Fungal Infections in the Era of Immunobiologicals: The Good, Bad and Ugly

Session 199: Special Populations Requiring Special Considerations

John W. Baddley, MD, MSPH

September 8, 2014

Disclosures

- Pfizer: adjudication committee (biologic)
- BMS: research grant (biologic)
- Lilly: consulting (biologic)
- Astellas: data review committee (antifungal)
- Merck: consulting (antifungal)

Outline

- Case (the Ugly)
- Impact of immunobiologicals (the Good)
- Overview of immunobiologicals and fungal infections
- The Future (The Good and the Bad)

Case (the Ugly)

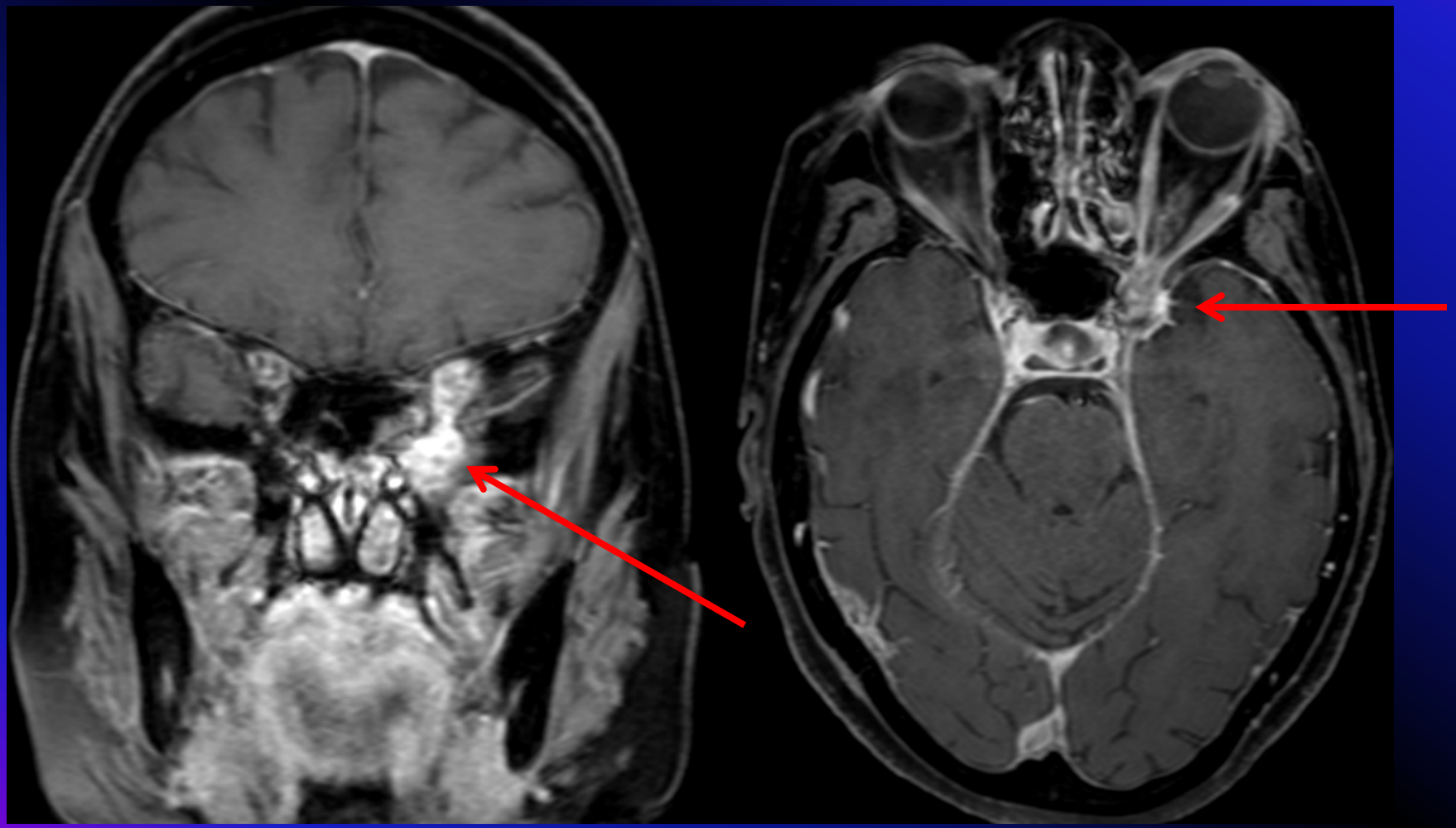
- HPI: 72-year-old AAF with RA presents with loss of vision in her left eye
  - One month prior to admission she was seen in the clinic with nasal congestion, sinus pain. Treated with azithromycin, with some improvement.
  - Two weeks ago noted blurred vision in left eye, which progressed to complete loss of vision & ptosis x 1 day
  - No fever. Notes headache, left temporal pain & pain behind her left eye

