

# Toxicities Associated with IBD Therapies

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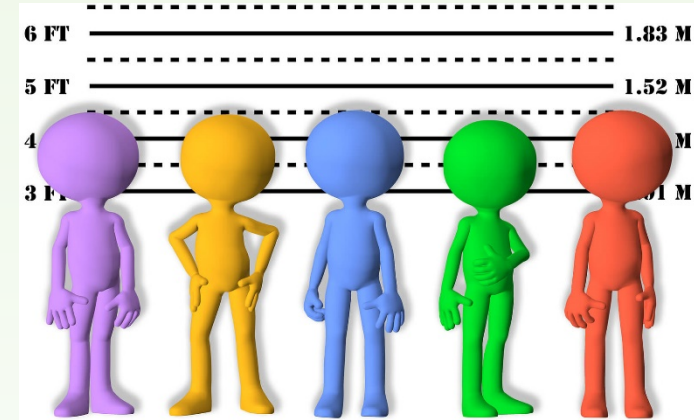


# Disclosures

- Janssen DSMB Member

# The usual suspects: Infections

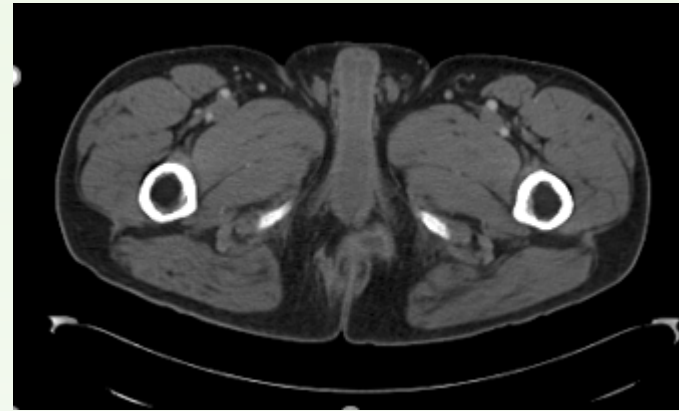
- Opportunistic infections
  - Tuberculosis
  - Listeriosis
  - Histoplasmosis
  - Coccidioidomycosis
- Chronic viral infections
  - HBV
  - CMV
  - VZV
  - C difficile



Queiroz N and Regiero M (2020) Curr Opin Gastroenterol 36:

# Case 1

- 49 year old male from India with small bowel and perineal Crohn's disease x 7 years
- Intermittent 6 MP
- Colonoscopy now with active ileo-colonic disease
- Presents now with severe perirectal pain and fistula tract on CT
- Discussed initiation of infliximab after drainage of abscess



**But**



# Risk factors for reactivation of TB

Disease	Relative Risk for Reactivation
AIDs	110 - 170
HIV Infection	50 - 110
Solid Organ Transplant	20 - 74
Chronic Renal Failure	10 - 25
<b>TNF alpha therapy</b>	1.7 - 9
<b>Glucocorticoid Therapy</b>	4.9
Diabetes	2 - 3.6
Under weight (BMI < 20)	2-3
Smoker (1 ppd)	2-3
Healthy Individual	1

Test for and treat latent TB before anti-TNF and before steroids  
Testing for TB recommended for all biologics

Lobue P and Menzies D (2010) Respirology 15:603-622

## Case 2

- 58 year old male
- Severe Crohn's perineal disease
- Well controlled on infliximab x 10 years
- Now with recurrent skin infections and rash around his feet, nails and glans of the penis



# Psoriasis and anti-TNF therapy

## EPIDEMIOLOGY

- Incidence 1.6 – 10% of patients treated with anti-TNF agents
- More common in Crohn's disease (90-96%) than ulcerative colitis (4-10%)
- Risk factors
  - Smoking (active or past)
  - Increased BMI
  - FH of inflammatory skin disease
  - Short disease duration
  - Women > Men

