Hôpitaux Universitaires Genève

UNIVERSITÉ DE GENÈVE
FACULTÉ DE MÉDECINE

Anticorps monoclonaux utilités pratiques

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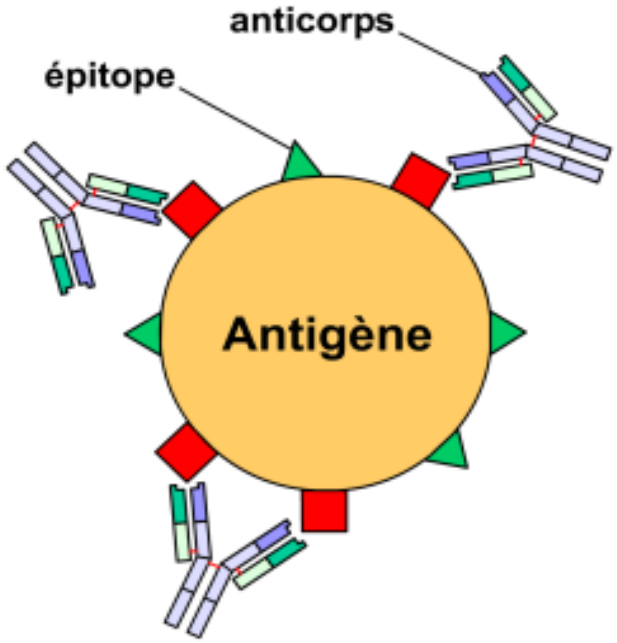
Hôpital de SION

Jean Villard MD,PhD

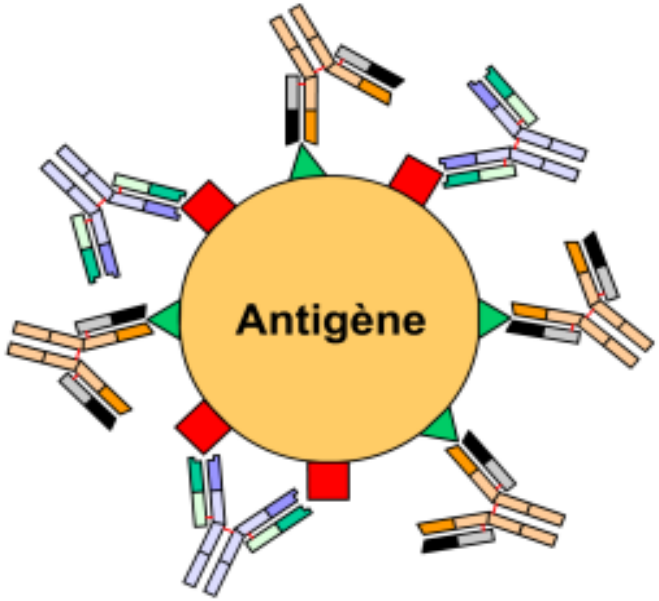
Unité d'Immunologie de Transplantation ,
Service de néphrologie
Service de Médecine de Laboratoire
HUG, Genève

Anticorps monoclonaux

Anticorps monoclonaux



Anticorps polyclonaux



HISTORIQUE

- Début du XX^{ème} siècle
  - utilisation des anticorps en sérothérapie ou en séroprophylaxie
  - Von Behring découvre la protection conférée par les anticorps anti-diphtériques
  - utilisation des immunoglobulines spécifiques animales dans le traitement de nombreuses maladies infectieuses
- Abandon de cette immunothérapie:
  - progrès de la Vaccination et de l'Antibiothérapie
  - survenue de la maladie sérique

- Vers 1960, utilisation d'anticorps hétérologues du sérum de cheval anti-lymphocytaire (SAL), dans la prévention et le traitement du rejet de greffe

- Tournant en 1975:
  - découverte de la possibilité de produire, par hybridation cellulaire, des anticorps d'une seule spécificité, issus d'un clone de lymphocytes B immortalisés.
- Naissance des anticorps monoclonaux murins

- **1975**: premiers AC monoclonaux murins
  - obtenus par fusion de lymphocytes B normaux de souris préalablement immunisées (par des GR de moutons) avec des cellules de myélome (lymphocytes B immortalisés)

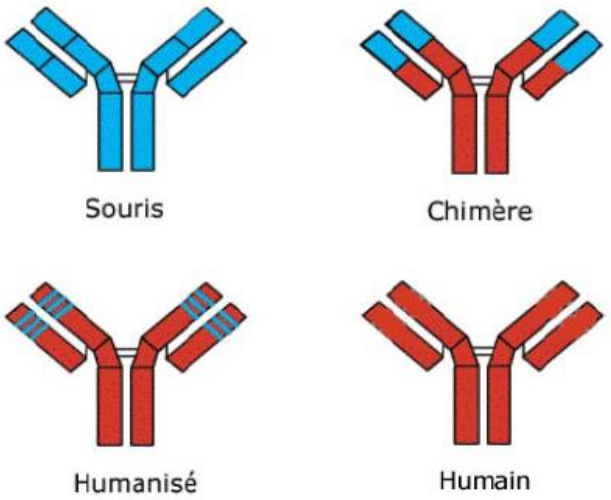
    cellules hybrides produisant un AC monoclonal dirigé contre les GR de mouton (Köhler et Milstein)

- **1984**: AC monoclonaux chimériques souris/homme

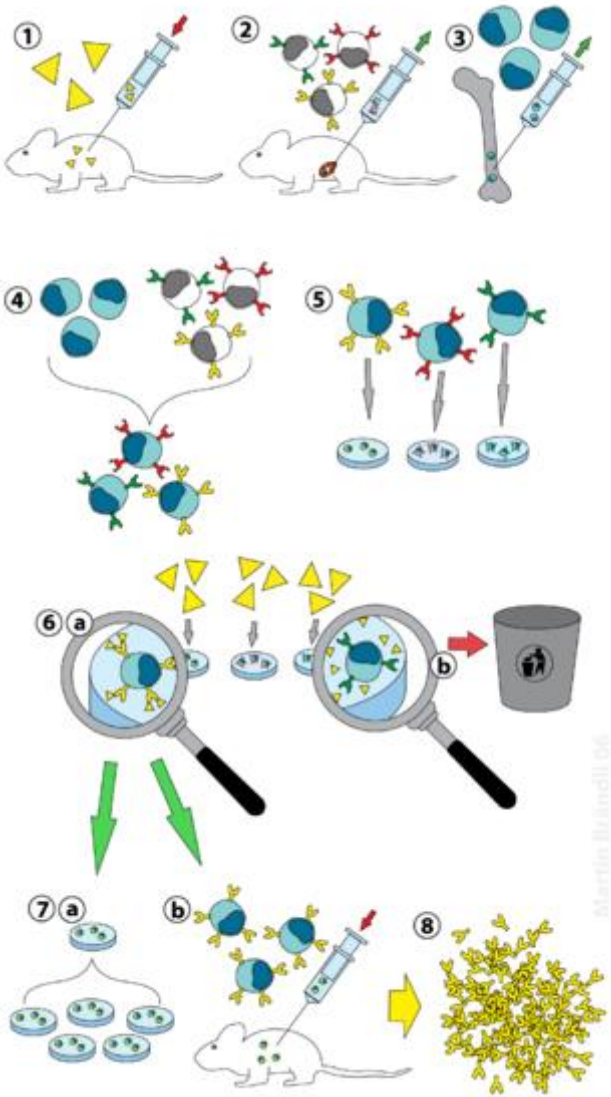
- **1986**: premier AC monoclonal mis sur le marché: Muromomab (anti CD3)

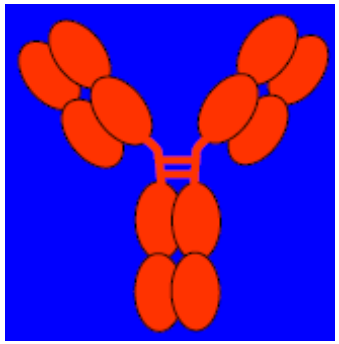
- **1989**: AC monoclonaux humanisés

- **1994**: production d'AC monoclonaux humains par des souris transgéniques ou trans-chromosomiques

