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Antiviral therapy for COVID-19: Derivation of optimal strategy based on past antiviral and favipiravir experiences



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ABSTRACT

Favipiravir, a broad-spectrum RNA-dependent RNA polymerase inhibitor, inhibits the replication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) at significantly lower concentrations than the plasma trough levels achieved by the dosage adopted for influenza treatment and exhibits efficacy against coronavirus disease 2019 (COVID-19) pneumonia. Although high doses of favipiravir are required due to the molecule being a purine analog, its conversion into the active form in infected cells with active viral RNA synthesis enhances the antiviral specificity and selectivity as a chain terminator with lethal mutagenesis. Another characteristic feature is the lack of generation of favipiravir-resistant virus. COVID-19 pneumonia is caused by strong cell-mediated immunity against virus-infected cells, and the inflammatory response induced by adaptive immunity continues to peak for 3 to 5 days despite antiviral treatment. This has also been observed in herpes zoster (HZ) and cytomegalovirus (CMV) pneumonia. Inflammation due to an immune response may mask the effectiveness of favipiravir against COVID-19 pneumonia. Favipiravir significantly shortened the recovery time in patients with mild COVID-19 pneumonia by 3 days with the start of treatment by the 5th day of symptom onset. Since both CMV and COVID-19 pneumonia are caused by adaptive immunity and prevention of cytomegalovirus pneumonia is the standard treatment due to difficulties in treating refractory CMV pneumonia, COVID-19 pneumonia should be prevented with early treatment as well. In the present study, we have comprehensively reviewed the optimal antiviral therapy for COVID-19 based on clinical trials of favipiravir for the treatment of COVID-19 pneumonia and the concurrently established therapies for other viral infections, particularly HZ and CMV pneumonia. Optimally, antivirals should be administered immediately after COVID-19 diagnosis, similar to that after influenza diagnosis, to prevent COVID-19 pneumonia and complications resulting from microangiopathy.

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Abbreviations: AUC, the area under the curve; CMI, cell-mediated immunity; COVID-19, coronavirus disease 2019 caused by SARS-CoV-2 virus; CMV, cytomegalovirus; EC₅₀, half maximal effective concentration; FTP, favipiravir-4-ribofuranosyl-5'-triphosphate; HSV, herpes simplex virus; HZ, herpes zoster; IFN, interferon; IL, interleukin; RdRp, RNA-dependent RNA polymerase; SARS, severe acute respiratory syndrome; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SOC, standard of care; TERT, telomerase reverse transcriptase; TLR, toll like receptor; TNF- α , tumor necrosis factor- α ; VZV, varicella-zoster virus.

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1. Introduction

The Coronavirus family affects the human respiratory system. The family includes severe acute respiratory syndrome (SARS) coronavirus, Middle East respiratory syndrome coronavirus, and the seventh novel coronavirus, which have caused a pandemic of severe pneumonia similar to SARS pneumonia (WHO, 2020c). The causative virus has been named “severe acute respiratory syndrome coronavirus 2” (SARS-CoV-2) (ICTV, 2020) and the disease has been termed “coronavirus disease 2019” (COVID-19) (WHO, 2020b).

Immediately after the outbreak, Chinese researchers scanned more than 70,000 drugs or compounds through rigorous *in silico* simulations and *in vitro* enzyme activity tests and identified 5,000 potentially effective drug candidates. These drugs were then examined at the cellular level against the common coronavirus infection, and approximately 100 drugs were selected for further investigation. Among these drugs, chloroquine, favipiravir, and remdesivir were selected for testing in clinical trials (China, N. H. C. O. T. P. S. R. O, 2020; Wang et al., 2020). Favipiravir has been developed as an anti-influenza drug in collaboration with Toyama Chemical Co., Ltd., Japan (Furuta et al., 2002; Shiraki & Daikoku, 2020) and has been shown to be therapeutically effective against COVID-19 pneumonia in several clinical trials (Cai et al., 2020; Ivashchenko et al., 2021; Shinkai et al., 2021).

