Effectiveness of autologous haematopoietic stem cell transplant in comparison with anti-CD20 therapies in relapsing-remitting MS

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Introduction

- anti-CD20 monoclonal antibodies are amongst the most potent disease modifying therapies for multiple sclerosis
- autologous hematopoietic stem cell transplantation (AHSCT) is associated with significant immune suppression or myeloablation, followed by immune reconstitution
- our previous comparison of AHSCT with ocrelizumab was not sufficiently powered to yield conclusive results

Aim

- to compare the effectiveness of AHSCT with ocrelizumab or rituximab in relapsing-remitting MS

Methods

Data source

- 7 AHSCT MS centres in Ottawa, Uppsala, Sheffield, Bergen, Prague, Sydney, Melbourne [RESCUE-MS]
- the international MSBase registry

Inclusion criteria

- relapsing-remitting MS
- commencing AHSCT, ocrelizumab or rituximab
- followed for ≥2 months before and ≥3 months after commencing study therapy

Outcomes

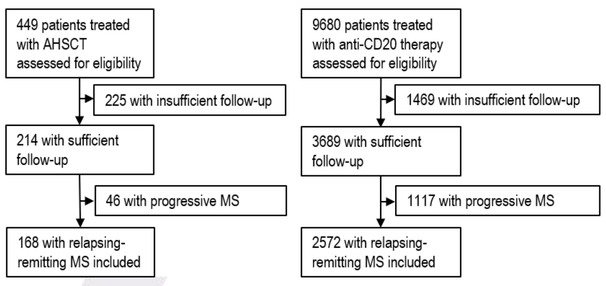
- annualized relapse rate (ARR)
- 6-month confirmed disability worsening
- 6-month confirmed disability improvement

Statistical methods

- Indication bias was controlled with 1:10 variable propensity score-matching on: sex, age, MS duration, disability (EDSS), relapse rate during the prior 12 and 24 months, prior MS therapy, geographic region.
- Data were analysed using 'as-treated' paradigm (censoring at treatment cessation).
- Inferential statistics: negative binomial models (ARR) and Cox proportional hazards models (disability worsening, disability improvement) weighted for matching ratio.

Results

Patient disposition



Classification of AHSCT treatment protocols

	High intensity (myeloablative)	Intermediate intensity (myeloablative)	Low intensity (lymphoablative)
stem cell mobilisation	G-CSF +/- ATG	G-CSF +/- ATG	G-CSF +/- methylprednisolone
leukoapheresis +/- CD34+ graft selection	+CD34+ selection	+/- CD34+ selection	usually no CD34+ selection
conditioning	total body irradiation or busulfan + cyclophosphamide	BEAM – carmustine, cytosine-arabinoside, etoposide, melphalan	cyclophosphamide 100 mg/kg or 200 mg/m2
post-conditioning therapy (typically administere on days 0-14)	+/- ATG	ATG	ATG Rituximab

