Biothérapies et risque infectieux

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DESC Infectiologie – 1er février 2019

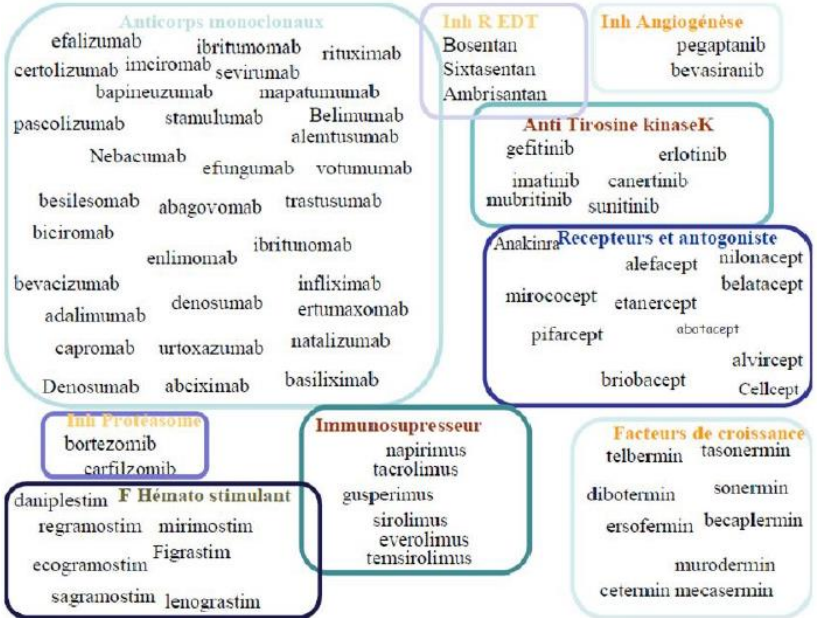
Biothérapies et infections

- Objectifs:
  - Identifier les principales biothérapies utilisées
    - Focus sur affections rhumatologiques et anti-TNF
  - En se plaçant du point de vue de l'infectiologue « généraliste »=
    1. Évaluation
    2. Gestion
    3. Prévention

    } du risque infectieux

Biothérapie: définition

- Biothérapie = immunomodulateur biologique
- Va impacter sur les déterminants de nombreuses affections inflammatoires à médiation immunitaire
- Et contribuer à améliorer la prise en charge/le devenir des patients atteints de ces affections



La nomenclature: Ac monoclonaux

- Dernière syllabe = mab = Monoclonal AntiBody
- **Avant-dernière syllabe = structure**
  - mo- : murin
  - xi- : chimérique murin-humain (infliximab, rituximab …)
  - zu- : humanisé
  - mu- : humain (adalimumab …)
- **Antépénultième syllabe = cible**
  - tu- : anti-tumoral (alemtuzumab …)
  - li- : anti-inflammatoire (adalimumab …)
  - vi- : antiviral (pavilizumab …)
  - ki- : cytokine (secukimumab)

Les biothérapies…ciblant les antigènes de surface lymphocytaires **CD19, CD20 et CD52**

Description of the main agents targeting surface antigens on lymphoid cells

Agent	Mechanism of action	Status of development (year of approval)	Approved indications	Off-label or experimental uses	Use as single agent	Use as first-line treatment	Cellular expression	Type of immunity impairment
Blinatumomab	Bispecific CD19-directed $CD3^+$ T-cell engager	Approved, EMA (2015), FDA (2014)	Ph-negative and Ph-positive relapsed or refractory B-cell precursor ALL	DLBCL	Yes	No	B cells (including earlier stages), follicular dendritic cells	B cells, HGG, impaired B-cell-dependent T-cell activation
Inebilizumab (previously MEDI-551)	Anti-CD19 monoclonal antibody	Phase 2 and 3 studies in NMO; phase 2 in CLL, SS, B-cell lymphoma and MS; phase 1 in MM	NA	NA	Yes	No		
Combotox	Immunotoxins targeting CD22 and CD19	Phase 2 studies in ALL ongoing	NA	NA	Yes	No	See CD19 and CD 22 agents	See CD19 and CD22 agents
Rituximab	Anti-CD20 monoclonal antibody	Approved, EMA and FDA (1998)	DLCBL, low-grade NHL or follicular lymphoma, CLL, RA, Wegener granulomatosis, microscopic polyangiitis	MS, GvHD, ITP, SLE, PTLD, autoimmune neuropathies or cytopenias, Rasmussen encephalitis, pemphigus vulgaris	Yes	Yes	B cells excluding plasma cells and B-cell precursors	T- and B-cell subsets
Obinutuzumab	Anti-CD20 monoclonal	Approved, EMA (2014), FDA	CLL, relapsed or refractory	ODD for marginal disorder	Yes	Yes	Same as other	Potentially T- and B-cell
Ocaratuzumab	Anti-CD20 monoclonal antibody	Phase 1 and 2 trials in haematological malignancies; phase 3 in pemphigus	NA	No	Potentially yes	NA	Same as other CD20-targeted agents	Potentially T- and B-cell subsets (no long-term data available)
^{90}Y-ibritumomab tiuxetan	Anti-CD20 monoclonal antibody, delivery of radioactive isotope	Approved (2002)	Relapsed low-grade NHL or follicular lymphoma, consolidation therapy in follicular lymphoma	No	Yes	No	Same as other CD20-targeted agents	T- and B-cell subsets and granulocytes (proximal radio-toxicity)
Alemtuzumab (MabCampath®)	Anti-CD52 monoclonal antibody	Approved, FDA (2001), EMA (2001, withdrawn in 2011)	CLL	MS, GvHD, conditioning regimens	Yes	No	Mature lymphocytes (not plasma cells)	Thymocytes, lymphocytes (not plasma cells), monocytes, macrophages and epithelial cells
Alemtuzumab (Lemtrada®)	Anti-CD52 monoclonal antibody	Approved, EMA (2013), FDA (2014)	MS	No	Yes	No		

ALL, acute lymphoblastic leukaemia; CLL, chronic lymphocytic leukaemia; DLBCL, diffuse large B-cell lymphoma; EMA, European Medicines Agency; FDA, Food and Drug Administration; GvHD, graft versus host disease; HGG, hypogammaglobulinaemia; ITP, immune thrombocytopenic purpura; MS, multiple sclerosis; MTX, methotrexate; NHL, non-Hodgkin's lymphoma; NMO, neuromyelitis optica; ODD, orphan drug designation; Ph, Philadelphia chromosome; PTLD, post-transplant lymphoproliferative disorder; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SS, systemic sclerosis.

CD19: *blinatumomab, inebilizumab, combotox*
CD20: *rituximab, obinutuzumab, ofatumumab, ocrelizumab, veltuzumab, ublituximab, ocaratuzumab,*
CD52: *alemtuzumab*

Clinical Microbiology and Infection 24 (2018)

Les biothérapies…ciblant les antigènes de surface lymphocytaires/myéloïdes **CD22, CD30, CD33, CD38, CD40, SLAMF-7 CCR4**

Description of the main agents targeting lymphoid and myeloid cell surface antigens

Agent	Mechanism of action	Status of development (year of approval)	Approved indications	Off-label or experimental uses	Use as single agent/ combination	Use as first-line treatment	Cellular expression
Epratuzumab	Anti-CD22 monoclonal antibody (also conjugated with the topoisomerase I inhibitor SN-38)	Phase 1 and 2 trials in follicular lymphoma, NHL, ALL; phase 3 RCT in SLE	NA	Refractory or relapsed DLBCL, previously untreated DLBCL, refractory or relapsed follicular lymphoma, ALL	Yes/yes	Yes	B-cells (mature and malignant)
Inotuzumab ozogamicin	Anti-CD22 monoclonal antibody conjugated with a calicheamicin agent	Approved, FDA (2017) Studies as single agent or combined with rituximab in refractory or relapsed NHL	Relapsed or refractory B-cell ALL	Follicular lymphoma, aggressive NHL (DLBCL)	Yes/yes	No	
Moxetumomab pasudotox	Variable fragment of anti-CD22 monoclonal antibody conjugated with *Pseudomonas* ex	Phase 3 trial in hairy cell leukemia; phase 1 studies in NHL and CLL; phase 2 trial in ALL	FDA ODD (2016) for hairy cell leukemia	ALL, NHL, CLL	Yes/no	No	
Brentuximab vedotin	An an an MM						
Gemtuzumab ozogamicin	An an wi ag						s,
Daratumumab	An						1 B-
	antibodies, enhancing	FDA (2015)	MM	amyloidosis, MDS			cells, activated T-cells and
Isatuximab	antitumor activity, modulation of CD38 ectoenzyme function (immunomodulation)	Phase 2 study in MM	NA	ALL, CD38-positive haematological malignancies	Yes/yes	No	germinal centre B-cells
Dacetuzumab	Anti-CD40 monoclonal antibody	Phase 2 in DLBCL; phase 1 in MM and CLL	NA	MM, CLL	Yes/yes	No	B-cells, monocytes, macrophages, follicular DCs, fibroblasts and keratinocytes
Elotuzumab	Anti-CD319 (SLAMF7) monoclonal antibody	Approved, EMA (2016), FDA (2015)	Previously treated MM	Naive MM	No/yes	No	Germinal centre B-cells, follicular DCs
Mogamulizumab	Anti-CCR4 monoclonal antibody	Approved, Japanese Ministry of Health, Labour and Welfare (2012)	Relapsed or refractory ATLL, peripheral and cutaneous T-cell lymphoma	Solid tumors and HTLV-1-associated myelopathy/tropical spastic paraparesis	Yes/no (only in ongoing studies)	Yes	ATLL cells, highly immunosuppressive Treg subset

Epratuzumab, inotuzumab, moxetumomab, brentuximab, gemtuzumab, daratumumab, isatuximab, dacetuzumab, elotuzumab,mogamulizumab, …

ALL, acute lymphoblastic leukaemia; ATLL, adult T-cell leukaemia/lymphoma; CLL, chronic lymphocytic leukaemia; DCs, dendritic cells; DLBCL, diffuse large B-cell lymphoma; EMA, European Medicines Agency; FDA, Food and Drug Administration; HTLV-1, human T-cell lymphotropic virus type 1; MDS, myelodysplastic syndrome; MM, multiple myeloma; MMAE, monomethyl auristatin A; NA, not available; NHL, non-Hodgkin's lymphoma; ODD, orphan drug designation; SLE, systemic lupus erythematosus.

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Les biothérapies…voies de signalisation intracellulaires

Agents	Pathway affected	Approved indications (regulatory agency)	Type of regimen	Expected impact of immune function
Imatinib, dasatinib, nilotinib, bosutinib, ponatinib	BCR-ABL, c-Kyt, other off-target kinases	**Imatinib:** Ph+ CML and ALL, MDS/MPD, hypereosinophilic syndrome and/or chronic eosinophilic leukemia, GIST (FDA and EMA), systemic mastocytosis, dermatofibrosarcoma protuberans (FDA only) **Remaining agents:** Ph+ CML	Monotherapy or sequential therapy	Neutropenia, reduced T-cell activation and proliferation, inhibition of CD34+ DCs differentiation (imatinib)
Vemurafenib, dabrafenib, encorafenib, trametinib, cobimetinib, selumetinib,				
Ibrutinib, acalabrutinib				haling HGG
Idelalisib, buparlisib, rigosertib, duvelisib				haling,
Venetoclax	Bcl-2	del(17p) CLL (FDA and EMA)	Monotherapy	Depletion of DCs, reduced IFN-α production (animal model only)
Ruxolitinib, tofacitinib, baricitinib	**JAK**/STAT	**Ruxolitinib:** polycythemia vera, myelofibrosis (FDA and EMA) **Tofacitinib:** rheumatoid arthritis (FDA and EMA) **Baricitinib:** rheumatoid arthritis (EMA only)	Monotherapy or combined with methotrexate or non-biologic DMARDs (rheumatoid arthritis)	Inhibition of Th1 and Th17 cells differentiation, inhibition of cytokine secretion, reduction of Tregs, impaired DCs function and migration

Tyrosine kinase Bruton: ibrutinib, acalabrutinib,
JAK/STAT: ruxolinitib, tofacitinib, baricitinib
Autres: Imatimib, dasatinib, nilotinib, bosutinib, ponatinib, vemurafenib, dabrafenib, encorafenib, trametinib, cobimetinib, selumetinib, idelalisib buparlisib, rigosertib, duvelisib, venetoclax, …

Clinical Microbiology and Infection 24 (2018)

Les biothérapies…récepteurs cellulaires de surface et voies de signalisation associées

Agents	Targeted molecule or pathway	Currently approved indications	Increased risk of infection	Observations and recommendations
Bevacizumab, panitumumab, aflibercept	VEGF-A/B, PlGF	CRC, breast cancer, NSCLC, RCC, ovarian cancer, fallopian tube cancer, primary peritoneal cancer, cervical cancer	Major	• Increase in risk of infection (likely due to drug-induced neutropaenia) • Increased risk of gastrointestinal perforation (with secondary peritonitis and bacteraemia), particularly in patients with CRC, previous diverticulitis, radiotherapy or recent surgical or endoscopic procedures • No expected benefit from universal use of anti-infective
Ramucirumab, sorafenib, sunitinib, axitinib, pazopanib, regorafenib vandetanib, cabozantinib				
Cetuximab, panitumumab				steroids, moisturizer and sunscreen for first 6 weeks; doxycycline or minocycline for first 6–8 weeks)
Trastuzumab, trastuzumab emtansine, pertuzumab	ErbB2/HER2	HER2-positive breast cancer, HER2-positive gastric cancer	None	• No apparent increase in risk of infection (lower incidence of neutropaenia compared to conventional chemotherapy)
Erlotinib, gefitinib, afatinib, neratinib, lapatinib, osimertinib	Tyrosine kinase domains of EGFR/HER1, ErbB2/HER2 and other ErbB family members	NSCLC, pancreatic cancer	None	• No apparent increase in risk of infection (lower incidence of neutropaenia compared to conventional chemotherapy)

VEGFR: bevacizumab, panitumumab, aflibercept,
VEGFR tyrosine kinase: ramucirumab, sorafenib, sunitinib, axitinib, pazopanib, regorafenib, vandetanib, cabozantinib,
Autres: cetuximab, panitumumab, trastuzumab, pertuzumab, elrotinib, gefitinib, afatinib, neratinib, lapatinib, osimertinib…

CRC, colorectal carcinoma; EGFR, epidermal growth factor receptor; GIST, gastrointestinal stromal tumour; HCC, hepatocellular carcinoma; HER, human epidermal growth factor receptor; HNSCC, head and neck squamous cell carcinoma; NSCLC, non–small cell lung cancer; PDGF, platelet-derived growth factor; PlGF, placental growth factor; RCC, renal cell carcinoma; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

Clinical Microbiology and Infection 24 (2018)

Les biothérapies…inh checkpoints immuns, adhesion cellulaire, proteasome, …

Agent	Pathway affected	Current indications	Increased risk of infection	Observations
Ipilimumab, tremelimumab	CTLA-4	Melanoma	Variable	• No intrinsic increase in risk of infection. • Increased risk of infection in patients developing irAEs and treated with additional immunosuppressive (i.e. corticosteroids and/or TNF-α–targeted agents).
Nivolumab, pembrolizumab, atezolizumab	PD-1 or PD-L1	Melanoma, NSCLC, HNSCC, Hodgkin lymphoma, urothelial carcinoma, bladder carcinoma, metastatic RCC, tumour with microsatellite instability	Variable	• No intrinsic increase in risk of infection. • Increased risk of infection in patients developing irAEs and treated with additional immunosuppressive (i.e. corticosteroids and/or TNF-α–targeted agents).
Alefacept				
Natalizumab, vedolizumab, efalizumab				
				IgG antibody index, prior immunosuppression, and duration of treatment.
Fingolimod	Sphingosine-1-phosphate receptor	Relapsing-remitting MS	Mild	• Increase in risk of opportunistic infections, mainly due to herpesviruses (VZV). • Sustained, albeit reversible, peripheral blood lymphopenia (mostly affecting naive and central memory $CD4^+$ and $CD8^+$ T-cell subsets).
Bortezomib, carfilzomib, ixazomib	Ubiquitin proteasome pathway	MM, relapsed or refractory mantle-cell lymphoma	Major	• Increased risk of HZ and respiratory tract infections (including pneumonia). • Likely increased risk of influenza-related complications.

Ipilumab, tremelimumab, nivolumab, pembrolizumab, atezolizumab, alefacept, natalizumab, vedolizumab, efalizumab, fingolimod, bortezomib, carfilzomib, ixazomib, …

CTLA-4, cytotoxic T-lymphocyte–associated antigen 4; HNSCC, head and neck squamous-cell carcinoma; HZ, herpes zoster; irAE, immune-related adverse effect; JCV, John Cunningham polyomavirus; LFA, lymphocyte function-associated antigen; MS, multiple sclerosis; NSCLC, non–small-cell lung carcinoma; PD, programmed death; PD-L, PD programmed death ligand; PML, progressive multifocal leukoencephalopathy; RCC, renal-cell carcinoma; TNF, tumour necrosis factor.

