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The impact of influenza A(H1N1)pdm09 infection on immunosuppressed patients

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ABSTRACT

Before the advent of the influenza A(H1N1)pdm virus in 2009, the information available about the clinical manifestations and prognosis of influenza in immunosuppressed patients was scarce. With the 2009 pandemic, knowledge of the behavior, severity and importance of antiviral therapy for influenza A infection in immunocompromised hosts has increased considerably. The aim of the present manuscript is to review the main challenges of influenza in the most representative immunosuppressed populations such as solid organ transplant recipients, hematopoietic stem cell transplant recipients, patients with solid and hematological cancer and human immunodeficiency virus infected patients.

Impacto de la infección por gripe A(H1N1)pdm09 en los pacientes inmunodeprimidos

Palabras clave:
Pacientes inmunodeprimidos
Gripe
Pronóstico
Trasplante
Pacientes con cáncer
Virus de la inmunodeficiencia humana

RESUMEN

Antes de 2009, momento en que se produjo la aparición de la gripe A(H1N1)pdm, no existía mucha información sobre las manifestaciones clínicas y el pronóstico de la gripe en los pacientes inmunodeprimidos. Sin embargo, desde la pandemia de 2009, el conocimiento de la conducta, la gravedad y la importancia del tratamiento antiviral para la infección por gripe A en huéspedes inmunodeprimidos han aumentado considerablemente. En este artículo se describen cuáles son los principales desafíos de la gripe en las poblaciones inmunodeprimidas más representativas como son los pacientes infectados por el virus de la inmunodeficiencia humana, pacientes con cáncer sólido o hematológico y los receptores de trasplante de órganos o de células madre hematopoyéticas.

Introduction

The survival of patients with malignancies, autoimmune disorders, and end-stage organ diseases has improved in recent decades; however this improvement has led to an increase in the number of immunosuppressed patients (ISP). These patients are at risk for opportunistic infections and also for community acquired infections such as respiratory virus infections, with considerable related morbidity and mortality.[1-3].

Several studies regarding risk factors, clinical manifestations and outcomes of influenza A(H1N1)pdm09 have been published since the 2009 pandemic, which has led to advances in the understanding of influenza infection in an immunosuppressed setting. The aim of the present manuscript is to review the main challenges of influenza in the most representative ISP such as solid organ transplant (SOT) recipients, patients with solid and hematological cancer, human immunodeficiency virus (HIV) infection and hematopoietic stem cell transplant (HSCT).

Solid organ transplant recipients

Before the advent of the influenza A(H1N1)pdm virus in 2009, the information available about the clinical manifestations and prognosis of influenza in SOT hosts was scarce. With the 2009 pandemic, knowledge of the behavior, severity and importance of antiviral therapy of influenza A infection in organ transplant recipients has increased considerably.

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The incidence of influenza A(H1N1)pdm09 is higher in lung recipients (30-400 cases/1000 persons year[4-6]) than in other organ recipients such as kidney (19-22/1,000 persons/year[5-7]), liver (29/1,000 persons year[5]) or heart (37/1,000 patients year[5]). Although influenza A(H1N1)pdm09 infection can occur at any time after transplantation, it can occur in the early post-transplant period with increased severity and mortality.[8-12]

Influenza A(H1N1)pdm09 virus infection in SOT recipients is associated with considerable morbidity and mortality, greater than that described in the general population.[1,5,8,13-25] Between 22 and 81% of patients had images compatible with pneumonia, usually with multilobar involvement[4-6,8,12-14,17-22,26-28]; 30% to 100% of patients required hospital admission, one fifth suffered severe complications and a median of 7% died (range: 0-26%).[4-6,8,12-14,22,26-28]

As with the general population, delays in hospitalization and oseltamivir therapy were associated with mortality and intensive care admission in SOT recipients.[5,8,14,16,20,29] Bacterial co-infection, which occurs in 3.5% to 60% of SOT recipients with influenza, is another factor that significantly influences prognosis.[6,8,14,16,26] Thus, patients with influenza and bacterial infections experience higher mortality (43% vs. 2%), greater severity (87% vs. 2%) and a longer hospital stay (26 days vs. 5 days). Other factors associated with an adverse outcome are diabetes mellitus, pneumonia, antilymphocyte globulin and influenza infection occurring within the first 3 months post- transplant.[14,24]

