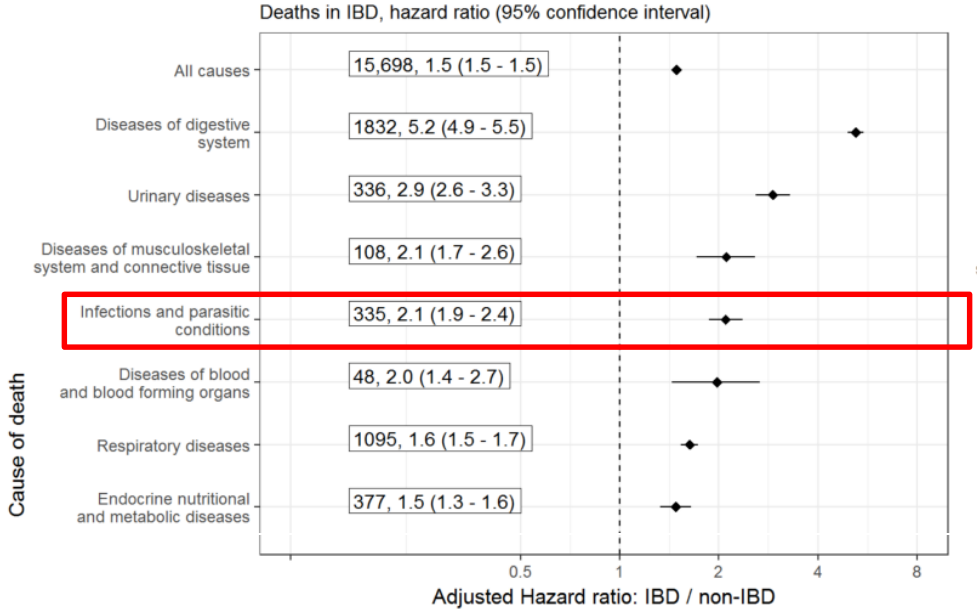


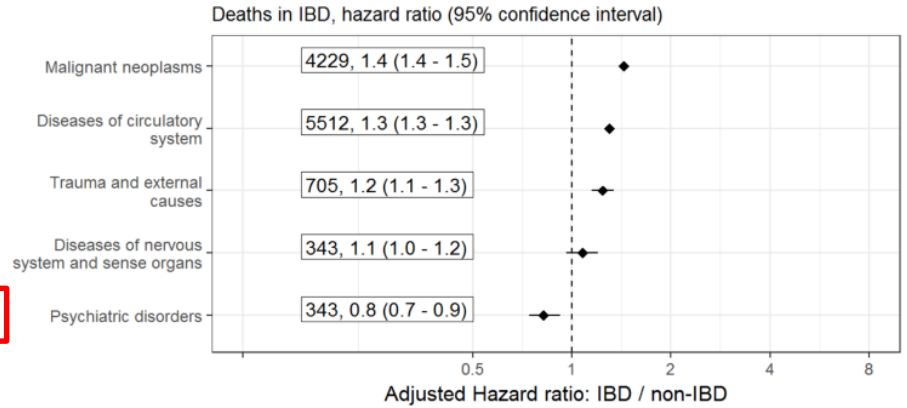
Veiligheid van biologische therapieën: infecties en Leuvense data rond vaccinaties

Marc Ferrante MD PhD
Dienst Maagdarmleverziekten

Mortality in IBD

- Swedish nationwide register-based cohort study 1964-2014
- 82718 incident IBD cases and 801180 matched reference individuals





Olén O, *Gut* 2019

Infection-related hospitalizations in IBD

- Nationwide USA hospitalization database
  - 67221 infection-related hospitalizations in IBD patients in 2007
    - ➔ 27.5% of all IBD hospitalizations
    - ➔ Associated with an estimated 2.3 days excess hospital stay
    - ➔ Associated with a 4-fold greater mortality: Odds ratio 4.4 (95% CI 3.7-5.2)

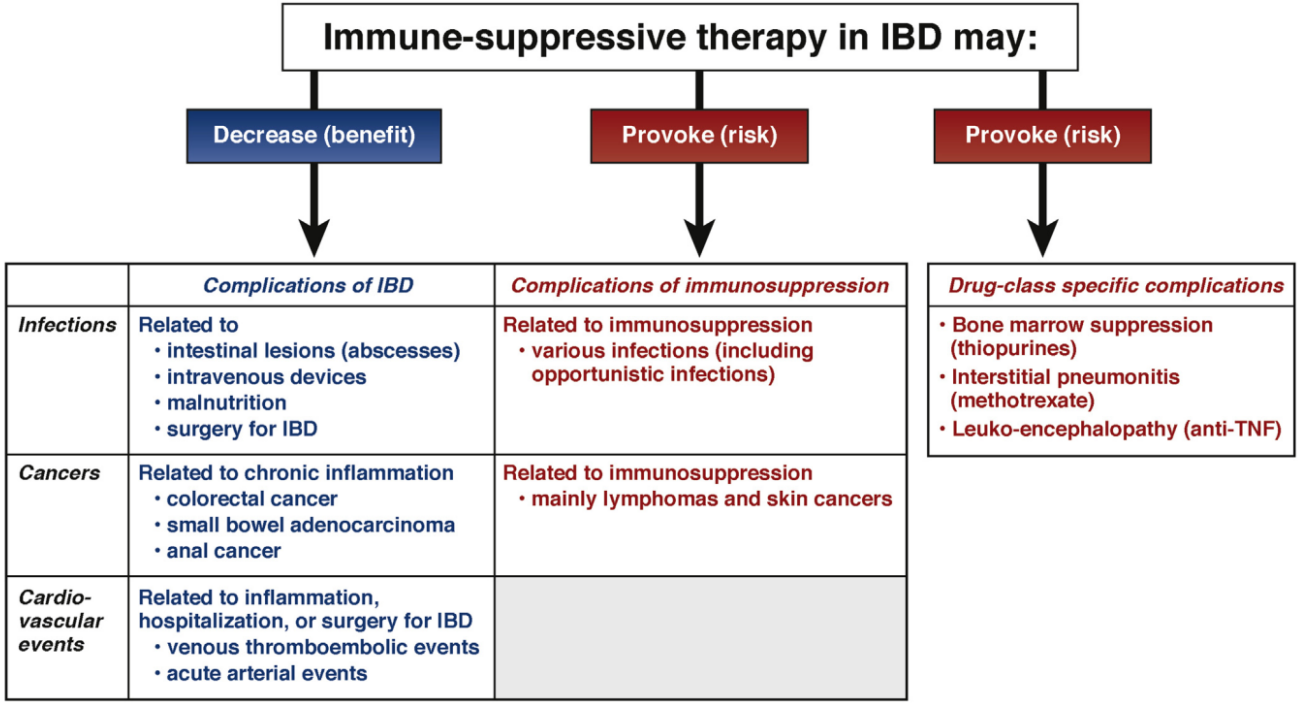
      Sepsis: Odds ratio 15.3 (95% CI 12.4-18.6)

      Pneumonia: Odds ratio 3.6 (95% CI 2.9-4.5)

      Clostridium difficile: Odds ratio 3.2 (95% CI 2.6-4.0)
    - ➔ Infections were independently associated with age, co-morbidity, malnutrition, TPN and bowel surgery



Infectious complications due to IBD or IBD therapy?



