Advanced Therapies for IBD:

IBD*:*

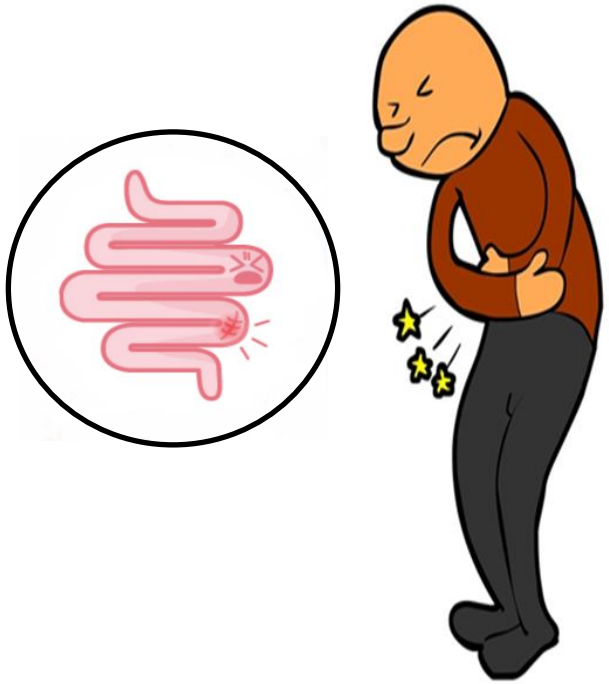
The diseases

Treatment options and strategy:

The new treatment strategies

The medicine cabinet

how to choose?



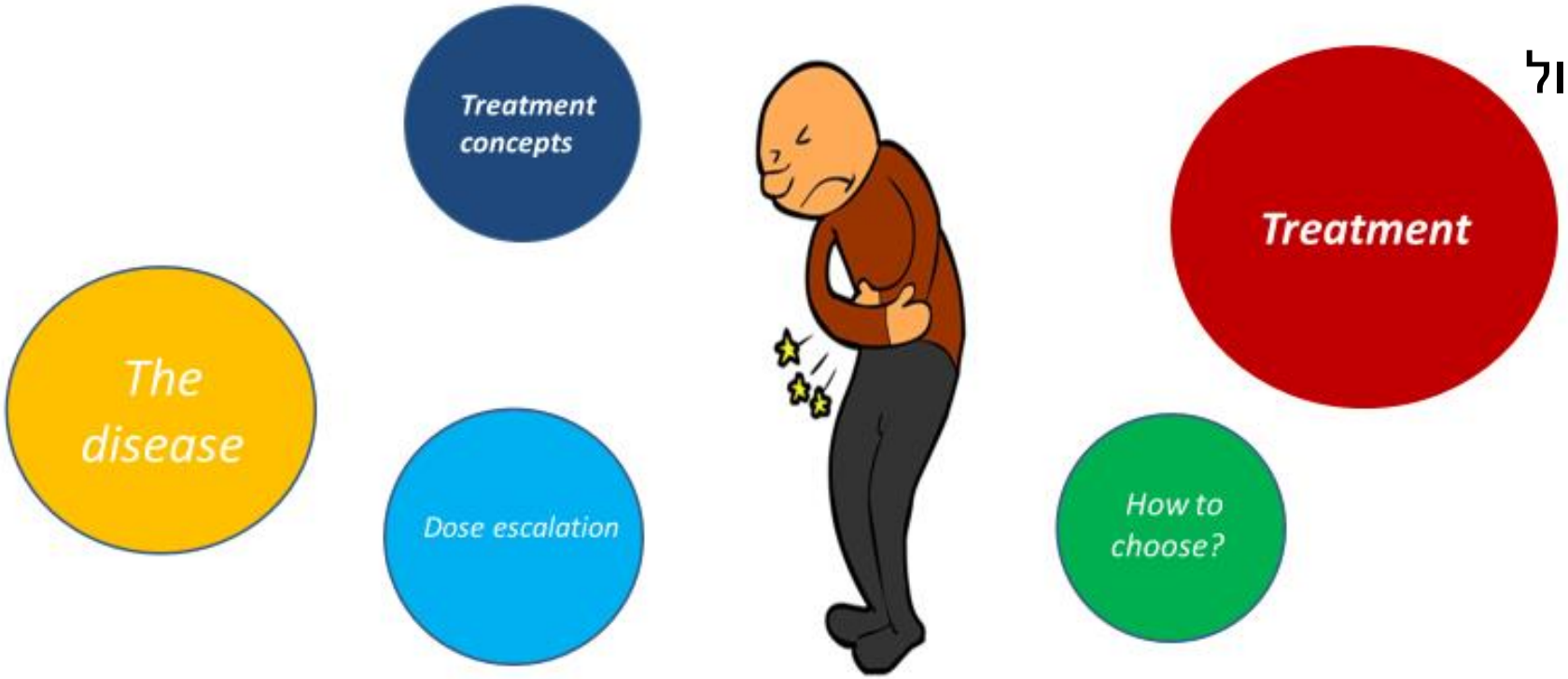
Eyal Shachar, M.D, M.H.A

- *The Institute of Gastroenterology, Chaim Sheba Medical Center, Tel Hashomer*
- *IBD service Batyamon medical center, Clalit health services*

EYAL SHACHAR
Eyal Shachar
GASTROENTEROLOGY

נושאים

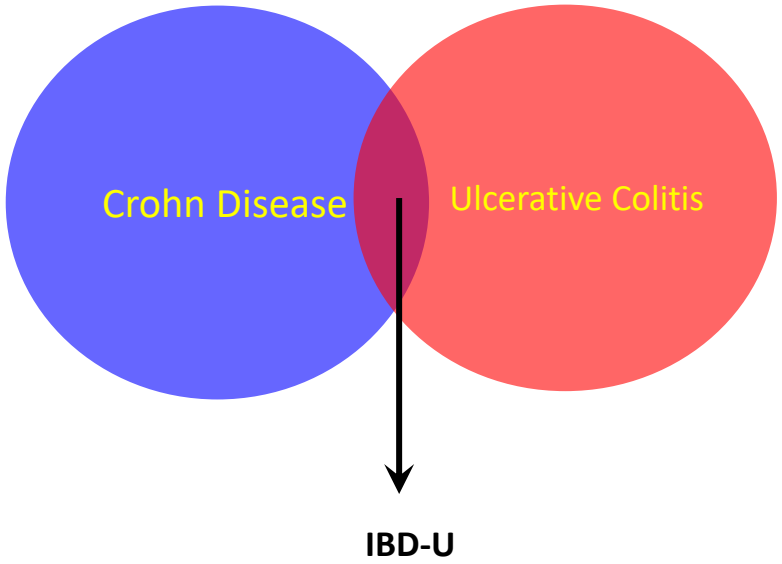
- הצגת מחלות המעי הדלקתיות וההבדלים בניהן
- הטיפול:
  - מטרות הטיפול – שינוי הגישה
  - קונספטים טיפוליים: התחלה מהירה, תרופות יעילות, Treat to target
- משפחות התרופות
- שיקולים בבחירת הטיפול



The disease

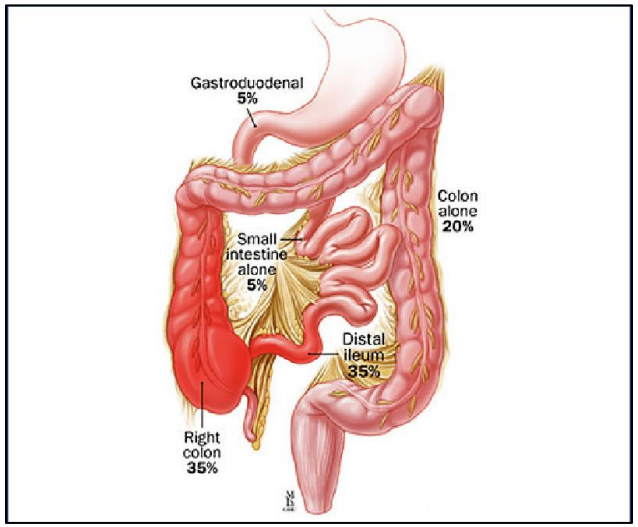
מחלות המעי הדלקתיות

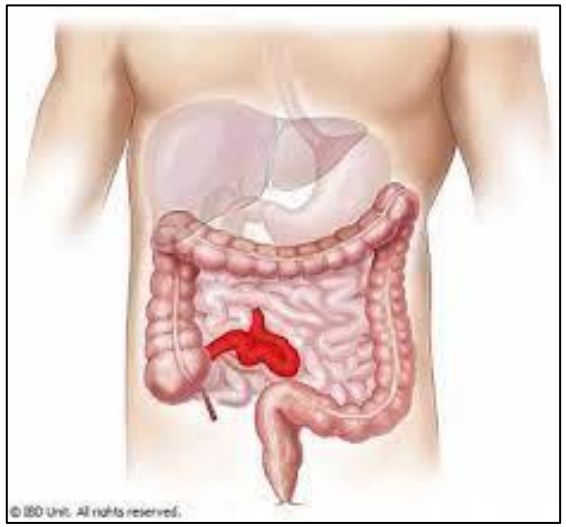
- מחלת קרון
- קוליטיס כיבית
- Indeterminate colitis



מחלת קרוהן Crohn’s Disease

- יכולה להתבטא בכל חלק של המעי, מחלל הפה ועד פי הטבעת, ב 60% מחולי קרוהן יש ביטוי של הדלקת בסוף המעי הדק.
- ביטויי המחלה תלויים במיקום הדלקת במעי, אך מאוד אופייניים לה: שלשול, כאב בטן, ירידה במשקל, חולשה, עייפות וחום.



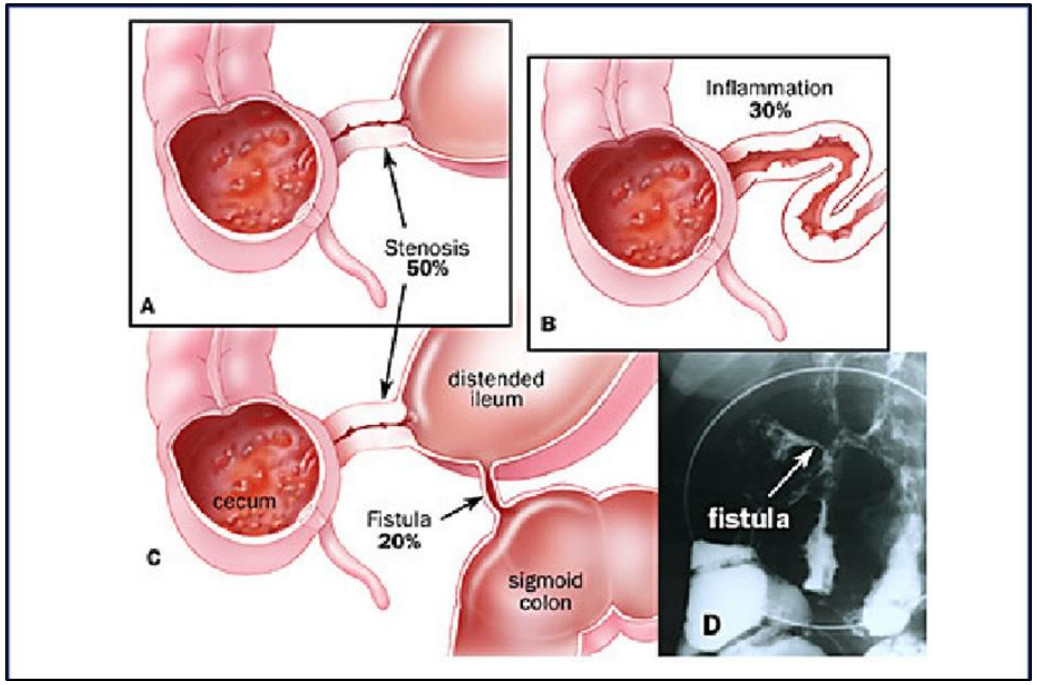


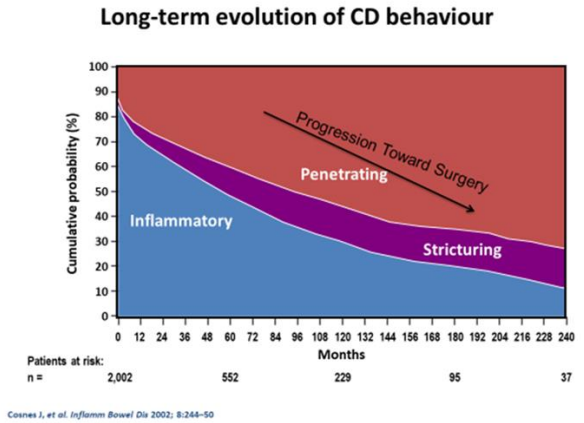
מחלת קרוהן - מאפיינים:

