What Did We Learn From the Emergency Use Authorization of Peramivir in 2009?

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(See the Major Articles by Sorbello et al, on pages 1–7, and Yu et al, on pages 8–15.)

“A crisis is a terrible thing to waste.” —Paul Rohmer

The recent pandemic caused by influenza A 2009 pH1N1 virus caused a substantial amount of severe disease, and disproportionately affected younger persons, pregnant women, and those with certain health conditions [1, 2]. These critically ill patients focused attention on gaps in our available antiviral agents for influenza. The most critical gaps include the need for parenteral agents for critically ill patients and agents active against influenza virus resistant to currently available antiviral drugs. Like most influenza viruses circulating in recent years, pH1N1 was uniformly resistant to 2 of the 4 licensed agents, rimantadine and amantadine. Fortunately, it was sensitive to the licensed neuraminidase inhibitors, oseltamivir and zanamivir, in contrast to the oseltamivir-resistant H1N1 viruses that had been circulating before the pandemic [3, 4]. Resistance to oseltamivir emerged in some patients with pH1N1 receiving oseltamivir as treatment or prophylaxis, but at low frequency [5], and only small clusters of secondary transmission were identified [6].

Two parenteral neuraminidase inhibitors were under development in 2009, peramivir and zanamivir. Both agents were initially available on a limited basis through expanded access program under an emergency investigational new drug application [7]. On 23 October 2009, during the second wave of the pandemic, the US Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for intravenous peramivir for the treatment of documented or suspected pH1N1 infection [8]. Two articles in this issue describe the available data from the experience [9, 10]. Unfortunately, they leave many questions unanswered about the efficacy, safety, and impact of peramivir on pH1N1 infection.

Yu and colleagues from the Centers for Disease Control and Prevention (CDC) analyzed requests for peramivir under the EUA using an electronic request system and sent out 3 surveys [10]. The MedWatch reporting reminder survey was designed to remind clinicians about reporting requirements for adverse events, to determine if the drug was administered, and to collect additional information on the patient and any adverse events. The pharmacy survey targeted hospital pharmacies that received peramivir to determine how many patients were treated, patient demographics, and the disposition of the drug. The clinician survey was designed to collect epidemiologic and clinical data on peramivir recipients. Response rates for the MedWatch reporting reminder survey and the pharmacy survey were 70% and 73%, respectively. Unfortunately, only 12% of clinicians contacted through the clinician survey responded.

There were 1371 requests resulting in 2129 five-day treatment courses of peramivir being delivered to 563 hospital pharmacies in the United States and Puerto Rico. The MedWatch reporting reminder survey provided data on 844 patients who were treated. One or more adverse events occurred in 260 patients (31%) but most, including death, renal complications, and neuropsychiatric events, were events that could have been the result of influenza or underlying disease. Because of the survey design and the lack of a comparison group, the relationship of reported adverse events to peramivir could not be determined. The clinician survey was completed by only 12% of physicians who requested peramivir, providing data on 127 patients. The results paint a picture of very ill patients and late treatment. The majority (72%) of peramivir recipients had underlying medical conditions. The median time from the onset of illness to starting peramivir treatment was 9 days (range, 0–33 days) and the median time from hospitalization to starting peramivir was 5 days (range, 0–26 days). At the time peramivir...
was started, 94% were in an intensive care unit, 92% were on mechanical ventilation, and 23% were on hemodialysis. At the end of treatment, 30 (24%) had died. It was not possible to determine from these data if treatment with peramivir influenced outcome.

An interesting and disturbing finding of the CDC experience with the peramivir EUA was the difficulty in determining the number of patients who were actually treated. Using survey responses, the investigators identified 1274 distinct peramivir recipients. With the use of capture recapture methodology using 3 different pairwise comparisons of the surveys, it was estimated that 1185, 1485, and 1490 patients were treated.

Sobello and colleagues [9] from the FDA described reports about patients receiving peramivir under the EUA to the FDA’s MedWatch system and entered into the Adverse Event Reporting System (AERS). According to the conditions of the EUA, reports were required for all medication errors, selected adverse events, serious adverse events, and deaths occurring during peramivir treatment. The FDA received 369 reports describing 900 adverse events (including medication errors and deaths) in 344 patients. Similar to the patients described by Yu and colleagues [10], the patients reported to MedWatch had a high prevalence of underlying medical conditions and many were on mechanical ventilation or renal replacement therapy. Despite careful review by an interdisciplinary safety committee, the FDA investigators were unable to determine if any adverse events other than rash could be attributed to peramivir. Missing data, severity of illness, and the high rate of organ system dysfunction complicated the review. The estimated overall mortality among patients treated with peramivir (roughly 16%) did not differ from the overall mortality of 14%–46% in published series of hospitalized patients with pH1N1 influenza.

