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Aggressiv MS

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Akademiska sjukhuset

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Forskningsfinansiärer

- ALF
- Akademiska Sjukhusets utvecklingsfond
- Svenska Sällskapet för Medicinsk Forskning
- Svenska Läkaresällskapet

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Introduktion

- Patienter med aggressiv MS har ökad risk för att snabbt utveckla funktionsnedsättning
- Traditionella behandlingsparadigm kan inte tillämpas
- Aggressiv sjukdom motiverar aggressiv behandling

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RESEARCH PAPER

Characterising aggressive multiple sclerosis

Suresh Menon,[1] Afsaneh Shirani,[2] Yinshan Zhao,[3] Joel Oger,[2] Anthony Traboulsee,[1] Mark S Freedman,[4] Helen Tremlett[2]

Patienter med MS från British Columbia, Kanada med prospektivt insamlade data (1980–2009)

- EDSS 6 eller mer inom 5 år från sjukdomsdebut = 5,5%
- EDSS 6 eller mer vid 40 års ålder = 14%
- SPMS < 3 år från debuten = 4,0%

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Menon et al. JNNP 2013.

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Skov

Definition

Ett MS-skov definieras vanligen som nya eller förvärrade fokala bortfalls- eller retningssymptom som pågått i minst 24 timmar i avsaknad av feber eller infektion.

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Skovbehandling

Högdosssteroider

Corticosteroids or ACTH versus placebo for acute exacerbations in multiple sclerosis					
Patient or population: multiple sclerosis patients with acute exacerbations **Settings:** hospital setting **Intervention:** corticosteroids or ACTH versus placebo					
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of participants (studies)**	**Quality of the evidence (GRADE)** **Comments**
	Assumed risk	**Corresponding risk**			
	Control	**Corticosteroids or ACTH versus placebo**			
Worse or unimproved within 5 weeks from randomisation Follow-up: 5 weeks	**Study population**		**OR 0.37** (0.24 to 0.57)	330 (5 studies)	⊕⊕⊕○ **moderate**
	61 per 100	**36 per 100** (27 to 47)			
	Medium-risk population				
	75 per 100	**53 per 100** (42 to 63)			
Mean disability (EDSS) score-at 1 week after randomisation Follow-up: 1 week		Treated participants' EDSS was **1.47 lower** (2.25 to 0.69 lower) than placebo	Mean difference	62 (2 studies)	⊕⊕⊕○ **moderate**[1]
Participants with new exacerbations during follow-up-at 6 months Follow-up: 6 months	**Study population**		**OR 1.72** (0.57 to 5.19)	51 (1 study)	⊕○○○ **very low**[2,3]

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Filippini et al. Cochrane Database Syst Rev 2000.

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Skovbehandling

Plasmaferes

Table 3. Primary Analysis of Efficacy

Group Treatment Assignment	Phase I	Phase II	*z* Score	n	Mean[a] *z* Score
Active treatment first	S	—	+1	5	
	F	S	−1	0	0.4 ± 0.5
	F	F	0	6	
Sham treatment first	S	—	+1	1	
	F	S	−1	3	−0.2 ± 0.6
	F	F	0	7	

- patienter med koma, afasi, uttalade pareser
- 7 plasmafereser under 14 dagar

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Weinshenker et al. Ann Neurol 1999.

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Plasmaferes

Biverkningar

TABLE II. Total Complications

Total complications	873
Total number of treatments with complications	614
Fever	133 (7.7%)
Urticaria	128 (7.4%)
Hypocalcemic symptoms	126 (7.3%)
Pruritis	101 (5.8%)
Tachycardia	96 (5.6%)
Mild hypotension (SBP < 95 mmHg)	96 (5.6%)
Nausea	56 (3.2%)
Vomiting	47 (2.7%)
Dizziness	23 (1.3%)
Severe hypotension (SBP < 85 mmHg)	22 (1.3%)
Exit site bleeding	21 (1.2%)
Exit site infection	9 (0.5%)
Headache	6 (0.3%)
Chest pain	6 (0.3%)
Dyspnea	4 (0.2%)
Back pain	3 (0.2%)
Abdominal pain	2 (0.1%)
Anxiety	2 (0.1%)
Arrhythmia	2 (0.1%)
Leg cramps	2 (0.1%)
Pharyngitis	2 (0.1%)
Epistaxis	1 (0.1%)
Hemoptysis	1 (0.1%)

TABLE III. Comparison of Complications Using Albumin/NS as Replacement Fluid Compared with FFP

Complication	Albumin/NS	FFP	*P* value
Fever	69 (7.1%)	64 (8.5%)	NS
Urticaria	2 (0.2%)	126 (16.8%)	<0.0001
Hypocalcemic symptoms	80 (8.2%)	46 (6.1%)	NS
Pruritis	3 (0.3%)	98 (13.0%)	<0.0001
Tachycardia	43 (4.4%)	53 (7.1%)	NS
Mild hypotension	79 (8.1%)	17 (2.3%)	<0.01
Nausea	46 (4.7%)	10 (1.3%)	<0.01
Vomiting	40 (4.1%)	7 (0.9%)	<0.01
Dizziness	21 (2.2%)	2 (0.3%)	<0.01
Severe hypotension	21 (2.2%)	1 (0.1%)	<0.01
Exit site bleeding	10 (1.0%)	11 (1.5%)	NS
Exit site infection	3 (0.3%)	6 (0.8%)	NS
Headache	4 (0.4%)	2 (0.3%)	NS
Chest pain	1 (0.1%)	5 (0.7%)	NS
Dyspnea	2 (0.2%)	2 (0.3%)	NS
Back pain	1 (0.1%)	2 (0.3%)	NS
Abdominal pain	1 (0.1%)	1 (0.1%)	NS
Anxiety	2 (0.2%)	0	NS
Arrhythmia	1 (0.2%)	1 (0.1%)	NS
Leg cramps	2 (0.2%)	0	NS
Pharyngitis	2 (0.2%)	0	NS
Epistaxis	1 (0.1%)	0	NS
Hemoptysis	1 (0.1%)	0	NS
Total complications	435	454	
Mean complication rate/treatment	0.45	0.61	<0.0001
No. of treatments with complication	295	319	<0.0001

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Shemin et al. Journal of Clinical Apheresis 2007.

