7e Journée des Référents en Antibiothérapie

Tours le 13 juin 2012

Les infections sous biothérapies sont-elles évitables ?

Matthieu Revest
Maladies Infectieuses et Réanimation Médicale
CHU Rennes

Table 6. New molecular entities (NMEs) publicly disclosed in the research and development programs of the world's 7 largest biotechnology companies.

Indication or type of agent	No. of NMEs
Inflammation/immunodulator	24
Metabolic/endocrine	15
Cancer	13
Inherited enzyme deficiencies	9
Cardiovascular condition	6
Hematologic condition	3
Dermatologic condition	3
Renal condition	3
Neurology	2
COPD/asthma	2
Antibacterial agent	1

NOTE. COPD, chronic obstructive pulmonary disease.

Shlaes et al., CMI, 2004

Therapeutic monoclonal antibodies	Key targets
Alemtuzamab	CD52
Adalimumab, Infliximab, Certolizumab pegol, Etanercept	TNF-α
Anakinra, Rilonacept	IL-1
Gemtuzumab ozogamicin	CD33
Alefacept	CD2
Muromonab	CD3
Abatacept, Efalizumab	T-cell activation
Basiliximab, Daclizumab	IL-2
^{90}Y-Ibritumomab tiuxetan, Rituximab, ^{131}I-Tositumomab	CD20

Tocilizumab IL-6

Salvana et Salata

CLINICAL MICROBIOLOGY REVIEWS, Apr. 2009, p. 274–290

Infections et biothérapies

- Quel risque infectieux pour quelle biothérapie ?
  - Anti-TNF$_{\alpha}$
  - Rituximab
  - Anakinra
  - Abatacept
  - Tocilizumab
- Comment prévenir ce risque ?

Anti-TNF$_\alpha$ et infections

- Essais randomisés:
  - Etanercept: étude ERA[1]:
    - MTX vs etanercept 10 mg x 2/sem ou 25 mg x 2/sem
    - 632 patients, suivi de 2 ans
    - Pas de sur-risque d'infection grave
  - Infliximab:
    - Etude ATTRACT[2]: pas de sur-risque d'infection grave
    - Etude ASPIRE[3]: sur-risque d'infection grave (pneumonies)
  - Adalimumab[4,5]:
    - Risque si associé au MTX
    - Pneumonies
  - Certolizumab pegol:
    - Etude Fast4ward[6]: pas de sur-risque infectieux

[1]Genovese, 2002; [2]Maini, 2004; [3]St Clair, 2004; [4]Weinblatt, 2003; [5]Breedveld, 2006; [6]Fleischmann, 2009

The New England Journal of Medicine

TUBERCULOSIS ASSOCIATED WITH INFLIXIMAB, A TUMOR NECROSIS FACTOR α–NEUTRALIZING AGENT

JOSEPH KEANE, M.D., SHARON GERSHON, PHARM.D., ROBERT P. WISE, M.D., M.P.H., ELIZABETH MIRABILE-LEVENS, M.D., JOHN KASZNICA, M.D., WILLIAM D. SCHWIETERMAN, M.D., JEFFREY N. SIEGEL, M.D., AND M. MILES BRAUN, M.D., M.P.H.

N Engl J Med, Vol. 345, No. 15 · October 11, 2001

- 70 T pour 149 000 patients
- Incidence:
  - 24,4/100 000 PR + infliximab
  - 6,2/100 000 PR

- Fréquence des formes extra-pulmonaires +++ (50%)
- Gravité +++
- Réactivation d'ITL

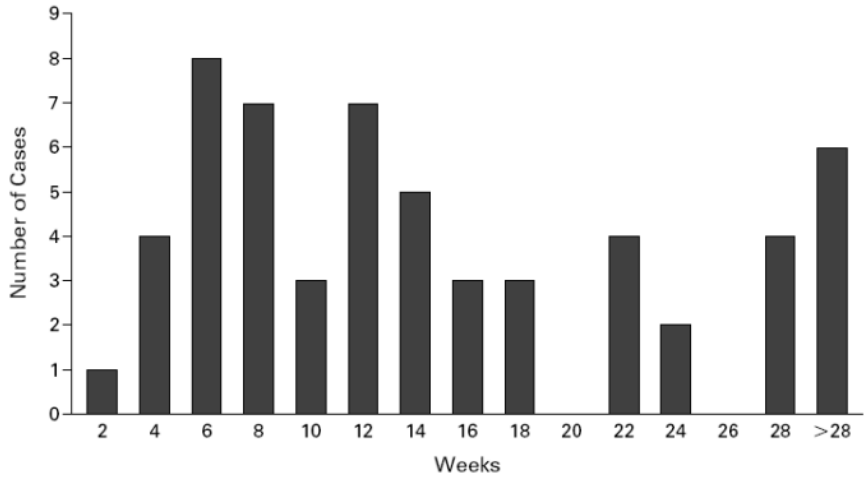
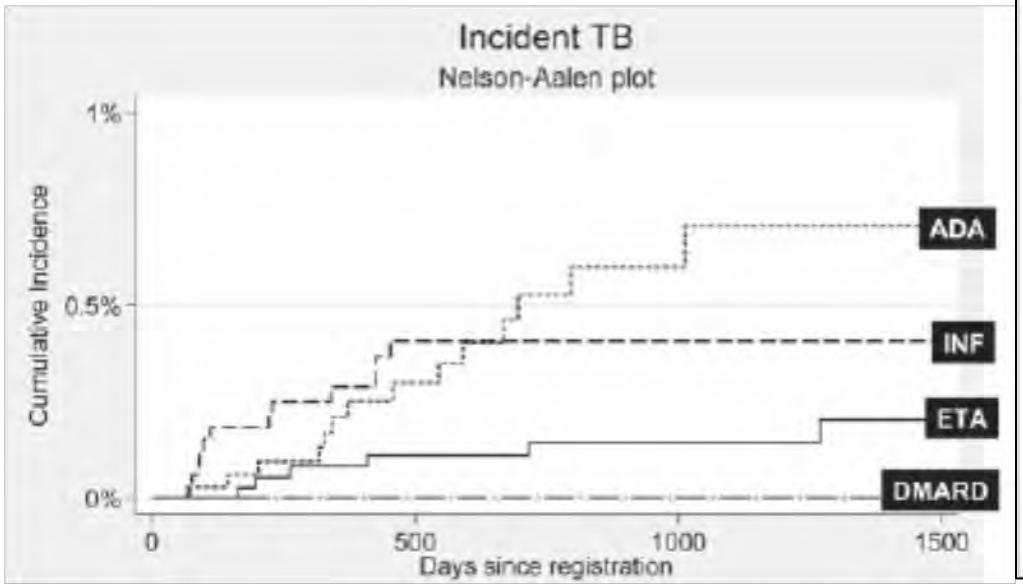


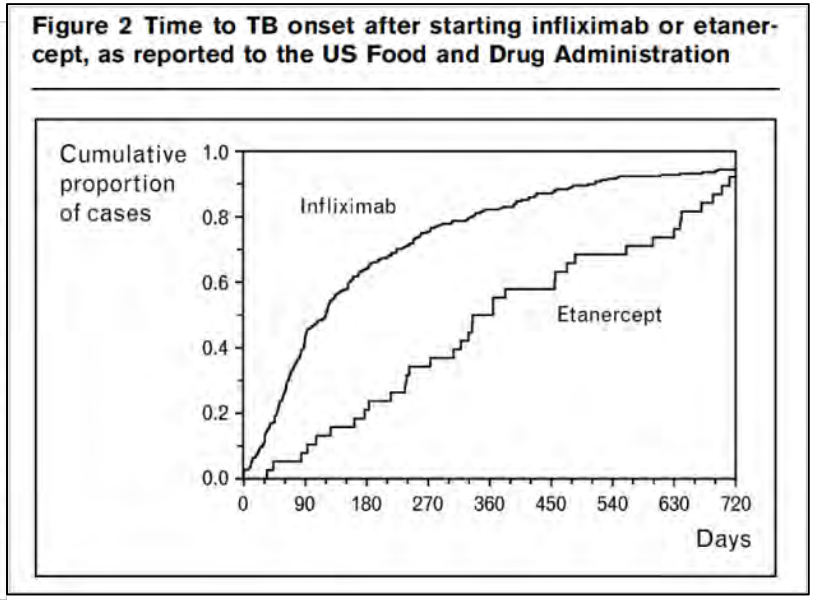
Figure 1. Time from the Initiation of Infliximab Therapy to the Diagnosis of Tuberculosis. Data were available for 57 patients, most of whom had received monthly infusions of infliximab.

