disease
- Failure of AZA, MTX
- Currently on adalimumab mono therapy X 6 months.
- Although luminal disease well controlled now (HBI =0) has severe psoriasis on her scalp (pic) non-responsive to topical therapies

Case presentation 1

- What would you do next?

- Any other investigations?

Case Presentation 1

Near normalization of CRP

FC= 200

Colonoscopy reveals mild disease activity (SES-CD = 6)

What would you do now?

Combination Biologic Therapy Overview: An IBD Perspective

- Biologic therapy has revolutionized the care of inflammatory bowel disease (IBD).
- Despite multiple options, clinical remission rates at one year are approximately 40% for any single biologic agent.
- In addition, questions surround the efficacy of newer agents in controlling extra-intestinal manifestations (EIMs).
- This has raised interest in whether combination biologic therapies with different mechanisms of action (MOA) can be used safely to increase overall efficacy and to control EIMs.

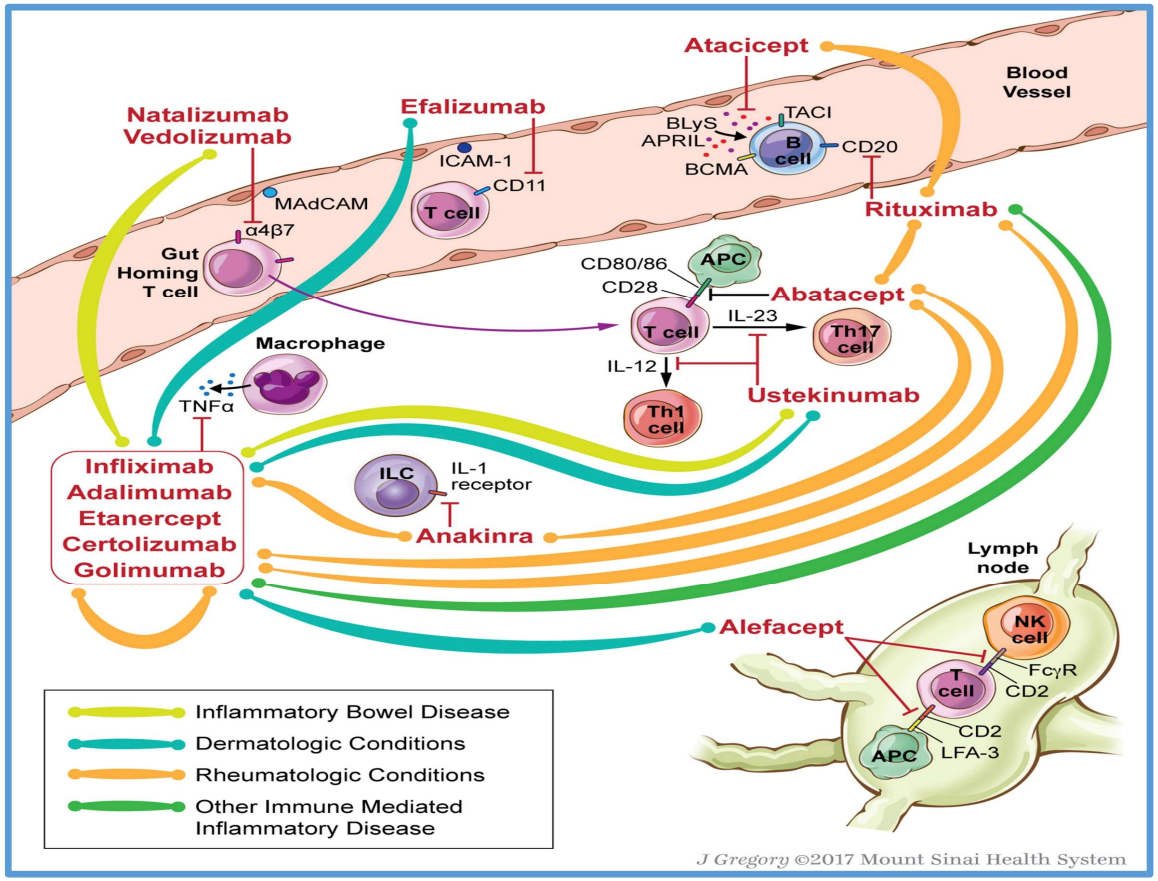
The challenge in IMID management

How can we identify the right strategy for the right patient at the right time?

Consider the following

- IBD phenotype & EIMIBD
- Concomitant IM disease characteristics
- Probable inflammatory mechanism
  - Response to past medications
  - Pattern of non or loss of response to medications
- RFs for medication-related adverse events
- Patient preference
- Risk profile

What treatment options are available for dermatologic and gastrointestinal disorders?



Reports of combination therapy in Dermatologic Conditions

Table 2. Publications on the Use of Combined Biologic Agents in the Treatment of Dermatologic Conditions

Reference	Year	Study type	Disease	Number of subjects	Medications (n)	Efficacy	Adverse events	Follow-up period
Cuchacovich et al[10]	2012	Case report	Psoriasis + PSA	1	Etanercept + UST	Composite psoriatic disease activity index, significant improvement	None	11 mo
Babalola et al[11]	2015	Case report	Psoriasis + PSA	1	Etanercept + UST	Resolved joint and skin manifestations	Unstable angina/cardiac stent	6 mo
Heinecke et al[12]	2013	Case report	Psoriasis + PSA	1	UST + etanercept → adalimumab	Skin improved but joint symptoms continued	Furuncles + autoimmune hemolytic anemia	—
Gniadecki et al[13]	2016	Case series	Psoriasis + PSA	4	UST + etanercept (2) or adalimumab → golimumab (1) or adalimumab → certolizumab (1)	Improved skin and joint symptoms	Herpes zoster, retrotonsillar abscess, erysipelas, bacterial pneumonia, cellulitis	7–62 mo 18.2 patient-years of exposure
Adisen et al[15]	2008	Case report	Psoriasis + PSA	1	Efalizumab + etanercept	Improved skin and joint symptoms	None	1.5 mo
Kitamura et al[16]	2009	Case report	Psoriasis + PSA	1	Efalizumab + etanercept	Improved skin and joint symptoms	Pulmonary tuberculosis	~18 mo
Hamilton[17]	2008	Case series	Psoriasis + PSA	20	Efalizumab + etanercept or etanercept → infliximab	Improved skin and joint symptoms	URI, LRI, SCC, BCC, dysplastic nevus, actinic keratoses	16 mo (range, 8–46 mo)
Krell[19]	2006	Case series	Psoriasis + PSA	3	Alefacept + etanercept	Improved skin and joint symptoms	None	—