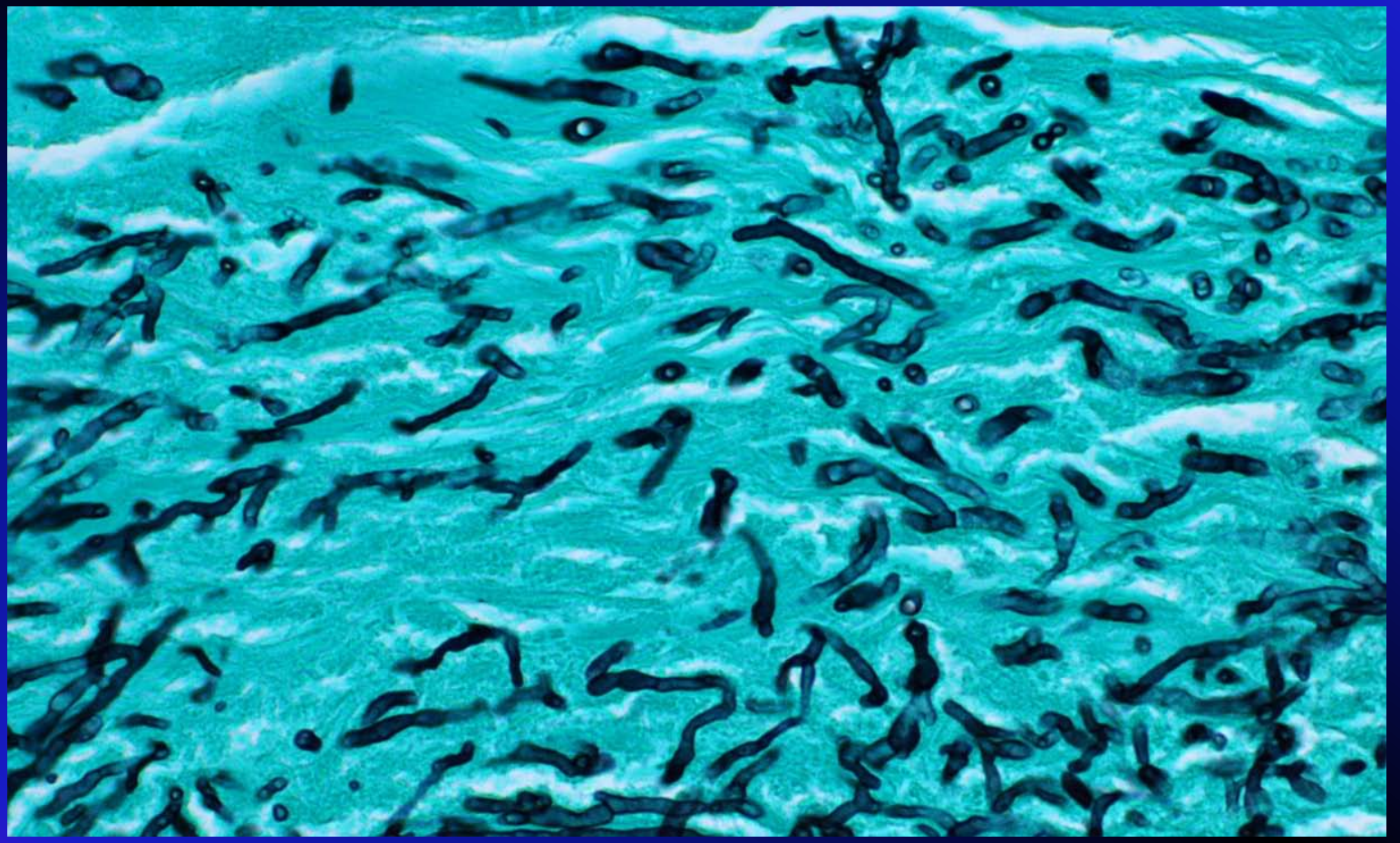
Case (2)

- PMH: RA, HTN, Dyslipidemia
- Meds: Etanercept
  Azathioprine
  Prednisone 5mg/d

- V/s: T 100.8, HR 88, RR 20, BP 113/69
- HEENT: Left pupil, 6mm, no reaction to light; ptosis and ophthalmoplegia
- Lung: Clear

Soft tissue mass in the left pterygopalatine fossa with extension into the orbital apex and anterior cavernous sinus





