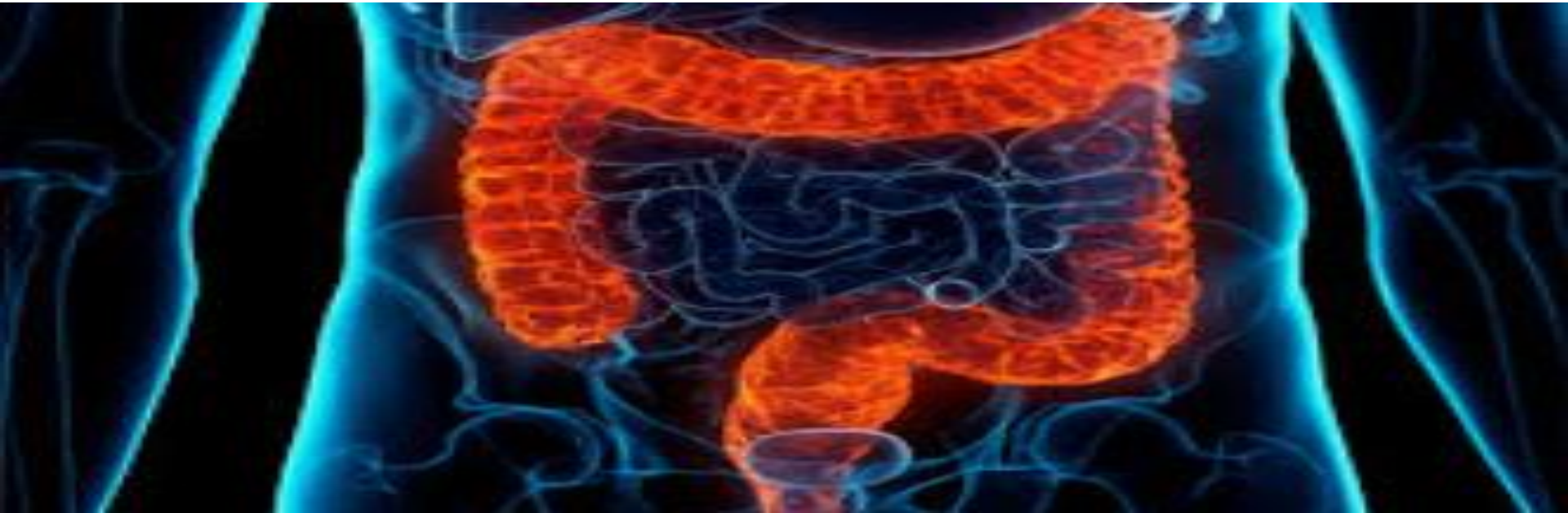
New treatments for severe ulcerative colitis

Shohreh Maleknejad MD
associate professor
GUMS



Introduction

- Acute severe ulcerative colitis (ASC), a medical emergency in children, is defined by a Pediatric Ulcerative Colitis Activity Index (PUCAI) score of at least 65 points.
- Pediatric onset ulcerative colitis (UC) is often more extensive than in adults and more dynamic in progression.

PUCAI scores are interpreted as follows

- **0 to 9 – Remission**
- **10 to 34 – Mild disease**
- **35 to 64 – Moderate disease**
- **65 to 85 – Severe disease**

Item

1-Abdominal pain, 2-Rectal bleeding, 3-Stool consistency of most stools, 4-Number of stools per 24 hours, 5-Nocturnal stools, 6- Activity level

TABLE 1. Paediatric Ulcerative Colitis Activity Index

Item	Points
(1) Abdominal pain	
No pain	0
Pain can be ignored	5
Pain cannot be ignored	10
(2) Rectal bleeding	
None	0
Small amount only, in <50% of stools	10
Small amount with most stools	20
Large amount (>50% of the stool content)	30
(3) Stool consistency of most stools	
Formed	0
Partially formed	5
Completely unformed	10
(4) Number of stools per 24 hours	
0–2	0
3–5	5
6–8	10
>8	15
(5) Nocturnal stools (any episode causing wakening)	
No	0
Yes	10
(6) Activity level	
No limitation of activity	0
Occasional limitation of activity	5
Severe restricted activity	10
Sum of PUCAI (0–85)	

Severe ulcerative colitis

- Children with ASC should be ***admitted to hospital for immediate evaluation and intensive medical treatment with intravenous corticosteroids (IVCS).***
- A PUCAI 65 is associated with a more refractory disease course in pediatric UC, both at disease onset and thereafter.
- The occurrence of ASC was associated with an increased risk of colectomy .
- The advent of calcineurin inhibitors and infliximab has reduced the short-term colectomy rate from between 40% to 70% to approximately 10% to 20% in children and the 1-year colectomy rate from 60% to between 18% to 22% .

Toxic megacolon

- Toxic megacolon is life-threatening complication.
- Toxic megacolon occurs in approximately 5 percent of patients with severe UC and may be triggered by hypokalemia or opiate use.

Suggested criteria for diagnosing toxic megacolon in children with colitis are:

- Acute dilation of the transverse colon, with loss of haustral folds – **Diameter >4 cm on children younger than 10 years or diameter >5.6 cm in patients 10 years or older**

AND

- Systemic symptoms, such as fever, tachycardia, dehydration, electrolyte disturbance, altered level of consciousness, and hypotension

- Patients with toxic megacolon should be promptly evaluated and ***followed closely by surgeons***. Emergency or urgent colectomy may be indicated, depending on the patient's condition.

