Nouvelles cibles thérapeutiques dans les maladies neuromusculaires auto-immunes

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Liens d'intérêt

- À peu près tous les labos travaillant dans le domaine de la SEP et des neuropathies (boards, consulting, invitation congrès, symposia). La liste est longue et donc j'ai peur d'en oublier
- Pour plus de précision : https://www.transparence.sante.gouv.fr

  https://eurosfordocs.fr/

21/01/2022

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Quels sont les acteurs de la maladie auto-immune ?

- Cellules T
- Macrophages
- Cellules B
- Auto-anticorps
- Complément
- Cytokines
- Autres ?

Cibler les cellules T

- Rien de très nouveau…

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Inhibition of TLR4 signaling protects mice from sensory and motor dysfunction in an animal model of autoimmune peripheral neuropathy

Oladayo Oladiran[1], Xiang Qun Shi[1], Mu Yang[1], Sylvie Fournier[2*] and Ji Zhang[1,2,3,4*]

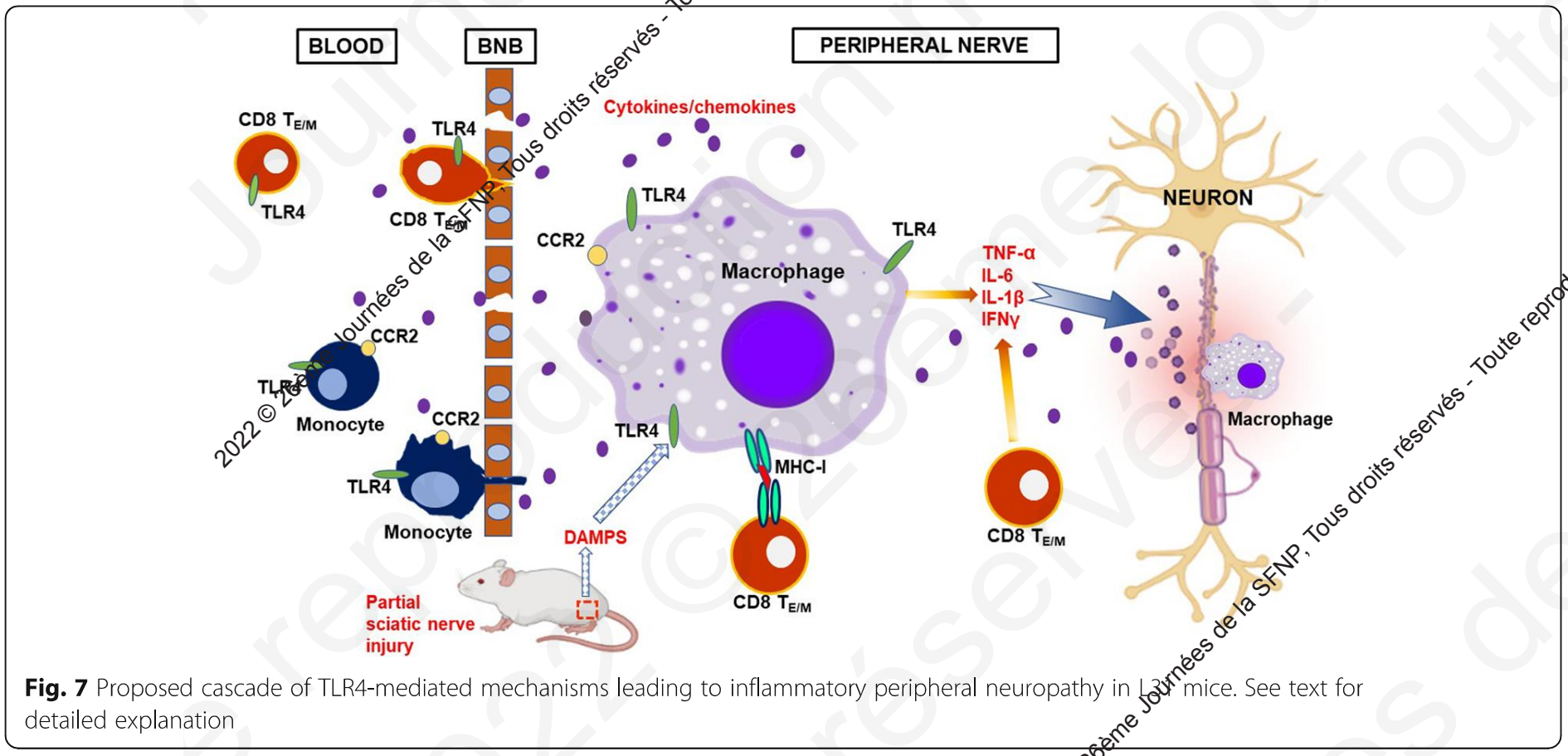
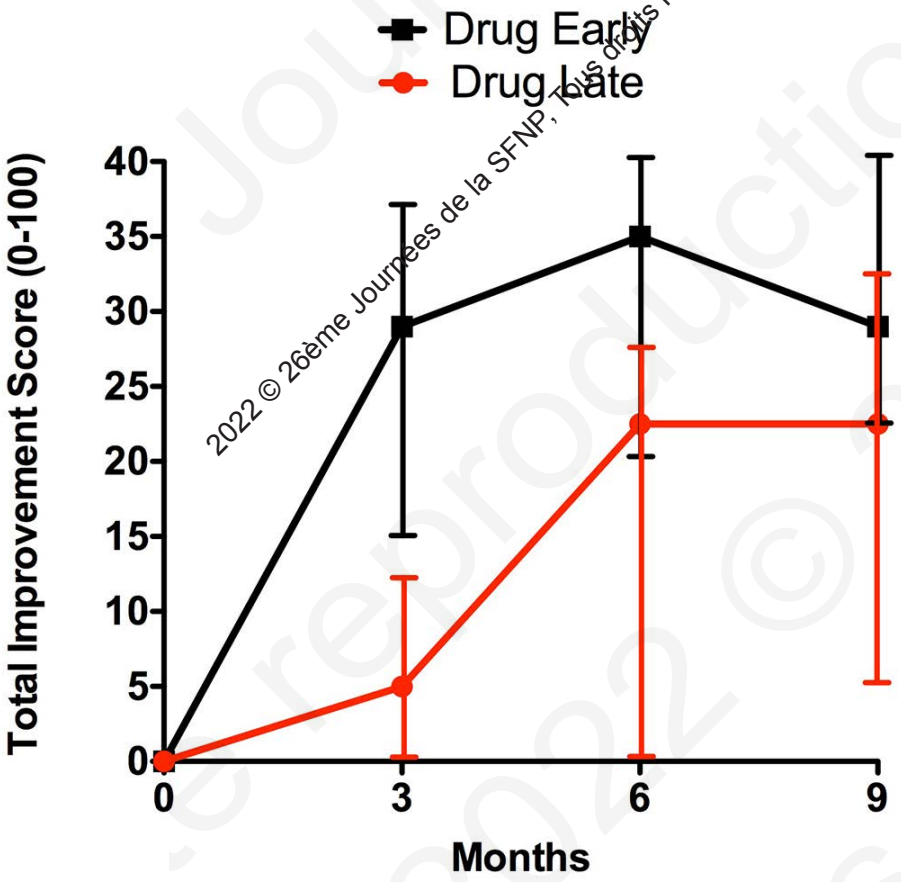


Fig. 7 Proposed cascade of TLR4-mediated mechanisms leading to inflammatory peripheral neuropathy in L3[1] mice. See text for detailed explanation

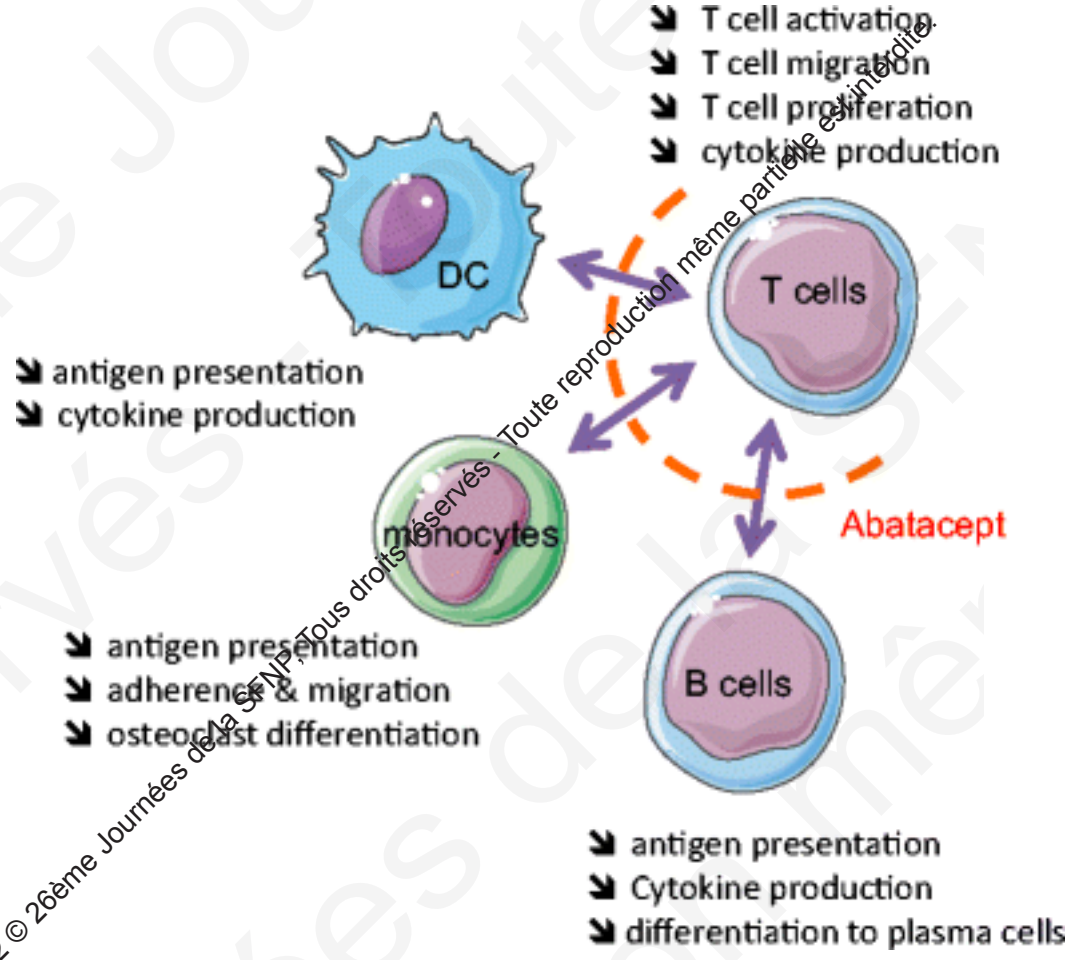
Abatacept in the treatment of adult dermatomyositis and polymyositis: a randomised, phase IIb treatment delayed-start trial

Tjärnlund A, *et al*. *Ann Rheum Dis* 2018;**77**:55–62

Anna Tjärnlund,[1] Quan Tang,[1] Cecilia Wick,[1] Maryam Dastmalchi,[1] Herman Mann,[2] Jana Tomasová Studýnková,[2] Radka Chura,[3] Nicola J Gullick,[3] Rosaria Salerno,[3] Johan Rönnelid,[4] Helene Alexanderson,[5] Eva Lindroos,[1] Rohit Aggarwal,[6] Patrick Gordon,[3] Jiri Vencovsky,[2] Ingrid E Lundberg[1]



module sélectivement un signal clé de costimulation nécessaire à l'activation complète des lymphocytes T exprimant le CD28



Cibler les cellules B

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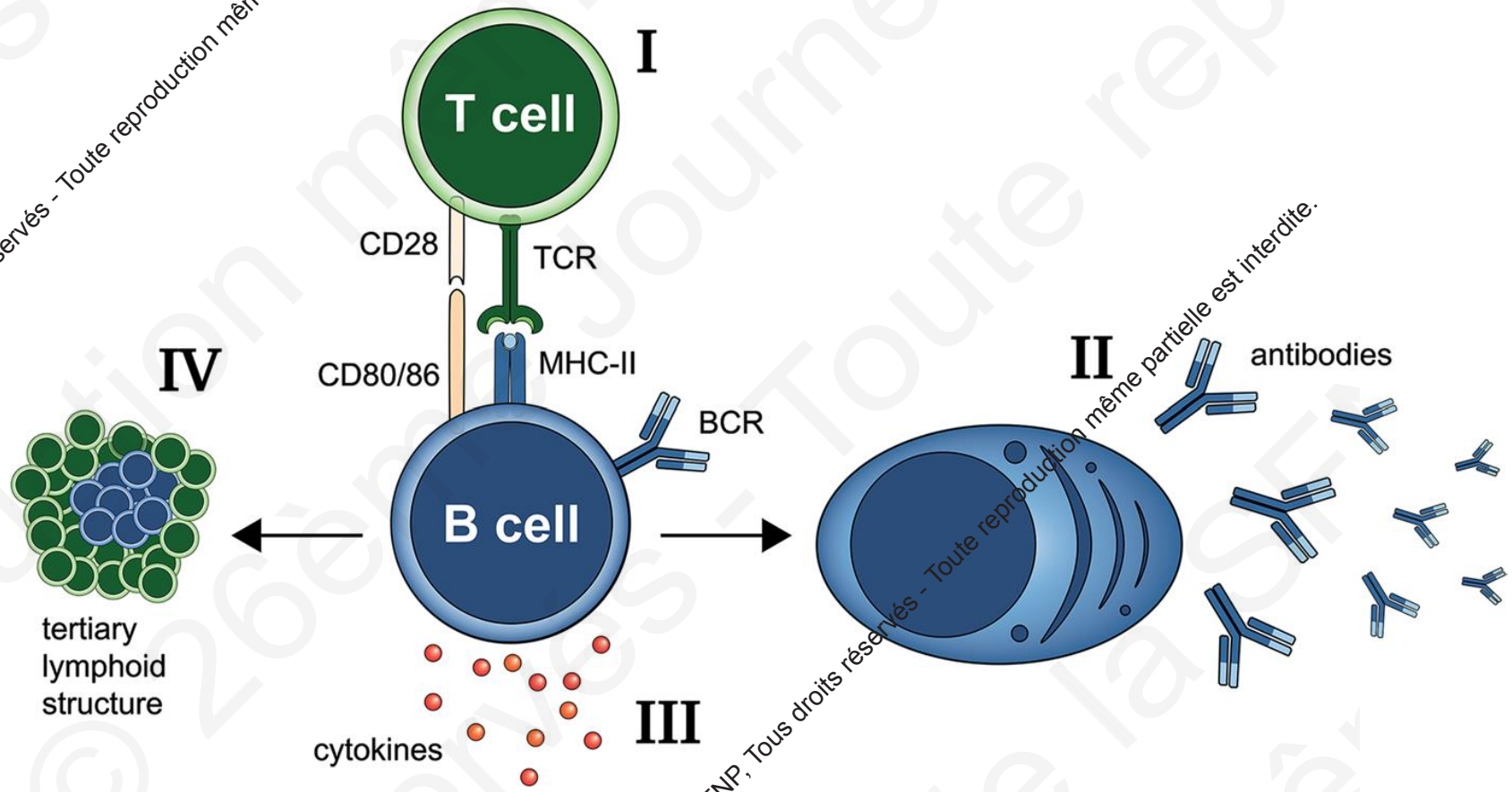
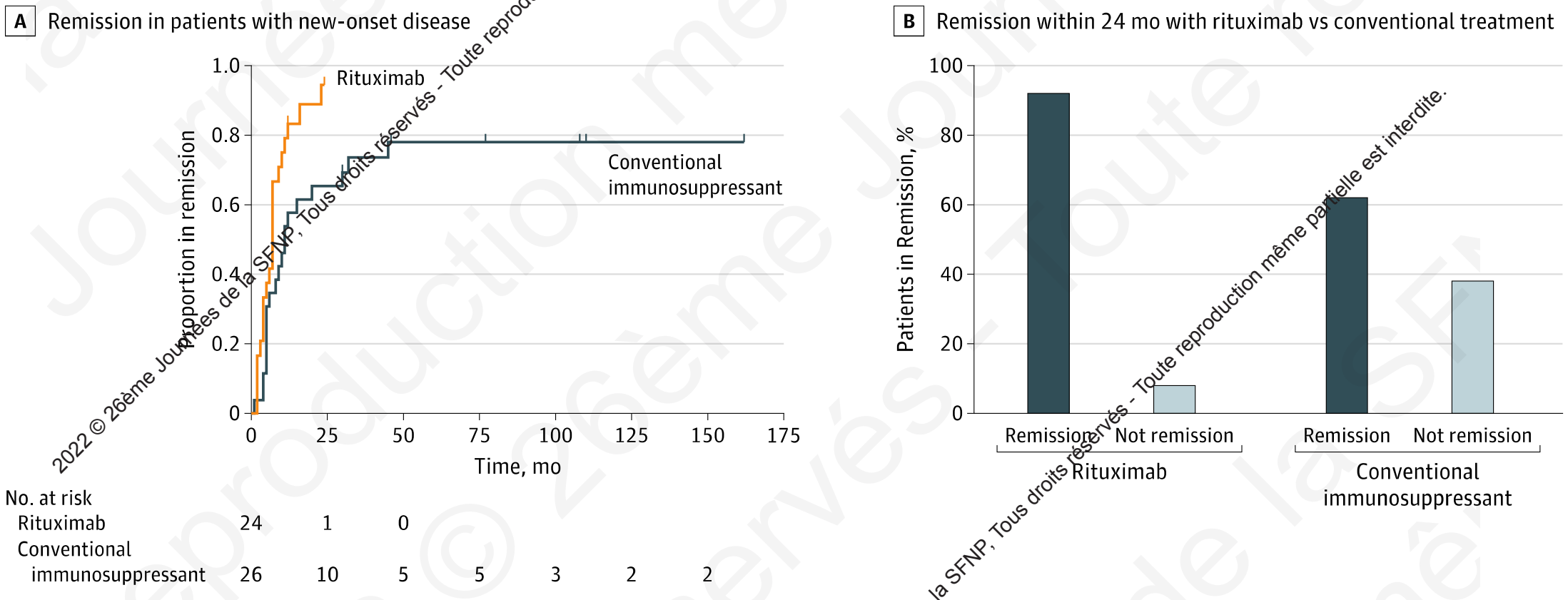


