The Juliet Keidan Institute of
Paediatric Gastroenterology and Nutrition
Shaare Zedek Medical Center, Jerusalem, Israel

ANNE & JOE TURNER
PEDIATRIC IBD CENTER
Shaare Zedek Medical center

ניהול מחלות מעי דלקתיות בילדים כשרשימת התרופות המאושרות גדלה והולכת

Dan Turner MD, PhD

Institute of Pediatric Gastroenterology
Shaare Zedek Medical Center
The Hebrew University of Jerusalem
Israel

המרכז הרפואי
שערי צדק
SHAARE ZEDEK
MEDICAL CENTER

Disclaimer

- Entyvio® is approved for:
  - The treatment of adult patients with moderate to severe active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNFα) antagonist.
  - The treatment of adult patients with moderately to severely active Crohn's Disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNFα) antagonist.
- As of January 2015 Vedolizumab is reimbursed in the national health basket for patients with moderate to severe UC/CD who failed or were intolerant for previous treatment biologic or non biologic
- The data on this presentation is based on published clinical studies
- For further information refer to the approved prescribing information, including warnings and precautions and adverse reaction http://www.old.health.gov.il/units/pharmacy/Trufot/ShowAlon.asp?tmpPath=/units/pharmacy/trufot/alonim/Entyvio-DR_1445248686864.pdf
- This presentation is sponsored by Takeda

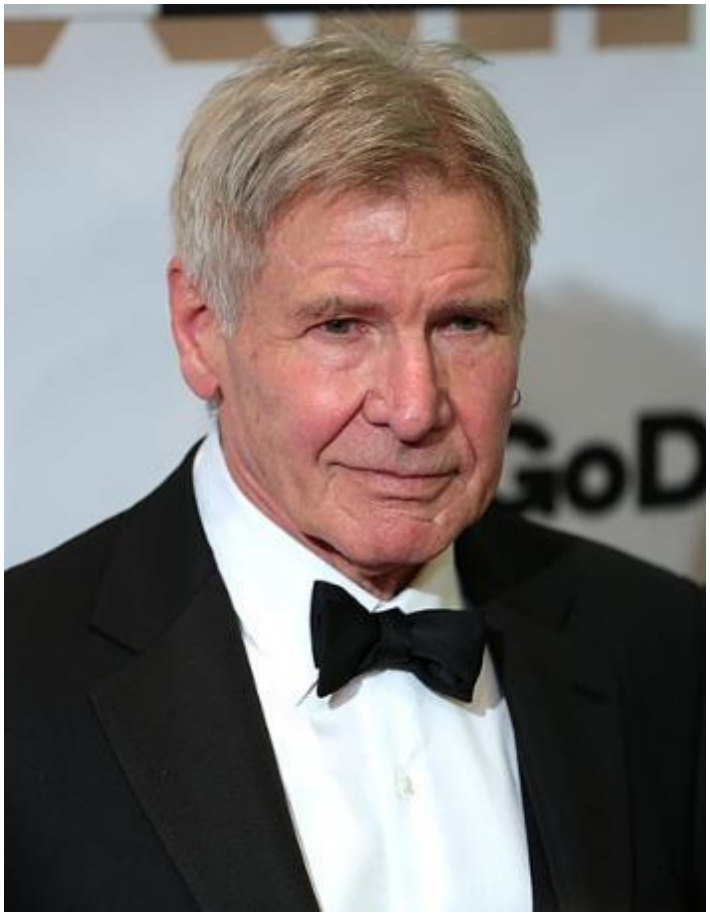
COI

Last 3 years DT received consultation fee, research grant, royalties, or honorarium from:

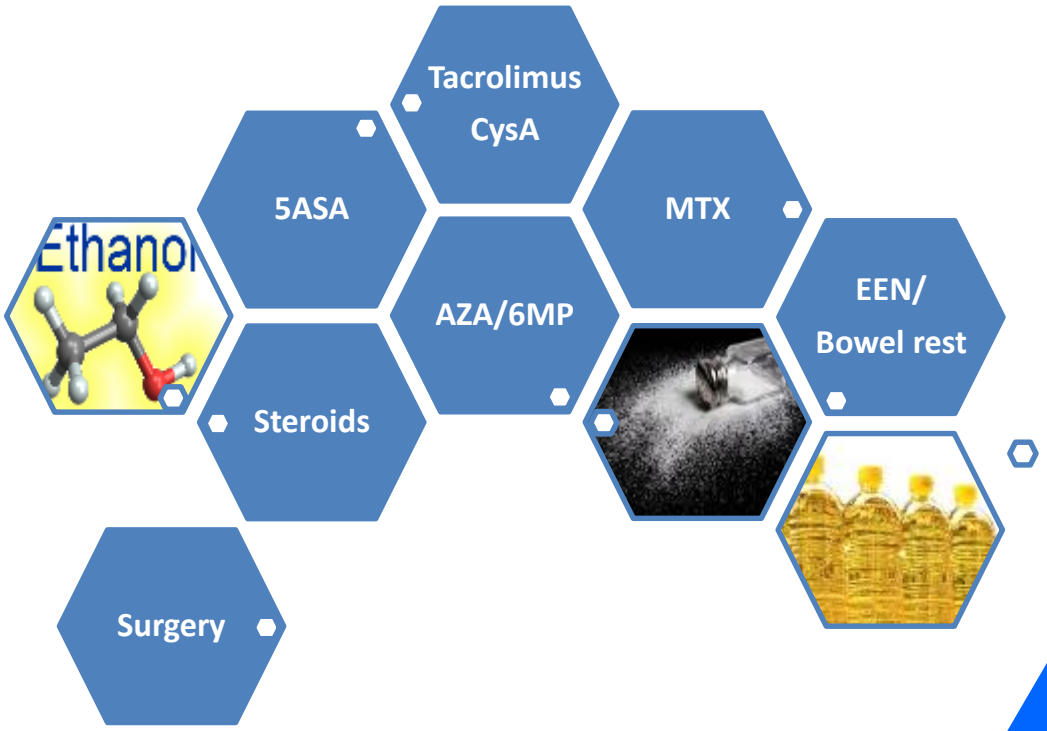
Janssen, Pfizer, Ferring, Hospital for Sick Children, AstraZeneca, Abbvie, Takeda, BMS, Boehringer Ingelheim, Biogen, Atlantic Health, Celgene, Lilly, Shire, Neopharm, Lilly

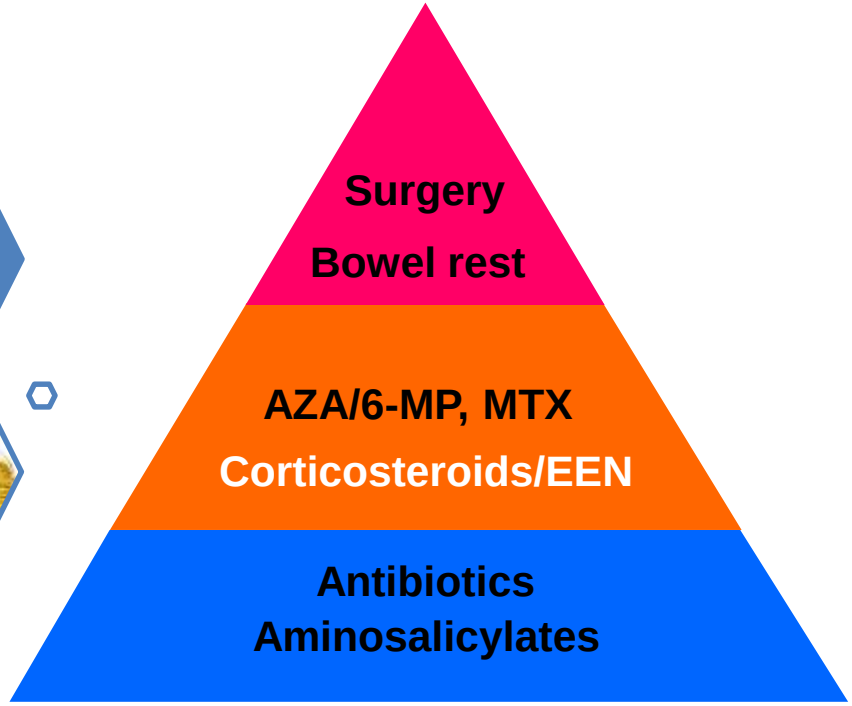
DT declares receiving speaker's fee for the current lecture from Takeda

