Research in Myasthenia gravis - challenges and opportunities

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Disclosures

Received research support, travel support, speaker honoraria and served as consultant on advisory boards

- Octapharma,
- CSL Behring,
- NMD Pharma,
- Pfizer,
- Novo,
- Alexion,
- Sanofi Genzyme
- UCB Pharma
- Amicus Pharmaceuticals
- Lundbeck

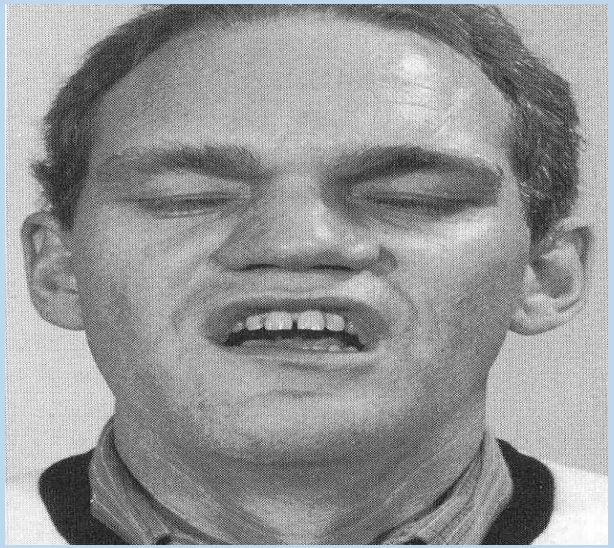
Established medical treatments in MG

Corticosteroids	Inhibition of T cells and monocyte-macrophage activation
Azathioprine	Purine analogue inhibiting DNA and RNA replication
Mycophenolate	Inhibition of inositol monophosphate dehydrogenase
Methotrexate	Folic acid antimetabolite
Cyclosporine	Inhibits calcineurin
Tacrolimus	Macrolide antibiotic that inhibits calcineurin

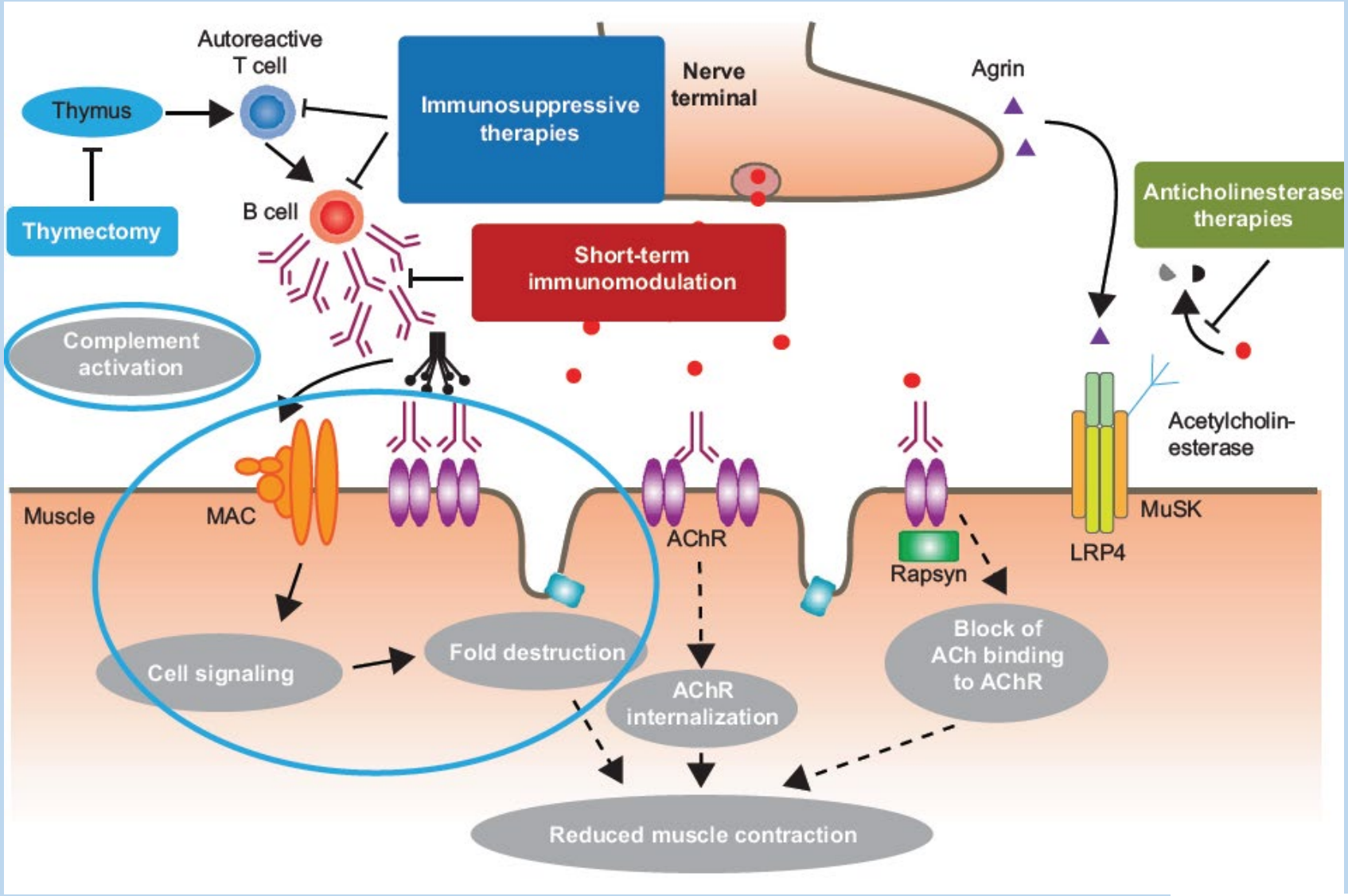
PLEX	Removal of pathogenic antibodies by ‘apheresis
IVIG	Multiple mechanism, predominantly FcRn saturation