Infectious Screening

Recommendations

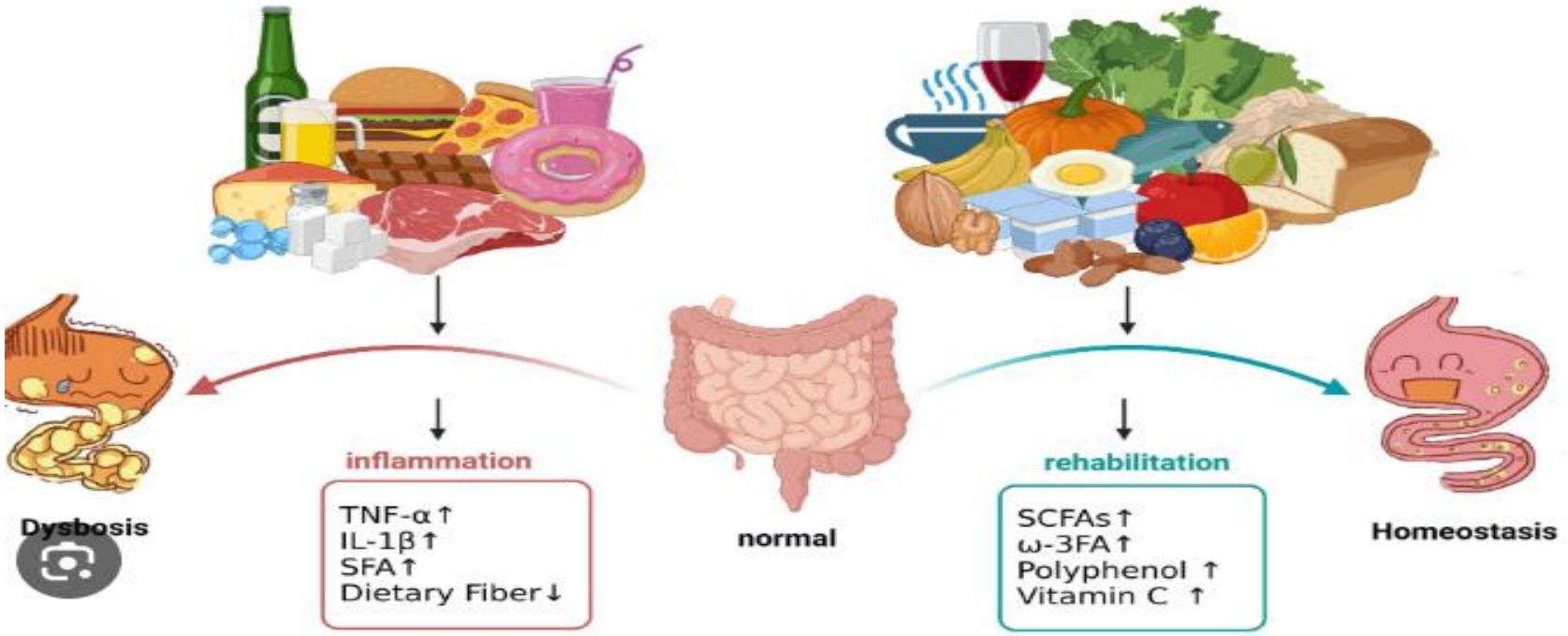
- 1.Bacterial causes for ASC should be excluded by a stool culture including **Clostridium difficile** toxins A and B (100% agreement).
- 2. **Cytomegalovirus (CMV)** colitis should be excluded in children not responding to 3 days of IVCS (98% agreement).
- 3. Other infections should be considered when relevant, including viral and parasitic(**e.g., cryptosporidium and amoebiasis**), such as in the presence of fever, other affected household members or non-bloody diarrhea; stool testing for Entamoeba histolytica should be performed in endemic areas or recent travel to these areas (100% agreement).

Antibiotics

- Antibiotics are not routinely recommended in children with ASC at admission. (100% agreement).
- Antibiotics are indicated in ***cases of suspected bacteremia, C. difficile or other enteric infection, and toxic megacolon*** and are continued until blood and stool cultures are negative.
- In children who are not suspected to have these conditions, antibiotics are not routinely recommended. However, some clinicians utilize oral, multidrug antibiotic regimens empirically and/or for colon salvage therapy in corticosteroid-refractory patients with severe colitis.

Nutritional Support

- ***Regular diet should be continued in most ASC cases***. Enteral (or parenteral in those not tolerating enteral) nutrition may be used if oral feeding is not tolerated or in malnutrition (98% agreement).
- ***Oral or enteral feeding is contraindicated in cases of megacolon, or when surgery is imminent*** (100% agreement).
- Electrolyte imbalance (especially hypokalaemia and hypomagnesaemia) can promote colonic dilatation. Thus, electrolytes should be monitored, at least every 1 to 3 days, according to the degree of the baseline values and clinical status (98% agreement).



Corticosteroids

- ***Intravenous methylprednisolone*** 1 mg/k/day (up to 40 mg/day) once daily in the morning is recommended as the initial treatment at admission ; a higher dose of **1.5 mg/k/day** (up to 60 mg/day) in 1 or 2 divided daily doses should be reserved to the more severe end of the spectrum and for children who have failed oral steroids before admission (100% agreement).
- ***Oral 5-aminosalicylate (5-ASA) preparations should be stopped at the time of hospital admission*** because 5-ASA preparations are usually ineffective in acute severe exacerbations of colitis and are responsible for worsening colitis in approximately 3 percent of patients.

Monitoring Disease and When to Start Second-line Therapy

- A PUCAI >45 points on the third day of IVCS treatment should dictate planning for second-line therapy between days 3 to 5 (100% agreement).
- Second-line therapy should be initiated on the fifth day of IVCS treatment in children with a PUCAI >65 points (100% agreement).
- IVCS should be continued for an additional 2 to 5 days in children with a PUCAI of 35 to 65 on day 5; daily monitoring for confirming gradual response is recommended before a decision on second-line therapy is made in most cases within a total of 7 to 10 days of treatment (100% agreement).

