Real-world effectiveness of ocrelizumab in a UK multi-centre paediatric-onset multiple sclerosis cohort

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INTRODUCTION

- **Paediatric-onset Multiple Sclerosis (POMS) is rare** with incidence ranging between around 0.1 and 0.7 per 100,000 children per year.[1]
- Compared to adult MS patients, **children have a more inflammatory** disease course and a **higher relapse rate[2]**.
- In the UK there are 18 licensed disease modifying therapies (DMTs) for MS; to date, **only three clinical trials** have been **published in POMS**.
- **Current standards-of-care** for POMS are **centre-specific and based on adult protocols.**
- There is a growing consensus favouring earlier **use of highly effective disease modifying therapies (DMTs)** in POMS[3].
- A number of **real-world studies** have demonstrated **superiority of higher efficacy DMTs** over injectables and older DMTs in POMS[4,5].
- Real-world effectiveness data on ocrelizumab, **a humanised monoclonal antibody** that selectively depletes CD20+ B cells, in POMS are limited.

OBJECTIVES

- The aim of the current study was to **evaluate the efficacy and safety of ocrelizumab for children with MS** in a real-world clinical setting.

METHODS

- We conducted a **prospective study** including consecutive paediatric MS patients (<18 years) from **three UK tertiary paediatric neurosciences centres** who received ocrelizumab (Great Ormond Street Hospital for Children and Evelina Children's Hospital in London and Birmingham Children's Hospital).
- We recruited patients as part of the 'Predicting Individual Treatment responses towards personalised medicine in Multiple Sclerosis (PITMS)' study**, a large NIHR-funded prospective observational cohort** (recruitment target of 800 adults and 80 children).
- **We assessed patients at baseline and measured outcomes at 6 monthly** follow-up intervals.
- We collected data on **demographics, clinical variables, MRI, Brief International Cognitive Assessment for MS or BICAMS) and patient reported outcome measures**.
- Recruitment is ongoing with 2-year follow-up planned per patient.

RESULTS

- **A total of of 60 POMS patients** (all relapsing remitting) were included; 49 female (81.7%), 41 non-white (68.0%), with a median age of 14.6 yrs (IQR 13.3, 15.5) **(Table 1).**
- **Over 2/3 of patients presented with polyfocal CIS** with 23% presenting with optic neuritis and 5% with transverse myelitis.
- All children had a **positive EBV IgG serology, abnormal MRI at onset and positive intrathecal OCBs**.
- **Median follow-up period so far was 1.0 yrs** (range, 0.1-2.6). Forty-three patients (71.7%) had ocrelizumab as their first-line DMT.
- The **median number of relapses** per **patient pre-treatment was 2** (range 1-5).
- **Two patients relapsed within 1 month of starting ocrelizumab**.
- During the follow-up period, a **median of 2 (**range 1-5) **repeated MRI** scans were performed (total scans, n=140).

	N= 60
Age at presentation, Median yrs (IQR)	14.6 (13.3-15.5)
Sex (M : F)	11:49 (1:4.5)
Ethnicity (white : other)	19:41 (1:2.2)
CIS phenotype at onset	
Polysymptomatic (Involvement of brainstem or cerebellum; cerebral hemisphere)	43 (71.7%)
Optic neuritis	14 (23.3%)
Transverse Myelitis	3 (5%)
Vitamin D, mean (nmol/L)	45
Immunoglobulin G/ A / M, mean (g/L)	11.0 / 1.8 / 1.3
EBV IgG positive	60 (100%)
Intrathecal oligoclonal bands	60 (100%)
Abnormal brain MRI at onset	60 (100%)

Table 1: Baseline demographic, clinical and paraclinical data for our POMS cohort

RESULTS

- **Forty out of 43 (93.0%) patients** achieved **no evidence of disease activity (NEDA-3) at 12-months follow-up.**
- Two patients had one new brain lesion each at 6-months and a different patient had a relapse (optic neuritis) without new brain lesions at 6 months.
- **Annualised relapse rate (ARR)** was reduced from 2.54 pre-treatment to 0.001 post-treatment (p<0.0001).
- **Median EDSS score remained stable during follow-up**; 1.0 at baseline and at follow-up (p=0.21) **(Figure 1).**
- There was **no change in BICAMS scores at follow-up**; baseline SDMT mean score 46 vs follow-up SDMT mean score 48 (p=0.39) **(Figure 2).**
- The **most common adverse events** reported were **infusion-related reactions (33/60, 55%),** all of which were grade 1 or 2.
- **Serious adverse events** were recorded **in one patient with enterovirus meningitis,** who made a full recovery and decided to continue ocrelizumab.

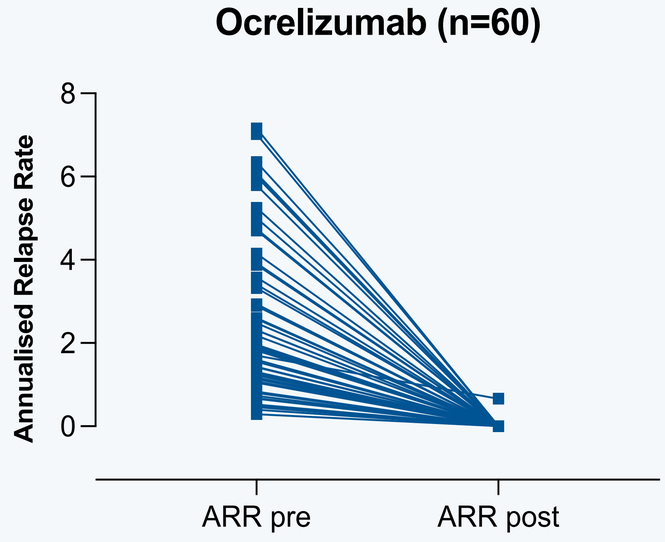

Figure 1: Annualised Relapse Rate (ARR) was reduced in our cohort from 2.54 pre-treatment to 0.001 on treatment. Each blue line corresponds to an individual patient from the 60 included so far.

