Imperial College London

Multiple sclerosis – treatment strategies

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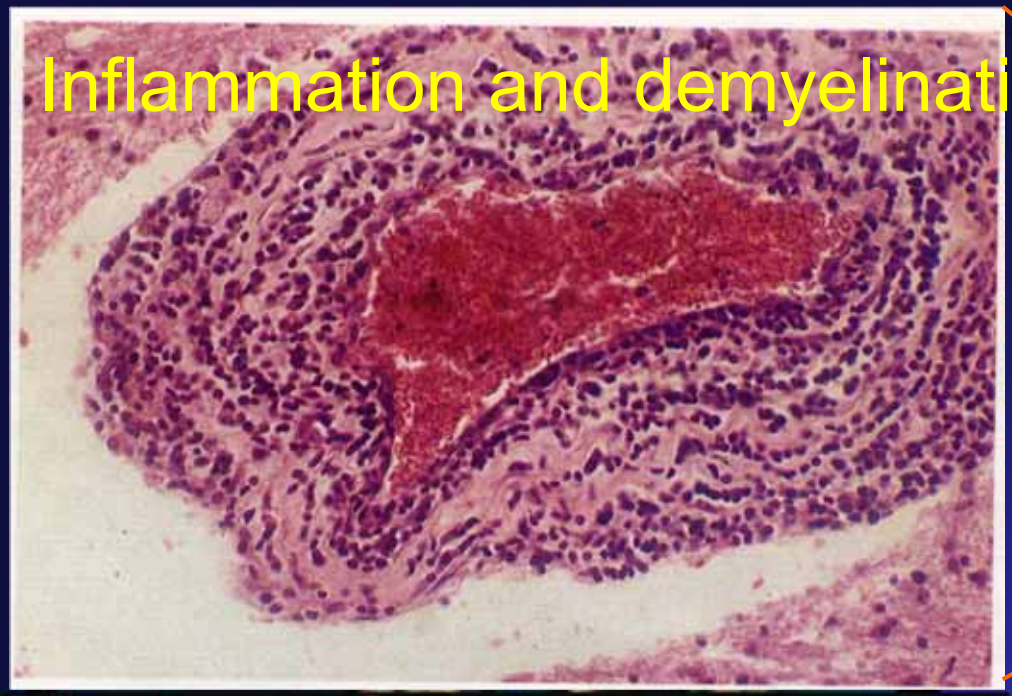
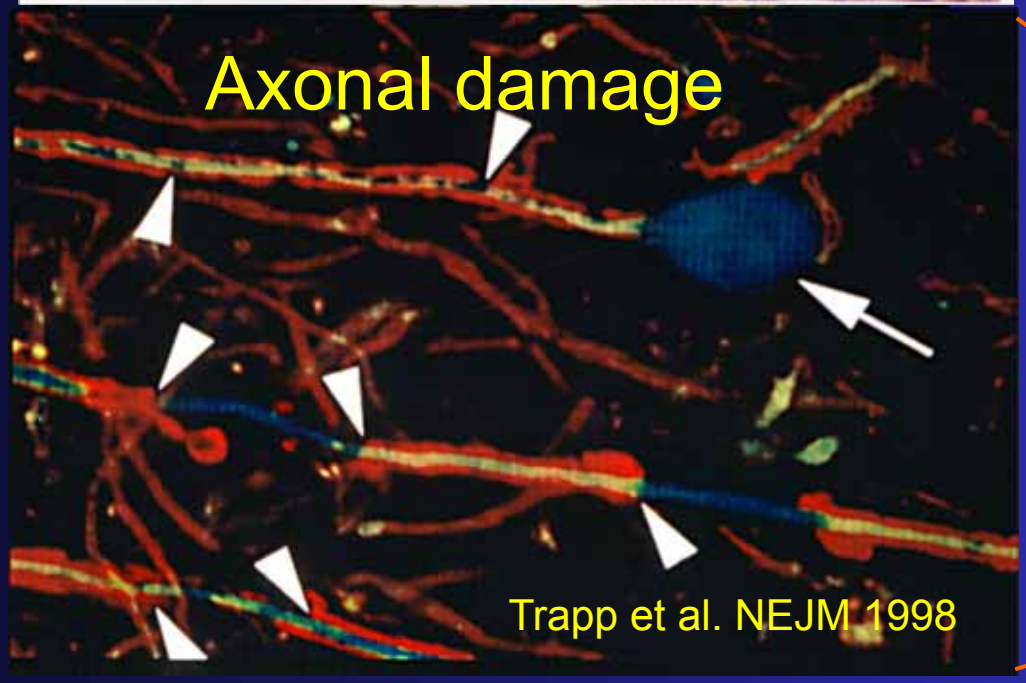
Clinical Reader in Neuroimmunology and Honorary Consultant Neurologist

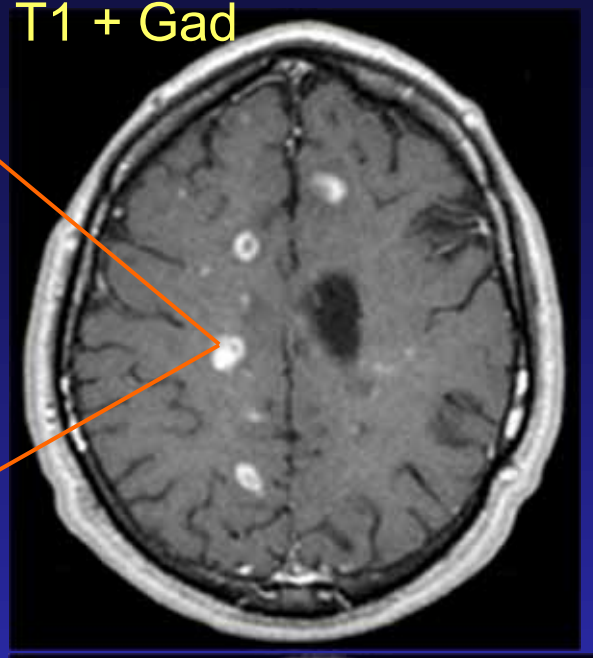
Learning objectives

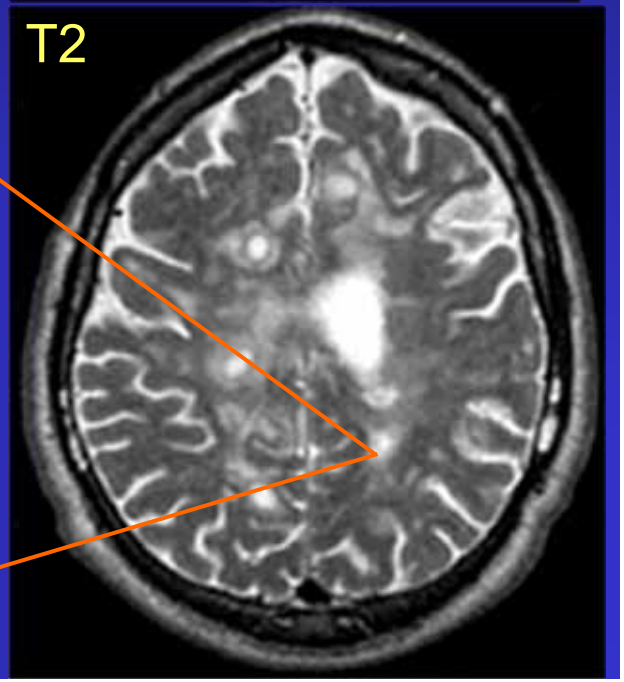
- Understand the main categories of treatments for MS (what can we treat)
- Learn about the main symptomatic treatments and the management of common complications
- Learn about the main approved disease-modifying treatments
- Have a notion on what new treatments are in late stage of clinical development


Inflammation and demyelination


Axonal damage
Trapp et al. NEJM 1998

MRI


T1 + Gad


T2

Management of MS

- Education and counselling
- Management of acute attacks
- Prevention of relapses and progression of disability
- Symptomatic therapy
- Physical therapy
- Treatment of complications

Education and counselling

- Information on MS
- MS societies, web sites
- Well-balanced diet
- Regular exercise, avoid heat
- Work or habits adjustment
- Psychosocial and multidisciplinary management

Overview of pharmacological treatments for MS

- **Of acute attacks**
  - High dose steroids

- **Symptomatic**
  - Anti-spastic drugs
  - Drugs to reduce neuropathic pain
  - Medication to improve bladder control

- **To prevent relapses and accumulation of disability (Disease Modifying Treatments, DMTs)**
  - Immunomodulatory or Immunosuppressive

Management of acute attacks

- Exclude pseudo-relapses (heat or fever-related)
- Decide on necessity for treatment
- Standard treatment given to accelerate recovery
  - **High-dose IV methylprednisolone (500-1000 mg/day x 3-5 days**
  - **Can also be given orally**
  - Commonly given in day hospital setting
  - High-dose oral prednisone
  - Standard-dose oral steroids (eg Prednisone 60mg od) not recommended

Symptomatic treatment

- Spasticity
- Sphincter disturbances
- Pain
- Fatigue
- Depression
- In-coordination and tremor
- Sexual dysfunction

Treatment of spasticity

- Stretching, physical therapy
- Pharmacological
  - Baclofen
    - When given orally limited by side effects: drowsiness and hypotonia
    - Can be given intrathecally with implanted pump
  - Tizanidine
  - Benzodiazepines
  - Botulinum toxin
    - More selective effect

Treatment of sphincter disturbance: Bladder dysfunction

- Small, spastic bladder (failure to store, detrusor hyperactivity →frequency/urgency)
  - Oxybutinine chloride 5mg tds (up to 40 mg/day)
  - Imipramine (0.5-1mg/kg/day)
- Flaccid, big bladder (failure to empty, residual volume >400 cc)
  - intermittent self-catheterisation
- Dyssynergic bladder (“conflicting”, urgency followed by hesitation)
  - Alpha blockers

Treatment of pain

- **Establish origin of pain**
- Paroxysmal pain:
  - Gabapentin 900mg/day to max 1.8g/day
  - Carbamazepine 100-800mg/day
- Chronic dysaesthetic pain:
  - Amitriptyline 20-100 mg/day
  - Other antiepileptic and antidepressant drugs can be effective or better tolerated
- Narcotics and NSAIDs are ineffective and not recommended for neuropathic pain