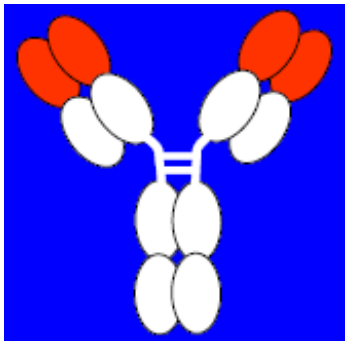


Production d'anticorps monoclonaux

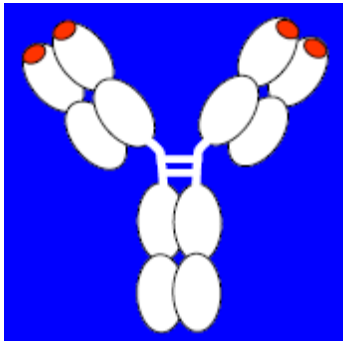




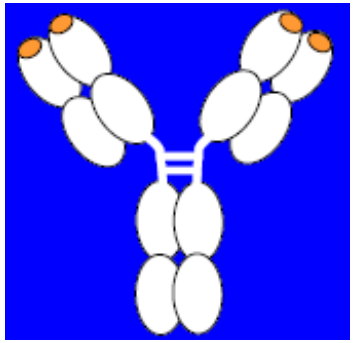
de souris
1975
…momab



chimérique
1984
…ximab



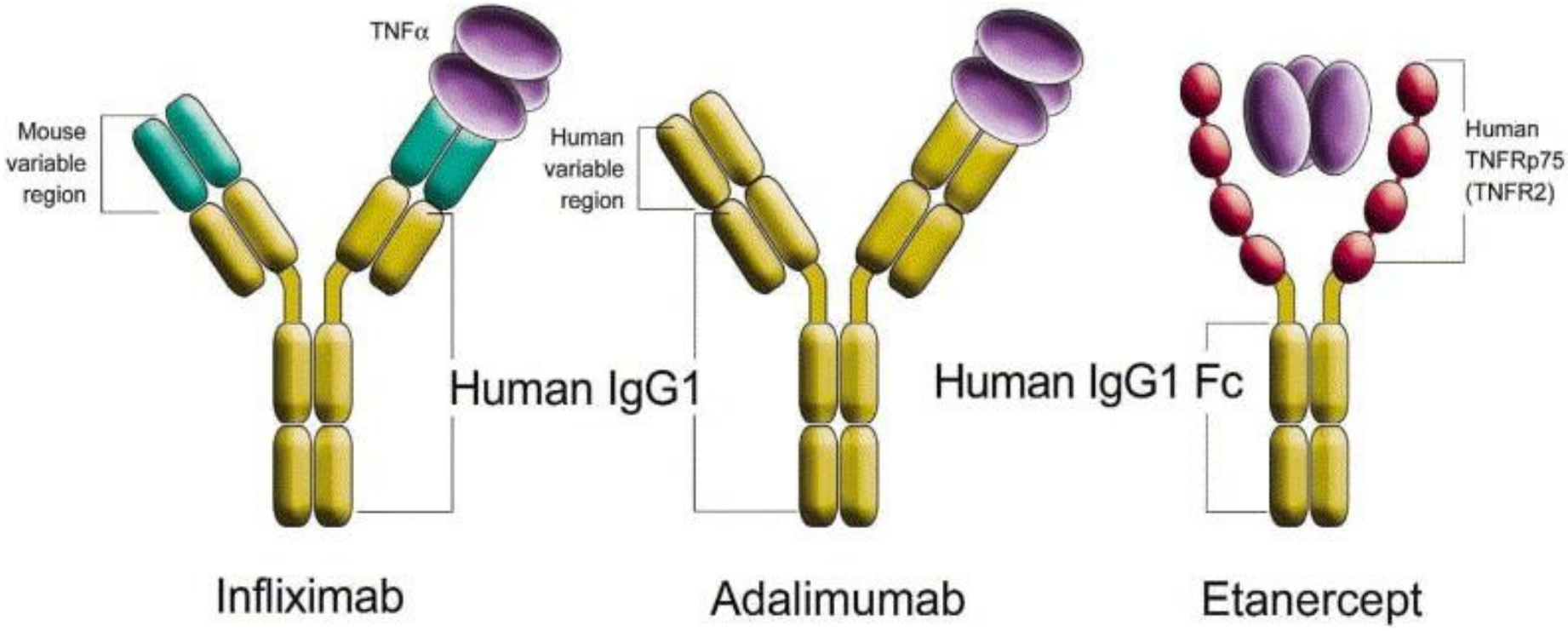
humanisés
1988-1991
…zumab



humains
1994-1999
…mumab

Immunogéniques

Moins immunogéniques


TNFα
Mouse variable region
Human IgG1
Infliximab
Human variable region
Adalimumab
Human IgG1 Fc
Human TNFRp75 (TNFR2)
Etanercept

MECANISMES D'ACTION

- Les anticorps monoclonaux peuvent fonctionner selon trois principaux modes d'action
  - en **bloquant** l'action de molécules ou de récepteurs spécifiques
  - en **ciblant** des cellules spécifiques
  - en fonctionnant comme des molécules de **signalisation**

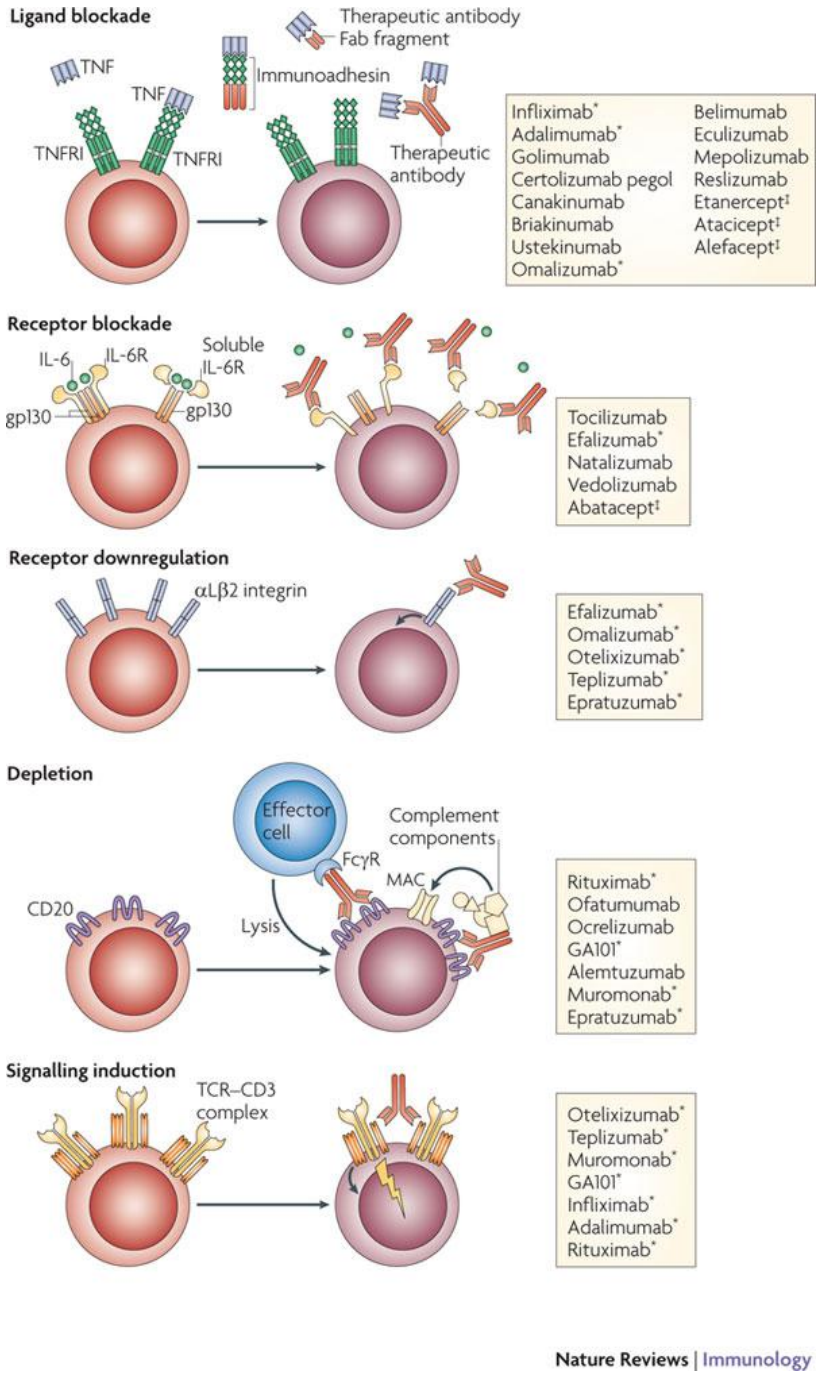
Blocage:
bloquer de façon spécifique, la fonction de facteurs de croissance, cytokines ou autres médiateurs solubles

Ce blocage se fait par liaison directe au facteur lui-même ou à son récepteur

Downregulation:
Induit l'anergie en internalisant la molécule cible

Déplétions: deux mécanismes existent
- Cytotoxicité cellulaire dépendante des anticorps (ADCC)
- Cytotoxicité dépendante du complément au CDC

Signalisation:
-génère des signaux transmembranaires permettant de contrôler la croissance et l'apoptose des cellules cibles,
- miment le ligand naturel et inhibent les fonctions de transmission de signal associées
- induction dérégulation, modification de signalisation intracellulaire