BCC, basal cell carcinoma; LRI, lower respiratory tract infection; PSA, psoriatic arthritis; SCC, squamous cell carcinoma; URI, upper respiratory tract infection; UST, ustekinumab.

Hirten RP et al, Clin Gastroenterol Hepatol. 2018 Sep;16(9):1374-1384

Biologic agent	UC	CD	AS	PsA	PsO	Uveitis	HS	nr-Ax SpA
Adalimumab	✓	✓*	✓	✓	✓	✓**	✓	No
Certolizumab pegol	No	No	✓	✓	No	No	No	No
Etanercept	No	No	✓	✓	✓	No	No	No
Golimumab	✓	No	✓	✓	No	No	No	✓
Infliximab	✓	✓	✓	✓	✓	No	No	No
Secukinumab	No	No	✓	✓	✓	No	No	No
Ustekinumab	No	✓	No	✓	✓	No	No	No
Vedolizumab	✓	✓	No	No	No	No	No	No

What treatment options are available for dermatologic and gastrointestinal disorders?

What safety events should I be concerned about?

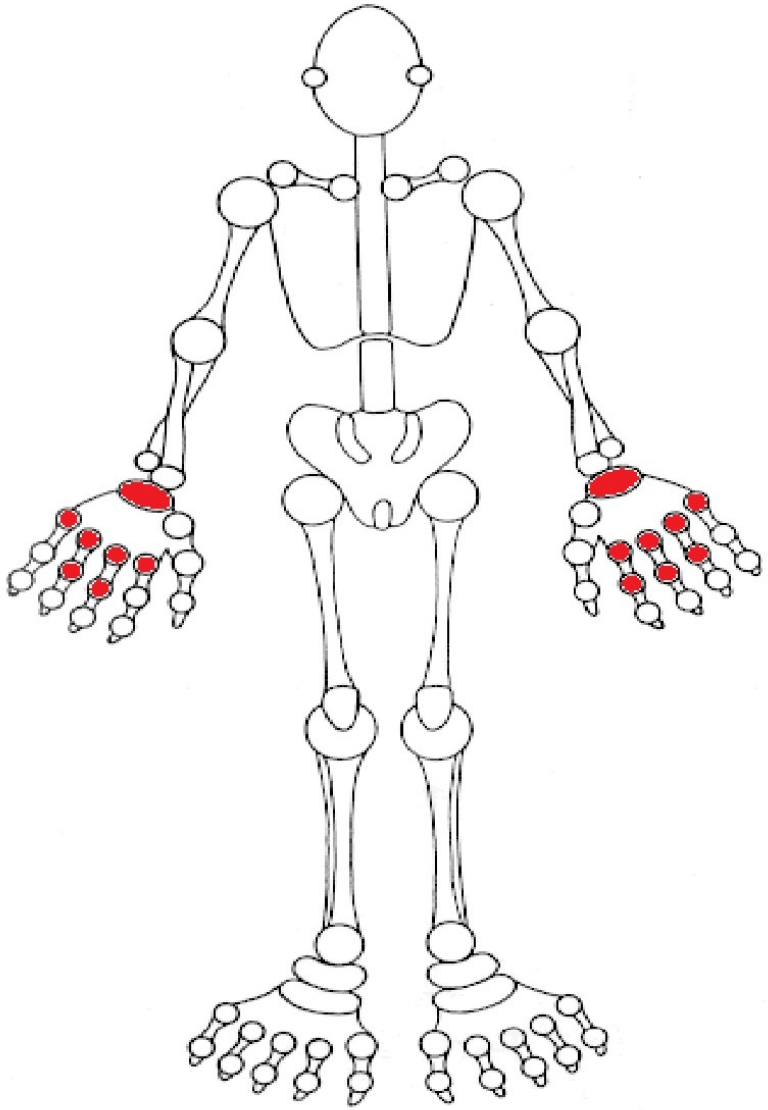
- Infections (cell mediated immunity)
  - HSV
  - Pneumonia
  - Derm: furuncles, cellulitis
  - Shingles
- Reactivation TB
- PJP (depending on the level of IS patient is on)
- Vaccine preventable illness

Case Presentation 1

- After a lengthy discussion regarding risk vs. benefit a decision is made to initiate ustekinumab in combination with adalimumab
- 4 months later patient has near resolution of the scalp psoriasis and remains in clinical remission.
- She has been able to successfully wean off the prednisone
- A repeat FC = 100
- To date this patient has not developed adverse events on dual biologic therapy

Case Presentation 2

- 67 year-old man diagnosed with ulcerative pancolitis x 25 years
  - Previously maintained in long-term remission on Asacol 2.4g PO daily
  - Last colonoscopy 2018: pseudopolyps in the left colon and scarring but no active inflammatory disease
  - Incomplete compliance with 5ASA therapy
- Past Medical History
  - Rheumatoid arthritis: currently on Methotrexate 15mg SC weekly
  - HTN
  - Dyslipidemia