Residual myasthenic symptoms and deficits

”Unmet medical needs”



Currently available therapies for MG



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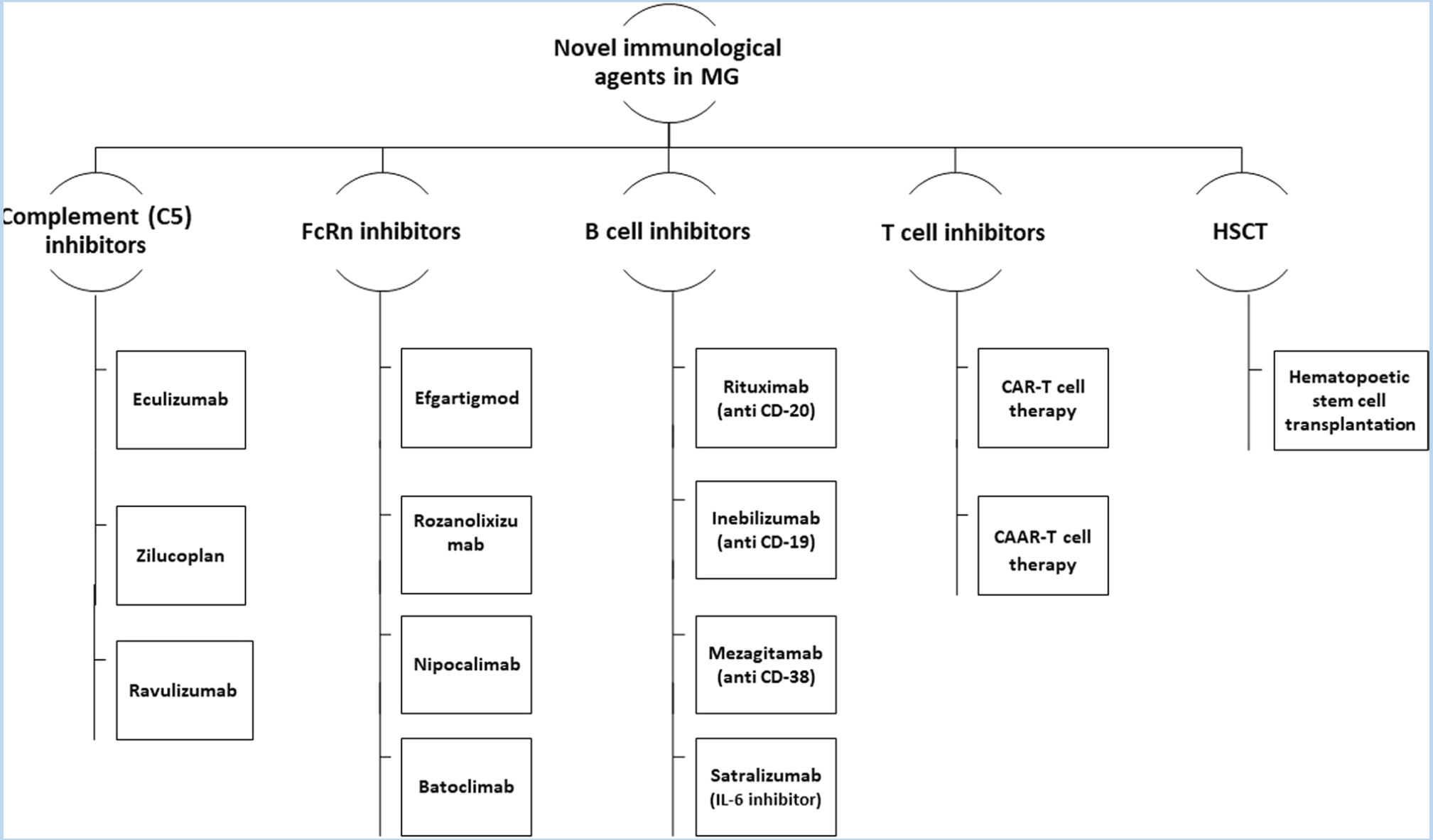
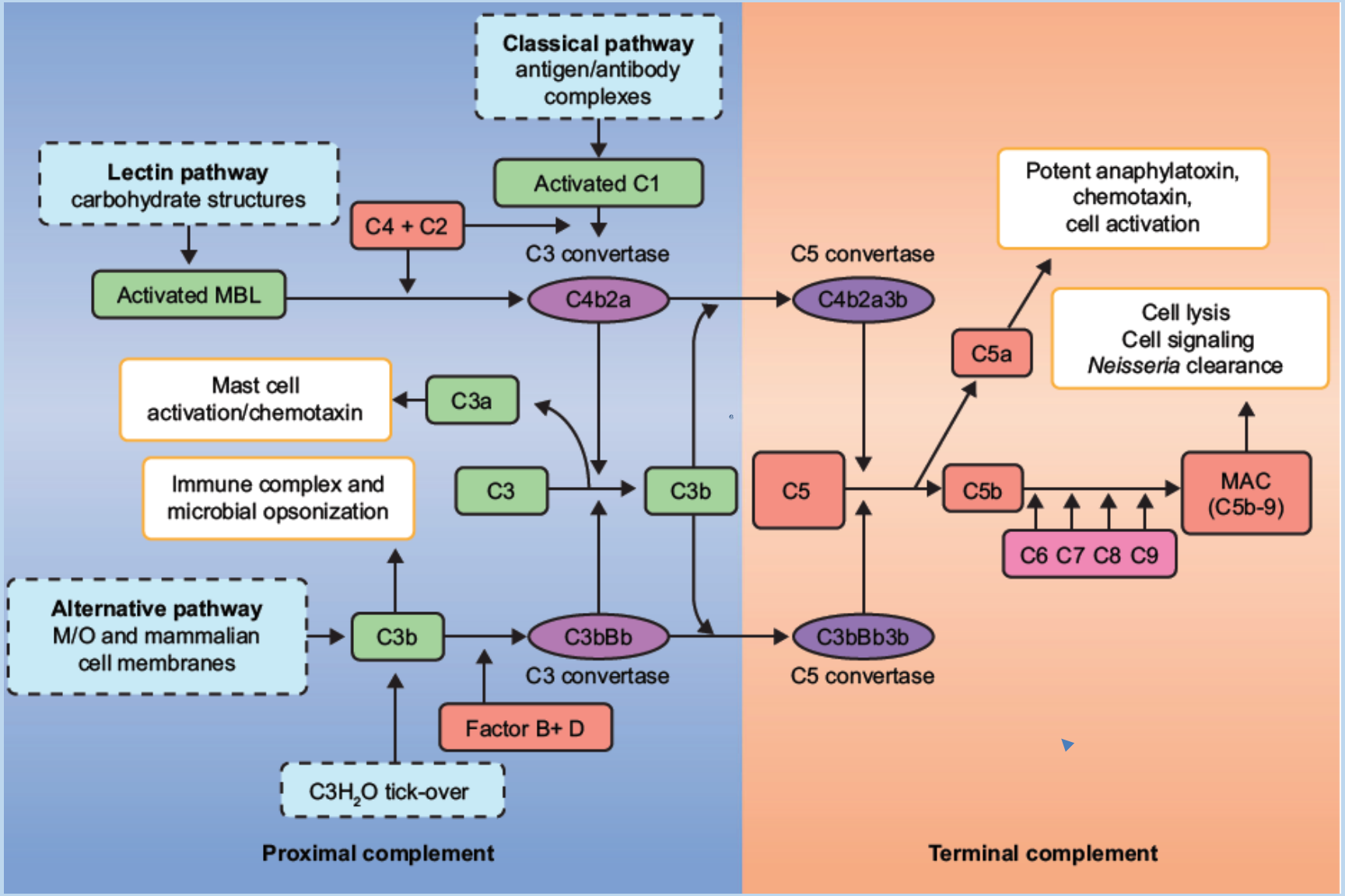
Established treatments in MG