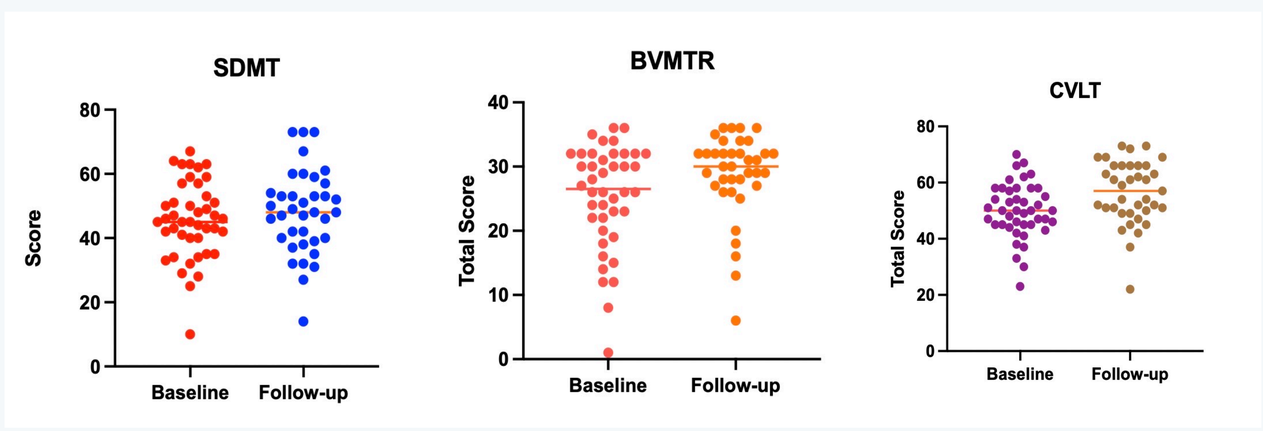

Figure 2: BICAMS scores for our cohort at baseline vs last follow-up for all 60 patients. This demonstrates no significant difference between the two timepoints for all 3 measures

DISCUSSION

- **In the OPERA phase III** randomised controlled trials, **Ocrelizumab** was shown to be **associated with lower rates of disease activity and disability accumulation** vs. **interferon beta-1a** over in adult patients with relapsing remitting MS[6].
- In addition, recent trials have shown that in **adults with primary progressive multiple sclerosis,** ocrelizumab was associated with lower rates of clinical and MRI progression than placebo[7].
- Our preliminary results show that **ocrelizumab is highly effective with a reassuring short-term safety profile in POMS.**
- A **large reduction in ARR was observed in this cohort**, with almost all children achieving NEDA-3 at 12 months with stable EDSS and BICAMS.
- This data adds weight for the early use of **higher efficacy therapies in POMS.**
- Due to systemic limitations of RCTs in paediatric MS, **multicenter real-world observational cohort studies** can provide a valuable alternative to analyse DMT efficacy and safety in POMS[8].
- **Assessment for long-term efficacy and safety of ocrelizumab in POMS** is ongoing with more comprehensive 2-year follow-up data.

REFERENCES

1. Waldman A, Ghezzi A, Bar-Or A, Mikaeloff Y, Tardieu M, Banwell B. Multiple sclerosis in children: an update on clinical diagnosis, therapeutic strategies, and research. Lancet Neurol. 2014;13(9):936-948.
2. Gorman MP, Healy BC, Polgar-Turcsanyi M, Chitnis T. Increased relapse rate in pediatric-onset compared with adult-onset multiple sclerosis. Arch Neurol. 2009; 66(1):54-59.
3. Hacohen Y, Banwell B, Ciccarelli O. What does first-line therapy mean for paediatric multiple sclerosis in the current era?. Multiple Sclerosis Journal. 2021 Nov;27(13):1970-6.
4. Krysko KM, Graves JS, Rensel M, Weinstock-Guttman B, Rutatangwa A, Aaen G, Belman A, Benson L, Chitnis T, Gorman M, Goyal MS. Real-world effectiveness of initial disease-modifying therapies in pediatric multiple sclerosis. Annals of neurology. 2020 Jul;88(1):42-55.
5. Abdel-Mannan OA, Manchoon C, Rossor T, Southin JC, Tur C, Brownlee W, Byrne S, Chitre M, Coles A, Forsyth R, Kneen R. Use of disease-modifying therapies in pediatric relapsing-remitting multiple sclerosis in the United Kingdom. Neurology-Neuroimmunology Neuroinflammation. 2021 Jul 1;8(4).
6. Hauser SL, Bar-Or A, Comi G, Giovannoni G, Hartung HP, Hemmer B, Lublin F, Montalban X, Rammohan KW, Selmaj K, Traboulsee A. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. New England Journal of Medicine. 2017 Jan 19;376(3):221-34.
7. Montalban X, Hauser SL, Kappos L, Arnold DL, Bar-Or A, Comi G, De Seze J, Giovannoni G, Hartung HP, Hemmer B, Lublin F. Ocrelizumab versus placebo in primary progressive multiple sclerosis. New England Journal of Medicine. 2017 Jan 19;376(3):209-20.
8. Sormani MP, Waubant E. Paediatric multiple sclerosis: a lesson from TERIKIDS. The Lancet Neurology. 2021 Dec 1;20(12):971-3.

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