Clinical Microbiology and Infection 24 (2018)

Les biothérapies…ciblant les effecteurs solubles (IL, complément, Ig)

Agents	Targeted molecule or pathway	Currently approved indications[a]
Anakinra, cabakinumab, gevokizumab, rilonacept	Interleukin-1α (IL-1α) and/or IL-1β	Rheumatoid arthritis, juvenile idiopathic arthritis,: cryopyrin-associated periodic syndromes, familial Mediterranean fever, tumour necrosis factor receptor-associated periodic syndrome, hyper-IgD syndrome/mevalonate kinase deficiency, Still's disease, gout
Mepolizumab, reslizumab		
Tocilizumab, siltuxumab		
Ustekinumab		
Secukinumab, ixekizumab, broda		
Omalizumab		
Eculizumab		

IL1: anakinra, cabakinumab, gevokizumab, rilonacept,
IL5: mepolizumab, reslizumab,
IL6: tocilizumab, siltuxumab,
IL12/23: ustekinumab,
IL17 secukimumab, brodalumab, ixekizumab
IgE: omalizumab,
Complément: eculizumab, …

Clinical Microbiology and Infection 24 (2018)

Les biothérapies…ciblant les effecteurs solubles: antiTNF

Agent (trade mark)	Type and mode of action	Approved indications	Off-label uses
Infliximab (Remicade®)	Human–mouse chimeric IgG1 monoclonal antibody	IBD (CD and UC), RA, AS, PsA, plaque psoriasis	Graft-versus-host disease, uveitis, Behçet's disease, skin disorders
Etanercept (Enbrel®)	Fusion protein of the soluble 75-kDa TNF-α receptor and human IgG1 antibody (hinge and FC regions)	RA, AS, JIA, PsA, plaque psoriasis	Pemphigus vulgaris, Behçet's disease, skin disorders
Adalimumab (Humira®)	Fully human IgG1 monoclonal antibody	IBD (CD and UC), RA, AS, JIA, PsA, plaque psoriasis, hidradenitis suppurativa and uveitis	Sarcoidosis, Behçet's disease, skin disorders
Golimumab (Simponi®)	Fully human IgG1 monoclonal antibody	UC, RA, AS, JIA, PsA	Plaque psoriasis, systemic lupus erythematosus, uveitis
Certolizumab pegol (Cimzia®)	Pegylated F(ab') fragment of humanized monoclonal antibody	CD (only FDA), RA, AS, PsA	Plaque psoriasis

AS, ankylosing spondylitis; CD, Crohn's disease; FDA, US Food and Drug Administration; IBD, inflammatory bowel disease; JIA, juvenile idiopathic arthritis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; TNF-α, tumour necrosis factor α; UC, ulcerative colitis.

Clinical Microbiology and Infection 24 (2018)

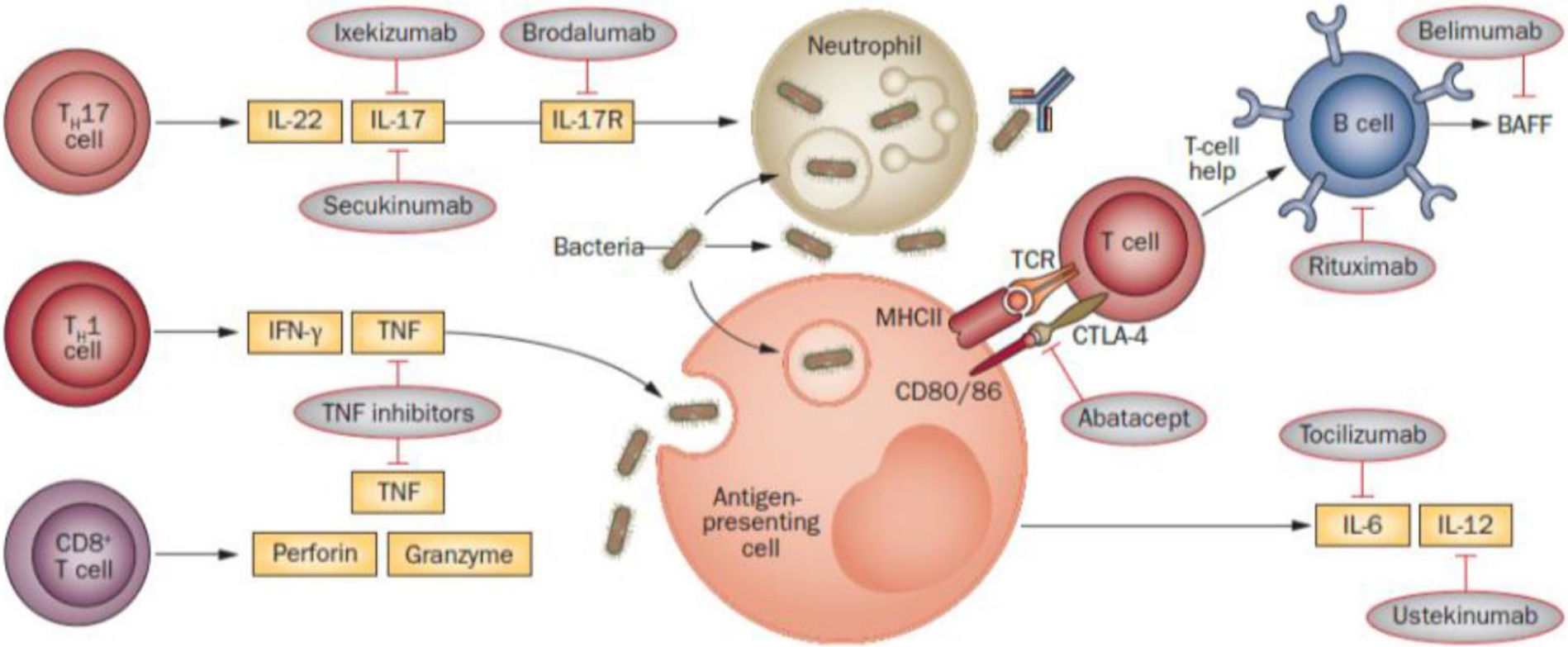
Les biothérapies… sans compter …

Targeted molecule	Agent	Approved or intended use
Platelet glycoprotein IIb/IIIa receptor	Abciximab	Platelet aggregation inhibitor
Dabigatran	Idarucizumab	Reversal of anticoagulant effects of dabigatran
Human cardiac myosin	^{111}In-imciromab	Cardiac imaging
Proprotein convertase subtilisin kexin type 9 (PCSK9)	Atezolizumab, evolocumab	Primary hypercholesterolaemia or mixed dyslipidaemia
Interleukin 2 receptor chain α (CD25)	Basiliximab, daclizumab	Prevention of rejection in solid organ transplantation
Vascular endothelial growth factor (VEGF)	Ranibizumab	Age-related macular degeneration
Receptor activator of nuclear factor κB ligand (RANKL)	Denosumab	Osteoporosis
Bacillus anthracis protective antigen	Obiltoxaximab	Inhalational anthrax
Respiratory syncytial virus (RSV) F protein	Palivizumab	Prevention of RSV infection
Clostridium difficile toxin B	Bezlotoxumab	*Clostridium difficile* infection
Fungal heat-shock protein 90 (Hsp90)	Efungumab	Invasive fungal disease

ESGICH, European Society of Clinical Microbiology and Infectious Diseases Study Group for Infections in Compromised Hosts.

Clinical Microbiology and Infection 24 (2018)

Focus affections rhumatologiques



Infections… avec ou sans biothérapie!

Table 1 Objectively confirmed infections in 609 rheumatoid arthritis (RA) and 609 non-RA subjects[a] with data from Doran et al. [16]

Patients, no.			Infections, no.		Incidence/100 person-years			
Infection type	RA	Non-RA	RA	Non-RA	RA	Non-RA	Rate ratio[b]	95 % CI[c]
Total	389	343	1481	1137	19.64	12.87	1.53	1.41–1.65
Bacteremia/septicemia	53	39	60	47	0.78	0.51	1.50	1.10–2.08
Septic arthritis	22	2	31	2	0.40	0.02	14.89	6.12–73.7
Osteomyelitis	11	1	13	1	0.17	0.01	10.63	3.39–126.8
Pneumonia	179	135	311	218	4.02	2.39	1.68	1.46–1.95
Lower respiratory tract	52	35	83	52	1.07	0.57	1.88	1.41–2.53
Urinary tract infections	234	224	658	662	8.72	7.49	1.16	1.05–1.30
Urosepsis/pyelonephritis	28	29	38	40	0.49	0.44	1.12	0.77–1.63
Skin/soft tissue	132	59	231	83	2.99	0.91	3.28	2.67–4.07
Gastroenteritis	8	7	10	8	0.13	0.09	1.46	0.68–3.28
Intra-abdominal	17	7	17	7	0.22	0.08	2.76	1.39–6.22
Other	23	15	29	17	0.38	0.19	1.99	1.22–3.36

Doran Arthritis Rheum 2002

Infections… avec ou sans biothérapie!

Risk and predictors of infection leading to hospitalisation in a large primary-care-derived cohort of patients with inflammatory polyarthritis

Table 2 Incidence of serious infections by site

	Incidence/1000 person-years, mean (95% CI)		
	Men	Women	Total
Respiratory tract	8 (5.7 to 10.8)	5 (3.8 to 6.5)	5.9 (4.8 to 7.2)
Urinary tract	2.1 (1to 3.7)	3.1 (2.2 to 4.3)	2.8 (2 to 3.7)
Skin	2.8 (1.6 to 4.7)	1.5 (0.9 to 2.4)	1.9 (1.3 to 2.7)
Septicaemia	1.5 (0.7 to 3)	0.6 (0.3 to 1.3)	0.9 (0.5 to 1.5)
Infectious arthritis	0.8 (0.2 to 1.9)	0.4 (0.1 to 1)	0.5 (0.2 to 1)
All combined	15.2 (12 to 18.9)	10.7 (8.9 to 12.8)	12.1 (10.5 to 13.9)

Toutes infections graves = 12/1000.années

Table 3 Relative risk of serious infections by site

	Age- and sex-adjusted RR (95% CI)
Respiratory tract	3.5 (2.3 to 5.4)
Urinary tract	2 (1.2 to 3.4)
Skin	1.9 (1.1 to 3)
Septicaemia	4 (2 to 7.8)
Infectious arthritis	2.2 (0.4 to 12.5)
All combined	2.7 (2 to 3.4)

Franklin J Ann Rheum Dis 2007

Infections… avec ou sans biothérapie!

Table 1. Rates of serious infections in a cohort of 86,039 seniors with rheumatoid arthritis: overall, organ-specific, and organism-specific infection event rates for serious infections

Types of infection*	No. of events	Event rate, events/1,000 patient-years
Infections, overall†	20,575	46.36
Respiratory infections, overall	11,545	23.50
Bacterial pneumonia	8,839	17.43
Herpes zoster	4,368	8.54
Skin or soft tissue infections	4,198	8.12
Septicemia	2,056	3.87
Postoperative infections	853	1.61
Pyelonephritis	574	1.08
Septic arthritis	232	0.43
Osteomyelitis	195	0.36
Fungal infections	49	0.09
Endocarditis	35	0.07
Tuberculosis	30	0.05
Meningitis	19	0.04
Central nervous system abscess	16	0.03
Encephalitis	11	0.02

Serious Infections in a Population-Based Cohort of 86,039 Seniors With Rheumatoid Arthritis

JESSICA WIDDIFIELD,[1] SASHA BERNATSKY,[2] J. MICHAEL PATERSON,[3] NADIA GUNRAJ,[4] J. CARTER THORNE,[5] JANET POPE,[6] ALFRED CIVIDINO,[7] AND CLAIRE BOMBARDIER[1]

Arthritis Care & Research
Vol. 65, No. 3, March 2013, pp 353–361

Toutes infections graves = 46/1000.années

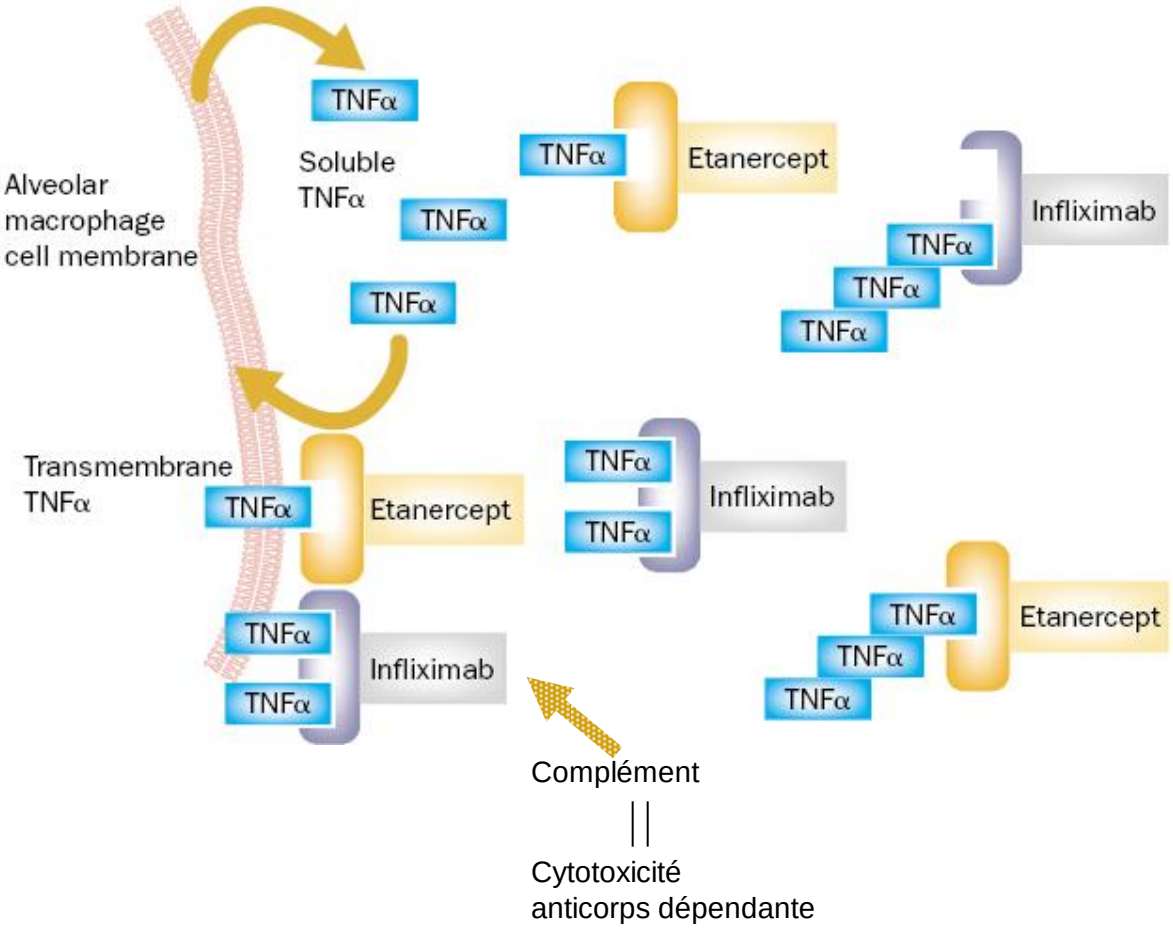
Les biothérapies…

les anti-TNF (PAR, …)

	Etanercept	Infliximab	Abatacept	adalimumab	tocilizumab	certolizumab	Golimumab	rituximab
Posologie	25*2 ou 50mg	3 à 7,5mg/kg	500 à 1000 mg selon pds	40mg	IV : 8mg/kg SC : 162 mg	400mg	50mg	1000 mg
Fréquence	hebdo-madaire	0,2,6 puis 8 semaines	0,2,4 puis toutes les 4 semaines	Toutes les 2 semaines	SC:hebdoma-daire IV : mensuel	0,2,4 puis toutes les 4 semaines	mensuel	J1-15
IV ou SC	SC	IV	SC OU IV	SC	SC OU IV	SC	SC	IV
Classe	AntiTNF	AntiTNF	CTLA-4 mimétique	AntiTNF	Anti R.IL6	AntiTNF	AntiTNF	AntiCD20
Biosimilaire	oui	oui	non	non	non	non	non	bientôt
Prix	250 euros la seringue à 50 mg	450 euros le flacon	250 à 1500 euros	500 euros la seringue/stylo	250 euros la seringue/stylo	400 euros la seringue	1000 euros la seringue	2650 euros/gram me

