Tuberculose IRIS et anti-TNF

Quelles données, quelles indications?

Nathalie DE Castro

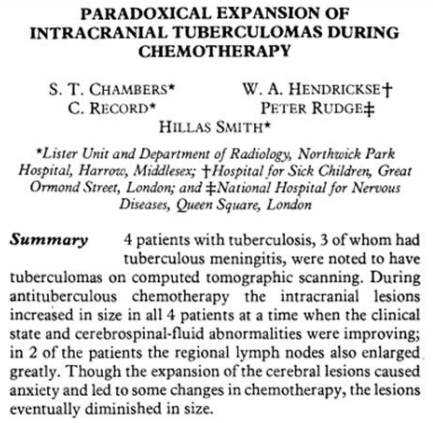
SMIT SAINT-LOUIS LARIBOISIÈRE, AP-HP

Journée G2I

13 JANVIER 2023

Introduction
Réactions/TB paradoxales

- Aggravation « paradoxale » sous traitement anti-infectieux d'une pathologie infectieuse décrit dans les infections à mycobactéries depuis les années 60-70:
  - Lèpre : réactions de réversion
  - tuberculomes cérébraux et pleurésie de l'enfant



PARADOXICAL EXPANSION OF INTRACRANIAL TUBERCULOMAS DURING CHEMOTHERAPY

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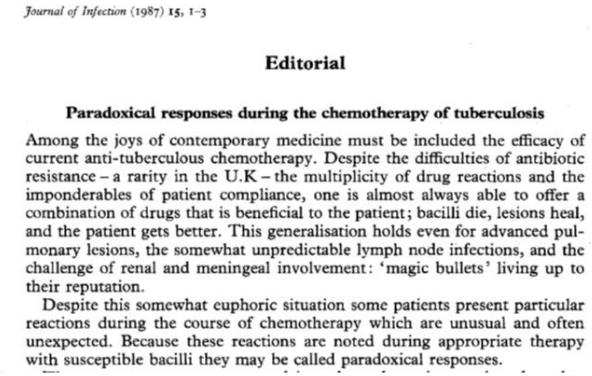
Summary 4 patients with tuberculosis, 3 of whom had tuberculous meningitis, were noted to have tuberculomas on computed tomographic scanning. During antituberculous chemotherapy the intracranial lesions increased in size in all 4 patients at a time when the clinical state and cerebrospinal-fluid abnormalities were improving; in 2 of the patients the regional lymph nodes also enlarged greatly. Though the expansion of the cerebral lesions caused anxiety and led to some changes in chemotherapy, the lesions eventually diminished in size.



Journal of Infection (1987) **15**, 1–3

Editorial

Paradoxical responses during the chemotherapy of tuberculosis

Among the joys of contemporary medicine must be included the efficacy of current anti-tuberculous chemotherapy. Despite the difficulties of antibiotic resistance – a rarity in the U.K – the multiplicity of drug reactions and the imponderables of patient compliance, one is almost always able to offer a combination of drugs that is beneficial to the patient; bacilli die, lesions heal, and the patient gets better. This generalisation holds even for advanced pulmonary lesions, the somewhat unpredictable lymph node infections, and the challenge of renal and meningeal involvement: 'magic bullets' living up to their reputation.

Despite this somewhat euphoric situation some patients present particular reactions during the course of chemotherapy which are unusual and often unexpected. Because these reactions are noted during appropriate therapy with susceptible bacilli they may be called paradoxical responses.

- Chez les immunodéprimés
  - VIH+++
  - « unmasking » IRIS lors de la reconstitution immunitaire
  - Sortie d'aplasie : infections fongiques
  - diminution/arrêt de traitements immunosuppresseurs quels qu'ils soient: **corticothérapie**, **biothérapies**…

Chambers AT. *Lancet* 1984
Smith H. *J Infect* 1987

Introduction
TB paradoxales ⇨ IRIS chez l'immunodéprimé

Type IRIS	Pathogène	Immunodépression	Pathologie sous-jacente	Cause IRIS
TB	***M. tuberculosis***	**Lymphopénie CD4**	**VIH**	**Début ARV**
TBM	***M. tuberculosis***	**Lymphopénie CD4**	**VIH**	**Début ARV**
TB	***M. tuberculosis***	**Anti-TNF**	**PR, sarcoïdose, psoriasis…**	**Arrêt anti-TNF**
LEMP	JC virus	Lymphopénie CD4	VIH	Début ARV
LEMP	JC virus	Natalizumab (inhib α-4 intégrine)	SEP	Arrêt natalizumab
Kaposi	HHV8	Lymphopénie CD4	VIH	Début ARV
Cryptoccocose	*C. neformans*	corticothérapie	Transplantation d'organe	Arrêt corticothérapie
Cryptoccocose méningée	*C. neformans*	Lymphopénie CD4	VIH	Début ARV
CHS	*Candida spp*	Chimiothérapie	Hémopathies malignes	Reconstitution hématologique

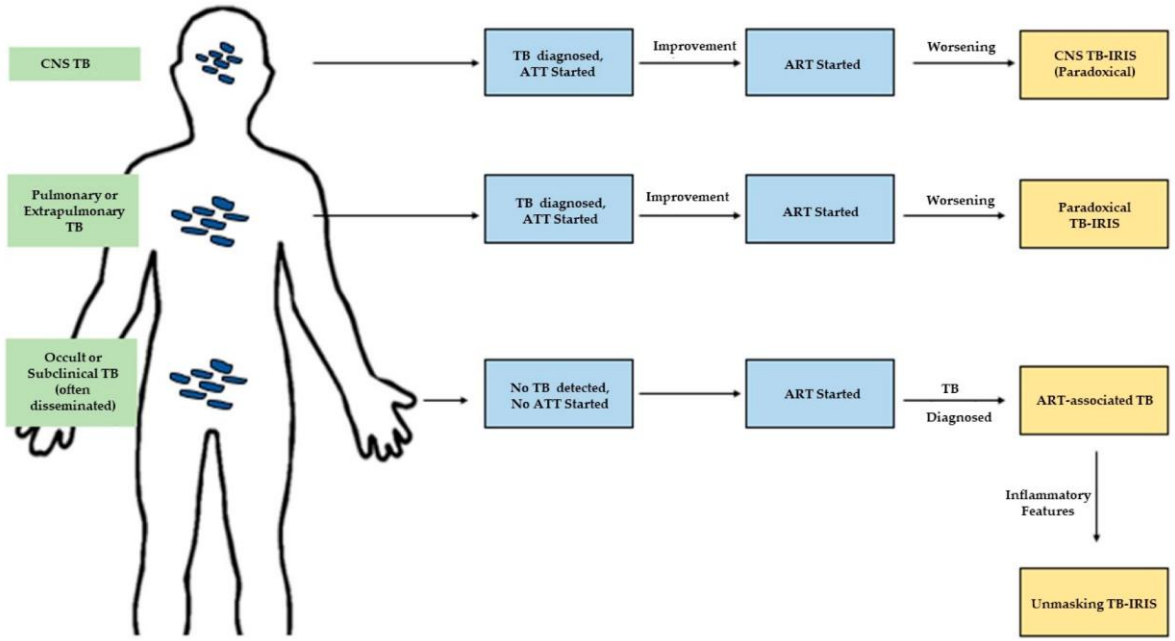
Cevaal et al. Tuberculosis 2019
https://doi.org/10.1016/j.tube.2019.101863

IRIS chez les PVVIH

IRIS TB : diagnostic d'élimination

CD4<100
CV élevée
Fort inoculum (TB disséminée)

Délai ART-IRIS < 3 mois



Fréquence 15-18%

Eliminer autre dg

Autre diagnostic
Infections bactériennes
Infections fongiques
MAC
Lymphomes…

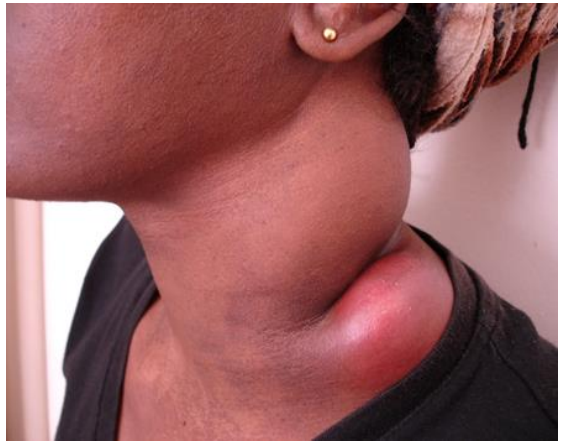
Echec du traitement anti-TB
Résistance+++
Inobservance
Sous-dosage…

