Treatment of MS: from Charcot to Sherlock

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Treatment of MS - Overview

- Background
- Progress in the treatment of MS
- Benefits and risks of new treatments
- Yorkshire Brain Research Centre
- Embedding research in the MS Clinic
Charcot: the father of neurology

- Paris 1825-1893
- First link between clinical features of MS and post mortem changes
- Recognition of MS as a distinct disease
- ‘La sclérose en plaque’
Background: what is MS?

- MS is the most common cause of neurological disability in young adults in the UK
- 900 people living with MS in Leeds
- 50 new cases of MS / year in Leeds
Clinical course of MS

- Relapsing-remitting
- Secondary progressive (following relapsing-remitting)
- Primary-progressive
- Progressive-relapsing
Brain imaging diagnostic criteria

Natural history of brain atrophy in MS

Images acquired over the course of 7 years from a single MS patient
Progress in the treatment of MS

- Early Trials
- First injectable treatments
- Powerful infusions
- New tablet treatments
Early MS trials

In 1954 Kurtzke and Berlin reported their results in the treatment of 30 multiple sclerosis patients with isoniazid. Using their own classification scale, they estimated that 90\% of these patients were improved as compared with 33\% improved in their control series.
Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial.

The IFNB Multiple Sclerosis Study Group

Neurology. 1993 Apr;43(4):655-61
Interferon beta in relapsing-remitting MS

- Reduces clinical attacks by about 30%
- Reduces MRI activity by up to 80%
Problems with interferon beta

- Expensive (£8,000 per patient per year)
- NICE approval – Risk Sharing Scheme
- Side-effects:
  - Injection site problems
  - Flu-like symptoms
  - Rarely: liver inflammation/hepatitis or low white blood cell count
Natalizumab (Tysabri)
Natalizumab

- Licence and NICE approval 2007
- Monoclonal antibody
- Stops white blood cells crossing into the brain
- 2 year phase 3 trial in relapsing remitting MS showed a 68% reduction in relapse rate
Shares in Irish drugmaker Elan have plummeted once more after a third case of disease linked to Tysabri, its multiple sclerosis treatment.

Elan suspended the drug after two patients were found to have caught the rare disease, one of whom later died.

The newly revealed case - which also ended with the death of the patient - could mean Tysabri never makes it back onto the market, analysts warned.

By the close of trading, Elan shares were down 56% to 2.43 euros.
Risk Stratification Tool: The Presence of Anti-JCV Antibodies, Prior Immunosuppressant Use, Treatment Duration

Anti-JCV Antibody Status

- Negative
- Positive

Prior IS Use

- No: 1 in 1,667
- Yes: 1 in 556

Natalizumab Exposure

- No Prior IS Use
- Prior IS Use

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<tr>
<th>Exposure</th>
<th>No Prior IS Use</th>
<th>Prior IS Use</th>
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<tr>
<td>1–24 months</td>
<td>0.6/1000 (95% CI 0.4–0.9)</td>
<td>1.8/1000 (95% CI 1.1–2.8)</td>
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<tr>
<td>25–48 months</td>
<td>5.2/1000 (95% CI 4.3–6.2)</td>
<td>10.6/1000 (95% CI 8.1–13.8)</td>
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1 in 14,286 (0.07/1000; 95% CI 0–0.38)

1 in 1,667

1 in 192

1 in 94

Data beyond 4 years of treatment are limited.

*Based on natalizumab exposure and 285 confirmed PML cases as of September 5, 2012. Prior IS data in overall natalizumab-treated patients based on proportion of patients with IS use prior to natalizumab therapy in TYGRIS as of May 2011; and prior IS data in PML patients as of September 5, 2012. The analysis assumes that 55% of natalizumab-treated MS patients were anti-JCV antibody positive and that all PML patients test positive for anti-JCV antibodies prior to the onset and diagnosis of PML. The estimate of PML incidence in anti-JCV antibody negative patients is based on the assumption that all patients received at least 1 dose of natalizumab. Assuming that all patients received at least 18 doses of natalizumab, the estimate of PML incidence in anti-JCV antibody negative patients was generally consistent (0.1/1000; 95% CI 0.00–0.62).

