Day 1

# Highlights from the 9th ECTRIMS Focused Workshop, 2022



## Plenary

### Plenary Session 1

**Thursday, 10 March 14:00 – 15:10 CET**
**Speakers: Roland Martin, Matilde Inglese**
**Chairs: Bruno Stankoff, Paolo Muraro, Raffaella Greco**

**Conclusion:** An increasing body of clinical evidence supports haematopoietic stem cell transplant (HSCT) as a highly effective treatment for multiple sclerosis (MS). New understanding of the immunological basis of this efficacy has shown B- and T-cell immune renewal to be an important mechanism underpinning the disease-blocking activity of HSCT. In the clinical setting, data from a recent meta-analysis of HSCT in MS demonstrated that phase and form of disease were significantly associated with lower progression rate and treatment-related mortality. No evidence of disease activity (NEDA) rates compared favourably with those reported for disease-modifying therapies (DMTs), suggesting that HSCT could be considered a more effective treatment option in specific cases. Leading MS bodies have updated their guidelines to reflect this new clinical understanding – now recommending HSCT as a therapeutic option in selected patients with MS.

**What's New:** Research into the immunological rationale for HSCT efficacy has revealed new insights into the underlying mechanisms of immune renewal. Some T-cells, notably effector memory T-cells, and few B-cells survive HSCT transiently, while central memory T-cells, T-naïve and switched memory B-cells remain reduced for more than 2 years. T-cells that carry over to the post-transplant period are characteristically senescent, with shorter telomeres, less proliferative capacity and lacking full functionality. New naïve T- and B-cells renew their repertoire and longer-term immune renewal becomes more and more complete. Currently, the role played by renewed or more effective T-regulatory cells and regulatory natural killer cells remains unclear, as does the recurrence (or not) of autoreactive T-cells and their functional phenotype. Beyond immune renewal, additional mechanisms may be at play involving effects in the periphery versus brain.

Large cohort studies and randomised controlled clinical trials (RCTs) have confirmed the 'remarkable' efficacy of HSCT, delivering suppression of MS activity and long-term clinical stabilisation. Uncontrolled real-world studies comparing HSCT to DMTs have also revealed superior efficacy to agents such as alemtuzumab in inflammation control and suppression of relapses. Evidence from a meta-analysis of 15 HSCT studies identified year of transplant performance (pre-/post-2005), baseline Expanded Disability Status Scale and proportion of relapsing-remitting MS (RRMS) patients (<44%/≥44%) as significant predictors of treatment-related mortality. The only factor significantly associated with 2-year progression rate was the proportion of RRMS patients. Across these pooled studies, 2-year and 5-year NEDA averaged 83.4% and 67% respectively.

**Background:** HSCT has been increasingly used in recent years as a treatment option for MS. It is assumed that post-HSCT, MS-associated adaptive and innate immune components are eliminated and a new immune system generated. However, HSCT does not abrogate the quantitative MS trait or eliminate the main environmental risk factor Epstein-Barr virus. Therefore, more remains to be discovered as to why HSCT has such a profound impact on the immune pathogenesis of MS and is so clinically effective. Insights from cohort studies, RCTs and real-world experience have helped to improve the benefit/risk profile of HSCT, with refinement of treatment selection and protocols successfully reducing treatment-related mortality and toxicity burden. However, important clinical questions also remain to be addressed. These include the optimal profiling of patients for treatment, a better understanding of when in the disease course to undertake transplant, clear consensus on the optimal conditioning regimen and use of HSCT in patients previously treated with alemtuzumab.

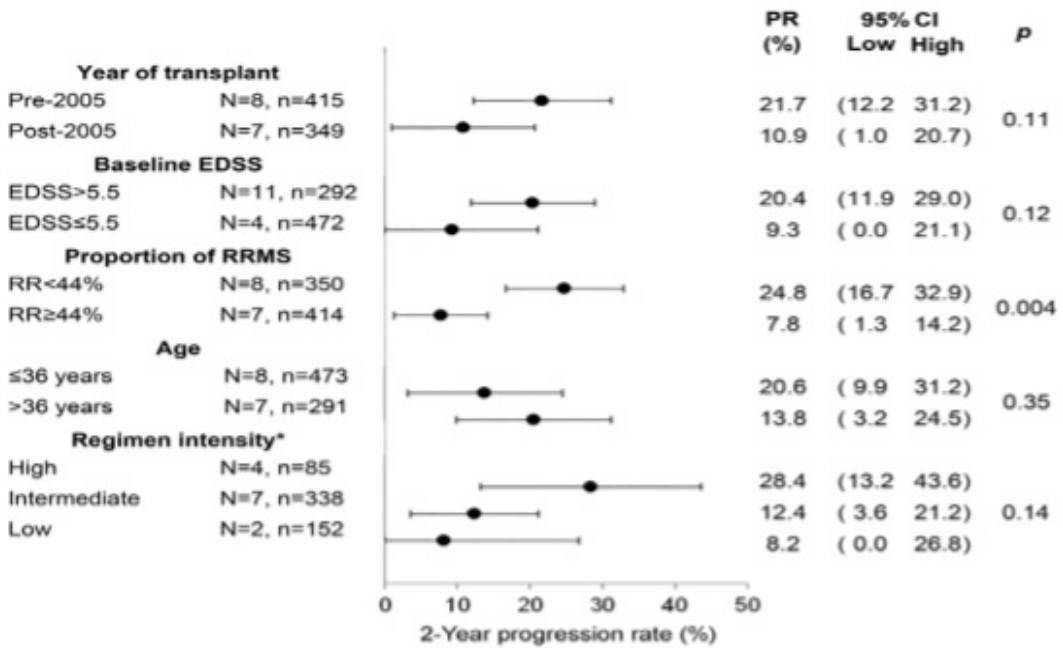
## Immune renewal after HSCT
*(Martin presentation)*

