Table 4 Duration of fever after the first dose of oseltamivir for pandemic or seasonal A(H1N1) by age (mean hours ± SD)

	After the first dose		*P* between oseltamivir and zanamivir	After the onset		*P* between oseltamivir and zanamivir
	Oseltamivir	Zanamivir		Oseltamivir	Zanamivir	
Seasonal A(H1N1) in the 2007–2008 season	32.0 ± 18.9 ($n = 41$) a	31.5 ± 14.9 ($n = 27$)	NS	50.2 ± 21.4 ($n = 41$) d	48.1 ± 16.9 ($n = 27$)	NS
Seasonal A(H1N1) in the 2008–2009 season	49.7 ± 32.3 ($n = 87$) b	27.3 ± 18.6 ($n = 106$)	<0.001	67.2 ± 33.8 ($n = 87$) e	43.2 ± 20.5 ($n = 106$)	<0.001
2009 Pandemic A(H1N1)	23.0 ± 11.6 ($n = 149$) c	26.9 ± 15.4 ($n = 212$)	<0.01	40.7 ± 15.8 ($n = 149$) f	44.7 ± 16.9 ($n = 212$)	<0.05

a versus b, b versus c: $P < 0.001$

a versus c: $P < 0.01$

d versus e, d versus f: $P < 0.01$

e versus f: $P < 0.001$

pandemic H1N1 between patients ≤15 years of age (oseltamivir 22.5 ± 10.8 h and zanamivir 27.1 ± 16.5 h) and those >15 years of age (23.5 ± 12.5 and 26.6 ± 13.9 h, respectively).

Duration of fever after the onset

The duration of fever after the onset was significantly shorter for patients with pandemic 2009 (40.7 ± 15.8 h) than for patients with H1N1 in both the 2008–2009 (67.2 ± 33.8 h, $P < 0.001$) and 2007–2008 (50.2 ± 21.4 h, $P < 0.01$) seasons (see Table 4). Significant differences were shown between oseltamivir and zanamivir therapy for patients with pandemic in 2009 ($P < 0.05$) and seasonal H1N1 in 2008–2009 ($P < 0.001$).

N1 sequence analysis

Sequence analysis revealed that all 88 of the H1N1 virus isolates in the 2008–2009 season but none in the 2007–2008 or 2009–2010 seasons contained the H275Y mutation.

Discussion

In the 2008–2009 season, almost 100% of the seasonal H1N1 virus in Japan was resistant to oseltamivir because of H275Y mutation [1, 2], but it was reported to be susceptible to amatadine or rimantadine [12]. We reported a lower effectiveness of oseltamivir to the H275Y mutated H1N1 virus in the 2008–2009 season compared to H1N1 virus without H275Y mutation in the 2007–2008 season, especially for children [1, 2]. From August 2009 until February 2010 in Japan, the pandemic H1N1 2009 virus was prevalent, with the seasonal influenza H1N1 and H3N2 viruses rarely found [13]. This pandemic H1N1 2009 influenza virus was genetically different from seasonal H1N1 and had a swine component. It was reported in a genetic and phenotypic analysis to be susceptible to oseltamivir and zanamivir [5]. Therefore, we felt it was important to compare the clinical symptoms of the pandemic H1N1 virus infection and the effectiveness of NAIs against this pandemic virus with seasonal H1N1 virus infection.

The percentage of pandemic 2009 patients with fever (97.0%, >37.4°C) was similar to the report by Dawood et al. [5] (93%). The percentage of patients with sore throat (32.7%) or diarrhea (2.8%) was similar to a report by Cao et al. [6] (36.6% or 2.8%, respectively). The percentages of 2009 pandemic patients with cough (78.9%), fatigue (41.3%), rhinorrhea (47.4%), headache (30.5%), or vomiting (3.6%) of our study were higher than those reported by Cao et al. [6] (69.5%, 10.3%, 23.7%, 19.5%, or 1.9%, respectively).

The clinical symptoms of pandemic and seasonal H1N1 virus infection are said to be similar or rather milder than those of seasonal H1N1 infection, but they have not been adequately compared. In this study, the peak body temperature and the percentage of patients with body temperature ≥37.5° or ≥38.0°C at the start of NAI therapy were equivalent in the three seasons, and the frequency of symptoms was the same or lower for pandemic influenza compared with seasonal H1N1. The pandemic H1N1 2009 infection was a self-limiting illness, as is seasonal influenza, and most patients recovered without complications [5]. However, severe outcomes, including respiratory failure, encephalopathy, myocarditis, and death, have in rare cases been reported. The percentage of patients with intestinal symptoms, such as diarrhea, vomiting, or abdominal pain, was higher for hospitalized or serious patients [5, 7, 14, 15].

The duration of fever after the first dose of a drug and from the onset was analyzed to evaluate the clinical effectiveness of NAIs [10, 11, 16] because it is difficult to evaluate the clinical effectiveness of drugs in outpatient clinics by estimating the mortality rate or incidence of hospitalization. There is a limit to the findings of our study in that it was performed in a general practice setting and not in the context of a rigorous clinical protocol. The body temperature of our outpatients was obtained from reports self-recorded by the patient or a family member. In our previous analysis, the duration of fever after the first dose of oseltamivir or zanamivir of patients with influenza A was approximately 30 h [10, 11], with no significant difference in the duration of fever between seasonal H1N1 and H3N2 virus infection [16]. Oseltamivir was less effective for influenza B than for influenza A [10, 16].

The data obtained using these self-recorded reports seem quite adequate and informative.

In this study of the three most recent influenza seasons, zanamivir was equally effective for pandemic and seasonal H1N1. Zanamivir is inhaled as a dry powder and is reported to be deposited at various sites after administration: oropharynx, 77.6%, whole lung, 13.2% (5.1% central lung region, 4.2% intermediate lung lobe, 3.9% peripheral lung region), and trachea, 1.2% [17]. The effectiveness of zanamivir was not different between pandemic and seasonal H1N1, probably because zanamivir acts on the respiratory system directly and is not affected by H275Y mutation.

However, the effectiveness of oseltamivir differed by season. In 2007–2008, oseltamivir had similar effectiveness to zanamivir. In 2008–2009, oseltamivir had reduced effectiveness in comparison with zanamivir and oseltamivir in the previous season, especially for children, as we previously reported [1, 2], because the seasonal H1N1 in the 2008–2009 season had acquired resistance to oseltamivir by H275Y mutation.

No H275Y mutation was detected for our 34 patients with pandemic H1N1 2009. Our data on the duration of fever showed that oseltamivir was more effective for the pandemic influenza than for seasonal H1N1 in both the 2008–2009 and 2007–2008 seasons. Oseltamivir was more effective than zanamivir for 2009 pandemic patients. The reason for the greater effectiveness of oseltamivir for pandemic H1N1 is unclear, and further study is necessary.

In Japan, the administration of zanamivir is not recommended for children under 5 years, and oseltamivir was prohibited for use by patients aged from 10 to 19 years in the 2007–2008 and 2008–2009 seasons. This restriction makes controlled studies of antiinfluenza drugs that include patients at all ages difficult in Japan, for ethical reasons. Although there was no control (untreated) group in this study, comparisons were made between the H1N1 strains from 2007 to 2008, 2008 to 2009, and 2009 to 2010; thus, the lack of traditional controls is mitigated.

The very few patients in serious condition taken immediately to the hospital were excluded from this study. For these serious patients a combination therapy that includes antivirals and other therapies to mitigate complications may be necessary. The mortality rate (death per million population) by pandemic H1N1 2009 was extremely low in Japan (0.2) compared with other countries (Canada, 2.8; UK, 2.2; Mexico, 2.9; US, 3.3; South Africa, 1.8; Argentina, 14.6; Australia, 8.6; Brazil, 7.0; Chile, 8.1; New Zealand, 4.4) [18], probably because the wide use of commercial antigen detection kits in Japan by skilled physicians promotes accurate diagnosis and the early start of antiinfluenza drug therapy, and because universal coverage by healthcare insurance allows for the testing and treatment to be done at a reasonable cost to the patient, which allows more patients to seek timely treatment. Also, the effectiveness of an antiinfluenza drug in shortening the febrile period confirmed in this study seems to have contributed to reductions in the mortality rate and the rate of complications.

It is common for Japanese patients to be examined by commercial antigen detection kits at clinics near their homes and to start taking antiinfluenza drugs immediately after influenza infection is diagnosed. The effectiveness of commercial antigen detection kits for the detection of both seasonal and AH1N1 pandemic 2009 influenza has been reported in laboratory or clinical studies [19, 20].

As of February 3, 2010, 225 oseltamivir-resistant cases were reported and confirmed worldwide [21]. All these oseltamivir-resistant isolates had the same mutation in the neuraminidase gene (H275Y). In Japan, the frequency of H275Y mutation was also very low for patients with 2009 pandemic influenza (1.10%: 76 of 6,916 analyzed viruses had the H275Y mutation) in a report on October 1, 2010 [22]. However, the situation could change in the future, because the rapid emergence of oseltamivir resistance was confirmed in a patient 4 days after early treatment with the standard dosage of oseltamivir for pandemic 2009 pneumonia [22, 23].