Seasonal influenza virus seems to activate immunological mechanisms in the transplant organ leading to acute rejection in kidney, liver and lung transplant recipients and chronic rejection in lung transplant recipients.[30-32]. Several cases of allograft rejection in lung, liver and pancreas recipients have also been reported with influenza A(H1N1)pdm09 infection.[8,11,33,34]This risk is higher in lung recipients, of whom 39% may experience a progression or worsening of bronchiolitis obliterans syndrome.[6]

One issue of concern at the beginning of the influenza A(H1N1) pdm09 pandemic was the possibility of transmission of influenza from the donor to the recipient. Although influenza A(H1N1)pdm09 can cause viremia in mild and severe disease,[35,36] transmission from donor to recipient has not been reported in short published series.[37-39] Based on the limited available evidence, good short-term outcomes can be achieved with select organs procured from H1N1-infected donors. However, it remains important that transplanting teams have a high index of suspicion of influenza A(H1N1)pdm09 infection in donors, offer prophylaxis and undertake active surveillance of the recipients.

Patients with solid cancer

There are few studies regarding influenza A(H1N1)pdm09 in patients with solid cancer. Chemaly et al.[40] recently published a multicenter retrospective study of 115 cases of influenza A(H1N1) pdm09 infection in patients with solid tumors. Although, most patients with cancer are elderly, in this study severe influenza A(H1N1)pdm09 mostly affected young patients who were moderately or severely immunosuppressed.[40] This is a distinctive epidemiological feature of the 2009 pandemic that was also observed in the general population[41] and HSCT.[42] This fact has been explained by partial baseline immunization from former infections in the elderly population.[41,43,44] Obesity has been described as a new risk factor for influenza severity and mortality during the 2009 pandemic in the general population.[23] Although cancer patients are commonly underweight, in one study up to a third of cancer patients with influenza were obese.[40]

Clinical symptoms of influenza infection in solid cancer patients did not differ from non- ISP, but oncological patients had more frequent laboratory disturbances such as neutropenia, leukopenia and, anemia.[22] Bacterial co-infections were also more frequent in cases of influenza A(H1N1)pdm09 infection in the oncological setting (21% vs. 6.4%). Bacterial co-infections are especially important in neutropenia patients due to their frequency (40%) and mortality (40%).[22] The degree of immunosuppression (moderate to severe) at the time of diagnosis was the only independent factor associated with mortality among cancer patients with solid tumors in a multicenter study.[40]

The incidence of pneumonia in patients with cancer ranged from 23%-31%, many of whom needed intensive care unit support and up to one third of them dying.[22,40,45,46] In general, high rates of hospitalization (50%), and death (9-21%) have been reported in adults with cancer and influenza A(H1N1)pdm09 infection.[22,40,46,47] When compared with seasonal flu, children with influenza A(H1N1)pdm09 had more frequent low respiratory tract infections and died.[48] Patients who developed pneumonia and those who died were moderately to severely immunocompromised patients (70% vs. 27%).[40]

As previously mentioned, delayed hospital admission and antiviral therapy have been associated with unfavorable outcomes in the general population and in SOT recipients.[8,14,29] In a REIPI multicenter study, all patients with complicated diseases started therapy after the first 48 h of symptoms. Indeed, this was the only modifiable risk factor for complicated influenza A (H1N1)pdm09 infection in this population.[22] In other studies, the onset of treatment beyond the first 48 h of symptoms was independently associated with an increased risk of pneumonia and a trend towards greater mortality.[40] Although the proportion of patients receiving antiviral therapy was much higher than that described in series of seasonal influenza[1] an effort should be made to decrease the time to treatment with antivirals, especially in neutropenia patients.

Patients with hematological malignancies and hematopoietic stem cell transplant

Therapies required in HSCT and other hematological malignancies leave patients profoundly immunosuppressed and place them at a high risk for complications from seasonal influenza. A retrospective study of prepandemic seasonal influenza carried out in 4797 patients found an incidence of infection of 1.3% with a mortality rate of 28% among patients with pneumonia.[49] The incidence of influenza A(H1N1)pdm09 has not been widely studied, but retrospective studies report an incidence of 20-38 per 1000 patient-years.[50,51]

It has been speculated that the cytokine response associated with seasonal influenza infection may be decreased due to underlying disease and corticosteroid therapy in HSCT,[52] which determines infrequent systemic symptoms.[40] However, with influenza A(H1N1) pdm09, all studies have found that fever was the most common symptom, appearing in more than 80% of the cases.[22-25,29-42,45,50,51,53]

