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[Review article]

Pharmacologic background and clinical issue of anti-influenza drugs

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Abstract

Since 2000, rapid antigen detection kits and anti-influenza drugs have been used for the early diagnosis and treatment of influenza in Japan, respectively. The main drugs available in clinical practice are the neuraminidase inhibitors oseltamivir, zanamivir, laninamivir, and peramivir, as well as the cap-dependent endonuclease inhibitor baloxavir marboxil. Antiviral therapy with neuraminidase inhibitors has been practiced for many years, especially in Japan ; it can shorten the febrile period and reduce complications. Despite having similar structures, the pharmacologic background of neuraminidase inhibitors differs significantly, as reflected in their varying clinical efficacy. Due to its inhibitory mechanism, baloxavir marboxil can rapidly reduce the viral load than neuraminidase inhibitors. However, the duration of symptoms was similar after the administration of baloxavir marboxil and oseltamivir, and variants with reduced drug susceptibility have been detected in 20%–30% of pediatric patients treated with baloxavir marboxil. Clinical trials of several novel anti-influenza drugs are currently underway. When these drugs are first marketed, the characteristics of the influenza virus and the pharmacologic background of the drugs must be clarified before their administration to patients in clinical practice.

Key words : anti-influenza drug, antiviral, influenza, children

Introduction

Oseltamivir and zanamivir are the first neuraminidase (NA) inhibitors approved in Japan, which were launched in 2000–2001, followed by laninamivir and peramivir, launched in 2010–2011. Since then, rapid antigen detection kits and the abovementioned NA inhibitors have been used for the early diagnosis and treatment of influenza, respectively. In 2018, baloxavir marboxil (herein referred to as baloxavir), a cap-dependent endonuclease (CEN) inhibitor, was introduced to the clinical setting.

However, these drugs are associated with many issues, such as differences in clinical efficacy based on each drug's pharmacologic background and selection of variants with reduced drug susceptibility. In line with these issues, this review has discussed the efficacy and concerns of anti-influenza drugs.

Clinical significance and research implications of anti-influenza drugs

Influenza virus

Structures

Influenza viruses belong to the family *Orthomyxoviridae* and are classified into types A, B, C, and D according to antigenic differences between each nuclear and membrane protein[1-3)]. In humans, epidemics are mainly caused by type A and B viruses, which have envelopes and eight-segmented single-stranded negative-sense RNA genomes. Type A viruses are further classified into 16 hemagglutinin (HA) and 9 NA subtypes based on antigenic differences. Currently, two subtypes of type A viruses, namely, H1N1 (A/H1 subtype) and H3N2 (A/H3 subtype), are circulating among the human community. Type B viruses are not as diverse as

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type A viruses and are classified into two lineages—Yamagata and Victoria—based on differences in HA antigenicity.

Life cycle

Influenza viruses adsorb on the surface of airway epithelial cells by recognizing sialic acid and galactose α2-6-linked sugar chains expressed on the cell surface as receptors (Figure 1). The virus entry requires approximately 25 min after adsorption[4]. Through endocytosis, the virus is internalized into the cell. Next, the viral envelope fuses with the host cell membrane (endosomal membrane), resulting in the uncoating of the virus and the release of viral RNA into the cytoplasm. The released RNA then moves into the host cell nucleus, where it is replicated and transcribed. As influenza viruses are minus-stranded RNA viruses and cannot directly produce mRNA, they need to cut out approximately 15 bases from the host-derived mRNA containing a cap structure at the 5′-end. This is mediated through the action of CEN in the PA subunit of the virus' RNA polymerase. Using these 15 bases as a primer, the virus transcribes the negative-stranded RNA to obtain viral mRNA, which is translated on the host cell ribosome to synthesize viral proteins. After the replicated RNA and newly synthesized viral proteins produce progeny viruses, budding occurs. When the assembled virions bud on the cell surface, the viral HA is bound to sialic acid, preventing the release of the virus. Through the sialic acid–degrading action of its own NA, the virus can detach itself from the cell surface and release itself outside the cell. Infected cells begin producing progeny influenza virus 6 h after adsorption, continuing for 5 hours[5].

Anti-influenza virus drugs

M2 inhibitor

The type A virus has an ion channel formed by the M2 protein, and when outside hydrogen ions enter the virus through this channel, uncoating occurs.

Amantadine, an M2 inhibitor, exhibits antiviral effects by targeting this M2 protein ion channel and inhibiting uncoating. This drug has been used in the United States and other countries since the 1960s. However, most type A viruses isolated today are resistant to amantadine[6], and type B viruses do not have the M2 protein, making amantadine ineffective. Thus, M2 inhibitors are not currently administered.

