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et l'interrégion Nord-Pas-de-Calais-Picardie

Les virus grippaux émergents (H5N1 ou H7N9) en 2016 Aspects thérapeutiques

Xavier Duval
Hôpital Bichat Claude Bernard, Paris
Universités Paris 7-CIC 1425
IAME-Inserm 1138

Déclaration de liens d'intérêt avec les industries de santé en rapport avec le thème de la présentation (loi du 04/03/2002) :

Intervenant : Duval Xavier

Titre : Les virus grippaux émergents (H5N1 ou H7N9) en 2016

○ L'orateur ne souhaite pas répondre ☐

● Consultant ou membre d'un conseil scientifique	☐ OUI	☑ NON
○ Conférencier ou auteur/rédacteur rémunéré d'articles ou documents	☐ OUI	☑ NON
● Prise en charge de frais de voyage, d'hébergement ou d'inscription à des congrès ou autres manifestations	☐ OUI	☑ NON
● Investigateur principal d'une recherche ou d'une étude clinique	☑ OUI	☐ NON


H5N1

H5N1

- Sous-type A(H5N1) – virus de la grippe aviaire hautement pathogène
- 1997: 1ère infection humaine:
- 2003 et 2004:
  - Réémergence à une vaste échelle
  - Propagation de l'Asie à l'Europe et à l'Afrique
- Période d'incubation
  - de 2 à 8 jours
  - parfois jusqu'à 17 jours

H5N1_ pronostic

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

CURRENT CONCEPTS

Update on Avian Influenza A (H5N1) Virus Infection in Humans

Writing Committee of the Second World Health Organization Consultation on Clinical Aspects of Human Infection with Avian Influenza A (H5N1) Virus*

Table 2. (Continued.)

Variable	Vietnam, Thailand, Cambodia, 2004–2005, Clade 1†	Indonesia, 2005–2006, Clade 2.1‡	China, 2005–2006, Clade 2.3§	Egypt, 2006–2007, Clade 2.2¶	Turkey, Azerbaijan, 2006, Clade 2.2‖
Deaths — no./ total no. (%)	32/41 (78)	41/54 (76)	7/8 (88)	15/38 (39)	9/16 (56)

H5N1 _Epidémiologie

Cumulative number of confirmed human cases for avian influenza A(H5N1) reported to WHO, 2003-2016

Country	2003-2009*		2010-2014**		2015		2016		Total	
	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths
Azerbaijan	8	5	0	0	0	0	0	0	8	5
Bangladesh	1	0	6	1	1	0	0	0	8	1
Cambodia	9	7	47	30	0	0	0	0	56	37
Canada	0	0	1	1	0	0	0	0	1	1
China	38	25	9	5	6	1	0	0	53	31
Djibouti	1	0	0	0	0	0	0	0	1	0
Egypt	90	27	120	50	136	39	4	0	350	116
Indonesia	162	134	35	31	2	2	0	0	199	167
Iraq	3	2	0	0	0	0	0	0	3	2
Lao People's Democratic Republic	2	2	0	0	0	0	0	0	2	2
Myanmar	1	0	0	0	0	0	0	0	1	0
Nigeria	1	1	0	0	0	0	0	0	1	1
Pakistan	3	1	0	0	0	0	0	0	3	1
Thailand	25	17	0	0	0	0	0	0	25	17
Turkey	12	4	0	0	0	0	0	0	12	4
Viet Nam	112	57	15	7	0	0	0	0	127	64
Total	**468**	**282**	**233**	**125**	**145**	**42**	**4**	**0**	**850**	**449**

* 2003-2009 total figures. Breakdowns by year available on subsequent tables.
** 2010-2014 total figures. Breakdowns by year available on subsequent tables.

Total number of cases includes number of deaths
WHO reports only laboratory cases
All dates refer to onset of illness

World Health Organization

H5N1 oseltamivir

Table 4. Effects of Treatment and Time to Treatment with Oseltamivir on Survival among Patients with Influenza A (H5N1) Infection.*

Type of Infection and Location of Patients	Year	Survival		Days from Onset of Illness to Initiation of Antiviral Therapy		Comment	Reference
				Nonfatal Illness	Fatal Illness		
		no. of survivors/ no. treated (%)	*no. of survivors/ no. not treated (%)*	*median (range)*			
Presumed clade 1 virus infections		45/82 (55)	6/26 (23)			Significant survival benefit with oseltamivir treatment as compared with no treatment (P=0.006, Fisher's exact test)	
Thailand	2004–2005	3/10 (30)	2/7 (29)	5 (4–7)	9 (5–22)		Chotpitayasunondh T (unpublished data)
Vietnam (southern)	2004–2005	5/17 (29)	0/1 (0)	6 (4–12)	5.5 (2–7)		de Jong M (unpublished data)
Vietnam (northern)	2004–2005	37/55 (67)	4/12 (33)	NR	NR	Significant survival benefit with oseltamivir treatment as compared with no treatment (P=0.048); most patients (73%) began to receive oseltamivir after 4 days of illness	Cao T, Thanh Liem N, and Duc Hien N (personal communication)
Cambodia	2005–2006	NA	0/6 (0)			Median time to hospitalization, 6 days	Buchy et al.[37]
Presumed clade 2 virus infections		43/106 (41)	1/30 (3)			Significant survival benefit with oseltamivir treatment as compared with no treatment (P<0.001)	
Turkey, clade 2.2 virus infections	2005	4/7 (57)	0/1 (0)	4 (1–10)	8 (8–10)		Oner et al.[21]
Egypt, clade 2.2 virus infections	2006–2007	20/34 (59)	NA	1 (0–3)	4 (1–14)	Significantly shorter time from onset of illness to oseltamivir treatment among patients who survived than among those who did not survive (P=0.001, Kruskal–Wallis test)	Abdel-Ghafar A (unpublished data)
Indonesia, clade 2.1 virus infections	2005–2007	19/65 (29)	1/29 (3)	NR	NR	Significant survival benefit with oseltamivir treatment as compared with no treatment (P=0.005)	Sedyaningsih et al.[63]
Total		88/188 (47)	7/56 (12)			Significant overall survival benefit with oseltamivir treatment as compared with no treatment (P<0.001)	

N ENGL J MED 358;3 WWW.NEJM.ORG JANUARY 17, 2008

Recommandations OMS Traitement

« Chez les cas présumés, un traitement par l'oseltamivir doit être prescrit aussi vite que possible (idéalement dans les 48 heures suivant l'apparition des symptômes) pour maximiser les effets thérapeutiques. »

« Toutefois, compte tenu de la forte mortalité actuellement associée à l'infection à A(H5N1) et A(H7N9) et des données indiquant une réplication prolongée du virus dans ces maladies, l'administration de ce médicament doit aussi être envisagée chez les patients qui consultent à un stade plus tardif de l'évolution de la maladie.