Case Presentation 2

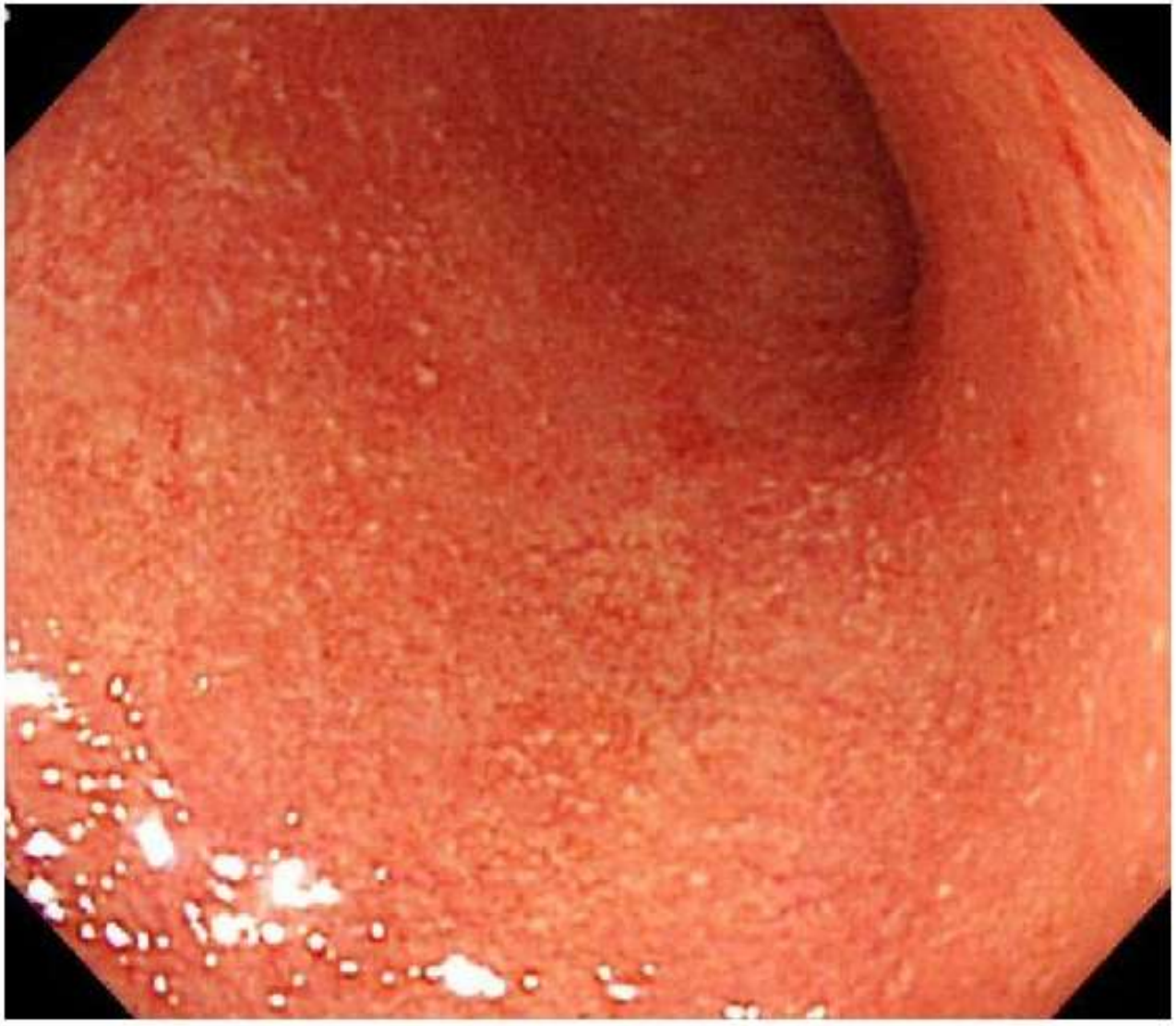
- Over last 3 months, flaring symptoms:
  - **5-10 bowel movements per day with urgency and tenesmus, 50% with rectal bleeding**
  - Tried 2-week course of Salofalk 1g suppository without significant improvement
  - Tried 8 weeks of Asacol 4.8g PO daily without significant improvement
  - Increasing hour-long morning stiffness, swelling, and pain in hands/wrists

- **What would you do next?**

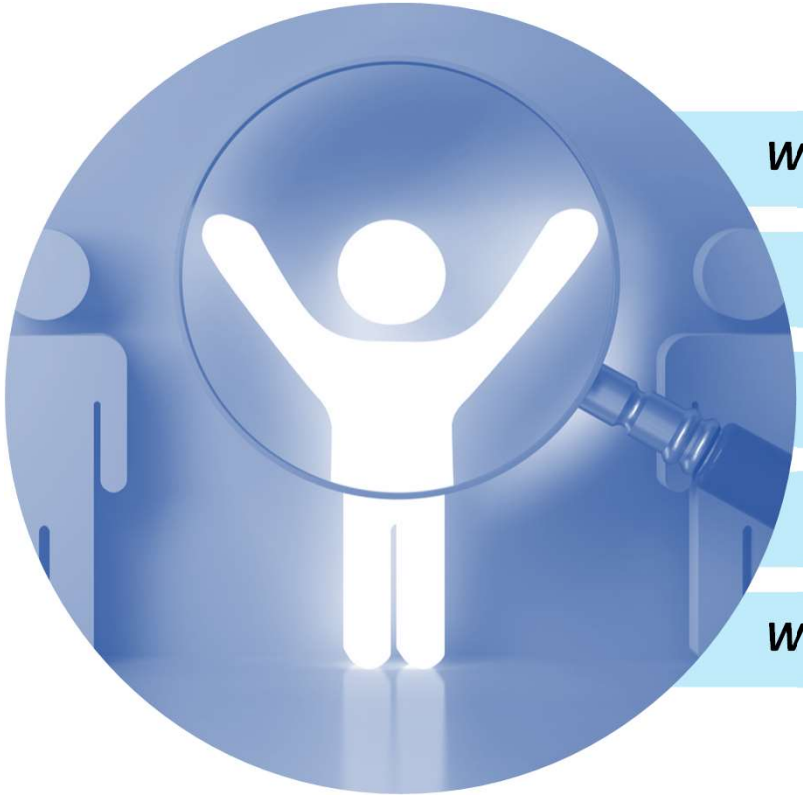
Case Presentation 2

- Infectious workup negative
- Pre-biologic workup:
  - TST negative, CXR negative
  - HBsAg negative, anti-HBc total negative, anti-HBs (+)
- Flexible sigmoidoscopy:

- **What would you do next?**



What factors do you consider in treating patients with multiple immune mediated diseases?