	Complications of IBD	*Complications of immunosuppression*	*Drug-class specific complications*
Infections	Related to • intestinal lesions (abscesses) • intravenous devices • malnutrition • surgery for IBD	Related to immunosuppression • various infections (including opportunistic infections)	• Bone marrow suppression (thiopurines) • Interstitial pneumonitis (methotrexate) • Leuko-encephalopathy (anti-TNF)
Cancers	Related to chronic inflammation • colorectal cancer • small bowel adenocarcinoma • anal cancer	Related to immunosuppression • mainly lymphomas and skin cancers	
Cardio-vascular events	Related to inflammation, hospitalization, or surgery for IBD • venous thromboembolic events • acute arterial events		

Beaugerie L, *Clin Gastroenterol Hepatol* 2019

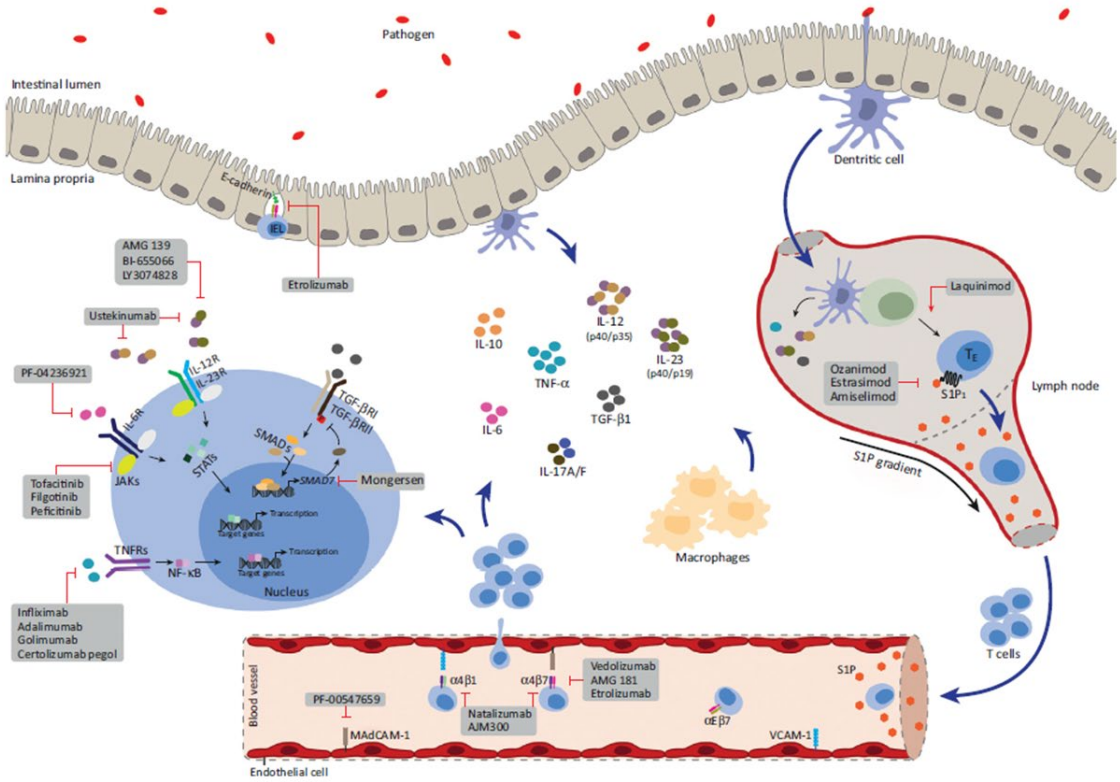
Safety plays a major role in treatment selection

Anti-IL23

Anti-IL12/23

Anti-JAK

Anti-TNF



S1PR agonists

Anti-integrin

Coskun M, *Trends Pharmacol Sci* 2017

Safety plays a major role in treatment selection

Your physician has proposed treatment with a targeted anti-inflammatory drug. This leaflet will give you an overview of the various anti-inflammatory therapies.

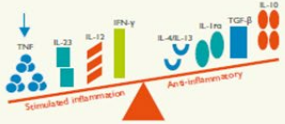
REQUIRED PRELIMINARY EXAMINATIONS IN ORDER TO EXCLUDE TUBERCULOSIS:

✗ X-ray of the lungs ✗ Mantoux test or QuantiFERON test

ANTI-TNF

OPERATING MECHANISM

These are proteins or antibodies that block the excess production of TNF. This way they can reduce the inflammation process that is one of the causes of the disease.



ONSET OF ACTION AND ADMINISTRATION

Days to weeks



INFLIXIMAB (Flixabi®, Inflectra®, Remicade® and Remsima®) If necessary combined with Imuran®, Purinethol®, Ledertrexate® or Metoject®.



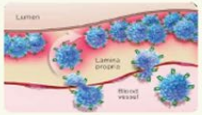
ADALIMUMAB (Amgevita®, Hulio®, Humira®, Hyrimoz®, Imraldi®)

POTENTIAL SIDE EFFECTS

Allergic reactions (including infusion reactions), arthralgia, dry skin, more prone to infections (cold, bronchitis, sinusitis …)

ANTI-ADHESION

These are proteins or antibodies that prevent white blood cells from travelling out of the blood vessels into the surrounding tissue, and this selectively in the gut area.



ONSET OF ACTION AND ADMINISTRATION

Weeks to three months



VEDOLIZUMAB (Entyvio®)

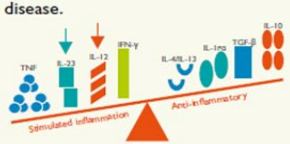
POTENTIAL SIDE EFFECTS

Possible more gastrointestinal infections, but other than that practically no side effects as a result of bowel selectivity.

ANTI-IL12/23

OPERATING MECHANISM

These are proteins or antibodies that block the excess production of interleukin 12 and interleukin 23. This way, they reduce the inflammation process which is one of the causes of the disease.



ONSET OF ACTION AND ADMINISTRATION

Weeks



USTEKINUMAB (Stelara®)#

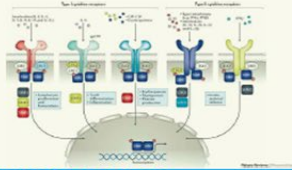
POTENTIAL SIDE EFFECTS

Infections of the upper airways (limited available data)

ANTI-JAKs

OPERATING MECHANISM

This oral therapy is blocking one or more JAK proteins. By blocking these JAKs the production of several pro-inflammatory proteins (interleukins) will be reduced.