ENBREL **REMICADE** **HUMIRA** **CIMZIA** **SIMPONI**

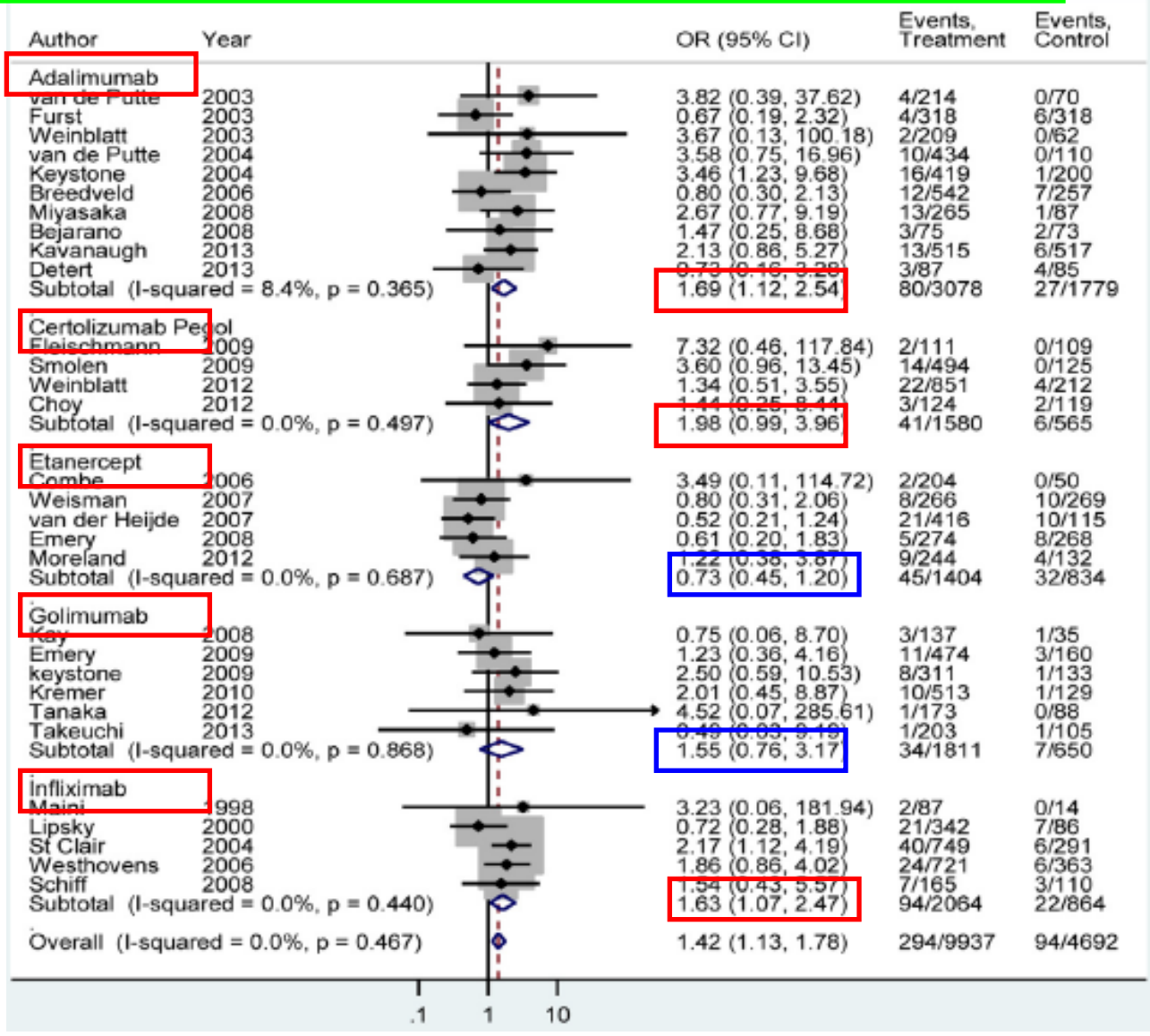
Les biothérapies…



Adapté d'après Gardam et al, Lancet Infect Dis, 2003

Infection et anti-TNF alpha

- Méta-analyse de 44 essais thérapeutiques (PR)



Tzeyu L. Michaud,

- *The American Journal of Medicine (2014) 127, 1208-1232*

Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly

James B. Galloway[1], Kimme L. Hyrich[1], Louise K. Mercer[1], William G. Dixon[1], Bo Fu[1], Andrew P. Ustianowski[2], Kath D. Watson[1], Mark Lunt[1], BSRBR Control Centre Consortium* and Deborah P. M. Symmons[1] on behalf of the British Society for Rheumatology Biologics Register

Rheumatology 2011;50:124–131

Infection et anti-TNF alpha:

le facteur temps

- Cohorte Britannique (BSR)
  - 11798 patients sous anti-TNF, 3598 sous DMARD
  - infections sévères (ttt iv, hospitalisation, décès)

TABLE 2 Overall and time-dependent risk of SI

Results	nbDMARD	All TNF	ETN	INF	ADA
Follow–up, pyrs	9259	36 230	15 874	9622	10 733
Number of SIs	296	1512	609	441	462
Rate/1000 pyrs (95% CI)	32 (28, 36)	42 (40, 44)	38 (35, 42)	46 (42, 50)	43 (39, 47)
Unadjusted HR	Ref.	1.5 (1.3, 1.7)	1.4 (1.2, 1.6)	1.6 (1.4, 1.9)	1.4 (1.2, 1.7)
adjHR[a] (95% CI)	Ref.	1.2 (1.1, 1.5)	1.2 (1.0, 1.4)	1.3 (1.1, 1.6)	1.3 (1.1, 1.5)
Follow-up, months					
0–6	Ref.	1.8 (1.2, 2.6)	1.8 (1.2, 2.7)	1.7 (1.1, 2.6)	1.8 (1.2, 2.7)
6–12	Ref.	1.4 (0.9, 2.0)	1.3 (0.8, 2.0)	1.4 (0.9, 2.2)	1.4 (0.9, 2.1)
12–24	Ref.	1.2 (0.8, 1.6)	1.1 (0.8, 1.5)	1.1 (0.7, 1.5)	1.3 (0.9, 1.8)
24–36	Ref.	0.9 (0.6, 1.3)	0.8 (0.6, 1.2)	1.2 (0.8, 1.8)	0.8 (0.6, 1.3)

[a]Adjusted for age, gender, COPD, diabetes, smoking, disease duration, DAS, HAQ, entry year, steroid use and MTX use. pyrs: patient-years.

Risque infectieux sous anti-TNF dépendant du temps…

Table 2. Number and incidence rates for serious adverse events (SAEs) in rheumatoid arthritis (RA) patients treated with and without the tumor necrosis factor (TNF) antagonists, infliximab or etanercept.

Analyse Régression Poisson: risque relatif lié à l'utilisation continue des anti-TNF après ajustement sur les variables initiales et temps-dépendantes:

Global **1.97 (1.25-3.19)**

1ère année **2.40 (1.20-5.03)**

2ème et 3ème année combinées **1.38 (0.80-2.43)**

Serious infection	No. of events	30	82	28	44	1.16	2.04
	IR (/100-PY)	2.72 (1.87-3.83)	5.54 (4.44-6.84)	4.80 (3.26-6.84)	5.58 (4.11-7.42)	(0.72-1.87)	(1.34-3.10)
Serious respiratory tract infection	No. of events	17	42	16	26	1.20	1.96
	IR (/100-PY)	1.45 (0.86-2.30)	2.84 (2.07-3.80)	2.74 (1.63-4.35)	3.30 (2.21-4.76)	(0.65-2.24)	(1.10-3.48)

Sakai R et al, Arthritis Care & Research 2012, 64 (8); 1125-1134

Risque infectieux sous anti-TNF dépendant du temps… et du reste

Long-term anti-TNF therapy and the risk of serious infections in a cohort of patients with rheumatoid arthritis: Comparison of adalimumab, etanercept and infliximab in the GISEA registry

Univariable and multivariable predictors of serious infections.

	Univariate				Multivariate			
	HR[a]	95% CI[b]		p	AHR[c]	95% CI[b]		p
Age at start of anti-TNF treatment	1.03	1.02	1.04	<.0001	1.036	1.02	1.053	<.0001
Disease duration	1.009	0.99	1.03	0.3	1.004	0.98	1.025	0.709
DAS28	1.055	0.94	1.19	0.381	0.946	0.81	1.107	0.49
DI-HAQ	1.443	1.15	1.81	0.002	1.156	0.85	1.576	0.358
Etanercept	1				1			
Adalimumab	1.942	1.2	3.15	0.0007	2.224	1.12	4.421	0.023
Infliximab	4.291	2.84	6.47	<.0001	4.916	2.71	8.906	<.0001
DMARDs	2.178	1.59	2.98	<.0001	2.145	1.28	3.595	0.004
Corticosteroids	1.849	1.36	2.51	<.0001	1.633	1.01	2.644	0.046
Comorbidity	0.899	0.67	1.21	0.479	1.246	0.87	1.791	0.234

DAS 28 = Disease activity score; DI-HAQ = Disability Index-Health Assessment Questionnaire; DMARDs = Disease-modifying antirheumatic drugs.

[a] HR: hazard ratio.

[b] 95% CI: 95% confidence interval.

[c] AHR: adjusted hazard ratio.

Atzeni F Autoimmun Rev 2012;2:225-229

Risque infectieux sous anti-TNF dépendant du temps… et du reste

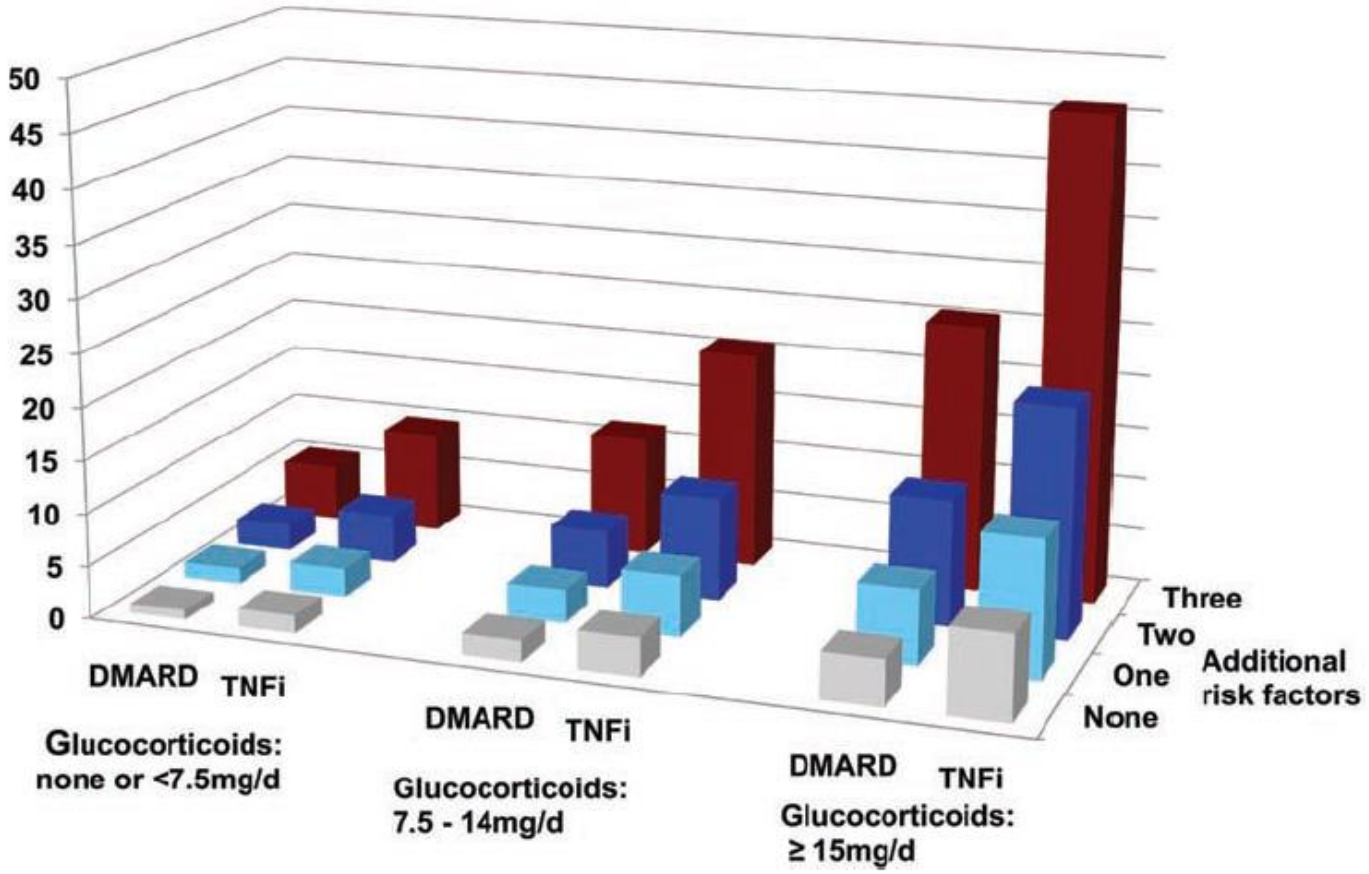


Figure 3 Estimated incidences of serious infections in 100 patients per year by treatment and risk profile. Additional risk factors are one or two of the following: age >60 years, chronic lung disease, chronic renal disease or high number of treatment failures; three risk factors: two of the above risk factors plus prior serious infections. DMARD, disease-modifying antirheumatic drug; TNFi, tumour necrosis factor inhibitor.

Strangfeld ACR 2011

Risque infectieux sous anti-TNF dépendant du temps… et du reste

Question = peut-on « individualiser » le risque?

Rabbit score

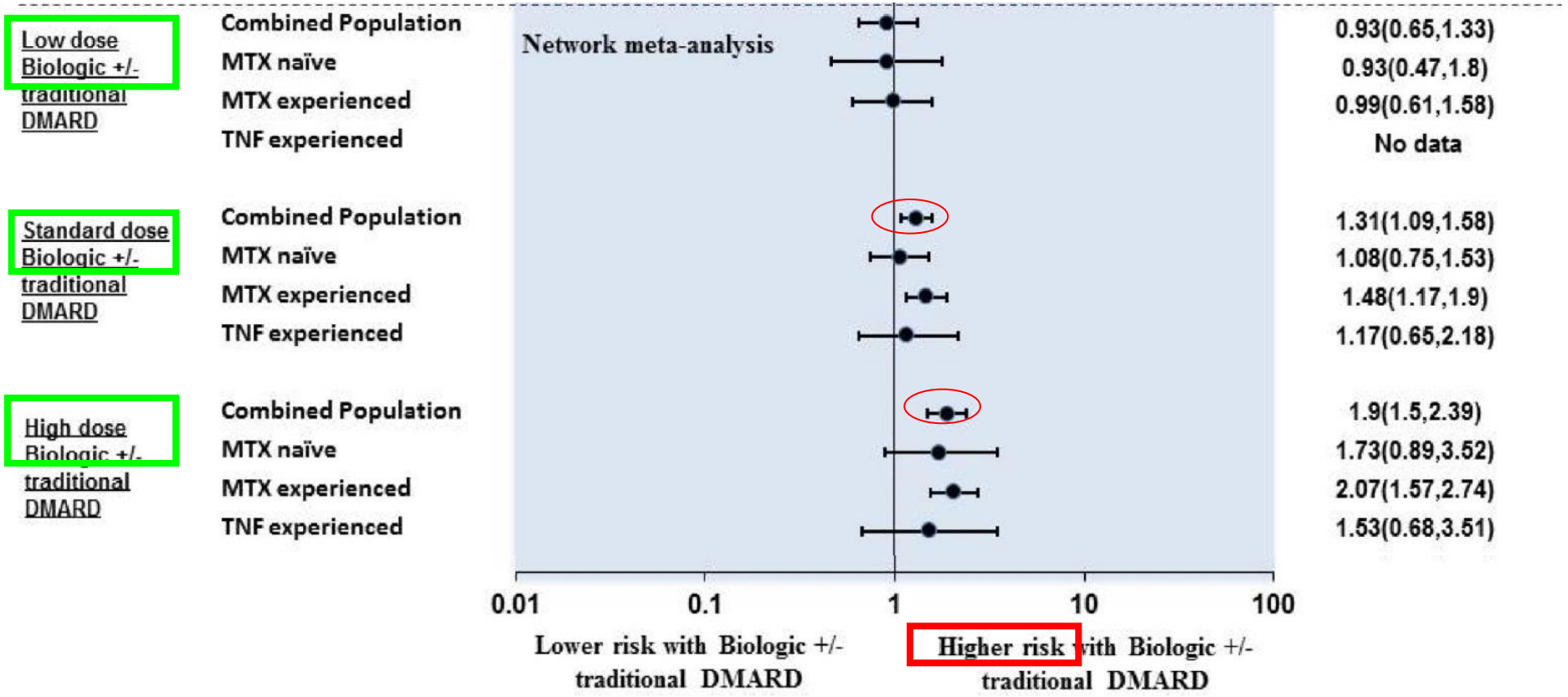
To calculate the risk score

60 years of age or older?	○ Yes ◉ No
HAQ-Score (0-3)	1.25
Severe infection (last 12 months)	○ Yes ◉ No
COPD or other chronic lung disease	◉ Yes ○ No
Chronic kidney disease	○ Yes ◉ No
Number of previous treatments with non-biologic /biologic DMARDs	◉ < 5 ○ >= 5
Treatment: Glucocorticoids (average dose of prednisone equivalent /d):	◉ < 7.5mg ○ 7.5 - 14mg ○ >=15mg
	○ TNF-inhibitor ○ Abatacept ○ Rituximab ○ Tocilizumab ◉ Non-biologic DMARDs