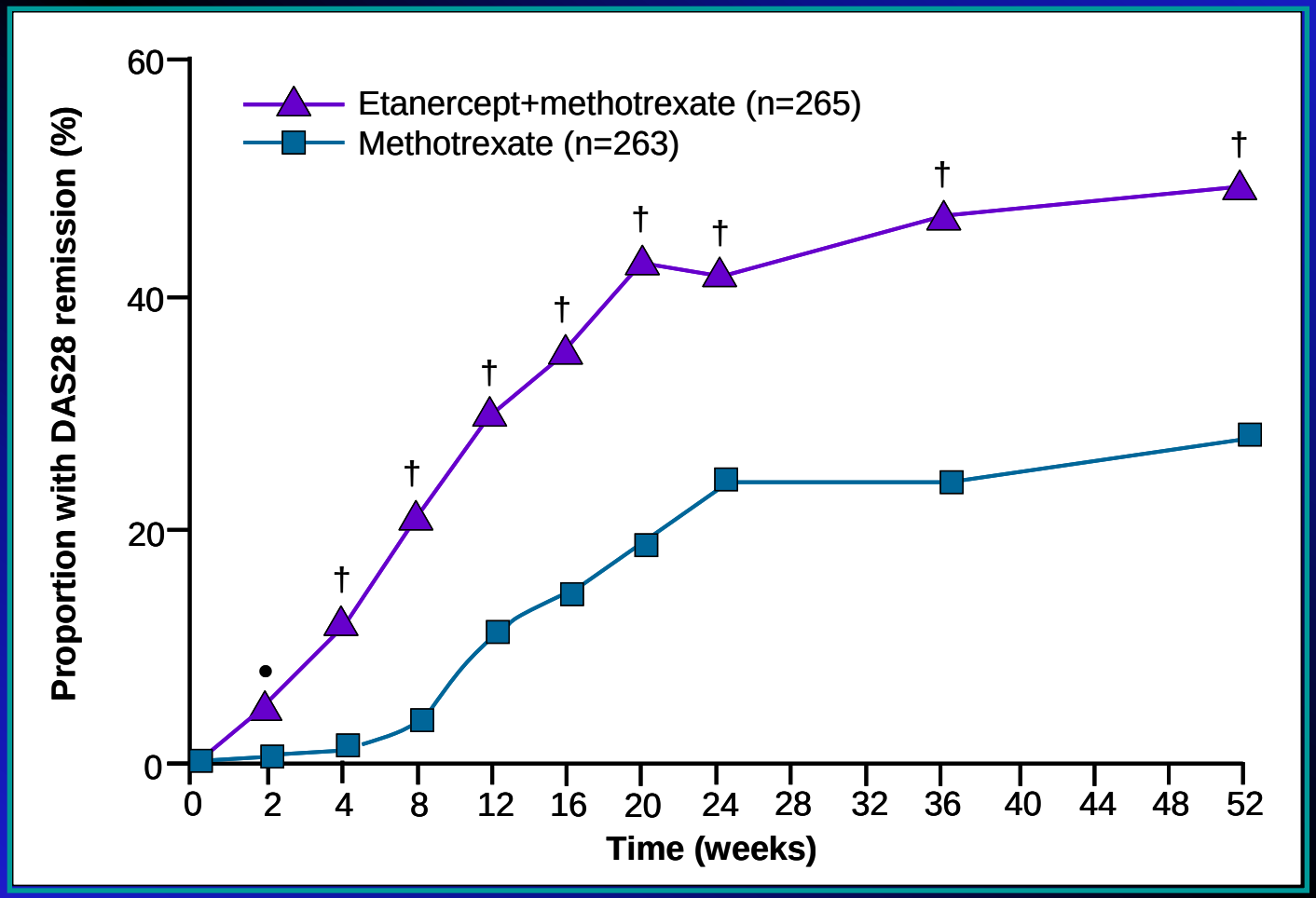
Culture: *Aspergillus fumigatus*

Biologic Therapies

- More than 35 approved for human therapy
- 350 in clinical development
- **Areas of indications**: inflammation, cancer, autoimmunity, cardiovascular, organ transplantation, infection, ophthalmology
- Economic impact: annual worldwide sales of $45 billion in 2011
- Adalimumab $7.9 billion in 2011 US Sales

Chan and Carter, *Nature Reviews: Immunology* 2010
Bipharm.com 2013

DAS28 Remission Over 52 Weeks of Treatment (GOOD)

