ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

Alloréactivité cellulaire et Humorale

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Hôpital Bichat

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Fréquence du Rejet en Tx pulmonaire

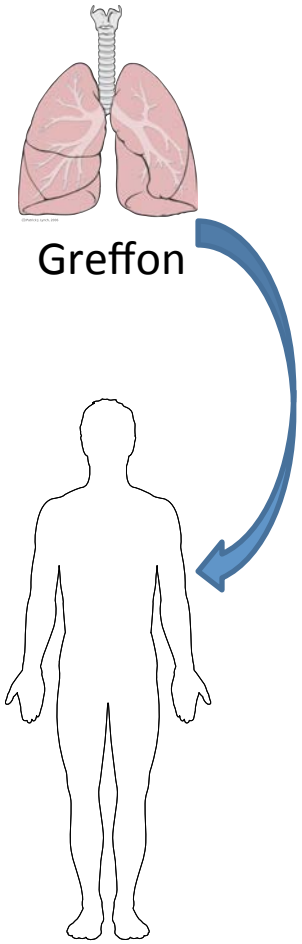
Table 1. – Chronic allograft dysfunction in solid organ transplantation

Organ	Pathological features	Incidence 5 yrs after transplant %
Liver	Vanishing bile duct syndrome	5
Kidney	Glomerular sclerosis/tubular atrophy	30
Heart	Coronary artery sclerosis	20
Lung	Bronchiolitis obliterans	50–60

Tx pulmonaire: incidence du rejet la plus élevée comparée aux autres greffe d'organe

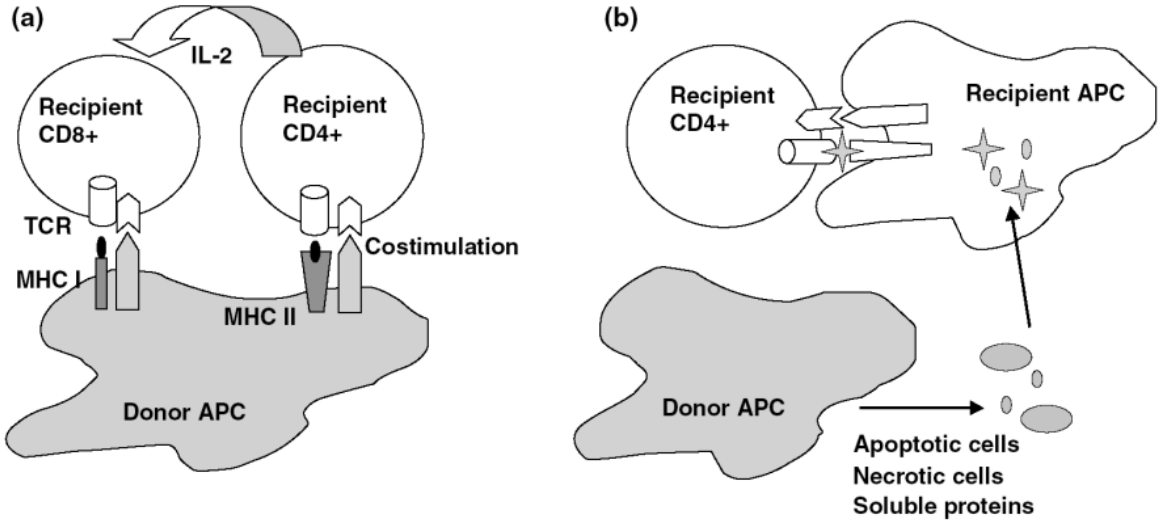
Rejet aigu cellulaire

Mécanismes cellulaires du rejet de greffe



(a) Présentation directe de l'Ag

(b) Présentation indirecte de l'Ag



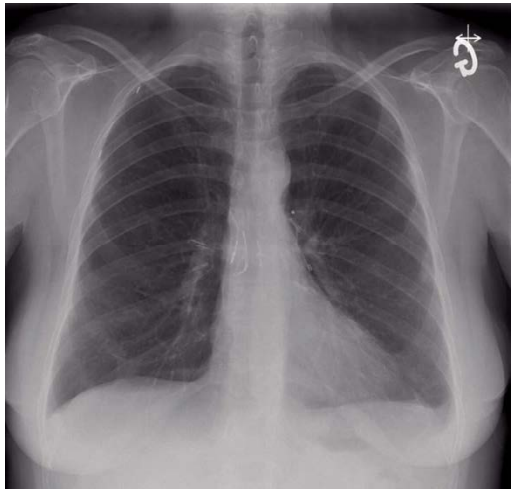
Reconnaissance du non-soi via système HLA/CMH

Rejet aigu cellulaire

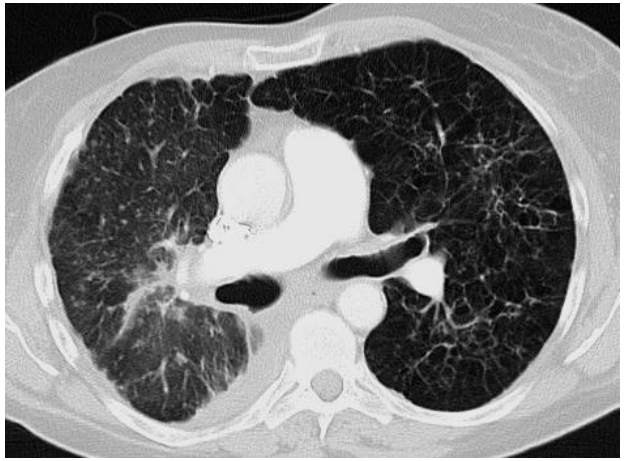
Présentation clinico-radiologique du rejet aigu classique

Non spécifique

RA précoce: 80% des cas bruyant / tardif : plus souvent insidieux
- Dyspnée, Fièvre, signes bronchiques…
- Baisse VEMS et paO2
- RX/TDM non spécifiques



Rx normale



Signes TDM aspécifiques
verre dépoli en mosaïque péribronchique
Reticulations
Epanchement pleural

Indication Fibroscopie avec biopsies transbronchiques + LBA

Rejet aigu cellulaire

Diagnostic de confirmation du rejet aigu cellulaire
= histologie des BTB

Infiltration Lymphocytes périvasculaire
= RA classique (grade A)

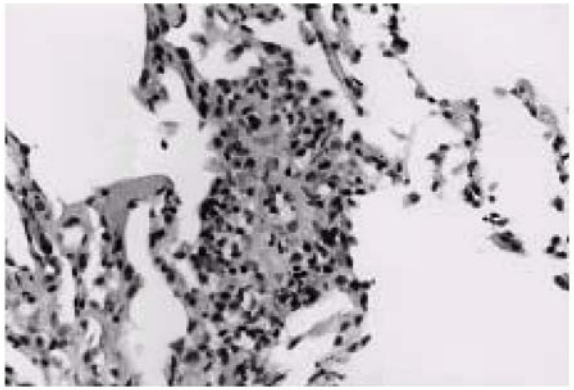


Fig. 2. – A dense perivascular infiltrate of mononuclear cells including small and large lymphocytes and macrophages with intimitis. The infiltrate does not extend into adjacent alveolar walls and the alveolar spaces are clear. Grade A2 acute rejection. Haematoxylin and eosin.