ONSET OF ACTION AND ADMINISTRATION

Days to weeks

Induction dose

2 x 1 tablet of 10 mg, during 8 weeks

Maintenance dose

2 x 1 tablet of 5 mg

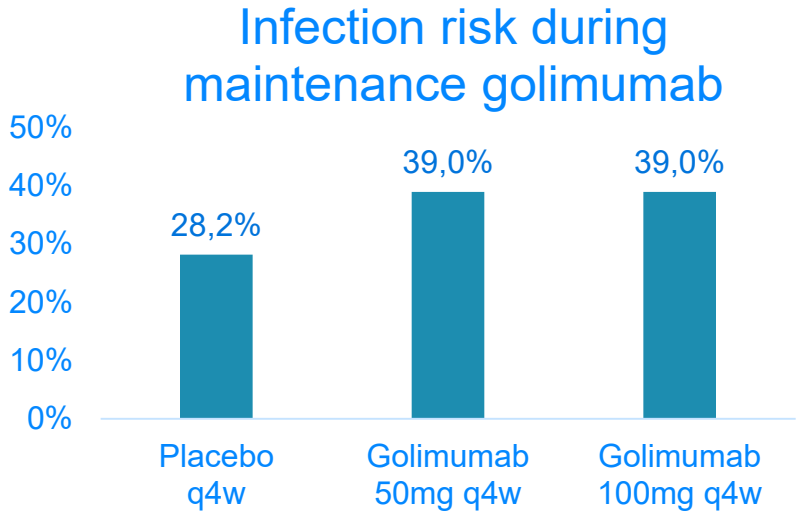
TOFACITINIB (Xeljanz®)*

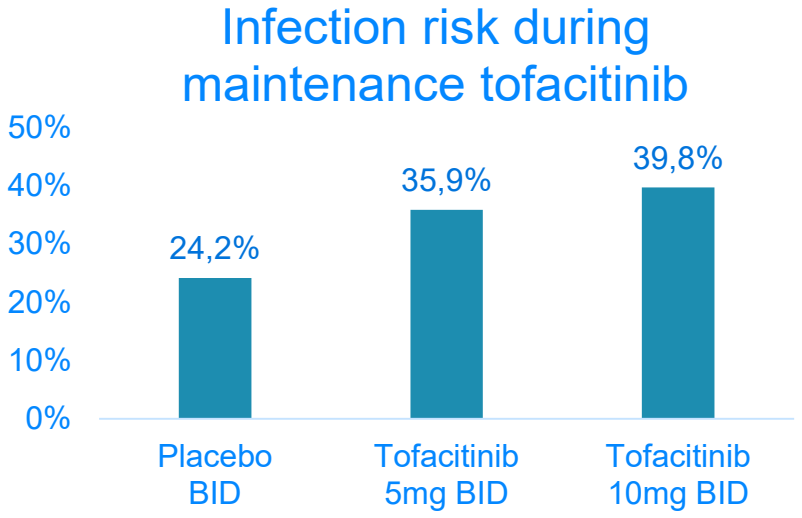
POTENTIAL SIDE EFFECTS

Infections (mainly viral), increased cholesterol, increased CKs, thrombosis in patients with a cardiovascular risk profile.

Infection risk in randomized controlled trials for IBD

- No link with the use of infliximab, adalimumab and certolizumab pegol
- No link with the use of vedolizumab
- No link with the use of ustekinumab





Sandborn WJ, *Gastroenterology* 2014; Sandborn WJ, *N Engl J Med* 2017

Safety should be assessed beyond clinical trials

- Randomized controlled trials (RCTs) only pick up frequent side effects:
  - Modern trial design eliminates the denominator: few patients receive only placebo
  - The size and duration of RCTs does not allow to assess long term safety
  - Patients have been highly selected at study entry

- Examples of important side effects that appeared after approval
  - Risk of tuberculosis reactivation with anti-TNFs
  - Risk of melanoma skin cancer with anti-TNFs
  - Risk of John Cunningham (JC) viral progressive multifocal leukoencephalopathy with natalizumab and sphingosine-1 phosphate receptor agonists



Pooled analyses of clinical trials in IBD

- 49 randomized placebo-controlled trials reporting adverse events
  - 47 trials including 14439 patients reporting any infections
    - ➔ Use of biologics: Odds ratio 1.19 (95% CI 1.10-1.29)
    - ➔ Use of anti-TNF: Odds ratio 1.21 (95% CI 1.10-1.33)
    - ➔ Use of anti-integrin: Odds ratio 1.14 (95% CI 0.99-1.32)



Bonovas S, *Clin Gastroenterol Hepatol* 2016

Pooled analyses of clinical trials in IBD

- 49 randomized placebo-controlled trials reporting adverse events
  - 24 trials including 8832 patients reporting opportunistic infections: *Mycobacterium tuberculosis*, JC virus infection, *Nocardia* infection, cytomegalovirus or Epstein-Barr virus infection, oral or esophageal candidiasis, varicella-zoster virus infection, herpes zoster infection, *Pneumocystis jirovecii* infection, *Histoplasma capsulatum* infection, *Legionella*-induced pneumonia, herpes simplex infection, or other unspecified opportunistic infection
    - ➔ Use of biologics: Odds ratio 1.90 (95% CI 1.21-3.01)
    - ➔ Use of anti-TNF: Odds ratio 1.89 (95% CI 1.15-3.12)
    - ➔ Use of anti-integrin: Odds ratio 1.99 (95% CI 0.64-6.18)



Bonovas S, *Clin Gastroenterol Hepatol* 2016

Pooled analyses of clinical trials in IBD

- 49 randomized placebo-controlled trials reporting adverse events
  - 44 trials including 14032 patients reporting serious infections: infections associated with hospital admission, use of intravenous antibiotics, or death
    - ➔ Use of biologics: Odds ratio 0.89 (95% CI 0.71-1.12)
    - ➔ Use of anti-TNF: Odds ratio 0.90 (95% CI 0.69-1.17)
    - ➔ Use of anti-integrin: Odds ratio 0.87 (95% CI 0.54-1.39)



Bonovas S, *Clin Gastroenterol Hepatol* 2016

Pooled analyses of clinical trials in RA

- 106 randomized placebo-controlled trials reporting adverse events
  - 106 trials including 42330 patients reporting serious infections: infections associated with hospital admission, use of intravenous antibiotics, or death

➔ Low dose biologics:

Odds ratio 0.93 (95% CI 0.65-1.33)

➔ Standard dose biologics:

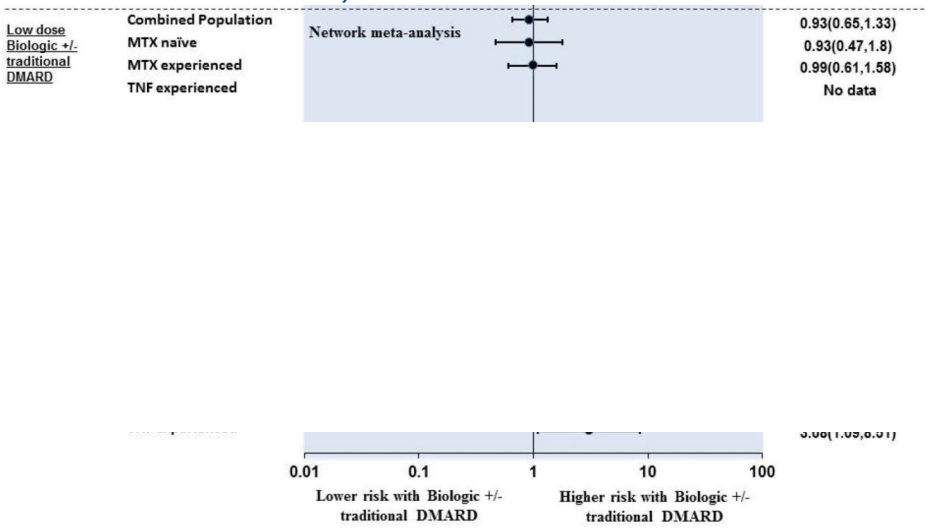
Odds ratio 1.31 (95% CI 1.09-1.58)

➔ High dose biologics:

Odds ratio 1.90 (95% CI 1.50-2.39)

➔ Combination of biologics:

Odds ratio 4.14 (95% CI 1.87-9.05)



Singh JA, *Lancet* 2015

Registries on the safety of anti-TNF agents in IBD

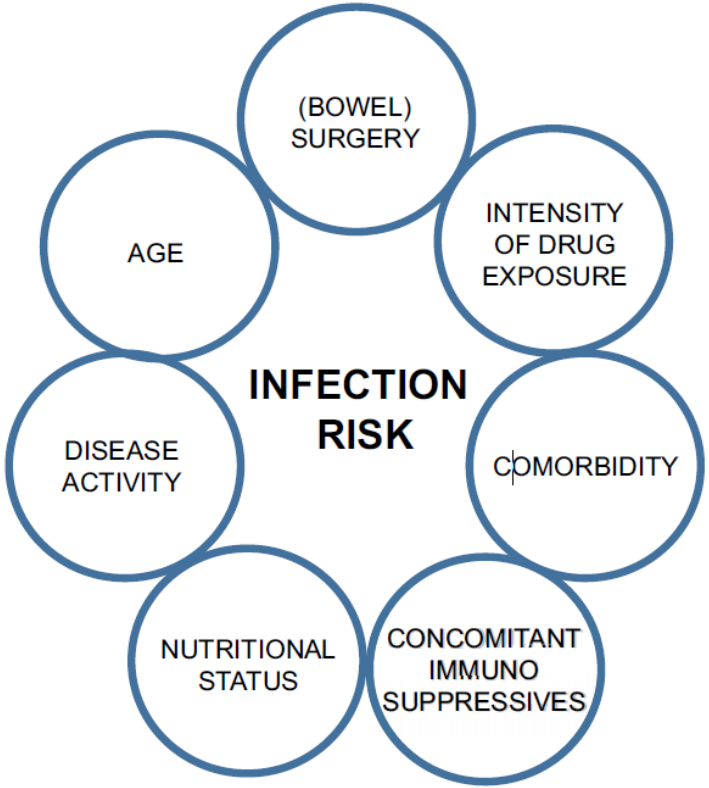
Registry	Population	Risk of serious infections
ENCORE	IFX: n=1839 No IFX: n=1121	Odds ratio 1.64 (95% CI 1.17-2.31)
TREAT	IFX: n=3440 No IFX: n=2833	Odds ratio 2.46 (95% CI 1.80-3.36)
PYRAMID	ADM: n=5025 16680 patient years	4.7 events per 100 patient years