In conclusion, the reduced clinical effectiveness of oseltamivir against influenza in the 2008–2009 season, in which most isolated virus was seasonal H1N1 with the H275Y mutation, was not found in the 2009–2010 season, in which almost all isolated viruses were pandemic H1N1 2009. The effectiveness of zanamivir was unchanged over the three seasons. However, H275Y mutation related to oseltamivir resistance has occurred sporadically in the virus of patients with pandemic H1N1 virus infection in some parts of the world; thus, clinicians must bear in mind that oseltamivir resistance to this new influenza virus may

become more widespread, as has been seen with seasonal H1N1 virus, especially in immunocompromised or high-risk patients [25, 26]. In the 2009–2010 season, no seasonal influenza virus was detected, and oseltamivir and zanamivir were very effective in this study. However, we must continue careful surveillance because seasonal influenza H1N1 with the H275Y mutation may again become the most prevalent form in the near future, and 2009 pandemic H1N1 virus may acquire resistance to oseltamivir or zanamivir.

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治　療

新型インフルエンザH1N1の症状と治療

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2009年秋に大流行した新型H1N1の症状と抗インフルエンザ薬(抗イ薬)の治療効果などを2007/2008年および2008/2009年のH1N1と比較した．対象はPCRで確定したH1N1例で2007/2008年(68例)と2008/2009年(256例)はソ連型，2009/2010年(300例)は新型である．新型は平均年齢が低く(18.2歳)，10代が54.2％を占めた．37.5℃または38℃以上の発熱，咳，咽頭痛，嘔吐，下痢の出現頻度は有意差がなかったが，倦怠感，鼻汁，筋肉痛，頭痛，食欲不振の頻度は新型で低い傾向にあった．ザナミビル解熱時間は3シーズン間で有意差を認めなかったが，オセルタミビル解熱時間は新型では2008/2009年のソ連型(同薬耐性)より短く，2007/2008年のソ連型よりもさらに短い傾向にあった．新型は一部で重症例もあるが，一般的には前2年のH1N1よりも症状は同程度かやや軽い傾向にあり，両抗イ薬の有効性も高いと思われた．

KEY WORDS

■新型H1N1
■ソ連型
■H274Y変異
■オセルタミビル
■ザナミビル

はじめに

2009年春にメキシコで初めて発生したブタ由来の新型インフルエンザH1N1(以下，新型)[1]は国内では5月に第1例が発生し，7月24日に全例把握が終了するまでに4,986例が発症した(この間の死亡例はゼロ)[2]．さらに8月に流行開始の基準である定点あたりの患者数1人を超え，特に沖縄では大流行となった．9月以降，流行は全国に拡がり，11月頃をピークとして全国的な大流行となった．また2008/2009年シーズンにはH274Y変異によるオセルタミビル耐性H1N1ウイルス(ソ連型)が流行し，われわれはこれらの感染例でオセルタミビルの有効性低下を報告しており[3][4]，新型についてもオセルタミビルの耐性化が懸念されている[5]．

われわれは昨秋の迅速診断A型例の大部分が新型であったことから，すでに昨秋の迅速診断A型例について症状

表1　過去3シーズンのPCRによるH1N1診断症例の背景比較

	H1N1ソ連型		H1N1新型	p値		
	2007/2008[a]	2008/2009[b]	2009/2010[c]	(a)vs(b)	(b)vs(c)	(a)vs(c)
n	68	256	300			
年齢	26.1±20.2	22.0±18.5	18.2±12.9	NS	<0.01	<0.01
性別(男/女)	39/29	133/123	149/151	NS	NS	NS
季節性ワクチン(接種/非接種/不明)	28/40/0	106/146/4	59/234/7	NS	<0.001	<0.001
最高体温	39.0±0.8	39.0±0.6	39.0±0.6	NS	NS	NS

などを解析し速報として報告した[6]．今回はPCRで確定した新型例について，同じくPCRで確定した2007/2008年と2008/2009年のH1N1ソ連型(以下，ソ連型)と比較して，患者背景，症状と抗インフルエンザ薬(抗イ薬)の治療効果について2010年1月時点で中間解析した．今回はこの中間解析結果に，若干の考察を加えて述べたい．

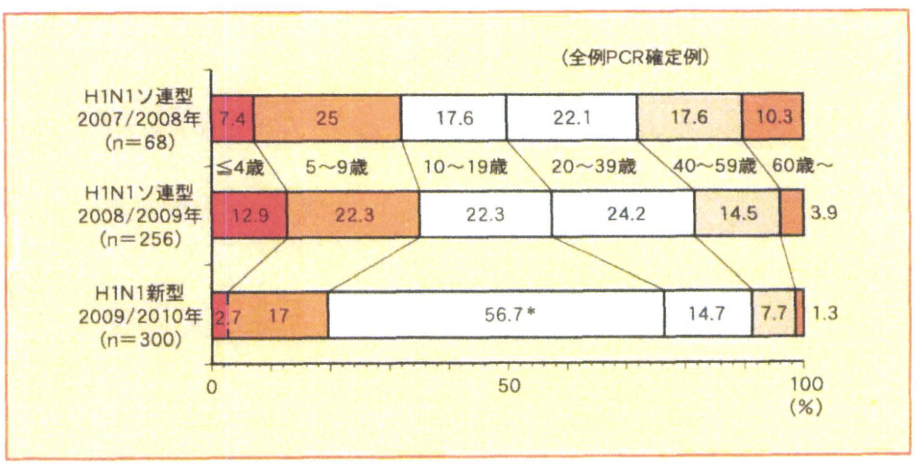

図1　過去3シーズンのH1N1症例の年齢分布

同じH1N1でも新型では2007/2008年，2008/2009年のソ連型よりも10代での発症者の比率が有意に高かった．

＊：10代の比率は新型では2007/2008年および2008/2009年のソ連型よりも有意に高い(いずれもp<0.001)．

1　新型H1N1の背景

前2シーズンのソ連型と比較した新型の患者背景を表1に示す．なお新型例の発症日は2009年8月19日～2010年1月9日であり，2例以外は2009年12月末までに発症した．また外来にて救急搬送されたような重症例は今回の対象には含まれていない．年齢は新型(18.2±12.9歳)では2008/2009年のソ連型(22.0±18.5歳)よりも有意に平均年齢が低かった(p<0.01)．性差は3シーズンともほとんどみられなかった．季節性インフルエンザワクチンの接種率は新型では流行時期が例年よりも早かったため低かった．最高体温の平均は新型，ソ連型(2007/2008年)，ソ連型(2008/2009年)のいずれも39.0℃であった．

新型の患者年齢について，4歳以下，5～9歳，10～19歳，20～39歳，40～59歳，60歳以上に分けた分布を過去2シーズンと比較して図1に示す．新型では10代が56.7％と半数以上を占めており，2007/2008年(17.6％)および2008/2009年(22.3％)の各ソ連型よりも有意に10代の比率が高かった(いずれもp<0.001)．

2　新型H1N1の症状

次に症状出現から迅速キットによる診断確定時までにみられた各症状の出

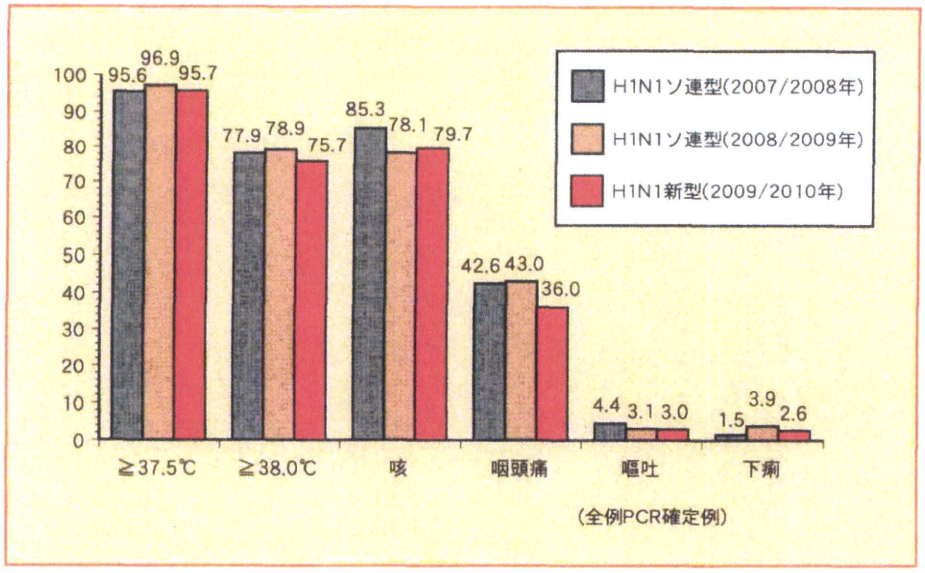

図 2　過去 3 シーズンにおける H1N1 症例の診断時の症状(有意差のない症状)