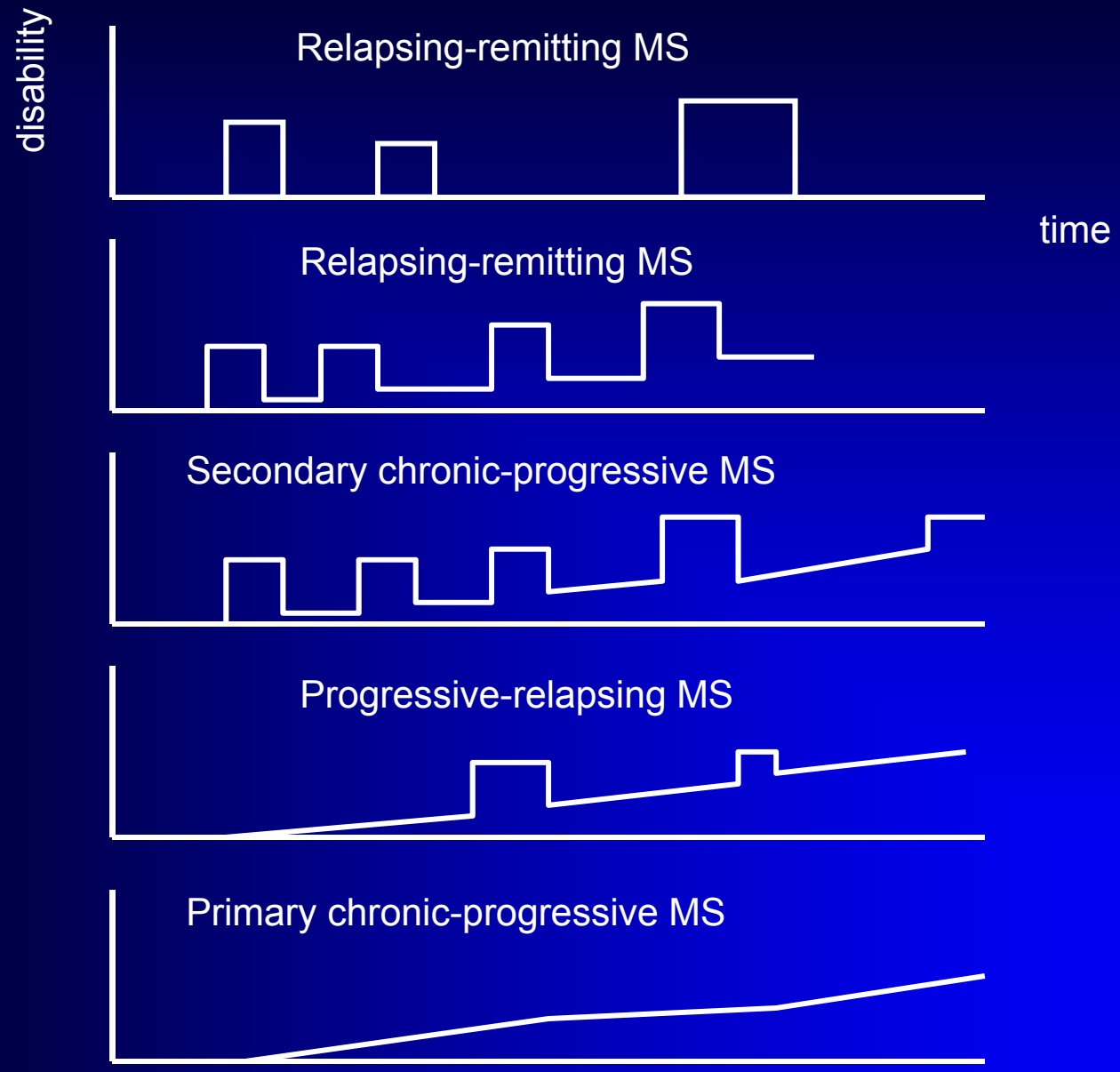
Treatment of fatigue

- Limited options
- Energy savings (day planning, devices)
- Pharmacological treatment
  - Amantadine (unconfirmed)
  - Some antidepressants

Management of complications

- Depression: **psychosocial and pharmacological Tx**
- Urinary tract infection: **antibiotics**
- Limb contractures due to spasticity: **orthoses, tendon surgery**
- Gastroparesis and intestinal pseudo-obstruction: **pharmacological or mechanical evacuation**
- Dysphagia, malnutrition: **nutritionist evaluation, percutaneous endoscopic gastrostomy (PEG)**
- Aspiration pneumonia and bronchopneumonia: **medical, antibiotics**
- Pulmonary thromboembolism: **anticoagulation, ICU**
- Pressure sores: **debridement surgery, water mattress**

Disease courses of multiple sclerosis



Prevention of relapses and ?progression of disability ? (disease-modifying treatments, DMTs)

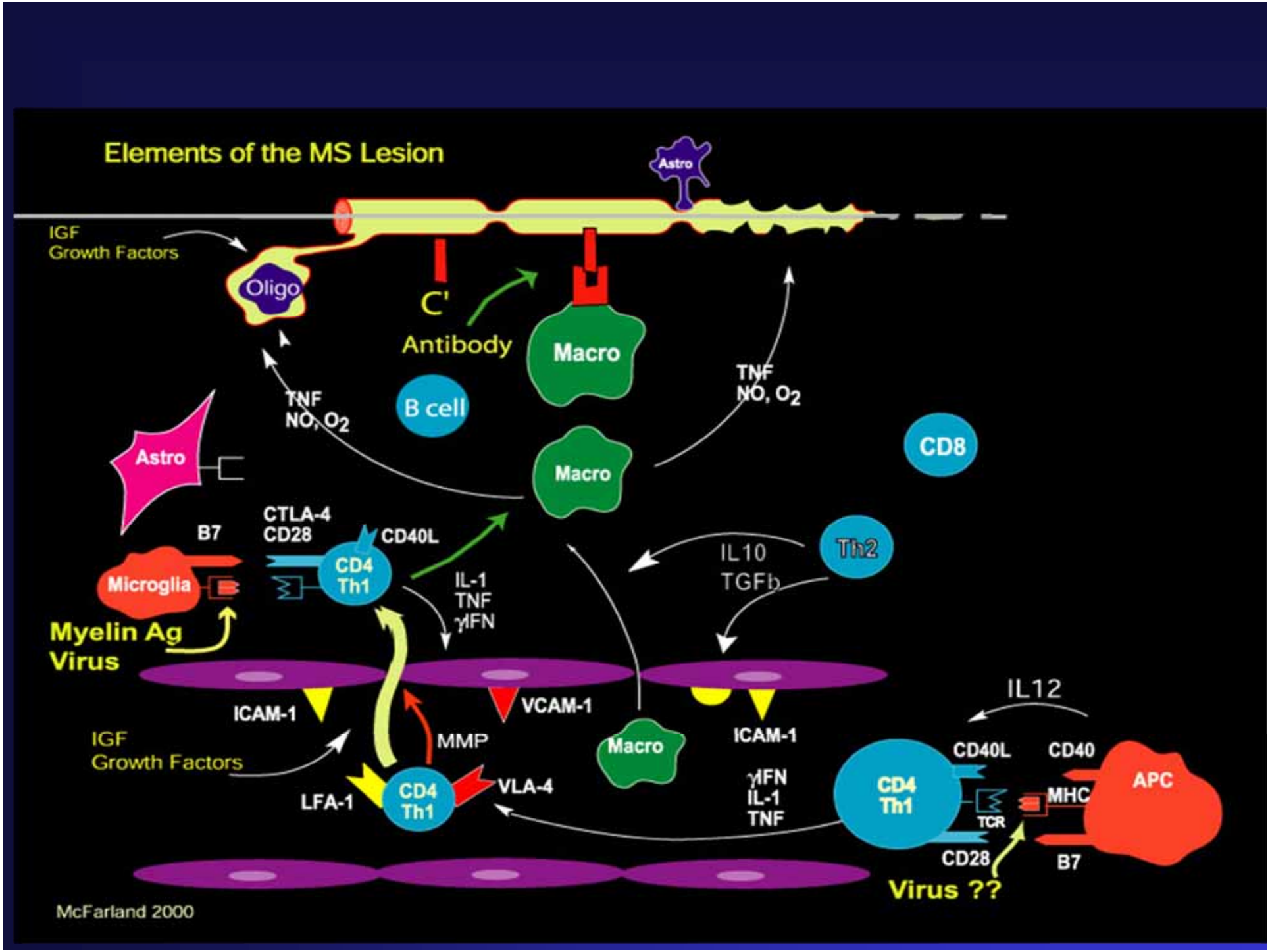
- RR MS
  - Interferon beta
  - Glatiramer acetate
  - Natalizumab
  - Fingolimod
  - *Azathioprine*
  - *Intravenous Immunoglobulin (IVIg)*

- SP MS
  - Interferon beta
  - *Mitoxantrone* *

- Primary progressive
  - No treatment proven effective
  - *Low dose immunosuppression (Methotrexate)*

Italic typeface: unlicensed treatment

**licensed in other countries*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Virus ??
McFarland 2000

Approved immunomodulatory treatments for RR-MS

- **Interferon-β**

Interferon-β (Betaferon,Rebif, Avonex)

- First immunomodulatory Tx for MS
- Naturally secreted cytokine, Type I IFN
- Thought to act on several components of immune response:
  - Suppresses lymphocyte proliferation
  - T helper immune deviation?
  - Downregulation of MHC expression
  - Pro-/anti apoptotic effects on lymphocytes
  - Interference with cell adhesion

Interferon-β for treatment of MS

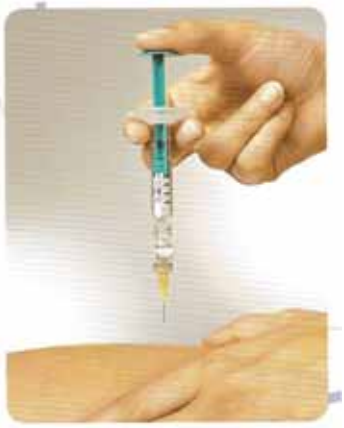
- Relapsing-remitting or early secondary progressive
- Prevents about 1/3 of relapses
- Reduces accumulation of disability (controversial)
- Neutralising antibodies develop in 15-30% and may reduce efficacy

Self-injection of interferon beta

step two

Inject your Betaferon dose at a right angle to your skin with a quick, firm motion. Hold the syringe like a pencil or a dart. Administer the dose with a slow, steady push on the syringe plunger all the way in until the syringe is empty.

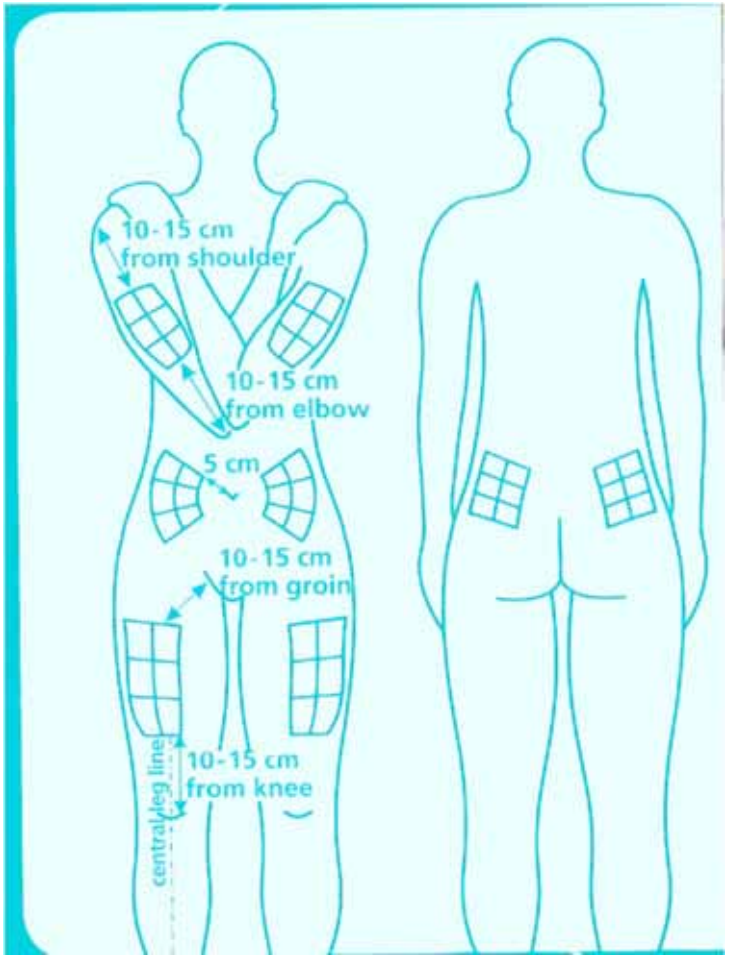
Some people cool the injection site after the injection process. You may find it helpful but don't need to if it's not helpful to you.



