BEST OF
Infections et Biothérapies

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Déclaration de liens d'intérêt avec les industries de santé en rapport avec le thème de la présentation (loi du 04/03/2002) :

Intervenant : FAURE Karine

Titre : Best of « Infections et biothérapies »

☐ L'orateur ne souhaite pas répondre

Consultant ou membre d'un conseil scientifique	☐ OUI	☑ NON
Conférencier ou auteur/rédacteur rémunéré d'articles ou documents	☐ OUI	☑ NON
Prise en charge de frais de voyage, d'hébergement ou d'inscription à des congrès ou autres manifestations	☐ OUI	☑ NON
Investigateur principal d'une recherche ou d'une étude clinique	☐ OUI	☑ NON

BIOTHÉRAPIES ET CANCERS HÉMATOLOGIQUES

Inhibiteur de la Bruton Thyrosine Kinase: Ibrutinib

Inhibiteur de protéosome: Carfilzomib

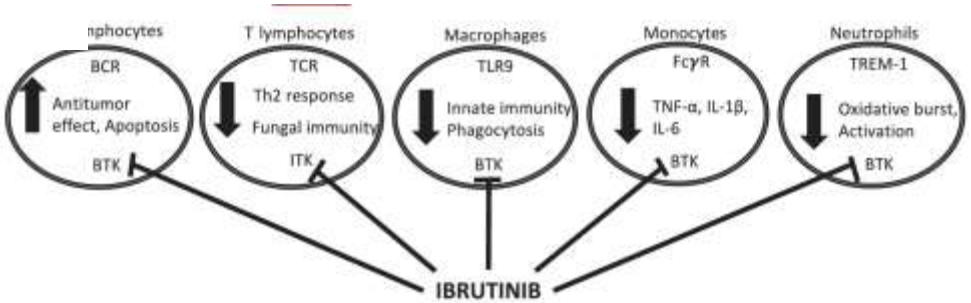
Anti-CD38: Daratumumab

Biothérapies et cancers hématologiques

Inhibition de la Bruton thyrosine kinase: Ibrutinib

Systematic review of infectious events with the Bruton tyrosine kinase inhibitor ibrutinib in the treatment of hematologic malignancies

Tillman BF et al. Eur J Haematol. 2018 Apr; 100(4): 325-334



Ibrutinib - Cancer lymphoïde

EI infectieux avec classement CTCAE (grade 1 à 5)

	Tous EI	EI grade 3-4	EI grade 5
Patients sous monothérapie	56%	26%	2%
Patients sous associations	52%	20%	2%

% habituel dans LLC sous chimiothérapie

Biothérapies et cancers hématologiques

Inhibition de la Bruton thyrosine kinase: Ibrutinib

Serious Infections in Patients Receiving Ibrutinib for Treatment of Lymphoid Cancer

Varughese T et al. CID 2018

- New-York – 5 ans
- Rétrospective – K lymphoïde
- Ibrutinib seul ou en association
- ≥ 30 jours de suivi

- Infection grave = nécessitant une hospitalisation ou un trt IV
- IFI = définition EORTC

Patient Characteristics	Patients, No. (%)[a]			
	All Patients (N = 378)	CLL (n = 165)	NHL (n = 213)	*P* Value
Age, mean (SD), y	66 (12)	67 (10)	65.1 (13)	.36
Male sex	246 (66)	115 (70)	131 (62)	.10
Ibrutinib daily dose, mean, mg	485	420	536	<.001
Ibrutinib daily dose				
280 mg	9 (2)	5 (3)	4 (2)	
420 mg	250 (66)	157 (95)	93 (44)	
560 mg	86 (23)	2 (1)	84 (39)	
840 mg	33 (9)	1 (1)	32 (15)	
Prior treatment regimens, mean (range), No.	2.31 (0–10)	1.55 (0–8)	2.90 (0–10)	<.001
Ibrutinib as 1st-line treatment	71 (19)	54 (33)	17 (8)	<.001
Rituximab before ibrutinib	271 (72)	99 (60)	172 (81)	<.001
Fludarabine before ibrutinib	37 (10)	28 (17)	9 (4)	<.001
Alemtuzumab before ibrutinib	2 (0.5)	2 (1)	0 (0)	.19
Prior HSCT[b]	43 (11)	5 (3)	38 (18)	<.001
Autologous	36 (10)	1 (0.6)	35 (16)	<.001
Allogeneic	10 (3)	4 (2)	6 (3)	.99
Ibrutinib monotherapy	316 (84)	157 (95)	159 (75)	<.001
Neutropenia	12 (3)	8 (5)	4 (2)	.14
Lymphopenia	28 (7)	4 (2)	24 (11)	.001
Corticosteroid use	37 (10)	11 (7)	26 (12)	.08
Antimicrobial prophylaxis				
PJP prophylaxis	60 (16)	21 (13)	39 (18)	.16
Antifungal prophylaxis	16 (4)	5 (3)	11 (5)	.44
Infection	43 (11)	20 (12)	23 (11)	.75
Bacterial	23 (6)	9 (5)	14 (7)	.83
Fungal	16 (4)	10 (6)	6 (3)	.13
Viral	4 (1)	1 (0.6)	3 (1)	.64

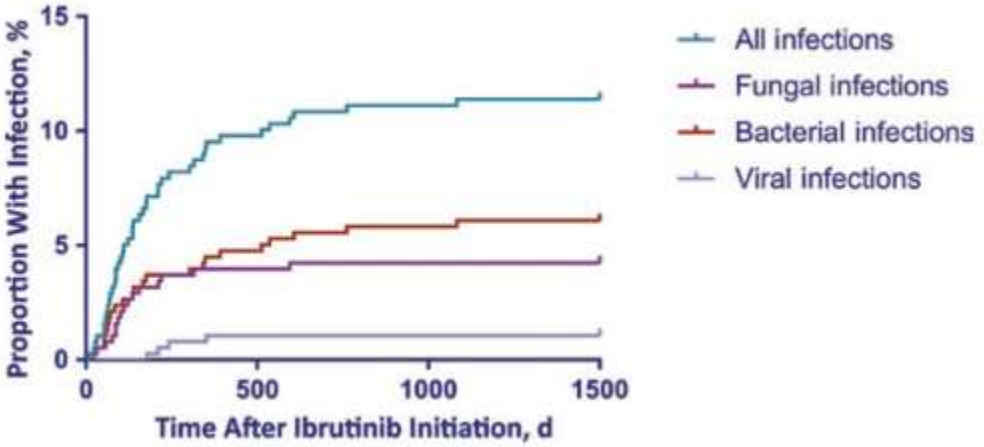
Biothérapies et cancers hématologiques

Inhibition de la Bruton thyrosine kinase: Ibrutinib

Infection grave chez 43 patients - 6 décès attribués à une infection évolutive

Infection dans la 1ère année (84%) - délai médian = 136 jours

Facteurs de risque: ≥ 3 traitements antérieurs et neutropénie



Inf. bact.: 23 patients

Infection respiratoire = 10, bactériémie = 7

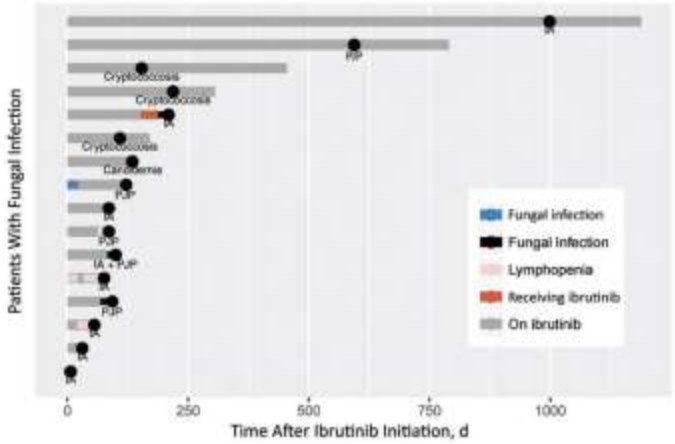
Majoritairement *S. aureus*

Facteur de risque: neutropénie

IFI: 16 patients (aucun greffé), sans prophylaxie

IA (prouvé ou probable) = 8 (dont 2 atteintes cérébrales), PJP = 3, crypto = 3, candidémie = 1

Facteurs de risque: ≥ 3 traitements antérieurs, neutropénie (au moins 1 fois durant le traitement), corticothérapie



Varughese T et al. CID 2018

Biothérapies et cancers hématologiques

Inhibition de la Bruton thyrosine kinase: Ibrutinib

Chronic lymphocytic leukemia and infection risk in the era of targeted therapies: Linking mechanisms with infections

Hilal T et al. Blood review 2018

Nombre de patients sous Ibrutinib en augmentation +++

Nombreuses descriptions d'IO mais une incidence qui reste faible

Recommandation de surveillance étroite en particuliers pour les IFI

Class of therapy with corresponding immune dysfunction and potential infectious risks.

