Supplemental material

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Detailed description of treatment episodes

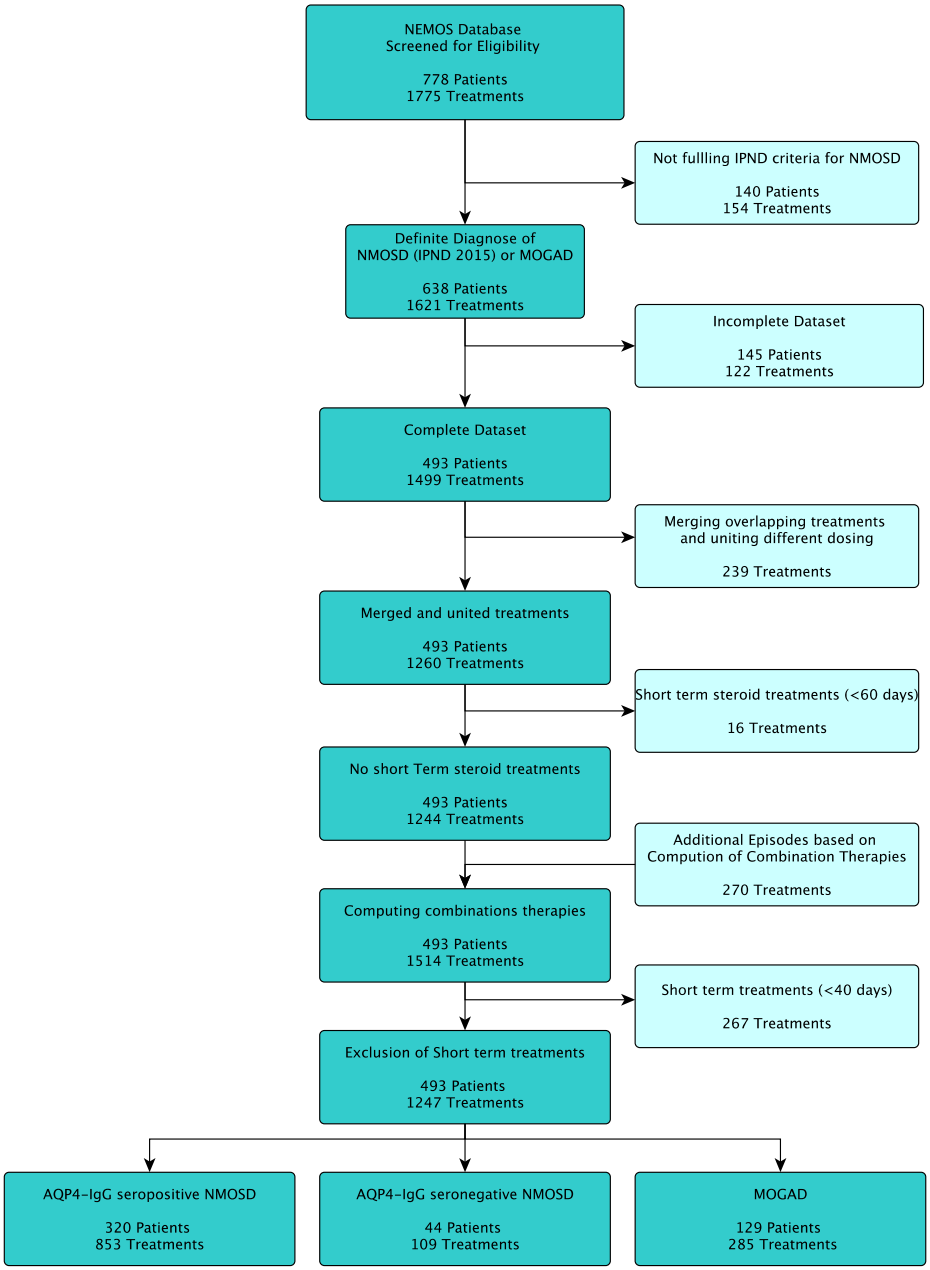
To account for persisting pharmaceutical effects after the last dose, we defined persisting effects after the last dose in concordance with our previous analysis[1] as follows: 365 days for alemtuzumab; 180 days for rituximab (RTX) and other intravenous anti-CD-20 treatment; 180 days for inebilizumab, 90 days for mitoxantrone, intrathecal steroids and teriflunomide; 30 days for azathioprine (AZA), cyclophosphamide (CYC), ciclosporin A, dimethyl fumarate (DMF), fingolimod, mycophenolate mofetil (MMF), natalizumab, intravenous immunoglobulin (IVIG), intravenous steroids, satralizumab (STZ) and tocilizumab (TCZ); 14 days for eculizumab (ECU) and 7 days for interferon-β (IFN), glatiramer acetate (GLAT), methotrexate (MTX) and oral steroids. Multiple entries of the same treatment were merged into one treatment episode if the first dose of the second treatment was administered less than 30 days after the assumed end of effectiveness. Treatment episodes shorter than 40 days were excluded from the analysis. Untreated episodes were defined as episodes with no treatment 30 days after the initial manifestation or the assumed end of a discontinued treatment´s effectiveness. In case of overlapping treatment episodes of different treatments, based on the start and end date or the estimated efficacy period, the treatment episode was defined as a combination therapy. Based on available data and the latest recommendation regarding therapies [2], we then defined 19 categories of either monotherapy or combinations of immunotherapies.