- Major confounders: age, disease duration, disease severity, concomitant therapy (prednisone, immunomodulator), narcotic use



D'Haens G, *J Crohns Colitis* 2016; Lichtenstein GR, *Inflamm Bowel Dis* 2018; D'Haens G, *Am J Gastroenterol* 2018

Many confounding factors



Hindryckx P S, *Clin Pharmacol Ther* 2017

Concomitant medication as a confounding factor

	Incidence rate (cases per 1000 person-years) in total IBD population	Adjusted HR (95% CI) in patients with IBD exposed to immunosuppressive therapy versus those not exposed to immunosuppressive therapy		
		Thiopurines alone	Anti-TNF agents alone	Thiopurines in combination with anti-TNF agents
Benign infections				
Overall	ND	ND	ND	ND
Zoster[a]	7.6	1.5 (1.3–3.7)	1.2 (0.9–1.4)	1.7 (1.2–2.2)
Serious infections	9.8[b]	1.3 (1.2–1.4)[b]	1.6 (1.0–2.6)[c]	2.8 (2.4–3.2)[b]
Opportunistic infections				
Overall[b]	0.8	3.7 (3.0–4.6)	4.0 (3.1–5.3)	7.9 (5.40–11.4)
Viral[b]	0.3	9.0 (6.6–12.3)	5.2 (3.2–8.3)	10.2 (5.5–19.0)
Bacterial[b]	0.2	1.9 (1.1–3.3)	4.5 (2.7–7.4)	9.0 (4.5–18)
Fungal	0.2[d]	1.5 (0.7–3.6)[b]	1.9 (0.8–4.8)[b]	1.5 (0.4–5.7)[b]
Infection-related mortality	0.4[b]	ND	ND	ND



Beaugerie L, *Clin Gastroenterol Hepatol* 2019

Concomitant medication as a confounding factor

TABLE 3: Predictors of Time to First Serious Infection—All Patients (Using Exposure Any Time After Registration)

Risk Factors	Adjusted Hazard Ratios (95% CI)	*P* Value*
Age 31 to ≤41 vs ≤30 y	0.704 (0.482–1.028)	0.069
42 to vs ≤30 y	0.861 (0.591–1.255)	0.437
>52 vs ≤30 y	1.316 (0.907–1.910)	0.148
Sex: female vs male/unknown	1.020 (0.802–1.299)	0.870
Race: Caucasian vs other/unknown	0.735 (0.495–1.091)	0.126
Diseased area:[a] ileum only vs ileum and colon	0.845 (0.637–1.120)	0.241
Diseased area:[a] colon only vs ileum and colon	0.760 (0.559–1.032)	0.079
Diseased area:[a] unknown vs ileum and colon	1.341 (0.487–3.691)	0.570
Years between diagnosis and enrollment	1.020 (1.008–1.032)	0.001
Severity:[b] mild vs remission	0.980 (0.736–1.304)	0.889
Severity:[b] moderate/severe vs remission	2.182 (1.531–3.109)	<0.001
Severity:[b] unknown vs remission	0.000 (0.000–8E222)	0.967
Infliximab vs no infliximab[c]	1.456 (1.131–1.874)	0.004
Prednisone vs no prednisone[c]	1.569 (1.175–2.097)	0.002
Immunomodulators vs no immunomodulators[c]	1.199 (0.941–1.528)	0.141
Narcotic analgesics vs no narcotic analgesics[c]	1.977 (1.435–2.723)	<0.001

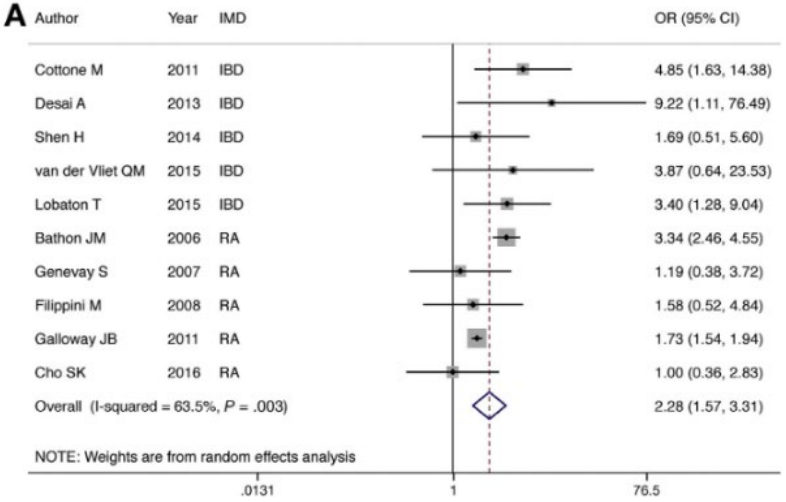


Lichtenstein GR, *Inflamm Bowel Dis* 2018

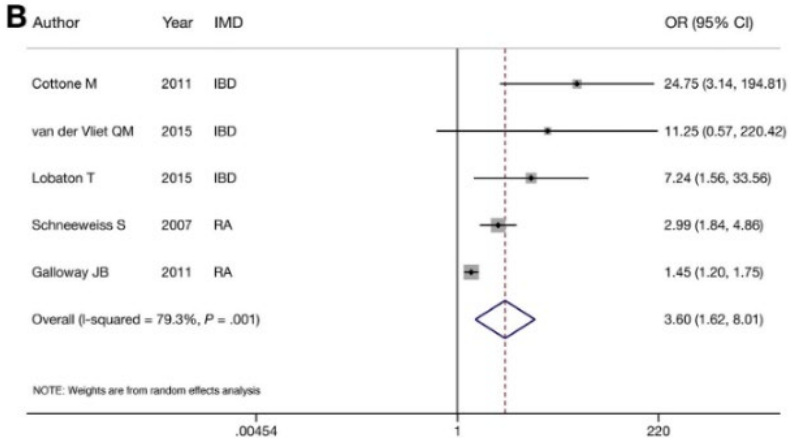
Age as a major confounding factor

- Meta-analysis including 14 unique (mostly retrospective) studies
  - Pooled infection risk among older IMID patients on any type of biological

Compared to younger IMID patients on biologicals
Odds ratio 2.28 (95% CI 1.57-3.31)



Compared to older IMID patients not on biologicals
Odds ratio 3.60 (95% CI 1.62-8.01)



Borren NZ, *Clin Gastroenterol Hepatol* 2019

Tuberculosis

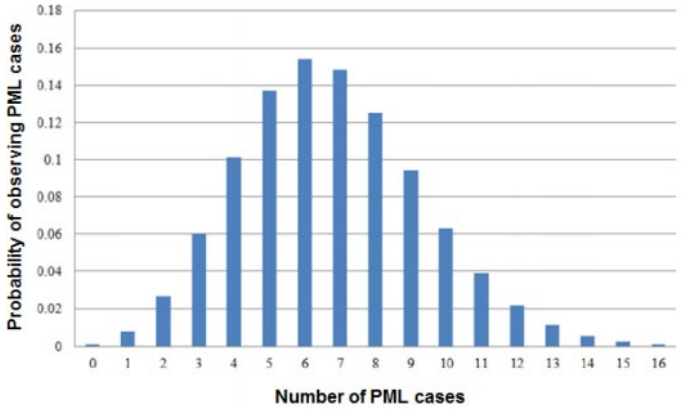
- Patients should be screened for latent tuberculosis before starting immunosuppression.
  - Tuberculosis reactivation is a risk for patients on anti-TNF.
  - But also for patients on glucocorticoids, leflunomide, teriflunomide, mitoxantrone and alemtuzumab.
  - The Food and Drug Administration (FDA) suggests tuberculosis screening also before starting ustekinumab or vedolizumab, until the risk is clearly settled.