Class of therapy	Immune dysfunction	Infections
Alkylating agents (e.g. chlorambucil, cyclophosphamide, bendamustine)	Neutropenia Lymphopenia (T cell dysfunction)	Bacterial Fungal, if prolonged PJP Cryptococcus
Purine analogues (e.g. fludarabine, pentostatin)	Neutropenia Lymphopenia (T cell dysfunction)	Bacterial Fungal, if prolonged PJPCryptococcus
Anti-CD20 antibodies (e.g. rituximab, ofatumumab, obinatuzumab)	Lymphopenia (B cell dysfunction)	Bacterial Hepatitis B reactivation Viruses (e.g. enterovirus, JC virus)
Anti-CD52 antibody (i.e. alemtuzumab)	Lymphopenia (B and T cell dysfunction)	Viruses (e.g. CMV, HSV, VZV) Fungal PJP
BTK inhibitors (e.g. ibrutinib, acalabrutinib)	Lymphopenia (B cell dysfunction, possible T cell dysfunction)	Hepatitis B reactivation Fungal (Aspergillus, Cryptococcus) PJP
PI3K inhibitors (e.g. idelalisib)	Neutropenia Lymphopenia (B and T cell dysfunction)	Bacterial Fungal, if prolonged Viruses (e.g. CMV, HSV) Aspergillus PJP
BCL2 inhibitors (e.g. venetoclax)	Neutropenia Lymphopenia (B cell dysfunction)	Bacterial Viruses (e.g. enterovirus)

ESCMID Study Group for Infections in Compromised Hosts (ESGICH)

ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an infectious diseases perspective (Intracellular signaling pathways: tyrosine kinase and mTOR inhibitors)

Reinwald M et al. CMI 2018

Agent	Increased risk of overall infection	Risk of OI	Risk of PCP	Risk of HBV reactivation	Observations and recommendations
Vemurafenib, dabrafenib, encorafenib, trametinib, cobimetinib selumetinib,	None	No	No	No	• No apparent increase in risk of infection • Some of most common drug-related adverse effects (pyrexia, fatigue, arthralgia and skin rash) may mimic ongoing infection
Ibrutinib, acalabrutinib	Modest	PCP, IFI, PML	Yes (particularly in presence of additional risk factors)	No	• Modest increase in risk of infection (contributing role of prior or concurrent therapies or inherent immune defects) • No expected benefit from universal use of antibacterial or antifungal prophylaxis • Anti-*Pneumocystis* prophylaxis for CLL patients with additional risk factors (e.g. purine analogues or high-dose corticosteroids) • PML occasionally associated with use of ibrutinib

Biothérapies et cancers hématologiques

Inhibiteurs de protéosome: Carfilzomib

The European Medicines Agency Review of Carfilzomib for the Treatment of Adult Patients with Multiple Myeloma Who Have Received at Least One Prior Therapy

Tzogani K et al. The Oncologist 2017; 22: 1339-1346

11 études cliniques - 2 123 patients

EI les plus fréquents (> 20% des patients): anémie, thrombocytopénie, fatigue, diarrhées, nausées, fièvre, dyspnée, infections respiratoires, toux, œdème

Comparaison EI grade ≥ 3 bras avec carfilzomib (CRd) versus bras sans carfilzomib (Rd):

EI avec une différence ≥ 5%: aucun

EI avec une différence entre ≥ 2% et 5%: neutropénie, thrombocytopénie, **pneumonie**, hypophosphatémie

Décès: 7,7% versus 8,5%: cause la plus fréquente de décès = infection (pas d'imputabilité directe au carfilzomib)

Biothérapies et cancers hématologiques

Inhibiteurs de protéosome: Carfilzomib

New Agents in Multiple Myeloma: An Examination of Safety Profiles

Bringhen S et al. Clin Lymph Myel Leukemia 2017; 17(7): 391-407

Table 2 Most Common Grade 3, 4, and 5 Adverse Events Reported in Phase III Trials, by Agent

	Grade 3	Grade 4	Grade 5
Proteasome inhibitors			
Carfilzomib[40]	Anemia (25%)[a] Thrombocytopenia (24%)[a] Neutropenia (8%)[a] Acute renal failure (8%)[a] Pneumonia (6%)[a] Renal failure (5%)[a]		Deaths owing to AE: Cardiac event[b] (4%) Acute renal failure or infection (2%) Pneumonia (1%) Sepsis (1%) Multi-organ failure (1%) Pulmonary edema (1%) Upper GI hemorrhage (1%)
Carfilzomib (+ dex)[42]	Anemia (14%) Hypertension (9%) Pneumonia (6%) Thrombocytopenia (5%) Fatigue (5%) Dyspnea (5%)	Thrombocytopenia (4%) Anemia (<1%) Pneumonia (<1%)	Pneumonia (<1%) Acute renal failure (<1%) Cardiac failure (<1%)
Ixazomib (+ len + dex)[57]	Neutropenia (18%) Thrombocytopenia (12%) Anemia (9%) Diarrhea (6%) Rash (5%) Arrhythmia (5%)	Thrombocytopenia (7%) Neutropenia (5%) Arrhythmia (<1%)	Arrhythmia (<1%) Thromboembolism (<1%) Hypotension (<1%) Heart failure (<1%) Myocardial infarction (<1%)

EI grade ≥ 3 les plus fréquents: hématologique mais identiques au groupes contrôles (neutropénie fébrile peu fréquent)

Pneumonie et infections des voies respiratoires de tous grades fréquents:

Etudes de phase II: 13% et 28%

Etudes de phase III: grade ≥ 3, pas de différence carfilzomib versus contrôle

	carfilzomib	controle
pneumonie	6%	12%
Infections voies respiratoires	7%	8%

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ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an infectious diseases perspective (Immune checkpoint inhibitors, cell adhesion inhibitors, sphingosine-1-phosphate receptor modulators and proteasome inhibitors)

Redelman-Sidi G et al. CMI 2018

Agent	Increased risk of PCP	Anti-*Pneumocystis* prophylaxis	Increased risk of VZV or HSV infection	Vaccinations	Other prophylaxis or recommendations
Bortezomib, carfilzomib, ixazomib	No	May be considered for selected MM patients with additional risk factors (i.e. prolonged high-dose corticosteroid therapy)	Yes	Live attenuated varicella vaccination for VZV-seronegative patients without history of varicella (at least 1 month before starting therapy); HZ/su may be considered for VZV-seropositive patients aged ≥50 years; seasonal TIV (at least 2 weeks before starting therapy and annually thereafter); completed pneumococcal vaccination series (PCN7 or PCN13 followed by PPV23) (at least 2 weeks before starting therapy) with revaccination 5 years later with PPV23	• Antiviral prophylaxis with (val)acyclovir for VZV-seropositive patients during induction therapy and for at least 4 weeks after discontinuation.

