New research in primary and secondary progressive multiple sclerosis

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Overview

- What is multiple sclerosis?
- What treatments are currently available?
- Developing a new drug
- Approval of a new drug for prescribing
- What drugs are currently in trials for:
  - Secondary progressive MS?
  - Primary progressive MS?
Multiple Sclerosis (MS)

- An auto-immune, inflammatory disorder of the central nervous system
- Inflammatory plaques arise within the brain or spinal cord resulting in demyelination
- Affects females twice as frequently as men
- Peak age onset 30-40 years
The immune system damages myelin covering the nerves
Visible on MRI scans…
The immune system also damages the axons of nerves
Over years, demyelinated nerves degenerate

Not driven by immune cells

Trapp NEJM 1999
Types of MS

- Relapsing-remitting 85%
- Secondary Progressive
- Primary Progressive 10-15%
Clinical Course

Inflammation

Nerve Degeneration

Brain Atrophy

1. PREVENT

2. REMYELINATION

3. NEUROPROTECTION

Compston A, Coles A, Lancet 2002
Clinical Commissioning Policy: Disease Modifying Therapies for Patients with Multiple Sclerosis (MS)

- NHS Commissioning Board published April 2013
- Provides guidance on the use of disease modifying therapies for patients with MS in England
- Allows beta interferon, glatiramer acetate, natalizumab and fingolimod to be commissioned without the need for prior approval
- Identifies starting and stopping criteria for the use of these drugs
- Provides definitions to describe the different presentations of MS
Definitions for NHS Clinical commissioning

Secondary progressive MS
Following a period of relapsing-remitting MS, the frequency of relapses is decreased and disability increased

- Disease modifying treatments are only recommended in relapsing secondary progressive MS when relapses are the predominant cause of increasing disability.

Primary progressive MS
Disability increases from the outset, usually with the absence of distinct relapses

- No disease modifying treatment is indicated.
Main starting criteria, the patient:

- has had at least **two disabling relapses in two years**
- **is able to walk 10m or more**
- has had minimal increase in disability due to gradual progression over the past 2 years

Main stopping criteria, one or more of the following are met:

- No reduction in frequency or severity of relapses following a minimum 6 month period of treatment
- Development of **inability to walk, persistent for more than 6 months**, unless unable to walk for reasons other than MS.
- Intolerable adverse effects of the drug
- The patient is pregnant, breast feeding or attempting conception
Unmet need for new drugs in progressive MS

• All current approved therapies target inflammation and aim to prevent relapses

• No licensed drugs that promote remyelination or protect neurones to stop degeneration and progression

• Stages of drug development:
  - Pre-clinical i.e. laboratory testing of drugs in models of MS
  - Clinical trials
  - Approval for licensing – FDA, EMA
  - Approval for prescription in England and Wales (NICE) or local approval
Development of new drugs, stages of clinical trials

Licensing approval: Medicines and Healthcare products Regulatory Agency (MHRA) or the European Medicines Agency (EMA)

10 to 15 years*

£ 1.15 billion*

* The Association of the British Pharmaceutical Industry
Expanded disability status scale (EDSS)
Multiple sclerosis functional composite

1. Ambulation -> timed 25-foot walk
2. Arm and hand function -> a nine hole peg test
3. Cognitive function -> Paced Auditory Serial Addition Test
ALEMTUZUMAB in relapsing-remitting MS

- Humanised monoclonal antibody, targets a protein on lymphocytes
- Single dose leads to the long term depletion of T-cells
- Licensed for chronic lymphocytic leukaemia
- Used since the early 1990’s in Cambridge as an experimental treatment of MS
- Given by intravenous infusion (once per year for minimum of two cycles)

Phase II and III trials in relapsing-remitting MS shows:
- At least 50% reduction in annual relapse rate compared to beta-interferon
- Reduction in accumulation of disability
- Reduction in brain shrinkage (atrophy)
ALEMTUZUMAB in relapsing-remitting MS

First used in MS in 1991

Licensed by EMA in Sept 2013

Under NICE review 2014


Phase 2

CAMMS223
N=334
Treatment-naïve vs. SC IFNB-1a 44 µg
3 years & extension (2+ years)
COMPLETED: 2007

Phase 3

CARE-MS I
N=581
Treatment-naïve vs. SC IFNB-1a 44 µg
2 years
COMPLETED: Summer 2011

CARE-MS II
N=840
Treatment-experienced and relapsed on prior therapy vs. SC IFNB-1a 44 µg
2 years
COMPLETED: Autumn 2011

Extension study

CARE-MS Extension Protocol
4 years
ONGOING

RRMS=relapsing, remitting MS; SC IFNB=subcutaneous interferon beta
National Institute for Health and Clinical Excellence (NICE) the final hurdle?