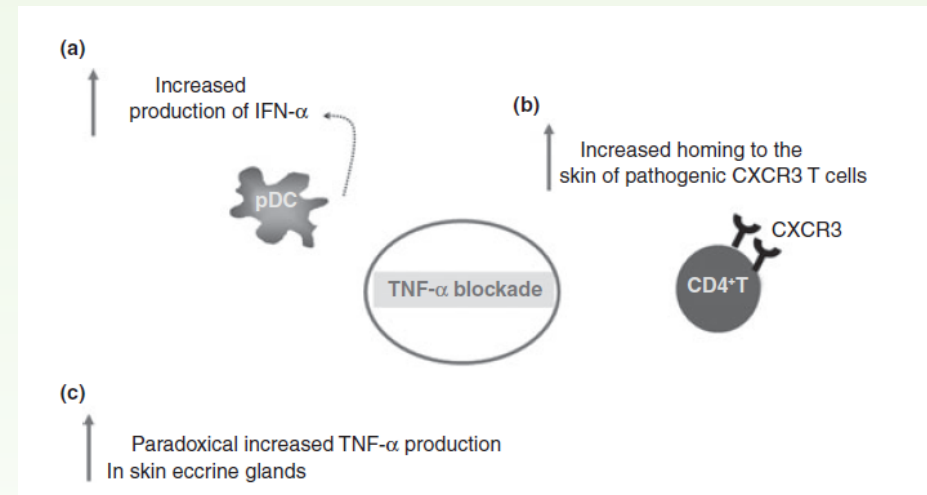
## CLINICAL

- Most common sites → hand/palm, feet/plantar, and flexures, scalp, genitalia
- ANA and ds DNA more common in patients with skin lesions
- Higher incidence of psoriasis and atopic dermatitis risk loci
- No difference in anti-TNF trough levels with and without skin lesions

Gravina et al (2016) United Eur Gastro J 4:165-171  
Freyling et al (2015) Am J Gastro 110:1186-1196  
Cleyner, I et al (2016) Ann Internal Med 164:10-22

# Possible Mechanism of Development of Psoriasis

- Balance between  $\text{IFN}\gamma$  and TNF
- $\text{IFN}\gamma$  is produced by the dermal plasmacytoid dendritic cells (DPDC) – this is an important cytokine for induction of psoriasis
- Blockade of  $\text{TNF}\alpha$  leads to uncontrolled production of  $\text{IFN}\gamma$



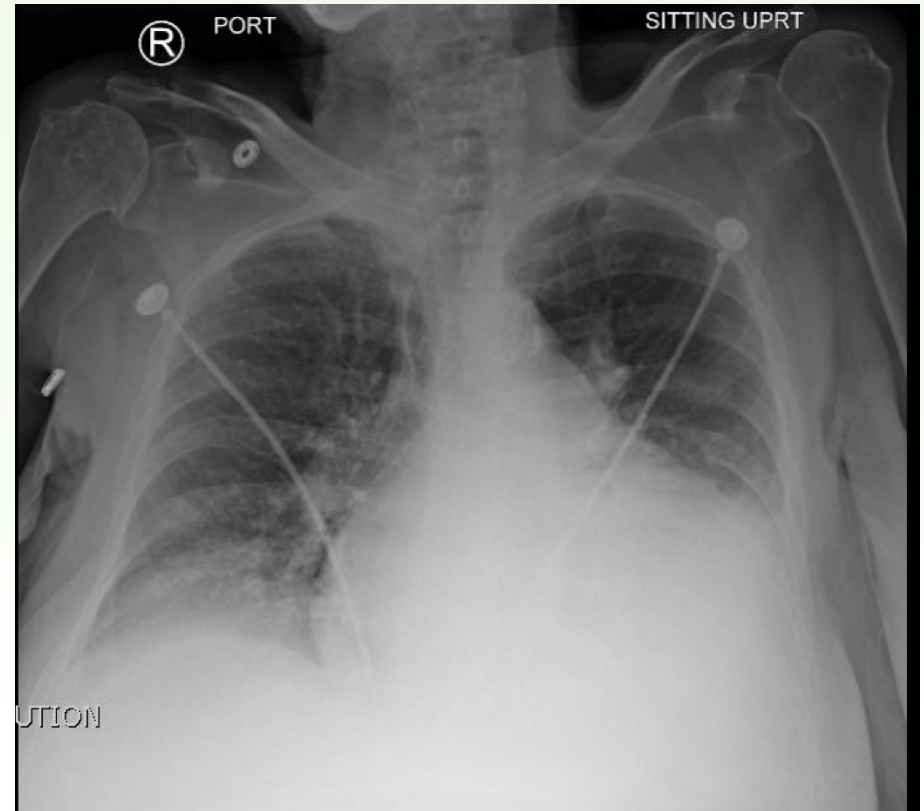
If mild psoriasis -> can use topical therapy  
If severe or non-responsive to topical therapy  
switch class of drug → ustekinumab effective  
for both IBD and psoriasis

