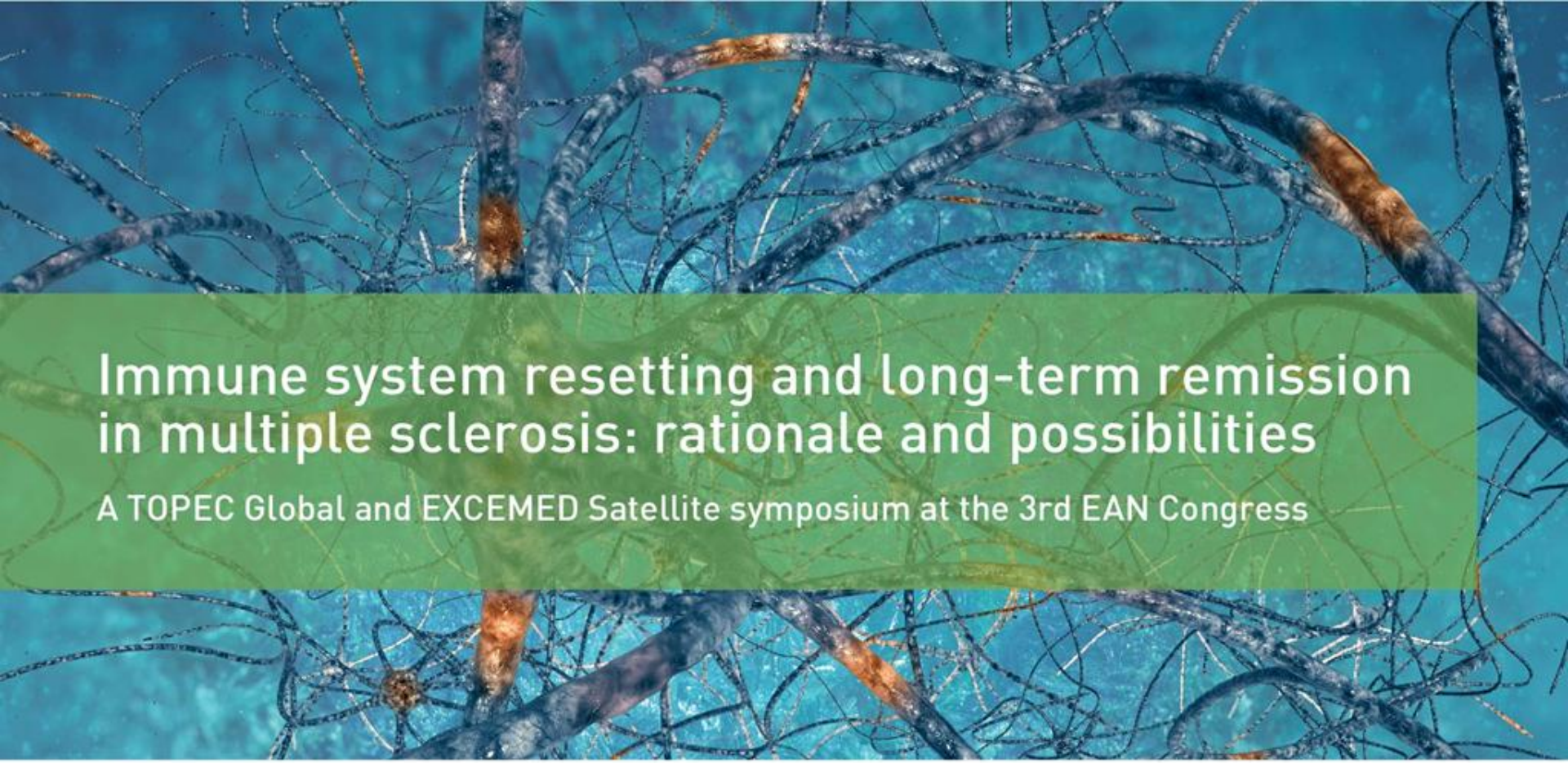

Immune system resetting and long-term remission in multiple sclerosis: rationale and possibilities

A TOPEC Global and EXCEMED Satellite symposium at the 3rd EAN Congress

gna Global Neurology Academy

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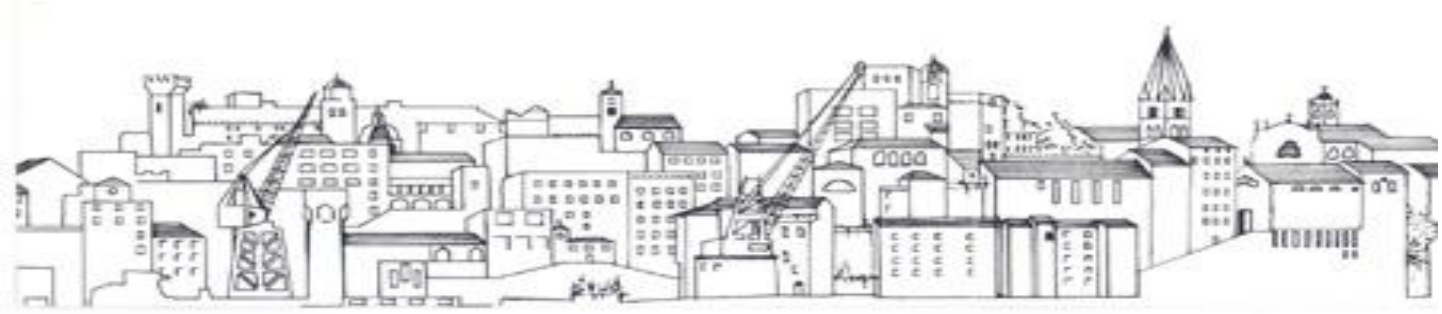


Evidence from bone marrow transplantation

Gianluigi Mancardi

Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, Ospedale Policlinico San Martino, University of Genova, Italy

3rd EAN Congress and Excemed Satellite Symposium
Amsterdam June 25 2017

Disclosure

Lecture fees and economic support for institutional research from Novartis, Merck Serono, Biogen Idec, Sanofi Aventis, Teva, Genzyme and Bayer

EXPERIMENTAL HSCT IN ADs

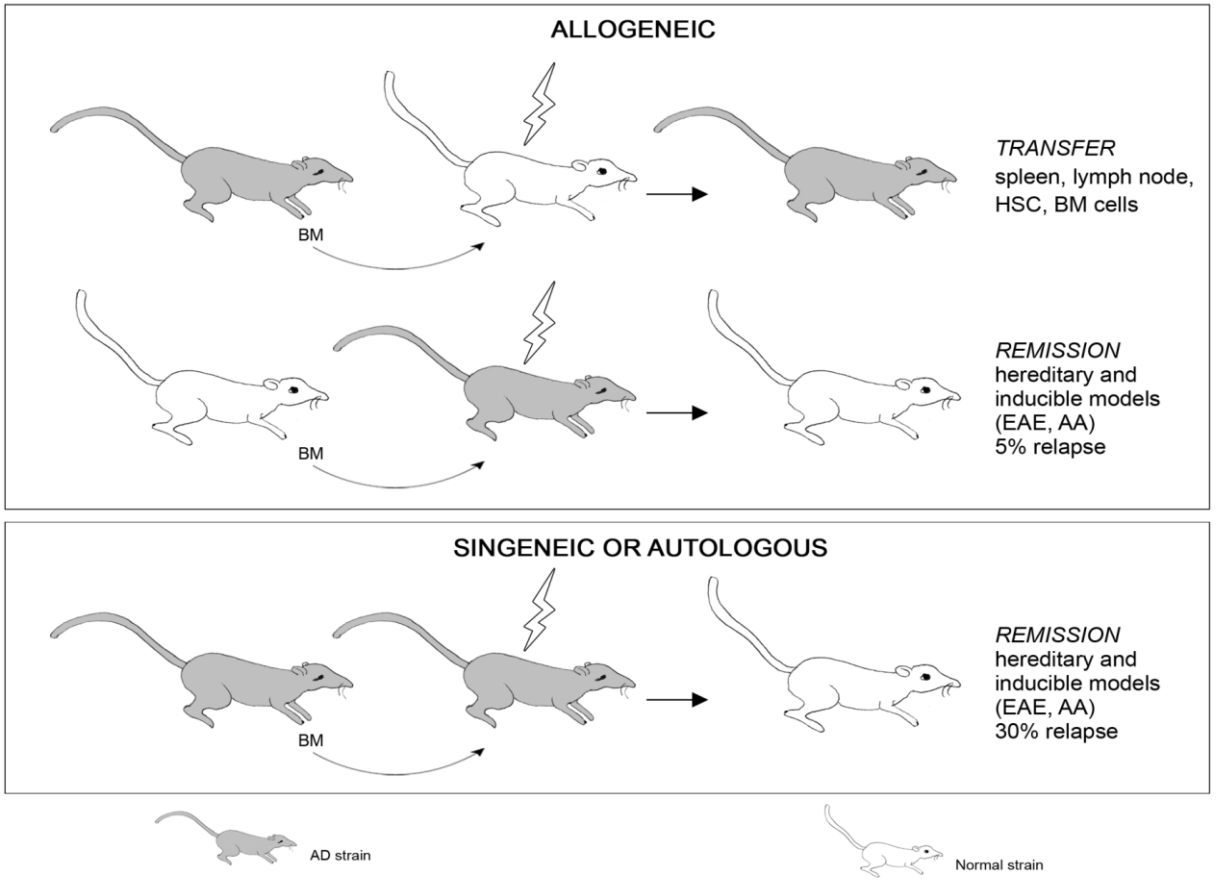
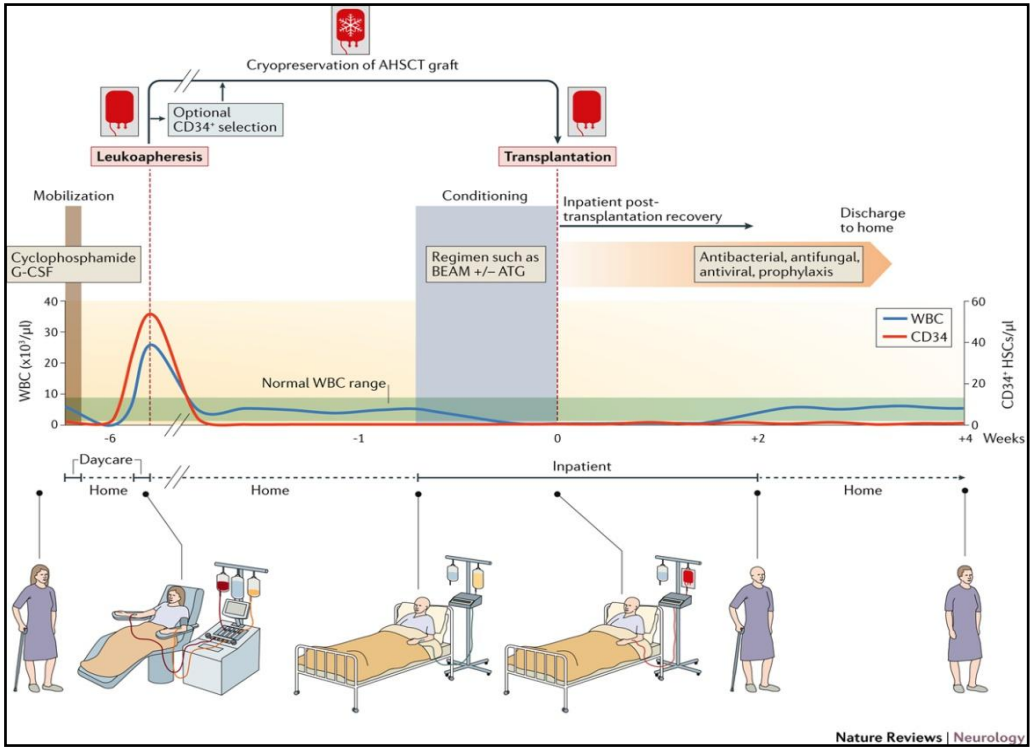