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MS-sällskapet rekommenderar

- Vid skov av måttlig eller allvarlig svårighetsgrad rekommenderas i.v. Methylprednisolon 1000 mg 3 dagar i följd, (eller peroral motsvarighet).
- Plasmaferes kan övervägas vid svåra skov då man bedömer att effekten av metylprednisolon är otillräcklig.

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Aggressiv MS

En praktisk definition

- EDSS 4 inom fem år från debut
- Multipla skov (två eller fler) med inkomplett återhämtning under det senaste året
- Mer än två MR-undersökningar med sjukdomsaktivitet trots behandling
- Uteblivet terapisvar efter behandling med bromsmedicin ett år

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Rush et al. Nature Reviews Neurology 2015.

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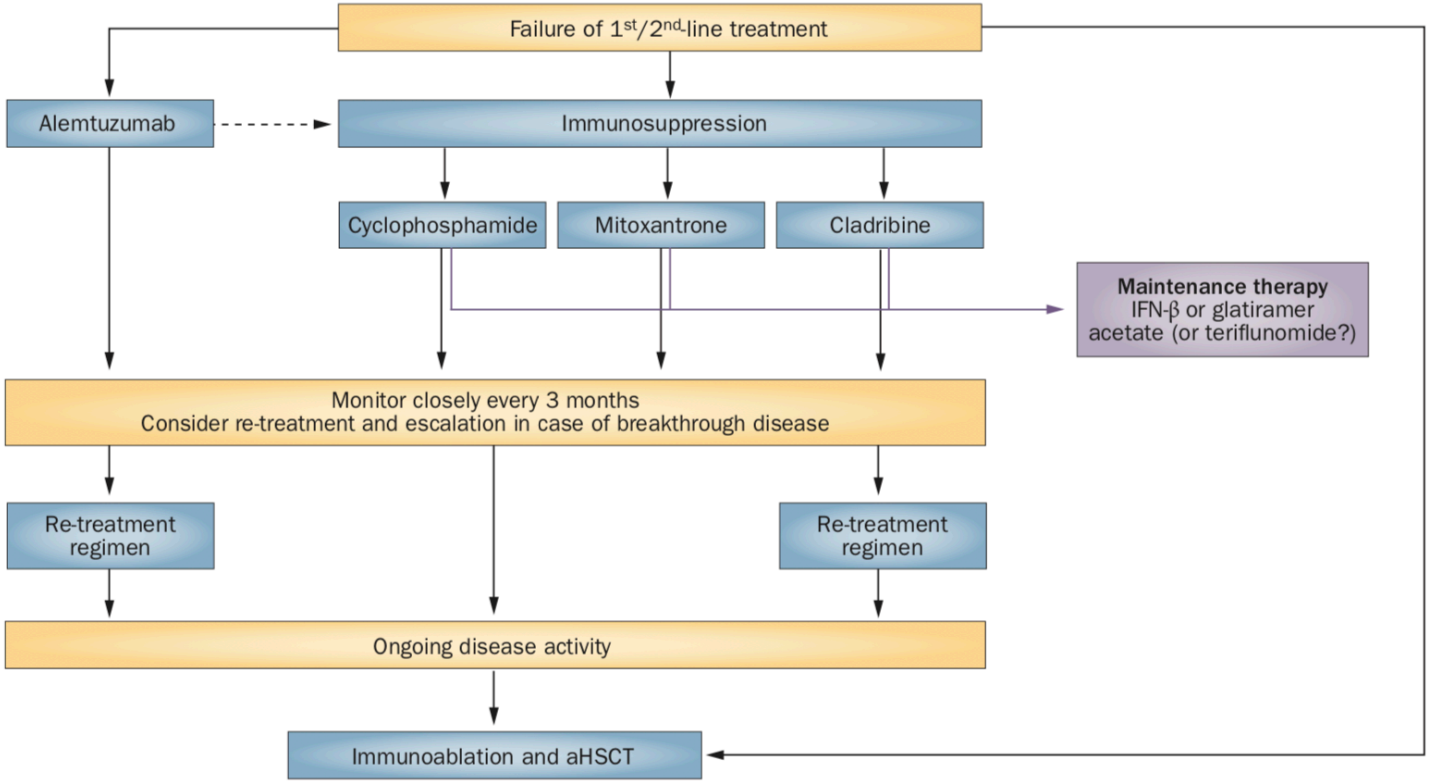

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Rush et al. Nature Reviews Neurology 2015.

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Rituximab

Efficacy of rituximab in refractory RRMS

- RRMS
- sjukdomsaktivitet trots behandling med fingolimod, natalizumab, mitoxantrone, cyklofosfamid eller alemtuzumab)
- en eller flera kontrastladdningar och/eller nya T2 lesioner vid MR undersökning under de senaste 12 månaderna
- behandling med rituximab

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Durozard et al. Multiple Sclerosis Journal 2018.

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Rituximab

Efficacy of rituximab in refractory RRMS

Age (years)	37.5 (19–63)
Sex ratio (F/M)	3.17 (38/12)
Follow-up duration (years)	
Before rituximab	10.1 (1.6–27.4)
After rituximab	1.1 (0.4–6.4)
EDSS at rituximab initiation	4.5 (0–7)
Annualized relapse rate	
Since the onset of the disease	0.8 (0.3–3.5)
During second-line therapy	0.6 (0–3.8)
Last year before rituximab	1 (0–5)
Last treatment	
Natalizumab	4
Fingolimod	43
Mitoxantrone	3

EDSS: Expanded Disability Status Scale.

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Durozard et al. Multiple Sclerosis Journal 2018.