The probability of a serious infection during the next 12 months is: 1.4 %.

http://www.biologika-register.de/en/home/risk-score/

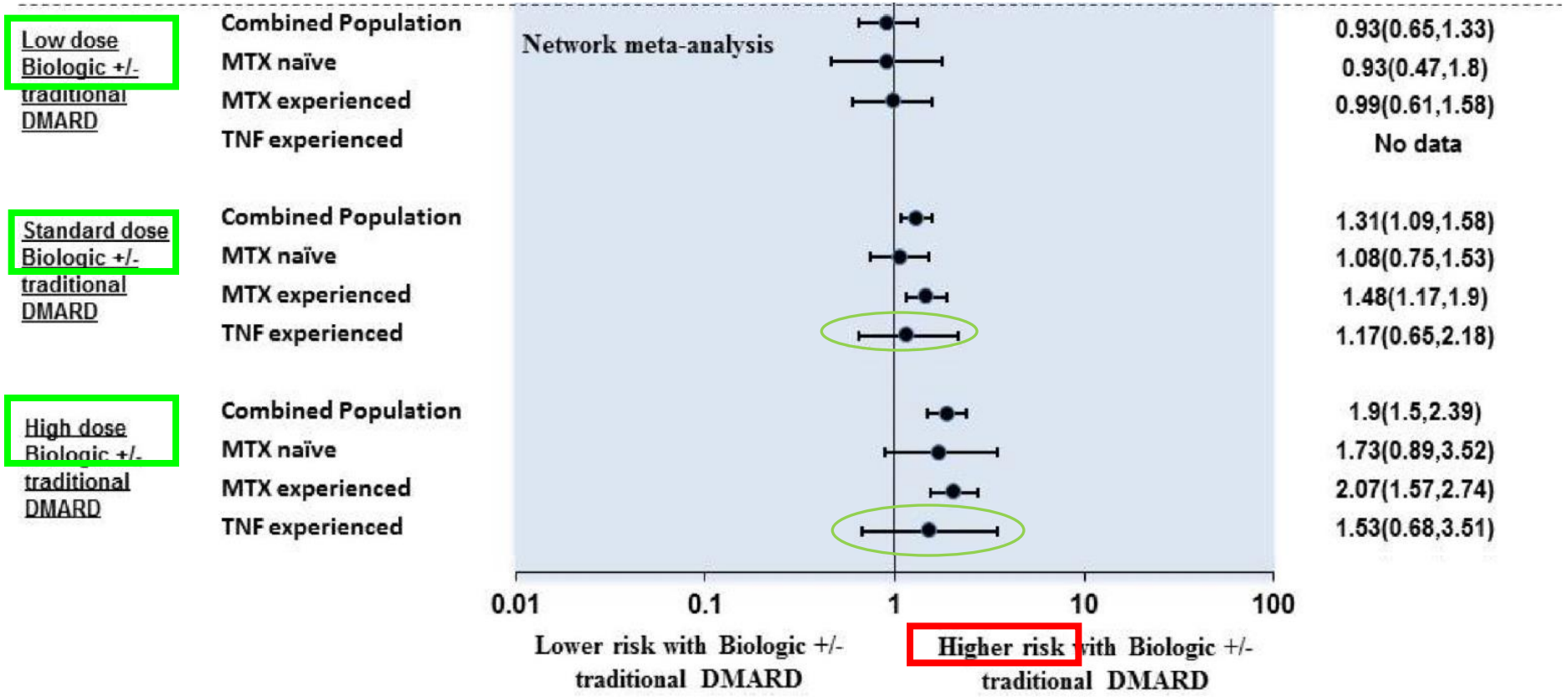
Risque infectieux sous anti-TNF dépendant du temps… et de la dose?



The risk of serious infection with biologics in treating patients with rheumatoid arthritis: A Systematic Review and Meta-analysis

Singh JA Lancet 2015

Risque infectieux sous anti-TNF dépendant du temps… et de la dose?



The risk of serious infection with biologics in treating patients with rheumatoid arthritis: A Systematic Review and Meta-analysis

Singh JA Lancet 2015

Infection et anti-TNF alpha: quels pathogènes?

Table 2 Pathogens and/or presentations of specific pathogens to be considered as opportunistic (or 'indicator') infections in the setting of biologic therapy (level of evidence I–V)

Definite*†	Probable‡
Pneumocystis jirovecii (II)	Paracoccidioides infections (V)
BK virus disease including PVAN (V)	*Penicillium marneffei* (V)
Cytomegalovirus disease (V)	*Sporothrix schenckii* (V)
Post-transplant lymphoproliferative disorder (EBV) (V)	Cryptosporidium species (chronic disease only) (IV)
Progressive multifocal leucoencephalopathy (IV)	Microsporidiosis (IV)
Bartonellosis (disseminated disease only) (V)	Leishmaniasis (Visceral only) (IV)
Blastomycosis (IV)	Trypanosoma cruzi infection (Chagas' disease) (disseminated disease only) (V)
Toxoplasmosi	
Coccidioidom	
Histoplasmosi	
Aspergillosis (	
Candidiasis (i	
Cryptococcosi	
Other invasive *Scedosporium*	
Legionellosis (II)	
Listeria monocytogenes (invasive disease only) (II)	
Tuberculosis (I)	
Nocardiosis (II)	
Non-tuberculous mycobacterium disease (II)	
Salmonellosis (invasive disease only) (II)	
HBV reactivation (IV)	
Herpes simplex (invasive disease only) (IV)	
Herpes zoster (any form) (II)	
Strongyloides (hyperinfection syndrome and disseminated forms only) (IV)	

TUBERCULOSE,
pneumocystose, nocardiose, coccidioidomycose, aspergillose, candidose, cryptococcose, legionellose, listeriose, salmonellose, herpès…

Winthrop KL, *et al. Ann Rheum Dis* 2015;**74**:2107–2116.

Infection et anti-TNF alpha: quels pathogènes?

- Intra-cellulaires / mettant en jeu l'immunité cellulaire réponse Th1
  - Listeriose légionellose,
  - salmonellose, …
  - cryptococcose
  - Coccidioidomycose
  - Syphilis
  - pneumocystose
  - virus

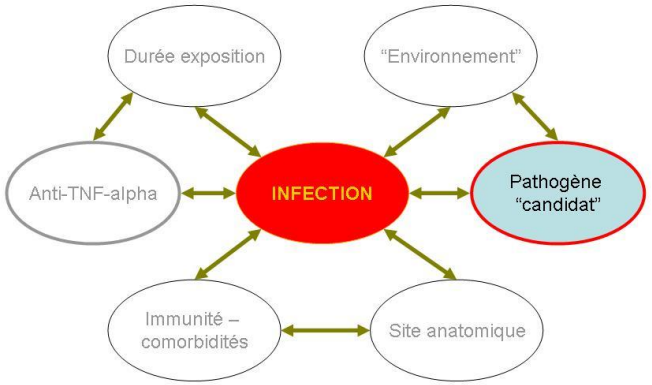
Kelesidis J Infect 2010

Bories-Haffner Joint Bone Spine 2010

- +/- capacité à générer un granulome (acquisition – réactivation)
  - mycobactérioses
  - histoplasmose

Raychaudhuri Autoimmun Rev, 2010

Infection et anti-TNF alpha: quels pathogènes?



- **Légionellose:**
  - 13 cas survenus en 18 mois, d'origine communautaire : 100%
  - Age moyen : 51 ans (40-69)
  - Durée moyenne d'anti TNFα = 8,9 mois (0,7- 17,0)
  - Incidence en pop générale : 2/100 000
  - Incidence chez les patients sous anti TNF pendant la période : 33 à 42/100 000 (nombre estimé de patients traités par anti-TNFα pendant la période : 24 à 30 000)

  ➔ Risque relatif entre 16,5 et 21 (acquisition)

Tubach et al, Clin Infect Dis, 2006 - Observatoire RATIO, juin 2007

Infection et anti-TNF alpha: quels pathogènes?

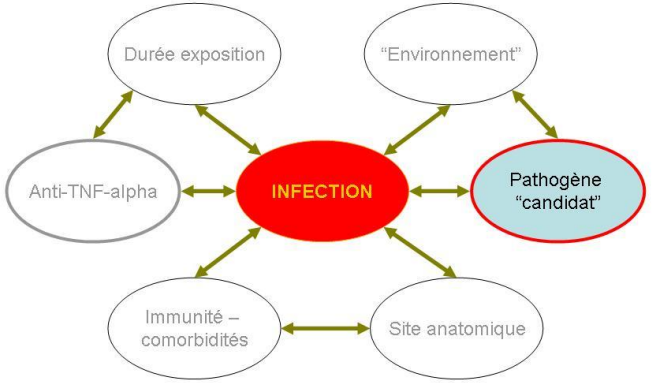
Recommandations

Conseils d'utilisation des traitements anti-TNF et recommandations nationales de bonne pratique labellisées par la Haute Autorité de santé française☆,☆☆

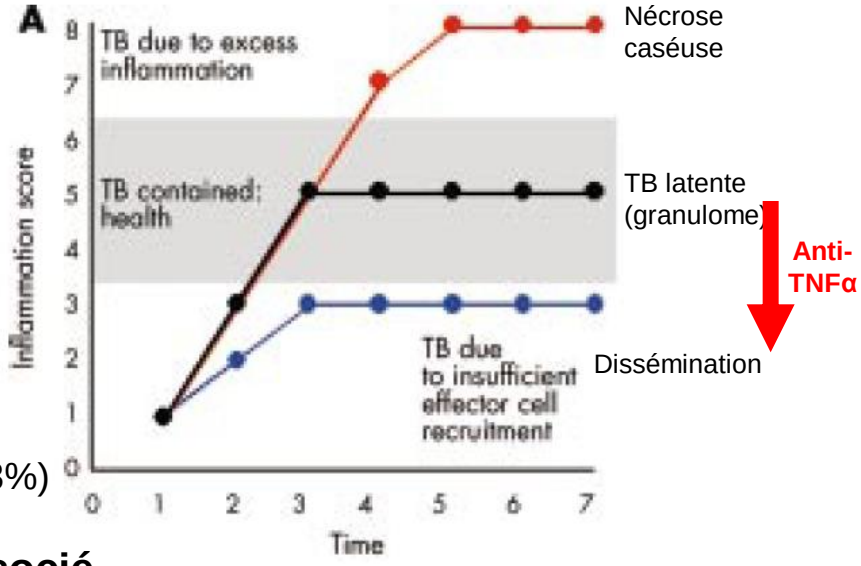
Revue du rhumatisme 80 (2013) 459–466

- Toute pneumopathie infectieuse chez un patient sous anti-TNF justifie
  - la recherche de l'antigénurie légionelle et une imagerie pulmonaire,
  - ainsi que la mise en place d'une antibiothérapie active sur Streptococcus pneumoniae et Legionella pneumophila (AE).
- En cas de doute persistant sur une légionellose chez un patient ayant une antigénurie négative, une sérologie ou une recherche directe de légionelle pourra être proposée (AE).
- Il est recommandé de suspendre le traitement anti-TNF jusqu'à la guérison (AE).

Infection et anti-TNF alpha: quels pathogènes?



- **Tuberculose:**
  - **Sexe ratio : F: 65%/ H: 35%**
  - **âge médian :** 59.5 ans (21-86)
  - **Comorbidités**
    - Polyarthrite rhumatoïde: 63%
    - Spondylarthrite ankylosante : 29%
    - Maladie de Crohn: 8%
  - **Présentation clinique**
    - Pleuro-pulmonaire : 20 (33%)
    - Ganglionnaires : 9 (18%)
    - Extra-pulmonaire ou disséminée : 20 (33%)
    - Décès : 2%
  - **Traitement immuno-suppresseur associé**
    - Au moins un : 89%
    - Méthotrexate : 71.4%
    - Leflunomide : 16.3%
    - Azathioprine : 8.2%
    - Salazopyrine : 24%
    - Corticothérapie : 70.8% (dose médiane: 13 mg/j (3- 50))

