Imperial College London

Multiple sclerosis – treatment strategies

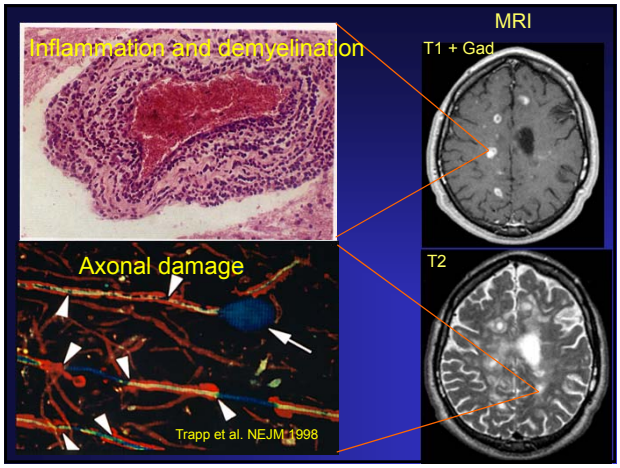
Paolo A. Muraro, MD PhD
Clinical Reader in Neuroimmunology and Honorary Consultant Neurologist

Learning objectives

- Understand the main categories of treatments for MS (what can we treat)
- Be familiar with the main approved disease-modifying treatments
- Be familiar with the main symptomatic treatments and the management of common complications
- Have a notion on what new treatments are being experimented

MS pathogenesis – brief recap

- Inflammation
- Demyelination
- Axonal damage and loss



Management of MS

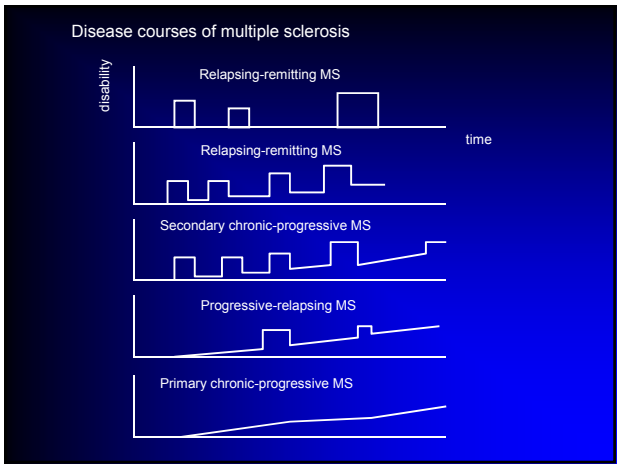
- Education and counselling
- Management of acute attacks
- Prevention of relapses and progression of disability
- Symptomatic therapy
- Physical therapy
- Treatment of complications

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
- **To prevent relapses and accumulation of disability**
  - Immunomodulatory treatments
  - Immunosuppressive treatments
- **Symptomatic**
  - Anti-spastic drugs
  - Drugs to reduce neuropathic pain
  - Medication to improve bladder control

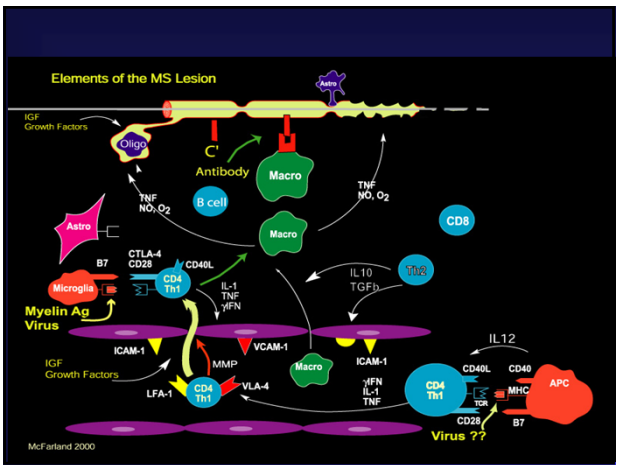


Management of acute attacks

- 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
  - High-dose oral prednisone
  - Standard-dose steroids not recommended
  - Commonly given in day hospital setting

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

- RR MS
  - Interferon beta
  - Glatiramer acetate/copolymer 1
  - Azathioprine
  - Intravenous Immunoglobulin (IVIg)
  - Natalizumab
- SP MS
  - Interferon beta 1b
  - Mitoxantrone
- Primary progressive
  - Low dose Methotrexate
  - No treatment proven effective



Approved immunomodulatory treatments for RR-MS

- Interferon-β
- Glatiramer acetate
- Natalizumab

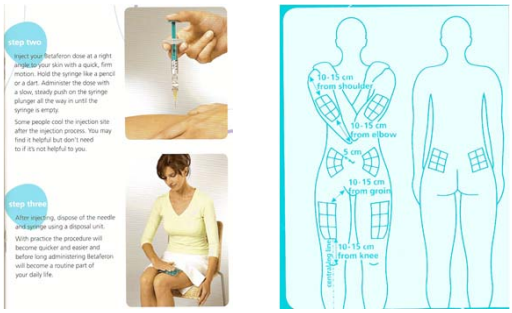
Interferon-β (Betaferon,Rebif, Avonex)

