Oseltamivir Prescription Practices during the 2017-2018 Influenza Season

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Background: Influenza is an acute contagious respiratory illness caused by influenza A and B viruses worldwide. Influenza is estimated to cause approximately three to five million severe illnesses and 250,000 – 350,000 deaths annually. It is considered an economic burden costing approximately $87.1 billion annually. The use of Oseltamivir can act as a chemoprophylactic and therapeutic agent to reduce the duration and severity of the infection.

Objective: To review and analyze influenza cases treated with Oseltamivir during the influenza season of 2017-2018.

Design: A Retrospective Cross-Sectional Study.

Setting: King Hamad University Hospital, Bahrain.

Method: Two hundred and twenty-one prescriptions of antiviral Oseltamivir were reviewed from 1 October 2017 to 31 March 2018. Ten patients were excluded due to incomplete medical records.

Result: Two hundred eleven Oseltamivir were prescribed, 121 (57.35%) prescribed for hospitalized patients, 9 (4.27%) for out-patients and 81 (38.39%) in emergency department. Fourteen (11.57%) patients required ICU/NICU admission. The mean age was 36.37 years±26.05 SD. Ninety-two (43.60%) patients were ≥41 years old. Peak prescribing rate was between December and January. Lab test was performed for the majority of the patients, 192 (91%). Ninety-three (44.08%) of the patients had their treatment initiated in ≤48 hours and 117 (55.45%) initiated in ≥48 hours. Earlier treatment was not significant in reducing the length of stay (P=0.3082). Four (1.9%) patients died due to influenza infection.

Conclusion: All patients received doses adjusted based on their renal function and body weight. Patient and family education need to be emphasized because approximately 40% of the cases acquired the infection due to contact with an influenza-positive patient.

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Influenza is transmitted through sneezing and coughing via large droplets. In addition, some studies suggest transmission via small aerosols (≤5 microns) that are released into the air during breathing[1]. The influenza envelope consists of two main glycoproteins that are important in the duplication of the virus, hemagglutinin and neuraminidase. Influenza is estimated to cause approximately three to five million severe illness and 250,000–350,000 deaths annually. In the European Union, there are approximately 40,000–220,000 annual deaths attributable to influenza[2]. On average, severe cases and mortality are more likely to be among elderly patients aged ≥65 years, pediatric patients aged ≤2 years and persons with medical co-morbidities classified as "high risk influenza complications"[3].

Influenza infection and its complications can be prevented with an annual vaccination which is known to be the most effective method in influenza prevention. It is recommended for any individual aged ≥6 months[4]. The use of neuraminidase inhibitors such as Oseltamivir can act both as a chemoprophylactic agent as well as a therapeutic agent to reduce the duration and severity of infection[5]. It is a sialic acid analog, competitively inhibiting the virus neuraminidase enzyme which in-turn prevents the release of the newly developed virions. Oseltamivir is a pro-drug metabolized by liver enzymes from oseltamivir phosphate to its active form, oseltamivir carboxylate. It is known to be more effective when administered within ≤48 hours from the onset of symptoms[6]. Starting treatment ≥48 hours is known to decrease its efficacy.

It is still recommended to administer oseltamivir for suspected or confirmed infected persons even if the onset of illness is ≥48 hours[7]. The recommended dose for adults is 75 mg twice daily for therapeutic cases, 75 mg once daily for chemoprophylaxis and weight based dose for pediatrics[6]. Doubling the dose of oseltamivir to 150 mg in adults has been suggested for severely ill patients. However, it is found that there are no observable benefits for larger doses compared to standard doses[8,9]. The risk of neuraminidase resistance has been reported among influenza viruses[10].

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The aim of this study is to evaluate the Oseltamivir use for influenza infection patients during season 2017 and 2018.