Fig. 2 The four main pathogenic roles of B cells in the context of systemic autoimmune disease. (I) Initiation or enhancement of autoimmune responses by presenting auto-antigens to T cells and concomitantly providing co-stimulatory signals. (II) B cells can differentiate into autoantibody-producing plasma cells. (III) B cells can produce pro-inflammatory cytokines. (IV) B cells are involved in stimulating the development and maintenance of these tertiary lymphoid structures

Neys et al. Drugs 2021

Myasthénie

Figure 3. Time to Remission After Exposure to Rituximab or Conventional Immunotherapy in New-Onset Myasthenia Gravis

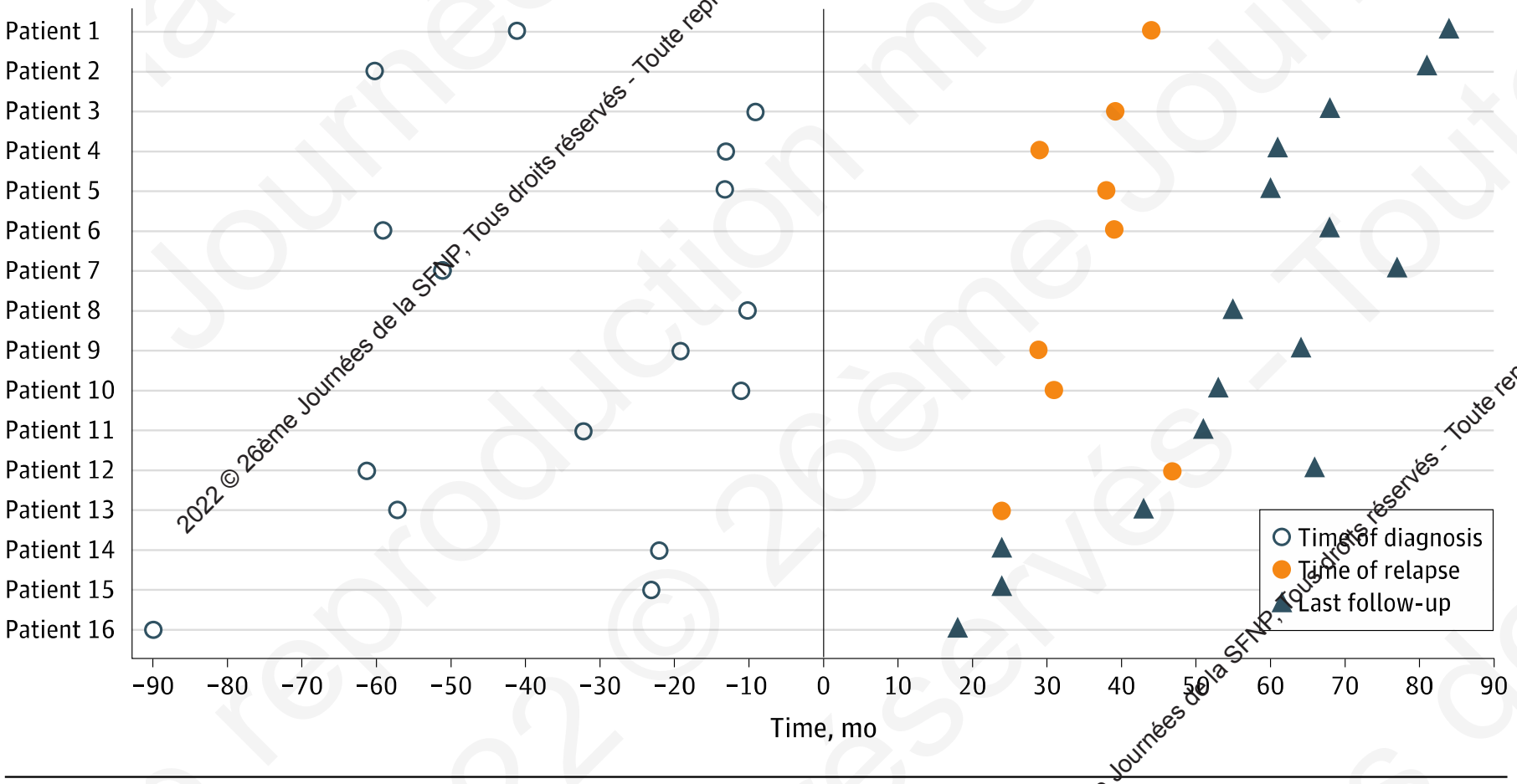


Kaplan-Meier curve of patients reaching clinical remission in new-onset patients treated with rituximab or conventional immunotherapy (A), and proportion of patients in remission within 24 months after treatment start (B).

Brauner et al. Jama Neurol 2020

Myasthénie

Figure 1. Durability of Response to Rituximab



Time of diagnosis, last follow-up visit, and time of clinical relapse are displayed. The black vertical line crossing the x-axis at 0 indicates initiation of treatment with rituximab.

Robeson et al. Jama Neurol 2016

Molécules candidates développées pour la déplétion des auto-anticorps

Molécule	Type	Voie d'administration	Stade de développement dans la myasthénie
Molécules de déplétion des lymphocytes B			
Inébilizumab (Viela Bio)[1]	 Anticorps IgG4 monoclonal humanisé	IV	Phase 3 (en cours)
TAK-079 (Takeda)[2,3]	 Anticorps IgG1 monoclonal entièrement humain	SC	Phase 2 (en cours)

FcRn, récepteur Fc néonatal ; IgG, immunoglobulines G ; IV, intraveineux ; SC, sous-cutané.

1. Huda R. *Front Immunol.* 2020;11:240. doi: 10.3389/fimmu.2020.00240. **2.** Smithson G, et al. *J Immun*. 2017;198(1 Suppl). 3. ClinicalTrials.gov. Consulté le 26 février 2021. https://clinicaltrials.gov/ct2/show/NCT04159805. **4.** Vaccaro C, et al. *Nat Biotechnol.* 2005;23:1283-1288. **5.** ClinicalTrials.gov. Consulté le 26 février 2021. https://clinicaltrials.gov/ct2/show/NCT03971422. **6.** Kiessling P, et al. *Sci Transl Med.* 2017;9:eaan1208. **7.** Ling LE, et al. *Clin Pharmacol Ther.* 2019;105:1031-1039. 8. Habib AA. Neurol Rev.2020:34-36.(Supplément). 9. Blumberg L, et al. Sci Adv. 2019;5:eaax9586. 10. Collins J, et al. Neurology. 2019;92(15 Supplément). **11**. Howard J.F Jr. *Lancet Neurol*. 2021 Jul;20(7):526-536.

Nodopathies auto-immunes

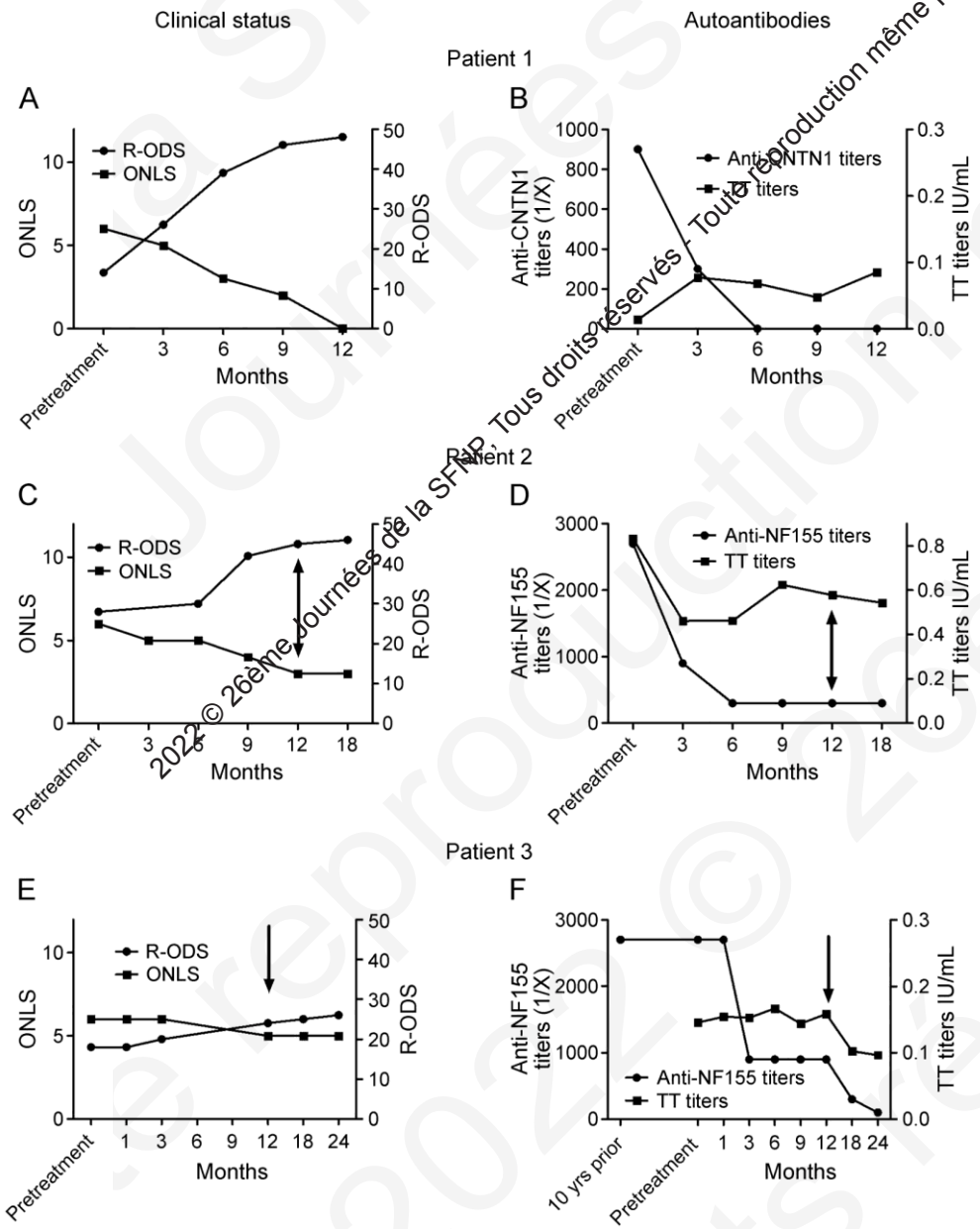


Table 2 Treatment and Clinical Response

Treatment	No. of patients (n, %)	Response (n, %)	Dose/Protocol
IVIg	38 (95%)	Yes: 5 (13.1%) Partial: 9 (23.7%) No: 24 (63.2%)	2g/kg per course
Steroids	36 (90%)	Yes: 10 (27.8%) Partial: 16 (44.4%) No: 10 (27.8%)	1 mg/kg/d: 23 (63.9%) MP iv pulse: 4 (11.1%) MP iv pulse + mg/kg/d: 5 (13.9%) Others: 4 (11.1%)
PLEX	18 (46.2%)	Yes: 7 (38.9%) Partial: 6 (33.3%) No: 5 (27.8%)	No of sessions (median, IQR): 6 (5–9)
Rituximab[a,b]	23 (57.5%)	Yes: 17 (77.3%) Partial: 3 (13.6%) No: 2 (9.1%)	4 + 2: 8 (36.4%) 4: 6 (27.3%) 4 + 1: 6 (27.3%) Others: 2 (9.1%)
Azathioprine	9 (22.5%)	Yes: 1 (11.1%) Partial: 4 (44.4%) No: 4 (44.4%)	—
Mycophenolate	3 (7.5%)	Partial: 1 (33.3%) No: 2 (66.7%)	—
Methotrexate	3 (7.5%)	Partial: 1 (33.3%) No: 2 (66.7%)	—
Cyclosporine	1 (2.5%)	No: 1 (100%)	—
Interferon beta 1a	1 (2.5%)	No: 1 (100%)	—