Once upon a time…

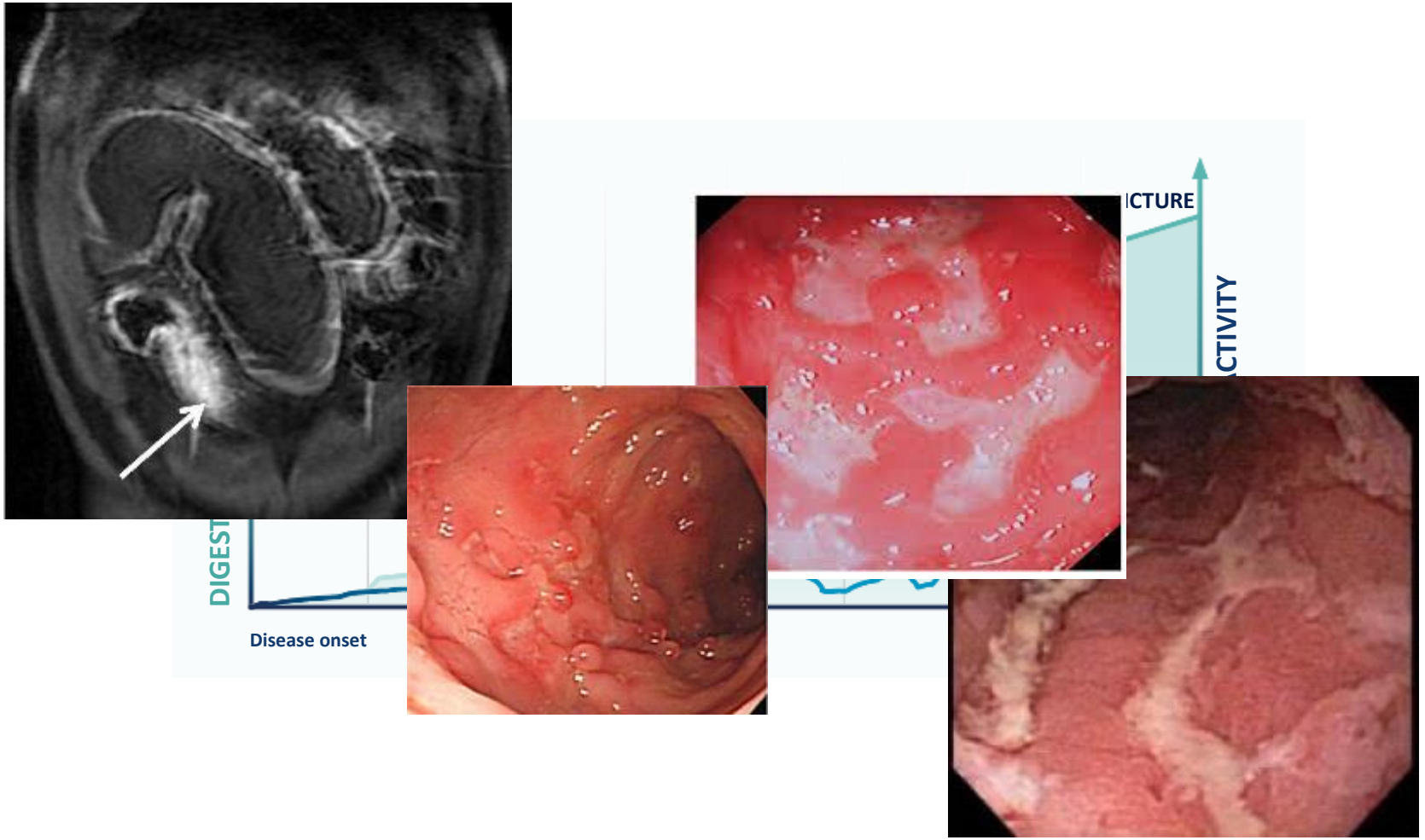


Once upon a time…

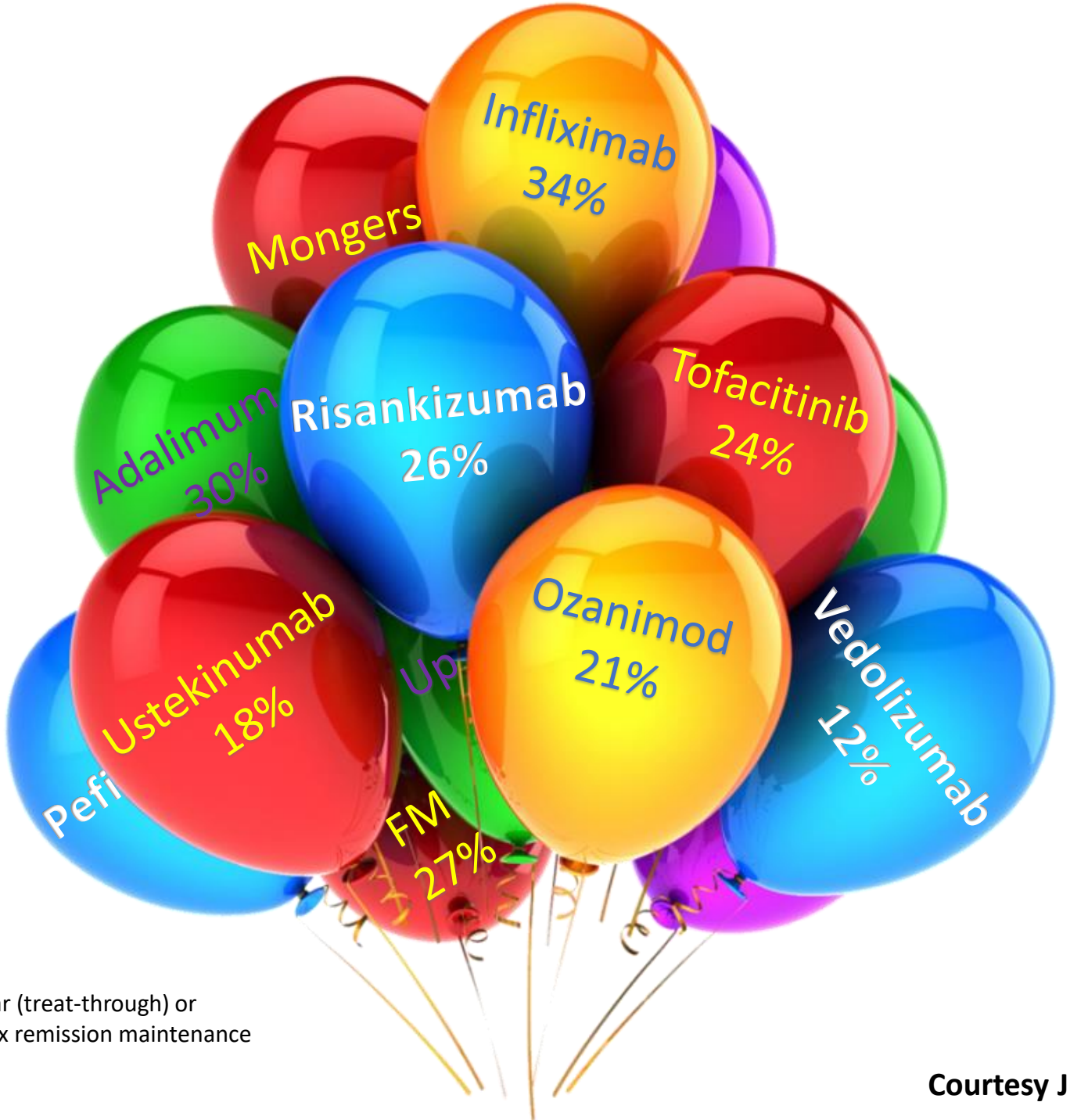




Natural history of Crohn's disease

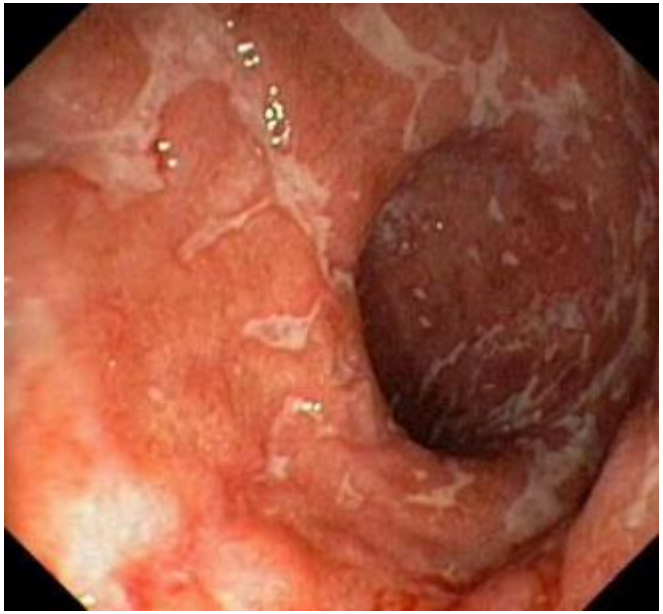


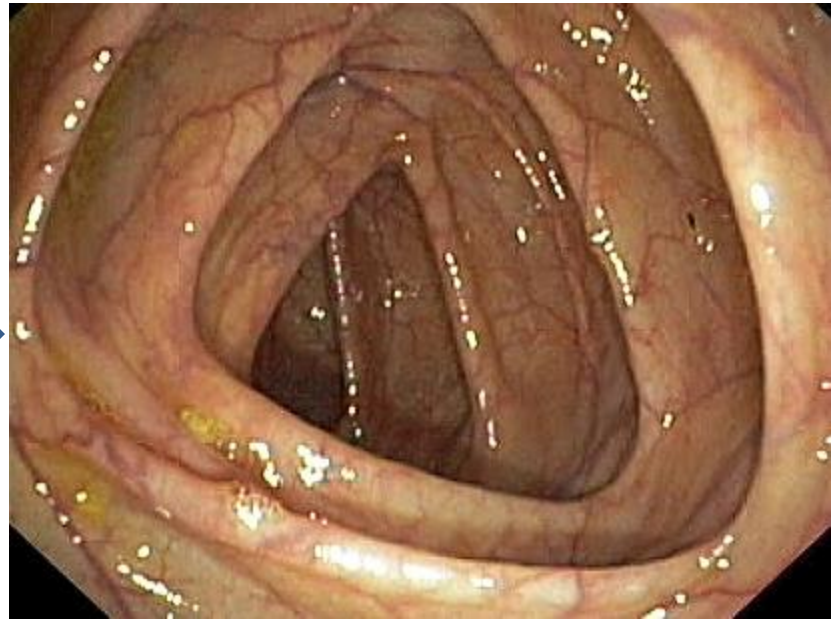
Pariente B, et al. *Inflamm Bowel Dis*. 2011;17:1415–22.



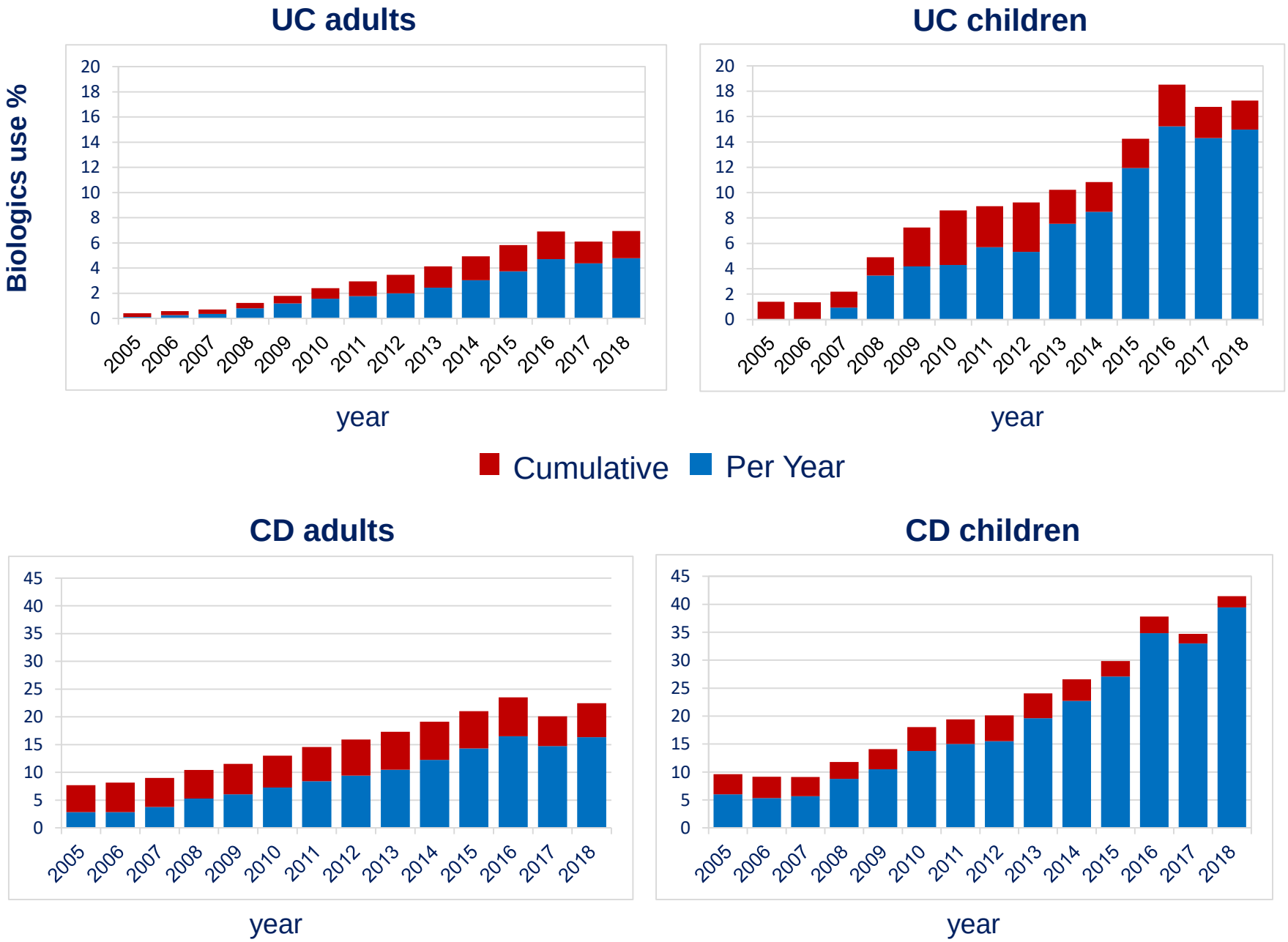
Remision rates 1 year (treat-through) or
Response induction x remission maintenance

Courtesy Julian Panes





Use of biologics in IBD Israel 01.2005-10.2018



Approved biologics

	CD	UC
Infliximab	+	+
Adalimumab	+	+ (Adults)
Golimumab		+ (Adults)
Cymzia	+ (Adults, not by EMA)	
Vedolizumab	+ (Adults)	+ (Adults)
Ustekinumab	+ (Adults)	
Tofacitinib		+ (Adults, FDA)

