Immune system resetting and long-term remission in multiple sclerosis: rationale and possibilities

A TOPEC Global and EXCEMED Satellite symposium at the 3rd EAN Congress
Immune system resetting and long-term remission in multiple sclerosis: rationale and possibilities

How to transfer the concept in the clinical practice

Prof. Gavin Giovannoni
Barts and The London School of Medicine and Dentistry
Disclosures

Over the last 15 years Professor Giovannoni has received personal compensation for participating on Advisory Boards in relation to clinical trial design, trial steering committees and data and safety monitoring committees from: Abbvie, Almirall, Atara Bio, Bayer-Schering Healthcare, Biogen-Idec, Canbex, Eisai, Elan, Fiveprime, Genzyme, Genentech, GSK, GW Pharma, Ironwood, Merck, Merck-Serono, Novartis, Pfizer, Roche, Sanofi-Aventis, Synthon BV, Teva, UCB Pharma and Vertex Pharmaceuticals.
The clinical context
The cause of progression is inflammation

Trapp, et al. NEJM 1998;338:278-85
MS Iceberg

- Relapses
- Unreported relapses
- Clinical disease progression
- Subclinical relapses: focal MRI activity
  - Focal gray and white matter lesions not detected by MRI
- Brain atrophy
- Spinal fluid neurofilament levels
- OCB-ve

Clinical activity
Focal MRI activity
Hidden focal and diffuse MRI activity
Microscopic or biochemical pathology
Defining a cure
**Induction and Assessment of Chronic Relapsing Experimental Allergic Encephalomyelitis**

**Day 0**

Spinal cord homogenate in Freund’s complete adjuvant

**Day 7**

Clinical Score

- Normal
- Limp tail
- Remission
- Impaired righting reflex
- Partial paralysis
- Hindlimb paralysis
- Moribund

- Spasticity & Tremor Develops
- Remission 1
- Remission 2
- Remission 3
- Remission 4

Time (Days)

Slide courtesy David Baker
Curing animal MS
Average disease course

Slide courtesy Sam Jackson & Ian Duncan.
Post-inflammatory SPMS

Day 29

Day 58

Day 105

Early-tolerisation

Late-tolerisation

Slide courtesy David Hampton
Prevention of relapsing CREAE after three paralytic episodes does not inhibit secondary progression and deterioration of mobility.
BARTS-MS T2T-NEDA ALGORITHM

T2T = treating-to-target; NEDA = no evident disease activity

1. Define the individual’s MS
2. Choose a therapeutic strategy
   - Maintenance-escalation
   - Immune reconstitution therapy (IRT)

   Maintenance-escalation:
   - Choose therapy
     - A, B, C
   - Initiate or Switch or Escalate Rx
     - Rebaseline
     - Monitoring
     - Treatment failure?

   Immune reconstitution therapy (IRT):
   - Choose therapy
     - X, Z, Y
   - Complete course / Re-treat
     - Rebaseline
     - Monitoring
     - Breakthrough disease

IFNβ = interferon-beta; NABs = neutralizing antibodies; Rx = treatment
What is a pulsed immune reconstitution therapy or IRT?

An immune reconstitution therapy, or IRT, is by definition given as a short course, i.e. intermittently and not continuously, and has the ability to induce long-term remission and in some cases the **possibility of a cure**.

Please note that a IRT is not given continuously and additional courses of the therapy are only given if there is a recurrence of inflammatory activity*.

* Inflammatory activity in multiple sclerosis typically refers to clinical relapses and/or focal MRI activity (new T2 lesions and or Gd-enhancing lesions).
What is a maintenance therapy?

A maintenance therapy is by definition given continuously, without an interruption in dosing, and although it has the ability to induce long-term remission it cannot result in a cure.

Please note that and maintenance therapy is given continuously and if while on therapy there is a recurrence of, or ongoing, inflammatory activity*, it is an indication that there is a suboptimal response.