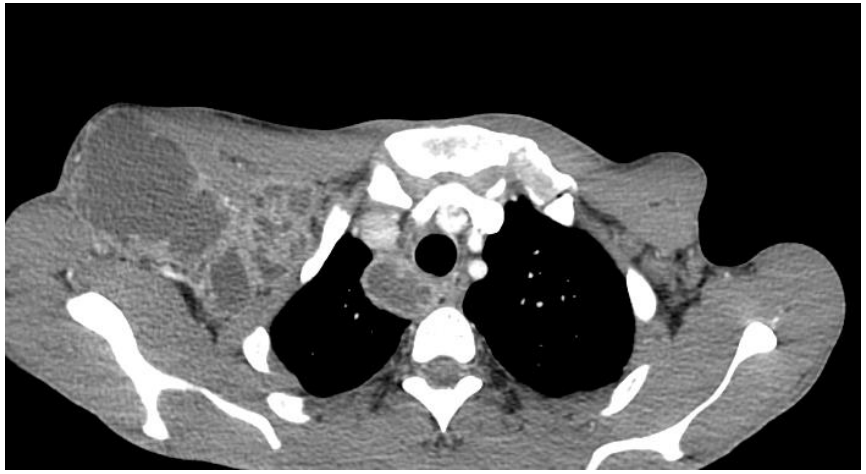
Allergie
Dress+++

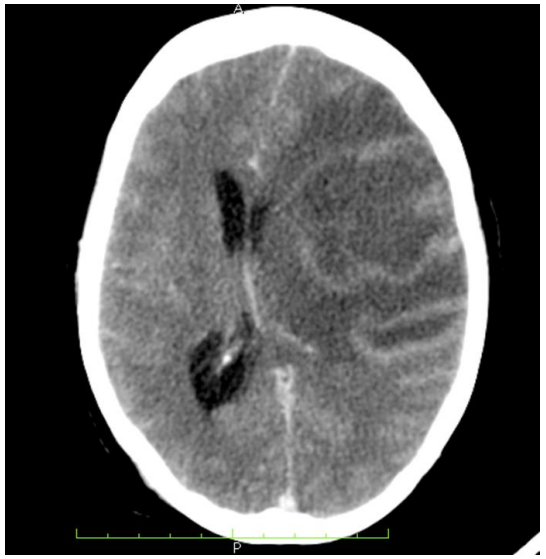
Quinn *et al. Life* 2020
Müller M *et al. Lancet Infect Dis* 2010
Walker NF *et al. Curr Opin HIV AIDS* 2018

IRIS chez les PVVIH

Présentation clinico-radiologique IRIS TB

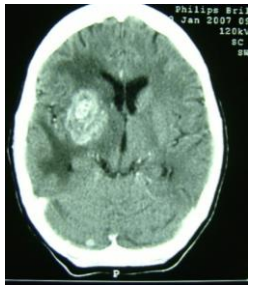






IRIS chez les PVVIH
IRIS neurologique

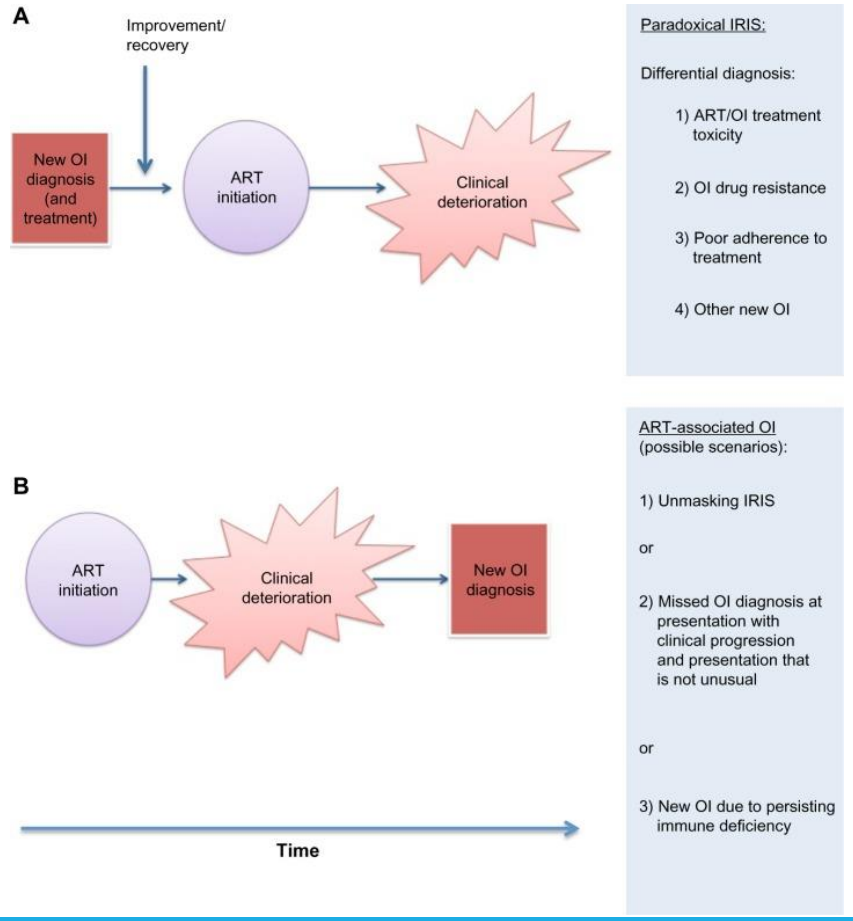
- Sévérité : IRIS neurologique
  - 12% des IRIS ont une atteinte neurologique
  - 47% des PVVIH avecTBM qui débutent les ARV developpent IRIS
- IRIS neurologique
  - Méningite, tuberculomes, radiculomyelopathie
  - Peut survenir chez des patients sans atteinte neurologique initiale
  - 25% à 75% de mortalité
  - Séquelles+++
  - Absence de bénéfice à débuter ARV à J15 dans un essai randomisé et plus d'EI grade 4 (mais pas plus d'EI neurologique) => OMS recommande ART à S4

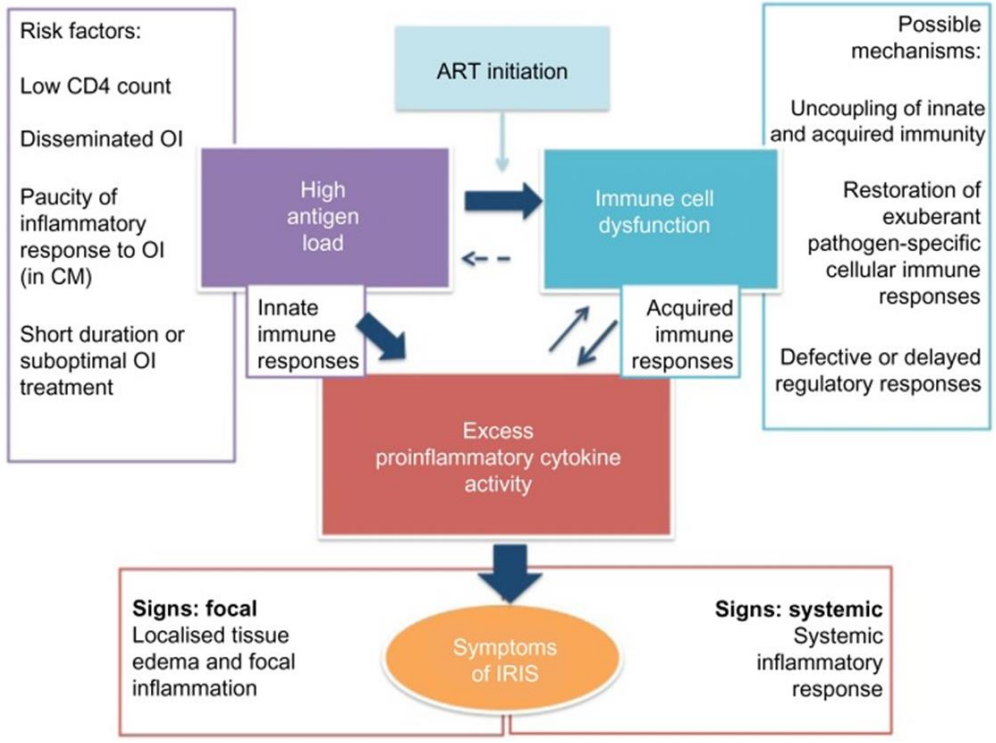


Pepper et al. *Clin Infect Dis* 2009
Marais et al. *Clin Infect Dis* 2012
Agarwal et al. *AIDS Res Ther* 2012
Török et a. *Clin Infect Dis* 2011

