Switching stable patients from Natalizumab to Alemtuzumab Efficacy and safety in the real world

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OBJECTIVE:

- **To assess evidence about efficacy and safety switching from natalizumab (NTZ) to alemtuzumab (ATZ) in stable MS patients due to risk of progressive multifocal leukoencephalopathy (PML) in a German MS center**

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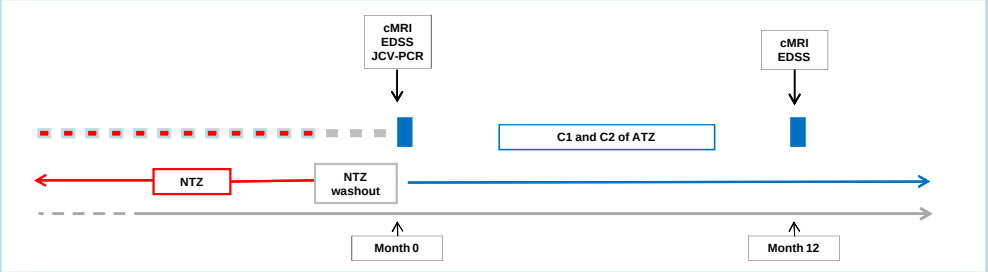
BACKROUND:

- Natalizumab (NTZ) is a highly effective therapeutic option in active relapsing MS and has proven to reduce relapse rates and disability progression (1).
- Unfortunately, it is associated with the risk of development of progressive multifocal leukoencephalopathy (PML) especially when positive for antibodies to the John Cunningham virus (JCV)(2,3).
- 2 courses of alemtuzumab (ATZ) demonstrated significantly greater improvements on clinical and MRI out-comes versus SC IFNB-1a over 2 years in patients with RRMS.(4,5)
- Therefore ATZ seems to be an alternative treatment option for patients with highly active RRMS.
- For the treatment of RRMS patients who discontinue NTZ being positive for John Cunningham virus (JCV) and change therapy to ATZ it is important to evaluate data on the efficacy and safety outcomes.
- Data from real-world clinical practice are still limited on treatment-sequencing strategies in patients on high-efficacy DMTs switching from NAT to ATZ for safety reasons (6,7).

DESIGN/ METHODS:

- 20 patients discontinued NTZ treatment (19 due to risk of progressive multifocal leukoencephalopathy (PML); 1 patient due to the experience of a massive rebound after NTZ cessation during a prior pregnancy). Prior NTZ treatment was in median 55,1 months (range 7-102).
- No patients experienced clinical or radiologic disease activity in at least 12 months prior to discontinuation.
- Our patients received the first course of ATZ 12 mg/day (C1) for 5 days between Sep. 2015 and Jul. 2017.
- To rule out asymptomatic PML, 19 patients received a recent contrast-enhanced brain MRI with DWI (median 15,5 days; range 2-65) and CSF-examination for JCV-PCR (median 14,6 days; range 7-27) prior to initiation of ATZ.
- Median washout period was 11,8 weeks (range 7-20) before receiving course 1 of ATZ 12 mg/day (C1): 5 days and course 2 (C2): 12 months later for 3 days 12 mg/day .
- At least one brain MRI and Expanded Disability Status Scale (EDSS) was performed 12 months after ATZ initiation.