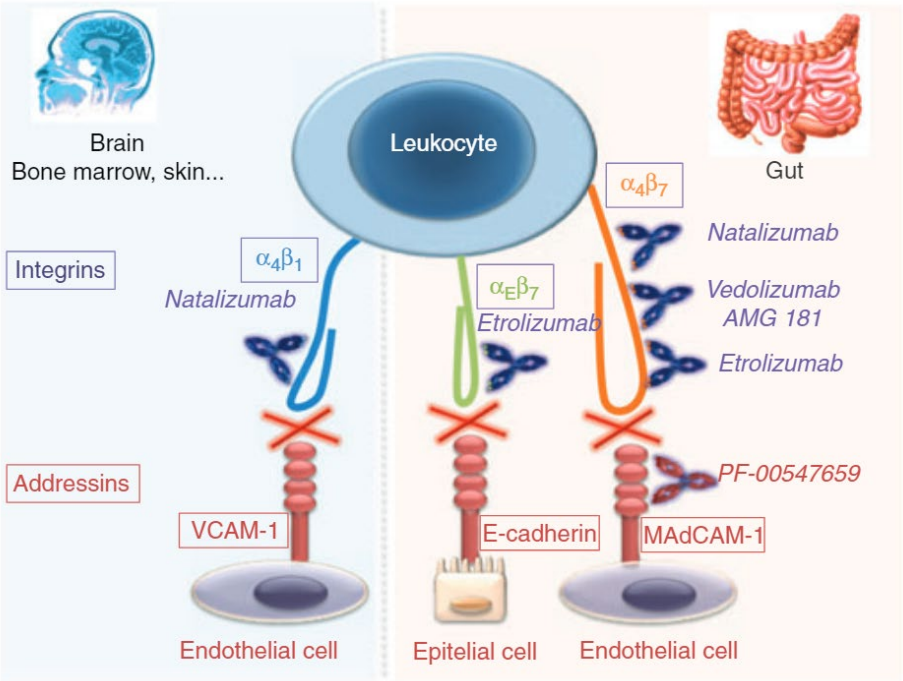
Abreu C, *Dig Liver Dis* 2017

Progressive multifocal leucoencephalopathy

- Vedolizumab
  - Neurological symptoms in 10%
  - No confirmed PML cases



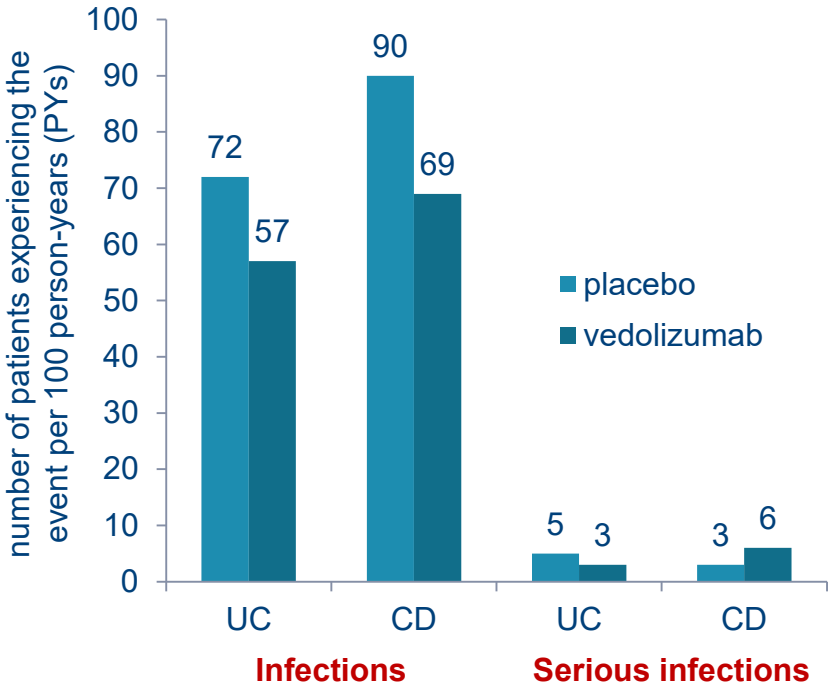
If risk were similar to that of natalizumab



Colombel J-F, *Gut* 2017

The safety of vedolizumab for IBD

- Exposure-adjusted incidence rates (2932 patients, up to 5 years)



Side effect	VDZ (n=2830)	PBO (n=504)
Any serious infection	4,3	3,8
Gastroenteritis	0,4	0,0
Abscess	1,4	1,4
Clostridial infection	0,3	0,0
Candida, tinea and other fungal infections	0,1	0,0
Sepsis	0,2	0,9
Tuberculosis	0,1	0,0
Cytomegalovirus infections	0,1	0,0
Meningitis	<0,1	0,0
Salmonella infections	<0,1	0,0

Colombel J-F, *Gut* 2017

The safety of ustekinumab

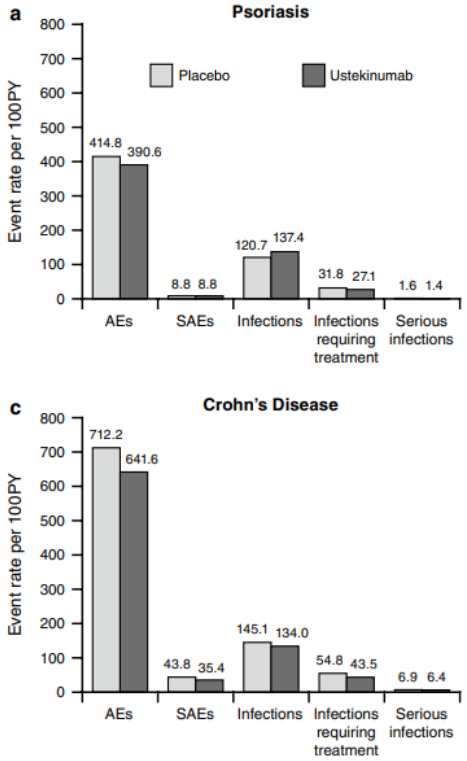
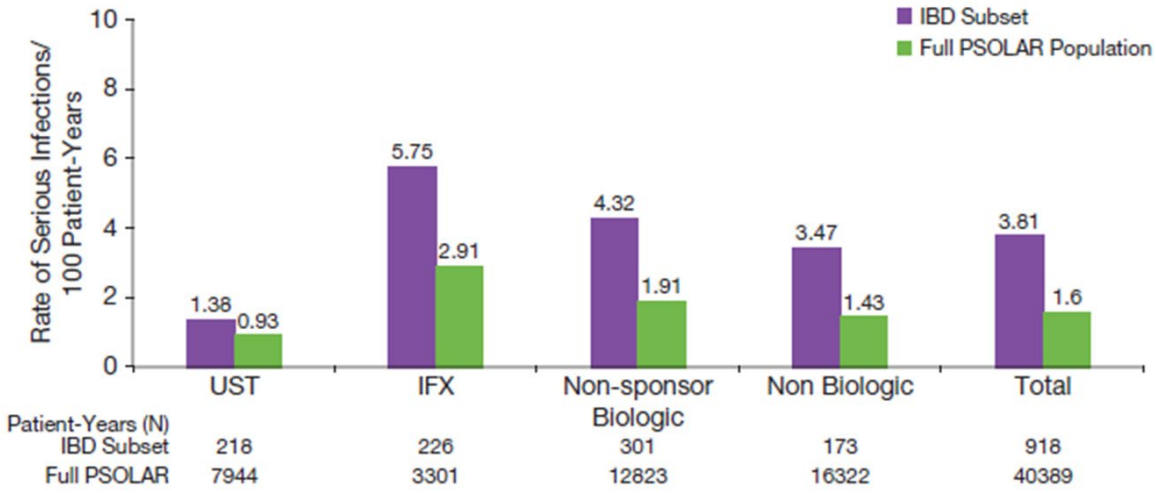