NA inhibitors

As described above, to release the replicated progeny virus from the cell surface, HA must be detached from sialic acid using the sialic acid–degrading enzymatic activity of NA (Figure 1). Current NA inhibitors prevent the enzymatic activity of sialic acid–based degrading enzymes. In other words, NA inhibitors are enzyme inhibitors. In the 1970s, the sialic acid derivative 2,3-dehydro-2-deoxy-*N*-acetylneuraminic acid (DANA) was reported to inhibit NA activity[7]. Subsequently, based on the DANA structure, a computer-aided drug design led to the development of drugs that inhibit NA activity more potently. Thus, current NA inhibitors, such

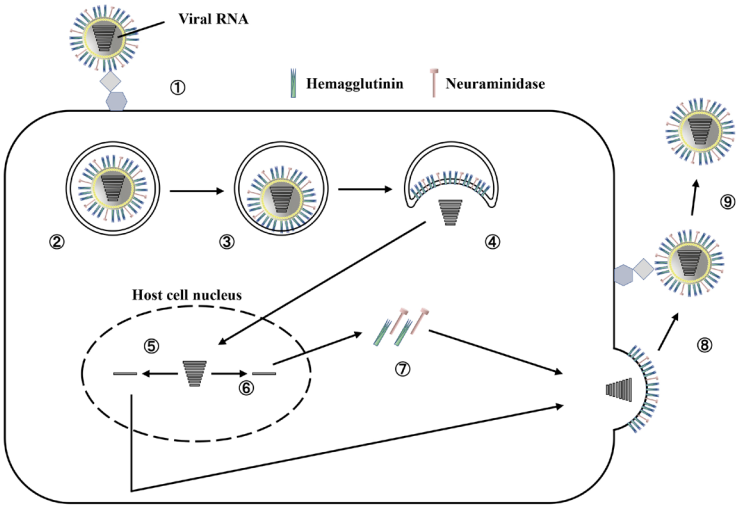

Fig. 1. Life cycle of influenza virus
① adsorption, ② endocytosis, ③ membrane fusion, ④ uncoating, ⑤ RNA replication, ⑥ mRNA transcription, ⑦ protein synthesis, ⑧ budding, and ⑨ release

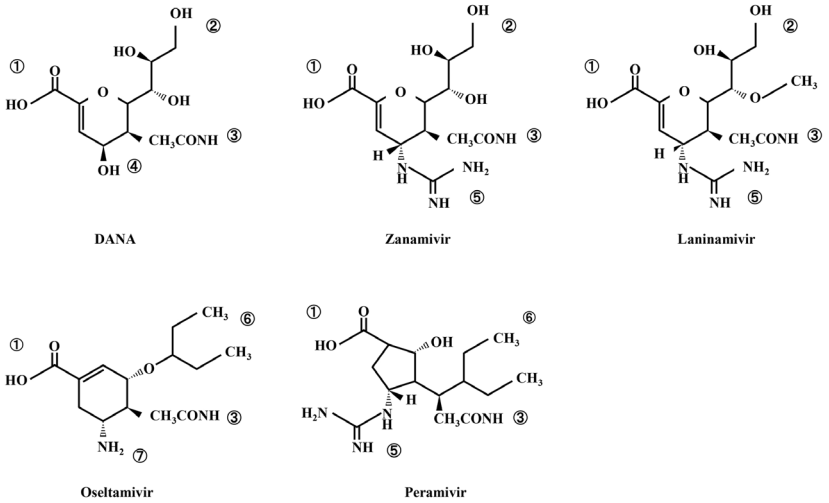

Fig. 2. Structure of neuraminidase inhibitors
① carboxyl group, ② glycerol group, ③ *N*-acetylamino group, ④ hydroxy group, ⑤ guanidino group, ⑥ 3-pentyl group, and ⑦ amino group
DANA, 2,3-dehydro-2-deoxy-*N*-acetylneuraminic acid

as oseltamivir, zanamivir, laninamivir, and peramivir, are DANA derivatives, and their analogs exhibit similar structures (Figure 2).

Oseltamivir

Oseltamivir is available in two dosage forms : 75 mg capsules and 3% dry syrup. It has been approved for use in the treatment of influenza and as a post-exposure prophylaxis regimen (Table 1).

