A RETROSPECTIVE COMPARISON OF RITUXIMAB VS CYCLOPHOSPHAMIDE IN NEUROMYELITIS OPTICA SPECTRUM DISORDERS PATIENTS

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Background

Neuromyelitis Optica Spectrum Disorders (NMOSD) is a severe demyelinating antibody-mediated disease with no approved treatment. Rituximab (RTX) has been proposed as a first-line therapy, but few comparative studies have been published so far. We retrospectively evaluated the effect of RTX treatment respect to cyclophosphamide (CFX) which is an immunosuppressive drug traditionally used in this disease.

Methods

From seventy NMOSD patients followed at our centre, we retrospectively selected patients receiving at least one course of RTX and at least two courses of CFX. For RTX, the treatment scheduled dosing changed during the course of the study. From 2009 however we used a fixed scheme constituted by an induction regimen of two courses of RTX of 1000 mg infused twice, with a 2 week interval between infusions and then a single cycle of 1000 mg every 6-7 months as maintenance regimen. CFX was administered i.v. at standard a dosage of 800 mg/m^2 . The cumulative dosage was adjusted during the follow-up according to haematological values in order to achieve a nadir value of lymphocytes < 1000/uL

Results

The demographic an clinical characteristics of the two groups

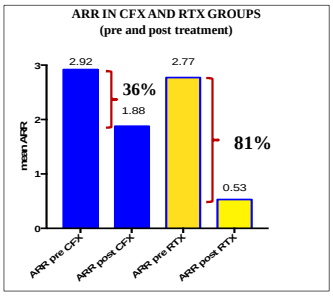
	RTX group 42 pts	CFX group 25 pts	P value
2006 diagnostic criteria	22/42 (52%)	12/ 25 (48%)	0.756
Age at disease onset (mean-SD)	39 (15)	39 (15)	0.921
Sex (F)	36/42 (86%)	20/25 (80%)	0.734
AQP4-IgG+	38/42 (90%)	20/25 (80%)	0.277
Disease duration pre RTX/CFX (median-range)	34m (0.5m-28y)	36m (1m-27y)	0.577
EDSS before RTX/CFX (median-range)	4.50 (2-9)	4.50 (2-8)	0.138
ARR before RTX/CFX (mean-SD)	2.76 (2.7)	2.92 (2.4)	0.622
Relapses before RTX/CFX (median-range)	5.0 (1-18)	3.0 (1-17)	0.369
Relapses 2 ys before RTX (median-range)	3.0 (1-7)	3.0 (1-5)	0.515
Therapies before RTX/CFX (mean-range)	1.2 (0-5)	0.6 (0-3)	**0.022**
Treatment naive patients	14/42 (33%)	16/25 (64%)	**0.022**

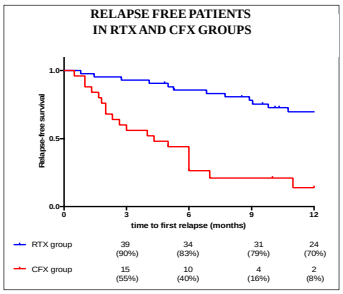
Overall 42 patients received at least one course of RTX and 25 patients received at least two courses of CFX. All patients satisfy the 2015 Wingerchuck criteria. We compared CFX group and RTX group and no statistical differences were found regarding epidemiological characteristics or disease activity characteristics. However, the mean number of therapies prior CFX was significantly lower than prior to RTX, and accordingly the number of treatment naïve patients was significantly higher in the CFX group.

NMOSD patients treated with CFX (25)	
Follow up (median)	11 months
CFX cycles per patient (mean)	7
Dose per cycle (mean)	1180 mg
Cumulative dosage per patient (mean)	8600 mg
Interval between cycles (mean)	43 days

NMOSD patients treated with RTX (42)	
Follow up (median)	33 months
RTX cycles per patient (median)	4
At least 2 RTX cycles	39 pts
At least 10 RTX cycles	5 pts
Cumulative dose per patient (median)	5000 mg
Interval between cycles (median)	7 months

In the RTX group, after a follow up of 33 months, 24 patients (57%) were relapse-free. The cumulative number of relapses was 33. In the CFX group after a median follow-up of 11 months only 5 patients (20%) were free from relapses and the cumulative number of relapses was 34. In both groups no significant changes were observed in the median EDSS.