Physiopathologie IRIS TB chez les PVVIH

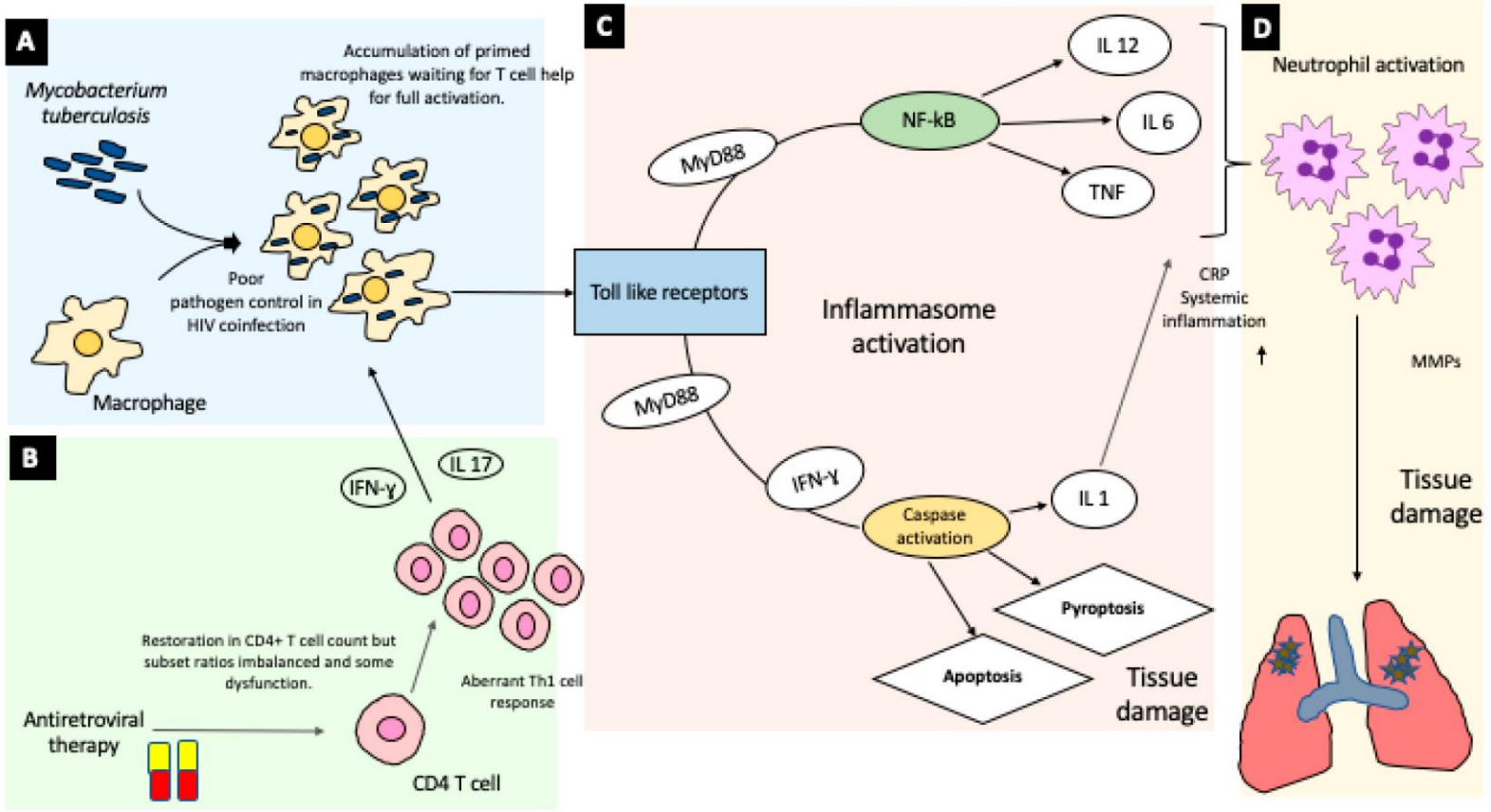
Facteurs liés à l'hôte et au pathogène





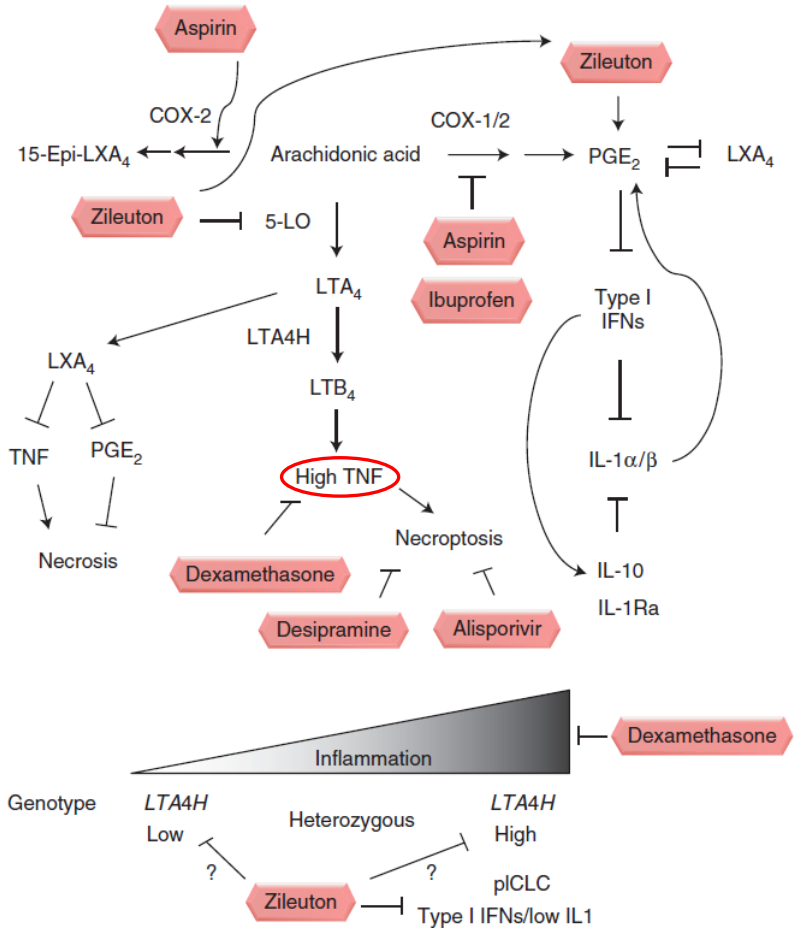
HIV/AIDS – Research and Palliative Care 2015:7 49–6

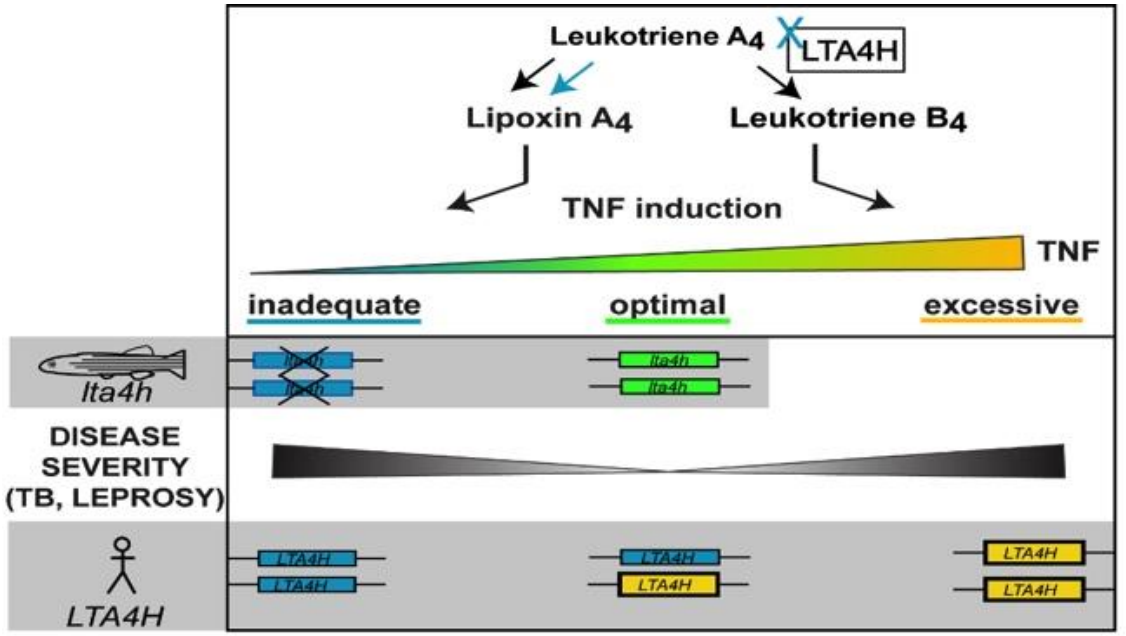
Physiopathologie IRIS TB chez les PVVIH
Rôle IFN et TNF



Physiopathologie IRIS TB chez les PVVIH

Cas particulier de la TBM





Homozygotes CC Hétérozygotes CT Homozygotes TT

1- WHO 2017
2-Torok ME *et al*. *Clin Infect Dis* 2011
3-Abdool Karim SS *et al*. *N Engl J Med* 2011
4-Strangfeld A *et al.* Ann Rheum Dis 2011

Traitement/prévention IRIS TB
Immunomodulateurs utilisés en clinique

- Corticothérapie dès les années 50 :
  - TBM+++
- Thalidomide:
  - réactions de réversion de la lèpre
  - TBM+++
- Anti-TNF
- AINS/Aspirine pour les formes moins sévères

IRIS TBM

"Prévention" par corticoïdes

ORIGINAL ARTICLE

Dexamethasone for the Treatment of Tuberculous Meningitis in Adolescents and Adults