Fiorino G et al (2009) Aliment Pharmacol Ther 29:921-927  
Mocci, G et al (2013) J Crohn's Colitis 7:769-729



# Case 3

- 81 year old woman with 10 years of ulcerative pan colitis
- Treated with mesalamine and steroids.
- Unable to taper steroids and continue activity while on steroids
- Biologic was added to her regimen
- Now presents with shortness of breath, poor exercise tolerance and difficulty laying flat to sleep



# What is this?

- Anti- TNF  $\alpha$  associated Congestive Heart Failure
  - TNF  $\alpha$  levels increased in CHF
  - Study using anti-TNF in patients with class II/IV hear failure → no clinical improvement and increased risk of death after 28 weeks
  - In Adalimumab registration trials – 32 new cases of CHF (0.3%) in patients with no medical history of CHF
  - PI – doses of infliximab > 5mg/kg contraindicated in patients with any class of heart failure and all doses are contraindicated in class III/IV heart failure.
  - Mixed results in terms of risk in population studies

Use different class of medication if known heart failure

Can use low dose cautiously in Class I/II heart failure if needed

Be aware if new symptoms of heart failure

Cole et al (2007) Rheum International 27:369-372  
Schiff et al (2006) Ann Rhuem Dis 65:889-894

# Case 4

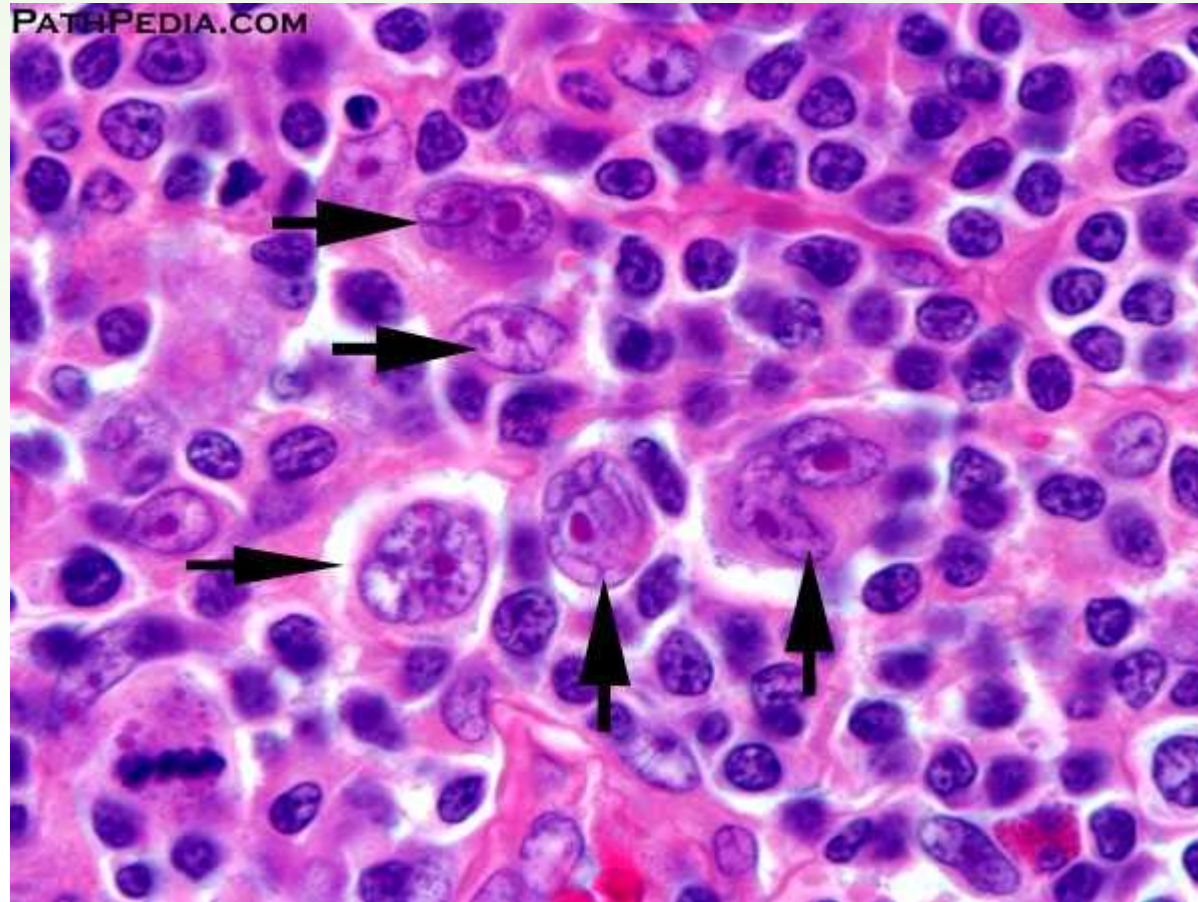
## CLINICAL

- 52 year old male with 30 year history of Crohn's colitis and peri-anal fistulas
- Multiple medications – anti-TNF, thiopurines, ustekinumab
- Subtotal colectomy age 38, completion colectomy age 51
- Presents with weight loss, night sweats, nausea and vomiting – 8 months after his completion colectomy and proctectomy

# Case 4



What do you think he has?

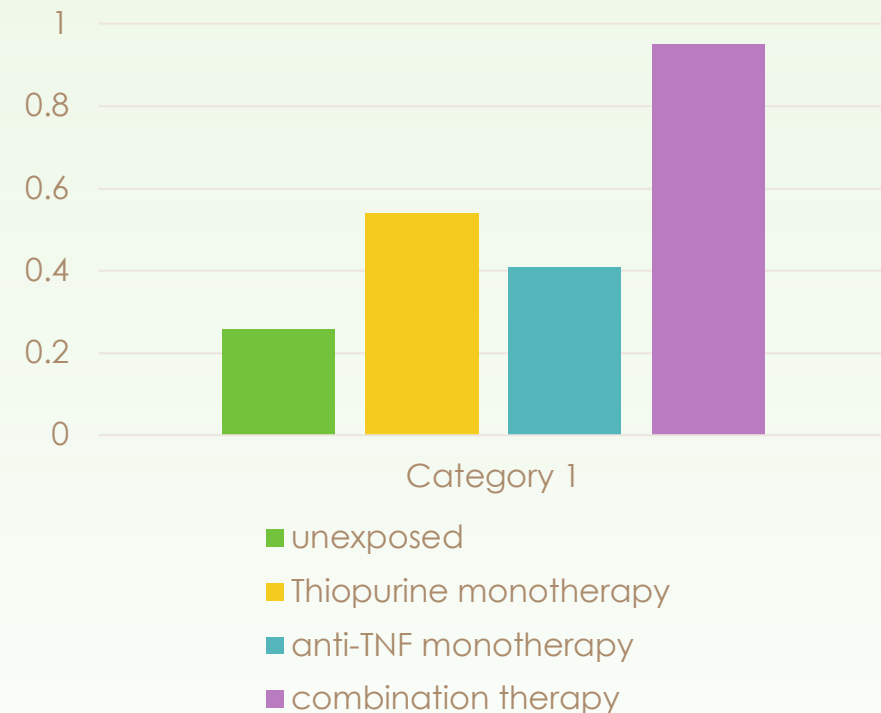


Pathopedia.com

# Lymphoma

- Nationwide cohort study – French National Health Insurance data bases.
- Patients 18 years and old with IBD
- Groups: thiopurine monotherapy, anti-TNF monotherapy, combination therapy and unexposed.
- 189,289 patients: 123,069 unexposed, 50,405 thiopurine monotherapy, 30,294 anti-TNF monotherapy, 14,229 combination therapy
- 2/3 of overall lymphomas see in patients not on thiopurines or anti-TNF therapy

Incidence Rate per 1000 PY



Thiopurine monotherapy or anti-TNF monotherapy were associated with a small but statistically significant increased risk of lymphoma that was higher in combination therapy