Figure 3. Rates of Serious Infections per 100 Patient-Years Within 91 Days of Biologic Administration



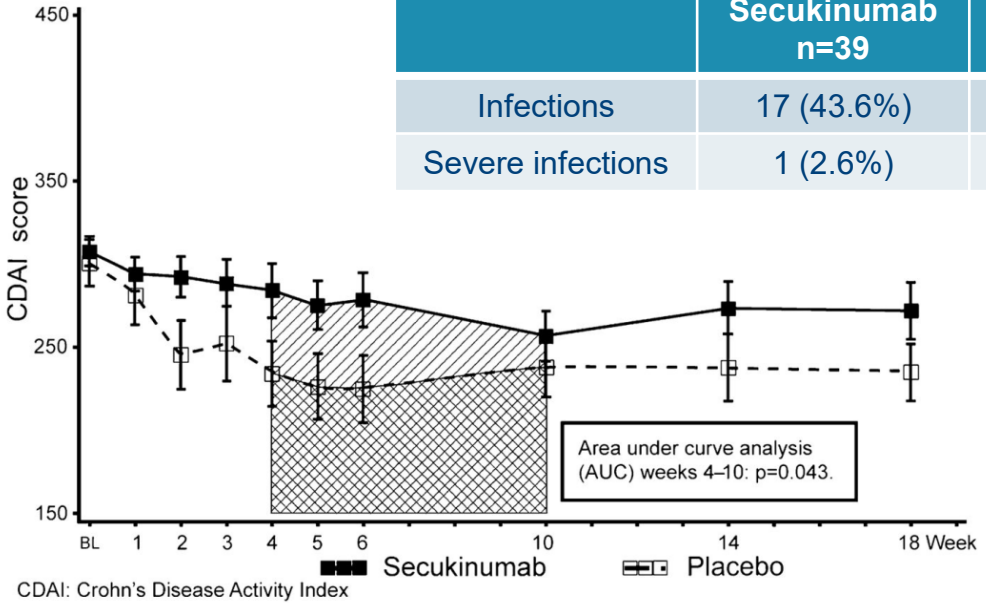
Patient-Years (N)	UST	IFX	Non-sponsor Biologic	Non Biologic	Total
IBD Subset	218	226	301	173	918
Full PSOLAR	7944	3301	12823	16322	40389

Ghosh S, *Drug Saf* 2019; Loftus EV, *ECCO* 2016

Anti-IL17 treatment in IBD

- Secukinumab for Crohn's disease

	Secukinumab n=39	Placebo n=20
Infections	17 (43.6%)	0 (0%)
Severe infections	1 (2.6%)	0 (0%)

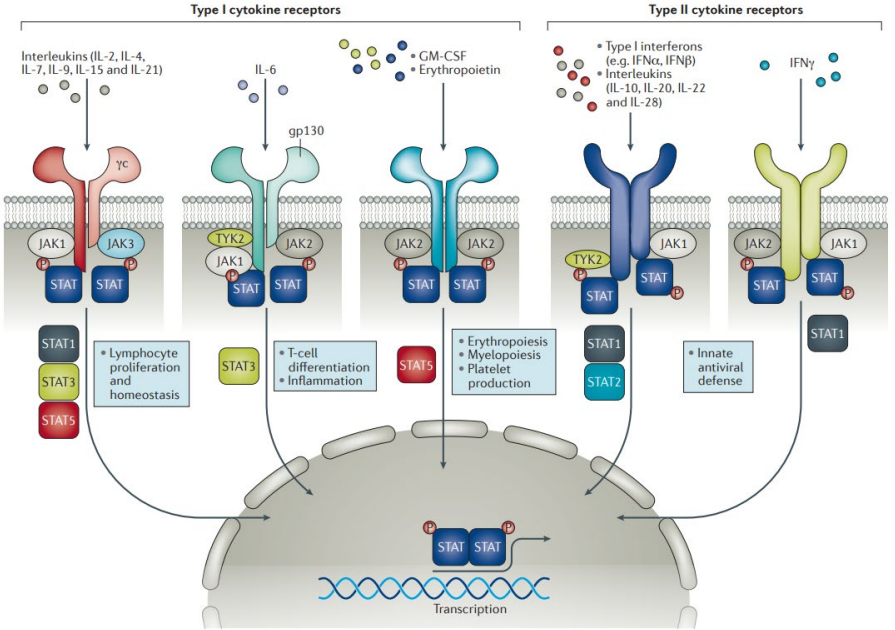


CDAI: Crohn's Disease Activity Index

Hueber W, *Gut* 2012

The safety profile of JAK inhibitors

- Incidence rate of serious infections similar between tofacitinib and TNF blockers or other biologic agents.
- An increased risk of viral infections (particularly herpes zoster) seems to distinguish the safety profile of tofacitinib from that of biologic agents.



Winthrop KL, *Nat Rev Rheumatol* 2017

The safety profile of JAK inhibitors

- Crude incidence rates of herpes zoster (HZ) in RA

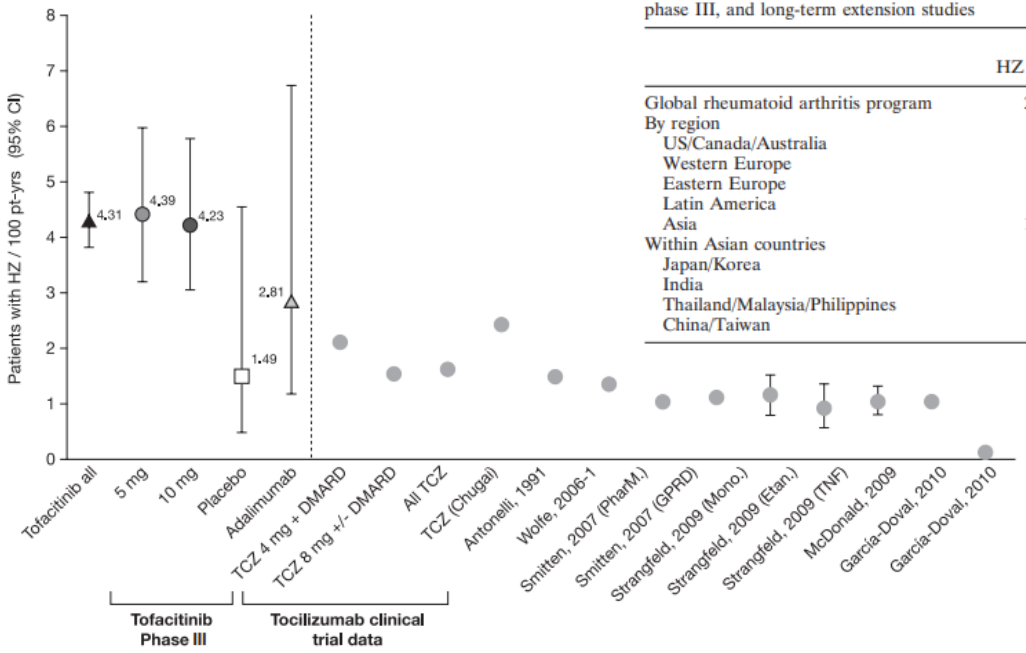


Table 4. Crude incidence rates of HZ overall and by geographic region of enrollment in the phase II, phase III, and long-term extension studies