* In multiple sclerosis inflammatory activity typically refers to clinical relapses and/or focal MRI activity (new T2 lesions and or Gd-enhancing lesions).
### A New Classification of Disease-Modifying Therapies for RMS

#### Maintenance/Escalation Therapy (MET)
- Chronic therapy that is maintained and/or escalated over time resulting in changes in immune function only during active treatment

#### Immune Reconstitution Therapy (IRT)
- Short course therapy resulting in long-term qualitative changes in immune function

<table>
<thead>
<tr>
<th>MET that results in continuous immunomodulation</th>
<th>MET that results in continuous immunosuppression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunomodulation</td>
<td>Immunosuppression</td>
</tr>
<tr>
<td>E.g. interferon-β</td>
<td>E.g. fingolimod</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Selective IRT (SIRT)</th>
<th>Non-Selective IRT (NIRT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRT that selectively affects the adaptive immune system</td>
<td>IRT that affects both the innate &amp; adaptive immune systems</td>
</tr>
<tr>
<td>E.g. cladribine</td>
<td>E.g. alemtuzumab</td>
</tr>
</tbody>
</table>

**Non-Selective IRT (NIRT)**
- IRT that affects both the innate & adaptive immune systems

**Selective IRT (SIRT)**
- IRT that selectively affects the adaptive immune system

E.g. cladribine

Maintenance Therapies vs. Immune Reconstitution Therapies (IRTs)

<table>
<thead>
<tr>
<th>Maintenance Therapies</th>
<th>IRTs</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Continuous treatment</td>
<td>• Short-courses or pulsed therapy</td>
</tr>
<tr>
<td>• Low to very high efficacy</td>
<td>• High to very high efficacy</td>
</tr>
<tr>
<td>• Reversible</td>
<td>• Irreversible</td>
</tr>
<tr>
<td>• Perceived to be lower risk</td>
<td>• Perceived to be higher risk</td>
</tr>
<tr>
<td>• Cumulative, or increased, risk with time</td>
<td>• Frontloading of risk or reduced risk with time</td>
</tr>
<tr>
<td>• Examples</td>
<td>• Examples</td>
</tr>
<tr>
<td>• Laquinimod, GA, IFNβ, teriflunomide, BG12, fingolimod, natalizumab, daclizumab, anti-CD20</td>
<td>• Non-selective: Mitoxantrone, alemtuzumab, HSCT- BMT</td>
</tr>
<tr>
<td>• Breakthrough disease</td>
<td>• Selective: cladribine, anti-CD20</td>
</tr>
<tr>
<td>• Suboptimal or failure to respond</td>
<td>• Breakthrough disease</td>
</tr>
<tr>
<td>• NEDA reliable metric for efficacy</td>
<td>• Marker for retreatment</td>
</tr>
<tr>
<td>• Rebound activity</td>
<td>• NEDA unreliable to assess efficacy</td>
</tr>
<tr>
<td>• Highly likely</td>
<td>• Rebound activity</td>
</tr>
<tr>
<td>• Can be life-threatening</td>
<td>• Less likely</td>
</tr>
<tr>
<td>• Pregnancy</td>
<td>• Unlikely to be life-threatening</td>
</tr>
<tr>
<td>• No potential for a cure</td>
<td>• Pregnancy</td>
</tr>
<tr>
<td>• Rebound</td>
<td>• Potentially ‘curative’?</td>
</tr>
<tr>
<td>• SPMS and progressive brain atrophy</td>
<td>• 15–20-year experiment</td>
</tr>
</tbody>
</table>
| The following are not licensed for MS in the UK: laquinimod, daclizumab mitoxantrone, cladribine, anti-CD20 therapies, and BMT IRTs = immune reconstitution therapies
Defining an MS cure?

Survival analysis

"Pulsed immune reconstitution therapy or PIRT"

"Moderately effective maintenance treatments"

Secondary Progression
MS is a neurodegenerative disease hypothesis

No Secondary Progression
MS is an autoimmune disease hypothesis

Remission

Cure

15-20 year experiment

Genes

Environment

Multiple Sclerosis
The evidence
Ocrelizumab
B cells play key functional roles in MS

The Reduction in Gd-Enhancing T1 Lesions by OCR Is Maintained Through 144 Weeks

Primary endpoint:
OCR vs placebo

Patients with baseline MRI
- Placebo (n=54)
- OCR 600 mg arm (n=55)
- OCR 1000 mg arm (n=55)
- IFN-β1a (n=54)

- ‘Core Study’ (0–96 weeks)
- ‘Follow-Up’ (97–144 weeks)

