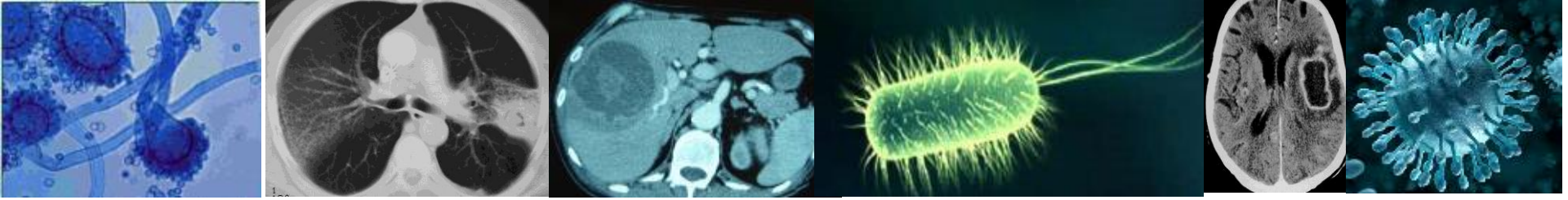


Recent biotherapies and infections

Olivier Lortholary, M.D.; Ph.D

Centre d'Infectiologie Necker-Pasteur

Université de Paris, Hôpital Necker Enfants malades,

IHU Imagine &

Centre National de Référence Mycoses Invasives & Antifongiques, Unité de Mycologie Moléculaire,

CNRS UMR 2000, Institut Pasteur, Paris, France.

JNI, June 6th 2019 Lyon

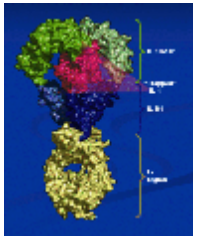
Conflits d'intérêt

- Orateur pour Astellas, MSD, Pfizer, Gilead Sciences
- Consultant pour Neteos, F2G, Gilead Sciences

Glossary of biologics

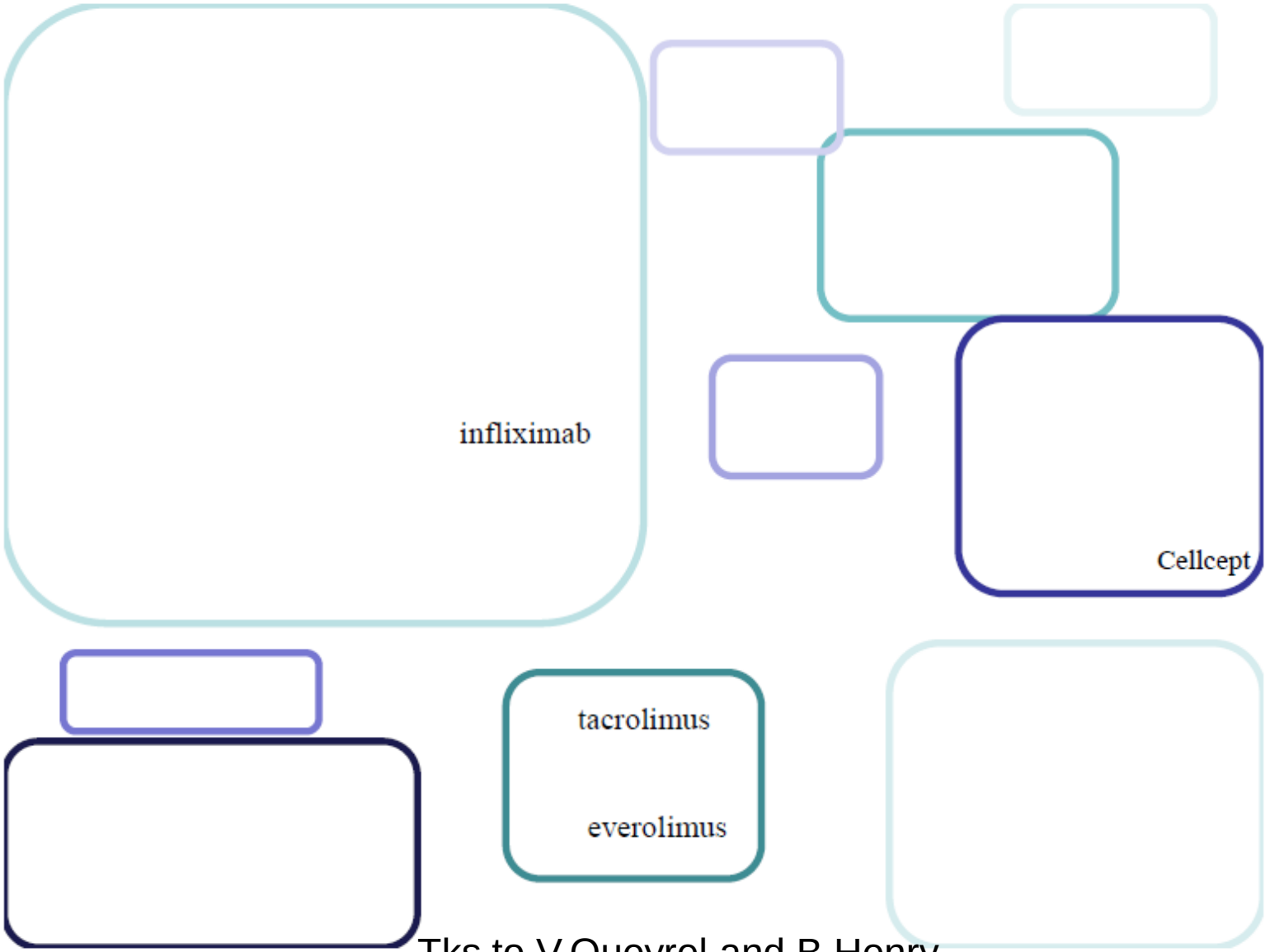
- Monoclonal antibodies *--mab*

- Fusion proteins: *--cept*



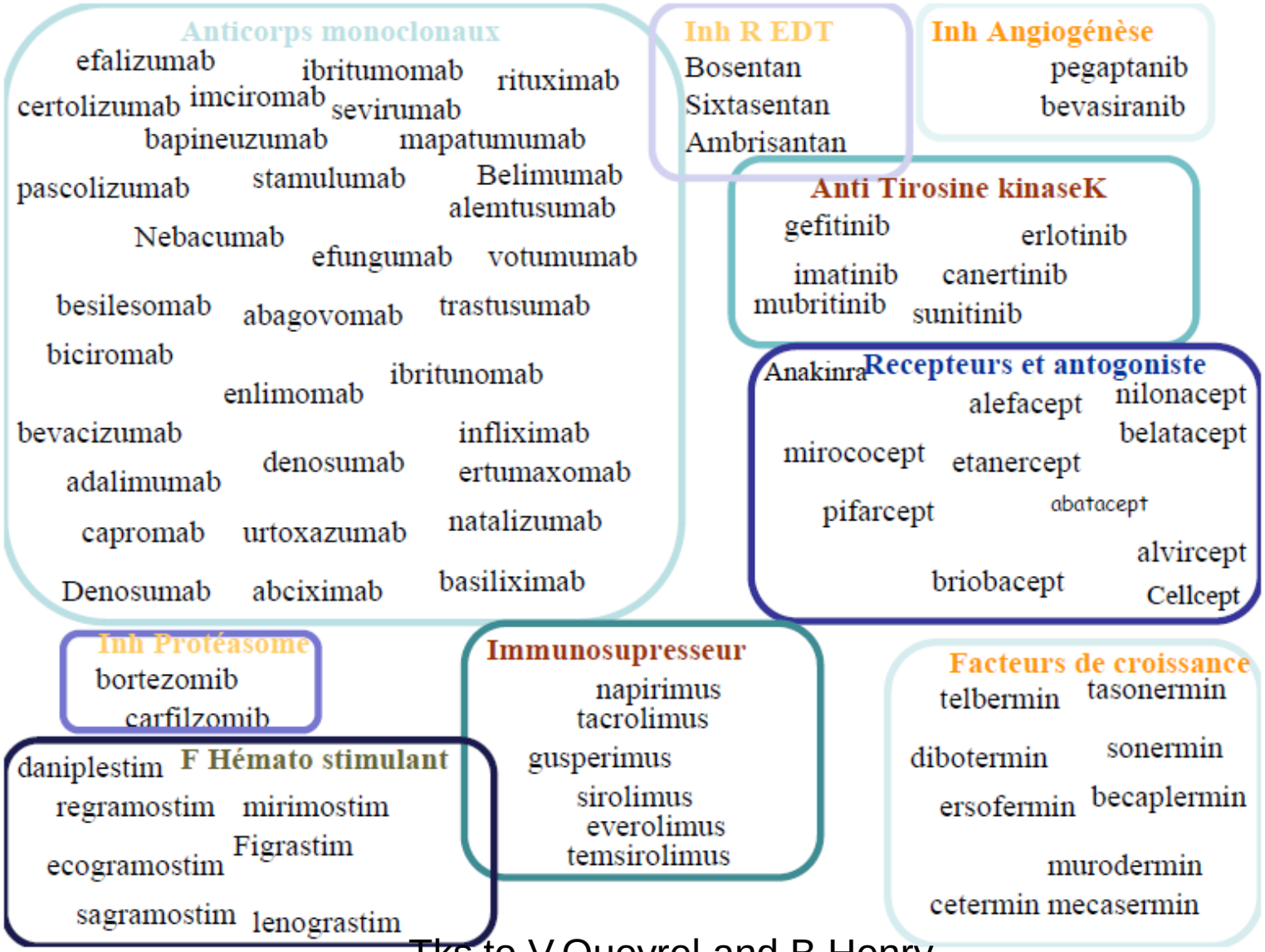
- Receptor analogs proteins: *--ra*

At biotherapy onset: « 1 mab, 1 cept, 2 mus !»



Tks to V.Queyrel and B Henry

And then…



Tks to V.Queyrel and B Henry

Biologics targeting soluble immune effector molecules

- **Pro-inflammatory cytokines**
  - **TNF-α** infliximab, adalimumab, golimumab, certolizumab pegol, etanercept
  - **IFN-γ** fontolizumab
- **Interleukins and their corresponding receptors**
  - **IL-1β** canakinumab, anakinra, rilonacept, gevokizumab
  - **IL-5** mepolizumab, reslizumab
  - **IL-6** tocilizumab, siltuxumab, olamkicept
  - **IL-12/23** ustekinumab
  - **IL-17A** secukinumab, ixekizumab, brodalumab
- **Immunoglobulins**
  - **IgE** omalizumab
- **Complement factors**
  - **C5** eculizumab

Biologics targeting cell surface receptors and antigens

- **Growth factor receptors**
  - **ErbB2/HER2** — trastuzumab, pertuzumab
  - **EGFR** — cetuximab, panitumumab
  - **VEGFR** — ramucirumab
- **Inhibitory coreceptors (immune checkpoints)**
  - **CTLA-4** — ipilimumab, tremelimumab
  - **PD-1/PD-L1** — nivolumab, pembrolizumab, atezolizumab
- **Cell-adhesion molecules**
  - **α4 integrins** — natalizumab, vedolizumab
  - **CD11a** — efalizumab
- **Chemokine receptors**
  - **CCR4** — mogalizumab
- **Lymphoid and myeloid cells surface antigens**
  - **CD19** — blinatumomab, inebilizumab, combotox
  - **CD20** — rituximab, ^{131}I-tositumomab, ocrelizumab, ofatumumab, veltuzumab, ocrelizumab, obinutuzumab, ocaratumomab,
  - **CD22** — epratuzumab, inotuzumab ozogamicin, moxetumomab pasedotox, combotox
  - **CD28** — abatacept
  - **CD30** — brentuximab vedotin
  - **CD33** — gemtuzumab ozogamicin
  - **CD38** — daratumumab, isatuxumab
  - **CD40** — lucatumumab, dacetuzumab
  - **CD52** — alemtuzumab
  - **SLAMF7** — elotuzumab

Biologics targeting intracellular signalling pathways

- **Cell-surface receptor-associated tyrosine kinases**
  - **VEGF receptor** — sorafenib, sunitinib, axitinib, pazopanib, regorafenib, cabozantinib
  - **ErbB receptor** — erlotinib, gefitinib, afatinib, osimertinib, lapatinib, neratinib
  - **Bruton's TK** — ibrutinib, acalabrutinib
- **Signalling pathway-associated tyrosine kinases**
  - **BCR-ABL** — imatinib, dasatinib, nilotinib, bosutinib, ponatinib
  - **BRAF/MEK** — vemurafenib, dabrafenib, trametinib, cobimetinib, selumetinib, encorafenib
  - **Bruton's TK** — ibrutinib, acalbrutinib
  - **PI3K** — idelalisib, buparlisib, rigosertib, duvelisib
  - **Janus kinases** — tofacitinib, ruxolitinib, baricitinib
- **Other signalling pathway-associated molecules**
  - **mTOR** — everolimus, temsirolimus