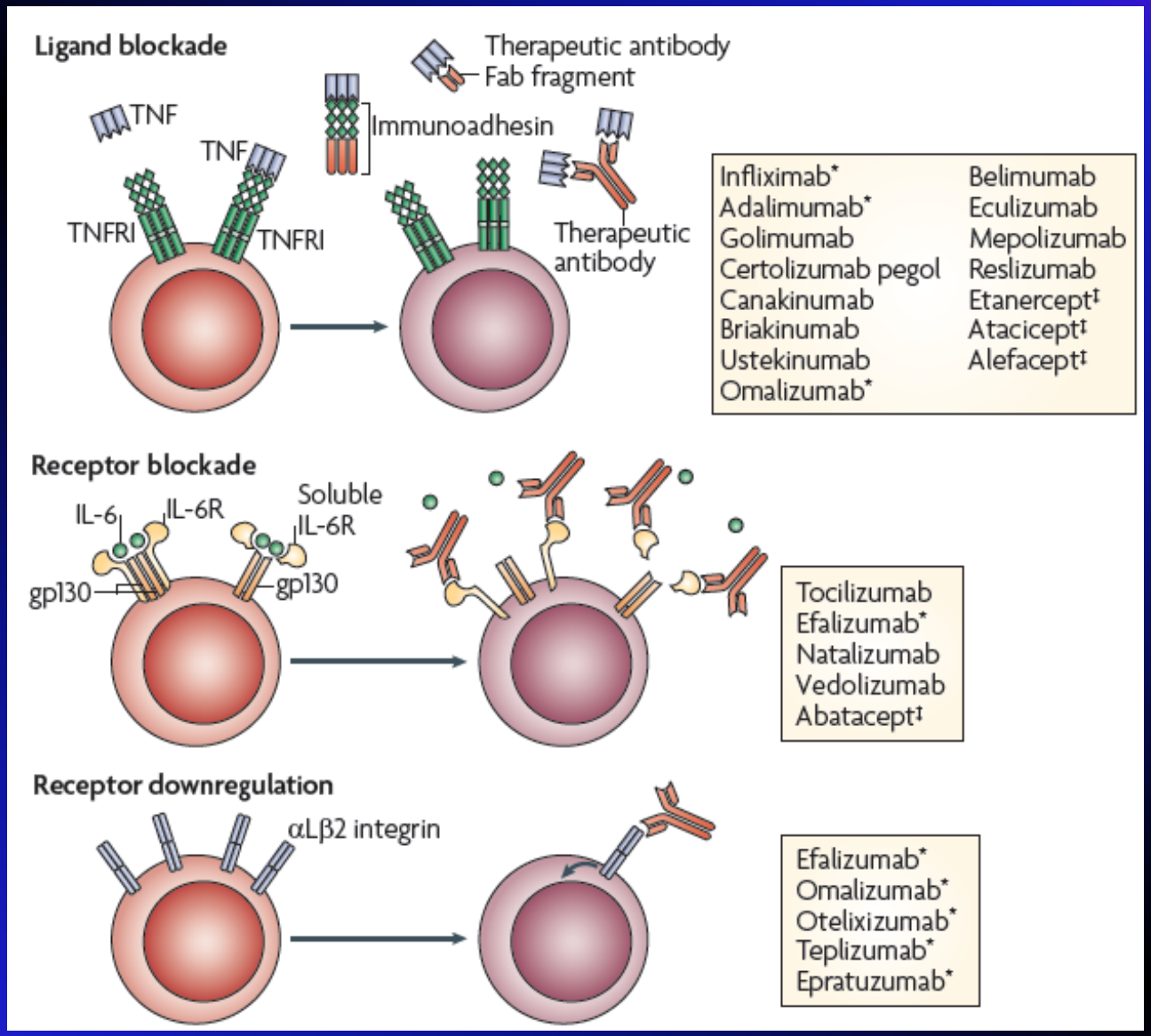


A significant difference in the proportion of patients in DAS28 remission was seen in week 2 and persisted for the study period. *p-0-002 †p<0.0001

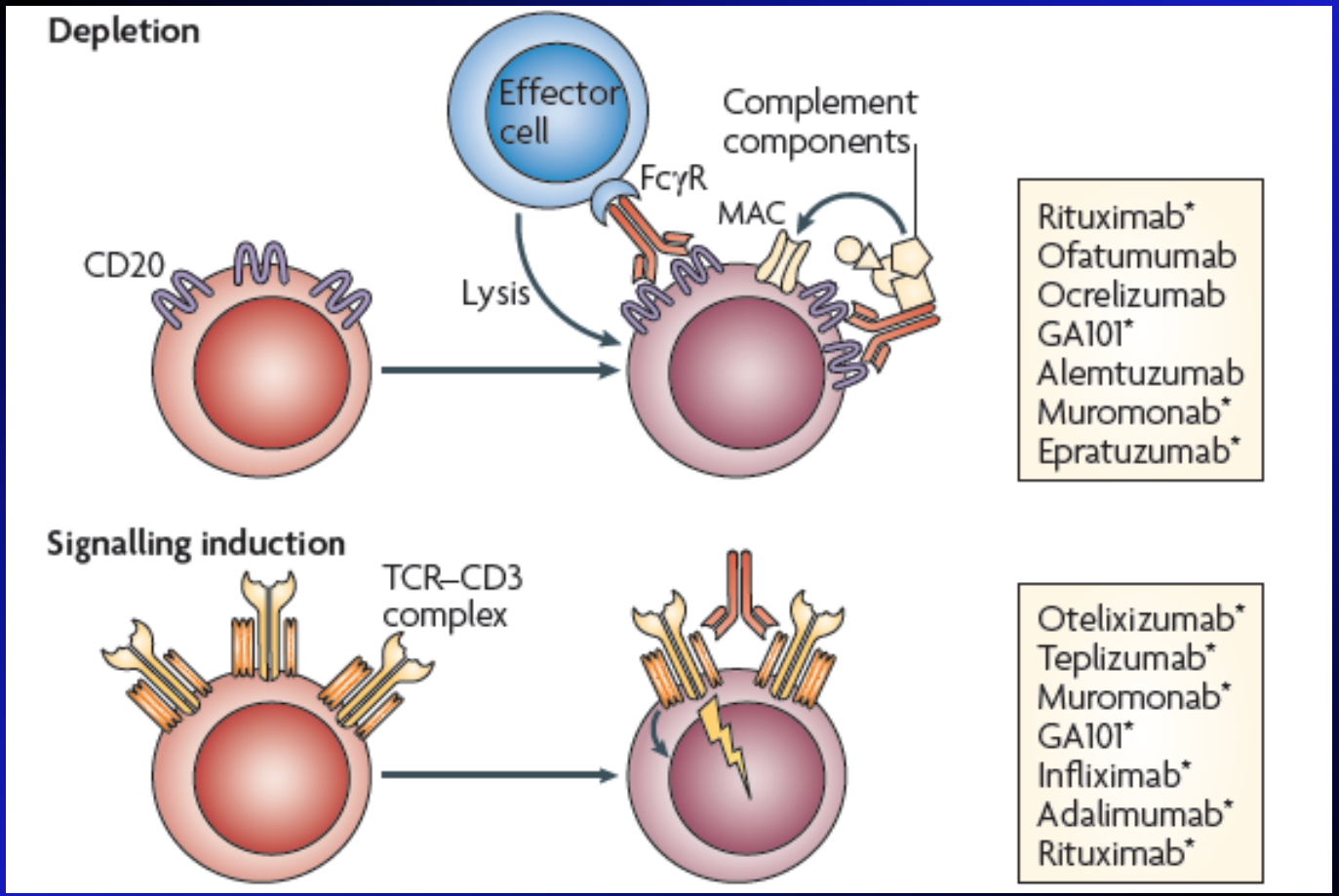
Emery P, Breedveld FC, Hall S, et al. *Lancet.* 2008;372:375-382.