*p<0.0001 for both OCR doses vs placebo, N (for primary analysis): Placebo=54, OCR 600 mg=51, OCR 1000 mg=52, IFN-β1a=52

Patients who withdrew during earlier treatment cycles were also included in the follow-up periods


Slide courtesy of Stephen Hauser
Primary Progressive MS

An Exploratory Analysis of 12- and 24-Week Confirmed Composite Disability Progression in Patients With Primary Progressive Multiple Sclerosis in the ORATORIO Trial

Figure 3. Time to onset of 12- and 24-week confirmed disability progression as measured by (a) EDSS, (b) ≥20% progression in T25FW and (c) ≥20% progression 9HPT

<table>
<thead>
<tr>
<th>Deaths</th>
<th>Placebo</th>
<th>Ocrelizumab 600 mg</th>
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<tr>
<td></td>
<td>n=239</td>
<td>n=486</td>
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<tr>
<td>Deaths</td>
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<td></td>
<td>1 (0.4)</td>
<td>4 (0.8)</td>
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<td>Road traffic accident</td>
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<tr>
<td>Sudden cardiac death</td>
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<td>Aspiration</td>
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<td>Pulmonary embolism</td>
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<td>Pneumonia</td>
<td></td>
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<tr>
<td>Pancreas carcinoma</td>
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<tr>
<td>Pneumonia aspiration</td>
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</table>

<table>
<thead>
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<th>Malignancies</th>
<th>Placebo</th>
<th>Ocrelizumab 600 mg</th>
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<tbody>
<tr>
<td></td>
<td>n=239</td>
<td>n=486</td>
</tr>
<tr>
<td>Malignancies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervix adenocarcinoma in situ</td>
<td>2 (0.8)</td>
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<tr>
<td>(N=1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal cell carcinoma</td>
<td>11 (2.3)</td>
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</tr>
<tr>
<td>(N=1)</td>
<td></td>
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<tr>
<td>Breast cancers (N=4)</td>
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<td>Endometrial adenocarcinoma (N=1)</td>
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<td></td>
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<tr>
<td>T-cell lymphoma (N=1)</td>
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<td></td>
</tr>
<tr>
<td>Histiocytoma (sarcoma) (N=1)</td>
<td></td>
<td></td>
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<tr>
<td>Basal cell carcinoma</td>
<td></td>
<td></td>
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<tr>
<td>(N=3)</td>
<td></td>
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</tbody>
</table>
Other adverse events


Antigen presentation
Autoantibody production
Ectopic lymphoid follicle-like aggregates
Cytokine production

Carryover PML
HSV
HZV
Hypogammaglobulinaemia
Alemtuzumab
Alemtuzumab: mechanism of action

1. Selection

Targets T and B cells thought to mediate MS inflammation\(^1\)
- Animal studies indicate that innate immune cells that express lower levels of CD52 are minimally or transiently impacted by alemtuzumab treatment\(^2\)

2. Depletion

Decreases MS inflammation
- Alemtuzumab selectively depletes circulating T and B cells\(^2,3\)
- Many lymphocytes remain present in lymphoid organs after treatment\(^2,3\)

3. Repopulation

Reduces MS disease activity
- Lymphocyte progenitor cells are presumably unaffected by alemtuzumab\(^2,4,5\)
- A distinctive pattern of T- and B-cell repopulation begins within weeks, potentially changing the balance of the immune system\(^2,4,5\)

T- and B-cell Pharmacodynamics

- Alemtuzumab depleted circulating lymphocytes in SPMS patients treated between 1994–1997 (N=29)
  - CD4 and CD8 counts were 30-40% of pretreatment values 18 months later\(^1\)
  - B cells repopulated more rapidly, with counts reaching 179% of pretreatment values at 18 months

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"Four alemtuzumab-treated patients (5%) fulfilled the definition of secondary progression of two consecutive SAD events."