L'administration de corticoïdes n'est pas recommandée. »

Recommandations OMS

- La plupart des virus A(H5N1) et A(H7N9) sont résistants aux adamantanes.

- En cas d'infection sévère à A(H5N1) et A(H7N9): Peut être envisagé d'accroître
  - la dose quotidienne recommandée
  - et/ou la durée du traitement d'oseltamivir

H5N1_Oseltamivir sonde gastrique

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PLoS one

Oseltamivir Is Adequately Absorbed Following Nasogastric Administration to Adult Patients with Severe H5N1 Influenza

Walter R. J. Taylor[1,2]*, Bui Nghia Thinh[3], Giang Thuc Anh[3], Peter Horby[1,2], Heiman Wertheim[1,2], Niklas Lindegardh[2,4], Menno D. de Jong[2,5], Kasia Stepniewska[2,4], Tran Thuy Hanh[3], Nguyen Duc Hien[6], Ngo Minh Bien[3], Ngo Quy Chau[3], Annette Fox[1,2], Nghiem My Ngoc[5], Martin Crusat[5], Jeremy J. Farrar[2,5], Nicholas J. White[2,4], Nguyen Hong Ha[6], Trinh Thi Lien[6], Nguyen Vu Trung[6], Nicholas Day[2,4], Nguyen Gia Binh[3]

Abstract

In the absence of a parenteral drug, oral oseltamivir is currently recommended by the WHO for treating H5N1 influenza. Whether oseltamivir absorption is adequate in severe influenza is unknown. We measured the steady state, plasma concentrations of nasogastrically administered oseltamivir 150 mg bid and its active metabolite, oseltamivir carboxylate (OC), in three, mechanically ventilated patients with severe H5N1 (male, 30 yrs; pregnant female, 22 yrs) and severe H3N2 (female, 76 yrs). Treatments were started 6, 7 and 8 days after illness onset, respectively. Both females were sampled while on continuous venovenous haemofiltration. Admission and follow up specimens (trachea, nose, throat, rectum, blood) were tested for RNA viral load by reverse transcriptase PCR. *In vitro* virus susceptibility to OC was measured by a neuraminidase inhibition assay. Admission creatinine clearances were 66 (male, H5N1), 82 (female, H5N1) and 6 (H3N2) ml/min. Corresponding AUC_{0-12} values (5932, 10,951 and 34,670 ng.h/ml) and trough OC concentrations (376, 575 and 2730 ng/ml) were higher than previously reported in healthy volunteers; the latter exceeded 545 to 3956 fold the H5N1 IC_{50} (0.69 ng/ml) isolated from the H5N1 infected female. Two patients with follow-up respiratory specimens cleared their viruses after 5 (H5N1 male) and 5 (H3N2 female) days of oseltamivir. Both female patients died of respiratory failure; the male survived. 150 mg bid of oseltamivir was well absorbed and converted extensively to OC. Virus was cleared in two patients but two patients died, suggesting viral efficacy but poor clinical efficacy.

H5N1 Résistance oseltamivir

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Oseltamivir Resistance during Treatment of Influenza A (H5N1) Infection

Menno D. de Jong, M.D., Ph.D., Tran Tan Thanh, M.Sc., Truong Huu Khanh, M.D., Vo Minh Hien, M.D., Gavin J.D. Smith, Ph.D., Nguyen Vinh Chau, M.D., Bach Van Cam, M.D., Phan Tu Qui, M.D., Do Quang Ha, M.D., Ph.D., Yi Guan, M.D., Ph.D., J.S. Malik Peiris, D.Phil., M.D., Tran Tinh Hien, M.D., Ph.D., and Jeremy Farrar, D.Phil., F.R.C.P.

SUMMARY

Influenza A (H5N1) virus with an amino acid substitution in neuraminidase conferring high-level resistance to oseltamivir was isolated from two of eight Vietnamese patients during oseltamivir treatment. Both patients died of influenza A (H5N1) virus infection, despite early initiation of treatment in one patient. Surviving patients had rapid declines in the viral load to undetectable levels during treatment. These observations suggest that resistance can emerge during the currently recommended regimen of oseltamivir therapy and may be associated with clinical deterioration and that the strategy for the treatment of influenza A (H5N1) virus infection should include additional antiviral agents.

H5N1 Résistance oseltamivir

Table 1. Patients' Characteristics and Clinical and Virologic Outcome.

Patient	Age (yr)/ Sex	Admission*		Virus Detectable at End of Treatment†	H274Y in N1 at End of Treatment†	Clinical Outcome
		Date	Day of Illness			
1	13/F	January 2005	2	Yes	Yes	Died on 8th day of illness
2‡	35/F	January 2005	6	NA	NA	Died on 7th day of illness
3	16/F	December 2004	7	Yes	NA	Died on 20th day of illness
4	18/F	January 2005	6	Yes	Yes	Died on 20th day of illness
5	26/F	January 2005	4	NA	NA	Survived
6§	8/F	January 2004	8	No	—	Survived
7§	23/M	February 2004	7	No	—	Survived
8	22/M	February 2004	6	No	—	Survived

* All patients started oseltamivir treatment on the day of admission.
† NA denotes not applicable owing to insufficient follow-up.
‡ Patient 2 was the mother of Patient 1.
§ This patient has been described previously.[2]

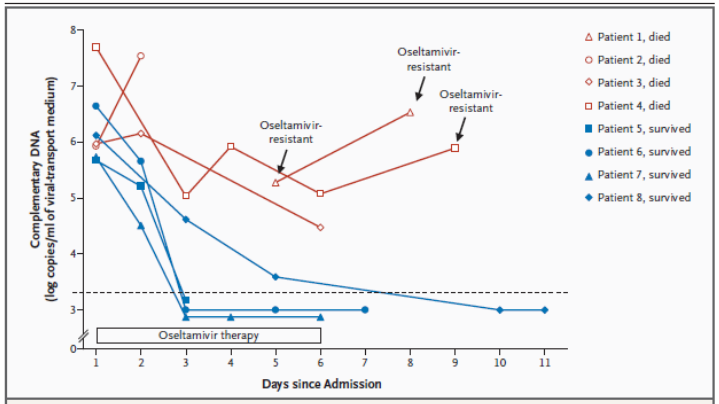

Figure 3. Influenza A (H5N1) Viral RNA Load in Throat Swabs from Eight Patients.
Blue lines represent patients who survived influenza A (H5N1) virus infection, and red lines represent patients who died. The dashed horizontal line denotes the limit of detection of the RT-PCR assay. The arrows indicate the specimens from which oseltamivir-resistant influenza A (H5N1) variants were isolated. No virus was isolated from any other specimen besides samples obtained at admission.

