Progressive multifocal leukoencephalopathy (PML) – FDA-Requested Listening Session

September 11, 2020

Objectives of session: To gain a better understanding of PML patient & caregiver perspectives on:

- Disease & symptom impact & burden
- Treatment burden
- Clinical trials – design, risk tolerance, and potentially clinically meaningful endpoints, etc.

Discussions in FDA Listening Sessions are informal and not meant to replace, but rather complement, existing patient engagement opportunities in the Agency. All opinions, recommendations, and proposals are unofficial and nonbinding on FDA and all other participants. This report summarizes the input provided by patients and those representing patients with PML at the meeting. To the extent possible, the terms used in this summary to describe specific manifestations of PML, and the health effects and impacts, reflect those of the participants. This report is not meant to be representative of the views and experiences of the entire PML patient population or any specific group of individuals or entities. There may be experiences that are not mentioned in this report.

Perspectives on participation in PML clinical trials

- At any time after being diagnosed with PML, did you (or the PML patient you cared for) ever think about joining in a clinical trial that was studying an investigational treatment for PML? Why or why not?
    - Half of the caregivers stated that they considered or would participate in a clinical trial. The caregivers of two patients shared that they researched clinical trials with the intention to participate; however, because of the rapid progression of PML after diagnosis, the patients passed away before they could participate.
    - One patient and one caregiver stated that they did not think about joining a clinical trial because it was not brought up by their doctor.
    - One caregiver indicated that they initially did not think about participating in a PML clinical trial, but they were able to be a part of a Natural History Study (NHS) for PML.
    - One caregiver shared that the patient participated in a clinical trial for another disease/condition and was open to participating in a PML clinical trial; however, none were available.
- What aspects of a clinical trial of an investigational treatment for PML might make you (or the PML patient you cared for) *more or less likely* to want to participate in a PML clinical trial?
    - A patient stated willingness to participate in a clinical trial if there was more access to doctors with PML expertise.
    - Two caregivers expressed interest in participating in a clinical trial if it meant a diagnosis for PML could be identified sooner.
    - One caregiver shared the importance of educating doctors and other patients on the medications or conditions that cause PML.

- One caregiver expressed interest in learning more about the benefits of the investigational treatment and the purpose of a placebo in a clinical trial.
- One caregiver indicated that it would be a waste of time to test an investigational treatment when given a short amount of time to live.
- One caregiver understood that there would be tests involved in a clinical trial in order to establish a baseline.

- Are there any aspects or features of a clinical trial that might *prohibit* you from participating?
    - A patient indicated that the use of drugs from a previous treatment for another disease/condition would prohibit him from participating in a clinical trial.
    - One caregiver reiterated that if the testing became too onerous, such as regular spinal taps, they wouldn't put the patient through that clinical trial.
    - Some caregivers stated they would not participate if there was a chance that the patient would receive a placebo. One caregiver felt that giving a placebo would give the patient poorer quality of life.
    - Two caregivers indicated that there were no aspects of a clinical trial that would deter them from participating in a clinical trial
- Do you have any other thoughts about what scientists and researchers should consider when planning clinical trials that study potential treatments for PML?
    - Responses from the caregivers varied. Most caregivers mentioned that fast progression of the disease would present a challenge. Due to the aggressive nature of the disease, two caregivers expressed concerns about the patients receiving a placebo.
    - Two caregivers noted constraints with travel between their homes and the clinical trial location, citing the patients' inability to travel back and forth due to mobility issues, schedule and financial constraints, and family commitment, etc.
    - One caregiver shared the need for PML prevention specifically for Non-Hodgkin's lymphoma patients. Another caregiver highlighted the need for doctors to consider and understand how the patient got PML.

Use of placebos in PML clinical trials

- What are your thoughts about randomized, placebo-controlled trials for PML, in which ***all*** participants receive the best available care, and ***some*** *will receive an additional investigational treatment* while others will receive a placebo?
    - A patient considered a randomized, placebo-controlled trial to be a good idea if it would help in having a better treatment for PML patients.