- **דלקת כרונית שאינה רציפה אנטומית המתפשטת לעומק כל שכבות דופן המעי.**
- אפטות וכיבים ע"פ רירית תקינה במעי (ובחלל הפה)
- גרנולומות

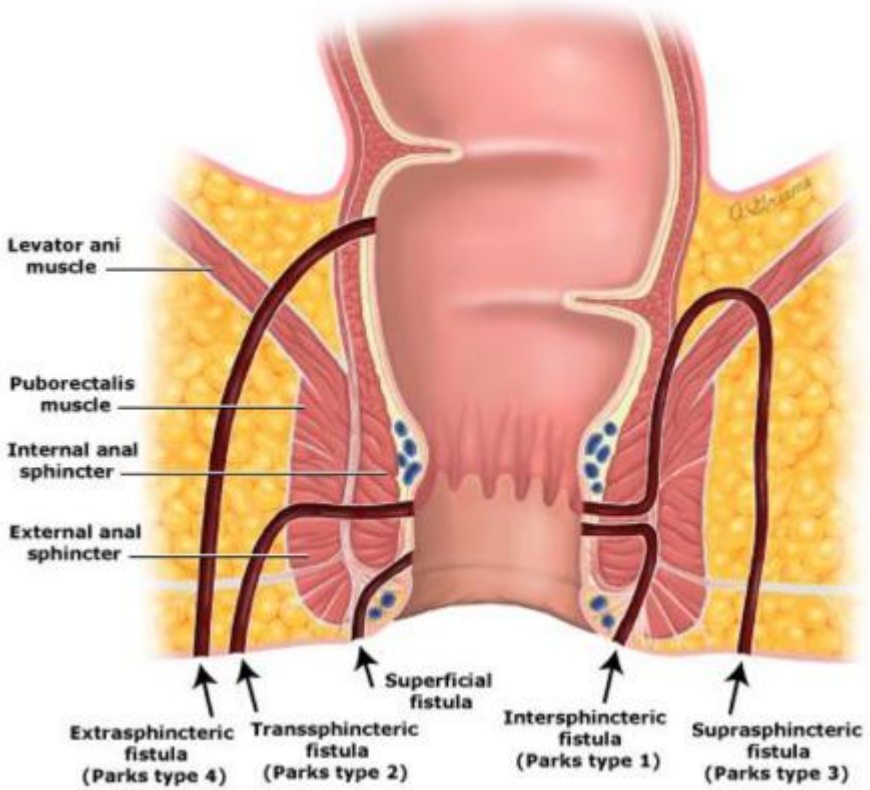
דלקת שיכולה לערב את כל עובי המעי:

- הצרות חלל המעי (סטריקטורות)
- פיסטולות: חיבור לא תקין בין 2 מבני גוף.
- אבצסים
- סינוסים: לולאות עוורות



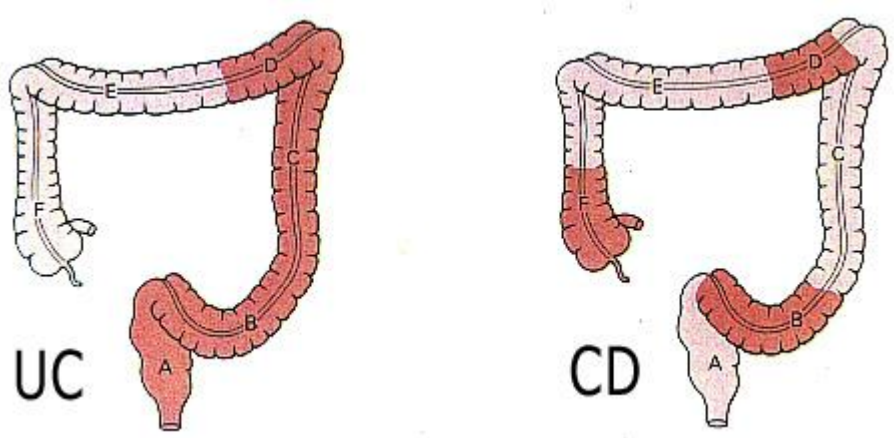


Perianal Crohn’s Disease

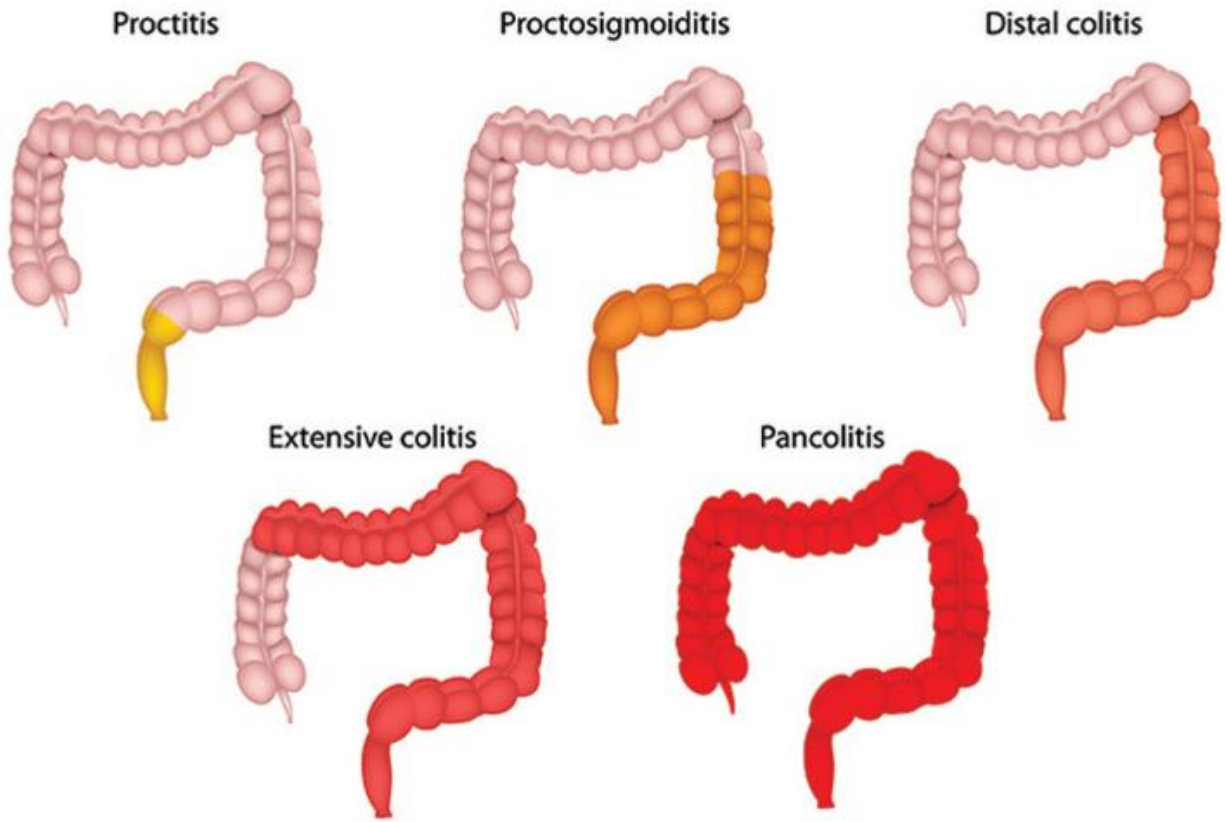


קוליטיס כיבית Ulcerative Colitis

- בקוליטיס כיבית, הדלקת מוגבלת רק למעי הגס.
- במחלה זו יש רצף של דלקת, המתחילה תמיד בפי הטבעת וממשיכה פנימה לאורך המעי הגס.
- הדלקת מתבטאת בצורה שטחית יחסית, על פני רירית המעי הגס.
- החולים סובלים בעיקר משלשול ודימום דרך פי הטבעת.