Biologics: Risks (more Ugly)

- **Infections**
- Autoimmune syndromes (e.g. SLE)
- Cancer
- Heart Failure
- Demyelinating Events (e.g. MS)
- Gastrointestinal perforation
- Ischemic events (MI, stroke)
- Hypersensitivity
- Leukopenia
- Liver failure
- Death



Chan and Carter, *Nature Reviews: Immunology* 2010



Chan and Carter, *Nature Reviews: Immunology* 2010

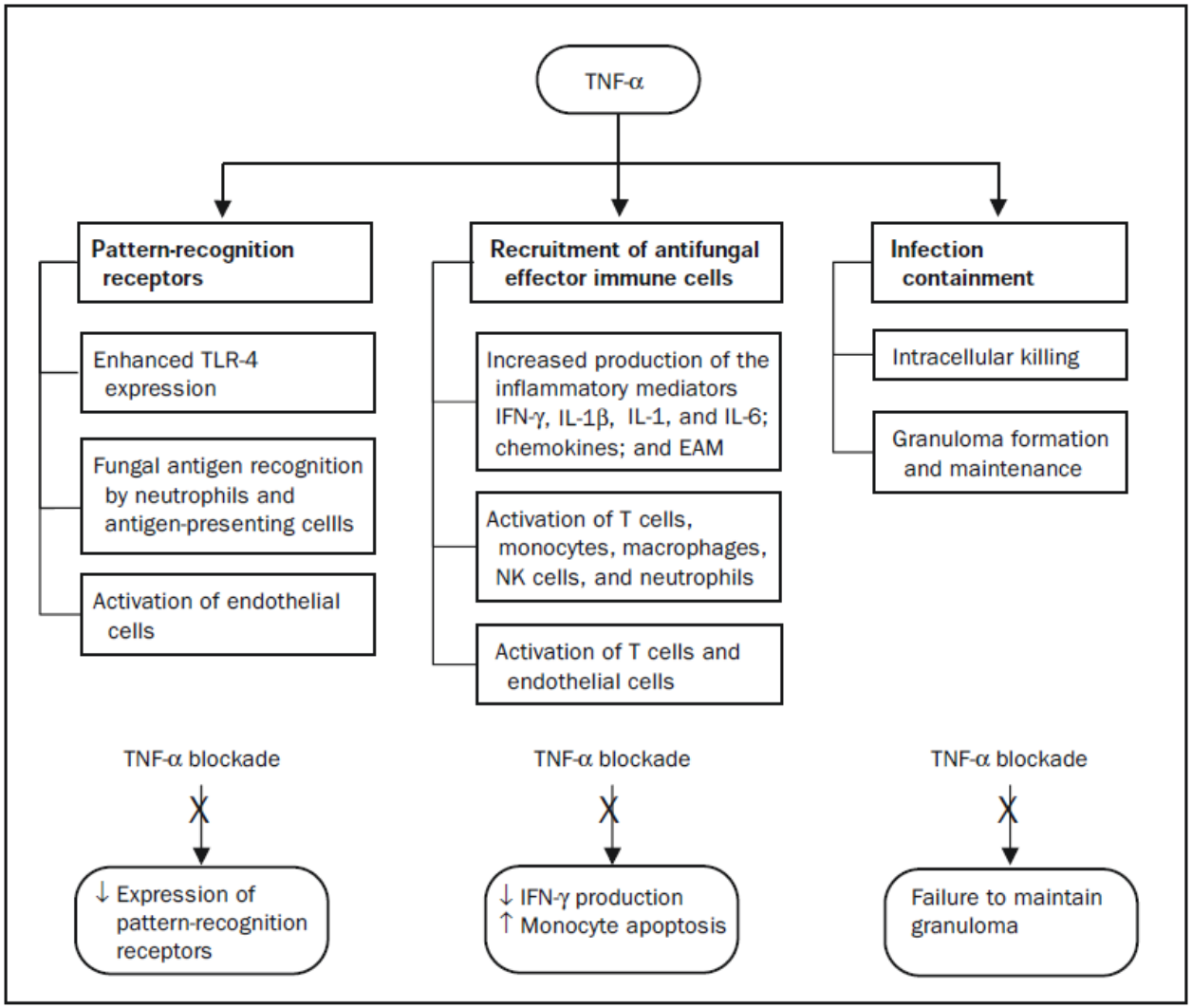


FIGURE. Key immunomodulatory effects of tumor necrosis factor α (TNF-α) pertaining to fungal immunity. Effects from TNF-α blockade are boldface. EAM = experimental autoimmune myocarditis; IFN-γ = interferon γ; IL = interleukin; NK = natural killer; TLR = toll-like receptor.

Tsiodras et al. *Mayo Clin Proc* 2008;83:181-194

TNF-α Antagonists

Generic	Trade	Type	TNF Binding	Diseases
Infliximab	Remicade®	Chimeric anti-TNF mAb	Soluble, membrane	RA, PA, spondyloarthropathies, IBD
Etanercept	Enbrel®	Soluble TNF-α receptor fusion protein	Soluble, membrane (weaker)	RA, PA, spondyloarthropathies; not effective in IBD
Adalimumab	Humira®	Human anti-TNF mAb	Soluble, membrane	RA, PA, spondyloarthropathies, IBD
Certolizumab pegol	Cimzia®	Pegylated Fab' fragment of a humanized mAb. No FC portion.	Soluble, membrane	Crohn's, RA
Golimumab	Simponi®	Human anti-TNF mAb	Soluble, membrane	RA, PA, spondyloarthropathies

mAb=monoclonal antibody; RA=rheumatoid arthritis; PA=psoriatic arthritis; IBD=inflammatory bowel disease

Infections in Patients Receiving Biologics

Important Considerations:

- Clinical trials not usually powered to detect adverse events such as rare infections
- High rate of co-morbidities in patients
- Immunosuppressant use associated with disease severity (confounding by indication)
- Patients receiving many immunosupressants

  (What is impact of prednisone?)