step three

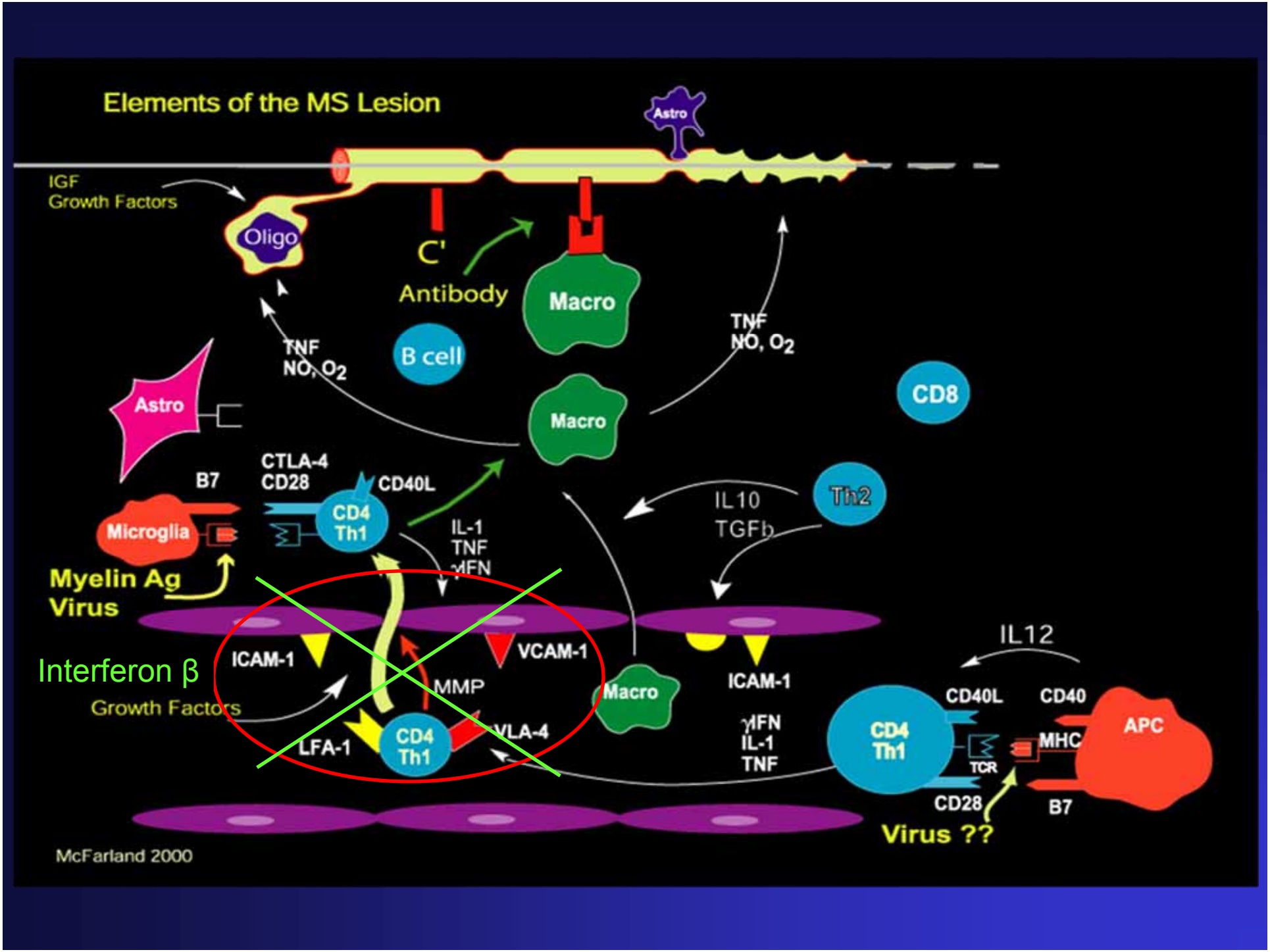
After injecting, dispose of the needle and syringe using a disposal unit.

With practice the procedure will become quicker and easier and before long administering Betaferon will become a routine part of your daily life.



Mechanisms of IFN-beta

- Anti-viral effect?
- Regulation of T cell activation
- IFN-β treatment reduces VLA-4 cell surface expression on T lymphocytes → decreased T cell entry to CNS across blood-brain barrier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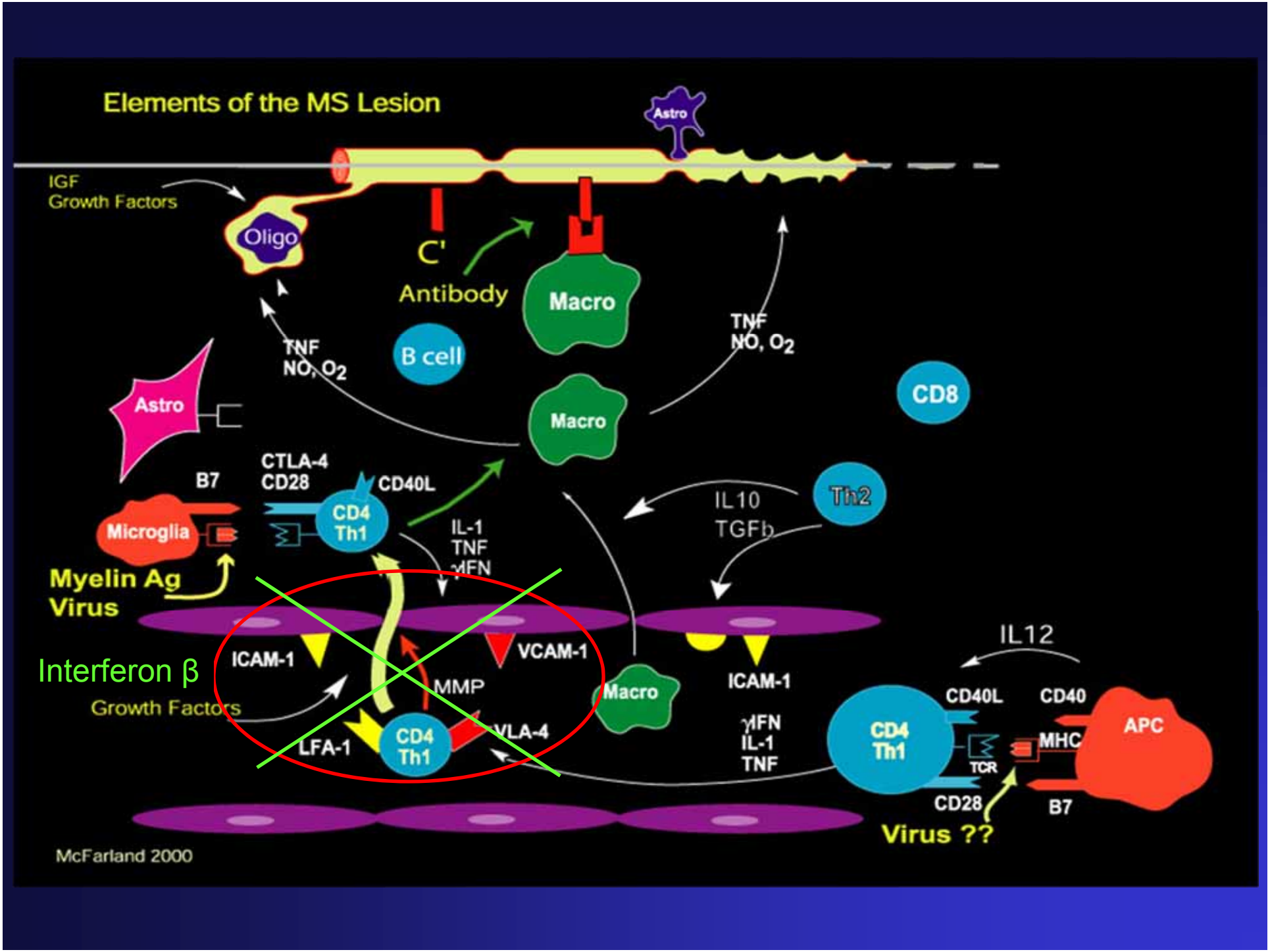
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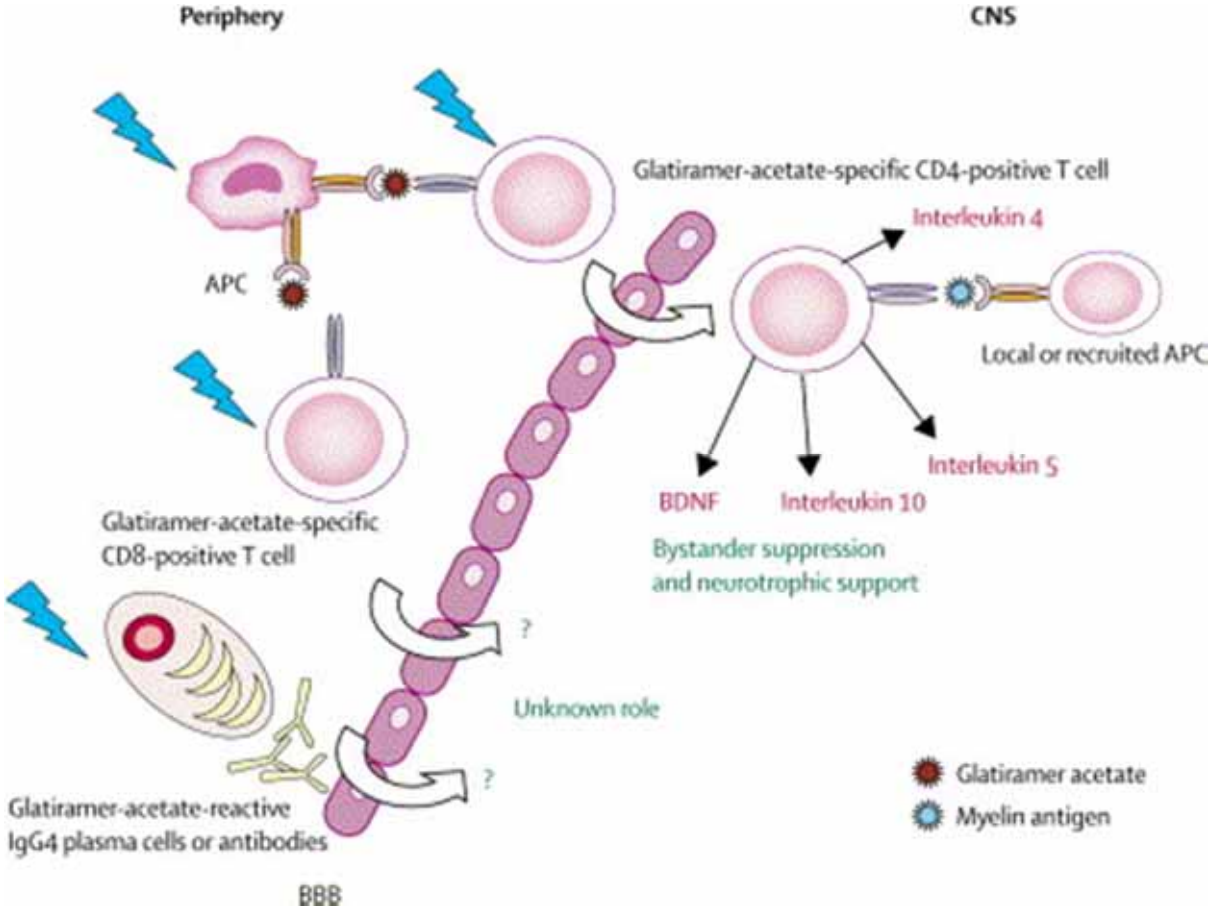
Approved immunomodulatory treatments for RR-MS