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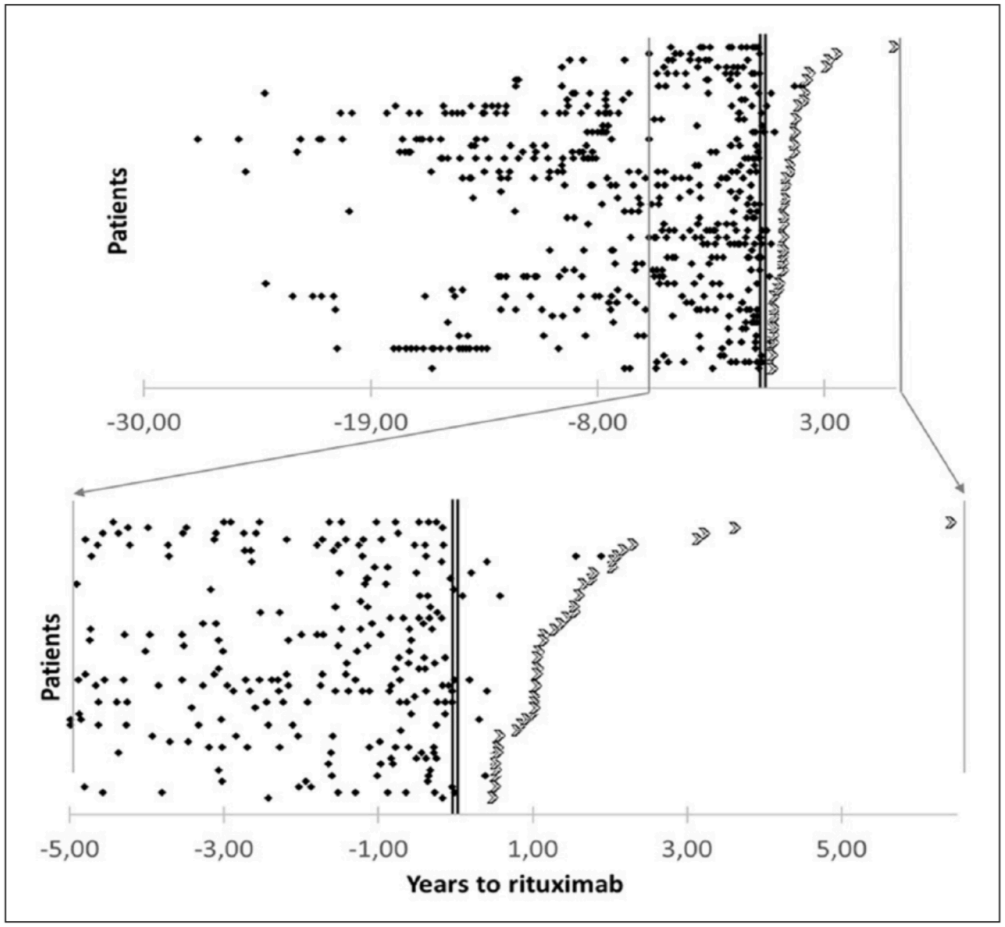
Rituximab

Efficacy of rituximab in refractory RRMS



Durozard et al. Multiple Sclerosis Journal 2018.

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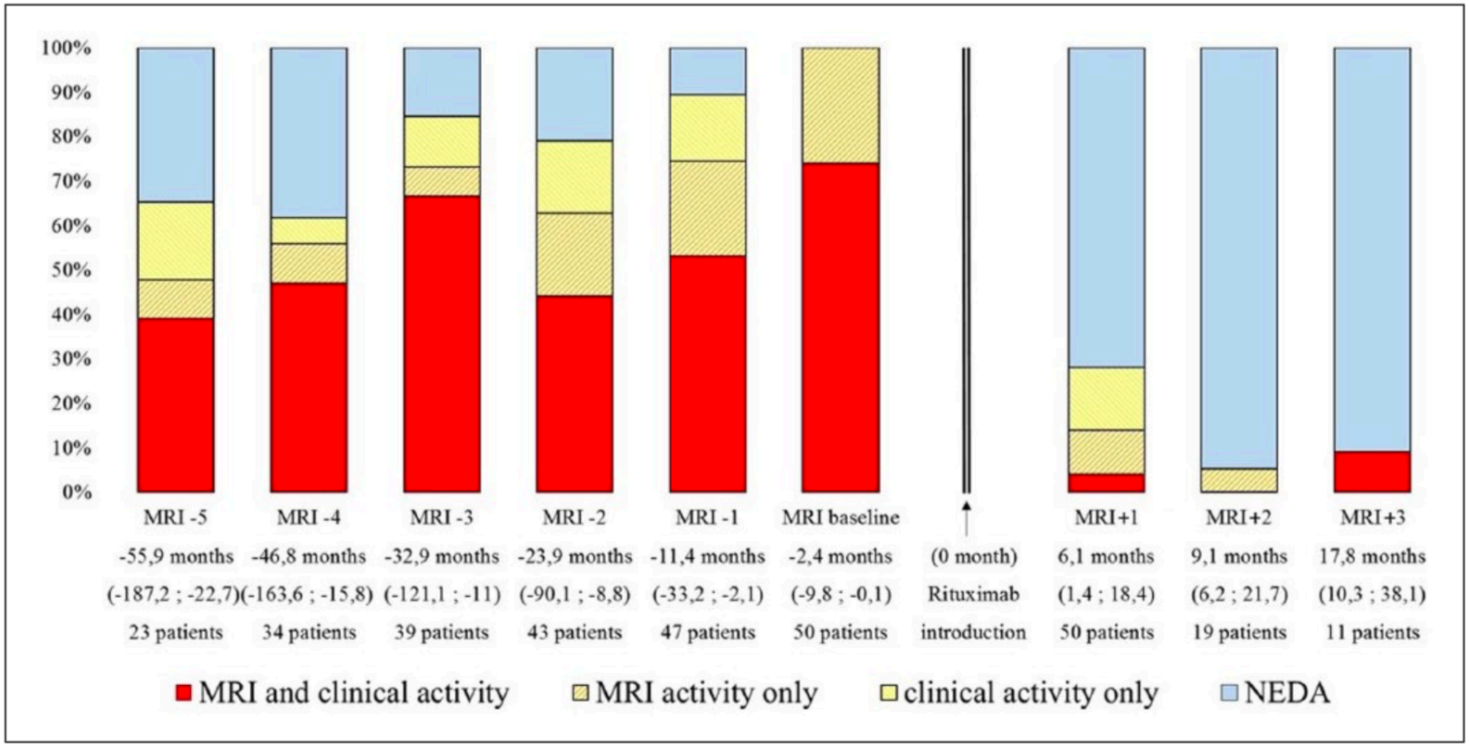
Rituximab