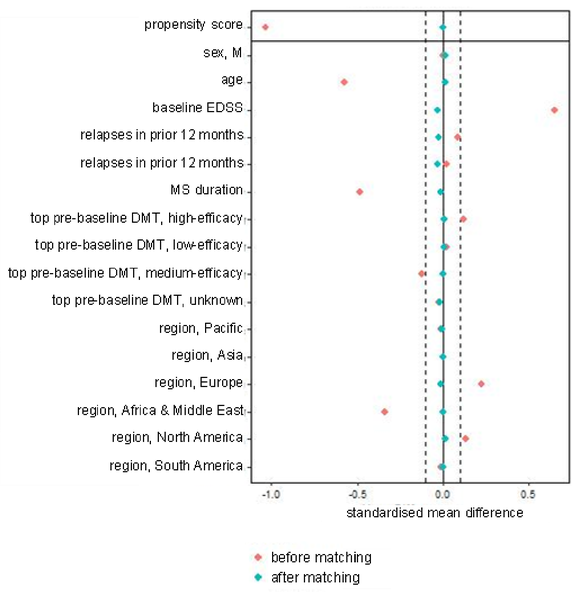
Representation of anti-CD20 therapies

ocrelizumab: 752 matched patients
rituximab: 107 matched patients

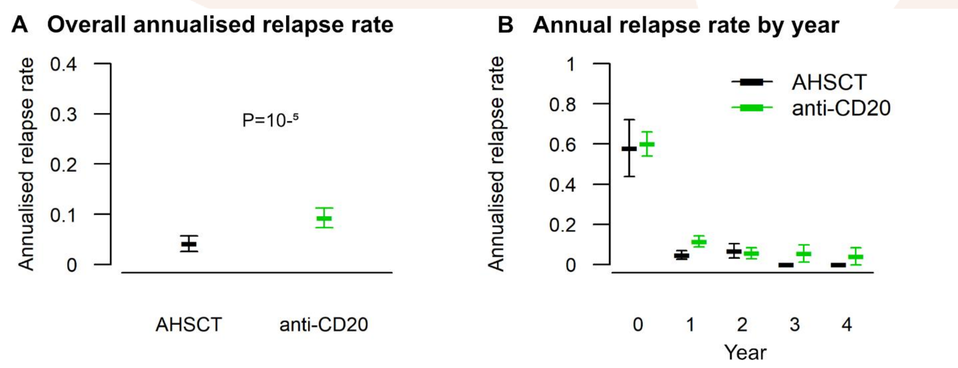
Patient characteristics)

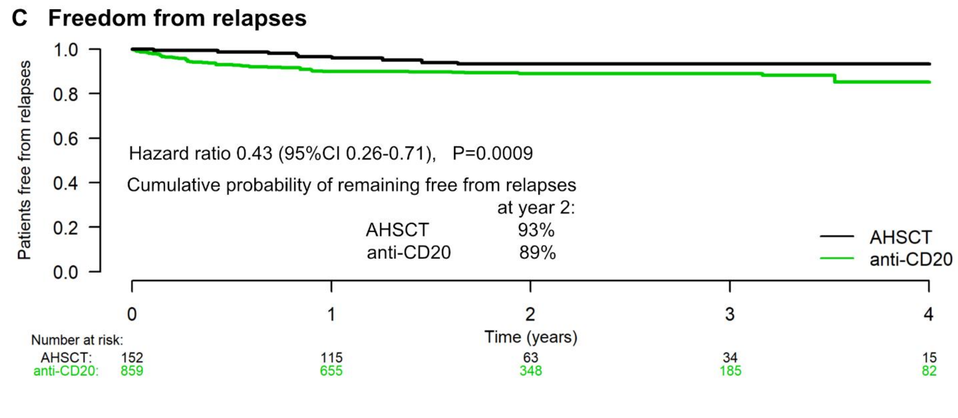
	after matching		
	AHSCT	anti-CD20 therapy	d
patients matched	152	859	
sex, M (%)	47 (30.9)	254 (29.6)	0.03
age (mean (SD))	36.3 (8.8)	36.1 (9.4)	0.02
Multiple sclerosis duration, y (mean (SD))	8.11 (5.26)	8.16 (6.40)	0.01
relapses in prior 12 months (mean (SD))	0.58 (0.90)	0.60 (0.90)	0.02
relapses in prior 24 months (mean (SD))	0.79 (1.18)	0.82 (1.11)	0.03
baseline EDSS (mean (SD))	3.77 (1.59)	3.81 (2.01)	0.03
patients with pre-baseline EDSS worsening (%)	25 (16.4)	165 (19.2)	0.12
top pre-baseline DMT (%)			0.06
low-efficacy	28 (18.4)	152 (17.7)	
medium-efficacy	32 (21.1)	179 (20.8)	
high-efficacy	71 (46.7)	391 (45.5)	
unknown	21 (13.8)	136 (15.9)	
region (%)			0.04
Asia-Pacific	51 (33.6)	292 (34.0)	
Europe	73 (48.0)	421 (49.0)	
North America	28 (18.4)	146 (17.0)	
Africa and Middle East	0 (0.0)	0 (0.0)	
South America	0 (0.0)	0 (0.0)	
study follow-up, y (mean (SD))	4.03 (2.61)	2.37 (1.59)	0.77
year of baseline (median [IQR])	2016 [2014, 2017]	2019 [2018, 2020]	1.25
brain MRI: T2 lesion number (%)			0.52
0	0 (0.0)	11 (1.3)	
1-2	1 (0.7)	11 (1.3)	
3-8	1 (0.7)	76 (8.8)	
9+	49 (32.2)	350 (40.7)	
unknown	101 (66.4)	412 (47.9)	
visit interval, months (mean (SD))	8.21 (3.70)	6.49 (5.14)	0.38