H5N1 résistance naturelle oseltamivir

J Gen Virol. 2016 Mar 2. doi: 10.1099/jgv.0.000444. [Epub ahead of print]

The significance of naturally occurring neuraminidase quasispecies of H5N1 avian influenza virus on resistance to oseltamivir: a point of concern.

Schaduangrat N[1], Phanich J[2], Rungrotmongkol T[3], Lerdsamran H[4], Puthavathana P[5], Ubol S[6].
Author information

Abstract

Viral adaptability and survival arise due to the presence of quasispecies populations that are able to escape the immune response or produce drug-resistant variants. However, the presence of H5N1 virus with natural mutations acquired without any drug selection pressure, poses a great threat. Cloacal samples collected from the 2004-2005 epidemics in Thailand from Asian open-billed storks revealed one major and several minor quasi species populations with mutations on the oseltamivir binding site of the neuraminidase gene (NA) without prior exposure to a drug. Therefore, this study investigated the binding between the NA containing novel mutations and oseltamivir drug (OTV) using molecular dynamic (MD) simulations and plaque inhibition assay. The results revealed that the mutant populations, S236F mutant, S236F/C278Y mutant, A250V/V266A/P271H/G285S mutant and C278Y mutant, had a lower binding affinity with OTV as compared to the wild-type virus due to rearrangement of amino acid residues and increased flexibility in the 150-loop. This result was further emphasized through the obtained IC50 values of the major population and wild-type virus, 104.74nM and 18.30nM respectively. Taken together, these data suggests that H5N1 viruses isolated from wild birds, have already acquired oseltamivir resistant point mutations without any exposure to a drug.

frontiers in Microbiology

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6.004

Peramivir: A Novel Intravenous Neuraminidase Inhibitor for Treatment of Acute Influenza Infections

*Malak M. Alame[1], Elie Massaad[2] and Hassan Zaraket[2,3]**

lower than those of the rest of the NAIs (Dapat et al., 2010; Ikematsu et al., 2014, 2015a,b; Zaraket et al., 2014). Importantly, peramivir has been also demonstrated to be highly effective *in vitro* against emerging avian influenza viruses of pandemic potential including H5N1, H7N9, and H9N2 (Govorkova et al., 2001; Zhang et al., 2014; Marjuki et al., 2015).

Survival improved to 55% with two IM peramivir doses. An 8-day regimen consisting of two daily IM injections starting 1 h post-exposure followed by seven daily IM doses provided mice with 100% protection from lethal H5N1 challenge, but survival decreased to 78 and 56% when treatment was delayed by 24 and 48 h, respectively (Boltz et al., 2008). The 8-day regimen of 30 mg/kg/day IM peramivir, with the first dose initiated at the time of infection, also resulted in reduction of lung virus titers and mortality in mice infected with a lethal dose of the H7N9 virus (Farooqui et al., 2015).

Repeated IV administration of peramivir over 5 days starting on the day of infection or 24 h after infection significantly reduced viral titers, inflammatory cytokines, and the period to virus clearance in the upper respiratory tract of cynomolgus macaques infected with H5N1 virus (Kitano et al., 2014).

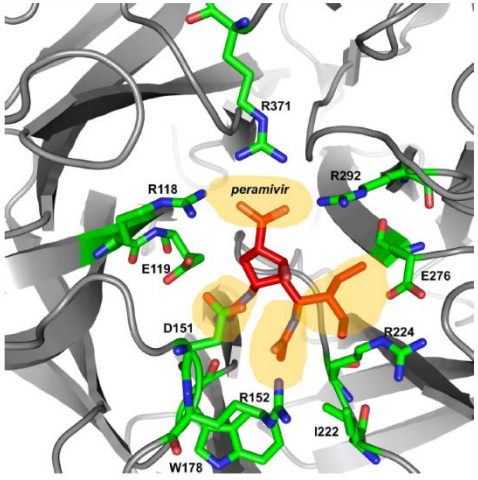

FIGURE 2 | Peramivir bound to influenza A/H7N9 neuraminidase. Crystal structure of peramivir and influenza A/H7N9 neuraminidase complex (4 MWV). The four binding pockets of the enzyme active site are shown in yellow shades.

H5N1_Peramivir

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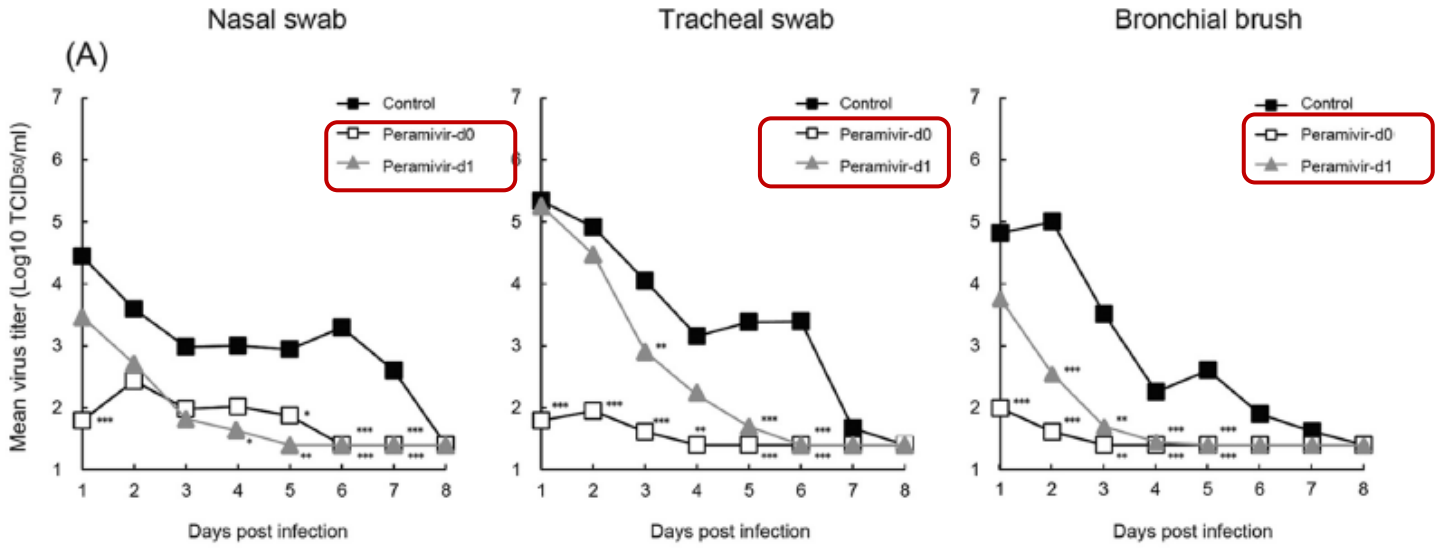
Efficacy of Repeated Intravenous Administration of Peramivir against Highly Pathogenic Avian Influenza A (H5N1) Virus in Cynomolgus Macaques