- Interferon-β
- **Glatiramer acetate**

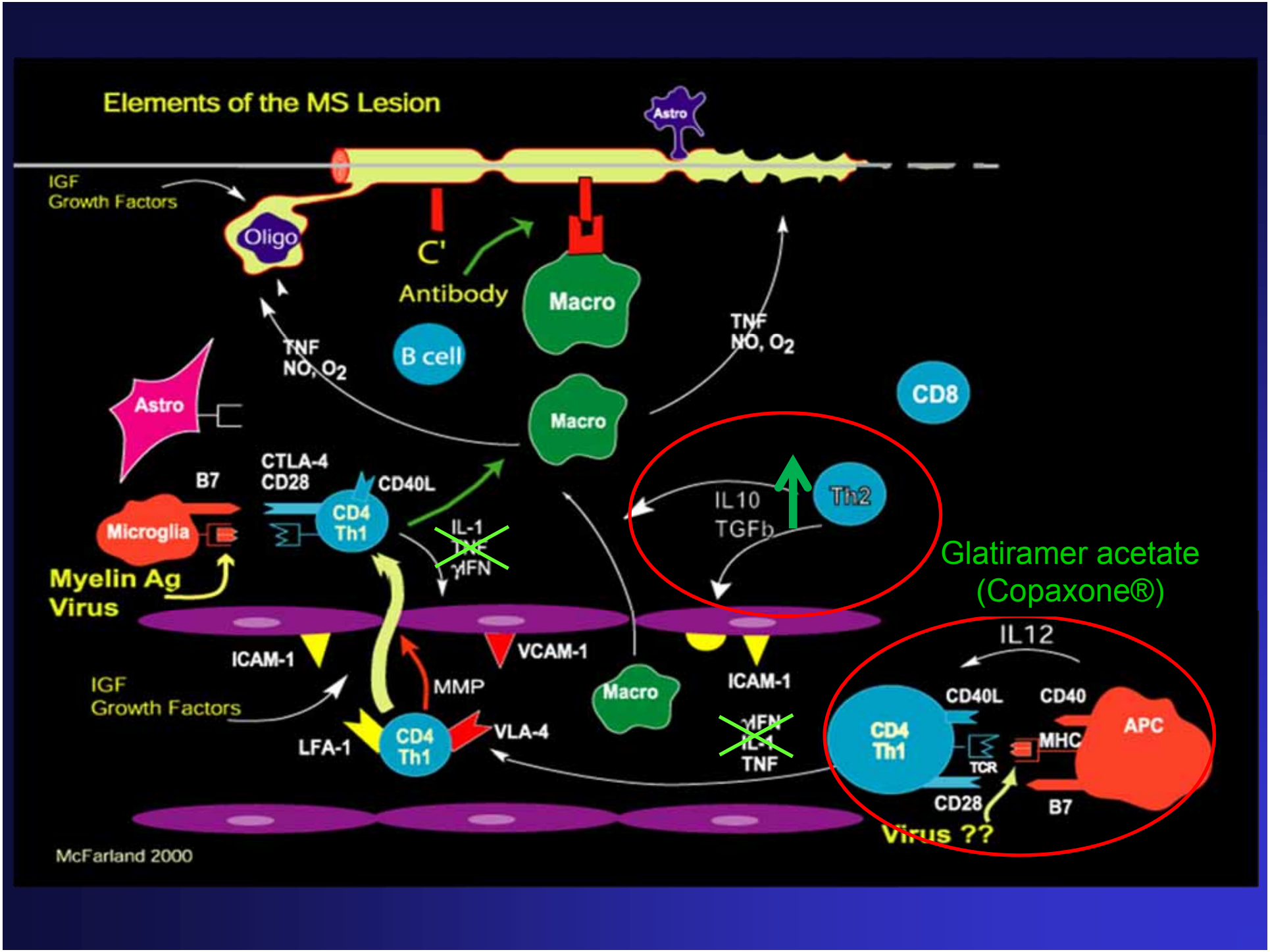
Glatiramer acetate (Cop-1, Copaxone, YEAK)

- Pool of 40-100 a.a. long synthetic peptides composed of random sequences of tyrosine, glutamate, alanine and lysine in a defined molar ratio
- Mechanisms include
  - immune deviation
  - bystander suppression
  - altered peptide ligand effect
  - Neurotrophic support

Glatiramer-acetate-mediated changes on adaptive immune system



Farina et al. Lancet Neurol 2005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Approved immunomodulatory treatments for RR-MS

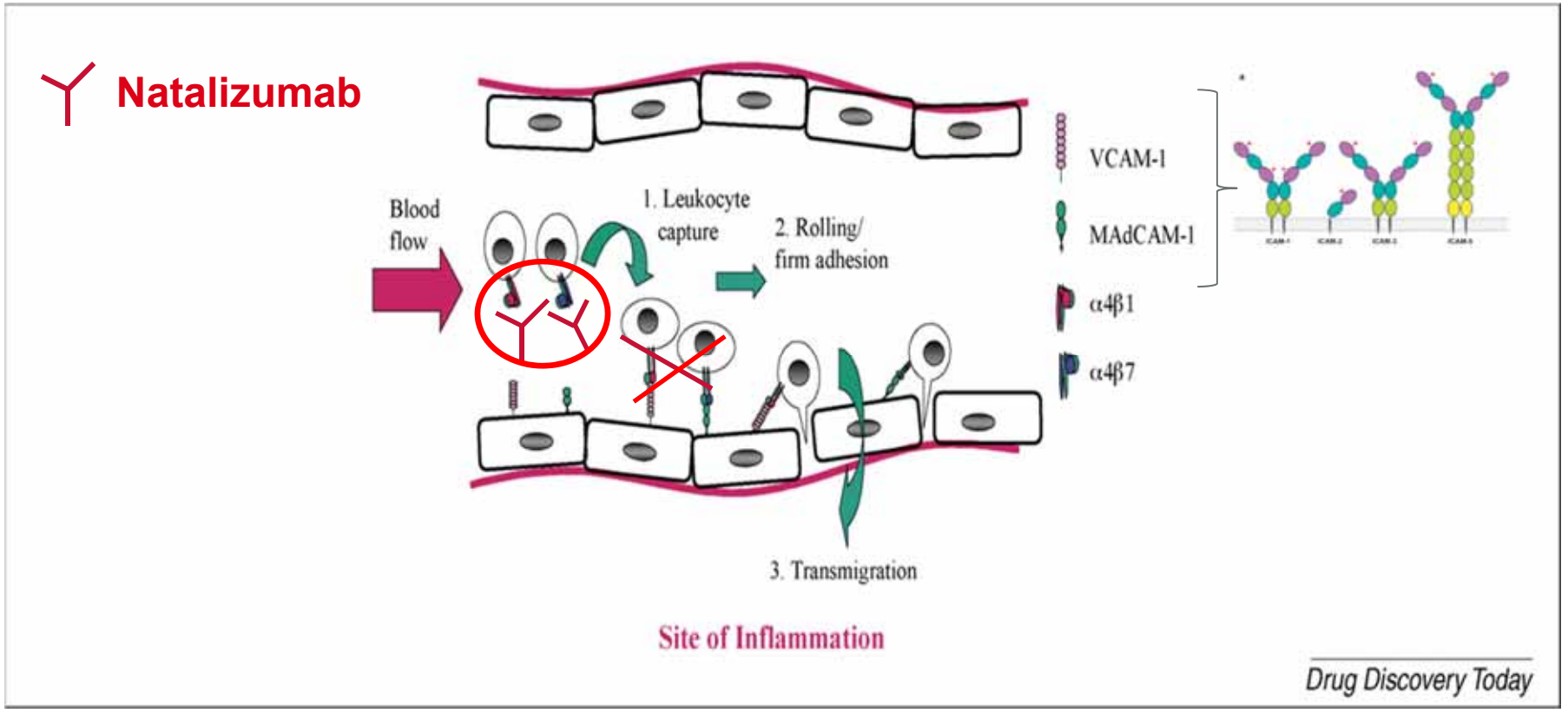
- Interferon-β
- Glatiramer acetate
- **Natalizumab**

Natalizumab (Tysabri)

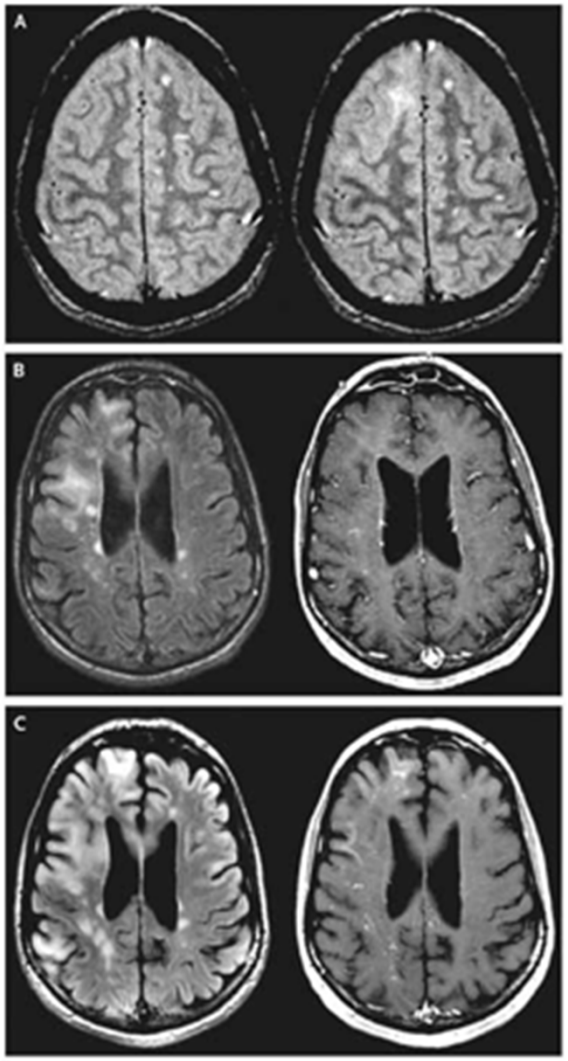
- Humanized mAb directed against α4 subunit of integrin
- Clinical efficacy on active inflammation and relapse rate
- Progressive multifocal leukoencephalopathy observed as complication of treatment (1/1,000 treated patients)

Imperial College
London

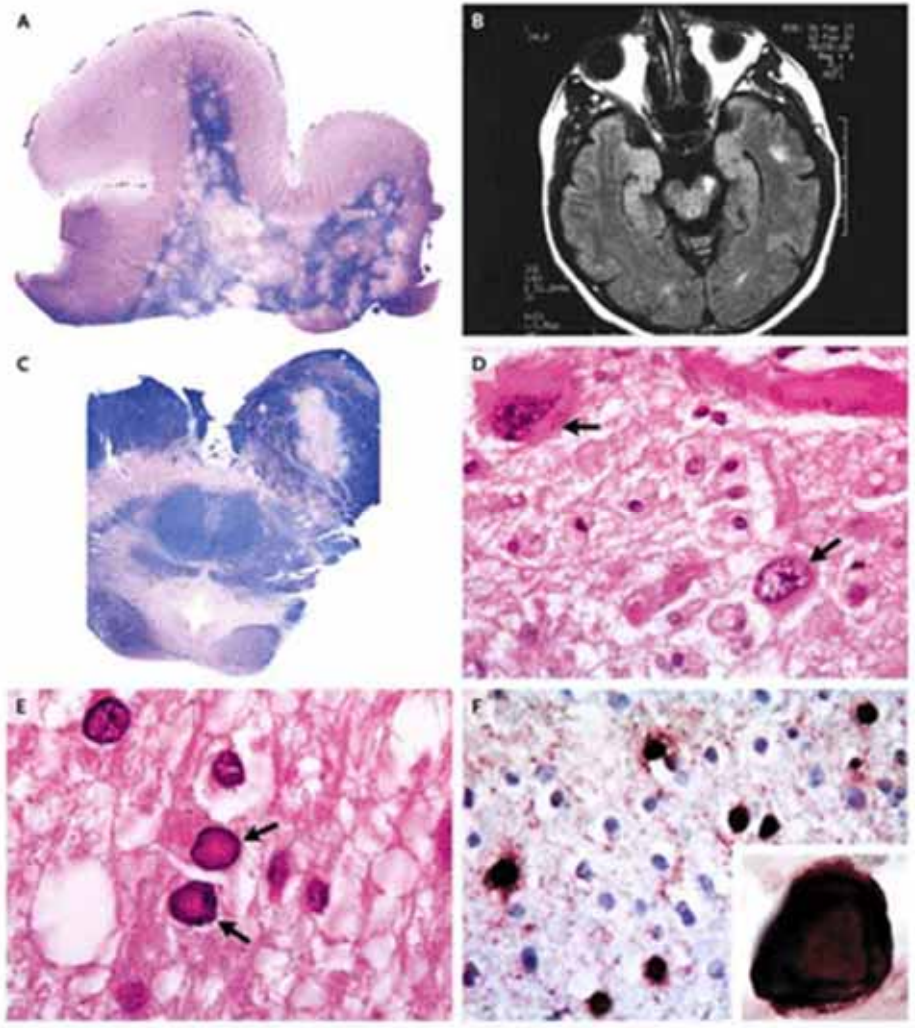
Natalizumab - an antibody blocking alpha-4 integrin