図は過去 3 シーズンの H1N1 で出現率に有意差がみられなかった症状を示す．各シーズンともに，発熱や咳の出現率が高いのに比し，消化器症状の出現率は全体としてはそれほど高くなかった．

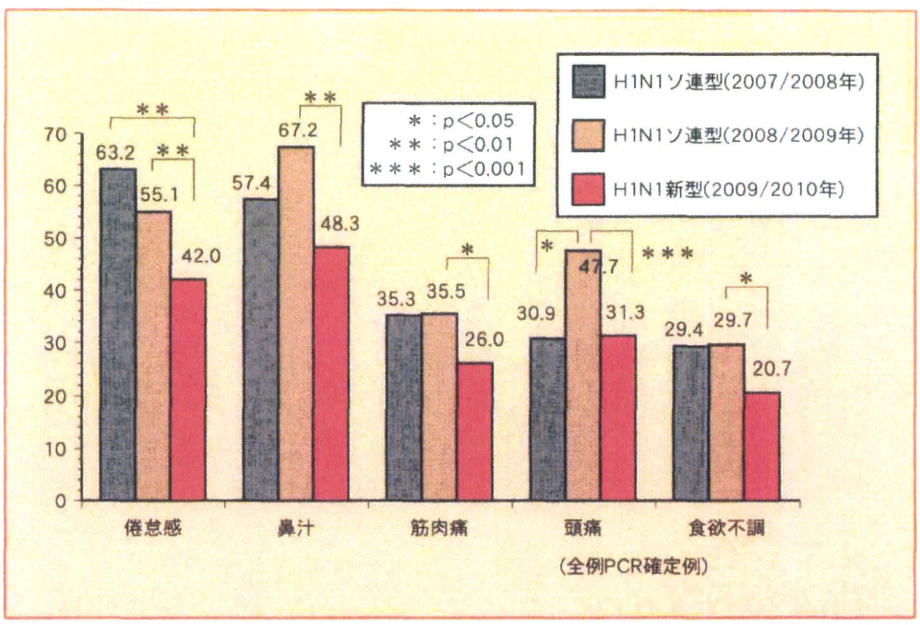

図 3　過去 3 シーズンにおける H1N1 症例の診断時の症状(有意差のある症状)

図中に示した各症状は 2008/2009 年のソ連型よりも新型のほうが有意に出現率が低かった．

現率について検討した．図 2 は新型と 2 シーズンのソ連型で出現率に差がなかった症状を示す．37.5℃および 38℃以上の出現率は各群ともおのおの 95.6～96.9 %，75.7～78.9 % であった．また咳の出現率は 78.1～85.3 %，咽頭痛は 36.0～43.0 %，嘔吐は 3.0～4.4 %，下痢は 1.5～3.9 % でいずれも 3 群間で有意な差を認めなかった．

一方，新型が 2008/2009 年のソ連型よりも有意に出現率が低かったのは倦怠感(42.0 % vs 55.1 %)，鼻汁(48.3 % vs 67.2 %)，筋肉痛(26.0 % vs 35.5 %)，頭痛(31.3 % vs 47.7 %)，食欲不振(20.7 % vs 29.7 %)であった(図 3)．また新型は 2007/2008 年のソ連型よりも倦怠感(ソ連型 63.2 %)の出現頻度は有意に低かった．

新型の症状出現頻度は米国では Dawood ら[1]，発熱 94 %，咳 92 %，咽頭痛 66%，嘔吐と下痢が各 25 % と報告しており，Lessler ら[7]もほぼ同様なデータを報告している．また中国の Cao ら[8]は咳 69.5 %，咽頭痛 36.6%，鼻汁 23.7 %，頭痛 19.5 %，倦怠感 10.3 %，筋肉痛 10.1 %，下痢 2.8 %，嘔吐 1.9 % と報告しており，今回のわれわれの成績もこれらの報告と比較的似ている．

新型とソ連型の症状の比較データはほとんど報告されていないが，今回の結果より，新型の各症状出現率は前 2 年の H1N1 とほぼ同程度か，若干低い可能性が示唆された．37.5℃あるいは 38℃以上の発熱，咳，咽頭痛，嘔吐，下痢などの出現率は従来のソ連型と大差はみられなかったが，倦怠感，

筋肉痛，頭痛，食欲不振などの全身症状は2008/2009年のソ連型よりも頻度が低い傾向にあり，特に倦怠感は2007/2008年のソ連型よりも有意に頻度が低かった．ただ新型では一部で重症化する例が報告されており，このような症例では嘔吐などの消化器症状が高率にみられることも指摘されているので，注意が必要である[6]．

3 新型H1N1の治療効果

ザナミビル投与後の平均の解熱時間(投与開始～解熱)は新型が27.8時間と2007/2008年および2008/2009年の31.5時間，27.3時間と有意差を示さなかった(図4)．一方，オセルタミビル投与後の平均の解熱時間は，ソ連型が2007/2008年は32.0時間，2008/2009年は49.3時間と後者のほうが有意に長かった(図4，$p<0.001$)．また新型の平均の解熱時間は24.0時間と2008/2009年($p<0.001$)のみならず2007/2008年のソ連型($p<0.05$)よりもさらに有意に短かった(図4)．

この両抗イ薬投与後の解熱時間を10歳未満，10～19歳，20歳以上の各年齢層別に検討した(図5)．ザナミビル投与後の平均の解熱時間は新型では各年齢層で26.9～31.5時間の範囲にあり，有意な差はなかった．また2007/2008年，2008/2009年との有意差もいずれの年齢層でもみられなかった．

オセルタミビル投与後の平均の解熱時間は10歳以下では2008/2009年よりも2007/2008年および新型では有意

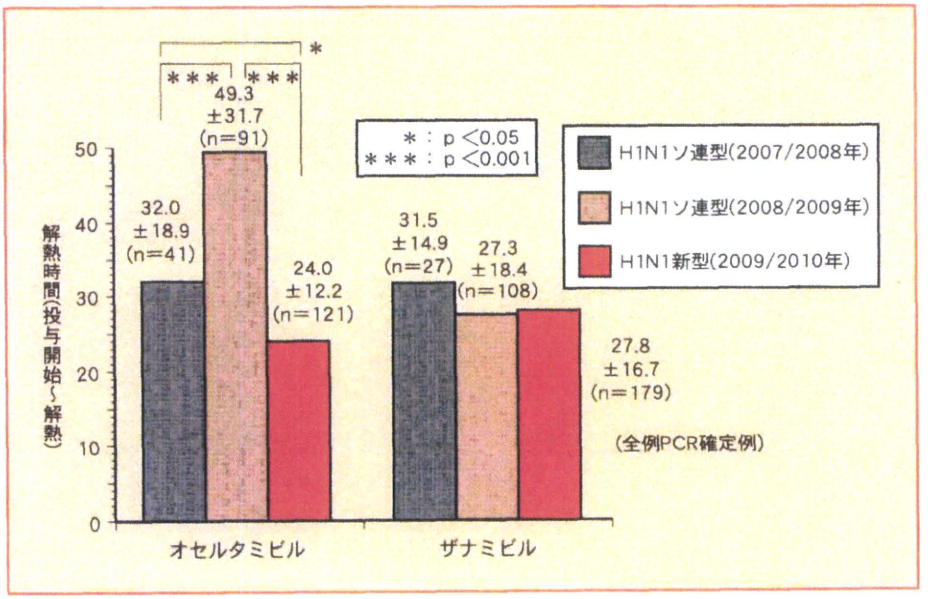

図4 過去3シーズンのH1N1症例における抗イ薬投与から解熱までの時間

ザナミビルは過去3シーズンとも解熱時間に有意な差がないのに比し，オセルタミビルではほぼ100％の症例にH274Y遺伝子変異がみられた2008/2009年のソ連型ではほかのシーズンよりも有意に解熱時間が長かった．一方，新型では2008/2009年のみならずH274Y変異のみられなかった2007/2008年よりもさらに解熱時間が短く有効性が高かった．