Figure 1: Outline of the AHSCT procedure



Muraro PA, et al. Nat Rev Neurol 2017:doi:10.1038/nrneurol.2017.81

NATURE REVIEWS NEUROLOGY | **REVIEW**

Autologous haematopoietic stem cell transplantation for treatment of multiple sclerosis

Paolo A. Muraro, Roland Martin, Giovanni Luigi Mancardi, Richard Nicholas, Maria Pia Sormani & Riccardo Saccardi

Nature Reviews Neurology (2017) doi:10.1038/nrneurol.2017.81
Published online 16 June 2017

Abstract

Autologous haematopoietic stem cell transplantation (AHSCT) is a multistep procedure that enables destruction of the immune system and its reconstitution from haematopoietic stem cells. Originally developed for the treatment of haematological malignancies, the procedure has been adapted for the treatment of severe immune-mediated disorders. Results from ~20 years of research make a compelling case for selective use of AHSCT in patients with highly active multiple sclerosis (MS), and for controlled trials. Immunological studies support the notion that AHSCT causes qualitative immune resetting, and have provided insight into the mechanisms that might underlie the powerful treatment effects that last well beyond recovery of immune cell numbers. Indeed, studies have demonstrated that AHSCT can entirely suppress MS disease activity for 4–5 years in 70–80% of patients, a rate that is higher than those achieved with any other therapies for MS. Treatment-related mortality, which was 3.6% in studies before 2005, has decreased to 0.3% in studies since 2005. Current evidence indicates that the patients who are most likely to benefit from and tolerate AHSCT are young, ambulatory and have inflammatory MS activity. Clinical trials are required to rigorously test the efficacy, safety and cost-effectiveness of AHSCT against highly active MS drugs.

Subject terms: Cell transplantation Haematopoietic stem cells Multiple sclerosis

	Patients (n)	EDSS score	Mobilisation	Ex-vivo T-cell depletion	Conditioning regimen	In-vivo T-cell depletion	Clinical outcome		Comments
							Follow-up (years)	PFS*	
Fassas et al[8,35]	25	4·5–8	CY and G-CSF	In 10 patients	BEAM	Yes	3·7	76%	After 10 years PFS is 47%†
Fassas and Kimiskidis[51]	10	4·5–8	CY and G-CSF	No	Busulfan	Yes	3	50%	After 6 years PFS remains at around 50%†
Kozak et al[36,37]	33	5–8·5	CY and G-CSF	In 20 patients	BEAM	In 13 patients	5	70%	
Mancardi et al,[38] Saccardi et al[39,56]	21	5–6·5	CY and G-CSF	No	BEAM	Yes	8·5	58%	Italian BMT Study Group
Nash et al[33]	26	5–8	G-CSF	Yes	TBI and CY	Yes	2	73%	
Burt et al[44]	21	3–8	G-CSF or CY and G-CSF	Yes	TBI and CY	No	1·8	61%	
Openshaw et al[47]	5	5·5–7·5	G-CSF	Yes	Busulfan and CY	Yes	1·8	40%	
Carreras et al,[52] Saiz et al[53,57]	14	4·5–6·5	CY and G-CSF	Yes	Carmustine and CY	Yes	6	62·5%	
Ni et al[42]	21	5–9·5	CY and G-CSF	Yes	CY and TBI or BEAM	Yes	3·5	75%	
Su et al,[40] Xu et al[41]	22	4·5–7·5	G-CSF	In 9 patients	BEAM	No	3	77%	
Samijn et al[45]	14	5·5–6·5	BM	Yes	TBI and CY	Yes	3	36%	
Atkins et al,[48] Freedman et al[49,50]	17	3–6	CY and G-CSF	Yes	Busulfan and CY	Yes	3	75%	Canadian MS BMT Study‡

*Probability of remaining alive without confirmed disability progression on EDSS after transplant compared with baseline.[58] †Personal communication, A Fassas (George Papanicolaou Hospital, Thessaloniki, Greece). ‡Personal communication, M S Freedman (The Ottawa Hospital, Ontario, Canada). BM=bone marrow. CY=cyclophosphamide. G-CSF=granulocyte colony-stimulating factor. PFS=progression-free survival. TBI=total body irradiation.

Table: **Prospective studies of AHSCT in MS**

Original Investigation

April 2017

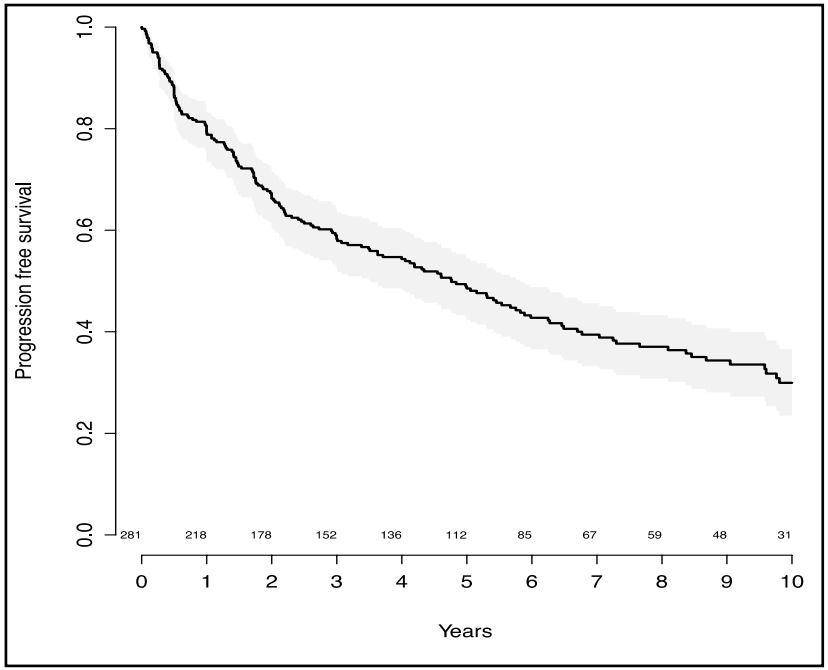
Long-term Outcomes After Autologous Hematopoietic Stem Cell Transplantation for Multiple Sclerosis

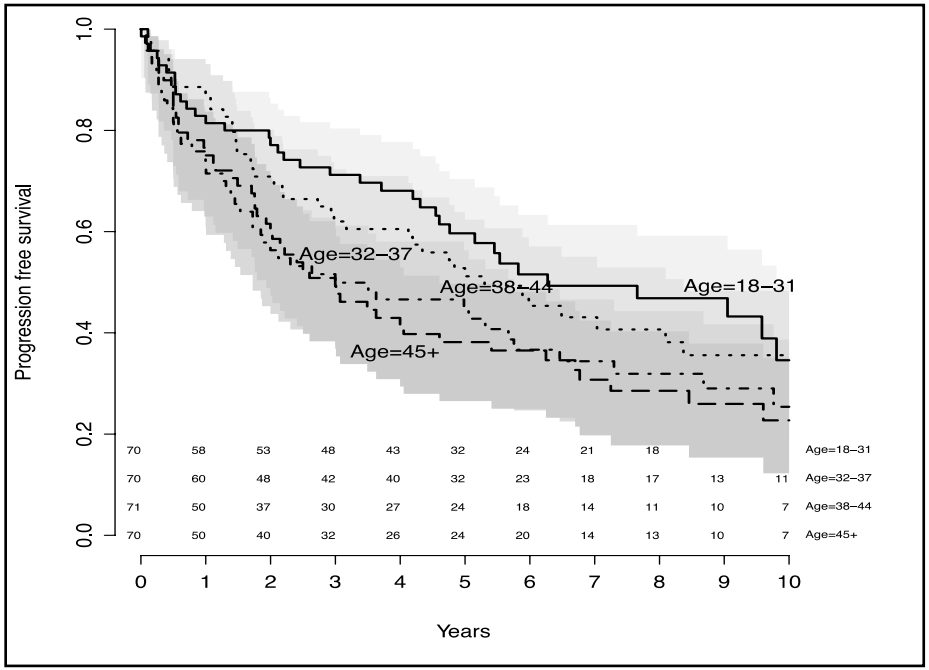
Paolo A. Muraro, MD[1]; Marcelo Pasquini, MD[2]; Harold L. Atkins, MD[3]; et al

» Author Affiliations

JAMA Neurol. 2017;74(4):459-469. doi:10.1001/jamaneurol.2016.5867

The first studies, 1995 – 2006: Progression-free survival





Progressive MS: 78%. Median EDSS score: 6.5. PFS 46% at 5 years

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Muraro PA, et al. JAMA Neurol 2017;74:459–69.