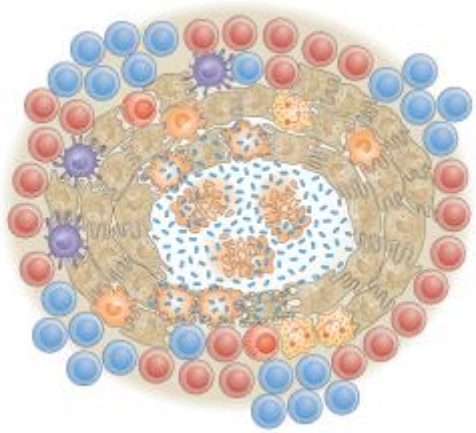
Infectious risk of biologics depends on…

- Mechanism of action: the presumable impact on immune response…
- Structure of the drug
- What has been evidenced during experimental infections/primary immunodeficiencies
- Epidemiology of pathogens

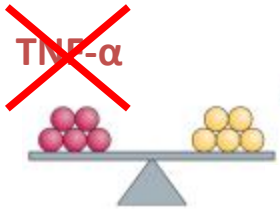
Impact on immune response

Infliximab

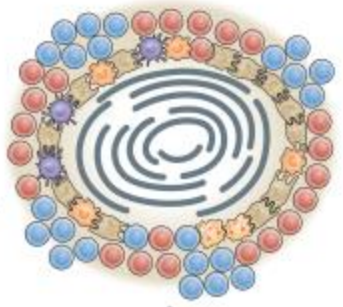
Monoclonal antibody targeting TNF-α



Tuberculous granuloma



Balance between pro-inflamatory and anti-inflamatory mediators



Resolved granuloma

Cadena et al. *Nat Rev Immunol* 2017;17:691-702.

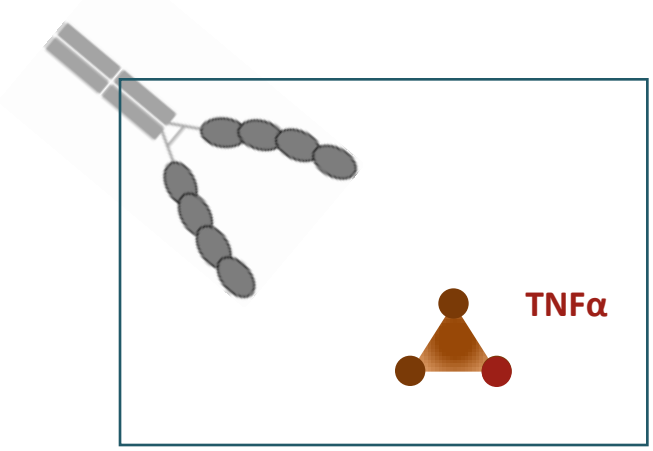
Structure of the drug

Etanercept

Dimeric soluble form of TNF-α receptor linked to hinge and Fc portions of IgG1

Rheumatoid arthritis, psoriatic arthritis, juvenile arthritis, spondylitis, psoriasis

Embrel® 50 mg twice weekly for 12 weeks



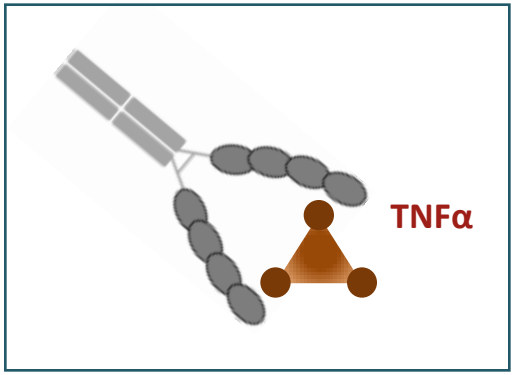
51-kDa homotrimer allowing simultaneous binding to 3 receptor molecules

one receptor-binding site remains free

1:1 stoichiometric complexes

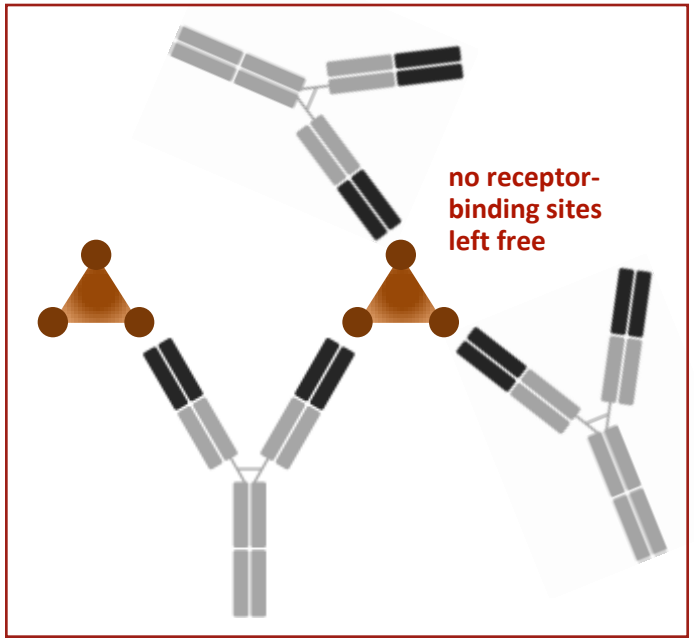
Structure of the drug

Etanercept versus anti-TNFα mAbs



1:1 stoichiometric complexes

lower infection risk with etanercept



3:1 stable complexes

Structure of the drug

Anti-CD20 monoclonal antibodies

First generation

Rituximab

^{90}Y-ibritumomab

murine or chimeric antibodies

Second generation

Ofatumumab

Ocrelizumab

Veltuzumab

^{131}I-tositumomab

humanized or fully human antibodies with reduced immunogenicity

Third generation

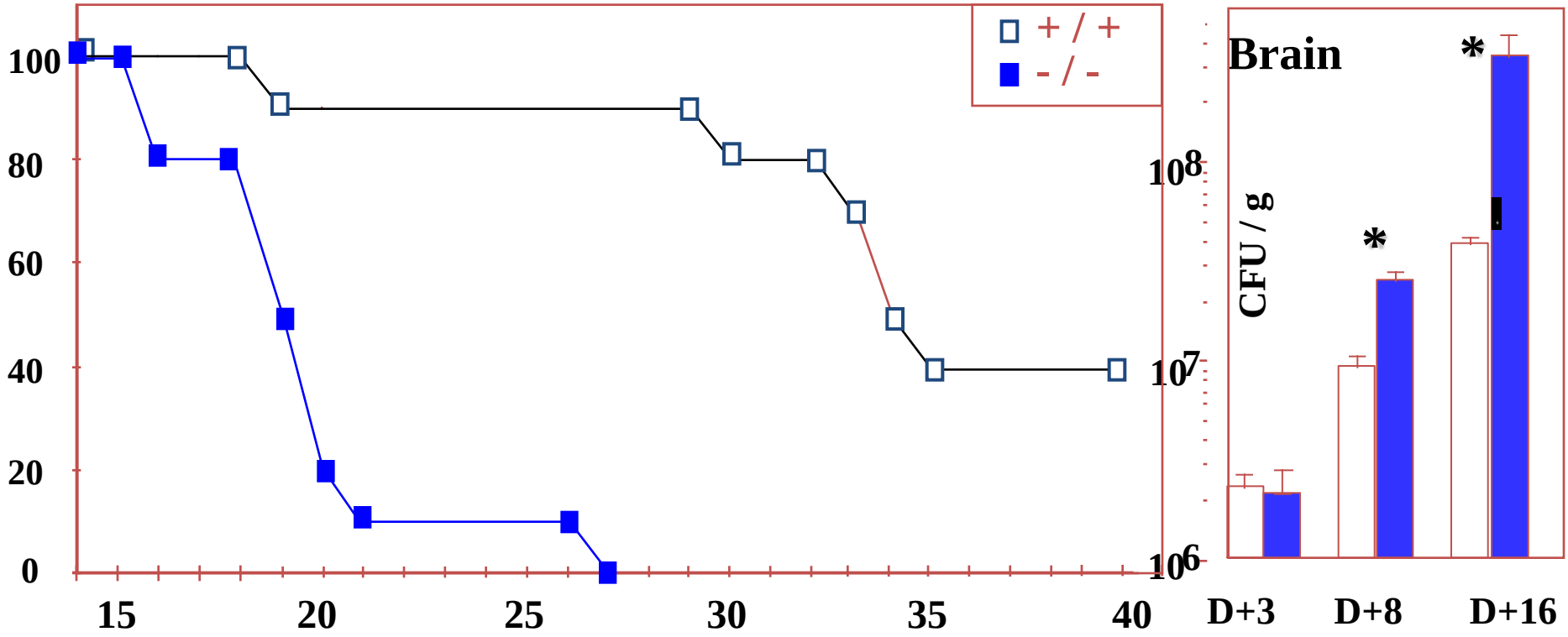
Obinutuzumab

Ocaratuzumab

antibodies with an engineered Fc region to boost CDC and ADCC

What has been evidenced during experimental infections

Cryptococcosis more severe in KO TNF-α/Lt-α mice



Days after inoculation of *C. neoformans* (2 x 10^6 i.v.)

Rayhane J. Infect. Dis. 1999

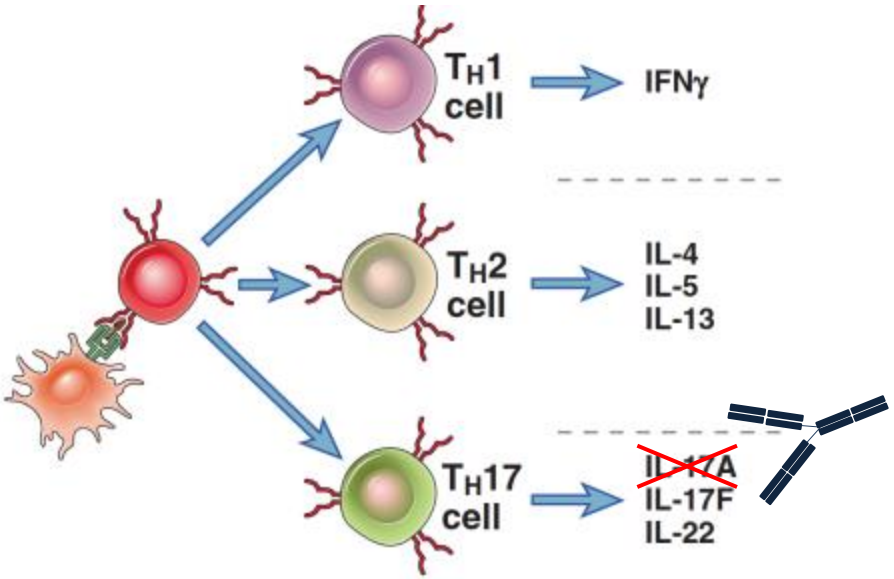
What has been evidenced during primary immune deficiencies