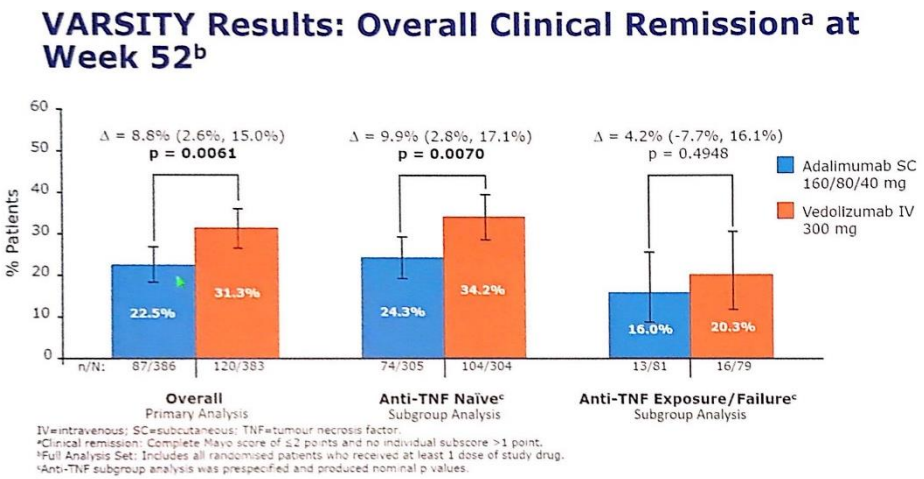
No doubt today that for effectiveness:
Biologics>thiourines/MTX> 5ASA

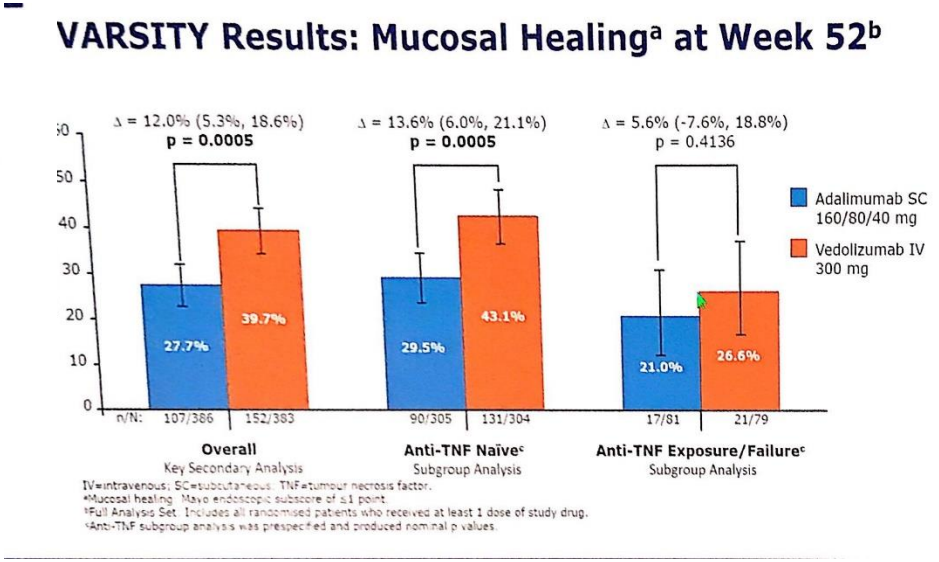
H2H trials in IBD

Vedolizumab (Entyvio) superior to adalimumab (Humira) in adults with UC

BUT!

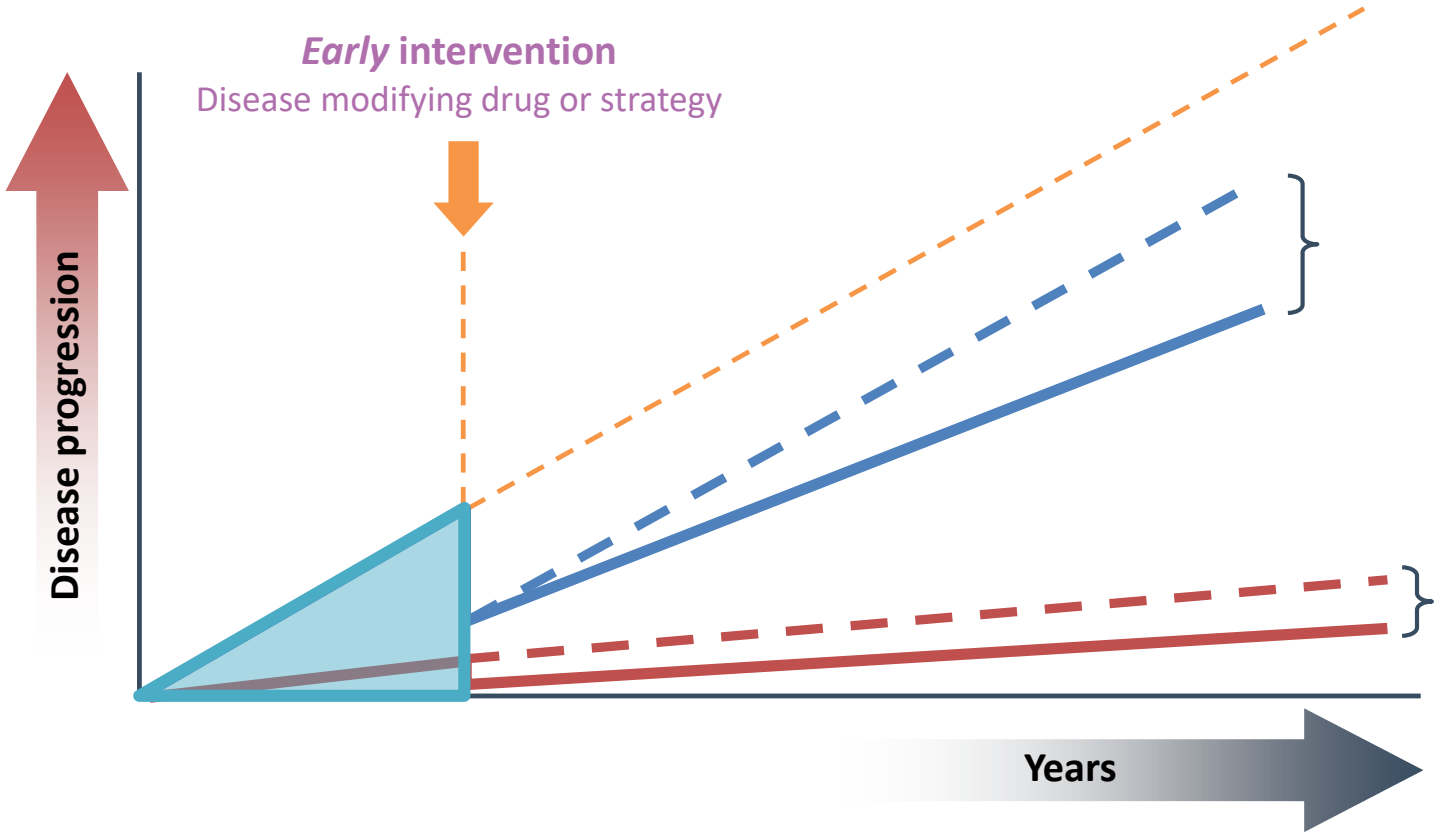
1. No intensification of humira
2. Adalimumab biosimilars are cheaper than VDZ





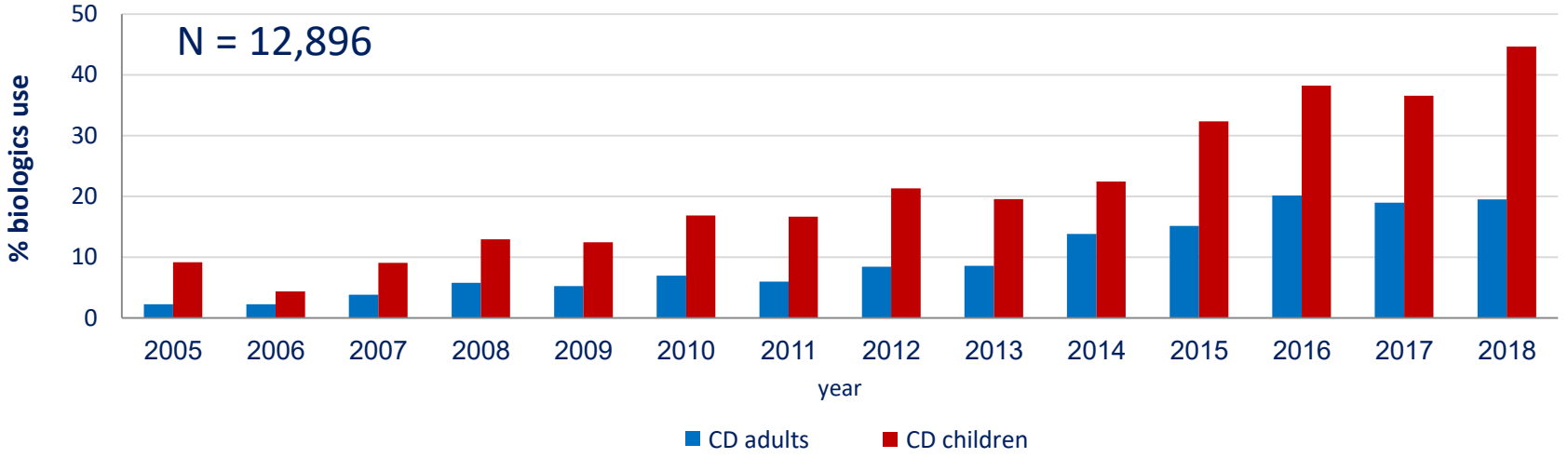
ECCO annual meeting, Copenhagen, March 2019

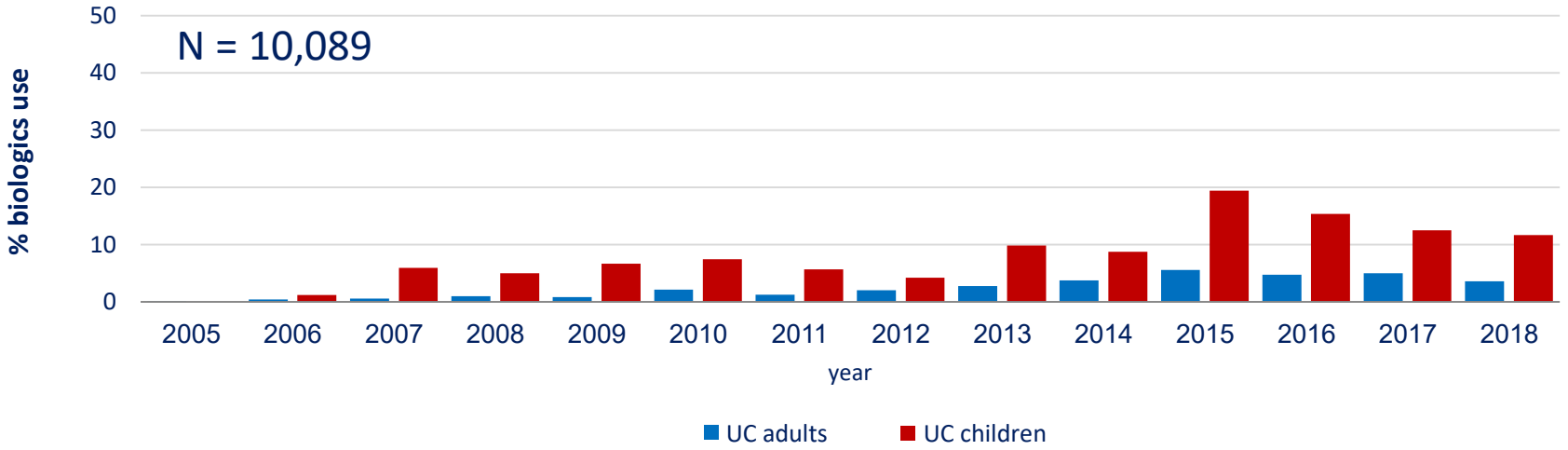
Modifying the natural history of disease