Practice Points

- Recommended planning for second-line therapy between days 3 and 5 in non-responders includes ***sigmoidoscopy (to detect infectious colitis (most notably CMV), granulomas, and degree of inflammation), surgical consult***, ***discussion with a stoma specialist, exclusion of latent tuberculosis, serology for HBV and HCV, and/or blood tests required before treatment with calcineurin inhibitors (creatinine, lipids, and magnesium)*** (95% agreement).
- ***Frequent monitoring of laboratory tests*** **(including complete blood count, c-reactive protein (CRP), ESR, albumin, and electrolytes)** is advisable as needed but at least at diagnosis and on days 3 and 5 thereafter. CRP, albumin, and ESR have some value to predict IVCS failure and should be monitored also for that purpose (100% agreement).
- Fecal inflammatory markers have no role in the diagnosis or management of ASC (95% agreemen).

WHEN STEROIDS FAIL Medical Second-line Therapies

This second-line therapy is sometimes known as ***"rescue" or "salvage" therapy***.

- 1. **Infliximab** is recommended as the second-line medical therapy for anti-TNF naive children failing IVCS (100% agreement).
- 2. **Calcineurin inhibitors (tacrolimus and cyclosporine)** can be considered as an alternative second-line medical therapy (100% agreement).
- 3. When introducing second-line therapy, the possibility of non-response and therefore need for colectomy must always be discussed (100% agreement)
- Adalimumab is also a first-line option for steroid-refractory disease. It is approved by the US Food and Drug Administration for use in children with moderate to severe pediatric UC. However, the role of adalimumab in acute severe UC is not clear. In practice, it is better to use **infliximab** rather than adalimumab in this setting.

Practice Points

- Due to rapid clearance of infliximab in ASC, **Doses of infliximab up to 10 mg/kg per dose** may be considered and may be given more frequently than usual (eg, **weeks 0, 1, and 4**). Drug levels obtained during induction may guide maximization of efficacy (95% agreement).
- Among responders to intensified induction, subsequent doses of infliximab during maintenance phase can often be gradually lowered and adjusted to standard dosing, ideally guided by therapeutic drug monitoring (100% agreement).
- Children who develop steroid-refractory ASC are at particular risk for colectomy within 1 year. Therefore, ***the addition of an immunomodulator is recommended in responders to infliximab for at least 6 months. Thiopurine therapy is preferred over methotrexate in UC*** given its superior effect on treating the colitis itself. (100% agreement).

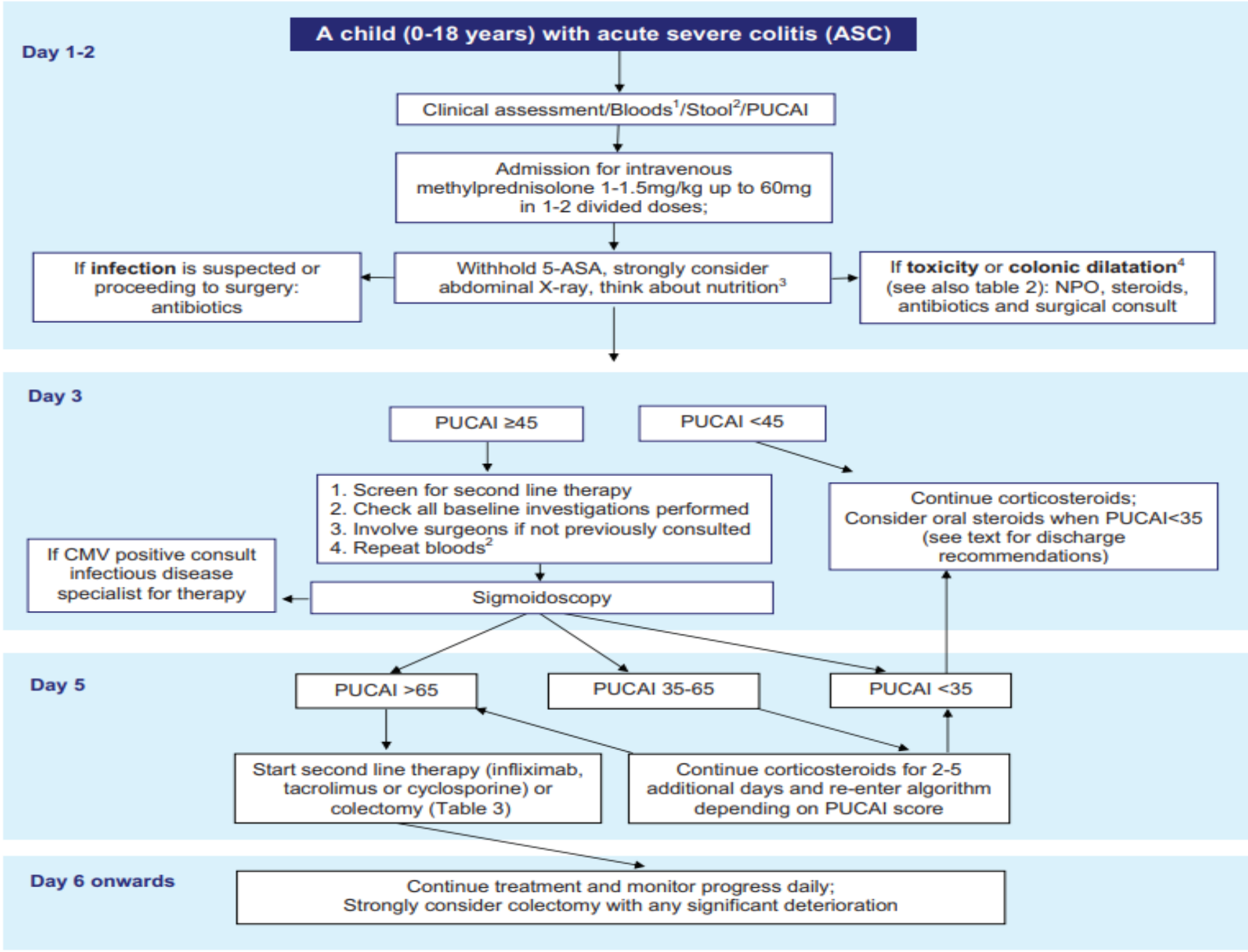
Third-line and Sequential Medical Therapy

Recommendation

- In general, prompt referral for urgent colectomy is recommended following failure of second-line medical therapy (95% agreement).

