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Low rate of oseltamivir prescription among adults and children with confirmed influenza illness in France during the 2018–19 influenza season

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Background: Oseltamivir shows effectiveness in reducing influenza-related symptoms, morbidity and mortality. Its prescription remains suboptimal.

Objectives: We aim to describe oseltamivir prescription in confirmed cases of influenza and to identify associated factors.

Methods: A prospective monocentric observational study was conducted between 1 December 2018 and 30 April 2019. All patients with a virologically confirmed influenza diagnosis were included. Factors associated with oseltamivir prescription were studied.

Results: Influenza was confirmed in 755 patients (483 children and 272 adults), of which 188 (25.1%) were hospitalized and 86 (11.4%) had signs of severity. Oseltamivir was prescribed for 452 patients (59.9%), more frequently in children than in adults [329/483 (68.1%) versus 123/272 (45.2%), $P < 0.001$]. Factors associated with oseltamivir prescription were evaluated in 729 patients (246 adults and 483 children). Patients with at least one risk factor for severe influenza received oseltamivir less frequently (50%, 137/274) than those without risk factors (70%, 315/452) ($P < 0.001$). Pregnant women received oseltamivir in 81% of cases (17/21). Severe influenza cases were treated with oseltamivir in only 45.3% (39/86). The median duration of symptoms was 24 h (IQR 12–48) in treated patients versus 72 h (IQR 48–120) in untreated patients ($P < 0.01$).

Conclusions: Oseltamivir should be administered as early as possible, preferably within 24–48 h after illness onset, for the best benefits. It is, however, very important to promote the use of neuraminidase inhibitor ('NAI') treatment beyond 48 h in some specific patient populations.

Introduction

Annual seasonal influenza epidemics are associated with high morbidity and mortality worldwide and affect both children and adults.[1] According to the WHO, about one billion influenza cases occur each year, of which 3–5 million are severe, causing 290 000 to 650 000 seasonal influenza-associated respiratory deaths. Adults 65 years of age or older, children younger than 5 years of age (especially under 2 years of age), pregnant women and people with certain chronic diseases are at particularly high risk of influenza-related complications.[2,3] It is for such complications that guidelines recommend prescribing a neuraminidase inhibitor (NAI) for adults and children with documented or suspected influenza illness. This recommendation is confirmed regardless of the duration of symptoms in patients hospitalized because of influenza disease, for children younger than 2 of age and adults 65 years of age or older, and for pregnant women and those within 2 weeks postpartum.[4,5] Outpatients of any age with severe or progressive illness and those at high risk of complications of influenza illness (chronic medical conditions and immunocompromised patients) should be treated regardless of the duration of symptoms.[4,5] The American Academy of Pediatrics supports the use of oseltamivir to treat influenza in both term and preterm infants from birth.[3] Initial studies showed that the benefit of oseltamivir was greater if

administration was done early (≤48 h) after the beginning of symptoms.[6–8] Recent evidence showed that a benefit of use is still present if administered after 48 h.[9–13] Despite these recommendations and evidence supporting the use of NAIs to reduce morbidity and mortality,[14,15] they remained underused.[8] A few studies have attempted to evaluate the prescription of oseltamivir in clinical practice.[16,17]

We aim to describe the prescription of oseltamivir and the associated factors during the 2018–19 influenza season in a French tertiary care hospital.

Methods

A prospective observational study was conducted between 1 December 2018 and 30 April 2019 at the University Hospital of Saint Etienne, France. All inpatients and outpatients, adults and children, with a confirmed diagnosis of influenza infection by rapid influenza diagnostic test,[18] RT–PCR or multiplex PCR using FilmArray (BioFire Diagnostics, Inc., a bioMérieux company) on nasopharyngeal aspirates or expectorations were included.

Demographic, clinical and biological data at admission were collected from the medical charts. Clinical signs of severity were defined for adults as a qSOFA score ≥2 or a qSOFA score = 1 with signs of respiratory failure (respiratory rate >22 breaths/min and oxygen requirement >2 L) and for children as seizure, asthma PRAM score >5, bronchiolitis WANG score >4 or respiratory failure (tachypnoea and/or oxygen requirement >2 L). Oseltamivir prescription, dosage, initiation date from start of influenza symptoms and duration of treatment were assessed. Patients with medical charts missing oseltamivir prescription information were considered as not treated.