Progressive multifocal leukoencephalopathy complicating treatment with natalizumab and interferon beta-1a for multiple sclerosis



Langer-Gould et al. NEJM 353 (4): 375, July 28, 2005



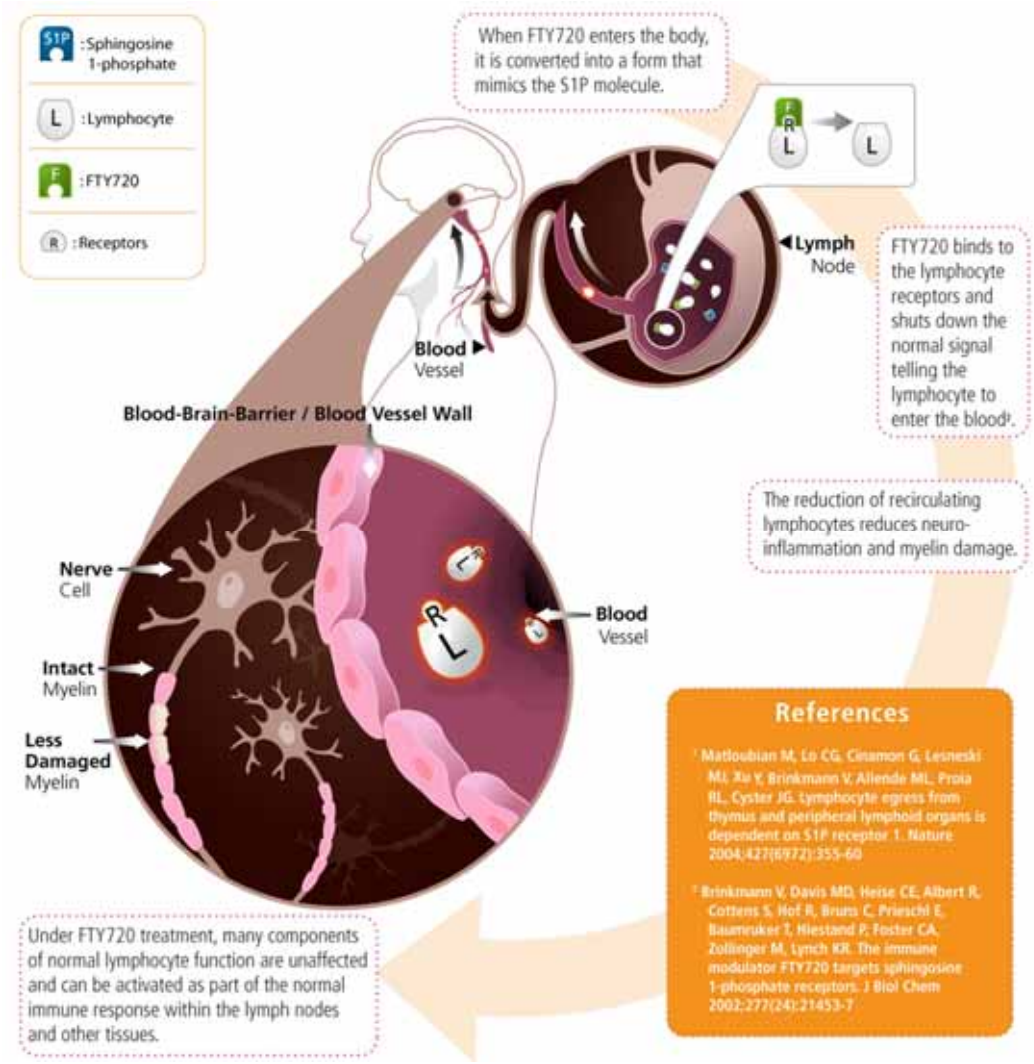
Kleinschmidt-DeMasters and Tyler NEJM 353 (4): 369 July 28, 2005

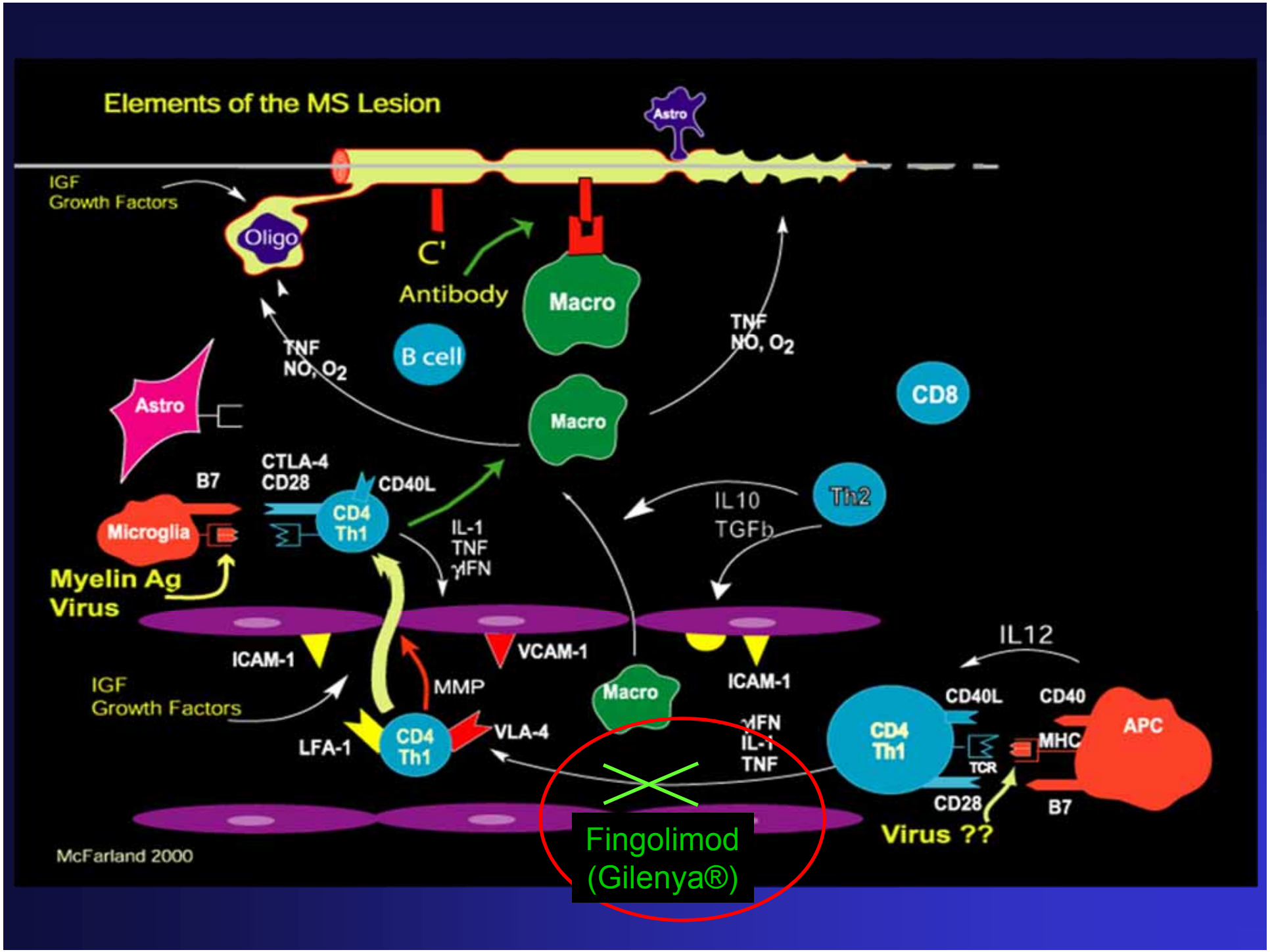
Approved immunomodulatory treatments for RR-MS

- Interferon-β
- Glatiramer acetate
- Natalizumab
- **Fingolimod**

Fingolimod (Gilenya)

- S1P antagonist
- Keeps lymphocytes in lymph nodes

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Virus ??
Fingolimod
(Gilenya®)
McFarland 2000

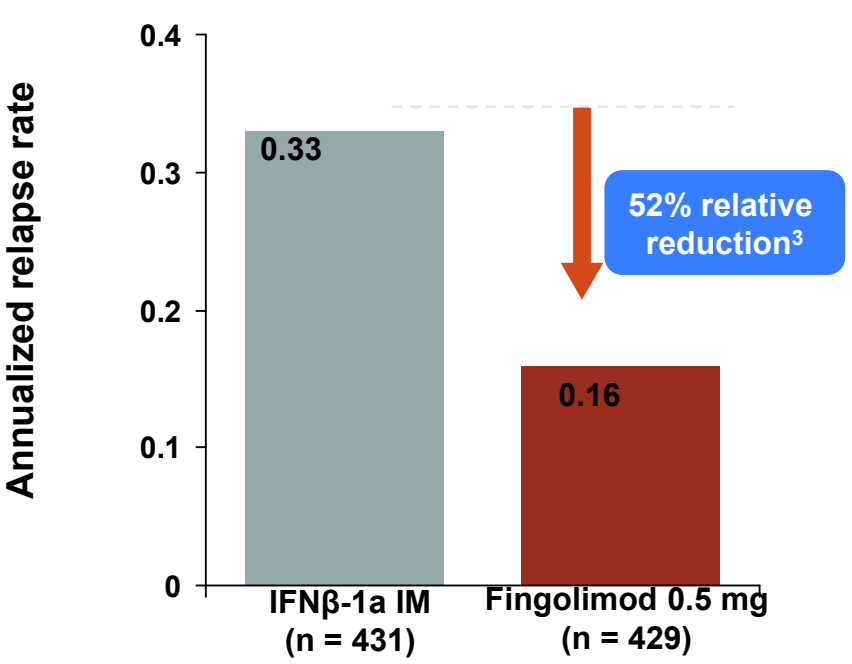
Isaria sinclairii

myriocin is a metabolite of the fungus *Isaria sinclarii*

Fingolimod significantly reduced ARR versus IFNβ-1a IM and placebo

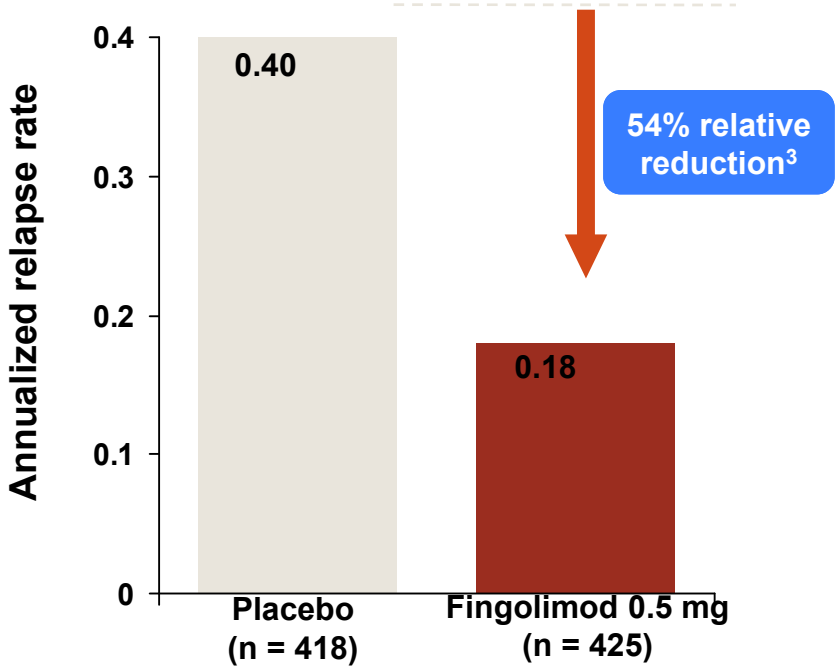
TRANSFORMS 1-year results[1]

p < 0.001 for fingolimod versus IFNβ-1a IM



FREEDOMS 2-year results[2]