| T cells | Early | | M12 | |
|---|---|---|---|---|
| | Persisting | New | Persisting | New |
| Percent of recent thymic emigrants? | Low | - | - | High |
| Telomere length? | Short | - | - | Long |
| TCR repertoire? | 25% of overlap in early CD4+ EM | - | | Overlap decreasing<br>Naïve compartment renewed |

| B cells | Early | | M12 | |
|---|---|---|---|---|
| | Persisting | New | Persisting | New |
| Somatic hypermutations? | High | - | - | Decreased |
| Clonal overlap? | About 2.2% | - | - | Decreased to 0.3% |

Ruder et al., in prep.

## Meta analysis: factors influencing 2-year progression after HST
*(Inglese presentation)*



# Parallel Sessions

## Parallel Session 1: Neurological indications (within MS and related diseases) and optimal patient selection

**Thursday, 10 March 15:20 – 17:35 CET**

**Speakers: Lars Bo, Maria Pia Amato, Joachim Burman, Alice Mariotinni, Lucia Moiola**

**Chairs: Mar Tintoré, Basil Sharrack**

**Conclusion:** Haematopoietic stem cell transplant (HSCT) has established itself as an important option within the overall multiple sclerosis (MS) treatment armoury, particularly for those patients with aggressive MS at risk of rapid accrual of disability and disease progression. Several important randomised controlled trials (RCTs) are ongoing that will help shed further light on the optimal therapeutic positioning of HSCT in MS and help guide the targeted selection of patients for transplant. Clinical and paraclinical prognostic markers remain important to identify ideal HSCT candidates and maximise the balance of benefit and risk.

**What's New:** To further explore the role of HSCT in relapsing-remitting MS (RRMS) several key clinical trials are planned or ongoing in patients who failed on prior disease-modifying therapy (DMT). These studies, which include StarMS, RAM-MS, NET-MS and BEAT-MS, all utilise no evidence of disease activity (NEDA) as the primary clinical outcome and have comparator arms consisting of commonly used highly effective therapies (HET) including alemtuzumab and ocrelizumab. Currently, the combined clinical data from HSCT studies indicate that transplant should be considered as a treatment option for patients with RRMS with poor prognostic factors and suboptimal response to DMT who show ongoing disease activity after re-treatment with an alternative HET. However, HSCT may also be preferred at an earlier stage in selected cases where patients show rapidly evolving disease.

Based on the available clinical evidence in the setting of treatment-naïve MS, first-line HSCT may also be considered for patients with aggressive disease presentation given the narrow window of opportunity for preventing disease progression. In the first and only study of first-line HSCT, progression-free survival (PFS) was 100% and no patients got worse after transplant. Overall, treatment-related mortality with HSCT appeared comparable to other procedures.

HSCT trials in progressive MS have yielded variable rates of PFS ranging from 36% to >70% at 5 years. The most encouraging results have been obtained in recent studies, suggesting a benefit on disability outcomes and potential reduction in brain atrophy. In this current therapeutic scenario, HSCT could be considered for patients with progressive MS who continue to progress despite the use of an active treatment such as siponimod or ocrelizumab.

In a further neurological indication, clinical studies have also highlighted an important role for HSCT in neuromyelitis optica spectrum disorder (NMOSD) both as rescue therapy in DMT non-responders and as induction therapy in patients with aggressive presentation. Conditioning with rituximab and selection of ambulatory patients may yield improved results, and potentially achieve prolonged disease-free remission.

**Background:** Several RCTs have confirmed the efficacy of HSCT in RRMS, notably the large-scale trial by Burt et al., which compared non-myeloablative HSCT to continued DMT in 100 patients with RRMS. HSCT significantly reduced both time to disease progression and first relapse compared with DMT, with significantly more HSCT patients achieving NEDA after 5 years of follow-up. HSCT has also demonstrated efficacy across a range of other neurological indications including treatment-naïve MS, progressive MS and NMOSD. However, important questions remain about where best to position HSCT within the overall MS treatment paradigm and how to select individual patients for treatment.