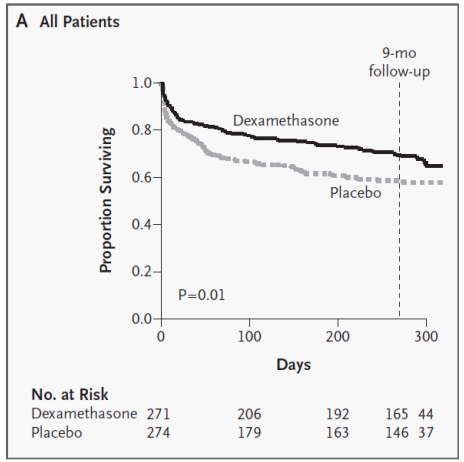
Guy E. Thwaites, M.R.C.P., Nguyen Duc Bang, M.D., Nguyen Huy Dung, M.D., Hoang Thi Quy, M.D., Do Thi Tuong Oanh, M.D., Nguyen Thi Cam Thoa, M.D., Nguyen Quang Hien, M.D., Nguyen Tri Thuc, M.D., Nguyen Ngoc Hai, M.D., Nguyen Thi Ngoc Lan, Ph.D., Nguyen Ngoc Lan, M.D., Nguyen Hong Duc, M.D., Vu Ngoc Tuan, M.D., Cao Huu Hiep, M.D., Tran Thi Hong Chau, M.D., Pham Phuong Mai, M.D., Nguyen Thi Dung, M.D., Kasia Stepniewska, Ph.D., Nicholas J. White, F.R.C.P., Tran Tinh Hien, M.D., and Jeremy J. Farrar, F.R.C.P.

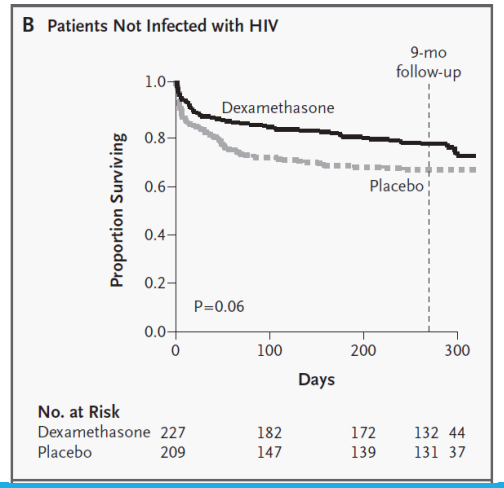
Table 3. Outcomes of 545 Patients Nine Months after Randomization.

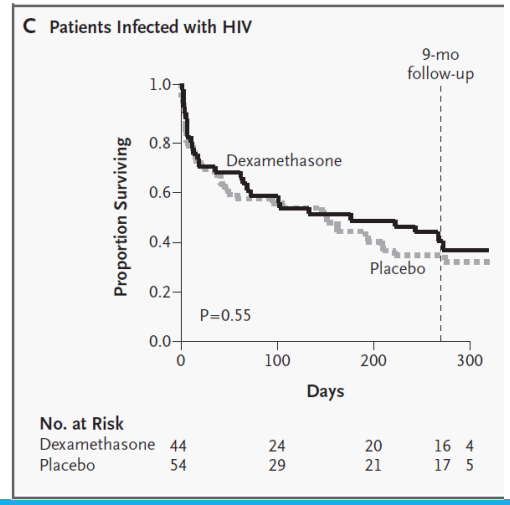
Group	No. of Patients	Outcome			
		Good	Inter-mediate	Severe Disability	Death
		number (percent)			
Dexamethasone*	274	104 (38.0)	49 (17.9)	34 (12.4)	87 (31.8)
Placebo	271	95 (35.1)	42 (15.5)	22 (8.1)	112 (41.3)

* Because of rounding, the percentages for the dexamethasone group do not total 100.

Pas de bénéfice chez les PVVIH (pré ART)







Thwaites et al. NEJM 2004

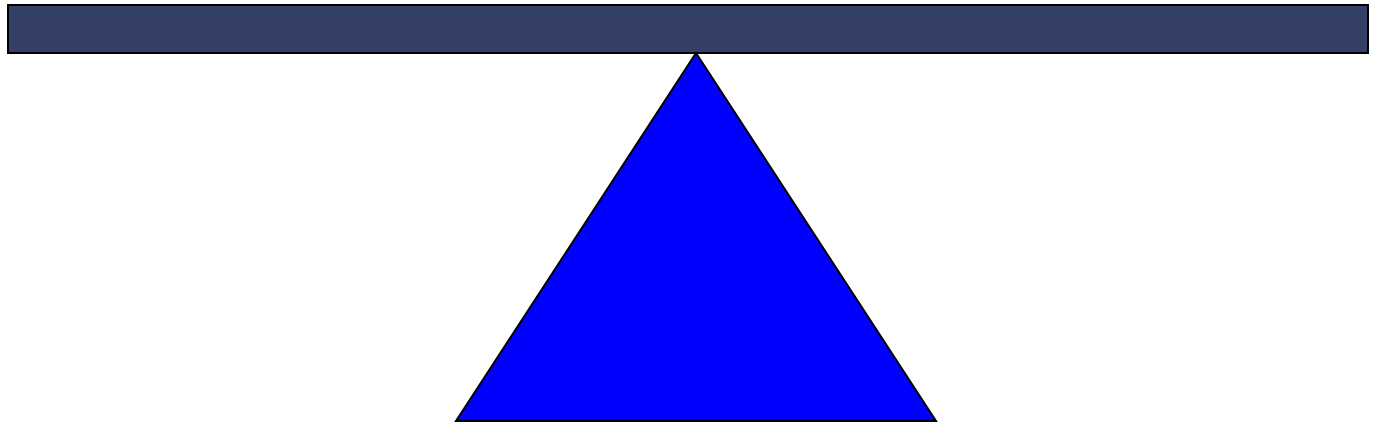
IRIS TB chez les PVVIH

Corticoïdes

Amélioration des symptômes
Réduction de l'hospitalisation?
Amélioration survie pour cas sévères?

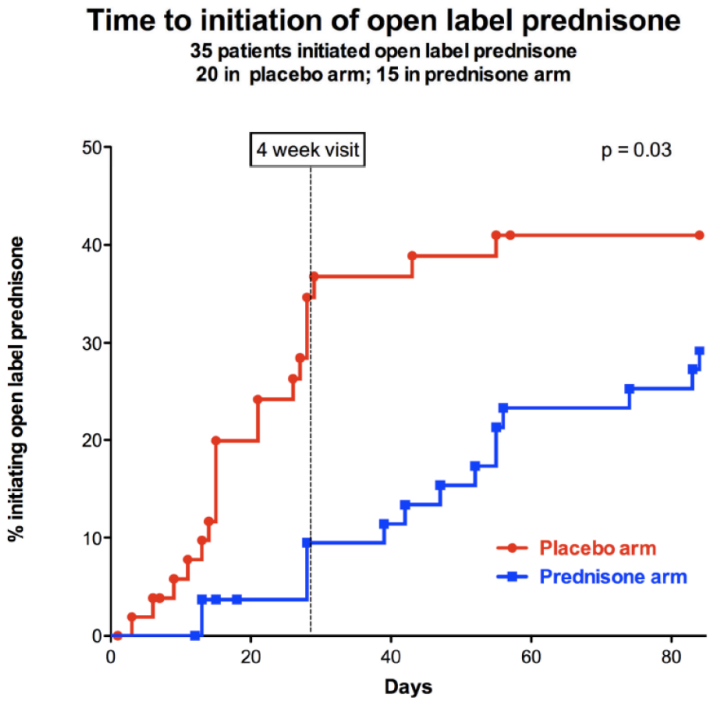
Complications potentielles
- Kaposi
- Infections
- Métaboliques

Absence de certitude dg de l'IRIS



IRIS TB chez les PVVIH
Traitement par corticoïdes

- 110 patients avec IRIS grave
- 0,75mg/kg/j prednisone 10j ou placebo
- Critère jugement: journées d'hospitalisation ou nécessité consultations/gestes en ambulatoire
- Pas de différence de mortalité: placebo 4% vs prednisone 5%



Meintjes et al. AIDS 2010; 24:2381-90

IRIS TB chez les PVVIH
Prévention par corticoïdes

ORIGINAL ARTICLE

Prednisone for the Prevention of Paradoxical Tuberculosis-Associated IRIS

G. Meintjes, C. Stek, L. Blumenthal, F. Thienemann, C. Schutz, J. Buyze, R. Ravinetto, H. van Loen, A. Nair, A. Jackson, R. Colebunders, G. Maartens, R.J. Wilkinson, and L. Lynen, for the PredART Trial Team

- VIH+ CD4<100/mm^3
- Exclusion TBM ou pericardique
- IRIS : adénopathies, abcès ou aggravation radio
- Pas de bénéfice sur mortalité