Bacterial Infections

- Occur early (<6 months) after staring anti-TNF
- Overall rates **2-14/100 person years**
- *Probably* an increase of 2-3 infections/100 person-years with a biologic (relative increase of 50-100%) compared to non-biologic DMARDS
- Increased risk with monoclonals (ada/inflix) when compared to etanercept
- Steroids and co-morbidities important contributors

Fungal Infections

- Numerous case reports
- Few large studies evaluating risk
- **Meta-analysis (RA):** -only 9 cases of non-PJP IFI (5 IA)*
  -no increased risk of IFI with biologics
- Infections occur within 1-6 months of starting a biologic
- Advanced disease; high morbidity and mortality (FDA black box warning)

-Pneumocystosis (0.5/100,000)

-Histoplasmosis (2-19/100,000)

-Coccidioidomycosis (1-5/100,000)

Kourbeti et al., *Clin Infect Dis* 2014

RATIO Group

- Collected all cases of OIs from Feb 2004-Feb 2007 (French Registry of cases)
- **Case definition**: standardized definitions, validated by ID physicians
- **Drug exposure:** Estimated patient-years of infliximab, etanercept and adalimumab during study period
- Estimated incidence rates and defined risk factors for infection
- **41 non-TB OIs were identified**
- **Risk factors for OIs: steroid therapy (>10mg/d) and monoclonal TNF antibodies**

Salmon-Ceron et al., *Ann Rheum Dis* 2011

RATIO Mycoses

Type of OI	N	Pathogen	Median age, years (Q1–Q3)	Underlying disease	Localisation	Admissionto intensive care unit	Lost to follow-up	Cured	Death
Fungi	Pneumocystosis 5	*Pneumocystis jiroveci*	51.0(50.0–63.0)	Crohn: 1 RA: 2 Polyarteritis nodosa: 1 Mesenteric fibrosis: 1	5 Interstitial pneumonia	2	0	4	1
	Aspergillosis 3	*2 Aspergillus fumigatus* *1 unknown*	58.0(13.0–69.0)	Crohn: 1 RA: 1 Pyoderma gangrenosum:1	1 Extensive sinusitis 1 Colitis 1 Pneumonia	1	0	1	1
	Cryptococcosis 2	*Cryptococcus neoformans*	51.0(47.0–55.0)	RA: 1 Sarcoidosis: 1	1 Arthritis left knee and fungaemia 1 Cutaneous lesion with lymph nodes	0	1	1	0

OI rates: 151.6 per 100,000 p-yrs

Salmon-Ceron et al., *Ann Rheum Dis* 2011

SABRE Study

- **Safety Assessment of Anti-TNF Agents used in Autoimmune Diseases**
- AHRQ funded
- **Participating Sites:** University of Alabama at Birmingham, Vanderbilt, Kaiser Permanente (KP), University of Pennsylvania, Brigham and Women's Hospital
- **Databases:**

  (1) Kaiser Permanente Northern California (KPNC)

  (2) Horizon Blue Cross Blue Shield of New Jersey

  (3) British Columbia Linked Health Database (BCLHD)

  (4) Nationwide Centers for Medicare and Medicaid Services (CMS) data

  (5) Tennessee Medicaid data (Tenn Care) linked to State birth certificates
- **108,000 users of TNF-blockers and other biologics**
- Infections diagnosed by ICD-9 codes; some validation (KPNC)

Table 2 Distribution of non-viral OI (n=80) among new TNFI users for all disease indications*

Infection	Frequency (%)
Pneumocystosis	16 (20)
Nocardiosis/actinomycosis	12 (15)
tuberculosis	10 (12.5)
Histoplasmosis	9 (11.3)
Toxoplasmosis	1 (1.3)
Coccidioidomycosis	1 (1.3)
Blastomycosis	1 (1.3)
Aspergillosis	1 (1.3)

*Only the first OI per patient is listed. One patient with tuberculosis was diagnosed with NTM several years later. That NTM case is not listed above but was used in analysis in table 5.
†Defined using ICD-9 484.7 (pneumonia in systemic mycoses). Not in table
NTM, non-tuberculous mycobacterial; OI, opportunistic infection, TNFI, tumour necrosis factor α inhibitor.

	Crude rate (/1000 p-yrs)	Adjusted Rate
Comparator	**1.7 (1.2, 2.5)**	**ref**
TNF users	**2.7 (2.2, 3.4)**	**1.6 (1.0, 2.6)**
Baseline steroids		**2.5 (1.5, 4.0)**

Baddley et al., *Ann Rheum Dis* 2013

U.S. Veteran's Cohort

- Cohort of RA patients from 1998-2012
- 56,392 with RA diagnosis (2 RA diagnosis codes by a rheumatologist or 1 code plus biologic use)
- 8207 new users of biologics (11,319 episodes):

  (ADA 4622; ETA 4184; INF 1022; RIT 755; ABA 545)
- **Cohort of "switchers" (3730 patients)**
- Fungal infections identified by ICD-9 codes and laboratory studies (serology, culture, some histopathology).
- All cases confirmed by ID clinician chart review

OI Rates in VA RA Patients

Opportunistic Infection[1]	Abatacept n=338 PY=486.5	Adalimumab n=1826 PY=2727.4	Etanercept n=741 PY=1180.6	Infliximab n=358 PY=511.2	Rituximab n=511 PY=650.8	Total N=3774 PY=5538
Zoster	5	38	16	2	4	65
Tuberculosis						
Pneumocystosis						
Legionellosis						
Coccidioidomyc						
Histoplasmosis						
Non-tuberculou mycobacteria						
Salmonellosis	0	1	0	0	1	2
Nocardiosis	0	0	0	1	0	1
TOTAL OIs	5	44	19	4	12	84
IR (95% CI) per 100 p-years	1.1(0.4, 2.6)	1.6 (1.2, 2.2)	1.6 (1.0, 2.5)	0.8 (0.3, 2.1)	1.8 (1.0, 3.2)	1.5 (1.2, 1.9)