## Balancing benefit and risk with HSCT in MS
*(Amato presentation)*

**Maximize efficacy**

**TARGET INFLAMMATION**

- Recent (≤ 1 y) MRI inflammatory activity
- Recente relapses (≤ 2y)
- Failure* of DMT(s) of which one (or two ) has to be highly-effective (preferably ≤ 2 DMTs) [1]

**SELECT THE BEST CANDIDATE**

- Age < 50 years
- Shorter disease duration (≤ 10 years)
- Still ambulatory, low to moderate EDSS (≤6.5)
- High disability may be acceptable when acutely and recently acquired

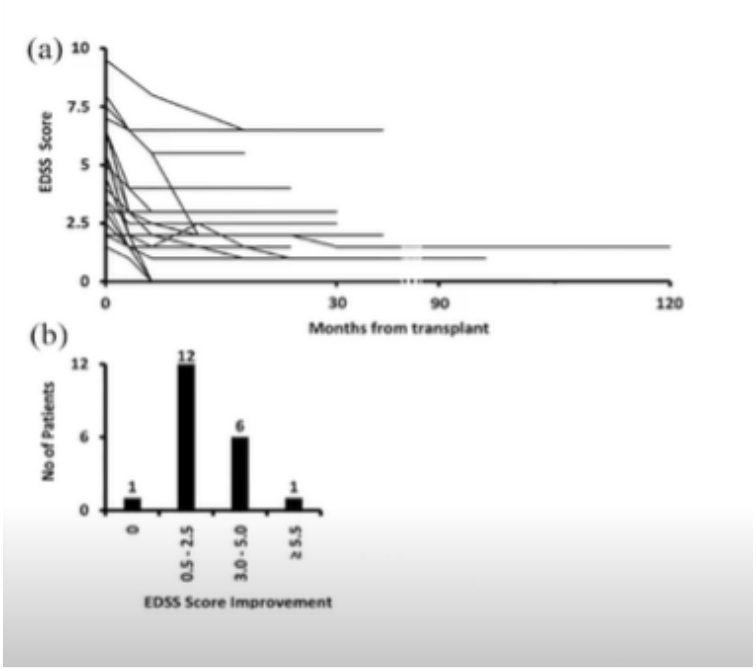
**Minimize risks**

**TREAT SAFELY**

- No significant comorbidities (especially heart, lung, liver, kidney)
- In young patients, address the risk of infertility
- Only in centres with substantial experience and expertise

* Failure = breakthrough disease activity

## HSCT as first-line therapy in aggressive MS
*(Burman presentation)*



# Parallel Sessions

## Parallel Session 2: Haematological evaluation (including fertility management) and transplant protocol

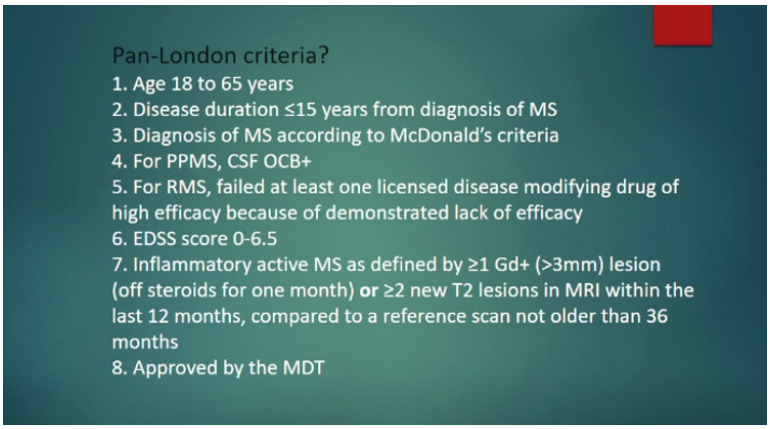
**Thursday, 10 March 15:20 – 17:20 CET**
**Speakers: Majid Kazmi, Maria Gaughan, Riccardo Saccardi, Raffaella Greco**
**Chairs: Riccardo Saccardi, Majid Kazmi**

**Conclusion:** The application of both autologous and allogeneic stem cell transplantation in patients with demyelinating disorders such as multiple sclerosis (MS) or neuromyelitis optica spectrum disorder (NMOSD) has demonstrated some of the greatest efficacy of all treatment options. However, several factors must be considered. The conditioning regimens required prior to stem cell transplantation are not without risks and may require refinement, in addition to necessitating a thorough assessment of patient fitness pre-transplant. In addition, patients should be informed of potential risks to fertility, the availability and appropriateness of fertility preservation measures and the risk of relapse that has been observed in some post-transplant patients who have received in vitro fertilization treatment.

**What's New:** When assessing the fitness of patients to undergo stem cell transplantation, pulmonary and cardiac workups are required. Ventilatory defects are common in patients with more progressive MS and a detailed assessment including lung volume measurement, overnight oximetry, earlobe blood gas and diaphragm muscle testing is recommended. Standard cardiac assessments should be performed, with serial measurement of serum N-terminal pro-B-type natriuretic peptide and troponin-I at start of conditioning required in any patient with significant cardiac risk factors. Peri-transplant monitoring is recommended, including use of polymerase chain reaction to assess reactivation of Epstein-Barr virus or cytomegalovirus between days 15 and 60 post-transplant; the potential role of anti-CD20 therapy in reducing the risk of viral reactivation remains to be confirmed. Assessment of the effects of stem cell transplantation on fertility have identified amenorrhoea, age and prior cyclophosphamide as risks for fertility impairment. However, studies have showed recovery of fertility post-transplantation and amenorrhoea should not be assumed to represent infertility. In patients with NMOSD, autologous stem cell transplantation may reduce inflammation, but relapse may occur; allogeneic stem cell transplantation may offer long-term disease control, however, there are few data at present in this area and a greater patient population needs to be observed.