Efficacy of rituximab in refractory RRMS



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Durozard et al. Multiple Sclerosis Journal 2018.

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Rituximab

Efficacy of rituximab in refractory RRMS

Adverse effect	Number
Death	0
PML	0
Severity of adverse effect	
Grade 1	7
Grade 2	6
Grade 3	3
Type of adverse effect	
Infectious	10
Hematological	2
Neoplastic	0
Obstetric	1
Reactions to infusion	3
Discontinuation of treatment	2
Pregnancy	1
Adverse effect	1

PML: progressive multifocal leukoencephalopathy.

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Durozard et al. Multiple Sclerosis Journal 2018.

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Rituximab

Efficacy of rituximab in refractory RRMS

- AAR minskade från 0,8 till 0,18
- EDSS förbättrades med 0,5 poäng (från 4,5 till 4)

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Alemtuzumab

Campath in patients with aggressive RRMS

Characteristic	
n	39
female/male	24/15
age	34 (18-58)
disease duration	3 (0-6)
AAR	2.5
EDSS	4.5 (0-8.5)
previous DMD	7/32

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Hirst et al. Journal of Neurology 2008.

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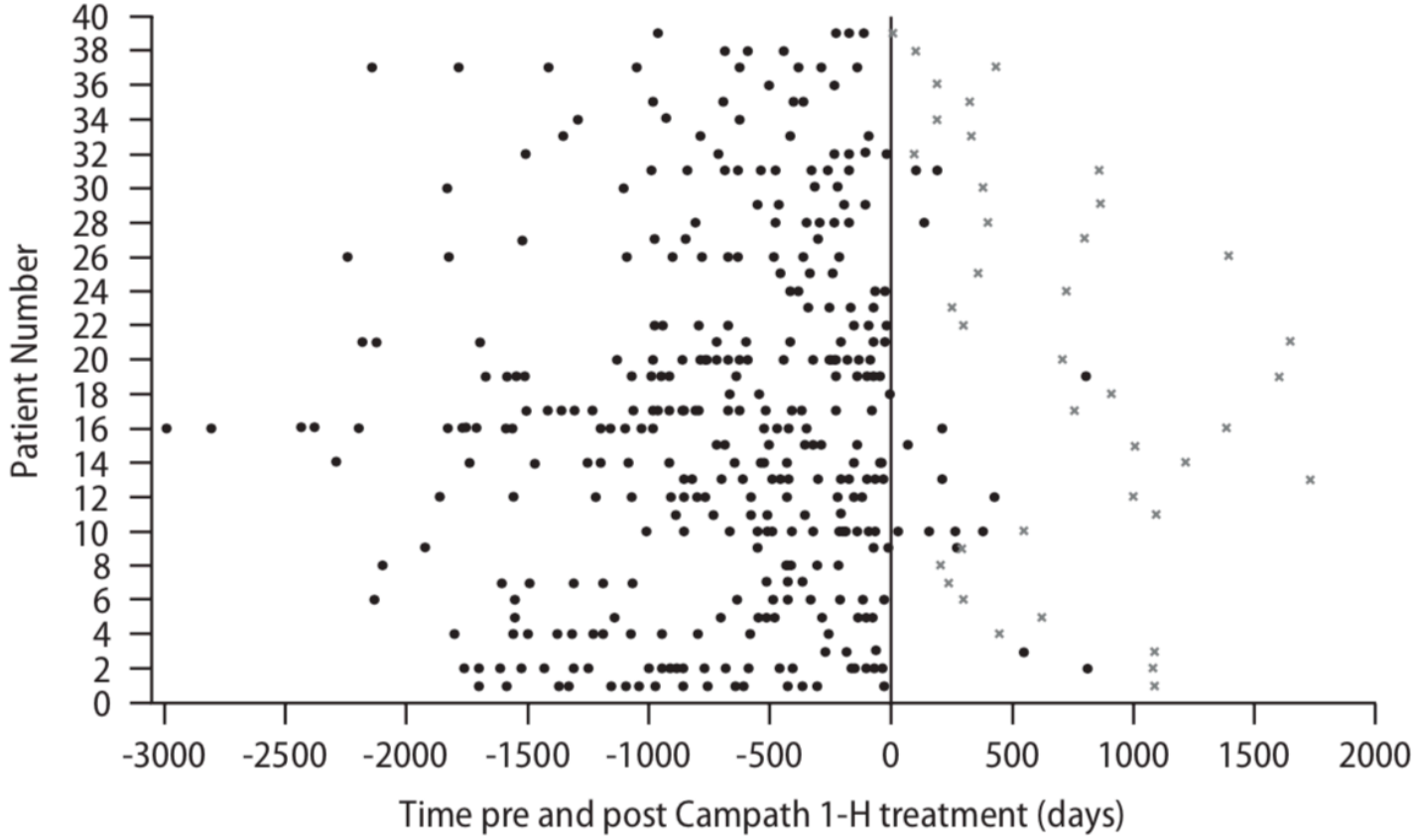
Alemtuzumab

Campath in patients with aggressive RRMS



Hirst et al. Journal of Neurology 2008.