Mitsutaka Kitano,[a,b] Yasushi Itoh,[a] Hirohito Ishigaki,[a] Misako Nakayama,[a] Hideaki Ishida,[a] Van Loi Pham,[a] Masahiko Arikata,[a] Shintaro Shichinohe,[d] Hideaki Tsuchiya,[c] Naoko Kitagawa,[a] Masanori Kobayashi,[b] Ryu Yoshida,[b] Akihiko Sato,[b] Quynh Mai Le,[e] Yoshihiro Kawaoka,[f,g,h] Kazumasa Ogasawara[a,c]



H5N1 Immunotherapie

Immunothérapie passive anti-infectieuse:

- Plasma de convalescent
- Anticorps polyclonaux spécifiques hautement purifiés.

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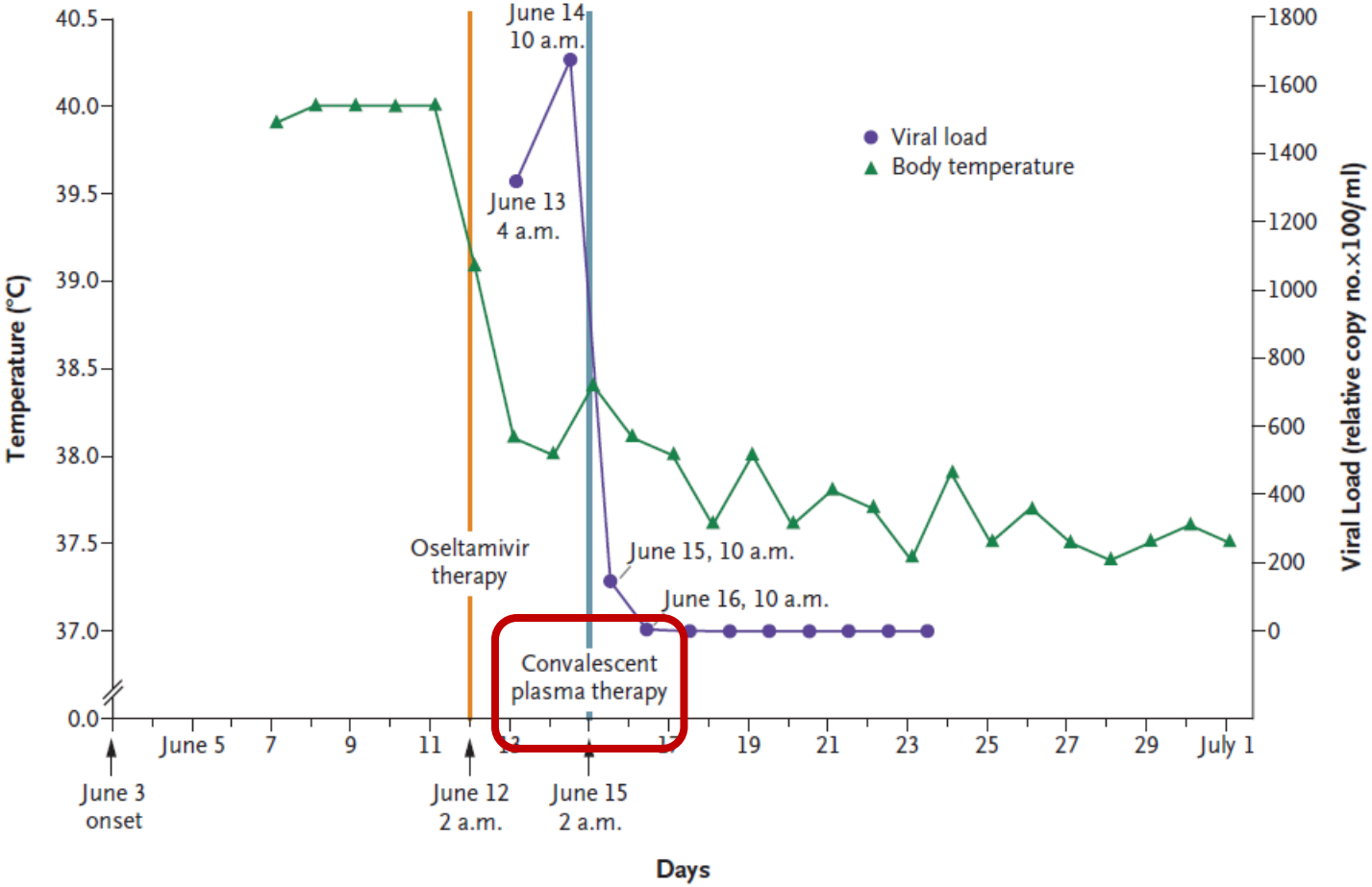
Treatment with Convalescent Plasma for Influenza A (H5N1) Infection



Zhou B; NEJM 2007

H5N1 Immunotherapie

solution d’immunothérapie passive anti-infectieuse, basée sur les anticorps polyclonaux spécifiques hautement purifiés. Ces anticorps administrés neutralisent spécifiquement le virus de façon immédiate et freinent le développement de la maladie.

Fab'entech
Specific Polyclonal Antibodies

FAB'ENTECH | PRODUITS & R&D | TECHNOLOGIE | ACTUALITÉS

Pipeline

Produits et portefeuil[illegible]

	CIBLE	PREUVE DE CONCEPT (POC)	STADE PRECLINIQUE	STADE CLINIQUE	DEVELOPPEMENT TERMINE
FBF-001	H5N1				2016
FBF-002	H7				2017
FBH-004	EBOLA				2017
FBH-001	CCHF*				2017
FBR-001	MERS-CoV				2018
FBN-001	HENDRA-NIPAH				2018
FBH-003	LASSA				2018
FBT-001	TOXINES				2018
FDX-000	AUTRES MALADIES EMERGENTES				

*Fièvre Hémorragique Crimée-Congo

Safety, potential efficacy, and pharmacokinetics of specific polyclonal immunoglobulin F(ab')$_2$ fragments against avian influenza A (H5N1) in healthy volunteers: a single-centre, randomised, double-blind, placebo-controlled, phase 1 study