Categories of immunotherapies

Classical Multiple Sclerosis (MS) therapeutics were summarized in one category and included three treatment episodes of alemtuzumab, six of dimethyl fumarate, three of fingolimod, 31 of glatiramer acetate, 43 of interferons, 24 of mitoxantrone, 16 of natalizumab, and three of teriflunomide.

Separate categories were selected for azathioprine and rituximab with additional oral steroids, rituximab in combination with other immunosuppressants, and eculizumab as well as satralizumab when used with other immunosuppressive therapies. Other combinations, in addition to those mentioned above, or the use of more than two agents are categorized as combination therapies. In this category, the combination of classical immunosuppressant (azathioprine, mycophenolate mofetil and methotrexate) with other substances was administered most frequently (n = 31) and 10 episodes with cyclophosphamide and other therapies were recorded. Regarding fixed categories the combination of mycophenolate mofetil and steroids (n = 8) as well as tocilizumab and steroids (n = 5) were used most frequently. Other treatment consisted of seven treatment episodes of ciclosporin A, four of hydroxychloroquine, two of regular plasma exchange, two of regular intravenous steroid treatment, one of intrathecal steroids and 17 unclassified treatment episodes.

Patient disposition (Suppl. Fig. 1)



Flow chart illustrating the selection of patients and treatment episodes for the analyses.

Characteristics of immunotherapies (Suppl. Table 1)

		AZA	AZA+STE	MS	COM.	CYC	ECU	ECU0	INE	IVIG	MTX	MMF	OTHER	RTX	RTX+STE	RTXO	STZ	STZO	STE	TCZ	NO THERAPY
PATIENTS RECEIVING TREATMENT	All, n	159	54	82	48	17	18	7	3	18	21	23	27	301	51	62	7	7	59	25	422
	AQP4-IgG seropositive NMOSD, n	98	30	48	35	17	18	7	2	10	13	17	21	218	29	40	7	7	34	17	269
	AQP4-IgG seronegative NMOSD, n	15	2	15	2	0	0	0	0	0	2	2	2	25	6	5	0	0	7	3	42
	MOGAD, n	46	22	19	11	0	0	0	1	8	6	4	4	58	16	17	0	0	18	5	111
TREATMENT EPISODES	All, n (%)	187 (15)	61 (4.9)	129 (10.3)	83 (6.7)	23 (1.8)	19 (1.5)	10 (0.8)	3 (0.2)	18 (1.4)	24 (1.9)	26 (2.1)	33 (2.6)	348 (27.9)	56 (4.5)	101 (8.1)	8 (0.6)	7 (0.6)	83 (6.7)	28 (2.2)	679 (54.5)
	AQP4-IgG seropositive NMOSD, n (%)	117 (13.7)	36 (4.2)	73 (5.9)	65 (7.6)	23 (2.7)	19 (2.2)	10 (1.2)	2 (0.2)	10 (1.2)	15 (1.8)	20 (2.3)	25 (2.9)	251 (29.4)	32 (3.8)	67 (7.9)	8 (0.9)	7 (0.8)	53 (6.2)	20 (2.3)	442 (51.8)
	AQP4-IgG seronegative NMOSD, n (%)	15 (13.8)	2 (1.8)	22 (1.8)	4 (3.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (2.8)	2 (1.8)	3 (2.8)	33 (30.3)	8 (7.3)	5 (4.6)	0 (0)	0 (0)	9 (8.3)	3 (2.8)	71 (65.1)
	MOGAD, n (%)	55 (19.3)	23 (8.1)	34 (2.7)	14 (4.9)	0 (0)	0 (0)	0 (0)	1 (0.4)	8 (2.8)	6 (2.1)	4 (1.4)	5 (1.8)	64 (22.5)	16 (5.6)	29 (10.2)	0 (0)	0 (0)	21 (7.4)	5 (1.8)	166 (58.2)
EPISODES WITHOUT ATTACK	All, n (%)	102 (54.5)	37 (60.7)	55 (42.6)	53 (63.9)	16 (69.6)	18 (94.7)	9 (90)	3 (100)	9 (50)	12 (50)	18 (69.2)	16 (48.5)	193 (55.5)	40 (71.4)	77 (76.2)	7 (87.5)	7 (100)	45 (54.2)	19 (67.9)	303 (44.6)
	AQP4-IgG seropositive NMOSD, n (%)	61 (52.1)	17 (47.2)	33 (45.2)	41 (63.1)	16 (69.6)	18 (94.7)	9 (90)	2 (100)	3 (30)	9 (60)	14 (70)	14 (56)	139 (55.4)	22 (68.8)	51 (76.1)	7 (87.5)	7 (100)	25 (47.2)	12 (60)	177 (40)
	AQP4-IgG seronegative NMOSD, n (%)	14 (93.3)	2 (100)	5 (22.7)	2 (50)	0	0	0	0	0	1 (33.3)	2 (100)	0 (0)	19 (57.6)	5 (62.5)	4 (80)	0	0	6 (66.7)	3 (100)	39 (54.9)
	MOGAD, n (%)	27 (49.1)	18 (78.3)	17 (50)	10 (71.4)	0	0	0	1 (100)	6 (75)	2 (33.3)	2 (50)	2 (40)	35 (54.7)	13 (81.2)	22 (75.9)	0	0	14 (66.7)	4 (80)	87 (52.4)
TREATMENT DURATION (DAYS)	All, mean (sd)	1324 (1594)	599 (973)	676 (743)	583 (687)	350 (578)	613 (536)	288 (316)	1370 (385)	1098 (1483)	1245 (1813)	838 (1059)	860 (813)	1165 (1098)	540 (728)	361 (401)	232 (147)	172 (96)	456 (700)	984 (1005)	1081 (2021)
	AQP4-IgG seropositive NMOSD, mean (sd)	1532 (1827)	724 (1211)	527 (615)	586 (714)	350 (578)	613 (536)	288 (316)	1355 (543)	858 (1308)	1162 (1922)	827 (1170)	923 (882)	1276 (1159)	695 (878)	345 (384)	232 (147)	172 (96)	544 (817)	1138 (1130)	1106 (2008)
	AQP4-IgG seronegative NMOSD, mean (sd)	1387 (1474)	496 (199)	950 (940)	433 (277)						503 (502)	874 (1121)	1096 (469)	1138 (1135)	233 (197)	356 (361)			386 (533)	956 (521)	803 (1185)