Sustained improvement of pre-existing disability in patients treated with Alemtuzumab

Mean EDSS Change From Baseline

No. of Patients

<table>
<thead>
<tr>
<th></th>
<th>IFNB-1a SC 44 µg</th>
<th>Alemtuzumab 12 mg</th>
<th>Alemtuzumab 24 mg</th>
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<td>112</td>
<td>110</td>
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<tr>
<td>3-6</td>
<td>100</td>
<td>107</td>
<td>108</td>
</tr>
<tr>
<td>6-12</td>
<td>91</td>
<td>103</td>
<td>105</td>
</tr>
<tr>
<td>12-18</td>
<td>83</td>
<td>99</td>
<td>105</td>
</tr>
<tr>
<td>18-24</td>
<td>73</td>
<td>99</td>
<td>101</td>
</tr>
<tr>
<td>24-30</td>
<td>71</td>
<td>92</td>
<td>97</td>
</tr>
<tr>
<td>30-36</td>
<td>68</td>
<td>88</td>
<td>89</td>
</tr>
</tbody>
</table>

Mean EDSS

- IFNB-1a SC 44 µg
- Alemtuzumab 12 mg
- Alemtuzumab 24 mg

Durable Efficacy of Alemtuzumab Over 10 Years: Long-term Follow-up of Patients With RRMS
From the CAMMS223 Study

Alasdair J Coles,† Mario Habeck,‡ Ann D Bass,† Vesna Bhrar,³ Anton Viadic,³ David H Margolin,¹ Edward J Fox; on behalf of the CAMMS223 Investigators

†University of Cambridge, Cambridge, UK; ‡University of Sydney, Sydney, Australia; and †Cambridge Medical School and University Hospital Center, Zagreb, Croatia

Objective

- To evaluate the 10-year efficacy and safety profile of flurbiprofen 3C Saga® in patients with active RRMS.

Introduction

- Alemtuzumab is a humanized anti-CD52 monoclonal antibody used for treatment of relapsing-remitting multiple sclerosis (RRMS) in HS clinical trials.

- The phase 3 CAMMS223 trial (10140222231001) showed efficacy of alemtuzumab in 12 mg-treated patients who entered the ongoing Extension Study.

- The phase 3 CAMMS223 trial (10140222231001) and the phase 3 CAVI-MSI (NCT01857456) trial in patients who were treatment-naive, and other phase 3 CAMMS223 trials (NCT01857456) in patients who had an inadequate response to prior therapy at baseline, demonstrated greater improvements in disability compared with placebo, with a reduction in annualized relapse rate (ARR) of 0.18 in patients with relapse-onset. The results of the beta-1a SC IFN-β1a in patients with active RRMS. The study was completed in 2012.

- Five-year data from the CAMMS223 study, the CAVI-MSI land 2 studies, and the Extension Study (NCT01857456) have demonstrated durable efficacy of alemtuzumab, with most patients remaining on alemtuzumab retreatment or early disease-modifying therapy (DMT) therapy.

- A consistent safety profile was demonstrated across all clinical development programs.

- A further 5 years of extension events (AEs) with alemtuzumab were in the ongoing extension of patients with relapse-onset RRMS.

- The study design aimed to evaluate the long-term safety and efficacy of alemtuzumab in patients with relapsing-remitting multiple sclerosis (RRMS) over 10 years.

Methods

- Study Design:
  - CAMMS223 was a phase 3, randomized, controlled 3-year study of alemtuzumab versus SC IFN-β1a (44 µg 3 times per week) in treatment-naive patients with active RRMS.
  - Patients randomized to alemtuzumab received up to 2 annual courses of 12 or 24 mg at 0, 12, and 24 months after initiation of treatment.
  - In the CAMEO study (NCT01857456), a phase 3 extension study, 5 years of safety and efficacy data were available for patients who entered the study.
  - Patients could participate in an extended follow-up period (baseline through Year 10) in the ongoing Extension Study.
  - The study design included a 3-year treatment period with continued re-treatment every 12 months after the initial retreatment dose.
  - Patients with a history of recurrent or severe infections, active malignancy, or other significant medical conditions were excluded from the study.

- Efficacy:
  - The primary outcome measure was the proportion of patients in the alemtuzumab treatment arm who remained in remission at the end of Year 10.
  - The secondary outcome measures included the proportion of patients achieving a sustained clinical response, as defined by a reduction in the primary outcome measure by at least 50% from baseline to Year 10.

- Safety:
  - The safety profile of alemtuzumab over 10 years was consistent with previous studies, with no new safety signals identified.

- Results:
  - A total of 158 patients randomized to alemtuzumab were eligible for the 10-year follow-up.
  - The median time on study was 10 years.
  - The proportion of patients in remission at Year 10 was 77.8% (122 of 158 patients).