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Alemtuzumab

Campath in patients with aggressive RRMS

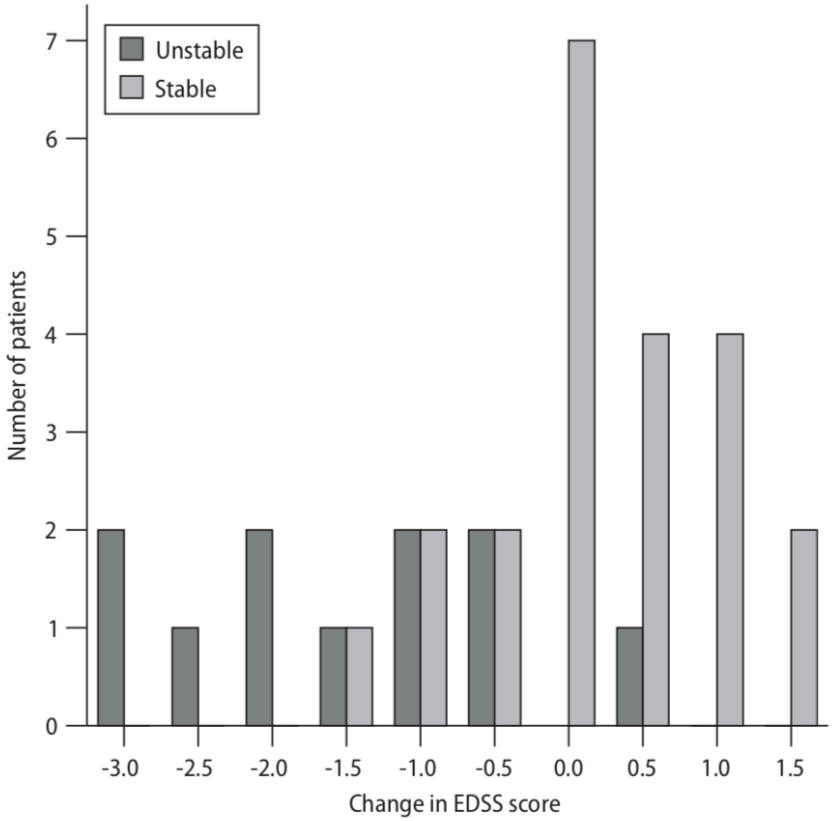

Fig. 2 Graph of change in EDSS scores over entire follow-up for those with stable and unstable baseline scores

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Hirst et al. Journal of Neurology 2008.

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Alemtuzumab

Campath in patients with aggressive RRMS

- AAR minskade från 2,44 till 0,30 (jfr Care-MS II 0,26)
- EDSS ökade med 0,2 (stabila patienter) resp minskade med 1,5 (patienter med skov)

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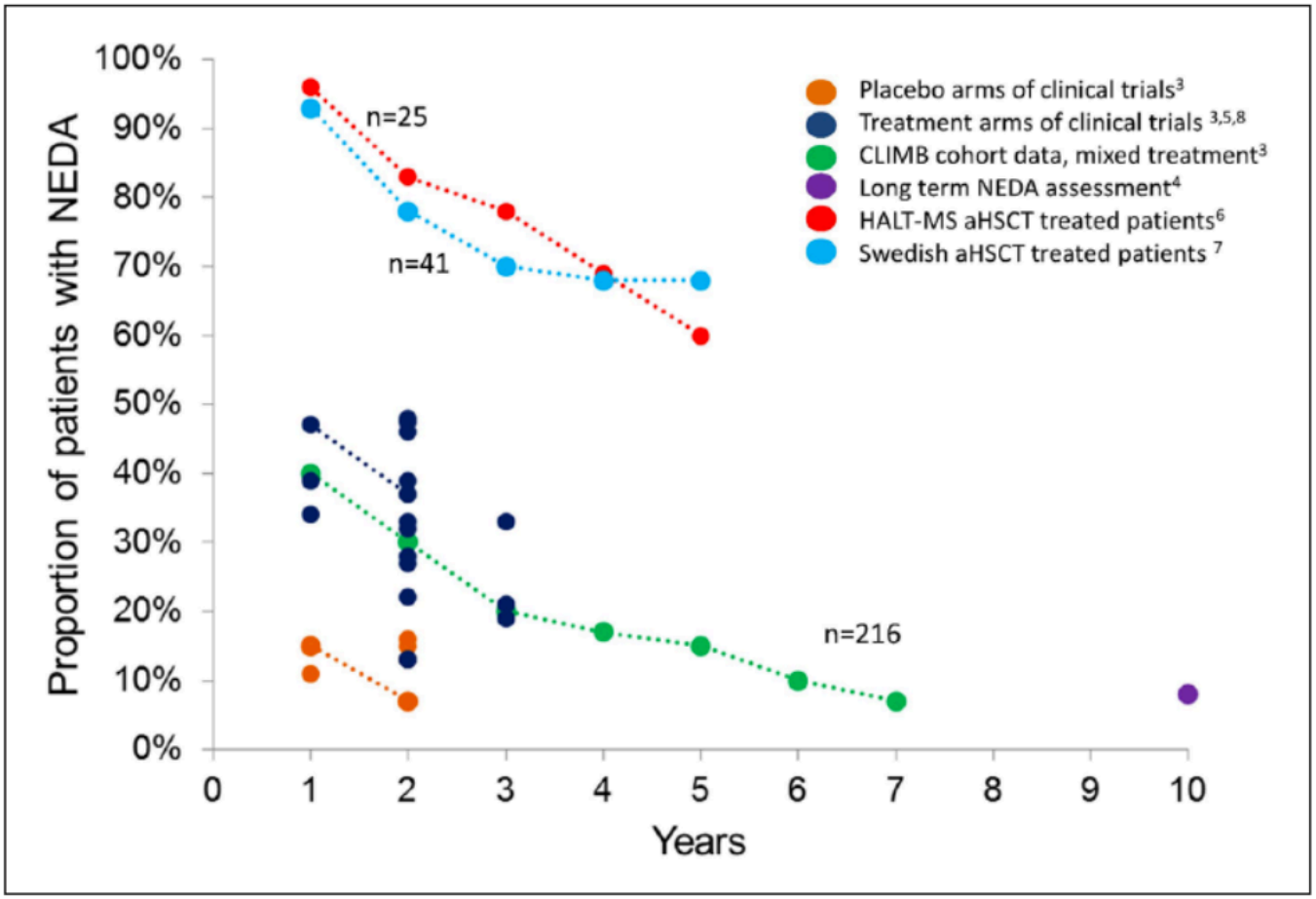
No Evidence of Disease Activity