Querol et al. Neurol Neuroimmunol Neuroinflamm 2015, Martin-Aguilar et al. Neurol Neuroimmunol Neuroinflamm 2021

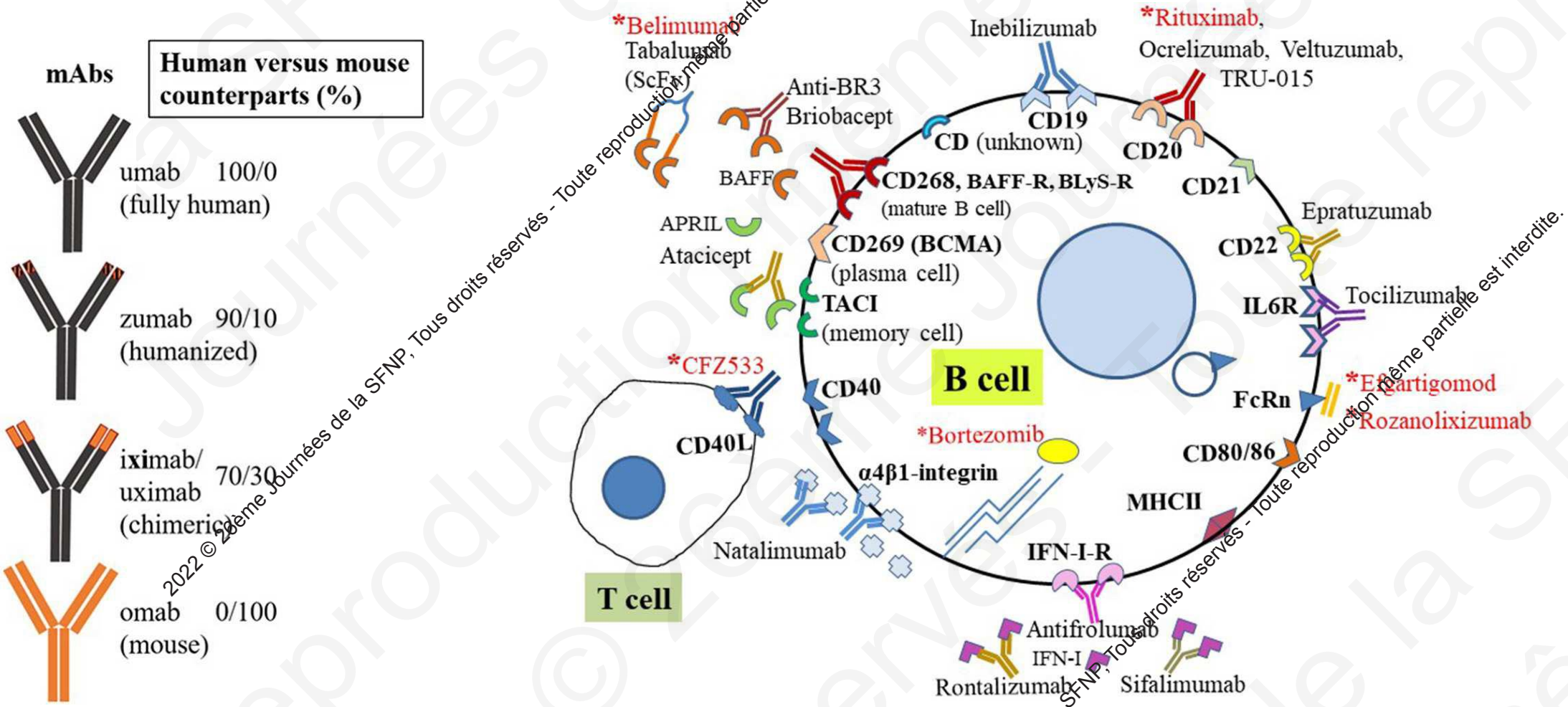
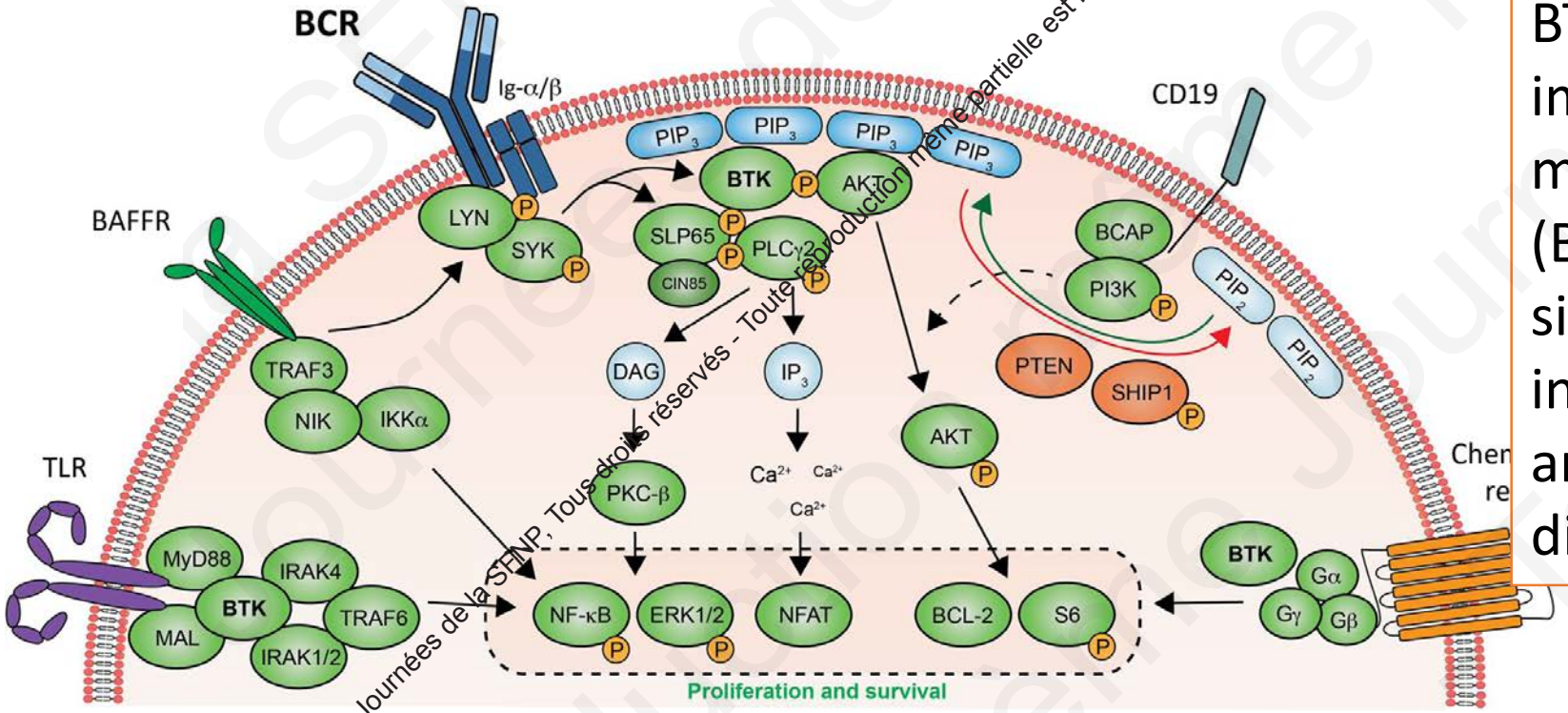


FIGURE 2 | B cell-targeting therapies using CD surface biomarkers. Schematic representation of representative CD antigens expressed on the human B cell surface and targeted for B cell-specific therapy in autoimmune diseases. Those with asterisks (red) have been targeted for potential treatment of MG and are either approved for treatment or under investigation. For direct targeting, biologics (e.g., mAb or mAb fragments) directly bind cell surface CD molecules or receptors. Indirect treatments involve targeting soluble ligands of receptors.

Huda Front Immunol 2020



BTK plays a major role in immune response and is a key mediator of B cell receptor (BCR) and Fc receptor signaling. BCR signaling is also involved with B cell activation and leads to chemotaxis, differentiation, and trafficking

Fig. 1 Role of BTK in B-cell signaling. Overview of BCR signaling and other important signaling modules for B cells. Upon BCR engagement, LYN will activate and phosphorylate Ig-α and Ig-β, subsequently activating SYK. Together with CD19-mediated activation of PI3K, this leads to the activation of SLP65, BTK, and PLCγ2. This in turn activates downstream signaling pathways crucial for proliferation and survival, including engagement of ERK, NF-κB, and downstream mediators of AKT like S6, and anti-apoptotic proteins like BCL-2. Signaling downstream of TLRs and BAFFR also involves BTK phosphorylation, leading to activation of these same proliferation and survival factors. Other receptor signaling pathways like chemokine receptor signaling also contribute to migration, proliferation, and survival of B cells. *BTK* Bruton's tyrosine kinase, *BCR* B-cell receptor, *Ig* immunoglobulin, *PTPN22* protein tyrosine phosphatase non-receptor type 22, *SYK* spleen tyrosine kinase, *PI3K* phosphoinositide 3-kinase, *SLP65* Src homology 2 domain-containing leukocyte adaptor protein of 65 kDa, *CIN85* Cbl-interacting protein of 85 kDa, *PLCγ2* phospholipase Cγ2, *DAG* diacylglycerol, *IP3* inositol triphosphate, *PKC-β* protein kinase C β, *TRAF3* TNF receptor-associated factor 3, *NIK* NF-κB-inducing kinase, *IKKα* inhibitor of NF-κB kinase, *MyD88* myeloid differentiation factor 88, *MAL* MyD88 adaptor-like, *IRAK2* interleukin-1 receptor-associated kinase 2, *ERK* extracellular signal-related kinase, *NFAT* nuclear factor of activated T cells, *BCAP* B-cell adaptor for PI3K, *PTEN* phosphatase and tensin homolog, *SHIP1* SH-2 containing inositol 5' polyphosphatase 1, *BCL-2* B-cell lymphoma-2

Développement des BTKi

Maladies prolifératives

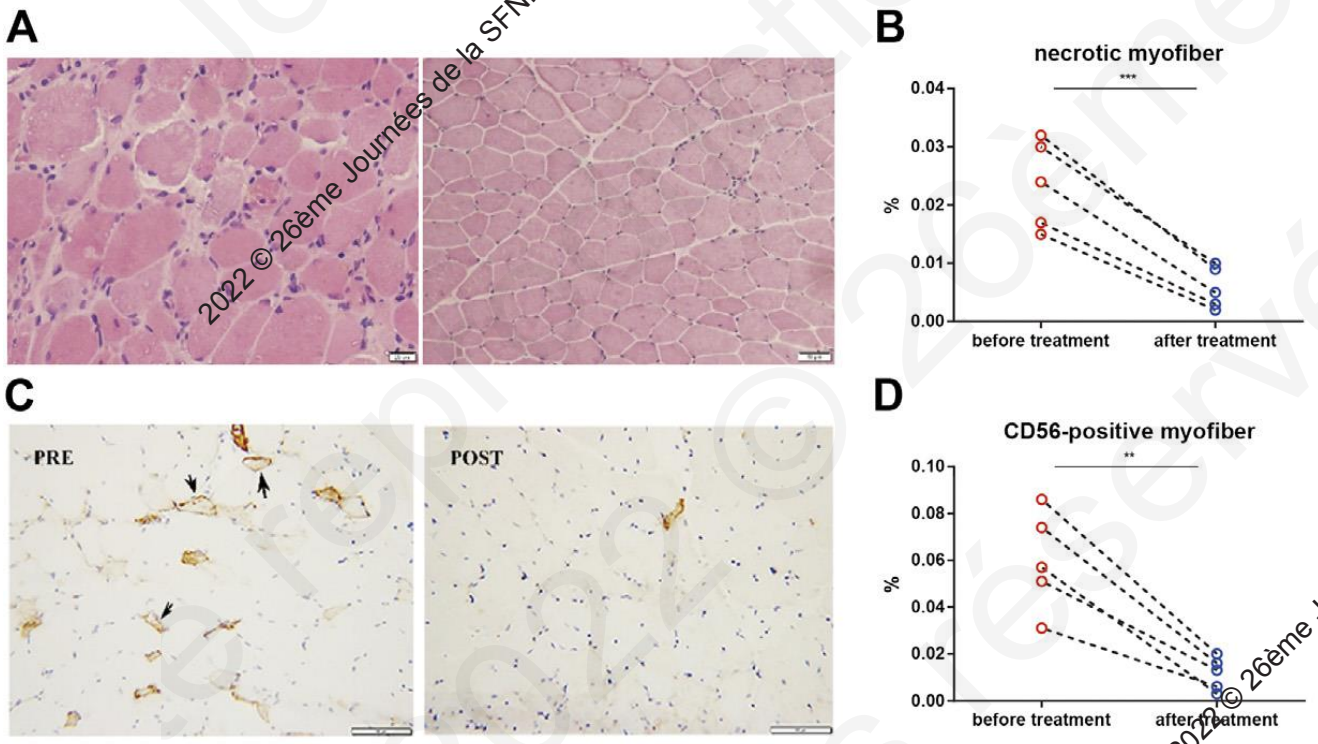
Maladies auto-immunes

Neys et al. Drugs 2021

Tocilizumab (anti-IL6R) et myosites

TABLE 2 | Six IMACS core set measures in patients with IMNM at the baseline and after 3 and 6 months of treatment with tocilizumab.