**Background:** The use of stem cell transplantation in demyelinating disorders has been a primarily patient-driven approach, with what was initially an experimental regimen becoming increasingly common. Indeed, the fastest growing indication for stem cell transplantation is MS. Transplantation can offer potential long-term control of disease. However, patient and treatment factors can affect outcomes, and transplantation using current conditioning regimens may not be suitable for the treatment of older patients. Given that the age at which transplantation is likely to occur is similar to that at which most individuals may start a family, there is a need to consider the impact of transplantation on fertility. In addition, the relative benefits and drawbacks of autologous and allogeneic stem cell transplantation techniques must be considered..

**Pre-transplant assessment and screening for comorbidities in HSCT candidates**
*(Kazmi presentation)*



## Fertility post AHSCT for Multiple Sclerosis
*(Gaughan presentation)*

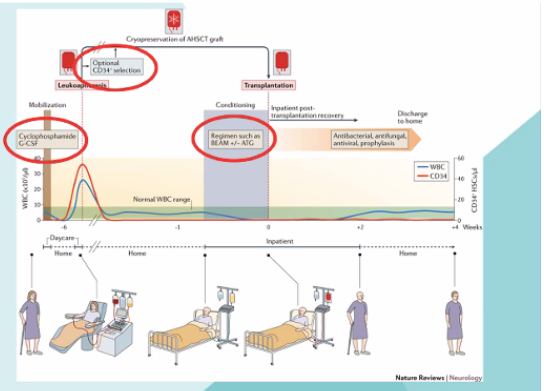
### Issues to consider

- Fertility preservation counselling
  - Risk of infertility AND
  - Possible options to preserve fertility
- Amenorrhoea common post-transplant, but frequently recover cycle
- Contraception
- Menopause
- Role of reproductive endocrinologist/access to gynaecology services

**Recovery of menstrual cycle no guarantee of fertility**

## Conditioning intensity or treatment intensity?
*(Saccardi presentation)*

- The final intensity of immunosuppression is also affected by the mobilization chemo, graft manipulation and inclusion/dosage of serotherapy in the conditioning regimen
- The role of immunosuppressive treatments prior to HSCT is still to be clarified




*Muraro et Al. Nat. Rev. Neurol, 2017*

## Transplant protocols and safety/tolerability in MOSD
*(Greco presentation)*

### Will HSCT cure NMO?

- **Autologous HSCT:** the ADWP EBMT analysis illustrates that HSCT can be used effectively to reduce high inflammation in the short term with a low toxicity profile, despite a tendency to progress/relapse in the long term. Chicago experience using NMA plus rituximab reported 80% of cases relapse-free off all immunosuppression at 5 years.

  *Feasible and safe approach.*
  *Able to control high inflammation in refractory and aggressive diseases.*
  *Optimized outcomes with early treatment (before significant chronic disability), Rituximab in the conditioning.*

- **Allogeneic HSCT:** long-term disease control was achieved in preliminary cases.

  *Feasible and safe in a preliminary experience.*
  *Long-term disease control (>10y).*
  *Further studies are warranted.*

  *Several concurring mechanisms:*
  *- eradication of autoreactive patient lymphohemopoiesis by the myeloablative conditioning regimen;*
  *- in vivo T and B cell depletion by ATG and rituximab, respectively;*
  *- elimination of long-lived plasma cells producing anti-AQP4 Ab by putative donor T cell-mediated alloreactivity;*
  *- renewal of the immune repertoire with re-establishment of thymic central tolerance.*

Day 2

# Highlights from the 9th ECTRIMS Focused Workshop, 2022



## Plenary

### Plenary Session 2 - Wrap-up Summaries

**Friday, 11 March 16:30 – 17:50 CET**

**Speakers: Mar Tintoré, Basil Sharrack, Ellen Iacobaeus, Gian Luigi Mancardi, Riccardo Saccardi, Raffaella Greco, John Snowden, Paolo Muraro, Tobias Derfuss**

**Conclusion:** Two years of planning work has culminated in this informative and productive ECTRIMS focused workshop. Key next steps will be to prepare manuscripts for publications in scientific journals – including the development of at least one ECTRIMS/European Society for Blood and Marrow Transplantation (EBMT) guidelines paper, ideally with endorsement from the European Academy of Neurology (EAN). The organising committee will summarise and refine the data presented at this workshop into practical guidelines that clinicians can utilise in daily practice to select patients for HSCT, together with evidence-based strategies for optimising both short- and long-term outcomes from transplant. Educational material will also be promoted via the ECTRIMS online library and disseminated to the wider public as part of the overarching ECTRIMS communication strategy.