Results are reported as number and percentage for categorical variables and as mean and range or median and IQR for continuous variables. Missing data for each variable were excluded. For univariate analysis, χ^2 test and Fisher's exact test were used as appropriate for categorical data and *t*-test and Mann–Whitney test were used as appropriate for numerical variables. To identify variables significantly associated with prescription of Tamiflu, we performed two forward logistic regression analyses, separately for children and adults. The models included variables yielding a *P* value of ≤0.20 in univariate analysis. Variables are reported as estimated ORs with their 95% CI. Co-linearity and interactions were tested. The Hosmer–Lemeshow test was used to check goodness of fit of the logistic regression. All tests were two-sided and $P < 0.05$ was considered to indicate statistical significance. Statistical tests were performed using MedCalc® Statistical Software v19.0.3 and Minitab® 18.1. This study was approved by the University Hospital of Saint Etienne Ethics Committee (approval ref. IRBN112019/CHUSTE).

Results

A total of 755 patients, 483 children and 272 adults, with laboratory-confirmed influenza illness were included during the study period. Influenza virus type A was detected in 749 patients, type B in 5 patients and there was one case of AB coinfection. The characteristics of the patients are given in Table 1. Among the overall population, 83.6% (631/755) were at risk of severe influenza. Among these at-risk patients, data on vaccination were available for 157/631 (24.9%), with a vaccine coverage of 57.9% (91/157) among them. Patients were hospitalized in 24.9% of cases (181/727), significantly more frequently among adults (47.1%, 115/244) (see Table 1). Percentages of severe influenza cases and ICU admission were 11.9% (86/720) and 4.0% (29/717), respectively. The mean time from symptom onset to confirmed influenza diagnosis was 48.4 h (SD 65.6) in children and 97.9 h (SD 93.40) in adults ($P < 0.01$).

Overall, 59.9% (452/755) of patients received treatment with oseltamivir, 68.1% (329/483) of children and 50% (123/246) of adults ($P < 0.01$). The factors associated with oseltamivir prescription are given in Table 2.

For patients at risk of severe influenza, oseltamivir was prescribed for 45.2% (76/168) of cases for patients >65 years and 72.1% (129/179) of cases for patients <2 years. In pregnant women, patients with chronic heart disease, patients with chronic respiratory disease and immunocompromised patients, oseltamivir was prescribed for 81% (17/21), 43.4% (46/106), 56.4% (75/133) and 56.3% (40/71), respectively.

Among patients hospitalized because of influenza, 55.2% (100/181) received treatment with oseltamivir [68.2% (45/66) for children and 47.8% (55/115) for adults]. Oseltamivir was prescribed for 45.3% (39/86) of patients presenting severity criteria as defined above and for 52% (15/29) of ICU admissions (see Table 1). In univariate analysis, the factors negatively associated with oseltamivir prescription were hospitalization for influenza ($P = 0.03$), severity criteria ($P < 0.01$), chronic heart disease ($P < 0.01$), chronic renal failure ($P < 0.01$), diabetes ($P = 0.01$) and obesity ($P = 0.05$). The only factor associated with increased likelihood of prescription was pregnancy ($P = 0.02$).

Patients with symptom onset ≤48 h were more likely to receive oseltamivir than patients with a longer history of symptoms ($P < 0.01$, total population). Among patients receiving oseltamivir, the median duration of symptoms was 24 h (IQR 12–48) versus 72 h (IQR 48–120) for untreated patients ($P < 0.01$). Of the 452 patients who received oseltamivir, a correct dosage was prescribed for 90% (296/329) of children and 72.9% (70/96) of adults ($P < 0.01$).

After adjustment for cofounders, only an increase in duration of symptoms before diagnosis was associated with a decrease in prescription of oseltamivir to paediatric patients (OR = 0.25, 95% CI = 0.19–0.33) (Table 3).

Discussion

In this prospective monocentric study, including a large population with laboratory-confirmed influenza in a teaching hospital, we found that oseltamivir was used only in approximatively 60% of cases (50% among adults and 68% among children). Prescription rates of oseltamivir reported here are in the range of those found in the literature. In fact, previous studies reported rates ranging from 12%[19] to 83.4%.[20] Overall, the global use of oseltamivir remains low in adults and children,[17,21,22] despite recommendations.[4,5]

The prescription rate of oseltamivir in our study was better in patients presenting fever for less than 48 h. Current guidelines[4,7] recommend to give oseltamivir as soon as possible, especially in the first 48 h, because of a maximized effect of oseltamivir at the beginning of the disease when the virus is in its replication phase.[11,23] Several data support that, when given early (≤48 h from symptom onset), NAI treatment may lead to several benefits for patients and could help reduce ICU mortality, complications of hospitalized patients, hospitalizations and hospital length of stay.[24–27]