Anti-TNF$_\alpha$ et tuberculose

- Risque retrouvé dans tous les pays:
  - Suède: RR x **4** (Askling, Arthritis Rheum, 2005)
  - Corée du sud: RR x **30** si infliximab par rapport à la population générale (x 9 si PR sans anti-TNF) (Seong, J Rheumatol, 2007)
  - Espagne: incidence TB (Gomez-Reino, Arthritis Rheum, 2003)
    - Pop générale: 21/100 000
    - PR sans anti-TNF: 95/100 000
    - PR avec infliximab: **1 893 / 100 000**

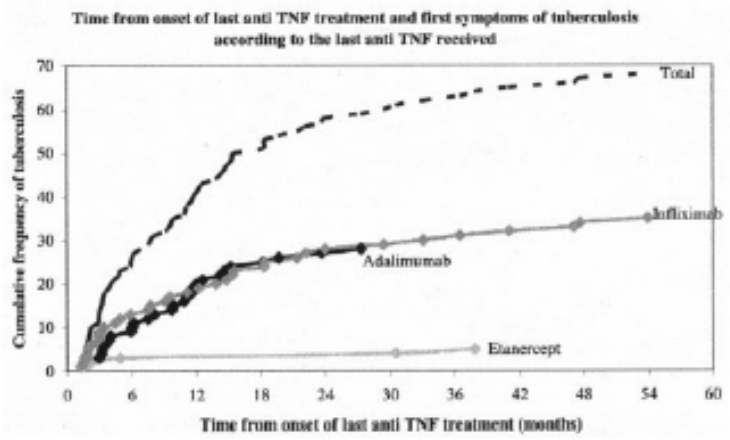
Anti-TNF$_\alpha$ et tuberculose

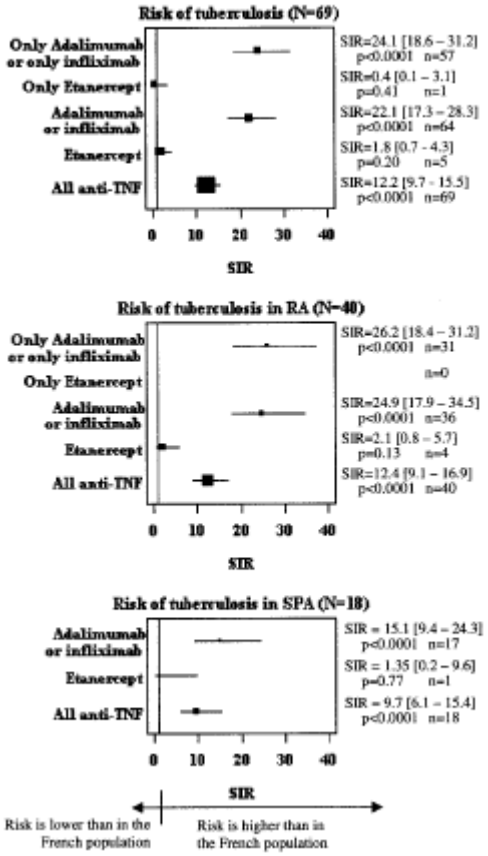




Dixon, Ann Rheum Dis, 2010

Anti-TNF$_\alpha$ et tuberculose: données françaises





69 cas de tuberculoses:

- 61% formes extra-pulmonaires
- 41% disséminées
- Microbiologie +: 63%
- 2 décès

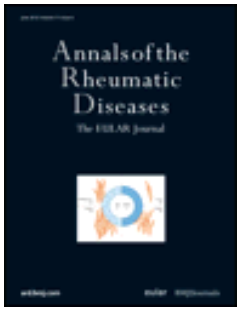
Tubach, Arthritis Rheum, 2009

Anti-TNF$_\alpha$ et tuberculose: Certolizumab pegol

Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomised controlled trial

J Smolen,[1] R B Landewé,[2] P Mease,[3] J Brzezicki,[4] D Mason,[5] K Luijtens,[6] R F van Vollenhoven,[7] A Kavanaugh,[8] M Schiff,[9] G R Burmester,[10] V Strand,[11] J Vencovský,[12] D van der Heijde[13]

Ann Rheum Dis 2009;**68**:797–804.



3 bras comparatifs après 1 mois de monothérapie:

- **MTX + PCB**
- **MTX + certolizumab 200 mg**
- **MTX + certolizumab 400 mg**

→

5 cas de tuberculose dans les bras certolizumab:

- **3 pulmonaires**
- **1 péritonéale**
- **1 disséminée**

Efficacité de la prévention

- **Screening:**
  - ATCD de TB non ou partiellement traitée
  - Contact proche d'un patient bacillifère
  - Séquelle de PIT sur RP
  - IDR ≥ 5 mm (ou 2ème test à S1 +)

⟶ **9 mois INH**

Table 1. Characteristics of the 2,833 rheumatoid arthritis patients treated with tumor necrosis factor (TNF) antagonists in the BIOBADASER registry*

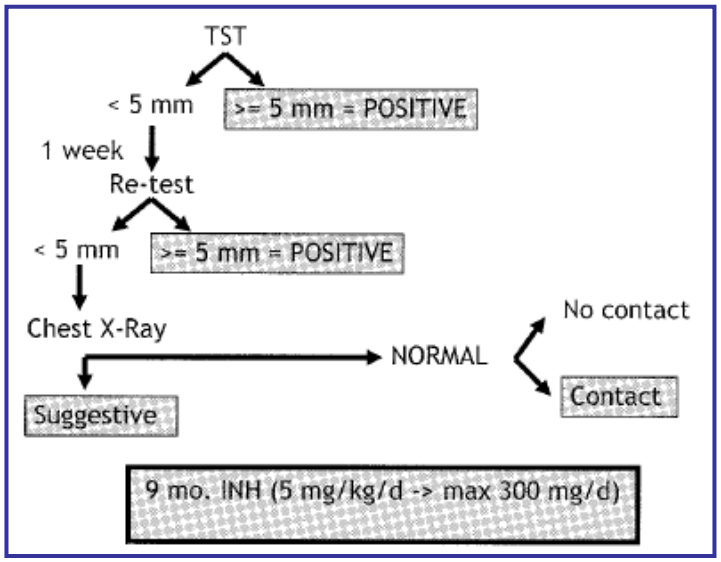
	Pre-OR	Post-OR
No. of patients	1,690	1,143
Women, %	78	78
Age, mean ± SD years	54 ± 13	50 ± 15
Disease duration, mean ± SD years	11 ± 8	10 ± 8
TNF antagonist, no. (%)†		
Infliximab	1,648 (87.6)	579 (46.7)
Etanercept	233 (12.4)	506 (40.8)
Adalimumab	0 (0)	154 (12.5)