Variable[a]	Baseline	Month 3	Month 6
Physician global activity, VAS (10 cm)	6.0 (5.7–6.5)	5.0 (3.8–5.5)	3.0 (1.5–5.5)
Patient global activity, VAS (10 cm)	7.0 (6.0–7.0)	4.2 (4.0–6.0)	2.5 (2.3–6.0)
MMT-8 (0–80)	49 (42–52)	51 (49–58)	60 (53–65)
HAQ (0–3)	1.6 (1.1–1.85)	0.9 (0.6–1.3)	0.55 (0.3–0.85)
CK, IU/L (26–200)	975 (730–1751)	491 (185–702)	240 (86–416)
Extramuscular activity, VAS (10 cm)	2.0 (1.5–2.2)	2.0 (1.5–2.2)	2.0 (1.5–2.2)



Li et al. Front Pharmacol 2021

TABLE 2 Drugs under continued investigation or drug development in neuromuscular diseases

	Drug Category	Route of Administration	Disease	Study Status
Efgartigimod	Neonatal Fc receptor inhibitor	IV	Generalized MG	Phase 2 complete; phase 3 underway
Rozanolixizumab	Neonatal Fc receptor inhibitor	IV	Generalized MG CIDP	Phase 2 complete. Phase 3 ongoing Phase 2 ongoing
M281	Neonatal Fc receptor inhibitor	IV	Generalized MG	Phase 2 ongoing
Ravulizumab	Terminal complement inhibitor	IV	Generalized MG	Phase 2 complete; phase 3 underway
Zilucoplan	Terminal complement inhibitor	SQ	Generalized MG Immune-mediated necrotyzing myopathy	Phase 2 complete; phase 3 in planning stage Phase 2 study in planning stage
Belimumab	B-cell depletion therapy (B-lymphocyte stimulator inhibitor)	IV	Dermatomyositis/polymyositis	Phase 2/Phase 3 ongoing
Tocilizumab	Cytokine inhibition (IL-6 receptor antagonist)	IV	Dermatomyositis/polymyositis	Phase 2 ongoing
Abatacept	T-cell activation inhibitor	SQ	Dermatomyositis/polymyositis	Phase 2 complete; phase 3 ongoing

Farmakidis et al. Muscle Nerve 2019

Cibler les auto-anticorps

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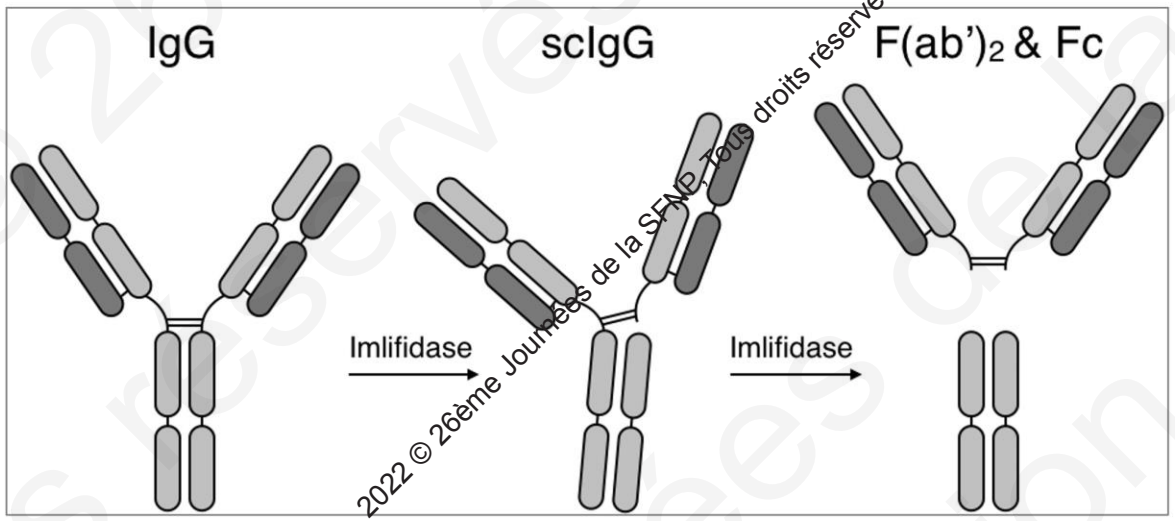
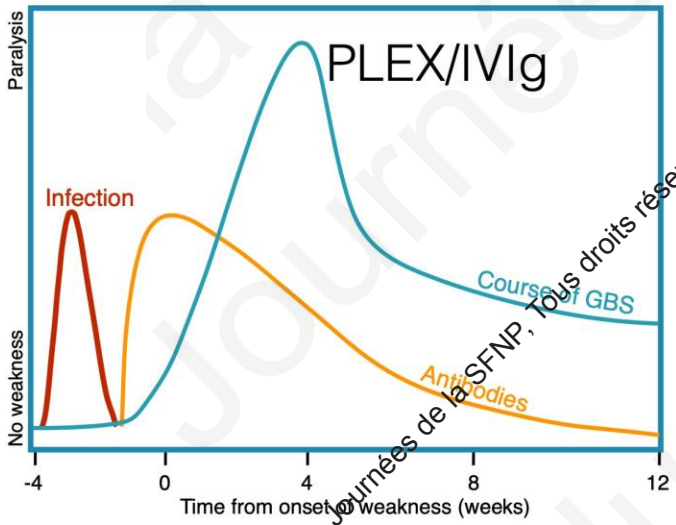
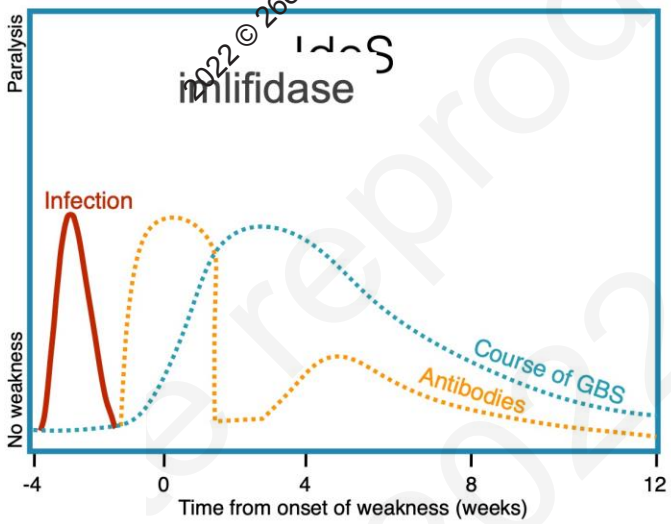
Imlifidase: IgG-degrading enzyme of *S. pyogenes* (IdeS)

- IgG-specific (not IgM, IgA, IgD or IgE)
- Cleaves all forms of IgG: free, bound to antigen and B-cell receptor (IgG-type)
- A two-step cleavage reaction
  - 1st heavy chain cleaved: single cleaved IgG (scIgG) – limited by ADA
  - 2nd heavy chain cleaved: one $F(ab')_2$ and one dimeric Fc fragment – limited by concentration
- Imlifidase treatment inhibits Fc-mediated activities
  - IgG mediated CDC (complement dependant cytotoxicity)
  - IgG mediated ADCC (antibody-dependent cell-mediated cytotoxicity)
  - IgG mediated phagocytosis



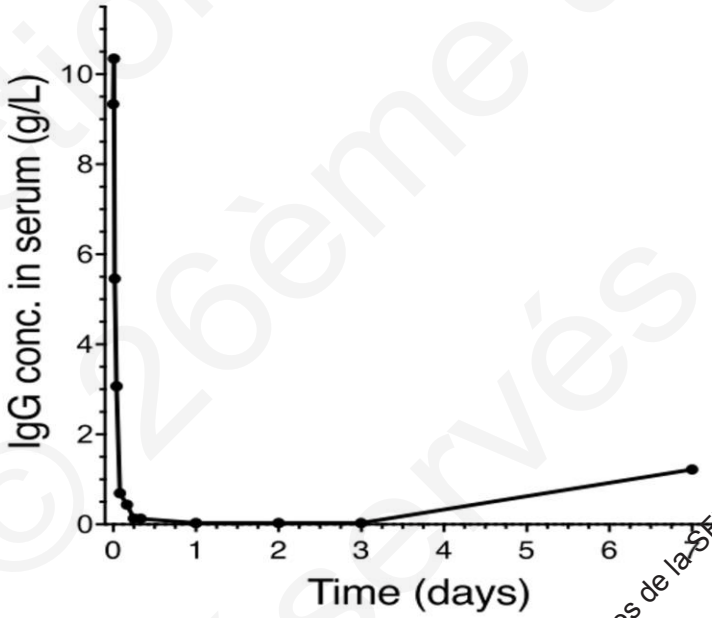
Une étude en cours dans le SGB



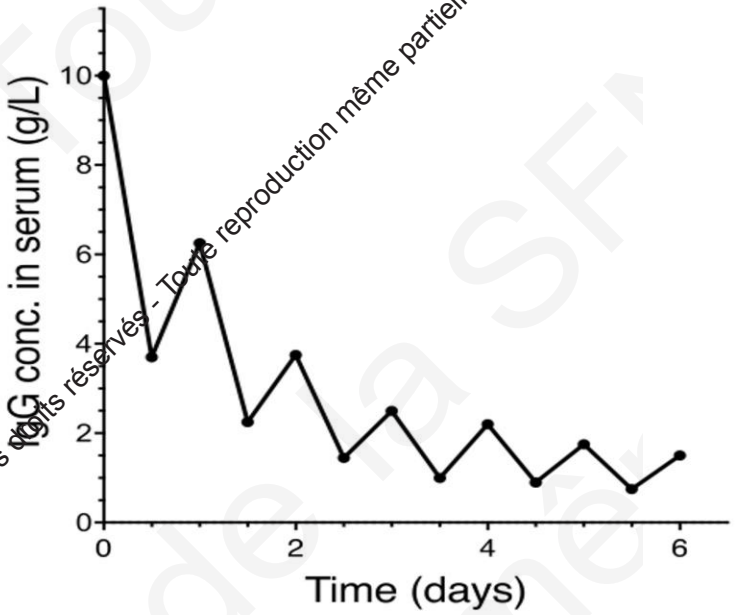


Rapidité d'action

imlifidase



PLEX



Adopted from Ismail et al., Plasmapheresis in Handbook of dialysis. Philadelphia: Lippincott Williams Wilkins. pp. 231–262.

Clinical Implications of Basic Research

The New England Journal of Medicine

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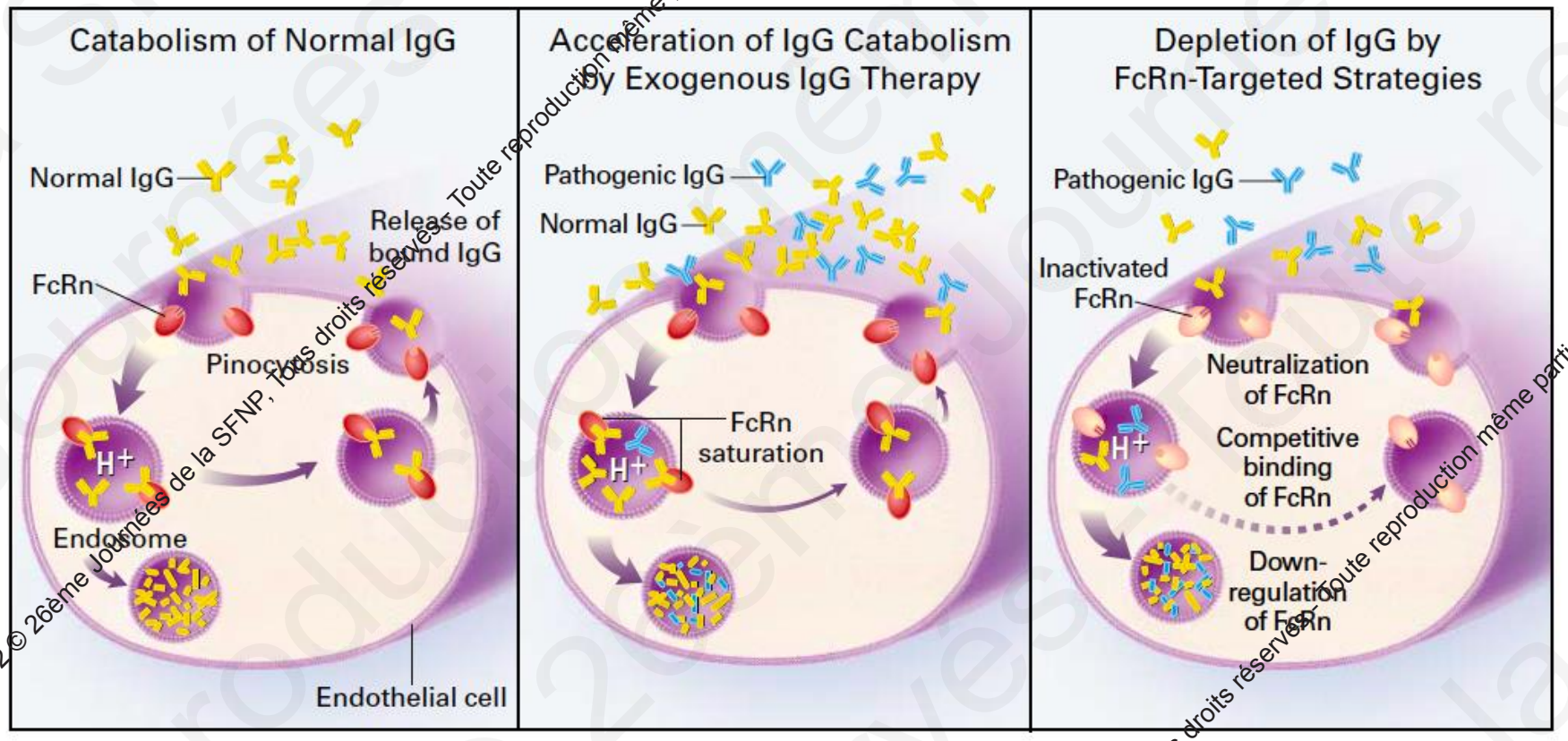


Figure 1. Regulation of the Catabolism of IgG by FcRn.

A specialized intracellular Fc receptor — FcRn — that is abundant in endothelial cells binds pinocytosed IgG only in the acidic environment of the endosome. It releases intact IgG when its transport vesicle is redirected to the neutral pH of the cell surface. Unbound IgG is transferred to lysosomes for degradation.[6] The saturation of FcRn in states of hypergammaglobulinemia accelerates the catabolism of IgG. This IgG-depleting mechanism plausibly explains the temporary benefit of intravenous therapy with high doses of normal IgG in autoimmune diseases mediated by pathogenic IgG. Alternative therapeutic strategies that inactivate the FcRn receptor would be effective for longer periods than immune globulin therapy, would be more economical, and would be devoid of the risk of infection. For example, one might design neutralizing monoclonal antibodies to modify FcRn covalently, synthetic ligands with a higher affinity than IgG for the receptor and that would thus saturate FcRn, or antisense nucleotides to down-regulate the expression of FcRn. With the use of such strategies, levels of IgG would not rebound because the synthesis of IgG is driven by immunogenic stimulation and is not affected by the rate of catabolism.