Practice Points

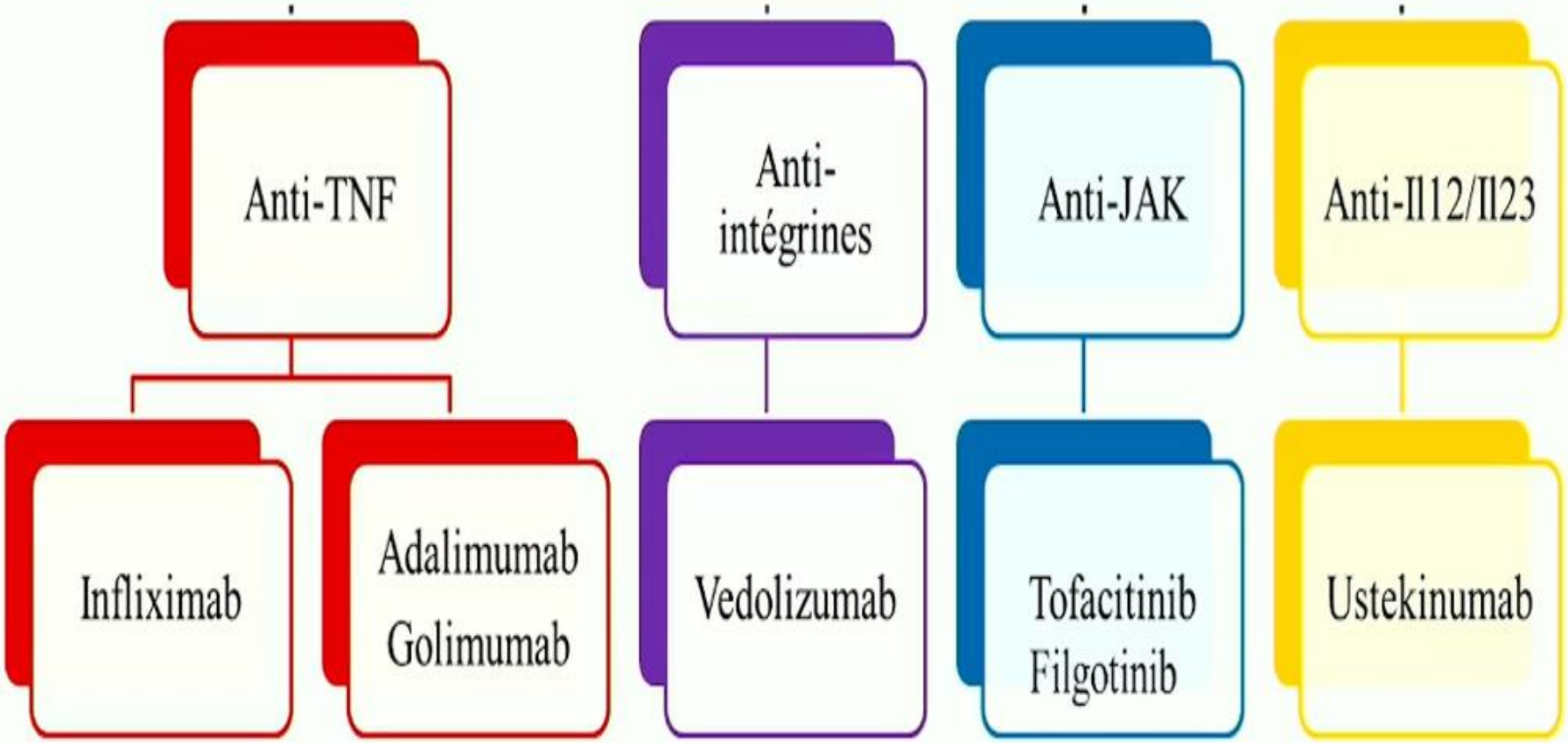
- 1. Despite the above recommendation, in highly specialized centers and in selected non-fulminant cases, ***sequential therapy of calcineurin inhibitors after infliximab or vice versa*** may be considered after weaning off steroids since concomitant steroid therapy is the main contributor for infections. (95% agreement).
- 2. Sequential therapy should not be considered unless an undetectable level of the previous drug has been documented (93% agreement).
- 3. If sequential therapy is used, ***Pneumocystis jiroveci pneumonia (PJP) prophylaxis*** (Trimethoprim-sulfamethoxazole dosing: for 3 days each week) should be considered especially if triple immunosuppressive treatment is used (98% agreement).


Day 1-2
A child (0-18 years) with acute severe colitis (ASC)
Clinical assessment/Bloods[1]/Stool[2]/PUCAI
Admission for intravenous methylprednisolone 1-1.5mg/kg up to 60mg in 1-2 divided doses;
If infection is suspected or proceeding to surgery: antibiotics
Withhold 5-ASA, strongly consider abdominal X-ray, think about nutrition[3]
If toxicity or colonic dilatation[4] (see also table 2): NPO, steroids, antibiotics and surgical consult
Day 3
PUCAI ≥45
PUCAI <45
1. Screen for second line therapy
2. Check all baseline investigations performed
3. Involve surgeons if not previously consulted
4. Repeat bloods[2]
Continue corticosteroids; Consider oral steroids when PUCAI<35 (see text for discharge recommendations)
If CMV positive consult infectious disease specialist for therapy
Sigmoidoscopy
Day 5
PUCAI >65
PUCAI 35-65
PUCAI <35
Start second line therapy (infliximab, tacrolimus or cyclosporine) or colectomy (Table 3)
Continue corticosteroids for 2-5 additional days and re-enter algorithm depending on PUCAI score
Day 6 onwards
Continue treatment and monitor progress daily; Strongly consider colectomy with any significant deterioration