		AZA	AZA+STE	MS	COM.	CYC	ECU	ECU0	INE	IVIG	MTX	MMF	OTHER	RTX	RTX+STE	RTXO	STZ	STZO	STE	TCZ	NO THERAPY
	MOGAD, mean (sd)	863 (837)	413 (429)	818 (797)	613 (668)	NaN (NA)	NaN (NA)	NaN (NA)	1399 (NA)	1399 (1718)	1822 (1981)	874 (489)	405 (431)	740 (648)	384 (455)	400 (456)			263 (310)	385 (228)	1136 (2318)
CUMULATIVE TREATMENT	All, years	678	100	239	132	22	32	8	11	54	82	60	78	1110	83	100	5	3	104	75	2010
	AQP4-IgG seropositive NMOSD, years	491	71	105	104	22	32	8	7	23	48	45	63	877	0	63	5	3	79	62	1338
	AQP4-IgG seronegative NMOSD, years	57	3	57	5	0	0	0	0	0	4	5	9	103	5	5	0	0	10	8	156
	MOGAD, years	130	26	76	23	0	0	0	4	31	30	10	6	130	17	32	0	0	15	5	516
FIRST-LINE	All, n (%)	112 (23.3)	27 (5.6)	70 (14.6)	4 (0.8)	8 (1.7)	8 (1.7)	0 (0)	2 (0.4)	8 (1.7)	6 (1.2)	1 (0.2)	10 (2.1)	163 (34)	22 (4.6)	3 (0.6)	0 (0)	0 (0)	34 (7.1)	2 (0.4)	0 (0)
	AQP4-IgG seropositive NMOSD, n (%)	69 (22.2)	16 (5.1)	39 (8.1)	4 (1.3)	8 (2.6)	8 (2.6)	0 (0)	1 (0.3)	4 (1.3)	5 (1.6)	0 (0)	8 (2.6)	120 (38.6)	12 (3.9)	1 (0.3)	0 (0)	0 (0)	14 (4.5)	2 (0.6)	0 (0)
	AQP4-IgG seronegative NMOSD, n (%)	10 (22.7)	1 (2.3)	14 (2.9)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.3)	11 (25)	3 (6.8)	0 (0)	0 (0)	0 (0)	4 (9.1)	0 (0)	0 (0)
	MOGAD, n (%)	33 (26.4)	10 (8)	17 (3.5)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.8)	4 (3.2)	1 (0.8)	1 (0.8)	1 (0.8)	32 (25.6)	7 (5.6)	2 (1.6)	0 (0)	0 (0)	16 (12.8)	0 (0)	0 (0)
ACUTE ATTACK RATE	All, ARR (95% CI)	0.46 (0.35-0.61)	0.59 (0.35-0.98)	1.13 (0.86-1.49)	0.46 (0.32-0.68)	0.92 (0.37-2.38)	0.03 (0-0.18)	0.23 (0.03-1.48)	0	0.79 (0.32-2.03)	0.43 (0.21-0.84)	1.13 (0.38-4.38)	0.43 (0.27-0.68)	0.5 (0.4-0.64)	0.44 (0.24-0.79)	0.46 (0.28-0.76)	0.33 (0.05-1.52)	0 (NA)	0.98 (0.66-1.46)	0.24 (0.12-0.48)	0.72 (0.63-0.82)
	AQP4-IgG seropositive NMOSD, ARR (95% CI)	0.41 (0.29-0.58)	0.52 (0.29-0.92)	1.32 (0.90-1.96)	0.47 (0.30-0.73)	0.92 (0.37-2.38)	0.03 (0-0.18)	0.23 (0.03-1.48)	0	1.37 (0.53-3.64)	0.43 (0.14-1.32)	1.24 (0.35-6.36)	0.39 (0.21-0.71)	0.43 (0.33-0.57)	0.35 (0.16-0.77)	0.46 (0.25-0.84)	0.33 (0.05-1.52)	0 (NA)	0.91 (0.59-1.38)	0.30 (0.13-0.66)	0.8 (0.69-0.93)
	AQP4-IgG seronegative NMOSD, ARR (95% CI)	0.07 (0.02-0.16)	0 (NA)	1.36 (0.82-2.28)	0.42 (0.07-1.3)						0.97 (0.3-2.24)	0 (NA)	0.44 (0.14-1.03)	0.34 (0.17-0.67)	0.79 (0.24-1.87)	0.2 (0.01-0.9)			0.99 (0.2-5.44)	0 (NA)	0.42 (0.3-0.59)
	MOGAD, ARR (95% CI)	0.66 (0.41-1.08)	0.52 (0.29-0.92)	0.62 (0.36-1.07)	0.48 (0.21-1.11)					0.17 (0.04-0.78)	0.27 (0.12-0.5)	1.24 (0.35-6.36)	0.72 (0.22-1.68)	0.85 (0.52-1.46)	0.44 (0.13-1.64)	0.56 (0.2-1.58)			1.31 (0.47-3.79)	0.19 (0.01-0.84)	0.64 (0.47-0.86)
ACUTE ATTACK RATE FIRST-LINE THERAPY ONLY	All, ARR (95% CI)	0.46 (0.31-0.67)	0.5 (0.18-1.42)	1.17 (0.83-1.67)	0.42 (0.02-1.84)	0.5 (0.08-1.56)	0.08 (0-0.37)		0 (NA)	0.72 (0.19-3.37)	0.13 (0.03-0.58)	0 (NA)	0.35 (0.14-0.95)	0.39 (0.28-0.54)	0.4 (0.15-0.94)	2.9 (0.9-6.72)			1.26 (0.65-2.42)	0.17 (0.07-0.28)	
	AQP4-IgG seropositive NMOSD, ARR (95% CI)	0.38 (0.25-0.58)	0.53 (0.19-1.42)	1.33 (0.82-2.2)	0.42 (0.02-1.84)	0.5 (0.08-1.56)	0.08 (0-0.37)		0 (NA)	1.49 (0.44-4.86)	0.22 (0.01-29.48)		0.33 (0.11-1.24)	0.42 (0.28-0.63)	0.3 (0.09-0.7)	0 (NA)			0.44 (0.14-1.19)	0.17 (0.07-0.28)	
	AQP4-IgG seronegative NMOSD, ARR (95% CI)	0 (NA)	0 (NA)	1.37 (0.75-2.55)										0.13 (0.02-1.2)	1.31 (0.32-3.37)				2.36 (0.73-5.47)		