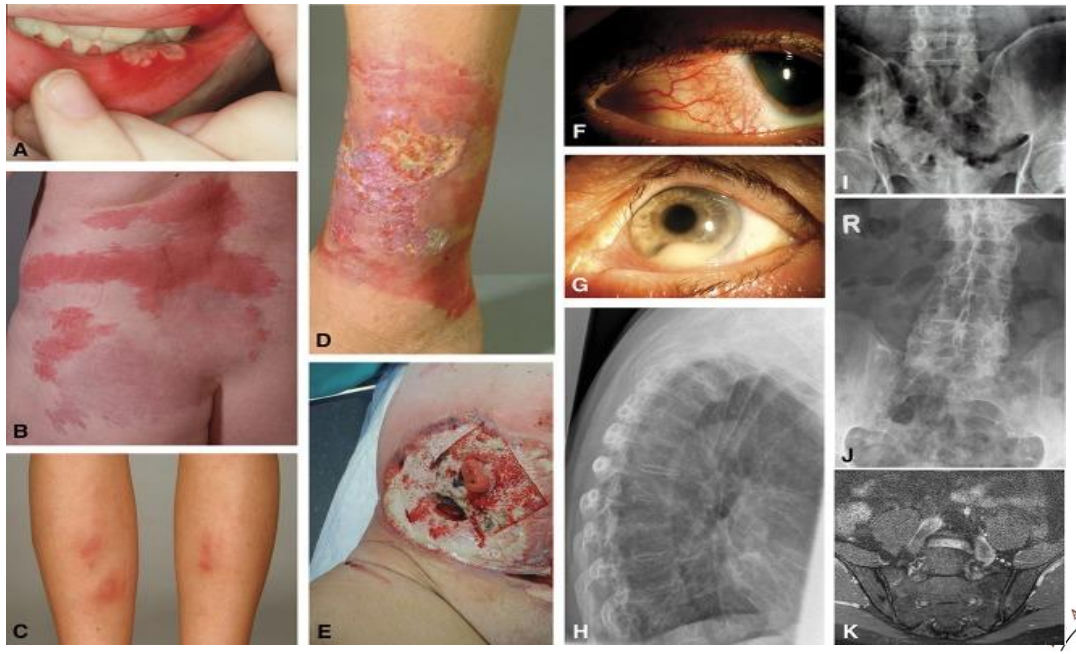
Ulcerative Colitis



Extraintestinal Manifestations of IBD

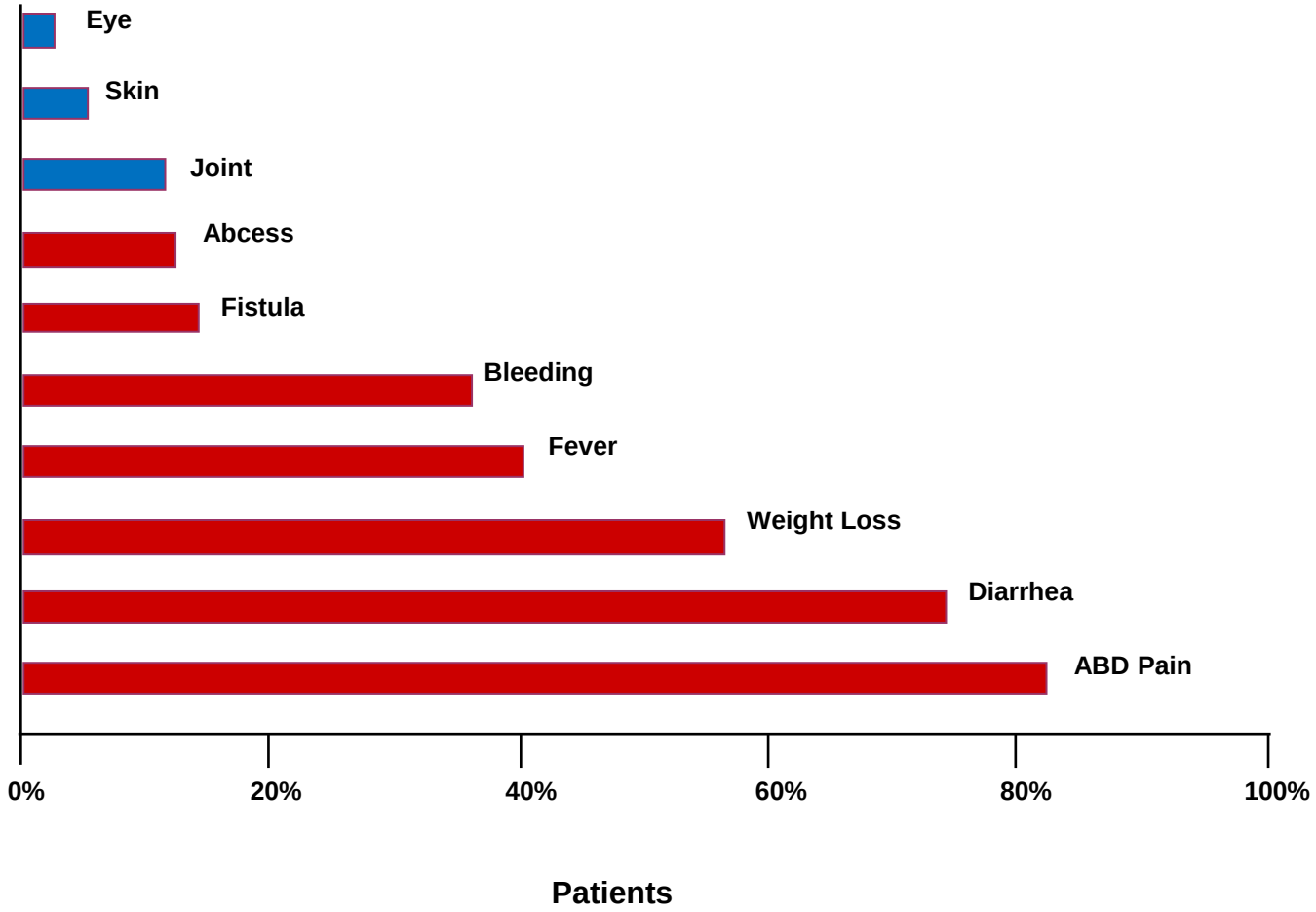
למחלות אלו , ששתיהן מתבטאות בהתקפים, יש ביטויים במערכות נוספות, כמו: הפרקים, העיניים, העור – שחלקם יכול להופיע בעת התקף, וחלקם שלא בהקשר להתקף.

A, Oral aphthous ulcers, (B) Sweet's syndrome, (C) erythema nodosum, (D) pyoderma gangrenosum, (E) peristomal pyoderma gangrenosum, (F) episcleritis, (G) uveitis with hypopyon and dilated iris vessels, (H) conventional x-ray of the lateral spine demonstrating syndesmophytes (bamboo spine), (I) plane radiograph of the ileosacral joints with bilateral sacroiliitis, (J) plane radiography of the sacrum with bilateral ankylosis, (K) coronal magnetic resonance image of the sacroiliac joints with active inflammation mainly on the left side and chronic inflammatory changes on both sides.



Vavricka SR, Schoepfer A, Scharl M, et al. Extraintestinal Manifestations of Inflammatory Bowel Disease. Inflammatory Bowel Diseases. 2015 Aug;21(8):1982-1992

Common CD Symptoms



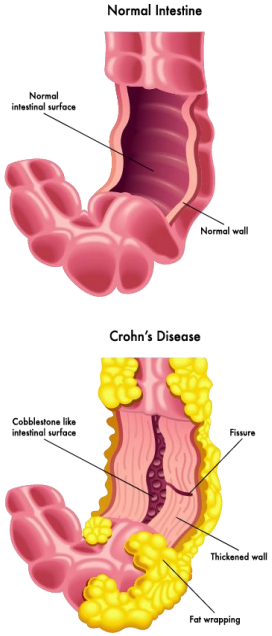
Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, Management (Gastrointestinal & Liver Disease (Sleisinger/Fordtran)) . Saunders; 10 edition 2015 . ISBN-10: 1455746924

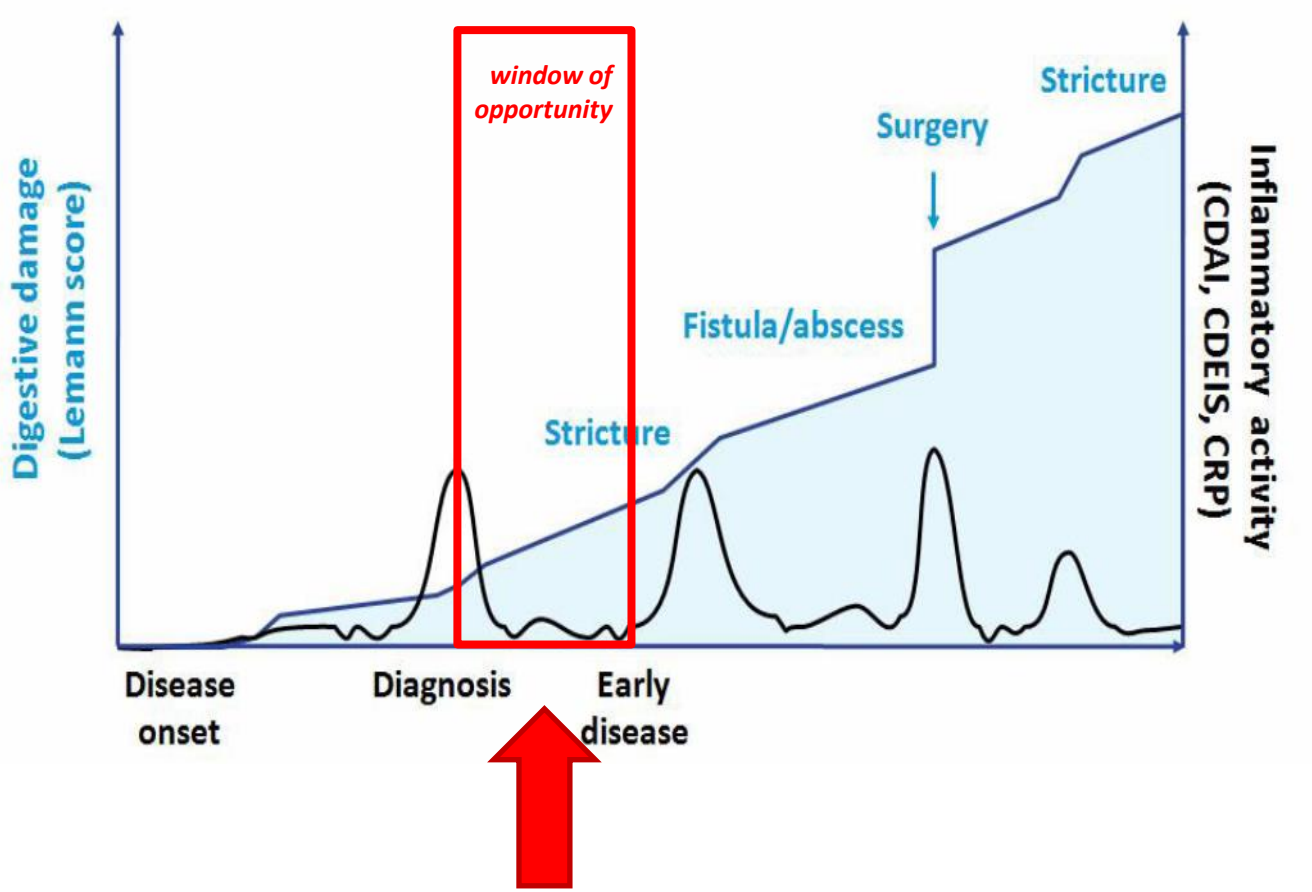
Treatment concepts

קונספטים טיפוליים ב IBD 2023

- מטרת הטיפול: אינה רק הרגשה טובה אלא שינוי מהלך המחלה
- התחלת טיפול יעיל בשלב מוקדם של המחלה
- תרופות יעילות
- Treat to target