- NICE is an independent organisation, it gives advice on which new and existing drugs should be available on the NHS
- NICE looks at how a new drug or treatment compares to the treatment already available and whether it's good value for money
- When all the evidence has been reviewed, a decision is made and guidance is issued
- If NICE haven’t reviewed a particular drug then local health bodies decide whether to provide a drug or treatment
- If NICE approves a medicine, this replaces any previous local decisions and promotes equal access for patients across the country
- If NICE does not approve a particular drug, it may still be accessible locally through exceptional funding
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Compston A, Coles A, Lancet 2002
Current research in progressive MS

Secondary progressive MS:
- Simvastatin
- Mastinib
- Nataluzimab
- Siponimod (BAF312)
- Riluzole, ibudilast and amiloride (MS-SMART)
- Autologous mesenchymal stem cells

Primary progressive MS:
- Mastinib
- Nataluzimab
- Fingolimod
- Rituximab
- Ocrelizumab
- Idebenone
- Autologous mesenchymal stem cells
Simvastatin in Secondary progressive MS

- Statins have numerous anti-inflammatory effects and a range of potential neuroprotective effects

THE MS-STAT TRIAL

- Phase II, London UCL
- 70 patients with secondary progressive MS given high dose Simvastatin (80mg) and 70 given placebo
- Results presented at ECTRIMS 2012, after 2 years those on simvastatin had:
  - A small but significant reduction in the rate of brain atrophy (brain shrinkage) over two years
  - Slightly better end-of study EDSS scores (a scale measuring disability levels)
- There was no difference in relapse rate or MRI disease activity
- Overall the drug was well tolerated
- Study results not yet published
Mastinib

- Tyrosine kinase inhibitor, targets mast cells (a type of cell involved in allergy and inflammation)

- Mastinib led to a significant reduction in disease in a mouse model of MS

- Phase II trial of mastinib in patients with primary progressive or relapse-free secondary progressive disease treated over 12 months

- 27 patients given mastinib tablets twice daily and 8 patients given placebo

- Multiple sclerosis functional composite (MSFC) score was the primary outcome measure:
  - Improvement in scores relative to baseline in mastinib group
  - Worsening MSFC score in patients receiving placebo
  - Not statistically significant

- Side effects: fatigue, rash, nausea, oedema (fluid retention) and diarrhoea
Nataluzimab (Tysabri)

- Licensed for highly active relapsing remitting MS (reduces relapse rate by approx. 65%)
- A monoclonal antibody, binds to molecules on the surface of specific immune cells and prevents them passing through the blood-brain barrier into the central nervous system
- Given as an intravenous infusion, once every four weeks
- A rare but potentially fatal side effect is progressive multifocal leukoencephalopathy, a viral disease of the brain, caused by JC virus
Natalizumab Treatment of Progressive Multiple Sclerosis (NAPMS)

- Single centre study in Copenhagen, Denmark
- Phase II study to investigate the safety and effectiveness of natalizumab treatment of primary and secondary progressive multiple sclerosis
- Completed, results awaited

Phase 3 trial ‘ASCEND’

- 850 participants with secondary progressive MS given natalizumab or placebo by intravenous infusion every four weeks for 96 weeks
- Primary objective is to investigate whether natalizumab slows the accumulation of disability
- UK centres: London, Manchester, Liverpool, Nottingham, Plymouth, Swansea, Birmingham, Brighton
- Study ongoing but no longer recruiting participants
Fingolimod (Gilenya®)

- Fingolimod approved by NICE in 2011 for relapsing-remitting MS patients with active disease who have failed treatment with interferon-beta (reduces relapses by approx. 50%)
- Taken as a tablet once daily
- Side effects include:
  - headache, diarrhoea, cough and dizziness
  - mild infections
  - slowing of the heart rate (first dose given in hospital with monitoring)
  - rarely visual problems (macular oedema)
- Phase II trial underway in primary progressive MS to study the safety and effect on delaying disability progression (INFORMS)
Siponimod (BAF 312)