Who is this patient?

What are the features of their disease?

What is their risk of disease?

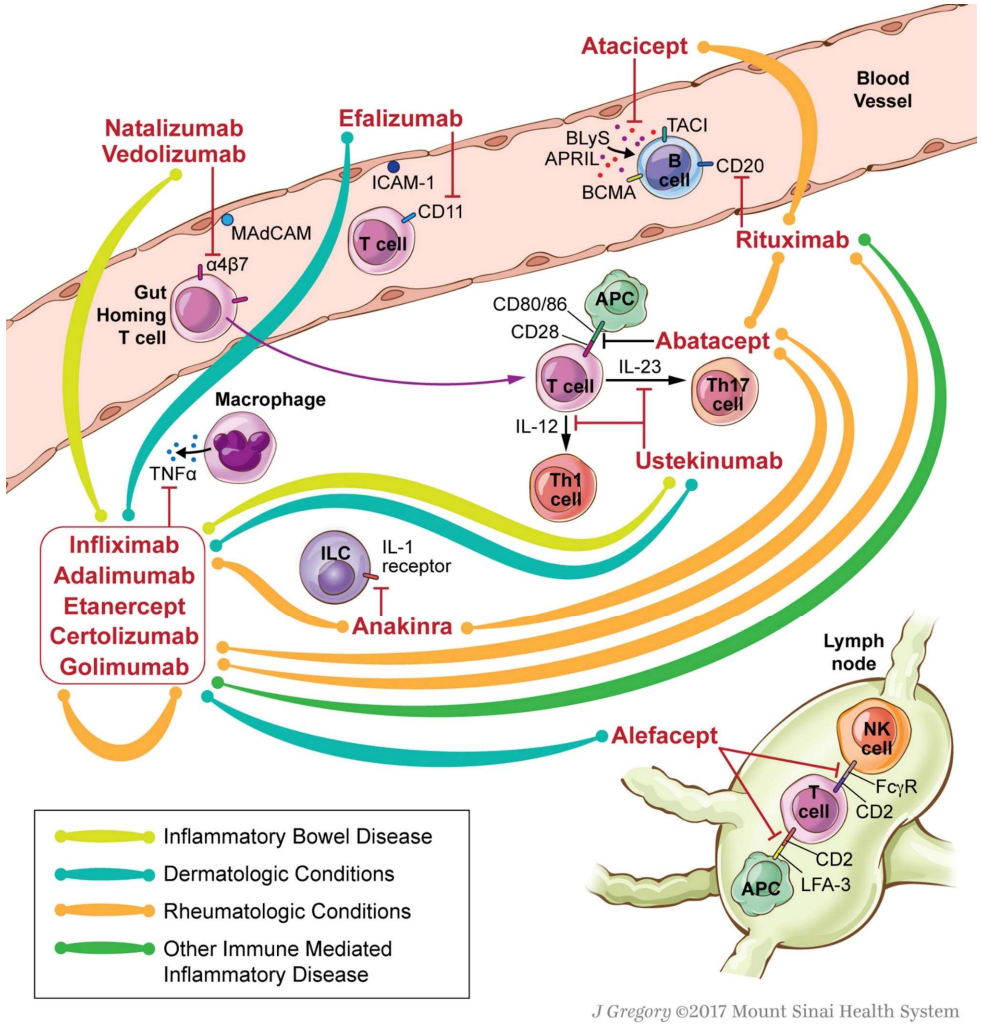
What is their likelihood of responding to therapy?

What is the likelihood of AEs from therapy?

Management of IMIDs

- Make the diagnosis quickly and accurately
- Assess disease severity and determine prognosis
- Select and initiate therapy to induce and maintain remission
- Adjust therapies to achieve a target
- Modify long-term outcomes of the disease
- Monitor for relapse
- Monitor for drug-related and disease-related complications

What treatment options are available for rheumatologic and gastrointestinal disorders?



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Secukinumab	No	No	✓	✓	✓	No	No	No
Ustekinumab	No	✓	No	✓	✓	No	No	No
Vedolizumab	✓	✓	No	No	No	No	No	No

What treatment options are available for rheumatologic and gastrointestinal disorders?

Case Presentation 2

- Patient started on **adalimumab** (standard induction, q2 week maintenance therapy) in combination with methotrexate
- Joint symptoms enter into remission: no swelling, pain after 2 months
- Bowel symptoms: incomplete response
  - Still 3-5 bowel movements per day, occasional bleeding
  - CRP persistently elevated 8-12 mg/L
  - Fecal calprotectin elevated 350 µg/mg
- Escalated to adalimumab weekly, maximized methotrexate to 25mg/week but still no response. Adalimumab level measured 12 µg/mL, no detectable anti-adalimumab antibodies.

Case Presentation 2

- **What would you do next?**
  - Switch to infliximab?
  - Switch/add vedolizumab?
  - Switch/add tofacitinib?
  - Switch/add ustekinumab?
  - Colectomy?
  - Other options?