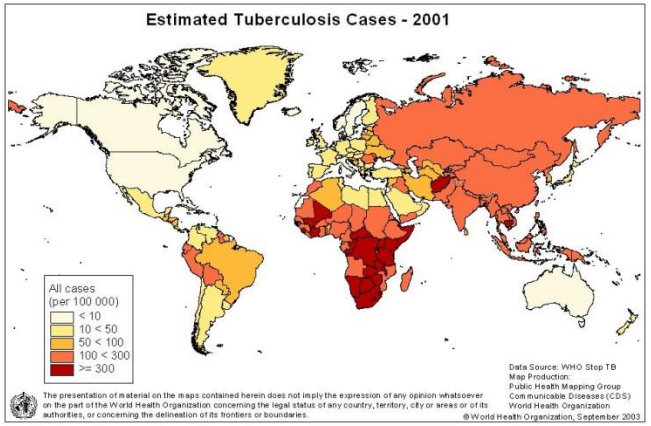


D'après Ehlers et al, Ann Rheum 2003

réactivation +

Observatoire RATIO, juin 2007

Infection et anti-TNF alpha: environnement



Europe / Amérique du Nord

Asie

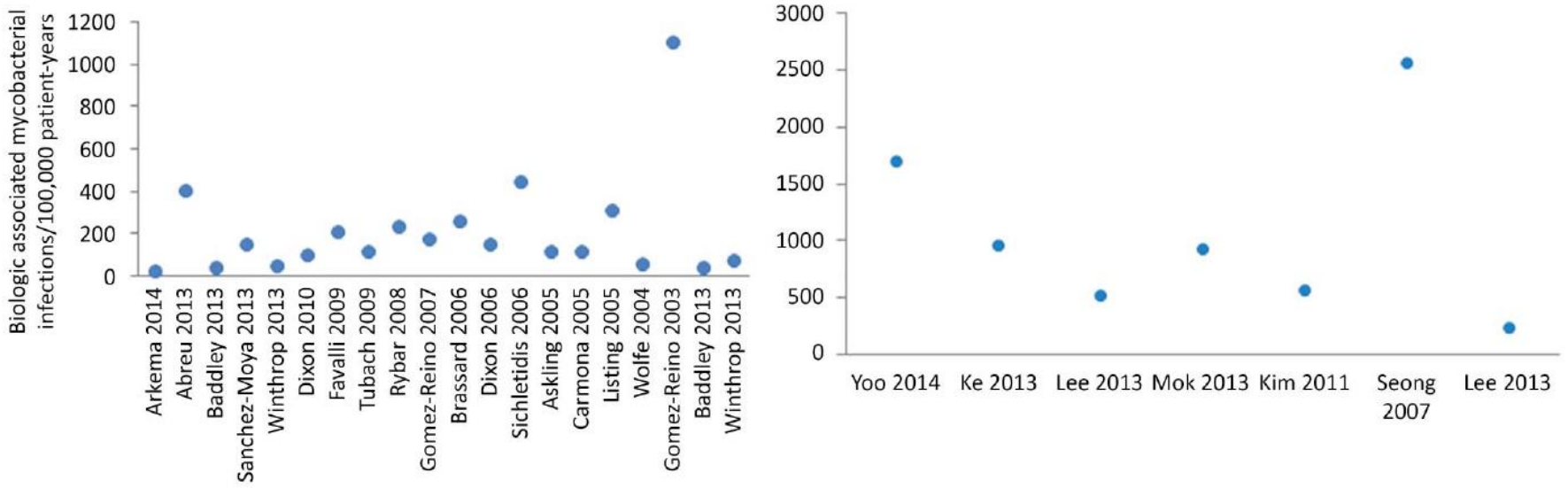
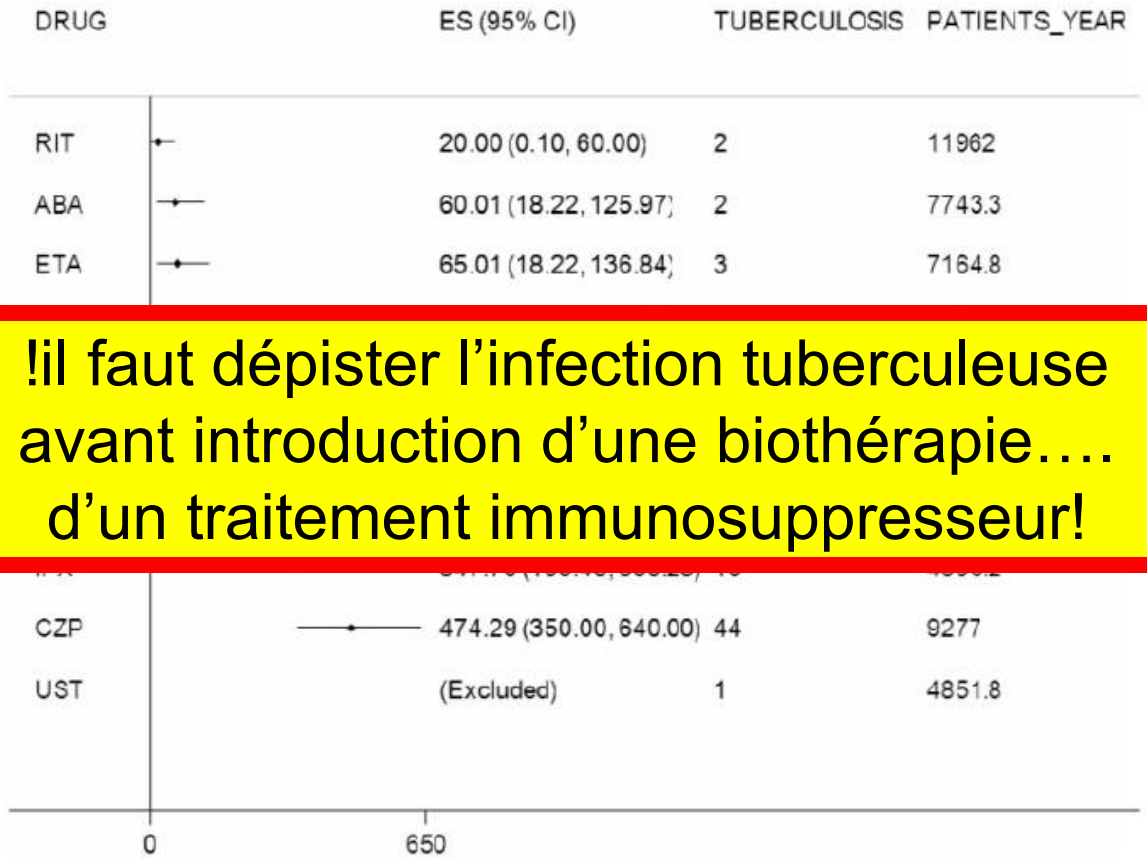


Figure 1 Postmarketing observational studies reporting incidence of mycobacterial infections in Europe/North American and Asia.[12 21–43]

Winthrop KL, *et al*. *Ann Rheum Dis* 2015;**74**:2107–2116.

Risque tuberculeux
avec toutes les biothérapies?

FIG. 3 Meta-analysis of incidence rates by treatment of long-term extension studies



!il faut dépister l'infection tuberculeuse avant introduction d'une biothérapie…. d'un traitement immunosuppresseur!

ES: incidence rate per 100 000 patient-years; ABA: abatacept; ETA: etanercept; TOC: tocilizumab; TOF: tofacitinib; GOL: golimumab; ADA: adalimumab; IFX: infliximab; CZP: certolizumab; UST: ustekinumab; RIT: rituximab.

Souto Rheumatology 2014

Dépistage tuberculose latente: limites

Influence of replacing tuberculin skin test with ex vivo interferon γ release assays on decision to administer prophylactic antituberculosis antibiotics before anti-TNF therapy

Table 3 Comparison of interferon γ (IFNγ) release assay and TST in the 57 patients with LTBI defined by questioning or x-ray

Test	N	Sensitivity	95% CI	N	Specificity*	95% CI
TST	57	0.32	0.20 to 0.45	335	0.54	0.69 to 0.70
QTF-Gold IT	57	0.21	0.11 to 0.34	335	0.92	0.89 to 0.95
T-SPOT.TB	57	0.25	0.14 to 0.38	335	0.87	0.82 to 0.90
QTF-Gold IT or T-SPOT.TB	57	0.28	0.17 to 0.42	335	0.85	0.81 to 0.89

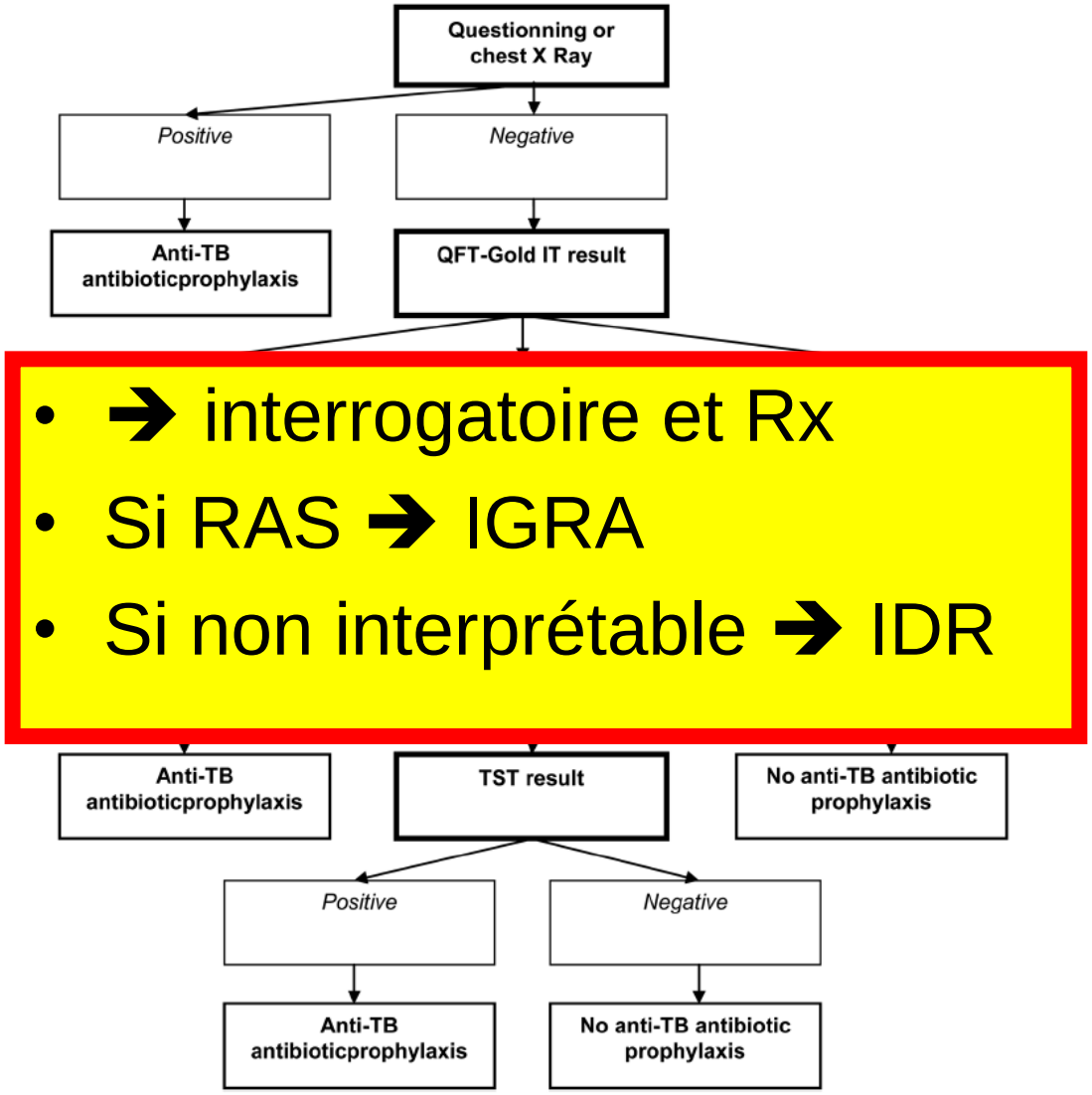
*Indeterminate and negative results were pooled.
LTBI, latent tuberculosis infection; QTF-Gold IT, QuantiFERON TB Gold in tube; TST, tuberculin skin test

Traitement antibiotique si IDR inclus dans la définition ITL = 177 patients (45,2%) vs 84 patients (21,4%) si remplacée par test interféron QTF

➔ Changement de l'attitude thérapeutique pour 113 patients (28,8%, IC95% 24,4% -33,6%) si IDR remplacée par test interféron

Mariette X, Baron G, Tubach F, *et al*. *Ann Rheum Dis* (2012). doi:10.1136/annrheumdis-2011-200408

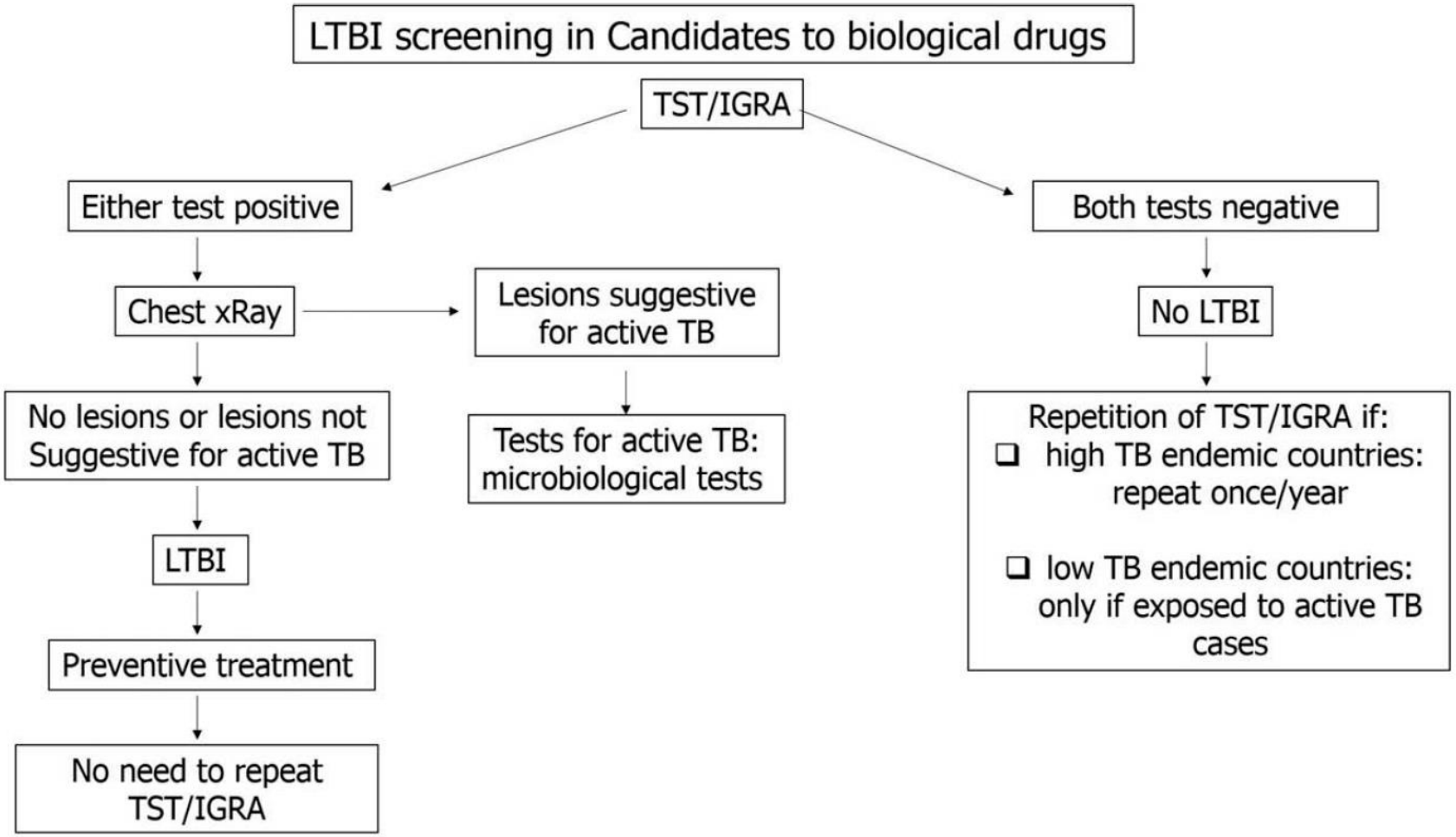
Dépistage tuberculose latente



- ➔ interrogatoire et Rx
- Si RAS ➔ IGRA
- Si non interprétable ➔ IDR

Mariette X, Baron G, Tubach F, *et al*. *Ann Rheum Dis* (2012). doi:10.1136/annrheumdis-2011-200408

Dépistage tuberculose latente

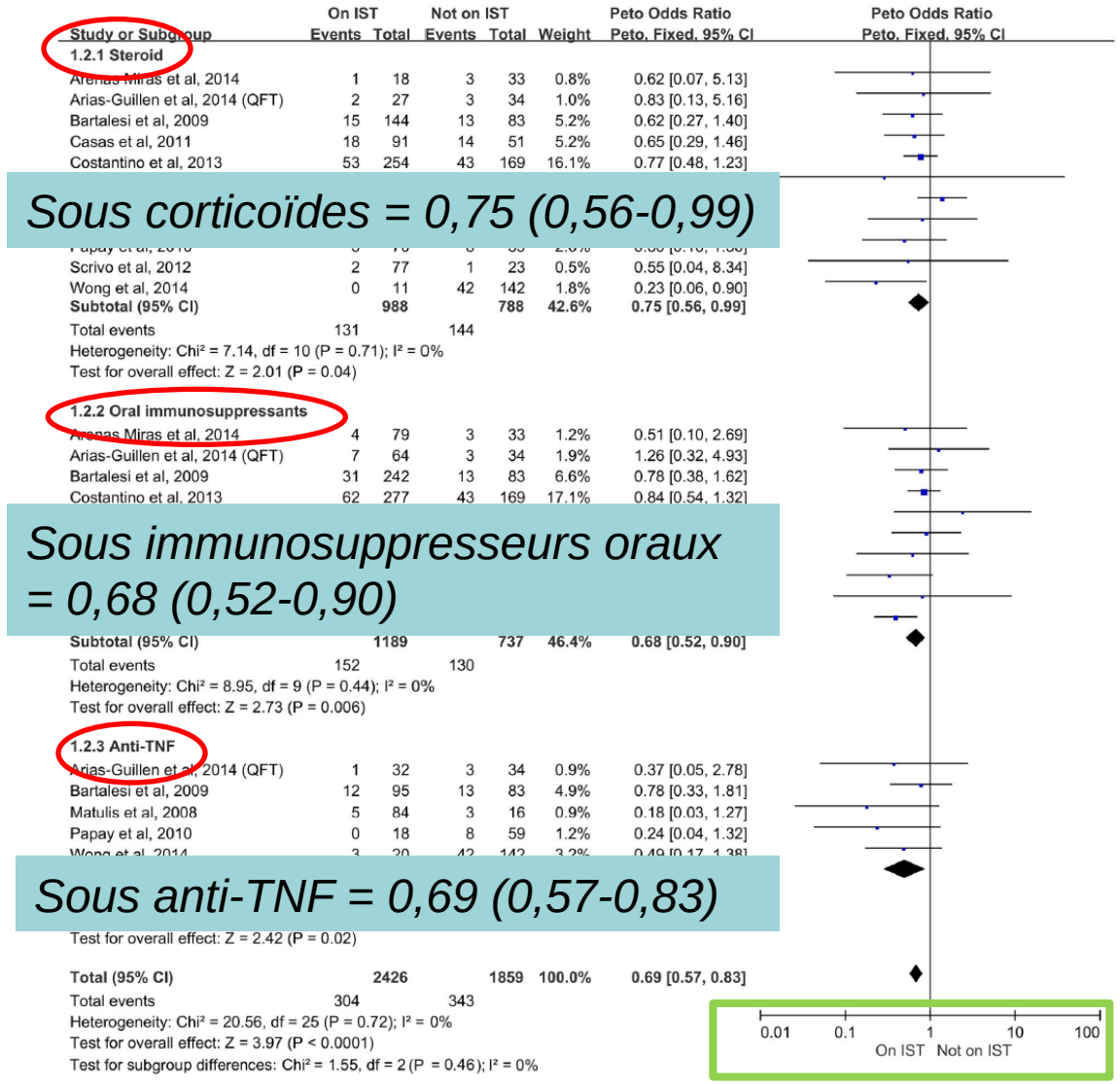


Goletti D et al, Expert review of anti-infective therapy, 2018 2018, VOL. 16, NO. 6, 501–512