The active form of oseltamivir (oseltamivir carboxylate) has low bioavailability when administered orally[8] ; hence, the precursor oseltamivir phosphate is administered orally, which is then converted into the active form in the body. In adults, when 75 mg per dose oseltamivir is administered orally, the maximum plasma concentration of the active form of the drug is approximately 1200 nM. However, because children have higher extracellular fluid per body weight and larger volume of distribution, as well as the higher clearance rate of the active form per body weight is inversely proportional to age[9,10], the maximum plasma concentrations of the active form is approximately 700 nM in children aged 9–12 years and 400 nM in those aged 1–2 years, with lower concentrations in younger age groups[11]. As influenza viruses infect and multiply in the airways, the extent to which the active form is transferred from the blood to the airways is a more significant issue than the blood drug concentration. In animal models, the highest concentration of the active form in the airways is ~70% of the highest plasma concentration[12] ; however, its concentration in the human lower respiratory tract remains unknown. In human saliva, the concentration of the active form is ~5% of the plasma concentration[13] ; nonetheless, it is considerably higher than 50% of the inhibitory concentration (IC_{50}) (Table 2)[14]. If the NA activity of susceptible type A virus is inhibited by 50%, a sufficient effect is expected.

In adults, oseltamivir has been demonstrated to shorten the symptomatic period and prevent complications compared with placebo[15]. In fact, during the H1N1 pdm09 epidemic, which caused many deaths worldwide, the oseltamivir group had a significantly lower mortality rate than the untreated group[16]. In children, the febrile period was reduced by approximately 25 h in the oseltamivir group compared with that in the placebo group ; consequently, complications such as otitis media were controlled, and unnecessary administration of antimicrobial agents was prevented[17]. A retrospective cohort study involving critically ill children who were systemically managed in an intensive care unit (ICU) showed that oseltamivir administration within 24 h of ICU admission contributed to reducing hospitalization duration compared with no oseltamivir treatment[18]. In Japan, compared with children not treated with oseltamivir, the fever duration in type A (H3N2) and type B influenza was reduced by approximately 20 h in children treated with oseltamivir[19]. However, patients treated with oseltamivir showed no reduction in the infectious virus shedding period compared with those who were not treated with oseltamivir, and infectious viruses continued shedding for 5–7 days after the onset of

Table 1. Four neuraminidase inhibitors and a cap-dependent endonuclease inhibitor in Japan

Classification	Neuraminidase inhibitors				Cap-dependent endonuclease inhibitor
Generic name	Oseltamivir	Zanamivir	Laninamivir	Peramivir	Baloxavir marboxil
Trade name	Tamiflu®	Relenza®	Inavir®	Rapiacta®	Xofluza®
Route	oral	inhalation	inhalation	intravenous	oral
Drug formulation	Capsule (75 mg) Dry syrup (3%)	Dry powder (5 mg)	Dry powder (20 mg) Inhalation suspension set (160 mg)[a]	Drip infusion (150, 300 mg)	Tablet (10 and 20 mg)
Dose	Adults	Adults	Adults	Adults	>12 years old (adults)
	75 mg/dose, twice daily for 5 days	10 mg/dose, twice daily for 5 days	Dry powder 40 mg/dose, single Inhalation suspension set 160 mg/dose, single	300 mg/dose (maximum: 600 mg/dose), single Possible daily administration	<80 kg body weight: 40 mg, single ≥80 kg body weight: 80 mg, single
	Children	Children	Children	Children	Children (<12 years old)
	<1 year old: 3 mg/kg/dose ≥1 year old: 2 mg/kg/dose (maximum: 75 mg/dose) Twice daily for 5 days	10 mg/dose, twice daily for 5 days	Dry powder <10 years old: 20 mg/dose, single ≥10 years old: 40 mg/dose, single Inhalation suspension set 160 mg/dose, single	10 mg/kg/dose (maximum: 600 mg/dose), single Possible daily administration	≥10 to <20 kg body weight: 10 mg, single ≥20 to <40 kg body weight: 20 mg, single ≥40 kg body weight: 40 mg, single
Indications for post-exposure prophylaxis	Yes Adults: 75 mg/dose, once daily for 7–10 days Children: ≥1 year old: 2 mg/kg/dose (maximum: 75 mg/dose), once daily for 10 days	Yes For both adults and children: 10 mg/dose, once daily for 10 days	Dry powder: Yes ≥10 years old and adults: 40 mg/dose single, or 20 mg/dose once daily for 2 days <10 years old: 20 mg/dose, single Inhalation suspension set: None	None	Yes For >12 years old (adults): <80 kg body weight: 40 mg, single ≥80 kg body weight: 80 mg, single For children (<12 years old): ≥20 to <40 kg body weight: 20mg, single ≥40 kg body weight: 40 mg, single

* a, a jet nebulizer required

illness[19]. Based on this previous report, the duration of suspension from school or preschool after the onset of influenza has been established by law in Japan. Both oseltamivir and zanamivir are equally effective in reducing fever duration in type A influenza ; however, in type B influenza, oseltamivir is less effective than zanamivir in reducing fever duration[20,21]. Oseltamivir can rotate the NA active center (E276) and induce a hydrophobic pocket with R224, binding to that site via a 3-pentyl group (Figures 2 and 3)[22-24]. However, compared with type A virus, E276 rotation is less likely to occur in type B virus. Therefore, the hydrophobic pocket accommodating the 3-pentyl group is not induced[25], and the IC_{50} value of oseltamivir for type B viruses is higher than that for type A viruses (Table 2)[14]. Consequently, the clinical efficacy of oseltamivir against type A influenza differs from that against type B influenza.