Cumulative incidence: 0.2%
Incidence rate: 144/100,000 p-yrs
6/8 in rituximab users

Baddley et al., ACR 2012

Management of IFIs

- Stop the biologic

  -beware of IRIS (42% in Histoplasmosis study[1])
- Standard course of antifungal therapy
- Document clinical resolution of infection
- Re-start the biologic?
- Chronic suppressive therapy/secondary prophylaxis?
- **Outcomes:**

  Histoplasmosis:

  -Restarted in 4/15; 1 had recurrence [2]

  -Resumption of TNF blockers post-histo was safe in 6 patients[1]

  Coccidioidomycosis

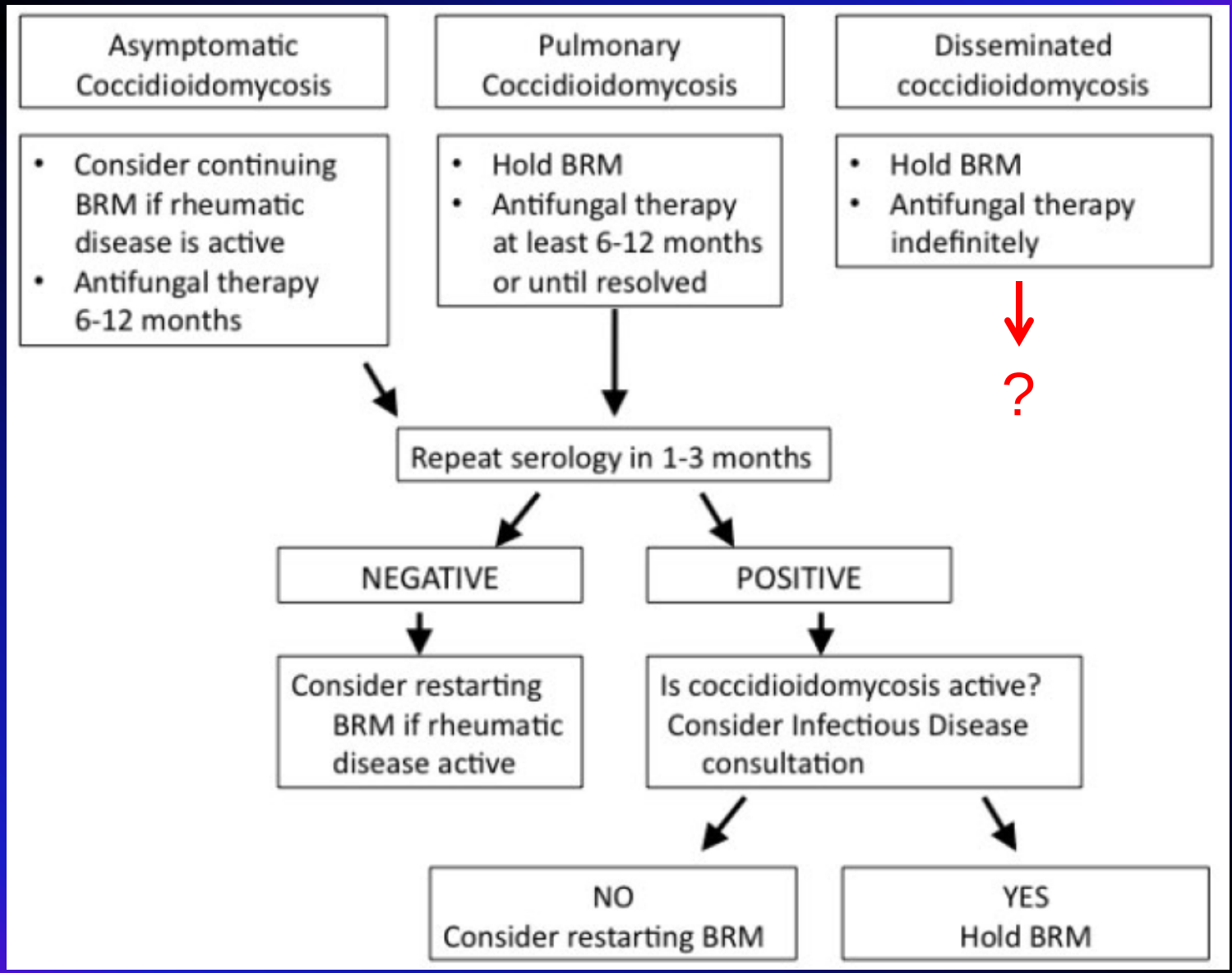
[1] Hage, C. et al. *Clin Infect Dis* 2010;50:85-92

[2] Olson et al *BMC ID* 2011

Management of Coccidioidomycosis

- Retrospective review of patients with cocci receiving DMARDS or biologic response modifiers (BRMs)
- 44 patients (29 pulmonary; 9 disseminated; 8 asymptomatic)
- 25 BRM/DMARD; 8 DMARD alone; 11 BRM alone
- 34 (77%) stopped one or more drugs; 23% did not change therapy at time of diagnosis of cocci.
- 93% started antifungal therapy (range, 0-96 months; median treatment 9 months)
- **Follow-up data in 38** (23 on BRMs/DMARDS; 10 DMARDS)
- Time to restart BRM, median 10 months; 16 remained on antifungal therapy
- **Outcomes: None** developed more severe cocci; one had possible reactivation