Influenza infection has usually a benign course when only the respiratory upper tract is affected.[51] The progression in hematological patients from the upper to the lower respiratory tract frequently lead to acute lung injury and death in seasonal influenza infection.[40,54,55] In a retrospective study in HSCT, influenza A(H1N1)pdm09 infection was independently associated with lower respiratory tract disease, hypoxemia and prolonged viral shedding compared to prepandemic influenza A and influenza B infection.[56] The proportion of cases with pneumonia in hematological patients with influenza A(H1N1)pdm09 infection ranges from 32% to 40%,[42,50,56,57] without significant differences when compared with allogeneic and autologous hematopoietic stem transplants. When influenza infection is complicated with pneumonia the prognosis worsens, with one-third requiring mechanical ventilation and with 9% to 25% dying.[22,42,45,50,51,53] Some studies have attempted to identify risk factors for pneumonia in this population. Schnell et al.[3] in a retrospective study of ISP (mostly hematological) with prepandemic seasonal influenza, found that the factors independently associated with pneumonia were influenza A (OR: 5.54; 95%CI, 1.16-26.47) and hematological

malignancies (OR: 3.85; 95%CI, 1.1-14.5). Ljungman et al.[42] found 2 independent risk factors for pneumonia: lymphopenia and age. In allogeneic HSCT an unrelated or mismatched family donor lymphopenia and age were also independently associated with respiratory inferior tract progression. George et al.[51] observed that low respiratory tract involvement was associated with severe immunosuppression, because of either a recent HSCT (<100 days) or immunosuppression due to graft vs. host disease.

The global mortality rate for influenza in hematological patients ranges from 7% to 20%,[22,42,45,50,51,53,58] and from 14% to 40% in hospitalized patients.[22,42,45,51,53,58] Age has also been found to be an independent risk factor for other adverse outcomes such as mechanical ventilation and death. Series of children with hematological disease and influenza A(H1N1)pdm09 usually report lower mortality (<3%).[1,22,45,47,50,53,59-62] Other factors related to adverse outcomes, such as mechanical ventilation or death, were hospital-acquired influenza infection, profound lymphopenia, neutropenia, lack or delayed antiviral treatment and graft vs. host disease treated with immunosuppressants.[1,51,56] Allogeneic vs. autologous transplants were not found to have an impact on patient outcomes in one study[42]; however that study may have a reporting bias.

The proportion of co-infected patients is higher in hematological patients than in non-ISP. This is especially relevant in severe cases, three quarters of whom had a confirmed bacterial co-infection. The isolated bacteria were also different from non-ISP, with a higher proportion of gram-negative bacilli and *Staphylococcus aureus* infections.[22] The high frequency of co-infections in severe cases and the presence of "non-strict" community-acquired respiratory pathogens would suggest, based on the local epidemiology, the need to use broad-spectrum antibacterial agents in severe cases of influenza. Invasive fungal infections are frequent among hematological patients. It has been suggested that prepandemic influenza may be related to a greater susceptibility to developing invasive aspergilosis.[63] The association of invasive aspergillosis and influenza has been reported in 5 ISP adults (2 liver transplants and 3 acute myeloid leukemia patients). Most of the cases occurred days after the influenza diagnosis as a worsening of respiratory symptoms once the infection had initially improved. Two of the 3 patients with leukemia died due to this infection.[63]

The rates of oseltamivir resistance have been quite low for influenza A(H1N1)pdm09 in the general population. The first cases of influenza A(H1N1)pdm09 that were resistant to oseltamivir were reported in ISP.[64] Thereafter, oseltamivir resistance has been demonstrated in this group of patients, especially in those with hematological malignancies or HSCT with a proportion greater than that of the general population (9.3% vs. 2.4%).[42,46,61,64-67] The H275Y NA mutation, a substitution known to confer a high level of oseltamivir resistance, was detected in 4 of 7 hematological patients who had detectable nucleic acids after more than 4 days of oseltamivir therapy. These 4 patients comprised 13.3% of those who received oseltamivir in this cohort. All viruses were susceptible to oseltamivir at baseline.[46] The resistance to oseltamivir seems to affect the severity of the disease in these patients, as most of the patients with resistant strains were admitted to the intensive care unit with a mortality rate between 50% and 100%.[42,46,61,66,67] These results must be biased, since it is likely that severe disease prompted testing for resistance. The oseltamivir-resistant H275Y mutants remain susceptible to the alternative neuraminidase inhibitor zanamivir, which should be considered in these cases.

