

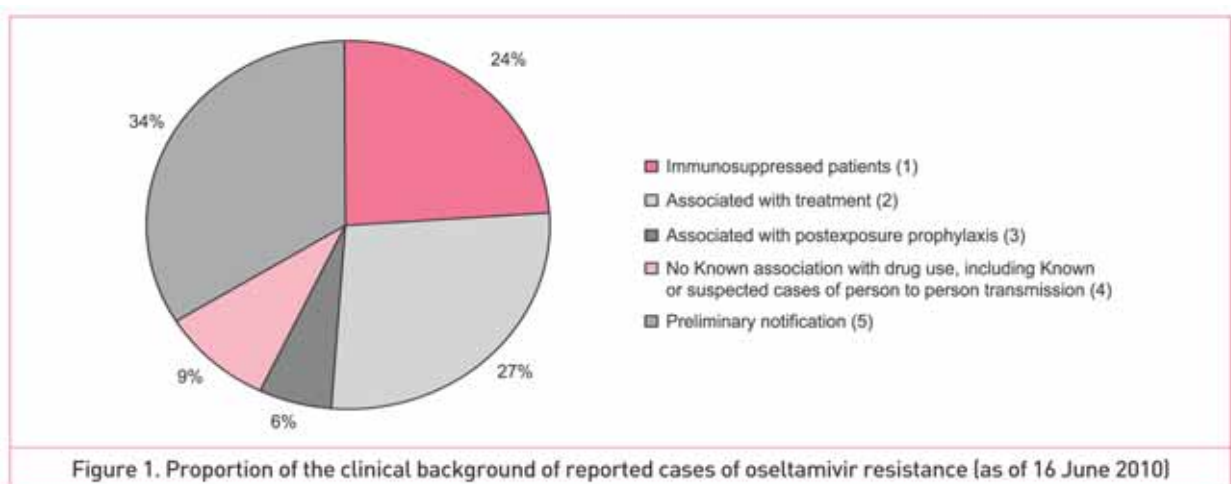
2009-2010 절기 인플루엔자 A(H1N1) 2009 바이러스의 항바이러스제 내성 분석

Antiviral drugs resistance of influenza A(H1N1) 2009 virus isolated in Korea during 2009-2010 season

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최장훈

I. 들어가는 말

2009 4 월, A(H1N1) 2009 가 (World Health Organization; WHO) ' 6 ' A(H1N1) 2009 가 WHO (Oseltamivir,) (neuraminidase; NA) 298 (WHO, 2010. 6. 16.), 116 , 99 , 82 , (24%), (27%), (9%) 가 (Zanamivir,) , M2 (Amanta-dine) , (Histidine; H) (Tyrosine; Y) NA 275 가 , 2009 5 , 2010 10 (가)



Cases are classified first by identifying those that occur in severely immunocompromised patients (1). The remaining cases are then classified as either occurring during or after oseltamivir treatment (2), associated with post-exposure prophylaxis (3), or occurring in patients who had not used antiviral drugs prior to occurrence of the resistant virus (4). The balance of cases (5) are those where insufficient clinical information is available[1].

II. 몸 말

2009-2010
526 , 2009 4 2010 12 15
1,018 , 67 1,611 M2

(genotypic assay)
(phenotypic assay) . M2

M2
(L26F, V27A, A30T, S31N, G34E) . NA
(E119V, R152K, D199N, H275Y, R293K
N295S)
(Table 1) (RT-PCR)
ABI 3730 DNA analyzer .
MDCK
(WHO Collaborating
Centre for Reference and Research on Influenza)
(Fluorometric Neuraminidase Inhibition Assay, WHO-025) NA IC₅₀ .
IC₅₀ 50-200 nM ,
>200 nM .
2009 4 24 2010 12 15 A(H1N1) 2009
, 1,611 M2 . NA
2009-2010 (526)
1,018 .
(67) 11 (11/67, 16.4%)
(Table 2). 2009 11 30 , 5
A(H1N1) 2009 5
(,) 10 가 .
가 5 가 54.5%(6), 40 36.4%(5)
, NA H275Y 가 [4](Table 3).
(0 /1,611 , 0%).
11 2 , IC₅₀
713.2 nM, 359.4 nM , 0.13 nM 0.78
nM . 가 ,
()
, 가
. Figure 2 (A)
, (B) (C)
(TAC; Tyrosine)
HA [4].
가

Table 1. List of primers for NA and M genes amplification

Gene	Primer	Sequence(5'-3')
NA	forward	AAATTAACGGGCAATTCCTCTCT
	reverse	CCGAAAATCCCACTGCATATGTAT
M	forward	CTAGCTCCAGTGCTGGTCTGA
	reverse	CTCAGGCACTCCTCCGTAGA

Table 2. Antiviral resistance of influenza A(H1N1) 2009 viruses in Korea [2009.4.24.-2010.12.15.]