Lemaitre M et al (2017) 318:1679-1686

# Studies looking at Risk of Lymphoma

MEDICATION	REPORTED LYMPHOMA RISK
<p><b>THIOPURINES</b>            Kandiel, Gut 2005 (meta-analysis)            Beaugerie, Lancet 2009 (CESAME)            Kotlyar, CGH 2015 (meta-analysis)            Lamaitre M JAMA 2017 French Insurance cohort</p>	<p>SIR 4.06 (2.01-7.28)            SIR 6.5 (3.5-11.2)            SIR 4.92 (3.10 – 7.78)            aHR 2.60 (1.96-3.44)</p>
<p><b>ANTI-TNFs</b>            Siegel CA, CGH 2009 (meta-analysis)            Anderson NN, JAMA 2014            Lamaitre M JAMA 2017 French Insurance cohort</p>	<p>SIR 3.23 (1.5-6.9)            RR 1.07 (0.85-1.36)            aHR 2.41 (1.60-3.64)</p>
<p><b>THIOPURINES + ANTI-TNFs</b>            Herrinton Am J Gastro 2011            Beaugerie, Lancet 2009 (CESAME)            Lamaitre M JAMA 2017 French Insurance cohort</p>	<p>SIR 6.6 (4.4-8.8)            SIR 10.2 (1.2-36.9)            aHR 6.11 (3.46-10.8)</p>



# Risk of lymphoma is age dependent

**Table 3 Number Needed to Treat (Harm) to Cause 1 Additional Lymphoma per Year**

Age (y)	Lymphoma incidence	NNH if relative risk of lymphoma = 2	NNH if relative risk of lymphoma = 3	NNH if relative risk of lymphoma = 4	NNH if relative risk of lymphoma = 5	NNH if relative risk of lymphoma = 6
20–29	7.25	6897	4598	3448	2759	2299
30–39	9.45	5291	3527	2646	2116	1764
40–49	15.6	3205	2137	1603	1282	1068
50–59	29.9	1672	1115	836	669	557
60–69	59.0	848	565	424	339	283
70–79	102.5	488	325	244	195	163

Thiopurine meta-analysis

Kotlyar DS et al. (2015) Clinical Gastroenterology and Hepatology 13:847-858



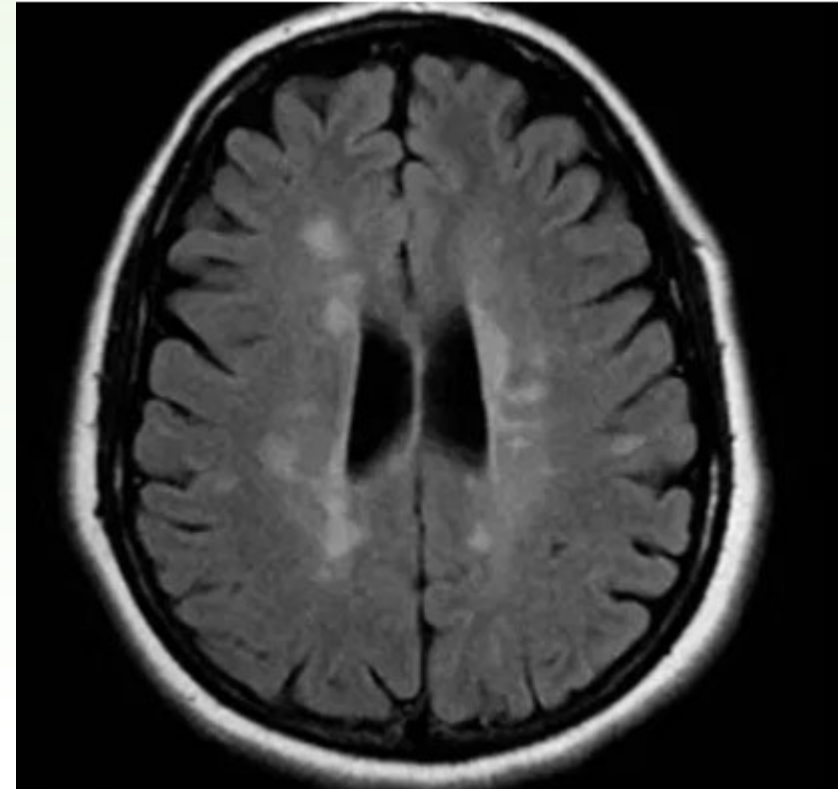
# Thiopurines and lymphoma

- Relative risk is moderate but absolute risk is low – less than 1 in 2000.
- Older adults may have absolute risk closer to 1:350 per year
- Men at greater risk than women.
- Appear to need 1 year of exposure to incur the increased risk.
- Risk appears to be diminished after discontinuation – suggesting that the immunosuppression rather than direct DNA damage may be more of a factor in the development of excess lymphomas

Kotlyar DS et al. (2015) Clinical Gastroenterology and Hepatology 13:847-858

## Case 5

- 38 year woman with 8 year history of Crohn's ileitis.
- Well controlled on infliximab 5 mg/kg every 8 weeks
- Presents complaining of fatigue and numbness
- She feels fuzzy and has trouble thinking. She also mentions that when she is working at the computer she has some double vision.