Céline Bal, Cécile H Herbreteau, Philippe Buchy, Sareth Rith, Masliza Zaid, William Kristanto, Velda Han, Charlotte Reynaud, Patrick Granjard, Bertrand Lépine, Caroline Durand, Paul A Tambyah**

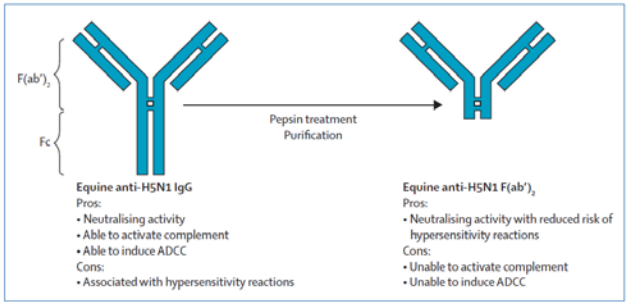


Figure: **Equine F(ab')$_2$ raised against avian influenza A virus (H5N1 subtype)**
ADCC=Antibody-dependent cell-mediated cytotoxicity

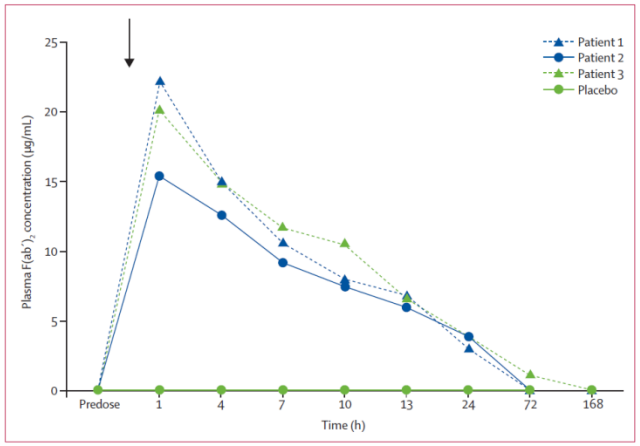


Figure 1: **Plasma concentrations of equine F(ab')$_2$ after one infusion**
Concentrations measured in participants over 1 week after infusion of FBF001 or placebo (point of infusion shown by the bold arrow).

Safety, potential efficacy, and pharmacokinetics of specific polyclonal immunoglobulin F(ab')$_2$ fragments against avian influenza A (H5N1) in healthy volunteers: a single-centre, randomised, double-blind, placebo-controlled, phase 1 study

Céline Bal, Cécile H Herbreteau, Philippe Buchy, Sareth Rith, Masliza Zaid, William Kristanto, Velda Han, Charlotte Reynaud, Patrick Granjard, Bertrand Lépine, Caroline Durand, Paul A Tambyah**

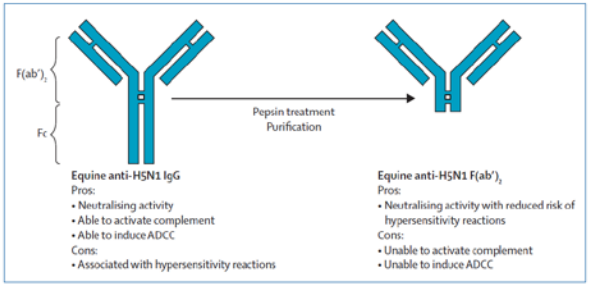


Figure: **Equine F(ab')$_2$ raised against avian influenza A virus (H5N1 subtype)**
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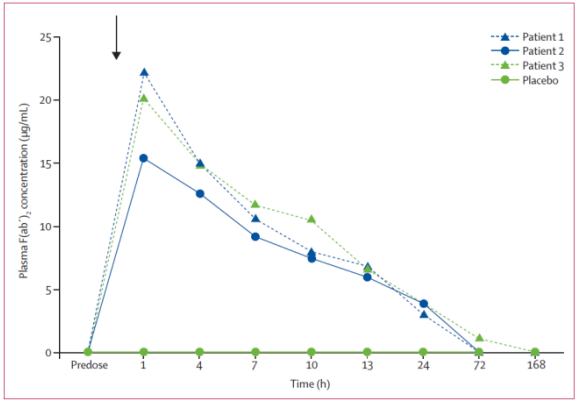

Figure 1: **Plasma concentrations of equine F(ab')$_2$ after one infusion**
Concentrations measured in participants over 1 week after infusion of FBF001 or placebo (point of infusion shown by the bold arrow).

	Description (MedDRA term)	Start	Finish	Duration	Intensity	Relation with treatment?
Stage 1						
Event	Eyelid twitching (blepharospasm)	Day 4	Day 6	2 days	Mild	Unlikely
Stage 2						
Event	Febrile reaction (general disorders)	Day 3	Day 3	37 min	Mild	Probable
Event	Mild sinusitis (infections)	Day 13	Day 23	10 days	Mild	Unlikely

MedDRA=Medical Dictionary for Regulatory Activities.

Table 2: **Treatment-emergent adverse events**

H7N9

H7N9

- Sous-type A(H7N9): virus grippe aviaire faiblement pathogène,
- Mars 2013: deux habitants de Shanghaï et un habitant de la province de l'Anhui,
- Aucun cas d'infection à virus A(H7N9) n'a été notifié en dehors de la Chine (cas importés canada)
- A(H7N9) touche particulièrement les personnes présentant des affections médicales préexistantes.

H7N9

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ORIGINAL ARTICLE

Clinical Findings in 111 Cases of Influenza A (H7N9) Virus Infection

Hai-Nv Gao, M.D., Hong-Zhou Lu, M.D., Ph.D., Bin Cao, M.D., Bin Du, M.D., Hong Shang, M.D., Jian-He Gan, M.D., Shui-Hua Lu, M.D., Yi-Da Yang, M.D., Qiang Fang, M.D., Yin-Zhong Shen, M.D., Xiu-Ming Xi, M.D., Qin Gu, M.D., Xian-Mei Zhou, M.D., Hong-Ping Qu, M.D., Zheng Yan, M.D., Fang-Ming Li, M.D., Wei Zhao, M.D., Zhan-Cheng Gao, M.D., Guang-Fa Wang, M.D., Ling-Xiang Ruan, M.D., Wei-Hong Wang, M.D., Jun Ye, M.D., Hui-Fang Cao, M.D., Xing-Wang Li, M.D., Wen-Hong Zhang, M.D., Xu-Chen Fang, M.D., Jian He, M.D., Wei-Feng Liang, M.D., Juan Xie, M.D., Mei Zeng, M.D., Xian-Zheng Wu, M.D., Jun Li, M.D., Qi Xia, M.D., Zhao-Chen Jin, M.D., Qi Chen, M.D., Chao Tang, M.D., Zhi-Yong Zhang, M.D., Bao-Min Hou, M.D., Zhi-Xian Feng, M.D., Ji-Fang Sheng, M.D., Nan-Shan Zhong, M.D., and Lan-Juan Li, M.D.