		AZA	AZA+STE	MS	COM.	CYC	ECU	ECU0	INE	IVIG	MTX	MMF	OTHER	RTX	RTX+STE	RTXO	STZ	STZO	STE	TCZ	NO THERAPY
	MOGAD, ARR (95% CI)	0.74 (0.39-1.42)	0.46 (0.03-137.79)	0.67 (0.34-1.37)						0.07 (0-0.66)				0.39 (0.22-0.67)	0.39 (0.01-18.18)	4.17 (10.59-2.34)			1.71 (0.64-4.58)		

AZA = Azathioprine, AZA+STE = Azathioprine and steroids, MS = Classical Multiple Sclerosis therapy, COM = Combination therapy, CYC = Cyclophosphamide, ECU = Eculizumab, ECUO = Eculizumab and other, INE = Inebilizumab, IVIG = Intravenous immunoglobulins, MTX = Methotrexate, MMF = Mycophenolate mofetil, RTX = Rituximab, RTXO = Rituximab and other, RTX+STE = Rituximab and steroids, STZ = Satralizumab, STZ = Satralizumab and other, OS = Steroids oral, TOC = Tocilizumab, AAR = Annualized attack rate.

Use of different immunotherapies over time (Suppl. Table 2)

All Subgroups

	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
Azathioprine	38 (24.7)	42 (24.7)	43 (22.5)	44 (19.5)	46 (17.5)	57 (20.3)	54 (18.7)	51 (16)	52 (15.1)	52 (15)	42 (12.2)	37 (14.6)	24 (14)
Azathioprine and Steroids	6 (3.9)	8 (4.7)	6 (3.1)	8 (3.5)	10 (3.8)	8 (2.8)	8 (2.8)	4 (1.3)	8 (2.3)	9 (2.6)	15 (4.3)	10 (3.9)	10 (5.8)
Classical MS	31 (20.1)	20 (11.8)	15 (7.9)	20 (8.8)	25 (9.5)	24 (8.5)	18 (6.2)	13 (4.1)	4 (1.2)	1 (0.3)	1 (0.3)	1 (0.4)	0
Combination Therapy	8 (5.2)	9 (5.3)	13 (6.8)	12 (5.3)	14 (5.3)	15 (5.3)	13 (4.5)	11 (3.4)	16 (4.7)	11 (3.2)	12 (3.5)	9 (3.5)	6 (3.5)
Cyclo-phosphamide	3 (1.9)	2 (1.2)	2 (1)	1 (0.4)	2 (0.8)	1 (0.4)	0	0	1 (0.3)	1 (0.3)	1 (0.3)	0	0
Eculizumab	0	0	0	0	1 (0.4)	2 (0.7)	2 (0.7)	3 (0.9)	2 (0.6)	3 (0.9)	12 (3.5)	15 (5.9)	8 (4.7)
Eculizumab and other	0	0	0	0	0	0	1 (0.3)	1 (0.3)	2 (0.6)	2 (0.6)	9 (2.6)	2 (0.8)	1 (0.6)
IVIG	3 (1.9)	4 (2.4)	4 (2.1)	5 (2.2)	4 (1.5)	6 (2.1)	5 (1.7)	5 (1.6)	7 (2)	9 (2.6)	7 (2)	6 (2.4)	4 (2.3)
Inebilizumab	0	0	0	0	0	0	1 (0.3)	3 (0.9)	3 (0.9)	3 (0.9)	3 (0.9)	2 (0.8)	NA
Methotrexate	6 (3.9)	6 (3.5)	7 (3.7)	7 (3.1)	6 (2.3)	5 (1.8)	6 (2.1)	7 (2.2)	6 (1.7)	7 (2)	4 (1.2)	4 (1.6)	4 (2.3)
Mycophenolate mofetil	2 (1.3)	1 (0.6)	5 (2.6)	8 (3.5)	9 (3.4)	11 (3.9)	9 (3.1)	10 (3.1)	8 (2.3)	9 (2.6)	8 (2.3)	2 (0.8)	1 (0.6)
Other	4 (2.6)	6 (3.5)	7 (3.7)	5 (2.2)	5 (1.9)	6 (2.1)	6 (2.1)	7 (2.2)	7 (2)	6 (1.7)	6 (1.7)	5 (2)	6 (3.5)
Rituximab	36 (23.4)	51 (30)	65 (34)	79 (35)	97 (36.9)	106 (37.7)	126 (43.6)	150 (47)	170 (49.4)	170 (49.1)	156 (45.2)	106 (41.7)	68 (39.5)
Rituximab and other	7 (4.5)	10 (5.9)	11 (5.8)	14 (6.2)	15 (5.7)	7 (2.5)	12 (4.2)	14 (4.4)	18 (5.2)	22 (6.4)	23 (6.7)	18 (7.1)	9 (5.2)