METHOD

Two hundred twenty-one prescriptions of antiviral Oseltamivir were prescribed for patients diagnosed with laboratory-confirmed influenza or had positive flu symptoms from 1 October 2017 to 31 March 2018. Ten patients were excluded due to incomplete medical records. Patient's data were documented and analyzed by SPSS and Microsoft Office Excel using applicable statistical test. P-values less than 0.05 were considered significant.

RESULT

Two hundred eleven Oseltamivir were prescribed; 121 (57.35%) were prescribed for hospitalized patients, 9 (4.27%) for out-patients and 81 (38.39%) as emergency. Influenza infection was the primary diagnosis for 116 (95.87%) of hospitalized patients. Five (4.13%) were hospitalized due to other medical diagnosis and acquired influenza while being hospitalized. Fourteen (11.57%) required intensive care (ICU/ NICU).

One hundred twenty-nine (61.14 %) were females, 100 (77.52%) were adults and 29 (22.48%) were pediatrics. Fifty-eight (70.73%) were adult males and 24 (29.27%) were pediatrics. The mean age was 36.37 years ± 26.05 SD. Most-treated age group was ≥41 years, 92 (43.60%) followed by 53 (25.12%) in the 0-10 years group, 31 (14.69%) in the 21-30 years group, 25 (11.85%) in the 31-40 years group and 10 (4.47%) in the 11-20 years group, see table 1. In the beginning of the influenza season oseltamivir utilization was the lowest and gradually increased until it reached the peak between December and January, 54 (25.59%) and 58 (27.49%), respectively. In addition, a clear decline was noticed by the end of January, see figure 1.

Table 1: Personal Characteristics of Patients (n=211)

Male		Female	
82 (38.86%)		129 (61.14%)	
Adult	**Pediatric**	**Adult**	**Pediatric**
58 (70.73%)	24 (29.27%)	100 (77.52%)	29 (22.48%)
Age group (%)			
Mean		36.37 years	
0-10 years		53 (25.12%)	
11-20 years		10 (4.47%)	
21-30 years		31 (14.69%)	
31-40 years		25 (11.85%)	
Above 41 years		92 (43.60%)	

One hundred ninety-two (91%) patients were tested for Reverse-Transcriptase Polymerase Chain Reaction (RT-PCR) and 19 (9%) started treatment without any laboratory investigations. In addition, laboratory test was requested for 7 (3.65%), but no reagent was in stock, 16 (8.33%) of investigated patients had a negative influenza infection; although, they were treated with oseltamivir. In addition, 35 (18.23%) of laboratory-confirmed influenza were infected with

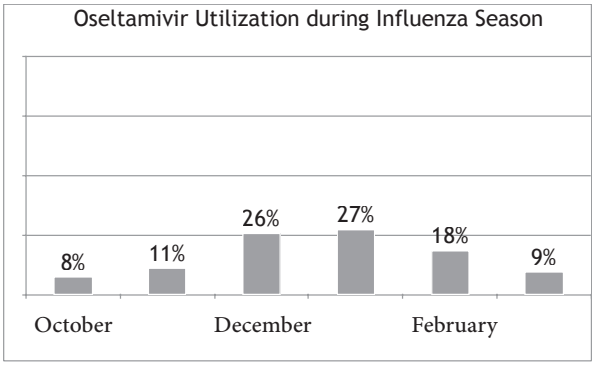

Figure 1: Oseltamivir Utilization during Influenza Season

influenza A, 113 (58.85%) A H1N1, 26 (13.54%) influenza B and 1 (0.51%) had mixed infection 'Influenza B and A H1N1'. Influenza A viruses were highly circulated at the beginning of influenza season compared to influenza B. All cases treated with oseltamivir were infected with influenza A in October and November, see table 2. Two hundred nine (99.05%) patients received a therapeutic dose of Oseltamivir and 2 (0.95%) received a prophylactic dose. Various dose regimens were prescribed for the patients according to their conditions. It was found that 137 (64.93%) received a standard dose of Oseltamivir (75mg) while 9 (4.27%) required a double dose (150 mg). Twelve (5.69%) patients needed regimen adjustment due to their impaired renal function. Fifty-three (25.12%) were pediatrics who received doses according to their body weight. Ninety-three (44.08%) patients' treatment was initiated within 48 hours whereas 117 (55.45%) was initiated after 48 hours.