Table 1. Characteristics and clinical presentation of the 755 influenza patients diagnosed during December 2018 to April 2019 at the University Hospital of Saint Etienne, France

	Overall, *N* = 755	Paediatric, *N* = 483	Adult, *N* = 272	*P*
Demographics				
age (years), mean (SD)	–	4 (3.6)	66.1 (21)	NR
age (years), *n* (%)				
0–2	179 (23.7)	179 (37.1)	–	–
>2–5	162 (21.5)	162 (33.5)	–	–
18–65	101 (13.4)	–	101 (37.1)	–
>65	168 (22.3)	–	168 (61.8)	–
gender[a], *n* (%) or *n*/*N* (%)				
male	372/729 (51)	260 (53.8)	112/246 (45.5)	**0.01**
female	357/729 (49)	223 (46.2)	134/246 (54.5)	**0.01**
Chronic diseases[a], *n* (%) or *n*/*N* (%)				
overall chronic diseases	361/753 (47.9)	109/483 (22.6)	252/270 (93.3)	<**0.01**
chronic respiratory disease	133/752 (17.7)	57/482 (11.8)	76/270 (28.1)	<**0.01**
chronic heart disease	106/728 (14.6)	12 (2.5)	94/245 (38.4)	<**0.01**
neurological disease	42/753 (5.6)	22 (4.6)	20/270 (7.4)	0.1
chronic renal failure	46/728 (6.3)	6 (1.2)	40/245 (16.3)	<**0.01**
diabetes	54/728 (7.4)	2 (0.4)	52/245 (21.2)	<**0.01**
immunosuppression[b]	71/751 (9.5)	5/481 (1)	66/270 (24.4)	<**0.01**
obesity[c]	36/611 (5.9)	5 (1)	31/128 (24.2)	<**0.01**
Clinical characteristics				
pregnancy[a], *n* (%) or *n*/*N* (%)	21 (2.8)	0	21/134 (15.7)	–
BMI[d] (kg/m^2), mean (SD)	–	15.8 (2.5)	26.2 (5.3)	NR
glomerular filtration rate (mL/min/1.73 m^2), mean (SD)	–	137.2 (55)	71.9 (31.6)	NR
Charlson comorbidity index, mean (range)	–	–	4.5 (0–13)	–
vaccination in current season[a], *n*/*N* (%)	93/174 (53.4)	15/34 (44.1)	78/140 (55.7)	–
Paraclinical findings, *n*/*N* (%)				
chest X-ray compatible with influenza infection[a]	108/240 (45)	13/43 (30.2)	95/197 (48.2)	**0.04**
Microbiological diagnosis, *n* (%)				
influenza A virus	749 (99.3)	481 (99.6)	269 (98.9)	–
influenza B virus	5 (0.6)	2 (0.4)	3 (1.1)	–
positive RIDT result	506 (67)	463 (95.9)	44 (16.2)	–
positive influenza RT–PCR	234 (31)	21 (4.3)	213 (78.3)	–
positive multiplex PCR	83 (11)	68 (14.1)	15 (5.5)	–
Clinical course				
duration of clinical signs before diagnosis (h), mean (SD)	–	48.4 (65.6)	97.9 (93.4)	<**0.01**
severity criteria[a,e], *n* (%) or *n*/*N* (%)	86/720 (11.9)	43 (8.9)	43/237 (18.1)	<**0.01**
hospitalization for influenza[a], *n* (%) or *n*/*N* (%)	181/727 (24.9)	66 (13.7)	115/244 (47.1)	<**0.01**
ICU admission[a], *n* (%) or *n*/*N* (%)	29/717 (4)	4 (0.8)	25/234 (10.7)	–
hospital length of stay (h), mean (SD)	–	48 (49)	144 (117.4)	<**0.01**
death during hospitalization, *n* (%)	9 (1.2)	1 (0.2)	8 (2.9)	<**0.01**
Oseltamivir prescription				
oseltamivir use[a], *n*/*N* (%)	452/729 (62)	329/483 (68.1)	123/246 (50)	<**0.01**
correct dosage prescribed[a], *n*/*N* (%)	366/425 (86.1)	296/329 (90)	70/96 (72.9)	<**0.01**
duration of prescription (days), mean (SD)	–	4.9 (0.5)	5.1 (0.8)	**0.01**
antibiotic prescription[a], *n* (%) or *n*/*N* (%)	218/715 (30.5)	66 (13.7)	152/232 (65.5)	<**0.01**