Agent	Mechanism	Earliest time to clinical benefit	Dosing
Corticosteroids	Inhibition of T cells and monocyte-macrophage activation	2–12 wk	Initiation at 10/20 mg daily and weekly uptitration to 50/60 mg daily
Azathioprine	Purine analogue inhibiting DNA and RNA replication	12 mo	Initiation at 50 mg daily and increased weekly to 2–3 mg/kg/d
Mycophenolate mofetil	Inhibition of inositol monophosphate dehydrogenase	6–12 mo	1–2 g/day in divided doses
Cyclosporine	Inhibits calcineurin	2–12 mo	Initiation at 3 mg/kg/d and increased to 6 mg/kg/d, titration based on clinical efficacy, therapeutic drug monitoring (400–600 ng/mL) and/or serum creatinine levels
Tacrolimus	Macrolide antibiotic that inhibits calcineurin	2–12 mo	3 mg/kg/d with further titration based on clinical efficacy or therapeutic drug monitoring (7–8 ng/mL)
Methotrexate	Folic acid antimetabolite	3–6 mo	Initiation at 10 mg/wk single dose, increased weekly up to 20–25 mg/wk
Cyclophosphamide	Alkylating agent preventing DNA replication	3–4 mo	Pulse of 1–1.5 mg/m^2 given over 5 d repeated monthly for 6 mo
IVIG	Multiple mechanism, predominantly FcRn saturation	10–15 d	2 g/kg divided over 2–5 d
SCIG	Same as IVIG but with lower peak and trough immunoglobulin levels and steadier state	2 wk	Weekly dose calculated by multiplying the maintenance dose of IVIG in grams by 1.37 divided by the interval between IVIG doses
PLEX	Removal of pathogenic antibodies by 'apheresis'	2–4 d	30–40 mL/kg of plasma exchanged per day for 5 d

