EDITORIAL COMMENTARY

Influenza Will Not Miss Opportunities

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(See the article by Baz et al. on pages 1555–61)

In healthy individuals, influenza causes self-limited disease. An appropriate immune response leads to a rapid viral clearance, thereby limiting the duration of viral shedding to <10 days in most adults. In contrast, subjects with an impaired immune response might not efficiently clear influenza infection, thereby leading to additional replication cycles and higher viral loads. In these circumstances, given the intrinsic abilities of this RNA virus to accumulate point mutations, the likelihood of the emergence of new quasi species increases rapidly. According to the resulting phenotypic changes, new emerging mutants can escape the different environmental constraints (antigenic drift), including the host's immune responses and drug pressures. At an individual level, such adapted viruses may contribute to viral persistence and decrease the efficacy of antiviral drugs. On a wider level, new drifted strains lead to vaccine escape and could promote progressive adaptation of animal strains to humans.

In this issue, Baz et al. [1] describe a stem cell transplant recipient presenting with a chronic influenza infection for months. This careful study described a case in which oral oseltamivir that was administered for weeks failed to clear the influenza infection, and resistant clones emerged. By sequencing several clones, the authors showed that isolates harboring resistance to neuraminidase inhibitors (mainly the E119V mutation on the neuraminidase gene) and amantadine (mainly the S31N mutation on the M2 gene) rapidly became dominant. Moreover, clones carrying both neuraminidase and M2-resistance mutations were detected. Although it is known that M2-resistant viruses can easily be selected, persist, and be transmitted, neuraminidase resistance was considered until very recently to be uncommon and associated with decreased fitness [2, 3]. However, in addition to the article by Baz et al. [1], similar reports of infection in immunocompromised patients [4, 5] and observations in children and recent cases of influenza A/H5N1 have tempered this relatively optimistic view. In hospitalized children receving oseltamivir, a resistance rate of 18% has been documented [6], and in patients treated for H5N1 avian influenza, resistant clones have rapidly emerged [7, 8]. Is there a common key point that could promote influenza resistance in immunocompromised hosts, in children with an acute primary infection, and in human cases of H5N1 avian influenza? This is possibly the combination of a delayed or failing immune response with a protracted infection and high viral loads. Given the intrinsic abilities of influenza to mutate or even to recombine, this is an invitation to select new mutants while exposed to drugs, particularly if drug levels are suboptimal. In the study by Baz et al. [1], oseltamivir selected a complex pattern of mutations on the neuraminidase gene that could combine and accumulate to increase resistance step-by-step or in a synergistic manner. The identification of concomitant mutations on the hemagglutinin gene also needs to be highlighted, because these mutations could possibly restore viral fitness [9] and also contribute to the transmissibility of multidrug-resistant viral quasi species. At this time and to the best of our knowledge, transmission of oseltamivir-resistant H3N2 influenza virus in humans has not been observed [10], but this seems just a question of time. In a ferret model, resistant H3N2 influenza virus carrying the E119V mutations has already proved to be transmissible [11]. In humans, a recent investigation suggests strongly that H5N1 influenza virus clones have been transmitted from brother to sister [8]. In the study by Baz et al. [1], multidrug-resistant virions were isolated even after cessation first of oseltamivir and then of amantadine—a definitive confirmation that these viruses can survive in immunocompromised hosts [4, 5]. It would be naive to consider oseltamivir-resistant or multidrug-resistant influenza viruses as uniformly unfit and nontransmissible.

From a clinical point of view, the study by Baz et al. [1] well complements pre-

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vious similar observations in immunocompromised patients [4, 5] and raises at least 4 important questions for clinicians caring for immunocompromised hosts: (1) What is the frequency of influenza infections in immunocompromised hosts and what is the relative importance of influenza compared with other respiratory viruses that are circulating in the community? Although every immunocompromised subject is at risk for influenza during seasonal outbreaks (the severity of which can vary from year to year), influenza seems not to be the most frequent respiratory virus affecting these subjects. The so-called common-cold viruses (rhinovirus and coronavirus), which are often not routinely detected, present similar clinical illnesses but are epidemiologically much more frequently present [12]. Thus, the real impact of respiratory virus as a whole (and not only influenza virus) needs to be better appreciated. (2) In the case of influenza infection, how often do severe complications occur? Many reports have shown that influenza can be relatively indolent in immunocompromised hosts [13], but could also lead to severe lower respiratory tract events [14]. The rate of influenza-related complications (e.g., viral pneumonia, bacterial or fungal complications, or graft rejection) needs to be systematically investigated. (3) Oseltamivir and other neuraminidase inhibitors are effective in healthy adults and adolescents and, to some extent, decrease the rate of complications leading to antibiotic prescriptions [3, 15]. Studies have suggested that neuraminidase inhibitors are also effective in the elderly and those with chronic lung diseases, but these drugs have never been evaluated systematically in hospitalized subjects or in immunocompromised hosts. Whether the expected benefit would be significant in these populations remains to be proven. (4) The usual oseltamivir or zanamivir regimens have been established and standardized again for healthy adults. Is there a dose-response relationship and should the dosage and the duration be increased in immunocompromised hosts as recommended by some experts? Could this prevent emergence of resistance? Is there an advantage to prescribe combination therapy, as was done in the present case? Combination therapy is an attractive concept and has been tested in a limited number of hospitalized subjects, with inconclusive results [16]. These issues also illustrate the need for new antiviral drugs and therapy that are efficiently distributed in the respiratory tract.

Good news confirmed by the present report is that cross-resistance between neuraminidase inhibitors is not the rule and that oseltamivir-resistant clones were still susceptible to zanamivir or other neuraminidase inhibitors in development. Less-good news is that amantadine resistance has been identified in up to 92% of influenza isolates recently surveyed in the United States, where amantadine and rimantadine are used for community-acquired influenza virus infection [17]. This is a dramatic increase compared with previous years and reveals that resistant strains can dominate a continent and rapidly spread worldwide. Amantadine-resistant avian influenza is also a common finding in animals [18]. Keeping in mind that millions of dollars have been spent to stockpile oseltamivir, the study by Baz et al. [1] emphasizes the need for investigation to assess the risk of neuraminidase inhibitor resistance where it matters the most—in hospitalized patients, immunocompromised hosts, persons with chronic lung diseases, young children, and, of course, in cases of avian influenza. As a first step, spending money to stockpile oseltamivir against H5N1 influenza is a wise move, but this should be complemented by significant support for clinical investigations in at-risk populations that provide the virus with an ideal setting for adaptation. Otherwise, empirical strategies and expert opinions will remain the rule for the future. Influenza will not miss opportunities to resist therapy—whether case-by-case in immunocompromised hosts or on a larger scale by spreading in the community—and why not in a pandemic fashion?

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