Zanamivir and laninamivir

Given that influenza spreads and multiplies in the airways, the concentration of antiviral drugs in the airways should be high. The inhalants zanamivir and laninamivir are the most reasonable agents. Both drugs have been approved for influenza treatment and post-exposure prophylaxis (Table 1).

When zanamivir is inhaled, most of the drug is distributed from the posterior pharyngeal wall to the larynx, with only approximately 15% reaching the lower respiratory tract ; nevertheless, more than 3000 nM of the drug is still thought to remain in the airways 6 h after inhalation[26]. The IC_{50} values for zanamivir against type B virus are lower than those of oseltamivir (Table 2)[14]. As mentioned above, its clinical efficacy is higher than that of oseltamivir[20,21,27], and the duration of virus shedding tends to be shorter in children[19]. The structure of lanina-

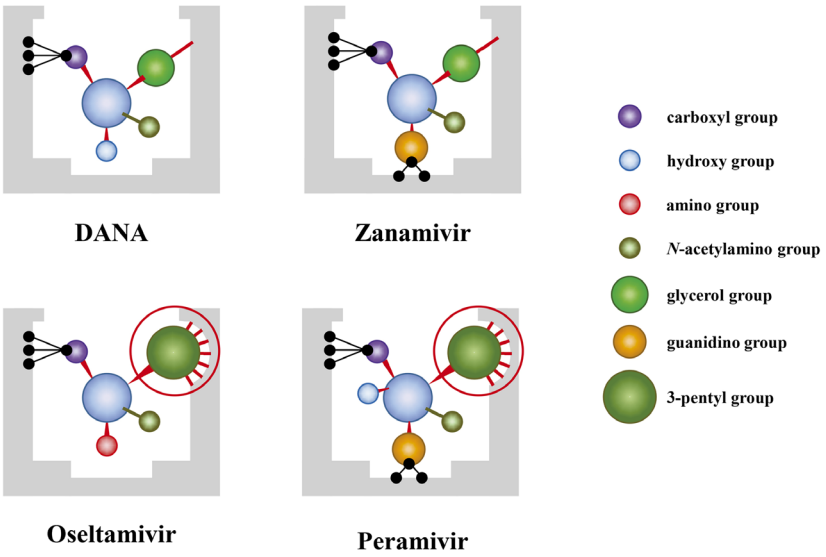

Fig. 3. Binding of drugs to virus neuraminidase
Each neuraminidase inhibitor binds to the active site of viral neuraminidase (gray solid) using its side chain. Oseltamivir and peramivir are required to induce the formation of hydrophobic pockets (red circle) on the viral neuraminidase for successful binding. DANA, 2,3-dehydro-2-deoxy-*N*-acetylneuraminic acid

Table 2. Drug concentrations required to inhibit virus neuraminidase activity by 50%[14]

Viruses		IC_{50} (nM)			
		Oseltamivir	Zanamivir	Laninamivir	Peramivir
Type A					
	H1N1 pdm09 (wild-type)	0.22 ± 0.08	0.23 ± 0.05	0.18 ± 0.03	0.06 ± 0.02
	H3N2 (wild-type)	0.13 ± 0.04	0.37 ± 0.13	0.37 ± 0.05	0.11 ± 0.04
Type B		10.43 ± 5.24	1.34 ± 0.53	1.50 ± 0.49	0.77 ± 0.44
	Yamagata lineage	6.57 ± 2.02	1.86 ± 0.53	1.35 ± 0.16	0.54 ± 0.14
	Victoria lineage	11.01 ± 5.33	1.23 ± 0.44	1.52 ± 0.52	0.83 ± 0.49

Mean ± standard deviation
IC_{50}: 50% of inhibitory concentration

mivir is very similar to that of zanamivir (Figure 2); both drugs also have a similar inhibitory effect on NA activity (Table 2)[14]. Given that zanamivir is water-soluble, its clinical efficacy was also confirmed in children by dissolving it in saline or other solutions and inhaling it using a nebulizer[19], but this inhalation method using a zanamivir solution is not currently approved.