Discharge Recommendations

- 1. Children should not be discharged from hospital unless the disease is at most mild (ie, PUCAI <35 points) but preferably closer to remission (ie, PUCAI <10 points) (98% agreement).
- 2. **Thiopurine maintenance** is generally recommended after ASC responsive to IVCS; exclusive **mesalamine maintenance therapy could be considered if a response to steroids has been rapid and the patient was mesalamine naı¨ve before admission** (100% agreement).
- 3. Patients responding to infliximab commenced during ASC should continue this drug as a maintenance treatment post discharge (100% agreement).
- 4. **Children should be reviewed clinically within 2 to 3 weeks of discharge post ASC and then as needed** (98% agreement)

✓ The number of therapeutic options has recently grown in ulcerative colitis



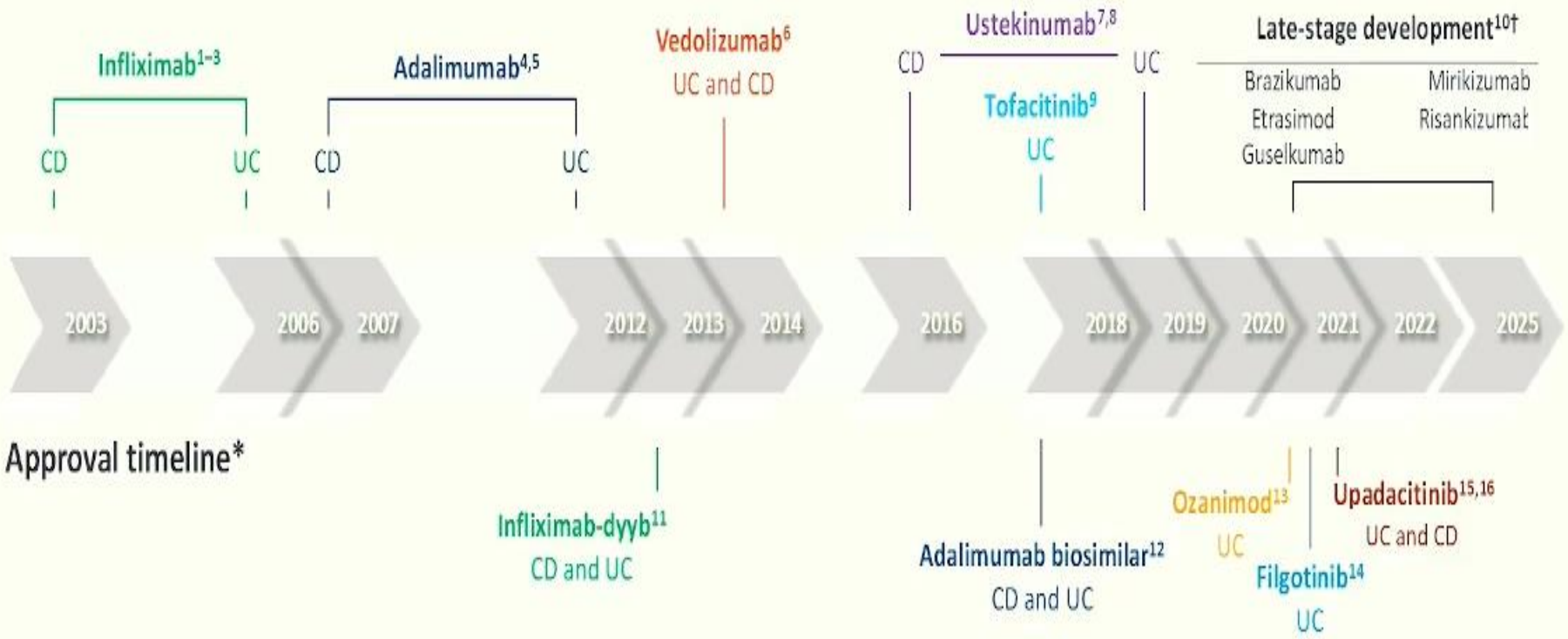
→ **Anti-JAK, anti-p19, modulateurs S1P**

There are a number of different drug classes for long term management of moderate to severe UC, including :

- **TNF-a antagonists (Infliximab, Adalimumab , Golimumab)**
- **anti-integrin agent (vedolizumab)**
- **Janus kinase inhibitor (Tofacitinib, Upadacitinib, Filgotinib)**
- **interleukin 12/23 antagonist (Ustekinumab, Risankizumab, Mirikisumab)**
- **Sphingosine-1-phosphate receptor modulators (Ozanimod)**

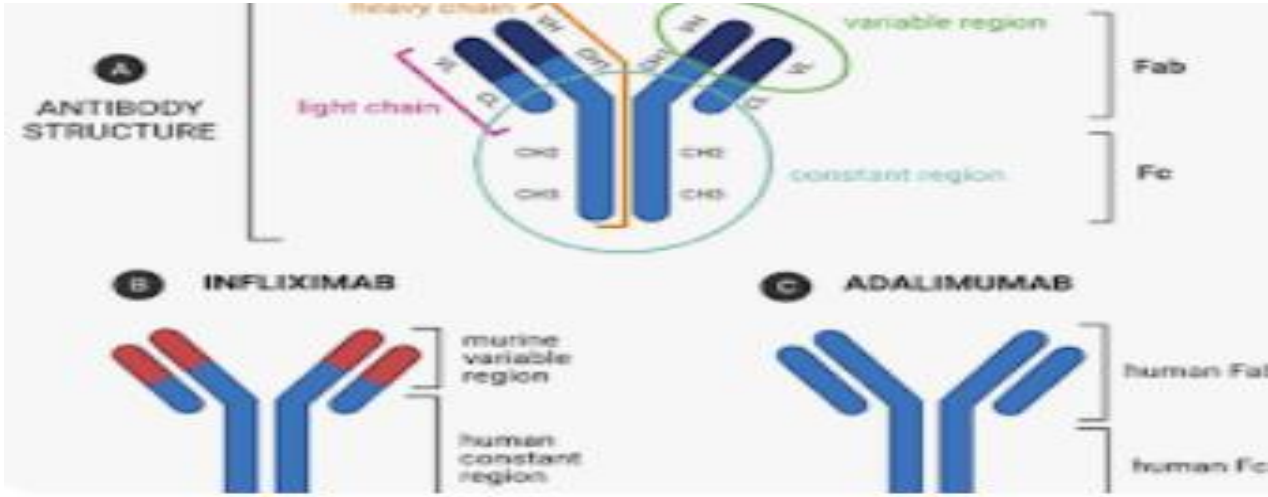
Ulcerative colitis - navigating a crowded therapeutic landscape

Biologics vs Small Molecules: which first?