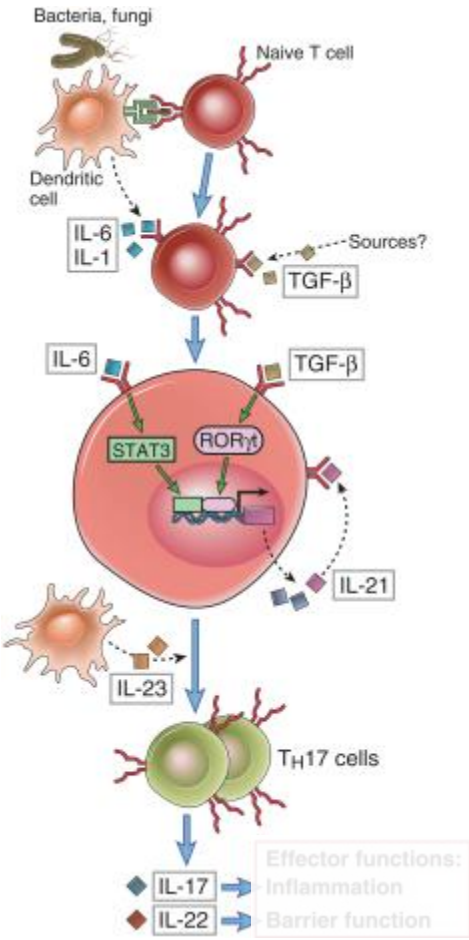
Secukinumab, ixekizumab and brodalumab

Monoclonal antibodies targeting IL17A or IL17-RA

Plaque psoriasis, ankylosing spondylitis and psoriatic arthritis

Cosentyx®, Taltz®, Siliq®





What has been evidenced during primary immune deficiencies

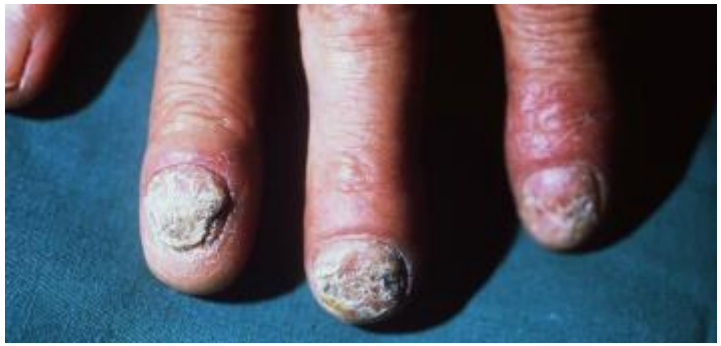
Secukinumab, ixekizumab and brodalumab

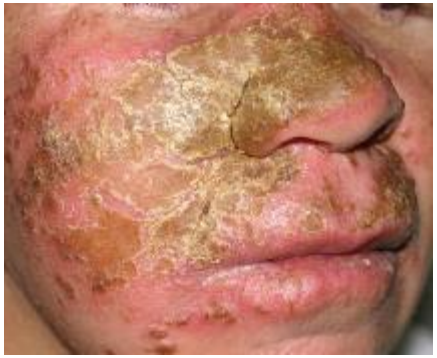
Monoclonal antibodies targeting IL17A or IL17-RA

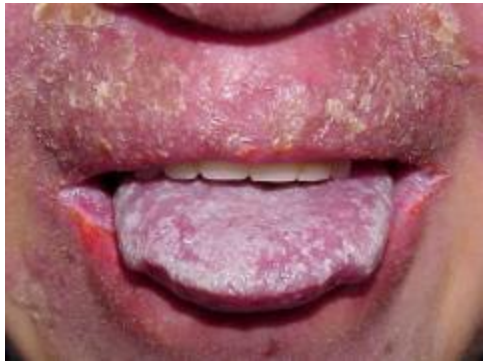
Plaque psoriasis, ankylosing spondylitis and psoriatic arthritis

Chronic mucocutaneous candidiasis

Inherited deficiencies in the IL-17 pathway







Saunte et al. *Br J Dermatol* 2016;45:345-56.
Huppler, et al. *Curr Opin Allergy Clin Immunol* 2012;12:616-22.

What has been evidenced during primary immune deficiencies

Secukinumab, ixekizumab and brodalumab

Monoclonal antibodies targeting IL17A or IL17-RA

Plaque psoriasis, ankylosing spondylitis and psoriatic arthritis

Cosentyx®, Taltz®, Siliq®

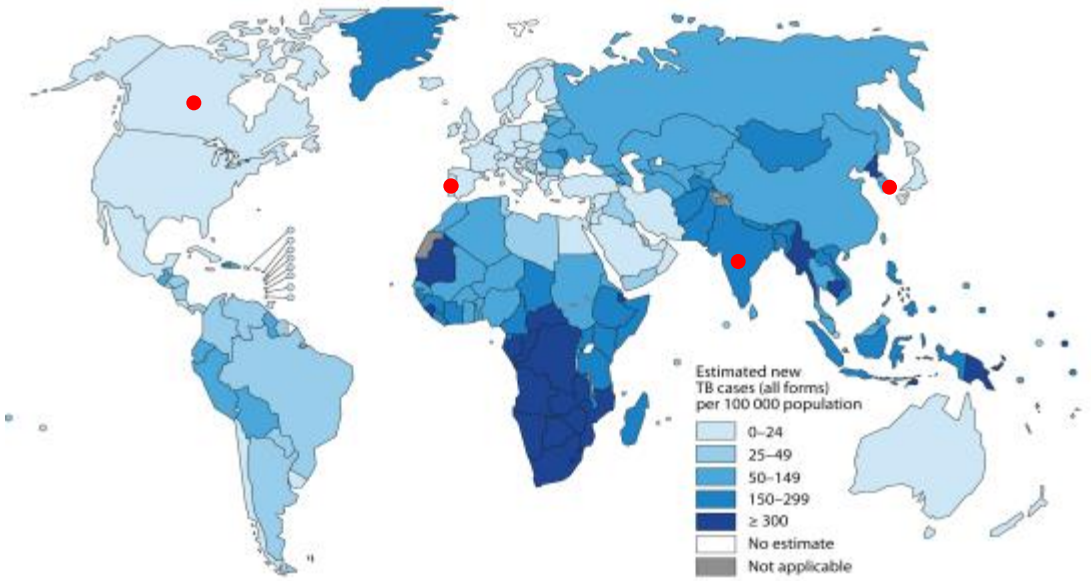
	Total no. patients included	Mild to moderate *Candida* infection (%)						Severe *Candida* infections (%)	Overall (%)
		Vulvovaginal /genital	Oral	Skin	Esophageal	Nail	Unknown infection site		Total
Secukinumab	4,277	7 (0.2%)	15 (0.4%)	2 (0.05%)	2 (0.05%)	0 (0%)	56 (1.3%)	1 (0.02%)	83 (2.1%)
Brodalumab	4,431	0 (0%)	7 (0.2%)	0 (0%)	1 (0.02%)	0 (0%)	169 (3.8%)	0 (0%)	177 (4.0%)
Ixekizumab	4,113	40 (1.0%)	63 (1.5%)	20 (0.5%)	2 (0.05%)	1 (0.025%)	9 (0.2%)	0 (0%)	135 (3.3%)
Etanercept	1,065	4 (0.4%)	1 (0.1%)	0 (0%)	0 (0%)	0 (0%)	4 (0.4%)	0 (0%)	9 (0.8%)
Ustekinumab	613	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	14 (2.3%)	0 (0%)	14 (2.3%)
Placebo	2,323	3 (0.1%)	2 (0.09%)	1 (0.04%)	0 (0%)	0 (0%)	1 (0.04%)	0 (0%)	7 (0.3%)

Saunte Br J Dermatol 2016

Epidemiology of pathogens

TNFα blockers

Tuberculosis incidence rates in the overall population



Canada

2.19 x 1,000 patient-years

Portugal

13.3 x 1,000 patient-years

South Korea

19.9 x 1,000 patient-years

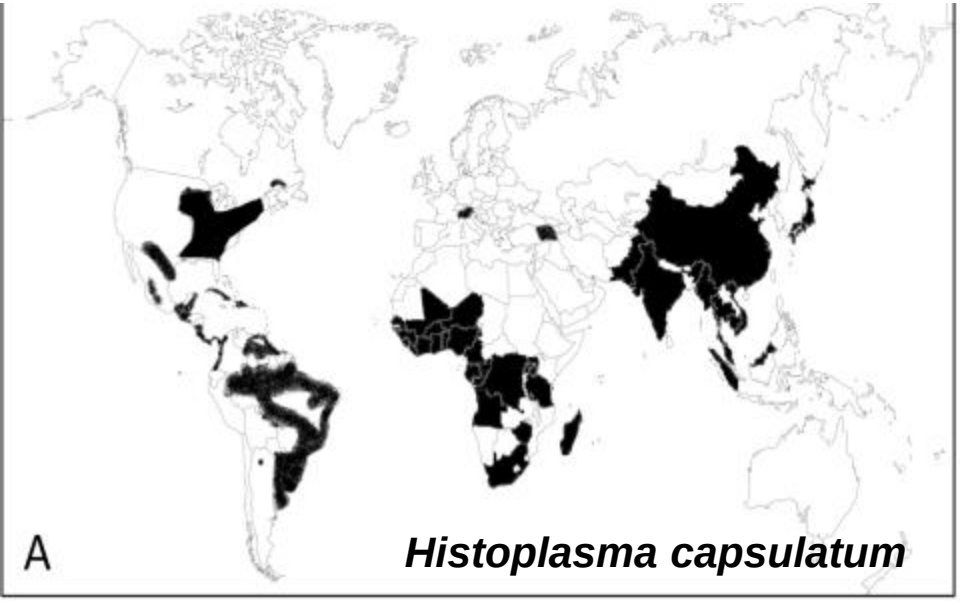
India

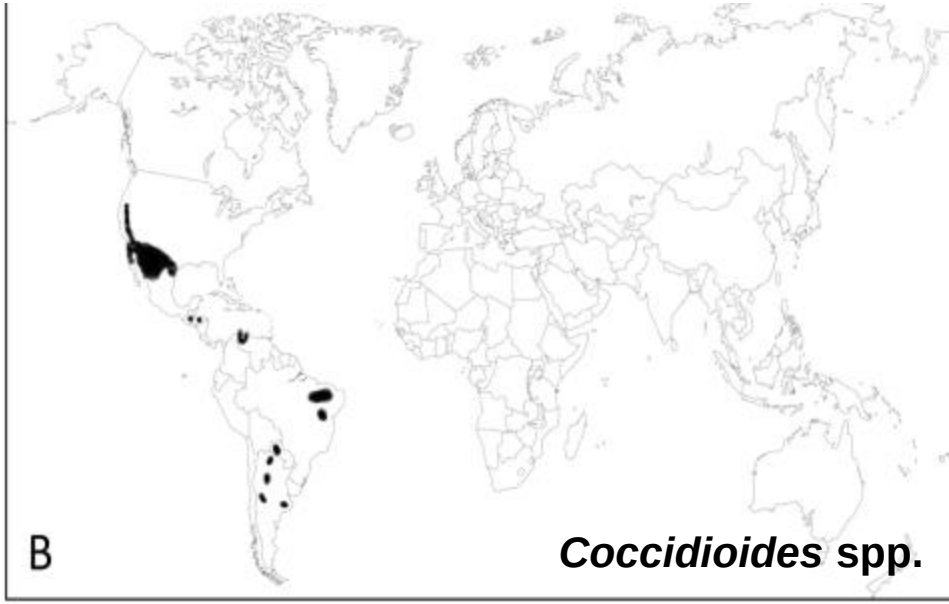
8.8% of treated patients

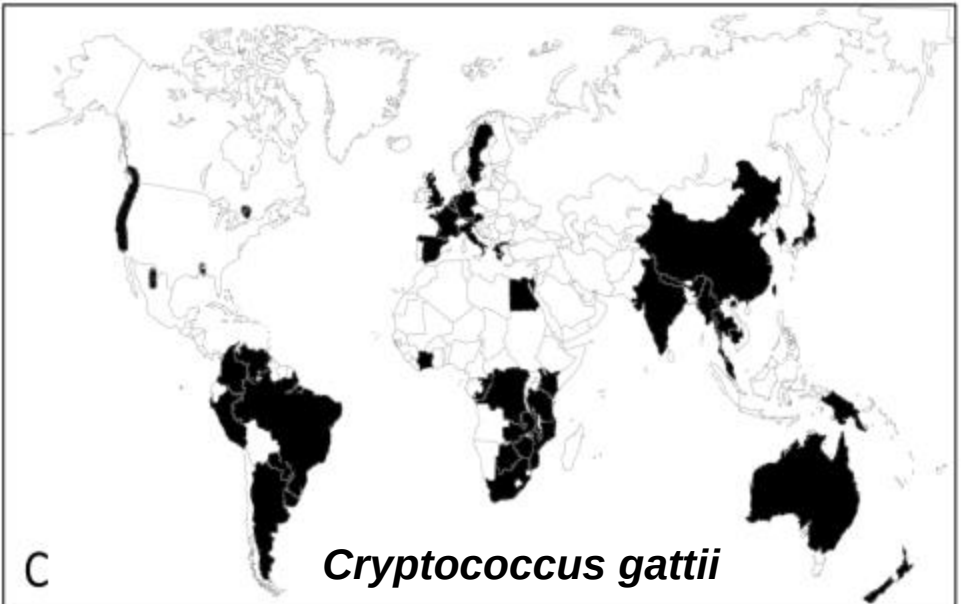
Brassard. Clin Infect Dis 2006.
Abreu J Crohnd Colitis 2013.
Kim World j Gastroenterol 2015.
Puri. J Gastroenterol Hepatol 2017