Meanwhile, laninamivir inhales its precursor called laninamivir octanoate, which is fat-soluble, allowing it to enter the cells in the airways, where it is hydrolyzed into the active form in the cells. Therefore, laninamivir is believed to bind to NAs intracellularly, whereas other NA inhibitors inhibit viral NAs extracellularly. Furthermore, considering that laninamivir has a long half-life in the airways of approximately 41 h[28], a single inhalation is sufficient to complete the treatment.

In noninferiority studies involving patients treated with laninamivir and oseltamivir in Japan and other Asian countries, the clinical efficacy of laninamivir was not inferior to that of oseltamivir[29,30]. Another noninferiority study investigating pediatric patients during an oseltamivir-resistant virus epidemic in Japan showed that laninamivir significantly reduced the duration of symptoms compared with oseltamivir[31]. These findings led to the approval of laninamivir use in Japan.

However, laninamivir is not approved in the United States because of the lack of clinical efficacy in a double-blind, placebo-controlled study[32].

In children, the inhalation dose differs between those younger and older than 10 years (Table 1). Of note, even children younger than 10 years may not receive a sufficient dose, depending on their size. When laninamivir can be successfully inhaled

in children, its clinical efficacy may be equivalent to that of zanamivir inhalation for five days[33]. When comparing the clinical efficacy of laninamivir with that of zanamivir (both are inhaled drugs), laninamivir is associated with more recurrent fever in younger age groups[34], possibly because it is a single-inhalation complete drug, whereas zanamivir can be inhaled twice daily for five days. Therefore, zanamivir or oseltamivir should be considered when full inhalation of laninamivir cannot be assured. In 2019, an inhaled suspension formulation of laninamivir was launched to allow younger children to inhale this drug. However, the administration of this new formulation has not been reported because of the outbreak of the novel coronavirus infection shortly after.

Peramivir

Peramivir is currently the only intravenous formulation of NA inhibitors ; it has the advantage of ensuring that the target dose is administered in patients with an available intravenous route. This drug binds more strongly to viral NA than oseltamivir and might inhibit NA activity for a relatively longer time[35]. In mild influenza cases, a single once-daily dose of peramivir is sufficient to achieve clinical efficacy. However, peramivir has not yet been approved for use as a post-exposure prophylaxis regimen.

A single intravenous dose of 300 mg of peramivir in adults reportedly provides sufficient effective concentrations in the upper and lower respiratory tracts[36], facilitating earlier resolution of fever and shorter symptomatic periods than the placebo group[37]. Furthermore, in hospitalized cases, its clinical efficacy is comparable to that of oseltamivir[38]. A single 10 mg/kg dose of peramivir in children has been shown to reach a maximum concentration of 5000 nM in the airways (Figure 4)[39] with clinical efficacy[39,40]. For type A virus, the viral load after 1 or 2 days of administration can be reduced to <1% of the pre-dose level[39]. Compared with oseltamivir and zanamivir[39,41], peramivir may reduce the viral load earlier, although making a general comparison is not possible because the studies were not conducted concurrently. However, in infants, peramivir is excreted from the respiratory tract approximately 35 h after administration (Figure 4)[39]. Therefore, in some children, type A virus may reappear 72 h after peramivir administration ; moreover, infectious virus has been isolated in 50% of these children with viral reappearance[39]. For the type B virus, the viral load cannot be sufficiently reduced even on the day following peramivir administration[39], possibly because peramivir concentrations in the blood and airways decrease rapidly immediately after administration[39]. Regarding peramivir, the IC_{50} value for type B virus is higher than that for type A virus (Table 2)[14].

Because peramivir concentration in the blood decreases rapidly after administration, peramivir can be administered repeatedly regardless of age. However, in patients with impaired renal function, the decrease in blood peramivir concentration is slower ; thus, the dosage should be adjusted accordingly[42].