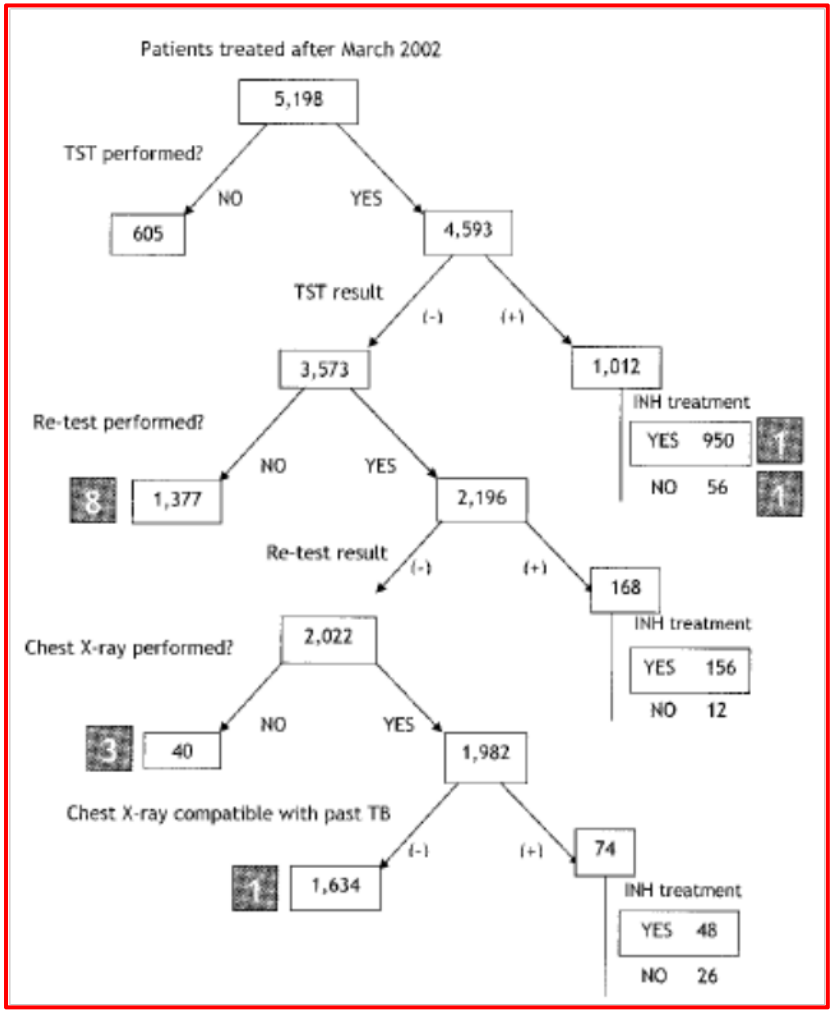
Table 2. Rate of active TB in the BIOBADASER cohort before and after the specific recommendations, and risk ratio for the incidence of active TB compared with the risk in the background Spanish population and in the EMECAR patients*

	Patient-years of exposure to TNF antagonists	No. of active TB cases	Active TB rate per 100,000 (95% CI)	IRR versus background (95% CI)	IRR versus EMECAR (95% CI)†
All TB cases					
Pre-OR	6,126	32	522 (369–738)	20.9 (12.0–36.8)	–
Post-OR	1,699	2	117 (29–470)	4.7 (0.5–18.9)	–
$IRR_{recommendations}$‡	–	–	0.22 (0.03–0.88)	–	–
TB cases with RA only					
Pre-OR	4,780	27	564 (387–823)	22.6 (12.6–40.6)	6.2 (2.6–16.9)
Post-OR	1,049	1	95 (13–676)	3.8 (0.1–23.3)	1.0 (0.02–8.2)
$IRR_{recommendations}$‡			0.17 (0.004–1.02)	–	–

Carmona, Arthritis Rheum, 2005

Efficacité de la prévention





Gomez-Reino, Arthritis Rheum, 2007

Recommandations françaises
Dépistage avant mise sous anti-TNF

- Interrogatoire soigné:
  - BCG
  - Contage
  - Pays d'origine
  - IDR antérieures,…
- Examen clinique: signe de TB ?
- RP
- IDR: positive si > 5 mm
- Peut être remplacée par elispot ou quantiféron

CRI, décembre 2010

Recommandations françaises
Conduite à tenir

- PIT non traitée
- Sujet à fort risque de réactivation:
  - ATCD de TB avant 1970 ou insuffisamment traitée (< 6 mois de traitement dont 4 mois de quadri-thérapie)
  - Contact proche du sujet bacillifère
  - RP anormale et incertitude quant à un traitement stérilisant
  - IDR > 5 mm

→ Traitement par Rifam-INH 3 mois ou INH 9 mois

Attendre 3 semaines pour débuter les anti-TNF

- Si TB maladie:
  - Traitement (6 à 9 mois)
  - Attendre la fin du traitement (au moins 2 mois si urgence thérapeutique)

CRI, décembre 2010

Intérêt des tests quantiféron ou elispot ?

- Tests qui detectent la sécretion d'IFN-γ en contact d'antigène de *Mycobacterium tuberculosis*
- Exploration de l'immunité mémoire
- Ne croise pas avec le BCG
- Ne croise pas avec les mycobactéries de l'environnement (sauf *M. kansasii, szulgaï, marinum* et *flavescens*)
- Culture cellulaire pour l'elispot

BSR and BHPR rheumatoid arthritis guidelines on safety of anti-TNF therapies

Tina Ding[1], Jo Ledingham[2], Raashid Luqmani[3], Sarah Westlake[4], Kimme Hyrich[5], Mark Lunt[5], Patrick Kiely[6], Marwan Bukhari[7], Rikki Abernethy[8], Ailsa Bosworth[9], Andrew Ostor[10], Kate Gadsby[1], Frank McKenna[11], Diana Finney[12], Josh Dixey[13] and Chris Deighton[1] on behalf of the Standards, Audit and Guidelines Working Group of BSR Clinical Affairs Committee and BHPR

Rheumatology, nov 2010

- Prix des tests: (France 100 €)
  - Quantiféron: 35 £
  - Elispot: 100 £
- Incidence d'ITL en GB à 50 ans: 50 / 100 000
- Nombre de tests requis pour dépister un cas: 2000
- Coût : 70 000 £ pour quantiféron et 200 000 £ pour elispot

→ Tests non recommandés

Efficacité de la prévention

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Carmona, Arthritis Rheum, 2005

Comparison of in vitro-specific blood tests with tuberculin skin test for diagnosis of latent tuberculosis before anti-TNF therapy

Ann Rheum Dis 2007;66:1610–1615.

Jérémie Sellam*, Haifa Hamdi*, Carine Roy, Gabriel Baron, Marc Lemann, Xavier Puéchal, Maxime Breban, Francis Berenbaum, Marc Humbert, Karin Weldingh, Dominique Salmon, Philippe Ravaud, Dominique Emilie, Xavier Mariette, for the RATIO (Research Axed on Tolerance of Biotherapies) Study Group

- 68 patients avec pathologies inflammatoires (PR, SPA, Crohn)
- ITL définie par IDR, RP, ou ATCD contage…
- Deux groupes:
  - I: ITL exclue
  - II: ITL certaine selon recommandations (IDR > 10 mm car inclusion avant 2005)
    - ITL sur IDR
    - ITL à IDR neg

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Table 3 Results of CFP-10 thymidine incorporation among patients with certain latent tuberculosis infection independent of the tuberculin skin test (TST) result

Patient	TST result	CFP-10 thymidine incorporation
Patient 1	Neg	Pos (3.0)
Patient 2	Neg	Pos (6.9)
Patient 3	Neg	Pos (6.2)
Patient 4	Neg	Pos (42.6)
Patient 5	Neg	Pos (35.7)
Patient 6	Pos	Pos (28.1)
Patient 7	Pos	Pos (90.1)
Patient 8	Pos	Pos (3.1)
Patient 9	Pos	Neg (1.8)
Patient 10	Pos	Pos (15.4)
Patient 11	Pos	Neg (1.3)
Patient 12	Pos	Pos (3.0)
Patient 13	Pos	Pos (8.1)
Total	**8/13 (61.5%)**	**11/13 (84.6%)**

TST is expressed as positive with a threshold of 10 mm. Results of each test for each subject are reported as Pos (positive) or Neg (negative) (exact value). Results for thymidine assay are expressed in the stimulation index (SI).