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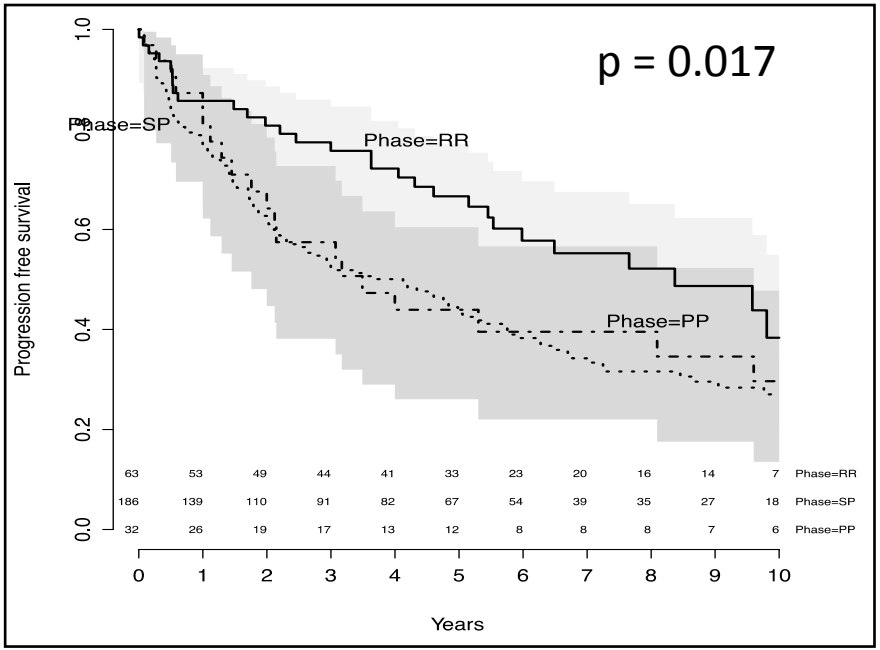
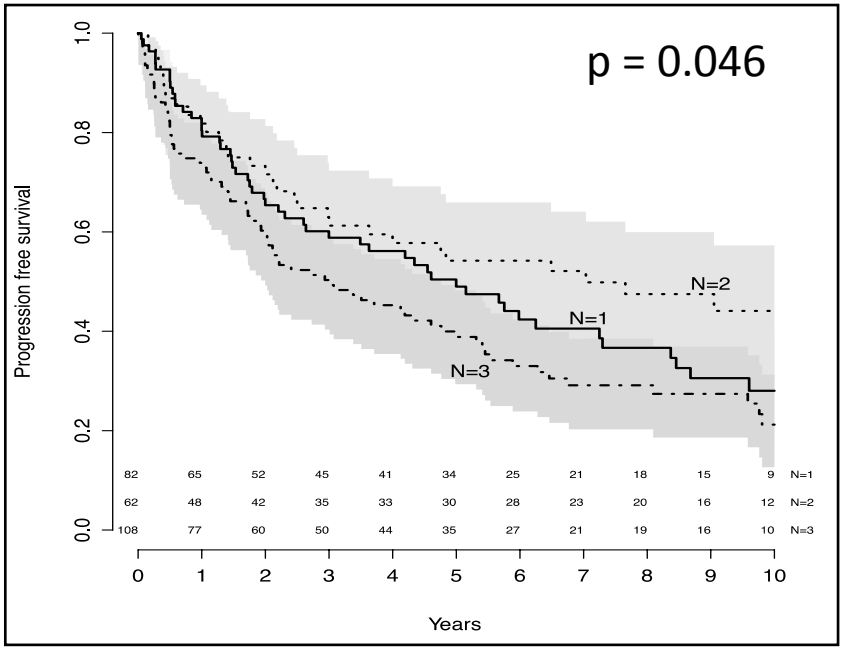
Progression-free survival: 2 of 2

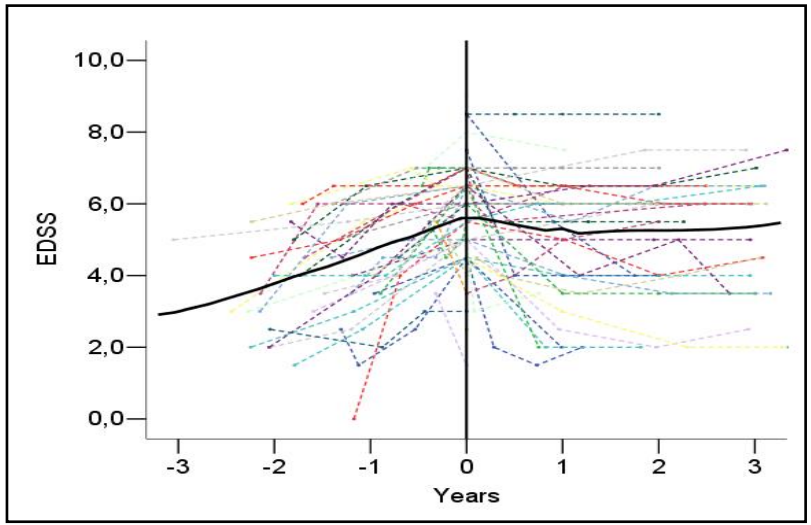




Muraro PA, et al. JAMA Neurol 2017;74:459–69.

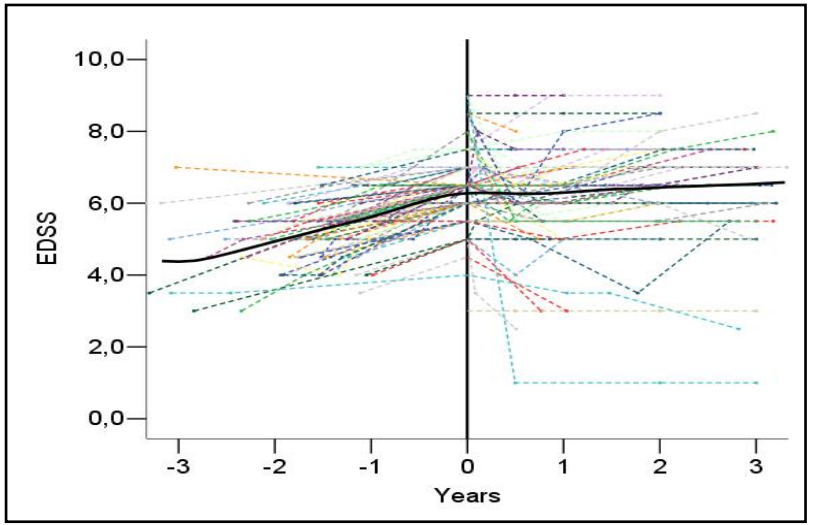
Evolution of EDSS score before and after AHSCT in patients with longitudinal EDSS data (n=170)

Relapsing MS (n=51)



EDSS change 1 year pre-transplant +1.42
EDSS change 1 year post-transplant -0.76

Progressive MS (n=119)



EDSS change 1 year pre-transplant +0.73
EDSS change 1 year post-transplant -0.14

Global Neurology Academy

Muraro PA, et al. JAMA Neurol 2017;74:459–69.

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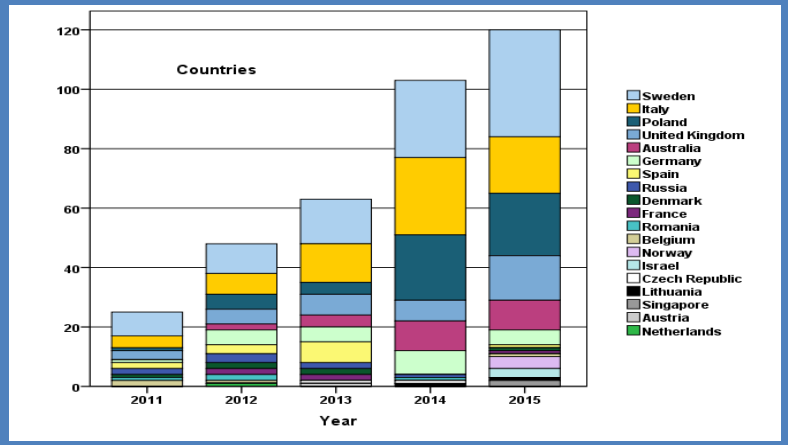
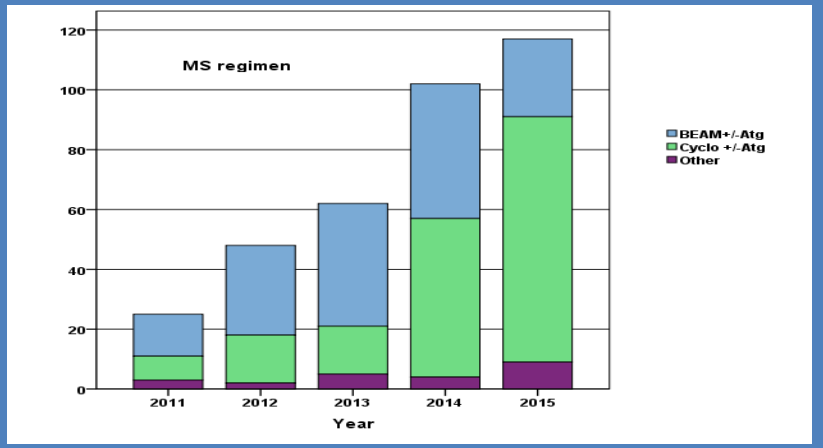
MS (n=915)
ADWP–EBMT Registry – October 2016

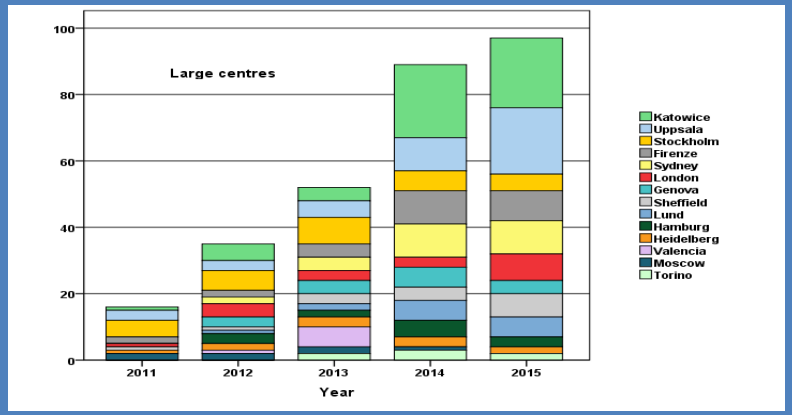
Transplant procedures	915
Patients	909
Auto / allo (nr)	911/4
Male/Female %	39/61
Paediatric/ adult / %	3/97
Median time from diag-1st auto HSCT	7y (<1-34)
Median age at 1st auto (adult)	36y (18-66)
Centers /Countries	116 / 29