Generic name (trade name; sponsoring companies)	Format	Targets	Development stages	Diseases	Proposed mechanisms of action
Natalizumab (Tysabri; Biogen Idec/Elan)	Humanized IgG4	α4 subunit of α4β1 and α4β7 integrins	Approved	MS and Crohn's disease	Receptor binding and antagonism; inhibits leukocyte adhesion to their counter receptor (or receptors)
Vedolizumab (MLN2; Millennium Pharmaceuticals/ Takeda)	Humanized IgG1	α4β7 integrin	Phase III	UC and Crohn's disease	Receptor binding and antagonism; inhibits leukocyte adhesion to their counter receptor (or receptors)
Belimumab (Benlysta; Human Genome Sciences/ GlaxoSmithKline)	Human (phage-produced) IgG1	BAFF	Phase III	SLE	Ligand binding and neutralization
Atacicept (TACI–Ig; Merck/Serono)	TACI ECD–Fc (IgG1) fusion protein, modified Fc to eliminate effector functions	BAFF and APRIL	Phase II/III	SLE	Ligand binding and neutralization; blocks activation of TACI
Alefacept (Amevive; Astellas)	LFA3 ECD–Fc (IgG1) fusion protein	CD2	Approved	Plaque psoriasis	Inhibits LFA3–CD2 interaction and blocks lymphocyte activation
			Phase III	GVHD	
Otelixizumab (TRX4; Tolerx/ GlaxoSmithKline)	Chimeric light chain, humanized heavy chain, IgG1 aglycosyl Fc	CD3	Phase III	T1D	Modulates T cell function
Teplizumab (MGA031; MacroGenics/Eli Lilly)	Humanized IgG1 with mutated Fc	CD3	Phase III	T1D	Modulates T cell function
Rituximab (Rituxan/ Mabthera; Genentech/ Roche/Biogen Idec)	Chimeric IgG1	CD20	Approved	Non-Hodgkin's lymphoma, RA (in patients with inadequate responses to TNF blockade) and CLL	Sensitizes cells to chemotherapy; induces apoptosis, ADCC and CDC
Ofatumumab (Arzerra; Genmab/ GlaxoSmithKline)	Human (mouse-produced) IgG1	CD20	Approved	CLL	CDC and ADCC
			Phase III	RA	
Ocrelizumab (2H7; Genentech/Roche/ Biogen Idec)	Humanized IgG1	CD20	Phase III	RA and SLE	ADCC and CDC
Epratuzumab (hLL2; Immunomedics/UCB)	Humanized IgG1	CD22	Phase III	SLE and non-Hodgkin's lymphoma	ADCC and downregulation of B cell receptor
Alemtuzumab (Campath/ MabCampath; Genzyme/Bayer)	Humanized IgG1	CD52	Approved	CLL	ADCC
			Phase III	MS	
Abatacept (Orencia; Bristol-Myers Squibb)	CTLA4 ECD–Fc, mutated IgG1 Fc	CD80 and CD86	Approved	RA and JIA	Inhibits T cell activation by binding to CD80 and CD86, thereby blocking interaction with CD28
			Phase III	UC and Crohn's disease	
			Phase II/III	SLE	

Table 1 (cont.) | **Monoclonal antibodies and Fc fusion proteins for autoimmunity and inflammation***

Generic name (trade name; sponsoring companies)	Format	Targets	Development stages	Diseases	Proposed mechanisms of action
Mepolizumab (Bosatria; GlaxoSmithKline)	Humanized IgG1	IL-5	Phase III	Hyper-eosinophilic syndrome	Ligand binding and receptor antagonism
Reslizumab (SCH55700; Ception Therapeutics)	Humanized IgG4	IL-5	Phase III	Eosinophilic oesophagitis	Ligand binding and receptor antagonism
Tocilizumab (Actemra/ RoActemra; Chugai/ Roche)	Humanized IgG1	IL-6R	Approved	RA	Receptor binding and ligand blockade
			Phase III	JIA	
Ustekinumab (Stelara; Centocor)	Human (mice) IgG1	IL-12 and IL-23	Approved	Plaque psoriasis	Ligand binding and receptor antagonism
			Phase III	Psoriatic arthritis	
			Phase II/III	Crohn's disease	
Briakinumab (ABT-874; Abbott)	Human (phage-produced) IgG1	IL-12 and IL-23	Phase III	Psoriasis and plaque psoriasis	Ligand binding and receptor antagonism
Etanercept (Enbrel; Amgen/Pfizer)	TNFR2 ECD–Fc (IgG1) fusion protein	TNF	Approved	RA, JIA, psoriatic arthritis, AS and plaque psoriasis	Neutralizes TNF activity by binding soluble and transmembrane TNF and inhibiting binding to TNFRs
Infliximab (Remicade; Centocor/Merck)	Chimeric IgG1	TNF	Approved	Crohn's disease, RA, psoriatic arthritis, UC, AS and plaque psoriasis	Neutralizes TNF activity by binding soluble and transmembrane TNF and inhibiting binding to TNFRs; induction of activated T cell and macrophage apoptosis
Adalimumab (Humira/ Trudexa; Abbott)	Human (phage-produced) IgG1	TNF	Approved	RA, JIA, psoriatic arthritis, Crohn's disease, AS and plaque psoriasis	Neutralizes TNF activity by binding soluble and transmembrane TNF and inhibiting binding to TNFRs; lyses TNF-expressing cells by CDC; induction of activated T cell and macrophage apoptosis
Certolizumab pegol (Cimzia; UCB)	Humanized Fab, PEG conjugate	TNF	Approved	Crohn's disease and RA	Neutralizes TNF activity by binding soluble and transmembrane and inhibiting binding to TNFRs
Golimumab (Simponi; Centocor)	Human (mouse-produced) IgG1	TNF	Approved	RA, psoriatic arthritis and AS	Neutralizes TNF activity by binding soluble and transmembrane TNF and inhibiting binding to TNFRs

Les anticorps monoclonaux pour quelles indications ?

beaucoup de OFF label !!!!!

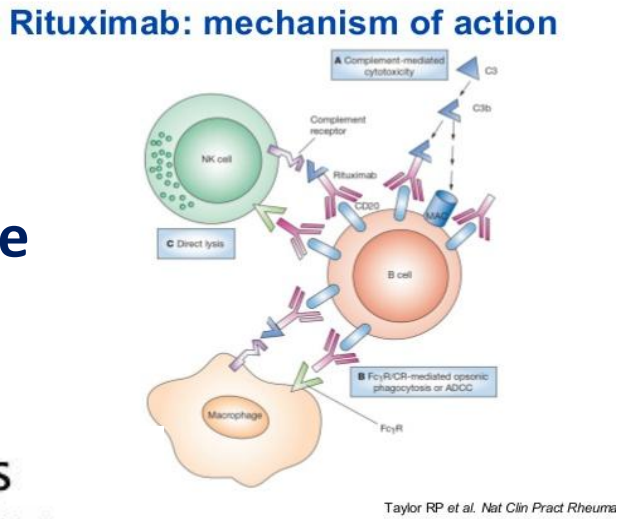
Table 5. Immunotherapeutic agents approved for use in autoimmune and autoinflammatory diseases (adapted from Lefranc, 2015; O'Shea, 2014; Ostrov, 2013).

Generic name	Brand name	Clinical use	Type	Target and mechanism of action
Abatacept	Orencia	RA, polyarticular JIA	CTLA-4 co-stimulatory blocker	CD28 inhibition
Adalimumab	Humira	RA, Psoriasis, AS, PsA, CrD, JIA	Human MAB	Inhibits TNF-α
Anakinra	Kineret	RA, CAPS	Recombinant protein	IL-1 receptor antagonist
Belimumab	Benlysta	SLE	Human MAB	Inhibits BLyS
Canakinumab	Ilaris	CAPS, JIA	Human MAB	Inhibits IL-1β
Certolizumab	Cimzia	RA, AS, PsA, CrD	Humanized FAB	Inhibits TNF-α
Etanercept	Enbrel	RA, JIA, Psoriasis, PsA, AS	Fusion receptor	Soluble TNFα receptor antagonist
Golimumab	Simponi	RA, Psoriasis, AS, PsA, CrD, UC	Human MAB	Inhibits TNF-α
Infliximab	Remicade	RA, AS, PsA, UC, CrD	Chimeric MAB	Inhibits TNF-α
IFN β 1a	Rebif	MS	Cytokine inhibitor	Targets Type 1 IFN
IFN β 1b	Betaseron	MS	Cytokine inhibitor	Targets Type 1 IFN
IFN β 1a	Avonex	MS	Cytokine inhibitor	Targets Type 1 IFN
Natalizumab	Tysabri	CrD, MS	Humanized MAB	Inhibits Integrin α-4
Rilonocept	Arcalyst	CAPS	Fusion receptor protein	Targets IL-1R1/IL-RAcP heterodimeric receptor
Rituximab	Rituxan	RA, ANCA associated vasculitis	Chimeric MAB	Inhibits CD20 receptor on B cells
Tocilizumab	Actemra	RA, polyarticular JIA, Systemic JIA	Humanized MAB	Inhibits IL-6 receptor
Tofacitinib	Xeljanz	RA	Small molecule; Janus kinase inhibitor	Specifically blocks JAK-STAT pathway
Ustekinumab	Stelara	Psoriasis, CrD	Humanized MAB	Anti-p40 antibody; Inhibits Th1/Th17 cells

MAB: monoclonal antibody, JAK: Janus kinase, IFN: interferon, FAB: antibody fragment, CTLA: cytotoxic T lymphocyte-associated protein-4, TNF: tumor necrosis factor, RA: Rheumatoid arthritis, AS: ankylosing spondylitis, SLE: systemic lupus erythematosus, JIA: juvenile idiopathic, MS: Multiple Sclerosis, PsA: Psoriatic arthritis, CAPS: cryopyrin associated periodic syndromes, CrD: Crohn Disease, BLyS: B lymphocyte stimulator, UC: ulcerative colitis.