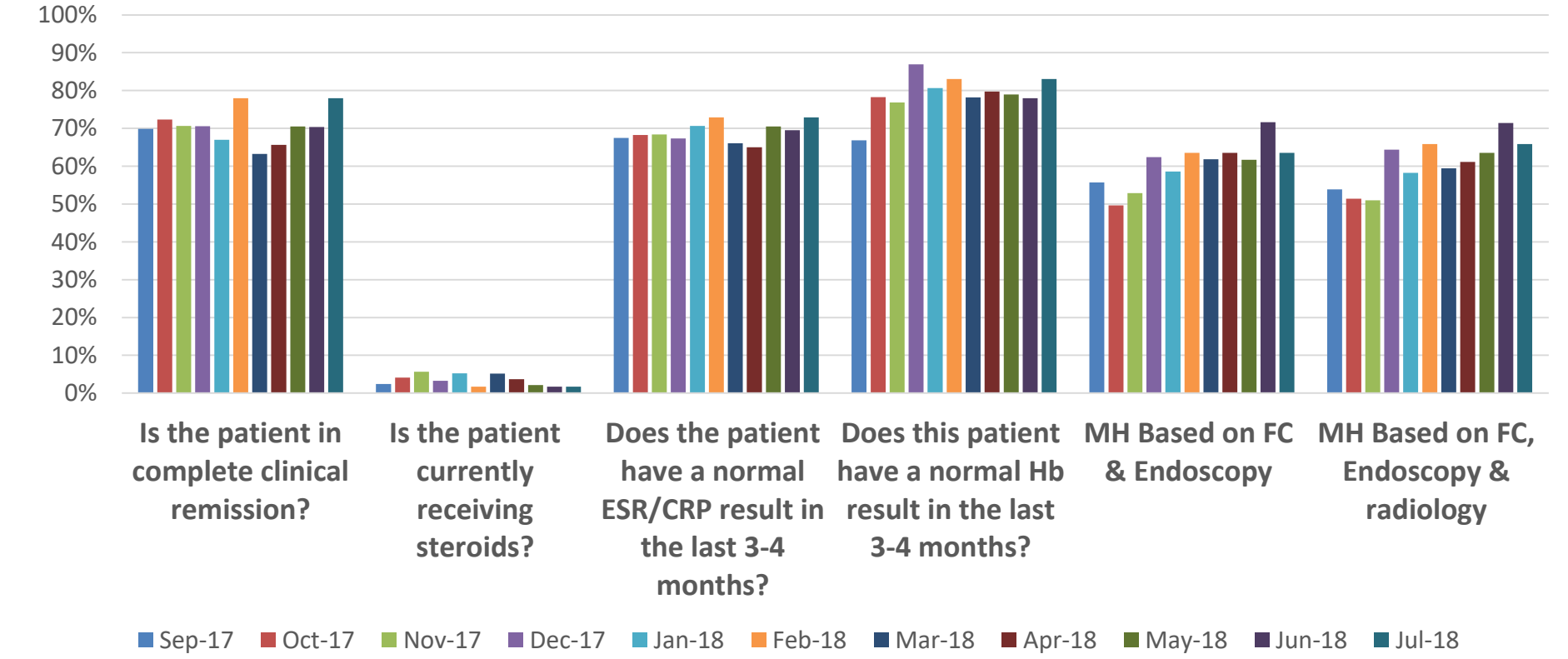
Commencement of biologics during the first year of diagnosis

p<0.001

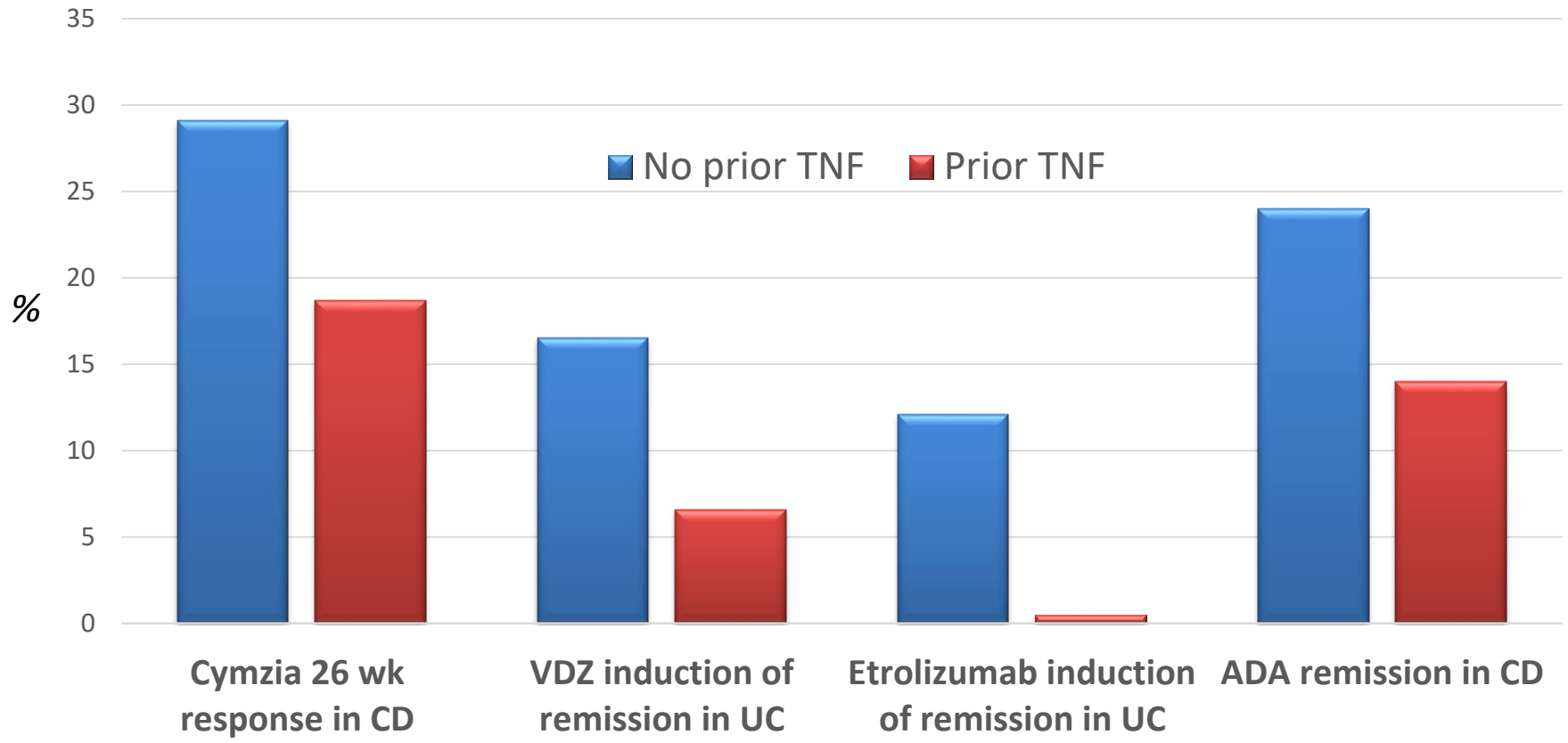




Quality improvement project of all 20 pediatric IBD centers in Israel – 2017-2018



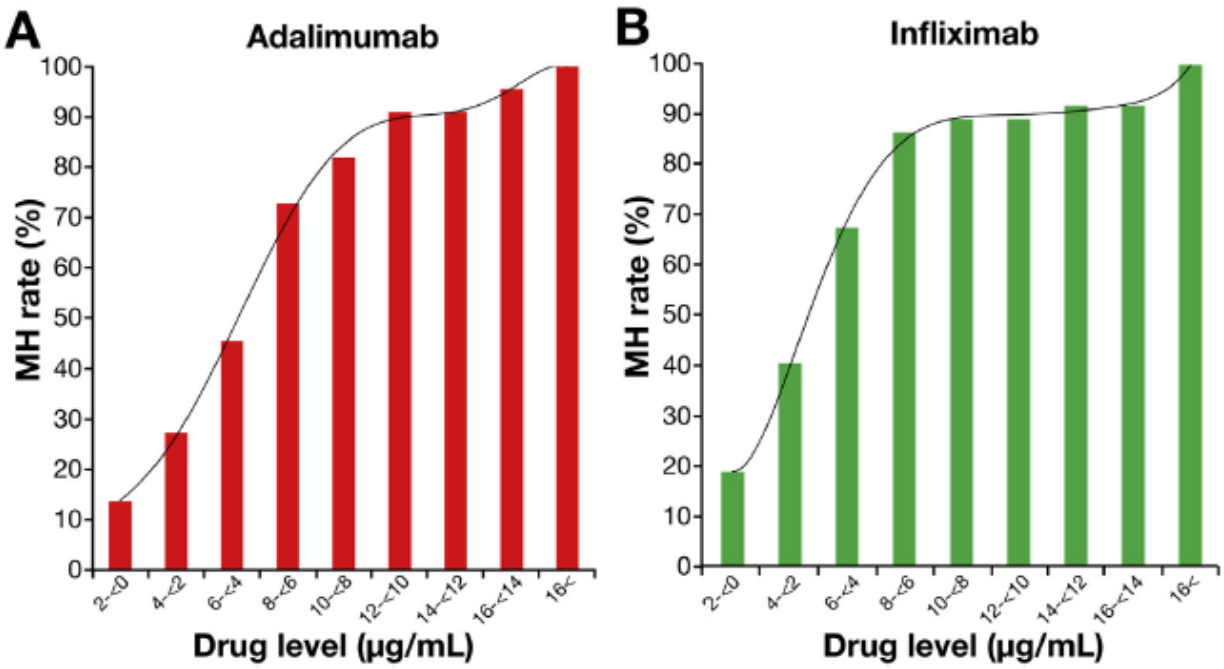
Δ outcome between biologics and placebo, stratified by prior TNF experience



Feagan B at al. NEJM 2013, Vermeire S et al. Lancet 2014 Hanauer SB et al. Gastroenterology. 2006;130(2):323 Sandborn WJ et al. Ann Intern Med. 2007;146(12):829

Don’t run <u>through</u> your treatment options….

Incremental mucosal healing by drug concentrations (UC and CD combined)



Ungar B. et al CGH 2016; 14: 550-557

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CD patient treated with adalimumab and MTX

מע' גסטרואנטרולוגית טל' 2905

Drug level & Immunogenicity

ADALIMUMAB Level	**undetectable 0.01**	micg/ml	28/11/2012
Anti ADALIMUMAB ab.	**positive 1.80**	micg/ml	28/11/2012

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40mg EOW->40mg weekly

מע' גסטרואנטרולוגית טל' 2905

Drug level & Immunogenicity

ADALIMUMAB Level	positive 3.80	micg/ml	24/03/2013
Anti ADALIMUMAB ab.	borderline 1.20	micg/ml	24/03/2013

Safety

Ustekinumab may be safer than anti-TNF?