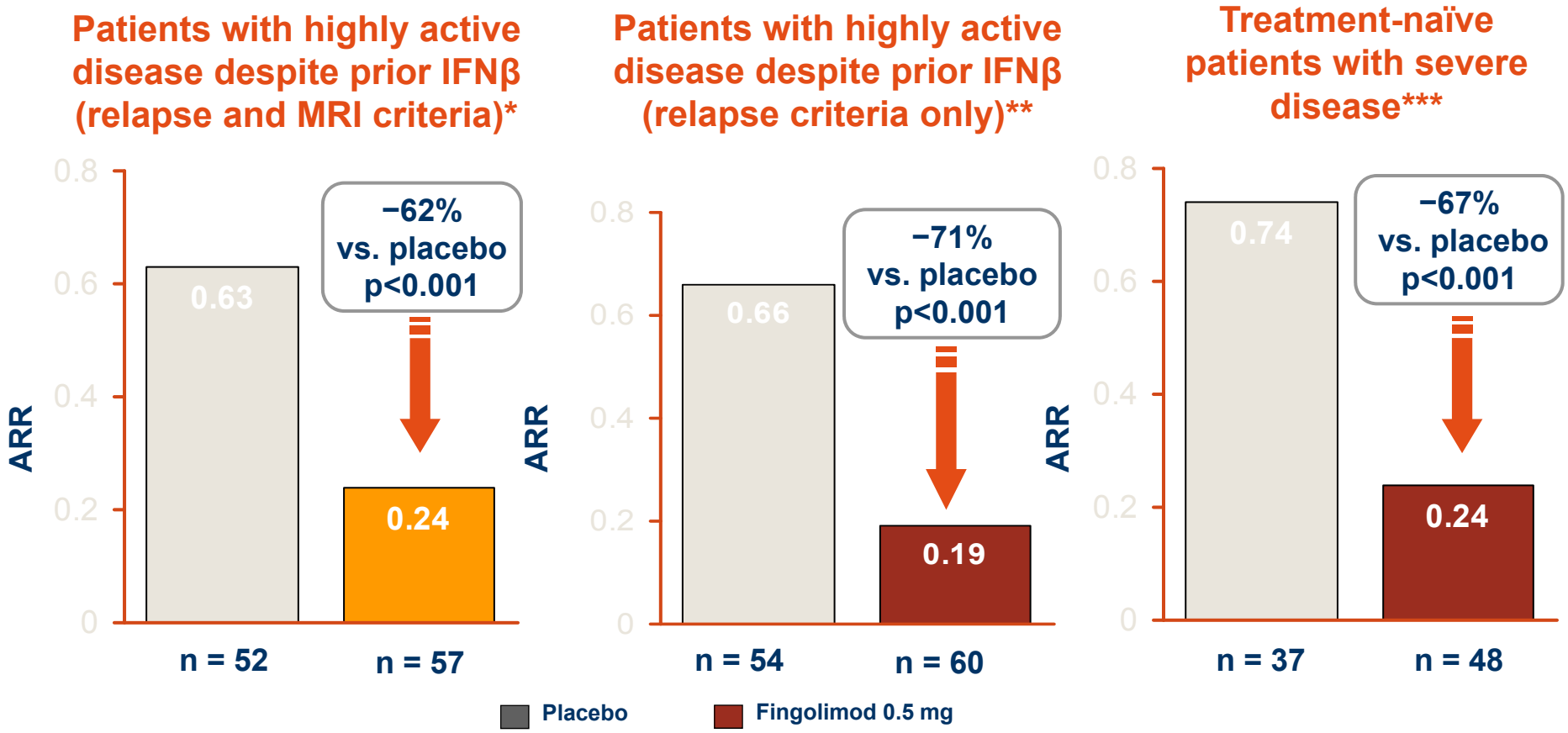
p < 0.001 for fingolimod versus placebo



Annualized Relapse Rate estimate and p value are calculated using negative binomial regression model adjusted for treatment group, country, number of relapses in previous 2 years and baseline EDSS score.

EDSS, Expanded Disability Status Scale; IM, intramuscular 1. Cohen JA *et al. N Engl J Med* 2010;362:402–15. 2. Kappos L *et al. N Engl J Med*. 2010;362:387–401. 3. FDA Advisory Committee presentation (10 June 2010).

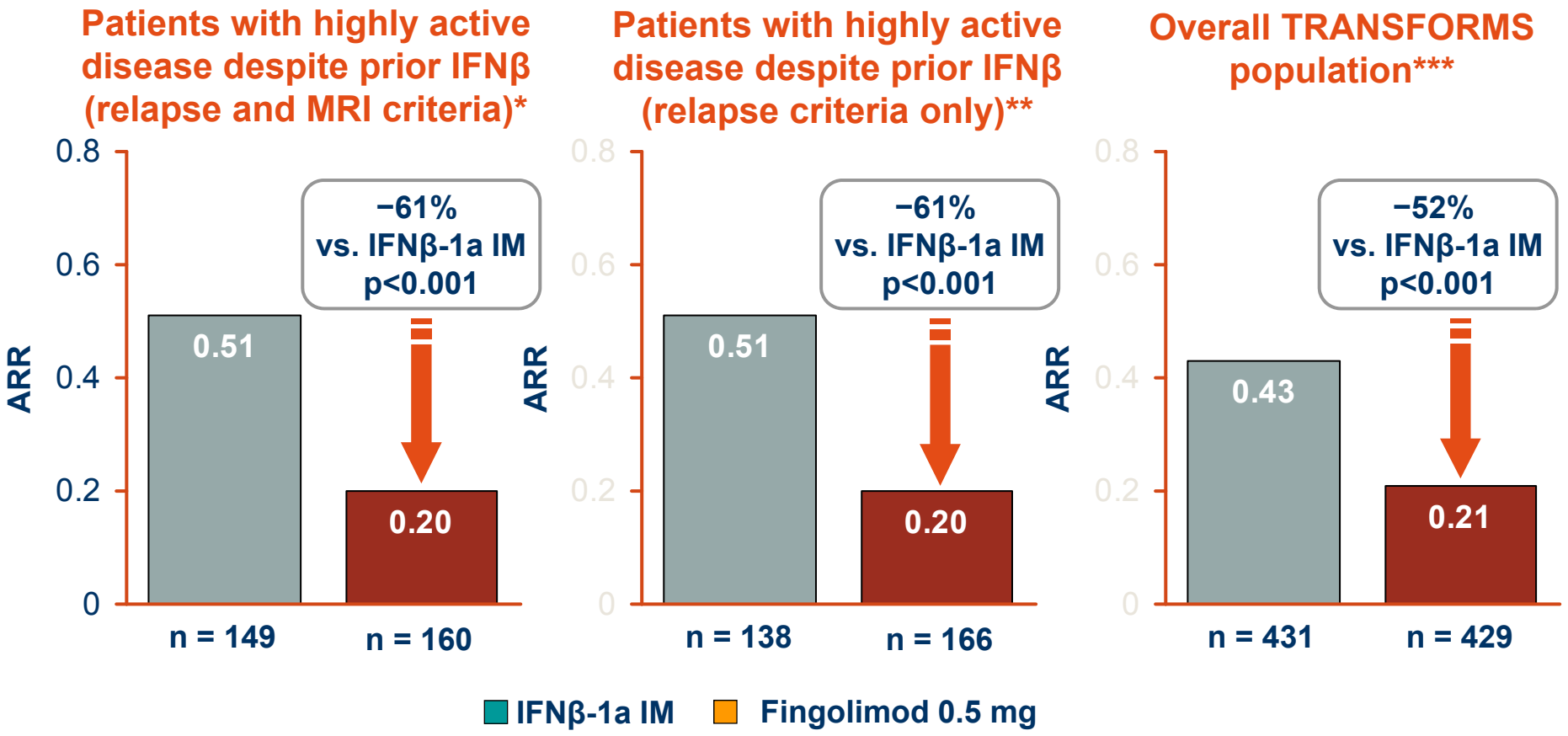
Fingolimod reduced ARR in patients with highly active RRMS at 2 years (FREEDOMS)



FREEDOMS overall population included RRMS, EDSS 0-5.5, ≥1 relapse in the year prior to study or ≥ 2 relapses in the previous 2 years, ARR primary endpoint at 2 years: 0.18 for fingolimod 0.5 mg (n=425) and 0.40 for placebo (n=418) representing 54% relative reduction in ARR.

*IFN and ≥1 relapse in the year prior to study, plus either ≥1 Gd-enhancing lesions or ≥9 T2 lesions at baseline;**IFN in the year prior to study, plus equal or more relapses in Year -1 than in Year -2; ***rapidly evolving severe RRMS defined as ≥2 relapses in the previous year and ≥1 Gd-enhancing lesion at baseline; based on relapse rate ratio. Kappos L *et al. N Engl J Med* 2010, Francis G and Haering D, Apr 2011 Data on file

Fingolimod reduced ARR in patients with highly active RRMS despite prior DMT, at 1 year (TRANSFORMS)