- 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

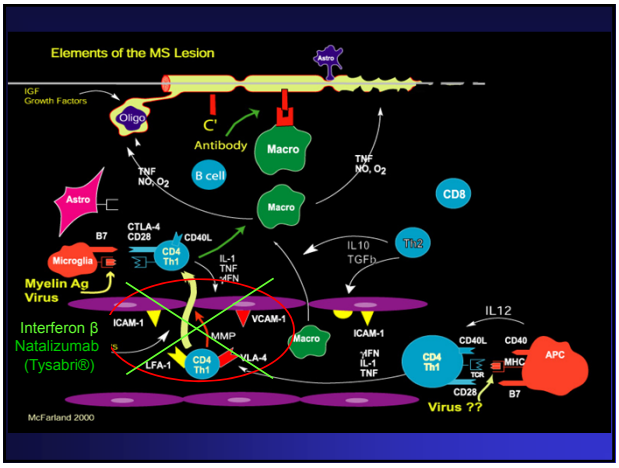
- Relapsing-remitting or early secondary progressive
- Prevents about 1/3 of relapses
- Reduces accumulation of disability (controversial)
- Neutralising antibodies develop in 15-30% and may reduce efficacy

Self-injection of interferon beta



Mechanisms of IFN-beta

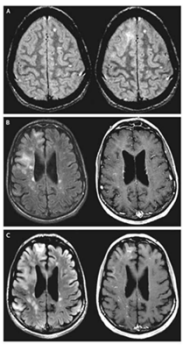
- Anti-viral effect?
- IFN-β treatment reduces VLA-4 cell surface expression on T lymphocytes



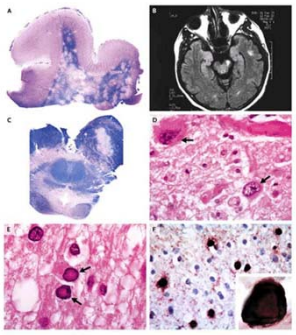
Natalizumab (Tysabri)

- 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)

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

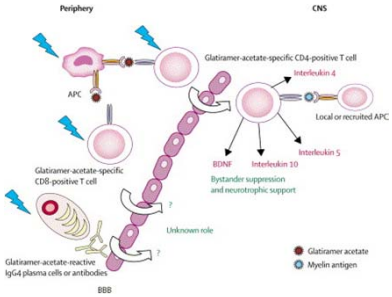


Kleinschmidt-DeMasters and Tyler NEJM 353 (4): 369 July 28, 2005

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

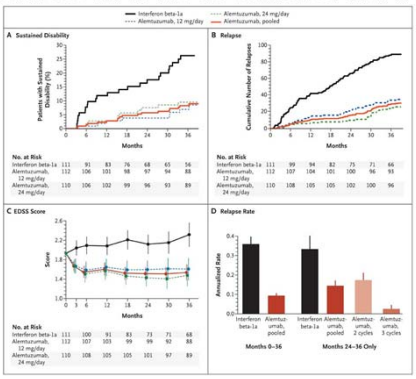
Emerging/experimental therapies

- New monoclonal antibodies
  - Campath-1H (anti-CD52)
  - Rituximab (anti-CD20)
  - Daclizumab (anti-CD25)
- Bone marrow/haematopoietic stem cell transplantation
- Mesenchymal stem cell transplantation

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

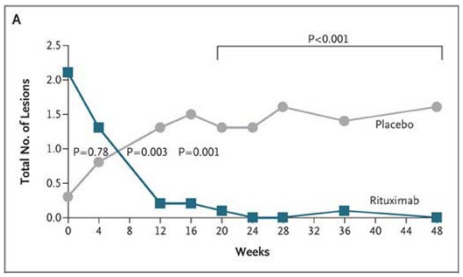


CAMMS study group, NEJM 2008

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[33]
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[55]
J695 (fully human)	IL-12	Tested in phase I/II trials	National Multiple Sclerosis Society USA[55]
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[55]

Further details about ongoing trials can be found at the website of the National Multiple Sclerosis Society USA.[55] 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.

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

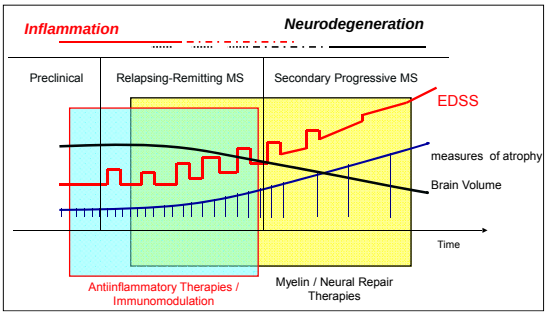
Management of complications

- 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**

Future

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

Therapeutic windows in MS



Muraro, Cassiani and Martin, *Cytotherapy* 2004

Recommended reading

- Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG. Multiple sclerosis. *N Engl J Med* 2000;**343**(13): 938-52.
- Wekerle H and Hohlfeld R, Drug insight: using monoclonal antibodies to treat multiple sclerosis. Nat Clin Pract Neurol. 2005 Nov;1(1):34-44
- McAlpine's Multiple Sclerosis, Fourth Edition, Churchill Livingston, 2005 (relevant sections)
- Muraro and Bielekova. Emerging treatments for multiple sclerosis. Neurotherapeutics. 2007 Oct;4(4):676-92