Infiltration lymphocytaire bronchiolaire
RA Bronchiolaire (grade B)

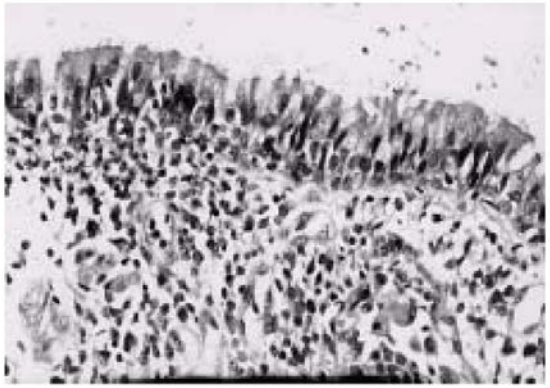


Fig. 5. – Bronchiolar mucosa showing a diffuse infiltrate of lymphocytes in subepithelial tissue and within the epithelium itself. The ciliated respiratory epithelial cells are intact with no evidence of ulceration or metaplasia. Grade B2 acute airways rejection. Haematoxylin and eosin.

Dogme jusqu'aux années 90's = Le rejet de greffe est médié par les Lymphocytes T

Rejet aigu cellulaire

Prévention : Traitement anti-rejet

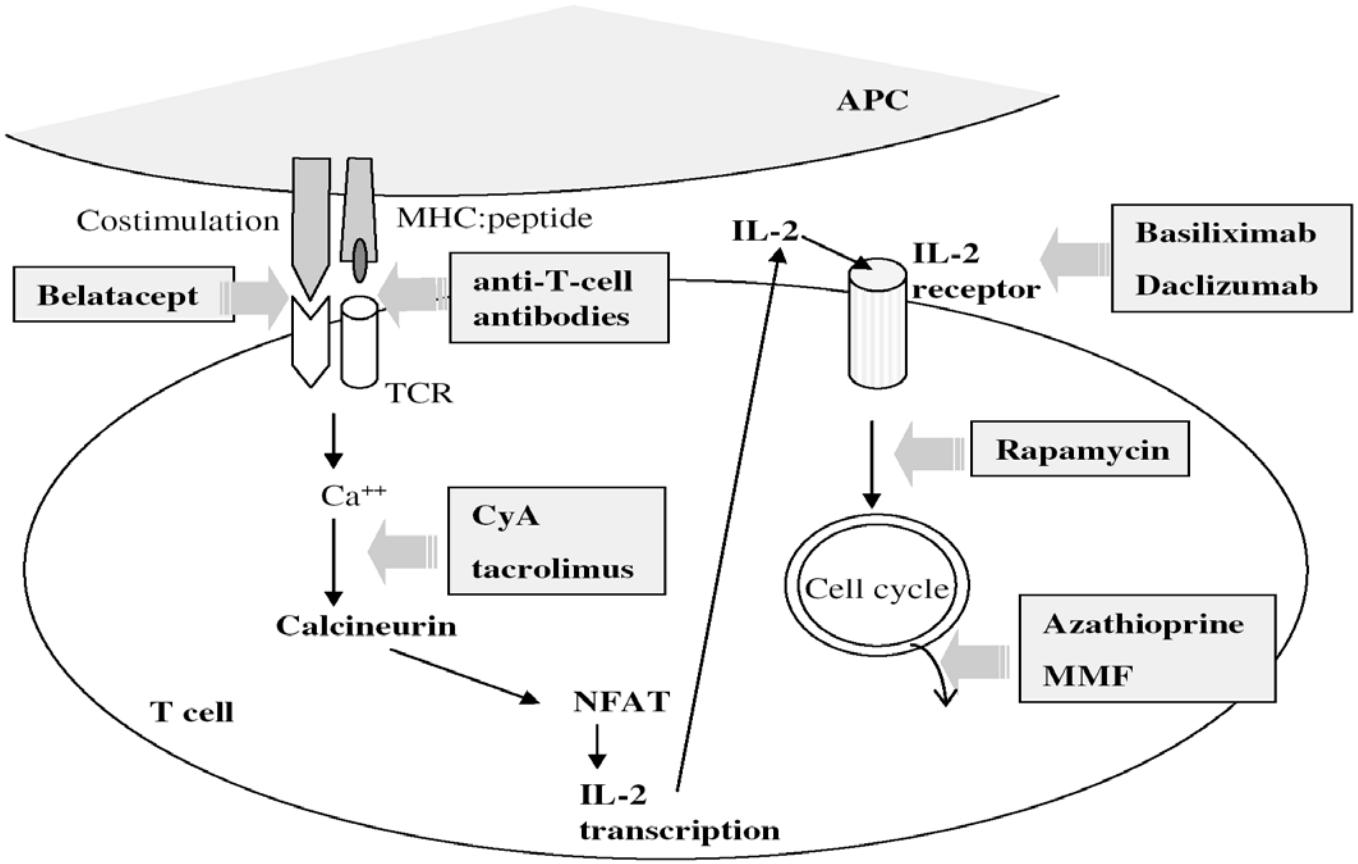
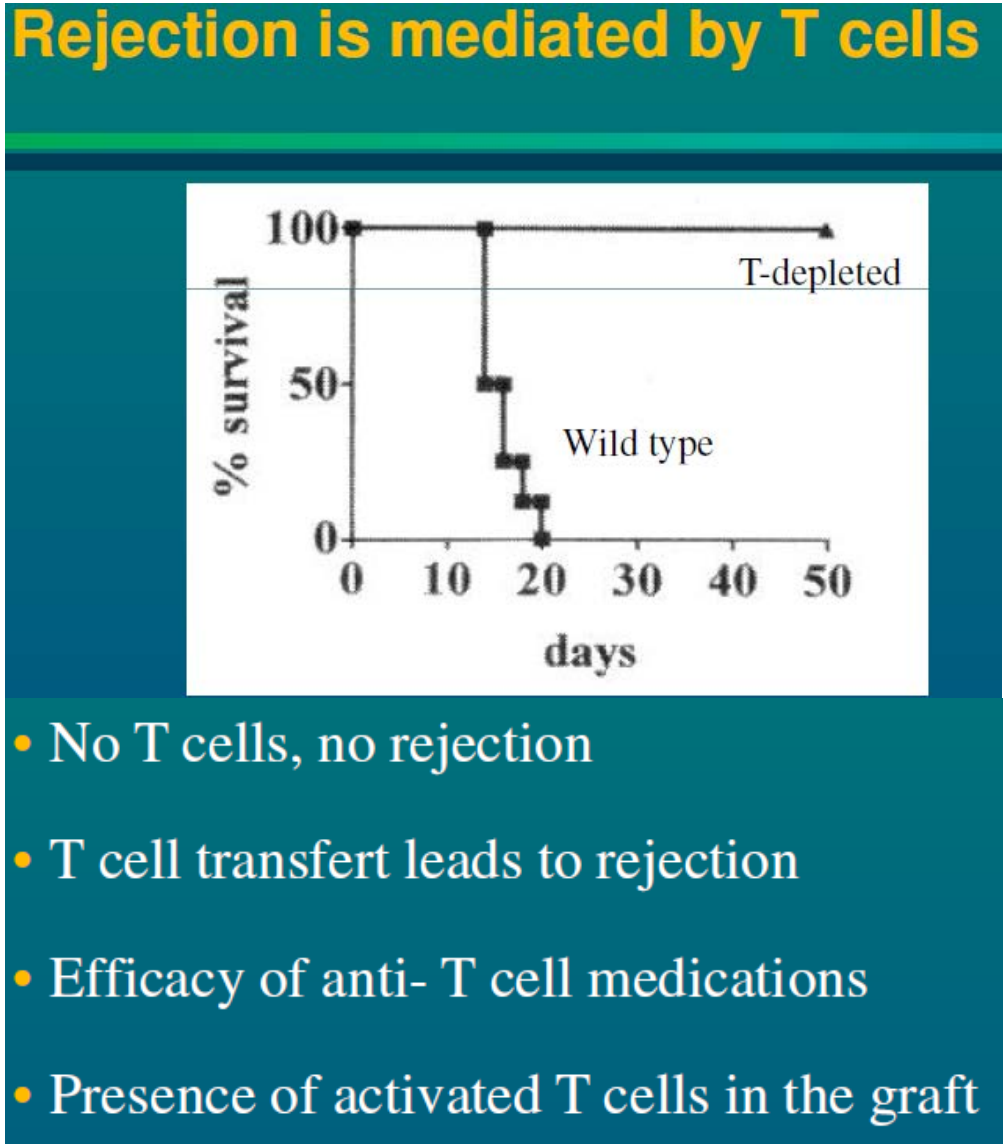