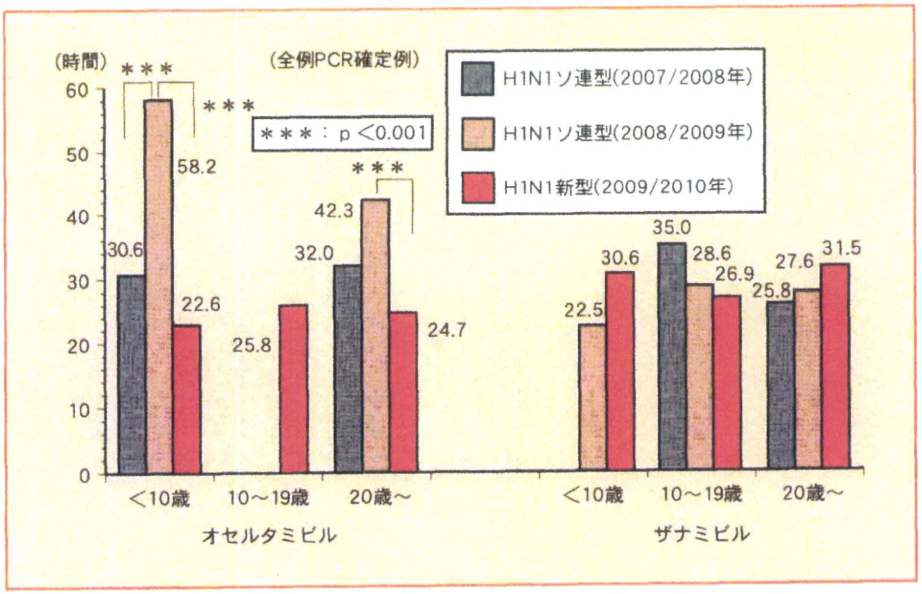

図5 過去3シーズンのH1N1症例における年齢層別の解熱時間

オセルタミビルはほぼ100％耐性ウイルスであった2008/2009年のソ連型を除いて，またザナミビルは3シーズンすべてで，各年齢層における解熱時間は20～30数時間と有効性が高い，と考えられた．

に短かった(ともに $p<0.001$)．また同解熱時間は20歳以上では2008/2009年よりも新型では有意に短かった($p<0.001$)．

4 治療効果とH274Y遺伝子変異について

2008/2009年のソ連型はその前シーズンにはほとんどみられなかったオセルタミビル耐性のH274Y遺伝子変異がほぼ100％の症例でみられた[3)4)]．このH274Y変異によるオセルタミビル耐性ウイルスではオセルタミビルの臨床的な有効性が特に小児で低下していることをわれわれは世界で初めて論文報告した[3)4)]．具体的には投与5±1日目のウイルス残存率が15歳以下の小児では50％と15歳超の11.8％よりも有意に高かった．また15歳以下では2007/2008年よりも2008/2009年は投与後3，4病日の平均体温が有意に高く，解熱時間も有意に長かった．

なお *in vitro* でもオセルタミビルの感受性の指標である IC_{50} は2007/2008年に比し，2008/2009年は約200倍に増加しており，感受性が1/200に低下したことをわれわれは報告した[3)]．われわれの検討では IC_{50} は小児と成人で有意差がなかったことを考えると，小児と成人における有効性の差は生体側の防御反応の年齢的な差に起因する可能性が考えられた．小児では既感染歴やワクチン接種歴が乏しく，インフルエンザに対する免疫防御能が成人ほど高くないため，罹患時にウイルス量がより多くなる可能性がある．一般にオセルタミビル感受性は1/200に低下しても同薬の血中濃度は500～1,000 nM程度あるため[9)10)]，小児に比べると成人での有効性の低下がそれほど顕著でなかったことは理解できる．なおこのようなH274Y変異例でもザナミビルの有効性低下はみられなかった[4)]．

新型に対するオセルタミビルの有効性は同薬の耐性がみられた2008/2009年ソ連型よりも高いだけでなく，耐性のみられなかった2007/2008年ソ連型よりもさらに高い可能性が示唆された．A型のオセルタミビル感受性は亜型によって若干異なること，一般にH3N2のほうがH1N1よりも IC_{50} は低く，感受性が高いことが報告されている[11)]．われわれの臨床研究でもオセルタミビルの有効性はH3N2では高く，H1N1ではやや劣る傾向にあることを報告した[12)]．今回の結果より，同じオセルタミビルに耐性のないH1N1でも新型のほうが2007/2008年のソ連型よりも有効性が高い傾向にあることが示唆され，かつわれわれが以前に報告したH3N2に対する効果よりもさらに高い可能性が示された[12)]．

また今回，新型では症状出現率からみて従来のソ連型よりもやや症状の軽いことがオセルタミビルの効果が高かった原因である可能性もある．ただわれわれは過去に最高体温が高いほど解熱時間が長いことを報告しているが[13)14)]，今回新型は過去2シーズンのソ連型と比して最高体温は39.0℃と有意差がなく，かつザナミビルでは過去3シーズンの有効性がほぼ不変であることを考慮すると，単に症状が軽いことが理由なのかはまだ定かではない．このように新型では同じH1N1で耐性のないソ連型よりもさらに有効性が高かった理由については現時点では不明であり，今後さらに検討したい．

なお国立感染症研究所感染症情報センター[5)]からは2009年12月時点での国内でのH274Y変異によるオセルタミビル耐性化率が国内では総解析数1,403株中22株(発生頻度1.6％)であること，うち19例は予防または治療投与による薬剤の選択圧によって，また2例は薬剤投与がなく耐性株がヒトーヒトによって感染したと考えられることが報告されている．なおこれらの耐性株はザナミビルに対しては感受性を保持しており，国内外においてこれら耐性株が広範囲に拡がっている事例は今のところ報告されていないようである[5)]．しかし，英国・米国では耐性株の院内感染が報告されていることから，今後も新型H1N1耐性株の発生動向に注意が必要であることもあわせて注意喚起されている[5)]．われわれも現在，新型における遺伝子解析を実施中であり，後日報告したいと考えている．

5 重症化例について

新型インフルエンザでは発症後早い時期に急激に症状が悪化し，重症化する例があることが報告されている[6)15)]．この原因としてウイルス性肺炎や脳症，心筋炎などが考えられ，特に喘息などの慢性呼吸器疾患をもった患者ではウイルス性肺炎に注意する必要がある[15)]．今回の検討ではこのような重症例，救急搬送例は含まれておらず，全般的に

症状が軽かったが，一部このような重症化例があることにも常に留意して診療にあたる必要がある．

結語

PCRで確定された新型H1N1について，2007/2008年および2008/2009年のH1N1ソ連型と比較して，症状，抗イ薬の有効性などについて述べた．現状では新型は一部の重症例を除いて症状は同程度かやや軽い傾向にあり，オセルタミビルもザナミビルも著効している．しかし，今後オセルタミビル耐性化も懸念されており，注意は必要と思われる．

*

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ORIGINAL ARTICLE
Myocardial Disease

A National Survey on Myocarditis Associated With the 2009 Influenza A (H1N1) Pandemic in Japan

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with the 2009 Influenza A (H1N1) Pandemic in Japan organized
by the Japanese Circulation Society

Background: An influenza pandemic occurred in 2009 and myocarditis associated with the 2009 influenza A (H1N1) pandemic was reported among hospitalized patients from August 2009.

Methods and Results: The Japanese Circulation Society organized the Clinical Research Committee on Myocarditis Associated with Influenza Pandemic A (H1N1) 2009 and called for a case report on myocarditis for a national survey. The diagnosis of myocarditis was performed using the Guidelines for the Diagnosis and Treatment of Myocarditis (JCS 2009). Fifteen patients were reported to the committee. Fulminant myocarditis developed in 10 patients. Mechanical circulatory support (intra-aortic balloon pumping (IABP) and/or percutaneous cardiopulmonary support (PCPS)) was used on all 10 patients, 8 of whom were rescued. Abnormalities on echocardiography and elevated cardiac enzymes were seen in most of the patients. Myocarditis was found by endomyocardial biopsy in 6 patients. Three patients had complications with pneumonia.

Conclusions: In reality, myocarditis associated with pandemic influenza A (H1N1) seemed to be more common in hospitalized patients, compared with previous seasonal influenza virus outbreaks. To avoid misdiagnosis of acute myocarditis associated with influenza pandemic A (H1N1) 2009, it is essential to determine the characteristic symptoms, signs, and laboratory findings of acute myocarditis during influenza pandemics. Mechanical circulatory support (IABP and/or PCPS) was required to rescue patients with fulminant myocarditis. (*Circ J* 2010; **74:** 2193–2199)

Key Words: Influenza; Myocarditis; Pandemic

Influenza pandemics occur every 10 to 50 years, and the 2009 influenza A (H1N1) pandemic has been spreading worldwide since the first cases were identified in the USA and the United Mexican States in April 2009.[1–6] Most people infected with the 2009 influenza A (H1N1) pandemic recovered without any sequelae, and hospitalizations were quite rare in Japan until June 2009.[4,5] However, some Japanese cases of myocarditis including fulminant myocarditis caused by the 2009 influenza A (H1N1) pandemic began to be reported in hospitalized patients from August 2009.[6] Thus, a Japanese National Survey, to investigate what is going on in the real world around myocarditis associated with the 2009 influenza A (H1N1) pandemic, was initiated by the Japanese Circulation Society.