RA patients receiving biologics and worldwide fungal risk

Lortholary O *et al*. CID 2013



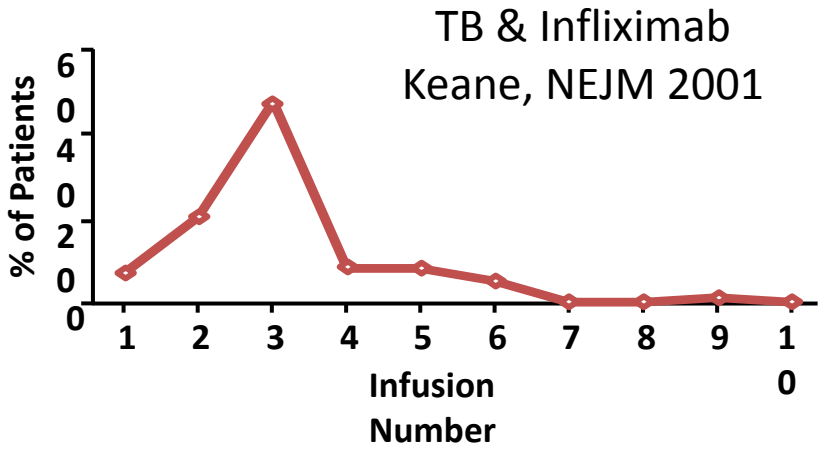




Biotherapy in rheumatoid arthritis

- **Biological (targeted) therapies**
  - Improved quality of life
  - Increased the risk of infection by 1.7
  - Increased serious infections [Ramiro ARD 2017] and hospitalizations
  - Mostly during first year
  - Serious infections: leading global cause of death

- **Particular concern:**
  - Severe bacterial infections
  - Mycobacterial / Fungal infections
  - Zoster / HBV replication
  - Travel-associated infections



- **Definition of OI** [Winthrop, ARD 2015]

Biologics-related infections and RA: not so easy to decipher !

Infections are increased in RA patients

High rate of co-morbidities in patients (diabetes, etc.)

Immunosuppressant use associated with disease severity (confounding by indication)

Pts receive multiple immunosuppressant (impact of steroids?)

How do we best to determine risk of individual drug?

Randomized clinical trials are not typically powered to detect adverse events such as rare infections

For registration

Relatively low number of highly selected patients with a limited exposure to the tested drug

Registries

- Heterogenous but real life patients
- Biger sample size for detecting a rare event

Infectious complications may not be observed during pivotal studies

Infliximab

Monoclonal antibody targeting TNF-α

IBD, rheumatoid arthritis, psoriatic arthritis, spondylitis, psoriasis

Remicade® 3-5 mg/Kg at weeks 0, 2 and 6

THE LANCET

Randomised double-blind comparison of chimeric monoclonal antibody to tumour necrosis factor α (cA2) versus placebo in rheumatoid arthritis

The New England Journal of Medicine

INFLIXIMAB AND METHOTREXATE IN THE TREATMENT OF RHEUMATOID ARTHRITIS

No reports on the occurrence of tuberculosis in patients treated with infliximab

The New England Journal of Medicine

INFLIXIMAB FOR THE TREATMENT OF FISTULAS IN PATIENTS WITH CROHN'S DISEASE

Elliot et al. *Lancet* 1994;344:1105-10.
Lipsky et al. *N Engl J Med* 2000;343:1594-602.
Present et al. *N Engl J Med* 1999;340:1398-405.

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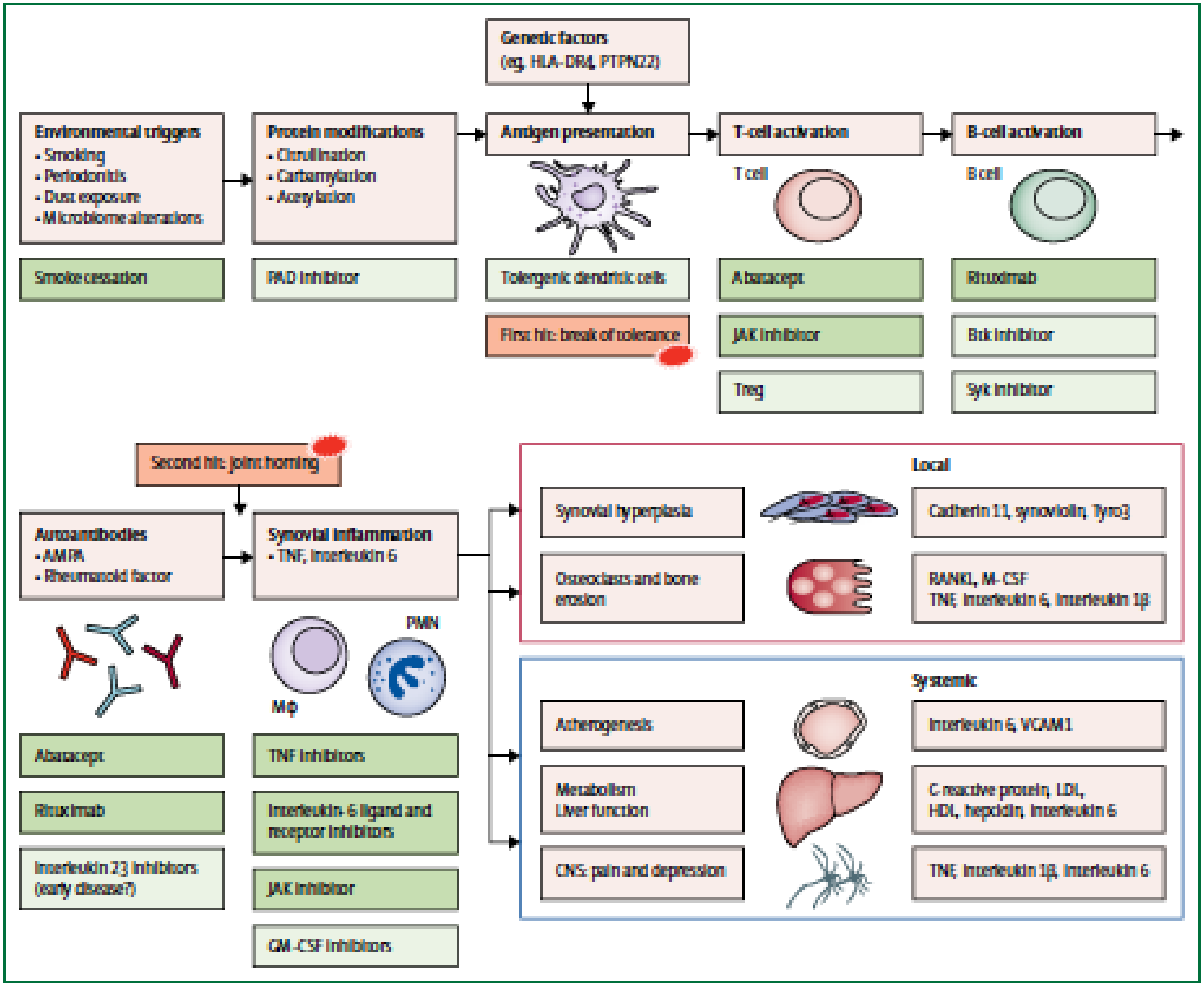
Data from the FDA's Adverse Events Reporting System (spontaneous AE reporting program)

Keane et al. *N Engl J Med* 2001;345:1098-104.

Current and future therapeutic approaches in RA



McInness & Schett, Lancet 2017

RHEUMATOLOGY

Rheumatology 2017;56:1746–1754
doi:10.1093/rheumatology/kex238
Advance Access publication 14 July 2017

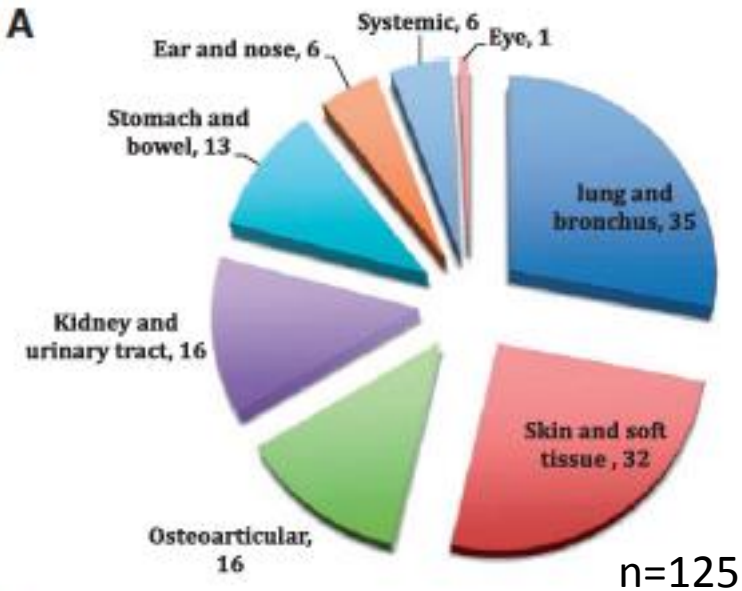
Original article

Risk factors of serious infections in patients with rheumatoid arthritis treated with tocilizumab in the French Registry REGATE

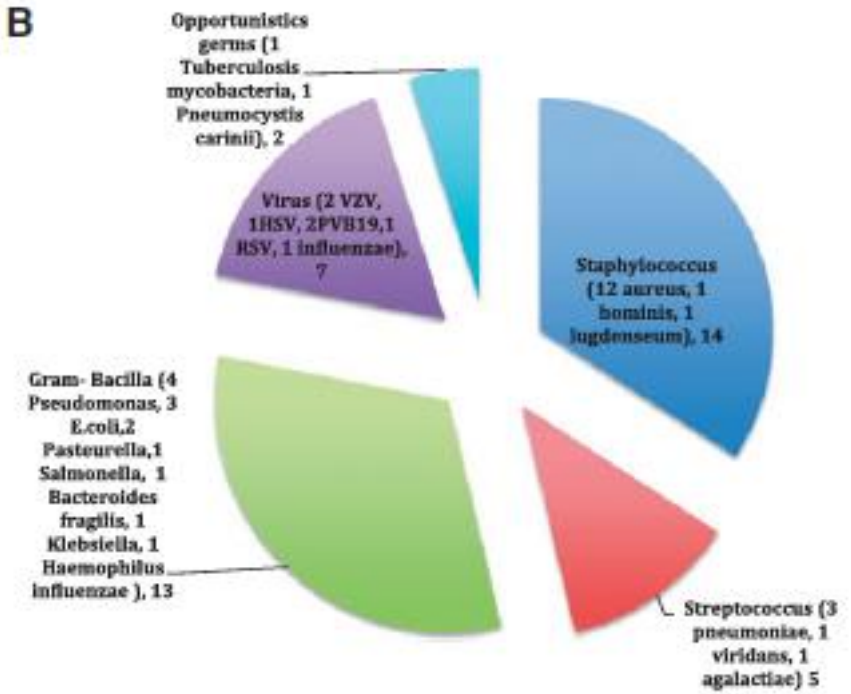
Jacques Morel[1], Arnaud Constantin[2], Gabriel Baron[3], Emmanuelle Dernis[4], René Marc Flipo[5], Stéphanie Rist[6], Bernard Combe[1], Jacques Eric Gottenberg[7], Thierry Schaeverbeke[8], Martin Soubrier[9], Olivier Vittecoq[10], Maxime Dougados[11], Alain Saraux[12], Xavier Mariette[13], Philippe Ravaud[3] and Jean Sibilia[7]

1491 pts, TCZ mean duration 12.8 mo

Risk factors at baseline	Hazard ratio (95% CI)	*P*-value
Age, per 10 years	1.14 (0.99, 1.32)	0.064
Disease duration, per 6 months	1.07 (0.96, 1.19)	0.21
APCA positive	0.56 (0.36, 0.88)	0.012
Initial ANC >5.0 G/l	1.94 (1.32, 2.85)	0.001
DMARDS combination, *n* (%)		
None	1	
MTX alone	1.14 (0.76, 1.71)	0.53
LEF alone	2.18 (1.22, 3.88)	0.009
Other	0.84 (0.33, 2.14)	0.72



n=125



n=41

Incidence 4.7/100 pt-years (4.1 Abatacept, 5 Rituximab, 3-6 anti-TNF)