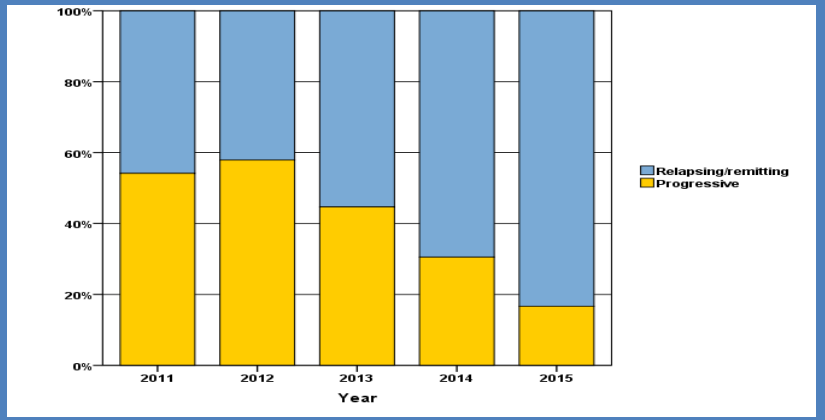
CONDITIONING REGIMENS (auto HSCT)	Nr (%)
Cyclo	27 (3.0)
Cyclo + ATG	262 (28.8)
BEAM	154 (16.9)
BEAM + ATG	321 (35.2)
Melphalan containing	41 (4.5)
Other /Missing	*20/75*

MS - 1st auto-HSCT per large center 2011 – 2015 (n=359) October 2016









Autologous hematopoietic stem cell transplantation in multiple sclerosis

A phase II trial

Giovanni L. Mancardi, MD
Maria P. Sormani, MD
Francesca Gualandi, MD
Albert Saiz, MD
Eric Carreras, MD
Elisa Merelli, MD
Amedea Donelli, MD
Alessandra Lugaresi, MD
Paolo Di Bartolomeo, MD
Maria R. Rottoli, MD
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Massimo Di Gioia, MD
Luisa Vuolo, MD
Daniela Currò, MD
Luca Roccatagliata, MD
Massimo Filippi, MD
Umberto Aguglia, MD
Paolo Iacopino, MD
Dominique Farge, MD
Riccardo Saccardi, MD
For the ASTIMS Haemato-Neurological Collaborative Group, On behalf of the Autoimmune Disease Working Party (ADWP) of the European Group for Blood and Marrow Transplantation (EBMT)

ABSTRACT

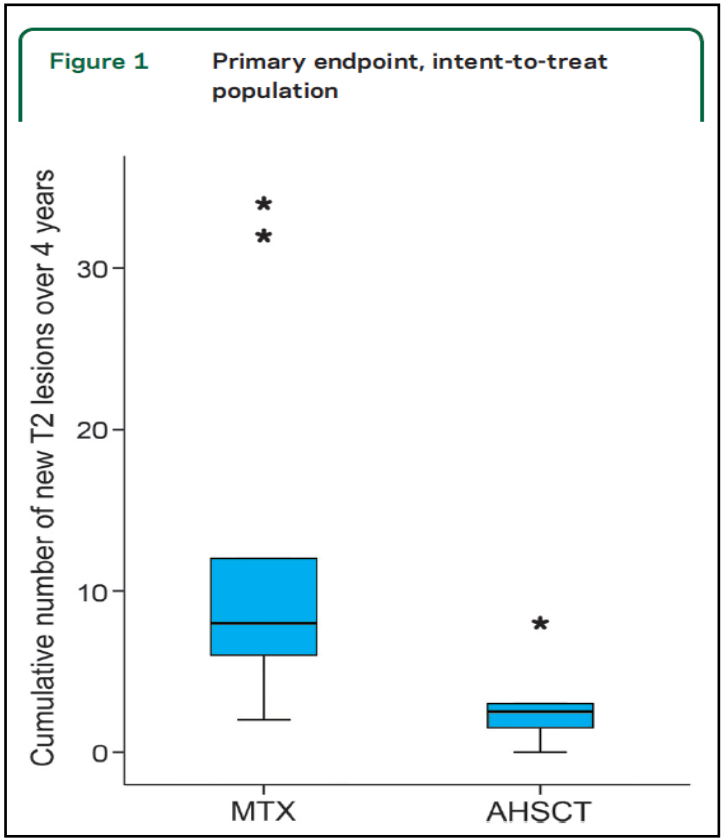
Objective: To assess in multiple sclerosis (MS) the effect of intense immunosuppression followed by autologous hematopoietic stem cells transplantation (AHSCT) vs mitoxantrone (MTX) on disease activity measured by MRI.

Methods: We conducted a multicenter, phase II, randomized trial including patients with secondary progressive or relapsing-remitting MS, with a documented increase in the last year on the Expanded Disability Status Scale, in spite of conventional therapy, and presence of one or more gadolinium-enhancing (Gd+) areas. Patients were randomized to receive intense immunosuppression (mobilization with cyclophosphamide and filgrastim, conditioning with carmustine, cytosine-arabinoside, etoposide, melphalan, and anti-thymocyte globulin) followed by AHSCT or MTX 20 mg every month for 6 months. The primary endpoint was the cumulative number of new T2 lesions in the 4 years following randomization. Secondary endpoints were the cumulative number of Gd+ lesions, relapse rate, and disability progression. Safety and tolerability were also assessed. Twenty-one patients were randomized and 17 had postbaseline evaluable MRI scans.

Results: AHSCT reduced by 79% the number of new T2 lesions as compared to MTX (rate ratio 0.21, $p = 0.00016$). It also reduced Gd+ lesions as well as the annualized relapse rate. No difference was found in the progression of disability.

Conclusion: Intense immunosuppression followed by AHSCT is significantly superior to MTX in reducing MRI activity in severe cases of MS. These results strongly support further phase III studies with primary clinical endpoints. The study was registered as EUDRACT No. 2007-000064-24.

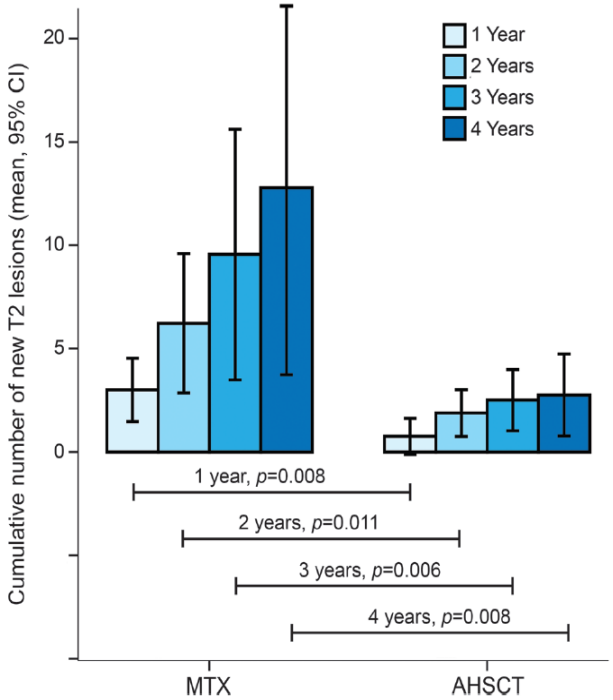
Neurology® 2015;84:1–8



The cumulative number of new T2 MRI lesions counted over 4 years is significantly reduced in the autologous hematopoietic stem cell transplantation (AHSCT) arm as compared to the mitoxantrone (MTX) arm: MTX = median 8 (range 2–34), AHSCT = median 2.5 (range 0–8), rate ratio = 0.21 (95% confidence interval 0.10–0.48), $p = 0.00016$. Black lines: medians; box = interquartile range. *Rate ratio, negative binomial regression analysis.

Mancardi GL, et al. Neurology 2015;84:1–8.

Figure 2 Cumulative number of new T2 MRI lesions over 1, 2, 3, and 4 years



AHSCT = autologous hematopoietic stem cell transplantation; CI = confidence interval; MTX = mitoxantrone.

The more recent studies:
Mainly RRMS with an aggressive clinical course

Multiple sclerosis

RESEARCH PAPER

Autologous haematopoietic stem cell transplantation for aggressive multiple sclerosis: the Swedish experience

Joachim Burman,[1,2] Ellen Iacobaeus,[3] Anders Svenningsson,[4] Jan Lycke,[5] Martin Gunnarsson,[6,7] Petra Nilsson,[8] Magnus Vrethem,[9,10] Sten Fredrikson,[11] Claes Martin,[12] Anna Sandstedt,[13] Bertil Uggla,[7,14] Stig Lenhoff,[15] Jan-Erik Johansson,[16] Cecilia Isaksson,[17] Hans Hägglund,[18] Kristina Carlson,[18] Jan Fagius[1,2]

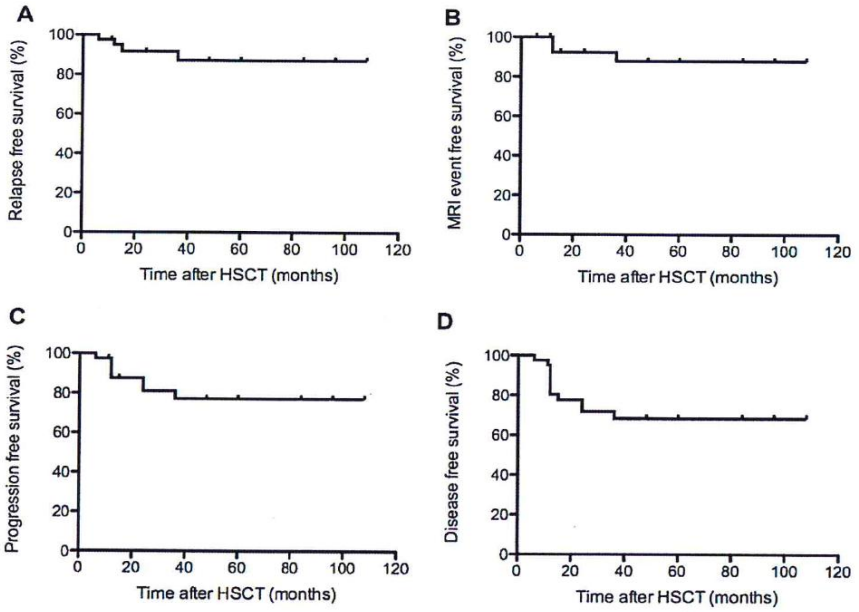


Figure 1 Kaplan–Meier survival curves of relapse-free survival, MRI event-free survival, progression-free survival and disease-free survival. Relapse-free survival, MRI event-free survival, progression-free survival and disease-free survival (no relapses, no new MRI lesions and no EDSS progression) after haematopoietic stem cell transplantation for all patients with follow-up time at least 1 year (n=41). EDSS, expanded disability status scale.

48 patients, 83% RRMS; 5 years, disease free survival 68%

Burman J, et al. J Neurol Neurosurg Psy 2014;85:1116–21.