The reduction of the ARR was significantly higher in the RTX group **(p<0,001)**

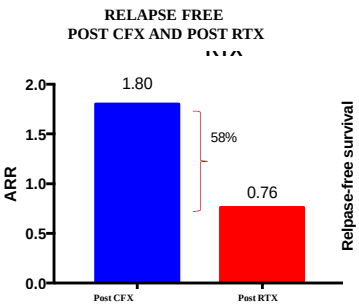
The mean ARR post CFX was 1.88, whereas after RTX was 0,53.

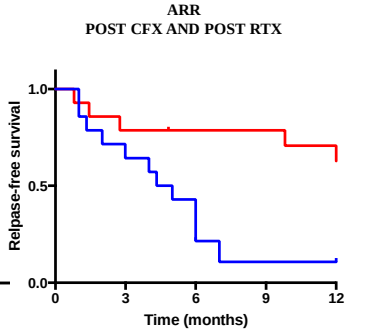
The proportion of relapse-free patients was significantly higher in the RTX group **(p <0.001)**

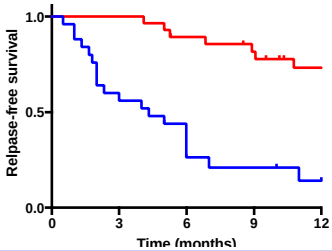
After 6 months of follow-up, 83% of RTX group was relapse-free respect to only 40% in the CFX group. After 1 year the proportion of relapse free patients decreased to 8% in the CFX group whereas it was 70% in the RTX group

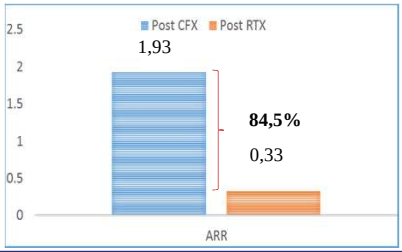
Since fourteen patients were treated with RTX after the failure of CFX, a subgroup analysis to confirm the results was performed..

14 patients	Pre CFX	Pre RTX	P value
Disease duration before RTX/CFX	35m (0.5y-27y)	77m (0.5y- 27y)	0.202
EDSS before RTX/CFX (median-range)	4.5 (2-7)	7 (4-9)	**0.033**
ARR before RTX/CFX (mean-SD)	2.71 (2.43)	2.53 (2.43)	0.776
Relapses before RTX/CFX (median-range)	3 (2-17)	6 (3-18)	**0.022**
Relapses 2 years before RTX (median-range)	3 (1-4)	4 (1-7)	**0.014**
Therapies before RTX (mean-range)	0.62 (0-3)	2.07 (1-5)	**0.004**
Treatment naive patients	9/14 (64%)	0/14 (64%)	**0.001**









Finally, to exclude the possible long term effect of CFX during RTX therapy, we compared patients treated with CFX (25 patients) with the subgroup of RTX patients who did not receive CFX (28 patients). The two groups were comparable in terms of baseline characteristics of disease activity, disability and previous immunosuppressive treatments.

Conclusions

Our study demonstrated a more efficacy of RTX in NMO patients respect to CFX. Despite the several limitations of the study, our results justify an earlier use of the monoclonal antibody and confirm that RTX can be considered the best treatment option in NMO SD patients. However as CFX was used at the standard dose of 800 mg/m^2 we cannot exclude a possible better outcome with higher dosages of the immunosuppressive drug. More comparative studies are needed to establish a treatment algorithm in patients with NMOSD and to confirm a major efficacy of RTX respect to other immunosuppressive drugs.