N Engl J Med 2013;368:2277-85.

H7N9

Table 3. Complications, Treatment, and Clinical Outcomes in 111 Patients Infected with H7N9 Virus.*

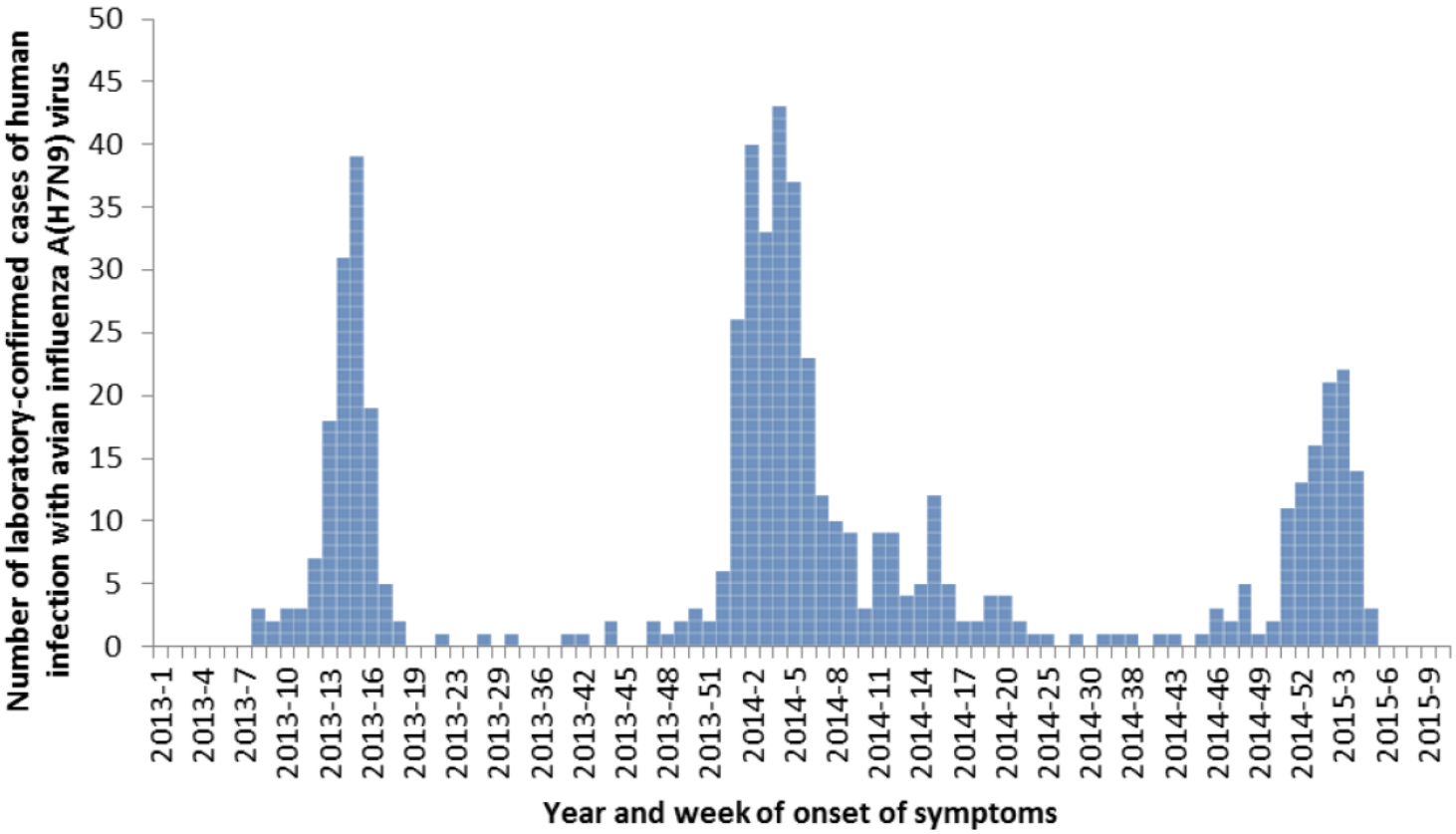
Variable	Value
	no. of patients (%)
Complications	
Pneumonia	108 (97.3)
Acute respiratory distress syndrome	79 (71.2)
Shock	29 (26.1)
Acute kidney injury	18 (16.2)
Rhabdomyolysis	11 (9.9)
Treatment	
Bacteria isolation from culture	29 (26.1)
Administration of oseltamivir or peramivir	108 (97.3)
Timing from onset of illness to administration of antiviral therapy	
0–2 days	11 (9.9)
3–5 days	32 (28.8)
≥6 days	65 (58.6)
Clinical outcome	
Death	30 (27.0)

Table 4. Multivariate Analysis of Risk Factors for the 79 Patients with the Acute Respiratory Distress Syndrome.

Risk Factor	Odds Ratio (95% CI)*	P Value
Age ≥65 yr	1.01 (0.99–1.03)	0.30
Coexisting medical condition	3.42 (1.21–9.70)	0.02
Lymphocyte count <1000 cells/mm³	2.73 (0.60–12.52)	0.20
Aspartate aminotransferase level >40 U/liter	1.37 (0.42–4.43)	0.60
Creatine kinase level >200 U/liter	1.80 (0.59–5.48)	0.30
Time from symptom onset to initiation of antiviral therapy >3 days	2.42 (0.49–11.99)	0.28

N Engl J Med 2013;368:2277-85.

H7N9 600 cas déclarés en 2016



Mortalité: 30%

H7N9

RESEARCH ARTICLE Open Access

Efficacy of oseltamivir-peramivir combination therapy compared to oseltamivir monotherapy for *Influenza A* (H7N9) infection: a retrospective study

Yan Zhang, Hainv Gao, Weifeng Liang, Lingling Tang, Yida Yang, Xiaoxin Wu, Liang Yu, Ping Chen, Shufa Zheng, Huilin Ou and Lanjuan Li*

Abstract

Background: Since the novel H7N9 avian influenza outbreak occurred in China in 2013, neuraminidase inhibitors (NAIs) such as oseltamivir and peramivir have been used as first-line drugs to treat the influenza virus infection. This study aimed to compare the efficacy of oseltamivir-peramivir combination therapy versus oseltamivir monotherapy.