Biothérapies et cancers hématologiques

Anti-CD38: Daratumumab

Daratumumab plus Bortezomib, Melphalan, and Prednisone for Untreated Myeloma

Mateos MV et al. NEJM 2018; 378: 518-528

- Etude randomisée multicentrique (25 pays) de phase III
- Patients non éligible à une greffe
- Pas de ligne antérieure de traitement

- Arrêt de traitement lié à une infection: 0,9% vs 1,4%
- Décès liés à une infection: 5 patients vs 4 patients

Daratumumab +Bortezomib +Melphalan + Prednisolone

Bortezomib +Melphalan + Prednisolone

Table 3. Most Common Adverse Events during Treatment in the Safety Population.*

Event	Daratumumab Group (N=346)		Control Group (N=354)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Hematologic adverse events				
Neutropenia	172 (49.7)	138 (39.9)	186 (52.5)	137 (38.7)
Thrombocytopenia	169 (48.8)	119 (34.4)	190 (53.7)	133 (37.6)
Anemia	97 (28.0)	55 (15.9)	133 (37.6)	70 (19.8)
Nonhematologic adverse events				
Peripheral sensory neuropathy	98 (28.3)	5 (1.4)	121 (34.2)	14 (4.0)
Diarrhea	82 (23.7)	9 (2.6)	87 (24.6)	11 (3.1)
Pyrexia	80 (23.1)	2 (0.6)	74 (20.9)	2 (0.6)
Nausea	72 (20.8)	3 (0.9)	76 (21.5)	4 (1.1)
Infections	231 (66.8)	80 (23.1)	170 (48.0)	52 (14.7)
Upper respiratory tract infection	91 (26.3)	7 (2.0)	49 (13.8)	5 (1.4)
Pneumonia	53 (15.3)	39 (11.3)	17 (4.8)	14 (4.0)
Second primary cancer†	8 (2.3)	NA	9 (2.5)	NA
Any infusion-related reaction	96 (27.7)	17 (4.9)	NA	NA

ESCMID Study Group for Infections in Compromised Hosts (ESGICH)

ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an infectious diseases perspective (Agents targeting lymphoid or myeloid cells surface antigens [II]: CD22, CD30, CD33, CD38, CD40, SLAMF-7 and CCR4)

Drgona L et al. CMI 2018

Agent	Type of study	Treatment arms	No. of subjects	Rate of infection (novel agent vs. comparator)
Daratumumab	Phase 3 RCT for relapsed or refractory MM [43]	Daratumumab plus bortezomib plus dexamethasone vs. bortezomib plus dexamethasone	251 vs. 247	Serious infection (grade 3–4): 21.4% vs. 19%; pneumonia (grade 3–4): 8.2% vs. 9.7%; neutropenia (grade 3–4): 12.8% vs. 4.2%; VZV: 5% vs. 3%
	Phase 3 RCT for relapsed or refractory MM [42]	Daratumumab plus lenalidomide plus dexamethasone vs lenalidomide plus dexamethasone	286 vs. 283	Serious infection (grade 3-4): 28.3% vs. 22.8%; pneumonia (grade 3-4): 7.8% vs. 8.2%; neutropenia (grade 3-4): 51.9% vs. 37%; febrile neutropenia (grade 3–4): 5.7% vs. 2.5%; VZV: 2% vs. 2%

Group	Agent	Risk of neutropenia	Risk of HSV and VZV (anti-herpesvirus prophylaxis warranted)	Risk of PCP (anti-*Pneumocystis* prophylaxis warranted)	Risk of HBV reactivation (prophylaxis warranted for HBsAg+/HBsAg-antiHBc+)	Risk of CMV infection (monitoring warranted)	Other infections to be considered
CD38-targeted agents	Daratumumab (no data yet available for isatuximab)	Yes	Yes (VZV)	Possible (consider if concomitant corticosteroid therapy)	Possible (consider if concomitant corticosteroid therapy)	No	ND

BIOTHÉRAPIES ET CANCERS SOLIDES

Anti-PD1: Pembrolizumab

Nivolumab

Biothérapies et cancers solides
anti-PD1

- **Pembrolizumab**: plusieurs cas cliniques publiés (mélanomes):
  - **Gastrite, entérite, colite**: documentation endoscopique et anatomopathologique – guérison avec arrêt du pembrolizumab +/- corticoïthérapie *(Gonzalez RS et al. Histopathology 2017; 70(4): 558-567)*
  - **Pneumopathie**: documentation avec imagerie, fibroscopie-LBA, examens microbiologiques négatifs, traitement par arrêt du pembrolizumab +/- corticothérapie *(Leroy V et al. ERJ Open Res 2017; 3(2))*

Biothérapies et cancers solides
anti-PD1

- **Nivolumab**: études de phase II

  - **Sarcome**: en association avec ipilimumab (anti-CTLA-4): Pas d'événement infectieux parmi les EI graves déclarés *(D'Angelo SP et al. Lancet Oncol. 2018 Mar;19(3):416-426)*

  - **Carcinome hépatocellulaire**: Pas d'événement infectieux parmi les EI graves déclarés *(El-Khoueiry AB et al. Lancet. 2017 Jun 24;389)*

  - **Carcinome de l'œsophage**: Pneumonies parmi les EI graves: 4/65 patients (6%) *(Kudo T et al. Lancet Oncol. 2017 May;18(5):631-639)*

Biothérapies et cancers solides
anti-PD1

- **Pembrolizumab ou Nivolumab**

  - **Infection VIH et K pulmonaire non à petites cellules**: 7 patients, tous sous traitement antirétroviral, pas d'événement signalé *(Garcia-Ostios L et al. J Thorac Oncol 2018; Apr 6)*

  - **Infection VHB/VHC et mélanome ou K pulmonaire non à petites cellules** : 7 patients: augmentation ALAT de grade 2 chez 1 patient avec retour rapide à la normale sous ledipasvir/sofosbuvir, augmentation ALAT de grade 1 chez 4patient avec retour à la normale *(Kothapalli A, Melanoma Res 2018; 28(2): 155-158)*

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Reinwald M et al. CMI 2018

Agent	Increased risk of PCP	Anti-*Pneumocystis* prophylaxis	Increased risk of VZV or HSV infection	Vaccinations	Other prophylaxis or recommendations
Nivolumab, pembrolizumab, atezolizumab	Increased risk in patients developing irAEs and receiving corticosteroids	Patients with irAEs expected to receive 20 mg of prednisone daily (or equivalent) for ≥4 weeks	No	As per standard practice	• Potential risk of IRIS with unmasking of latent (dormant) infections (i.e. LTBI).

BIOTHÉRAPIES ET TRANSPLANTATION D'ORGANE SOLIDE

Anti-CD52: Alemtizumab

Inhibiteurs de mTOR: Everolimus, Sirolimus

Biothérapies et transplantation d'organe solide

Anti-CD52: Alemtuzumab

Efficacy and Safety of Induction Therapy in Kidney Transplantation: A Network Meta-Analysis

Hwang SD et al. Transplant Proc. 2018 May;50(4):987-992

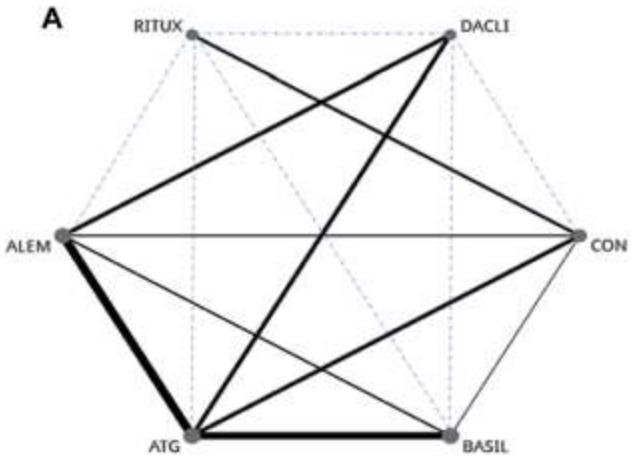
27 essais randomisés (dont 10 USA, 3 UK, 4 France, 2 Allemagne)