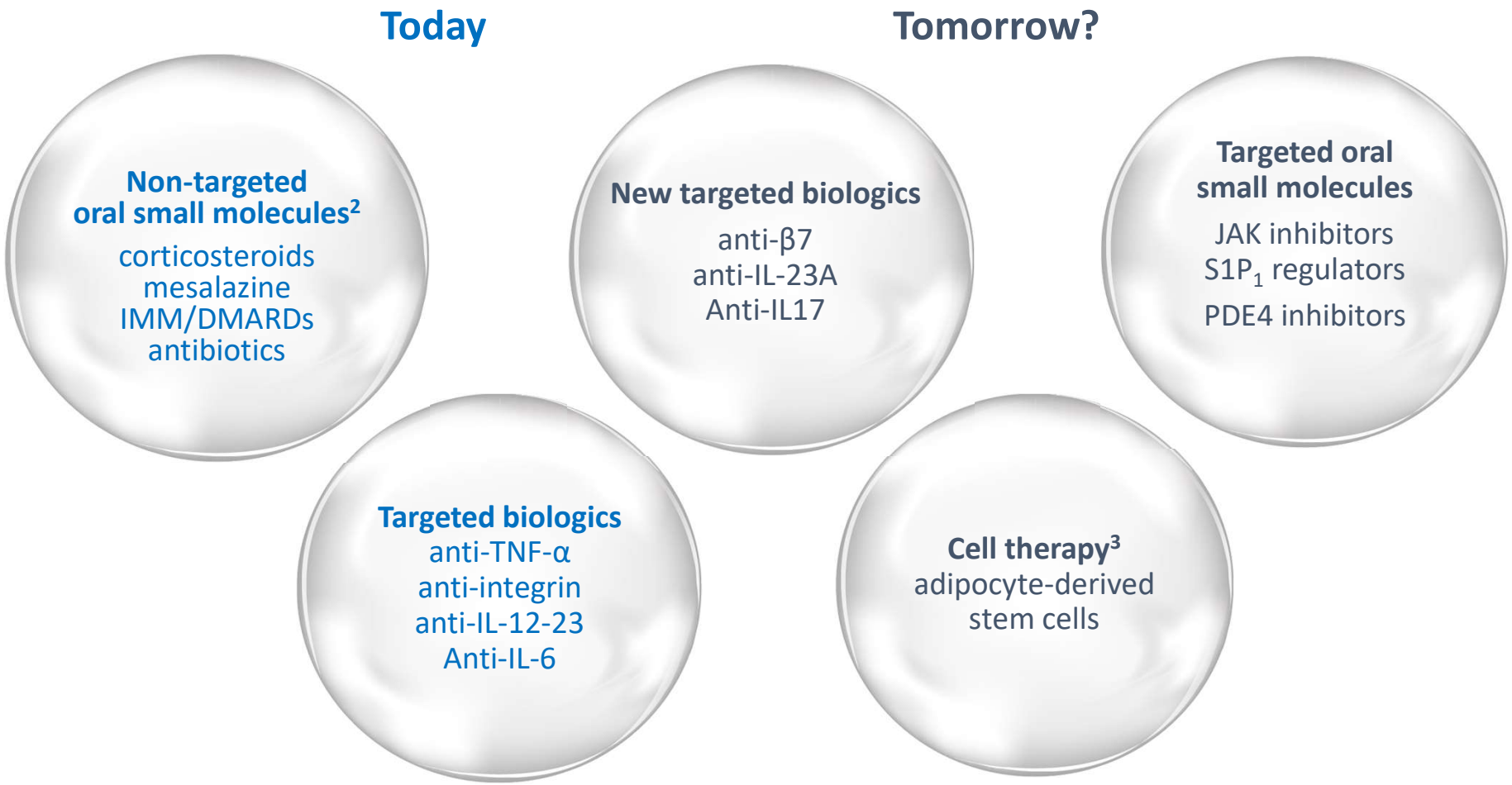
Case Presentation 2

- Decided to add vedolizumab
  - Excellent response: clinical and endoscopic remission
- Adalimumab discontinued a year later due to development of anti-TNF related psoriasis but joints re-flare approximately 3 months after adalimumab discontinuation
- **Now what to do?**

Table 3. Publications on the Use of Combined Biologic Agents in the Treatment of Rheumatologic Conditions

Reference	Year	Study type	Disease	Number of subjects	Medications (n)	Efficacy	Adverse events (n)	Follow-up
Sheehy et al[21]	2006	Case report	HLA-B27-associated arthropathy	1	IFX + etanercept	Improved joint inflammation and pain	None	>6 mo
Weinblatt et al[24]	2007	RCT + LTE	RA	121	Etanercept + abacacept or placebo	No differences at 6 and 12 mo	Combination: higher AEs, SAEs, related SAEs, discontinuation because of AEs at 1 year; trend continued in LTE	RCT- 12 mo LTE- 24 mo
Genovese et al[26]	2004	RCT	RA	242	Anakinra + etanercept vs etanercept	No difference	Combination: higher SAEs (14.8% vs 2.5%), discontinuation because of AEs (7.4% vs 0%), injection reactions (70.4% vs 40%), 1 death	24 wk
Morgan et al[28]	2008	Observational study	RA	8	CD4 monoclonal antibody + bivalent TNF antagonist	Improved joint swelling and pain	Maculopapular rash (5), infusion reactions	17–49 mo
Koumakis et al[32]	2009	Case series	RA	2	RTX + etanercept	Resulted in remission	None	4 y; 18 mo
Feuchtenberger et al[33]	2009	Case series	RA	2	RTX + etanercept	Significantly improved disease activity	Pneumonia, acute bronchitis in 1 patient	6 y
Blank et al[34]	2009	Retrospective cohort	RA	6	RTX → etanercept + RTX if no response	Significant improvement with combination	Oral herpes simplex	18.5 mo of mean exposure
Rigby et al[36]	2013	Open label study	RA	176	RTX + background biologic	Physical function improved at 24 and 48 wk	24.3 SAEs/100 patient-years, cellulitis, pneumonia, bronchitis, septic shock, 3 deaths	48 wk
Greenwald et al[37]	2011	RCT	RA	51	RTX or placebo + adalimumab or etanercept	____	Placebo vs rituximab: AEs (83% vs 94%), SAEs (0% vs 6%); similar infectious rates	24 wk
Van Vollenhoven et al[38]	2015	RCT	RA	27	RTX + placebo or atacicept	No difference in clinical response	Combination vs placebo, treatment period: AEs (94.4% vs 100%), discontinuation because of AEs (22.2% vs 11.1%), infections (44.4% vs 66.7%) Follow-up: 12 SAEs	25-wk treatment period 32-wk follow-up
Weinblatt et al[39]	2006	RCT	RA	169	Abatacept or placebo + background biologic	Lack of clinical benefit with combination	Combination vs placebo: AEs (95.1% vs 89.1%), discontinuation because of AEs (8.7% vs 3.1%), infection (5.8% vs 1.6%); malignancy (7% vs 2%)	1 y
Record et al[40]	2011	Case series	Juvenile idiopathic arthritis	4	Abatacept + anakinra	Improved disease control in all subjects	None	8–17 mo