Figure 2 Targets for current immunosuppressive drugs. Signal 1 is delivered through the T-cell receptor (TCR) by recognition of peptide antigens presented in the context of major histocompatibility complex (MHC) molecules on the antigen-presenting cells. This stimulation results in calcineurin activation, a process blocked by cyclosporine A or tacrolimus. Activated calcineurin dephosphorylates the nuclear factor of activated T cells so that it can enter the nucleus and bind to the interleukin-2 (IL-2) promoter. Costimulatory signals (signal 2) are necessary for optimal IL-2 gene transcription in the T cell. IL-2 receptor stimulation induces the T cell to enter cell cycle and proliferate; this can be blocked by IL-2 receptor antibodies or by rapamycin which inhibits signalling induced by IL-2 receptor ligation. By blocking purine synthesis, azathioprine and mycophenolate mophetil MMF interrupt DNA replication and cell proliferation.

Rejet aigu cellulaire

Historique (1) : Tx organe solide < années 2000



Rejet aigu humoral

Rôle destructeur AC anti-HLA préTx démontré: rejet suraigu

Evènement rare mais le plus souvent fatal

Hyperacute Rejection Following Lung Transplantation*

Adaani E. Frost, MD; Cory T. Jammal; and Philip T. Cagle, MD

Table 1—*HLA Status*

Patient Type	Donor Antibody
A2	A1
A11	Ablank
B35	B8*
C4	C4
C3	CBlank
DR11	DR15
DR13	DR17

*Donor antigen to which patient reacted.

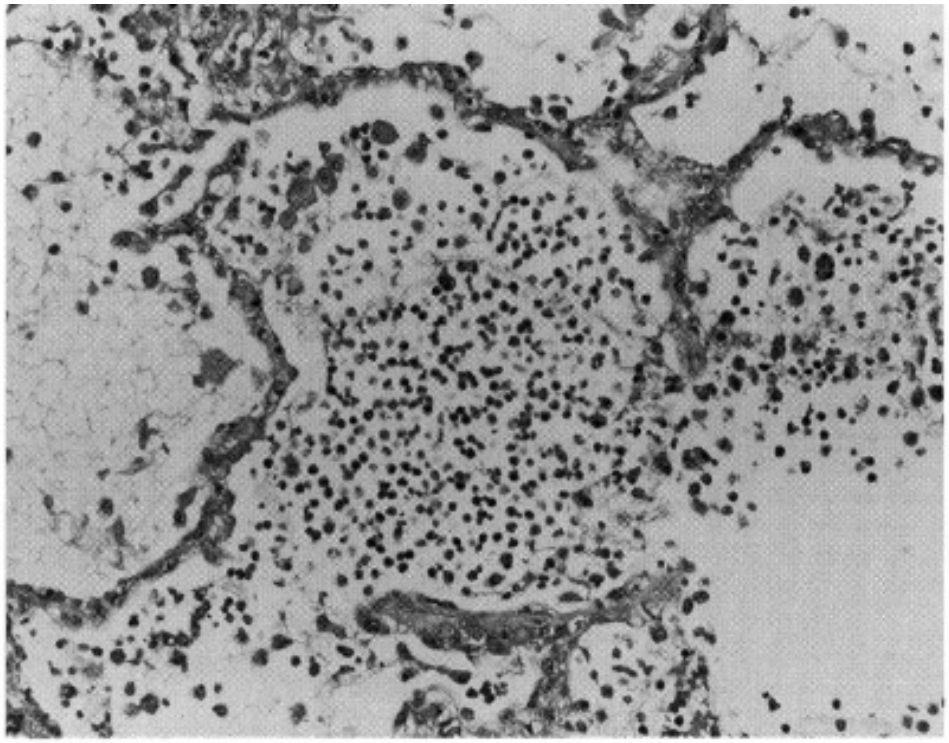
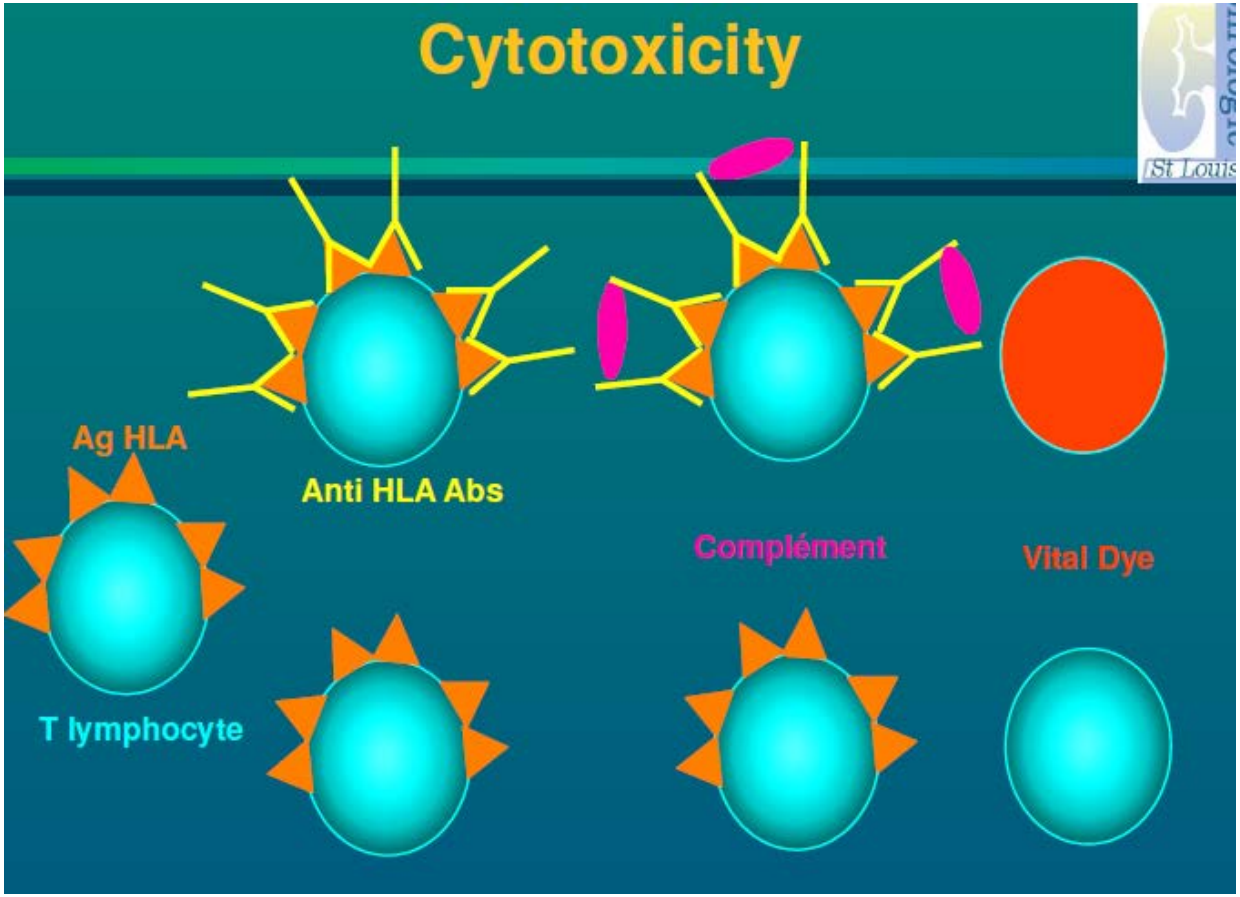