RIDT, rapid influenza diagnostic test; NR, not relevant.
P values are shown in bold when ≤0.05.
[a]Missing data, the denominator corresponds to the number with known data.
[b]Including immunosuppressive drugs, cancer, chemotherapy, transplant, HIV, leukaemia, drepanocytosis and asplenia.
[c]Including obese children from grade 1 (IOTF ≥30) and obese adults from grade 1 (BMI ≥30).
[d]BMI was calculated for patients with available height and weight data to assess obesity.
[e]Signs of severity in adults included qSOFA score ≥2 or qSOFA score = 1 with signs of respiratory failure (respiratory rate >22 breaths/min and oxygen requirement >2 L). Signs of severity in children included seizure, asthma PRAM score >5, bronchiolitis WANG score >4 or respiratory failure (tachypnoea and/or oxygen requirement >2 L).

Table 2. Factors associated with oseltamivir prescription in univariate analysis

	Overall			Paediatric			Adult		
	oseltamivir +, $N=452$[a]	oseltamivir −, $N=277$[a]	*P*	oseltamivir +, $N=329$[a]	oseltamivir −, $N=154$[a]	*P*	oseltamivir +, $N=123$[a]	oseltamavir −, $N=123$[a]	*P*
Demographics									
age (years), median (IQR)	–	–	–	2.97 (1.01–5.65)	3.5 (1.5–5.4)	0.13	71 (51.8–84)	71 (55–82.8)	0.89
male, *n/N* (%)	225/452 (49.8)	147/277 (53.1)	0.39	179/329 (54.4)	81/154 (52.6)	0.71	46/123 (37.4)	66/123 (53.7)	**0.01**
Chronic diseases, *n/N* (%)									
risk factor for severe influenza[b]	137/452 (30.3)	119/277(43.0)	<0.01	52/329 (15.8)	26/154 (16.9)	0.79	85/123 (69.1)	93/123 (75.6)	0.32
chronic respiratory disease	75/452 (16.6)	52/275 (18.9)	0.43	39/329 (11.9)	18/153 (11.8)	0.98	36/123 (29.3)	34/122 (27.9)	0.81
chronic heart disease	46/452 (10.2)	60/276 (21.7)	<**0.01**	7/329 (2.1)	5/154 (3.2)	0.46	39/123 (31.7)	55/122 (45.1)	**0.03**
neurological disease	26/452 (5.8)	16/276 (5.8)	0.98	18/329 (5.5)	4/154 (2.6)	0.24	8/123 (6.5)	12/122 (9.8)	0.34
chronic renal failure	17/452 (3.8)	29/276 (10.5)	<**0.01**	2/329 (0.6)	4/154 (2.6)	0.09	15/123 (12.2)	25/122 (20.5)	0.08
diabetes	25/452 (5.5)	29/276 (10.5)	**0.01**	2/329 (0.6)	0/154 (0)	1	23/123 (18.7)	29/122 (23.8)	0.33
immunosuppression	40/451 (8.9)	24/275 (8.7)	0.95	4/328 (1.2)	1/153 (0.7)	1	36/123 (29.3)	23/122 (18.9)	0.06
obesity	18/399 (4.5)	18/212 (8.5)	**0.05**	3/329 (0.9)	2/154 (1.3)	0.66	15/70 (21.4)	16/58 (27.6)	0.42
Clinical characteristics									
pregnancy, *n/N* (%)	17/77 (22.1)	4/57 (7)	**0.02**	–	–	–	17/77 (22.1)	4/57 (7)	**0.02**
BMI (kg/m^2), median (IQR)	16.6 (15.2–23.1)	19.3 (15.1–25.8)	**0.03**	15.6 (14.7–16.8)	15.5 (14.1–16.7)	0.4	26 (23.1–27.4)	25.9 (23.3–30)	0.48
glomerular filtration rate (mL/min/1.73 m^2), median (IQR)	88 (58–106)	75 (45.5–96.4)	**0.03**	129 (101.3–169.5)	130 (118.5–153)	0.72	78.0 (54.5–96)	69.5 (42–158)	**0.05**
Charlson comorbidity index, median (IQR)	–	–	–	–	–	–	5 (1.5–6)	5 (2–6)	0.53
Paraclinical findings									
chest X-ray compatible with influenza infection	56/111 (50.5)	52/129 (40.3)	0.12	7/20 (35)	6/23 (26.1)	0.53	49/91 (53.8)	46/106 (43.4)	0.14
Clinical course									
duration of clinical signs before diagnosis (h), median (IQR)	24 (12–48)	72 (48–120)	<**0.01**	24 (12–24)	72 (48–120)	<**0.01**	72 (24–96)	96 (48–120)	**0.03**
severity criteria, *n/N* (%)	39/449 (8.7)	47/271 (17.3)	<**0.01**	20/329 (6.1)	23/154 (14.9)	<**0.01**	19/120 (15.8)	24/117 (20.5)	0.35
hospitalization for influenza, *n/N* (%)	100/451 (22.2)	81/276 (29.3)	**0.03**	45/329 (13.7)	21/154 (13.6)	0.99	55/122 (45.1)	60/122 (49.2)	0.52
ICU admission, *n/N* (%)	–	–	–	2/45 (4.4)	2/22 (0.9)	0.11	13/116 (11.2)	12/118 (10.2)	0.83
hospital length of stay (h), median (IQR)	72 (27.8–192)	144 (72–234)	**0.01**	26.5 (13.8–54)	72 (48–96)	<**0.01**	144 (78–384)	144 (96–270)	0.91
died during hospitalization, *n/N* (%)	3/452 (0.7)	5/277 (1.8)	0.16	0/329 (0)	1/154 (0.6)	0.32	3/123 (2.4)	4/123 (3.3)	1.00
antibiotic prescription, *n/N* (%)	111/450 (24.7)	107/265 (40.4)	<**0.01**	31/329 (9.4)	35/154 (22.7)	<**0.01**	80/121 (66.1)	72/111 (64.9)	0.84