Methods: A retrospective study of 82 H7N9 confirmed patients was conducted by reviewing medical charts at the First Affiliated Hospital of ZheJiang University in China from April 1, 2013 to Feb 28, 2014. The patients' clinical information was collected systematically, and we compared the virology and clinical data between oseltamivir monotherapy group (43 patients) and oseltamivir-peramivir combination group (39 patients).

Results: The median duration from NAIs administration to H7N9 virus-negative in oseltamivir monotherapy group and oseltamivir-peramivir combination group was 6.50 and 7.00 days ($p > 0.05$), respectively. The median decline of Day 2 to Day 0 (initiation of NAIs therapy) viral load was 0.00 and 0.69 log10 copies/μl ($p > 0.05$) respectively in the monotherapy vs. combination therapy groups. The incidence of new Acute Respiratory Distress Syndrome during NAI administration was 63.89 and 77.78 % ($p > 0.05$); while the mortality rates were 25.58 and 43.59 % ($p > 0.05$) in the oseltamivir group vs. oseltamivir-peramivir group.

Conclusions: Our results suggest that in adults with H7N9 virus infection, the use of oseltamivir-peramivir combination therapy was not superior to oseltamivir monotherapy.

Keywords: *Influenza A*, H7N9 virus, Oseltamivir, Peramivir

H7N9

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Etude rétrospective 1er Avril 2013 28 Fev 2014, HangZhou Chine

82 patients:

- Oseltamivir + Peramivir: 39 pts
- Oseltamivir monothérapie: 43 pts

H7N9_Oselta+ Pera_Caractéristiques inclusion

Table 2 Baseline information and the duration from NAIs therapy to H7N9 virus-negative

Patients	Characteristics	O + P	O	*P* Value
All patients		*n* = 39	*n* = 43	
Patients whose virus still positive till death		*n* = 7	*n* = 5	
Study patients		*n* = 32	*n* = 38	
	Age (years): mean (SD)	55.22(14.25)	60.21(14.89)	0.64
	No. of male (%)	22(68.75 %)	27(71.05 %)	1.00
	Time from symptom onset to NAIs administration (days):median (IQR)	7.00(4.25, 8.75)	5.00(4.00, 7.00)	0.52
	APACHE II score: mean(SD)	17.47(8.08)	20.82(8.17)	0.87
	Viral load(log10 /ul) at day 0: median(IQR)	3.30(2.91, 4.1)	3.29(2.70, 4.47)	0.12
	Duration from NAIs taken to H7N9 virus negative(days): median(IQR)	7.00(6.00, 9.75)	6.50(4.00, 8.00)	0.67

O oseltamivir monotherapy, *O+P* oseltamivir-peramivir combination therapy, *IQR* interquartile range, percentile 25 – percentile75

H7N9_Oselta+ Pera_Décroissance charge virale

Table 3 Baseline information and the decrease of log10 virus load between Day 0 and Day 2

Patients	Characteristics	O+P group	O group	*P* value
All patients		*n* = 39	*n* = 43	
Patients with both day 0 and day 2 available specimens		*n* = 31	*n* = 29	
	Age (years): mean (SD)	55.45(14.80)	60.79(14.62)	0.94
	No. of male (%)	22(56.41)	22(51.16)	0.45
	Time from symptom onset to NAIs administration (days):median(IQR)	7.00(5.00, 8.00)	5.00(4.00, 7.00)	0.46
	APACHE II score: mean(SD)	18.53(8.83)	22.69(8.53)	0.83
	Viral load decrease between day 2 and day 0 (log10 /ul): median(IQR)	0.69(0.31, 1.56)	0.00(−0.59, 1.18)	0.06

O oseltamivir monotherapy, *O+P* oseltamivir-peramivir combination therapy, *IQR* interquartile range, percentile 25 – percentile75

H7N9_Oselta+ Pera_Evolution clinique

Table 4 Baseline and the incidence of ARDS

Patients	Characteristics	O+P group	O group	*P* value
All patients		*n* = 39	*n* = 43	
patients had already got ARDS before received NAIs		*n* = 3	*n* = 7	
Study patients		*n* = 36	*n* = 36	
	Age (years): mean (SD)	52.58(12.70)	59.31(13.85)	0.44
	No. of male (%)	24	24	1.00
	Time from symptom onset to NAIs administration (days):median(IQR)	7.00(4.25, 8.00)	6.00(4.00,8.00)	0.57
	Viral load(log10 /ul) at day 0: median(IQR)	4.07(3.00, 4.47)	3.58(2.89,4.47)	0.73
	APACHE II score: mean(SD)	19.17(8.28)	20.22(7.76)	0.58
	New ARDS developed patients (%)	28(77.78)	23(63.89)	0.30

O oseltamivir monotherapy, *O+P* oseltamivir-peramivir combination therapy, *IQR* interquartile range, percentile 25 – percentile75

H7N9_Oselta+ Pera_Mortalité

Table 5 Baseline information and in-hospital mortality

Patients	Characteristics	O+P group	O group	*P* value
all patients included in the study *n* = 82		*n* = 39	*n* = 43	
	Age (years): mean (SD)	56.51(13.86)	59.74(14.71)	0.53
	No. of male (%)	27(69.23 %)	29(67.44 %)	1.0
	Time from symptom onset to NAIs administration (days):median(IQR)	7.00(5.00,8.00)	5.00(4.00,7.00)	0.16
	APACHE II score: mean(SD)	19.05(8.41)	21.09(8.33)	0.86
	Viral load(log10 /ul) at day 0: median(IQR)	3.34(3.06, 4.45)	3.53(2.84, 5.07)	0.08
	Mortality(%)	17(43.59)	11(25.58)	0.11

O oseltamivir monotherapy, *O+P* oseltamivir-peramivir combination therapy, *IQR* interquartile range, percentile 25 – percentile75

H7N9_Oselta+ Pera_Mortalité

Table 5 Baseline information and in-hospital mortality

Patients	Characteristics	O+P group	O group	*P* value
all patients included in the study *n* = 82		*n* = 39	*n* = 43	
	Age (years): mean (SD)	56.51(13.86)	59.74(14.71)	0.53
	No. of male (%)	27(69.23 %)	29(67.44 %)	1.0
	Time from symptom onset to NAIs administration (days):median(IQR)	7.00(5.00,8.00)	5.00(4.00,7.00)	0.16
	APACHE II score: mean(SD)	19.05(8.41)	21.09(8.33)	0.86
	Viral load(log10 /ul) at day 0: median(IQR)	3.34(3.06, 4.45)	3.53(2.84, 5.07)	0.08
	Mortality(%)	17(43.59)	11(25.58)	0.11

O oseltamivir monotherapy, *O+P* oseltamivir-peramivir combination therapy, *IQR* interquartile range, percentile 25 – percentile75