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Acute myocarditis is a potentially lethal disease, and the etiological agents of viral myocarditis are enteroviruses including coxsackieviruses, adenoviruses, parvoviruses, hepatitis C virus, human immunodeficiency virus, influenza, and others.[7–13] Fulminant myocarditis causes severe hemodynamic dysfunction and requires high-dose catecholamine and mechanical circulatory support. Fulminant myocarditis caused by viral infection is an uncommon type of myocarditis.[7–9] The frequency of myocardial involvement in influenza infection has varied and fulminant myocarditis associated with influenza infection is exceedingly rare as shown by previous papers, although this probability depends on low affinities

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Table 1. Profile, Baseline Disease, Symptoms and Laboratory Findings of 15 Patients With Myocarditis Associated With Pandemic Influenza A (H1N1) 2009 in Japan

Patient No.	Age/sex	Baseline disease	Symptoms of influenza	Cardiac symptom/ onset (day post symptoms of influenza)	Type of myocarditis and complication	ECG findings	CAG	Cardiac enzyme (peak)	UCG
1	6/M	Asthma	Cough, dyspnea, fever (37.5°C)	Dyspnea/day 3	Fulminant myocarditis, viral pneumonia	VF, Torsade de pointes	Not done	CPK (25,244 IU/L)	Diffuse hypokinesis EF 33.5%, effusion
2	11/F	None	Cough, dyspnea, fever (39.8°C)	Shock/day 3	Fulminant myocarditis, shock	ST elevated	Not done	CPK (4,793 IU/L)	Diffuse hypokinesis EF 25%, pericardial effusion
3	24/F	None	Fever, vomiting	Dyspnea, hypotension/day 6	Fulminant myocarditis, alveolar hemorrhage	ST elevated	Normal CAG	CPK (2,681 IU/L)	Diffuse hypokinesis EF 11%, pericardial effusion
4	30/M	None	Fever, dyspnea, chest pain	Chest discomfort/ day 10	Fulminant myocarditis	T inverted	Normal CAG	CPK (971 IU/L)	Diffuse hypokinesis EF 10%, edema of LV wall
5	31/M	None	Cough, arthralgia, fever (39°C)	Orthopnea, hypotension/day 9	Fulminant myocarditis, shock	ST elevated	Normal CAG	CPK (800 IU/L)	Diffuse hypokinesis, edema of inferior LV wall, pericardial effusion
6	31/F	Hyperthyroid	Dyspnea, fever (39°C)	Dyspnea, hypotension/day 2	Fulminant myocarditis, MOF, DIC	SVT, AF	Normal CAG	CPK elevated	Severe hypokinesis and akinesis
7	34/F	None	Vomiting	Chest discomfort/day 1	Fulminant myocarditis	VF, complete AV block	Normal CAG	CPK (3,808 IU/L)	Diffuse hypokinesis EF 32%, LV wall thinning
8	44/M	Asthma	Fever	Dyspnea/day 21	Congestive heart failure	Multifocal PVCs SVT	Normal CAG	No information	Diffuse hypokinesis EF 16%
9	44/F	Asthma	Fever (38.3°C)	Dyspnea, hypotension/day 3	Fulminant myocarditis, shock	VF, frequent VT	Normal CAG	CPK (2,911 IU/L)	Diffuse hypokinesis EF 24%
10	53/M	None	Fever	Syncope/day 3	Complete AV block	Complete AV block	Normal CAG	CPK elevated	Diffuse hypokinesis EF 40%
11	61/M	DM	Nausea, dyspnea, fever (38.8°C)	Dyspnea/day 2	Fulminant myocarditis	AF, T inverted	Normal CAG	Troponin I elevated	Diffuse hypokinesis EF 20%
12	61/F	None	Fever, abdominal pain, disorientation	Dyspnea, hypotension/day 2	Renal failure, septic shock, DIC	ST elevated	Not done	CPK (2,811 IU/L)	Diffuse hypokinesis EF 20%
13	66/M	Emphysema	Common cold-like symptoms	CPA/day 7	CPA, pneumonia (Streptococcus pneumonia)	VF, complete AV block	Normal CAG	CPK (1,842 IU/L)	Almost normal wall motion
14	69/M	Emphysema, cancer, DM	Fever	CPA/day 8	Fulminant myocarditis, cardiac tamponade	Asystole, complete AV block	Normal CAG	CPK elevated	Diffuse hypokinesis EF 29%
15	72/M	IHD (OMI of posterior wall)	Dyspnea, fever	Dyspnea/day 2	Congestive heart failure, viral pneumonia	Giant negative T	No stenosis (s/p PCI)	CPK (827 IU/L)	Diffuse hypokinesis (anterior+posterior wall) EF 38%

Abbreviations see in text.

Table 2. Viral Diagnosis, Treatment and Outcome of 15 Patients With Myocarditis Associated With Pandemic Influenza A (H1N1) 2009 in Japan

Patient No.	Age/ sex	Rapid influenza diagnostic testing	RT-PCR	Ventilator/ days	Mechanical support/days	Other treatment	Biopsy or autopsy	Outcome
1	6/M	Negative (day2,3)	2009A (H1N1) (day 3)	Used/ 14 days	PCPS/11days	Steroid 2mg/kg, large amount of γ-globulin	Not done	Improved (EF 63%)
2	11/F	Negative (day1) →positive (day3)	Not done	Used/ 22 days	PCPS/3days IABP/4days	Steroid pulse, large amount of γ-globulin	Not done	Improved (EF 70%)
3	24/F	Positive (day1)	Not done	Used	PCPS/7days IABP	Usual dose γ-globulin	Not done	Improved (EF 71%)
4	30/M	Negative (day1) →positive (day2)	Negative (day 20)	Not used	IABP/3days	Not used	Active myocarditis	Improved
5	31/M	Negative (day1)	2009A (H1N1) (day 9)	Not used	IABP/3days	Not used	Myocarditis (mild)	Improved
6	31/F	Positive (day1)	2009A (H1N1) (day 1)	Used/ 15days	PCPS/7days IABP/12days	CHDF, plasmapheresis	Myocarditis	Improved
7	34/F	Negative (day1)	2009A (H1N1) (day1)	Used/ 5 days	PCPS/4days IABP/5days	Plasmapheresis	Not done	Death on day 5
8	44/M	Positive (day2)	Not done (A/CF32X day45)*	Not used	Not used	Not used	Healing myocarditis (day 67)	Incompletely improved (EF 25%)
9	44/F	Negative (day2)	2009A (H1N1) (day 3)	Used	PCPS/6days IABP/12days	Usual dose γ-globulin	Myocarditis (day 3 and 24)	Improved (EF 60%)
10	53/M	Positive (day 1)	2009A (H1N1)	Not used	Not used	Pacemaker	Done	Improved
11	61/M	Positive	2009A (H1N1)	Used	IABP	Not used	Myocarditis (day 4 and 10) negative RT-PCR	Improved
12	61/F	Positive (day1)	Not done	Not used	Not used	Usual dose-globulin	Not done	Improved (EF 50%)
13	66/M	Not done	2009A (H1N1) (day7)	Used/ 4 days	Not used	Not used	Interstitial fibrosis (day 31)	Improved
14	69/M	Positive (day1)	2009A (H1N1) (day1)	Used/ 2 days	PCPS/2days	Not used	Interstitial fibrosis (Autopsy)	Death on day 9
15	72/M	Positive (day2)	2009A (H1N1) (day4)	BiPAP	Not used	Usual dose γ-globulin	Interstitial fibrosis (day 8)	Incompletely improved (EF 44%)

*CF titer to Influenza virus A was 1:32 on day 45.
Abbreviations see in text.

to cardiac involvement of the influenza virus and/or the methods used to diagnose myocardial involvement and influenza infection.[7–9] Although usually both the diagnosis and treatment of the pathogen involved in myocarditis are difficult, good diagnostic methods, such as influenza tests, which were quickly checked and reverse transcription polymerase chain reaction (RT-PCR) for the 2009 influenza A (H1N1) pandemic, and treatment with neuraminidase inhibitors were already available in this 2009 pandemic.[1–6]

Methods

To investigate what is going on in the real world around myocarditis associated with the 2009 influenza A (H1N1) pandemic, the task forces directed by the Japanese Circulation Society organized a Clinical Research Committee for Myocarditis associated with the pandemic. The Japanese Circulation Society called for a case report on myocarditis associated with the 2009 influenza A (H1N1) pandemic to all members (24,203 persons in total) from all regions of Japan through direct e-mail in November 2009. Fifteen cases were immediately reported to the task forces within 4 months, and all cases were analyzed. The diagnosis of myocarditis was performed using the Guidelines for the Diagnosis and Treatment of Myocarditis (JCS 2009).[10] Compatible clinical symptoms, echocardiographic abnormalities in the absence of cardiac ischemia, leakage of cardiac enzymes and/or other evidence of myocardial damage provided the highly probable diagnosis for myocarditis. Myocardial biopsy or autopsy provided the histological diagnosis for myocarditis. Laboratory diagnosis of influenza pandemic A (H1N1) 2009 was made by quick influenza diagnostic testing and/or probe-based RT-PCR using a nasopharyngeal swab or sputum.