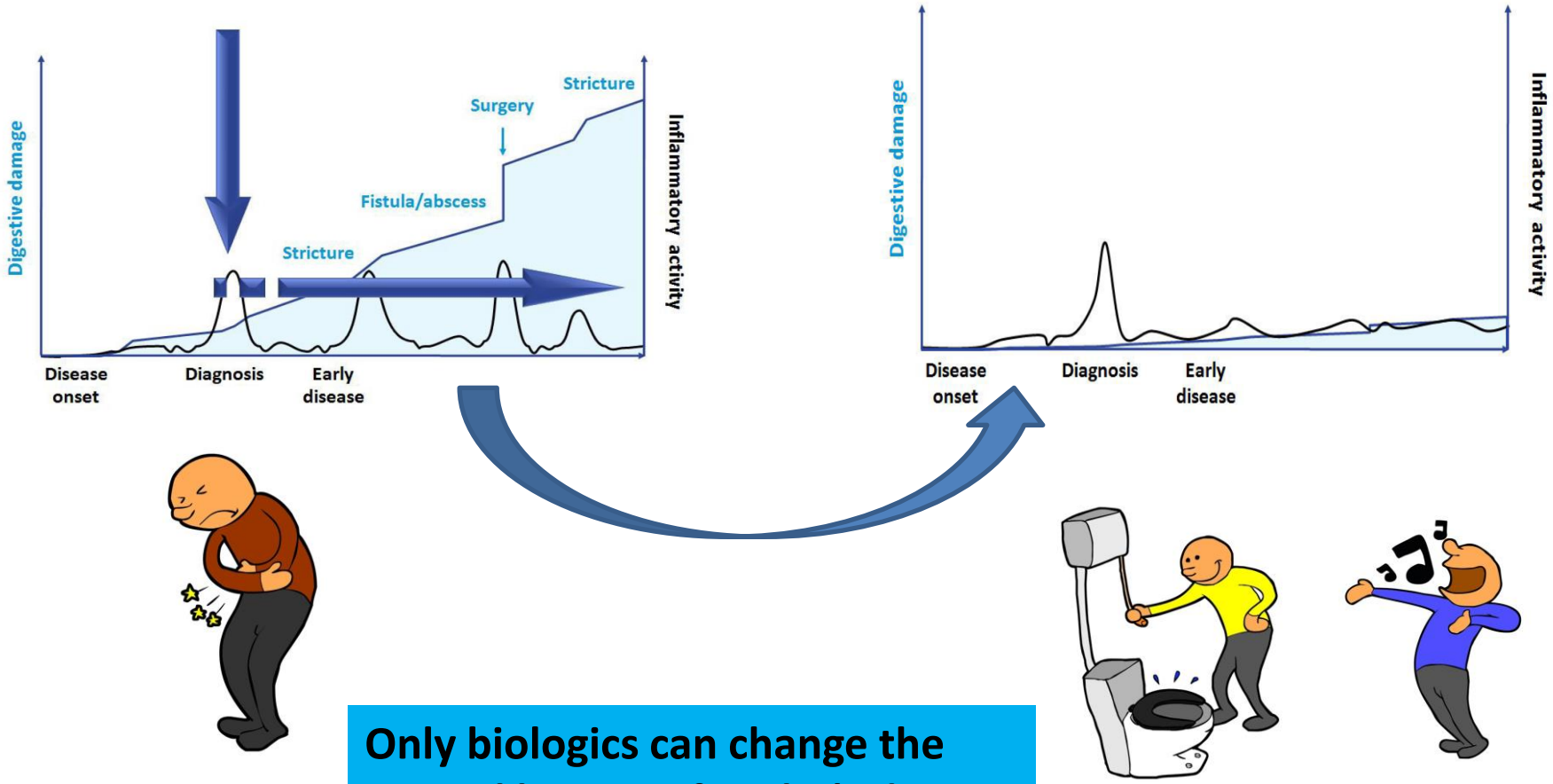
Crohn's disease natural history





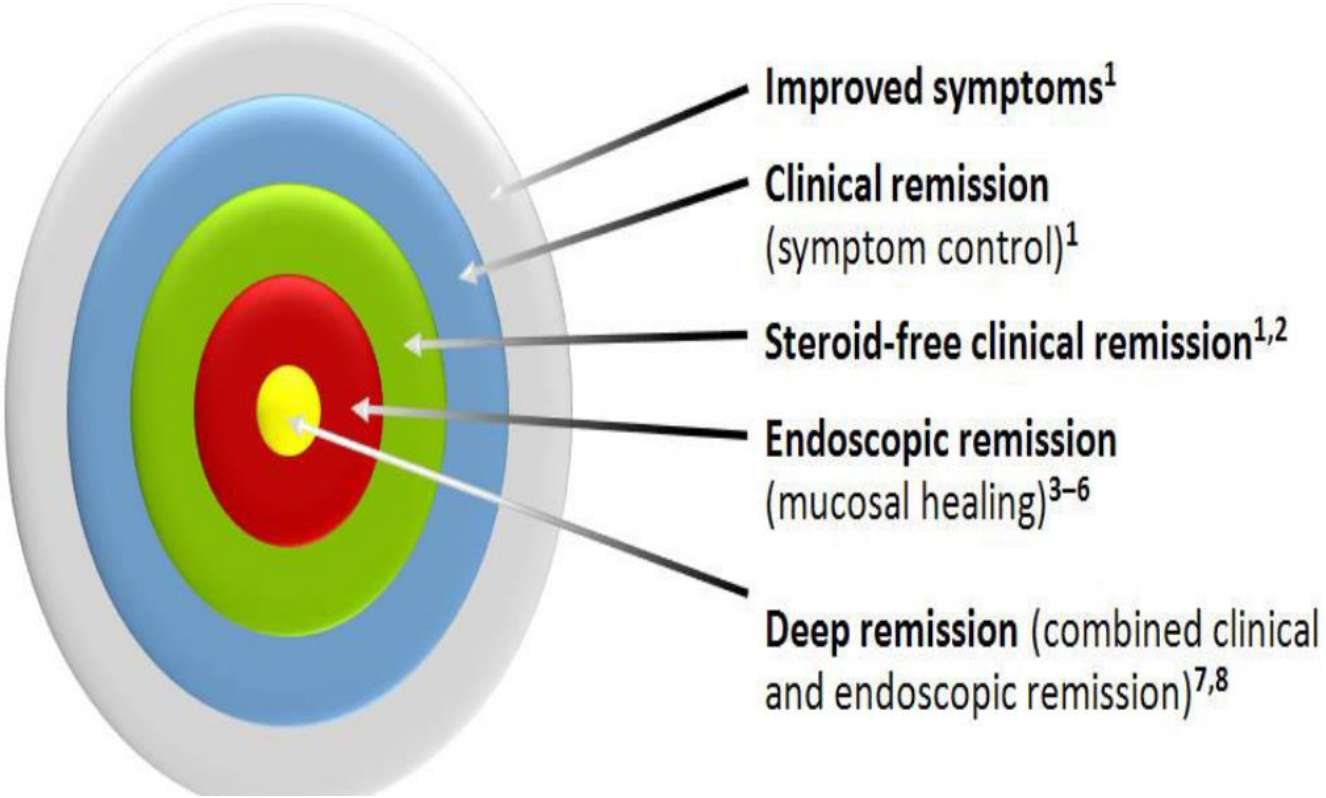
Pariente B, Cosnes J, Danese S, Sandborn WJ, Lewin M, Fletcher JG, Chowers Y, D'Haens G, Feagan BG, Hibi T, Hommes DW, Irvine EJ, Kamm MA, Loftus EV Jr, Louis E, Michetti P, Munkholm P, Oresland T, Panés J, Peyrin-Biroulet L, Reinisch W, Sands BE, Schoelmerich J, Schreiber S, Tilg H, Travis S, van Assche G, Vecchi M, Mary JY, Colombel JF, Lémann M. Development of the Crohn's disease digestive damage score, the Lémann score. Inflamm Bowel Dis. 2011 Jun;17(6):1415-22.

The right treatment at the ***right time*** ***May change the natural course of Crohn's disease***

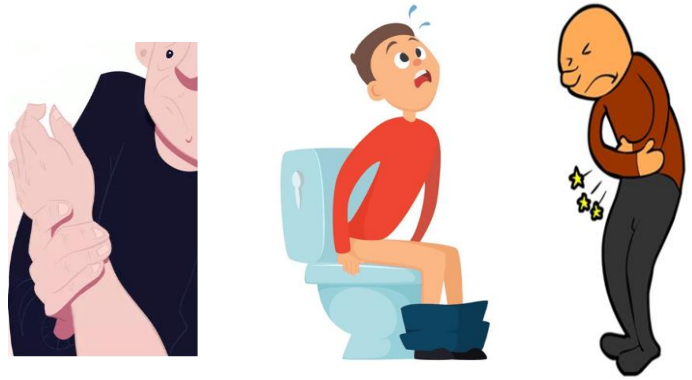


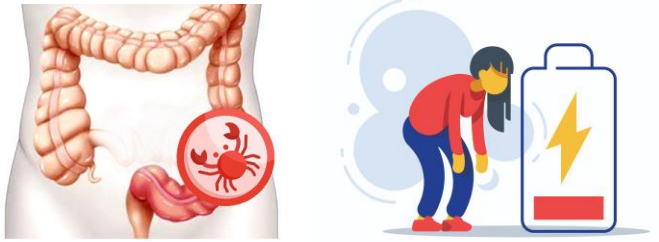
Only biologics can change the natural history of Crohn's disease

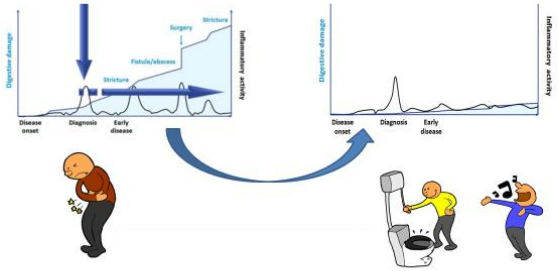
מטרת הטיפול



SUSTAINED REMISSION







STRIDE: selecting therapeutic targets in IBD: Treat to target

Resolution of abdominal pain, normalization of bowel habit should be the target

Outcome assessment

- **Every 3 months until symptom resolution**
- **Every 6 to 12 months after symptom resolution**

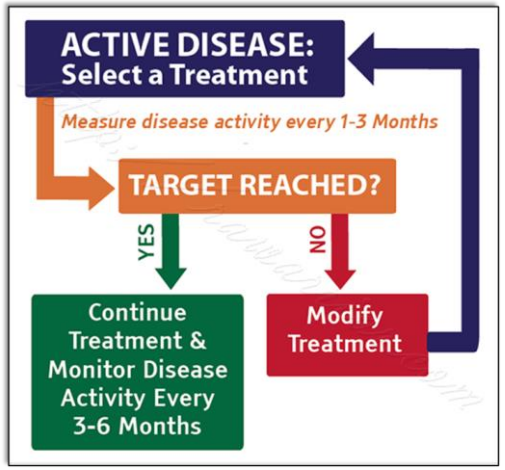
IN CROHN'S DISEASE

Endoscopic or cross-sectional imaging

assessment should be performed within 6–9 months after the start of therapy. Absence of ulceration is the target (when endoscopy cannot adequately evaluate inflammation, resolution of inflammation as assessed by cross-sectional imaging is a target)

Biomarkers including CRP and fecal calprotectin are not targets

but adjunctive measures of inflammation for monitoring



Peyrin-Biroulet L, et al. m J Gastroenterol. 2015;110:1324–38

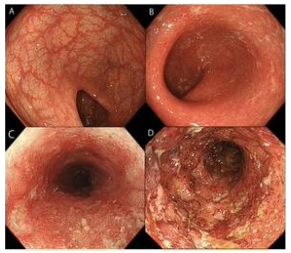
Assessing Response

Clinical: symptoms relief

Laboratory:

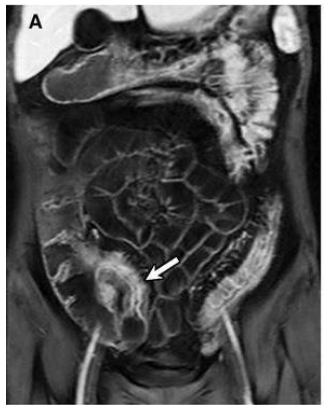
Fecal calprotectin+ C-reactive protein, Hemoglobin, Albumin

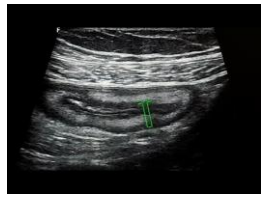
Endoscopy



Imaging:

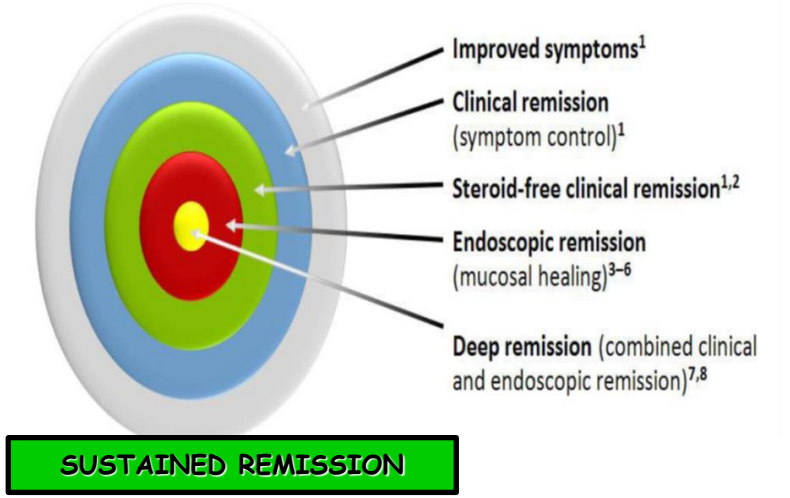
CT, MRI US





Treatment

- התחלת טיפול בשלב מוקדם של המחלה
- תרופות יעילות
- Treat to targets



זהו "ארון התרופות" לטיפול ב IBD בשנת *2023*

First line therapy for UC

- **5-ASA**

Immunomodulators

Corticosteroids

- **budesonide**

- **Azathioprine/6-MP**
- **Methotrexate**

Other Immunomodulators

- **Ciclosporin/ Tacrolimus**
- **mycophenolate mofetil**

Nutritional therapy

- **elemental diet**
- **TPN**
- **CDED/ Mediterranean diet**

Biologic Therapy

Anti-TNF

- **Infliximab**
- **Adalimumab**
- **Golimumab**
- **Certolizumab pegol**

Anti-cytokine

- **Ustekinumab anti-il 12/23**
- **Risankizumab anti-il 23**

Anti Migration

- **Vedolizumab**

Small Molecules

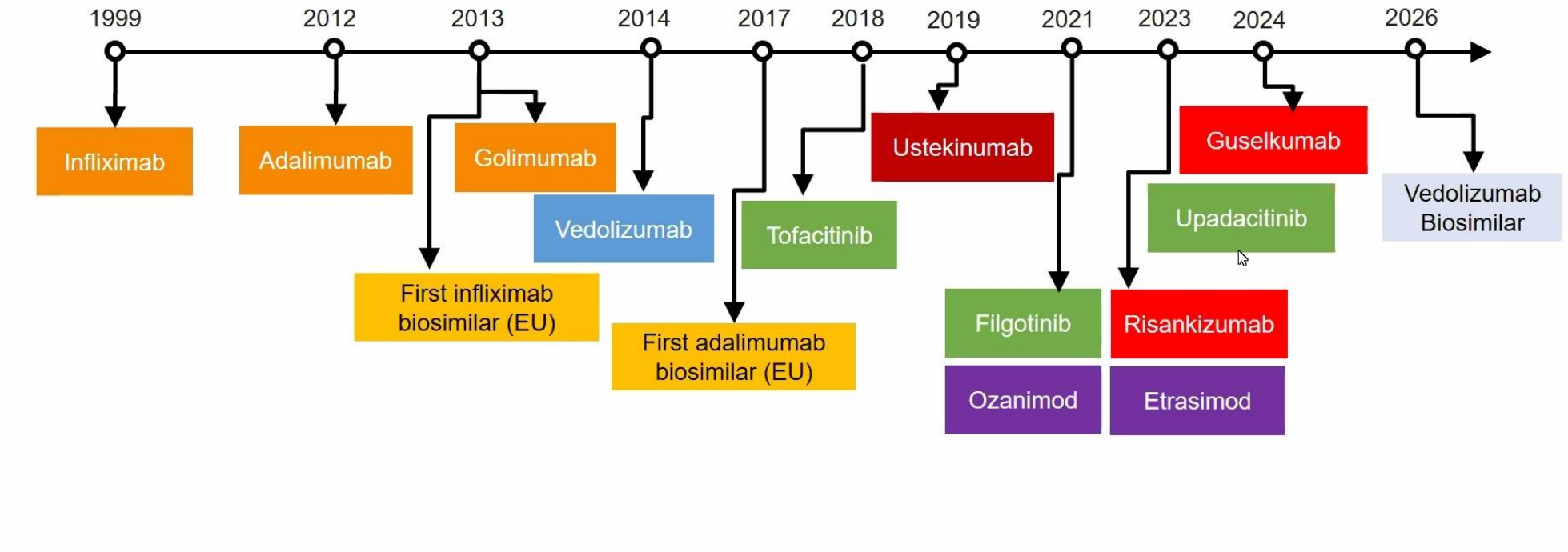
JAK inhibitor

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

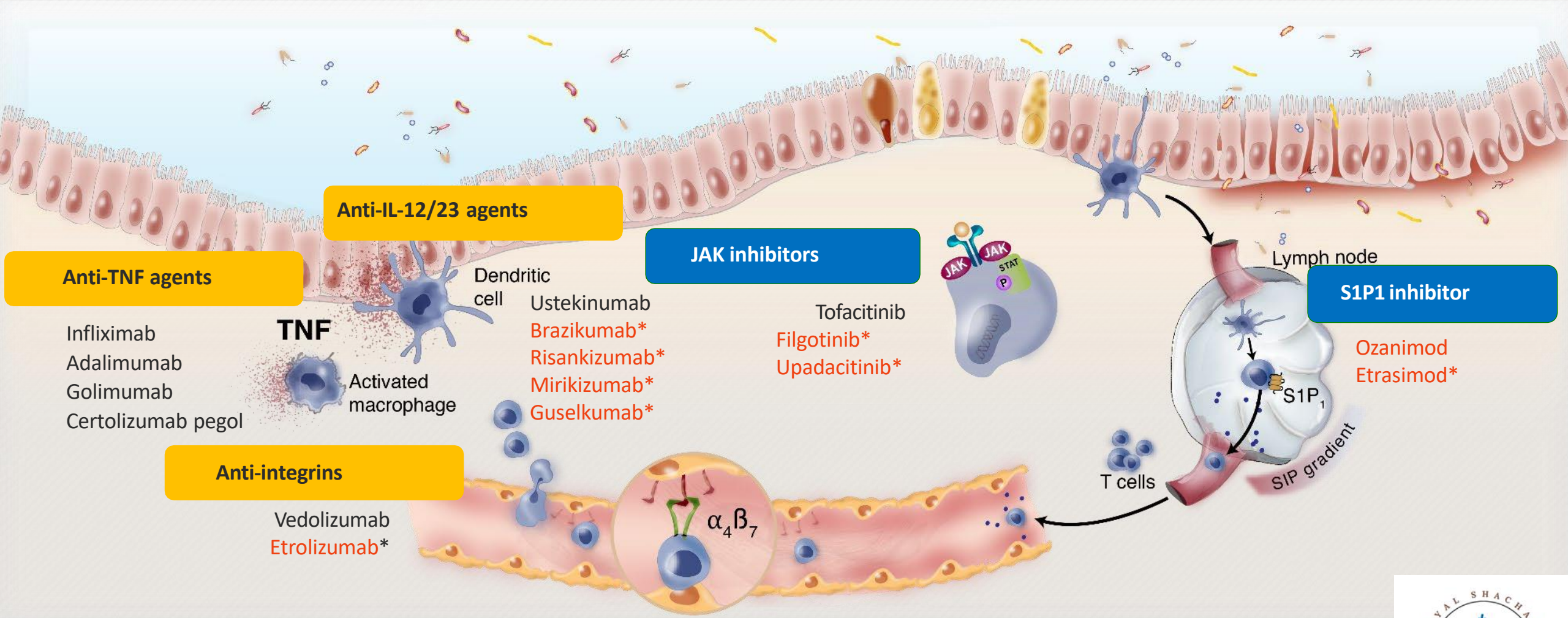
Sphingosine-1-phosphate (S1P) inhibitor

- **Ozanimod**

Therapies in IBD



Current and Emerging drug therapy for IBD

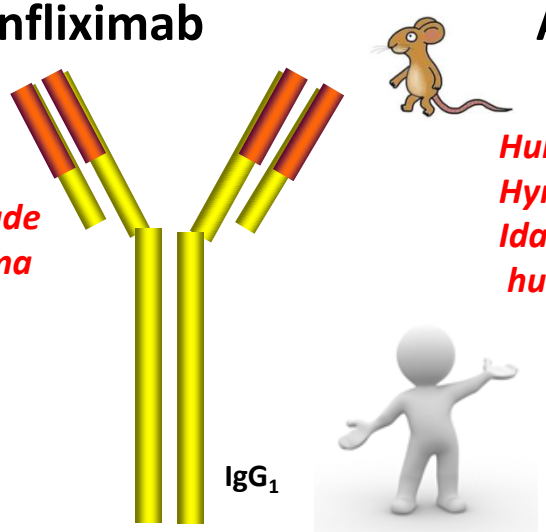


**Investigational. IL = interleukin; TNF = tumor necrosis factor; S1P1 = sphingosine-1 phosphate-1.*

Adapted from Coskun M, et al. Trends Pharmacol Sci. 2017;38(2):127-142.

נוגדי TNF

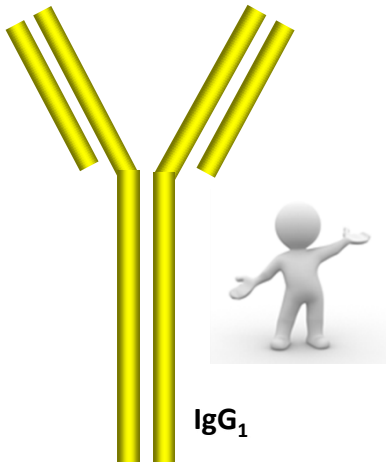
Infliximab



Remicade
Remsima
Ixifi

Chimeric monoclonal antibody (75% human IgG_1 isotype) 1998

Adalimumab



Humira
Hyrimoz
Idacio
hulio

Human recombinant antibody (100% human IgG_1 isotype) 2002

Golimumab

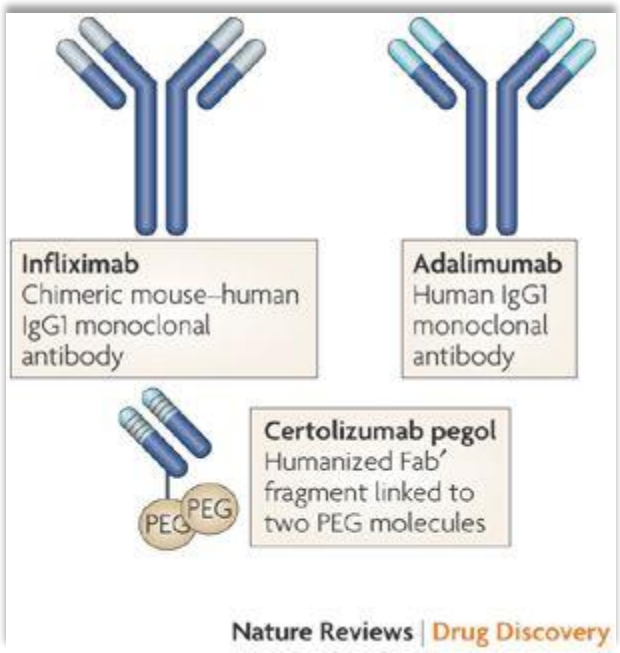
Fully Human antibody IgG1, FDA approved for UC 2013

Simponi

Certolizumab pegol

Crohn's 2018

Cimzia



Mouse
Human

Challenges With TNFis

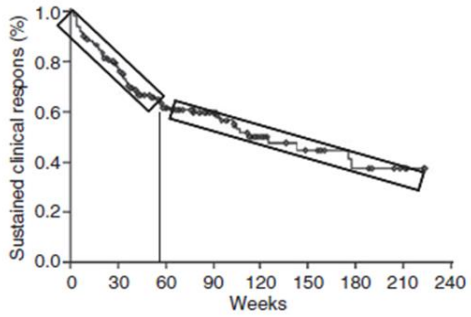
One third of patients will not respond to induction therapy with TNFis (primary nonresponse)

WHY?

Neutralizing antidrug antibodies/low serum trough levels?

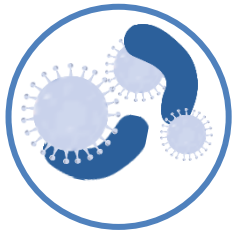
Other immune pathways that are driving inflammation?