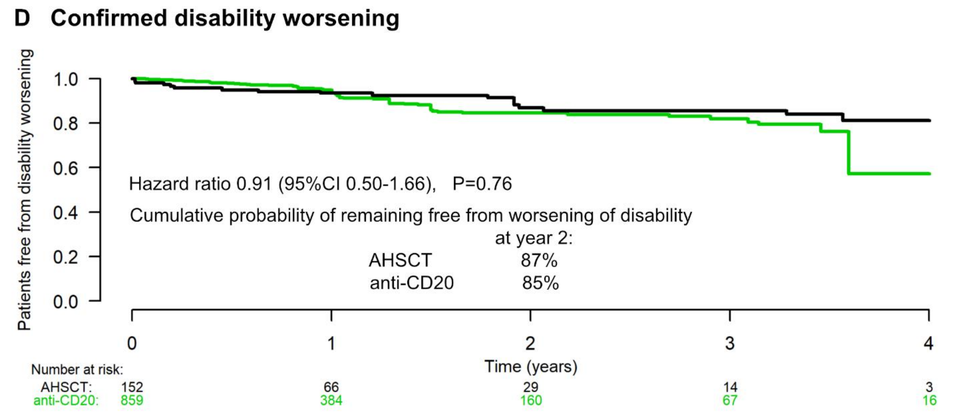
Love plot of group balance

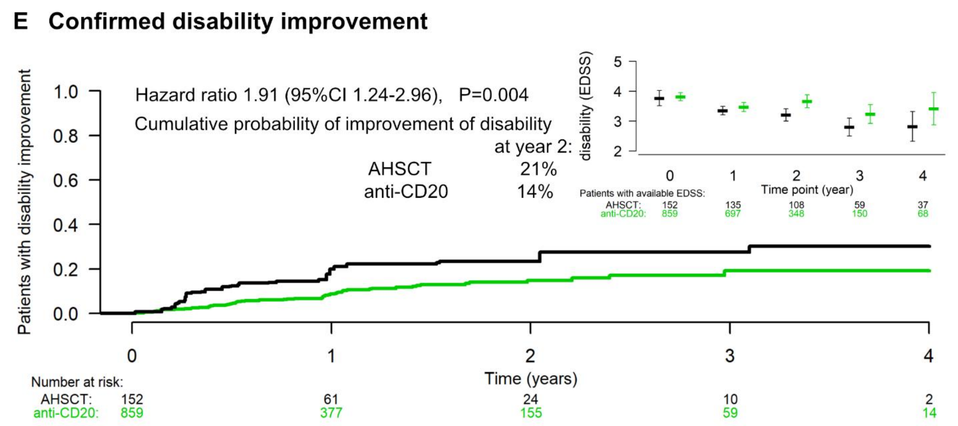


Comparisons of clinical outcomes in matched groups









Safety of AHSCT

Safety profile of AHSCT among the 152 matched patients:
- febrile neutropenia during mobilization: 33 patients
- serum sickness: 17 patients
- ICU admission: 9 patients
- treatment-related adverse events after discharge post-AHSCT: 70 in 50 patients (mainly of infections)
- treatment-related deaths: 0

Conclusion

In highly active relapsing–remitting MS:

- Both AHSCT and anti-CD20 therapy are associated with a substantial reduction of relapse risk.
- The ability of AHSCT to prevent relapses is mildly superior to anti-CD20 therapy.
- AHSCT is superior to anti-CD20 therapy at allowing recovery from previously accrued disability.
- No treatment-related mortality was reported among the 152 matched AHSCT-treated patients. Safety profile of AHSCT was consistent with previous clinical experience.
- This study is limited by the small size of the matched groups and missing saety information in the anti-CD20 groups. The available on-treatment follow-up does not allow comparisons of long-term treatment effects.
- Randomised trials comparing AHSCT with composite groups of alemtuzumab, natalizumab, anti-CD20 therapies and cladribine (RAM-MS, STAR-MS, BEAT-MS, NET-MS) are underway.

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