Results

Fifteen patients (9 men and 6 women, mean age 42.4±20.8 years) were reported to the task force of the Clinical Research for Myocarditis associated with the 2009 influenza A (H1N1) pandemic. They were admitted to hospitals from August 2009 to February 2010. The profiles, baseline disease, symptoms and laboratory findings of these 15 patients are shown in **Table 1**, and the results of diagnostic tests for influenza infection, treatment, histological findings and outcome in **Table 2**. Myocarditis was proven by endomyocardial biopsy in 6 patients, and myocarditis was clinically diagnosed based on clinical figures, leakage of cardiac enzymes, abnormalities on echocardiography, and other findings in the other 9 patients.[10] History was useful in obtaining the correct diagnosis. Thirteen patients complained of typical symptoms of

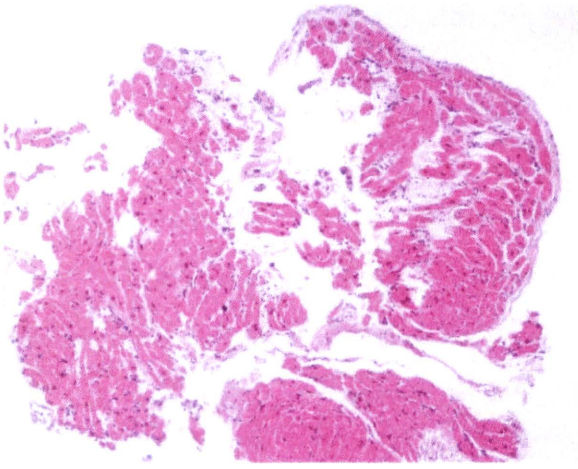

Figure. Endomyocardial biopsy (HE staining) from a 31-year-old woman who developed multi-organ failure (case 6) is shown. She was rescued with mechanical circulatory support (IABP and PCPS). Myocyte degeneration with lymphocyte infiltration and interstitial edema can be seen. IABP, intra-aortic balloon pumping; PCPS, percutaneous cardiopulmonary support.

influenza, such as high fever, cough, headache, and arthralgia. Three patients (20%) complained of abdominal symptoms (abdominal pain, nausea, and vomiting), and one patient complained of common cold-like symptoms. Cardiac symptoms such as dyspnea, chest discomfort, hypotension and syncope developed on the 2nd–21st day of sickness. The most frequent baseline disease was a respiratory disorder in 5 (33%) patients (bronchial asthma in 3 patients and emphysema in 2 patients), and others were diabetes in 1 patient and ischemic heart disease in 1 patient. Three patients with myocarditis were complicated by pneumonia: viral pneumonia in 2 patients and bacterial pneumonia in 1 patient.

Most patients exhibited electrocardiogram (ECG) abnormalities, including ventricular fibrillation in 3 patients, complete AV block in 4 patients, ST elevation in 4 patients, giant negative T-waves in 1 patient, and atrial fibrillation in 1 patient. Two patients were emergently admitted because of cardiopulmonary arrest due to ventricular fibrillation or complete AV block. Echocardiography revealed abnormalities of left ventricular wall motion in 14 patients and pericardial effusion in 2 patients. Cardiac dysfunction almost completely recovered in 11 patients but only incompletely in 2 patients. Coronary angiography was performed on 12 patients, which yielded normal results in all. Cardiac enzymes were elevated in 14 patients, with a peak serum creatine kinase concentration of 800 to 25,244 (IU/L). Quantitative troponin testing was measured in 4 patients and was found to be elevated in all patients. Qualitative quick troponin testing was measured in 3 patients, and was positive in 1 patient.

The clinical manifestations of myocarditis caused by influenza pandemic A (H1N1) varied greatly, and 10 patients were diagnosed with fulminant myocarditis with fatal arrhythmias, and/or varying degrees of cardiogenic shock. Cardiopulmonary arrest was the first cardiac symptom in 2 patients. Syncope due to complete AV block was the first cardiac symptom in 1 patient, who was rescued with temporary pacemaker implantation. The clinical course of patients also varied. Cardiac dysfunction progressed rapidly in 12 patients; 10 of these (83%) recovered to their previous condition and 2 died. Cardiac dysfunction developed after recovery from flu-like symptoms in 2 patients, and myocarditis appeared to have persisted for 1.5 months in 1 patient.

Quick diagnostic testing for influenza, performed on the first visit to the clinic, was negative in 5 patients and positive in 8 patients.[4–6] Quick diagnostic testing, when performed a second time was positive in 2 patients who initially had negative results. RT-PCR testing for the 2009 influenza A (H1N1) pandemic yielded positive results in 10 patients. RT-PCR or quick diagnostic testing yielded positive results in all patients.

Endomyocardial biopsy was performed in 8 patients and an autopsy was performed in 1 patient. Endomyocardial biopsies demonstrated histological myocarditis in 6 patients. Histological findings of an endomyocardial biopsy from case 6, who developed multi-organ failure, are shown in **Figure**. She was rescued with mechanical circulatory support. Lymphocyte infiltration and interstitial edema could be seen. RT-PCR testing for pandemic influenza A (H1N1) from a biopsy specimen was performed only in 1 case, but it was negative.

A ventilator was used in 6 patients and a biphasic positive airway pressure support system (BIPAP) was used in 1 patient. Mechanical circulatory support with intra-aortic balloon pumping (IABP) and/or percutaneous cardiopulmonary support (PCPS) was emergently inserted in 9 patients. Seven patients were rescued with mechanical circulatory support, and 2 patients died. A temporary pacemaker was implanted into the patient with complete AV block. All patients were treated with neuraminidase inhibitors, and high-dose immunoglobulin was used in 2 patients. Corticosteroid was used only in 2 children, but not in any adult patients.

Discussion

The influenza pandemic began in Kobe and Osaka, the middle region of Japan, in May 2009, and all patients recovered until July 2009 without any sequelae.[4,5] It was reported that, in Canada, critical illness due to the 2009 influenza A (H1N1) pandemic occurred rapidly after hospital admission, often in young adults, and was associated with severe hypoxemia, multisystem organ failure, which necessitated prolonged mechanical ventilation, and the frequent use of rescue therapy.[1–3] Hospitalization and death caused by the 2009 influenza A (H1N1) pandemic increased from August 2009, but this was rare in Japan. The Ministry of Health, Labor and Welfare (MHLW) of Japan confirmed only 85 deaths by 1st December 1, 2009, although the estimated number of cases was about 12.6 million by the end of November.[6] Japanese data obtained from the MHLW website showed that the proportion of influenza-like illness cases in those aged 0–4 years and in adults was lower in Japan, compared with other countries. More than 75% of cases were those aged 5–19 years with a low rate of fatalities in Japan. The mortality rates, both per reported rates and per hospitalizations, increased significantly with age. The mean age of the 15 myocarditis cases associated with the 2009 influenza A (H1N1) pandemic was 42 years, which was higher than the mean of estimated cases and similar to other fatal cases during the pandemic in Japan.[6]

Acute myocarditis is a potentially lethal disease, and the etiological agents of viral myocarditis are enteroviruses including coxsackieviruses, adenoviruses, parvoviruses, hepatitis C virus, human immunodeficiency virus, influenza, and others.[7–10] Coxsackievirus B has been described as the most common pathogen of viral myocarditis, and hepatitis C virus is associated with many different forms of heart disease world-

wide, however, influenza myocarditis is relatively rare.[11–16] Bratinssak et al reported four fulminant myocarditis cases in patients aged from 3 to 9 associated with the 2009 influenza A (H1N1) pandemic within a 30-day period, and this suggested that the 2009 influenza A (H1N1) pandemic was more commonly associated with myocarditis than seasonal influenza.[14] Martin et al identified 6 patients with reversible cardiac dysfunction associated with pandemic influenza A (H1N1) out of 123 hospitalized pandemic influenza A (H1N1) patients.[15] There was only 1 case report of fulminant myocarditis with the 2009 influenza A (H1N1) pandemic in Europe.[16] We report herein 15 myocarditis patients varying in age from a child to an old man over 70-year-old as a result of cross-sectional national survey by assist from all members of the Japanese Circulation Society using direct e-mailing system. We suggest that myocarditis is, along with pneumonia and encephalopathy, an important cause of clinical deterioration in influenza patients in Japan. Myocarditis associated with the 2009 influenza A (H1N1) pandemic seemed to be more common in hospitalized patients, compared with previous seasonal influenza virus.[6]

The diagnosis of myocarditis was performed using the Guidelines for the Diagnosis and Treatment of Myocarditis (JCS 2009) with a hybrid of compatible clinical symptoms, evidence of cardiac dysfunction, abnormality of cardiac enzymes in the absence of active coronary ischemia or other evidence of myocardial damage.[10] Clinical symptoms of these patients were not specific; however, most patients complained of not only upper respiratory symptoms but also systemic symptoms. ST elevation was seen in 4 patients and giant negative T-wave was seen in 1 patient, so ECG findings were not specific. Echocardiography revealed reversible abnormalities of left ventricular wall motion, and cardiac enzymes were elevated in most patients. Quantitative troponin was measured in 4 patients and elevated in all; however, qualitative quick troponin testing was measured in 3 patients, but was positive in only 1 patient in this study. Reichlin et al reported that sensitive cardiac troponin assays improve the early diagnosis of myocardial infarction, so we recommend that these assays might be useful for the diagnosis and management of myocarditis.[17] Cardiac scintigram is also useful.[10,18,19] A new approach to diagnose myocarditis is cardiovascular magnetic resonance (CMR) imaging.[10] Liu and Yan observed that CMR imaging is helpful for the detection of myocarditis, because CMR can visualize the entire myocardium.[18] CMR probably has good sensitivity in detecting patchy processes and changes in tissue composition associated with inflammation. To avoid misdiagnosis of acute myocarditis as a complication of influenza infection, it is essential to determine the characteristic symptoms, signs, and laboratory findings of acute myocarditis during influenza infection. Myocarditis is probably underdiagnosed, so we have to strongly suspect myocarditis in hospitalized patients during an influenza pandemic.