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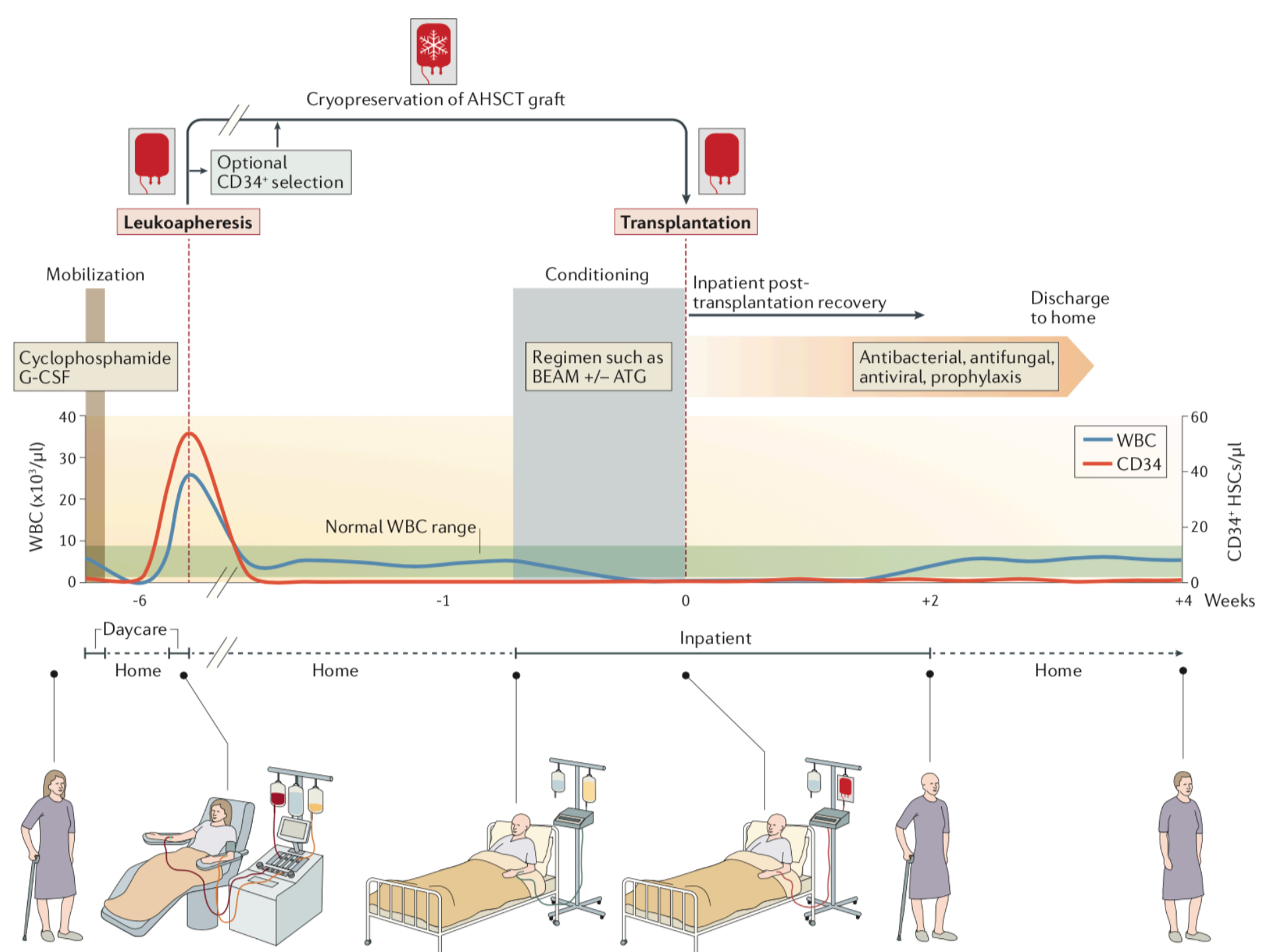
Cryopreservation of AHSCT graft
Optional CD34+ selection
Leukoapheresis
Transplantation
Mobilization
Conditioning
Inpatient post-transplantation recovery
Discharge to home
Cyclophosphamide G-CSF
Regimen such as BEAM +/– ATG
Antibacterial, antifungal, antiviral, prophylaxis
WBC (x10³/µl)
CD34+ HSCs/µl
WBC
CD34
Normal WBC range
40
30
20
10
0
60
40
20
0
-6
-1
0
+2
+4
Weeks
Daycare
Home
Home
Inpatient
Home

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MIST

ClinicalTrials.gov Id: NCT00273364

- internationell multicenterstudie med deltagare från USA, Storbritannien, Brasilien och Sverige
- randomiserad kontrollerad prövning av blodstamcellstransplantation jämfört med bästa alternativa behandling
- studien startade 2006
- sista patienten inkluderades hösten 2016

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MIST

Resultat (AAN 2018)

Abstract

Objective: To determine if non-myeloablative HSCT is superior to continuing DMD therapy.

Background: We previously reported that non-myeloablative HSCT can be performed safely and is accompanied by long-term improvement in neurological disability in patients with RRMS.