- One caregiver shared that the patient would be willing to participate in a placebo-controlled trial because although the patient may not benefit from receiving the investigational treatment or the placebo, the patient's participation would help researchers better understand the effects of the treatment for other PML patients.

- Three caregivers stated that they would not participate in a placebo-controlled trial because of the risks and that it would be cruel, inhumane or a waste of time.

- Two caregivers understood the need for a placebo but would like more information on how the investigational treatment works. One caregiver noted the need to study the effects on the treatment on patients with other conditions, such as Non-Hodgkin's lymphoma, human immunodeficiency virus (HIV), or Multiple Sclerosis (MS).

PML symptoms & disease burden

- As you think about the different PML symptoms you (or the patient you cared for) experience, which symptom(s) would you say is the most problematic, or impacts you (or them) the most?

    - Nearly all caregivers and patient cited difficulty with communication and loss of sight/blindness.

    - Some caregivers mentioned loss of motor function, such as the lack of balance and the inability to walk or swallow. Two caregivers shared that patients use a wheelchair.

    - Some caregivers indicated personality changes, such as depression.

- What do you feel is the biggest burden of living with PML?

    - Responses to this question varied. Some caregivers mentioned that patients have to totally depend on someone else. Some caregivers noted the change and significant impact in not only the patient's life, but also the caregiver's and family's lives.

    - Some caregivers shared their challenges with getting an early diagnosis. One caregiver highlighted the need to educate living with the disease for the patient and caregiver and the grieving process for the caregiver and family.

    - Patient and caregivers referenced loss of dexterity, loss of vision, and inability to read and function.

Additional Comments

- Some caregivers shared concerns about Rituximab.
- Some caregivers emphasized the need to educate oncologists and other healthcare professionals about PML and the need for them to test for the John Cunningham (JC) virus and PML.

Partner organizations

The National Organization for Rare Disorders (NORD) helped identify and prepare patient community participants.

The Reagan-Udall Foundation for the FDA assisted with producing the summary of this meeting. NORD and the Foundation were present during the listening session.

FDA divisions represented

- **Office of the Commissioner**
    - Patient Affairs Staff (*organizer*)
    - Attendees: Office of Orphan Products Development
- **Center for Biologics Evaluation and Research (CBER)**
    - Requestors: Office of Tissues and Advanced Therapies, Division of Clinical Evaluation and Pharmacology/Toxicology, Clinical Hematology Branch; Office of Tissues and Advanced Therapies, Division of Clinical Evaluation and Pharmacology/Toxicology, General Medicine Branch I
    - Attendees: Office of the Director; Office of Tissues and Advanced Therapies; Office of Tissues and Advanced Therapies, Division of Clinical Evaluation and Pharm/Toxicology; Office of Tissues and Advanced Therapies, Division of Clinical Evaluation and Pharmacology/Toxicology, General Medicine Branch II
- **Center for Drug Evaluation and Research (CDER)**
    - Requestors: Office of Infectious Diseases, Division of Antivirals; Office of Neurology, Division of Neurology II; Office of Regulatory Operations, Division of Regulatory Operations for Neuroscience; Office of Medical Policy Initiatives, Division of Clinical Trial Quality
    - Attendees: Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine, Division of Rare Diseases and Medical Genetics; Office of Drug Evaluation Science, Division of Clinical Outcome Assessment

NIH Centers represented

- Requestor: National Institute of Neurological Disorders and Stroke (NINDS)

Patients and caregivers represented

1 patient and 7 caregivers participated in the listening session representing a total of 8 PML patients.

- Patient ages ranged from 40 to 83 years old.
- Age of diagnosis varied. Patients' time of diagnosis ranged from less than a year ago to 10 years ago.

Prior to the Listening Session, patients and caregivers shared:

- PML symptoms: falls, immobility, loss of motor skills, loss of vision and sense of space, loss of speech and ability to swallow, loss of dexterity, personality changes, seizures

- Management of PML: physical therapy, occupational therapy, speech therapy, T-cell therapy, Keytruda, Memantine, Mirtazapine for depression

Financial Interest

Caregivers/Patients did not identify any conflict of interest relevant to this listening session and are not receiving compensation.