~ one half of patients who do respond may lose response within a few yrs



Cohen. BMJ. 2017;357:j25050. Ford. Am J Gastroenterol. 2011;106:644.
Karmiris K et al. Gastroenterology 2009; 137: .40–1628

Safety Considerations With TNFi Monotherapy and Combination Therapy

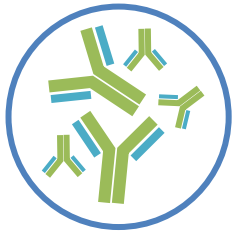


Infection

Including reactivation of TB and hepatitis B

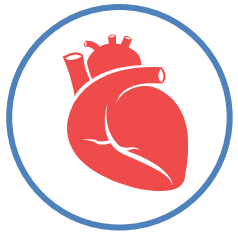
Demyelination

Avoid in patients with known CNS demyelination



Immunogenicity

Potential antidrug antibody formation



Heart failure

Avoid in patients with severe heart failure

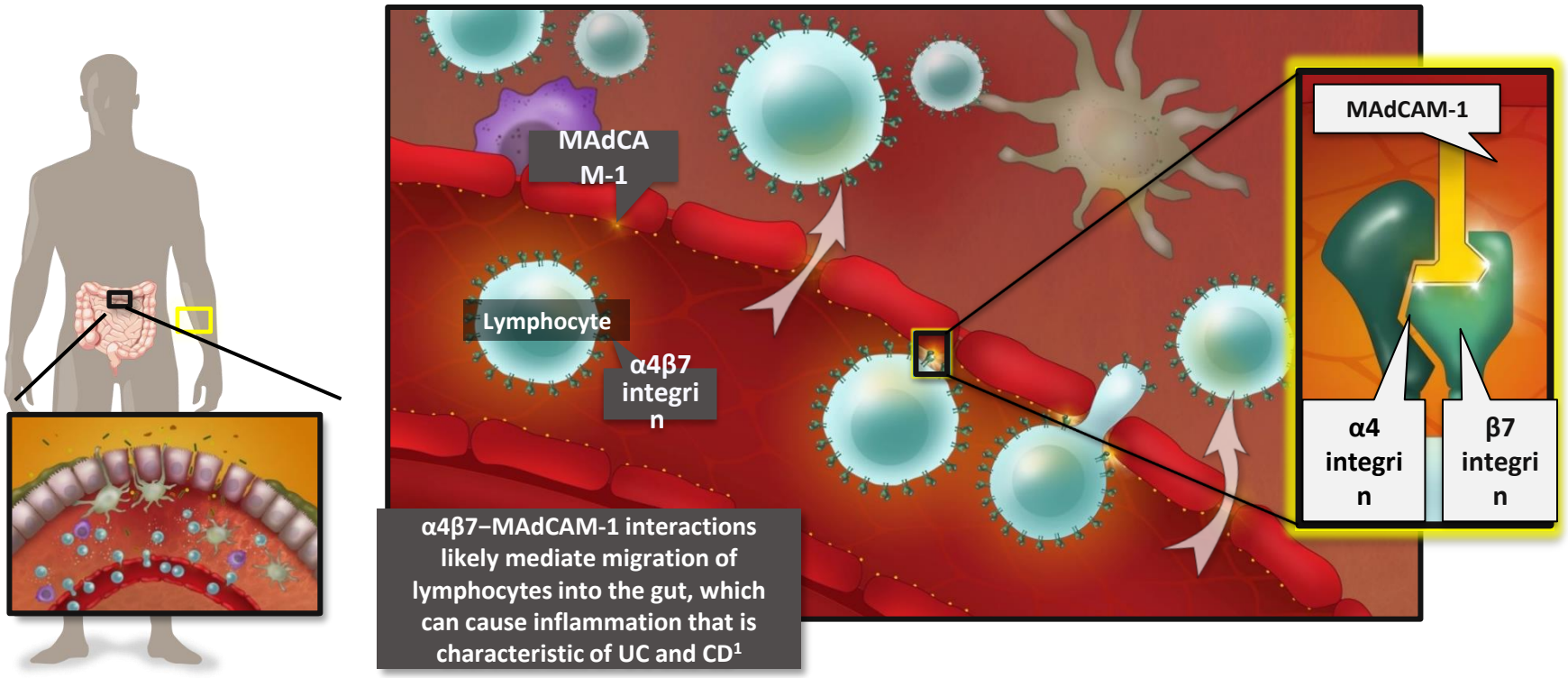
Neoplasia

Increase in risk of lymphoma (1/1000-2500), skin cancer

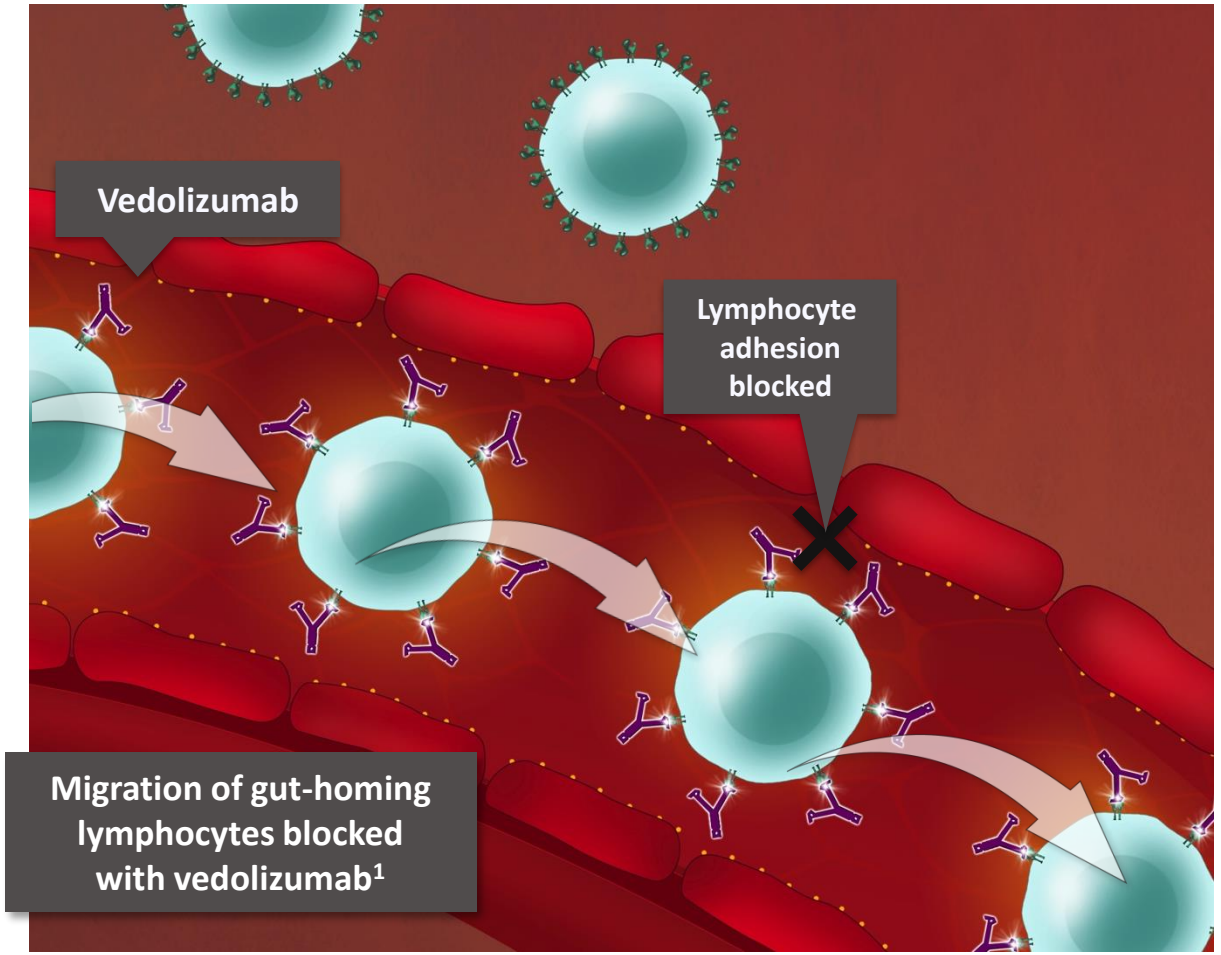
מעכבי אינטגרינים:

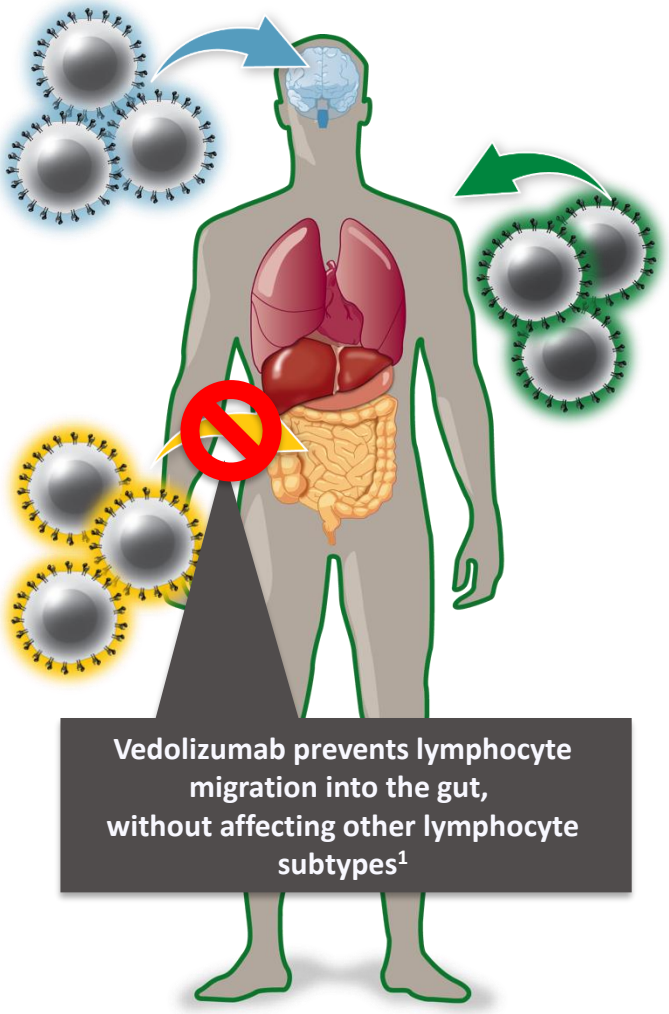
Vedolizumab (Entyvio) בסל הבריאות מינואר 2015

נוגדן הנקשר ל α4β7 על הלימפוציט ומונע הידבקות שלו לאנדותל כלי הדם במעי ובכך מעבר של הלימפוציט למעי



By targeting the α4β7 integrin Vedolizumab prevents migration of lymphocytes only into the gut



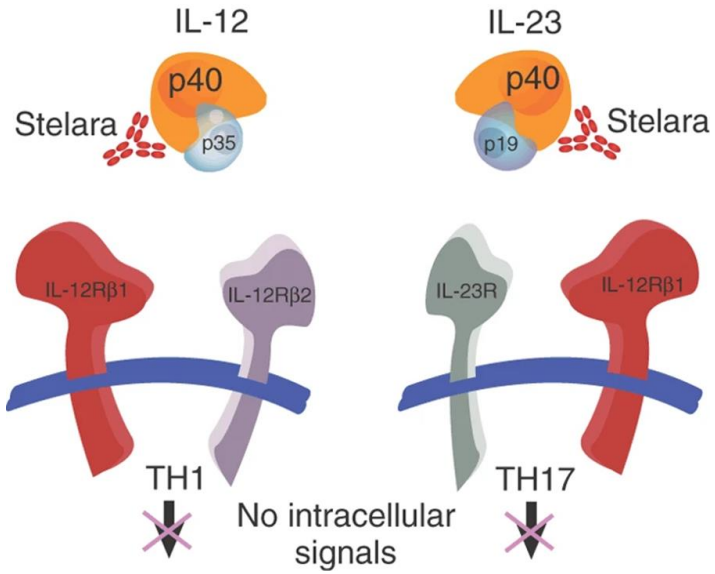


מעכבי אינטרלוקין 23/12

Stelara - Ustekinumab

בסל מ2017- ביולוגי קו 2 לקרוהן
הוגשה לסל הבריאות 2021/2 ל UC וקו ראשון ביולוגי לקרוהן