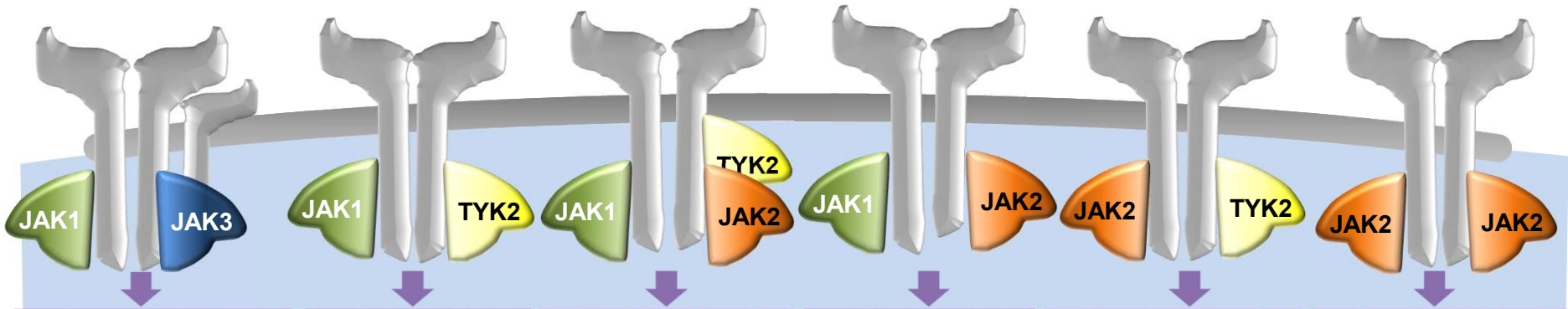
AE, adverse event; IFX, infliximab; LTE, long-term extension; RA, rheumatoid arthritis; RCT, randomized controlled trial; RTX, rituximab; SAE, serious adverse event; TNF, tumor necrosis factor.


Today
Tomorrow?
Non-targeted oral small molecules[2]
corticosteroids
mesalazine
IMM/DMARDs
antibiotics
New targeted biologics
anti-β7
anti-IL-23A
Anti-IL17
Targeted oral small molecules
JAK inhibitors
S1P1 regulators
PDE4 inhibitors
Targeted biologics
anti-TNF-α
anti-integrin
anti-IL-12-23
Anti-IL-6
Cell therapy[3]
adipocyte-derived stem cells

Case Presentation 2

- Decided to add tofacitinib to treatment regimen in combination with vedolizumab
- Discontinued methotrexate given degree of immunosuppression
- **What are the considerations for starting combination biologic therapy with an oral small molecule/JAK inhibitor?**

Upadacitinib (ABT-494)	More potently inhibits **JAK1** over JAK2 and JAK3
Baricitinib	More potently inhibits **JAK1 and JAK 2** over JAK3
Filgotinib	More potently inhibits **JAK1** over JAK2 and JAK3
Peficitinib	More potently inhibits **JAK3** over JAK 1and JAK 2
Tofacitinib	Non-selective (inhibits **JAK1, JAK2 and JAK3**)

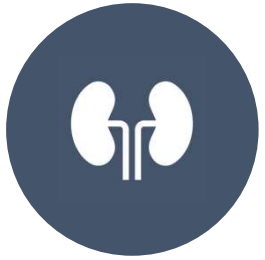


FUNCTION						
	• Growth/maturation lymphoid cells • Differentiation/ homeostasis T cells, NK cells • B-cell class switching • Inflammation	• Antiviral • Inflammation • Antitumor	• Naive T-cell differentiation • T-cell homeostasis • Inflammation • Granulopoiesis	• Antiviral • Inflammation	• Innate immunity • Differentiation/ proliferation of Th17 cells • Inflammation	• Erythropoiesis • Myelopoiesis • Megakaryocyte/ platelet production • Growth • Mammary development

Adapted from Clark et al, J Med Chem 2014;57:5023-5038.

Case Presentation 2

RISK OF HERPES ZOSTER?



RISK OF VENOUS THROMBOEMBOLISM?

RISK OF ELEVATED CK AND DYSLIPIDEMIA?

TOFACITINIB DOSING CONSIDERATIONS?

THE USE OF COMBINATION BIOLOGIC THERAPY IN INFLAMMATORY BOWEL DISEASE: THE CALGARY EXPERIENCE: METHODS

- A retrospective single center cohort study was performed at the University of Calgary of adult (≥18 years) IBD patients receiving combination biologic therapy between May 2015 and September 2018.

- All patients received “add on” biologic therapy either to control medically refractory disease or to control extra-intestinal manifestations not controlled by a single agent.