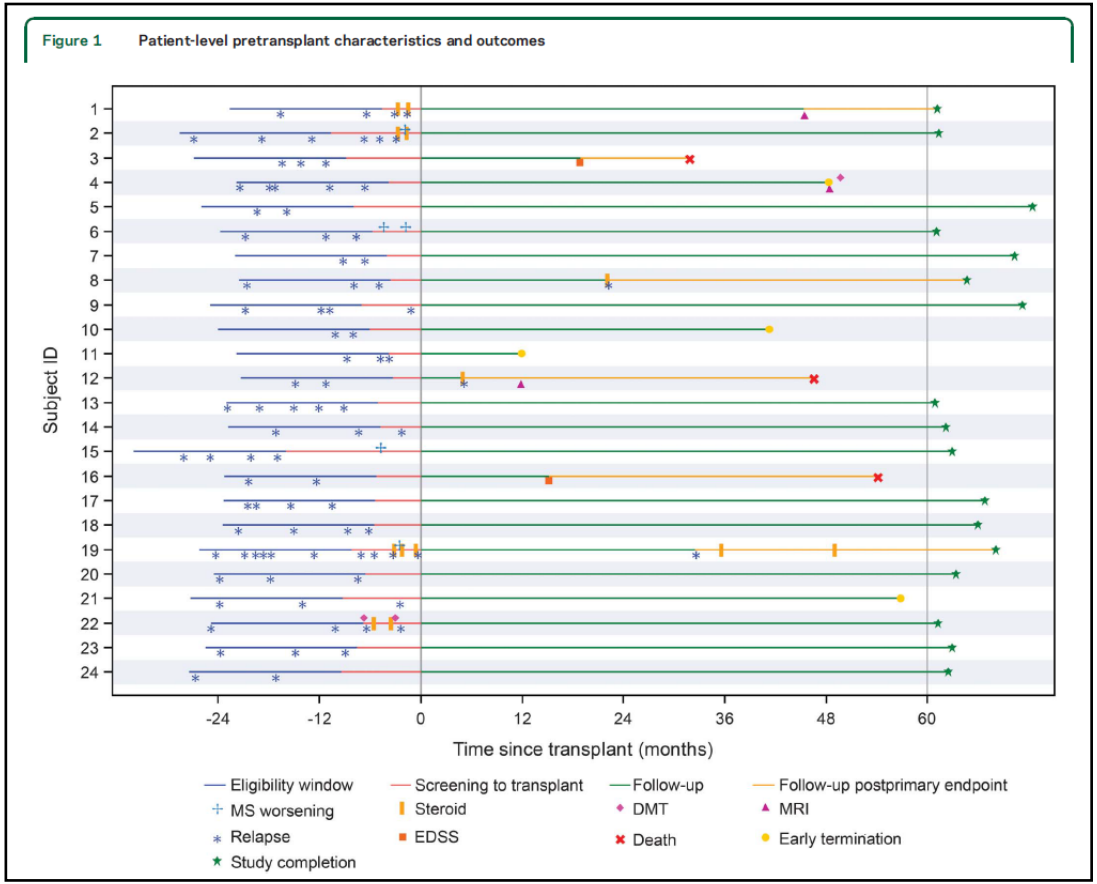
The more recent studies:
Mainly RRMS with an aggressive clinical course

Research

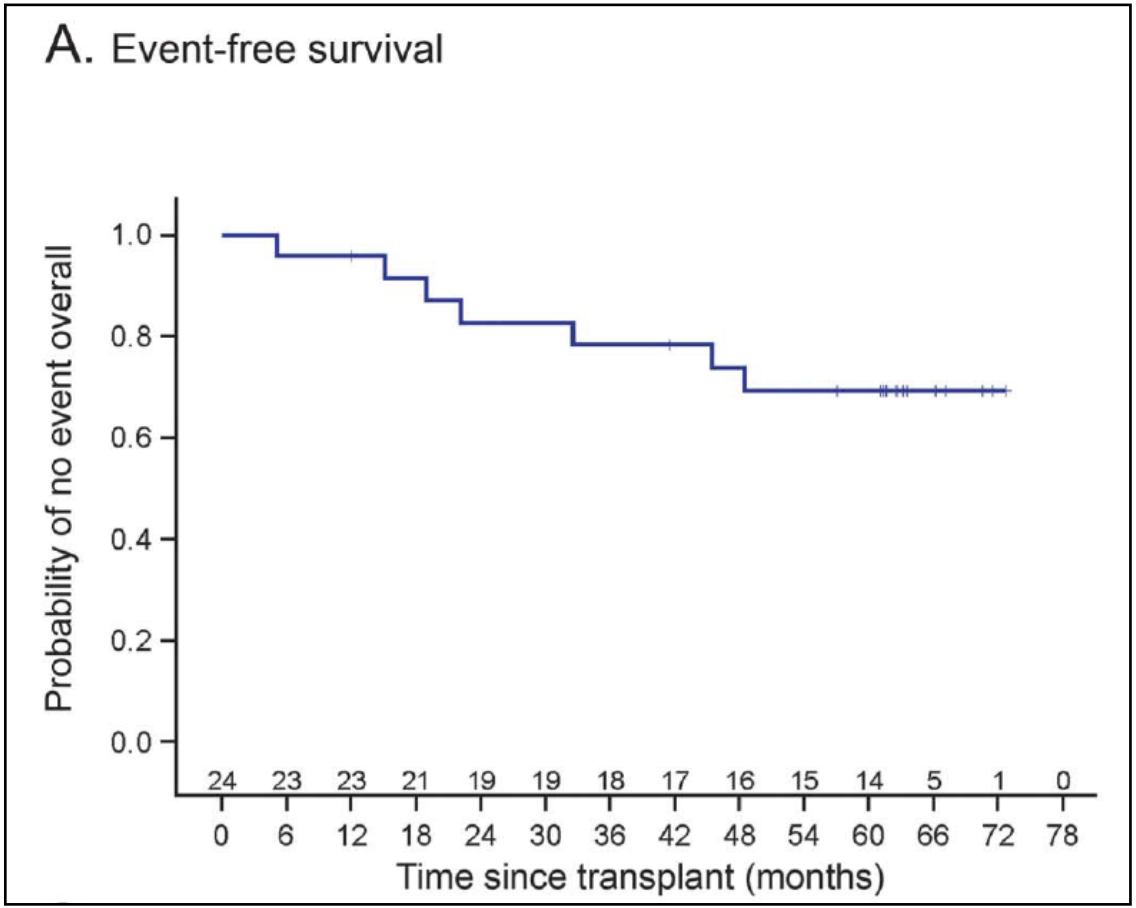
Original Investigation | CLINICAL TRIAL

High-Dose Immunosuppressive Therapy and Autologous Hematopoietic Cell Transplantation for Relapsing-Remitting Multiple Sclerosis (HALT-MS)
A 3-Year Interim Report

Richard A. Nash, MD; George J. Hutton, MD; Michael K. Racke, MD; Uday Popat, MD; Steven M. Devine, MD; Linda M. Griffith, MD, PhD; Paolo A. Muraro, MD, PhD; Harry Openshaw, MD; Peter H. Sayre, MD, PhD; Olaf Stüve, MD, PhD; Douglas L. Arnold, MD; Meagan E. Spychala, DrPH; Kaitlyn C. McConville, MS; Kristina M. Harris, PhD; Deborah Phippard, PhD; George E. Georges, MD; Annette Wundes, MD; George H. Kraft, MD, MS; James D. Bowen, MD



Nash RA, et al. Neurology 201;88:842–52.



Nash RA, et al. Neurology 201;88:842–52.

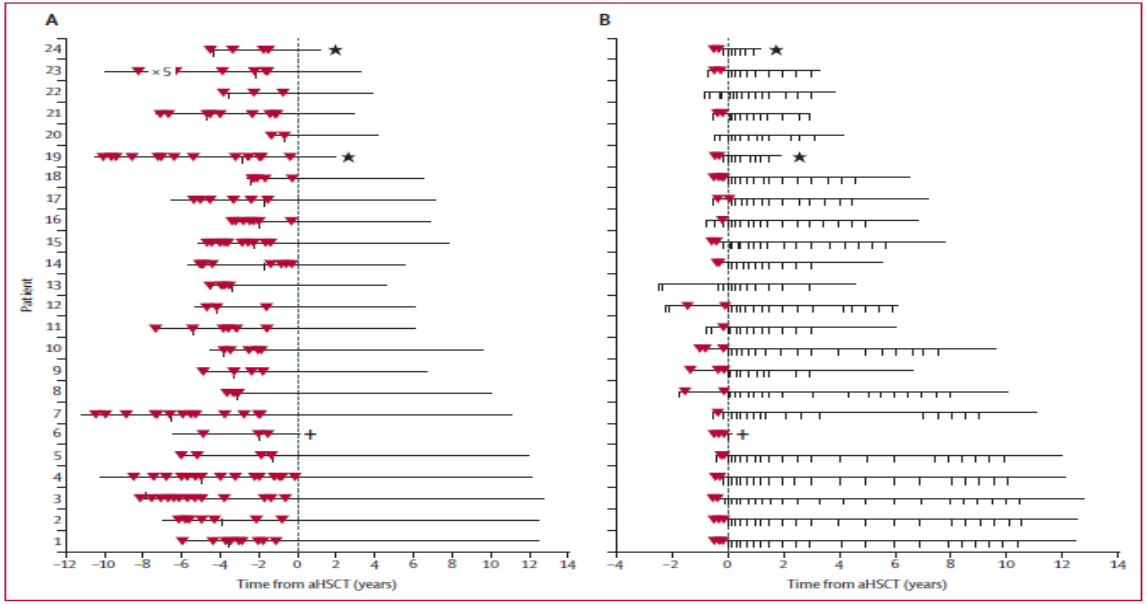
The more recent studies

Immunoablation and autologous haemopoietic stem-cell transplantation for aggressive multiple sclerosis: a multicentre single-group phase 2 trial

Harold L Atkins, Marjorie Bowman, David Allan, Grizel Anstee, Douglas L Arnold, Amit Bar-Or, Isabelle Bence-Bruckler, Paul Birch, Christopher Bredeson, Jacqueline Chen, Dean Fergusson, Mike Halpenny, Linda Hamelin, Lothar Huebsch, Brian Hutton, Pierre Laneuville, Yves Lapierre, Hyunwoo Lee, Lisa Martin, Sheryl McDiarmid, Paul O'Connor, Timothy Ramsay, Mitchell Sabloff, Lisa Walker, Mark S Freedman

Atkins HL, et al. Lancet. 2016;388:576-85.