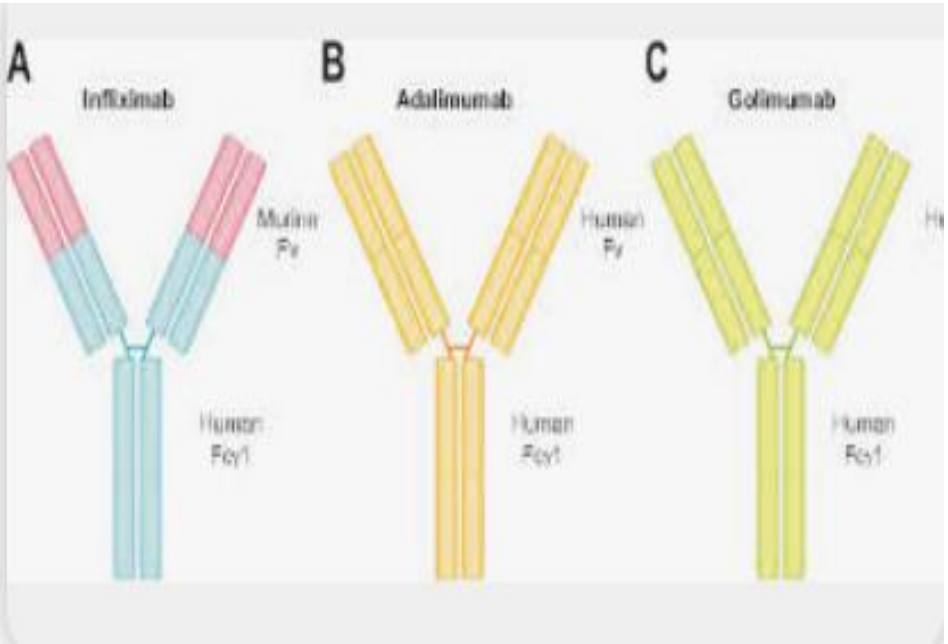
Anti-tumour necrosis factors

- Anti-TNF therapy has revolutionised the treatment of UC offering options for both medical rescue in the setting of ASUC and as a maintenance strategy in those where conventional medical strategies have already failed them.
- Anti-TNFs are not universally effective with ***a significant proportion of patients not responding to treatment or losing response, in part due to immunogenicity.***
- Concerns regarding the anti-TNF side effect profile, namely ***infection risk, malignancies, worsening heart failure and demyelinating disorders***, open the opportunity for the development of biological agents that mitigate these issues.



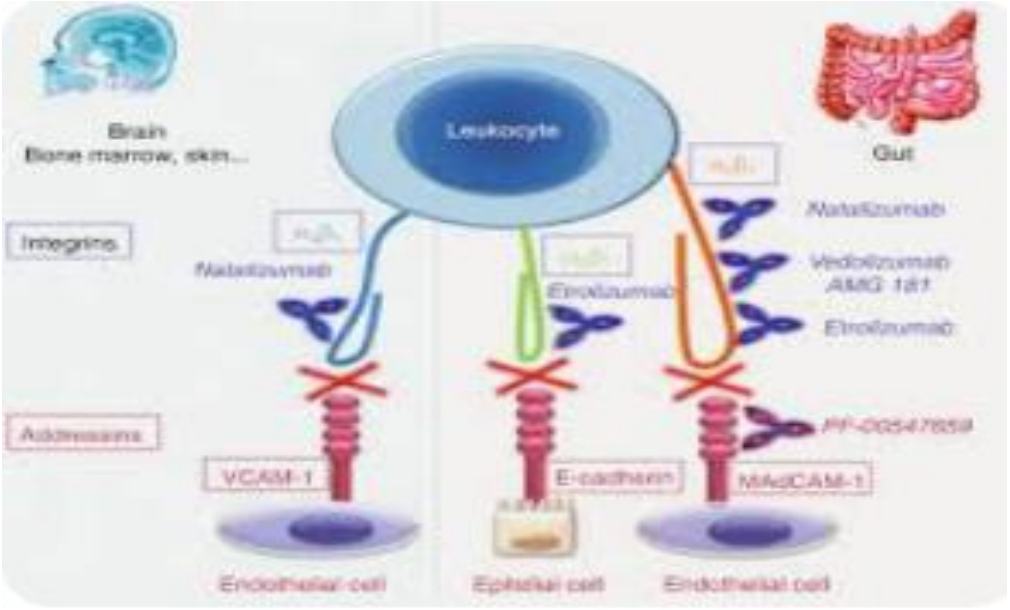
Golimumab

- ***Golimumab*** is a subcutaneously delivered human monoclonal antibody targeted against TNFα. In vitro and in vivo studies have demonstrated golimumab as ***having higher affinity to TNFα*** then both infliximab and adalimumab suggesting the possibility of a more potent clinical response.
- It was approved in 2013 for adult patients with moderate to severe active UC. It is not yet licensed for use in children, but small studies with 35 paediatric participants with UC showed 54% mucosal healing at week 6 with no significant clinical safety concern



Anti-integrin agents

- Although anti-TNF agents have transformed the treatment landscape for UC, it was noted that up to 10–30% of patients did not respond to antiTNF therapy (**primary non-response**).
- A significant proportion **lose response and while antibody formation or pharmacokinetic issues** were seen as the likely causal factor it has also been postulated that a proportion of patients may have an adaptive change in their immunopathogenesis from one which is TNFα mediated to one that is not primarily mediated by TNFα.