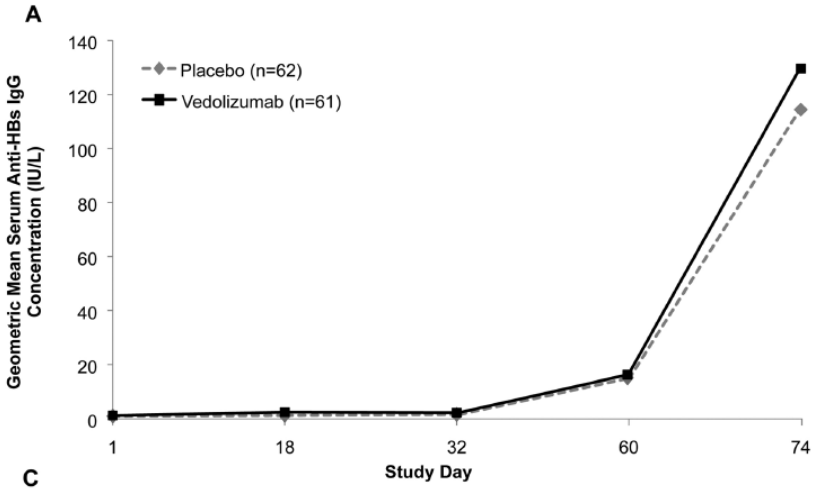
UNITI-1- wk 8 safety	PBO	UST 130 mg	UST ~6mg/kg*	UST combined
Treated subjects in induction phase – n	245	246	249	495
Duration of follow-up (weeks) – mean	7.9	7.9	7.8	7.8
Subjects with ≥1 – n (%)				
Death	0	0	0	0
AE	159 (64.9)	159 (64.6)	164 (65.9)	323 (65.3)
SAE	15 (6.1)	12 (4.9)	18 (7.2)	30 (6.1)
Infection	58 (23.6)	57 (23.2)	64 (25.7)	121 (24.4)
Serious infection	3 (1.2)	3 (1.2)	7 (2.8)	10 (2.0)
Infusion reaction	5 (2.0)	11 (4.5)	9 (3.6)	20 (4.0)
Malignancy	0	0	0**	0
MACE	0	0	0	0

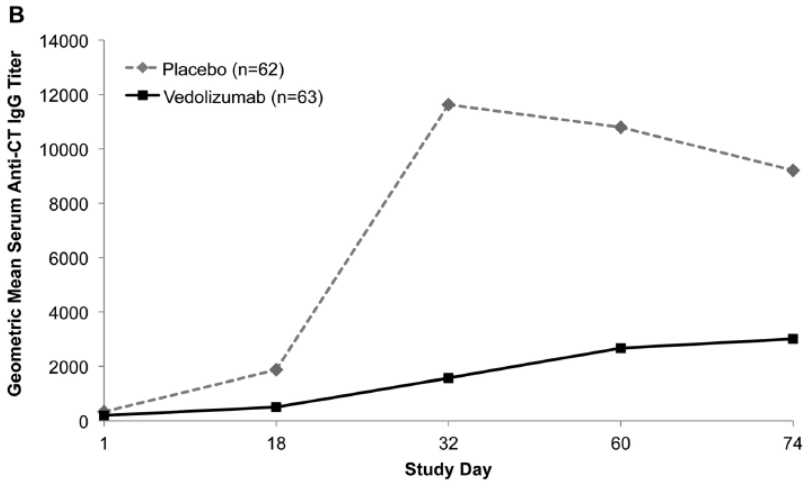
- No serious infusion reactions reported (UNITI 1, 2 and PSORIASIS registries) and less immunogenic
- PSOLAR: No increased risk for malignancy, cardiovascular event, serious infections, or mortality

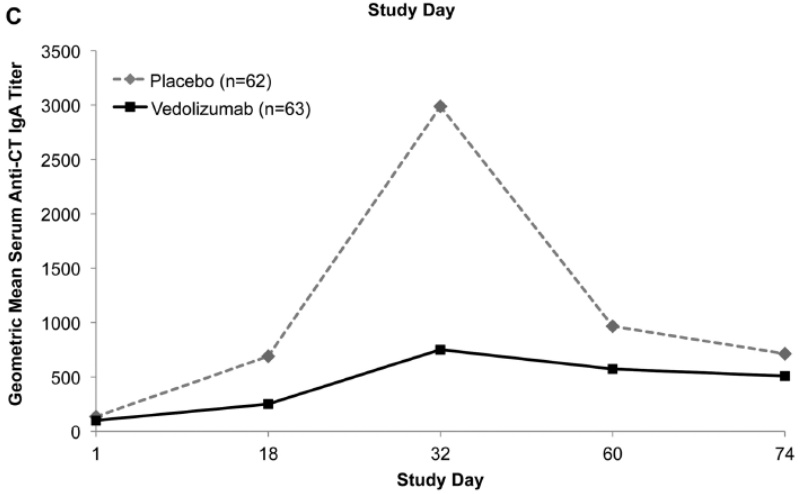
Adapted from Rutgeerts et al. ECCO 2016 OP014

Papp K, et al. J Drugs Dermatol 2015 Jul;14(7):706-14

Vedolizumab inhibits response to oral CT but not to systemic HBV vaccine



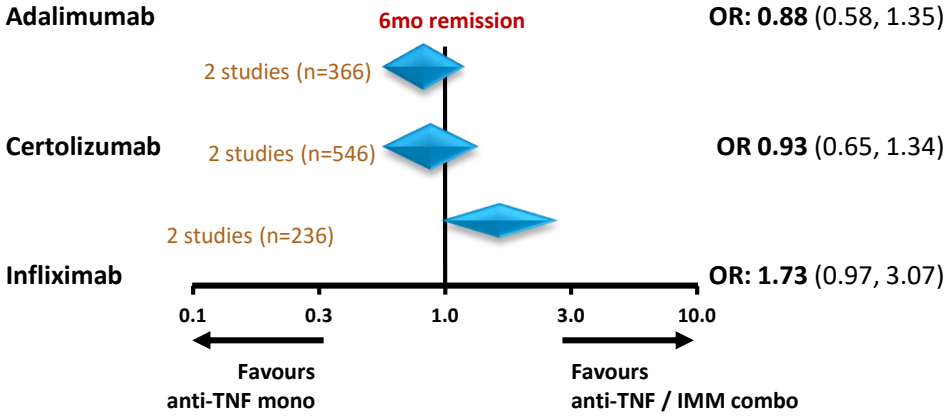




Oral JAK inh may be more risky (infections, hyperlipidemia, VTE)

Wyant T et al. Gut 2015;64:77

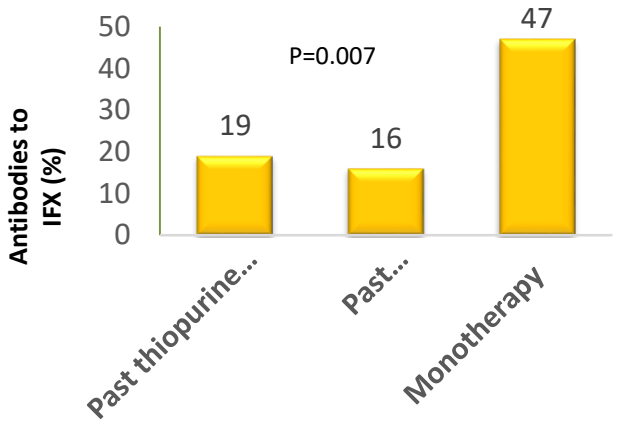
MTX/AZA increase IFX levels and improves outcome
Also for ADA but with a much smaller effect size
No such evidence for other biologics



Overall, combination therapy was not associated with increased ADE except for lower infusion reaction in the IFX-combo group

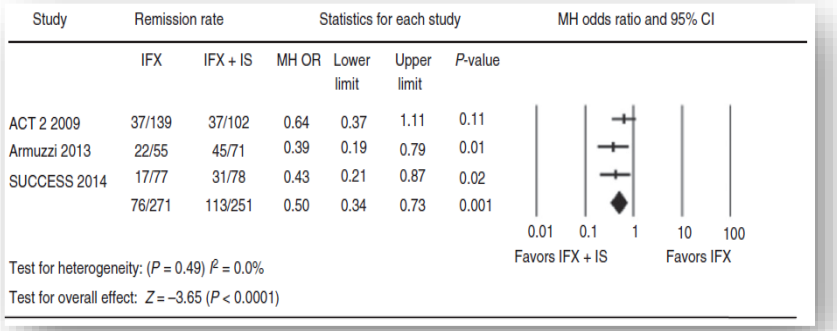
Jones JL, et al. CGH 2015;13:2233–40.e2

- **Past thiopurines failure/response**



Bar Yoseph H et al. 2017;15:69-75

Remission rate at 4-6 months

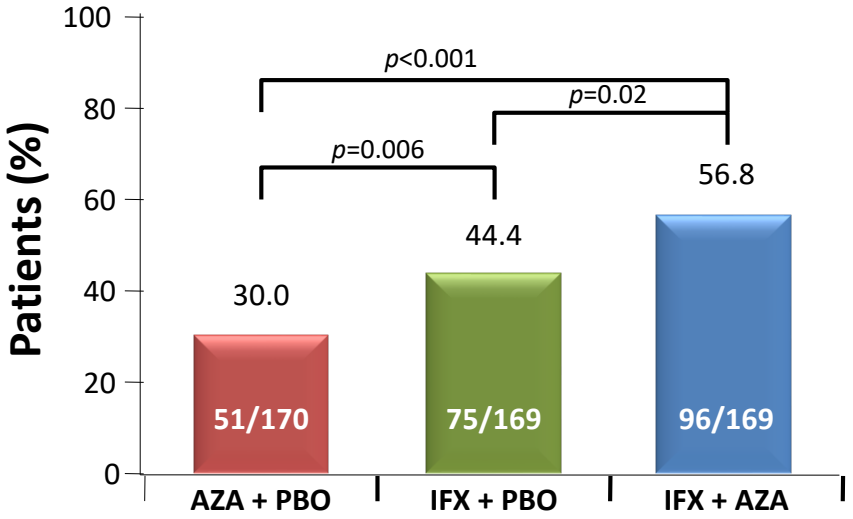


Study	Remission rate		Statistics for each study				MH odds ratio and 95% CI
	IFX	IFX + IS	MH OR	Lower limit	Upper limit	*P*-value	
ACT 2 2009	37/139	37/102	0.64	0.37	1.11	0.11	
Armuzzi 2013	22/55	45/71	0.39	0.19	0.79	0.01	
SUCCESS 2014	17/77	31/78	0.43	0.21	0.87	0.02	
	76/271	113/251	0.50	0.34	0.73	0.001	

Test for heterogeneity: ($P = 0.49$) $I^2 = 0.0\%$

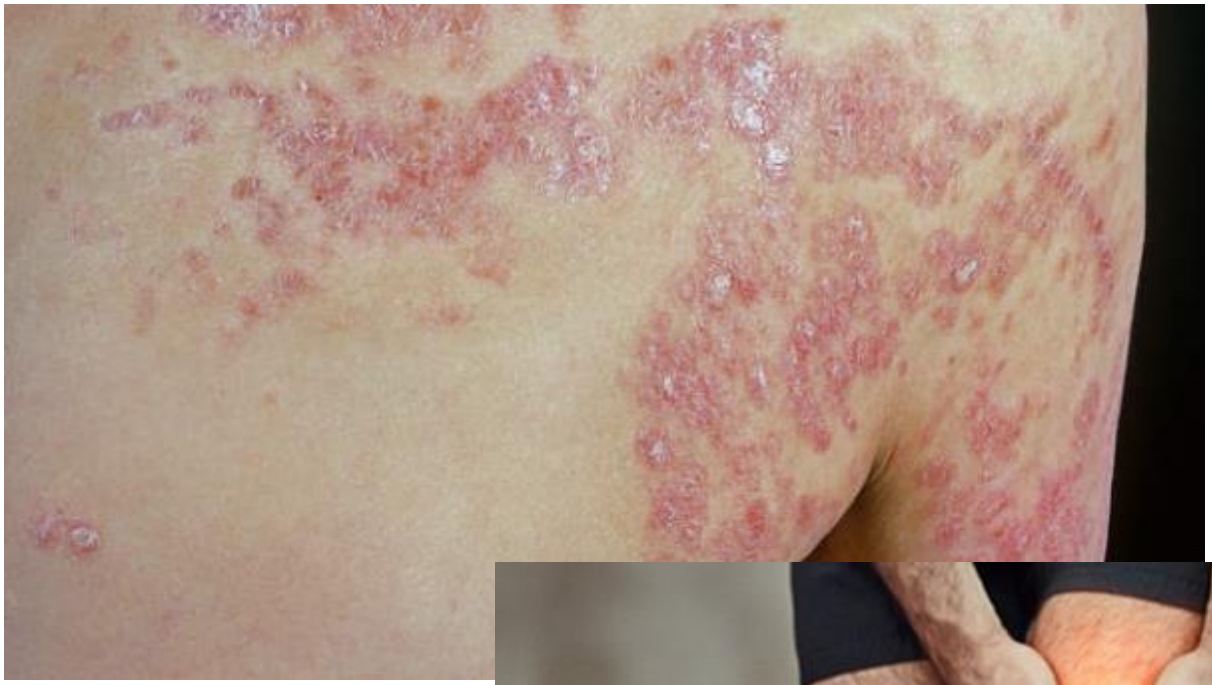
Test for overall effect: $Z = -3.65$ ($P < 0.0001$)