**What's New:** Evidence presented during the neurological stream of the ECTRIMS workshop has led to important clinical consensus on indications for haematopoietic stem cell transplant (HSCT), as well as post-transplant management and monitoring approaches. HSCT is an appropriate rescue therapy for patients with highly active multiple sclerosis (MS) who have failed high efficacy disease-modifying therapies (DMTs), and this indication should be widely adopted with equitable access across geographical areas. The position of HSCT within the overall MS treatment algorithm remains to be defined, but ongoing trials will help to answer this question. HSCT may also be considered first-line treatment for very active MS within the context of a clinical trial. Based on the available evidence, HSCT is not recommended in established progressive MS without inflammatory features or in neuromyelitis optica spectrum disorder (NMOSD). There may be a role for HSCT in progressive MS with inflammatory features and in subjects on high efficacy DMTs who demonstrate progression in the absence of relapsing activity (PIRA). Concerns exist surrounding reports of people travelling to receive HSCT in non-Joint Accreditation Committee ISCT-Europe & EBMT (JACIE) or Foundation for the Accreditation of Cellular Therapy (FACT)-accredited centres. Moving forward, there is a need for future clinical trials of HSCT in treatment-naïve patients and progressive disease; to study different treatment regimens; and to measure different outcome measures that extend beyond the anti-inflammatory effect of transplant. In the field of magnetic resonance imaging (MRI) monitoring, harmonisation and standardisation of scan protocols (potentially using MAGNIMS guidelines) will be important for robust long-term data collection, particularly in patients who fail on HSCT.

Expert clinical consensus was also reached during the neurological stream of this ECTRIMS workshop on key issues such as haematological evaluation, transplant protocol, virological and immune monitoring and vaccinations. Evidence supports a focus on treatment, not conditioning, intensity, with no role for very low intensity regimens in the majority of patients. In order to improve patient selection, it will be important to develop risk scores that facilitate the early identification of HSCT-eligible patients. Updated transplant guidelines are important to provide detailed information on specific complications related to HSCT for MS and their management. In particular, there exists a need for better guidance on fertility preservation and improved access to this resource for non-cancer patients. Protocols for vaccination after HSCT require harmonisation and regular updates, particularly given the ongoing threat of COVID-19. More research is still needed on the treatment and monitoring of

cytomegalovirus/Epstein-Barr virus reactivations and secondary autoimmunity, which may be encompassed within broader EBMT consensus guidelines and collaboration on immune monitoring. Although modern conditioning regimens have helped to improve outcomes and reduce the acute toxicity of HSCT, long-term surveillance to capture late complications remains essential as the number of survivors increases.

**Background:** Large cohort studies and meta-analysis provide clinical evidence of the high efficacy of HSCT in relapsing/remitting MS, with an improving safety profile. Preliminary randomised controlled trial evidence also suggests that HSCT may be more effective than some DMTs for relapsing-remitting MS. However, guidelines and consensus on the therapeutic position and optimal practical application of HSCT in MS disease

*(Iacobaeus talk)*

**Significant suppression of MRI activity (new T2 lesions and Gd ) post aHSCT in both RRMS and progressive MS**

Demonstrated in several studies with MRI measures as primary outcome

***Retrospective studies***
- Italian report, (Mancardi 2012) (n=74)
- Swedish report (Burman 2014) (n=41)
- Northwestern University report, USA (Burt 2015), n=145)

***Single arm studies, phase 1, 2***
- Canadian trial (Atkins 2016) (n=24)
- HALT-MS (Nash 2015-2017) (n=24)
- Australian trial (Moore 2018) (n=35)

***RCT***
- ASTIM phase 2 (Mancardi 2015) (n=9/21 AHSCT)
- MIST phase 3 (Burt 2018 (n=55/110 AHSCT)

**Transplant intensity**
*(Saccardi presentation)*

- Focus on treatment intensity not conditioning intensity.
- Consider chemo-mobilisation/ graft manipulation/ Chemotherapy intensity/ serotherapy type and intensity.
- Consider CNS penetrative chemoTx vs non-penetrative
- Very low intensity regimens (eg low-dose CYC w/o serotherapy) probably have no role in majority of patients. More intensive are likely more effective but trade off more risk and off target toxicity.
- Changing the natural history of the disease- Immune reset vs Immune suppression so if done earlier could avoid the development of progression or disability accumulation completely.
- Develop risk scores to identify early HSCT eligible patients. Improve patient selection further.
- Few, selected early-progressive patients might have some benefit (stabilization)
- MSBase contribution from HSCT groups

*(Snowden presentation)*

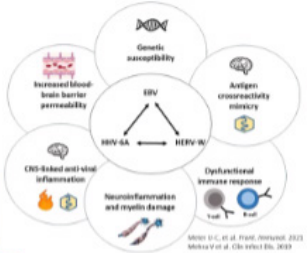
**CMV/EBV in MS patients after autologous HSCT**

In patients reconstituting immune system after HSCT, there is a period of impaired T-cell surveillance > *risk of infections*<.

- 'Cy-ATG' Experience in 84 MS pts (*Mehra et al.* 2021)
  - 100% patients with **EBV viremia**:
    - 41% patients had high viral load (>50,000 IU/mL);
    - 35% PET (Rituximab) on high viral load EBV.
  - 35% patients with **CMV viremia:**
    - 15% required PET on significant CMV reactivation;
    - no CMV disease.
- 'Cy-ATG' Experience in 507 MS pts (*Burt et al.* 2021)
  - 58/507 CMV reactivations (no disease).
- 'Cy-ATG' in 26 MS/1 SPS/1 CIDP pts (*Mapplebeck et al.* 2016)
  - 22/28 EBV viremia (no PTLD, 4 pts > 100000)
  - 18% asymptomatic CMV reactivation (no PET/disease)
- 'BEAM-ATG' Experience in 31 MS pts (*Saccardi et al. 2010*)
  - 38% EBV reactivations (median 29 days),
  - 35% CMV reactivation (median 35 days), 20% PET,
  - 1 CMV disease.