Influenza is an acute respiratory illness caused by infection with influenza viruses. The most frequent baseline disease in the present study was lung disease, in 5 (33%) patients (asthma in 3 patients and emphysema in 2 patients). RT-PCR assays or quick diagnostic testing yielded positive results in 15 patients, and viral pneumonia were complicated in 2 patients in this study. Nasopharyngeal smears or sputum were positive for influenza pandemic A (H1N1) 2009 virus on RT-PCR assay in 10 patients. RT-PCR assay was not performed or was negative, and further characterization of the virus was not performed in the other 5 patients. However, pandemic influenza A (H1N1) infection was strongly suspected, because it was previously revealed that over 99% of influenza A positive samples were identified with pandemic influenza A (H1N1) during this period by RT-PCR analysis. Although quick diagnostic testing for influenza is usually performed in Japan, the sensitivity of this type of testing is not high enough.[4–6] Quick diagnostic testing for influenza, which was performed at the first visit to the clinic, was negative in 5 patients. One child who was hospitalized in the Osaka Medical College Hospital under the diagnosis of viral pneumonia caused by pandemic influenza A (H1N1) was found to be positive for viral pneumonia based on the chest X-ray, accumulated white blood cell counts in the absence of bacterial infection, high serum C-reactive protein concentrations and negative quick diagnostic testing for influenza on the 2nd day of sickness. Itoh et al reported that the 2009 influenza A (H1N1) pandemic caused more severe pathological lesions in the lungs of infected mice, ferrets, and non-human primates than the seasonal human H1N1 virus.[20] Nakajima et al reported that the concentrations of various cytokines/chemokines in the serum and autopsied lung tissue were elevated in both of the first autopsy cases in Japan.[21] Muneuchi et al reported that myocarditis associated with influenza B virus appeared to be caused by endothelial impairment and disturbance of microcirculation rather than direct injury to cardiac myocytes.[22] These findings suggest that a negative quick diagnostic test of patients with systemic symptoms might lead to hospitalization due to symptomatic viral pneumonia, or myocarditis, and the pathogenesis of systemic complications of influenza might be related to the induction of inflammatory cytokines produced by infected alveolar cells.

The clinical manifestations of myocarditis quite varied. Cardiac dysfunction progressed rapidly in 12 patients, and cardiac dysfunction developed after recovery from flu-like symptoms in 2 patients, and probably persisted for 1–1.5 months in 1 patient. Cases including slow progressive myocarditis and repetitive myocarditis are very rare. Takehana et al reported that a 75-year-old man who recovered from myocarditis associated with influenza A developed cardiogenic shock and died of fulminant myocarditis.[23] Most patients who survived recovered without any cardiac sequelae in this study, quite similar to previous reports. The degree of myocarditis associated with the 2009 influenza A (H1N1) pandemic was in the present study relatively mild even in patients with fulminant myocarditis.[24] Kotaka et al reported that murine influenza myocarditis was histologically mild and brief in duration compared to coxsackievirus B3 myocarditis.[25] We suggest that the pathogenesis and pathomechanism of pandemic influenza myocarditis differ depending on the pathogen,[25] and moreover, that significant mechanisms of cardiac injury, such as cytokine storm, endothelial dysfunction, oxidative stress and other factors, might play significant roles in the pathogenesis of pandemic influenza myocarditis.[21–27] RT-PCR testing for pandemic influenza A (H1N1) from biopsy specimens was performed in only 1 case, and was negative. To evaluate influenza viral persistence in the myocardium in cases with myocarditis, further evaluation of viral replication in the myocardium using RT-PCR or in situ hybridization methods for pandemic influenza A (H1N1) from myocardial specimens is inevitable.

The first therapy for myocarditis patients with heart failure is supportive intervention. The recent application of PCPS and/or IABP to serious cases of viral myocarditis has yielded good outcomes.[5,29] The severity and grade of cardiac and renal

dysfunction are important factors in connection with the prognosis. In this study, 8 patients were rescued using mechanical circulatory support and 2 patients died. It is important to recognize that patients with influenza infection might have acute myocarditis with heart failure, and that early diagnosis is required for adequate treatment.

Neuraminidase inhibitors work by blocking the function of the viral neuraminidase protein and thus prevent the virus from reproducing by budding from the host cell, and are useful for treating and preventing influenza virus infections.[1-6,20] Itoh et al reported that the 2009 influenza A (H1N1) pandemic is sensitive to neuraminidase inhibitors, suggesting that these drugs could function as a first line of defense against the 2009 influenza A (H1N1) pandemic.[1-6,20] Treatment with neuraminidase is also recommended by the Japanese Association of Infection. The low rate of case fatality in Japan could be a result of aggressive early intervention using with antiviral drugs such as oseltamivir and zanamivir. All of the present patients were treated with oseltamivir. In Japan, 3 types of neuraminidase inhibitors are available: oseltamivir, zanamivir, and peramivir. Adamantine, a M2 protein blocker, is resistant to the 2009 influenza A (H1N1) pandemic, while oseltamivir and zanamivir exhibit lower frequencies of antiviral resistance.[29] Oseltamivir is orally available, while zanamivir is inhaled.[25] Halvala et al identified 10 patients who developed the H275Y oseltamivir-resistance mutation out of 1,802 samples in Scotland.[30] The new neuraminidase inhibitor, peramivir, is formulated for intravenous administration and it has resulted in a good IC_{50} response for pandemic influenza virus. Peramivir is recommended for patients requiring ventilation with difficulty in absorption of oseltamivir.[29] Treatment with high-dose immunoglobulin was used in 2 patients, which is still controversial.[31] Corticosteroid was used only in 2 children, but not in adult patients. We know that inflammatory cytokines are important in the infection course of influenza; however, immunosuppression therapy with corticosteroids is not recommended, and this is supported by previous evidence.[2,10] Moderate- to high-dose steroids are not recommended by the World Health Organization, because they are of unproven benefit and potentially harmful.

Conclusion

As a result of the present national survey in Japan, myocarditis associated with the 2009 influenza A (H1N1) pandemic seemed to be more common, compared with previous seasonal influenza viruses. To avoid misdiagnosis of acute myocarditis caused by influenza pandemic A (H1N1) 2009, the characteristic symptoms, signs, and laboratory findings of acute myocarditis during influenza pandemics must be determined. Mechanical circulatory support (IABP and or PCPS) was required to rescue myocarditis patients by all means. Appropriate treatment using neuraminidase inhibitors must be recommended for patients with myocarditis associated with the influenza A (H1N1) pandemic.

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Appendix

Members of the Clinical Research Committee on Myocarditis Associated with Pandemic 2009 H1N1 in Japan organized by the Japanese Circulation Society

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インフルエンザA（H1N1）心筋炎

Myocarditis associated with Influenza A (H1N1)

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注目される心筋炎

インフルエンザA(H1N1)心筋炎

Myocarditis associated with Influenza A (H1N1)

特集

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心筋症・心筋炎－基礎と臨床の最前線2010
Key words 心筋炎 インフルエンザ パンデミック

2009年春，新型インフルエンザPandemic2009A(H1N1)が北米で発生，全大陸に感染は拡大しWHOはパンデミックと判断した[1)2)]．国立感染症研究所は，2009年12月13日までの新型インフルエンザ受診者数を約1,539万人と推計しているが，これは自宅療養の患者や不顕性感染患者を含まない集計である[3)]．また入院サーベイランスでは，7月28日～12月15日までに11,723人が入院し，747人が人工呼吸器を使用，もしくは急性脳症と診断された．自治体からの報告では12月15日の時点で新型インフルエンザ感染と診断された122人が死亡した[3)]．この厚生労働省の報告において，100例の死亡者の直接死因のうち6例が心筋炎と報告され(重複を含む)，心筋炎は新型インフルエンザ重症例では決してまれではない合併症である(**図1**)．また，その後パンデミックはいったん収束したが，ウイルス変異や次の流行の発生が予想される．