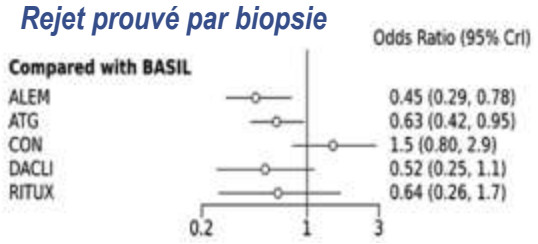
4 484 patients

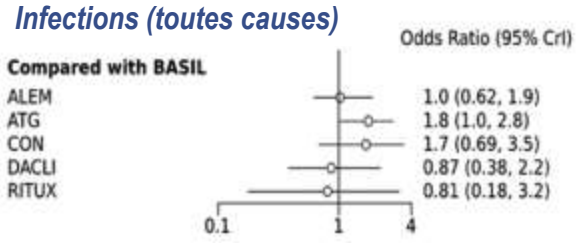
Survie (durée de suivi: 11 à 38 mois): pas de différence significative

Rejet: OR plus bas pour Alemtuzumab et rATG

Infections: aucun bénéfice, OR plus élevé pour rATG (en particuliers pneumonies)







Biothérapies et transplantation d'organe solide

Anti-CD52: Alemtuzumab

Alemtuzumab dose adjusted for body weight is associated with earlier lymphocyte repletion and less infective episodes in the first year post renal transplantation – a retrospective study

Willicombe M et al. Transpl Int. 2017 Nov;30(11):1110-1118

Etude rétrospective monocentrique

2005-2011: dose standard 30mg

2011: 0,4 mg/kg (max 50 mg)

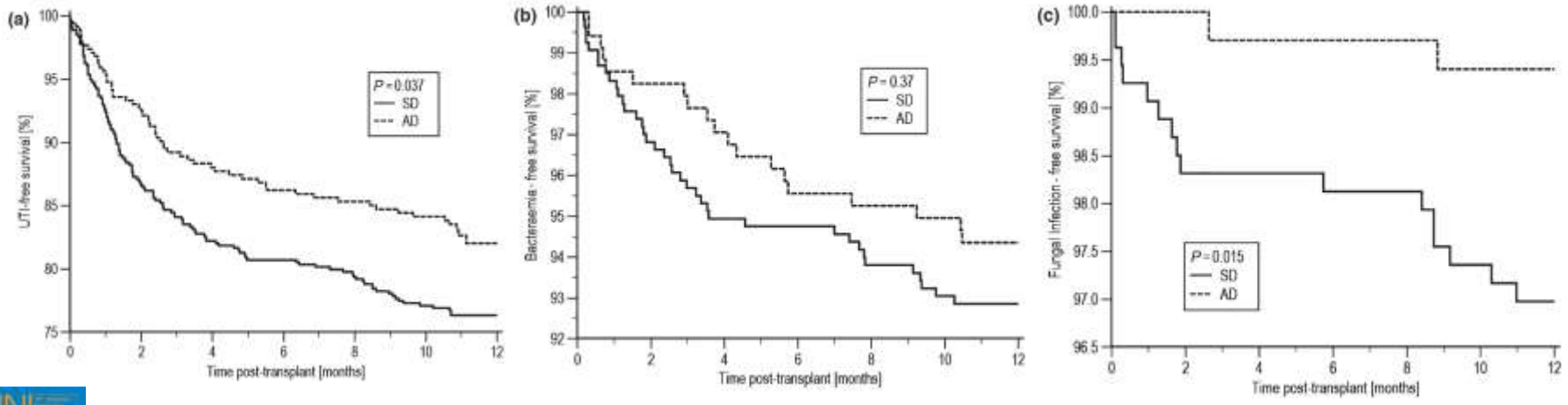
Trt immunosuppresseur associés identiques

Prophylaxies anti-infectieuses identiques

SD: 544 patients – AD: 344 patients (patients + âgés, + hyperimmunisation HLA)

Rejet: pas de différence à 1 an, à 4 ans

Normalisation GB (quantité et proportion) en faveur du bras AD



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ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an infectious diseases perspective (Agents targeting lymphoid cells surface antigens [I]: CD19, CD20 and CD52)

Mikulska M et al. CMI 2018

Agent	Type of study	Treatment arms	No. of participants	Rate of infection (novel agent versus comparator)	Specific infections reported in the literature
Alemtuzumab	Systematic review of RCTs for NHL [72]	Alemtuzumab 90 mg/week for 12 weeks plus chemotherapy vs chemotherapy	175 vs 175	CMV infection: 6% vs 0%	CMV, HSV and VZV infection, PCP
	2 multicentre phase 2 to 4 RCTs for SOT recipients [73,74]	Alemtuzumab 30 mg once vs basiliximab 20 mg (plus long-term tacrolimus and MMF in both arms)	760 vs 766	Overall infection: 73% vs 75%; serious infection: 32% vs 32%; CMV infection[a]: 9.6% vs 9.5%; BKV infection: 7 vs 5%, IFI: 1% vs 1%	
	3 phase 2/3 RCTs for MS [75–77][a]	Alemtuzumab (12 mg/day for 5 days) vs IFN-β	1180 vs 496	Overall infection: 73% vs 58%; serious infection: 3% vs 1%; CMV infection: 0% vs 0%; HSV: 10% vs. 2%; VZV: 5% vs 1%	HSV, VZV, HPV infection, TB, listeriosis, mucosal candidiasis (mainly oral or vaginal)
	Case series, case reports [78–81]	NA	NA	PCP, invasive aspergillosis, nocardiosis, listeriosis, PML; mycobacterial, BKV, CMV, VZV and HSV infections; HBV reactivation	

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Mikulska M et al. CMI 2018

Group	Agent	Risk of neutropenia	Risk of HSV and VZV (anti-herpesvirus prophylaxis warranted)	Risk of PCP (anti-*Pneumocystis* prophylaxis warranted)	Risk of HBV reactivation (prophylaxis warranted for $HBsAg^+/HBsAg^-$ anti-HBc^+)	Risk of CMV infection (monitoring warranted)	Other infections to be considered
CD52-targeted agents	Alemtuzumab (MabCampath®)	Yes	Yes	Yes	Yes/prophylaxis or monitoring	Yes	IFI, BK and JC polyomaviruses reactivation
	Alemtuzumab (Lemtrada®)	No	Yes	No (lower dose, no need of additional immunosuppression)	Probably yes/prophylaxis or monitoring	No	HPV, TB, listeriosis, candidiasis