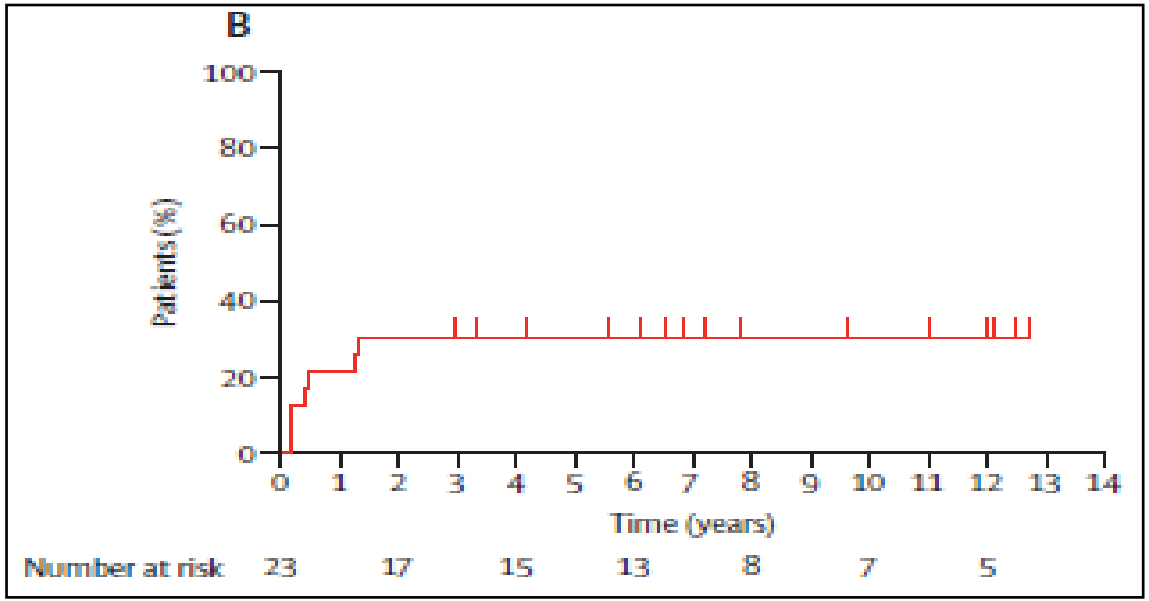
24 patients, RR MS 50% and SPMS 50%



167 relapses and 188 Gd+ lesions before. No relapses and no Gd+ lesions after
Median follow up: 6.7 years

Atkins HL, et al. Lancet. 2016;388:576-85.

Progression of disability



70% had no progression of disability after AHSCT
Median follow up: 6.7 years

Atkins HL, et al. Lancet. 2016;388:576-85.

MULTIPLE SCLEROSIS JOURNAL | MSJ

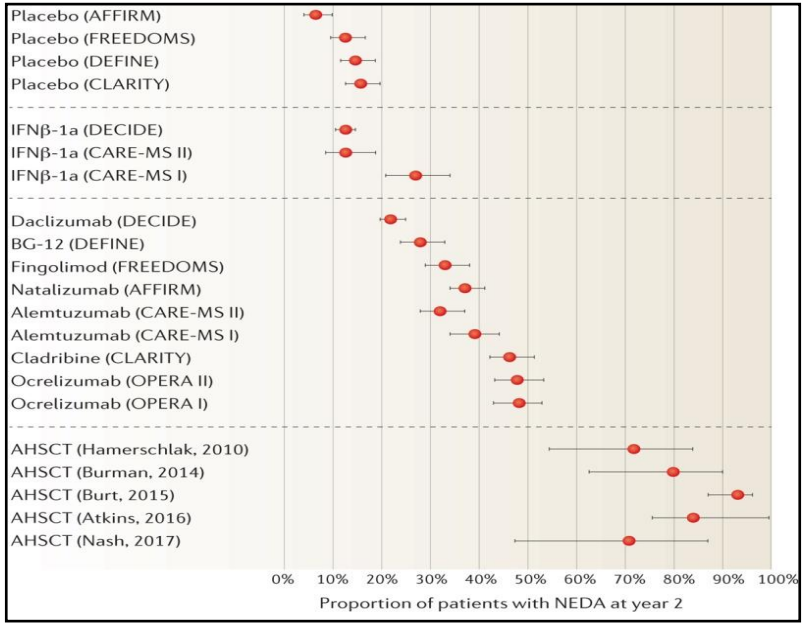
Personal Viewpoint

NEDA status in highly active MS can be more easily obtained with autologous hematopoietic stem cell transplantation than other drugs

Maria Pia Sormani, Paolo A Muraro, Riccardo Saccardi and Gianluigi Mancardi

Autologous hematopoietic stem cell transplantation for treatment of multiple sclerosis

Figure 3: Proportion of patients for whom NEDA was achieved at 2 years with disease-modifying therapies and AHSCT



Muraro PA, et al. Nat Rev Neurol 2017:doi:10.1038/nrneurol.2017.81

No doubt that AHSCT is effective in aggressive MS, especially in the RR phase of the disease. but there are still many problems

Progression of disability

Transplant related mortality

Mechanism of action

The method and the intensity of AHSCT

The patient who would be more likely to benefit from AHSCT

A phase 3 study?

Autologous hematopoietic stem cell transplantation in multiple sclerosis

A meta-analysis

Maria Pia Sormani, PhD
Paolo A. Muraro, MD
Irene Schiavetti, PhD
Alessio Signori, PhD
Alice Laroni, MD
Riccardo Saccardi, MD
Gian Luigi Mancardi, MD

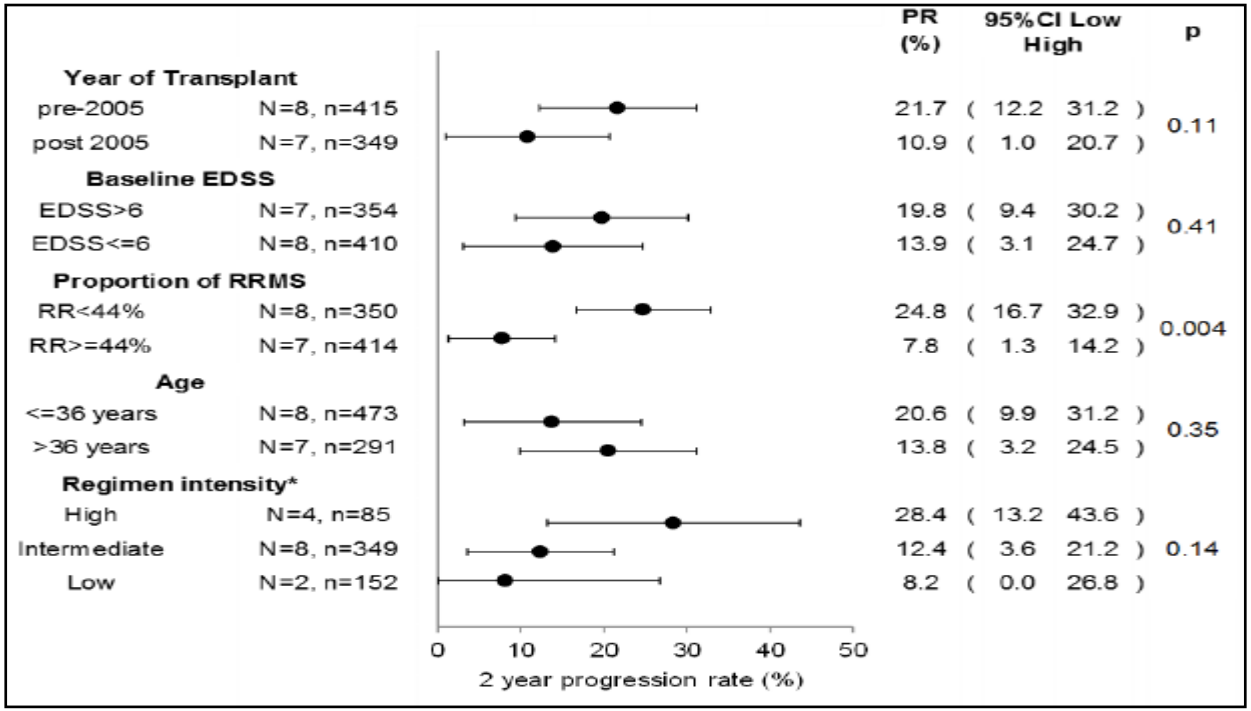
ABSTRACT

Objective: To summarize the evidence on immunoablative therapy followed by autologous hematopoietic stem cell transplantation (aHSCT) to manage severe and treatment-refractory multiple sclerosis (MS).

Methods: We collected all the published studies of aHSCT in any form of MS from 1995 to 2016, carefully excluding reports that were updated in subsequent studies. Endpoints were transplant-related mortality (TRM), rate of disease progression, and no evidence of disease activity (NEDA) status. A weighted metaregression based on a Poisson model was run, assessing whether there were study-specific characteristics with an effect on TRM and progression.

Sormani MP, et al. Neurology 2017;88:1–8.

Progression of disability



Sormani MP, et al. Neurology 2017;88:1–8.

No doubt that AHSCT is effective in aggressive MS, especially in the RR phase of the disease…. but there are still many problems

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The method and the intensity of AHSCT

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A phase 3 study?