FIGURE 1. Intra-alveolar hemorrhage (hematoxylin-eosin, original ×300).

Rejet aigu humoral

Détection des AC anti-HLA

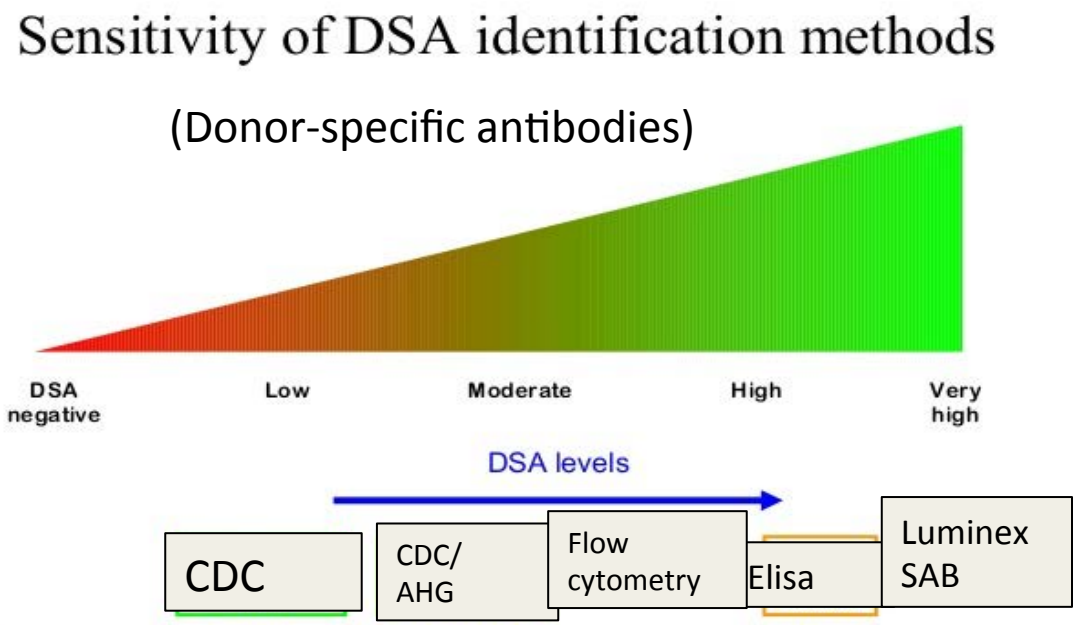
CDC complement-dependent cytotoxicity < année 2000



Détection d'AC anti HLA via CDC= 2% des patients

Rejet aigu humoral

2000's = technique Luminex pour détection AC anti-HLA



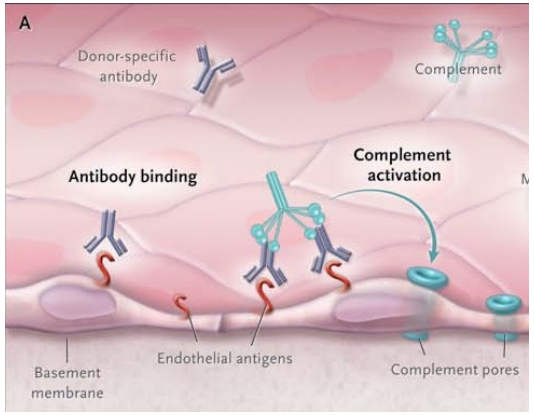
	< année 2000 CDC = cytotoxicité complément -dépendante	> 2000 Luminex
% de patients avec AC anti-HLA post-Tx	2-3%	13%-60%