PR= polyarthrite rhumatoïde (anti-cytokines, anti-CD20,CTLA4Ig))
Psoriasis (anti-cytokines)
Crohn (anti-cytokines, anti-integrin)
Sclérose en plaque (anti-CD20, anti-integrin)
Vasculite à ANCA (anti-DD20)
Lupus (anti-cytokines)
Maladies auto-inflammatoires (anti-récepteur des cytokines)

Rituximab (MabThera) dans la néphrite lupique

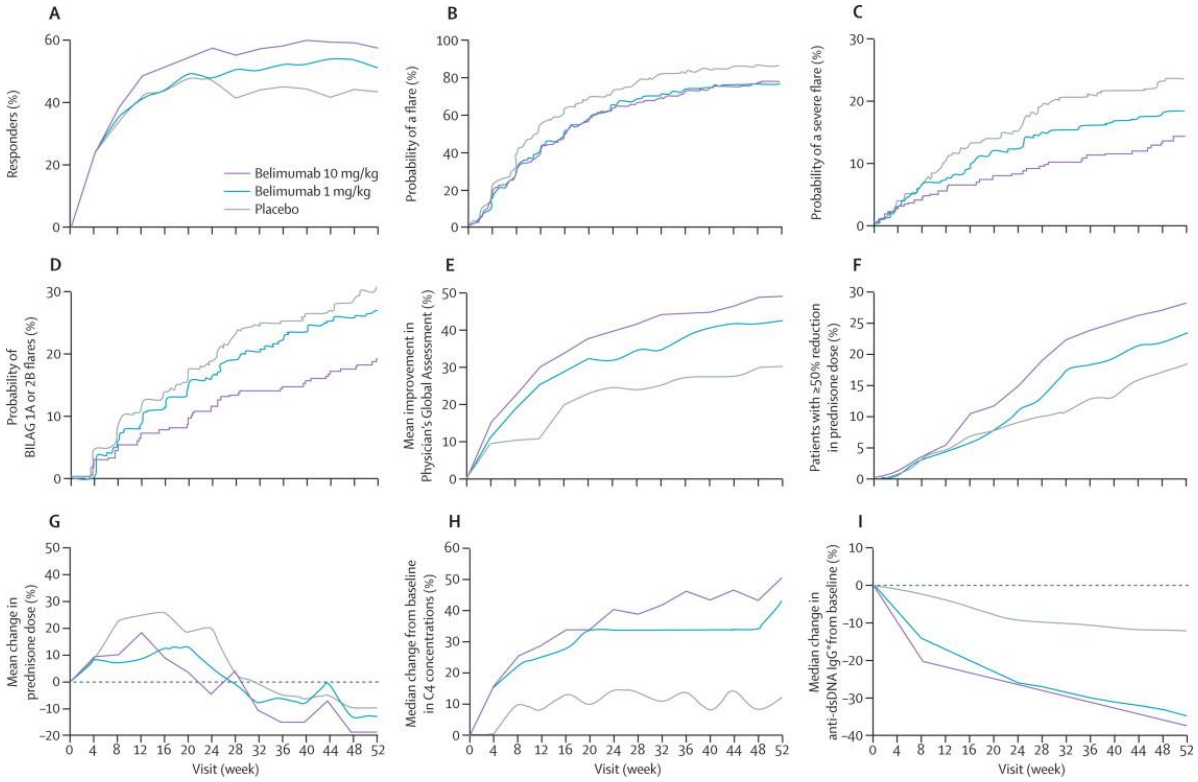


- ***LUNAR study:*** a trial on stage III and IV lupus nephritis showed that add on rituximab had no clinical impact in patients treated with corticosteroid and MMF.(Furie et al.Ann Rheum Dis.2010;69(suppl 3):549a

- ***EXPLORER study*** : Rituximab(anti CD20 monoclonal antibody) showed an impact on serological parameters but not on clinical efficacy in patients with active nonrenal lupus.*(Merrill et al.Lupus.2011;20:709-716)*

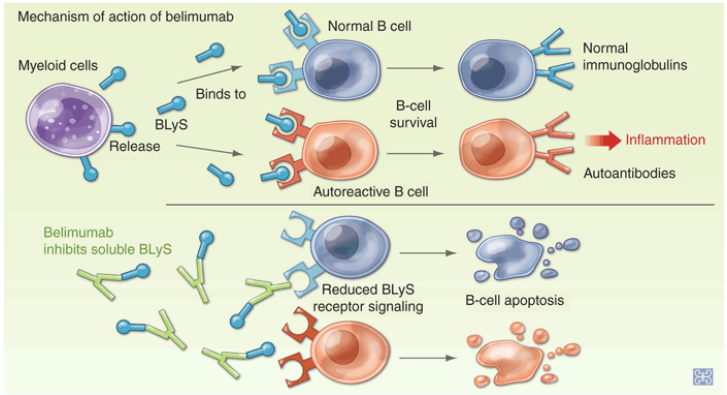
Le rituximab n'est pas admis pour le traitement du LUPUS

Belimumab (Benlysta) dans le lupus (sans atteinte rénale)



Navarra et al Lancet 2011

Le Belimumab est admis pour le traitement du LUPUS (mais pas pour la néphrite lupique)



Rituximab dans le lupus

Meta analyse

	Absolute No.	Percentage
Dose/interval	297	100%
4 × 375 mg/m^2 per week	150	49%
2 × 750 mg/m^2 per 2 weeks	5	2%
2 × 500 mg per 2 weeks	3	1%
3 × 500 mg per 2 weeks	1	0%
4 × 500 mg per 2 weeks	1	0%
2 × 1000 mg per 2 weeks	113	37%
Other regimen	24	8%

reports containin
responses were n
frequent in type I
showed a comple
Any response (co
in type III (87%)
74% (mixed typ
type V membran
with 1 out of 3
RTX within the n

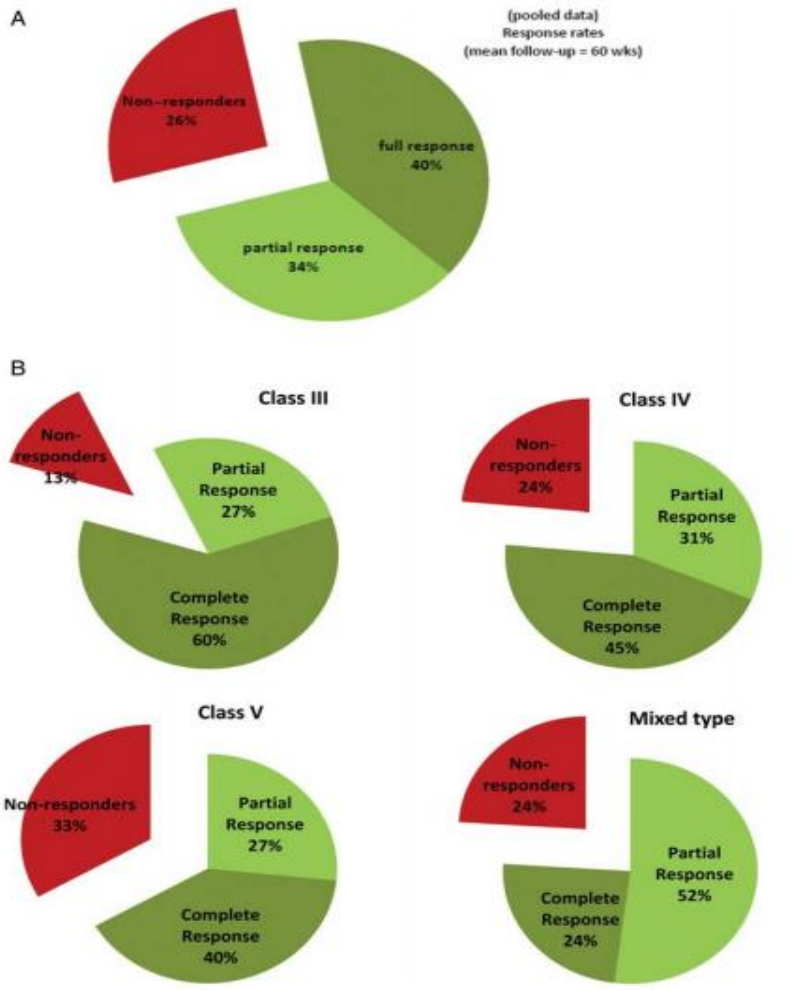


Fig. 2. Response rates upon RTX treatment. (A) The diagram illustrates the percentages of complete, partial o
RTX in a mean follow-up period of 60 weeks. (B) The same type of graph illustrates the respective percent
indicated.