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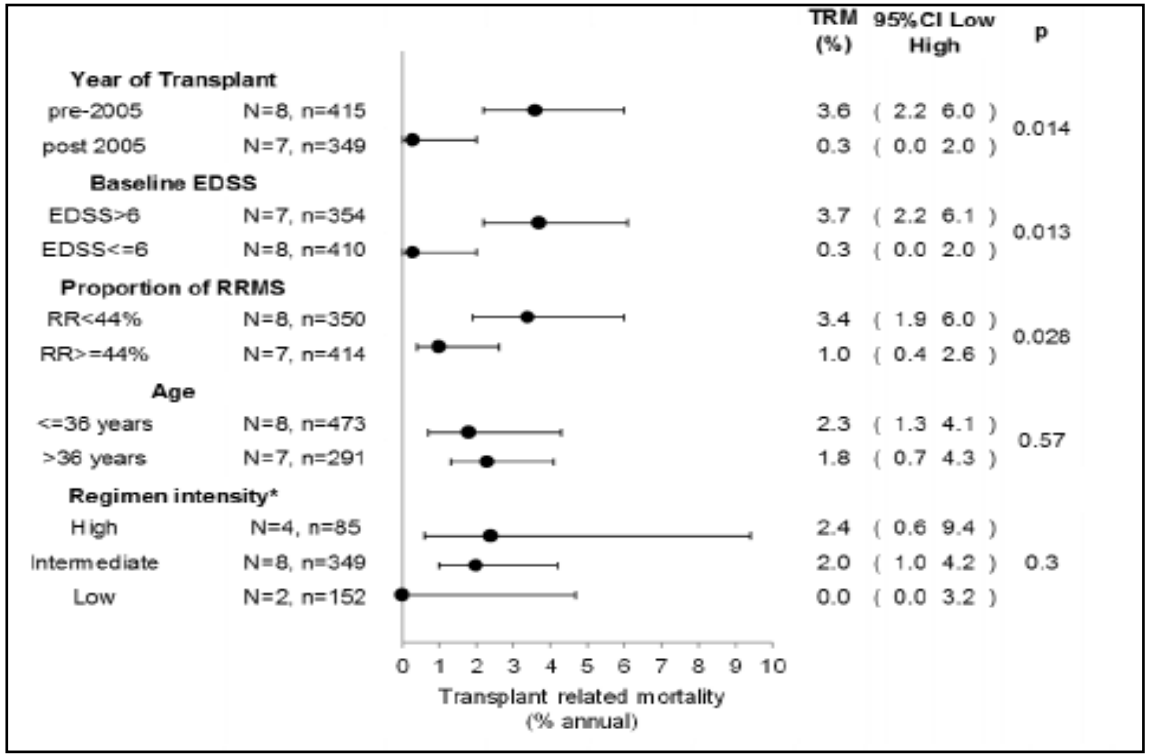
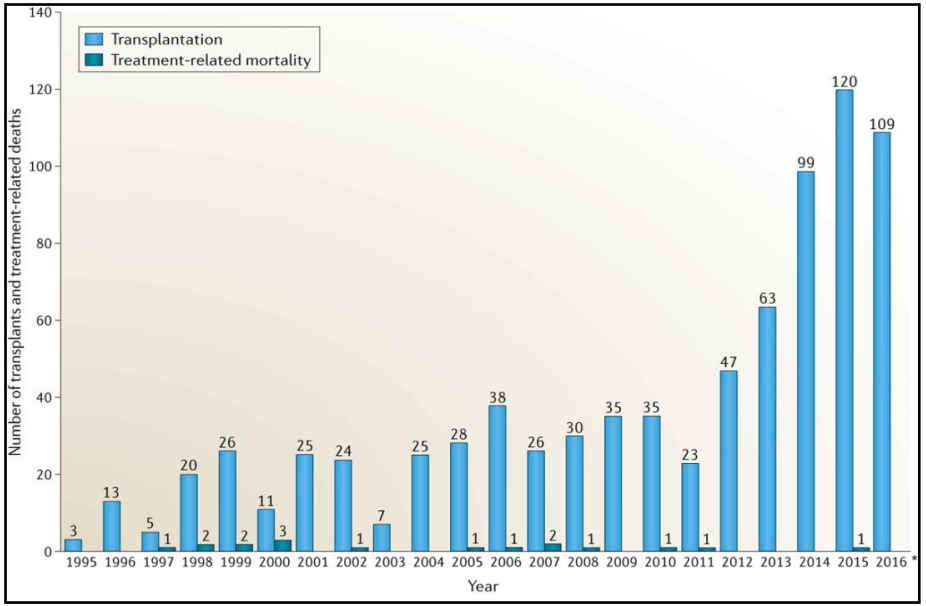
Transplant-related mortality



Sormani MP, et al. Neurology 2017;88:1–8.

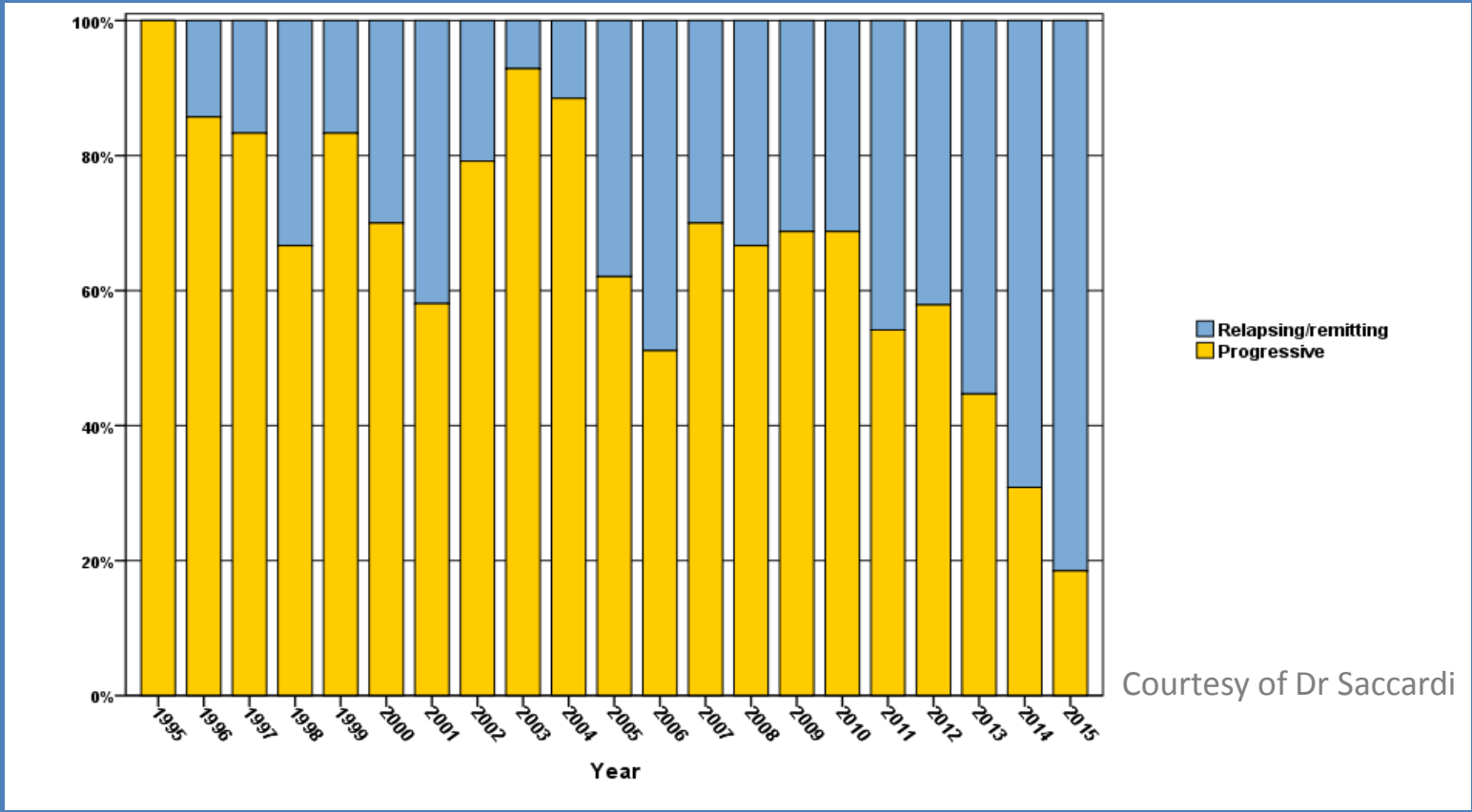
Autologous hematopoietic stem cell transplantation for treatment of multiple sclerosis

Figure 5: Number of AHSCT procedures for the treatment of multiple sclerosis and treatment-related mortality



Muraro PA, et al. Nat Rev Neurol 2017:doi:10.1038/nrneurol.2017.81

MS EBMT Registry
Relapsing vs Progressive
1995 – 2015 (n=671) March 2016



Courtesy of Dr Saccardi

No doubt that AHSCT is effective in aggressive MS, especially in the RR phase of the disease…. but there are still many problems

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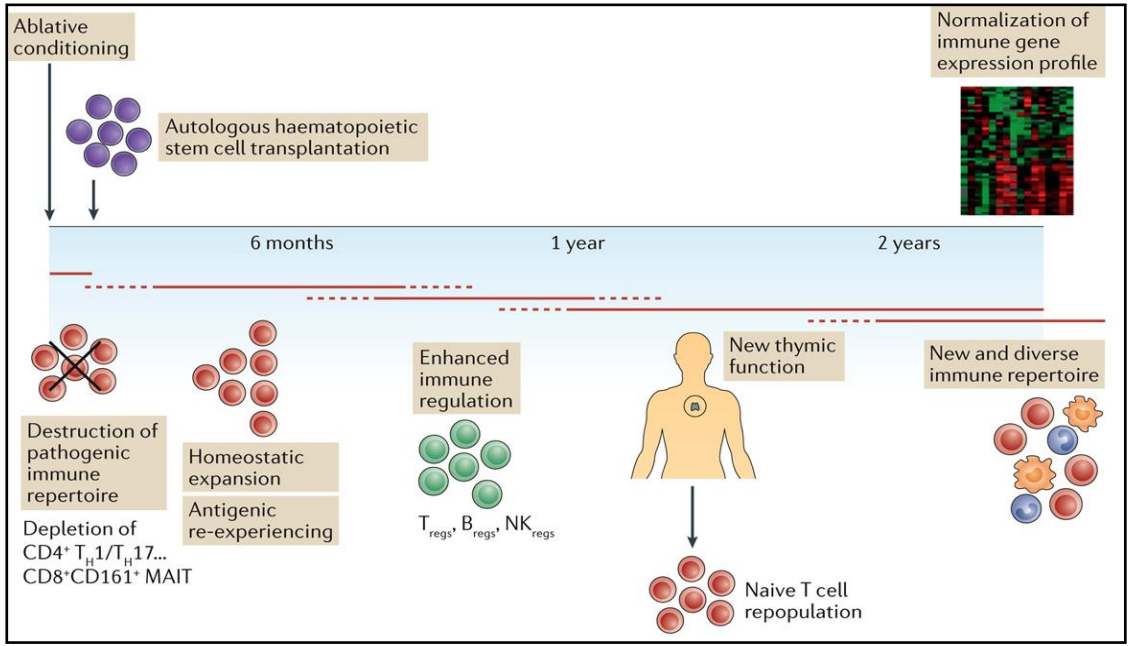
The patient who would be more likely to benefit from AHSCT

A phase 3 study?