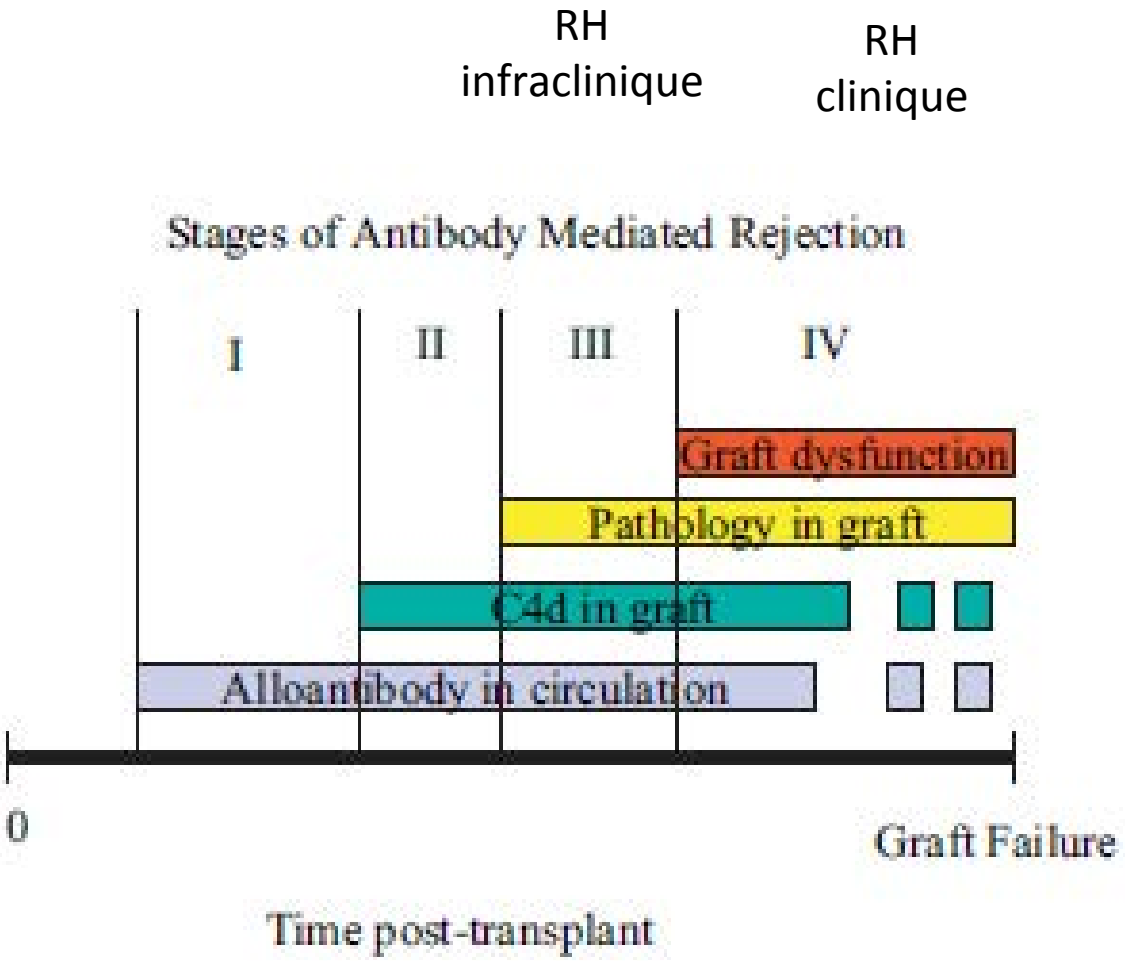
(1) Hachem 2010, (2) Brugière 2013, (3) Morell 2014, (4) Snider 2013 Tikkanen (2016, Le Pavec 2016.

Rejet aigu humoral

2000: Identification du Rejet humoral en Tx rénale

Responsable de > 50% perte du greffon rénale





Robert B. Colvin *J Am Soc Nephrol* 2007

Théorie humorale de l'immunité en Tx

Rejet aigu humoral

Rejet médié par anticorps en Tx pulmonaire

2013

EDITORIAL COMMENTARY

Antibody-mediated rejection in lung transplantation: Turning myth into reality

Allan R. Glanville, MBBS, MD

From the Lung Transplant Unit, St. Vincent's Hospital, Sydney, New South Wales, Australia.

2016

ISHLT CONSENSUS REPORT

Antibody-mediated rejection of the lung: A consensus report of the International Society for Heart and Lung Transplantation

Deborah J. Levine, MD,[a] Allan R. Glanville, MBBS, MD,[b]

Glanville JHLT 2013, Levine D, JHLT 2016

Rejet aigu humoral
= Place clinique en Tx pulmonaire

2016: reste mal définie

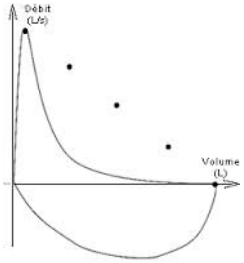
Littérature: 10 cas cliniques, 5 cases-series

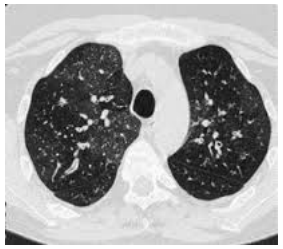
R.Humoral	N (%)	DSA	Histo	C4d	TTT	Outcome
Witt 2013	21 (4%)	+	+	+	PP, IVIg ritux	71% deaths (6 AMR, 9 CLAD)
Daoud 2013	2 (3%)	+	+	+	PP, IVIg, ritux	alive
Ottani 2014	9 (4%)	+	+/-	+/-	PP, IVIg, ritux	6 deaths CLAD (66%)
Lobo 2013	10 (19%)	+	Not detailed	ND	ND	5 deaths (AMR)
Roux A 2016	22 (10%)	+	+ or C4d+	+ or histo+	PP, IVIg, ritux	57% graft loss

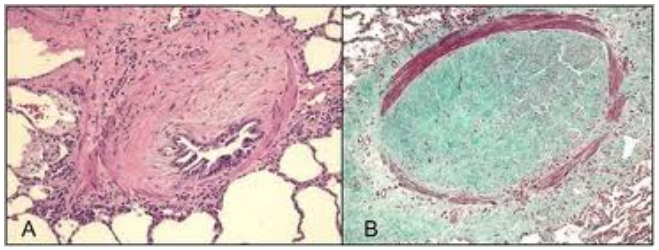
Rejet chronique: obstructif

s'intègre dans la « Dysfonction chronique du greffon »= CLAD*

- Principal phénotype de CLAD: bronchiolite oblitérante 80%

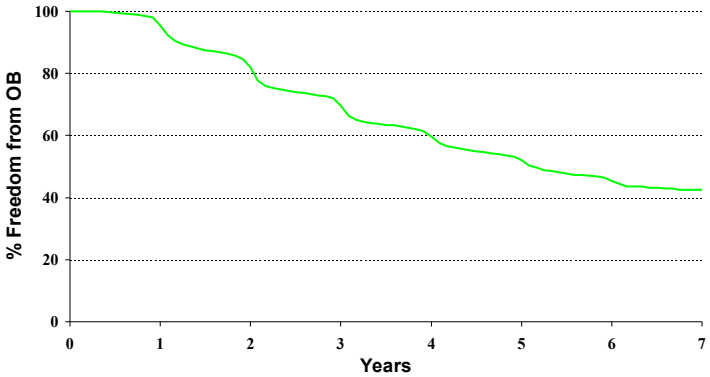






- Syndrome obstructif progressif/bronchiolite = définition fonctionnelle

50% des greffés à 5 ans. 1ère cause de mortalité



*BOS= chronic allograft dysfunction

Rejet chronique obstructif

Présentation de la BO post-TxP

Baisse spirométrique isolée, puis DE, signes bronchiques

Phase tardive: colonisation/infection

(*Pseudomonas* spp, *Staphylococcus* spp *Aspergillus* spp)

Mode de progression variable

- déclin rapide ou insidieux VEMS
- Phase de plateau

Evolution vers décès par Ins. Respir.

