MS disease Modifying Therapy Sequencing – Natalizumab to Cladribine tablets – Experience in 50 patients

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- **TZ** has received honoraria for speaking at scientific meetings, serving at scientific advisory boards and consulting activities from Almirall, Bayer Pharma, Biogen, Celgene, Sanofi-Genzyme, Merck Serono GmbH, an affiliate of Merck KGaA, Novartis, Roche, and Teva. He has received research support from Biogen, Sanofi-Genzyme, Novartis and Teva.
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CLEVER: DRKS00013587

(DRKS German Register for clinical trials)

INTRODUCTION

- Natalizumab proved to be very effective in patients with active relapsing-remitting multiple sclerosis (RRMS) but harbors the risk of progressive multifocal leukoencephalopathy (PML), especially in combination with specific risk factors.
- Accordingly, a safe and effective therapeutic alternative is warranted in this patient group.
- Cladribine tablets are a short course oral therapy with high efficacy for relapsing multiple sclerosis and are approved in Europe and the USA since 2017 and April 2019, respectively.
- Safety of switching from natalizumab to cladribine tablets has been investigated in a limited number of patients and with limited observational time.

OBJECTIVES

Analyzing the safety of switching from natalizumab to cladribine tablets in the subgroups of post-natalizumab patients from two non-interventional studies (NIS): CLEVER and CLADQoL.

METHODS

Studies

Analysis of safety data from two ongoing non-interventional studies*

50 patients who switched from natalizumab to oral cladribine tablets

CLEVER (N=23)

- Patients from Germany
- Follow-up as per study duration: **24 weeks**
- Data Cut-off: January, 2nd 2020

CLADQoL (N=27)

- Patients from Germany and Austria
- Mean follow-up: **12.8 months**
- Data Cut-off: June, 2nd 2020

- Patients were closely monitored, and data was collected regarding disease activity and possible adverse events

* Different study designs accounted for different timings in data collection; **CLEVER,** CLadribine Tablets – EValuation of thERapy satisfaction; **CLADQoL,** CLADribine Tablets – evaluation of Quality of Life

RESULTS

Demographic and baseline data: CLEVER and CLADQoL

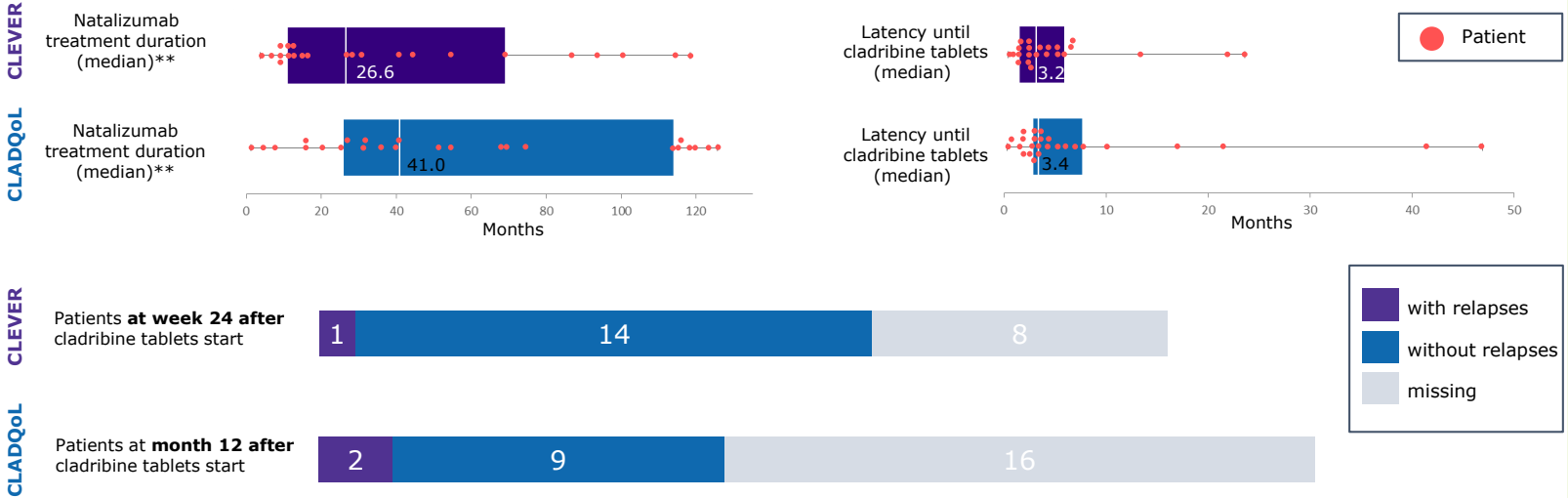
Characteristic	CLEVER (N=23)	CLADQoL (N=27)
Gender, % Female Male	 78.3 21.7	 70.4 29.6
Age, years	41.6	39.2
Type of MS, % RRMS SPMS	 87.0 13.0	 92.6 7.4
Time since MS diagnosis, months (median)	95.1	142.2
Main reason for treatment modification, n (%) "JCV positive or increase and increased risk of PML"	 8/23 (34.7)	 16/27 (59.3)
EDSS score at baseline, mean ±SD	3.50 ±1.79 (n=18)	3.06 ±1.76 (n=16)

- In both studies the most frequent reason for therapy switch was increased JCV antibody titer/risk of PML and additionally, lack of efficacy (4/23) in CLEVER.