These reports highlight the first effective use of the EUA to provide a potentially lifesaving medication that was not yet licensed during a large-scale bioemergency. The delivery of drug to >1100 critically ill patients within 24 hours of the request represents an enormous effort and logistical tour de force. However, the reports also highlight limitations of the EUA mechanism as currently described in legislation and interpreted in practice.

The EUA was not initiated until close to the peak of the second wave of the pandemic, and there may have been missed opportunities to make drug available earlier. Only limited data were collected on who was treated, their response, and possible adverse events, and little data were collected in real time. Despite extensive and thoughtful efforts, the post hoc data collection described in this issue provided a limited and incomplete view of the experience. The EUA mechanism as described in the Project BioShield Act of 2004 was not designed for prospective data gathering. However, this means that tremendous opportunities to learn about the efficacy and safety of emergency countermeasures during emergencies are lost. Clinical trials, such as those conducted to date with peramivir in hospitalized patients [11], usually exclude children, pregnant women, and some critically ill patients; thus, EUA use could provide critical information on these groups.

We can do better. Data collection forms or links to secure Web-based instruments could be included with certain drugs when they are released under an EUA. Careful collection of clinical data on patients who are and are not treated in real time during an emergency could be accomplished through clinical research networks. These networks would need to be established in advance and be able to be rapidly funded and activated in the event of a severe infectious disease emergency or pandemic. Rapid institutional review board review would be expedited by a central institutional review board [12]. With careful matched analysis and controlling for confounders, this type of analysis could provide important and reliable insights into the efficacy, effectiveness, and safety of the agents, as well as providing other vital data. Well-designed clinical trials will remain the gold standard; however, trials are unlikely to be conducted in these situations. As demonstrated in a recent meta-analysis of observational studies of antivirals for influenza [13], high-quality observational data will remain essential for evidence-based clinical decision making in high-risk patients.

These mechanisms will need to be designed and readied in advance, and resources must be available. Provisions in the reauthorization of the Pandemic and All Hazards Preparedness Act approved by the US House of Representatives includes language that would expand the FDA’s ability to plan in advance for EUAs and to collect data during and after an emergency; the Senate version does not. It is critical that this provision, which the FDA has requested [14], be passed so that future EUA release will not be wasted.

There are looming crises not addressed by the EUA experience with peramivir and by potential improvements to the EUA process. We face a dire absence of antiviral drugs in the development pipeline that can be used if influenza viruses become resistant to oseltamivir. We have limited ability to develop and evaluate drugs for patients with influenza who are at high risk or are critically ill. Of the small number of parenteral agents in development, only intravenous zanamivir is fully active against neuraminidase-resistant viruses containing the H275Y mutation. The reasons for these crises are complex. New influenza antivirals have not been seen as financially attractive drugs by the pharmaceutical industry, despite the toll of seasonal and pandemic influenza. Development of these drugs typically focuses on healthy outpatients, where the benefits are modest. There is currently no clear pathway for licensure in critically ill patients. New trial designs

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and endpoints will need to be developed and accepted.

To address the growing crisis in pharmaceutical development, innovative ideas have been proposed that can speed development and lead to limited approval of critically needed drugs in special populations. These concepts, sometimes referred to as “adaptive licensing,” are being actively considered by the FDA and regulators in other countries [15]. Another concept receiving favorable FDA attention was proposed by the Infectious Diseases Society of America, which has asked Congress to create a new approval pathway for Special Population Limited Use (SPLMU) drugs [16] as part of the FDA user fee reauthorization legislation. SPLMU products would be studied more rapidly in smaller and less expensive clinical trials than the traditional approval mechanism requires. Because the risk profiles for SPLMU drugs likely will be less well characterized, a special designation and labeling would be created to indicate that their use is to be reserved for seriously ill patients for whom no other treatments are available. The SPLMU mechanism can prove useful for a variety of critical needs in infectious diseases, from influenza antivirals to drugs for extensively drug-resistant, gram-negative bacterial infections.

Responding to the continued emergence of new infectious disease threats requires scientific, policy, and regulatory innovation. We are beginning to see creative ideas put forward from within the Infectious Diseases Society of America, academia, the FDA, the CDC, the National Institutes of Health, industry, and Congress. Many differences and challenges remain, however, and the path from ideas to effective action will be difficult.

Note

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