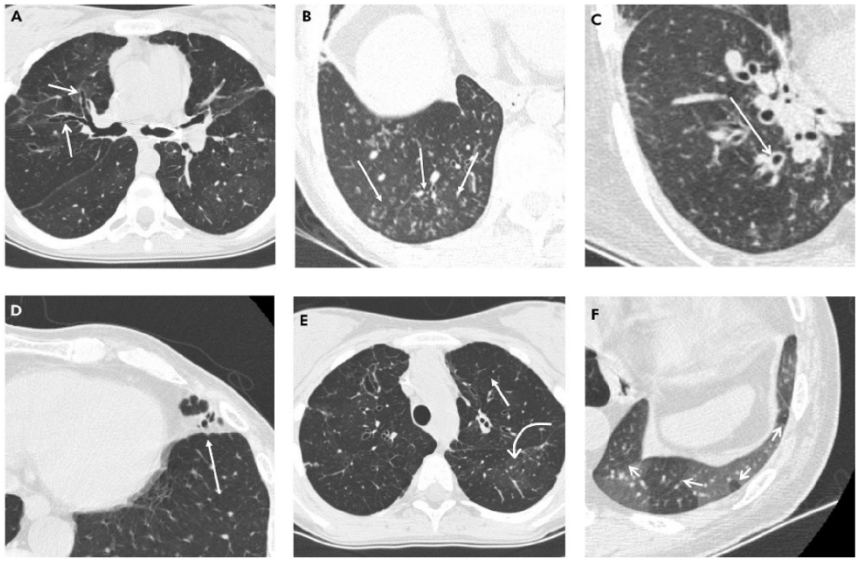


Figure 1 Representative CT images showing the CT_{BO} scoring system abnormalities. A collection of transaxial 1.25 mm CT sections in different patients viewed at lung window and level setting (width 1500 HU, level −500 HU) showing (A) bronchiectasis (arrows) identified by the absence of normal bronchial diameter tapering; (B) peripheral mucus plugging shown as multiple centrilobular nodules (arrows); (C) dilated bronchus with associated wall thickening (arrow); (D) lingular consolidation (arrow) shown as an area of increased density obscuring the underlying pulmonary vasculature; (E) generalised mosaic pattern in both upper lobes shown by areas of decreased attenuation and vessel size (straight arrow) compared with regions of normal attenuation and normal vessel size (curved arrow); and (F) expiratory image showing areas of air trapping (arrows).

Rejet chronique obstructif

Facteurs de risque de BO/CLAD

Alloimmuns

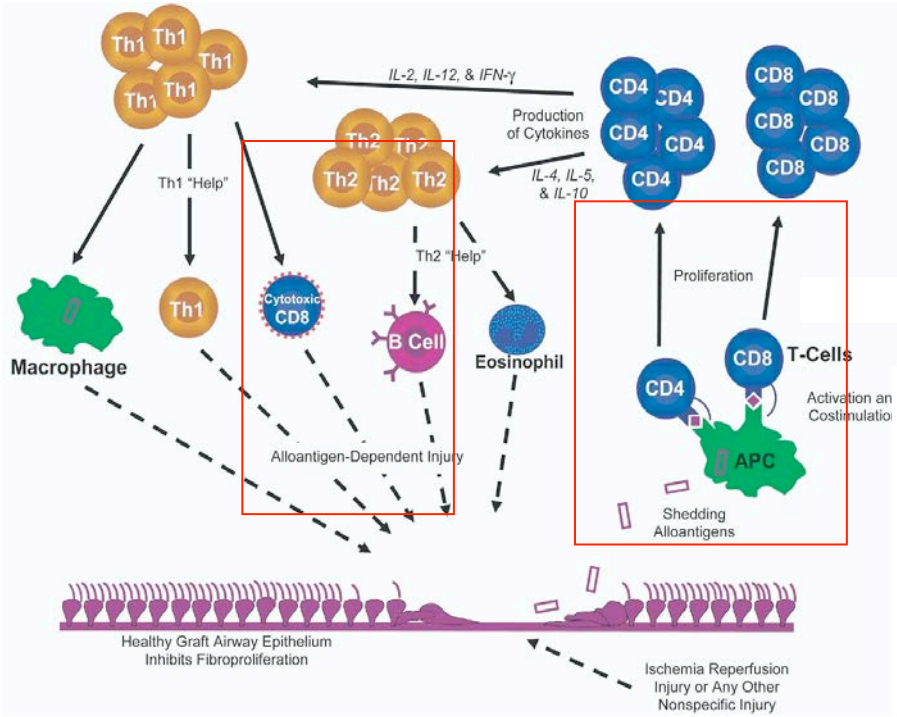
- Rejet aigu cellulaire (A)
- Rejet aigu bronchiolaire (B)
- Mismatch Ag HLA donneur/receveur
- AlloAC anti-HLA (cf infra)

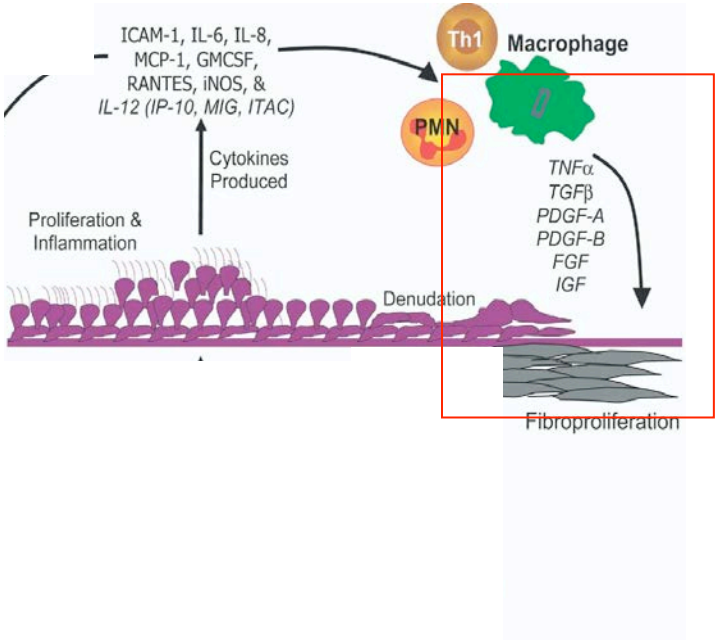
Non alloimmuns

- Pneumopathie à CMV
- Ischémie reperfusion du greffon sévère grade 3
- Viroses respiratoire communautaire
- Reflux gastro-oesophagien
- Auto-immunité (Collagène V, K-alpha tubuline)

Rejet chronique obstructif
mécanismes cellulaires Physiopathologie de la BO

Lésions de l'épithélium et prolifération/différentiation lymphocytaire (1) → **Fibroprolifération**