Rituximab and Steroids	2 (1.3)	2 (1.2)	6 (3.1)	9 (4)	10 (3.8)	11 (3.9)	11 (3.8)	16 (5)	14 (4.1)	16 (4.6)	17 (4.9)	10 (3.9)	7 (4.1)
Satralizumab	0	0	0	0	0	0	0	0	0	0	0	5 (2)	6 (3.5)
Satralizumab and other	0	0	0	0	0	0	0	0	0	0	0	3 (1.2)	6 (3.5)
Steroids oral	7 (4.5)	6 (3.5)	3 (1.6)	6 (2.7)	10 (3.8)	14 (5)	9 (3.1)	15 (4.7)	16 (4.7)	12 (3.5)	17 (4.9)	10 (3.9)	7 (4.1)
Tocilizumab	1 (0.6)	3 (1.8)	4 (2.1)	8 (3.5)	9 (3.4)	8 (2.8)	8 (2.8)	9 (2.8)	10 (2.9)	13 (3.8)	12 (3.5)	9 (3.5)	5 (2.9)

AQP4-IgG seropositive patients

	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
Azathioprine	30 (24)	30 (23.1)	29 (20.1)	30 (18.1)	33 (16.8)	40 (19.8)	38 (18.7)	32 (15)	29 (13)	26 (11.6)	16 (7.5)	16 (10.2)	8 (8)
Azathioprine and Steroids	6 (4.8)	8 (6.2)	6 (4.2)	6 (3.6)	8 (4.1)	6 (3)	4 (2)	2 (0.9)	4 (1.8)	3 (1.3)	3 (1.4)	4 (2.5)	2 (2)
Classical MS	20 (16)	10 (7.7)	6 (4.2)	5 (3)	5 (2.6)	7 (3.5)	4 (2)	1 (0.5)	0	0	0	0	0
Combination Therapy	7 (5.6)	6 (4.6)	10 (6.9)	9 (5.4)	10 (5.1)	11 (5.4)	9 (4.4)	9 (4.2)	12 (5.4)	7 (3.1)	6 (2.8)	4 (2.5)	4 (4)
Cyclophosphamide	3 (2.4)	2 (1.5)	2 (1.4)	1 (0.6)	2 (1)	1 (0.5)	0	0	1 (0.4)	1 (0.4)	1 (0.5)	0	0
Eculizumab	0	0	0	0	1 (0.5)	2 (1)	2 (1)	3 (1.4)	2 (0.9)	3 (1.3)	12 (5.6)	15 (9.6)	8 (8)
Eculizumab and Other	0	0	0	0	0	0	1 (0.5)	1 (0.5)	2 (0.9)	2 (0.9)	9 (4.2)	2 (1.3)	1 (1)
IVIG	2 (1.6)	3 (2.3)	3 (2.1)	3 (1.8)	2 (1)	3 (1.5)	2 (1)	2 (0.9)	3 (1.3)	4 (1.8)	3 (1.4)	1 (0.6)	1 (1)
Inebilizumab	0	0	0	0	0	0	1 (0.5)	2 (0.9)	2 (0.9)	2 (0.9)	2 (0.9)	1 (0.6)	0
Methotrexate	4 (3.2)	3 (2.3)	3 (2.1)	3 (1.8)	3 (1.5)	3 (1.5)	4 (2)	4 (1.9)	4 (1.8)	5 (2.2)	2 (0.9)	1 (0.6)	1 (1)
Mycophenolate mofetil	2 (1.6)	1 (0.8)	4 (2.8)	6 (3.6)	9 (4.6)	11 (5.4)	8 (3.9)	7 (3.3)	5 (2.2)	0	4 (1.9)	1 (0.6)	0
Other	2 (1.6)	3 (2.3)	5 (3.5)	3 (1.8)	4 (2)	6 (3)	5 (2.5)	5 (2.3)	5 (2.2)	5 (2.2)	5 (2.3)	4 (2.5)	5 (5)
Rituximab	33 (26.4)	46 (35.4)	57 (39.6)	70 (42.2)	85 (43.4)	88 (43.6)	99 (48.8)	110 (51.6)	118 (52.9)	121 (53.8)	110 (51.6)	73 (46.5)	47 (47)
Rituximab and Other	6 (4.8)	8 (6.2)	9 (6.2)	12 (7.2)	12 (6.1)	4 (2)	7 (3.4)	10 (4.7)	9 (4)	11 (4.9)	12 (5.6)	9 (5.7)	4 (4)
Rituximab and Steroids	2 (1.6)	2 (1.5)	4 (2.8)	6 (3.6)	8 (4.1)	6 (3)	8 (3.9)	9 (4.2)	10 (4.5)	11 (4.9)	10 (4.7)	7 (4.5)	4 (4)
Satralizumab	0	0	0	0	0	0	0	0	0	0	0	5 (3.2)	6 (6)
Satralizumab and Other	0	0	0	0	0	0	0	0	0	0	0	3 (1.9)	6 (6)
Steroids_oral	7 (5.6)	5 (3.8)	3 (2.1)	5 (3)	6 (3.1)	7 (3.5)	4 (2)	7 (3.3)	7 (3.1)	8 (3.6)	9 (4.2)	6 (3.8)	3 (3)
Tocilizumab	1 (0.8)	3 (2.3)	3 (2.1)	7 (4.2)	8 (4.1)	7 (3.5)	7 (3.4)	9 (4.2)	10 (4.5)	11 (4.9)	9 (4.2)	5 (3.2)	