- Conclusions:
  - Alemtuzumab demonstrated durable clinical efficacy through Year 10.
  - Safety findings were consistent with those of other alemtuzumab clinical trials.

Acknowledgments and Disclosures

Supported by Biogen Idec, Inc. (Cambridge, MA). The authors report no conflicts of interest relevant to this article.

Alemtuzumab innate immunity & T-cell pharmacodynamics

1. Non-selective leukocyte depletion
   a. Leukopaenia (neutrophils & monocytes)
   b. Lymphopaenia (prolonged)
   c. Infusion reactions (moderate to severe)
   d. Complications of corticosteroids
2. Immunosuppression
   a. Opportunistic infections
      i. Acute bacterial, e.g. Listeriosis
      ii. Typical opportunistic, e.g. CMV
3. Aberrant immune reconstitution
   a. Secondary autoimmunity
   b. Anti-drug antibodies

AVN = avascular necrosis, HPV = human papilloma virus, PCP = Pneumocystis carinii pneumonia, VZV = varicella zoster virus
# Risks identified

<table>
<thead>
<tr>
<th>Identified Risk</th>
<th>Rate in Alemtuzumab-Treated Patients</th>
<th>Notes</th>
</tr>
</thead>
</table>
| **ITP**         | ~1% (1 fatality prior to implementation of monitoring program)
|                 | • Onset generally occurred 14-36 mo after first exposure<br>• Most cases responded to first-line medical therapy |
| **Nephropathies Autoimmune Events** | 0.3% (anti-GBM n=2)
|                 | • Generally occurred within 39 mo after last administration<br>• Responded to timely medical treatment and did not develop permanent kidney failure |
| **Thyroid disorders (Hypo-hyper-)** | ~36% (serious, 1%)
|                 | • Onset occurred 6-61 mo after first Alemtuzumab exposure; peaked in year 3 and declined thereafter<br>• Most mild to moderate, most managed with conventional medical therapy, however, some patients required surgical intervention<br>• Higher incidence in patients with history of thyroid disorders |
| **IARs**        | >90% (serious, 3%)
|                 | • Occurred within 24 h of Alemtuzumab administration<br>• Most mild to moderate; rarely led to treatment discontinuation<br>• May be caused by cytokine release following mAb-mediated cell lysis |
| **Infections**  | 71% (serious, 2.7%)
|                 | • Incidence highest during first mo after infusion; rate decreased over time<br>• More common with Alemtuzumab; mostly mild to moderate<br>• Generally of typical duration; resolved following conventional medical treatment |

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**Switching**

Oral cladribine
Cladribine must enter cells and be activated in order to exert its effect

Cladribine works by a 4-step mechanism:
1. Cladribine enters cell via nucleoside transporter
2. Accumulates intracellularly due to ADA resistance
3. Cladribine is activated by specific kinases
4. Activated Cladribine induces selective lymphocyte reduction

* One of the kinases is deoxycytidine kinase (DCK). The phosphatase is 5'-nucleotidase.


Efficacy & Safety


VZV

TB

Treatment with Cladribine reduces the risk of conversion to McDonald 2005 MS in treatment-naïve patients with an FCDE\(^a\)

Patients at risk (conversions):
- Cladribine 5.25 mg/kg
  - 203 (0)
- Cladribine 3.5 mg/kg
  - 204 (0)
- Placebo
  - 201 (0)

Time to McDonald MS conversion from randomization date (Months)

Hazard ratio vs placebo\(^b\)
- 5.25 mg/kg: 0.425, p<0.0001
- 3.5 mg/kg: 0.496, p<0.0001

Risk reduction
- 5.25 mg/kg: 57.5%
- 3.5 mg/kg: 50.4%

\(a\)Patients enrolled in ORACLE-MS were treatment-naïve with an FCDE at high risk of converting to MS. \(b\)Cox proportional hazards model controlling for the randomization stratification factor (region). FCDE, first clinical demyelinating event; M, Month. Leist TP et al. Lancet Neurol 2014;13:257-67
A changing treatment philosophy
**Active**