Dépistage tuberculose latente: limites

Wong SH, et al. Thorax 2016;71:64–72

Probabilité d'avoir un IGRA positif



Sous corticoïdes = 0,75 (0,56-0,99)

Sous immunosuppresseurs oraux = 0,68 (0,52-0,90)

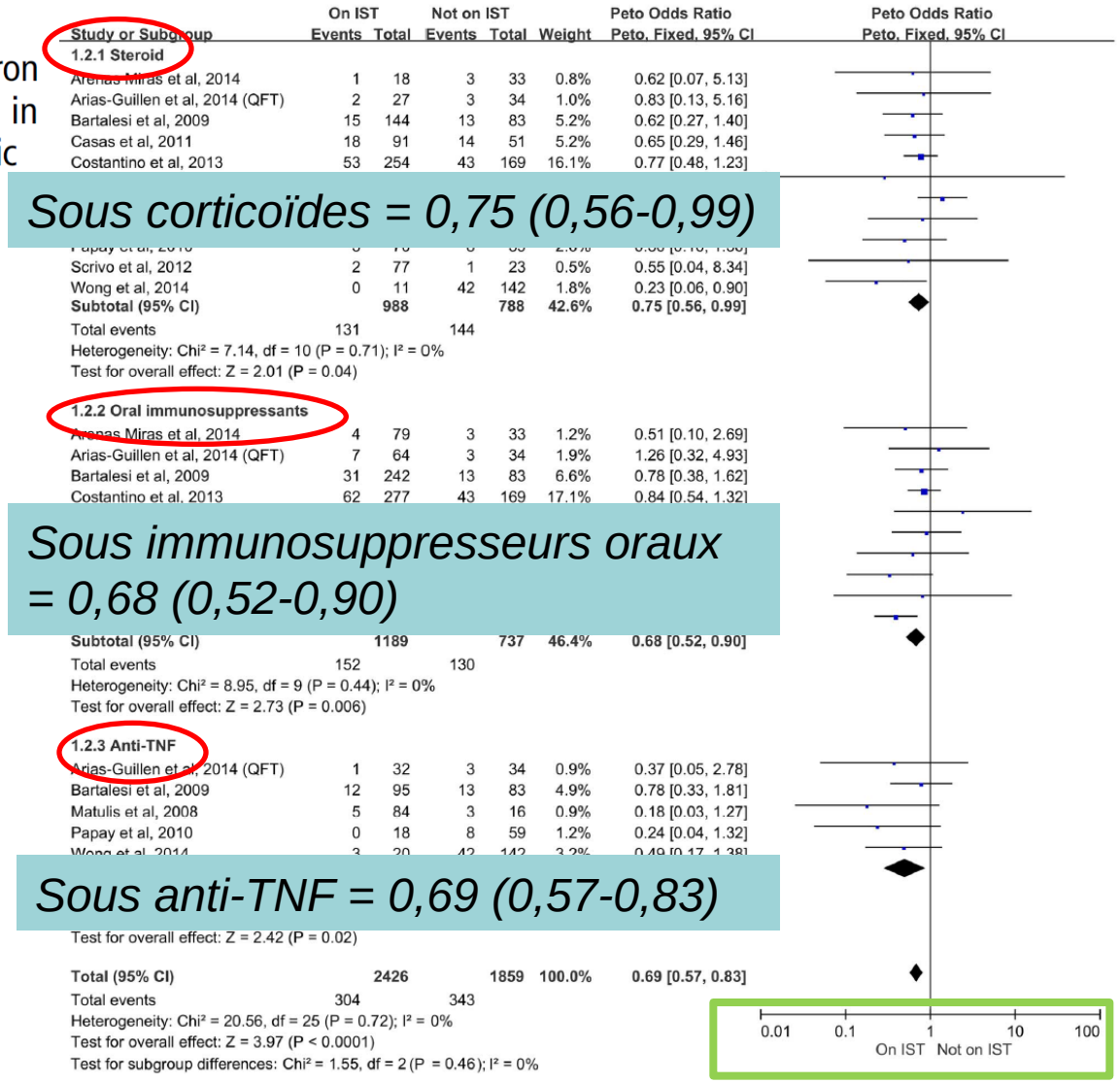
Sous anti-TNF = 0,69 (0,57-0,83)

Dépistage tuberculose latente: limites

Effect of immunosuppressive therapy on interferon γ release assay for latent tuberculosis screening in patients with autoimmune diseases: a systematic review and meta-analysis

Wong SH, et al. Thorax 2016;71:64–72

- ➔IGRA à faire
  - Avant anti-TNF
  - Avant tout traitement immuno-suppresseur!



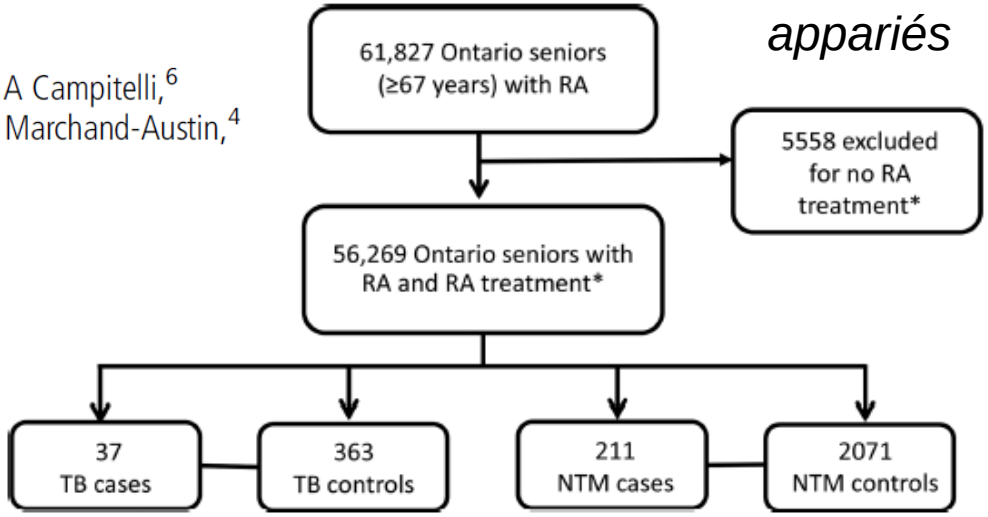
Mycobactéries: mais aussi….

ORIGINAL ARTICLE

Increased risk of mycobacterial infections associated with anti-rheumatic medications

Sarah K Brode,[1,2,3] Frances B Jamieson,[4,5] Ryan Ng,[6] Michael A Campitelli,[6] Jeffrey C Kwong,[4,6,7,8] J Michael Paterson,[6,9,10] Ping Li,[6] Alex Marchand-Austin,[4] Claire Bombardier,[9,11] Theodore K Marras[1,3]

Etude cas contrôles appariés



- This is the first study to describe an association between anti-TNF use and NTM disease after controlling for several potential confounders,

Anti-TNF en cours

NTM

ORajusté = 2,19

Table 2 ORs for TB and NTM disease according to anti-rheumatic medication use

Exposure	TB						NTM disease					
	TB cases N=37	TB controls N=363	Crude OR (95% CI)	p Value	Adjusted* OR (95% CI)	p Value	NTM cases N=211	NTM controls N=2071	Crude OR (95% CI)	p Value	Adjusted* OR (95% CI)	p Value
Anti-TNF use												
No use	[illegible] (84)	350 (96)	1.0 (ref)		1.0 (ref)		194 (92)	1997 (96)	1.0 (ref)		1.0 (ref)	
Past use	0 (0)	0 (0)	N/A		N/A		NR	7 (0.3)	2.94 (0.61 to 14.2)	0.18	1.09 (0.15 to 8.09)	0.93
Current use	6 (16)	13 (4)	**6.44 (2.02 to 20.6)**	**0.002**	**5.04 (1.27 to 20.0)**	**0.02**	NR	67 (3)	**2.42 (1.34 to 4.37)**	**0.003**	**2.19 (1.10 to 4.37)**	**0.03**

Brode SK, *et al*. *Thorax* 2015;**70**:677–682.

Risque d'infection VZV chez les patients atteints de PR et traités par antiTNF

Risk of herpes/herpes zoster during anti-tumor necrosis factor therapy in patients with rheumatoid arthritis. Systematic review and meta-analysis

Helene Che*, Cedric Lukas, Jacques Morel, Bernard Combe

Joint Bone Spine 2013

➔ sérologie VZV chez tout patient avant mise sous anti-TNF

- si sérologie négative:
  - vaccination avant instauration de tout traitement immunosuppresseur (si possible)
  - informer le patient d'éviter tout contact avec une personne présentant une varicelle ou un zona
  - immunoglobulines dans les 96 heures suivant un contact
- En cas de varicelle ou zona sous anti-TNF, interrompre le traitement par anti-TNF au moins jusqu'à la guérison complète.

Cohorte GB: **formes « sévères »** (nécessitant hospitalisation et/ou antiviraux en perfusion, et/ou plusieurs dermatomes) sous anti-TNF: **6%vs 0,02%**

Risque d'infection/réactivation VHB

TABLE 4. Main C… ts With Chronic HBV Infection After Tre… TNF Therapy

AgHBs+

Outcome (Post-Treatment)	No. (%)
Follow-up, mean (range), mo	14.00 ± 2.07 (0–77)
Death	4 (5)

Ac antiHBc isolés

Plusieurs cas de réactivation VHB rapportés

➔ **Patient avec AgHBs positif =**

➔ instaurer un traitement pré-emptif systématique par analogues nucléos(t)idiques - *il est recommandé d'attendre la négativation de l'ADN du VHB avant de débuter le traitement par anti-TNF …??*

➔ **Patient avec Ac anti-HBc isolé =**

- Si hépatite B occulte = prise en charge idem que pour Ag HBs +
- Si PCR ADN VHB négative = dépend du risque intrinsèque (antiCD20/antiCD52= ttt / anti-TNF= *traiter? Vacciner!?)*

➔ **Patient avec Ac anti-HBs positifs « faibles » =** *monitorer?*

Anti-TNF et risque chirurgical

Tumor Necrosis Factor Inhibitor Therapy and Risk of Serious Postoperative Orthopedic Infection in Rheumatoid Arthritis

2006

JON T. GILES, SUSAN J. BARTLETT, ALLAN C. GELBER, SHIKHA NANDA, KEVIN FONTAINE, VICTORIA RUFFING, AND JOAN M. BATHON

Table 1. Demographic and clinical parameters at the time of orthopedic surgery in patients with and without a serious postoperative orthopedic infection*

Parameter	No infection (n = 81)	Infection (n = 10)	*P*
Female sex	69 (85)	8 (80)	0.649
Age at surgery, mean ± SD years	59.4 ± 12.5	59.7 ± 9.66	0.950
Diabetes	14 (17)	2 (20)	1.000
RA disease duration, mean ± SD years	16.3 ± 9.6	17.2 ± 10.9	0.790
Oral glucocorticoids	36 (44)	3 (30)	0.507
RF positive	59 (73)	6 (60)	0.463
Treatment			
TNF inhibitor	28 (35)	7 (70)	0.041
Nonbiologic DMARDs			
Any conventional DMARD	64 (79)	8 (80)	1.000

OR : 4

Anti-TNF et risque chirurgical

PAR
Chirurgie orthopédique

TABLE 4 Multivariate logistic regression analysis of putative risk factors for post-operative SSI

	OR	95% CI	*P*-value
Gender, male	0.384	0.024, 6.276	0.50
Age, years	1.067	0.974, 1.170	0.16
Disease duration, years	1.169	1.030, 1.326	0.015
TNF-α blockers	21.8	1.231, 386.1	0.036
MTX	0.157	0.011, 2.321	0.18
SSZ	2.26E-07	Inf	0.99
PSL dosage	1.433	1.007, 2.040	0.046
NSAIDs	0.125	0.012, 1.346	0.09
Anti-platelet agent	0.106	0.002, 4.633	0.24
CRP	1.346	0.950, 1.907	0.10
Diabetes mellitus	5.48E-08	Inf	0.997

OR: odds ratio; PSL: prednisone; Inf: infinity.

Kawakami et al 2010

Anti-TNF et risque chirurgical

Recommandations CRI :
délai d'arrêt des biothérapies avant chirurgie selon risque septique

Risque septique	Faible	Moyen	Elevé	Très élevé	Reprise Biothérapie
Infliximab	20j à 3 sem	30j à 4 sem	40j à 6 sem	50j à 8 sem	Après accord du chirurgien et 2 semaines après cicatrisation complète
Adalimumab	30j à 4 sem	45j à 6 sem	60j à 8 sem	75j à 10 sem	
Certolizumab	30j à 4 sem	45j à 6 sem	60j à 8 sem	75j à 10 sem	
Golimumab	30j à 4 sem	45j à 6 sem	60j à 8 sem	75j à 10 sem	
Etanercept	10j à 2 sem	15j	20j	25j à 4 sem	
Abatacept	2 Mois minimum				
Rituximab	6 mois minimum				
Tocilizumab	4 semaines minimum				

Réduire le risque infectieux = changer de biothérapie?

- Réduit on le risque infectieux si on change le traitement anti-TNF après une infection ayant conduit à une hospitalisation?

Table 3 Absolute incidence rates (IRs) and pairwise comparison of each biologic* to every other for subsequent hospitalised infection

	Referent group				
Biologics	Infliximab	Adalimumab	Etanercept	Rituximab	Abatacept
Crude IR per 100 years (n/person-years)	33.8 (1382/4087)	34.9 (497/1423)	36.1 (661/1831)	28.5 (38/133)	26.5 (88/333)
Adjusted HR (95% CI)†					
Abatacept	0.80 (0.64 to 0.99) (p value=0.048)	0.88 (0.68 to 1.12)	0.97 (0.76 to 1.23)	0.93 (0.64 to 1.36)	1.0 (Ref)
Rituximab	0.87 (0.63 to 1.20)	0.94 (0.67 to 1.32)	1.04 (0.74 to 1.46)	1.0 (Ref)	
Etanercept	0.83 (0.72 to 0.97) (p value=0.013)	0.91 (0.76 to 1.08)	1.0 (Ref)		
Adalimumab	0.92 (0.79 to 1.09)	1.0 (Ref)			
Infliximab	1.0 (Ref)				

> 10 000 patients

Yun H, *et al*. *Ann Rheum Dis* 2014;**0**:1–7.

Autres mesures préventives = vaccinations

- **Triple problématique:**
  - Impact potentiellement négatif de la biothérapie sur la réponse vaccinale
    - Complexe, dépendant du type de vaccin, du type de biothérapie, et du timing de la vaccination – et des traitements associés !
  - Risque majoré d'EI post vaccinaux du fait de la biothérapie
    - Concerne essentiellement les vaccins vivants atténués
  - Risque d'aggravation de la pathologie sous jacente du fait du vaccin
    - Déterminisme auto-immun sous jacent

Impact vaccin sur affection chronique - PAR

- 28 patients avec PR légère-modérée (sous anti-TNF + <10mg de corticoïdes + MTX) vaccinés contre 3 souches grippales saisonnières (Vaxigrip*) 3 ans de suite
- 20 contrôles PR non vaccinés appariés (sexe, age, sous antiTNF) / 20 sains vaccinés

Table 1 DAS for RA vaccinated and non-vaccinated patients at T0 (before vaccination), T1 (30 days) and T2 (180 days) after flu vaccination.

Influenza seasons 2005–2006, 2006–2007, 2007–2008

	RA vaccinated	RA non-vaccinated	*p*
N patients	28	20	NS
Mean age (years)	53 ± 3	49 ± 3	NS
Sex (F/M)	23/5	17/3	NS
DAS T0 [a]	2.47 ± 0.2	2.7 ± 0.3	NS
DAS T1 [a]	2.52 ± 0.2	2.66 ± 0.1	NS
DAS T2 [a]	2.3 ± 0.2	2.8 ± 0.3	NS

F, females; M, males.
[a] Data shown are the mean of 3-year values, being representative of the behavior observed in each year.