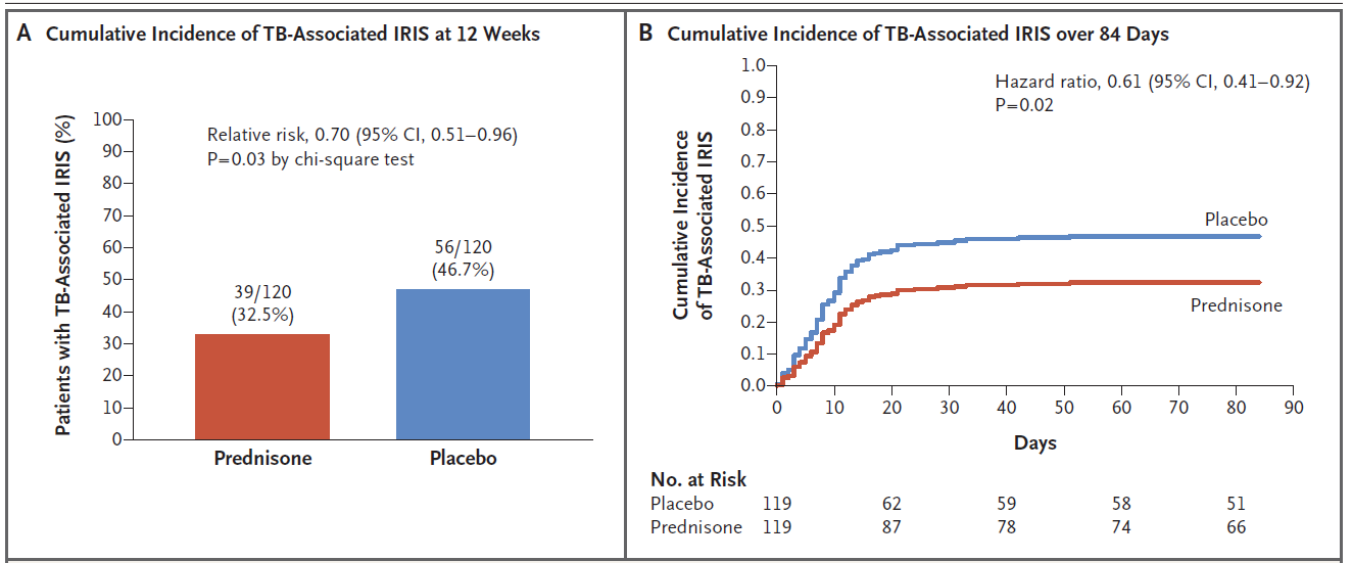


Figure 2. Cumulative Incidence of Paradoxical TB-Associated Immune Reconstitution Inflammatory Syndrome (IRIS).
Panel A shows the cumulative incidence of the primary end point of paradoxical TB-associated IRIS at 12 weeks. If paradoxical TB-associated IRIS had not developed before a patient died, withdrew, or was lost to follow-up, the patient was considered not to have had the syndrome. Panel B shows the cumulative incidence of TB-associated IRIS over 84 days. Diagnosis of TB-associated IRIS was determined according to the International Network for the Study of HIV-associated IRIS criteria.[14] Day 0 is the day ART was initiated.

Meintjes et al. NEJM 2018; 24:2381-90

IRIS TBM

“Prévention” par thalidomide

Enfants inclus entre 1998 et 2000
TBM
Anti TB + Corticoïdes

Original Article

Adjunctive Thalidomide Therapy for Childhood Tuberculous Meningitis: Results of a Randomized Study

Johan F. Schoeman, MBChB, MD; Priscilla Springer, MBChB, FCP; Anita Janse van Rensburg, Dipl Nurs; Sonja Swanevelder, MSc; Willem A Hanekom, MBChB, FCP; Patrick A. J. Haslett, MB, MRCP; Gilla Kaplan, PhD

Journal of Child Neurology / Volume 19, Number 4, April 2004

Table 2. Details of the Two Treatment Groups on Admission and After the First Month of Treatment

	Admission			*After 1 Mo*		
	Thalidomide (n = 30)	*Control (n = 17)*	P	*Thalidomide (n = 28)*	*Control (n = 17)*	P
Clinical						
Mean age (mo)	58	43	.17			
Stage 3 TBM	8 (29%)	2 (16%)	.49			
Mean GCS score	10.3	11	.57	13.9	**15**	.04
Brainstem signs	10 (20%)	2 (4%)	.16	3 (10%)	**0**	
Hemiparesis	21*	4*	.002	13	2	.70
Cranial nerve palsies	9 (30%)	5 (29%)	1.00	7 (23%)	3 (17%)	1.0
ICP (mm Hg)						
Baseline pressure	20.7	**14.0**	.07	13.2	10.6	.40
CT findings						
VP ratio	**.24**	.20	.08	.21	.19	.17
Severe basal enhancement	14 (47%)	6 (38%)	.55	12 (46%)	9 (56%)	.52
Basal ganglia infarcts	9 (30%)	2 (12%)	.28	12 (43%)	4 (24%)	.19
Tuberculoma	4 (14%)	**1 (6%)**	.64	1 (3%)	2 (12%)	.54

CT = computed tomography; GCS = Glasgow Coma Scale; ICP = intracranial pressure; TBM = tuberculous meningitis; VP = ventriculoparietal.
*These figures indicate the total number of hemipareses on admission (some patients had bilateral hemiparesis) and their course during the first month of treatment.

Table 1. Summary of Adverse Effects and Deaths in the Thalidomide Group

Patient Number/ Age (mo)	*Stage of TBM*	*Adverse Effects*	*Duration of Therapy*	*Outcome*
1/33	2	Diffuse morbiliform rash; thrombocytopenia; hepatitis	Day 27	Rash and hepatitis resolved; neurologically normal; IQ: 73
2/28	**3**	Diffuse morbiliform rash/no fever	Day 13	Rash resolved; bilateral hemiparesis resolved; IQ: 64
3/31	**2**	Stevens-Johnson syndrome; laryngotracheobronchitis; neutropenia; hepatitis	Day 17	Rash, hepatitis, and neutropenia resolved; severe left hemiplegia; IQ: 36
4/19	**3**	None	8 d	Died 8 d after admission
5/13	**3**	Fever, rash, and hepatosplenomegaly; coma deepened with onset of neurogenic hyperventilation	23 d	Died 1 d after thalidomide was stopped
6/32	3	Rash and fever; coma deepened with onset of seizures and decerebration	19 d	Rash and fever resolved; severe spastic quadriparesis; IQ: 4
7/96	2–3	Rash and fever; progressed from stages – 2–3 TBM after VP shunt	26 d	Fever and rash resolved; died 3 mo after start of treatment

TBM = tuberculous meningitis; VP = ventriculoparietal.

Shoman et al. J Child Neurol 2004

IRIS TB chez les PVVIH
Thalidomide

Thalidomide for steroid-dependent immune reconstitution inflammatory syndromes during AIDS

Anne-Sophie Brunel[a], Jacques Reynes[a,b], Edouard Tuaillon[c,d,e], Pierre-Alain Rubbo[c,d], Olivier Lortholary[f,g], Brigitte Montes[e], Vincent Le Moing[a,b] and Alain Makinson[a,b]

Management of relapsing or refractory immune reconstitution inflammatory syndromes (IRISs) despite corticosteroid therapy is yet to be defined. We describe three HIV-infected patients with corticosteroid-dependent and life-threatening paradoxical immune reconstitution inflammatory syndrome for whom thalidomide treatment induced rapid clinical remission and permitted complete corticosteroid withdrawal without clinical relapse.

HAART in advanced phases of HIV-1 infection may induce immune reconstitution inflammatory syndrome (IRIS), requiring brief corticosteroid therapy in severe cases [1,2]. Clinical manifestations in 'paradoxal IRIS' are primarily a worsening of clinical signs or the appearance of new events in patients with a known infection after starting HAART, most often without detectable or viable opportunistic infection and despite a successful suppression of HIV plasma viremia [3]. More rarely, in a form called 'unmasking IRIS', in which the opportunistic infection preexisted but was clinically silent, symptoms develop after the introduction of HAART. A switch from

AIDS Patient Care and STDs > Vol. 28, No. 11 > Letter to the Editor

Thalidomide in the Treatment of Immune Reconstitution Inflammatory Syndrome in HIV Patients with Neurological Tuberculosis

Camille Fourcade, Jean-Marc Mauboussin, Catherine Lechiche, Jean-Philippe Lavigne, and Albert Sotto

Published Online: 3 Nov 2014 | https://doi.org/10.1089/apc.2014.0083

Brunel et al AIDS 2012
Fourcade *et al.* AIDS patient care and STDs 2014

IRIS TB/crypto chez les PVVIH

Anti-TNF

Table 1 - Patient characteristics.