NA – no data

AQP4-IgG seronegative patients

	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
Azathioprine	3 (23.1)	5 (26.3)	8 (34.8)	8 (26.7)	7 (24.1)	7 (25)	5 (16.7)	4 (11.8)	3 (10.3)	4 (15.4)	4 (13.8)	5 (21.7)	4 (30.8)
Azathioprine and Steroids	0	0	0	0	0	0	0	0	1 (3.4)	1 (3.8)	1 (3.4)	0	0
Classical MS	6 (46.2)	6 (31.6)	4 (17.4)	5 (16.7)	6 (20.7)	5 (17.9)	4 (13.3)	4 (11.8)	1 (3.4)	0	0	0	0
Combination Therapy	0	0	1 (4.3)	2 (6.7)	2 (6.9)	1 (3.6)	1 (3.3)	0	0	0	0	0	0
Methotrexate	0	0	1 (4.3)	2 (6.7)	1 (3.4)	1 (3.6)	1 (3.3)	1 (2.9)	0	0	0	0	0
Mycophenolate mofetil	0	0	0	1 (3.3)	0	0	1 (3.3)	1 (2.9)	1 (3.4)	1 (3.8)	1 (3.4)	0	0
Other	1 (7.7)	1 (5.3)	0	0	0	0	0	1 (2.9)	1 (3.4)	1 (3.8)	1 (3.4)	1 (4.3)	0
Rituximab	3 (23.1)	5 (26.3)	6 (26.1)	7 (23.3)	8 (27.6)	6 (21.4)	11 (36.7)	19 (55.9)	19 (65.5)	19 (73.1)	17 (58.6)	12 (52.2)	6 (46.2)
Rituximab and Other	0	0	0	1 (3.3)	1 (3.4)	1 (3.6)	1 (3.3)	0	0	0	2 (6.9)	2 (8.7)	1 (7.7)
Rituximab and steroids	0	0	2 (8.7)	2 (6.7)	1 (3.4)	2 (7.1)	2 (6.7)	2 (5.9)	1 (3.4)	0	0	1 (4.3)	0
Steroids oral	0	0	0	0	2 (6.9)	4 (14.3)	3 (10)	2 (5.9)	2 (6.9)	0	0	NA	0
Tocilizumab	0	0	1 (4.3)	1 (3.3)	1 (3.4)	1 (3.6)	1 (3.3)	0	0	0	1 (3.4)	2 (8.7)	2 (15.4)