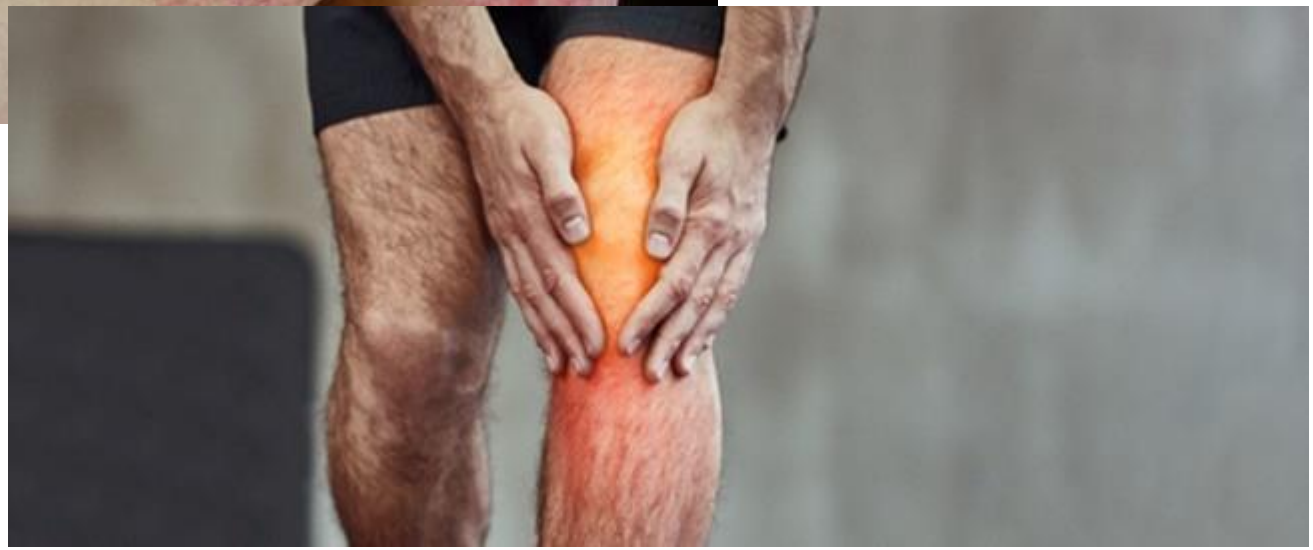
Christophorou D et al. 2015 APT; 41: 603–612



Colombel JF, N Engl J Med 2010

Ustekinumab





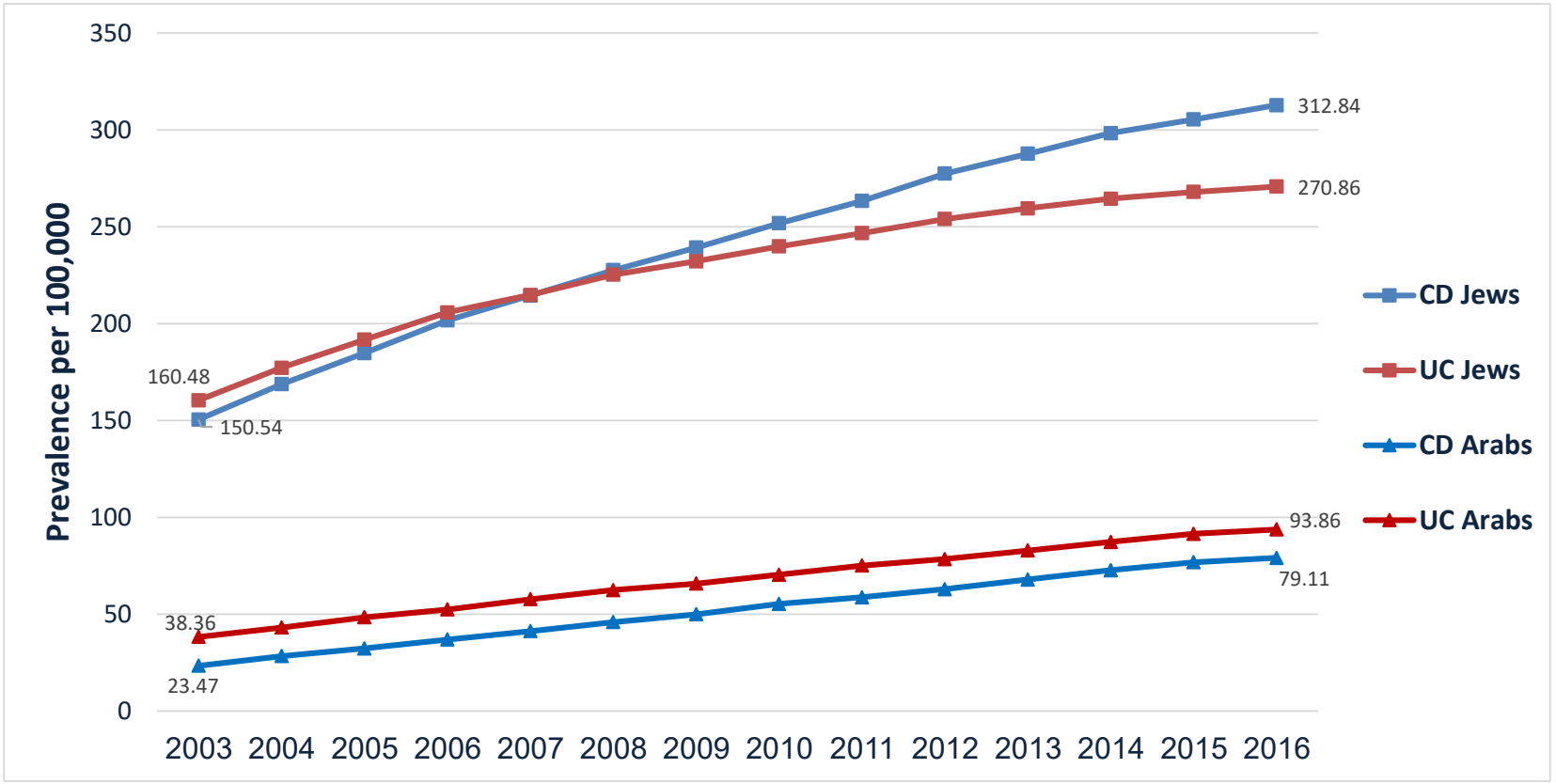
Patient

Characteristics

- Comorbidity
- Age
- Preference
- Cost
- EIM
- Perforating/stenosis
- Disease location
- TDM

- **Anti - TNF**
- **Vedolizumab**
- **Ustekinumab**
- **Surgery**
- **Tofacitinib**
- **Others**

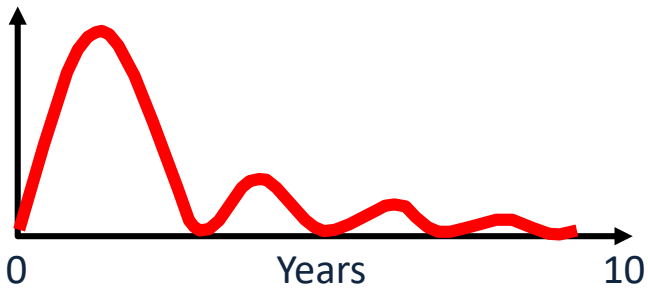
Israeli IBD prevalence trends



- Since 2003, the Jewish prevalence doubled from 0.31% to 0.59%
- The Arab prevalence increased threefold, from 0.06% to 0.17%.

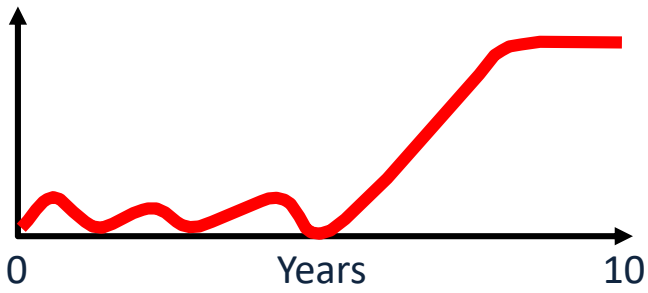
Disease course in CD

43% (n=85)



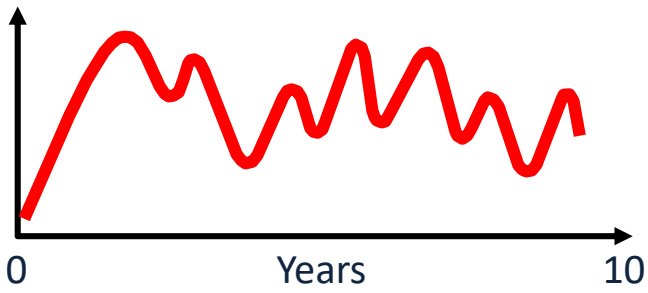
Remission or mild severity of intestinal symptoms after initial high activity

3% (n=6)



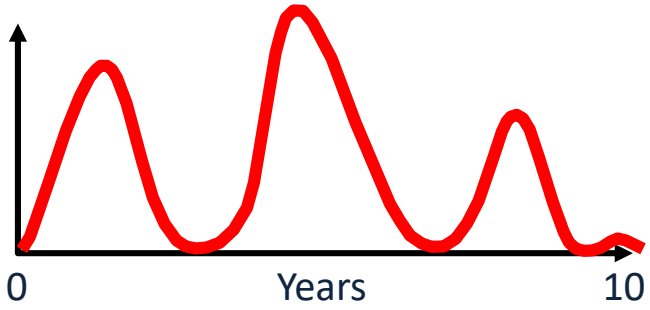
Increase in the severity of intestinal symptoms after initial low activity

19% (n=37)



Chronic continuous symptoms

32% (n=63)



