Routine Laboratory Measures in the Controlled Treatment Period of Phase III Ocrelizumab Trials in Relapsing and Progressive Multiple Sclerosis

JS Wolinsky,[1] L Kappos,[2] X Montalban,[3,4] C Chognot,[5] H Koendgen,[5] C Li,[5] A Pradhan,[6] SL Hauser[7]

[1]McGovern Medical School, UTHealth, Houston, TX, USA; [2]University Hospital Basel, University of Basel, Basel, Switzerland; [3]Division of Neurology, University of Toronto, Toronto, ON, Canada; [4]Vall d'Hebron University Hospital, Barcelona, Spain; [5]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [6]Genentech, Inc., South San Francisco, CA, USA; [7]University of California, San Francisco, San Francisco, CA, USA

BACKGROUND

- The safety and efficacy of ocrelizumab (OCR) have been characterized in a Phase II study in patients with relapsing-remitting multiple sclerosis (RRMS; NCT00676715),[1] and in the ORCHESTRA Phase III studies encompassing patients with relapsing multiple sclerosis (RMS; OPERA I [NCT01247324] and OPERA II [NCT01412333])[2] or primary progressive multiple sclerosis (PPMS; ORATORIO [NCT01194570])[3]
  - OCR reduced disease activity and disability progression in patients with RMS (vs interferon [IFN] β-1a)[2] and PPMS (vs placebo)[3]
- Findings from the double-blind OCR exposure period of the Phase III trials showed that the most common adverse events (AEs) associated with OCR included infusion-related reactions (IRRs), nasopharyngitis, upper respiratory tract infections, headache and urinary tract infections (UTIs)[2,3]
  - Serious AEs, serious infections and malignancies were reported in 7.0%, 1.3% and 0.5% of OCR-treated patients, respectively (vs 8.8%, 2.9% and 0.2% of patients treated with IFN β-1a), during the double-blind treatment period in the pooled Phase III RMS population;[2] in the Phase III PPMS population, these events were reported in 20.4%, 6.2% and 2.3% of OCR-treated patients, respectively (vs 22.2%, 5.9% and 0.8% of patients treated with placebo)[3]
  - Few patients had AE-related treatment withdrawals (approximately 2–4%) with OCR across studies[1–3]

OBJECTIVE

- To present the results of routine laboratory measures in the controlled treatment period of the Phase III OCR trials in RMS and PPMS

METHODS

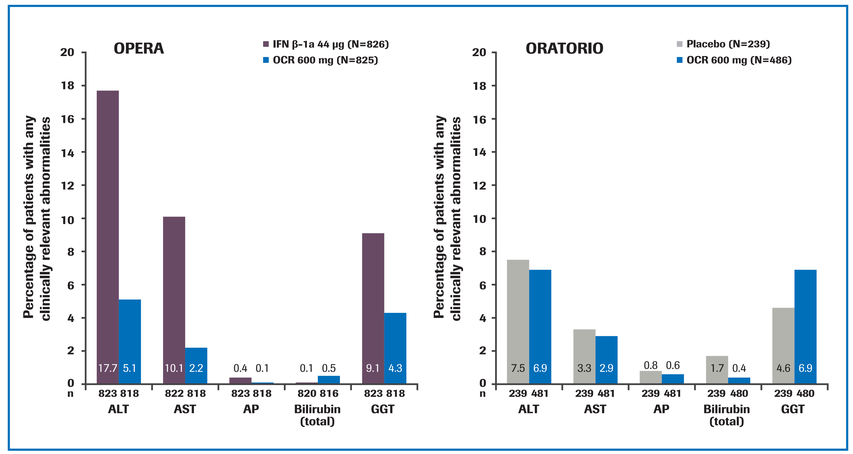
- In the OPERA I, OPERA II and ORATORIO studies, routine safety laboratory tests, including liver function, hematology and urinalysis, were conducted at baseline and every 12 weeks until the study end (**Table 1**)
  - In addition, routine safety laboratory tests were also conducted on Day 15 of the OPERA I and OPERA II studies
  - All laboratory samples collected during the OPERA I, OPERA II and ORATORIO studies were shipped to a central laboratory
  - Patient numbers were:
    - OPERA I and OPERA II (pooled): OCR N=825; IFN β-1a N=826
    - ORATORIO: OCR N=486; placebo N=239
- At infusion visits, urine and blood samples were collected prior to the infusion of methylprednisolone
- Laboratory abnormalities were defined as values outside the normal range for each specific parameter
  - For each laboratory test, a Marked Abnormality Range was predefined, above and/or below which a value is considered potentially clinically relevant
    - This Marked Abnormality Range is wider than the Reference Range
  - In addition, for each laboratory test, a percentage change (increase and/or decrease) has been defined, which represents a clinically relevant change from baseline
  - A Marked Abnormality is defined as a test result that is outside of the Marked Abnormality Range, which also represents a clinically relevant change from baseline of at least the designated value, during treatment or within 30 days after the end-of-trial treatment
- The two trial populations have not been adjusted for key baseline demographic characteristics such as age, comorbidities and comedication, all of which could impact laboratory parameters