Number of patient	Age, sex, infection	HIV historyCD4⁺ cell count and HIV viral load at infection diagnosisART used	Time to IRIS onset after infection diagnosis and after ART initiationDelay between ART and anti-infectious drug initiation	IRIS descriptionIncrease in CD4⁺ cell countHIV viral load at IRIS onset	Duration of corticosteroids before TNF-I initiationDuration of corticosteroids after TNF-I initiationEffect of corticosteroids	Clinical situation at TNF-I initiationSteroids dose at TNF-I initiation, anti-TB or antifungal treatment at TNF-I initiationCD4⁺ cell count and HIV viral load	TNF-I administration scheduleTime to TNF I initiationDuration of TNF-I therapy/total infusion)	OutcomesFollow-up after TNF-I initiationTotal duration of anti-TB or antifungal treatment
1	37, MTBLungs and lymph nodes	Concomitant diagnosis of HIV/TBCD4⁺ 124 cells/µlHIV VL 5.8 logTenofovirLamivudine Efavirenz	15 daysSpontaneous IRIS- 15 days	Worsening of preexisting conditionCD4⁺ 131 cells/µlHIV VL 3.48 log	0.5 months7 monthsResistance to corticosteroids	Persistent feverSteroids dose: 1 mg/kg/dayConcomitant use of anti-TB therapyHIV VL 2.8 logCD4⁺ 285 cells/µl	Infliximab(5 mg/kg, D1 D15 M1 then every 6 weeks)16 daysFour infusions	Cure without sequelae1 year12 months
2	34, MTBLymph nodes and psoas abscess	HIV previously knownCD4⁺ 147 cells/µlHIV VL 3.1 log Maraviroclopinavir	16 days23 days71 days	New TB siteCD4⁺ 562 cells/µl HIV VL <200 copies/ml	5 yearsNADependence to steroids	Persistent fever, psoas abscess and spondylodiscitisNo steroids (patient treated with lenalidomide)TNF-I without anti-TB therapyHIV VL undetectableCD4⁺ 623 cells/µl	Infliximab (5 mg/kg, D1 D15 then every 6 weeks)3100 dayssix infusions	Cure without sequelae4.2 years34 months
3	41, MTBLungs and lymph nodes	Concomitant diagnosis of HIV/TBCD4⁺ 35 cells/µl HIV VL 6 logTenofovirEmtricitabineDarunavir	19 days29 days8 days	New TB siteCD4⁺ 70 cells/µl 1430 copies/ml	4 monthsNAResistance to corticosteroids	Persistent fever, necrotic lymph nodes, psoas abscessNo steroidsConcomitant use of anti-TB therapyHIV VL 4 logCD4⁺ 141 cells/µl	Infliximab(5 mg/kg D1 D14)390 daystwo infusions	Unfavorable outcomeIncreased size of LN and psoas abscess3.9 years10 months
4	53, FTBINH-RCNS and lungs	HIV previously knownCD4⁺ 106 cells/µl HIV VL 6 log copies/mlTenofovir Emtricitabine efavirenz	17 days24 days7 days	Worsening of preexisting conditionCD4⁺ 19 cells/µl HIV VL 5.6 log	3 months5 monthsDependence to corticosteroids	Tuberculoma, intracranial hypertension syndromeSteroids dose: 1 mg/kg/dayConcomitant use of anti-TB therapyHIV VL undetectableCD4⁺ 205 cells/µl	Adalimumab (40 mg/2 weeks)54 days360 days	Cure with neurological sequelae6.5 months23 months
5	37, FTB MDRCNS and lungs	HIV previously knownCD4⁺ 106 cells/µl HIV VL 5 log copies/mlLamivudineAbacavirefavirenz	28 daysSpontaneous IRIS- 49 days	New TB siteCD4⁺ 65 cells/µl HIV VL 4 log	3 months8 monthsResistance to corticosteroids	Cerebral vasculitisSteroids dose: 1.3 mg/kg/day + cyclophosphamide IVConcomitant use of anti-TB therapyHIV VL 1 logCD4⁺ 452 cells/µl	Adalimumab (40 mg/2 weeks)285 days84 days	Cure with neurological sequelae1.2 years20 months
6	39, FCryptoCNS and lungs	HIV previously knownCD4⁺ 46 cells/µl HIV VL 2 log copies/mlTenofovir Emtricitabineefavirenz	25 days52 days64 days	Worsening of preexisting conditionCD4⁺ 361 cells/µl HIV VL < 100 copies/ml	1 month1 monthDependence to corticosteroids	Reduced visual acuity, intracranial hypertension syndromeSteroids dose: 0.3 mg/kg/dayTNF-I without antifungal therapyHIV VL undetectableCD4⁺ 302 cells/µl	Adalimumab (40 mg/2 weeks)570 days345 days	Cure with neurological sequelae11.5 months3 months

Laparra A. *AIDS* 2021

IRIS TBM
Traitement curatif par biothérapies anti-TNF

- Case reports n = 15, 2PVVIH
- Délai apparition IRIS/ anti-TB : <3mois
- Anti-TNF utilisé:
  - Infliximab n= 12
  - Adalimumab n=3
- Evolution
  - Guérison sans séquelles : n=6
  - Séquelles : n=9
  - Décès : 0
- Durée anti-TNF : 1 à 3 mois

Blackmore TK *et al. Clin Infect Dis* 2008
Molton JS *et al. Med J Aust* 2015
Lwin N *et al. Open forum Infect Dis* 2018
Lee H-S *et al. J Infect Chemother* 2012
Santin M *et al. Medicine* 2020
Marais BJ *et al. Open Forum Infect Dis* 2021
Jorge JH *et al. J Clin Rheumatol* 2012
Abo YN *et al. Pediatr Infect Dis J* 2020

IRIS TBM
Traitement curatif par biothérapies anti-TNF

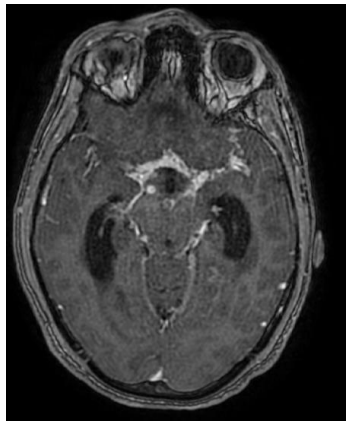
VIH -
IRIS cortico-dépendant+++++

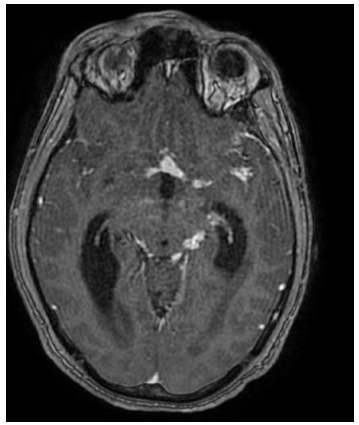
	Ateinte TB	Traitement TBM	Délai Tx-IRIS (jours)	IRIS	Traitement IRIS avant anti-TNF	Traitement anti-TNF	Evolution
H 65 ans Immunocompétent	SNC, poumon	HRZE Dexaméthasone	13	SNC, foie	Réascension dose de corticothérapie	Adalimumab x 3	Guérison sans séquelles
H 41 ans Immunocompétent	SNC, poumon	HRZE Dexaméthasone	22	SNC	Poursuite corticothérapie fortes doses	Adalimumab x 8	Guérison avec séquelles
H 29 ans Immunocompétent	SNC, poumon	HRZE Dexaméthasone	14	SNC	Corticoïdes fortes doses (corticorésistance) Dérivation	Adalimumab x 18	Guérison avec séquelles
H 50 ans Immunocompétent	SNC	HRZE Dexaméthasone	30	SNC	Reprise corticothérapie fortes doses	Adalimumab x 4	Guérison avec séquelles
H 42 ans Immunocompétent	Disséminée (CNS, miliaire)	HRZE Dexaméthasone	12	SNC, foie	Poursuite corticothérapie fortes doses	Adalimumab x 4	Guérison sans séquelles

Conan P. *Données SMIT Saint-Louis non publiées*

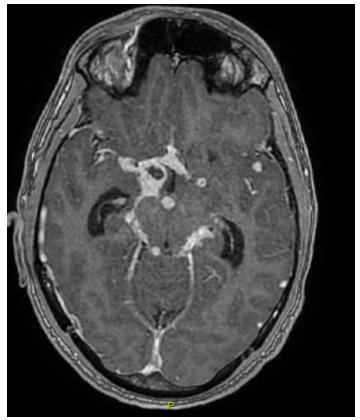
Cas 3
29 ans, VIH -, tuberculose méningée