T0 = avant vaccination
T1 = 30 jours après vaccination
T2 = 180 jours après

Salemi S Clinical Immunology (2010) 134, 113–120

Effect of vaccination (non-live vaccines) on IMID disease activity

Vaccine	Disease activity	RA	JIA	SLE	IBD
Hepatitis B	=	Clin, Lab (CCT) [74]	Clin (CCT) [101]	Clin, Lab (UCT) [75]	
Pneumococcal vaccine	=	Clin, Lab (CCT) [77]		Clin, Lab (CCT) [77] Clin, Lab (UCT) [102]	
Influenza	=	Clin, Lab (RCT) [103] Clin, Lab (CCT) [84, 86, 88, 93]		Clin, Lab (CCT) [86] Clin (UCT) [87]	Clin (CCT) [89]

Summary of literature data on the effect of vaccination on IMID disease activity. '=' indicates no significant effect. Non-live vaccines are well-tolerated in IMID patients and do not increase either clinical (Clin) or laboratory (Lab) markers of disease activity. Study design is recorded in parentheses: CCT: controlled clinical trial; UCT: uncontrolled clinical trial; RCT: randomized controlled trial.

Vaccinations recommandées

Anti-TNF

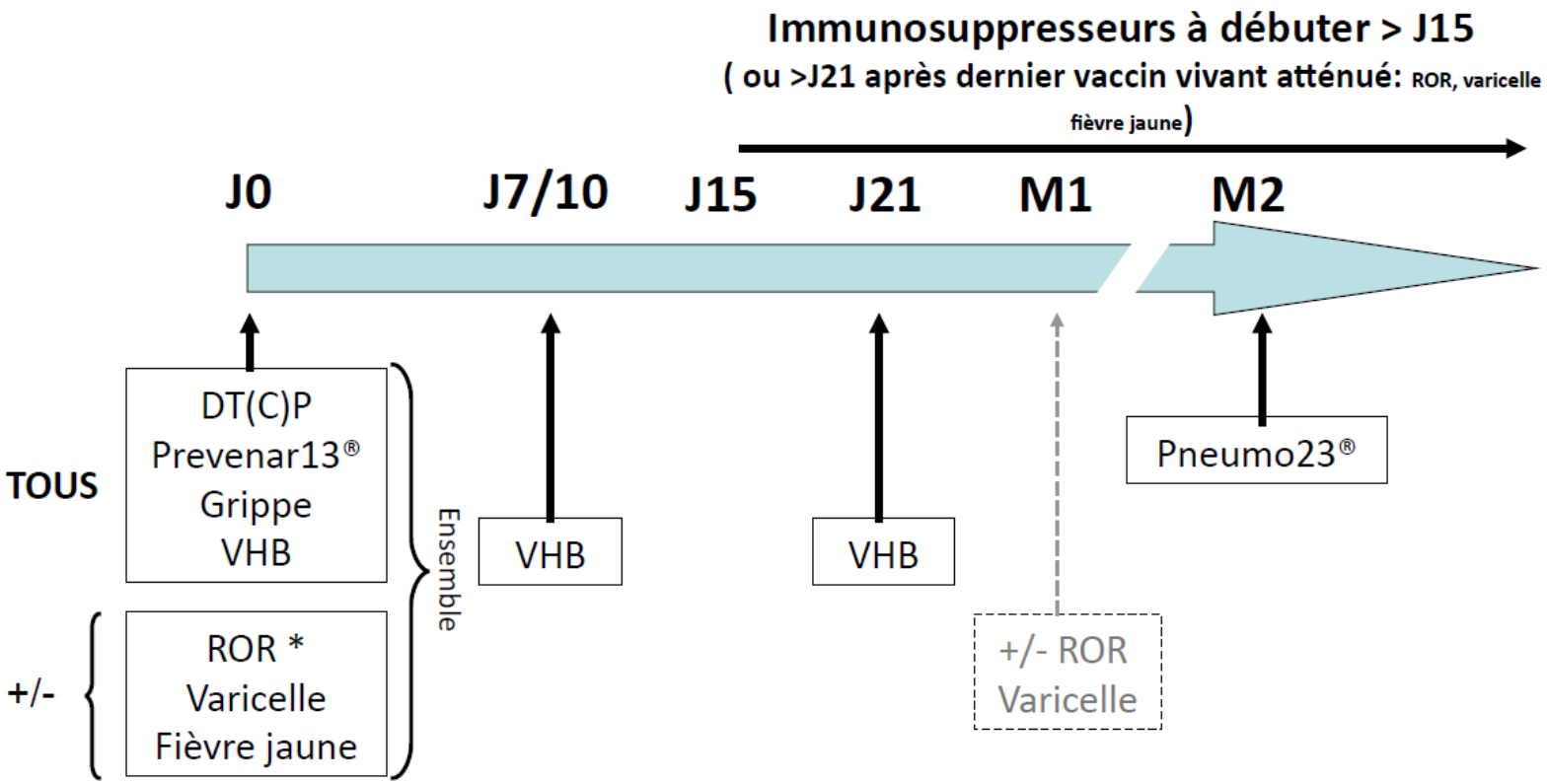
Non encore traité

Vaccins vivants atténués	Vaccins inactivés et sous-unités
- Grippe saisonnière (vaccin nasal) - BCG - Rougeole-Oreillons-Rubéole - Varicelle - Rotavirus - Fièvre jaune	- Grippe saisonnière (vaccin injectable) - Diphtérie-Tétanos-Polio-Coqueluche acellulaire (DTCaP) - *Haemophilus influenzae* de type b - Hépatite B - Méningocoque C conjugué - Pneumocoque - Papillomavirus - Hépatite A

Vaccinations recommandées

Anti-TNF

Département Infectiologie CHU Dijon décembre 2014



ROR = Personnes nées après 1980 et n'ayant pas reçu 2 doses de vaccin (1 ou 2 doses à 1 mois d'intervalle) ou
Personnes nées avant 1980, sans antécédent de rougeole, non vaccinées ET personnels de santé/petite enfance ➔ 1 dose

Varicelle = Pas d'antécédent de varicelle et sérologie varicelle négative - 2 doses espacées de 4 à 8 ou 6 à 10 semaines selon le vaccin utilisé

Fièvre jaune = Voyageurs

Si doute (notamment pour fièvre jaune si déjà vacciné ou originaire de zone d'endémie) = contrôle sérologie avant vaccination

Vaccinations recommandées

Anti-TNF

Déjà traité

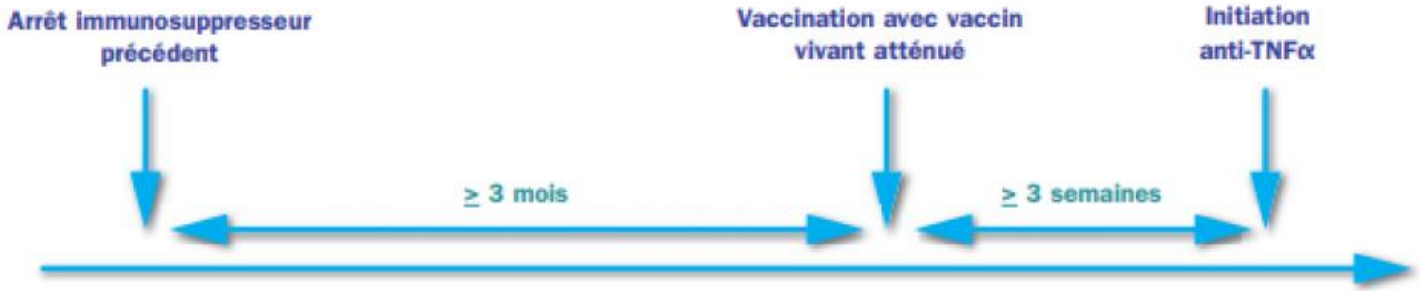
Haut Conseil de la Santé Publique

Vaccination des **personnes immunodéprimées** ou **aspléniques**

Recommandations

	Vaccins contre-indiqués = vaccins vivants	Vaccins particulièrement recommandés	Vaccins inertes recommandés en population générale
Patients atteints d'une maladie auto-immune traités par corticothérapie et/ou immunosuppresseurs et/ou biothérapies.	• BCG • Fièvre jaune • Grippe vivant atténué • ROR • Varicelle • Zona	• **Grippe saisonnière (vaccin inactivé)** • **Pneumocoque privilégier le vaccin conjugué 13 valences**	• Diphtérie, Tétanos, Polio et Coqueluche • Hépatite B • Méningocoque • Papillomavirus

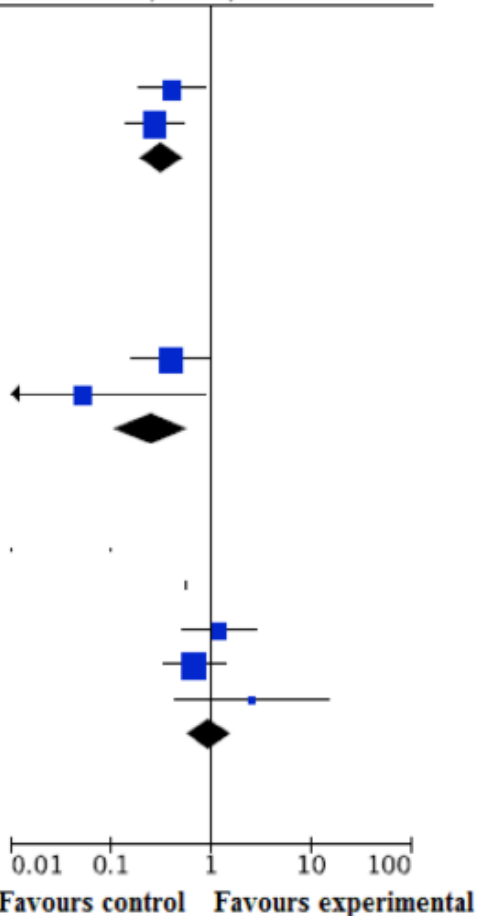
Sinon pour vaccins vivants



Vaccination anti-pneumococcique

: 6B serotype

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
•Treatment by Methotrexate :						
Kapetanovic 2006	24	50	43	62	38.3%	0.41 [0.19, 0.88]
Kapetanovic 2011 (A&R)	18	89	38	79	61.7%	0.27 [0.14, 0.54]
Subtotal (95% CI)		**139**		**141**	**100.0%**	**0.33 [0.20, 0.54]**
Total events	42		81			
Heterogeneity: $Chi^2 = 0.58$, df = 1 (P = 0.45); $I^2 = 0\%$						
Test for overall effect: Z = 4.32 (P < 0.0001)						
•Treatment by Rituximab:						
C.O.Bingham III 2010	24	63	17	28	57.7%	0.40 [0.16, 0.99]
Kapetanovic 2011 (ACR)	0	25	23	85	42.3%	0.05 [0.00, 0.89]
Subtotal (95% CI)		**88**		**113**	**100.0%**	**0.25 [0.11, 0.58]**
Total events	24		40			
Heterogeneity: $Chi^2 = 2.15$, df = 1 (P = 0.14); $I^2 = 54\%$						
Test for overall effect: Z = 3.25 (P = 0.001)						
•Treatment by anti-TNF:						
Kapetanovic 2006	24	50	16	37	31.9%	1.21 [0.52, 2.85]
Kapetanovic 2011 (A&R)	18	89	23	85	62.6%	0.68 [0.34, 1.38]
Visvanathan 2007	6	20	2	14	5.5%	2.57 [0.44, 15.19]
Subtotal (95% CI)		**159**		**136**	**100.0%**	**0.96 [0.57, 1.59]**
Total events	48		41			
Heterogeneity: $Chi^2 = 2.36$, df = 2 (P = 0.31); $I^2 = 15\%$						
Test for overall effect: Z = 0.17 (P = 0.86)						



Hua C et al, Arthritis Care Res, 2014; 66: 1016-1026

Vaccination anti-pneumococcique

Persistence of antibody response 1.5 years after vaccination using 7-valent pneumococcal conjugate vaccine in patients with arthritis treated with different antirheumatic drugs

Meliha Crnkic Kapetanovic[1*], Tore Saxne[1], Lennart Truedsson[2] and Pierre Geborek[1]

Kapetanovic *et al. Arthritis Research & Therapy* 2013, **15**:R1

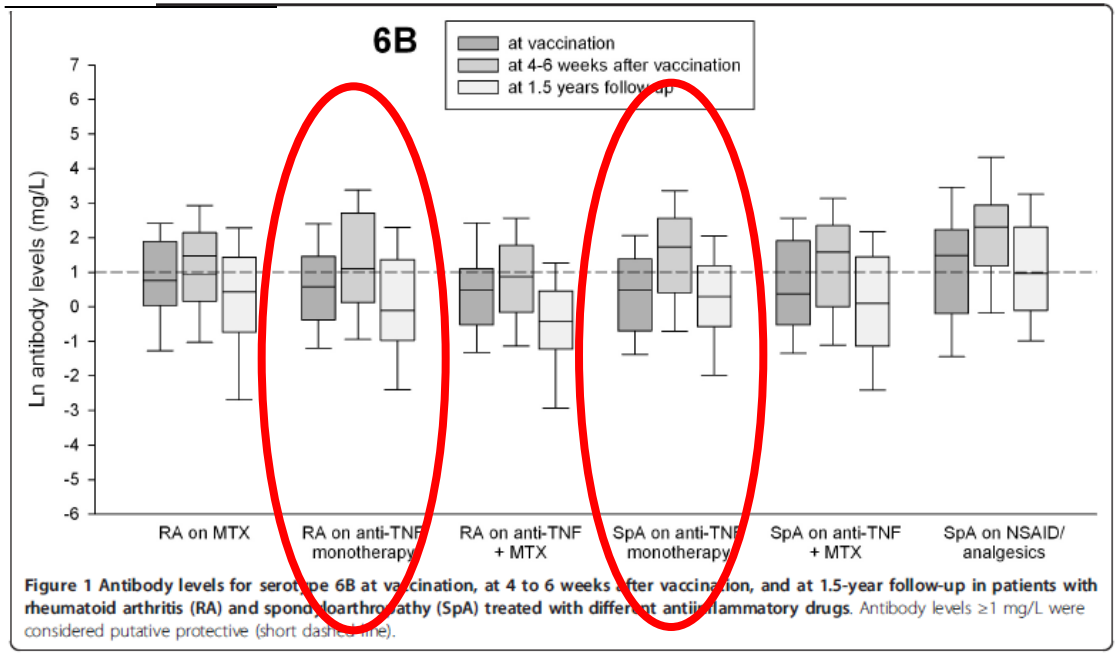


Figure 1 Antibody levels for serotype 6B at vaccination, at 4 to 6 weeks after vaccination, and at 1.5-year follow-up in patients with rheumatoid arthritis (RA) and spondyloarthropathy (SpA) treated with different antiinflammatory drugs. Antibody levels ≥1 mg/L were considered putative protective (short dashed line).

To boost antibody response, early revaccination with conjugate vaccine might be needed in patients receiving potent immunosuppressive remedies.

Vaccination antigrippale

anti-TNF alpha

At least 2 strains

•Treatment by Methotrexate

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Kaine 2007	33	59	36	50	52.8%	0.49 [0.22, 1.10]
Kivitz 2011	29	57	23	27	47.2%	0.18 [0.06, 0.59]
Total (95% CI)		**116**		**77**	**100.0%**	**0.35 [0.18, 0.66]**
Total events	62		59			

Heterogeneity: $Chi^2 = 1.92$, df = 1 (P = 0.17); $I^2 = 48\%$

Test for overall effect: Z = 3.20 (P = 0.001)

Odds Ratio M-H, Fixed, 95% CI

0.01 0.1 1 10 100

•Treatment by anti-TNF

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Kaine 2007	-0.0299	0.3166	36.8%	0.97 [0.52, 1.81]
Kapetanovic 2007	-1.9661	0.5957	26.1%	0.14 [0.04, 0.45]
Kivitz 2011	-0.901	0.3071	37.1%	0.41 [0.22, 0.74]
Total (95% CI)			**100.0%**	**0.42 [0.17, 1.09]**

Heterogeneity: $Tau^2 = 0.53$; $Chi^2 = 9.38$, df = 2 (P = 0.009); $I^2 = 79\%$

Test for overall effect: Z = 1.79 (P = 0.07)

Odds Ratio IV, Random, 95% CI

0.01 0.1 1 10 100

Favours control Favours experimental

Hua C et al, Arthritis Care Res, 2014; 66: 1016-1026

Vaccination antigrippale

anti-TNF alpha

- 28 sujets avec PR activité basse-modérée sous anti-TNF alpha
- Objectif: taux de séroprotection>70% (60% chez sujets de 60 ans)

Table 3 Response to flu vaccine by RA patients and healthy controls during three influenza seasons.