Comparison of in vitro-specific blood tests with tuberculin skin test for diagnosis of latent tuberculosis before anti-TNF therapy

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Table 5 Comparison of positive results of in vitro assays among patients without latent tuberculosis infection (LTBI) and tuberculin skin test (TST) results ⩽5 mm, those without evidence of LTBI except a TST result between 6 and 10 mm (intermediate TST) and those with LTBI (corresponding to group II)

Antigen	Test	Patients without LTBI and TST ⩽5 mm	Patients with TST 6–10 mm	Patients with LTBI Group II	P[1]	P[2]
CFP-10	Thymidine	1/13 (7.7)*	0/10 (0)	23/35 (65.7)	0.99	<0.0001
	PKH-26	1/13 (7.7)*	0/10 (0)	16/35 (45.7)	0.99	0.008
	ELISPOT	0/13 (0)	1/10 (10)	18/35 (51.4)	0.43	0.03
ESAT-6	Thymidine	0/8 (0)	0/3 (0)	10/19 (52.6)	1.0	0.22
	ELISPOT	1/8 (12.5)	1/3 (33.4)	16/19 (84.2)	0.50	0.12

Table 2. TB risk factors in patients and control subjects receiving anti-TNF therapy, by univariate analysis*

	TB patients (n = 68)	Controls (n = 136)	OR (95% CI)	*P*
Age, mean ± SD years†	58.3 ± 15.5	52.6 ± 16.3	1.35 (1.08–1.68)	0.008
Born in a TB-endemic area				
No	54 (79.4)	128 (94.1)	1	0.005
Yes	14 (20.6)	8 (5.9)	3.50 (1.47–8.34)	
Duration of underlying inflammatory disease, mean ± SD years	11.4 ± 8.8	13.6 ± 11.1	0.98 (0.95–1.01)	0.11
Tuberculin skin test reaction diameter at screening				
<5 mm	30 (66.7)	80 (77.7)	1	0.38
5–10 mm	11 (24.4)	13 (12.6)	2.04 (0.74–5.60)	
>10 mm	4 (8.9)	10 (9.7)	1.47 (0.37–5.73)	
Chest radiography findings at screening favoring TB sequelae				
No	50 (90.9)	90 (96.8)	1	0.07
Yes	5 (9.1)	3 (3.2)	4.59 (0.88–23.84)	

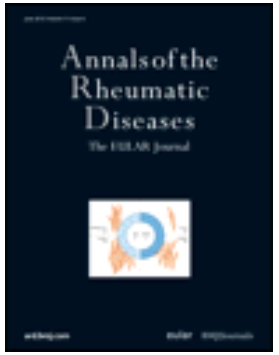
22 patients sans IDR et 13 sans RP

Tubach, Arthritis Rheum, 2009

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

Ann Rheum Dis (2012)

Xavier Mariette,[1] Gabriel Baron,[2] Florence Tubach,[3] Frédéric Lioté,[4] Bernard Combe,[5] Corinne Miceli-Richard,[1] René-Marc Flipo,[6] Philippe Goupille,[7] Matthieu Allez,[8] Dominique Salmon,[9] Dominique Emilie†,[10] Guislaine Carcelain*,[11] Philippe Ravaud*[2]



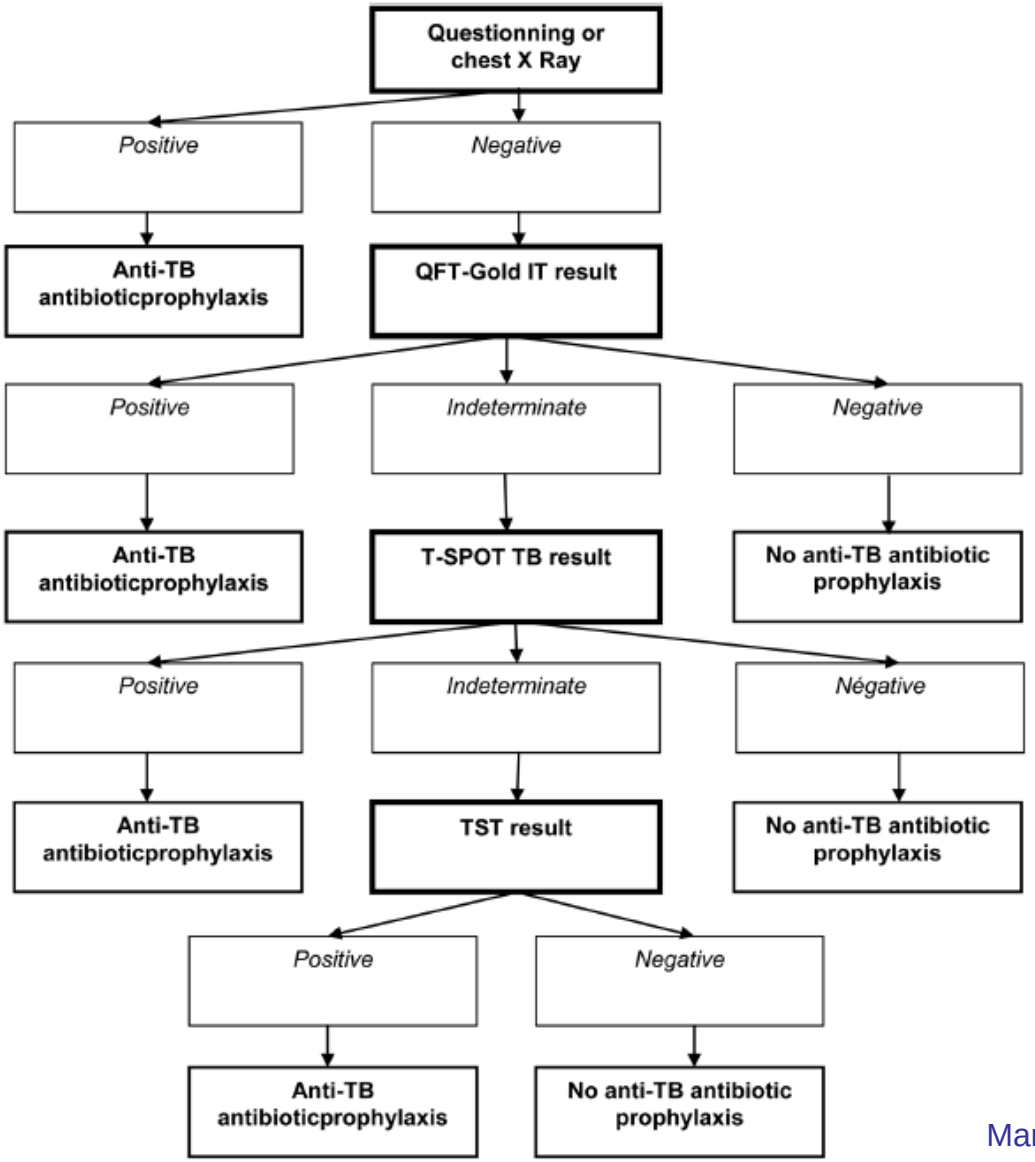
429 patients de 15 centres

429 patients de 15 centres

Traitement d'une ITL chez:

- **177 patients si on considère l'IDR**
- **107 patients si considère 1 IGRA**

Modification du choix de traiter ou pas pour 113 patients



Mariette, Ann Rheum Dis, 2012

Reprise anti-TNF après TB ?

- **Tuberculose-maladie**
  - Attendre **fin du traitement**
  - Avec les anti-BK majeurs (au moins 2 mois RMP + PZA)
  - Certitude d'éradication (**observance, BK sensible**)
  - Quelques séries rassurantes
    - Cohorte **Ratio**
    - 21 tuberculoses maladies documentées après anti-TNF
    - 1 décès (5%)
    - **6 reprises anti-TNF**
      - **après anti-BK complété**
      - **pas de rechute**

Long-term follow-up of patients with tuberculosis as a complication of tumour necrosis factor (TNF)-α antagonist therapy: safe re-initiation of TNF-α blockers after appropriate anti-tuberculous treatment

B. Denis[1], A. Lefort[2], R. M. Flipo[3], F. Tubach[4], M. Lemann[5], P. Ravaud[4], D. Salmon[6], X. Mariette[7] and O. Lortholary[1] on behalf of the RATIO Group

CMI, 2008

Il n'y a pas que la tuberculose dans la vie

Risk of Serious Bacterial Infections Among Rheumatoid Arthritis Patients Exposed to Tumor Necrosis Factor α Antagonists

Jeffrey R. Curtis,[1] Nivedita Patkar,[1] Aiyuan Xie,[1] Carolyn Martin,[2] Jeroan J. Allison,[1] Michael Saag,[1] Deborah Shatin,[2] and Kenneth G. Saag[1]