Long-term safety of tofacitinib for the treatment of rheumatoid arthritis up to 8.5 years: integrated analysis of data from the global clinical trials

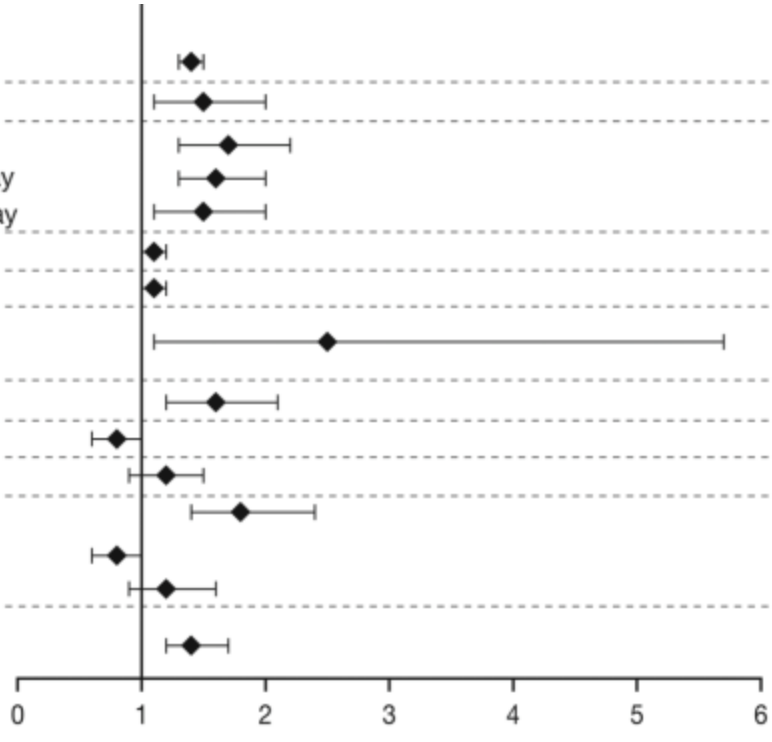
Stanley B Cohen,[1] Yoshiya Tanaka,[2] Xavier Mariette,[3] Jeffrey R Curtis,[4] Eun Bong Lee,[5] Peter Nash,[6] Kevin L Winthrop,[7] Christina Charles-Schoeman,[8] Krishan Thirunavukkarasu,[9] Ryan DeMasi,[10] Jamie Geier,[10] Kenneth Kwok,[10] Lisy Wang,[11] Richard Riese,[11] Jürgen Wollenhaupt[12]

Phase I to III up to March 2015; 6194 pts, 3.4 yrs

IR serious infections 2.7 (2.5-3); Herpes zoster 3.9 (3.6-4.2); 92% monodermatome

IR OI 0.3, tuberculosis 0.2; no significant increase overtime

Factors	Comparisons	HR	95% CI	p-value
Baseline age, years	Unit=10†	1.4	1.3, 1.5	<0.0001
Baseline COPD*	Yes vs No	1.5	1.1, 2.0	0.0145
Baseline glucocorticoid use	≥7.5 mg/day vs 0 mg/day	1.7	1.3, 2.2	0.0001
	0-<7.5 mg/day vs 0 mg/day	1.6	1.3, 2.0	
	Unknown dose vs 0 mg/day	1.5	1.1, 2.0	
Baseline HAQ-DI score	Unit=0.5†	1.1	1.0, 1.2	0.0078
Baseline body mass index	Unit=5†	1.1	1.0, 1.2	0.0320
Prior confirmed post-baseline lymphopenia <500 cells/μL‡	Unit=1†	2.5	1.1, 5.7	0.0249
Baseline diabetes	Yes vs No	1.6	1.2, 2.1	0.0009
Gender	Female vs Male	0.8	0.6, 1.0	0.0299
Line of therapy	3rd line vs 2nd line	1.2	0.9, 1.5	0.0399
Geographic region	Asia vs USA/Canada	1.8	1.4, 2.4	<0.0001
	Europe vs USA/Canada	0.8	0.6, 1.0	
	LA vs USA/Canada	1.2	0.9, 1.6	
Time-varying tofacitinib dose, mg BID	Unit=5†	1.4	1.2, 1.7	0.0003



Role of baseline co-factors

ARD 2017

Steroids increase the infectious risk in RA

40,933 eligible RA pts, 53 yrs, 77.4% women

	No GC	Very low dose GC[a] (≤5.0 mg)	Low-dose GC (≤7.5 mg)	High-dose GC (>7.5 mg)	Very high dose GC[b] (>20.0 mg)
All ages					
Total patient-years	23,654.2	4375.4	4603.1	1211.6	45.0
IR per 100 patient-years	3.9	6.4	6.4	13.3	24.5
(95% CI)	(3.63–4.13)	(5.65–7.17)	(5.68–7.16)	(11.32–15.51)	(12.21–43.76)
Ages <65 years					
Total patient-years	20,085.2	3463.1	3634.0	995.2	35.8
IR per 100 patient-years	3.2	4.7	4.7	11.7	22.3
(95% CI)	(2.91–3.40)	(4.04–5.52)	(4.00–5.44)	(9.63–13.98)	(9.64–43.98)
Ages ≥65 years					
Total patient-years	3,569.0	912.3	969.1	216.4	9.1
IR per 100 patient-years	8.0	12.6	12.8	20.8	32.9
(95% CI)	(7.06–8.94)	(10.41–15.13)	(10.64–15.26)	(15.17–27.83)	(6.77–95.99)

Schenfeld, Rheumatol Int 2017

Look for infectious sources: exogenous !

RMD Open
Rheumatic & Musculoskeletal Diseases

ORIGINAL ARTICLE

Risks of smoking and benefits of smoking cessation on hospitalisations for cardiovascular events and respiratory infection in patients with rheumatoid arthritis: a retrospective cohort study using the Clinical Practice Research Datalink

Rebecca M Joseph,[1,2] Mohammad Movahedi,[2] William G Dixon,[2,3,4] Deborah PM Symmons[2,4]

UK primary care electronic health records/hospital inpatient data

5677 RA pts, median age 61 years

RA patients should stop smoking !

Table 6 Cox regression analysis for time to first hospitalised respiratory tract infection after rheumatoid arthritis diagnosis

	Unadjusted, HR (95% CI)	Age-adjusted and sex-adjusted, HR (95% CI)	Fully adjusted*, HR (95% CI)
Smoking status			
Current vs never	1.62 (1.28 to 2.06)	2.18 (1.71 to 2.78)	1.78 (1.38 to 2.29)
Current vs former	0.79 (0.64 to 0.97)	1.34 (1.09 to 1.67)	1.29 (1.04 to 1.61)
Former vs never	2.06 (1.69 to 2.52)	1.62 (1.32 to 1.99)	1.38 (1.12 to 1.7)
Smoking cessation			
Per year since cessation, light smoker	0.92 (0.84 to 1.01)	0.86 (0.78 to 0.94)	0.84 (0.76 to 0.92)
Per year since cessation, heavy smoker	0.91 (0.82 to 1)	0.83 (0.75 to 0.92)	0.83 (0.75 to 0.92)
Heavy vs light smoker†	1.43 (0.9 to 2.27)	1.95 (1.21 to 3.14)	1.37 (0.82 to 2.26)
Interaction‡	0.98 (0.9 to 1.08)	0.96 (0.88 to 1.06)	0.99 (0.9 to 1.09)

Joseph, RMD Open 2017

Clinical Infectious Diseases

VIEWPOINTS

Call for Action: Invasive Fungal Infections Associated With Ibrutinib and Other Small Molecule Kinase Inhibitors Targeting Immune Signaling Pathways

Georgios Chamilos,[1,2] Michail S. Lionakis,[3] and Dimitrios P. Kontoyiannis[4]

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One fungus may hide another

Mrs C., 52 years-old

- Medical history :

  Chronic lymphocytic leukemia diagnosed in 2014 :

  – First line treatment (anemia, lymphocyte doubling time) : Fludarabine, Cyclophosphamide and Rituximab 5 cycles from March to June 2015

  – Second line treatment (fever, swelling of lymph nodes, neutropenia 0,6G/L): **Ibrutinib** started in September 2017

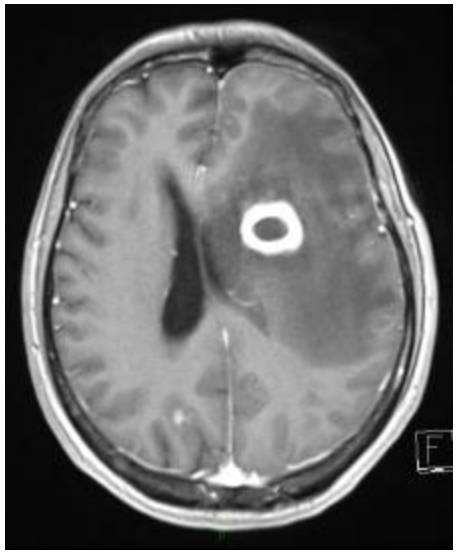
- Active smoking, several episodes of undocumented pneumonia in 2014-2015

- In February 2018, after 5 months of Ibrutinib : deterioration of general status with fever. Fluctuating neutropenia around 0,6G/L

- On March 18, 2017 : presented to hospital for two weeks history of confusion, behavior disorders, aggressiveness. No focal neurologic signs.
- Fever 38.3°C

- At that time, neutrophils = 0.6G/L

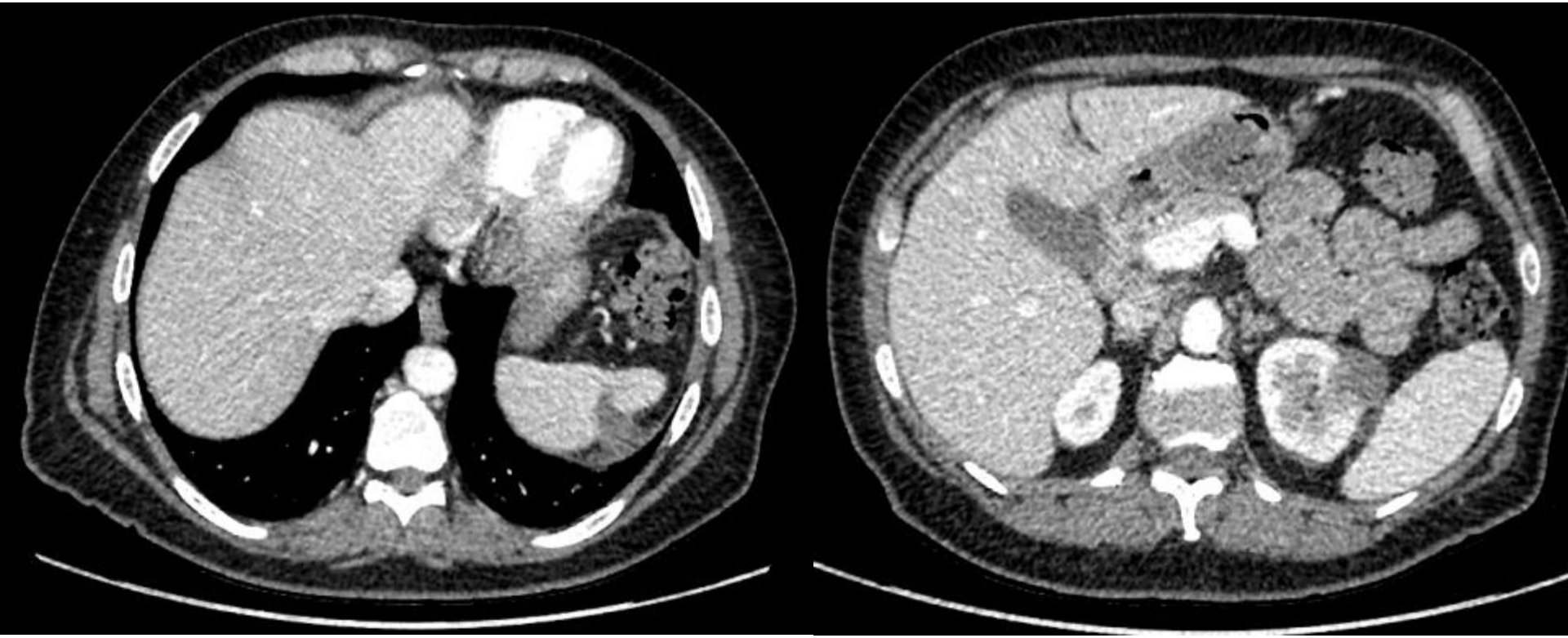
- Cerebral MRI was performed



- Mycological cultures were positive for ***Aspergillus fumigatus*** with negative direct examination.
- Serum galactomannan was negative.
- (1,3)-beta-d-glucan titers = 84 pg/mL.
- *Aspergillus fumigatus* PCR in serum was negative but not performed in cerebral tissue.