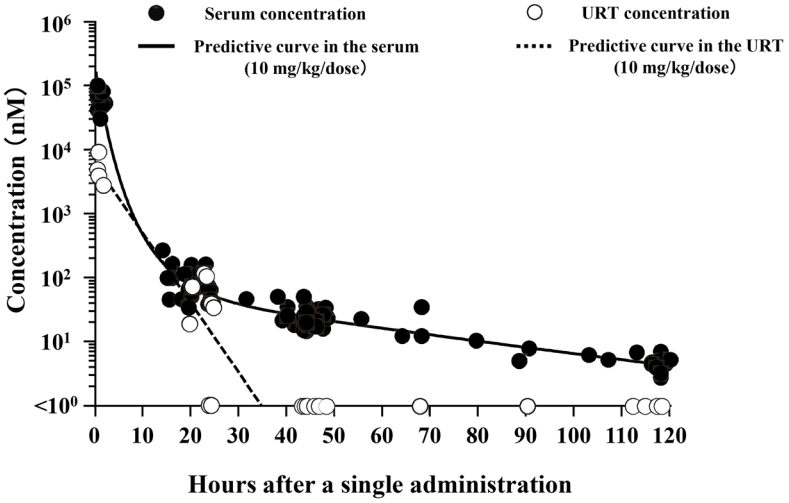

Fig. 4. Peramivir concentration after a single intravenous administration
After a single administration of peramivir, a maximum concentration of 5000 nM of peramivir in the URT is expected, but in children, this drug may be eliminated from the URT approximately 35 h after administration[39].
URT, upper respiratory tract.

CEN inhibitor

As described in the section on the life cycle of influenza, influenza viruses utilize the CEN activity of the RNA polymerase PA subunit of the virus itself to cut out approximately 15 bases from the host-derived mRNA with a cap structure at the 5′-end. These short bases are used as a primer to transcribe the genetic information from the viral negative-stranded RNA to mRNA and synthesize viral proteins. The drug baloxavir inhibits this CEN activity[43]. It inhibits the transcription of viral RNA to mRNA, thereby reducing viral protein synthesis. Considering that current NA inhibitors prevent the release of replicated progeny from infected cells, baloxavir may reduce viral load in the early infection stages even more than NA inhibitors. In fact, compared with oseltamivir-treated patients, baloxavir-treated patients showed significantly lower viral load immediately after administration[44]. Therefore, it was expected that patients treated with baloxavir would recover from clinical symptoms earlier than those treated with oseltamivir, but no significant difference in symptomatic time was observed between these two patient groups[44]. The indication for prophylactic dosing has been approved for baloxavir because of its ability to suppress infection spread within the family, according to the early post-dose decrease in viral load[45].

However, some variants with reduced susceptibility to baloxavir are detected after treatment in 20%–30% of children receiving this drug[46-48]. A higher percentage of these variants are detected in the A/H3 subtype than in the A/H1 subtype[46-48]. In these cases, viral load re-increases, the viral shedding period lengthens[46-48], and perhaps, the clinical symptom duration increases[46-48]. Baloxavir is marketed in 10 and 20 mg tablets, and although a 2% granule formulation is approved for production, it has not yet been marketed.

Variants with reduced susceptibility to anti-influenza drugs

Variants with reduced susceptibility to NA inhibitors

Substitutions of specific amino acids in the NA inhibitor-binding site on the NA of influenza viruses can reduce drug susceptibility. Representative viruses with low susceptibility to NA inhibitors include the NA/H275Y variant of the A/H1 subtype[49] and the NA/R292K variant of the A/H3 subtype[50]. The former involves an amino acid substitution affecting the induction of a hydrophobic group pocket that can store 3-pentyl groups, thereby decreasing susceptibility to oseltamivir and peramivir. This virus has been detected after oseltamivir administration in 10% of patients aged <3 years and <5% of patients aged ≥5 years[51]. However, susceptibility to zanamivir and laninamivir is maintained, making them the drugs of choice. Peramivir also shows decreased susceptibility, but not as much as oseltamivir, because peramivir has a guanidino group in its side chain, which is a key side chain of zanamivir and laninamivir that binds strongly to the virus. It may also be effective against NA/H275Y of the A/H1 subtype through a different administration method[39]. However, currently, baloxavir, which has a mechanism of action different from that of NA inhibitors, might be preferred for patients with these variants.

The A/H3 subtype of the NA/R292K variant has a weakened binding of the carboxyl group, which is common to all NA inhibitors. Additionally, the binding of this variant to the glycerol group is also weakened, resulting in decreased susceptibility to all NA inhibitors[50].

Variants with reduced susceptibility to baloxavir marboxil

In previous clinical studies, patients with influenza A treated with baloxavir showed numerous isolated variants (I38X variants ; X is any amino acid, such as threonine [T], valine [V], methionine [M], or other amino acid that replaced isoleucine [I], the 38th amino acid in the PA subunit of RNA polymerase [the target site of baloxavir]). Moreover, the variants that replaced glutamic acid (E), the 23rd amino acid, with glycine (G) or lysine (K) (E/23/G/K variant) were also isolated[46,52,53]. Among these variants, the PA/I38T variant has a high detection rate, especially in children. In addition, a summary of clinical studies conducted solely in children aged ≤15 years revealed a higher detection rate of PA/I38X or PA/E23/G/K variant in the A/H3 subtype than in the A/H1 subtype (28.7% vs. 16.9%)[46-48,53-55]. Among these clinical studies, when limited to the three studies of Yokoyama *et al.*[53] and our previous studies[47,48] in which the number of cases of subtype A that could be analyzed was specified, 8/35 (22.9%) and 9/17 (52.9%) cases were found for subtypes A/H1 and A/H3 variants, respectively. Additionally, the frequency of detection of variants in the A/H3 subtype was high. Moreover, Sonoyama *et al.*[55] revealed that the variants with reduced susceptibility were detected even more frequently in patients who had administered a double dose (2 mg/kg/dose) of a