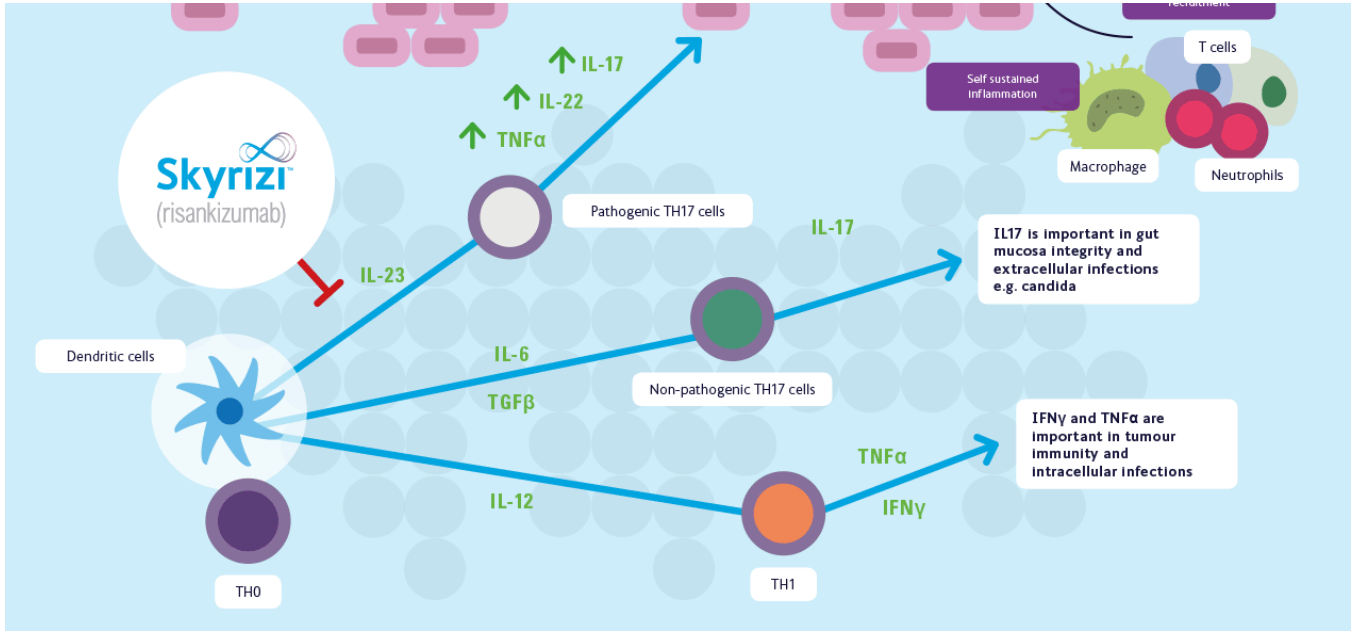
IGG1 אשר נקשר ליחידה p40 ומונע פעילות אינטרלוקין 23/12
ושיפעול הלימפוציטים TH17 TH1 ע"י ה APC



מעכבי אינטרלוקין 23

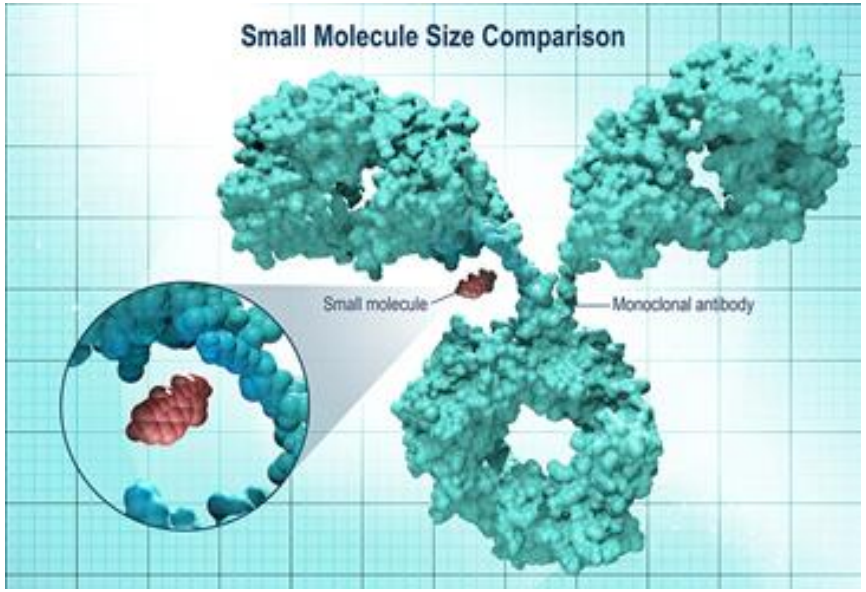
Skyrizi – Risankizumab תוגש ב 2023 לסל

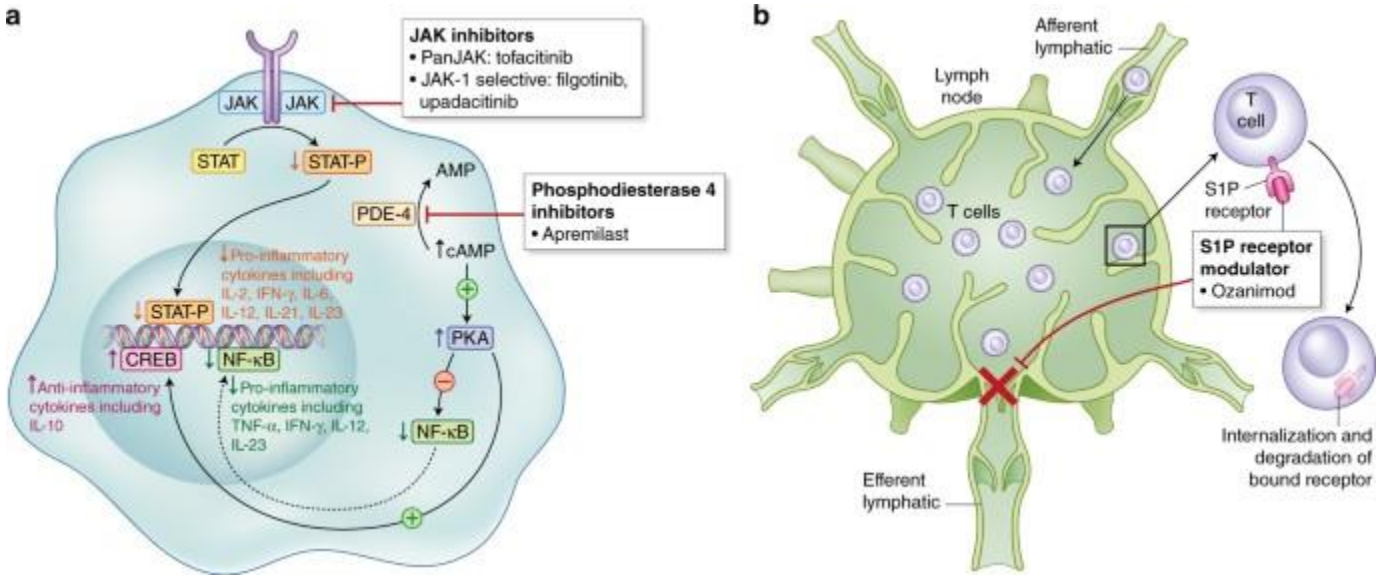
IGG1 אשר נקשר וחוסם את פעילות ה IL23 R
ושיפעול הלימפוציטים TH17 ע"י ה APC



Small molecules: JAKi , S1P1Ri

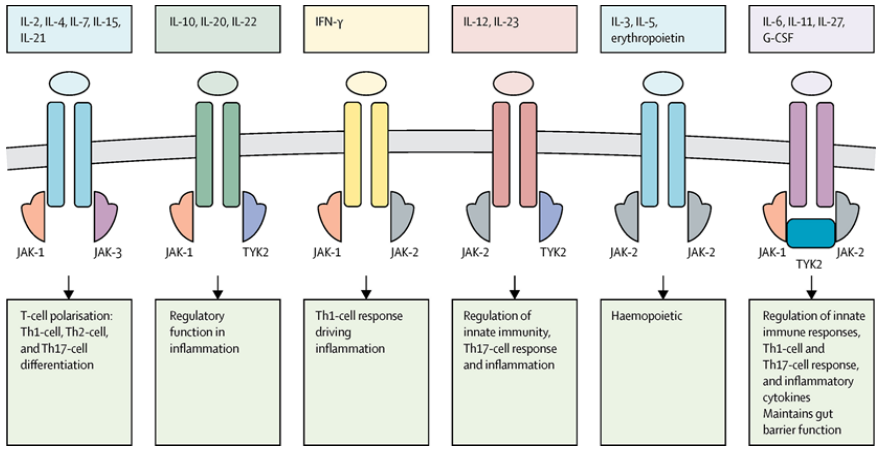
- Oral
- Well tolerated
- Short half life
- No immuno-genicity

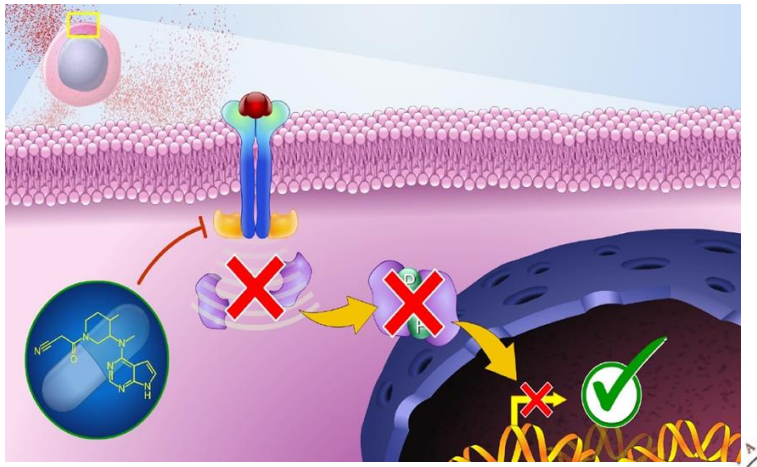




JAK :Janus kinases

- Janus kinases or JAKs are a family of four **tyrosine kinase proteins**, JAK1, JAK2, JAK3, and Tyk2
- JAK Inhibitor prevents JAKs from phosphorylating (activating) STATs, STATs don't dimerize, don't enter the nucleus = block intracellular signals that activate and differentiate lymphocytes





•*Small molecule oral targeted therapies in ulcerative colitis March 2020. The Lancet Gastroenterology & Hepatology 5(9)*

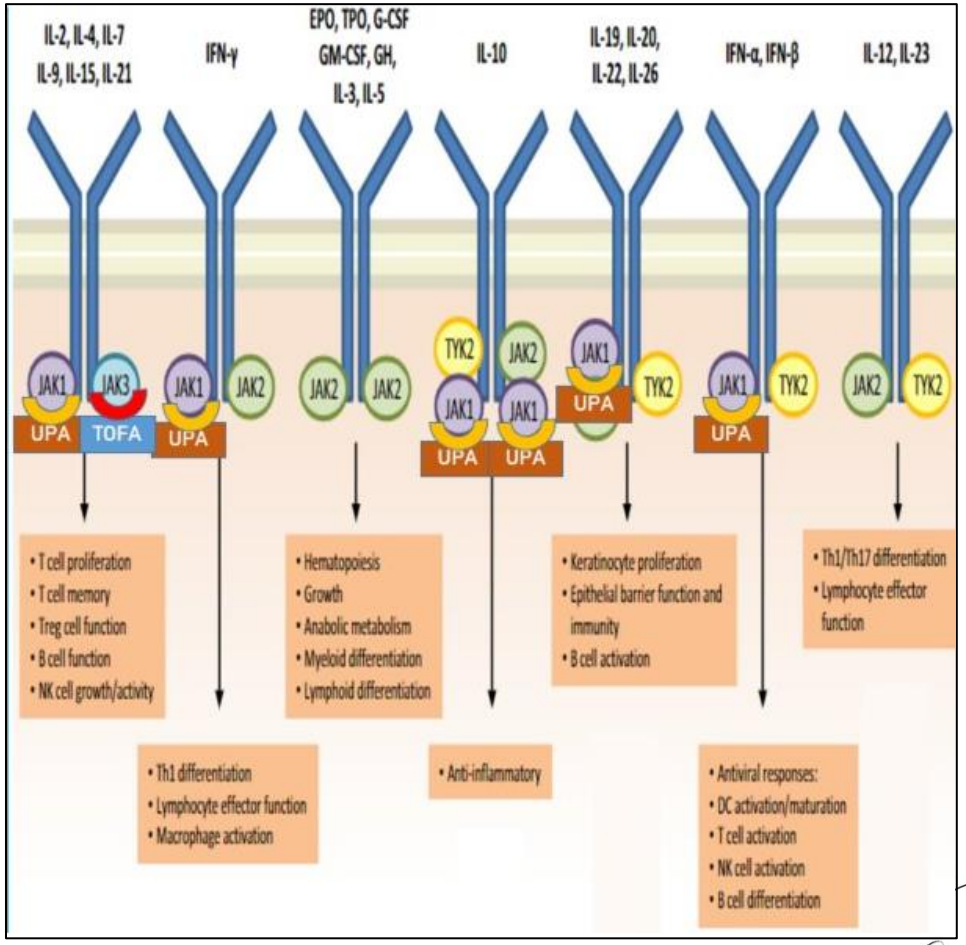
- *The mechanism of action of tofacitinib - an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis Jennifer A Hodge 1, Thomas T Kawabata 2, Sriram Krishnaswami 2, James D Clark 3, Jean-Baptiste Telliez 3, Martin E Dowty 3, Sujatha Menon 2, Manisha Lamba 2, Samuel Zwillich 2 Clin Exp Rheumatol . Mar-Apr 2016;34(2):318-28.*