- **MICs (EUCAST method):**
  - Voriconazole 0.19mg/L
  - Isavuconazole 0.25mg/L
  - Posaconazole 0.094mg/L
  - Itraconazole 0.36mg/L
  - Caspofungin 0.094mg/L

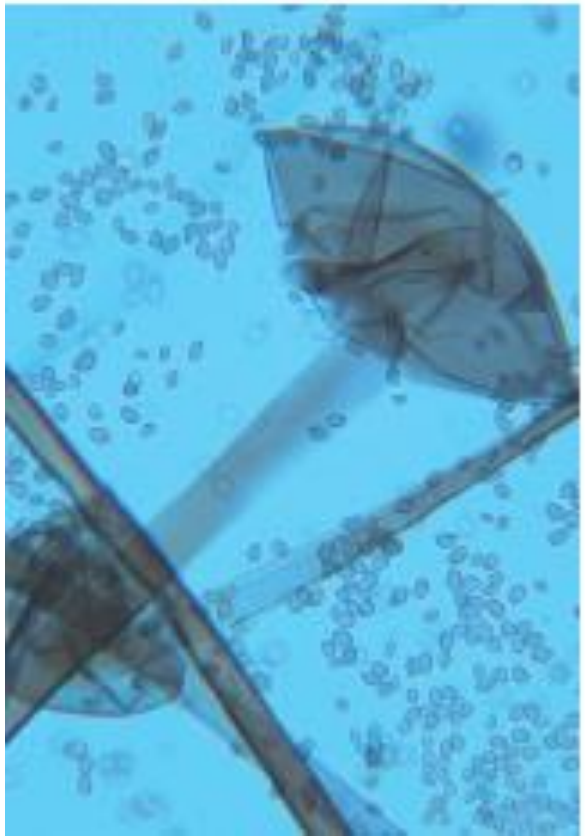
Sinus and thoracic CT scans were normal. Systematic abdominal scan :



Two lesions consistent with abscesses

- Lesion of the spleen
- Lesion of the upper pole of the left kidney

- CT guided biopsy of the kidney lesion :
  - Ischemic necrosis
  - Non-septate broad hyphae

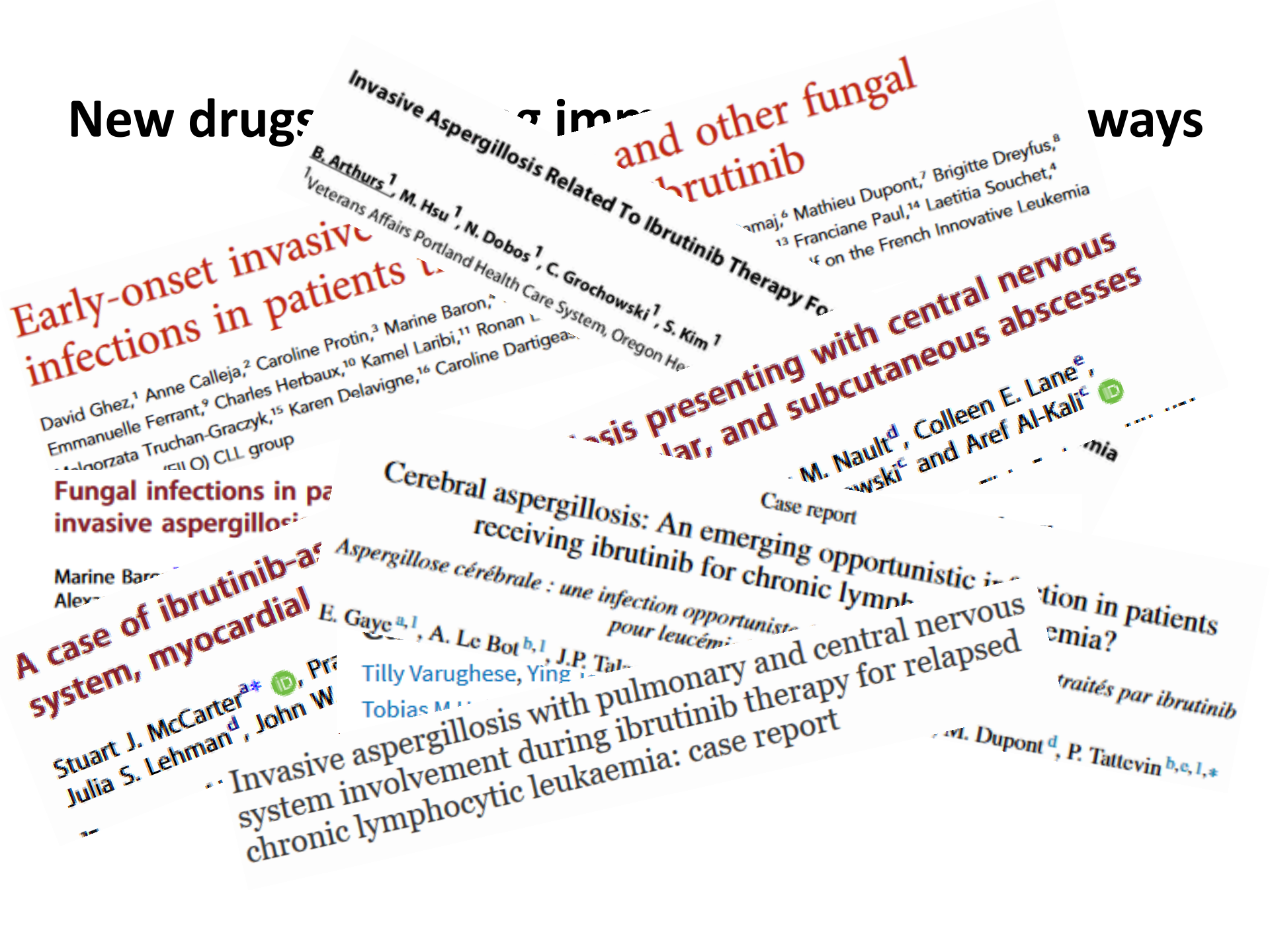


Diagnosis ?

Invasive mucormycosis confirmed by Mucorales fungal PCR which identified ***Lichtheimia* spp.**

Aspergillus fumigatus PCR was negative

Photograph from « Mucomycoses Actualités thérapeutiques » médecine/sciences 2013; 29:25-30


New drugs
ways
Invasive Aspergillosis Related To Ibrutinib Therapy
B. Arthurs, M. Hsu, N. Dobos, C. Grochowski, S. Kim
Veterans Affairs Portland Health Care System, Oregon
and other fungal
brutinib
Mathieu Dupont, Brigitte Dreyfus,
Franciane Paul, Laetitia Souchet,
on the French Innovative Leukemia
Early-onset invasive
infections in patients
David Ghez, Anne Calleja, Caroline Protin, Marine Baron,
Emmanuelle Ferrant, Charles Herbaux, Kamel Laribi, Ronan
Małgorzata Truchan-Graczyk, Karen Delavigne, Caroline Dartigea
(FILO) CLL group
sis presenting with central nervous
lar, and subcutaneous abscesses
M. Nault, Colleen E. Lane,
wski and Aref Al-Kali
Fungal infections in pa
invasive aspergillos
Marine Bar
Alex
A case of ibrutinib-as
system, myocardial
Stuart J. McCarter, Pra
Julia S. Lehman, John W
Cerebral aspergillosis: An emerging opportunistic i
receiving ibrutinib for chronic lymph
Case report
Aspergillose cérébrale : une infection opportunist
pour leucém
E. Gaye, A. Le Bot, J.P. Tal
Tilly Varughese, Ying
Tobias M
Invasive aspergillosis with pulmonary and central nervous
system involvement during ibrutinib therapy for relapsed
chronic lymphocytic leukaemia: case report
tion in patients
emia?
traités par ibrutinib
M. Dupont, P. Tattevin

blood

Brief Report

LYMPHOID NEOPLASIA

Early-onset invasive aspergillosis and other fungal infections in patients treated with ibrutinib

David Ghez,[1] Anne Calleja,[2] Caroline Protin,[3] Marine Baron,[4] Marie-Pierre Ledoux,[5] Gandhi Damaj,[6] Mathieu Dupont,[7] Brigitte Dreyfus,[8] Emmanuelle Ferrant,[9] Charles Herbaux,[10] Kamel Laribi,[11] Ronan Le Calloch,[12] Marion Malphettes,[13] Franciane Paul,[14] Laetitia Souchet,[4] Malgorzata Truchan-Graczyk,[15] Karen Delavigne,[16] Caroline Dartigeas,[17] and Loïc Ysebaert,[3] on behalf on the French Innovative Leukemia Organization (FILO) CLL group

Characteristics of invasive fungal infection	
Isolated microorganism	
Aspergillus fumigatus	16
Aspergillus nidulans	1
Zygomycetes (*Lichtheimia corymbifera*)	1
Cryptococcus neoformans	3
Pneumocystis jirovecii	1
Outcome	
Alive at last follow-up	16
Death	17
Because of IFI	9
Because of CLL	5
Other causes	3

Type of infection	
IA	27
Category	
Proven	17
Probable	9
Possible	1
Localization	
Pulmonary	15
Pulmonary + CNS	10
CNS + muscle abscess	1
Sinus	1
Cryptococcosis	4
Pneumocystis pneumonia	1
Mucormycosis	1

Major concern : high rate of CNS involvement in aspergillosis (11 of 27)

The first 6 months after starting Ibrutinib : 85%

Additionnal risk factor : anti-cancer chemotherapy within the last 6 months, neutorpenia, corticosteroid use. But not always…

Données récentes

Etude rétrospective MSKCC

378 patients traités par ibrutinib

Cancer	Patients, No. (%)
Chronic lymphocytic leukemia	165 (44)
Non-Hodgkin lymphoma	213 (56)
Mantle cell lymphoma	61 (16)
Diffuse large B-cell lymphoma	52 (13)
Waldenström macroglobulinemia	34 (9)
Follicular lymphoma	23 (6)
Marginal zone lymphoma	15 (4)
Primary central nervous system lymphoma	14 (4)
Other[a]	14 (4)

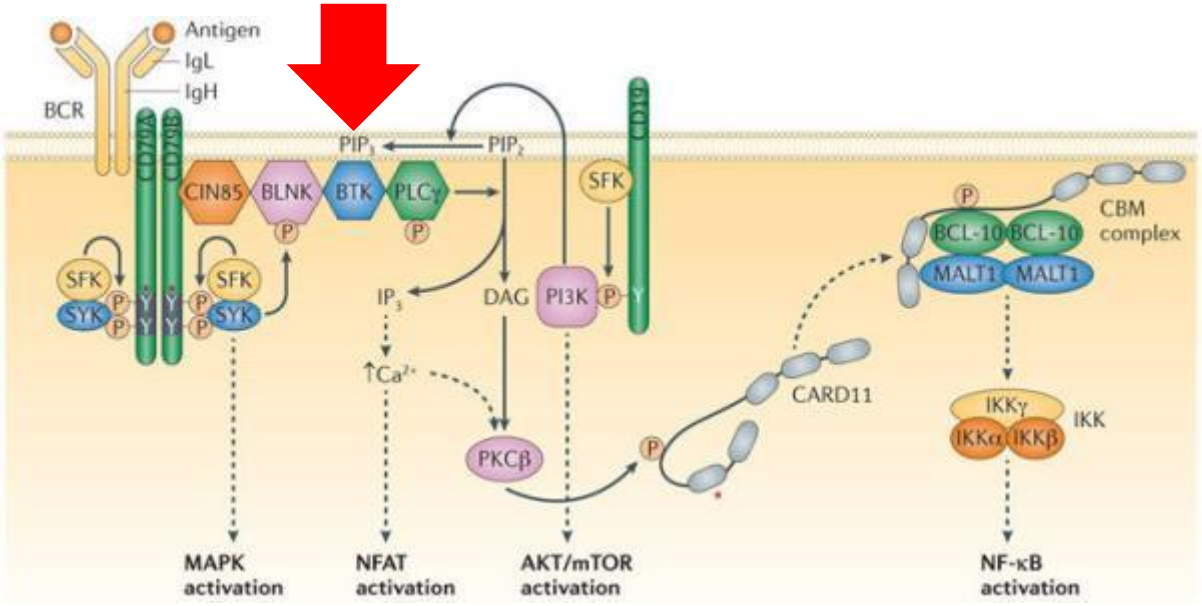
[a]Other cancers included multiple myeloma (5 patients), mycosis fungoides (4 patients), primary mediastinal large B-cell lymphoma (2 patients), and anaplastic large cell, γδ T-cell, and enteropathy-associated T-cell lymphoma (1 patient each).