- Similar drug to fingolimod, causes lymphocytes to be retained in lymph glands
- Taken as a tablet once daily
- In phase II relapsing remitting MS studies, siponimod reduced relapse rates compared to placebo (0.58 on placebo to 0.2 siponimod).
- Most common side effects were headache, slowing of heart rate, dizziness, and nose and throat infections.
- Phase III trial ‘EXPAND’ in secondary progressive MS
  - Multiple centres worldwide (including the UK) recruiting approx. 1500 patients
  - Randomised to either siponimod or placebo
  - Primary objective of the study is to demonstrate the efficacy of siponimod in delaying disability progression (measured by EDSS)
Rituximab in primary progressive multiple sclerosis

- Rituximab is a monoclonal antibody that depletes B cells in the blood
- Given by intravenous infusion 6 monthly
- OLYMPUS Phase II trial 2009
  - 439 primary progressive MS patients received rituximab or placebo infusions
  - Overall no significant difference in disease progression
  - Subgroup analysis showed time to disease progression was delayed in patients aged less than 51 years and in those with active inflammatory lesions on their MRI
- Rituximab owned by Roche (US patent expires 2015)
- No phase III trials planned
Ocrelizumab in primary progressive multiple sclerosis

- Ocrelizumab is a monoclonal antibody that is very similar to rituximab and depletes B cells in the blood
- Ocrelizumab also owned by Roche
- Ocrelizumab Phase II trial in relapsing-remitting MS published in Lancet 2011
  - Significant reduction in MS activity seen on MRI scans compared to placebo
  - Significant reduction in relapses compared to placebo
  - One patient died in the high-dose ocrelizumab group
  - Ocrelizumab associated with a serious risk of infection in studies of other diseases (trials suspended in rheumatoid arthritis and lupus)
- Phase III trial in primary progressive MS ongoing
  - 630 patients randomised to Ocrelizumab or placebo
  - Investigating the effect on disability progression
• Will recruit 440 secondary progressive MS patients in multiple UK centres

• MS-SMART will evaluate three drugs with potential neuro-protective effects:

1. Ibudilast
   - phosphodiesterase inhibitor
   - anti-inflammatory
   - used to treat asthma

2. Riluzole
   - inhibits the release of glutamate from nerve endings which is toxic in excess
   - used to treat motor neurone disease

3. Amiloride
   - blocks an ion channel (ASIC1) preventing sodium and calcium transport into nerve cells
   - studied in 14 primary progressive patients and reduced brain volume loss over three years on MRI

Arun et al, Brain 2013
Stem cells

- Stem cells are cells that can both reproduce themselves and ‘differentiate’ i.e. develop into different cell types.
Only produce cells found in the blood e.g. immune system cells

1. Hematopoietic -> blood cells
2. Mesenchymal stem cells (stromal) -> fat, cartilage and bone
3. Endothelial -> blood vessels

Adult stem cells
- Neural stem cells in the brain ->
  - nerve cells (neurons)
  - astrocytes and
  - oligodendrocytes
- Olfactory (lining of the nose)
- Intestinal (gut)
- Testicular

Embryonic stem cells

Bone marrow

Cord blood stem cells

most of the specialist cells in the body

- In Vitro Fertilized Egg
- Blastocyst Stage
- Inner Stem Cell Mass
- Cultured Undifferentiated Stem Cells

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Bone marrow mesenchymal stem cells could have an effect in Multiple Sclerosis by several mechanisms:

1. Modulation of the immune system
2. Modification of the cellular environment in the brain by producing an environment which is supportive to repair or anti-inflammatory effects
3. Repair of myelin in the brain and spine
Autologous mesenchymal stem cells for the treatment of secondary progressive multiple sclerosis

- Phase I/II trial completed in Cambridge and London, UK.
- 10 patients with secondary progressive multiple sclerosis involving the visual pathways
- Bone marrow (mesenchymal) stem cells harvested and cultured
- Administered intravenously
- Primary objective was to assess feasibility and safety
- Secondary outcomes were assessment of the anterior visual pathway
- No serious adverse events
- Small improvement after treatment in visual acuity

Connick et al Lancet Neurol 2012
Autologous mesenchymal stem cells safety and efficacy in MS

- Recruiting at Imperial college London

- STREAMS study:
  - Stem cells in Rapidly Evolving Active Multiple Sclerosis
  - Relapsing-remitting, secondary progressive or primary progressive MS
  - Visible MRI activity
  - EDSS 3-6.5
  - Age 18-50 years

- Primary outcome measure is MRI activity
Summary

- Drug development takes approximately 15 years
- Beta interferon is the only current approved therapy for Secondary Progressive MS
- No approved therapies for primary progressive MS
- Lots of current research in progressive MS