心筋炎(Myocarditis)は「心筋を主座とした炎症をきたす疾患」と定義されている．組織学的には，心筋細胞壊死とリンパ球，マクロファージなどの炎症性細胞浸潤によって確定診断がなされる．急性期には重症で致死的な経過をとることもあり，早期診断，早期治療が必要であるにもかかわらず，このような確定診断に至る臨床例は必ずしも多くはない[4)]．心筋炎の病因はウイルスが多いが多様である．ウイルス性心筋炎の病因として，筆者らはとくにコクサッキーB群を含むエンテロウイルスが重要と報告してきた．このほか，アデノウイルス，C型肝炎ウイルス，パルボウイルスやインフルエンザも心筋炎の病因ウイルスとされる．これまで，インフルエンザウイルスの頻度はさほど高くはないと考えられていたが[5)～10)]，今回のパンデミックにおいては従来の季節性のインフルエンザA(H1N1)よりも心筋炎の合併頻度は高い可能性が示唆される．

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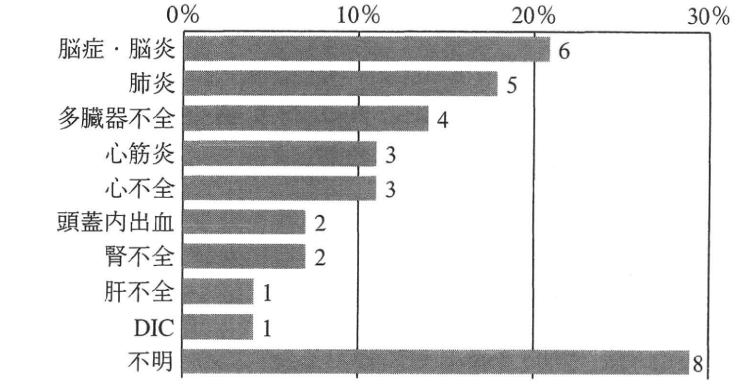
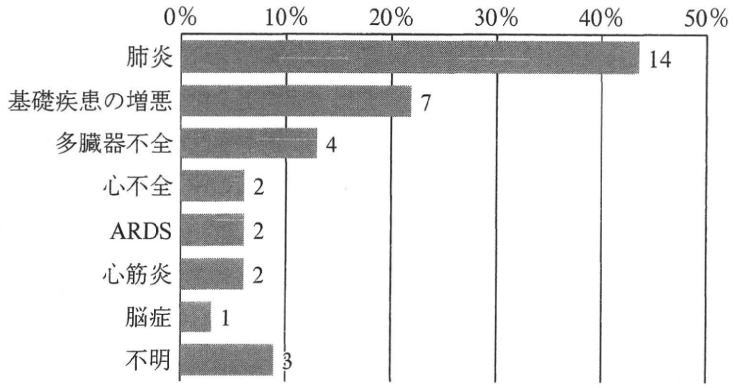
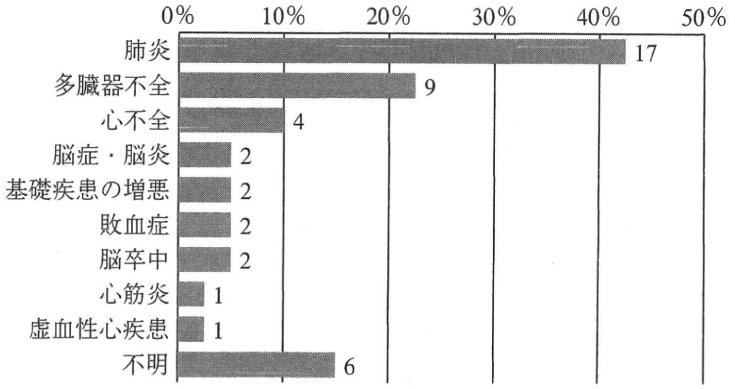


a. 小児(15歳未満)N=28(重複あり)



b. 15歳以上65歳未満(N=40)(重複あり)



c. 65歳以上の高齢者N=32(重複あり)

図1 死亡例の直接死因

(a, b, c:厚生労働省新型インフルエンザ対策推進本部:新型インフルエンザの発生動向~医療従事者向け疫学情報~ Ver. 2. 2009年12月25日より引用)

新型インフルエンザウイルスA(H1N1)について

インフルエンザにはA, B, Cの3つの型があり, A型のみがパンデミック(世界的大流行)を引き起こす. これは, A型のインフルエンザウイルス蛋白の赤血球凝集素(HA)に16種類, ノイラミニダーゼ(NA)に9種類, 合計16×9=144種類の亜型が存在し, そのため抗原性が異なり, 多くの人が基礎免疫を持たないためである. 2009年まではAソ連型(H1N1)とA香港型(H3N2), およびB型が流行株であった. これまで, H2N2(アジアかぜ型)や高病原性のH5N1型がパンデミックの原因ウイルスと考えられてきたが, 今回の新型はAソ連型と同じH1N1であった. さらに, この新型はかなり前に流行したと思われるヒト, 鳥, 豚の遺伝子の混じり合ったウイルスと, 豚由来のウイルスとが再び混じり合ったハイブリッドウイルスであった. NAとM蛋白の分節はユーラシア

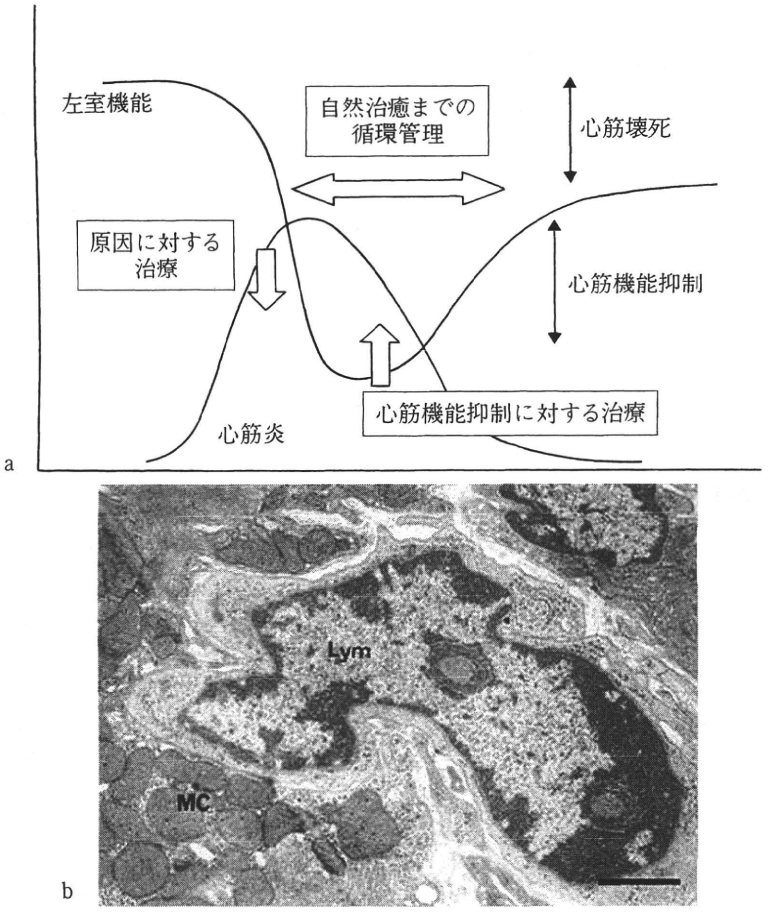


図 2
a：心筋炎における心機能障害の発症機序と介入ポイント
(急性および慢性心筋炎の診断・治療に関するガイドライン(2009年改訂版)(JCS 2009)2009より引用)
b：マウスのインフルエンザA(H1N1)心筋炎電子顕微鏡写真．MC：心筋細胞，Lym：リンパ球
(Am J Pathol 136：409-419, 1990より引用)

サージカルマスクを着用し，接触感染および飛沫感染予防策を遵守する．ただし感染性を有する時期にエアロゾルを生じるような処置(高流量酸素投与，気管挿管，気管支鏡など)を行うときには空気感染対策を考慮する．

心筋炎の発症機序

心筋炎の発症機序については「急性および慢性心筋炎の診断・治療に関するガイドライン」に一つの仮説が掲載されている(**図2a**)[4]．ウイルス増殖のピークは，心機能障害のピークと必ずしも一致せず炎症反応等が大きく関与すると考えられる．今回の新型A(H1N1)心筋炎の限られた症例の検討では，組織所見は臨床的に重症な症例でもあまり強い変化がなく，われわれが以前経験した季節性A(H1N1)でも同様であった[6]．さらに，われわれの研究室では季節性インフルエンザウイルスA(H1N1)をマウスに感染させ心筋炎モデルを作成した[17]．このモデルでは心筋からウイルスが分離され，感染5日後に限局性の心筋炎病巣が出現し，電顕ではリンパ球が心筋細胞に接して浸潤する像が認められた(図2b)．しかし，心臓親和性が強いコクサッキーBウイルスの病変[5]と比べると，このインフルエンザ心筋炎モデルでは，心筋炎は軽度かつ限局的であるなどいくつかの相違点が見られた．

インフルエンザ感染に関連した心機能障害において，ウイルスの直接侵襲のみならずサイトカイン等の関与が注目される．今後インフルエンザ心