Table 1. Overview of laboratory parameters for safety reporting

Laboratory test	Reference Range[a]	Marked Abnormality Range	Direction of change	Clinically relevant change from baseline
ALT	M 0–55 U/L[a] F 0–30 U/L[b]	0–110 U/L	Increase	≥50%
AST	M 0–40 U/L[a] F 0–25 U/L[b]	0–80 U/L	Increase	≥50%
AP	M 0–115 U/L[a] F 0–100 U/L[b]	0–220 U/L	Increase	≥50%
Bilirubin (total)	0–17 µmol/L[a]	0–34 µmol/L	Increase	≥75%
GGT	M 0–94 U/L[a] F 0–70 U/L[b]	0–190 U/L	Increase	≥50%
Sodium	135–145 mmol/L	130–150 mmol/L	Increase Decrease	≥7% ≥7%
Potassium	3.4–4.8 mmol/L	2.9–5.8 mmol/L	Increase Decrease	≥20% ≥20%
Creatinine	0–133 µmol/L	0–154 µmol/L	Increase	≥50%
Hemoglobin	M 130–180 g/L F 120–160 g/L[b]	110–200 g/L	Increase Decrease	≥15% ≥15%
Erythrocyte counts	M 4.5–5.3 $\times 10^{12}$/L F 4.1–5.1 $\times 10^{12}$/L[b]	3.8–6.1 $\times 10^{12}$/L	Increase Decrease	≥15% ≥15%
White blood cells	4.5–11.0 $\times 10^{9}$/L	3.0–18.0 $\times 10^{9}$/L	Increase Decrease	≥30% ≥30%
Thrombocyte counts	150–350 $\times 10^{9}$/L	100–550 $\times 10^{9}$/L	Increase Decrease	≥50% ≥30%
TSH	0–5.0 µU/ml[b]	0–10.0 µU/ml	Increase	≥30%