- Médiane survenue : 136 jours
- IFI = 16 patients (37,2 %)
  - AI probable/prouvée : 8
  - Pneumocystose : 3
  - Cryptococcose : 3
  - Fongémie *C. albicans* : 1
- FDR : corticoïdes

Infections sévères chez 43 patients (11,4 %)

Varughese et al. CID 208

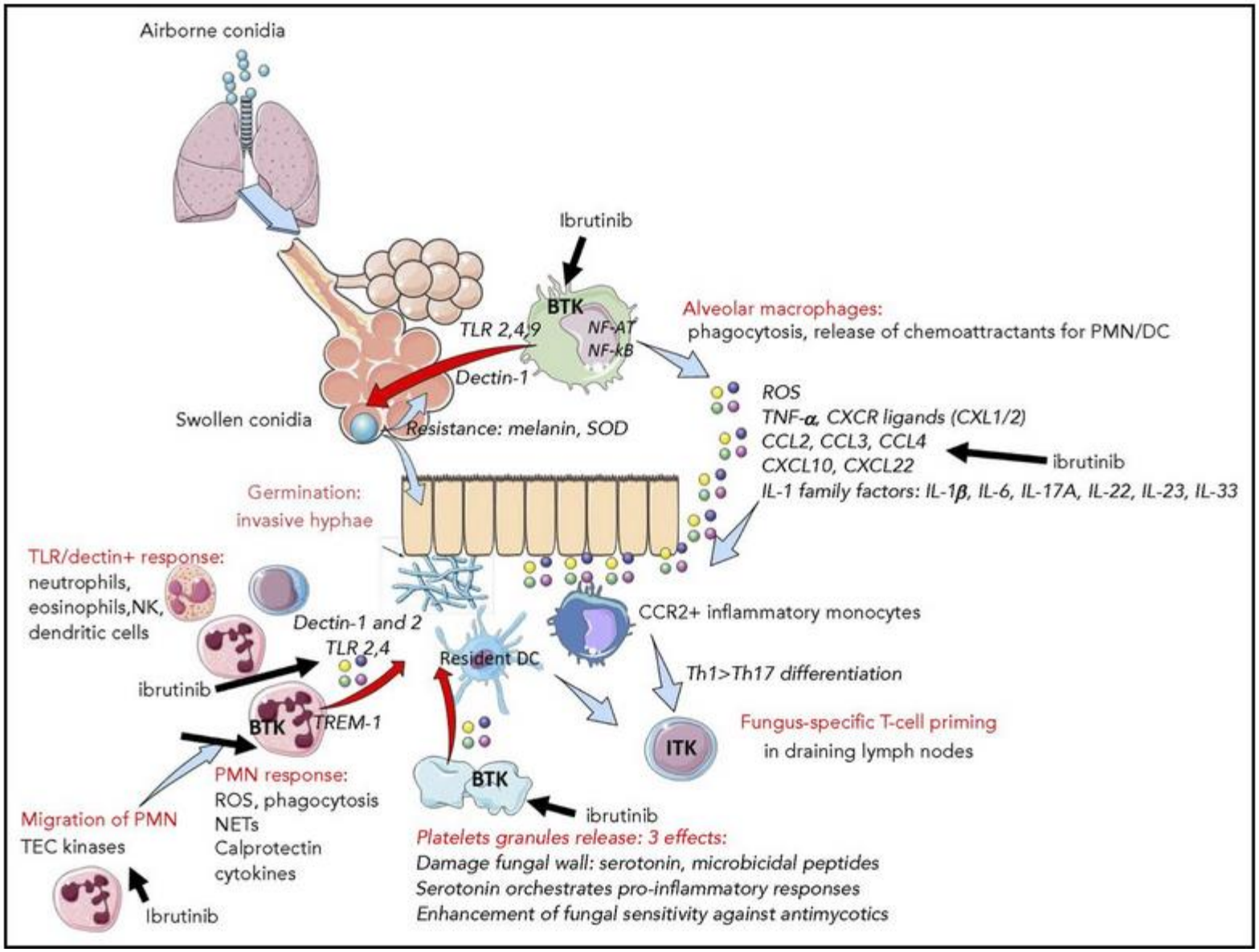
BTK : rôle central signalisation du BCR



1952 : Colonel Ogden Bruton: publication de la première description d'un déficit immunitaire primitif. Agammaglobulinemia. Pediatrics, 1952;9:722–728

1993 : Mise en évidence de mutations de BTK dans l'hypogammaglobulinémie liée à l'X (XLA)

From Young & Staudt. Nature reviews, 2013



Kerry Rogers. Ibrutinib and fungus : an invasive concern. Blood 2018;131:1882-4

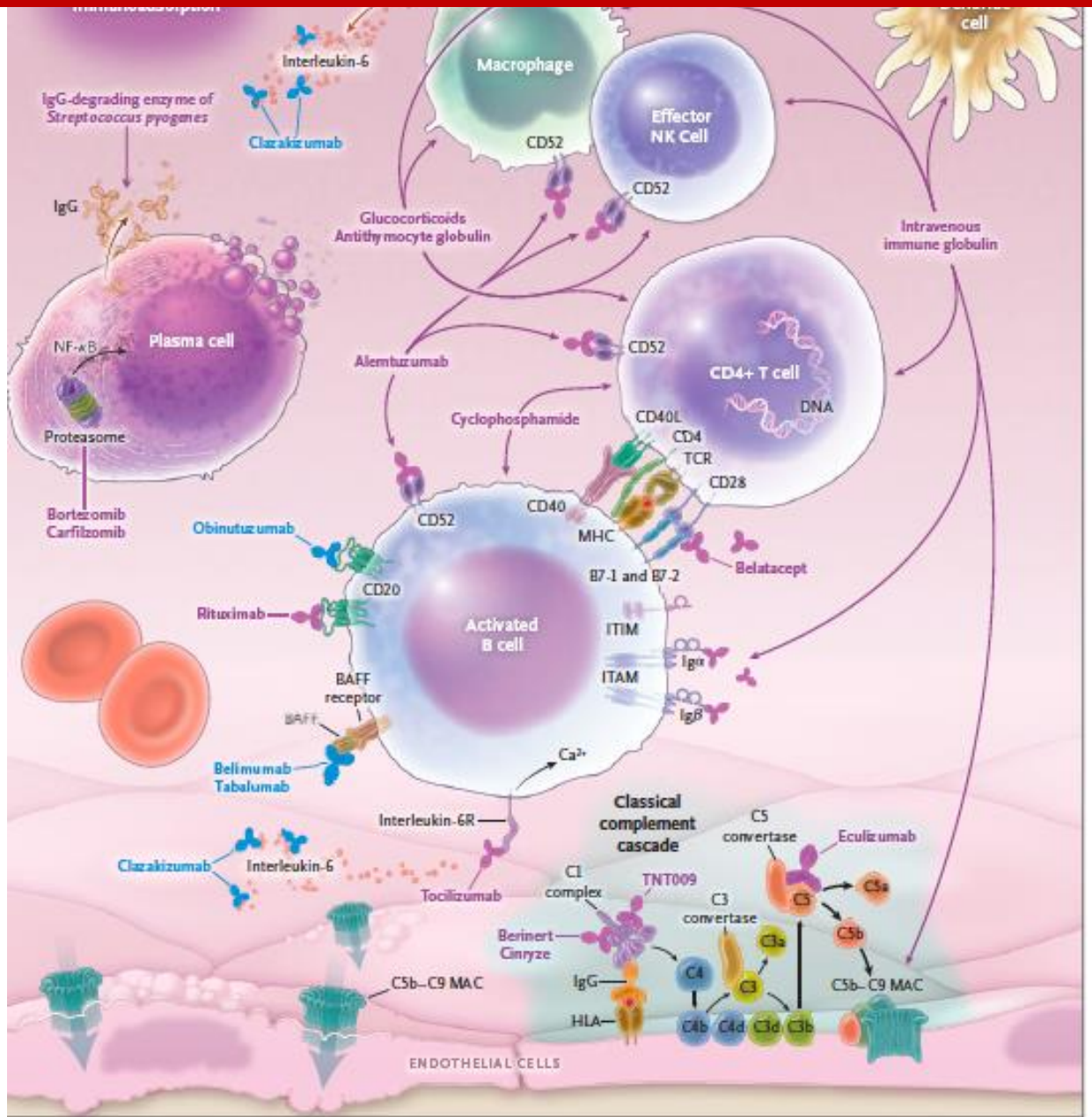
Table 4. Full List of FDA-Approved SMKIs and Relative Risk for Development of IFIs*

Compound (Trade Name; Manufacturer)	Mode of Action	Targets	Indication	Year of Approval	Comments
Imatinib (Gleevec; Novartis)	TKI	BCR-abl, Kit, PDGFR	Ph+ CML or ALL, aggressive systemic mastocytosis, CEL, DFSP, HES, GIST, MDS/MPD	2001	No evidence of OI
Gefitinib (Iressa; Astrazeneca)	TKI	EGFR	NSCLC	2003–2005, 2015	No evidence of infection
Erlotinib (Tarceva; OSI Pharmaceuticals)	TKI	EGFR	NSCLC, pancreatic cancer	2004	No evidence of OI; minimal risk for infection
Sorafenib (Nexavar; Bayer)	Dual TKIs	B/C-Raf, B-Raf (V600E), Kit, Flt3, RET, VEGFR1/2/3, PDGFRβ	Hepatocellular carcinoma, RCC, DTC	2005	No evidence of infection
Sunitinib (Sutent; Pfizer)	Multiple TKIs	PDGFRα/β, VEGFR1/2/3, Kit, Flt3, CSF-1R, RET	RCC, GIST, PNET	2006	Postmarketing reports of severe bacterial infections (sepsis, UTI, SSTI, respiratory); no evidence of OI
Dasatinib (Sprycel; Bristol-Myers Squibb)	TKI	BCR-Abl, Src, Lck, Yes, Fyn, Kit, EphA2, PDGFRβ	Ph+ CML, ALL	2006	**Bacterial infections, including sepsis, pneumonia, several cases of PJP, pos-**
Crizotinib (Xalkori; Pfizer)	Multiple TKIs	ALK, c-Met (HGFR), ROS, MST1R	ALK-positive NSCLC (2011), ROS-1–positive NSCLC (2016)	2011, 2016	URTIs, no evidence of OI
Ruxolitinib (Jakafi; Incyte)	TKI	JAK1/2	Myelofibrosis, PV	2011	**Warning box: serious bacterial (UTI), mycobacterial, fungal, viral (VZV, PML) infections**
Axitinib (Inlyta; Pfizer)	TKI	VEGFR1/2/3, PDGFRβ	RCC	2012	No evidence of infection
Bosutinib (Bosulif; Wyeth)	TKI	BCR-Abl, Src, Lyn, Hck	CML	2012	Respiratory tract infections; no evidence of OI
Regorafenib (Stivarga; Bayer)	Multiple TKIs	VEGFR1/2/3, BCR-Abl, B-Raf, B-Raf (V600E), Kit, PDGFRα/β, RET, FGFR1/2, Tie2, Eph2A	CRC	2012	No evidence of OI
Tofacitinib (Xeljanz; Pfizer)	TKI	JAK 1/3	Rheumatoid arthritis	2012	**Warning box: serious infections, including significant risk for OIs; significant risk for disseminated tuberculosis and IFIs, including cryptococcosis, PJP, *Candida* esophagitis; disseminated VZV; CMV**
Cabozantinib (Cometriq/ Cabometyx; Exelixis)	TKI	RET, Met, VEGFR1/2/3, Kit, TrkB, Flt3, Axl, Tie2	Metastatic medullary thyroid cancer, advanced RCC	2012, 2016	No evidence of OI; sepsis reported

Infections opportunistes surviennent avec traitements ciblant des voies de signalisation impliquées dans la réponse immunitaire :
Lck, Fyn, BTK, PI3K, JAK/STAT