Table 2: Circulated Influenza Types during the Season

	Influenza A	Influenza B	H1N1	Mixed infection
October	13 (6.16%)	0	1 (0.47%)	0
November	6 (2.84%)	1 (0.47%)	16 (7.58%)	0
December	9 (4.27%)	5 (2.37%)	29 (13.74%)	1 (0.47%)
January	7 (3.32%)	12 (5.69%)	32 (15.17%)	0
February	0	4 (1.90%)	28 (13.27%)	0
March	0	4 (1.90%)	7 (3.32%)	0

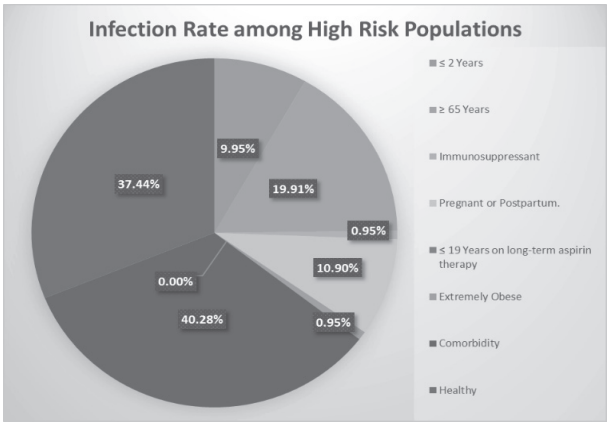

Figure 2: Infection Rate on High-Risk Populations

Table 3: Influenza Consequences Based on Age Groups

	Age Group					Mortality
	0-10	**11-20**	**21-30**	**31-40**	**>41**	>41
	53 (23.98%)	11 (4.98%)	34 (15.83%)	28 (12.67%)	95 (42.99%)	4
Test Result						
Negative	1 (1.87%)	2 (18.18%)	2 (5.88%)	3 (10.71%)	12 (12.63%)	0
Positive	48 (90.57%)	7 (63.64%)	24 (70.59%)	20 (71.43%)	77 (81.05%)	4 (100%)
Influenza type						
Influenza A	0	0	8 (33.33%)	4 (20%)	24 (31.1%)	0
Influenza A (H1N1)	48 (100%)	6 (85.71%)	14 (58.33%)	13 (65%)	32 (42.56%)	2 (50%)
Influenza B	0	1 (14.29%)	2 (8.33%)	3 (15%)	20 (25.97%)	2 (50%)
Mixed infection	0	0	0	0	1 (1.23%)	0
Hospitalization						
Normal Ward	22 (41.51%)	3 (27.27%)	18 (52.94%)	7 (25%)	57 (60%)	1 (25%)
ICU/NICU	1 (1.89%)	1 (9.09%)	2 (5.88%)	0	10 (10.53%)	3 (75%)
Onset of treatment						
<48 hours	13 (24.53%)	8 (72.73%)	17 (50%)	16 (57.14%)	39 (41.05%)	1 (25%)
>48 hours	40 (75.47%)	2 (18.18%)	13 (38.24%)	9 (32.14%)	53 (55.79%)	3 (75%)

As shown in figure 2, 132 (62.56%) patients had single or multiple risk factors compared to 79 (37.44%) risk free, P≥0.01. Eighty-five (40.28%) patients were known to have single or multiple comorbidities, 42 (19.91%) were ≥65 years, 23 (10.90%) were pregnant or 2 weeks postpartum, 21 (9.95%) were ≤2 years and 2 (0.95%) were either immunosuppressant or obese patients (BMI ≥40). Furthermore, 83 (39.34%) were infected due to contact with influenza-positive patients. By the end of the influenza season, four (1.90%) patients treated with oseltamivir died due to influenza infection (two were infected with influenza A H1N1 and two with influenza B), see table 3.