**EBV**

EBV reactivation and monoclonal paraproteinemia were PFS in MS (viral-mediated neuro-inflammation).
Correlation between high EBV levels (viremia >500,000 copies/mL or >50,000 IU/mL) and clinical events (i.e. neurological events) in MS-HSCT patients.




**PET per local practice. Need of harmonization for methods/samples.**

Need of comparison with DMTs! ↔ No clear viral infection data in ADs after HSCT → Monitoring CMV/EBV pre/post HSCT (100 days) ← ADWP survey on CMV/EBV ongoing

V. Mehra

# Parallel Sessions

## Parallel Session 3: Post-HSCT management; including neurological and MRI f/u, neuro-rehabilitation

**Friday, 11 March 14:00 – 16:00 CET**
**Speakers: Chris Heesen, Olga Ciccarelli, Giacoma Boffa**
**Chairs: Ellen Iacobaeus, Gian Luigi Mancardi**

**Conclusion:** The monitoring and management of patients after autologous haematopoietic stem cell transplant (HSCT) is continuing to evolve. Moving forward, clinical monitoring of multiple sclerosis (MS) disease course after HSCT may encompass traditional techniques such as magnetic resonance imaging (MRI), in conjunction with adapted disability measures and outcomes that include cognition and quality of life, as well as key biomarkers such as neurofilament light. Ecologically valid digital tools such as accelerometry will also be important in future MS monitoring paradigms post HSCT. Efforts to understand optimal management approaches for MS reactivation after HSCT remain ongoing and the collection of safety data on disease modifying therapy (DMT) reintroduction will be an important element of this. Neurorehabilitation may also have an important role to play both before and after HSCT, with the latter setting offering a unique opportunity to study brain neuroplasticity.

**What's New:** Consensus on optimal secondary outcomes for monitoring MS disease activity after HSCT has yet to be reached and endpoints used in current clinical trials remain insufficient. Adapting the existing Expanded Disability Status Scale (EDSS) to incorporate components of the Multiple Sclerosis Functional Composite (MSFC) such as the 9-Hole Peg Test (9-HPT) and Timed 25-Foot Walk (25FWT) may yield a composite confirmed disability accrual (CDA) definition with increased sensitivity to change. Emerging research has also shown accelerometery to be an attractive tool for monitoring disease trajectory that closely reflects what is happening in patients' daily lives. Other important measures that could be incorporated into the clinical monitoring of disease post HSCT include cognition (e.g., the Brief International Cognitive Assessment for MS (BICAMS)), contrast sensitivity and patient-reported outcomes such as fatigue, depression and quality of life.

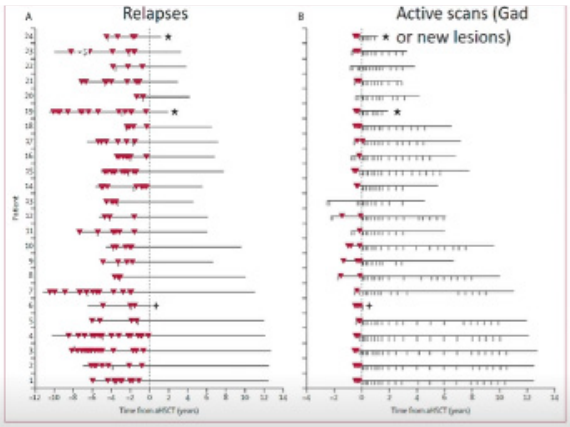
Available evidence shows that suppression of MRI disease activity is clear and almost complete for 3 years or more after HSCT. The improved responses seen in patients with active MRI prior to transplant advocates for use of MRI activity as a key requirement for treatment. Data also indicate that the level of MRI suppression may be linked with the preconditioning regimen, with around 8-10% of patients treated with intermediate-intensity regimens such as BEAM (carmustine, etoposide, cytarabine, melphalan) showing new or active MRI lesions 2-5 years post-HSCT.

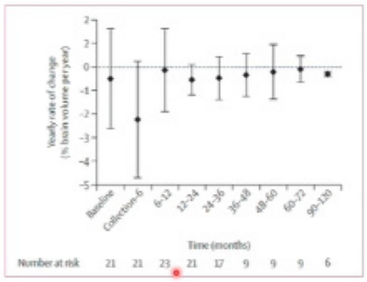
Although uncommon, MS reactivation after HSCT does occur and ensuing decisions on relapse management are complex. Moving forward, collaborative studies on neurological outcomes in patients with MS reactivation will be important to define the characteristics of the 'new MS' that emerges after HSCT. In particular, more data are needed to determine the potential benefit–and assess any safety risks–associated with the reintroduction of DMTs such as siponimod, ocrelizumab and Bruton's tyrosine kinase inhibitors in patients who experience disability progression after transplant.