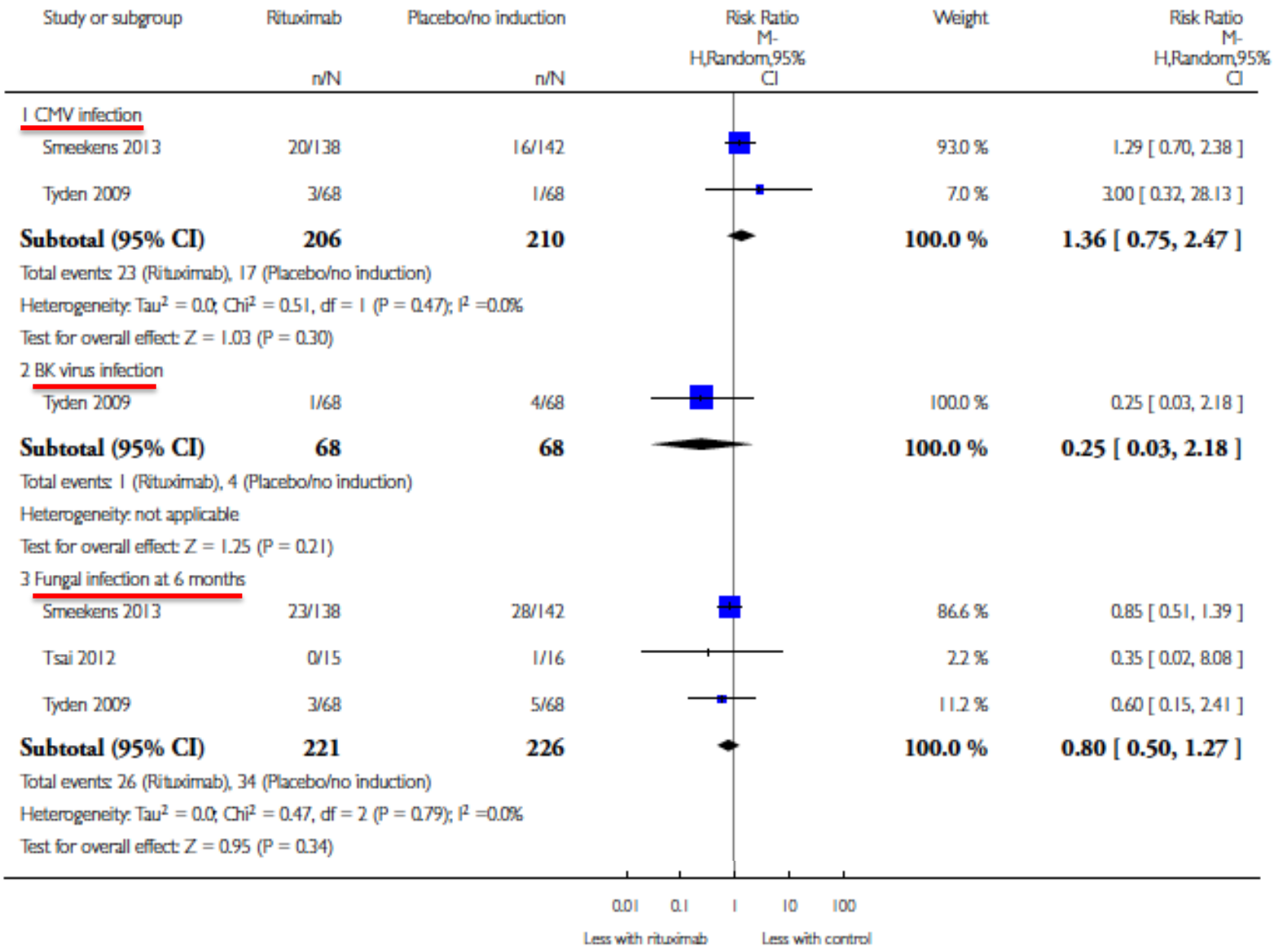
Chamilos et al.
CID 2018

« Non Conventional » induction therapy agents during kidney transplantation



Loupy, NEJM 2018

Rituximab alone does not increase the infection rate



Hill, Cochrane Databse of systematic reviews 2017

Rituximab Rituximab + ATG
High rate of infection-induced mortality

Infection-induced mortality (p=0.0007):
- Patients who received rituximab: 9.09%
- Patients who did not receive rituximab: 1.55%

Predictive factors for infection-induced mortality

	Odds ratio	$IC_{50\%}$ (ranges)	p
Recipient age	1.05	1.01–1.09	0.01
Diabetes mellitus	1.22	0.3–4.8	NS
Combined rituximab and RATG use	5.6	1.8–17.5	0.003
Cyclosporin A versus tacrolimus	3.23	0.87–12.02	NS
MPA use	0.47	0.15–1.47	NS
Bacterial infections	3.2	1.2–8.3	0.02
Fungal complications	3.32	1.07–10.3	0.04
Graft loss	0.98	0.25–3.95	NS

Kamar, AJT 2010

Belatacept (short focus)

- **Increased risk of viral infection:**
  - CMV
  - Polyoma viruses: PML…
  - EBV: PTLD

- **Increased risk of fungal infections** (Grinyo, AJKD, 2010)

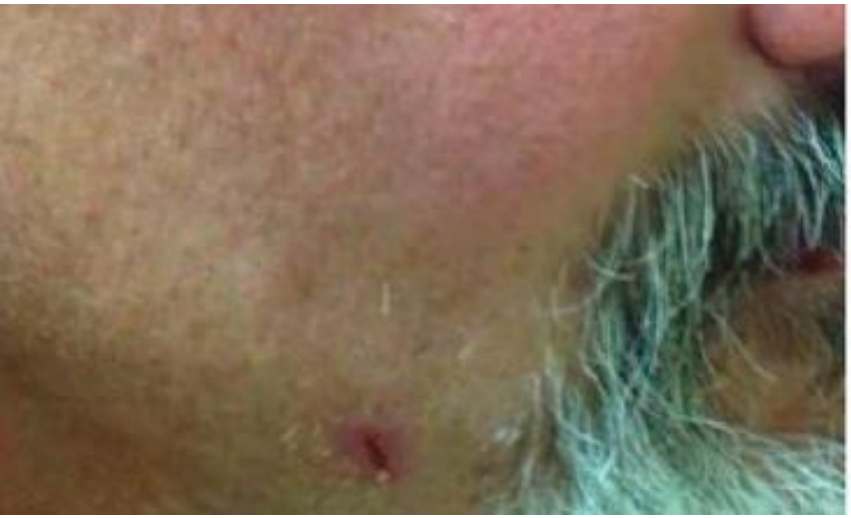
- **Increase risk of tuberculosis** (Viana, AJT 2019)

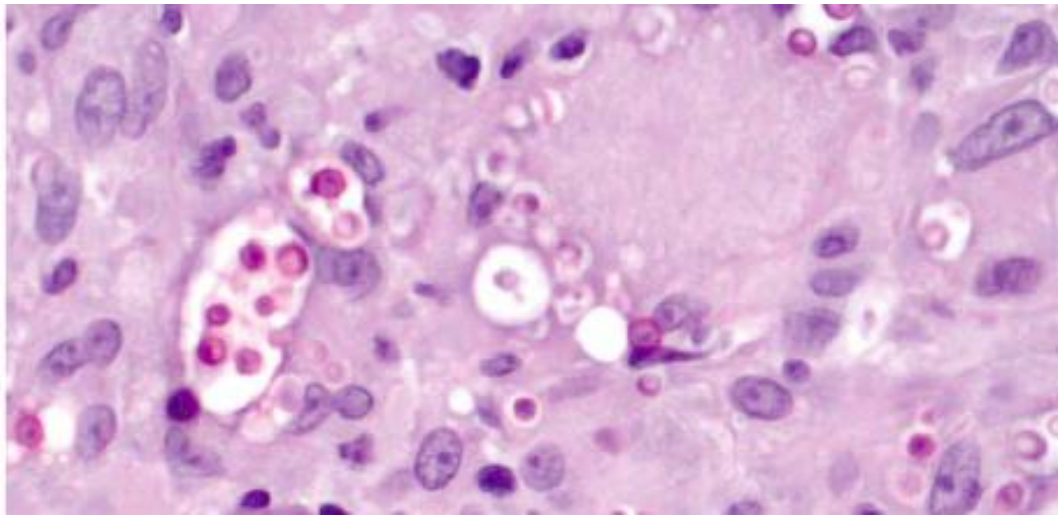
Parameters	Total	CNI/AZA	CNI/MPA	CNI/mTORi	Belatacept/MPA	Others
Patients at risk, n	11 453	6041	3915	807	34	656
Follow-up, days	1732 (745-3141)	1893 (831-3351)	1461 (617-2677)	2126 (968-3569)	3077 (2042-3077)	1642 (573-2946)
Time to TB diagnosis, mo	18·8 (7.3-58.6)	15 (7-550	18.3 (6.5-47.7)	31.4 (10.2-59.7)	12.5 (5.0-60.1)	61.9 (47.7-70.3)
Patients with TB, n	152	57	63	23	5	4
Cumulative incidence, %	1.32	0.94	1.60	2.85	14.7	0.60
Incidence density	235	156	326	450	2233	130
Relative risk, HR (95% CI)		Reference	1.62 (1.13-2.34)	2.45 (1.49-4.02)	13.14 (5.27-32.79)	1.54 (0.76-3.09)

DeRen Huang, MD, PhD

DISSEMINATED CRYPTOCOCCOSIS IN A PATIENT WITH MULTIPLE SCLEROSIS TREATED WITH FINGOLIMOD

Neurology 85 September 15, 2015





- 50-year old man with MS
- No DMT for 3 years and previously IFN
- Fingolimod 0.5 for 3 years 1/2
- Lymphopenia : 500/mm^3; no monocytopenia
- Initially afebrile, headache with no nuchal rigidity
- Disseminated cryptococcosis (CSF/skin and …?)
- Serum CrAg: 1/128

Cryptococcosis and fingolimod
(Sept 9th, 2015)

Cryptococcal meningitis : 9 cases

- Median age : 51 yrs;
- Fingolimod 21 to 52 months, median 36 months
- No history of HIV, SOT, malignancy, sarcoidosis or cirrhosis
- Chronic or recent use of steroids 4/9 patients
- Prior Isuppr: natalizumab 8y, 1 azathioprine, none (notified) 5
- Lymphocytes usual values found during fingolimod with CD4 26 to 66/mm^3 in 5/9 notified
- Eight cured, one death

Seven other cases : 2 pulmonary (1 asymptomatic nodule with granuloma) and 5 cutaneous infections (3 isolated)

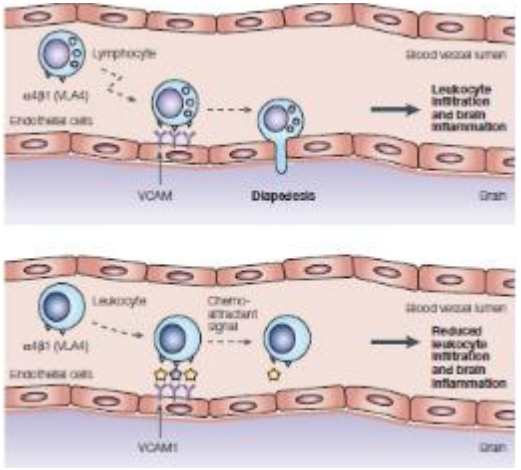
Cryptococcal meningitis in a multiple sclerosis patient taking natalizumab

Ac monoclonal anti intégrine α4

Reuben Mari Valenzuela [a], John H. Pula [a], Dennis Garwacki [a], John Cotter [b], Jorge C. Kattah

Journal of the Neurological Sciences 340 (2014) 109–111

- 49 years-old man with MS
- Glatiramer acetate + IFN
- 2 years natalizumab
- Cryptococcal meningitis: ATF + natalizumab withdrawal
- 2 months later : lethargy with decreased visual acuity
- Inflammatory lesions of white matter
  - Cryptococcal IRIS ???; MS activity



Conclusion

- Ever increasing number of therapeutic families and indications: real challenge for the ID clinician
- Relative value of pivotal trials to detect rare infectious events
- Role of post-marketing surveillance and open label extension studies
- Complexities in the assessment of attributable risk of infection
- Role of co-morbidities AND STEROIDS
- Contributing factors beyond specific mode of action
- Need for multicenter registries and multidisciplinary approaches
- Need for new vaccines trials in biotherapy treated pts
- Better define when biologics can be restarted after severe infection

ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

CMI CLINICAL MICROBIOLOGY AND INFECTION

ESCMID

ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the Safety of targeted and biological therapies: an infectious diseases perspective

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