Antogonistes du FcRn en développement dans les maladies neuromusculaires

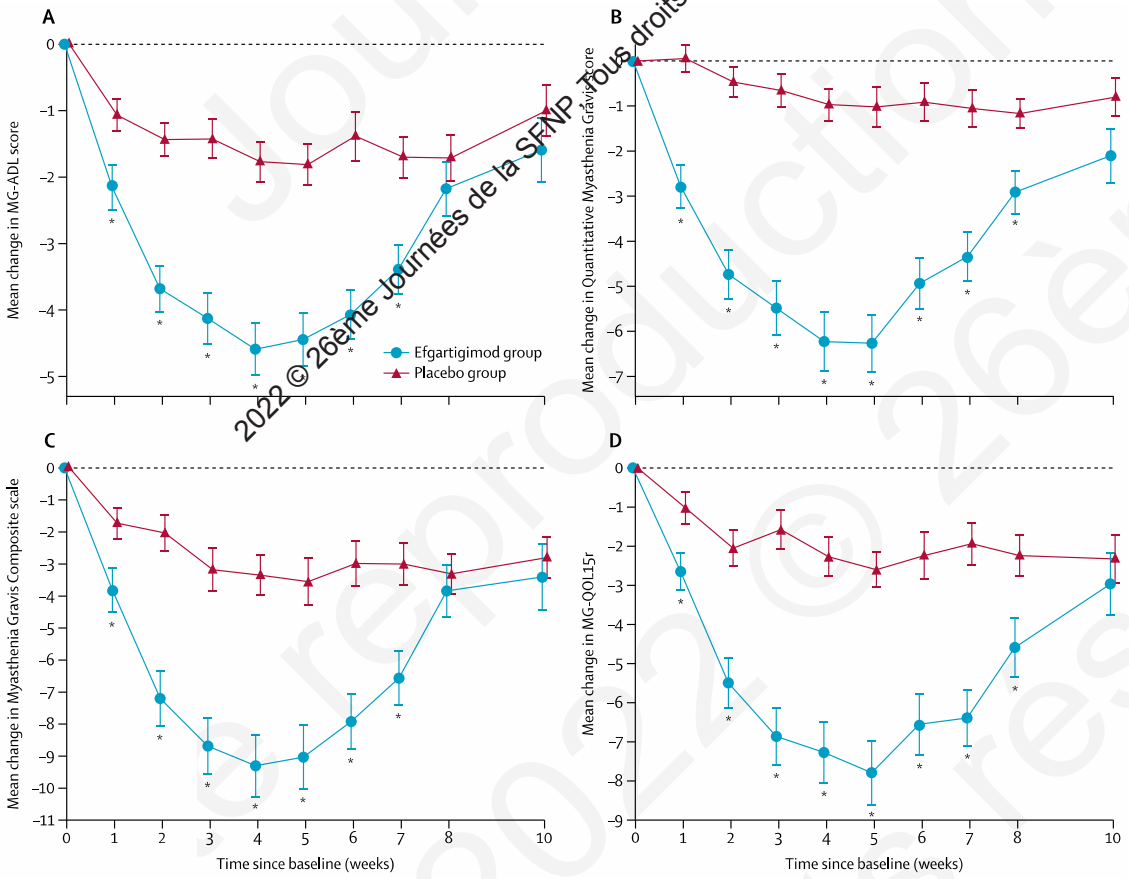
Molécule	Type	Développement dans les maladies neuromusculaires
Efgartigimod	Portion Fc d'IgG1 mutée	PIDC Myasthénie
Rozanolixizumab	Ac monoclonal (IgG4)	PIDC Myasthénie
Nipocalimab	Ac monoclonal (IgG1)	Myasthénie

Efgartigimod

	Efgartigimod group	Placebo group	OR (95% CI)	p value
MG-ADL responder in cycle 1 (primary endpoint)	44/65 (68%)	19/64 (30%)	4·95 (2·21–11·53)	<0·0001
Quantitative Myasthenia Gravis responder in cycle 1	41/65 (63%)	9/64 (14%)	10·44 (4·18–31·20)	<0·0001
MG-ADL responder in cycle 1 (all patients)	57/84 (68%)	31/83 (37%)	3·70 (1·85–7·58)	<0·0001
Percentage of time with ≥2-point improvement in MG-ADL up to day 126	48·7%	26·6%	..	0·0001
Median time from day 28 until no clinically meaningful improvement, days	35 (18–71)	8 (1–57)	..	0·26
Early MG-ADL responder (cycle 1)	37/65 (57%)	16/64 (25%)	..	Not assessed*

Data are n/N (%), or median (IQR), unless stated otherwise. Analyses were done in acetylcholine receptor antibody-positive patients unless otherwise stated. MG-ADL=Myasthenia Gravis Activities of Daily Living. *Secondary endpoints were tested in hierarchical order. The fifth secondary endpoint was not assessed because the fourth secondary endpoint was not significant.

***Table 2*: Summary of primary and secondary endpoints**



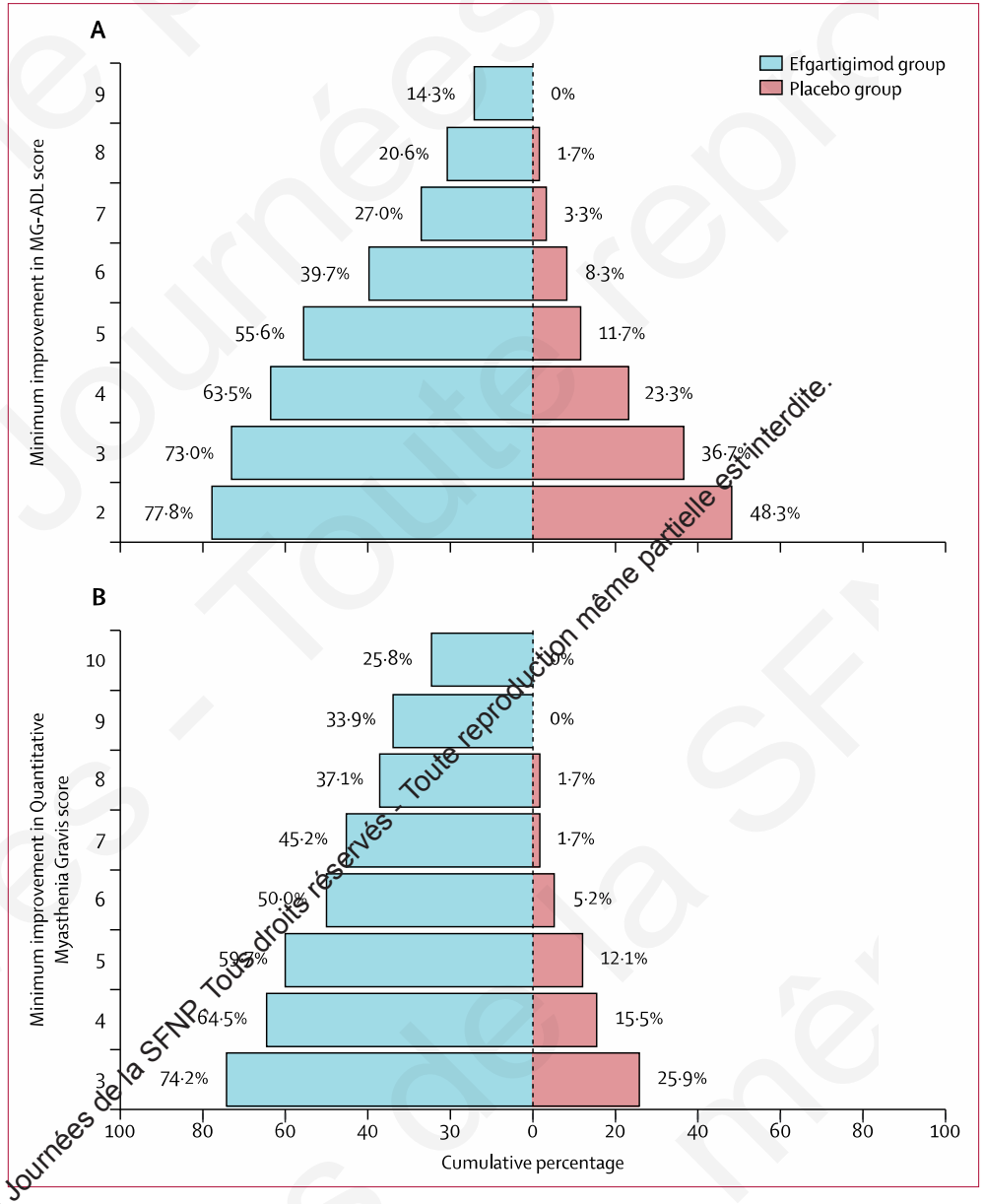
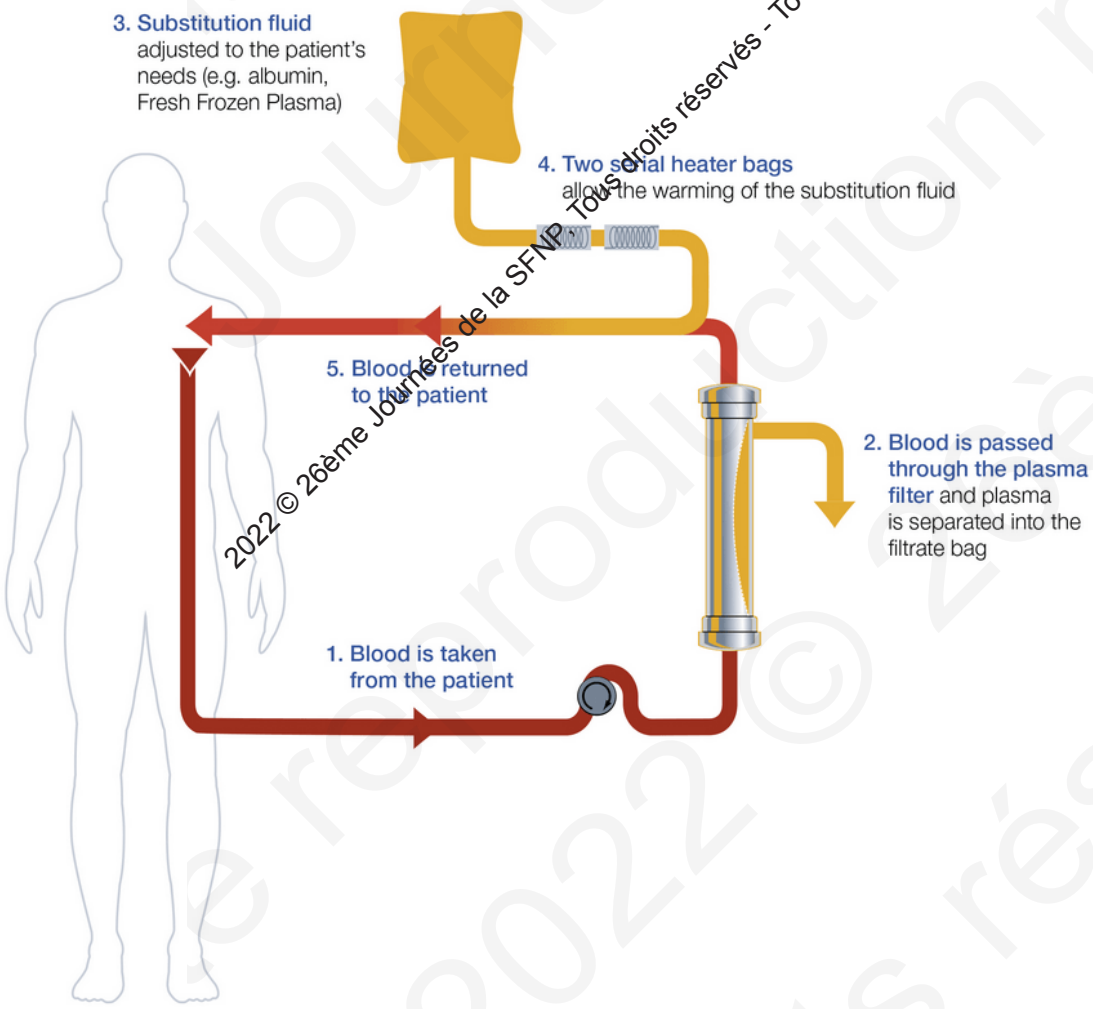
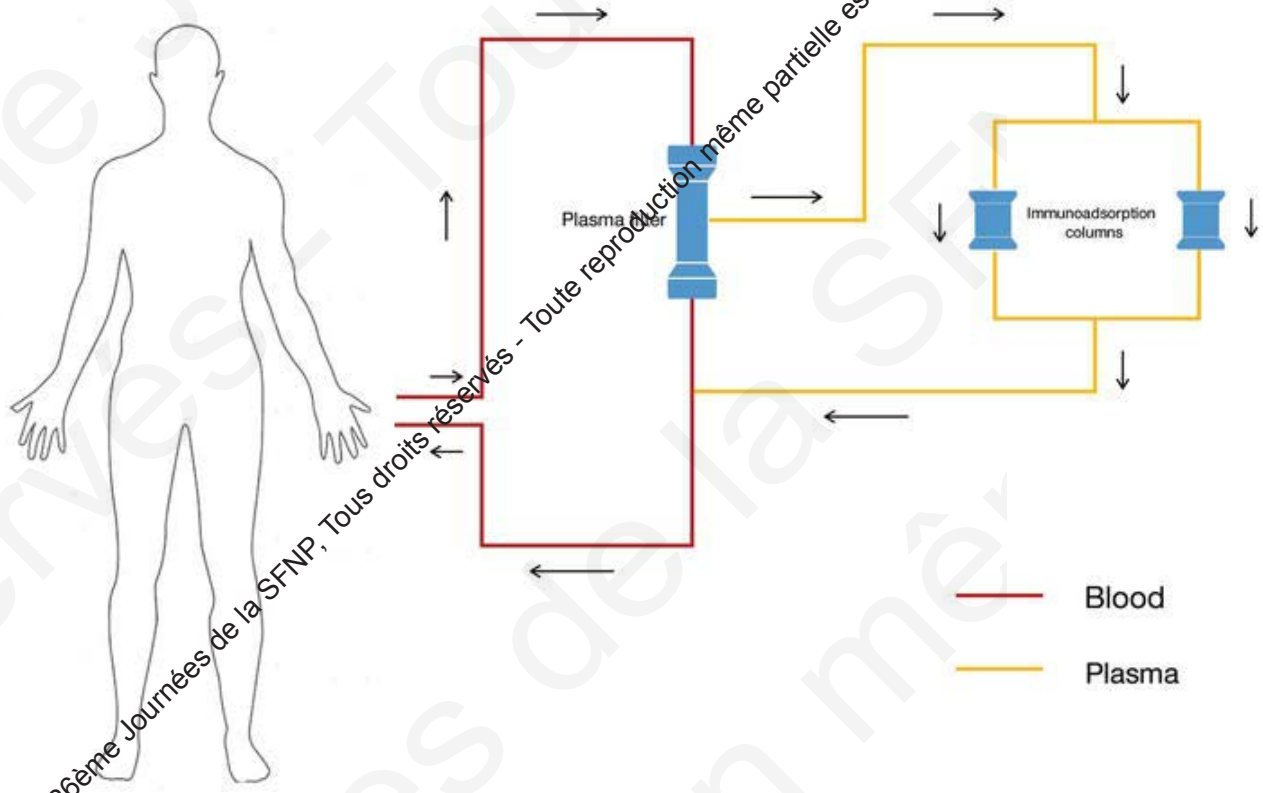


***Figure 3*: Minimum point improvement in MG-ADL (A) and Quantitative Myasthenia Gravis (B) score in cycle 1, in acetylcholine receptor antibody-positive patients**
Minimum improvements 1 week after the last infusion of cycle 1 (week 4). MG-ADL=Myasthenia Gravis Activities of Daily Living.