- Etude de cohorte américaine
- Infections bactériennes hospitalisées
- 2393 patients dans le groupe anti-TNF et 2933 patients dans le groupe MTX seul

→ Pas de différence entre anti-TNF

Table 2. Types of physician-confirmed "definite" bacterial infections during hospitalization*

	TNFα antagonist patients	MTX-only patients
No. (%) of patients with any infection	65 (2.7)	58 (2.0)
Site-specific infections, no.		
Pneumonia/empyema	25	23
Cellulitis/soft tissue	23	17
Bacteremia/sepsis	7	8
Kidney/urinary tract	8	10
Postoperative	7	5
Device-associated	6	4
Septic arthritis	4	4
Gastroenteritis	1	5
Abdominal abscess	1	2
Osteomyelitis	1	3
Bacterial sinusitis	3	0
Diverticulitis	0	1
Total†	86	82

ARTHRITIS & RHEUMATISM
Vol. 56, No. 4, April 2007, pp 1125–1133

Il n'y a pas que la tuberculose dans la vie

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Table 3. Factors associated with hospitalization with a "definite" bacterial infection*

	Crude HR (95% CI)	Adjusted HR (95% CI)
TNFα antagonist treatment	1.39 (0.97–1.98)	1.94 (1.32–2.83)

Dans les 6 premiers mois de traitement:

- 2,9 /100 patients –année dans le groupe anti-TNF vs 1,4 dans le groupe MTX seul
- HR: 4,2 (95% CI: 2,0-8,8)

ARTHRITIS & RHEUMATISM
Vol. 56, No. 4, April 2007, pp 1125–1133

- Régistre de Grande Bretagne des patients sous anti-TNF
- 11 798 patients sous anti-TNF
- 3 598 patients sous traitement conventionnels
- Recueil des infections sévères

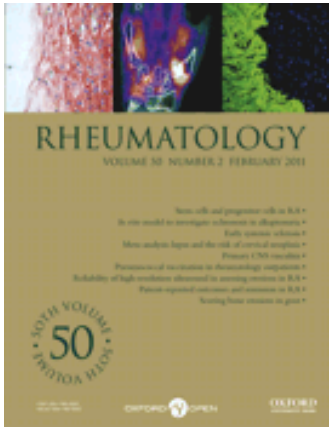


TABLE 2 Overall and time-dependent risk of SI

Results	nbDMARD	All TNF	ETN	INF	ADA
Follow–up, pyrs	9259	36 230	15874	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* (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)

Pas de différence de risque en fonction de l'âge

Galloway, Rheumatology, 2011

Infections virales

Risk of Herpes Zoster in Patients With Rheumatoid Arthritis Treated With Anti–TNF-α Agents

Anja Strangfeld, MD
Joachim Listing, PhD
Peter Herzer, MD
Anke Liebhaber, MD
Karin Rockwitz, MD
Constanze Richter, MD
Angela Zink, PhD

JAMA, February 18, 2009—Vol 301, No. 7

Table 5. Risk of Herpes Zoster: Andersen-Gill Model[a]

	Herpes Zoster Episodes, No.	Patient-years	Adjusted HR (95% CI)[b]	*P* Value
Characteristics at study entry				
Age, y[c]			1.50 (1.12-2.01)	.006
Propensity score				
Tertiles 1 and 2 (moderate/low)	18	1727	1 [Reference]	
Tertile 3 (high)	22	1342	1.53 (0.82-2.83)	.18
Characteristics at follow-up				
DMARDs	9	1301	1 [Reference]	
Anti–TNF-α	31	1736	2.24 (1.05-4.75)	.04
Etanercept	5	642	1.12 (0.39-3.17)	.84
Adalimumab/infliximab	26	1094	2.91 (1.35-6.30)	.007
Analyses for single agents				
Etanercept	5	642	1.09 (0.39-3.06)	.87
Adalimumab	18	717	3.01 (1.36-6.64)	.007
Infliximab	8	377	2.43 (0.94-6.26)	.07

Risk of Herpes Zoster in Patients Receiving Anti-TNF-α in the Prospective French RATIO Registry

Journal of Investigative Dermatology (2012) **132,** 726–729; doi:10.1038/jid.2011.383; published online 24 November 2011

Gaelle Serac[1,14], Florence Tubach[2], Xavier Mariette[3], Dominique Salmon-Céron[4], Philippe Ravaud[5], Frederic Lioté[6], David Laharie[7], Jean-Marc Ziza[8], Laurent Marguerie[9], Christine Bonnet[10], Geraldine Falgarone[11], Nathalie Nicolas[2], Olivier Lortholary[12,14] and Olivier Chosidow[13,14], for the RATIO group[15]

Table 2. Herpes zoster risk factors in patients receiving anti-TNF-α therapy considering anti-TNF-α agents in three molecules or two classes: multivariate analysis

	OR (95% CI)	*P*-value
Time from onset of last anti-TNF-α agent		
(for a 1-month increase)	0.96 (0.93–0.99)	0.0088
Last anti-TNF-α agent		0.0974
Etanercept	1	—
Adalimumab	3.25 (0.93–11.36)	0.0652
Infliximab	3.94 (0.93–16.65)	0.0619
Time from onset of last anti-TNF-α agent		
(for a 1-month increase)	0.96 (0.93–0.99)	0.0078
Class of last anti-TNF-α agent		
Soluble TNF-α receptor (etanercept)	1	—
mAb (adalimumab or infliximab)	3.49 (1.12–10.90)	0.0316

Abbreviations: CI, confidence interval; OR, odds ratio; TNF-α, tumor necrosis factor-α.

24 cas recensés,

7 à 202 semaines après le début du traitement

Emergence of *Legionella pneumophila* Pneumonia in Patients Receiving Tumor Necrosis Factor–α Antagonists

Clinical Infectious Diseases 2006; 43:e95–100

F. Tubach,[1,2,3] P. Ravaud,[1,2,3] D. Salmon-Céron,[4,5] N. Petitpain,[10] O. Brocq,[11] F. Grados,[12] J. C. Guillaume,[13] J. Leport,[14] A. Roudaut,[15] E. Solau-Gervais,[16] M. Lemann,[1,7] X. Mariette,[8,9] and O. Lortholary,[4,6] for the Recherce Axée sur la Tolérance des Biothérapies (RATIO) Group

- 13 cas survenus en 18 mois, 25% des patients en réanimation
- Aucun décès
- Age moyen: 51 ans (40-69)
- Incidences:
  - Population générale: 1,8/100 000
  - Patients traités pendant la période: 20 000
  - Incidence chez patients sous anti-TNF: 50/100 000

→ **RR x 28**

Autres infections opportunistes

- Registre Français (Ratio):
  - 4 listerioses
  - 4 nocardioses
  - 4 mycobactéries non tuberculeuses
  - 5 pneumocystoses
  - 3 aspergilloses
  - 2 cryptococcoses
  - 2 leishmanioses
  - 3 salmonelloses
  - 4 infections disséminées à CMV

Table 4 Risk factors of OI for patients receiving anti-TNF therapy (multivariate analysis, final model)

	OI cases and controls(38 cases and 114 controls)	
	OR (95% CI)	p Value
Last anti-TNF received		
Etanercept	1	
Adalimumab	10.0 (2.3 to 44.4)	0.002
Infliximab	17.6 (4.3 to 72.9)	<0.0001
Steroids >10 mg/day or boluses during the previous year		
No	1	
Yes	6.3 (2.0 to 20.0)	0.002

OI, opportunistic infection; TNF, tumour necrosis factor.