Design/Methods: Patients on stable DMDs with > 2 relapses within the prior 12 months were randomized (1:1) to treatment with cyclophosphamide and rabbit anti-thymocyte globulin followed by hematopoietic stem cell infusion or to a control arm with continued treatment with the most appropriate DMD as judged by their treating neurologist. The primary endpoint was treatment failure defined as an increase in EDSS, assessed by a blinded evaluating neurologist, by at least 1.0 point sustained for at least 6 months. Patients on DMDs who failed after at least 1 year of treatment were allowed to crossover to HSCT.

Results: 110 patients were randomized, 55 to each arm. Three HSCT patients were withdrawn: two for failing enrollment criteria, one for recurrent infections occurring before transplant. Five control patients were withdrawn after soliciting transplants at other centers. No deaths occurred and no CTC grade 4 non-hematopoietic toxicities occurred in the transplant arm. DMDs (number of patients) used in the control arm were: natalizumab (22), dimethyl fumerate (18), fingolimod (13) interferons (10), glatiramer acetate (8), and mitoxantrone (5). Other immune drugs used in the control arm were corticosteroids (39), cyclophosphamide (2) and rituximab (2). With a mean follow up of 3 years (range 1 to 5 years), treatment failure was 60% (30 of 50) for control arm and 6% (3 of 52) for HSCT ($P < 0.001$). During the first year after HSCT, mean EDSS improved from 3.5 to 2.4 while it worsened from 3.3 to 3.9 in the control arm ($P<0.001$).

Conclusions: HSCT for RRMS with > 2 relapses a year was superior to continued DMDs.

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Tio patienter

Tio års uppföljning

Characteristic	
n	10
female/male	7/3
age	27 (9-33)
disease duration	2 (0.5-9.5)
AAR	8 (3-12)
EDSS	6.5 (2-8.5)
enhancing lesions	11 (0-40)
previous DMD	2 (0-3)

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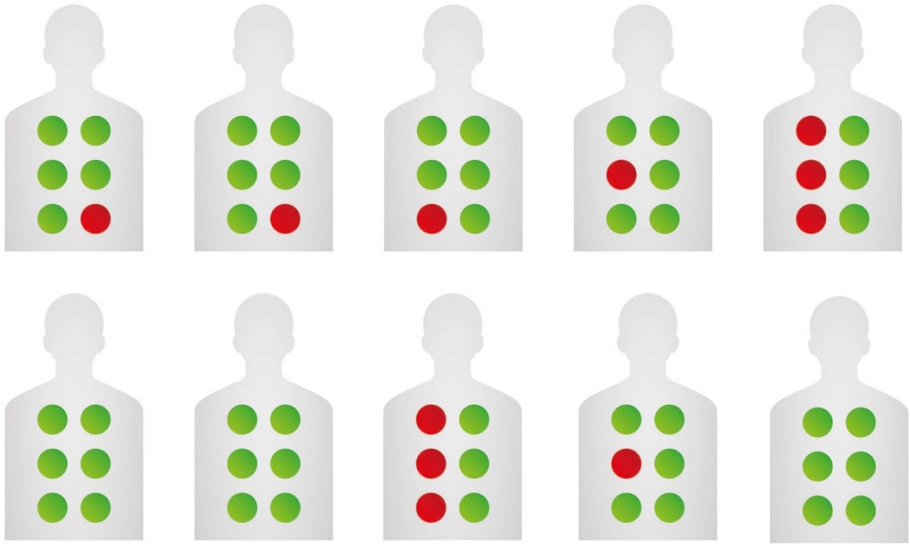
Tio patienter

Tio års uppföljning



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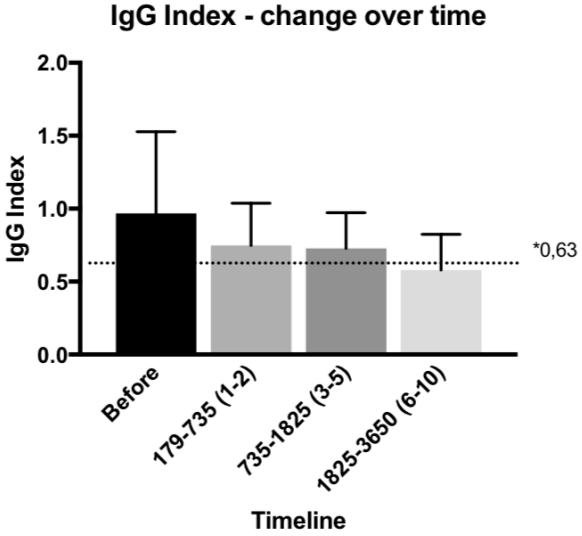
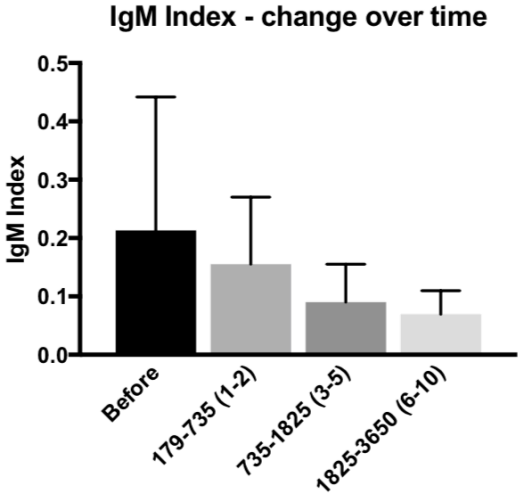