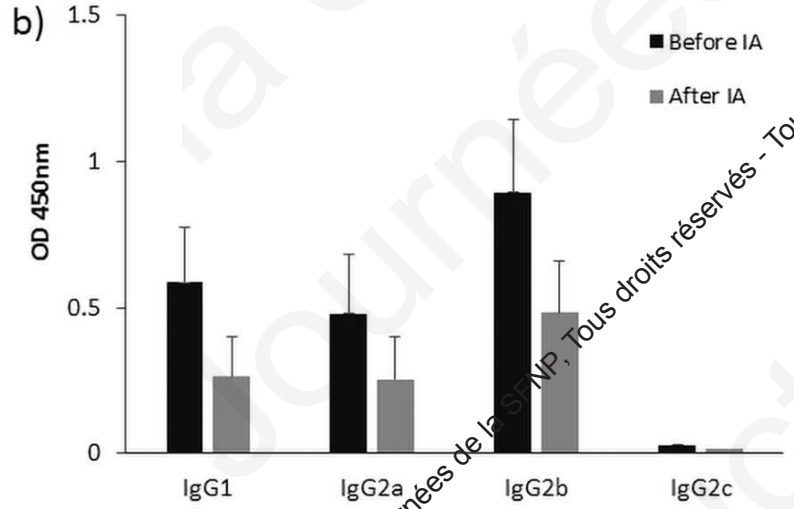
Howard et al. Lancet Neurol 2021

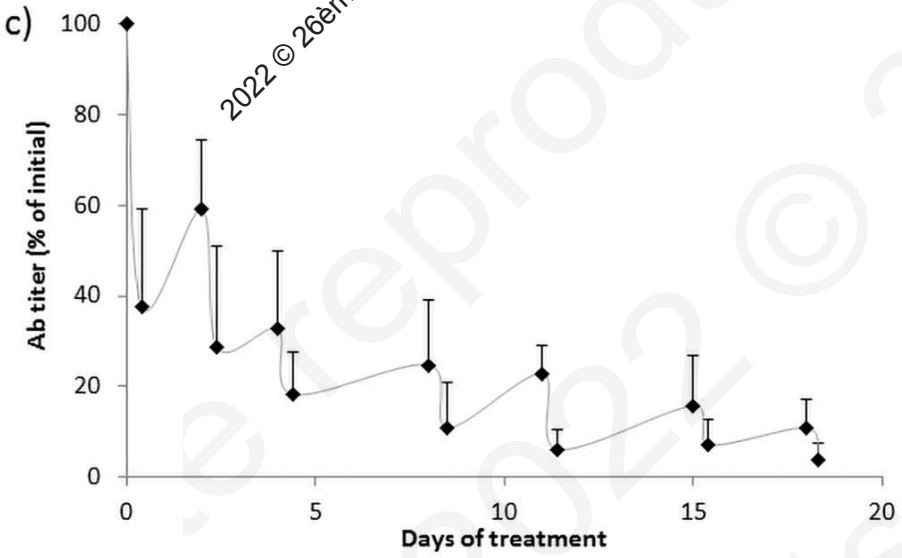
Échanges plasmatiques et immunoadsorption





Immunoadsorption ciblée sur l'antigène





Antigen-specific immunoadsorption of MuSK autoantibodies as a treatment of MuSK-induced experimental autoimmune myasthenia gravis

Konstantinos Lazaridis[a,*], Vasiliki Baltatzidou[a], Nikolaos Tektonidis[a], Socrates J. Tzartos[a,b,*]

Immunoadsorption :
Retirer IgG, IgM…

Antigen specific immunoadsorption :
Retirer sélectivement un anticorps

Théoriquement applicable à n'importe quelle maladie à auto-anticorp

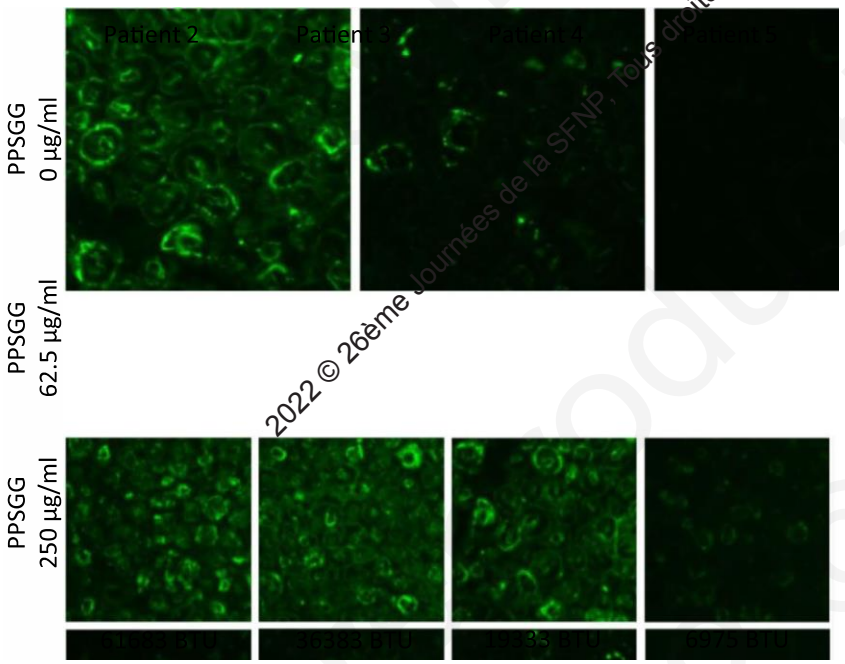
Lazaridis et al. J Neuroimmunol 2020

Selective inhibition of anti-MAG IgM autoantibody binding to myelin by an antigen-specific glycopolymer

Journal of Neurochemistry. 2020;154:486–501.

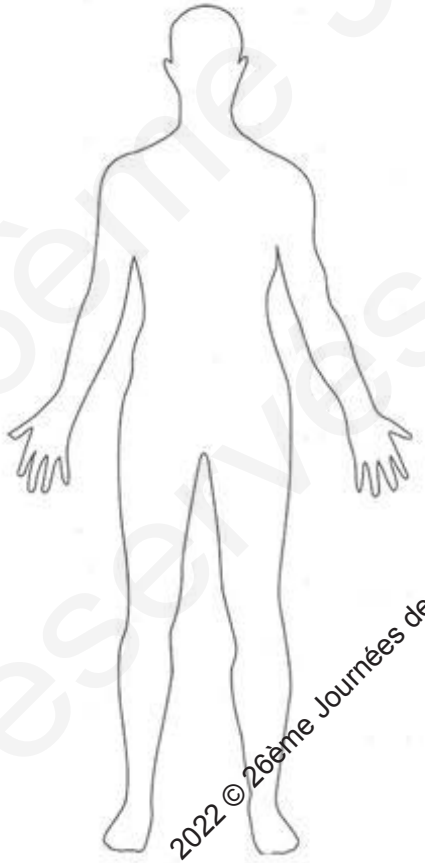
Butrint Aliu[1] | Delphine Demeestere[1] | Emilie Seydoux[2] | José Boucraut[3,4] | Emilien Delmont[5] | Alexandre Brodovitch[3,5] | Thomas Obenholzer[2] | Shahram Attarian[5] | Marie Théaudin[6] | Pinelopi Tsouni[6] | Thierry Kuntzer[6] | Tobias Derfuss[7] | Andreas J. Steck[7] | Beat Ernst[1] | Ruben Herrendorff[1,2] | Pascal Hänggi[1,2]

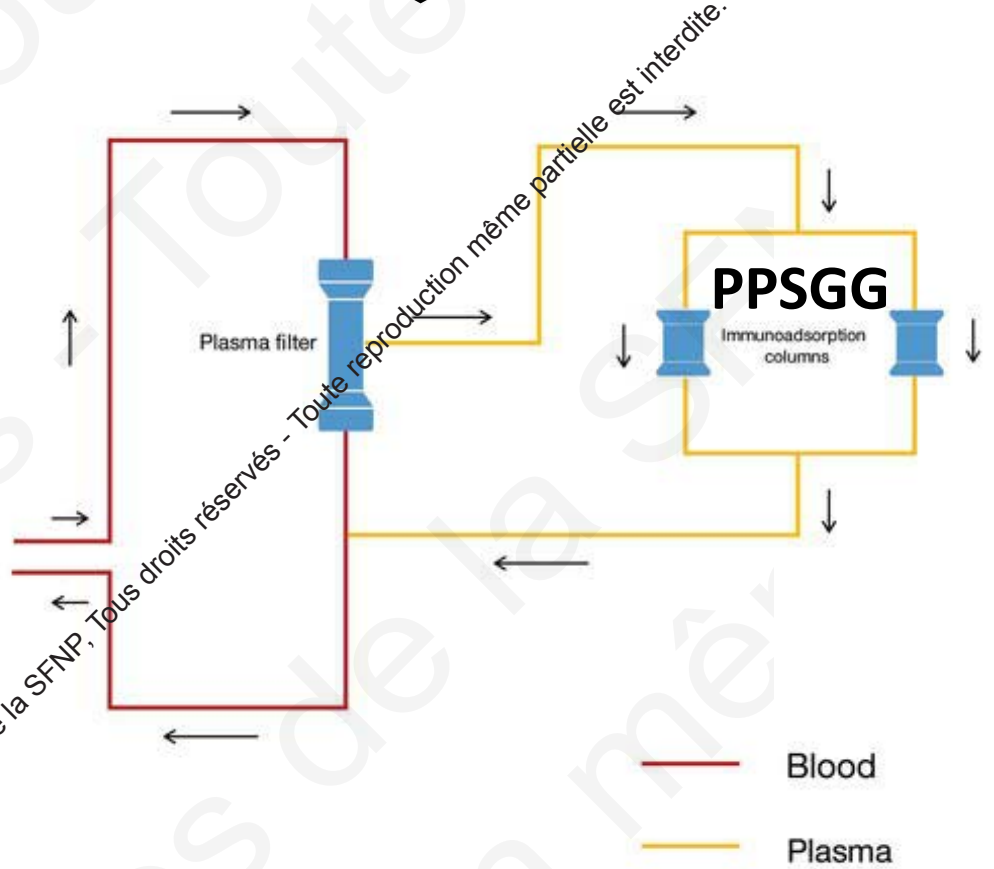
PPSGG



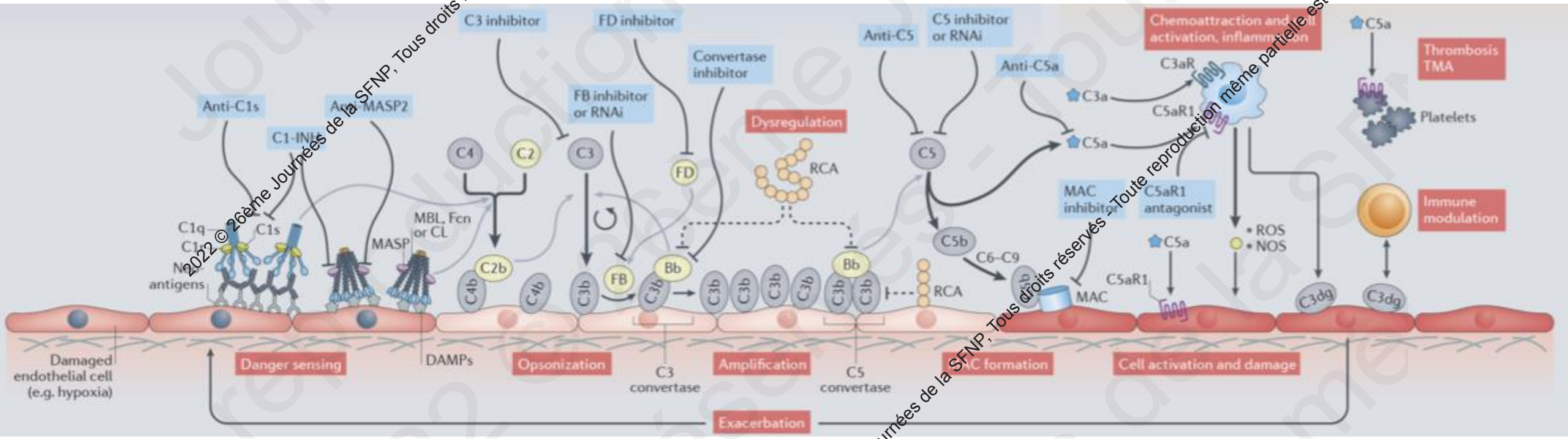
3.2 | Fast and efficient removal of circulating anti-HNK-1 IgM by PPSGG in BALB/c mice, while CD20$^+$ cell depletion showed no significant effect on the anti-MAG IgM titers in the immunological mouse model for anti-MAG neuropathy