Salmon-Ceron, Ann Rheum Dis, 2011

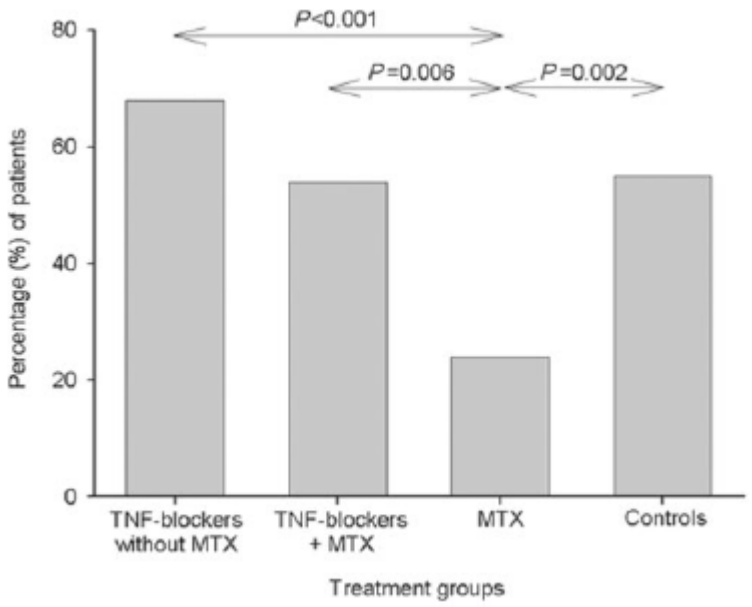
Prévention ?

- Anti-BK selon indications
- Vaccinations ?

Vaccinations et anti-TNF

- Vaccins vivants contre-indiqués sous biothérapies
  - Intérêt de protéger les patients contre rougeole et varicelle si sérologie négative (enfants)
  - Fièvre jaune:
    - 3 semaines à 1 mois avant anti-TNF
    - Arrêt de l'anti-TNF pendant 5 demi-vies
  - BCG: reste contre-indiqué
- Vaccins inertes:
  - Pas de contre-indication
  - Grand intérêt:
    - Vaccination **anti-pneumocoque** (tous les 5 ans)
    - Vaccination annuelle contre la grippe
    - Vaccination anti-hépatite B

Efficacité vaccination anti-pneumococcique



Kapetanovic, Rheumatology, 2006

- Etude comparative:
  - PR sous adalimumab ou placebo
  - Vaccin polysaccharidique anti-pneumococcique:
    - Efficacité 37,4% vs 40,4%
  - Vaccin anti-grippal:
    - Efficacité 73,3% vs 73,4%

Kaine, J Rheumatol, 2007

Salemi, Clin Immunol, 2010

Table 2 Systemic and local side effects in vaccinated RA patients and healthy controls.

Influenza seasons 2005–2006, 2006–2007, 2007–2008	RA patients	Healthy controls	*p*
Redness/swelling injection site	1	1	
Fever (>37.5 °C)	3	4	
Headache	0	1	
Asthenia/malaise	5	2	
Arthralgia/myalgia	3	0	
Total events	12	8	
Total events/*N* patients	12/28 (42%)	8/20 (40%)	NS
Total events/*N* flu shots	12/64 (18%)	8/28 (28%)	NS

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
Seroconversion rate							
Patients	20		40%		15%		15%
Healthy controls	7		43%		29%		29%
Seroprotection rate							
Patients	20	42%	80%	63%	85%	73%	85%
Healthy controls	7	60%	100%	40%	75%	60%	75%
Seroconversion factor							
Patients	20		5.66		2.73		2.55
Healthy controls	7		4.42		2		3.28

Prévention ?

- Anti-BK selon indications
- Vaccinations ?
- Autres ?

Rituximab: risque infectieux

- Risque modéré
- Augmentation modéré du risque d'infection bactérienne précoce mais non significatif
- Problèmes des hypogammaglobulinémies au long cours
- Autres:
  - HSV, VZV, erythrovirus B19
  - Réelle responsabilité ?
- LEMP ?
  - Quelques cas rapportés
  - Mais toujours des traitements associés (fludarabine)

Salvana et al, CMR, 2009

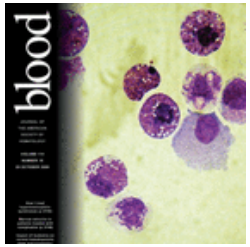
Progressive multifocal leukoencephalopathy after rituximab therapy in HIV-negative patients: a report of 57 cases from the Research on Adverse Drug Events and Reports project

Blood. **2009 May 14; 113(20): 4834–4840**

Kenneth R. Carson,[1] Andrew M. Evens,[2,3] Elizabeth A. Richey,[2] Thomas M. Habermann,[4] Daniele Focosi,[5]

1997-2008 : 57 LEMP post-rituximab documentées

- Indications
  - **52 hémopathies malignes lymphoïdes**
  - 2 Lupus, 2 cytopénies auto-immunes, 1 PR
- Présentation initiale **psychiatrique (54%)**
- **Médiane de survenue**
  - **début anti-CD20/diagnostic LEMP = 16 mois (6 perf.)**
  - **5,5 mois après la dernière perf. anti-CD20**
- **Mortalité 90% (100% si rituximab < 3 mois)**
- Pas de dénominateur => ni FDR, ni incidence (**lupus: 2 / 8 000 patients**)



Rituximab: hépatites virales


VOLUME 27 · NUMBER 4 · FEBRUARY 1 2009

JOURNAL OF CLINICAL ONCOLOGY

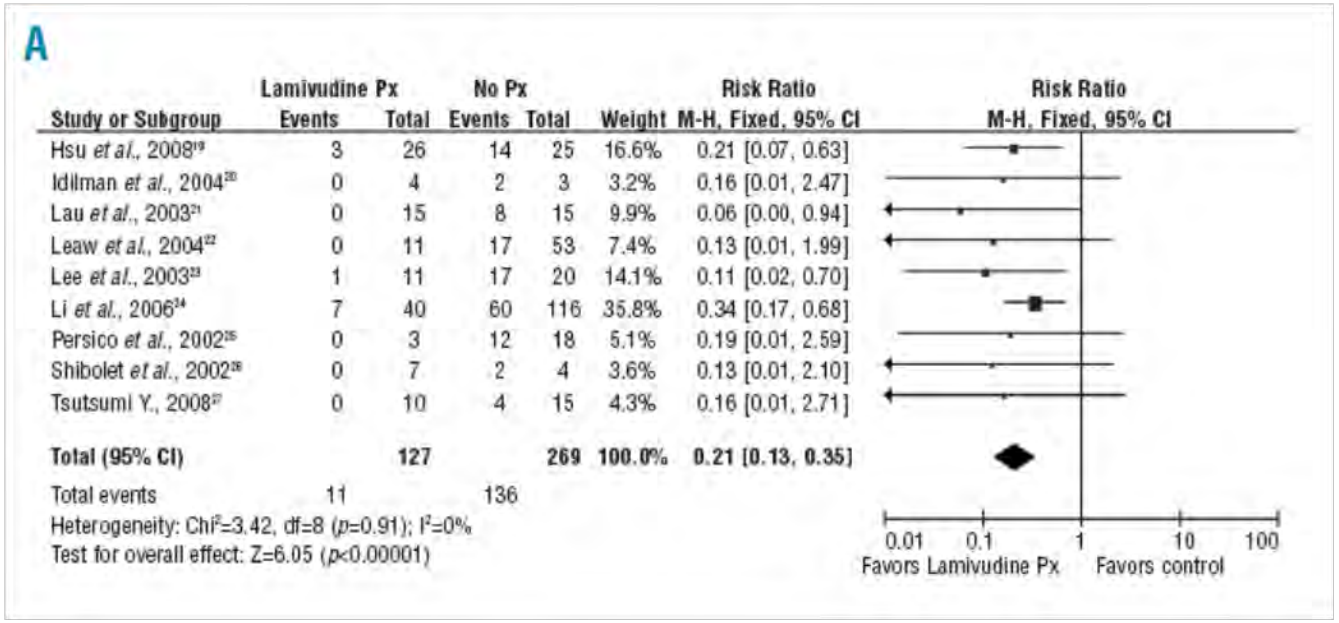
ORIGINAL REPORT

Hepatitis B Virus Reactivation in Lymphoma Patients With Prior Resolved Hepatitis B Undergoing Anticancer Therapy With or Without Rituximab

Winnie Yeo, Tung C. Chan, Nancy W.Y. Leung, Wai Y. Lam, Frankie K.F. Mo, Miu Ting Chu, Henry L.Y. Chan, Edwin P. Hui, Kenny I.K. Lei, Tony S.K. Mok, and Paul K.S. Chan