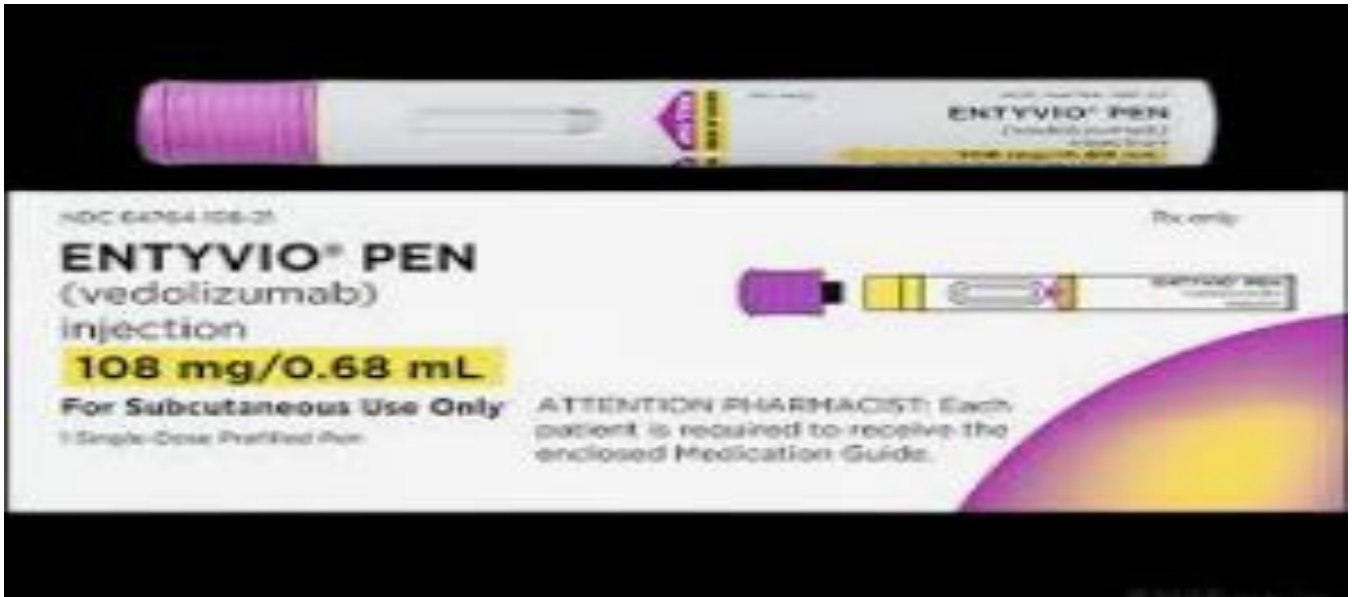


Vedolizumab

- Vedolizumab is a gut-selective humanised monoclonal antibody that inhibits the interaction between the α4β7 integrin and mucosal addressin cell adhesion molecule-1.
- This interaction leads to a gut-specific blockade of memory T cells into the gastrointestinal submucosa. **which inhibits a migration of T-lymphocytes into inflamed intestinal tissue.**
- In 2013, the GEMINI1 study group demonstrated the **efficacy and safety of vedolizumab as induction and maintenance therapy for UC.**
- The primary outcome for induction therapy was a clinical response at week 6 with secondary outcomes of clinical remission and mucosal healing.
- However, further analysis correlating higher trough serum concentrations with improved clinical outcomes suggests peak effect for vedolizumab would be expected closer to week 14, suggesting ***a slower inductive onset of vedolizumab, compared to other biologic therapy***.

Vedolizumab

- SC preparations of biologic treatments offer advantages in terms of patient preference and reduced healthcare-associated cost. **SC vedolizumab was investigated as a maintenance treatment option in patients with moderate to severely active UC.**
- This demonstrated that SC vedolizumab is effective as maintenance therapy in patients with moderate to severely active UC who had a clinical response to IV vedolizumab induction therapy.

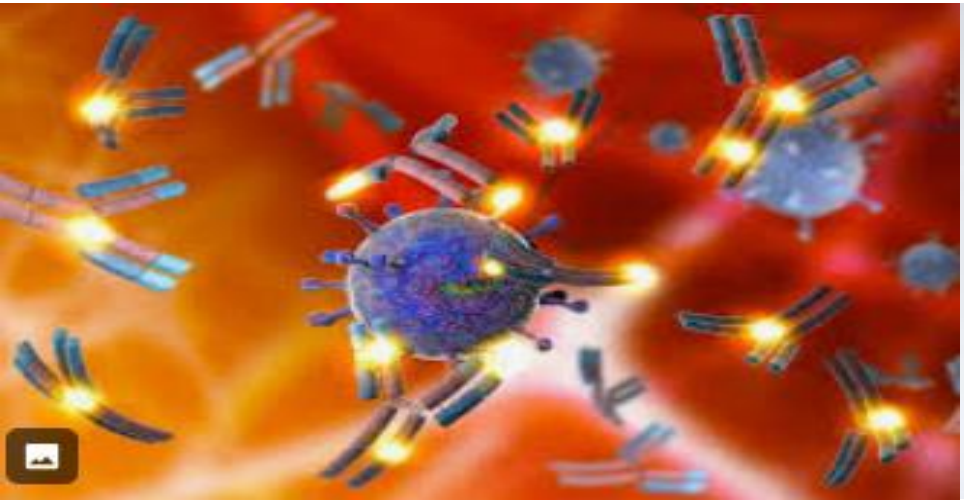


Anti-interleukin agent
Ustekinumab

- IBD appears to be mediated through an imbalance between the Th1 and the Th2 immune cells, but it is now known that another subset called Th17 and related cytokines are crucial mediators of inflammation independent of antiTNF drive.
- IL-12 has been noted to induce a predominant Th1 response in humans and IL-23 has been shown to upregulate Th17- driven inflammation.
- This knowledge has fuelled research into IL-12 and IL-23 and the development of an agent targeting the common p40 subunit of anti-IL12/23