Neurorehabilitation has shown positive effects after HSCT for MS, but efficacy hinges on the disease stage, presence and degree of disability, as well as medical therapy, rehabilitation type/duration and residual neuroplasticity of the central nervous system (CNS). From a research perspective, rehabilitation of a patient with MS after HSCT, where almost complete suppression of the main inflammatory pathological processes of the disease has been achieved, presents a unique opportunity to obtain the largest clinical effect due to potential reorganisation of the brain's capacity.

**Background:** HSCT is an effective treatment modality for MS and patients show clear benefit in clinical outcomes such as no evidence of disease activity and MRI measures of disease suppression. Long-term monitoring of patients after transplant is important in order to measure disease trajectories, accurately track outcomes, detect disease changes early and assess the impact of treatment on patients' everyday lives. Evidence-based therapeutic options also need to be decided upon for those patients who experience MS reactivation after transplant.

## MRI activity and brain atrophy post-AHSCT
*(Ciccarelli presentation)*




Mean yearly rate of brain atrophy increased in the first 6 months, but stabilized at -0.32% after 24 months post-aHSCT

- None of 327 scans showed Gd-enhancing lesions up to 12.7yrs

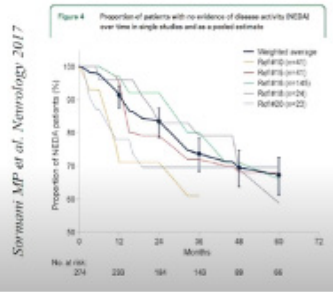
*Canadian trial (Atkins, Lancet 2016)*

## Prevalence of MS reactivation after AHSCT
*(Boffa presentation)*

**Table 1. Patient demographics, treatment protocols, and efficacy outcomes of AHSCT studies published from 2016 to 2020**

| Study | Nash [11] | Burt [12] | Boffa [13] | Zhukovsky [14] | Casanova [15] | Moore [16] | Mariottini [17] | Atkins [18] |
|---|---|---|---|---|---|---|---|---|
| Type of Study | Phase II | Phase III RCT | Observational | Observational | Observational | Phase II | Observational | Phase II |
| **Outcomes** | | | | | | | | |
| Follow-up, y | 5 (1-6) | 5 (1-5) | 5 (<1-5) | 3 (<1-5) | 8.4 (2-16) | 3 (1-5.5) | 8.2 (2-18.5) | 3 (2-13) |
| % Attack-free | 86.9% | 85% | 84% | 93% | 68 % | 90 % | 100% | 100 % |
| % MRI activity-free | 86.3% | N/A | 85% | 93% | 94 % | 86 % | 100% | 100 % |
| % Progression-free | 91.3% | 90% | 88% | 97% | 77 % | 73 % | 30% | 70 % |
| % NEDA | 69.2% | 78.5 % | 75% | 88% | 55 % | 60 % | 30% | 70 % |
| % DMT after AHSCT | 4% | 1 reported (2%) | 24% | 7% | 35% | 6 % | N/A | 0% |

*Bose G et al. J. Neurol Sciences 2021*




The proportion of patients who are relapse free and MRI-free after transplant ranges from 70 to 90%

# Parallel Sessions

## Parallel Session 4: Post-HSCT management; including early and late effects, virological and immune monitoring, vaccinations

**Friday, 11 March 14:00 – 16:15 CET**

**Speakers: Per Ljungman, Varun Mehra, Tobias Alexander, Joachim Burman, Kirill Kirgizov**

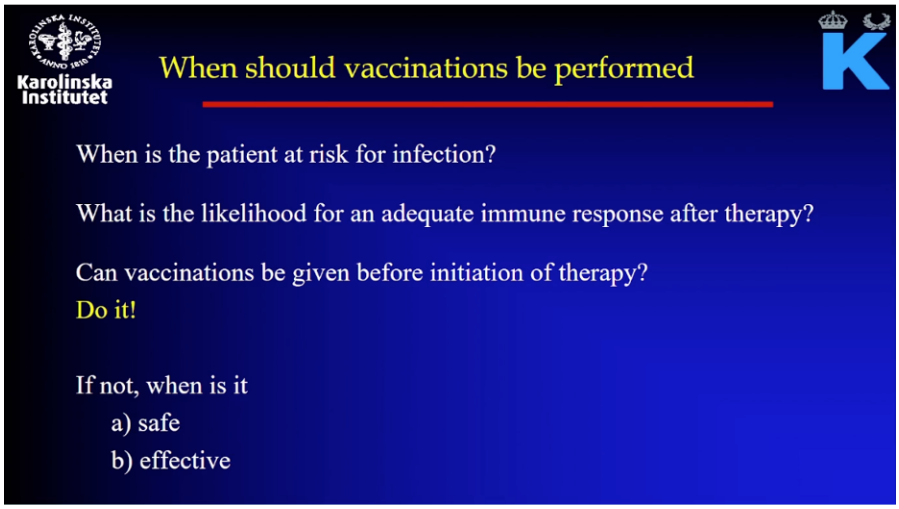
**Chairs: Raffaella Greco, John Snowden**

**Conclusion:** When planning a vaccination programme after stem cell transplantation, one may follow international recommendations or adapt to local practices. Many factors can influence the risks associated with stem cell transplantation, including epidemiology, previous disease, receipt of antibodies and transplant-related factors. In addition, poor rates of immunization in immunocompromised patients and the risk of secondary autoimmunity should be considered. The period of impaired T-cell surveillance that occurs during immune system reconstitution following stem cell transplantation can result in early manifestation of non-specific symptoms that might indicate viral reactivation, warranting viral and immune monitoring together with the development of an algorithm to assess late effects.