Weidenbush et al NDT 2013

Les anticorps monoclonaux: effets secondaires?

- ✓Fièvre
- ✓Frisson
- ✓Faiblesse
- ✓Maux te tête
- ✓Nausée
- ✓Vomissement
- ✓Diarrhée
- ✓Baisse de la PA
- ✓Rash cutané (urticaire, angiodème…)

= réactions d'hypersensibilités immédiate (IgE ou non-médiée), retardée (inflammation, activation du complément, complexe immuns..)

TTT: ralentir la vitesse de perfusion, ttt symptomatique, prévention avec anti-H1, stéroïdes

Induction de tolérance

Table 1: Rituximab desensitization protocol.

Step	Solution	Rate (mL/h)	Time (min)	Dose	Total dose
1	1	2.0	15	0.015	
2	1	5.0	15	0.037	
3	1	10.0	15	0.075	
4	1	20.0	15	0.150	0.277
5	2	5.0	15	0.375	
6	2	10.0	15	0.750	
7	2	20.0	15	1.500	
8	2	40.0	15	3.000	5.625 (1–8: 5.902) 750–5.902: 744 mg will be given in next steps
9	3	10.0	15		
10	3	20.0	15		
11	3	40.0	15		
12	3	75.0	240		

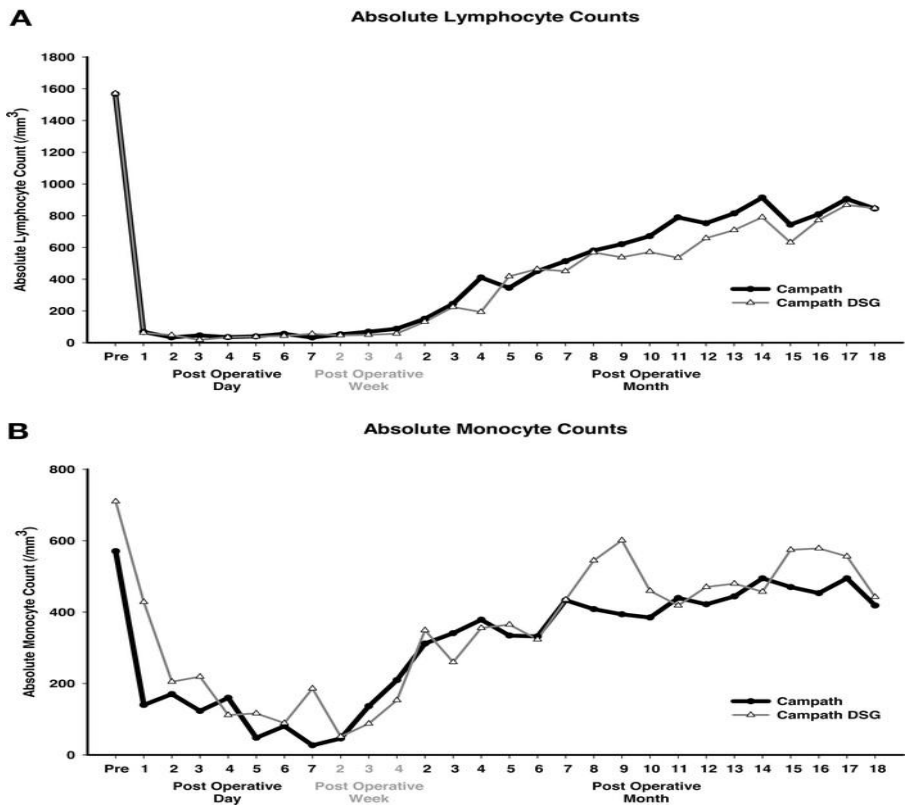
Solution 1: 250 mL, 5% dextrose, /0.8 mL rituximab (0.03 mg/mL: 1 : 100 of total dose, 250 mL/7.5 mg).
Solution 2: 250 mL, 5% dextrose, /7.5 mL rituximab (0.30 mg/mL: 1 : 10 of total dose, 250 mL/75 mg).
Solution 3: 250 mL, 5% dextrose, /74.4 mL rituximab.
Premedication: 20 minutes before pheniramine 45.5 mg IV, prednisolone 100 mg IV, and famotidine 20 mg IV.

Les anticorps monoclonaux: effets secondaires?

- Steven-Johnson
- Lyell
- Anémie hémolytique auto-immune
- Sclérose en plaque (?)
- Lupus-like (développement d'ANA)

Les anticorps monoclonaux: infections

Anticorps déplétant anti-lymphocytes T, NK (alemtuzumab= Campath)



Kirk et al Transplantation 80, 1051: 2005

Infection chez les patients sous anti-TNF

- TBC et PR
  - 6/100’000
- TBC et PR tt par anti-TNF
  - 58/100’000

X 10

Wolke Arth and Rheumat 50,372, 2004

Infection sous rituximab

Table 1. Rituximab Infectious Complications

	Evidence	Comments
Established increased infectious complications		
Overall infections	Meta-analyses in hematologic malignancies[11,12] Randomized trials in RA[1]	Increased severe infections (grade 3 or 4) when used as maintenance therapy in follicular lymphoma Mild infections in RA
Hepatitis B reactivation	Case series[13–15] Case reports[16–18]	Reports only in hematologic malignancies
PML	Case series,[19] case reports[20–22]	Most cases in hematologic malignancies, but a few in RA, SLE, and immune cytopenia
Possibly increased infectious complications		
Pneumocystis jirovecii pneumonia	Retrospective series compared to historical controls[23,24] Case series[25–27] Case reports[28–31]	Cases in hematological malignancies, RA, autoimmune diseases, solid organ transplant
Enterovirus encephalitis	Case reports[32–35]	Known complication of other B-cell immunodeficiencies
Parvovirus B19	Case reports[36–39]	Good response to IVIG
Cytomegalovirus	Case reports[20,28,40]	CMV disease is very uncommon except in HIV or following allogeneic transplant; there are several reports in hematologic malignancies treated with combination chemotherapy
West Nile virus	Case reports[41,42]	Increased severity and negative serology may be anticipated because of effect of rituximab on B cells
Babesiosis	Case-control study[43]	Most patients with persistent babesiosis had received rituximab
Mycobacterial disease	Case reports[44]	Severe *Mycobacterium avium* and *M kansasii*, no other reports

Abbreviations: PML, progressive multifocal leukoencephalopathy; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; IVIG, intravenous immunoglobulin; CMV, cytomegalovirus; HIV, human immunodeficiency virus.

Original article

Low pre-treatment B-cell counts are not a risk factor of infection in patients treated with rituximab for autoimmune diseases: An observational study

Ilias Lazarou [a,*], Axel Finckh [a], Lara Fischer [b], Camillo Ribi [b], Danielle Gascon [a], Jörg D. Seebach [b], Pierre-André Guerne [a]

[a] Division of Rheumatology, University Hospital and Medical Faculty of Geneva, 26, avenue Beau-Séjour, 1206 Geneva, Switzerland
[b] Division of Immunology and Allergology, University Hospital and Medical Faculty of Geneva, 1206 Geneva, Switzerland

Table 2
Comparison of baseline characteristics of patients who suffered severe infections versus patients who did not.