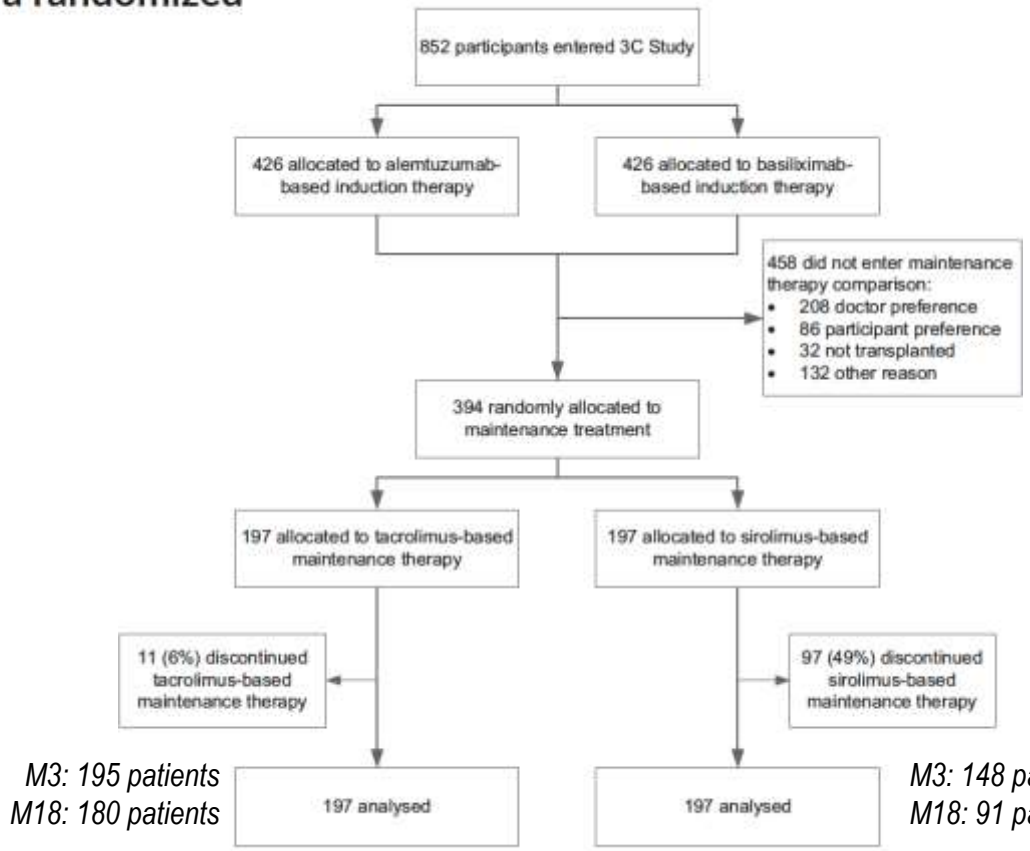
Biothérapies et transplantation d'organe solide

Inhibiteurs de mTOR: évérolimus, sirolimus

Campath, calcineurin inhibitor reduction, and chronic allograft nephropathy (the 3C Study) – results of a randomized controlled clinical trial

Haynes R et al. Am J Transplant. 2017 Dec 11

- Essai randomisé multicentrique
- 2/3 sous mycophénolate
- 1/3 sous prednisolone
- Motif d'arrêt de Sirolimus les 6 1er mois = rejet/infection

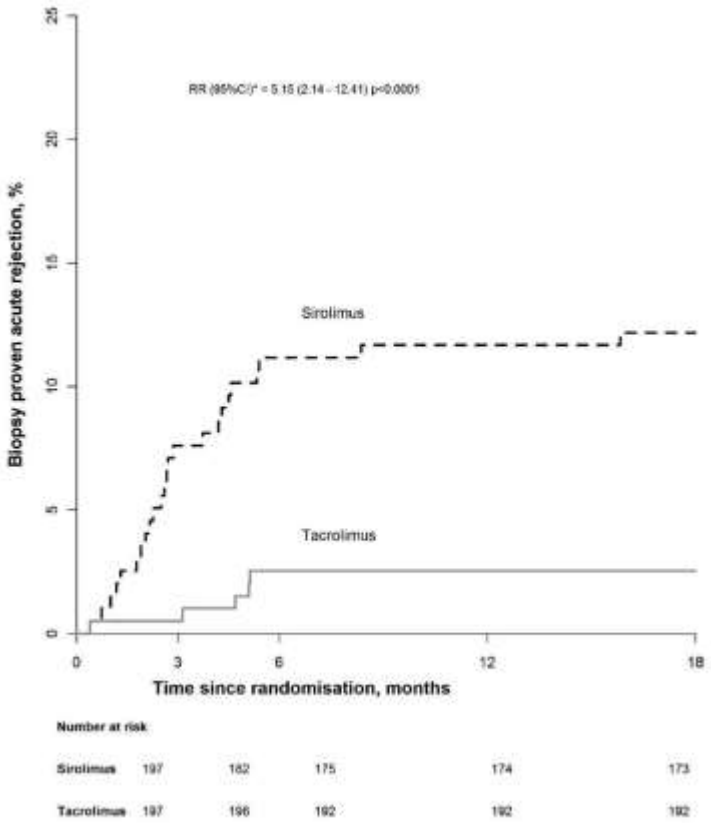


	Sirolimus (n = 197)	Tacrolimus (n = 197)
Induction therapy strategy		
Alemtuzumab-based	95 (48%)	97 (49%)
Basiliximab-based	102 (52%)	100 (51%)

Biothérapies et transplantation d'organe solide

Inhibiteurs de mTOR: évérolimus, sirolimus

	Sirolimus (n = 197)	Tacrolimus (n = 197)	Rate ratio (95% CI)	P value
Serious infections				
Opportunistic infections				
Cytomegalovirus infection	8 (4.1%)	8 (4.1%)	1.00 (0.38-2.68)	.99
BK virus infection	1 (0.5%)	3 (1.5%)		
Fungal infection				
Noninvasive	3 (1.5%)	2 (1.0%)		
Invasive	0 (0.0%)	1 (0.5%)		
Any	3 (1.5%)	3 (1.5%)	1.00 (0.20-4.97)	1.00
Other opportunistic infection				
PCJ	5 (2.5%)	1 (0.5%)		
Mycobaterial	0 (0.0%)	0 (0.0%)		
Other	8 (4.1%)	7 (3.6%)		
Any other opportunistic infection	12 (6.1%)	8 (4.1%)		
Any opportunistic infection	22 (11.2%)	22 (11.2%)	1.00 (0.56-1.81)	.99
Nonopportunistic infections				
Urinary tract	30 (15.2%)	29 (14.7%)		
Respiratory tract	32 (16.2%)	19 (9.6%)		
Gastrointestinal	26 (13.2%)	9 (4.6%)		
Central nervous system	1 (0.5%)	1 (0.5%)		
Other	33 (16.8%)	25 (12.7%)		
Any nonopportunistic infection	83 (42.1%)	60 (30.5%)	1.54 (1.11-2.15)	.010
Any serious infection	95 (48.2%)	70 (35.5%)	1.51 (1.11-2.06)	.008



Haynes R et al. Am J Transplant. 2017 Dec 11

ESCMID Study Group for Infections in Compromised Hosts (ESGICH)

ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an infectious diseases perspective (Intracellular signaling pathways: tyrosine kinase and mTOR inhibitors)

Reinwald M et al. CMI 2018

Agent	Increased risk of overall infection	Risk of OI	Risk of PCP	Risk of HBV reactivation	Observations and recommendations
Sirolimus, everolimus temsirolimus,	Major	HZ, tuberculosis	No	Yes	• Increased risk of infection in cancer patients, especially in those with additional risk factors (i.e. RCC, prior or concomitant cancer therapies, delay in wound healing or aphthous stomatitis). • Screening for chronic HBV infection and LTBI before starting therapy (followed by appropriate therapy if needed) • No expected benefit from universal use of antibacterial, antiviral or anti-*Pneumocystis* prophylaxis

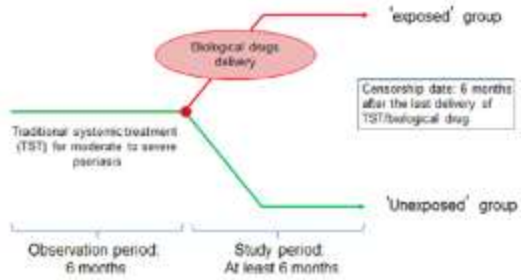
BIOTHÉRAPIES ET PSORIASIS

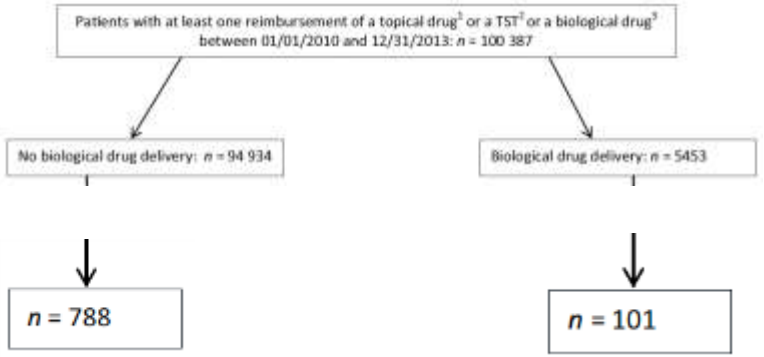
(dont Anti-IL17)

Biothérapies et psoriasis

Infectious risk of biological drugs vs. traditional systemic treatments in moderate-to-severe psoriasis: a cohort analysis in the French insurance database

Couderc S et al. Fundam Clin Pharmacol. 2018 Feb 15





Durée de la maladie >

≥ 1 hospitalisation durant la période « d'observation »

Table II Description of infectious risk by subgroups (study period: 2 years).