	HZ events	Patient-years of exposure	HZ incidence rate (95% CI)*
Global rheumatoid arthritis program	239	5,482	4.4 (3.8–4.9)
By region			
US/Canada/Australia	40	1,216	3.3 (2.4–4.5)
Western Europe	12	450	2.7 (1.5–4.7)
Eastern Europe	43	1,425	3.0 (2.2–4.1)
Latin America	37	991	3.7 (2.7–5.2)
Asia	107	1,388	7.7 (6.4–9.3)
Within Asian countries			
Japan/Korea	85	920	9.2 (7.5–11.4)
India	8	90	8.9 (4.4–17.7)
Thailand/Malaysia/Philippines	3	137	2.2 (0.7–6.8)
China/Taiwan	11	241	4.6 (2.5–8.2)

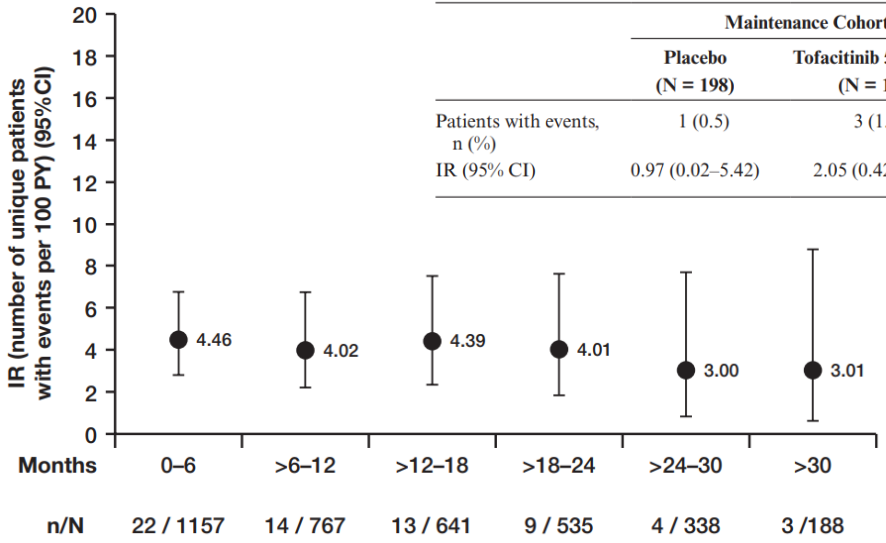
Winthrop KL, *Arthritis Rheumatol* 2014

The safety profile of JAK inhibitors

- Crude incidence rates of herpes zoster (HZ) in ulcerative colitis

TABLE 2: HZ IRs[a] by Dose Within the Maintenance (Phase III Maintenance) and Overall (Phase II/Phase III/OLE) Cohorts

	Maintenance Cohort (Phase III maintenance)			Overall Cohort (Phase II/Phase III/OLE)	
	Placebo (N = 198)	Tofacitinib 5 mg BID (N = 198)	Tofacitinib 10 mg BID (N = 196)	Tofacitinib 5 mg BID[a] (N = 186)	Tofacitinib 10 mg BID[b] (N = 971)
Patients with events, n (%)	1 (0.5)	3 (1.5)	10 (5.1)	12 (6.5)	53 (5.5)
IR (95% CI)	0.97 (0.02–5.42)	2.05 (0.42–6.00)	6.64 (3.19–12.22)	3.45 (1.78–6.02)	4.25 (3.18–5.56)



Winthrop KL, *Inflamm Bowel Dis* 2018

Prevention of infectious adverse events

Detailed interview
Infection history
Immunization status
Environmental risks

Poliomyelitis
Diphtheria Tetanus Pertussis
HPV

Tuberculosis screening



VZV
HBV +/- HAV
Yellow fever

Influenza
Pneumococcal

Laboratory tests
EBV, HAV, HBV, HCV,
HIV, (Measles), (VZV)

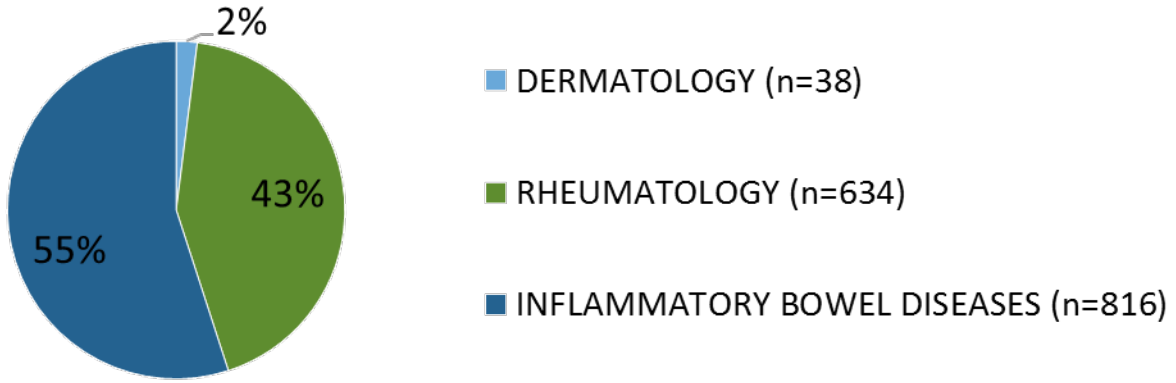
PJP prophylaxis



Rahier J-F, *J Crohns Colitis* 2014

Compliance to vaccination guidelines in UZ Leuven

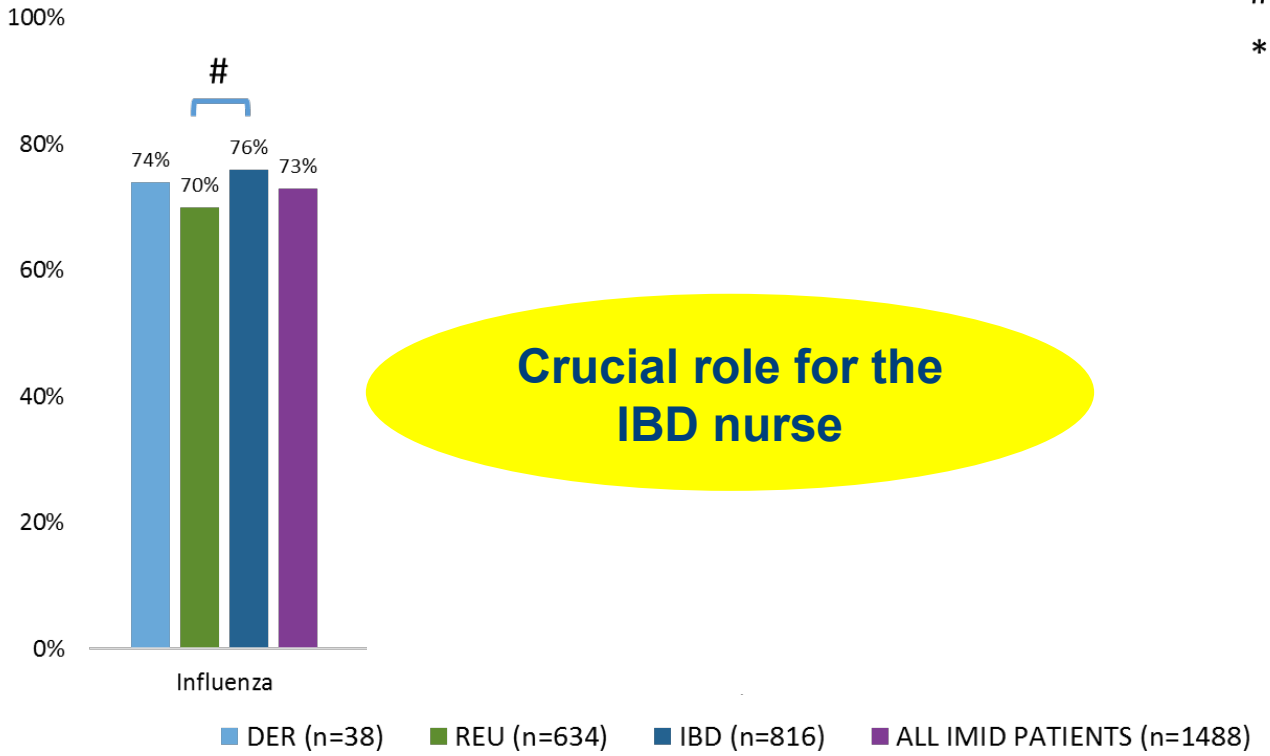
- Questionnaire on vaccination between Aug 2018 and Dec 2018
  - 1488 IMID patients were recruited