Taroumian et al., *Arthritis Care and Research*, 2012



Taroumian et al., *Arthritis Care and Research*, 2012

Future (Good and Bad)

Company	Name	Target(s)	Phase	Indication
Regeneron/Sanofi	Sarilumab	IL-6R	3	RA
Hoffmann-La Roche	Lebrikizumab	IL-13	3	Asthma
Lilly	Ixekizumab	IL-17A	3	RA, psoriasis
Novartis	Secukinumab	IL-17A	3	RA, psoriasis
Amgen	Broadalumab	IL-17R	3	Psoriasis
Merck	Tildrakizumab	IL-23 p19 subunit	3	Plaque psoriasis
Genentech	Ocrelizumab	CD20	3	Multiple Sclerosis
UCB	Epratuzumab	CD22	3	SLE
Merck	Lambrolizumab	PD1	3	Melanoma
BMS, AbbVie	Elotuzumab	CD2	3	Myeloma
Pfizer	Tofacitinib	JAK inhibitor	3	RA, psoriasis, IBD

Reichert, J. *mAbs* 2014

Mechanisms

IL-23/IL-17 Axis:

-crucial role in pathogenesis of autoimmune inflammation

-acts on multiple cell types (macrophages, neutrophils, lymphocytes)

-IL-17 illicits pro-inflammatory cytokines, TNF-α production

-**major role in preventing infections at mucosal sites**

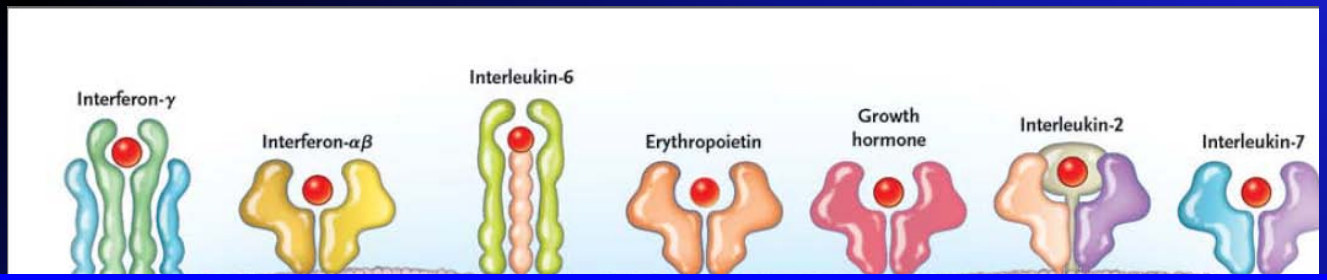
-**Concern for candidiasis, pulmonary aspergillosis**

Recent NEJM trial:

-Candida infections in 4.7% on secukinimab, greater than etanercept group[1]

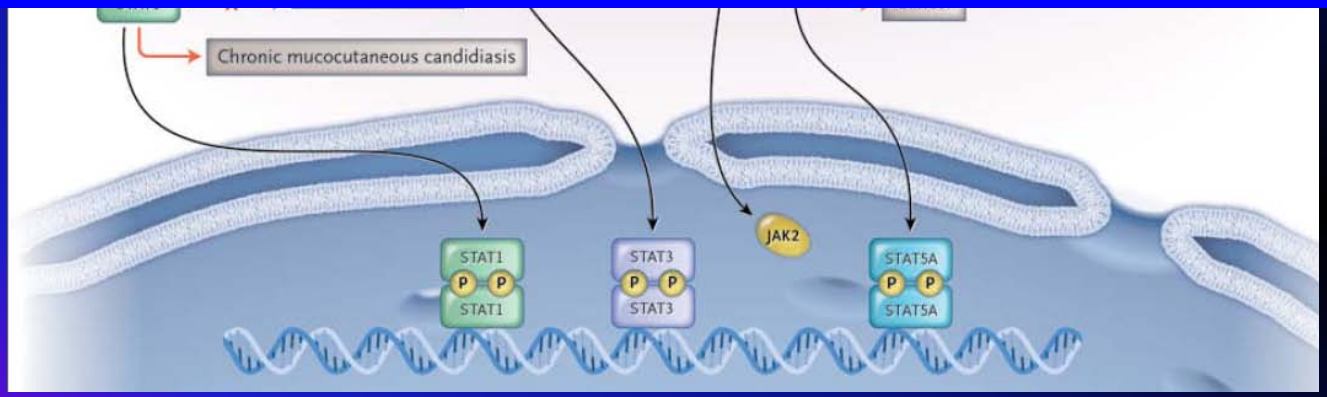
Langley et al., *NEJM* 2014

Janus Kinase (JAK) signal transducer and activator of transcription (STAT) pathway



Tofacitinib (RA): JAK3, JAK1 inhibitor, some JAK2
-no fungal cases reported (pulm. Cryptococcosis pending)

Ruxolitinib (myelofibrosis): JAK1, JAK2 inhibitor
-one pulmonary cryptococcosis case (Chest 2013)



O'Shea et al, *NEJM* 2013

Conclusions

- Immunobiologicals increase risk of IFI (BAD)
- Patients present with disseminated rather than localized disease (UGLY)
- ID specialists can help educate about disease presentation (GOOD)
- In general, treatment with biologics should be discontinued if a patient develops infection (GOOD). Beware of IRIS (UGLY).
- Need more data regarding re-starting biologics and duration of antifungal therapy (BAD)
- New biologics and new mechanisms of action mean more infections (BAD), but additional ID consults (GOOD)