JAK Inhibitors

- **Tofacitinib** – a pan-JAK inhibitor
  - Higher inhibitory activity for **JAK3**, less JAK 1+2
  - Approved for UC, 2018

- **Upadacitinib** – a JAK1 selective (inhibit more JAK- STAT pathways)
  - Approved for RA, 2019
  - Approved for UC, 2022

- **Filgotinib** – a JAK1 selective
  - In phase 2b/3 trials



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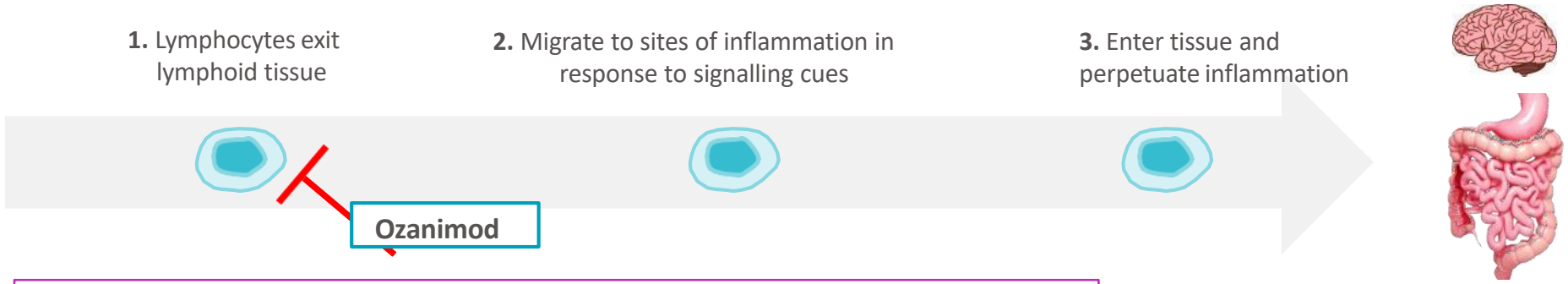
Sphingosine-1-phosphate (S1P) receptor modulators

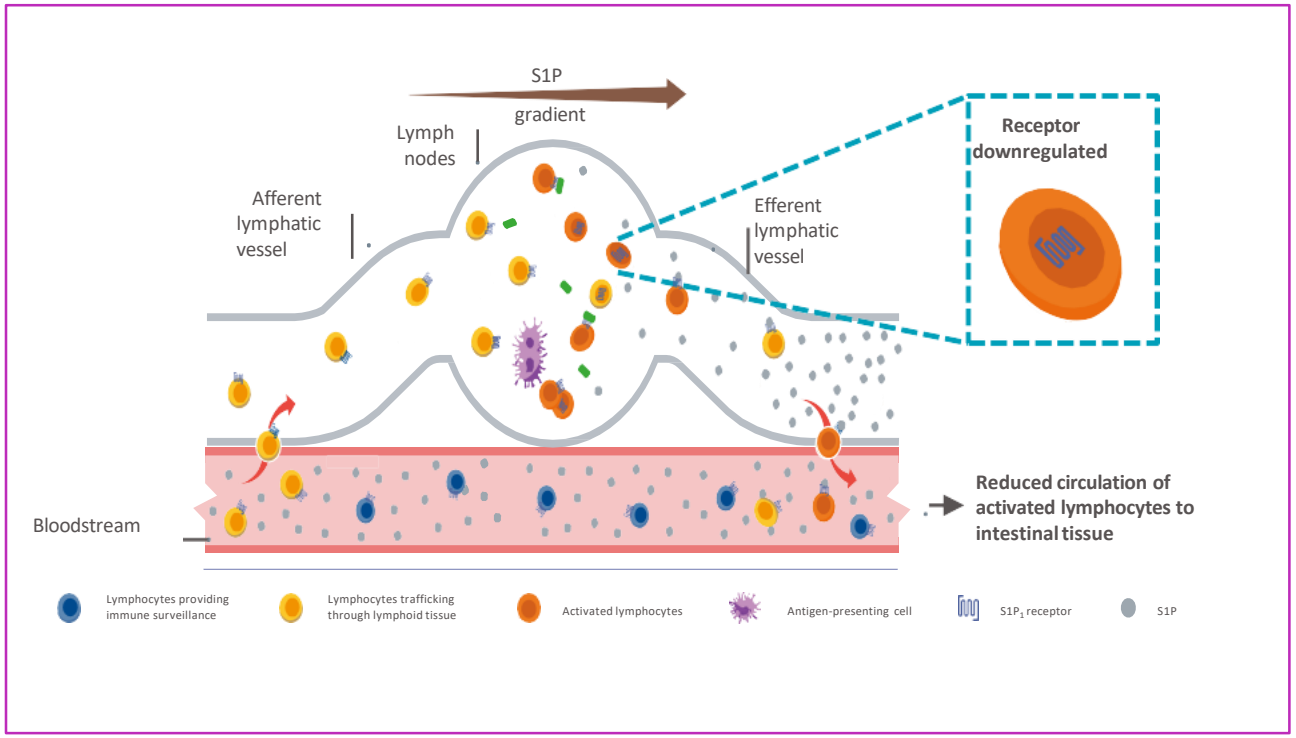
Ozanimod

1. Lymphocytes exit lymphoid tissue

2. Migrate to sites of inflammation in response to signalling cues

3. Enter tissue and perpetuate inflammation





- **Ozanimod binds to and internalizes the $S1P_1$ receptor, preventing some types of pro-inflammatory lymphocytes from exiting lymph nodes and reducing their circulation to intestinal tissue[1,3]**
- Cells involved in immune surveillance (eg, monocytes and NK cells) are not negatively affected and continue to circulate[4]

Drugs	Indication	Receptor selectivity	Status
Fingolimod[2]	Multiple sclerosis (MS)	S1P1, S1P3, S1P4 and S1P5	FDA approved 2010, EMA approved 2011
Ozanimod[2]	Multiple sclerosis (MS) and ulcerative colitits (UC)	**S1P1 and S1P5**	FDA approved 2020
Siponimod[2]	Multiple sclerosis (MS)	S1P1 and S1P5	FDA Approved 2019, EMA approved 2020
Ponesimod[2]	Multiple sclerosis (MS), psoriasis and graft vs. host disease	S1P1	FDA Approved 2021, In Phase III clinical trials and Phase II trials. (*)

CNS, central nervous system; GI, gastrointestinal; NK, natural killer.

1. Scott FL et al. *Br J Pharmacol*. 2016;173:1778-1792. 2. Danese S et al. *J Crohn's Colitis*. 2018;S678-S686. 3. Tran JQ et al. *J Clin Pharmacol*. 2017;57:988-996.
4. Harris S et al. *Neurol Neuroimunol Neuroinflamm*. 2020;7:e839.

How to choose?

How to choose?

Patient and drug

Characteristics

- Efficacy
- Safety
- EIM
- Comorbidity
- Age
- Preference
- Cost
- Onset of action
- TDM
- Disease location

Treatment

- Anti - TNF
- Vedolizumab
- Ustekinumab /Risankizumab
- Surgery
- JAKi
- Other

How to choose?

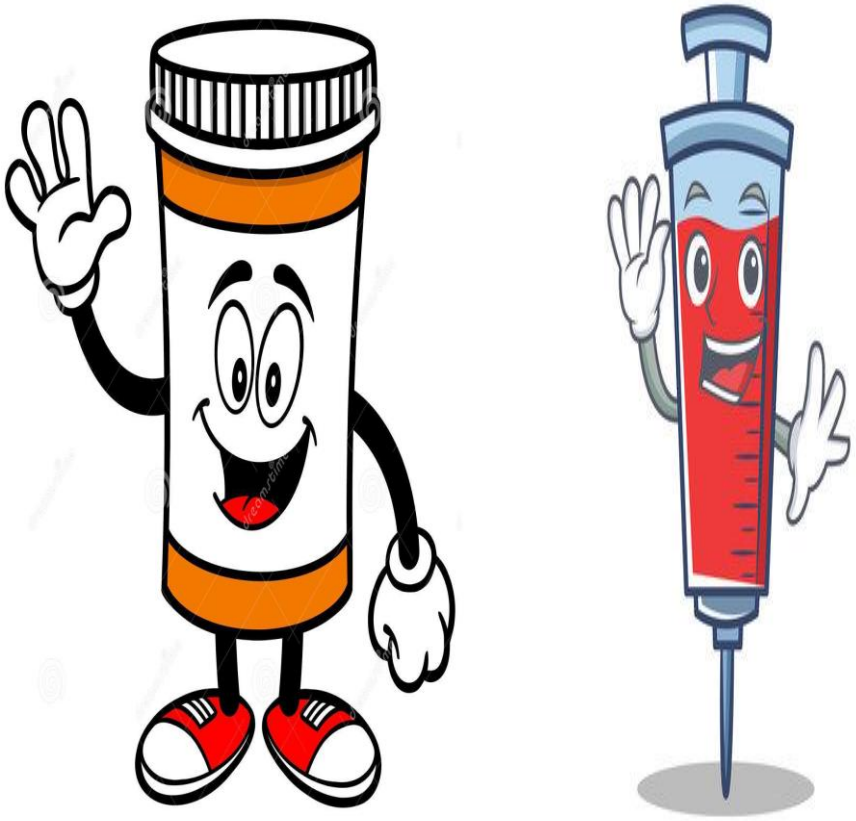
Patient oriented

- Efficacy- Prediction of success: **previous therapy failure and mechanism, Positioning and sequence**
- Safety- Age, comorbidity
- Comorbidity- Demyelination, CHF, Neoplasia, high risk of blood clots, psoriasis, cardiac conduction problems
- Preference- Route of Drug Administration
- Speed of onset- Acute severe colitis
- Pregnancy
- EIM

How to choose?

Drug oriented

- **Efficacy- Prediction of success**
  - **Treatment persistence**
- Safety
- Route of Drug Administration
- Speed of onset
- Preference
- TDM
- COST



Take-home messages

1. **הפרדיגמה הטיפולית היום**: על מנת להקל על הסימפטומים, הן במעי והן מחוצה לו, ולמנוע התקפים עתידיים וסיכון לפיתוח ממאירות יש לאמץ את קונספטים של התחלת טיפול יעיל מהר, הורדת הדלקת למינימום האפשרי, וכמו שאנו עושים בטיפול בסוכרת או ביל"ד, להשתמש באסטרטגיית ה **Treat to target** גם לסימפטומים וגם להעלמת הדלקת.

2. הטיפול הביולוגי/ במולקולות קטנות יעיל ובעל תחומי בטיחות טובים. למי שצריך יש מקום ברור מבחינת רווח מול הפסד להשתמש בו.

3. קיימים שיקולים רבים בבחירת התרופה הביולוגית המתאימה, בין אם התלויים בגורמים הקשורים למטופל ובין בתכונות התרופה עצמה.