- Risque de réactivation **hépatite B** +++
  - **25 %** des cas
  - Evolution vers l'hépatite fulminante et le décès possible
- Risque pour hépatite C également mais moins fréquent et grave

Rituximab: hépatites virales

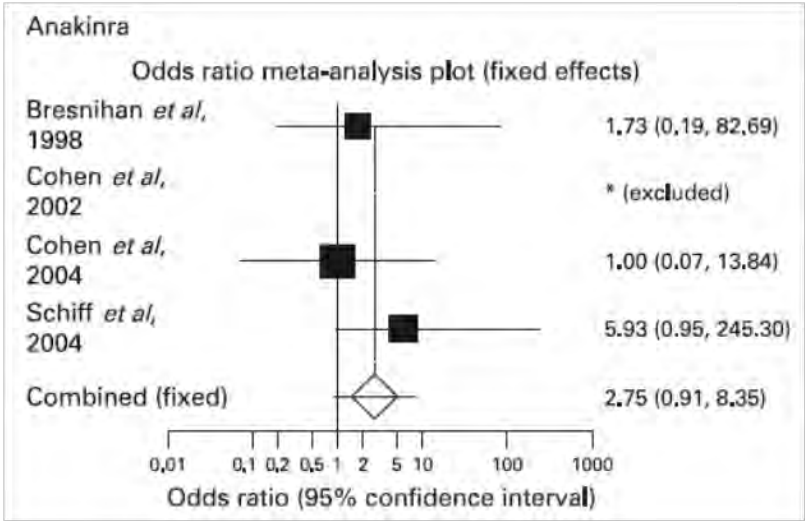


- Chez les patients Ag Hbs +
  - **Poursuivre lamivudine 6 mois après la fin du traitement**
  - Si HBV DNA > 2 000 copies /mL: poursuivre 12 mois

Zakias, Haemotologica, 2009

Anakinra et infections

- Antagoniste du récepteur de l'IL-1
- Pas de risque d'évènement infectieux grave en général
- Léger sur-risque si doses élevées (≥ 100 mg/j)
- Infections pulmonaires puis peau et tissus mous
- Pas de risque de TB ou d'autre infection opportuniste[1,2]

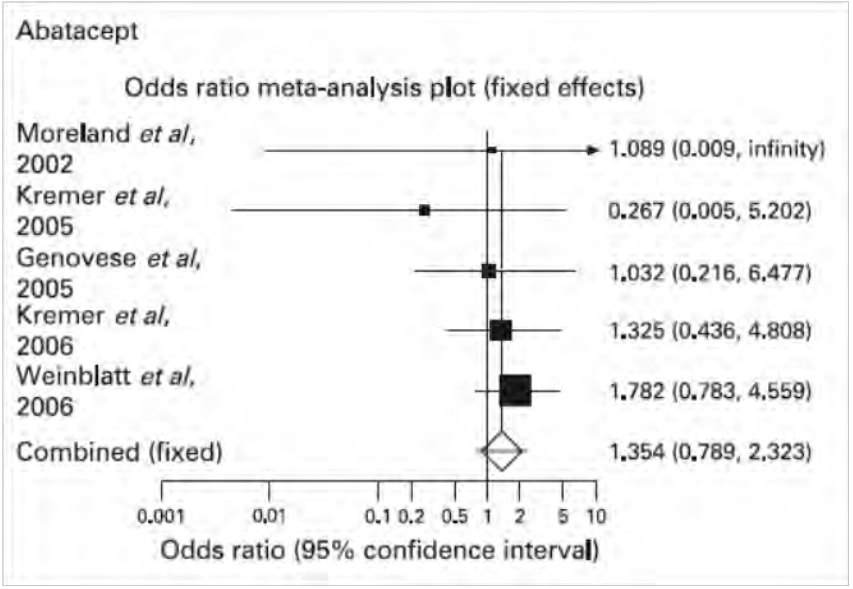


Saillot, Ann Rheum Dis, 2009

[1]Furst, Semin Arthritis Rheum, 2010; [2]Salvana, CMR, 2009

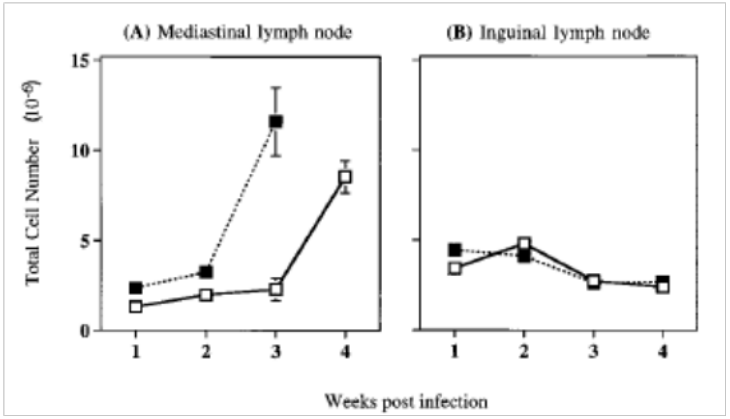
Abatacept et infections

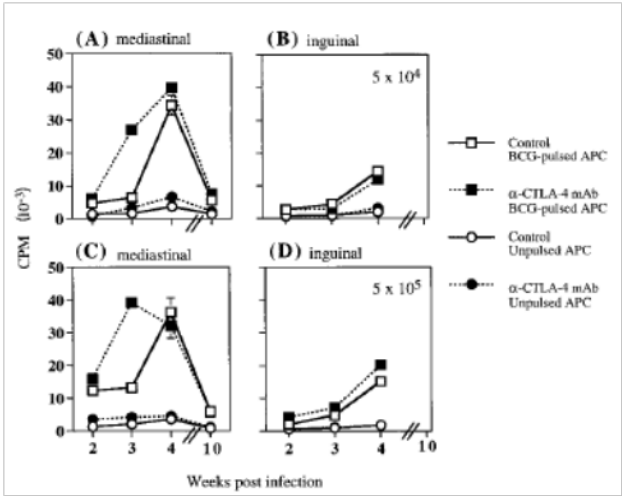
- Anti-CTLA-4: inhibe la co-stimulation lymphocytaire
- Méta-analyse: pas de risque d'évènement infectieux grave
- Ne pas associer avec autres biothérapies (Furst, 2010)
- Registre français: ORA (Mariette, Rheumatology, 2011)
  - 682 patients
  - 4,5 / 100 patients années infections sévères
  - Pulmonaires