granule formulation of baloxavir, with 2/10 (20.0%) and 14/22 (63.6%) cases for subtype A/H1 and subtype A/H3, respectively. This finding may be explained by the easier selection of variants as a result of eliminating susceptible wild-type viruses through the double-dose administration of baloxavir compared with the normal dose.

In many patients with detected PA/I38X variant, the viral load decreased after drug administration but then increased again because of the appearance of variants[46-48,52]. Furthermore, symptom duration is prolonged in children with detected PA/I38X variants compared with that in nondetected cases[46]; infectious virus shedding time is also prolonged[46-48]. Based on these results, the Japanese Pediatric Society has stated that "active administration of baloxavir in children under 12 years of age is not recommended"[56], and the Japanese Society of Infectious Diseases has recommended that "careful consideration of the indication for administration is required"[57]. Low HA antibody titer before baloxavir administration is a risk factor for the emergence of variants after baloxavir administration[46,52]. These results suggest that in actual clinical practice, identifying children who are likely to acquire the PA/I38X variant after baloxavir administration is extremely difficult.

Choice of anti-influenza drugs in clinical practice

Outpatients

Currently, all isolated A/H1 and A/H3 virus subtypes are susceptible to all NA inhibitors; hence, drug selection should be based on age and general condition (Figure 5). If treatment is available on an outpatient basis, oseltamivir is the drug of choice for younger children with difficulty inhaling the drug. However, for children who have difficulty taking oseltamivir dry syrup, inhalation of laninamivir suspension can be selected. If the patient is over 10 years old and can inhale, either zanamivir or laninamivir can be administered, although zanamivir is more appropriate for those without inhalation experience. With regard to baloxavir, in many cases of A/H3 subtype infection, a variant with low susceptibility to baloxavir is detected after administration, resulting in a prolonged viral elimination period and symptomatic period. Additionally, given that the drug is currently prescribed only in tablet form, the risk of aspiration should be considered in children under five years old.

For the type B virus, oseltamivir is less potent in inhibiting NA activity than zanamivir and laninamivir; its clinical efficacy is also inferior[20]. Nevertheless, its effect is still evident, with its clinical efficacy being confirmed compared with that of the drug-naive group[19,58]. In younger children, oseltamivir or nebulized laninamivir suspension inhalation is the treatment of choice, whereas, in older children, either zanamivir or laninamivir can be chosen. Baloxavir can shorten the duration of fever and symptoms more than oseltamivir in type B virus infection[59]. Considering that reports on viruses with low susceptibility to baloxavir following drug administration are still limited in type B virus infection cases, tablet administration should be consid-

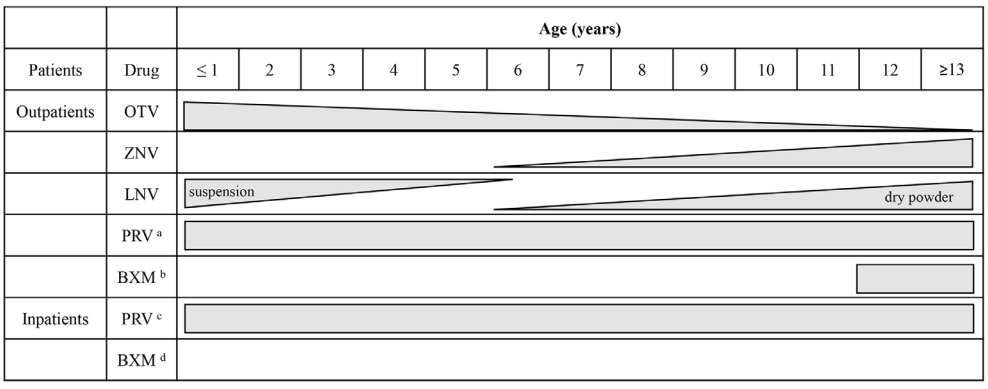

Fig. 5. Proposal of the selection of anti-influenza drugs in children
Peramivir may be administered to outpatients only if these patients have a secure intravenous route (a), but it can be the first choice for inpatients (c).
Baloxavir marboxil for outpatients aged <12 years should be administered after careful consideration for the frequent emergence of variants with reduced drug susceptibility (b), but it can be the first drug choice if patients have variants with reduced susceptibility against neuraminidase inhibitors (d). OTV, oseltamivir; ZNV, zanamivir; LNV, laninamivir; PRV, peramivir; BXM, baloxavir marboxil.

ered for patients who are able to take this drug form.