Subgroup	Number of patients	Number of patients with infection during the study period (%)
'Exposed' group (biological drugs)		
At least two different biological drugs	22	17 (77.3)
Ustekinumab only	37	22 (59.5)
Infliximab only	13	4 (30.8)
Adalimumab only	20	16 (80)
Etanercept only	9	9 (100)
Total	101	68 (67.3)
'Unexposed' group (traditional systemic treatments = TST)		
At least two different TST	197	95 (48.2)
Acitretin only	199	121 (60.8)
Phototherapy only	331	229 (69.2)
Methotrexate only	60	44 (73.3)
Ciclosporin only	1	1 (100)
Total	788	490 (62.2)

Table III Results of multivariate Cox model[a] evaluating the occurrence of the first infectious event.

Variables	HR	CI 95	*P* value
Gender (women vs. men)	1.23	1.04; 1.46	**0.02**
Universal Medical Coverage (CMU)	1.44	1.08; 1.92	**0.01**
Diabetes	0.70	0.52; 0.95	**0.02**
Chronic hepatitis B or C	2.74	1.35; 5.58	**0.005**
Cancer	1.70	1.20; 2.42	**0.003**
Chronic respiratory illness	1.18	0.91; 1.54	0.21
Infectious events (infectious screening drugs excluded) during the observation period	1.74	1.44; 2.08	**<0.0001**
Mean number of drugs per patient (anti-infective drugs excluded) during the observation period	1.03	1.01; 1.04	**0.002**
At least one hospitalization during the observation period	1.08	0.86; 1.36	0.52
Exposition to biological drugs	0.94	0.71; 1.22	0.62

Biothérapies et psoriasis

Infections in Moderate to Severe Psoriasis Patients Treated with Biological Drugs Compared to Classic Systemic Drugs: Findings from the BIOBADADERM Registry

Dàvila-seijoP et al. J Invets Dermatol 2017; 137: 313-321

Registre espagnol

Trt « classiques » et biothérapies

Comparateur = méthotrexate

2 153 patients

Table 3. Infection crude rates (per 1,000 person-years) and crude and adjusted incidence RR of infection compared with methotrexate[1]

	Person-time	Failures	Rate (95% CI)	Crude RR (95% CI)	Adjusted RR (95% CI)
Etanercept	1,228.6	183	148.9 (128.9–172.2)	1.23 (0.94–1.62)	1.34 (1.02–1.76)[2,5]
Infliximab	264.2	56	211.9 (163.1–275.4)	1.63 (1.09–2.44)[3]	1.71 (1.10–2.65)[3]
Adalimumab	1,329.7	195	146.6 (127.4–168.7)	1.22 (0.89–1.66)	1.27 (0.92–1.75)[3]
Ustekinumab	1,194.0	138	115.6 (97.8–136.6)	0.91 (0.62–1.34)	0.93 (0.64–1.36)[4]
Methotrexate	1,149.4	130	113.1 (95.2–134.3)	1.00	1.00
Cyclosporine	250.6	43	171.6 (127.3–231.4)	1.57 (1.17–2.12)[5]	1.58 (1.17–2.15)[5]
Acitretin	526.8	34	64.5 (46.1–90.3)	0.6 (0.42–0.86)[5]	0.6 (0.44–0.83)[5]
Etanercept combined with methotrexate	284.7	31	105.7 (73.0–153.1)	1 (0.50–1.99)	1.02 (0.52–1.99)[2]
Infliximab combined with methotrexate	225.6	25	104 (68.5–158.0)	1.12 (0.59–2.11)	1.23 (0.68–2.23)
Adalimumab combined with methotrexate	472.9	91	195.6 (157.7–242.6)	2.04 (1.28–3.26)[6]	2.13 (1.23–3.67)[3,6]
Ustekinumab combined with methotrexate	340.2	56	173.2 (132.0–227.3)	1.39 (0.96–2.02)	1.56 (1.08–2.25)[4,5]

Table 4. Serious and deadly infection crude rates (per 1,000 person-years) and crude and adjusted[1] incidence RR of serious and deadly infections compared with methotrexate

	Person-Time	Failures	Rate (95% CI)	Crude RR (95% CI)	Adjusted RR (95% CI)
Etanercept	1,228.6	2	1.6 (0.4–6.5)	0.17 (0.03–0.91)[5]	0.24 (0.04–1.29)[2]
Infliximab	264.2	5	18.9 (7.9–45.5)	1.27 (0.49–3.31)	2.52 (0.83–7.69)
Adalimumab	1,329.7	13	9.8 (5.7–16.8)	0.92 (0.46–1.84)	1.29 (0.72–2.32)[3]
Ustekinumab	1,194.0	7	5.9 (2.8–12.3)	0.59 (0.12–2.87)	0.75 (0.18–3.13)[4]
Methotrexate	1,149.4	11	9.6 (5.3–17.3)	1	1
Cyclosporine	250.6	5	20 (8.3–47.9)	2.21 (1.02–4.81)[5]	3.12 (1.11–8.77)[5]
Acitretin	526.8	4	7.6 (2.8–20.2)	0.8 (0.33–1.91)	0.82 (0.35–1.92)
Etanercept combined with methotrexate	284.7	2	7 (1.8–28.1)	0.37 (0.11–1.3)	0.56 (0.15–2.1)
Infliximab combined with methotrexate	225.6	2	8.9 (2.2–35.4)	2.11 (0.64–6.95)	3.4 (0.76–15.21)
Adalimumab combined with methotrexate	472.9	11	23.3 (12.9–42)	2.5 (0.7–8.89)	3.28 (0.8–13.46)[3]
Ustekinumab combined with methotrexate	340.2	3	8.8 (2.8–27.3)	1.05 (0.24–4.52)	1.63 (0.43–6.13)[4]

Table 5. Recurrent infections crude rates (per 1,000 person-years) and crude and adjusted[1] incidence risk ratio of recurrent infections compared to methotrexate

	Person-Time	Failures	Rate (95% CI)	Crude RR (95% CI)	Adjusted RR (95% CI)
Etanercept	1,228.6	70	57 (45.1–72)	1.18 (0.82–1.71)	1.4 (0.93–2.1)[2]
Infliximab	264.2	21	79.5 (51.8–121.9)	1.81 (0.86–3.82)	1.98 (1–3.94)
Adalimumab	1,329.7	66	49.6 (39–63.2)	1.03 (0.7–1.53)	1.06 (0.67–1.67)[3]
Ustekinumab	1,194.0	45	37.7 (28.1–50.5)	0.77 (0.36–1.61)	0.8 (0.37–1.75)[4]
Methotrexate	1,149.4	39	33.9 (24.8–46.4)	1	1
Cyclosporine	250.6	5	20 (8.3–47.9)	0.78 (0.43–1.43)	0.63 (0.3–1.31)
Acitretin	526.8	7	13.3 (6.3–27.9)	0.43 (0.23–0.8)[5]	0.45 (0.23–0.87)[5]
Etanercept combined with methotrexate	284.7	8	28.1 (14.1–56.2)	0.86 (0.37–2)	0.75 (0.37–1.49)[2]
Infliximab combined with methotrexate	225.6	3	13.3 (4.3–41.2)	0.61 (0.17–2.21)	0.66 (0.18–2.44)
Adalimumab combined with methotrexate	472.9	38	80.4 (58.5–110.4)	3.83 (2.47–5.95)[6]	4.33 (2.27–8.24)[3,6]
Ustekinumab combined with methotrexate	340.2	25	73.5 (49.7–108.8)	1.95 (0.49–7.71)	2.18 (0.63–7.48)[4]