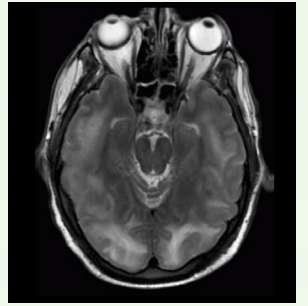


# What is it?

- Concerned about multiple sclerosis
- White matter lesions in the brain
- Sometimes complaints are very non-specific and can wax and wane
- White matter may be seen in up to 46% of patients with IBD as compared to 16% of healthy controls.
- Anti TNF therapy can cause central demyelination that mimics MS
- Natalizumab has been associated with PML due to reactivation of JC virus.
- Vedolizumab – 1 case of PML in patient who also had AIDs

Geissler et al (1995) Lancet 345:897-98

# Posterior reversible encephalopathy syndrome



- Rare – endothelial dysfunction that results in vasogenic edema in the brain.
- May be a result of inflammatory cytokines that increase vascular permeability
- Patients present with seizures and encephalopathy. Acute hemorrhage and obstructive hydrocephalus may occur in severe cases.
- Typical MRI findings → bilateral vasogenic edema in parietal and occipital white matter.
- This has been associated with infliximab and there is one case described in patient on ustekinumab

Evaluate fully any new neurologic symptoms in IBD patient – especially on biologics  
Avoid anti-TNF therapy in patients with significant white matter disease or other neurologic issues.

Chow et al (2016) J Clin Gastro;50:687

Haddock et al (2011) J Crohns Colitis 5:623-627

Mishra A and Seril DN (2018) Case Rep Gastroenterol 12:521 - 527

# Case 6

- 42 year old male on Tofacitinib 10 mg bid for induction of remission of ulcerative colitis.
- He has failed prior anti TNF therapy
- He has a marked improvement in his symptoms but calls thinking that he may be allergic to the new medication as he has developed a rash on his back.



# What is going on?

- Herpes Zoster

Patients at higher risk for *Herpes zoster on tofacitinib*:

- $\geq 65$  years
- Diabetes mellitus
- Concomitant steroids
- Asian race
- Prior anti-TNF failure

- Increased with biologics
- Risk factors age, immunodeficiency, chronic autoimmune or inflammatory disease
- Steroids increase risk of herpes zoster → higher dose worse risk
- Tofacitinib → up to 5% in higher dose maintenance arm. Twice the rate of anti-TNF and similar to thiopurines.

Tran et al (2017) Joint Bone Spine 84:21-27  
Olivera P (2020) Gastroenterology Jan 8  
EPUP ahead of print

# Case 7

- 60 year old male – hospitalized for acute ulcerative colitis.
- Had been well maintained on infliximab until 1 month prior to admission when he started to have increased bowel movements and bleeding.
- Started on Tofacitinib for his colitis.
- Now complaining of shortness of breath and chest pain.



Hu et al, Scientific reports &: Article 12741

# THROMBOEMBOLISM

**BLACK BOX WARNING**

- Where did this come from?
  - Post-marketing trial
  - RA patients > 50 years old with at least 1 cardiovascular risk factor.
  - Tofacitinib 10 mg bid vs. Tofacitinib 5 mg bid vs anti-TNF
  - PE 19 patients in 10 mg bid group and 3 in anti-TNF group.
  - Out of 3,994 patient years F/U and 3,982 patient years F/U
  - FDA warning 7/26/2019
- Post-hoc analysis of UC trial data
  - IR (95%) for DVT with Tofacitinib 0.04 (0.00-0.23)
  - IR (95%) for PE was 0.16 (0.04-0.41)
  - All DVT/PE events occurred in OLE after at least 7 months of treatment in patient receiving 10 mg bid.
  - IRs for DVT and PE comparable with those reported for patients with UC.