**What's New:** There is a need to improve the uptake of vaccination among patients with multiple sclerosis (MS) who have undergone stem cell transplantation. Many unknowns remain around efficacy of newer vaccines such as those against COVID-19, and with regard to immunization schedules and the impact of immune reconstitution. An alternative approach, particularly for prevention of viral reactivation, may be to adopt a prophylactic strategy of Epstein-Barr virus (EBV)/cytomegalovirus (CMV)-specific T-cell therapy post-transplantation. Standardised immune monitoring strategies should be integrated into follow-up assessments with several strategies available and recommendations published by the European Group for Blood and Marrow Transplantation (EBMT) and the Cellular Therapy and Immunobiology Working Party (CTIWP). It is vital that a consensus is met to ensure standardised protocols for sample collection, processing and handling are applied. Secondary autoimmunity, affecting primarily the thyroid, has thus far been underreported, and the risk of this occurring may be ameliorated by strategic B-cell depletion. However, the risk-benefit ratio of such an approach should be carefully assessed alongside the risks of contracting infections such as COVID-19. Late effects are also underestimated, highlighting the need for effective monitoring in those considered at risk of developing late complications.

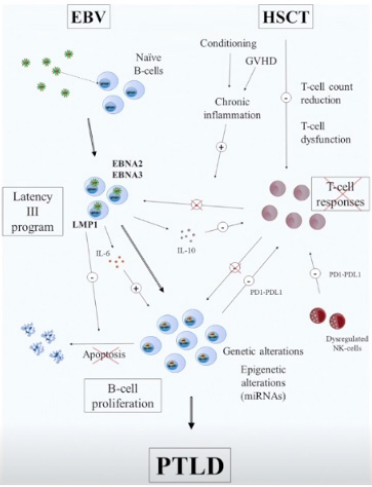
**Background:** Stem cell transplantation is increasingly being adopted as a standard of care across Europe for the treatment of autoimmune conditions such as MS, leading to the need to consider the safety of this therapeutic approach together with short- and long-term morbidity. Few true efficacy data exist to demonstrate the efficacy of vaccination, and it is possible that immunocompromised individuals may have a lower risk of direct side effects with inactivated vaccines than immune-competent individuals. Moreover, it should be noted that although stem cell transplantation is highly effective, it may also be associated with significant safety concerns, including reactivation of viral infections such as EBV or CMV, which may confer an increased risk of developing lymphoproliferative disorders, and secondary autoimmunity. Although most adverse events occur within the first 100 days following transplantation, some individuals may experience late effects after this benchmark.

**Vaccination programme after HSCT**
**is conducted weekly for the first 2 months post-transplantation and then every 2 weeks until Day 100**
*(Ljungman presentation)*



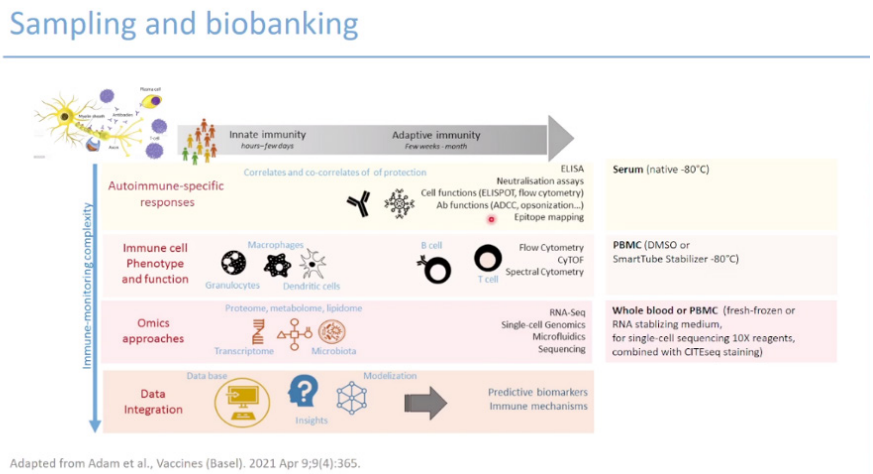
## CMV/EBV Reactivations
*(Mehra presentation)*

POST-TRANSPLANTATION LYMPHOPROLIFERATIVE DISORDER AFTER HAEMATOPOIETIC STEM CELL TRANSPLANTATION




Pegoraro, F., Favre, C. Post-transplantation lymphoproliferative disorder after haematopoietic stem cell transplantation. Ann Hematol 100, 865–878 (2021). https://doi.org/10.1007/s00277-021-04433-y

## Immune monitoring after autologous HSCT
*(Alexander presentation)*




Adapted from Adam et al., Vaccines (Basel). 2021 Apr 9;9(4):365.

## Late complications after autologous HSCT
*(Kirzigov presentation)*