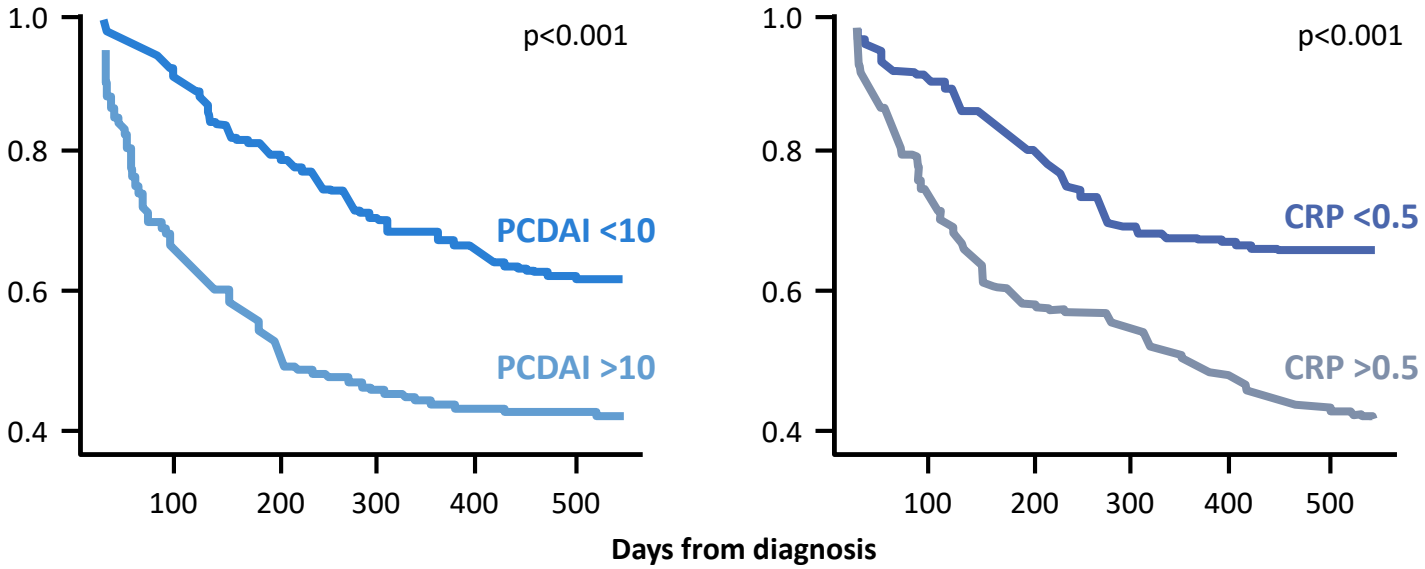
Chronic intermittent symptoms

Solberg IC, Clin Gastro Hepatol 2007

Prediction is a risky business….

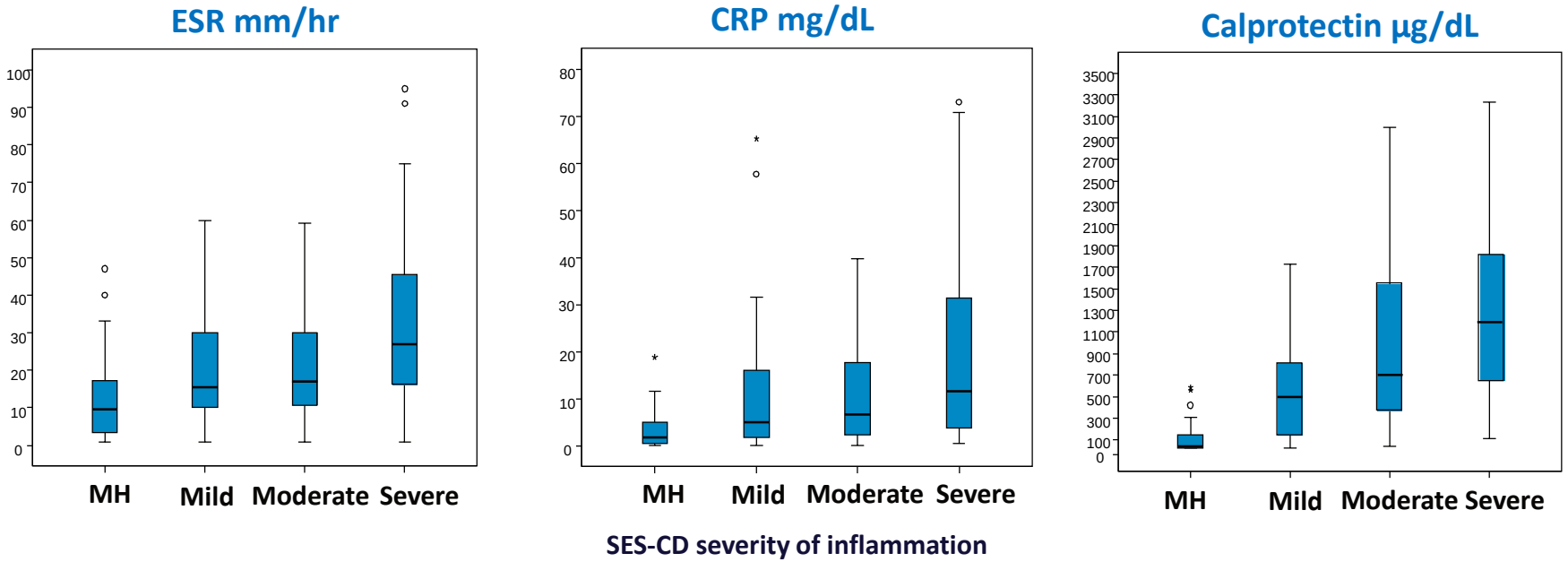
The GROWTH Crohn's disease study (n = 280)
Predicting relapse by 1 year

- Week 0: Nothing
- Week 12:



Courtesy Arie Levine – the GROWTH study

Data from the multicentre ImageKids study

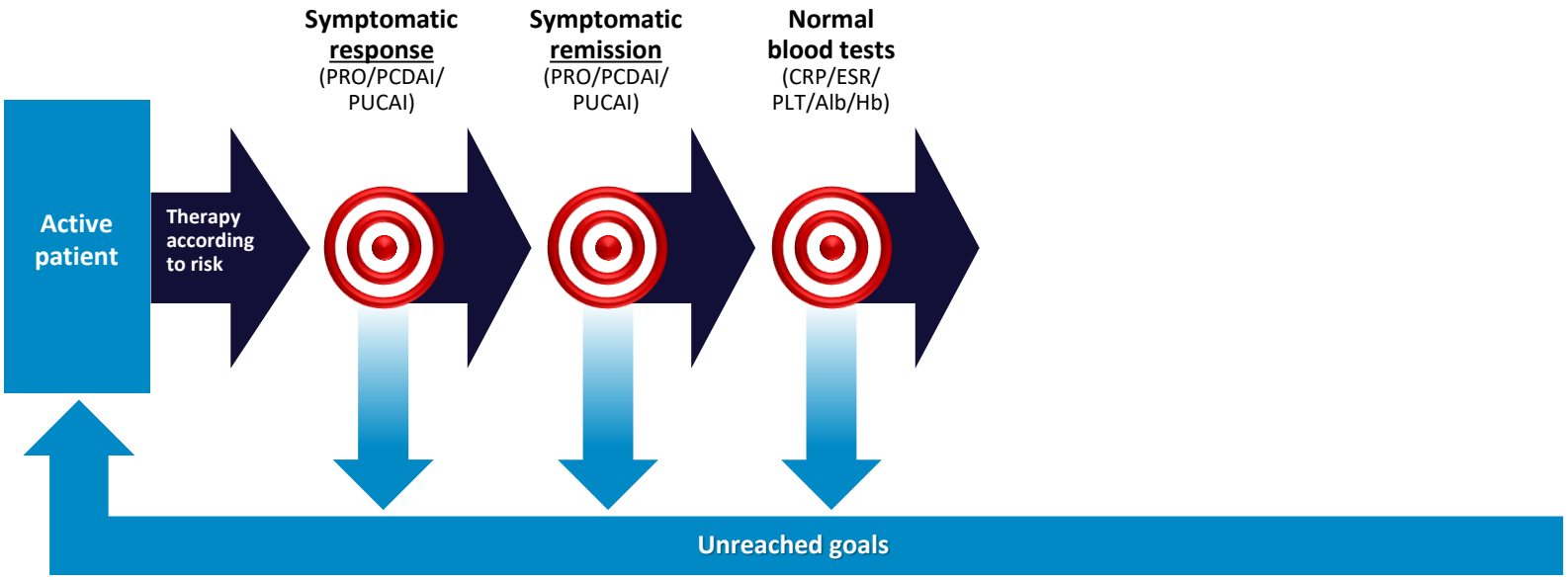


The ImageKids study has been funded by AbbVie.

Potential treat-to-target concepts in paediatric IBD

Alb, albumin; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hb, haemoglobin; MH, mucosal healing; PRO, patient-reported outcome; PCDAI, paediatric Crohn's disease activity index; PLT, platelets; PUCAI, paediatric ulcerative colitis activity index

Potential treat-to-target concepts in paediatric IBD



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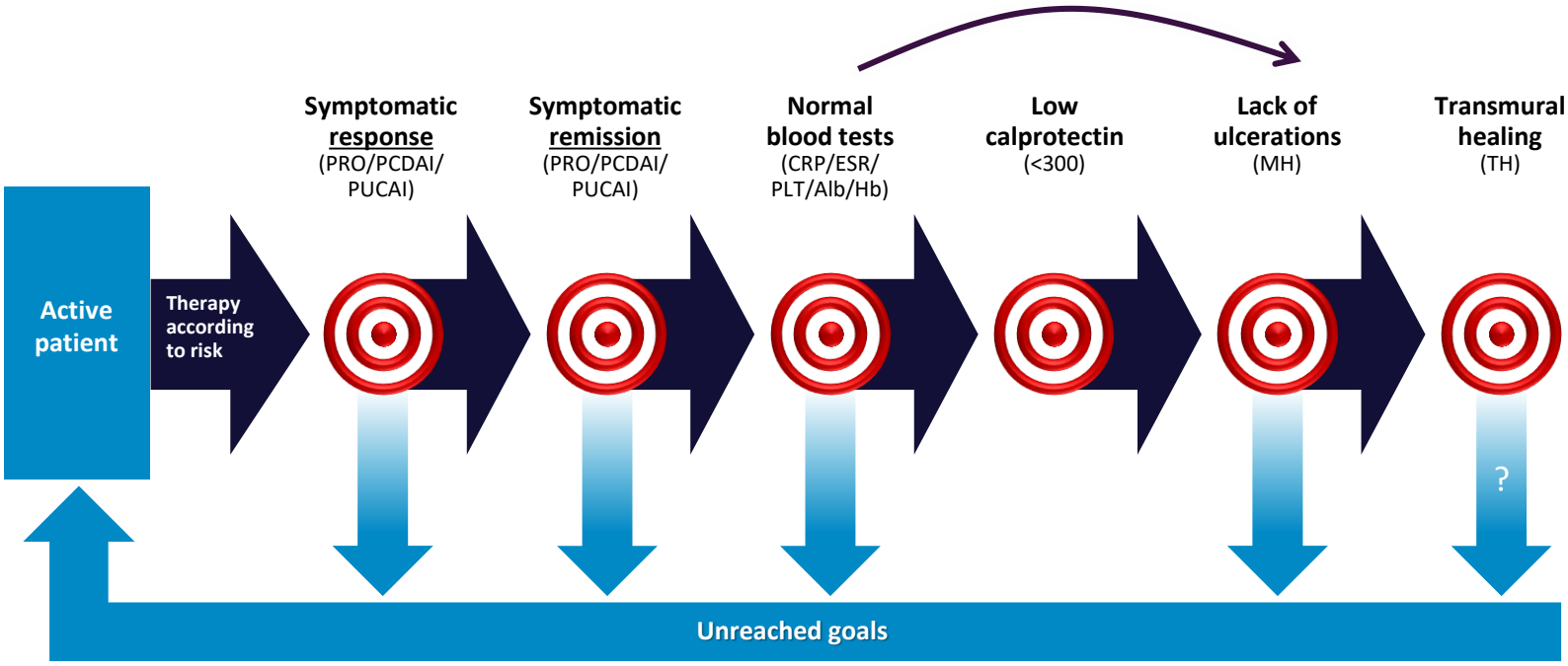


Alb, albumin; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hb, haemoglobin; MH, mucosal healing; PRO, patient-reported outcome; PCDAI, paediatric Crohn's disease activity index; PLT, platelets; PUCAI, paediatric ulcerative colitis activity index