n Baseline = 54
n 179-735 = 40
n 735 - 1825 = 17
n 1825 - 3650 = 13



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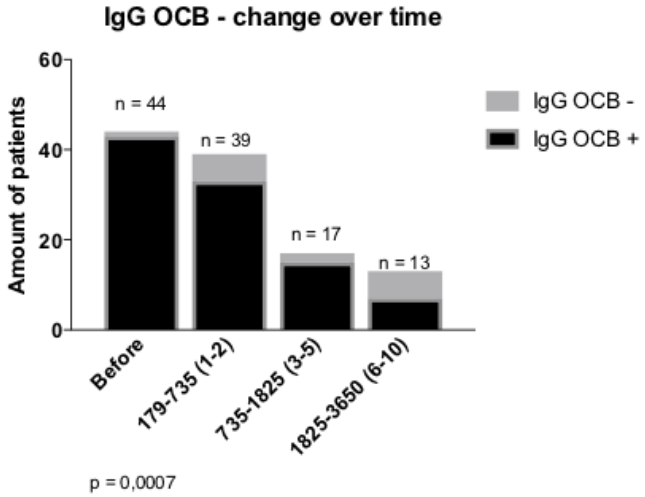
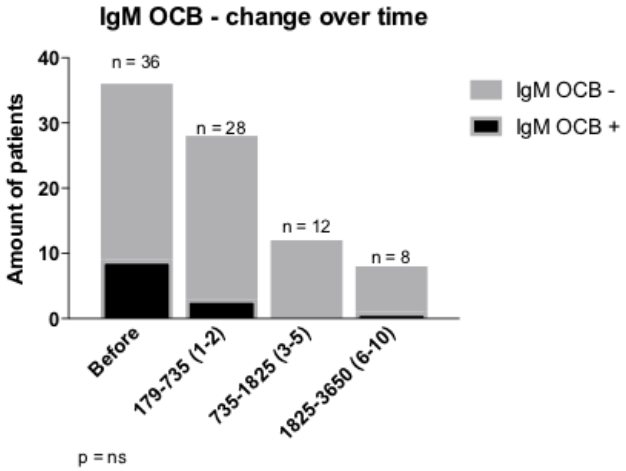
n 179-735 = 28
n 735 - 1825 = 12
n 1825 - 3650 = 8



p = 0,0007



p = ns

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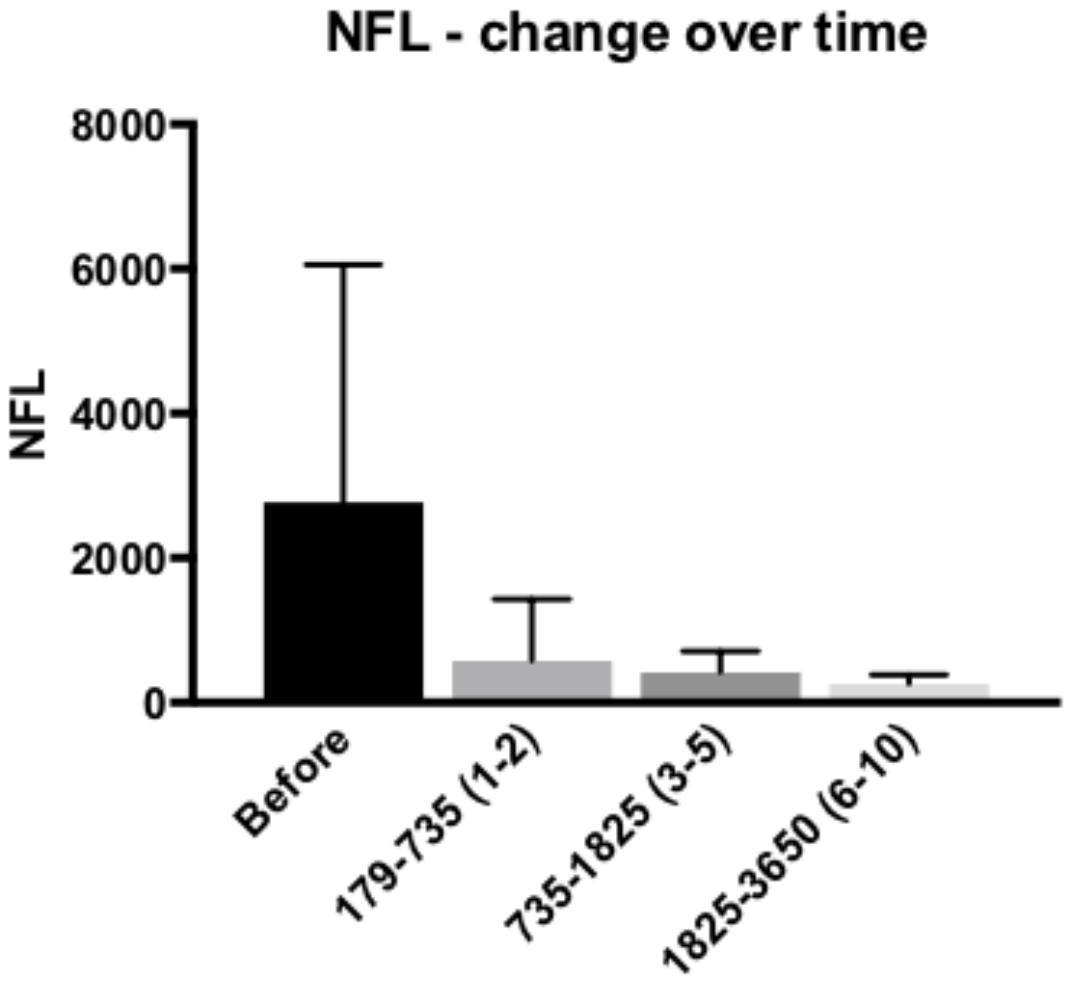

n Baseline = 34
n 179-735 = 33
n 735 - 1825 = 15
n 1825 - 3650 = 13

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NATIONELLA RIKTLINJER FÖR VÅRD VID MS OCH PARKINSONS SJUKDOM SOCIALSTYRELSEN

Rekommendationer

Hälso- och sjukvården bör

- erbjuda behandling med natalizumab till personer med aktiv skovvis MS utan antikroppar mot JC-virus *(prioritet 1)*
- erbjuda personer med aktiv skovvis MS behandling med fingolimod, alemtuzumab eller hematopoetisk stamcellstransplantation *(prioritet 3)*.

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