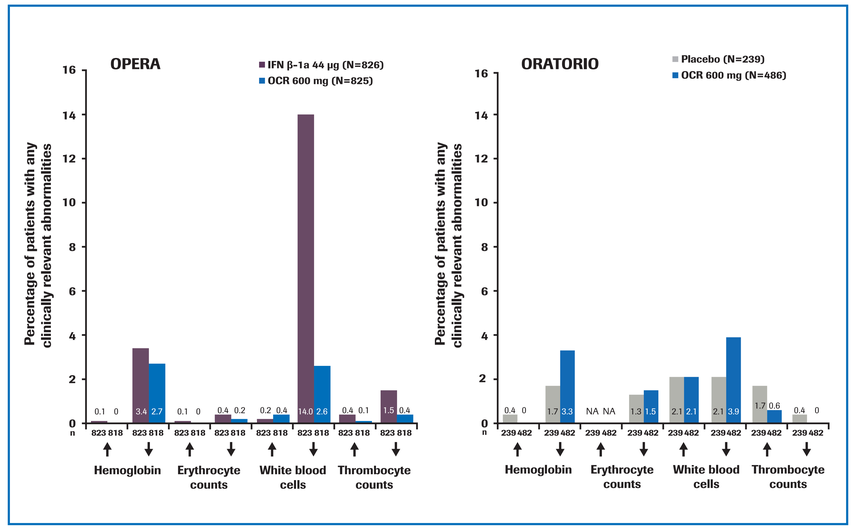
[a]For reporting and analyzing, the data are linearly transformed to the reference range according to the formula: $R_t = S_l + [(R_u - L_l)/(L_u - L_l)]*(S_h - S_l)$. To prevent transformed values becoming negative, the investigator lower limit is replaced by zero; [b]For reporting and analyzing, the data for females are linearly transformed to the reference range for males. For female-to-male transformation, replace L_l, L_u by the reference limits for female, and S_l, S_h by the reference limits for male.
ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; F, female; GGT, gamma-glutamyltransferase; I_l, I_u, investigator limits, low and high; M, male; R_t, transformed value; R_u, untransformed value; S_l, S_h, reference limits, low and high; TSH, thyroid-stimulating hormone.

Figure 1. Percentage of patients with any clinically relevant abnormalities in liver function



ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; IFN, interferon; OCR, ocrelizumab.

Figure 2. Percentage of patients with any clinically relevant abnormalities in hematology parameters (increase/decrease)



Upwards arrow (↑) represents increase; downwards arrow (↓) represents decrease.
IFN, interferon; NA, not applicable; OCR, ocrelizumab.

RESULTS

Liver Function

- The most common clinically relevant laboratory abnormalities were increases in liver enzymes in patients with RMS and PPMS, including alanine aminotransferase (ALT) and aspartate aminotransferase (AST), during the controlled treatment period (**Figure 1**)
  - In patients with RMS in the pooled OPERA studies, there were increases in ALT (OCR 5.1% vs IFN β-1a 17.7% of patients with clinically relevant abnormalities) and AST (OCR 2.2% vs IFN β-1a 10.1%)
  - In patients with PPMS in the ORATORIO study, there were increases in ALT (OCR 6.9% vs placebo 7.5%) and AST (OCR 2.9% vs placebo 3.3%)
- The proportions of patients with clinically relevant abnormalities for alkaline phosphatase (AP) in the pooled OPERA studies were OCR 0.1% vs IFN β-1a 0.4%, and in the ORATORIO study were OCR 0.6% vs placebo 0.8%
- For bilirubin (total), the proportions of patients with clinically relevant laboratory abnormalities in the pooled OPERA studies were OCR 0.5% vs IFN β-1a 0.1%, and in the ORATORIO study were OCR 0.4% vs placebo 1.7%
- In the ORATORIO study, a clinically relevant increase in gamma-glutamyltransferase (GGT) was observed in a higher percentage of patients in the OCR group (6.9%) compared with the placebo group (4.6%) during the controlled treatment period

Electrolytes

- The proportions of patients with clinically relevant abnormalities in electrolyte levels (sodium and potassium) during the controlled treatment period for the pooled OPERA studies and the ORATORIO study were small and did not follow any particular pattern with OCR, IFN β-1a or placebo treatment (data not shown)

Hematology

- The proportions of patients with clinically relevant abnormalities in hematology parameters during the controlled treatment period for the pooled OPERA studies and the ORATORIO study were small and did not follow any particular pattern with OCR, IFN β-1a or placebo treatment (**Figure 2**)
  - An exception was a decreased white blood cell count seen with IFN β-1a in the pooled OPERA studies (OCR 2.6% vs IFN β-1a 14.0%)

Renal Function

- The proportions of patients with clinically relevant abnormalities in renal function during the controlled treatment period for the pooled OPERA studies and the ORATORIO study were low, with no abnormalities reported for creatinine in the OCR group (n=818) in the pooled OPERA studies (vs IFN β-1a 0.2%; n=823), and 0.2% (n=481) in the ORATORIO study (vs placebo 0%; n=239) (data not shown)