- Rapidly-evolving severe
- Highly-active
- Active
- Inactive

**NEDA - 1 & 2**

Clinical activity

- Nz/Az
- Fingo/Dac/Clad
- IFNBeta/GA/Teri/DMF

**Conventional step-care**

**NEDA-3**

Focal MRI activity

- Nz/Az
- Fingo/Dac/Clad
- IFNBeta/GA/Teri/DMF

**Rapid Escalation**

**NEDA-4/5**

Brain atrophy and CSF neurofilament levels

- Nz/Az/Fingo/Dac/Clad

**“FLIPPING THE PYRAMID IN MS”**

NEDA = no evident disease activity; NEDA-2 = clinical only (relapse-free and progression free); NEDA-3 = clinical and focal MRI activity; NEDA-4/5 = clinical and focal MRI activity free and normalising brain atrophy loss & normalisation of CSF neurofilament levels. IFNbeta = interferon-beta; GA = glatiramer acetate; Teri = teriflunomide; DMF = dimethyl fumarate; Fingo = fingolimod; Nz = natalizumab; Az = alemtuzumab; Dac = daclizumab, Clad = oral cladribine.
Case studies
The cost of delayed access to highly active treatment

**20 month vs. 32 month delay or 2 relapses**

- **2004 1st attack**
- **2005 2nd attack**
- **Feb 2006 IFNbta**
- **Nov 2006 Alemtuzumab**
- **Nov 2007 Alemtuzumab**
- **2008 - 2014 NEDA**

**EDSS = 3.5:** unable to run, play tennis or walk down stairs quickly without the use of a handrail

**EDSS = 0.0:** fully functional
CASE REPORT

Timing is everything in the treatment of multiple sclerosis

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Summary

We present two similar cases of relapsing–remitting multiple sclerosis, both of whom received treatment with the monoclonal antibody alemtuzumab, but had significantly different long-term outcomes. Patient A is 12 years into his illness and was treated early in his disease course, he has no disability and continues to perform at a high level as a professional golfer. Patient B was initially started on interferon-β1a therapy and went on to have two disabling relapses on this treatment which resulted in a degree of fixed disability prior to the start of alemtuzumab. 10 years into his disease course he has moderate disability and daily symptoms of spasticity in his legs which impair his quality of life. These two contrasting cases highlight the difficult decision of when to start potent immune-modulating therapies for multiple sclerosis in young adults who appear well early in their disease but have the potential to rapidly accrue irreversible disability from future relapses.
Case study

42-yr old British journalist, married with 2 children
War correspondent - frequent travel to Afghanistan, Ukraine, Iraq and Syria

Diagnosed RRMS late 2014:
- Initial symptoms of sensory symptoms in feet and Lhermitte’s phenomenon
- Treated with dimethyl fumarate
- Two disabling attacks in 2015 - ataxia and spinal cord lesion with weak legs

Disease activity:
- Rapidly-evolving severe MS (RES)

Treatment:
- Eligible for Fingolimod, Natalizumab and Alemtuzumab

  Natalizumab contra-indicated as found to be JCV-seropositive (index 1.86)
  Offered fingolimod - was not keen about long-term immunosuppression
  Interested in HSCT (not eligible under London HSCT guidelines) or alemtuzumab

Major concerns about monitoring and accessing urgent treatment when abroad as war correspondent

Joint decision to treat him with parenteral cladribine (two cycles given - Jan/Feb 2016 and 2017)
Burden of Treatment
Treatment Burden

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<tr>
<th>Pre-dose</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>Total(^a)</th>
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<tr>
<td>sc IFN β-1a(^1)</td>
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<td></td>
<td></td>
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<td>Glatiramer acetate(^2)</td>
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<td>Dimethyl fumarate(^4)</td>
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<td>Cladribine tablets(^c,9)</td>
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Conclusion

• Treatment of MS is increasingly complex
  – Different modes of action vs. different treatment philosophies
    – maintenance escalation vs. IRTs (selective and non-selective)
  – Monitoring requirement, e.g. lymphopaenia, LFTs, etc.
  – De-risking strategies, e.g. JCV-testing
  – Long-term vs. short-term immunosuppression
    – cumulative vs. front-loading of risk
    – adaptive and/or innate immunity affected
    – Burden of treatment and monitoring
    – impact on adherence and outcomes

• Emerging therapies; ocrelizumab, oral cladribine and HSCT
  – all address an unmet need
Questions?