DISCUSSION

Earlier circulated influenza A was observed by other studies which match our findings. As reported in Saverio Caini's study, influenza A was circulated two or more weeks prior to influenza B in Bahrain, Egypt, Jordan, Qatar and Turkey, where opposite the scenario was observed in Algeria and Oman[11]. Peak influenza infection was found to occur at different times; in Jeddah and Kuwait, the highest incident rate was between October and November, which is earlier to what was found in this study[12,13,14]. However, a similar outcome was found in Lebanon (January to February)[12,13,14]. Influenza virus is known to be a highly contagious illness. Previously, it was believed that it has the ability to be transmitted via large air droplets (<5microns)[15]. Recently, it was found that influenza viruses could exceed this limit and be transmitted via small air aerosols (>5micron)[1].

In addition, it has been found that 39.34% of infected patients were in contact with a positive flu patient. Furthermore, such a high percentage could reflect that the community is not well educated or aware of how to protect themselves when in contact with flu positive patients. A higher percentage was observed in Saudi Arabia, 53%[14].

In this study, oseltamivir was used widely in patients above 41 years old (43.60%) which is justified as this group is more likely to have single or multiple risk factors, especially those below 5 years according to CDC finding. A similar observation found that most infected groups was above 65 years (45.2%) while in another study, the most infected age group were below 2 years followed by adults above 50 years old (75.2% and 20.36%, respectively)[2]. Administration of antiviral therapy within 48 hours of symptoms onset is known to be associated with better outcome compared to late administration. In this study, the difference between the two groups was not significant (P=0.3082)[6,15]. This finding could be a consequence of the fact that most of influenza infected patients were comorbid and their discharge delayed due to their underlying medical conditions.

In general, influenza is known to be a mild self-limiting infection. In our study, it was found that 42.66% were treated as outpatient and emergency while severe cases were hospitalized either in the normal ward or in the ICU/NICU (88.43% and 11.57%, respectively).

In this study, four patients died. The majority of hospitalized patients were having single or multiple risk factors. In a study, it was found that 33% of the influenza cases required ICU hospitalization and 12% died[2]. In another study, 62 infants had laboratory-confirmed influenza, 6.5% of them required ICU hospitalization[16]. In another study, 85.4% of the patients treated with oseltamivir and 7.7% out of 73% of hospitalized patients needed ICU hospitalization[12]. In the Middle East and North Africa, 76.5% and 23.5% of influenza infections were due to influenza A and B virus during the 2010-2016 influenza seasons, respectively[16]. Among influenza A subtypes; 61.9% cases were due to pandemic A(H1N1), 24% were due to A(H3N2) and the remaining were either unsubtyped (undifferentiated type of influenza virus) or pre-pandemic A(H1N1)[16]. Influenza infection could appear in single or multiple peaks during the season. It has been observed that in Bahrain and Qatar, the primary peaks were in November to December and the second peak is in March. While in Oman, the peaks were in January and March. Kuwait peaks were in October and November[11,16].

In 2017, a study which included Gulf Cooperation Council (GCC) healthcare workers found that the vaccination rate is low (17%) and that it was influenced by the individual type of work, gender, vaccine awareness, previous vaccination issues[13].

CONCLUSION

Oseltamivir utilization in this study was following the acceptable standards. It was found that the majority of patients initiated their treatment after lab investigations. Few complications required ICU and only 4 patients died; all of them with single or multiple risk factors. All patients received doses adjusted based on their renal function and body weight. Earlier administration of oseltamivir for hospitalized patients was not significantly helpful in shortening hospital stay compared to late administration.

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