Effets indésirables lors de la première administration à l'humain





Cibler le complément



Ricklin et al. Nat Rev Drugs Discov 2019

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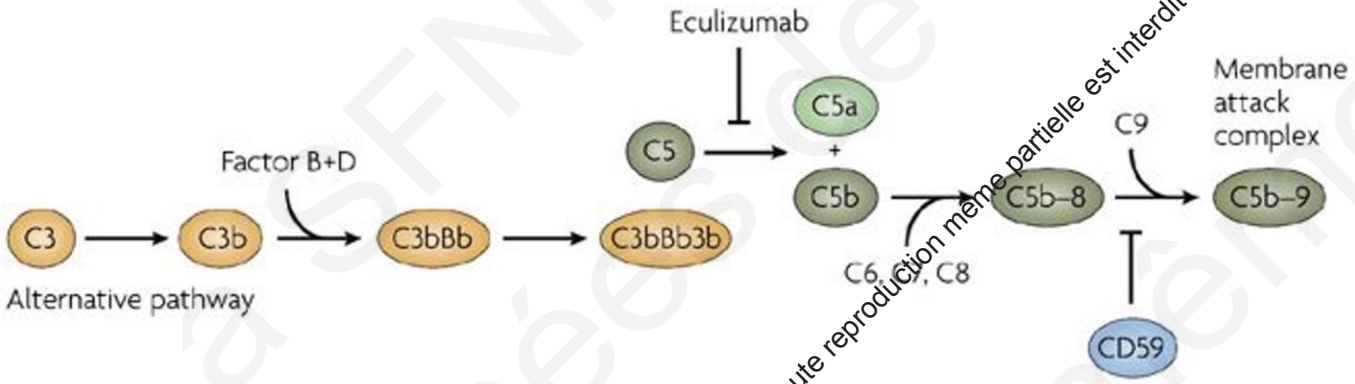
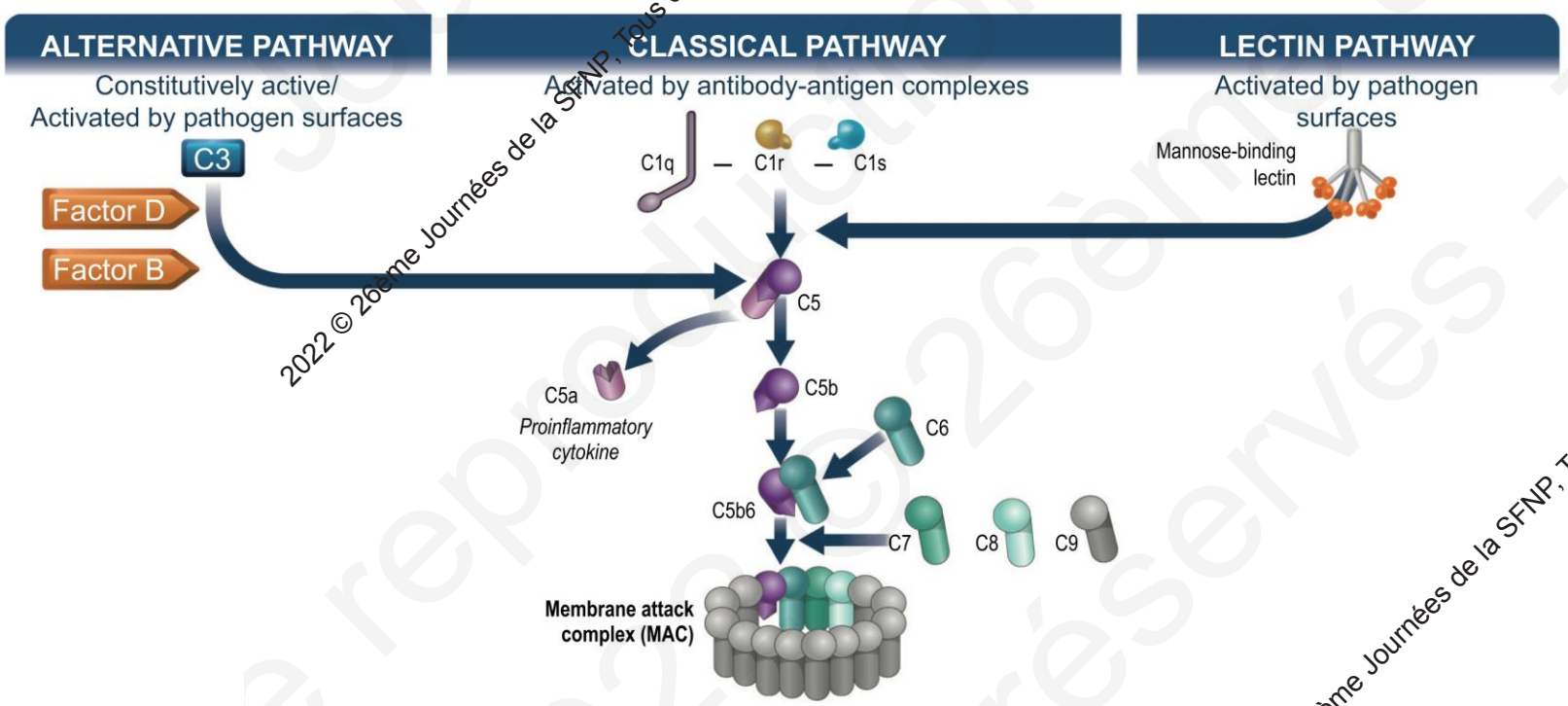
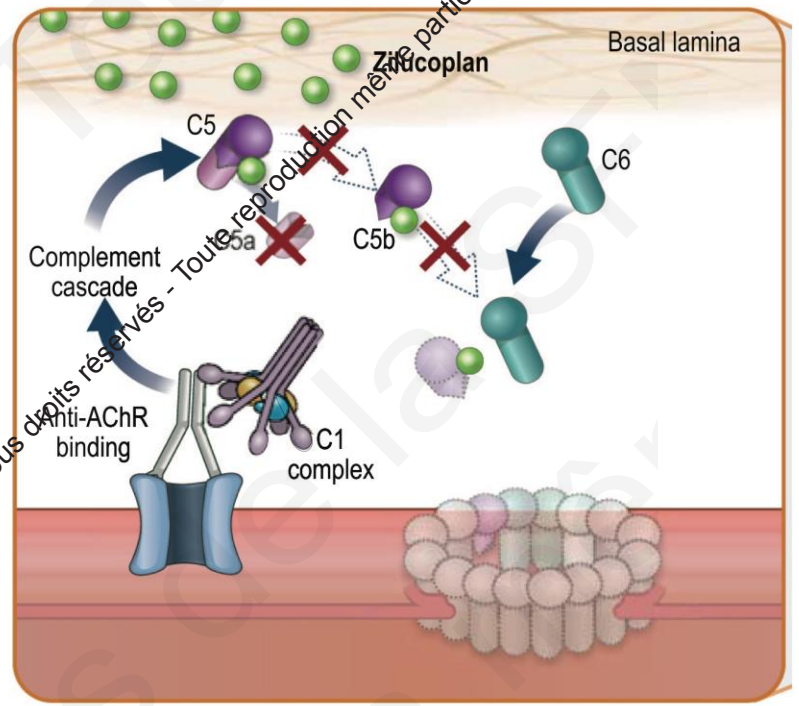


Direct inhibition of the complement pathway

Résultats 'négatifs' dans le SGB





Salles et al. Adv Therapy 2017, Howard et al. Exp Opin Investig Drugs 2021

Safety and efficacy of eculizumab in Guillain-Barré syndrome: a multicentre, double-blind, randomised phase 2 trial

Lancet Neurol 2018; 17: 519–29

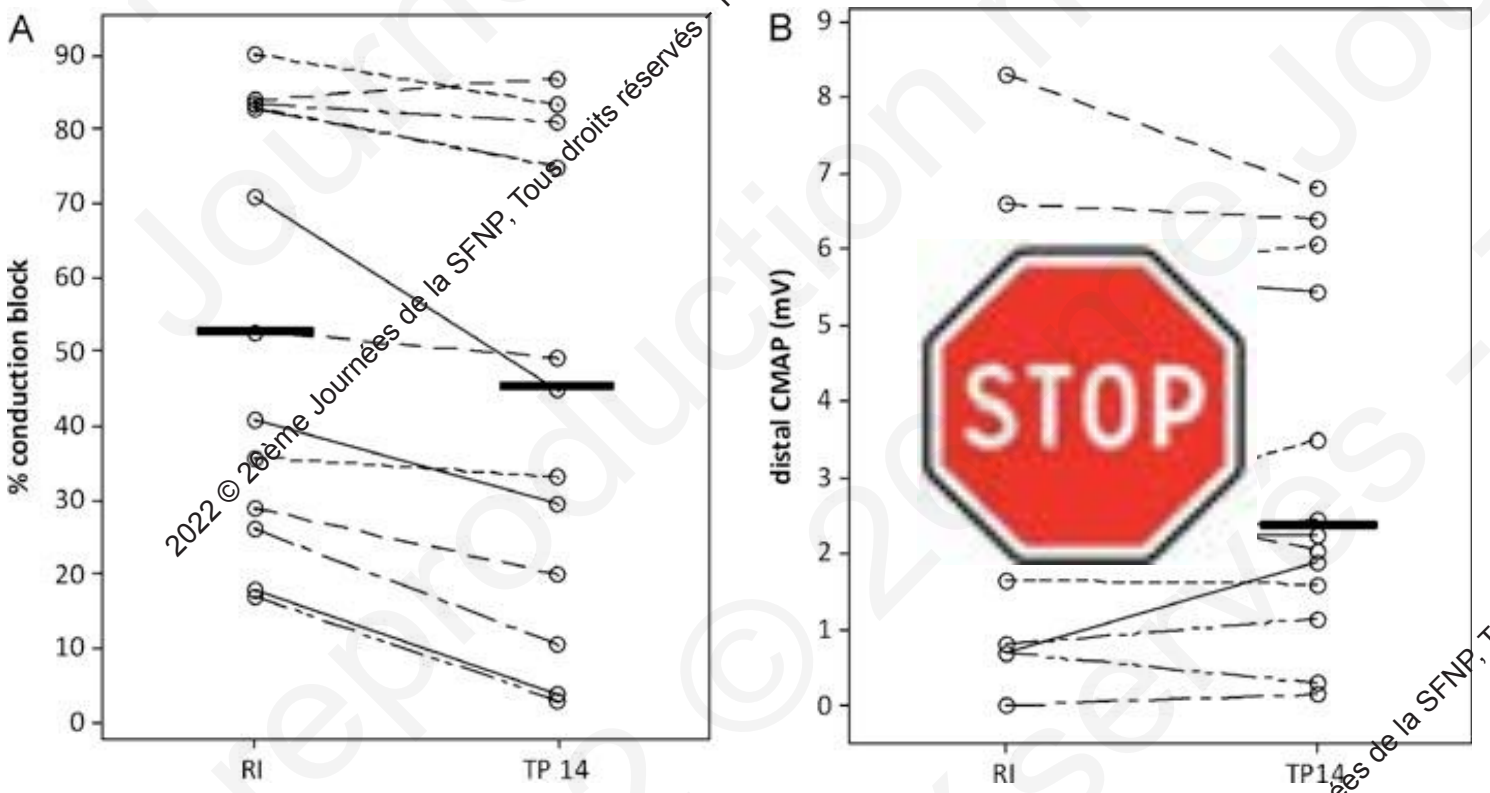
*Sonoko Misawa, Satoshi Kuwabara, Yasunori Sato, Nobuko Yamaguchi, Kengo Nagashima, Kanako Katayama, Yukari Sekiguchi, Yuta Iwai, Hiroshi Amino, Tomoki Suichi, Takanori Yokota, Yoichiro Nishida, Tadashi Kanouchi, Nobuo Kohara, Michi Kawamoto, Junko Ishii, Motoi Kuwahara, Hidekazu Suzuki, Koichi Hirata, Norito Kokubun, Ray Masuda, Junpedro Kaneko, Ichiro Yabe, Hidenao Sasaki, Ken-ichi Kaida, Hiroshi Takazaki, Norihiro Suzuki, Shigeaki Suzuki, Hiroyuki Nodera, Naoko Matsui, Shoji Tsuji, Haruki Koike, Ryo Yamasaki, Susumu Kusunoki, for the Japanese Eculizumab Trial for GBS (JET-GBS) Study Group**

	Eculizumab (n=23)	Placebo (n=11)	Between-group difference (95% CI)	p value
Primary outcome				
Able to walk 5 m independently (functional grade ≤2)				
Week 4, % (90% CI)	61% (42 to 78)		15% (−20 to 51)	..
Number of patients	14/23		..	..
Able to run (functional grade ≤1)§				
Week 24, % (95% CI)	74% (52 to 90)	18% (2 to 52)	56% (27 to 85)	0·004
Number of patients	17/23	2/11	..	..

An open label clinical trial of complement inhibition in multifocal motor neuropathy

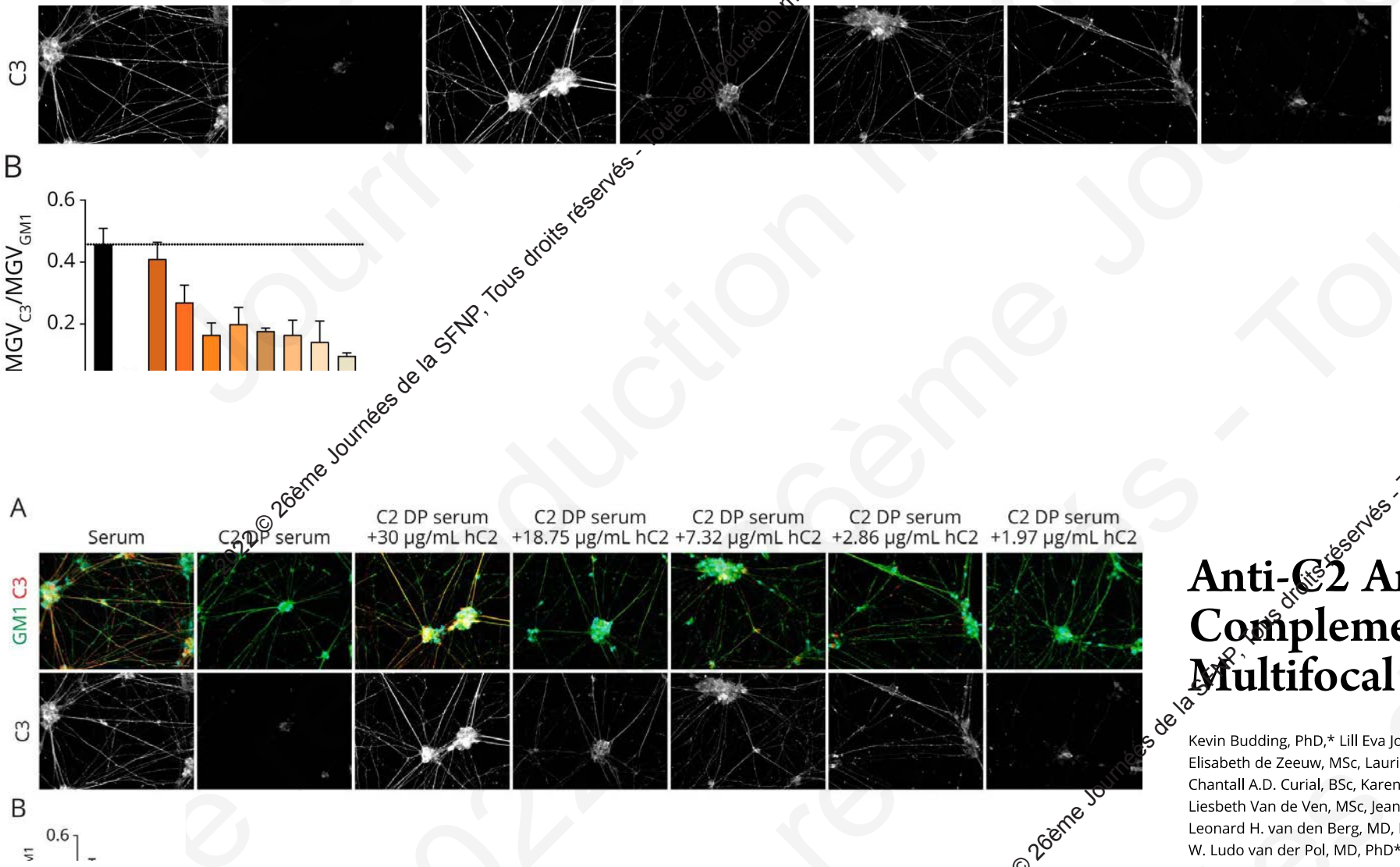
Journal of the Peripheral Nervous System 16:84–91 (2011)

Amanda M. Fitzpatrick[1,2], Cameron A. Mann[3], Sarah Barry[4], Katie Brennan[1,2], James R. Overell[2], and Hugh J. Willison[1,2]



Overall, a small treatment effect occurred in some patients that appeared supplementary to and independent of the IVIg treatment effect, and occurred more frequently in patients with higher baseline motor function.