Délai d'instauration des INA long
Pas de bénéfice sur la mortalité malgré tendance à la diminution plus importante de la CV J2
Biais d'indication

H7N9_Oseltamivir resistance

Characterization of Drug-Resistant Influenza A(H7N9) Variants Isolated From an Oseltamivir-Treated Patient in Taiwan

Henju Marjuki,[1] Vasiliy P. Mishin,[1] Anton P. Chesnokov,[1,2] Joyce Jones,[1] Juan A. De La Cruz,[1,2] Katrina Sleeman,[1] Daisuke Tamura,[1,3] Ha T. Nguyen,[1,2] Ho-Sheng Wu,[4] Feng-Yee Chang,[4] Ming-Tsan Liu,[4] Alicia M. Fry,[1] Nancy J. Cox,[1] Julie M. Villanueva,[1] Charles T. Davis,[1] and Larisa V. Gubareva[1*]

[1]Influenza Division, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, and [2]Battelle Memorial Institute, Atlanta, Georgia; [3]Oak Ridge Institute for Science and Education, Tennessee; and [4]Taiwan Centers for Disease Control, Taipei City

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Background. Patients contracting influenza A(H7N9) infection often developed severe disease causing respiratory failure. Neuraminidase (NA) inhibitors (NAIs) are the primary option for treatment, but information on drug-resistance markers for influenza A(H7N9) is limited.

Methods. Four NA variants of A/Taiwan/1/2013(H7N9) virus containing a single substitution (NA-E119V, NA-I222K, NA-I222R, or NA-R292K) recovered from an oseltamivir-treated patient were tested for NAI susceptibility in vitro; their replicative fitness was evaluated in cell culture, mice, and ferrets.

Results. NA-R292K led to highly reduced inhibition by oseltamivir and peramivir, while NA-E119V, NA-I222K, and NA-I222R caused reduced inhibition by oseltamivir. Mice infected with any virus showed severe clinical signs with high mortality rates. NA-I222K virus was the most virulent in mice, whereas virus lacking NA change (NA-WT) and NA-R292K virus seemed the least virulent. Sequence analysis suggests that PB2-S714N increased virulence of NA-I222K virus in mice; NS1-K126R, alone or in combination with PB2-V227M, produced contrasting effects in NA-WT and NA-R292K viruses. In ferrets, all viruses replicated to high titers in the upper respiratory tract but produced only mild illness. NA-R292K virus, showed reduced replicative fitness in this animal model.

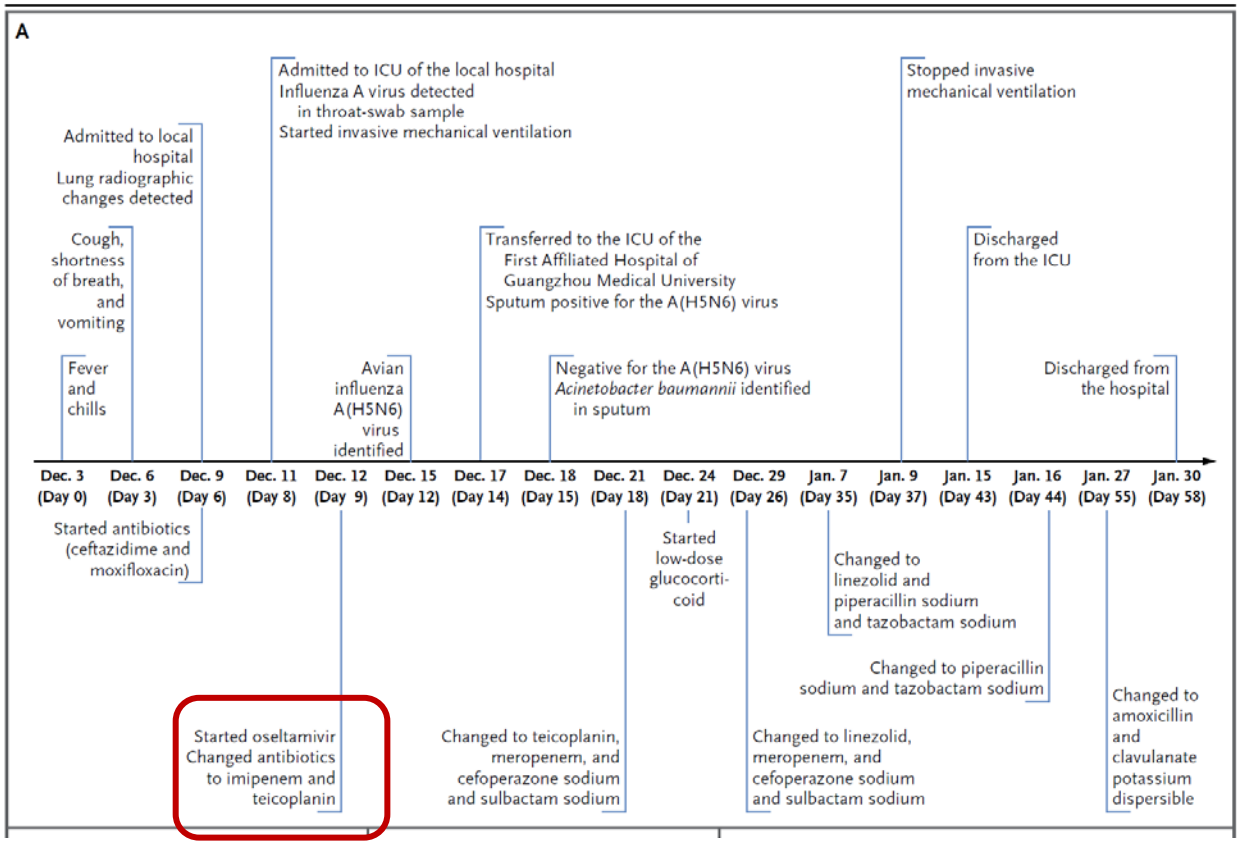
Conclusions. Our data highlight challenges in assessment of the replicative fitness of H7N9 NA variants that emerged in NAI-treated patients.

Keywords. influenza virus; H7N9; oseltamivir; peramivir; R292K; E119V; I222K; I222R; mice; ferrets.

H5N6

Human Infection with a Novel Avian Influenza A(H5N6) Virus

N ENGL J MED 373;5 NEJM.ORG JULY 30, 2015



Conclusion

- Oseltamivir pierre angulaire du traitement
- Le plus taux possible
- Intérêt des fortes doses ?
- Place du peramivir en association à déterminer
- Immunothérapie passive: stratégie en combinaison aux INA ?
- Résistance naturelle / Acquise