Compliance to vaccination guidelines in UZ Leuven

p=0.05

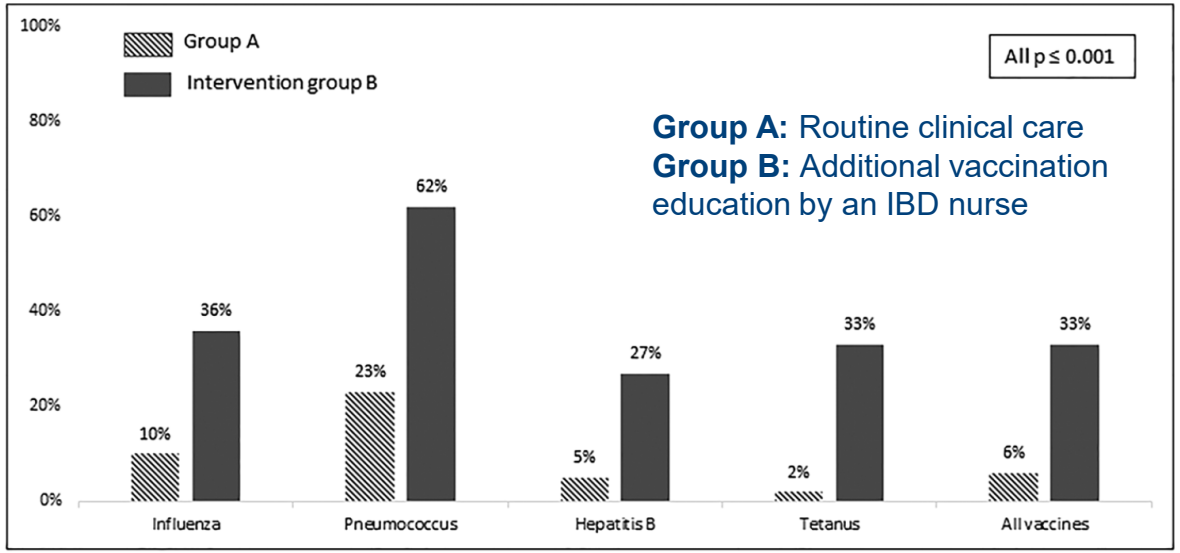
* p<0.001



Crucial role for the IBD nurse

Compliance to vaccination guidelines in UZ Leuven

- Vaccination rates 8 months after randomization

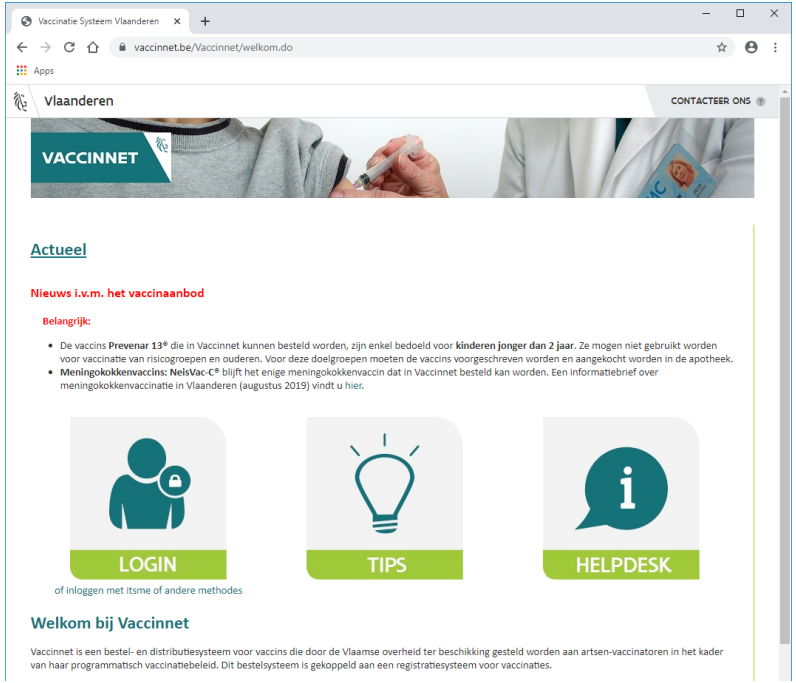


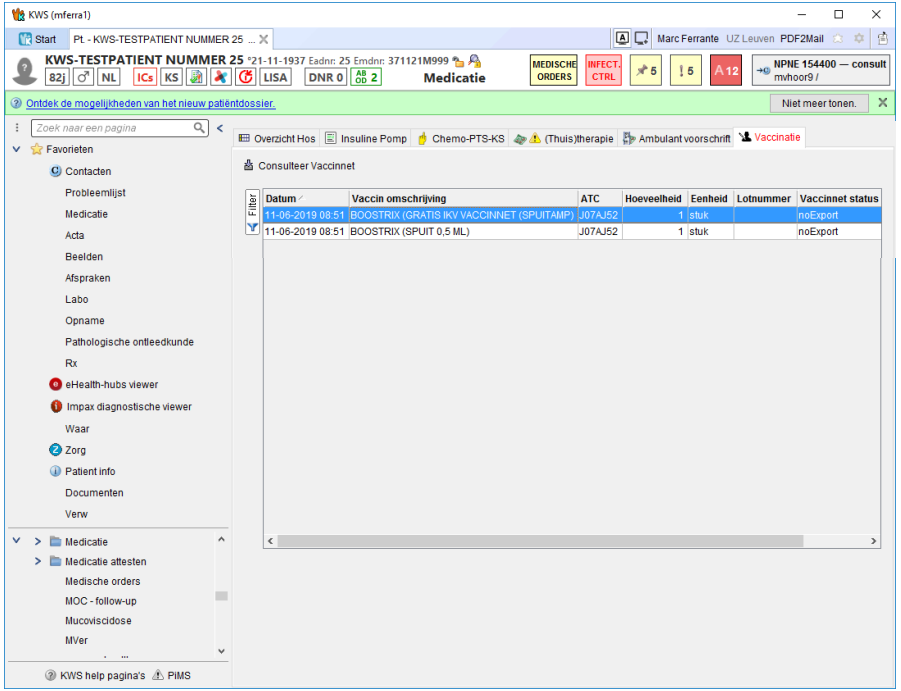
Group A	n = 5/52	n = 25/107	n = 7/151	n = 1/56	n = 13/206
Intervention group B	n = 18/50	n = 53/86	n = 24/89	n = 11/33	n = 46/140

Coenen S, *Inflamm Bowel Dis* 2017

Compliance to vaccination guidelines in UZ Leuven

- Role for Vaccinnet in improving vaccination rates





Conclusions

- Safety aspects should be taken into account when selecting appropriate therapy for an individual patient
- Indirect evidence suggests a better safety profile of vedolizumab and ustekinumab compared to anti-TNF and anti-JAK agents
- Confounding factors make data interpretation more difficult
- Vaccinations should be discussed with the patient from diagnosis onwards (checklists are available)
- Compliance to vaccination guidelines should be ameliorated
- Vigilance towards opportunistic infections remains required



Thank you