	Patients with severe infections $n = 33$	Patients without severe infections $n = 128$	Bilateral *P* value
Mean age, years (IQR)	56.7 (39.5–71.5)	52.4 (42–62)	NS
Female patients, n (%)	26 (78.8)	99 (77.3)	NS
Median disease duration, years (IQR)	2.8 (0.8–8.8)	6.3 (2.2–13.6)	NS
Mean follow-up, years (IQR)	2.7 (1.5–4.3)	2.3 (0.9–3.3)	NS
Diagnosis (%)			
RA ($n = 86$)	8 (24.2)	78 (60.9)	<0.001
SLE ($n = 26$)	4 (12.1)	22 (17.1)	NS
Primary vasculitis ($n = 15$)	8 (24.2)	7 (5.5)	0.001
Sjögren's syndrome ($n = 12$)	3 (9.1)	9 (7.0)	NS
Inflammatory myopathy ($n = 4$)	2 (6.1)	2 (1.6)	NS
Other ($n = 18$)	8 (24.2)	10 (7.8)	NS
Mean cumulative dose[a] of RTX in mg/m² (IQR)	1658 (1188–2368)	1919 (1198–3223)	NS
Concomitant therapy			
Systemic glucocorticoids, *n* (%)	26 (78.8)	85 (66.4)	NS
Median prednisone dose in mg (IQR)	17.5 (5–40)	7.5 (0–20)	0.025
Immunosuppressants, *n* (%)	26 (78.8)	97 (75.8)	NS
Concomitant disease			
Diabetes mellitus, *n* (%)	4 (12.1)	9 (7.0)	NS
Other comorbidities, *n* (%)	10 (30.3)	18 (14.0)	0.028
Baseline laboratory values, median (IQR)			
Neutrophils – total count, cells/mm³	5300 (3180–8760)	5060 (3530–6910)	NS
Lymphocytes – total count, cells/mm³	1302 (765–1807)	1734 (1258–2620)	0.004
B-cell count, cells/mm³	180 (82–185)	181.5 (117–294)	NS
IgG, g/L	10.2 (7.0–12.0)	11.4 (9.2–13.7)	NS
IgA, g/L	2.4 (1.8–3.5)	2.5 (1.8–3.6)	NS
IgM, g/L	0.9 (0.4–1.6)	1.2 (0.9–1.8)	NS
Creatinine, µmol/L	68 (60–78)	66.5 (57–77)	NS

IQR: interquartile range; NS: non-significant.
[a] At time of first infection versus last observation in patients without infection.

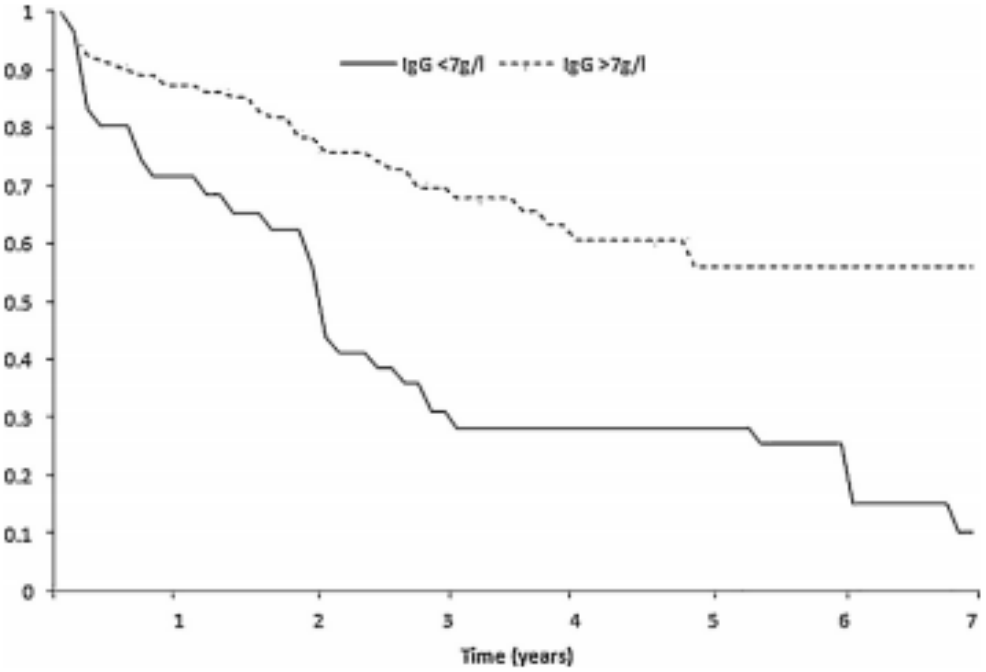


Fig. 1. Kaplan-Meier curbs: cumulative severe-infection-free survival rate over time (months) in patients with IgG levels >7 g/L (dotted line) versus <7 g/L (straight line).

Conclusion: pas de risque infectieux augmenté en fonction du taux de lymphocytes B mais importance du taux d'IgG = doser le IgG chez ls patients sous IS

Exp Clin Transplant. 2016 Jan 8. doi: 10.6002/ect.2014.0156. [Epub ahead of print]

Rituximab Therapy and Infection Risk in Pediatric Renal Transplant Patients.

Gulleroglu K[1], Baskin E, Moray G, Ozdemir H, Arslan H, Haberal M.

⊕ Author information

Abstract

OBJECTIVES: Rituximab is a monoclonal antibody directed against the CD20 molecule on pre-B and mature B cells and is used in transplant recipients for the prevention and treatment of alloantibody-mediated rejection or for the treatment of disease recurrence after transplant. In most patients, rituximab has been safe and well-tolerated, but the long-term adverse effects of rituximab are currently unknown.

MATERIALS AND METHODS: We retrospectively evaluated 78 pediatric renal transplant recipients for the occurrence of infectious disease. Patients who received rituximab therapy were divided into 2 groups: those who developed an infection and those who did not. The 2 groups were compared for serious infections, hospitalization, graft loss, and death rates.

RESULTS: Eighteen transplant patients received rituximab therapy for various causes. The number of rituximab courses given varied according to the cause and ranged from 1 to 8 courses. The dose at each course was 375 mg/m2. Median age of all recipients was 16.00 years (min-max:, 5.00-22.00 y), and median follow-up time was 2.00 years (min-max:, 1.00-3.00 y). Serious infections (bacterial sepsis, tuberculosis, Cytomegalovirus infection, varicella-zoster virus infection, Polyomavirus-associated nephropathy, and acute pyelonephritis) were observed in 8 patients who received rituximab therapy. We observed that patients with antibody-mediated rejection had significantly increased infection rate. Patients who had used rituximab combined with antithymocyte globulin and higher rituximab course number and higher pretreatment CD19 and CD20 levels had higher risk of infection ($P < .05$).

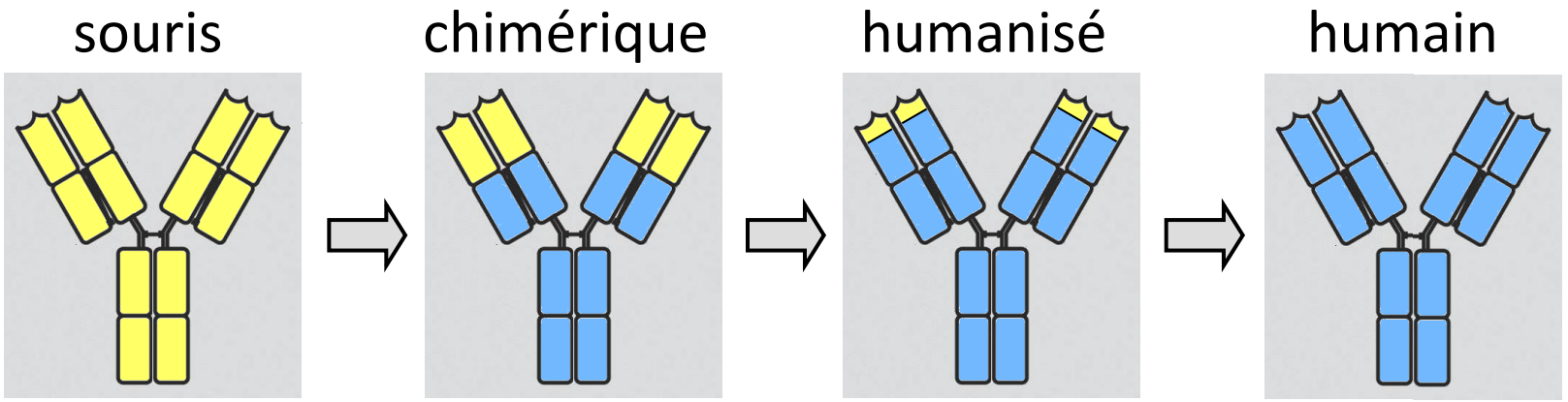
CONCLUSIONS: The combined use of rituximab with additional treatments such as antithymocyte globulin, intravenous immunoglobulin, and repeated plasma exchange may be associated with high risk of infectious disease. Especially for those patients who required intensive and repetitive treatment, such as antibody-mediated rejection, rituximab treatment should be used with caution. Infection risk should be closely monitored, although mainly in patients who receive T-cell-depleting agents.