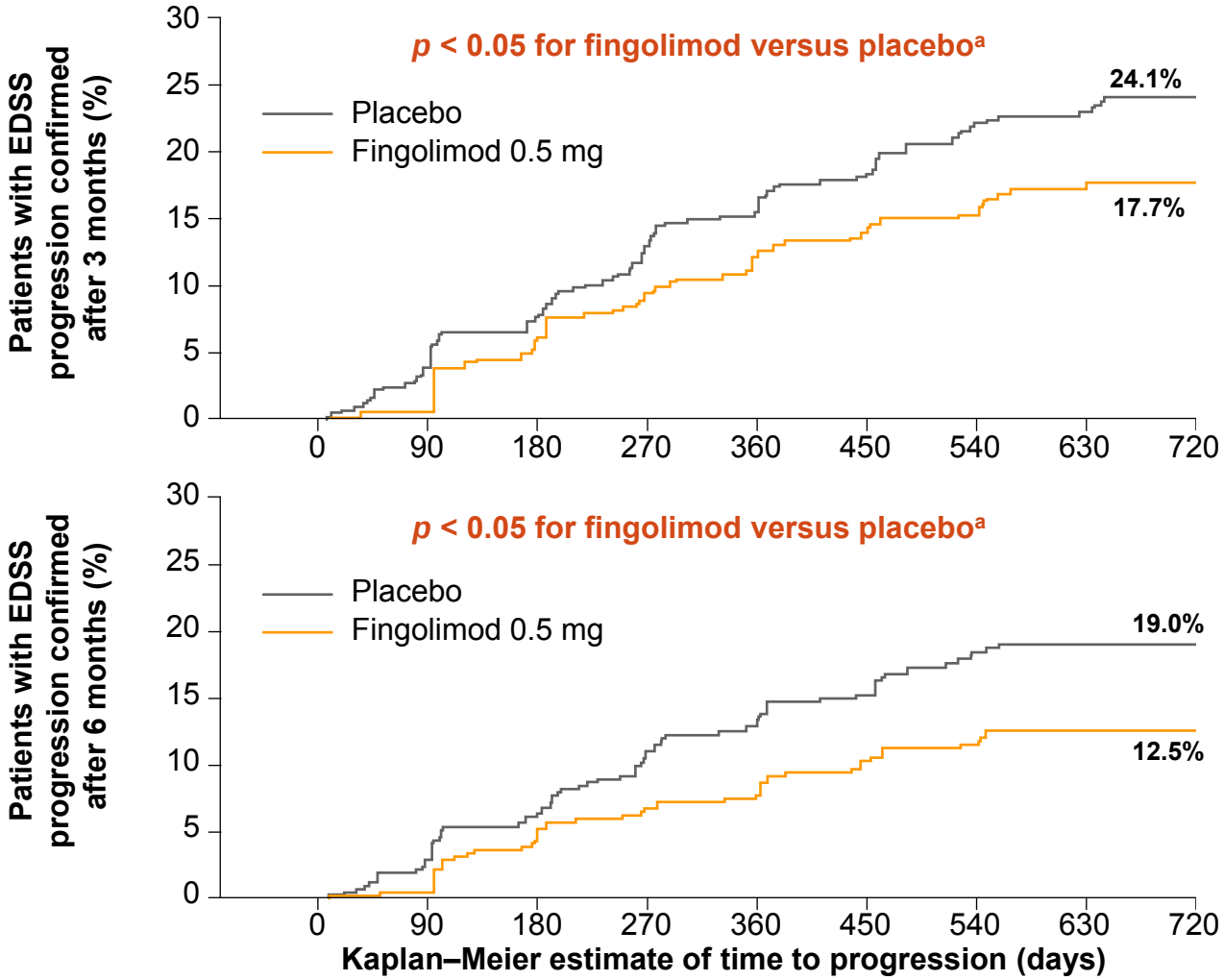


*IFN and ≥1 relapse in the year prior to study, plus either ≥1 Gd-enhancing lesions or ≥9 T2 lesions at baseline;**IFN in the year prior to study, plus equal or more relapses in Year -1 than in Year -2; based on relapse rate ratio; ***Aggregate ARR is presented

Cohen J *et al*. *ENS* 2011; poster P901

Fingolimod therapy reduced the risk of disability progression confirmed after 3 or 6 months versus placebo

FREEDOMS 2-year results[1,2]



[a]Log-rank test comparing the survival distributions between treatment groups. [b]Cox's proportional hazard model adjusted for treatment, country baseline EDSS and age. 1. Kappos L *et al. N Engl J Med*. 2010;362:387–401. 2. Kappos L *et al. J Neurology*. 2010;257:S144 (abstract).

GILENYA Label- European Union

- **GILENYA is indicated as a single disease-modifying therapy in highly active relapsing–remitting multiple sclerosis (RRMS) for the following adult patient groups:**
  - **patients with high disease activity despite treatment with a beta-interferon:**
    - **these patients may be defined as those who have failed to respond to a full and adequate course (normally at least 1 year of treatment) of beta-interferon. Patients should have had at least one relapse in the previous year while on therapy and have at least nine T2 hyperintense lesions in cranial MRI or at least one gadolinium-enhancing lesion. A "non-responder" could also be defined as a patient with an unchanged or increased relapse rate, or ongoing severe relapses, as compared with the previous year**

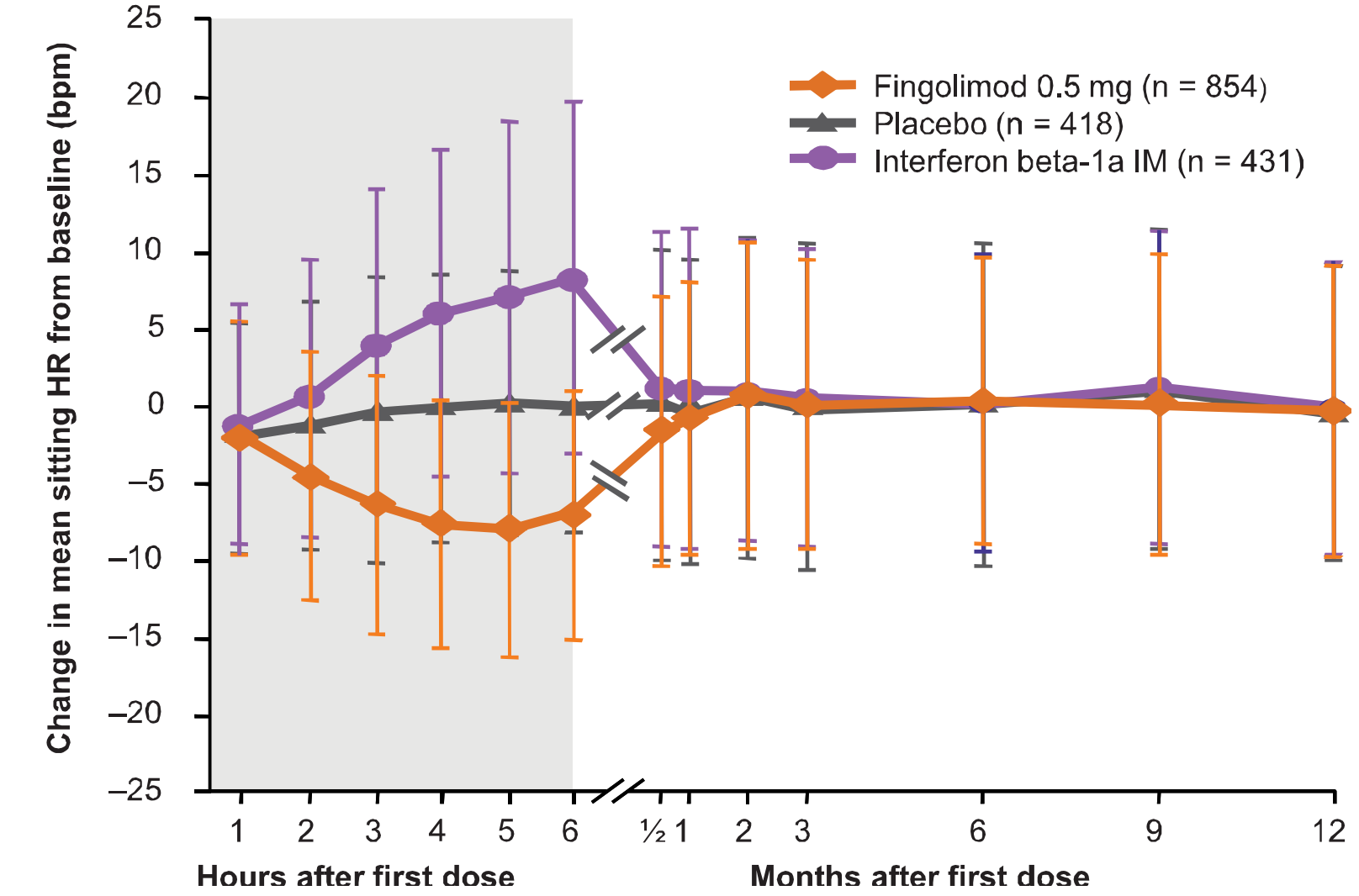
OR

  - **patients with rapidly evolving severe RRMS:**
    - **defined by two or more disabling relapses in 1 year and with one or more gadolinium-enhancing lesions on brain MRI, or a significant increase in T2 lesion load as compared with a previous, recent MRI**

GILENYA Summary of Product Characteristics (European Union). http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002202/WC500104528.pdf, accessed on 27 July, 2011

Safety summary

- Fingolimod has been extensively studied:
  - >4500 patient-years in >2600 patients included in the NDA submission
  - >11000 patient-years in >6000 MS patients as of February, 2011
  - comprehensive multi-organ safety assessments in all studies
- Well-characterized safety and tolerability profile in clinical trials
- Fingolimod 0.5 mg was selected as the dose for submission for marketing authorization approval
  - Overall incidence of SAEs and AEs leading to drug discontinuation similar between 0.5 mg dose and comparator (placebo & IFN beta-1a IM)
- Specific AEs that were reported more commonly in MS patients treated with fingolimod than in placebo-treated patients included:
  - Elevations of liver enzymes
  - Reductions in white blood cell counts (lymphocytes and total WBC) – an expected pharmacodynamic effect rather than an AE
  - Bradycardia – transient, on treatment initiation (Day 1)
  - Macular edema
  - Hypertension
  - Dyspnea
  - Bronchitis
  - Diarrhea



Data shown are mean ± SD. Shaded area indicates period of patient monitoring following the first dose

to Dear Healthcare Professional Communication

For all patients starting treatment, monitoring during the first 6 hours after dosing should include:

- A 12-lead ECG at baseline and 6 hours after the first dose
- Continuous 6-hour ECG monitoring
- Blood pressure and heart rate measurement every hour

In those patients with evidence of clinically important cardiac effects, monitoring should be extended until resolution. The following criteria for extended monitoring are recommended:

- The presence at the 6-hour time point after first dose of:
  - Heart rate less than 40 beats per minute
  - Decrease in heart rate of more than 20 beats per minute compared with baseline
  - Persistent new-onset 2nd degree atrioventricular block, Mobitz Type I (Wenckebach)
- The occurrence at anytime during the 6-hour monitoring of:
  - Symptomatic bradycardia
  - New onset 2nd degree atrioventricular block, Mobitz Type II
  - New onset 3rd degree atrioventricular block