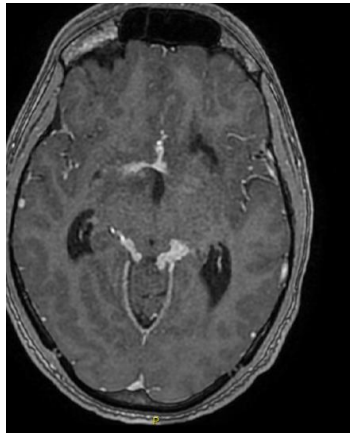
M0 anti-TB



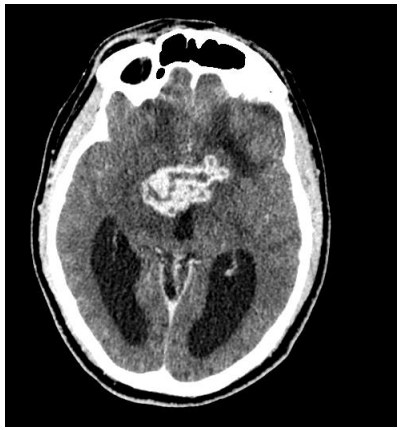


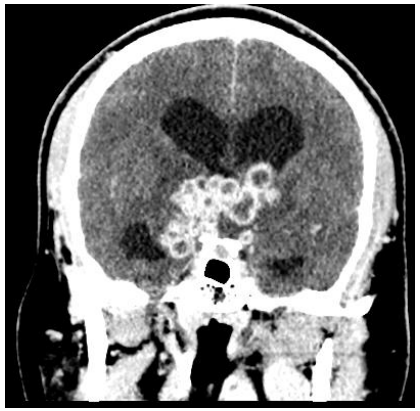
M1 anti-TB



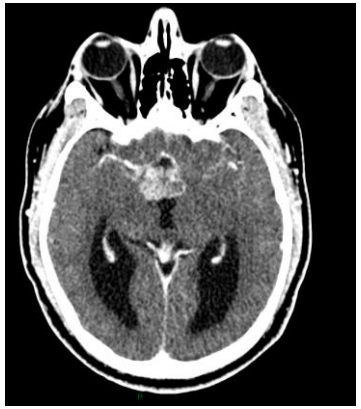


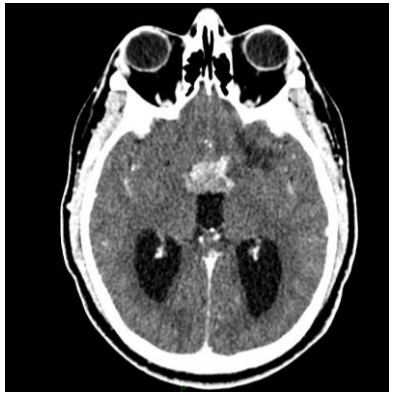
M12 anti-TB





Post-anti- TNF

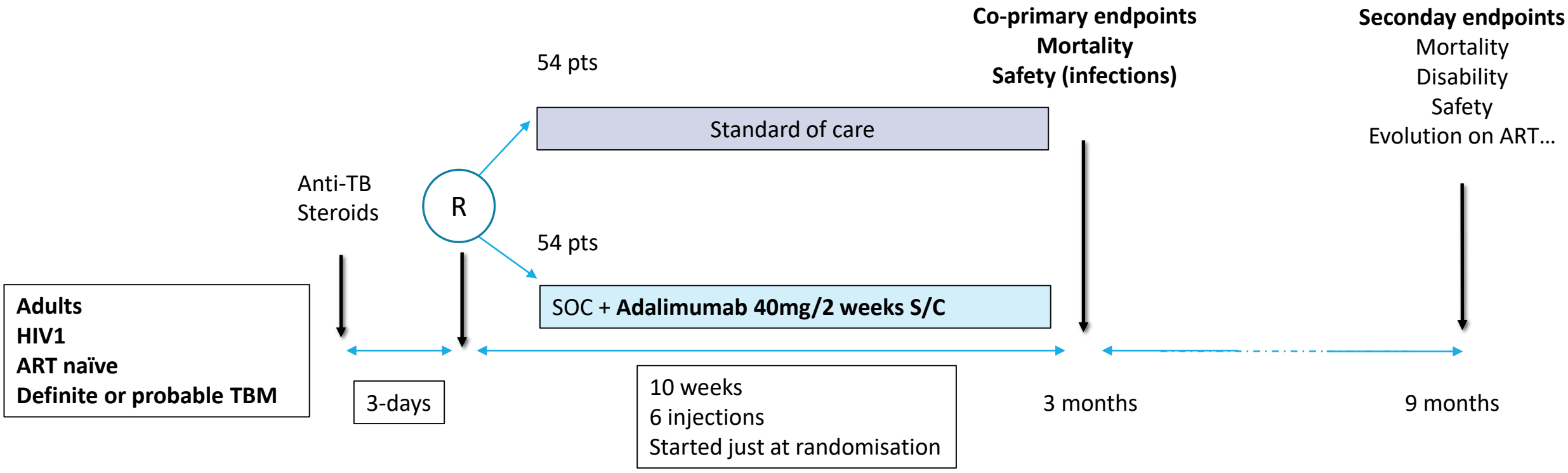




Tnf Inhibitors to reduce Mortality in HIV-1 infected PAtients with tuberculosis meNIngitis: a phase II, multicenter, randomized clinical trial

TIMPANI - ANRS 12 404

Study flowchart



En conclusion

- IRIS TB: entité bien décrite chez les patients VIH
  - Fréquent car initiation des ARV de plus en plus précoce
  - Pronostic et difficultés de prise en charge différents selon le pays où on se trouve
  - « Spectaculaire » et traitement parfois difficile mais mortalité directement imputable probablement faible en dehors des atteintes neurologiques.
  - Morbidité importante
  - Faut-il vraiment débuter corticothérapie systématique si CD4<100/mm^3?
- Traitement des IRIS TB sévères (TBM+++)
  - Corticothérapie en première intention
  - Anti-TNF si
    - Contre-indication, échec de la corticothérapie, corticodépendance
    - Effets secondaires de la corticothérapie
- Systématique dans la TBM?

Obrigada!

TB paradoxales
Avant la pandémie de VIH

Dès l'apparition des traitements antituberculeux (enfant)

- Méningite
- TB ganglionnaire
- Aggravation images pulmonaires

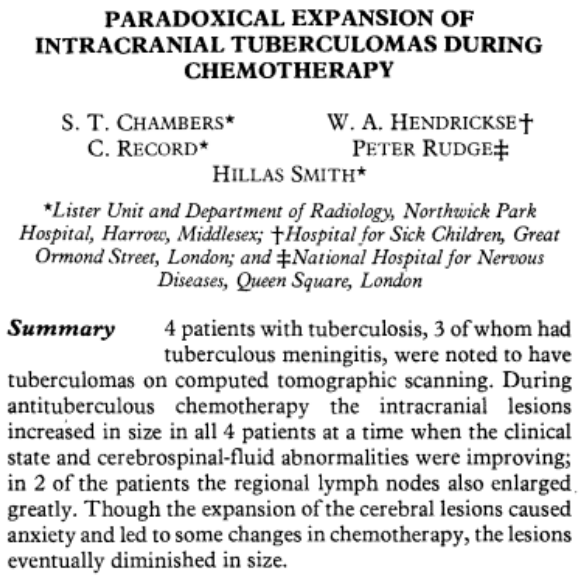
Temporaire et sans gravité

Gravité:

- Neurologique++
- SDRA/miliaire (exceptionnel)

Traitement :

- Corticoïdes
- (Thalidomide)



PARADOXICAL EXPANSION OF INTRACRANIAL TUBERCULOMAS DURING CHEMOTHERAPY

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C. RECORD* PETER RUDGE‡
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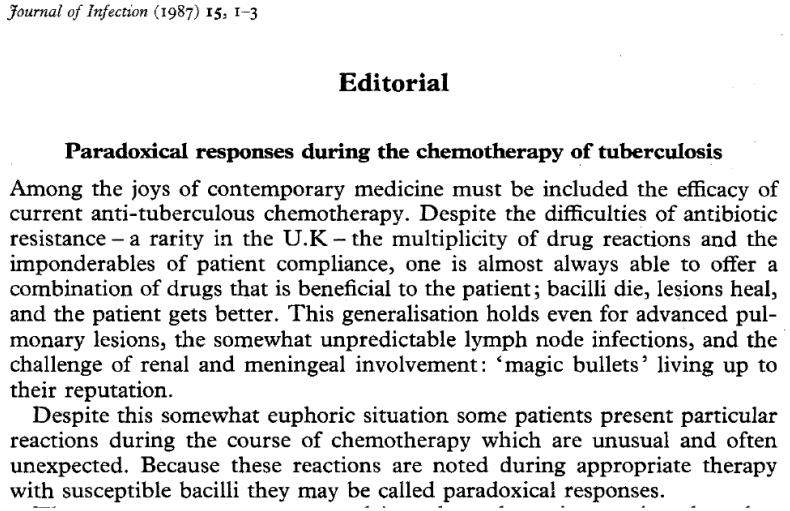
Summary 4 patients with tuberculosis, 3 of whom had tuberculous meningitis, were noted to have tuberculomas on computed tomographic scanning. During antituberculous chemotherapy the intracranial lesions increased in size in all 4 patients at a time when the clinical state and cerebrospinal-fluid abnormalities were improving; in 2 of the patients the regional lymph nodes also enlarged greatly. Though the expansion of the cerebral lesions caused anxiety and led to some changes in chemotherapy, the lesions eventually diminished in size.