Season 2005/2006	N	A/New Caledonia/20/99 H1N1		A/California/7/04 H3N2		B/Shanghai/361/02	
		T0	T1	T0	T1	T0	T1
Seroprotection rate							
Patients	22	23%	68%	35%	75%	23%	50%
Healthy controls	10	30%	90%	30%	80%	20%	40%
Season 2006/2007	**N**	**A/New Caledonia/20/99 H1N1**		**A/Wisconsin/67/05 H3N2**		**B/Malaysia/2506/04**	
		T0	T1	T0	T1	T0	T1
Seroprotection rate							
Patients	22	41%	73%	82%	82%	50%	59%
Healthy controls	8	88%	100%	88%	100%	63%	88%
Season 2007/2008	**N**	**A/Solomon Island/3/06 H1N1**		**A/Wisconsin/67/05 H3N2**		**B/Malaysia/2506/04**	
		T0	T1	T0	T1	T0	T1
Seroprotection rate							
Patients	20	42%	80%	63%	85%	73%	85%
Healthy controls	7	60%	100%	40%	75%	60%	75%

- Immunogénicité croissante année après année
- Fréquence de syndromes pseudo-grippaux moins importante dans le groupe des patients RA vaccinés (2/28 [7.14%] vs 5/20 [25%], p=0.08), (mais pas d'isolement du virus)

Salemi S Clinical Immunology (2010) 134, 113–120

Vaccins vivants

...

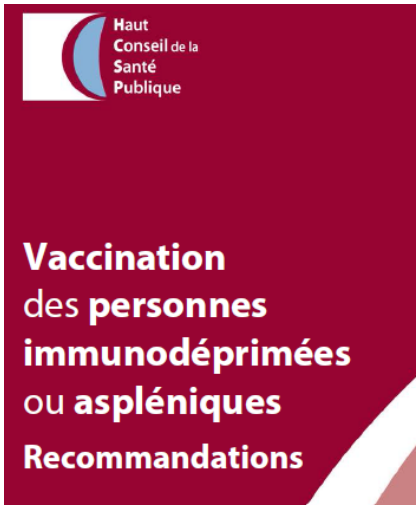
Vaccine	Biotherapy	TNFα antagonists				
		Etanercept	Adalimumab	Golimumab	Certolizumab	Infliximab
Live attenuated vaccines	Stop	2 to 12 weeks	10 to 12 weeks	8 to 12 weeks	10 to 12 weeks	6 to 12 weeks
	Re-start	3 weeks	3 weeks	3 weeks	3 weeks	3 weeks
Inactivated vaccines	Stop	No treatment interruption				
	Re-start					

French Society for Rheumatology (and based on drug half-life values) *J. Morel et al. / Joint Bone Spine 83 (2016) 135–141*

Durées **minimales** d'arrêt des anti-TNF avant vaccination = 3 mois!!

SANS OUBLIER: Pour la corticothérapie, la dose et la durée au delà desquelles l'administration d'un **vaccin vivant** est **contre indiquée** sont les suivantes **:**

- Chez l'adulte : 10 mg d'équivalent-prednisone par jour, depuis plus de 2 semaines.
- Chez l'enfant : 2 mg/kg d'équivalent-prednisone par jour - et au-delà de 20 mg par jour chez les enfants de plus de 10 kg -, depuis plus de 2 semaines.
- Les « bolus » de corticoïdes contre-indiquent l'administration d'un vaccin vivant durant les 3 mois qui suivent.



Des biothérapies particulièrement à risque (ou à risque particulier)

Rhumatismes inflammatoires

- **Tocilizumab** *(Roactemra®)*
  - Anticorps anti IL6
  - Infections = effets indésirables les plus fréquents sous tocilizumab, même si cas graves rares
  - !! anti-IL6 = peut limiter la fièvre et empêcher l'élévation de la CRP !! ➔ retard au diagnostic
  - Pneumonies+++

- **Anakinra** *(Kineret®)*
  - anticorps anti IL1
  - importance de la dose

- **Pas de sur-risque évident avec**
  - Abatacept *(Orencia®)*
  - Rituximab *(Mabthera®)*
  - Ustekinumab *(Stelara®)*

Table 4 Risk of serious infections stratified by high- and low-dose dose groups

Treatment	ORs (95% CIs)		
	High-dose* versus placebo groups	Low-dose† versus placebo groups	High-dose* versus low-dose† groups
Anakinra	3.40 (1.11 to 10.46)	0.51 (0.03 to 8.27)	9.63 (1.31 to 70.91)
	1.67 (0.51 to 5.41)§		6.41 (0.81 to 50.30)§

*High-dose groups were defined as 1000 mg for rituximab, 10 mg/kg for abatacept and ⩾100 mg for anakinra.
†Low-dose groups were defined as 500 mg for rituximab, ⩽2 mg/kg for abatacept and <100 mg for anakinra.
‡Calculated ORs when patients receiving biological DMARD as concomitant treatment were excluded.
§Calculated ORs when patients with comorbidity factors were excluded.

Des biothérapies particulièrement à risque (ou à risque particulier)

Sclérose en plaques

- **Natalizumab** *(Tysabri®)*
  - *Anticorps anti-α4-integrine*
  - *Inhibe l'adhérence du lymphocyte T à d'autres cellules/ SNC*
  - *Augmentation du risque de LEMP chez les SEP traitées par natalizumab*

  (650 cas fin 2017)

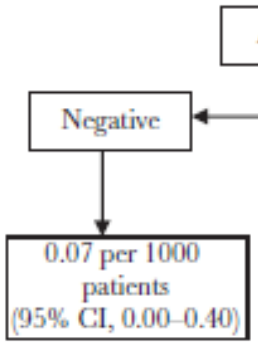
- *Efalizumab = idem*
- *Vedolizumab = mieux ? (intégrine plus sélective)*

Open Forum Infectious Diseases
INVITED REVIEW ARTICLE

IDSA Infectious Diseases Society of America · hivma hiv medicine association · OXFORD

Infectious Complications of Multiple Sclerosis Therapies: Implications for Screening, Prophylaxis, and Management

David J. Epstein,[1] Jeffrey Dunn,[2] and Stan Deresinski[1]



Natalizumab Exposure, mo[a]	Patients without previous immunosuppressant use, per 1000 patients (95% CI)			Patients with previous immunosuppressant use, per 1000 patients (95% CI)
	Index ≤ 0.9	Index 0.9–1.5	Index > 1.5	
1–12	0.01 (0.00–0.03)[b]	0.1 (0.0–0.2)	0.2 (0.0–0.5)	0.3 (0.0–1.9)
13–24	0.05 (0.00–0.14)[b]	0.3 (0.0–0.6)	0.9 (0.3–1.6)	0.4 (0.0–2.3)
25–36	0.2 (0.0–0.4)	0.8 (0.1–1.5)	2.6 (1.4–3.9)	3.6 (1.4–7.4)
37–48	0.4 (0.0–1.0)	2.0 (0.2–3.8)	6.8 (4.4–9.1)	8.3 (4.3–14.5)
49–60	0.5 (0.0–1.2)	2.4 (0.2–4.5)	7.9 (4.9–10.9)	8.4 (3.7–16.6)
61–72	0.6 (0.0–1.5)	3.0 (0.2–5.8)	10.0 (5.6–14.4)	5.5 (1.1–16.0)[c]

OFID 2018

Des biothérapies particulièrement à risque (ou à risque particulier)

Sclérose en plaques

- **Ocrelizumab***(Ocrevus®)*
  - *Anticorps anti-CD20*
  - *Risque élevé de réactivation VHB*

Table 3. Recommendations for Approach to Patients With Serologic Markers of HBV Infection by Drug

Drug	Risk of HBV Reactivation or Flare	HBsAg (+)	HBsAg (-) Anti-HBc (+)
Natalizumab	Moderate	Prophylaxis	Prophylaxis or preemptive
Alemtuzumab	High		
Ocrelizumab	Very high	Prophylaxis	
Mitoxantrone	Moderate	Prophylaxis	Prophylaxis or preemptive
Fingolimod	Low	Prophylaxis or preemptive	Preemptive or periodic LFT monitoring
Dimethyl fumarate	Low		
Teriflunomide	Low		

- **Pas de sur-risque évident avec**
  - Fingolimod *(Gylenia®)*

Des biothérapies particulièrement à risque (ou à risque particulier)

Lymphomes

- **Ibrutinib** *(Imbruvica®)*
  - inhibiteur tyrosine kinase ➔ *inhibe efficacement la prolifération et la survie in vivo des cellules B malignes ainsi que la migration cellulaire et l'adhésion*
  - en monothérapie 11,4% d'infections bactériennes et fongiques++ invasives *(via neutropénie, lymphopénie)* – mortalité infectieuse

Clinical Infectious Diseases
MAJOR ARTICLE

Serious Infections in Patients Receiving Ibrutinib for Treatment of Lymphoid Cancer

Tilly Varughese,[1] Ying Taur,[1,2] Nina Cohen,[3] M. Lia Palomba,[2,4] Susan K. Seo,[1,2] Tobias M. Hohl,[1,2] and Gil Redelman-Sidi[1,2]

Clinical Infectious Diseases® 2018;67(5):687–92

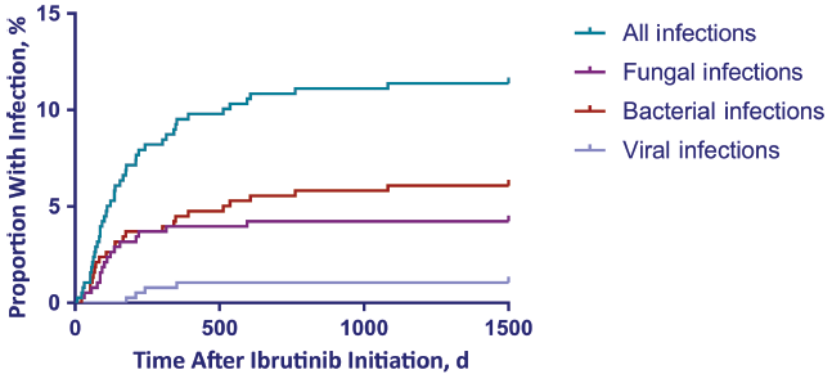


Figure 1. Serious infection after ibrutinib initiation. A Kaplan-Meier graph shows

- **Bortezomib** *(Velcade®)*
  - inhibiteur protéasome ➔ induction apoptose cellules tumorales mais aussi déplétion sélection lymphocytes T
  - sur-risque pneumonie (8%) et zona (13%)

Des biothérapies particulièrement à risque (ou à risque particulier)

- **Alemtuzumab** *(MabCampath®)*
  - Anticorps anti-CD52
  - Action anti lymphocytaire (anti CD4 ++++)
  - Risque infection CMV (6%), HSV, VZV, HPV, TB, listeriose, candidose muqueuses

Lymphomes

Infectious Complications Associated with Alemtuzumab Use for Lymphoproliferative Disorders

Stanley I. Martin,[1,5,a] Francisco M. Marty,[1,4,5] Karen Fiumara,[2] Steven P. Treon,[3,4,5] John G. Gribben,[6] and Lindsey R. Baden[1,4,5]

[1]Division of Infectious Diseases, [2]Department of Pharmacy, and [3]Division of Medical Oncology, Brigham & Women's Hospital, [4]Dana-Farber Cancer Institute, and [5]Harvard Medical School, Boston, Massachusetts; and [6]Cancer Research UK Medical Oncology Unit, Barts and The London School of Medicine, London, United Kingdom

Clinical Infectious Diseases 2006; 43:16–24

Des biothérapies particulièrement à risque (ou à risque particulier)

Cancers

- **Bevacizumab** *(Avastin®)*
  - anticorps anti-VEGF (Vascular Endothelial Growth Factor) – limite néoangiogénèse
  - risque d'infection majoré (lié à neutropénie – incidence 25%)
    ➔ RR d'infection grave = 1,59; IC95%, 1,42 -1,79
  - risque de perforation digestive (1%) ➔ risque de péritonite/bactériémie – mortalité 22%

- **Cetuximab** *(Erbitux®)*
  - anticorps monoclonal chimérique IgG1 spécifiquement dirigé contre le récepteur du facteur de croissance épidermique (EGFR)
  - risque d'infection majoré (lié à neutropénie – incidence 33%)
    ➔ RR d'infection grave = 1,34; IC95%,1,10 -1,62

Des biothérapies particulièrement à risque (ou à risque particulier)

Mélanomes

- **Pas de sur-risque intrinsèque**
  - Anti CTLA-4 Ipilimumab, tremelimumab
  - Anti PD-1 or PD-L1 Nivolumab, pembrolizumab, atezolizumab

  (améliorent/augmentent la fonction effectrice T cytotoxique)

- **Mais risque potentiel des traitement associés (corticoïdes!)**

Des biothérapies particulièrement à risque (ou à risque particulier)

Miscellanées

- **Eculizumab** *(Soliris®)*
  - Anticorps anti-complément (fraction C5 ➔ complexe d'attaque membranaire)
  - Indications HPN, microangiopathie thrombotique (SHU en particulier)
  - Risque : infections invasives
    - Méningocoque (incidence 1,5% !)
    - Gonococcie disséminée
    - (pneumocoque?) – car 42% d'infections respiratoires

- **Omalizumab** *(Xolair®)*
  - Anticorps anti-IgE
  - Indications asthme allergique grave
  - Risque infection parasitaire?
    - ➔ très peu évalué ! (OR infections helminthes 2,2; IC95% CI 0,94-5,15)

Des biothérapies y en a trop…

Club Rhumatismes et Inflammations

Fiches pratiques du CRI : Prise en charge pratique des patients sous...

Toutes les infos sur les dernières mises à jour des Fiches Pratiques du CRI

MISES A JOUR DECEMBRE 2017 !
De nouvelles fiches pratiques :

- **Prise en charge pratique des patients sous sécukinumab**

  Le champ des possibles continue à s'agrandir avec le ciblage d'une nouvelle voie, celle de l'interleukine 17. Le sécukinumab ouvre le bal de l'inhibition de cette voie qui a une véritable spécificité dans les affections articulaires et extra articulaires de la « nébuleuse » des spondyloarthrites et du psoriasis.
  Le CRI et son groupe d'experts multidisciplinaires poursuit son étroit partenariat avec le Groupe PSo de la Société Française de Dermatologie et a donc préparé pour vous les fiches pratiques afin de vous permettre d'utiliser le sécukinumab en maîtrisant le mieux possible tous les aspects importants.
  L'objectif est de vous accompagner dans votre quotidien par des réponses argumentées sur l'EBM (Evidence-Based Medicine) et le cas échéant, quand le sujet n'a pas été réellement étudié, en vous apportant un avis d'experts partagé.
  Nous remercions très sincèrement tous les experts multidisciplinaires qui contribuent depuis tant d'années avec enthousiasme et professionnalisme à la rédaction de ces documents très appréciés par nos collègues. C'est cet esprit scientifique et de générosité que nous souhaitons mettre en exergue et pérenniser. Merci à vous de nous accompagner avec autant de fidélité dans nos missions dont la priorité est toujours de faire le mieux possible pour nos patients !

Fiches pratiques & eSessions SCRIPT

→ Fiches pratiques du CRI : Prise en charge pratique des patients sous...
- Abatacept [Déc. 2015]
- Abatacept (English version)
- Anti-IL1 [Jan. 2014]
- Anti-TNFa [Jan. 2014]
- Belimumab [Déc. 2013]
- inhibiteurs de Janus Kinases (JAKi) [Juil. 2018]
- Méthotrexate [Déc. 2016]
- Rituximab [Jan. 2017]
- Rituximab chez l'enfant [Juil. 2009]
- Sécukinumab [Déc. 2017]
- Tocilizumab [Jan. 2017]
- Tocilizumab (English version)
- Ustékinumab [Fév. 2017]

→ eSessions SCRIPT

Conclusions biothérapies et infections…

- A la base, pathologies d'indication souvent associées à un sur-risque d'infections même en l'absence de biothérapie (par ex 2 fois plus important chez les sujets avec PR que dans la population générale)

- Majoration fréquente de ce sur-risque du fait:
  - Du fait des traitements « classiques » (corticoïdes, MTX, …)
  - des biothérapies (ne concerne pas que les anti-TNF)

Conclusions biothérapies et infections…

- Diminuer le risque infectieux
  - connaitre les risques spécifiques pour adopter des mesures de prévention spécifiques
  - Importance du bilan « infectieux » préthérapeutique (ex: dents, Rx thorax, QTF, sérologies VHB, VZV,…)
  - Mesures de prévention (individuelle et collective)

Conclusions biothérapies et infections…

- ➔ Vaccination, à évoquer/évaluer (! Timing !):
  - avant la mise en route de tout traitement IS/ biothérapie
  - lors du changement de biothérapie,
  - de façon annuelle à la fin de l'été et en cas de voyage à l'étranger
- Intérêt « cumulatif » des vaccins:
  - « transversal »= grippe + pneumocoque +/- haemophilus
  - « longitudinal » = grippe
- **Intérêt vaccination de l'entourage !!! (grippe, varicelle, rougeole)**

Conclusions biothérapies et infections…

- En cas d'infection déclarée,
  - privilégier arrêt biothérapie lorsque risque infectieux associé
  - toujours prendre en compte la balance bénéfices/risques pour la reprise

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