CONCLUSIONS

- No unconfirmed PML cases associated with ocrelizumab therapy have been reported.
- The confirmed cases of PML in ocrelizumab-treated patients have been associated with and confounded by prior treatment with natalizumab, fingolimod, or both.
- Approximately 17% (19,000) of post-marketing patients treated with OCR globally have previously received natalizumab.
- Cases of PML in patients with MS have been associated with other disease-modifying therapies (DMTs), e.g. fingolimod and dimethyl fumarate.
- Cases of PML were also reported with anti-CD20 therapies in a variety of different diseases and/or in concurrent immunosuppressive therapies.
- The purpose of these analyses was to describe cases reported as PML in OCR-treated patients with MS.

INTRODUCTION AND PURPOSE

- Ocrelizumab (OCR), a humanized monoclonal antibody that targets and selectively depletes CD20+ B cells, is approved for the treatment of relapsing and primary progressive multiple sclerosis.
- Progressive multifocal leukoencephalopathy (PML) is an opportunistic viral infection of the brain caused by the JC virus, typically occurring in immunocompromised patients, and may result in death or severe disability.
- JC virus is prevalent in >20% of the adult population as a latent or persistent infection.
- The vast majority of cases of PML in patients with multiple sclerosis (MS) have been associated with and described in those treated with natalizumab.

METHODS

Case Report Information

- For all cases, follow-up with the treating physician was attempted at several time points.
- Individual patient case narratives and brain MRI images prior to and after the initiation of OCR therapy (where available) were reviewed up to July 31, 2019.
- All assessments were supported by an external panel of expert advisors.
- Descriptive statistics were used.

PML Diagnostic Criteria

- The certainty of PML diagnosis was graded per American Association of Neurology (AAN) diagnostic criteria and considered “confirmed” if all criteria for the classification of “definite” were met (see Table 1).
- Definition of carry-over PML: OCR therapy that develops a few months after stopping a DMT associated with PML and starting a different DMT.
- In these cases, PML could have developed without causing symptoms while the patient was still on the previous treatment, an observation that suggests stopping the previous DMT.

RESULTS

Global OCR Patient Exposure

- As of July 31, 2019, more than 12,000 patients with MS have been exposed to OCR globally.
- Clinical trials: more than 2,000 patients.
- Post-marketing experience: more than 114,000 patients.

Overall Summary of Cases Reported as PML

- As of July 31, 2019, according to AAN diagnostic criteria for PML, there are:
  - Seven confirmed carry-over cases of definite PML.
  - Five confirmed carry-over cases reported as PML, or suspicion of PML, that do not meet AAN diagnostic criteria for definite PML.
  - One case with insufficient information for definite PML.
  - All 12 cases with information available are confounded by prior MS DMTs (natalizumab; n=11; fingolimod; n=1).

Confirmed PML Cases (BMI >25)

- The seven confirmed carry-over PML cases are summarized in Figure 1.
- Six patients had previously received treatment with natalizumab (treatment duration: 22-62 months) and all showed positive serum for anti-JCV virus antibodies (odds ratio, 12.35-4.11) prior to the diagnosis of PML.
- Time between initiation of OCR therapy and the diagnostic criteria of PML: 16-02 days.

Unconfirmed Reports of PML

- Five reports suggestive of carry-over PML, but not fully meeting AAN diagnostic criteria.
  - All five cases had MRI findings compatible with PML, one patient also had clinical symptoms and one other patient also had detection of JCV DNA in the cerebrospinal fluid.
  - All MRI scans in patients previously treated with natalizumab and already at higher risk for a natalizumab-associated PML.

Table 1. AAN diagnostic criteria for PML

<table>
<thead>
<tr>
<th>Category of PML</th>
<th>Definite</th>
<th>Confirmed</th>
<th>Suspicious</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>CSF/brain</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>MRI</td>
<td>3</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Ant-JCV antibody</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

ACKNOWLEDGMENTS

- The authors acknowledge assistance with data management from NeuroRx, Inc.
- The authors acknowledge assistance with medical writing from Roche Pharmaceuticals.
- All authors report no conflicts of interest.

REFERENCES

- The references are not provided in the image.