Medical Letter October 26, 2019

Sandborn W (2019) Alimen Pharm Ther On Line 9 Oct 2019

**FDA: Tofacitinib restricted to patients who have failed anti-TNF**



# Tofacitinib Adverse Events

- Herpes Zoster
- Non-melanoma skin cancer → both squamous cell and basal cell
- LDL and HDL increase → does not seem to be a cardiovascular impact but need to check cholesterol levels 4- 8 weeks after starting – may need to add a cholesterol lowering agent.
- No increased risk of gastrointestinal perforation.
- Serum CPK increase but no clear clinical impact.
- No immunogenicity.
- Likely a small malignancy risk.
- Anemia

Sandborn W et al (2016) Gastroenterology 15:  
S157

# Case 8

- 35 year old male with history of Crohn's disease x 15 years
- Ileocolonic distribution with perianal disease. S/P subtotal colectomy.
- On maintenance therapy with Adalimumab
- Mildly elevated LFTs.
- Brother died of cirrhosis – not a drinker
- Mother was from Viet Nam and Father US service member.

- Routine Hepatitis studies done
- Hepatitis C Negative
- Hepatitis B S Ag positive
- Hepatitis B Core total AB positive
- Hepatitis B Virus DNA 354 IU/ml
- Hepatitis B Virus DNA Log (10) 2.55
- Treated with entecavir – no detectable Hepatitis B viral DNA

# Hepatitis B reactivation with biologics

- TNF  $\alpha$  suppressed HBV replication and plays a role in eradicating HBV by stimulating HBV specific cytotoxic T cells.
- Anti TNF agents – allow HBV to escape immune control → viral replication.
- Study in RA patients found hepatitis B reactivation in 12.3% of 122 Hepatitis B surface antigen positive patients.
- Study in HBsAg negative, anti-HBc positive patients with RA showed reactivation in 1.7% of 468 HBsAg-negative and anti HBc positive patients undergoing anti-TNF therapy

Check hepatitis serologies in patients prior to starting anti-TNF – repeat periodically if risks  
Treat HBsAg positive patients during therapy with anti-viral  
Monitor Hepatitis B core antibody positive patients carefully for reactivation during therapy

Lee et al (2013) Int J Rheum Dis 16:527-531  
Lee et al (2013) Clin Exp Rheumatology 31:118-121



## Strange But Useful Medication Side-Effects

# Back up slides

# Adverse events with thiopurines

Event	Incidence/Risk
Pancreatitis	4%
Myelosuppression	2.2 – 15%
Hepatotoxicity	5-10 %
Non-melanoma skin cancer	Increased risk compared to control OR 1.9
Lymphoma	Age dependent – as high as .28%
Infections	.98% serious

Beaugerie and Krichgesner (2019) Clinical Gastroenterology and Hepatology 17:370-379  
Queiroz and Reguiero (2020) Current Opinion Gastro 36:

# Adverse Events Associated with anti-TNF treatment

Event	Frequency
Stop therapy due to adverse event	10%
Infusion or injection site reaction	3 – 20%
Drug related lupus-like reaction	1%
Serious infections	3%
Skin	1 – 20%
Tuberculosis	0.05% (5/10,000)
Non-Hodgkin's lymphoma (combo)	0.06% (6/10,000)
MS, heart failure, serious liver injury	Case reports

Siegle CA, Inflamm Bowel disease yearbook Volume 6 , 2009

# Adverse events associated with vedolizumab

Event	Rate
Serious Infections	< 0.6%
PML	0%
Infusion reactions	< 5%
Malignancy	< 1%

6 studies with follow-up to 5 years  
N = 2830, 4811 patient-years of Vedolizumab exposure.

One case of PML has been reported in patient who also had HIV related disease.

Colombel et al (2017) Gut 66:839-851



# Ustekinumab – Safety Profile – SQ Maintenance

	Ustekinumab 90 mg q 8 weeks	Placebo
Nasopharyngitis	11%	8%
Injection site reaction	5%	0%
Vaginal yeast infection	5%	1%
Bronchitis	5%	3%
Pruritis	4%	2%
UTI	4%	2%
Sinusitis	3%	2%
Malignancy	0.8%	0.8%

Unknown skin cancer risk. No other malignancy signal  
Low immunogenicity 2.3% had anti-drug antibodies  
One case of reversible posterior leukoencephalopathy  
in psoriasis studies. Case reports in Crohn's disease.

Feagan, BG et al. NEJM 2016; 375: 1946-1960.  
<https://www.stelarahcp.com/crohns-disease/safety-profile>