NA – no data

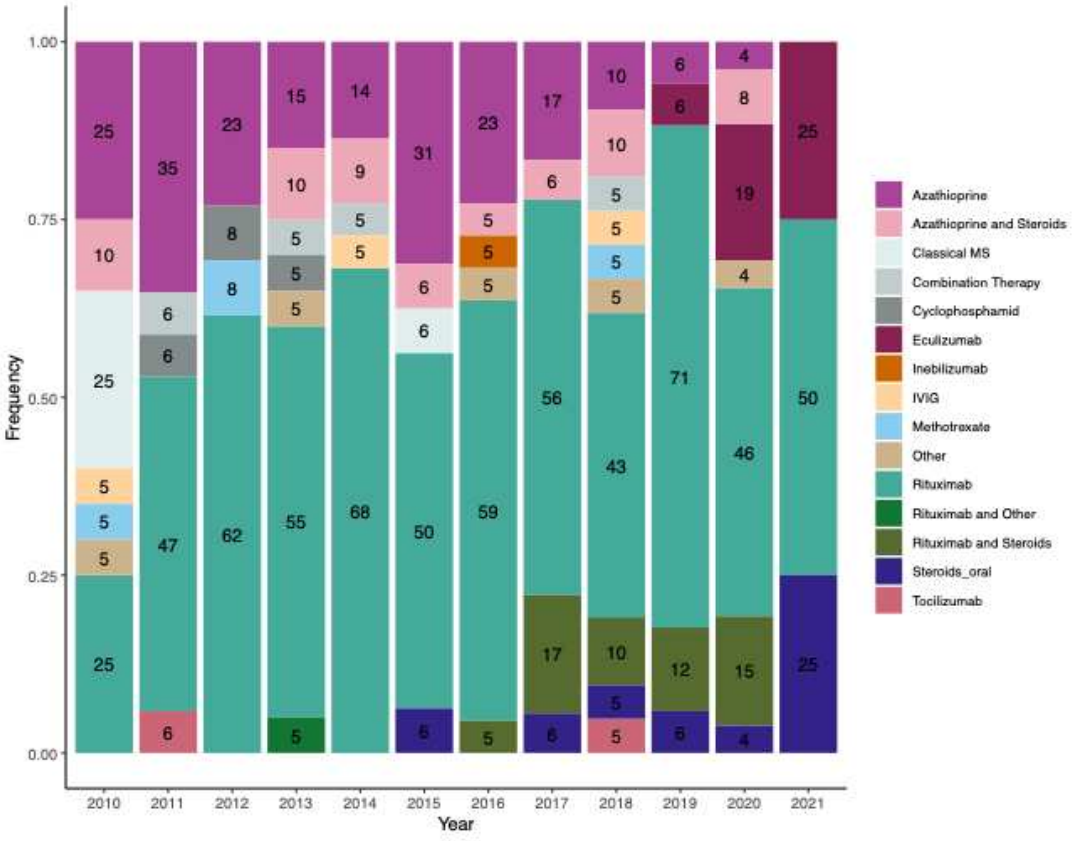
MOGAD

	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
Azathioprine	5 (31.2)	7 (33.3)	6 (25)	6 (20)	6 (15.8)	10 (19.6)	11 (19.6)	15 (20.8)	20 (21.7)	22 (23.2)	22 (21.4)	16 (21.6)	12 (20.3)
Azathioprine and steroids	NA	NA	NA	2 (6.7)	2 (5.3)	2 (3.9)	4 (7.1)	2 (2.8)	3 (3.3)	5 (5.3)	11 (10.7)	6 (8.1)	8 (13.6)
Classical MS	5 (31.2)	4 (19)	5 (20.8)	10 (33.3)	14 (36.8)	12 (23.5)	10 (17.9)	8 (11.1)	3 (3.3)	1 (1.1)	1 (1)	1 (1.4)	NA
Combination Therapy	1 (6.2)	2 (9.5)	2 (8.3)	1 (3.3)	2 (5.3)	3 (5.9)	3 (5.4)	2 (2.8)	4 (4.3)	4 (4.2)	6 (5.8)	5 (6.8)	2 (3.4)
IVIG	1 (6.2)	1 (4.8)	1 (4.2)	2 (6.7)	2 (5.3)	3 (5.9)	3 (5.4)	3 (4.2)	4 (4.3)	5 (5.3)	4 (3.9)	5 (6.8)	3 (5.1)
Inebilizumab	NA	NA	NA	NA	NA	NA	NA	1 (1.4)	1 (1.1)	1 (1.1)	1 (1)	1 (1.4)	NA
Methotrexate	2 (12.5)	3 (14.3)	3 (12.5)	2 (6.7)	2 (5.3)	1 (2)	1 (1.8)	2 (2.8)	2 (2.2)	2 (2.1)	2 (1.9)	3 (4.1)	3 (5.1)
Mycophenolate mofetil	NA	NA	1 (4.2)	1 (3.3)	NA	NA	NA	2 (2.8)	2 (2.2)	3 (3.2)	3 (2.9)	1 (1.4)	1 (1.7)
Other	1 (6.2)	2 (9.5)	2 (8.3)	2 (6.7)	1 (2.6)	NA	1 (1.8)	1 (1.4)	1 (1.1)	NA	NA	NA	1 (1.7)
Rituximab	NA	NA	2 (8.3)	2 (6.7)	4 (10.5)	12 (23.5)	16 (28.6)	21 (29.2)	33 (35.9)	30 (31.6)	29 (28.2)	21 (28.4)	15 (25.4)
Rituximab and other	1 (6.2)	2 (9.5)	2 (8.3)	1 (3.3)	2 (5.3)	2 (3.9)	4 (7.1)	4 (5.6)	9 (9.8)	11 (11.6)	9 (8.7)	7 (9.5)	4 (6.8)
Rituximab and steroids	NA	NA	NA	1 (3.3)	1 (2.6)	3 (5.9)	1 (1.8)	5 (6.9)	3 (3.3)	5 (5.3)	6 (5.8)	2 (2.7)	3 (5.1)
Steroids oral	NA	NA	NA	NA	2 (5.3)	3 (5.9)	2 (3.6)	6 (8.3)	7 (7.6)	4 (4.2)	7 (6.8)	4 (5.4)	4 (6.8)
Tocilizumab	NA	NA	NA	NA	NA	NA	NA	NA	NA	2 (2.1)	2 (1.9)	2 (2.7)	3 (5.1)