Source of Virus	Oseltamivir	Amantadine	No. Tested	No. Resistant (%)
	No. Tested	No. Resistant (%)		
Laboratory confirmed case	1,018	0	1,013	1,013 (100)
Laboratory surveillance (2009-2010 season)	526	0	526	526 (100)
Patients with complication or severe illness	67	11 (16.4)	100	100 (100)
Total	1,611	11 (0.68)	1,611	1,611 (100)

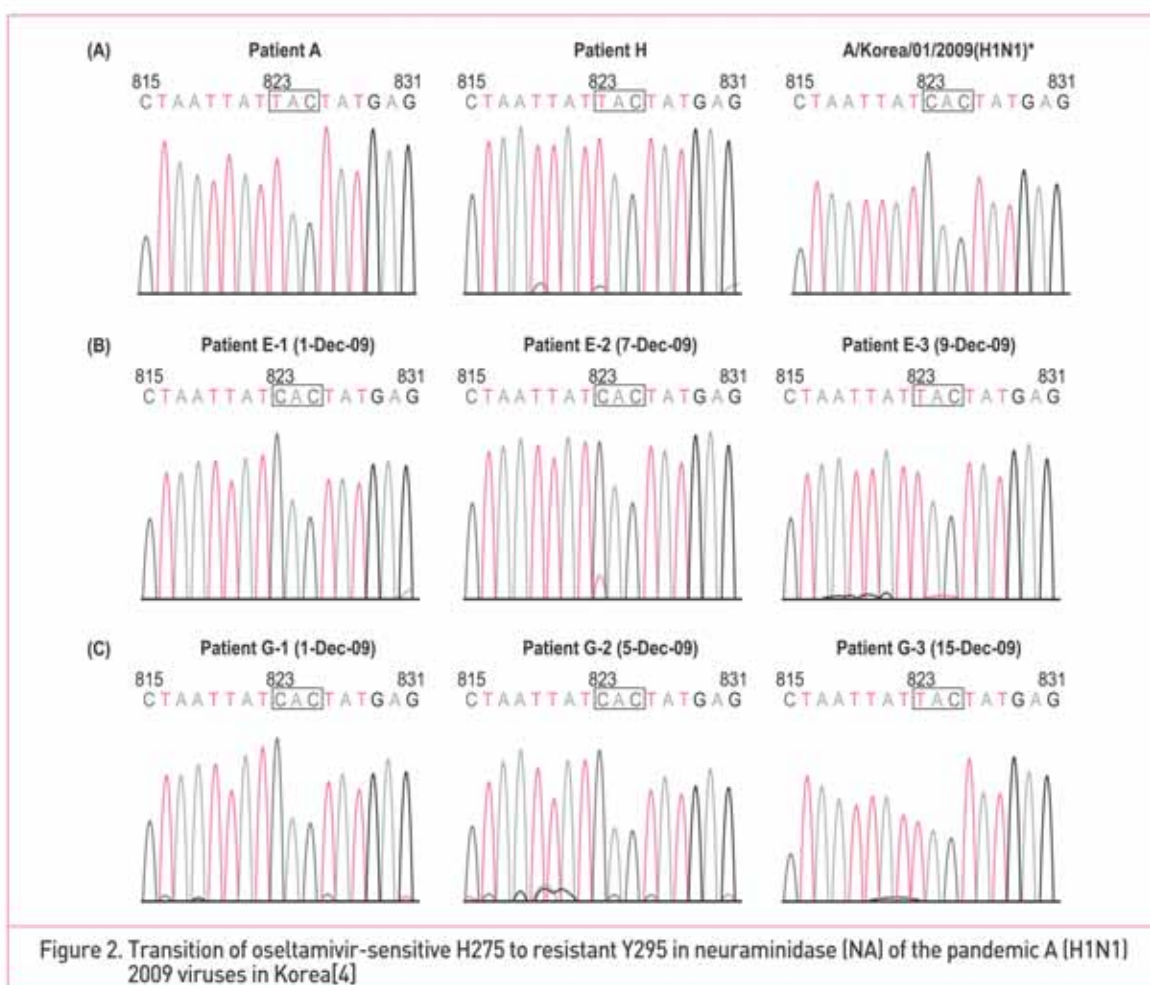


Figure 2. Transition of oseltamivir-sensitive H275 to resistant Y295 in neuraminidase (NA) of the pandemic A (H1N1) 2009 viruses in Korea[4]

(A) NA sequences of viruses from specimens of patient A, patient H and A/Korea/01/2009 (H1N1) (refer to Table). Viruses from patients A and H exhibited triplet TAC (encoding tyrosine) signals in NA 275 (in boxes), indicating that the patients were infected with oseltamivir-resistant virus, in contrast to A/Korea/01/2009 (H1N1) of the oseltamivir-sensitive case showing CAC (encoding histidine) in NA 275. (B) NA sequences from multiple specimens taken on different dates from patient E. Patient E was initially infected with oseltamivir-sensitive virus with CAC in NA 275 (1-Dec-2009). Next, the virus showed 823C (blue dominant peak) in the boxed CAC, with a minor signal 823T (red small peak) in NA 275 (7-Dec-09). In the third specimen (9-Dec-09), only TAC in NA 275 was recorded in the virus. (C) Oseltamivir-sensitive viral infection (CAC in NA 275) was recorded in the first two specimens of patient G (1-Dec-2009 and 5-Dec-2009, respectively). The mixed signals of dominant 823T (red peak) and minor 823C (blue peak) were seen in the latest specimen (15-Dec-2009), indicating a mixed viral infection of both oseltamivir-resistance and susceptibility. The nucleotide coordinates (815 and 831) refer to the NA gene sequence of pandemic (H1N1) 2009 virus. Amino acid residue 275 in NA encoded by the three nucleotides is indicated in boxes.