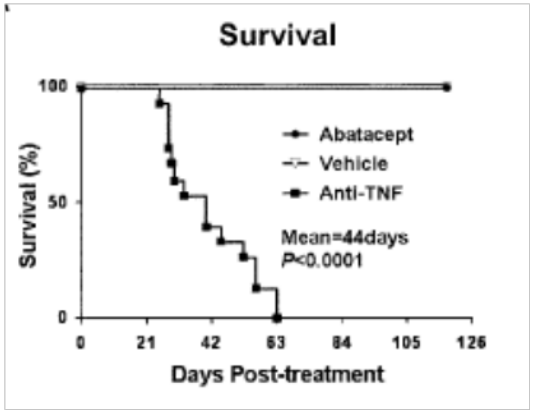
Saillot, Ann Rheum Dis, 2009

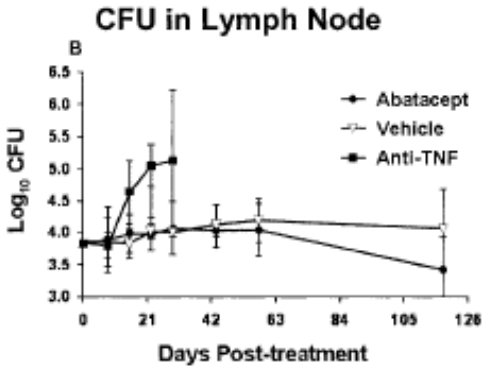
Abatacept et tuberculose





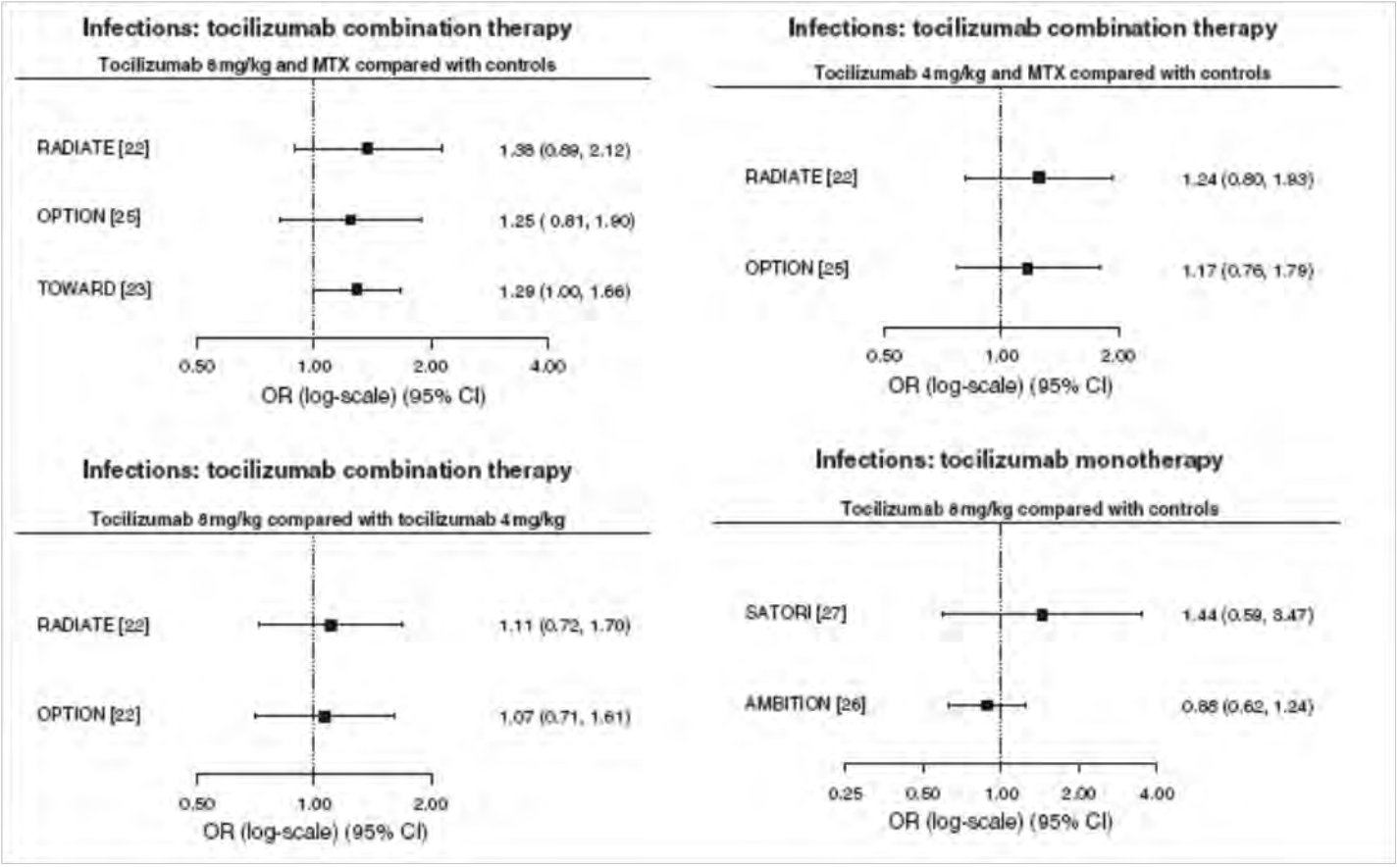
Kirman, Inf Immun, 1999





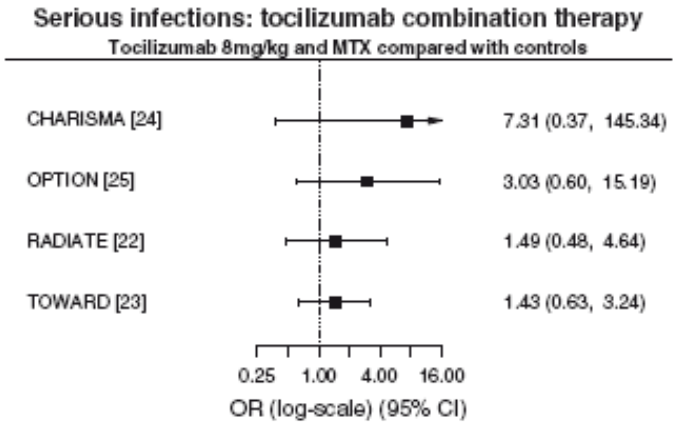
Bigbee, Arthriris Rheum, 2007

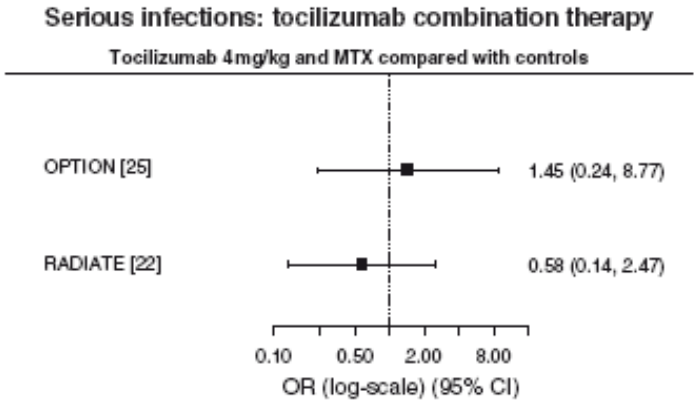
Tocilizumab et infections

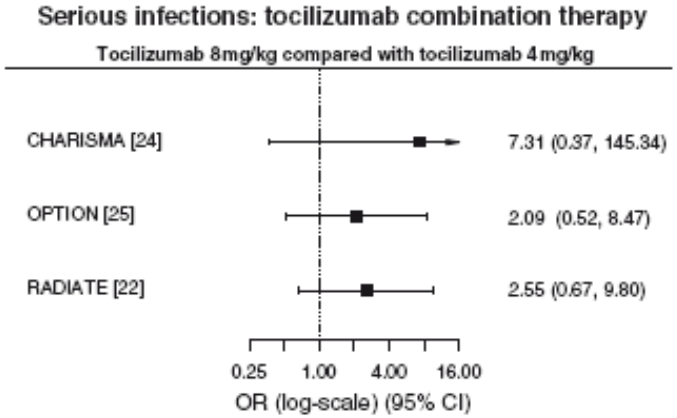


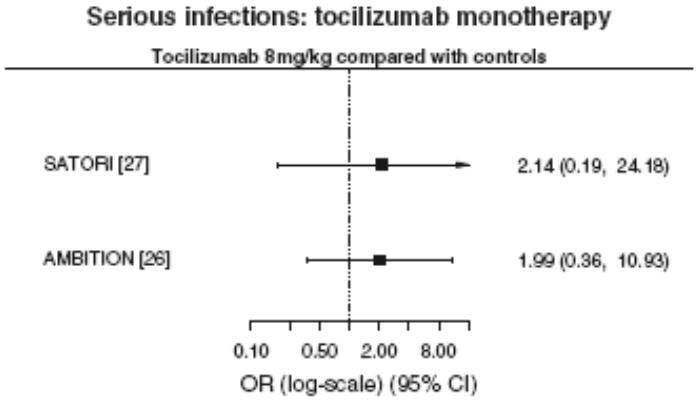
Campbell, Rheumatology, 2011

Tocilizumab et infections









Campbell, Rheumatology, 2011

Biothérapies: infections et prévention

- Anti-TNF_{α}:
  - Tuberculose: dépistage ITL
  - Infections pulmonaires: vaccination anti-pneumococcique
  - Vaccinations anti-grippales
- Rituximab:
  - Hépatite B
  - Se méfier des LEMP, hypogamma, effet à long terme
- Anakinra:
  - Se méfier si fortes doses
  - Vaccins pneumocoque
- Abatacept:
  - Peu de recul
  - Intérêt des vaccinations
- Tocilizumab: aucun recul