- The primary outcome of interest was to assess the safety of the combination biologic therapy. Secondary outcomes included proportion of patients who demonstrated clinical improvement, defined by physician global assessment, and evaluation of endoscopic response, defined as absence of deep ulceration or a Mayo score of one or less.

THE USE OF COMBINATION BIOLOGIC THERAPY IN INFLAMMATORY BOWEL DISEASE: THE CALGARY EXPERIENCE: RESULTS

- 10 patients (9 Crohn's disease (CD), 1 ulcerative colitis (UC)) were treated with combination biologic therapy.
- Primary indication to add a second biologic was
  - medically refractory disease in 6 and
  - control of EIMs in 4: 2 type II peripheral arthritis, 2 ankylosing spondylitis.
- Mean follow-up was 64.8 weeks (range 10-118 weeks). All patients were treated for at least three months.
- Clinical and endoscopic response was 50% in medically refractory patients and 100% to control EIMs
- One patient developed a community acquired pneumonia

Panaccione N et al, ECCO Copenhagen 2019

A first look at the Calgary Experience

Pt.	Age (Yrs.)	Gender	Disease Type	Previous Biologics	Combination Biologic Experience	PGA response	Endoscopic response
Primary indication to control medically refractory disease (n=6)							
1	54*	M	CD	IFX, ADA, USTE, Vedo, Goli	Vedo+Goli	Y	Y
2	28	M	CD	IFX, ADA, Vedo, USTE	USTE+ IFX	Y	Y
3	24+	F	UC	ADA, IFX, Goli, Vedo	Vedo+IFX	N	N
4	28	M	CD	IFX, ADA, USTE, Vedo	Vedo+IFX	N	N
5	28	F	CD	ADA, IFX, USTE, Vedo	Vedo+USTE	Y	Y
6	45++	F	CD	IFX, ADA, Goli, USTE, Vedo	Vedo+Cert	N	N
Primary indication to control extra-intestinal manifestations (n=4)**							
7	33	F	CD	ADA, IFX, Goli, USTE, Vedo	Vedo+IFX	Y	
8	47	M	CD	IFX, ADA, Goli, Vedo	Vedo+Goli	Y	
9	31	M	CD	IFX, ADA, USTE, Vedo	Vedo+ADA	Y	
10	34	F	CD	IFX, ADA, Goli, USTE, Vedo	Vedo+ADA	Y	

*patient developed community acquired pneumonia while on dual biologics and corticosteroids
** 2 type II arthropathy, 2 ankylosing spondylitis
PGA=Physician global assessment
IFX=infliximab, ADA=adalimumab, goli=golimumab, USTE=ustekinumab, Vedo=vedolizumab

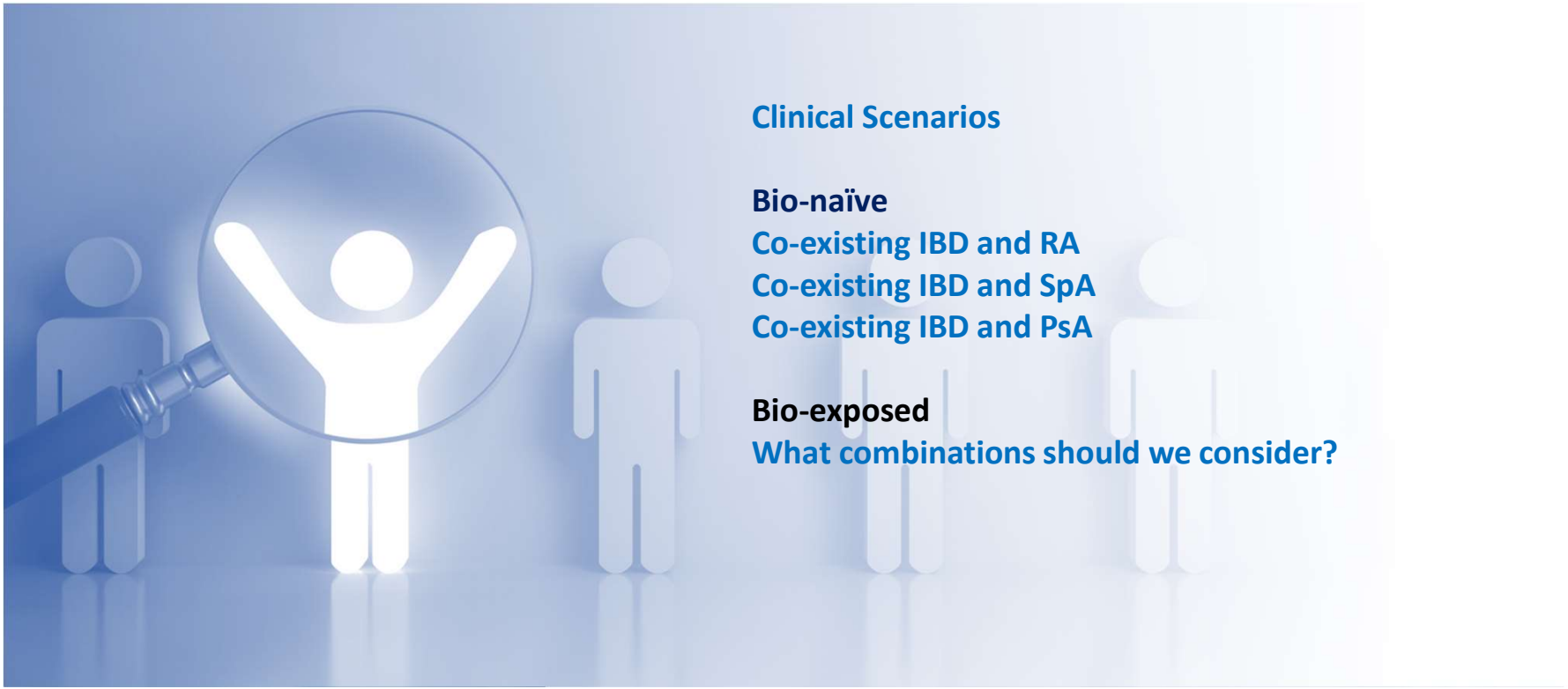
+patient required proctocolectomy 22 weeks after combination biologics started
++patient required ileal resection and diverting stoma 28 weeks after starting combination biologics

Panaccione N et al, ECCO Copenhagen 2019

How can we do this more effectively?