P values are shown in bold when ≤0.05.
[a]In the case of missing data, the denominator corresponds to the number with known data.
[b]Risk factors for severe influenza are defined as cardiac or renal chronic disease, diabetes or obesity.

In our study, we noted a real under-prescription of oseltamivir after 48 h of symptom onset. Data and communication about the better effect of NAIs before 48 h of symptom onset may lead to under-prescription or no prescription after that time although there is still a benefit of NAIs after 48 h in some situations.

Indeed, studies show a benefit to survival of oseltamivir prescription, even after 48 h of symptom onset, in hospitalized patients or those requiring ICU admission.[9,10] Adisasmito *et al.*[11] observed a benefit to survival up to 8 days from symptom onset. Regarding primary care, initiating oseltamivir after 48–72 h of illness onset or earlier might reduce the duration of flu symptoms in older patients who have comorbidities and who have been unwell for longer.[13] Finally, compared with no treatment, NAI treatment is associated with a reduction in mortality risk, regardless of the timing of antiviral administration.[23]

We found in our study a relatively low prescription rate in ICU patients (52%) and at-risk patients received oseltamivir significantly less frequently than patients without risk factors, which has

Table 3. Multivariate analysis

	OR	95% CI	*P*
Paediatric[a]			
time to diagnosis (days)	0.25	0.19–0.33	**<0.01**
age (years)	0.95	0.88–1.03	0.19
Adults[b]			
male	1.02	0.57–1.80	0.95
time to diagnosis (days)	0.97	0.89–1.05	0.48
estimated glomerular filtration rate (mL/min/1.73 m^2)	0.94	0.98–1.01	0.29

When forced in the model, male sex and severity signs (for paediatric analysis) and severity signs and hospitalization for influenza (for adult patients) were not retained, nor did they change the final model.
P values are shown in bold when ≤0.05.
[a]Hosmer–Lemeshow: $P = 0.56$.
[b]Hosmer–Lemeshow: $P = 0.33$.

been reported in other studies.[17,28] However, the prescription rate of oseltamivir for in critically ill patients remains very low despite evidence of treatment benefit[9,10,24] in this fragile population in whom the replication phase could be prolonged.[23]

At this time of viral emergence and pandemics, there is a great need to change the view of clinicians about antiviral drugs and their use, their indication and their management.

Conclusions

Oseltamivir should be administered as early as possible, preferably within 24–48 h after illness onset, for the best benefits. It is, however, very important to promote the use of NAI treatment beyond 48 h in some specific patient populations (e.g. patients with comorbidities and severely ill patients). This work shows it is important to improve the use of NAIs for influenza treatment. With the development of new antivirals for respiratory viruses, probably driven by the SARS-CoV-2 pandemic, strong antiviral stewardship will need to be implemented.

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Transparency declarations

None to declare.

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