Patients with human immunodeficiency virus-infection

Influenza is a common cause of respiratory infection in the HIV population. The studies before highly active antiretroviral therapy and pandemic influenza A(H1N1)pdm09 showed that patients with HIV infection were at increased risk for flu symptoms and complications with an increase of mortality if infected. Although antiretroviral therapy can partially restore alterations in cellular and humoral immunity in these patients, it remains unclear whether antiretroviral therapy reduces the risk of illness and complications.[68-72]

During the 2009 pandemic, studies were performed to determine the seroprevalence and the incidence of influenza A(H1N1)pdm09 in HIV-infected patients with respect to the general population. Kok et al.[73] in a cohort of HIV-infected patients in Sydney found that the seroprevalence was similar to that of the general population (36% vs. 40.1% in the 18-34 age group and 35.1% vs. 26.3% in the 35-64 age group). The seroconversion rate was also similar (23.8% vs. 24.3% for 18-34 years and 14.5% vs. 19.6% for 35-64 years), showing no increased incidence in patients with lower CD4 T cell counts or detectable HIV viral loads. A study on the WIHS cohort of U.S. women showed that seroconversion was 16.8 per 100 persons/year, similar to that of uninfected women. These studies did not specify the proportion of vaccinated patients in each group.[74]

From clinical studies during the 2009 pandemic in countries that ensure monitoring and treatment of HIV infection, 2 studies conducted in Spain deserve mention. Martínez et al.,[75] conducted a case-control study in patients with confirmed influenza A(H1N1) pdm09 virus infection. Patients with HIV infection were older and were more frequently tobacco smokers, but they had less comorbidity. Most patients had well- controlled HIV infection (95% HIV viral load <50 copies/mL). Patients with HIV infection presented more gastrointestinal symptoms but had less pneumonia or respiratory failure, with similar complications and length of hospital stay. A higher percentage of HIV-infected patients received oseltamivir. The CD4 T cell counts and HIV viral loads remained unchanged, a finding already reported by Golden et al.[76]

The study conducted by the influenza pandemic group of REIPI in 13 Spanish hospitals included 585 patients admitted to the hospital with pandemic flu, 26 of whom were infected with HIV. Most of the HIV patients had good control of the disease (84% with an undetectable HIV viral load and a median CD4 cell count of 503/mm^3), and 55% had received the seasonal influenza vaccine. Age was similar between groups, but HIV-infected patients were more frequently smokers and the prevalence of chronic obstructive pulmonary disease and liver disease was higher. There were no differences in clinical, laboratory or initial radiological findings. The proportion of patients receiving oseltamivir, complications, intensive care unit admission, length of hospital stay and death were also similar.[77]

Studies of influenza pandemic in other geographic areas such as South Africa or Peru found a higher HIV prevalence in patients dying with confirmed influenza A(H1N1)pdm09 infection than expected. In Mexico, 16 out of 30 HIV-infected patients diagnosed with influenza A(H1N1)pdm09 infection were hospitalized and 6 died. Most of them were profoundly immunosuppressed (CD4 cells count<100/mm^3). Mortality was higher in patients with opportunistic infections and delayed onset of oseltamivir therapy.[78] Therefore, mortality from influenza-related complications is elevated in patients with advanced HIV infection and/or AIDS, while well-controlled patients with proper antiretroviral treatment and recommended guidelines for influenza vaccination and treatment had a similar outcome as the non-HIV infected population. The management of patients with influenza and HIV infection should be similar to other populations at risk, including treatment with neuraminidase inhibitors. Although oseltamivir phosphate is hydrolyzed in the liver to its active form, no significant interactions between neuraminidase inhibitors and antiretroviral treatment have been reported.

Influenza A(H1N1)pdm09 in ISP causes disease with clinical symptoms similar to those of non-ISP, but with higher related mortality, especially in the most immunosuppressed, such as neutropenia patients, those with graft vs. host disease or advanced HIV infection or AIDS. Clinicians should have a high index of suspicion in all cases of pneumonia, even if there is evidence of bacterial

infection in pandemic or epidemic periods, and should initiate antiviral therapy early. Moreover, some of the complications that arise after influenza A(H1N1)pdm09 infection, such as secondary bacteria or fungal infections or selection of oseltamivir-resistant virus, may lead to a torpid clinical course in ISP. Clinicians should consider these possibilities in cases of relapse or lack of improvement from influenza infection.

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Conflicts of interest

All authors declare that they have no conflicts of interest in this article.

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