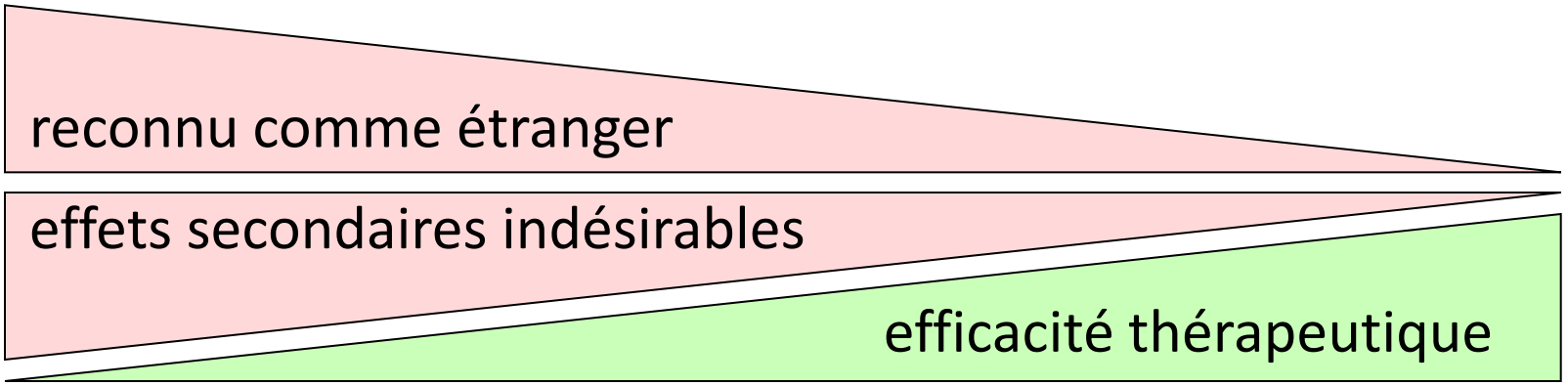
C'est la combinaison de plusieurs IS , prednisone + rituximab qui est associée à des risques infectieux significativement augmentés.

Les anticorps monoclonaux: épuisement de l'effet

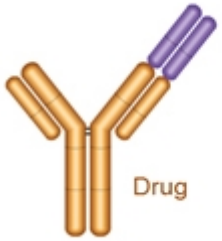
- développement d'anticorps anti-Moab (immunogénicité)

Anticorps monoclonaux thérapeutiques

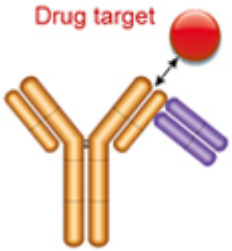




Détection des anticorps anti-Moab (ex: AC anti-Rituximab, anti-Infliximab…)



Type 1 anti-Moab (cible= site de reconnaissance)
Permet de détecter le taux de Moab libre

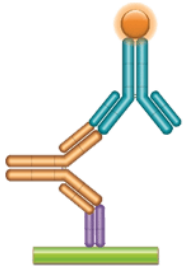


Type 2 anti-Moab (cible= en dehors du site)
Permet de détecter le taux de Moab total (libre et lié)

Type 3 anti-Moab (cible = site lié)
Permet de détecter le taux de Moab lié
(ex: infliximab lié au TNF)

Méthode de détection par ELISA

Taux de Moab



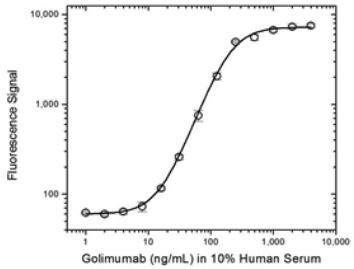
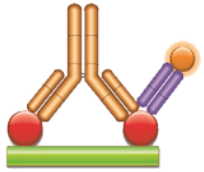


Figure 1 PK assay, bridging format, using antibodies HCA240 and HCA241

Taux de Moab lié



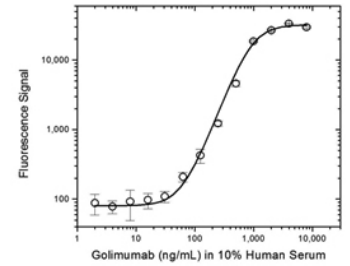
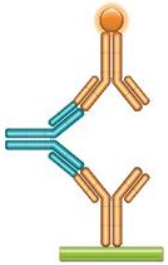


Figure 2 PK assay in antigen capture format ELISA, using Type 3 antibody

Taux d'anti-Moab libre



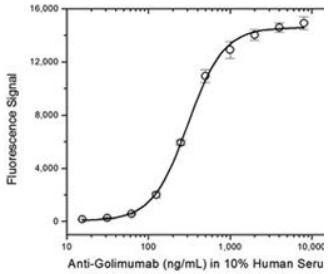
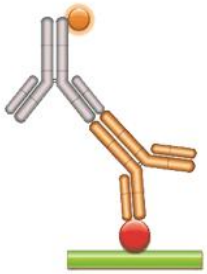


Figure 3 ADA assay development, using Type 1 anti-golimumab antibody HCA241

Taux d'inhibition du Moab par anti-Moab



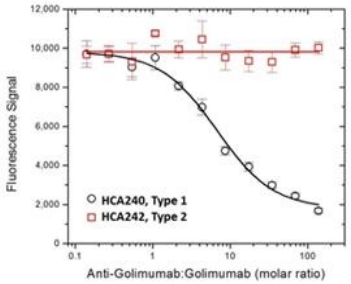


Figure 4 Inhibition of golimumab to TNF-α by Type 1 antibody HCA240, but not by Type 2 antibody HCA242

Importance du taux?

TABLE 1. Drug Concentration Thresholds and Associations with Various Outcome Measures[6,7,55,57,59–68,90]

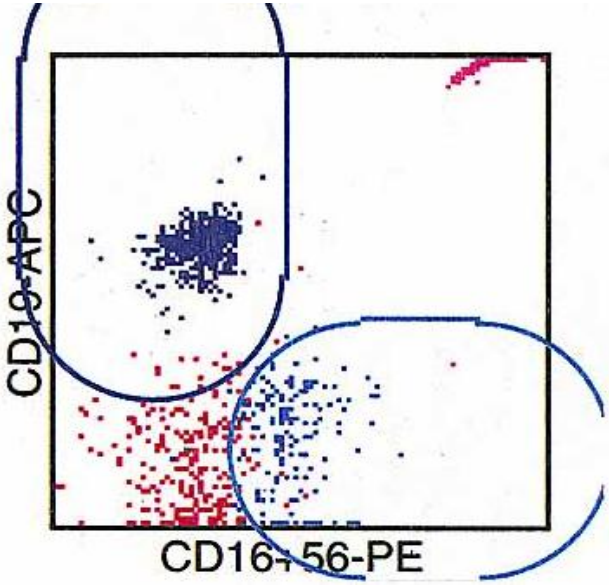
CD/UC (N)	Drug	Time Point of Sampling	Threshold, µg/mL	Sensitivity %, Specificity %, AUC	Outcome Measure
IBD (128)[60]	IFX	Induction	≥2.0	na, na, 0.76	Long-term clinical response after restart (≥W52)
UC (112)[59]	IFX	W14	≥2.5	81%, 75%, 0.77	Relapse-free survival (6 mo)
IBD (58)[51]	IFX	W14	≥4.0	53%, 75%, 0.64	Persistent remission (W54)
CD (144)[55]	IFX	W14	≥3.5	64%, 78%, 0.75	Sustained clinical response (throughout W54)
CD (85)[62]	IFX	Maintenance	<0.5	86%, 85%, 093	Clinical loss of response
UC (21)[62]	IFX	Maintenance	<0.8	75%, 100%, 0.90	Clinical loss of response
IBD (103)[63]	IFX	Maintenance	<2.0	76%, 82%, 0.68	Absence of clinical remission
CD (327)[54]	IFX	Maintenance	<2.7	63%, 76%, 0.72	CRP >5 mg/L
CD (483)[55]	IFX	Maintenance	≥2.8	53%, 78%, 0.68	Biochemical remission (CRP ≤5 mg/L)
UC (374)[57]	IFX	Maintenance	≥3.7	65%, 71%, 0.71	Clinical response
IBD (46)[56]	IFX	Maintenance	≥8.3	71%, 73%, 0.75	Mucosal healing
CD (81)[67]	IFX	Maintenance	≥5.0	na, na, na	Continued response after IMM withdrawal (FU)
UC (73)[68]	ADA	W4	≥4.6	80%, 56%, na	Clinical response (W12)
UC (73)[68]	ADA	W4	≥7.0	80%, 69%, na	Sustained clinical response (throughout W52)
CD (71)[69]	ADA	Maintenance	≥5.9	68%, 71%, 0.75	Clinical remission
IBD (40)[70]	ADA	Maintenance	<4.9	66%, 85%, 0.77	Absence of mucosal healing

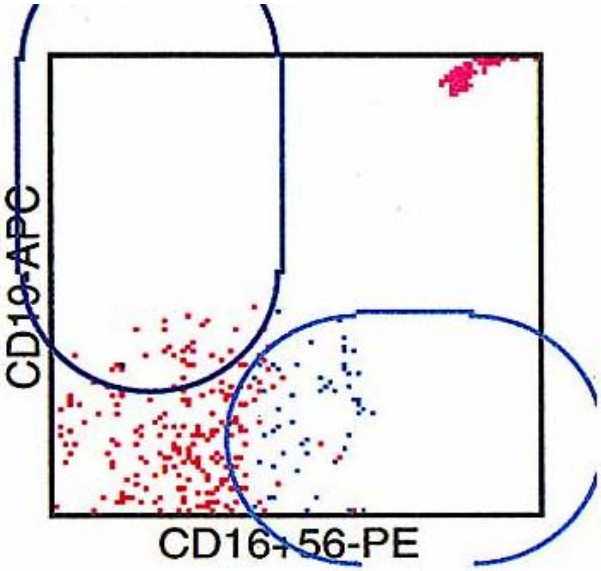
ADA, adalimumab; AUC, area under curve; CD, Crohn's disease; CRP, C-reactive protein; FU, follow-up; IBD, inflammatory bowel disease; IFX, infliximab; na, not available; UC, ulcerative colitis; W, week.