- Understanding therapy risk in the context of disease risk
- Embracing a 360 degree assessment of the IBD patient including psychosocial needs
- Embracing proven therapies earlier in the disease course
- Utilizing validated objective endpoints of disease control
- Adjusting therapies serially until endpoints are achieved (treating to a target)

Consider each patient's unique situation when choosing combination (dual) therapy



Clinical Scenarios

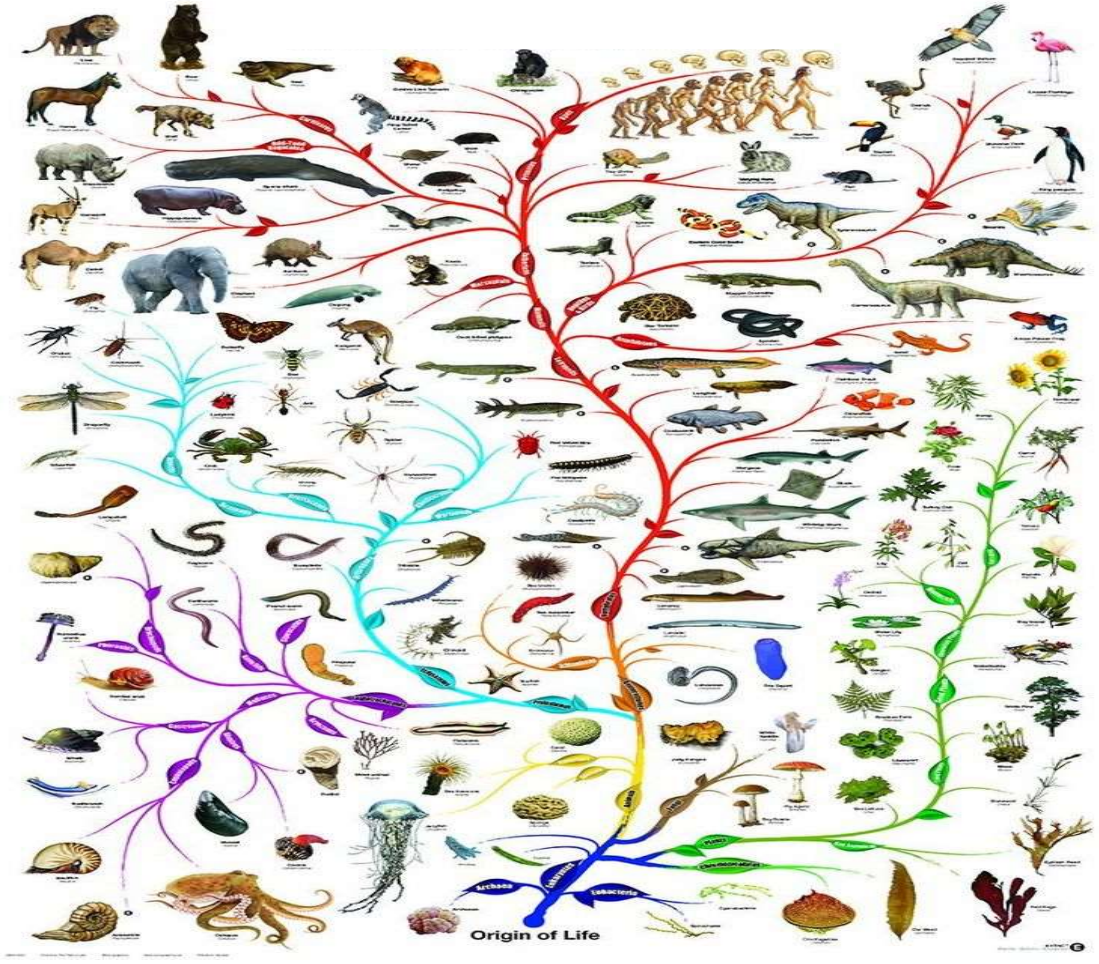
Bio-naïve
Co-existing IBD and RA
Co-existing IBD and SpA
Co-existing IBD and PsA

Bio-exposed
What combinations should we consider?

Kamp KJ et al. Patient 2018; doi: 10.1007/s40271-017-0294-0.

Summary : Combination Therapy in Evolution

- Combination biologic therapy has multiple advantages and may be where we are evolving to.
- It has disadvantages which are not inconsequential (cost, safety)
- Multiple options and the challenge will continue to be how to find the ideal combination for individual high risk patients.



Practical approaches for treatment of patients with IMIDs

Right patient

- Not everyone needs early aggressive therapy
- Prognostic factors are mainly clinical
  - Disease location, duration, severity
  - Comorbidities and complications
  - Other factors predicting risk for progression

Right therapy

- When choosing therapy, consider:
  - Risk:benefit ratio
  - Cost:benefit ratio
  - Predictive factors of response to therapy
  - Patient preference

Right time

- Intervene before it is too late
- Monitoring is essential
  - Preemptive optimisation of the dose and therapy

Early use of effective therapies, risk stratification, individualised treatment selection and frequent assessment of disease activity and treatment outcomes are key steps in achieving the full potential of biologic therapy in ulcerative colitis

Colombel JF et al. Gastroenterology. 2017;152:351-61.e5. Ordás I et al. Gut. 2011;60:1754-63. Khanna R et al. Gastroenterol Clin N Am. 2017;46:661-77.