Biothérapies et psoriasis
Anti-IL17 et Tuberculose

Inhibition of IL-17A by secukinumab shows no evidence of increased *Mycobacterium tuberculosis* infections

Kammüller M et al. Clin Trans Immunol 2017; 6

Résultats poolés de 5 essais thérapeutiques

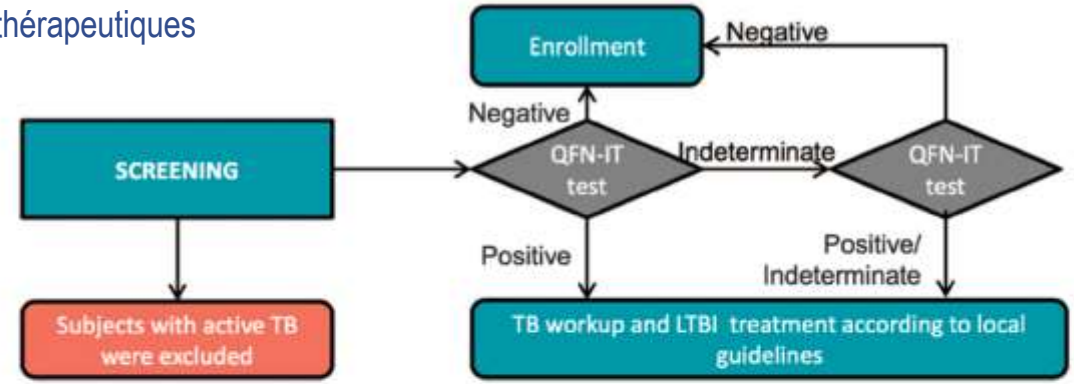


Figure 2 LTBI screening process in phase 3 trials. QFN-IT, Quantiferon-TB Gold in tube test.

Table 1 Subjects with a medical history of tuberculosis or LTBI showed no reactivation of tuberculosis during secukinumab treatment across five clinical studies

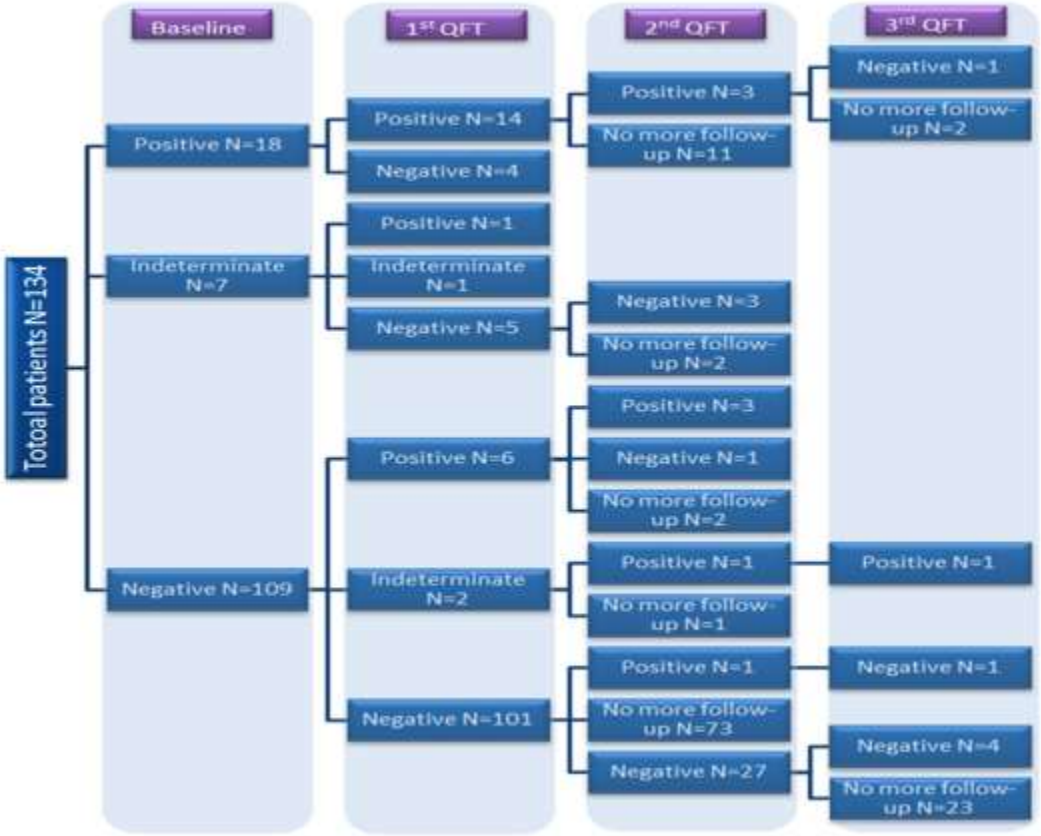
Treatment	*Subjects*		*Anti-tuberculosis medication*	*Secukinumab (mg)*[a]	*Median duration of secukinumab treatment (days)*	*Active tuberculosis*
Quantiferon tested positive	107	52	Yes	150	364	0
		55	Yes	300	364	0
Quantiferon tested negative	25	14	No	150	362	0
		11	No	300	363	0

Biothérapies et psoriasis
Tuberculose

Serial QuantiFERON-TB Gold testing in patients with psoriasis treated with ustekinumab

Hsiao CY et al. PlosOne 2017 12(9)

Age (years)	47.16 ± 13.14[a]
Sex, n (%)	Man: 101 (75.4)
	Woman: 33 (24.6)
With psoriatic arthritis, n (%)	42 (32.1)
Mean follow-up months	20.5 ± 10.52[a]
Previous biological treatment, n (%)	Etanercept: 24 (17.9)
	Adalimumab: 23 (17.2)
Combined treatment, n (%)	Methotrexate: 12 (9)
	Etanercept: 4 (3)
	Adalimumab: 1(0.7)



Majorité de patients naïfs de tout traitement

Majorité de patients en monothérapie

27 séroconversion - 81,5% traités

Parmi les séroconversion sous traitement:

- 7 patients sous ustekinumab seul vs 1 en association
- 5 patients naïfs de trt antérieur vs 2 avec trt antérieur

ESCMID Study Group for Infections in Compromised Hosts (ESGICH)

ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an infectious diseases perspective (Soluble immune effector molecules [II]: agents targeting interleukins, immunoglobulins and complement factors)

Winthrop KL et al. CMI 2018

Agents	Increased risk of overall infection	Risk of VZV/HBV infection	Risk of active TB	Observations and recommendations
Ustekinumab	Minor	Yes/yes (probably low in both cases)	Uncertain (theoretical risk of progression of LTBI)	• No apparent increase in the risk of infection • Screening for LTBI before starting treatment (followed by appropriate therapy if needed) due to theoretical risk of active TB • Screening for chronic HBV infection before starting therapy (followed by antiviral prophylaxis in HBsAg-positive patients) • Age-appropriate antiviral vaccinations
Secukinumab, ixekizumab, brodalumab	Minor	No/no	Probably low (theoretical risk of progression of LTBI)	• Minor increase in the risk of mild to moderate infection • Increased risk of mild to moderate mucocutaneous candidiasis (slightly higher for brodalumab and ixekizumab than secukinumab)

BIOTHÉRAPIES ET POLYARTHRITE RHUMATOÏDE

Anti-IL6: Tocilizumab

Biothérapies et polyarthrite rhumatoïde

Anti-IL6

Five-year Efficacy and Safety of Tocilizumab Monotherapy in Patients with Rheumatoid Arthritis Who Were Methotrexate- and Biologic-naive or Free of Methotrexate for 6 Months: the AMBITION Study