Biogen Idec, data on file.
First effective tablet drug for MS

A potent immunosuppressive activity was found in the culture broth of the fungus Isaria sinclairii (ATCC 24400). The metabolite was 10- to 100-fold more potent than cyclosporin A as an immunosuppressive agent of the immune response in vitro and in vivo, and appears to be a candidate for clinical application as a powerful immunosuppressant.
Fingolimod (FTY720)
Sphingosine 1-phosphate (S1P) receptor modulator

FTY720 results in internalisation of the receptor S1P1
This blocks lymphocyte egress from lymph nodes while sparing immune surveillance by circulating memory T cells

Prevents T cell invasion of CNS
FTY720 traps circulating lymphocytes in peripheral lymph nodes
Fingolimod

- TRANSFORMS Phase 3 Trial (n=1292)
- 52% reduction in relapse rate compared to IM Interferon 1a
- 2 incidences of fatal Herpes virus infection (type 1 encephalitis and disseminated Zoster)
New developments in 2014

- 3 new drugs licensed and NICE approved
- January 2014: Teriflunomide (tablet)
- May 2014: Alemtuzumab (infusion)
- August 2014: Dimethyl fumarate (tablet)
% reduction in relapse rate vs placebo

LOG frequency of serious adverse events
Lack of Progress – so far

- Secondary progressive MS: early promising results for Siponimod (Leeds is a trial centre)
- Primary progressive MS
- Neuroprotection – prevention of atrophy
- Myelin repair
MS Research Team
Welcome to the Yorkshire Brain Research Centre.

Latest News

Pride of Britain Awards
August 10, 2016
Yesterday the Fundraising Team was invited by The Pride of Britain Awards and TSB to Victoria Gardens in Leeds City...

Read More >

Latest Events
Embedding research in the MS Clinic

- Epidemiology
- Aetiology
- New treatment trials
- Patient reported outcome measures
- Impact of MS on employment
Epidemiology of MS

- Leeds MS Register – established 1996
- Prospective register – all new cases recorded with written consent
- Regularly updated
- Facilitates service development including the West Yorkshire MS Treatment Programme
Crude prevalence of MS in the Bradford population

112/10^5
Prevalence of total MS population in Bradford district PCT

306 196
Population of Bradford

79 603
South Asian population

46/10^5
Prevalence in South Asians

135/10^5
Prevalence in Non-South Asians

226 593
Non-South Asian population
Figure 4 Prevalence of Non-South Asian population with MS in Bradford

Figure 5 Prevalence of South Asian population with MS in Bradford
Causes of MS

- Genetics and MS (GAMS)
- University of Cambridge – international collaboration
- Immunological consequences of genetic variants
- Susceptibility to MS
- Clinical course of disease
Treatment trials

- Teriflunomide in relapsing remitting MS
- Combination study with interferon
- Siponimod in secondary progressive MS
- Ocrelizumab in relapsing remitting MS
- MS SMART
- Phase IV studies of fingolimod, teriflunomide, dimethyl fumarate and alemtuzumab
Natalizumab: Quality of Life study

![Bar chart showing the quality of life (QoL) scores over time for Beta interferon and Tysabri treatments.](image)
Psychological determinants of job retention in MS

- Prospective 3 year study of employed people with MS in Leeds and Bradford
- Funded by MS Society
- Aim to determine the psychological factors influencing job retention
- HF (CI), Co-investigators Alan Tennant, Amanda Stroud, Anna Madill
Progress

- Recruited 221 employed people with MS in the prospective study
- Trajectory of the working life of people with MS
- Identified self-efficacy and depression as key psychological factors
Epilepsy team
Summary

- Treatment of MS is evolving
- 11 licensed treatments for MS now available in the UK
- Leeds is a leading MS clinical trials centre
- Research can be embedded in a NHS clinical service