Thyroid Function

- In the pooled OPERA studies, clinically relevant abnormalities in thyroid-stimulating hormone (TSH) levels (increase) were observed in a lower percentage of patients in the OCR-treated group (0.4%; n=798) compared with the IFN β-1a group (1.9%; n=798) during the controlled treatment period (data not shown)
  - No clinically relevant abnormalities for TSH were reported for OCR and placebo in the ORATORIO study
    - TSH levels were determined in 39/486 (8.0%) OCR-treated patients and 14/239 (5.9%) placebo-treated patients
    - Note: Only a small number of ORATORIO patients had post-baseline TSH assessments (protocol requirement for TSH assessment was at screening only)

CONCLUSIONS

- Overall, the proportions of patients with clinically relevant abnormal electrolyte, hematological, renal and hepatic values were low with ocrelizumab
- These data support an acceptable risk profile for ocrelizumab treatment

ACKNOWLEDGMENTS

We would like to thank all patients, their families, and the investigators who participated in these trials. This research was funded by F. Hoffmann-La Roche Ltd, Basel, Switzerland. Writing and editorial assistance for this presentation was provided by Articulate Science, UK, and funded by F. Hoffmann-La Roche Ltd, Basel, Switzerland.

DISCLOSURES

JS Wolinsky has served on advisory boards, data monitoring or steering committees, has consulting agreements from the following entities: AbbVie, Actelion, Alkermes, Bayer HealthCare, Biogen, Bionest, Celgene, Clene Nanomedicine, EMD Serono, Forward Pharma A/S, GeNeuro, MedDay Pharmaceuticals, Novartis Pharmaceuticals, Otsuka, PTC Therapeutics, Roche Genentech, Sanofi Genzyme, Strategic Consultants International, Takeda, Teva Pharmaceuticals; royalties are received for out licensed monoclonal antibodies through UTHealth from Millipore Corporation. L. Kappos's institution, the University Hospital Basel, has received research support and payments that were used exclusively for research support for Prof Kappos' activities as principal investigator and member or chair of planning and steering committees or advisory boards for trials sponsored by Actelion, Addex, Almirall, Bayer HealthCare Pharmaceuticals, CLC Behring, F. Hoffmann-La Roche Ltd and Genentech, Inc., GeNeuro SA, Genzyme, Merck Serono, Mitsubishi Pharma, Novartis, Octapharma, Ono Pharmaceutical, Pfizer, Receptos, Sanofi, Santhera, Siemens, Teva, UCB and XenoPort; has received license fees for Neurostatus products; and has received research grants from the European Union, Gianni Rubatto Foundation, Novartis Research Foundation, Roche Research Foundation, Swiss Multiple Sclerosis Society and Swiss National Research Foundation. X Montalban has received speaker honoraria and travel expense reimbursement for participation in scientific meetings, been a steering committee member of clinical trials or served on advisory boards of clinical trials for Actelion, Almirall, Bayer, Biogen, F. Hoffmann-La Roche Ltd, Genzyme, Merck, Novartis, Octapharma, Receptos, Sanofi, Teva and Trophos. C Chognot is an employee of F. Hoffmann-La Roche Ltd. H Koendgen is an employee and shareholder of F. Hoffmann-La Roche Ltd. C Li is an employee of F. Hoffmann-La Roche Ltd. A Pradhan is an employee of Genentech, Inc. SL Hauser serves on the board of trustees for Neurona and on scientific advisory boards for Annexon, Bionure and Symbiotix and has received travel reimbursement and writing assistance from F. Hoffmann-La Roche Ltd for CD20-related meetings and presentations.

REFERENCES

1. Kappos L, *et al. Lancet* 2011;378:1779–1787.
2. Hauser SL, *et al. N Engl J Med* 2017;376:221–234.
3. Montalban X, *et al. N Engl J Med* 2017;376:209–220.
4. Kratz A, Lewandrowski KB. *N Engl J Med* 1998:339:1063–1072.

The data on this poster have previously been presented at the 70th American Academy of Neurology (AAN) Annual Meeting 2018; 21–27 April; Los Angeles, CA, USA.