- Autres voies : Axe TH-17, /l'IL-17/neutrophilie alvéolaire

(1) Neuringer 2005

Rejet chronique obstructif = rôle des AC

Association DSA (donor-specific Abs) et incidence de BO = HR le plus élevé

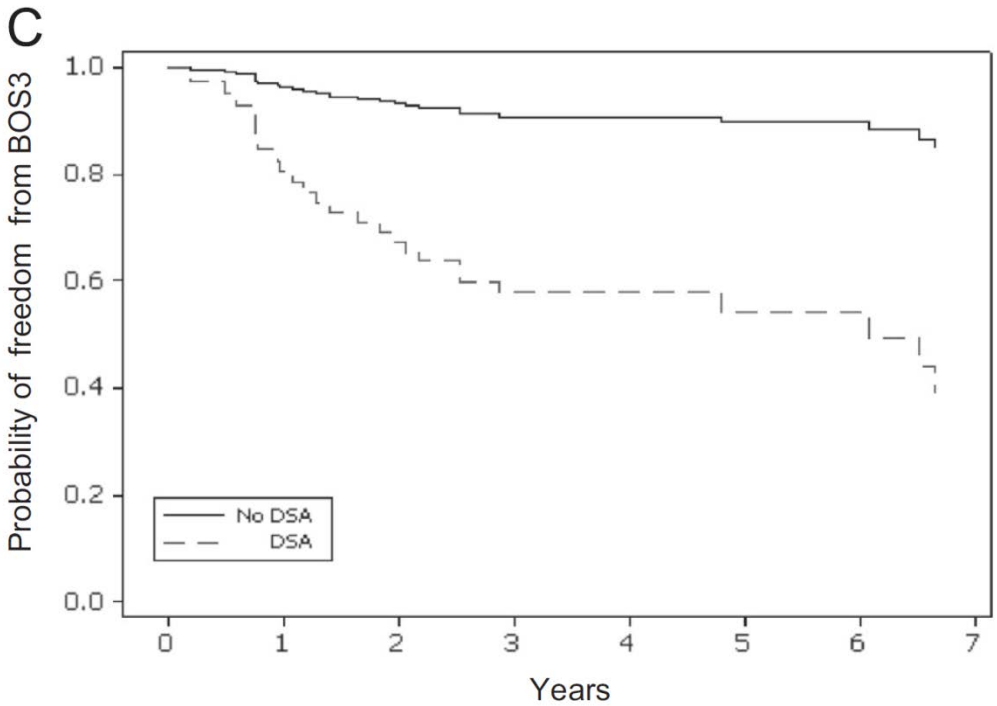


Figure 1 Survival curves based on the fitted Cox model with (C) Decreased tim_to BOS3.

N = 148

Variable
De novo DSA
De novo persistent DSA
Diagnosis
Cystic fibrosis
Emphysema
Fibrosis
Pulmonary hypertension
Other
Transplant type: single lung
Ischemic time
Pre-transplant HLA: NDSA
Recipient age
Recipient female
Donor age
Donor female
Donor CoD not brain pathology
HLA mismatch
HLA-A/B MM 0/1
HLA-A/B MM 2
HLA-A/B MM 3/4
HLA-DR/DQ MM 0/1
HLA-DR/DQ MM 2
HLA-DR/DQ MM 3/4
Crossmatch; IgM non-HLA
CMV status
R^-/D^-
R^+/D^+
R^-D^+
R^+/D^-
Primary graft dysfunction
Rejection
Persistent rejection
Infection
Persistent infection
Immunosuppressant switch
Tacrolimus
MMF
Sirolimus

ORIGINAL CLINICAL SCIENCE

De novo donor HLA-specific antibodies predict development of bronchiolitis obliterans syndrome after lung transplantation

Shahideh Safavi, 2014
J Heart Lung Transplant

Prise en charge 2017 de la BO/CLAD

Classique = freine l'évolution:

- Augmentation/modification de l' immunosuppression = décevant

–Inh mTOR? CS inhalés: Stéroides, CsA

–Bolus de solumédrol/thymoglobulines/

–Azithromycine: active sur BO avec neutrophilie >30%

–Chir anti-reflux

En cours d'évaluation:

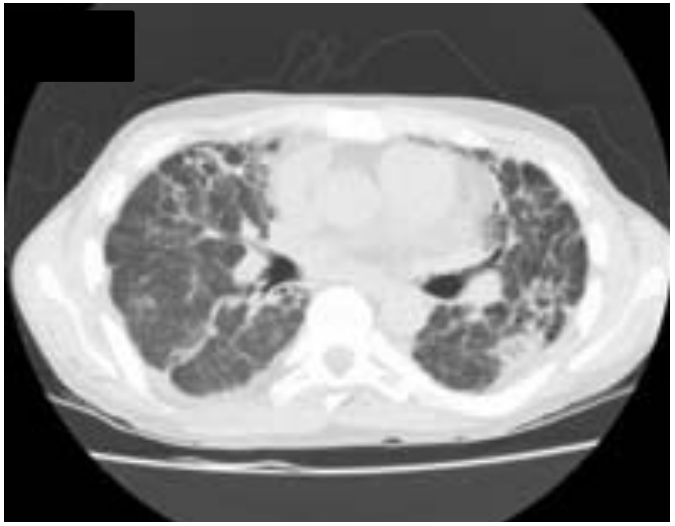
- Déimmunisation précoce si AC anti-HLA: IVIg, EP, ritux
- Inh signal de co-stimulation (belatacept)
- Photophérèse = induction TREG
- Médicaments anti-fibrosant: Nintedanib/Pirfenidone

Toujours à évaluer

- ReTx pulmonaire

Rejet chronique restrictif: 20%

Restrictive allograft syndrome (RAS): A novel form of chronic lung allograft dysfunction (CLAD) (1) environ 20% des CLAD



Images réticulaires interstitielles sur RP et TDM
+ consolidation sur TDM

Définition Fonctionnelle

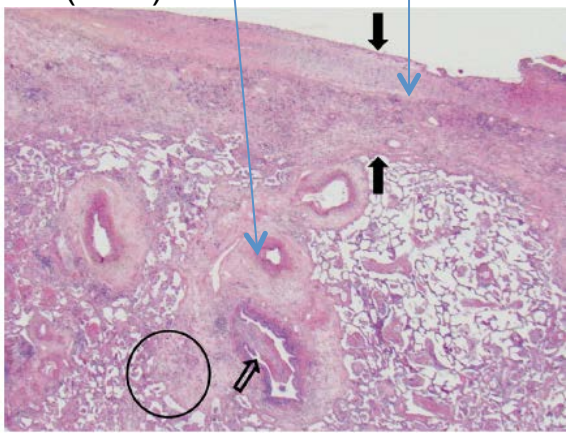
TLC< 90% of baseline
Or FVC <80% of baseline
Or FEV1<80% + tiffeneau > 0,7

+/- associée à TDM:

Verre dépoli, réticulations, pleurésie, prédominance sous pleurale

Histologie pleiomorphe (2)

- pleuroparenchymal fibroelastosis (PPFE) =90%
- Bronchiolitis obliterans (BO) 50%
- Diffuse alveolar damage
- Fibroblastic foci (37%)