Prévenir l'immunogénicité en ajoutant d'autres immunosuppresseur (methotrexate, imuek, cellcept, ciclosprorine….) si traitement chronique (ex infliximab…)

Intérêt des marqueurs ?

- Exemple d'anticorps déplétant le CD 20 (lymphocytes B = Rituximab)





Les anticorps monoclonaux: pourquoi c’est si cher?

Rituximab (Mabthera):
Ampoule 500 mg = 1875 CHF
2x1000 mg Mabthera = 7’500 CHF pour 1 cure (dose PR)

Adalimumab (Humira)
Ampoule 40 mg = 739 CHF
1 an = 17’736 CHF

Eculizumab (Soliris)
Ampoule 300 mg = 5948 CHF
1 an = 70’000 CHF le 1er mois puis mois 2 à 12 = 519’000 CHF total = 590’000 CHF

Rien à voir avec les coûts de production mais avec le coût de la vie…(Qualy)

……Attendons les biosimilaires (économies 20-30%)

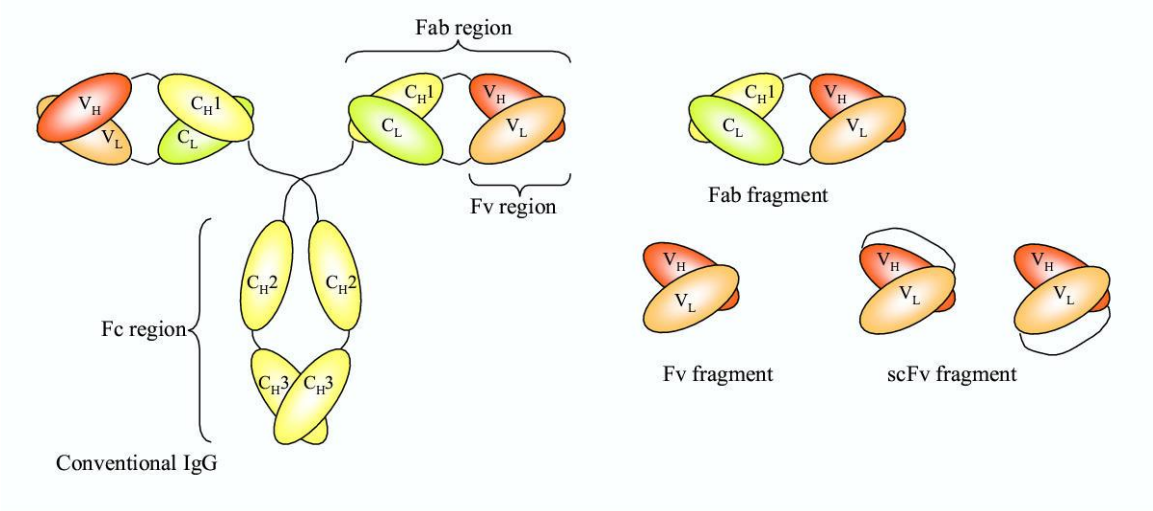
Les anticorps monoclonaux: la suite ?

Les anticorps monoclonaux: la suite ?

Voie d'administration

Curr Pharm Des. 2016 Feb 10. [Epub ahead of print]
Inhaled biologics: from preclinical to product approval.
Fathe K, Ferrati S, Moraga-Espinoza D, Yazdi A, Smyth HD[1]

Nouveau design: molécule plus petite, meilleure pénétration dans les tissus..

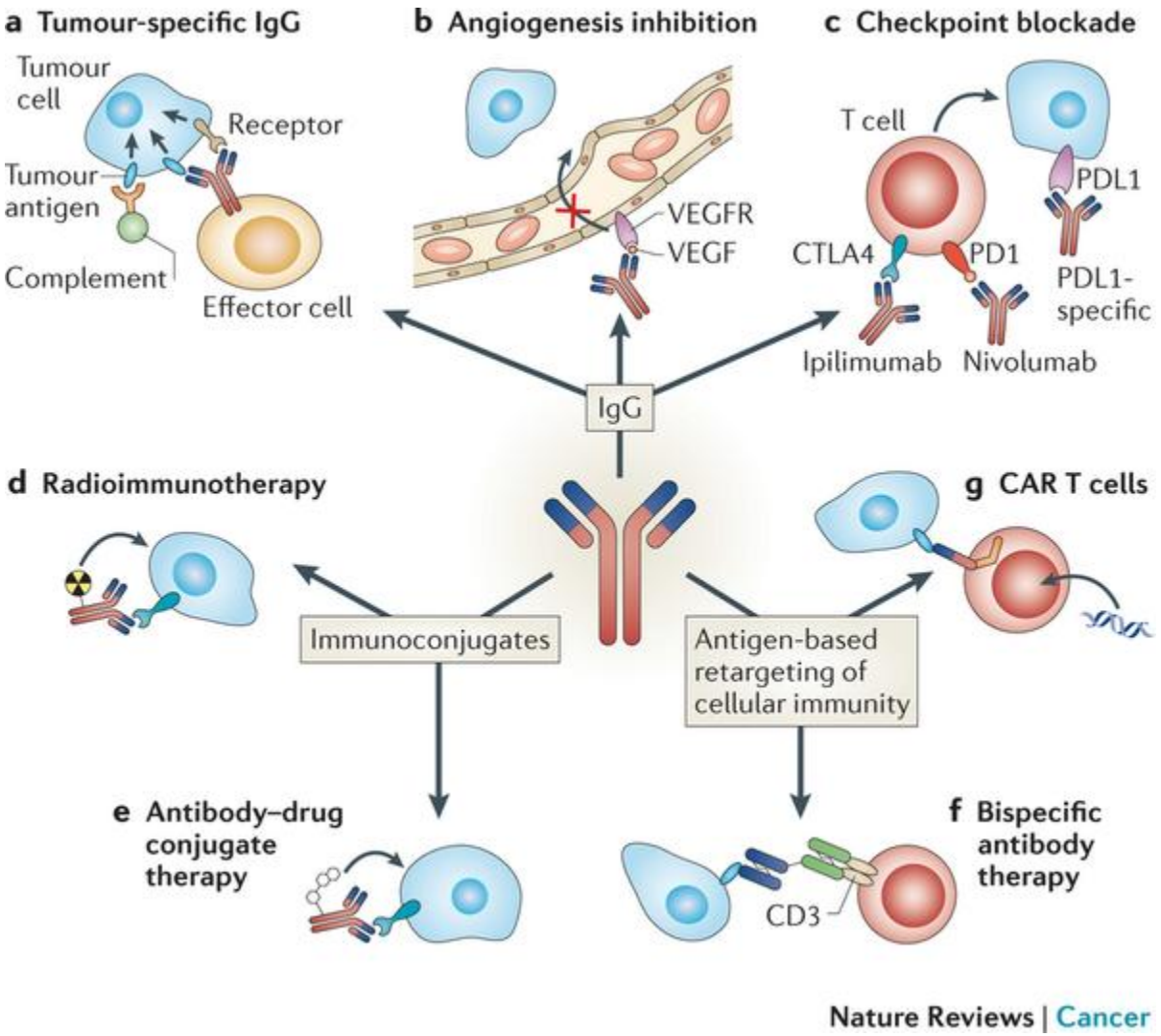


Les anticorps monoclonaux: la suite ?

Choisir le bon patient, c'est à dire

définir le bon phénotype, les paramètres génétiques, la pharmacocinétique

Les anticorps monoclonaux: la suite ?



CONCLUSION

- Un réel progrès lié aux AC monoclonaux qui réalisent une thérapeutique très ciblée.

- Préciser les bonnes pratiques d'utilisation
  - monothérapie
  - association à des moyens conventionnels
  - association à d'autres AC monoclonaux
  - durée d'utilisation
  - identifier les bons et les mauvais répondeurs
  - maîtriser les coûts

- Futur: poly-(bi)-spécificité, voie orale/inhalation