Figure 5 Complement Activation by IgM Anti-GM1 Bound to MNs Is C2 Dependent and Can Be Inhibited by ARGX-117



Anti-C2 Antibody ARGX-117 Inhibits Complement in a Disease Model for Multifocal Motor Neuropathy

Kevin Budding, PhD,* Lill Eva Johansen, MSc,* Inge Van de Walle, PhD, Kim Dijkxhoorn, BSc, Elisabeth de Zeeuw, MSc, Lauri M. Bloemenkamp, BSc, Jeroen W. Bos, MD, Marc D. Jansen, BSc, Chantall A.D. Curial, BSc, Karen Silence, PhD, Hans de Haard, PhD, Christophe Blanchetot, PhD, Liesbeth Van de Ven, MSc, Jeanette H.W. Leusen, PhD, R. Jeroen Pasterkamp, PhD, Leonard H. van den Berg, MD, PhD, C. Erik Hack, MD, PhD, Peter Boross, PhD,* and W. Ludo van der Pol, MD, PhD*

Neurol Neuroimmunol Neuroinflamm 2022;9:e1107. doi:10.1212/NXI.0000000000001107

Inhibiteurs du complément en développement dans les maladies neuromusculaires

Molécule	Cible	Type	Développement dans les maladies neuromusculaires
Eculizumab	C5	Ac monoclonal	SGB  Myasthénie
Ravulizumab	C5	Ac monoclonal	Myasthénie
Zilucoplan	C5	Peptide synthétique	Myasthénie
ARGX-117	C2	Ac monoclonal	NMM

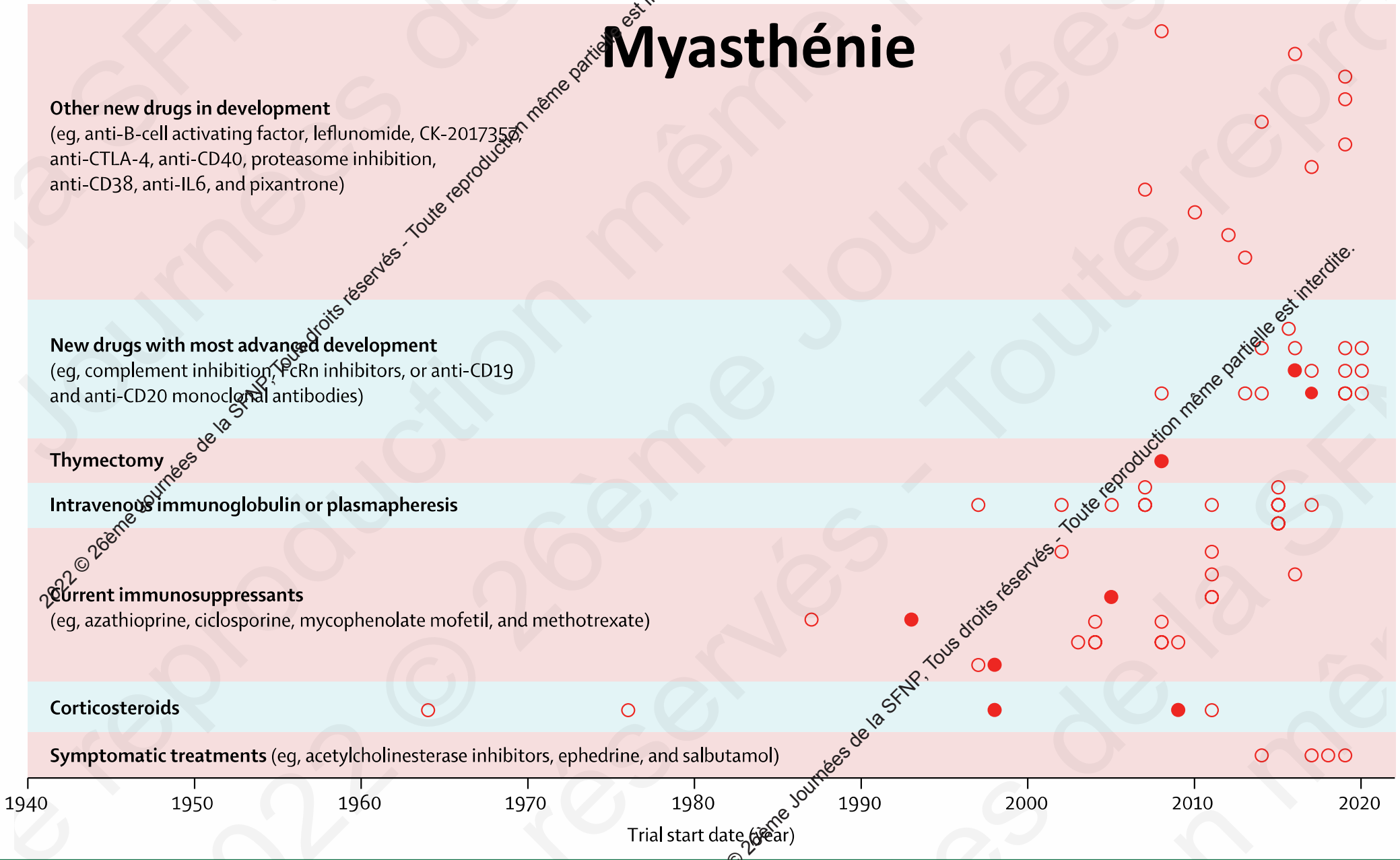
TABLE 2 Drugs under continued investigation or drug development in neuromuscular diseases

	Drug Category	Route of Administration	Disease	Study Status
Efgartigimod	Neonatal Fc receptor inhibitor	IV	Generalized MG	Phase 2 complete; phase 3 underway
Rozanolixizumab	Neonatal Fc receptor inhibitor	IV	Generalized MG CIDP	Phase 2 complete. Phase 3 ongoing Phase 2 ongoing
M281	Neonatal Fc receptor inhibitor	IV	Generalized MG	Phase 2 ongoing
Ravulizumab	Terminal complement inhibitor	IV	Generalized MG	Phase 2 complete; phase 3 underway
Zilucoplan	Terminal complement inhibitor	SQ	Generalized MG Immune-mediated necrotyzing myopathy	Phase 2 complete; phase 3 in planning stage Phase 2 study in planning stage
Belimumab	B-cell depletion therapy (B-lymphocyte stimulator inhibitor)	IV	Dermatomyositis/polymyositis	Phase 2/Phase 3 ongoing
Tocilizumab	Cytokine inhibition (IL-6 receptor antagonist)	IV	Dermatomyositis/polymyositis	Phase 2 ongoing
Abatacept	T-cell activation inhibitor	SQ	Dermatomyositis/polymyositis	Phase 2 complete; phase 3 ongoing

Farmakidis et al. Muscle Nerve 2019

2 exemples pour conclure

Myasthénie

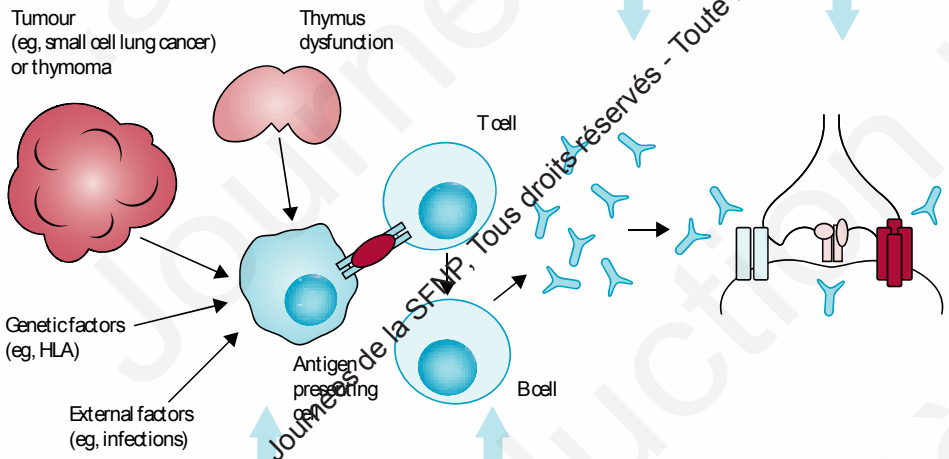


Verschuuren et al. Lancet Neurol 2022

Stratégie d'amont vs stratégie d'aval

Treatment with short-term onset of clinical effect (hours to weeks)

New	**Eculizumab** Ravulizumab Zilucoplan **Efgartigimod** Rozanolixizumab Nipocalimab	
Current	**Intravenous immunoglobulin** Plasmapheresis	Pyridostigmine **Amifampridine**



Current	**Thymectomy and chemotherapy for small cell lung cancer**	Corticosteroids Azathioprine Mycophenolate mofetil Methotrexate Ciclosporin Tacrolimus Cyclophosphamide
New	Stem cell transplantation	Rituximab Inebilizumab Belimumab Leflunomide CK-2017357 Abatacept Iscalimab (CFZ533) Bortezomib Descartes-08 TAK-079 Tocilizumab Pixantrone

Treatment with long-term onset of clinical effect (1–6 months)

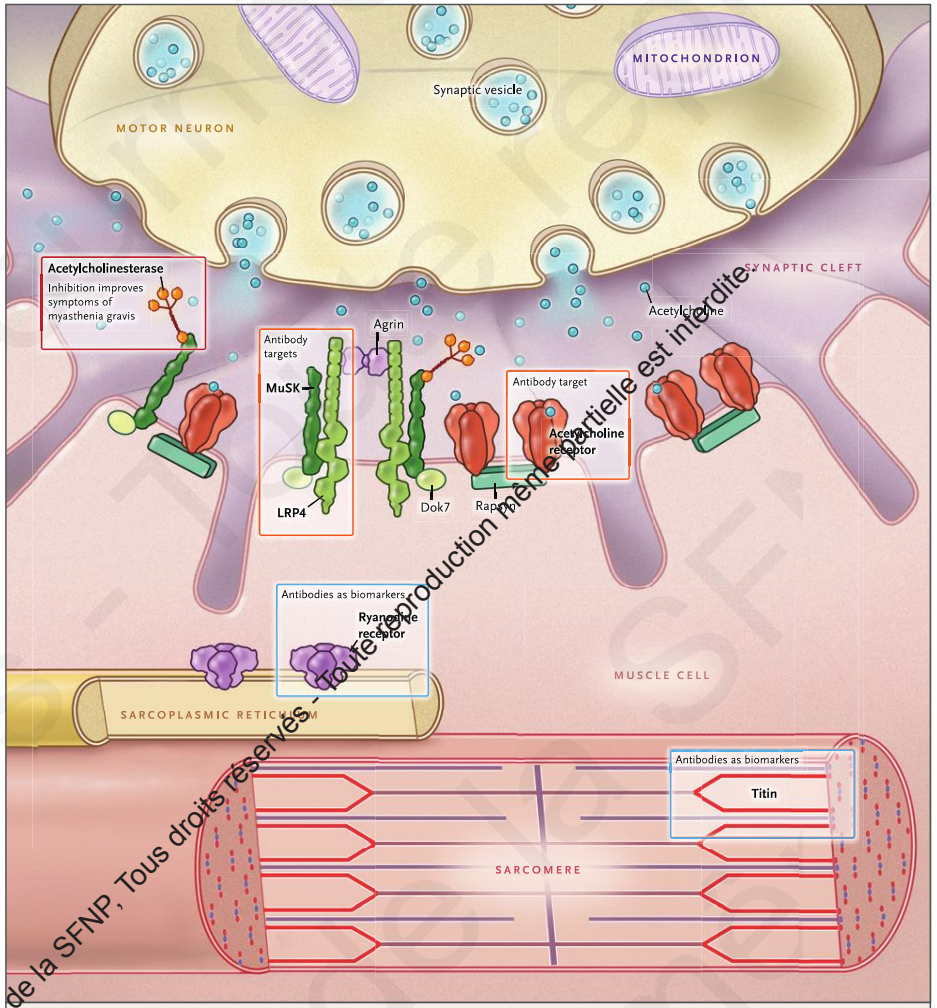
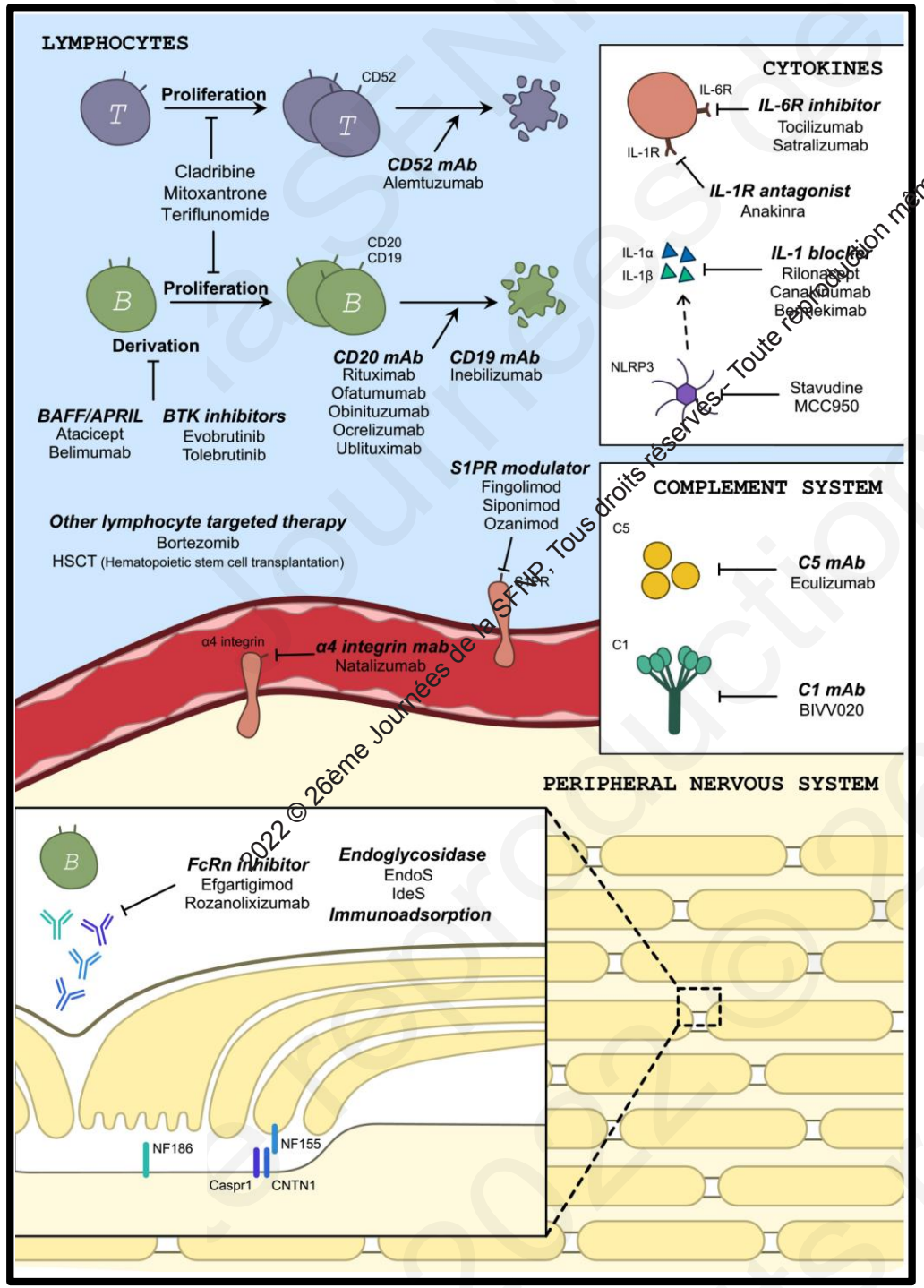


Figure 1. Neuromuscular Junction and Key Elements for the Pathogenesis of Myasthenia Gravis.
Neuromuscular transmission involves release of presynaptic acetylcholine, which binds to acetylcholine receptors in the postsynaptic membrane. The receptors interact with several other proteins in the membrane, including Dok7 and rapsyn. Mutant Dok7 and rapsyn are important in the development of congenital myasthenia. Antibodies against acetylcholine receptors, as well as antibodies against muscle-specific kinase (MuSK) and lipoprotein receptor–related peptide 4 (LRP4), induce myasthenic weakness. Antibodies against the intramuscular proteins titin and ryanodine receptor are relevant biomarkers in some subgroups of myasthenia gravis. Acetylcholine is degraded by local acetylcholinesterase, and acetylcholinesterase inhibition leads to symptomatic improvement in patients with myasthenia gravis.

Verschuuren et al. Lancet Neurol 2022, Gilhus N Engl J Med 2016

Approches thérapeutiques potentielles pour la PIDC



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Hu et al. Autoimmunity Rev 2022