מחשבות של ילדים בכנס התמודדות עם קרוהן וקוליטיס, שערי צדק

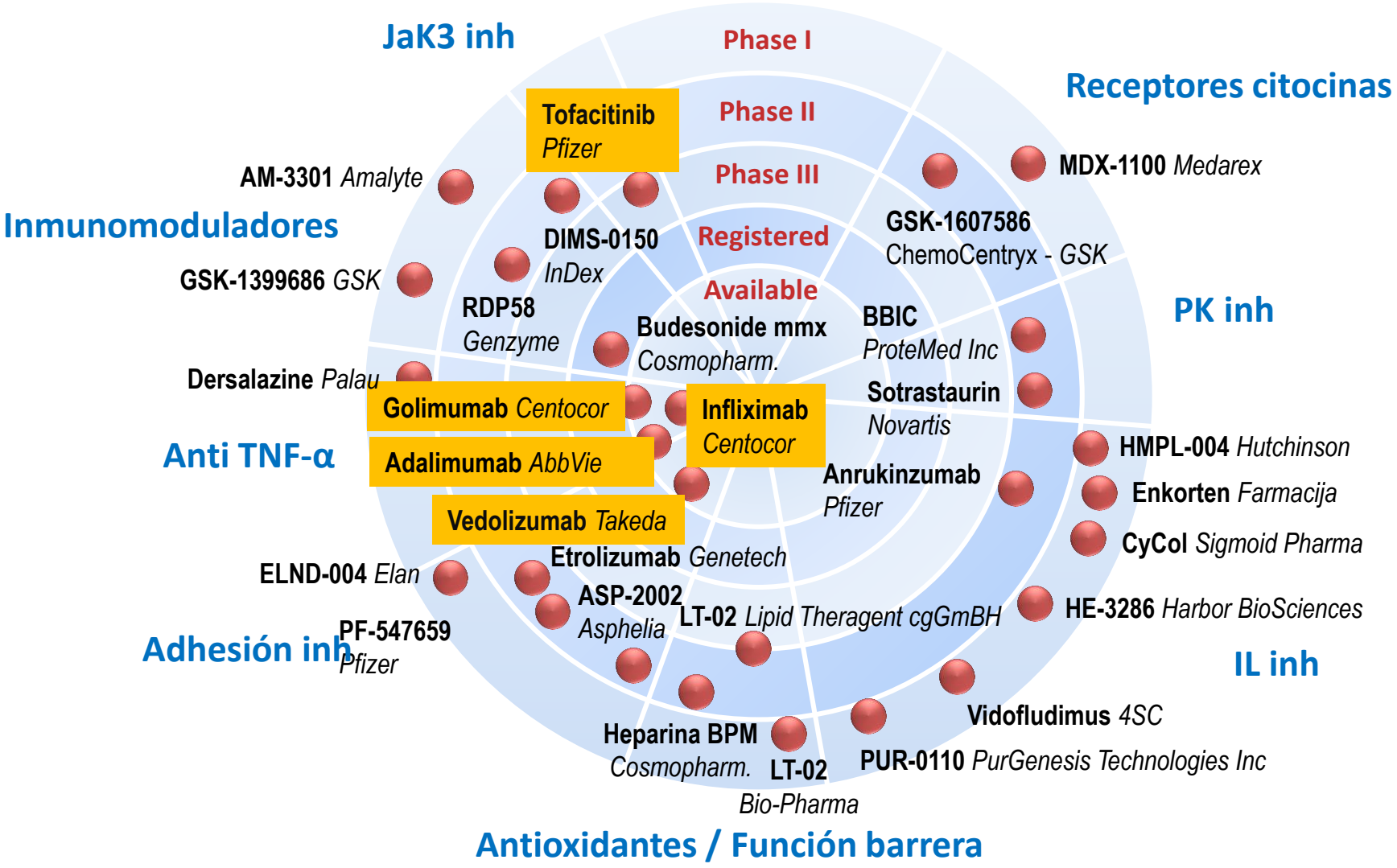
- הכאב הוא כמו סכין בבטן.
- קשה לא לאכול.
- אני צריך לחשוב על כל דבר שאני אוכל בעוד אחרים חופשיים לאכול כל דבר.
- אין כוח ואין אנרגיה.
- פרדניזון הופך את החיים לגהנום.
- אני מרגישה שאני מפספסת בחיים.
- הייתי רוצה לעשות הרבה דברים אבל כשלא בריאים אי אפשר.
- אני אף פעם לא יודע מתי יגיע הכאב.

מחשבות של ילדים בכנס התמודדות עם קרוהן וקוליטיס, שערי צדק

- הייתי רוצה להיות רגיל. בלי כאבים.
- כולם גדלים ואני מצטמק.
- אני מתביישת מאיך שאני נראית.
- אני פוחד לספר לחברים על המחלה. אולי הם יצחקו עלי.
- אני פשוט רוצה שיתייחסו אלי כמו שמתייחסים לכולם.

סדנאות התמודדות עם המחלה לבני נוער בשערי צדק

On the horizon:
More targets → more drugs



Adapted from Danese S. *Gut* 2012;61:918–32

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The Juliet Keidan Institute of
Paediatric Gastroenterology and Nutrition
Shaare Zedek Medical Center, Jerusalem, Israel

Gastroenterology

Research

המרכז הרפואי
שערי צדק
SHAARE ZEDEK
MEDICAL CENTER

Highlights of prescribing information

These highlights do not include all the information needed to use Entyvio® safely and effectively.

NAME OF THE MEDICINAL PRODUCT

Entyvio 300 mg powder for concentrate for solution for infusion Vedolizumab is a humanised IgG1 monoclonal antibody that binds to the human α4β7 integrin and is produced in Chinese hamster ovary (CHO) cells.

Therapeutic indications

Entyvio® is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis/ Crohn's disease, who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNFα) antagonist.

Posology and method of administration

Entyvio® treatment should be initiated and supervised by specialist healthcare professionals experienced in the diagnosis and treatment of ulcerative colitis or Crohn's disease. The marketing of Entyvio is subject to a risk management plan (RMP) including a 'Patient Alert Card'. The 'Patient Alert Card' emphasizes important safety information that the patient should be aware of before and during treatment. Please explain to the patient the need to review the card before starting treatment. This product is marketed with prescriber guide providing important safety information. Please ensure you are familiar with this material as it contains important safety information. The recommended dose regimen of Entyvio® is 300 mg administered by intravenous infusion at zero, two and six weeks and then every eight weeks thereafter.

Some patients who have experienced a decrease in their response may benefit from an increase in dosing frequency to Entyvio® 300 mg every four weeks.

In patients who have responded to treatment with Entyvio®, corticosteroids may be reduced and/or discontinued in accordance with standard of care.

If therapy is interrupted and there is a need to restart treatment with Entyvio, dosing at every four weeks may be considered.

Continued therapy for patients with ulcerative colitis should be carefully reconsidered if no evidence of therapeutic benefit is observed by Week 10.

Patients with Crohn's disease, who have not shown a response may benefit from a dose of Entyvio® at week 10. Continue therapy every eight weeks from Week 14 in responding patients. Therapy for patients with Crohn's disease should not be continued if no evidence of therapeutic benefit is observed by Week 14.

Paediatric population

No data is available on the safety and efficacy of vedolizumab in children aged 0 to 17 years.

Elderly patients

No dose adjustment is required.

Patients with renal or hepatic impairment

Entyvio® has not been studied in these patient populations. No dose recommendations can be made.

Contraindications

Hypersensitivity to the active substance or to any of its excipients. Active severe infections such as tuberculosis, sepsis, cytomegalovirus, listeriosis, and opportunistic infections such as Progressive Multifocal Leukoencephalopathy (PML).

Special warnings and precautions for use

Entyvio® should be administered in a healthcare setting equipped to allow management of acute hypersensitivity reactions including anaphylaxis, if they occur. Appropriate monitoring and medical support measures should be available for immediate use when administering Entyvio®.

All patients should be observed continuously during each infusion. Patients should continue to be observed for two hours following infusion completion for the first two infusions and one hour for subsequent infusions.

Infusion-related reactions (IRR)

IRR and hypersensitivity reactions have been reported, with the majority being mild to moderate in severity. Discontinue administration if a severe IRR, anaphylactic reaction, or other severe reaction occurs, and institute appropriate treatment. If a mild to moderate IRR occurs, the infusion rate can be slowed or interrupted and appropriate treatment initiated. Consider pre-treatment prior to the next infusion for patients with a history of mild to moderate IRR to vedolizumab.

Highlights of prescribing information

Infections
Entyvio® treatment is not to be initiated in patients with active, severe infections until the infections are controlled. Consider withholding in patients who develop a severe infection while on treatment with Entyvio®. Before initiating treatment, patients must be screened for TB. If latent TB is diagnosed, anti-tuberculosis appropriate treatment must be initiated prior to Entyvio® treatment.
Progressive Multifocal Leukoencephalopathy (PML)
No cases of PML were reported in clinical studies of vedolizumab however, healthcare professionals should monitor patients on vedolizumab for any new onset or worsening of neurological signs and symptoms, and consider neurological referral if they occur. If PML is suspected, treatment with vedolizumab must be withheld; if confirmed, treatment must be permanently discontinued.
Malignancies
The risk of malignancy is increased in patients with ulcerative colitis and Crohn's disease. Immunomodulatory medicinal products may increase the risk of malignancy. Overall, results from the clinical program to date do not suggest an increased risk for malignancy with vedolizumab however, the number of malignancies was small and long-term exposure was limited.
Prior and concurrent use of biological products
No vedolizumab clinical trial data are available for patients previously treated with natalizumab or rituximab. Caution should be exercised when considering the use of Entyvio® in these patients. Patients previously exposed to natalizumab should normally wait a minimum of 12 weeks prior to initiating therapy with Entyvio®. Entyvio® not recommended for concomitant use with biologic immunosuppressants as no clinical data are available.
Live and oral vaccines
Patients recommended to be up-to-date with all appropriate immunisations prior to initiating Entyvio®. Live vaccines may be administered concurrently only if benefit clearly outweighs risk. Patients may continue to receive non-live vaccines.
Interactions
No interaction studies have been performed. Concomitant administration of corticosteroids, immunomodulators (azathioprine, 6-mercaptopurine, and methotrexate) and aminosalicylates did not have a clinically meaningful effect on Entyvio® pharmacokinetics.
Fertility, pregnancy and lactation
Women of childbearing potential are strongly recommended to use adequate contraception to prevent pregnancy and to continue its use for at least 18 weeks after the last treatment with Entyvio®.
There are limited amount of data from the use of vedolizumab in pregnant women.
Entyvio® is to be used during pregnancy only if the benefits clearly outweigh any potential risk to both the mother and foetus.
Because maternal antibodies (IgG) are excreted in breast milk, it is recommended that a decision be made whether to discontinue breast-feeding or to discontinue/abstain from Entyvio® therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.
There are no data on the effects of vedolizumab on human fertility. Effects on male and female fertility have not been formally evaluated in animal studies.
Undesirable Effects
Very Common (≥1/10): nasopharyngitis, headache, arthralgia.
Common (≥1/100 to <1/10): bronchitis, gastroenteritis, URTI, influenza, sinusitis, pharyngitis, paraesthesia, hypertension, oropharyngeal pain, nasal congestion, cough, anal abscess, anal fissure, nausea, dyspepsia, constipation, abdominal distension, flatulence, haemorrhoids, rash, pruritis, eczema, erythema, night sweats, acne, muscle spasm, back pain, muscular weakness, fatigue, pain in the extremity, pyrexia.
For further information, please refer to the full prescribing information as approved by the Israeli MOH 2/2019

טקדה ישראל בע"מ, אפעל 25, קריית אריה, פתח תקוה, 4951125, טלפון: 40