New immunological treatments in MG



Complement system



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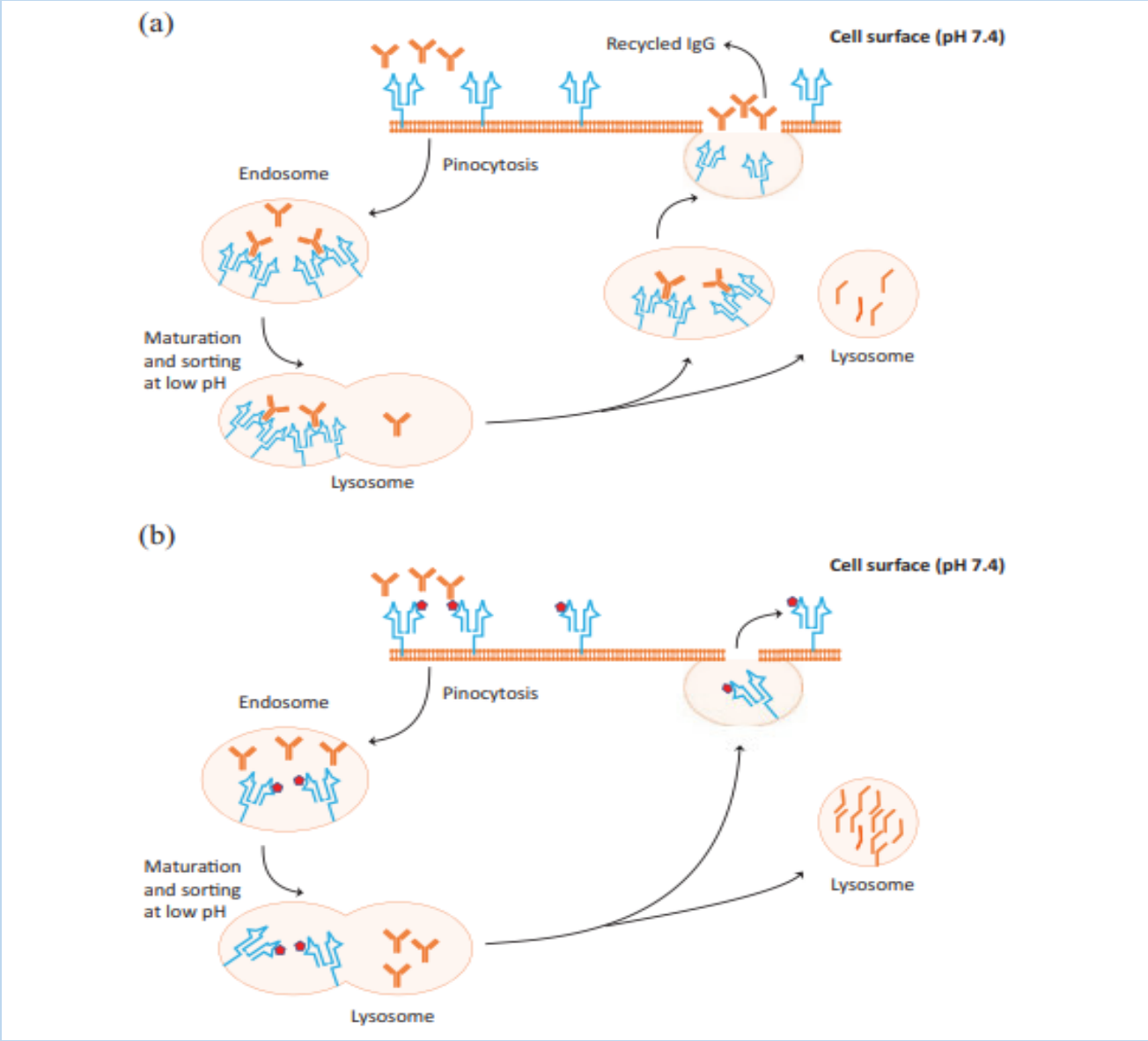
FcRn - working mechanism

Normal tilstand

Behandling med FcRN



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Newer immunological treatments in MG - Where are we ?