RRMS, relapsing-remitting MS**; SPMS,** secondary progressive MS; **JCV,** John Cunningham (JC-) virus; **PML,** progressive multifocal leukoencephalopathy

RESULTS

Medication characteristics and relapses: CLEVER (N=23) and CLADQoL (N=27)*



- In both studies duration of previous natalizumab therapy was very diverse and a portion of both patient populations showed relapses in the year before switching to cladribine tablets.

* Note: Values are not comparable due to different follow-up durations; ** Values used in graphs, median [q1; q3], [min, max] in months: CLEVER Natalizumab treatment duration 26.6 [10.8; 69.2], [3.7; 118.4]; CLEVER latency until cladribine tablets; 3.2 [1.5; 6.0], [0.4; 23.6], CLADQoL Natalizumab treatment duration 41.0 [25.9; 114.1], [1.2; 125.7], data from 2 patients missing; CLADQoL latency until cladribine tablets; 3.4 [2.8; 7.7], [0.3; 46.9], data from 1 patient missing

RESULTS

Safety: CLADQoL (N=27)

Patients with adverse events	n (%)
Subjects with ≥1 AE	9 (33.3)
Subjects with ≥1 SAE	3 (11.1)
Subjects with ≥1 TRAE	8 (29.6)
Subjects with ≥1 serious TRAE	2 (7.4)
Subjects with ≥1 AESI	0 (0)
Subjects with ≥1 serious AESI	0 (0)
Subjects with ≥1 (S)AE leading to death	0 (0)

Patients with (S)AE **		Number (% of total patient no)
Infections	Oral herpes (1), cystitis (1)	2 (7.4)
Nervous system	**MS relapse** (1 AE, **2 SAE**), headache (1)	4 (14.8)
Cardiac & vascular	**Myocardial infarction (1 SAE)**	1 (3.7)
Other	**Dyspnoe (1 SAE)**, listlessness (1), influenza-like illness (1), fatigue (1), myalgia (1)	4 (14.8)

- 9 patients experienced at least one AE, of which 3 had ≥1 SAE.
- No severe opportunistic infections, especially no PML, were reported.

***** All lymphopenia, all non-serious; ** Numbers in table may not add up as one patient may have more than one AE; **AE,** adverse event; **SAE,** serious adverse event; **TRAE,** treatment-related adverse event; **AESI,** adverse events of special interest. Definition according CLADQoL study protocol: Malignancies; severe and/or serious infections, that include 4 categories: severe and/or serious herpetic infections; severe and/or serious herpes zoster infection; severe and/or serious opportunistic infections (excluding herpetic infections), including progressive multifocal leukoencephalopathy (PML) and tuberculosis; other severe and/or serious infections; Severe lymphopenia (≥ grade 3)

RESULTS

Safety: CLEVER (N=23)

Patients with adverse events	n (%)
Subjects with ≥1 AE	7 (30.4)
Subjects with ≥1 SAE	0 (0)
Subjects with ≥1 TRAE	4 (14.4)
Subjects with ≥1 serious TRAE	0 (0)
Subjects with ≥1 AESI	0 (0)
Subjects with ≥1 serious AESI	0 (0)
Subjects with ≥1 (S)AE leading to death	0 (0)

Patients with (S)AE **		Number (% of total patient no)
Immune system	Lymphopenia (2)	2 (8.7)
Infections	Herpes simplex (1), cystitis (2)	3 (13)
Nervous system	Headache (2)	2 (8.7)
Other	Fatigue (1), abdominal pain (1), aphthous Ulcer (1), rhinorrhoea (1), tonsilitis (1)	4 (17.4)

- 7 patients experienced at least one AE.
- No SAE was reported.
- No severe opportunistic infections, especially no PML, were reported.

***** All lymphopenia, all non-serious; ** Numbers in table may not add up as one patient may have more than one AE; **AE,** adverse event; **SAE,** serious adverse event; **TRAE,** treatment-related adverse event; **AESI,** adverse events of special interest. Definition according CLADQoL study protocol: Malignancies; severe and/or serious infections, that include 4 categories: severe and/or serious herpetic infections; severe and/or serious herpes zoster infection; severe and/or serious opportunistic infections (excluding herpetic infections), including progressive multifocal leukoencephalopathy (PML) and tuberculosis; other severe and/or serious infections; Severe lymphopenia (≥ grade 3)

CONCLUSIONS

Based on data from 50 patients, **switching** from natalizumab to cladribine tablets **continued to be safe** during a follow-up of up to 1 year.

No cases of PML were observed.

In total, only **3 out of 50** patients reported **serious adverse events**.