NA – no data

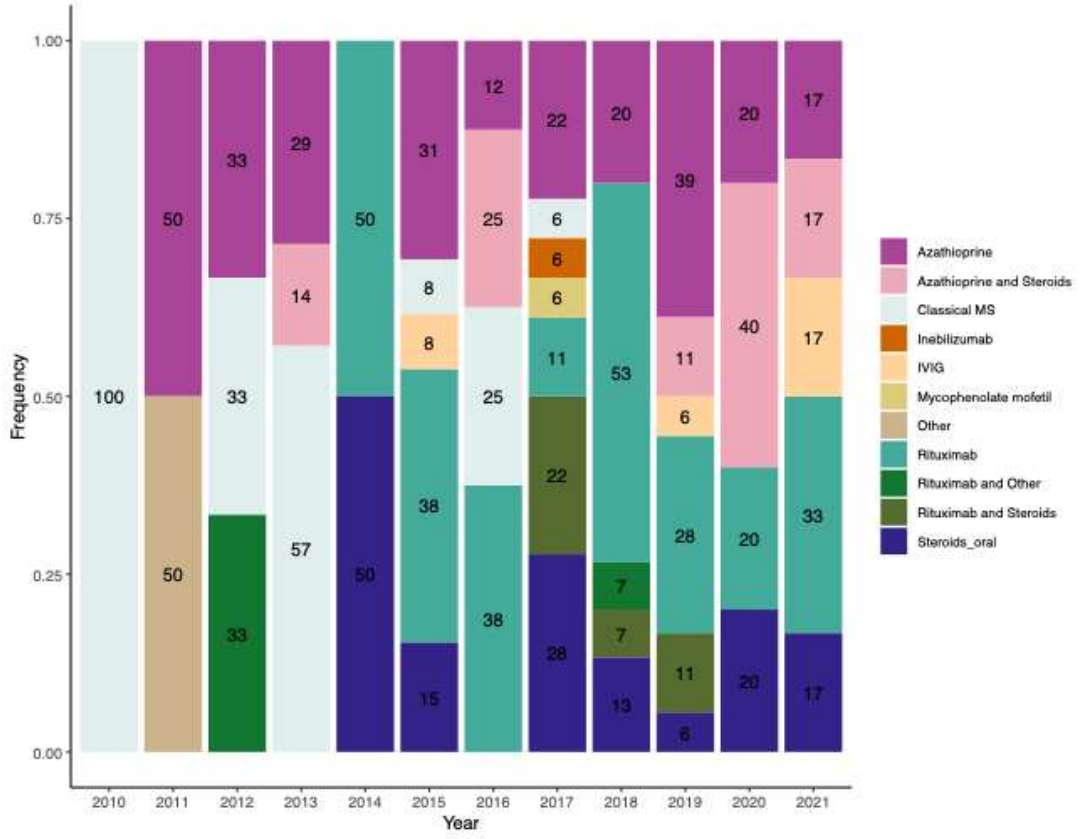
Use of different immunotherapies first line over time (Suppl. Fig. 2)

AQP4-IgG seropositive patients



Stacked bar plot illustrating changes in the first-line treatment landscape of AQP4-IgG seropositive NMOSD since 2010. Data are given as a percentage of all documented treatment episodes per year.

MOGAD



Stacked bar plot illustrating changes in the first-line treatment landscape of MOGAD since 2010. Data are given as a percentage of all documented treatment episodes per year.

Unadjusted hazard ratios for the effectiveness of immunotherapies (Suppl. Table 3)

	AQP4-IgG seropositive NMOSD			AQP4-IgG seronegative NMOSD			MOGAD		
	n	HR (CI)	p	n	HR (CI)	p	n	HR (CI)	p
Azathioprine	235	0.58 (0.47-0.71)	<0.001	21	0.23 (0.08-0.65)	0.005	109	0.96 (0.68-1.35)	0.798
Classical MS	106	1.15 (0.87-1.53)	0.325	54	1.79 (1.19-2.69)	0.005	59	1.09 (0.72-1.66)	0.679
Eculizumab	12	<0.001 (NA)	<0.001						
IVIG							13	0.63 (0.26-1.55)	0.314
Methotrexate	20	0.44 (0.21-0.94)	0.033				12	0.83 (0.39-1.78)	0.628
MMF	24	0.5 (0.25-1.02)	0.055						
Rituximab	398	0.47 (0.39-0.57)	<0.001	61	0.59 (0.36-0.98)	0.040	105	0.82 (0.56-1.19)	0.290
Rituximab and other	82	0.55 (0.34-0.87)	0.012				34	0.65 (0.32-1.33)	0.240
Steroids oral	83	1.03 (0.74-1.42)	0.859						
Tocilizumab	28	0.58 (0.34-1.01)	0.056						

IVIG = Intravenous Immunoglobulin, MMF = Mycophenolate mofetil

Hazard ratios treatment after RTX failure (Suppl. Table 4)

	n	HR (CI)	p
Rituximab	183	reference	
Classical immunosuppressives	21	1.15 (0.54-2.46)	0.718
Eculizumab	7	<0.001 (NA)	<0.001
Rituximab and other	43	0.48 (0.19-1.24)	0.131
anti-IL6R treatment	28	0.81 (0.37-1.74)	0.581

Supplemental references

1. Stellmann JP, Krumbholz M, Friede T, et al. Immunotherapies in neuromyelitis optica spectrum disorder: efficacy and predictors of response. *Journal of Neurology, Neurosurgery & Psychiatry*. 2017;88(8):639-647. doi:10.1136/jnnp-2017-315603

2. Kümpfel T, Giglhuber K, Aktas O, et al. Update on the diagnosis and treatment of neuromyelitis optica spectrum disorders (NMOSD) – revised recommendations of the Neuromyelitis Optica Study Group (NEMOS). Part II: Attack therapy and long-term management. *J Neurol*. Published online 2023:1-36. doi:10.1007/s00415-023-11910-z