Journal of Infection (1987) **15**, 1–3

Editorial

Paradoxical responses during the chemotherapy of tuberculosis

Among the joys of contemporary medicine must be included the efficacy of current anti-tuberculous chemotherapy. Despite the difficulties of antibiotic resistance – a rarity in the U.K – the multiplicity of drug reactions and the imponderables of patient compliance, one is almost always able to offer a combination of drugs that is beneficial to the patient; bacilli die, lesions heal, and the patient gets better. This generalisation holds even for advanced pulmonary lesions, the somewhat unpredictable lymph node infections, and the challenge of renal and meningeal involvement: 'magic bullets' living up to their reputation.

Despite this somewhat euphoric situation some patients present particular reactions during the course of chemotherapy which are unusual and often unexpected. Because these reactions are noted during appropriate therapy with susceptible bacilli they may be called paradoxical responses.

Chambers AT. *Lancet* 1984
Smith H. *J Infect* 1987

IRIS à l'arrêt des anti-TNF

INTERNAL MEDICINE

□ CASE REPORT □

Central Nervous System Manifestations of Tuberculosis-associated Immune Reconstitution Inflammatory Syndrome during Adalimumab Therapy: A Case Report and Review of the Literature

Toru Tanaka[1,2], Akimasa Sekine[1], Yoshiya Tsunoda[1], Hiroyuki Takoi[1], Shin-Yuan Lin[1], Yohei Yatagai[1], Kenji Hayasihara[1] and Takefumi Saito[1]

Intern Med 54: 847-851, 2015 DOI: 10.2169/internalmedicine.54.2828

Table. **Reports of the Development of IRIS Following the Discontinuation of Anti-TNF Therapy in the Previous Literature and the Current Case**

TNF antagonist	Case	Gender	Age	Underlying disease	Clinical manifestations of TB at diagnosis	Time to IRIS	Clinical manifestation of IRIS	Specific treatment for IRIS	outcome	Reference
adalimmab										
	1	F	17	SAPHO syndrome	Disseminated (miliary TB, pleural and pericardial effusion, brain tuberculomas, and meningitis)	4 weeks	Worsening meningitis and brain tuberculomas	Corticosteroids, ventriculo-peritoneal shunt	alive	1
	2	M	32	Proriasis	Disseminated (milliary TB and lymph node disease)	8 weeks	New-onset lymphadenopathies at several sites	None	alive	6
	3	F	29	RA	Pulmonary TB	13 days	Worsenig lung infiltrate	Corticosteroids (PSL 2.0 mg/kg), readministration of adalimumab	alive	9
	4	F	68	Inflammatory bowel disease	Disseminated (Multiple nodules in the liver and spleen)	4 weeks	New-onset lymphadenopathies at several sites and a cavity in the lung	None	alive	10
	5	F	64	RA	Disseminated (Miliary TB, lymph node disease, and multiple nodules in the kidney and spleen)	3 weeks	New-onset meningitis and brain tuberculomas, and reccurent lymphadenophathies at several sites	Corticosteroids (PSL 30mg/day)	alive	Our patient
infliximab										
	6	F	56	Ankylosing spondylitis	Disseminated (miliary TB, lymph node disease, and brain and splenic nodules)	12 weeks	Ruccurent lymphadenopathies at several sites	Corticosteroids (PSL 1.0mg/kg/day), tinzaparin	alive	2
	7	M	24	Crohn disease	Pulmonary TB	2 weeks	New-onset lymphadenopathies at several sites and miliary TB	None (continuation of PSL and AZA)	alive	3
	8	M	44	Ankylosing spondylitis	not descibed	4 weeks	Not described	Corticosteroids (PSL 1.0mg/kg/day)	alive	11
	9	M	20	Juvenile idiopathic arthritis	Disseminated (miliary TB)	24 weeks	New-onset meningitis and brain tuberculomas	Corticosteroids (PSL 75 mg/day), MTX, readministration of infliximab	alive	12
	10	F	49	RA	Disseminated (miliary TB and lymph node disease)	5 weeks	Worsening supraclavicular lymphadenopathy	Surgical excision of the lymph node disease	alive	13
	11	F	48	RA	Disseminated (miliary TB and lymph node disease)	8 weeks	New-onset lymphadonopathies at several sites	Surgical excision of the lymph node disease	alive	13
	12	M	56	Ankylosing spondylitis	Pulmonary and pleural TB	8 weeks	Worsenig infilitrates and pleural effusion	Corticosteroids (PSL 1.0mg/kg/day)	alive	13
	13	M	21	Chrohn disease	Anal TB	16 weeks	New-onset inguinal lymphadenopathy	NSAIDs	alive	13
	14	M	38	Chrohn disease	Disseminated (miliary TB and multiple nodules in the spleen)	12 weeks	New-onset lymphadenopathies at several sites	Surgical excision of lynph node disease	alive	14
	15	F	73	RA	Pulmonary and pleural TB	12 weeks	Worsening lung infiltrates	None	alive	15
	16	M	70	RA	Disseminated (Pleural effusion and ascites)	4 days	Reaccumulation of pleural effusion	Corticosteroids (PSL 60mg/day)	alive	16

TNF: tumor necrosis factor, TB: tuberculosis, IRIS: immune reconstitution inflammatory syndrome, M: male, F: female, SAPHO: (synovitis, acne, pustulosis, hyperostosis, osteitis), RA: rheumatoid arthritis, PSL: prednisolone, MTX: methotrexate, AZA: azathioprine, NSAIDs: non-steroidal anti-inflammatory drugs

IRIS à l'arrêt des anti-TNF Cohorte Ratio

Table 1
Description of 14 immune reconstitution inflammatory syndrome (IRIS) cases occurring during anti-tumor necrosis factor (TNF)-associated tuberculosis (TB).

Patient	Age (years)	Underlying disease		Anti-TNF regimen		TB			IRIS			TB
		Inflammatory	Duration	Last dose	Weeks	TST/QTF-TBG®/chest X-ray before anti-TNF agent	LTBI	Symptoms	Wks to IRIS[a]	Symptoms	Treatment	therapy, months
1	60	RA	18 yr	Adalimumab	138	<5 mm/NR/normal	Yes	Disseminated	37	Cervical lymph-node fistula	CS,RTX,new anti-TB treatment	23
2	47	Psoriasis	15 yr	Certolizumab	10	<4 mm/NR/normal	No	Disseminated	5	Upper left pulmonary cavitation	CS	22
3	83	RA	20 yr	Infliximab	172	NR/NR/normal	No	Extrapulmonary	22	Thickening around the sigmoid/gluteal abscess/left femoral osteitis	New anti-TB treatment, surgery	18
4	54	AS	8 yr	Infliximab	7	>10 mm/NR/normal	No	Disseminated	13	Supraclavicular lymph-node fistula, cerebral tuberculomas	CS, surgery	16
5	87	PA	30 yr	Adalimumab	140	>10 mm/NR/calcifications	Yes	Disseminated	3	Mediastinal lymphadenopathy onset, fever	None	13
6	67	GCA/UC	2 yr	Adalimumab	8	<5 mm/NR/normal	No	Disseminated	4	Right pulmonary cavitation, pleurisy, mediastinal lymphadenopathy onset	None	8
7	39	AS	4 yr	Infliximab	21	<5 mm/NR/normal	No	Disseminated	19	C6–C7 tuberculomas, mediastinal necrotizing lymphadenopathy with superior vena cava compression	CS, new anti-TB treatment, surgery	27
8	28	BD	4 mo	Infliximab	6	<5 mm/negative/normal	No	Disseminated	2	Lymphadenopathy	CS	12
9	46	AS	21 yr	Infliximab	4	<5 mm/NR/normal	No	Disseminated	10	Parietal cold abscess, axillary lymphadenopathy	Surgery	16
10	29	AS	9 yr	Infliximab	9	NR/NR/normal	No	Disseminated	49	Pericarditis, mesenteric and mediastinal lymphadenopathies	CS, TB tritherapy	36
11	65	RA	24 yr	Etanercept	272	NR/NR/NR	NR	Disseminated	8	Mesenteric lymphadenopathy, new nodular pulmonary lesions	CS	NR
12	41	BD	10 yr	Adalimumab	61	NR/NR/normal	No	Pulmonary	3	Larger pulmonary lesions	None	NR
13	59	AS	7 yr	Infliximab	261	<5 mm/NR/NR	NR	Disseminated	2	Cerebral encephalitis	TB treatment stopped, CS	13
14	50	RA	5 yr	Adalimumab	54	<7 mm/NR/normal	No	Disseminated	0	Ascites, cerebral tuberculomas	CS	12

RA: rheumatoid arthritis; AS: ankylosing spondylarthritis; PA: psoriatic arthritis; GCA: giant-cell arteritis; UC: ulcerative colitis; BD: Behçet's disease; TST: tuberculin skin test; QTF-TBG: Quantiferon TB gold®, Cellestis, Melbourne; LTBI: latent TB-infection treatment; NR: not reported; CS: corticosteroids; RTX: rituximab.
[a] Interval between anti-TB treatment onset and IRIS symptoms.

- Tuberculoses disséminées
- Masses ganglionnaires compressives
- Tuberculomes cérébraux
- Tt IRIS : Stéroïdes