Jones G et al. J Rheumatol. 2017 Feb;44(2):142-146

243 patients TCZ

134 poursuite de traitement

94 patients TCZ monothérapie à 5 ans

PR MTX-naïve ou free depuis 6 mois

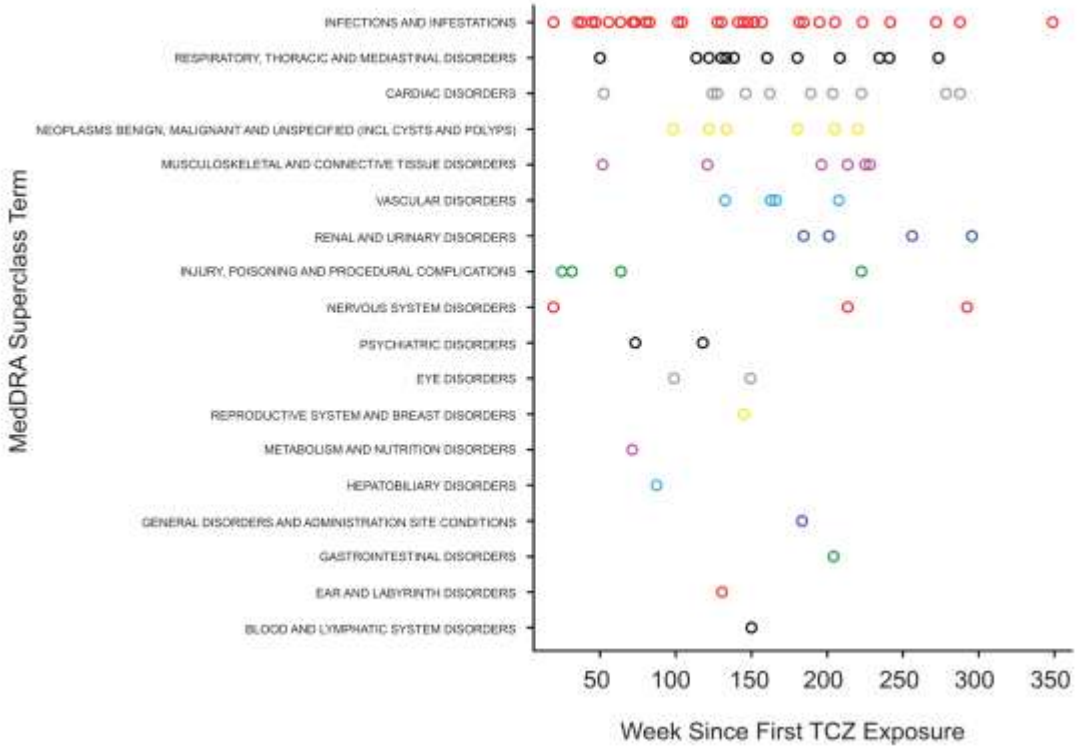
Randomisation TCZ 8 mg/kg IV / 4 sem ou MTX 7,5 – 20 mg/sem PO pdt 24 sem

Au-delà, possibilité de poursuivre ou non

Objectifs: efficacité et sécurité

Arrêt de Traitement pour EI = 19

Infections les + fréquentes = pneumonies



Biothérapies et polyarthrite rhumatoïde
Anti-IL6

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

Morel J et al. Rheumatol. 2017; 156: 1746-1754

REGATE: cohorte nationale prospective (78 centres)

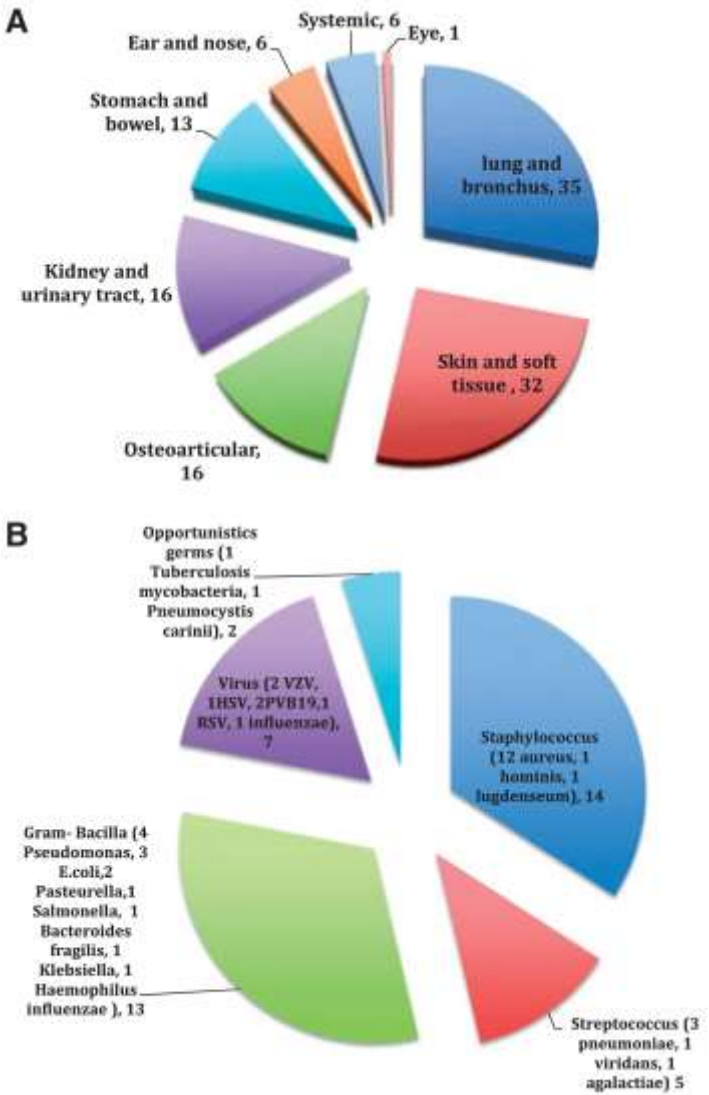
1 491 patients

ATCD: 30% anti-TNF, 13% rituximab, 18% abatacept

infection sévère/récidivante: 13%

125 infections sévères (hospitalisation/traitement IV/décès) chez 122 patients (sous traitement ou < 3 mois d'arrêt):
incidence = 4,7/100 patients-années

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



ACPA: anticorps anti-protéines citrullinées; LEF: léflunomide

Biothérapies et polyarthrite rhumatoïde

Anti-IL6

Subcutaneous tocilizumab in rheumatoid arthritis: findings from the common-framework phase 4 study programme TOZURA conducted in 22 countries

Choy Eet al. Rheumatol. 2018; 57: 499-507

Events	Total population (N = 1804), 943.3 PY	TCZ-SC monotherapy (n = 353), 175.7 PY	TCZ-SC + csDMARD (n = 1451), 767.6 PY
Serious infections and infestations Patients with ⩾1 event, *n* (%)	27 (1.5)	6 (1.7)	21 (1.4)

ESCMID Study Group for Infections in Compromised Hosts (ESGICH)

ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an infectious diseases perspective (Soluble immune effector molecules [II]: agents targeting interleukins, immunoglobulins and complement factors)

Winthrop KL et al. CMI 2018

Agents	Increased risk of overall infection	Risk of VZV/HBV infection	Risk of active TB	Observations and recommendations
Tocilizumab, siltuxumab	Modest	Yes/yes	Yes	• Risk comparable to that observed for anti-TNF-α agents (probably lower for TB) • Screening for chronic HBV infection before starting therapy • Antiviral prophylaxis while on therapy on HBsAg-positive patients • Monitoring for HBV viral load in anti-HBc positive, HBsAg-negative patients to assess eventual reactivation of occult HBV infection • Screening for LTBI before starting treatment (followed by appropriate therapy if needed) • Age-appropriate antiviral vaccinations