Anti-interleukin agent
Ustekinumab

- Following successful trials for ustekinumab in the treatment of moderate to severely active Crohn's disease, the UNIFI trial ***was established to determine the effectiveness of ustekinumab in patients with moderate to severely active UC.***
- The efficacy**, similar onset of action to infliximab**, **safety profile and low immunogenicity of ustekinumab make it an appealing option for those with refractory UC who have already failed conventional treatment and one or more biological agent.**



Janus kinase inhibitors

- The development of new molecules with the potential to target a myriad of cytokine targets such as the Janus kinase (JAK)-signal transducer and activator of transcription pathway have been shown to be effective in IBD.

- ***Tofacitinib***
- ***Upadacitinib***
- ***Filgotinib***

Tofacitinib

- It primarily inhibits JAK1 and JAK3 proteins, leading to downstream inhibition of cytokines that are implicated in the pathogenesis of UC.
- The OCTAVE trials were three distinct phase III randomised double-blind placebo-controlled trials evaluating ***the safety and efficacy of tofacitinib in patients with moderateto-severe UC despite previous conventional therapy or treatment with an anti-TNF age.***
- Post-hoc analysis of the trials moreover shows that ***induction of remission is particularly fast with these JAK inhibitors and occurs over a three-day period, making it a viable solution for treating ASUC.***
- Tofacitinib as a small molecule has distinct advantages over biologic agents with **no risk of immunogenicity**, ***predictable pharmacokinetics and rapid clearance attributed to its short half-life (3–4h) allowing for rapid discontinuation*** and resumption in the context of acute infections and surgery. Furthermore, as an ***oral compound***, it simplifies the process of drug administration as well as reducing the healthcare costs associated with delivering parenteral biologic.

Tofacitinib

- As JAKs play a key role in haematopoiesis, full blood counts should be periodically performed.
- It is important to note however that the OCTAVE trials did identify ***infections as being more common*** in patients treated with tofacitinib, specifically ***a higher prevalence of herpes zoster infections***.
- ***Non-melanoma skin cancer*** also occurred more frequently in those treated with tofacitinib, but it is important to consider a number of patients had previously received thiopurines.
- Tofacitinib treatment was also associated with ***higher lipid levels*** and an increased number of adjusted ***cardiovascular events.***

Upadacitinib

- Upadacitinib (UPA) is an FDA-approved JAK1 selective inhibitor that has demonstrated clinical efficacy for inducing clinical remission after 8weeks of treatment in phase IIb clinical trials for patients with moderate to severely active UC.

Filgotinib

- Filgotinib is another selective JAK-1 inhibitor with OD oral dosing and has been evaluated in the SELECTION study (phase IIb/III) with **an induction and maintenance phase in patients with moderately-to severely active UC**.
- Overall, the incidence of ARs, serious AEs and discontinuations due to AEs were similar in the filgotinib and placebo arms for both the induction and maintenance studies. Filgotinib is under regulatory review for use in UC.

Sphingosine-1-phosphate receptor modulators

- Similarities between the pathomechanism of relapsing multiple sclerosis and UC, via trafficking and accumulation of lymphocytes in inflamed tissue, have led to the development of sphingosine-1-phosphate (S1P) receptor modulators as a viable oral option for UC.
- **Ozanimod** is a S1P receptor modulator that binds to S1P subtypes 1 and 5. Specifically, the internalisation of S1P subtype 1 receptors **prevents lymphocyte trafficking to inflamed bowel.**
- **Ozanimod** has been approved in various countries for use in UC.

BRIEF REPORT

OPEN

The New Molecules Are Changing the Course of Pediatric Chronically Active Ulcerative Colitis: A Series of Pediatric Cases

*Rafael Martín-Masot, MD, *Pilar Ortiz Pérez, MD, *Encarnación Torcuato Rubio, MD, *Javier Blasco Alonso, PhD, *Marta Herrador López, †Carmen Gallego Fernández, PhD, and *Víctor Manuel Navas-López, PhD

CASE

- A 9-year-old boy with left-sided UC diagnosed based on typical endoscopy, histology, and elevated FC.
- Cytomegalovirus was suggested on biopsies by positive polymerase chain reaction and presence of inclusion bodies. Given moderately active disease at diagnosis (PUCAI = 40) treatment with prednisone, mesalazine, and ganciclovir was started.
- Disease worsened and he was admitted receiving treatment with intravenous corticosteroids. Given the lack of response in the following 5 days (PUCAI = 70), treatment with IFX (10mg/kg, 0-1-2) was started.

CASE

- Despite adequate IFX trough levels (25 µg/mL), remission was not achieved and an antibiotic cocktail (vancomycin, amoxicillin, metronidazole, and doxycycline) and tacrolimus (0.1mg/kg BID) were added. In the following 14 days, a decrease of >20 points in the PUCAI was observed but clinical remission was not reached.
- VDZ 300mg intravenously with a 0-2-6 scheme was started, without observing remission after 50 weeks of treatment, so it was withdrawn. During these 50 weeks, PUCAI was around 20–40 points, the tacrolimus dose was being adjusted, requiring withdrawal periods due to renal toxicity (creatinine 1.17mg/dL), and blood transfusions were also needed.
- Tacrolimus and VDZ were stopped and tofacitinib 5mg BID was started, with a progressive improvement achieving a complete clinical remission at week 20.
- After 16 months on tofacitinib (5mg BID) treatment, the patient maintained clinical remission (PUCAI = 0 points). There has been no alteration of the lipid profile since the start of the drug.


Thank You