Agent (pharmaceutical company)	Mechanism	Dosing	Adverse effects in trials	Current status
Eculizumab (Alexion)*	C5 complement inhibitor	900 mg IV qwk × 4, then 1200 mg IV q2wk	Risk of Neisseria meningitidis	Approved for AChR-positive GMG
Efgartigimod (Argenx)*	FcRn inhibitor	10 mg/kg IV qwk	Mild; headache, reduced monocyte count, rhinorrhoea, myalgia, pruritis, injection-site pain, herpes zoster	Approved for AChR-positive GMG by FDA in December 2021
Zilucoplan (UCB)	C5 and C5b complement inhibitor	0.3mg/kg SC qd	Mild; injection-site reactions, headache	Orphan drug status for moderate to severe AChR-positive MG; ongoing phase III trial
Ravulizumab (Alexion)	C5 complement inhibitor with extended half-life	Weight based (<60 kg: 2400 mg, 60–100kg: 2700 mg, >100 kg: 3000 mg) IV; 2nd dose 15 d after 1st dose, then q8wk maintenance	Risk of Neisseria meningitidis	Ongoing phase III trial
Rozanolixizumab (UCB)	High affinity FcRn blocker	7 mg/kg and 10 mg/kg qwk SC	Mild to moderate headache	Positive phase III trial results
Nipocalimab (Johnson & Johnson)	High affinity FcRn blocker	60 mg/kg IV q2wk	Well tolerated	Ongoing phase III trial
Batoclimab (Immunovant)	FcRn blocker	340 mg or 680 mg SC qwk × 4, then 340 mg q2wk	Influenza-like illness	Ongoing phase II trial
Rituximab (Genetech, Roche)	Anti-CD20 antibody	Induction with 375 mg/m^2 IV qwk × 4 or 1 g q2wk × 1 and repeat in 6 mo	Infusion reactions, minor risk of infections	MUSK MG and as a second-line agent for refractory AChR MG
Inebilizumab (Vielo Bio)	Anti-CD19 antibody	300 mg IV q2wk × 1, then 300 mg IV in 6 mo	Fever, urinary infection	Ongoing phase II trial
Mezagitamab (Takeda)	Anti-CD38 antibody	600 mg SC qwk	Fever, headache, postural hypotension	Ongoing phase II trial
Satralizumab (Hoffman-La Roche)	Anti-interleukin-6 antibody	120 mg SC q2wk (0, 2 and 4 wk) followed by q4wk	Headache, arthralgia, injection-related reaction	Ongoing phase III trial
CAR-T and CAAR-T cell therapies	Chimeric autoantibody receptor expressing T cells directed against autoreactive B cells		Serious cytokine-release syndrome	Ongoing phase I trial
Haematopoietic stem cell therapy	Eradication of all autoreactive T and B cells		Toxicity related to conditioning regimen	Ongoing phase I trial

Non-pharmacological treatments

Exercise and training ?

Nutrition, Nutritional supplements, Vitamines etc ?

Physiotherapy ?

Psychotherapy for psychological problems ?

Treatment of pain ? - and fatigue ?

Treatment of comorbidities ?

Biomarkers ? Thymoma ?

Patient reported Outcomes

- How to monitor disease and quality of life ?
- Can we improve our present ”Patient reported Outcomes” and clinical scales ?

”Drug price Toxicity”

”Institute for Clinical and Economic Review”
ICER

The Institute for Clinical and Economic Review (ICER) is a leading independent research organization providing clinicians with value-based price "benchmarks." All physicians must educate themselves in drug pricing principles and be prepared to have conversations regarding individual and societal value with the patients they serve.

INVITED REVIEW

Answer questions and earn CME https://education.aanem.org/URL/JR74.

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See article on pages 567–572 in this issue.

A crisis in US drug pricing: Consequences for patients with neuromuscular diseases, physicians, and society, part 2

Ted M. Burns MD[1] | Jason L. Crowell MD[2] | A. Gordon Smith MD[3]

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Commentary

FORMULARY EVALUATIONS

A Critical Examination for the Pricing of Eculizumab and Efgartigimod in Myasthenia Gravis

Paul C. Langley, Ph.D., Adjunct Professor, College of Pharmacy, University of Minnesota, MN

ABSTRACT

The purpose of this commentary is to focus on the downside of assumption-driven simulation modeling, the potential creation of a multitude of competing models, the mathematically impossible quality adjusted life year (QALY) and the failure to observe the axioms of fundamental measurement in mapping ordinal EQ-5D-5L preferences from the ordinal Quantitative Myasthenia Gravis (QMG) score. A second aspect of this commentary is to propose standards that should be set for the creation and evaluation of value claims in health technology assessment, in particular need fulfillment quality of life (QoL), that meet the demarcation test to distinguish science from non-science. The result is that the present ICER pricing claims for eculizumab and efgartigimod in myasthenia gravis should not be applied without consideration of more relevant evidence.

Danish Medicines Council

”Medicinrådet”

Role : To provide guidance about new medicines for use in the Danish hospital sector.

Two separate processes:

A) Assessments of new medicine, where a new compound is compared to the standard therapy used in Denmark.

B) Guidelines, where several medicines for a specified disease are compared.
The guideline process results in a recommendation with a prioritized list of medicines to be used.