Inpatients

Oseltamivir administration is also an option for children requiring intensive care because it reduces the length of ICU stay compared with the nontreated group[18]. However, children who require ventilator management are often treated with muscle relaxants and sedatives. Currently, the absorption of oseltamivir from the intestinal tract and distribution of the active drug has not yet been thoroughly investigated in these patients. Considering that oseltamivir levels in the blood are originally low and those in the airways are expected to be low in children, peramivir should be the first-line drug to achieve adequate antiviral efficacy.

If the vascular route is secured, peramivir can be reliably administered at the target dose, and its blood and airway concentrations are clearly higher than those of oseltamivir. Compared with oseltamivir, peramivir binds more strongly to viral NA, and it is expected to exert a greater inhibitory effect on viral replication. Although a single dose of peramivir can provide clinical efficacy in mild cases, it has a short half-life of approximately 2 h immediately after administration and is excreted from the respiratory tract approximately 35 h after administration, resulting in viral repopulation on the third day of administration[39]. As repeated once-daily administration of peramivir is permitted, we practice daily administration for three days in severe cases to inhibit viral repopulation.

Novel anti-influenza drugs

In Japan, four NA inhibitors and one CEN inhibitor are clinically available. Novel anti-influenza agents targeting viruses and host factors are currently under development (Figure 6)[60]. Many of these novel agents have inhibitory mechanisms different from the current NA inhibitors and baloxavir. Several of them are currently in phase III clinical trials, and understanding the inhibitory mechanism of each agent is important.

Conclusion

Currently, physicians can choose between the NA inhibitors and the CEN inhibitor as anti-influenza drugs, which have different inhibitory mechanisms. The NA inhibitors differ in formulation and antiviral effects ; consequently, they also differ in actual clinical efficacy. Selecting the best drug for patients according to the actual assessment is necessary, taking into consideration the issue of the emergence of variants with reduced susceptibility to such drugs.

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Conflict of interest disclosure

I declare no personal conflicts of interest.

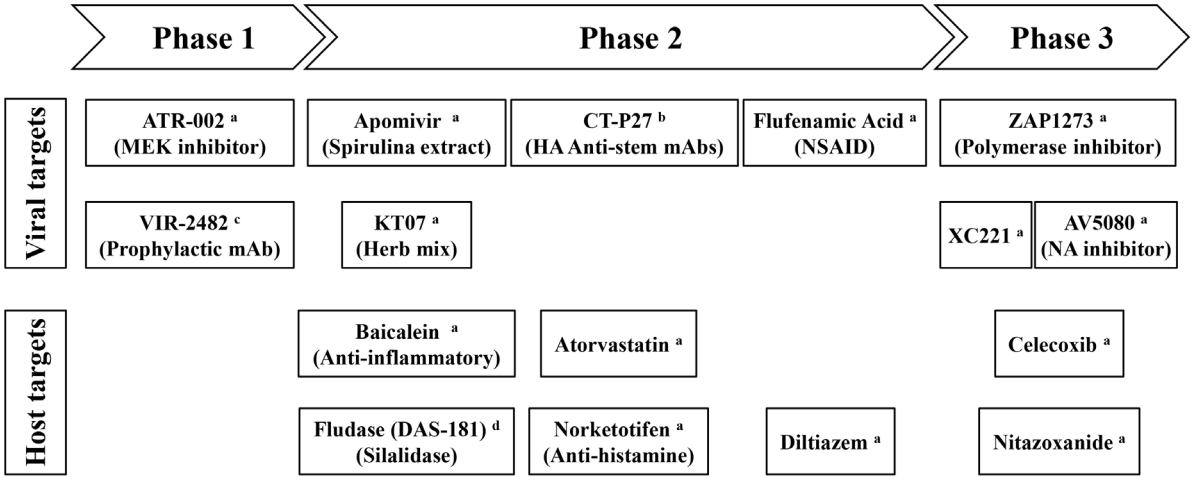

Fig. 6. Landscape of anti-influenza drugs under development
HA, hemagglutinin ; mAb, monoclonal antibody ; NSAID, nonsteroidal anti-inflammatory drug ; NA, neuraminidase
a, oral drug ; b, injection drug ; c, muscle injection drug ; d, inhalation drug

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Author contribution statement

Masatoki Sato : Conceptualization, writing—original draft, and editing.

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