Patient characteristics and outcome

Pat.-No.	Sex, Age at first dose ATZ	Year of MS onset	JCV-Index prior to switch	Duration NTZ (months)	Washout period NTZ to C1 ATZ (weeks)	cMRI prior to C1 ATZ (days)	JCV-PCR prior to C1 ATZ (days)	Adverse events (time after C1)	Relapses	MRI	EDSS, C1 to C2
1	m 26	2012	1,35	33	16	13	13		0	stable	2,5 → 2,5
2	f 34	2008	0,29	54	10	14	n.a.	Hyperthyreosis (year 3)	0	stable	2,0 → 2,0
3	f 35	2002	2,91	78	14	17	27	Stomatitis, urticaria (month 1)	0	3 active lesions prior C1	2,5 → 2,5
4	f 29	2008	1,94	66	20	2	9		0	5 active lesions prior C1	2,5 → 2,5
5	f 39	2009	2,15	11	10	16	16	Pityriasis rosea, transient lymphopenia (40 tsd. /µl)(month 3) Hypothyreosis (year 3)	0	stable	2,0 → 2,0
6	f 43	2001	3,44	39	15	11	16		0	stable	2,0 → 2,0
7	m 27	2013	2,33	26	11	11	13		0	stable	1,0 → 1,0
8	m 33	2002	1,85	86	14	24	14		0	stable	2,0 → 2,0
9	m 34	2000	3,81	102	13	4	7		0	2 active lesions month 7 1 active lesion month 12	1,0 → 1,0
10	m 46	2003	4,03	61	7	14	13	Fever 39,4°C (month 13), herpes zoster (month 19)	0	stable	3,0 → 3,0
11	f 51	2001	2,89	61	14	12	18	Herpes zoster (month 13)	0	stable	2,5 → 2,5
12	m 56	1997	3,10	100	12	65	13	Fever of unknown origin for 3 weeks, exanthema (month 13) Hypothyreosis (month 17) Fever, pneumonia. (month 18)	0	stable	3,5 → 3,5
13	f 41	1999	1,74	55	10	10	14	Fever 39,0°C (month 1 and 2) Infection-related exanthema (month 2)	0	stable	3,0 → 3,0
14	m 29	2006	3,16	74	12	3	12		0	stable	1,5 → 1,5
15	m 31	2003	2,22	77	9	6	18		0	stable	2,5 → 2,5
16	f 43	1999	3,12	43	11	13	19		0	stable	4,5 → 4,5
17	m 23	2014	2,40	8	10	11	7		0	stable	1,0 → 1,0
18	f 37	2007	2,13	40	11	10	13	Bilateral pneumonia (legionella) (1. month)	0	stable	1,5 → 1,5
19	m 27	2011	1,96	58	8	33	13	Herpes zoster (month 4)	0	stable	1,0 → 1,0
20	m 32	2006	1,71	30	10	14	23		0	stable	3,0 → 3,0
mean				**55**	**11,8**	**15,5**	**14,6**				

RESULTS:

- All 20 patients have follow-up data for at least 12 months after ATZ-C1. All patients received C2. None of the patients experienced a relapse or progression of disability. EDSS was unchanged in all patients.
- After start of ATZ only 1 patient (No. 9) had active or new brain MRI lesions (2 gadolinium-enhancing lesions at month 7[after C1] and 1 lesion at month 12 [just before C2]), without clinical signs of MS activity.
- Only 2 patients (No. 3,4) had active or new brain MRI lesions (3 and 5 gadolinium-enhancing lesions) before C1 (NTZ washout period 14 and 20 weeks).
- 6 of 20 patients required medical treatment due to infections:
- 4 patients had prolonged respiratory tract infections with high fever.
- 3 patients experienced herpes zoster.
- Thyroid AEs occurred in 3 patients (1 M. Basedow; 2 hypothyreosis).
- No PML was diagnosed.

CONCLUSIONS:

- **In this single center cohort of patients who discontinued natalizumab, alemtuzumab effectively maintained clinical stability over at least 12 months with no unexpected safety findings.**
- **A relevant proportion of patients required medical treatment due to infections.**
- **The median washout period for these patients was approximately 2,5 months. The washout period of NTZ should not exceed 12 weeks.**
- **Main AEs were respiratory tract infections with high fever within the first month after each course of ATZ.**
- **No carry-over PML occurred.**
- **The results in this cohort are similar to findings in other observations in the literature (6,7).**

References:

1. Polman, C.H., et al., *A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis.* N Engl J Med, 2006. 354(9): p. 899-910.
2. Schwab, N., et al., *Natalizumab-associated PML: Challenges with incidence, resulting risk, and risk stratification.* Neurology, 2017
3. Bloomgren G., et al. *N Engl J Med* 2012; 366:1870-80.
4. Cohen JA, et al. *Lancet* 2012;380:1819-28.
5. Coles AJ, et al. *Lancet* 2012;380:1829-39.
6. Berlotto A. et al. P6.357, Annual Meeting of the American Academy of Neurology (AAN), April 21–27, 2018.
7. Fortin J. et al. EP1498, Congress of the European Committee for Treatment and Research in MS (ECTRIMS), 14–17 September 2016, London, UK

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