Autologous hematopoietic stem cell transplantation for treatment of multiple sclerosis

Figure 2: Proposed model of therapeutic mechanisms of AHSCT



Muraro PA, et al. Nat Rev Neurol 2017:doi:10.1038/nrneurol.2017.81

No doubt that AHSCT is effective in aggressive MS, especially in the RR phase of the disease…. but there are still many problems

Progression of disability

Transplant related mortality

Mechanism of action

The method and the intensity of AHSCT

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Conditioning regimens

In animal studies, higher intensity regimens are associated with better clinical outcomes
However, in human studies, regimen intensity is associated with a higher TRM

Higher intensity regimens

Cyclophosphamide+ TBI+ ATG with T cell depletion of the graft

Busulfan+ Cyclophosphamide+ ATG+ with T cell depletion of the graft

Intermediate intensity regimens

BEAM (carmustine, etoposide, cytarabine, melphalan) +ATG with or without T cell depletion of the graft

Carmustine, Cyclophosphamide +ATG with T cell depletion of the graft

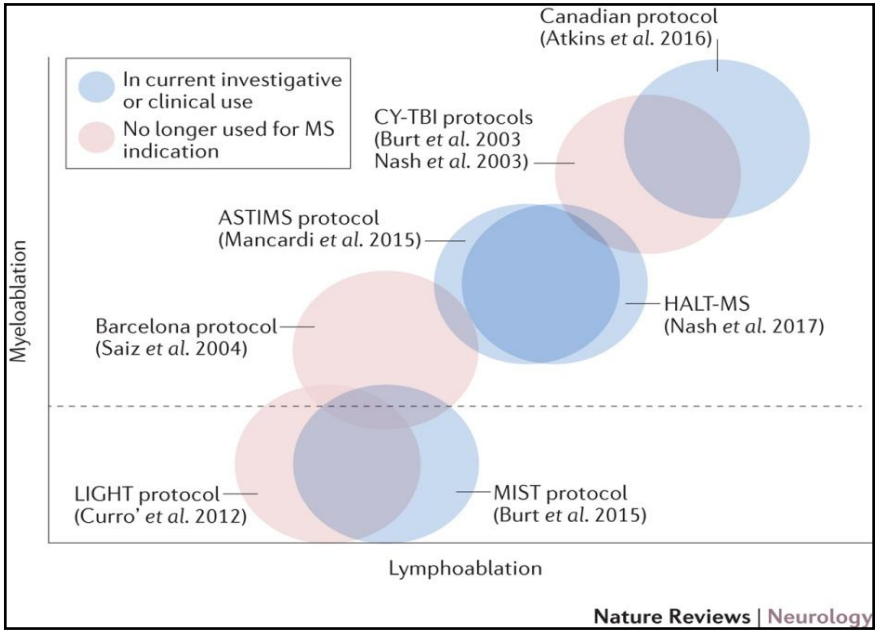
Low intensity regimens

Cyclophosphamide 200mg/kg plus alemtuzumab or ATG

Cyclophosphamide 120mg/kg plus ATG

Autologous hematopoietic stem cell transplantation for treatment of multiple sclerosis

Figure 4: Estimated lymphoablative and myeloablative effects of AHSCT protocols for multiple sclerosis



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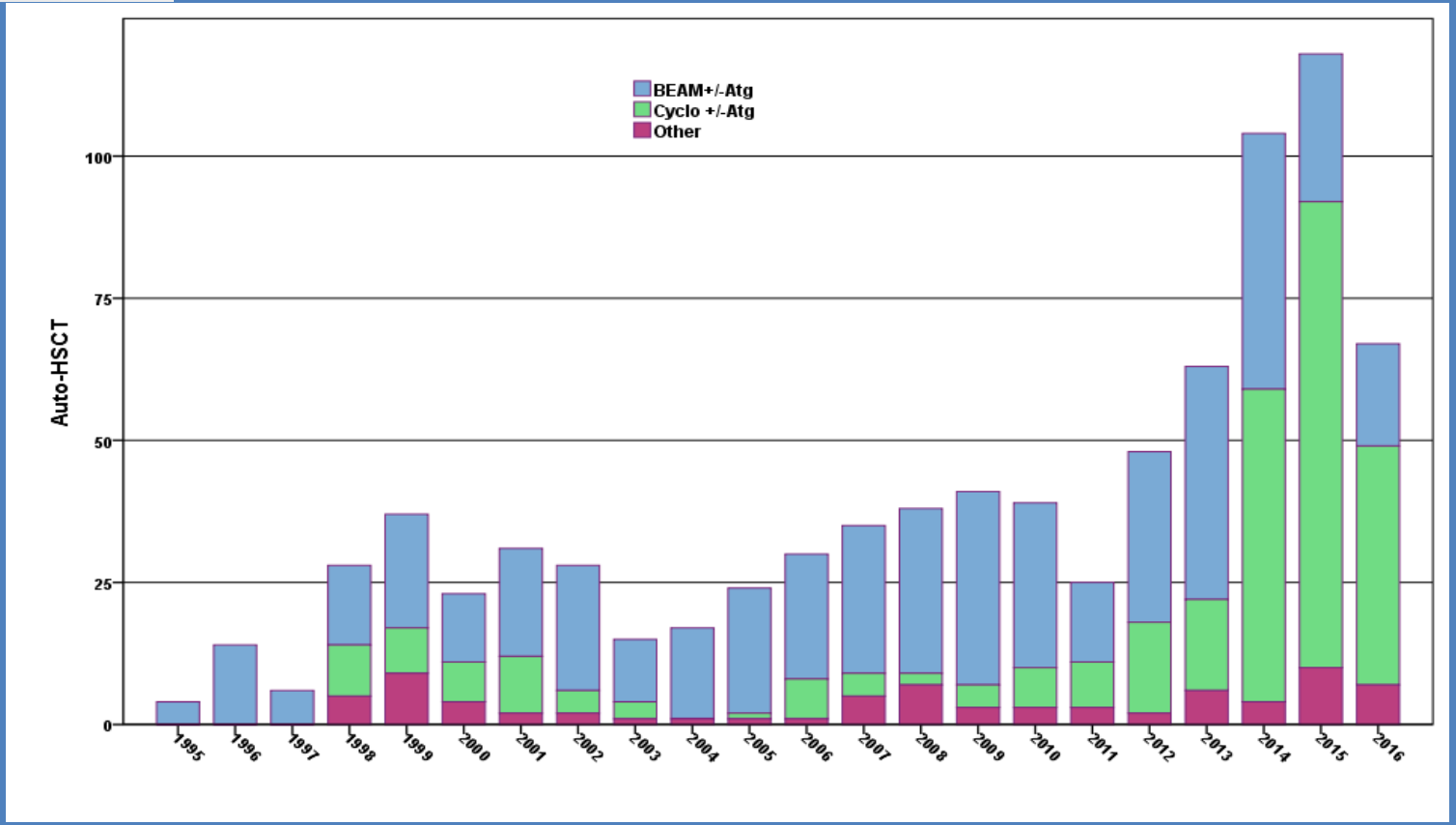
MS EBMT Registry
Conditioning regimen
1995 – 2015 (n=836) November 2016



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Still in the relapsing remitting phase of the disease or progressive phase (for a short time period), with clinical (relapses) and MR activity

Younger than 45 years of age with a disease duration no longer than 10 years

Score less than 6 at EDSS evaluation or with a higher EDSS if the score was reached within a short period of time (months) and the patient has active disease (clinical and MRI)

Failure of at least one first line and one second line therapy or one high efficacy approved DMT

- Lack of significant comorbidities
- Absence of relevant cognitive disturbances

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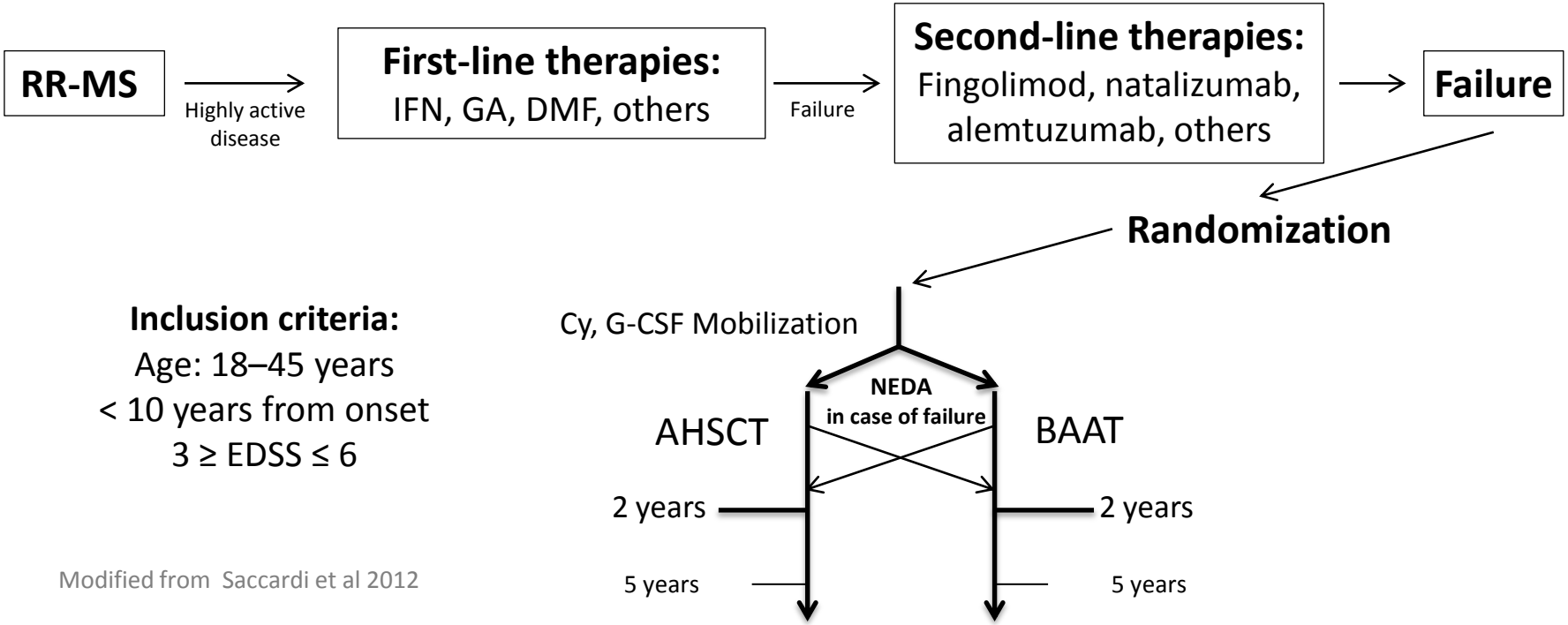
AHSCT: a prospective, randomized, controlled trial outline



Inclusion criteria:
Age: 18–45 years
< 10 years from onset
3 ≥ EDSS ≤ 6

Modified from Saccardi et al 2012

Saccardi R, et al. Mult Scler 2012;18:825–34.

Evidence from bone marrow transplantation

Gianluigi Mancardi

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Ospedale Policlinico San Martino, University of Genova, Italy

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