Table 3. Epidemiological information of patients infected with oseltamivir-resistant influenza A/H1N1 2009 in Korea[4]

Patients	Age /Sex	Antiviral treatments	Date of specimen collection	Sort of specimen	Underlying condition
A	5/M	Oseltamivir 30mg twice a day (29-October-2009 ~ 4-Nov-2009), Oseltamivir 60mg twice a day (5-Nov-2009 ~ 9-Nov-2009)	6-Nov-2009	Nasopharyngeal Swab	Mitochondria cytopathy
B	46/M	Oseltamivir 150mg twice a day (6-Nov-2009 ~ 15-Nov-2009), Zanamivir (16-Nov-2009 ~ 26-Nov-2009)	18-Nov-2009	Nasopharyngeal Swab	Leukemia
C	1/F	Oseltamivir 30mg twice a day (16-Nov-2009 ~ 21-Nov-2009), Oseltamivir 60mg twice a day (22-Nov-2009 ~ 8-Dec-2009)	21-Nov-2009 22-Nov-2009	Nasopharyngeal Swab	Death
D	2/M	Oseltamivir 90mg twice a day (26-Nov-2009 ~ 30-Nov-2009), Oseltamivir 180mg and Amantadine 65mg twice a day (2-Dec-2009 ~ 7-Dec-2009)	02-Dec-2009 26-Nov-2009	Nasal Suction	None
E	3/F	Oseltamivir 30mg twice a day (1-Dec-2009 ~ 5-Dec-2009), Oseltamivir 30mg twice a day (7-Dec-2009 ~ 11-Dec-2009)	01-Dec-2009 07-Dec-2009 09-Dec-2009	Oropharyngeal Swab (01,07-Dec-2009) Nasopharyngeal Swab (09-Dec-2009)	Asthma
F	3/F	Oseltamivir 45mg twice a day (10-Dec-2009 ~ 15-Dec-2009), Oseltamivir 75mg twice a day (16-Dec-2009 ~ 20-Dec-2009)	18-Dec-2009	Oropharyngeal Swab	Delayed development
G	1/F	Oseltamivir 30mg twice a day (1-Dec-2009 ~ 5-Dec-2009), Peramivir 75mg once a day (12-Dec-2009 ~ 18-Dec-2009)	01-Dec-2009 05-Dec-2009 15-Dec-2009	Nasal/Oropharyngeal Swab	Myelodysplasia (death)
H	63/M	Oseltamivir 150mg twice a day (7-Dec-2009 ~ 15-Dec-2009), Zanamivir (16-Dec-2009 ~ 20-Dec-2009)	16-Dec-2009	Oropharyngeal Swab	Diabetes mellitus
I	58/M	Oseltamivir 150mg twice a day (16-Dec-2009 ~ 18-Dec-2009), Peramivir 600mg intravenously once a day & Amantadine 100mg twice a day & ribavirin 300mg once a day (19-Dec-2009 ~ 25-Dec-2009), Zanamivir 10mg twice a day (26-Dec-2009 ~ 1-Jan-2009)	26-Dec-2010	Nasopharyngeal Swab	Myeloma
J	60/M	Oseltamivir 75mg twice a day (30-Nov-2009 ~ 2-Dec-2009)	26-Jan-2010	Viral RNA	Diabetes mellitus,(death)
K	54/F	Oseltamivir 75mg twice a day (9-Jan-2010 ~ 21-Jan-2010)	14-Jan-2010	Nasopharyngeal Swab	None

III. 맺는 말

A B

[2].

2009

A(H1N1) 2009

가

Global Influenza Surveillance Network(GISN)

2009

[3].

2009 - 2010

A(H1N1) 2009

0.68%

A(H1N1) 2009

가

가

(peramivir)

(GISN)

IV. 참고문헌

1. World Health organization (WHO), 2010. Weekly update on oseltamivir resistance to pandemic influenza A (H1N1) 2009 viruses. 2010. 06. 16.
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4. Hwajung Yi, Joo- Yeon Lee, Eun-Hye Hong, Mi-Seon Kim, Donghyok Kwon, Jang-Hoon Choi, Woo-Young Choi, Ki-Soon Kim, Jong-Koo Lee, Hee-Bok Oh, Chun Kang (2010). Oseltamivir-resistant infection of pandemic (H1N1) 2009 influenza virus in South Korea. Emerg. Inf. Dis. 16(12) 1938-1942