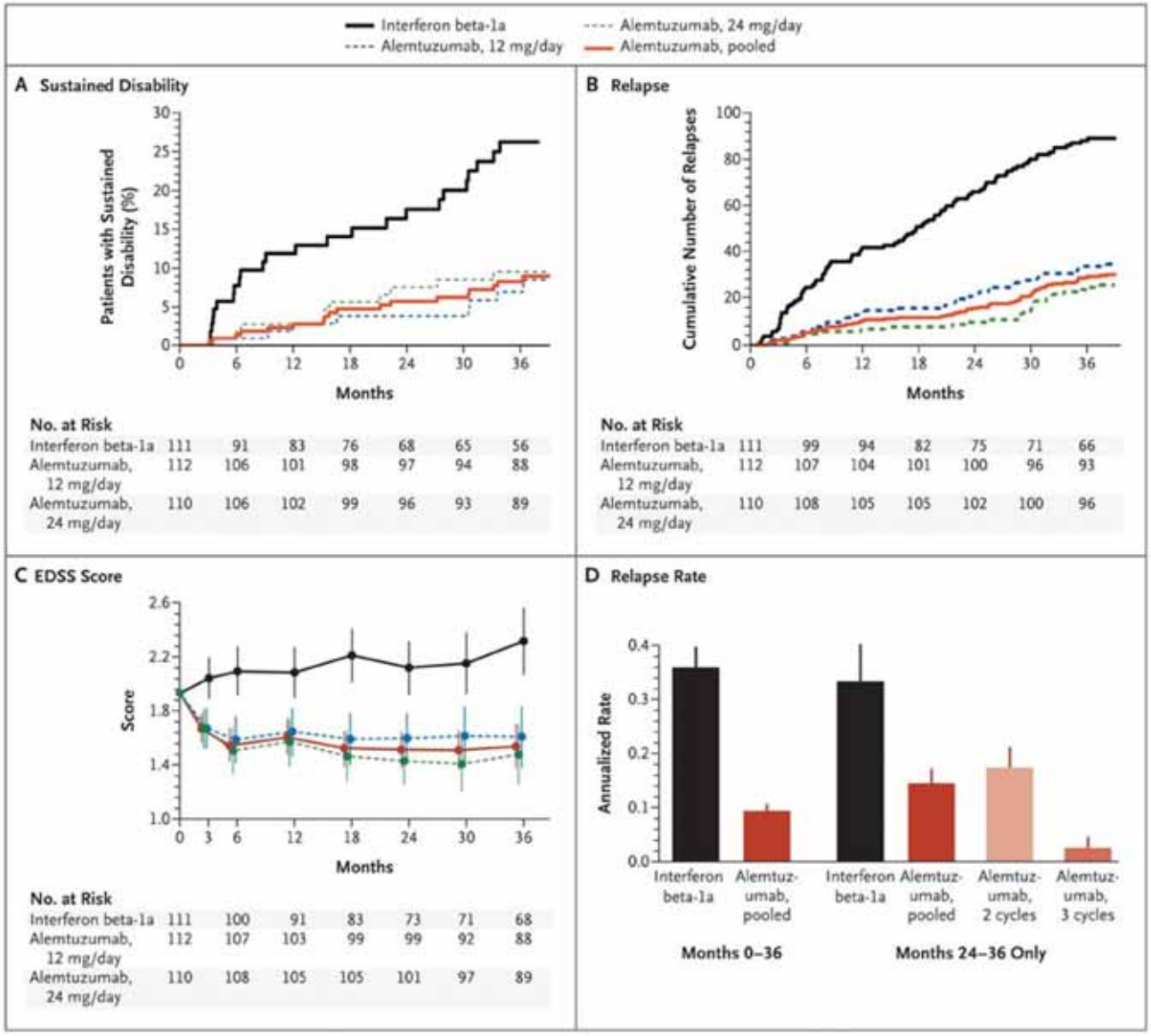
Immunomodulatory treatments in advanced clinical development (Phase 3)

- Alemtuzumab
- Rituximab

Alemtuzumab

- Formerly known as Campath-1H
- Anti-CD52 monoclonal antibody
- Profound and long-lasting T- and B-cell depleting effects
- Risk of secondary autoimmunity:
  - Hyperthyroidism/Graves' disease (up to 25-30%)
  - Immune thrombocytopoenic purpura

Alemtuzumab reduces accumulation of disability and relapses in RR-MS as compared with IFN-B1a

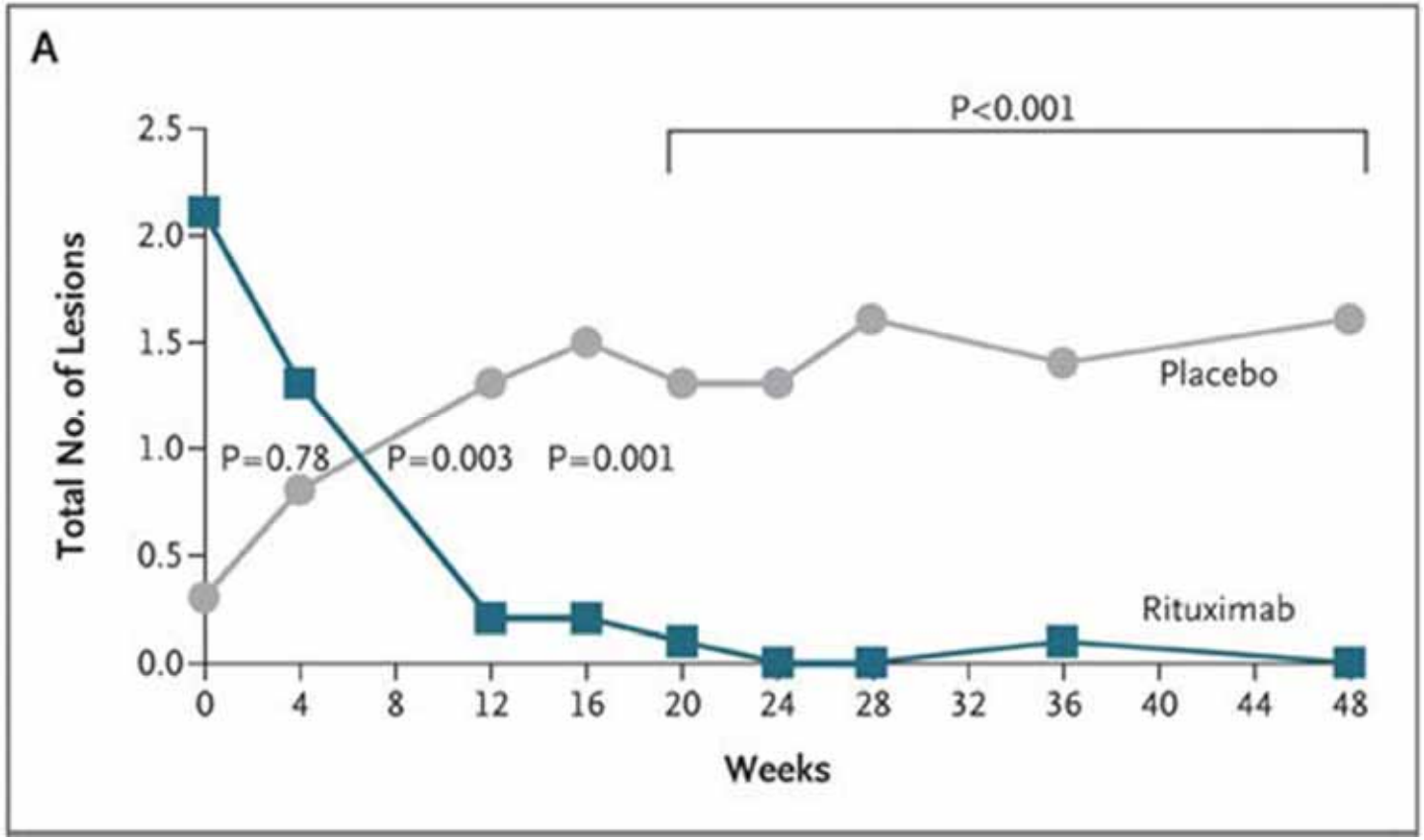


CAMMS study group, NEJM 2008

Rituximab

- Anti-CD20 monoclonal antibody
- Profound and long-lasting B-cell depleting effects
- Approved therapy for B cell lymphomas
- Risk of serious adverse events: PML
- May target specific B cell dependent pathogenic components, e.g. meningeal neolymphoid follicles

Effects of Rituximab on Gadolinium-Enhancing Lesions from Baseline to Week 48



Hauser et al. NEJM 358 (7): 676, Figure 2 February 14, 2008

Table 1 Monoclonal antibodies tested in multiple sclerosis.

Antibody	Therapeutic target	Comments	Study
Anti-T12 (mouse)	CD6 (expressed on all T cells and thymocytes)	Tested in pilot trials only; allergic reactions observed	Hafler *et al.* (1986)[14]
Anti-T11 (mouse)	CD2 (expressed on all T cells)	Tested in pilot trials only; mAb-labeled T cells found in CSF	Hafler and Weiner (1988)[13] Hafler and Weiner (1987)[16]
Anti-T4 (mouse)	CD4 (expressed on T-helper cells)	Tested in pilot trials only	Hafler and Weiner (1988)[13]
cM-T412 (mouse–human chimeric)	CD4 (expressed on T-helper cells)	Tested in phase II trials; long-lasting depletion of $CD4^+$ T cells; clinical and MRI findings not impressive	van Oosten *et al.* (1997)[23] Llewellyn-Smith *et al.* (1997)[24]
OKT®3 (Johnson & Johnson, New Brunswick, NJ) (mouse)	CD3 (expressed on all T cells)	Tested in phase I/II trials; side effects related to systemic cytokine release	Weinshenker *et al.* (1991)[18]
cA2 (humanized)	TNF-α	Treatment-exacerbated inflammatory activity	van Oosten *et al.* (1996)[29]
Natalizumab (Tysabri®, formerly Antegren®, Elan Pharmaceuticals, Inc., San Francisco, CA) (humanized)	α4 integrin on leukocytes	Impressive clinical results in phase II and III trials; marketing suspended because of serious adverse reactions (PML)	Miller *et al.* (2003)[36] and unpublished results[53]
Alemtuzumab (Campath®-1H, Burroughs Wellcome Co., Research Triangle Park, NC) (humanized)	CD52 on leukocytes	Long-lasting and sustained lymphocyte depletion; suppression of MRI evidence of inflammation but not atrophy; induction of cytokine release; autoimmune thyroid disease	Coles *et al.* (1999)[43,44] Moreau *et al.* (1994)[45]
Daclizumab (humanized)	CD25 on activated cells	Promising in phase II trials	Bielekova *et al.* (2004)[46] Rose *et al.* (2004)[47]
Rituximab (mouse–human chimeric)	CD20 on B cells	Promising in treating neuromyelitis optica	Rizvi and Bashir (2004)[50] Cree *et al.* (2005)[51]
ATM-027 (humanized)	TCR Vβ5.2/5.3 on T-cell subset	MRI results in phase II trials unimpressive	Killestein *et al.* (2002)[54]
CNTO 1275 (fully human)	IL-12	Tested in phase I/II trials	National Multiple Sclerosis Society USA[53]
J695 (fully human)	IL-12	Tested in phase I/II trials	National Multiple Sclerosis Society USA[53]
Hu23F2G (humanized)	LFA-1 (CD11/CD18)	Phase II trials unsuccessful	Lublin *et al.* (1999)[61]
IDEC-131 (humanized)	CD154 on immune cells and activated platelets	Phase I/II clinical trials halted because of thromboembolic complication	National Multiple Sclerosis Society USA[53]

Further details about ongoing trials can be found at the website of the National Multiple Sclerosis Society USA.[53] CSF, cerebrospinal fluid; IL-12, interleukin-12; LFA-1, lymphocyte function-associated antigen-1; mAb, monoclonal antibody; PML, progressive multifocal leukoencephalopathy; TCR, T-cell receptor; TNF-α, tumor necrosis factor-α.

Emerging/experimental therapies

- New monoclonal antibodies
  - Daclizumab (anti-CD25)
  - Ocrelizumab (anti-CD20 but ≠ epitope RTX)
  - Lots of other…zu/mumabs!
- New oral agents (BG-12, teriflunomide, laquinimod)
- Bone marrow/haematopoietic stem cell transplantation
- Mesenchymal stem cell transplantation

Future

- Improved understanding of the disease
  - Neuroimmunology
  - Neuropathology
  - Genomics and proteomics
  - Imaging
  - Pathophysiology of fatigue
- →More effective treatments
  - Immunotherapies
  - **Neuroprotective therapies**
  - **Regenerative approaches**

Recommended reading

- Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG. Multiple sclerosis. *N Engl J Med* 2000;**343**(13): 938-52.
- McAlpine's Multiple Sclerosis, Fourth Edition, Churchill Livingston, 2005 (relevant sections)
- Wekerle H and Hohlfeld R, Drug insight: using monoclonal antibodies to treat multiple sclerosis. Nat Clin Pract Neurol. 2005 Nov;1(1):34-44
- Muraro and Bielekova. Emerging treatments for multiple sclerosis. Neurotherapeutics. 2007 Oct;4(4):676-92
- Nicholas R, Giannetti P, Alsanousi A, Friede T, Muraro PA. Development of oral immunomodulatory agents in the management of multiple sclerosis. Drug Des Devel Ther. 2011;5:255-74
- PMID: 21625416 Free PMC Article

Questions?