(1) Sato. J Heart Lung Transplant 2011

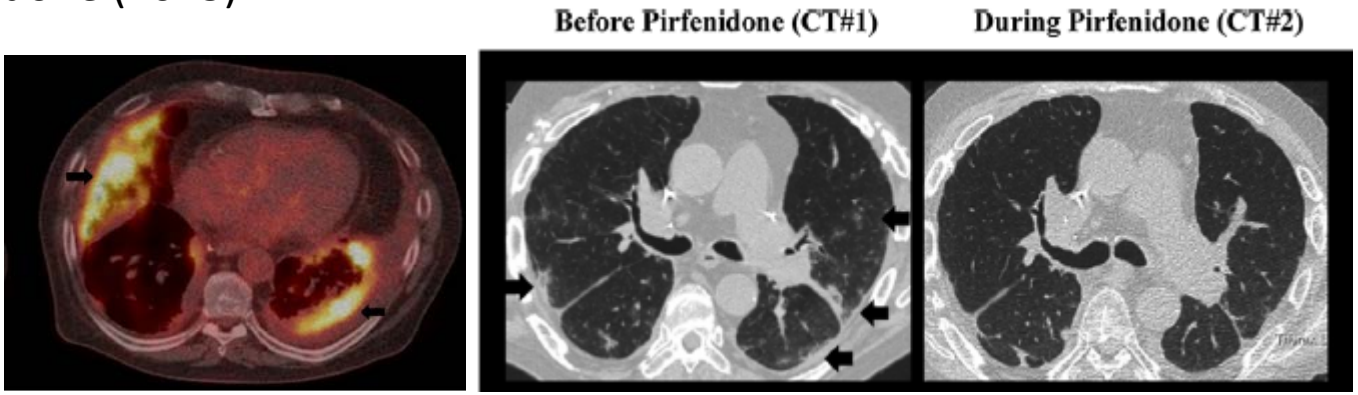
(2) Ofek E, 2013

Rejet chronique restrictif

Quel traitement pour le RAS ?
= Fibro-élastose pleuro-parenchymateuse post-TxP

- ❑ Majoration IS (bolus solumédrol, thymoglobuline)= décevant
- ❑ Traitement anti-fibrosant ?

1- Pirfinidone (2013)



2- Nintédanib (2016)

(1) Vos R. AJT 2013; (2) Suhling H. JHLT 2016

Conclusion
Rejet en Tx pulmonaire

- Incidence élevée de rejet/dysfonction chronique
- 2000: Identification du rôle crucial de l'immunité humorale
- 2001: identification d'une forme fibrosante de rejet chronique
- Nouveaux traitements de forme aiguë et chronique du rejet:
  - anti-fibrosant
  - désimmunisation
  - inh 2è signal activation Ly

Rejet aigu humoral *Historique (2):*

Rôle destructeur des AC anti-HLA démontré 1969

1969 Patel R, Terasaki PI.
Significance of the positive crossmatch test in kidney transplantation. *N Engl J Med* 1969; 280: 735-739

« The presence of recipient antibodies to antigens expressed on donor white cells is a major risk factor for immediate graft loss »

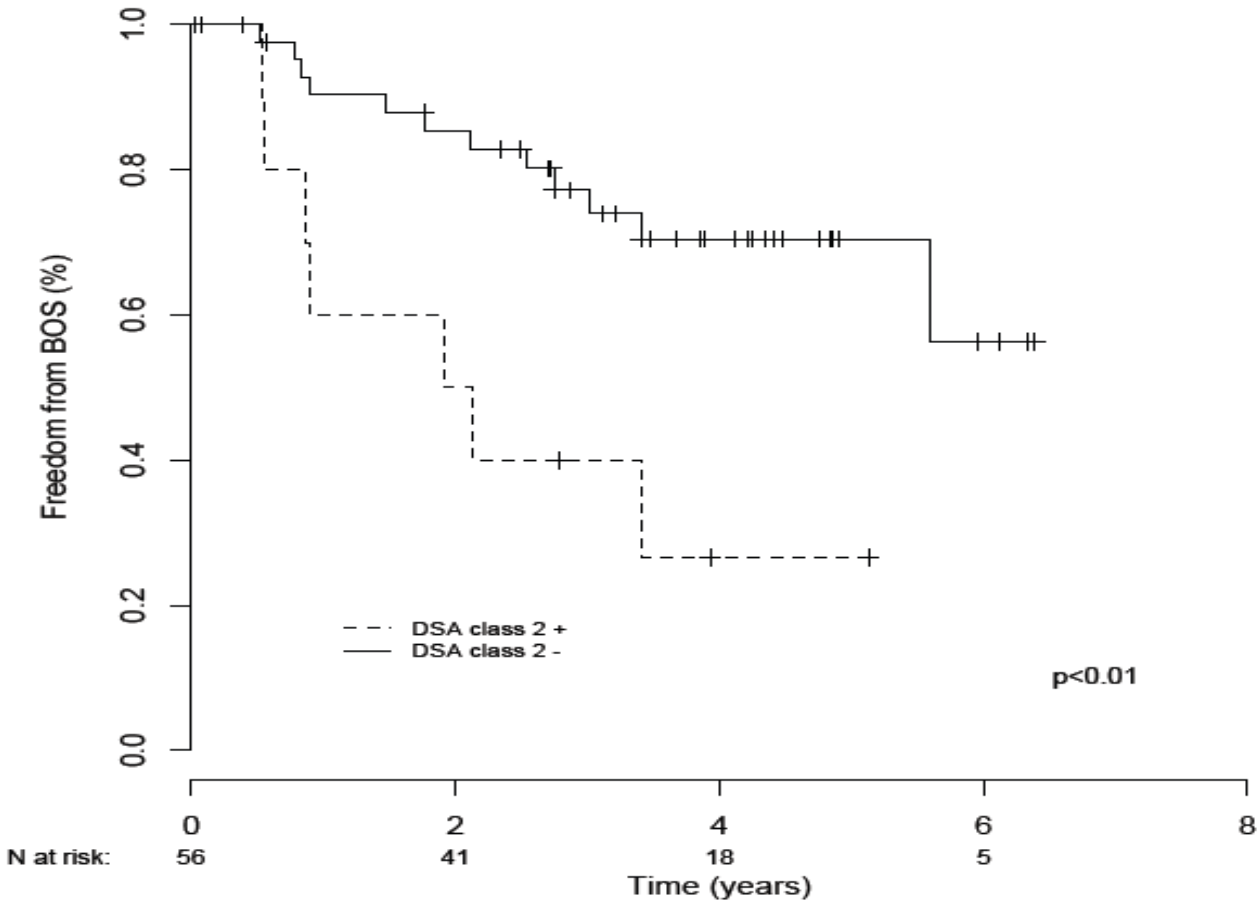
Hyperacute rejection

225 transplants :

= 24/30 with positive CXM failed to function immediately (minutes), in contrast to 8/ 195 with negative CXM($p < 0.001$).

Rejet chronique obstructif

DSA préformés et incidence de BO post-TxP



La survie indemne de BOS étaient inférieure en cas de DSA class II (p = 0.004)
Hypothèse d'un rejet humoral infra-clinique.

Brugière O. Transplantation 2013