We have previously reviewed the efficacy of favipiravir against influenza and Ebola virus infection (Shiraki & Daikoku, 2020). Favipiravir is expected to play an important role as a therapeutic drug against COVID-19. Shiraki, who co-developed favipiravir, started his virology and antiviral research studies under the guidance of Professor Takahashi, who developed the Oka varicella vaccine (Takahashi, Otsuka, Okuno, Asano, & Yazaki, 1974). Varicella skin tests have been developed to evaluate adaptive cell-mediated immunity (CMI) against herpes zoster (HZ) (Shiraki, Yamanishi, & Takahashi, 1984; Takahashi et al., 2003). Shiraki has conducted research on anti-herpes drugs such as acyclovir, famciclovir, ganciclovir, sorivudine, and amenamevir and analyzed their therapeutic efficacy in HZ (Shiraki, 2017, 2018; Shiraki & Daikoku, 2020). Both HZ and COVID-19 pneumonia show inflammation caused by adaptive CMI mediated by CD4 and CD8 lymphocytes and cytokines (Ackermann et al., 2020; Morizane, Suzuki, Tsuji, Oono, & Iwatsuki, 2005; Song et al., 2020). In this composite review, we have primarily focused on the successful antiviral treatment including HZ and cytomegalovirus (CMV) pneumonia and clinical studies on favipiravir for the treatment of COVID-19 pneumonia. We have proposed the optimal antiviral treatment, including favipiravir, to prevent COVID-19 pneumonia, microangiopathy and neurological complications.

2. Development and pharmacological actions of favipiravir

2.1. Development of favipiravir as an anti-RNA drug for life-threatening RNA viral infections

In the joint development of a new antiviral agent between the Shiraki laboratory and Toyama Chemical Co., Ltd. since 1992, approximately 30,000 compounds were synthesized. Favipiravir (6-fluoro-3-hydroxy-2-pyrazinecarboxamide) was selected for its potent anti-influenza activity in tissue culture screenings at the Toyama Chemical Co., Ltd. The Shiraki laboratory investigated the efficacy of favipiravir

in influenza-infected mice and ferrets in our Biosafety level 3 facility (Furuta et al., 2002). The control group died within 5 days of nasal infection with high-dose influenza virus, oseltamivir treatment extended survival by 3 days, and favipiravir treatment resulted in survival of all mice (Takahashi et al., 2003). Thus, the efficacy of favipiravir in animal experiments served as the basis for clinical trials of the drug against seasonal influenza.

The efficacy of favipiravir against seasonal influenza was established through clinical trials in the United States and Japan. Based on these results, favipiravir was approved for the treatment of novel or re-emerging influenza in Japan in 2014. Moreover, favipiravir has proven to be effective for the treatment of patients with severe fever with thrombocytopenia syndrome and Ebola virus infection (Bai et al., 2016; Sissoko et al., 2016; Suemori et al., 2021). Favipiravir offers broad-spectrum anti-RNA virus activity, and its effectiveness in both animal and human trials has been shown in the literature (Delang, Abdelnabi, & Neyts, 2018; Furuta et al., 2009; Furuta et al., 2013; Shiraki & Daikoku, 2020).

Favipiravir is a purine analog without ribose, unlike antiviral nucleoside analogs, and requires amidophosphoribosyltransferase action for the addition of phosphoribosylpyrophosphate to exhibit antiviral RNA-dependent RNA polymerase (RdRp) activity in its triphosphate form (Craig 3rd & Eakin, 2000). Therefore, the dose of favipiravir required is higher than that of other antiviral nucleoside analogs. Favipiravir is specifically taken up and activated in RNA virus-infected cells with abundant RNA synthesis, which increases the specificity of anti-RNA virus activity of favipiravir.

When the effect of favipiravir on RNA synthesis was analyzed biochemically, chain termination was detected and short RNA strands were formed in primer extension assays (Jin et al., 2013; Sangawa et al., 2013; Naydenova et al., 2021; Shannon et al., 2020). Favipiravir-4-ribofuranosyl-5'-triphosphate (FTP) is weakly incorporated into the replicating strand, and suppressed completion of RNA replication even when a high concentration of ribonucleotide triphosphates (rNTPs) is added (Naydenova et al., 2021).

2.2. Lack of generation of favipiravir-resistant virus

A previous review discussed the lack of generation of favipiravir-resistant viruses (Shiraki & Daikoku, 2020). Briefly, influenza virus and poliovirus were propagated in increasing concentrations of favipiravir for 1 month; however, favipiravir-resistant virus could not be isolated despite the presence of amino acid variations in the RdRp maintaining its enzyme activity and the susceptibility to favipiravir. This is unusual because the probability of generating favipiravir-resistant viruses under these conditions is high. Thus, favipiravir-resistant viruses have not become dominant among the entire virus population grown in the presence of favipiravir (Daikoku et al., 2018; Daikoku, Yoshida, Okuda, & Shiraki, 2014; Goldhill et al., 2018; Goldhill et al., 2021). Fifty-seven paired influenza viruses isolated from patients before and after favipiravir administration showed no change in susceptibility to favipiravir in a phase 3 clinical trial of seasonal influenza (Takashita et al., 2016). In contrast, acyclovir-resistant viruses have become dominant among the entire virus population grown in the presence of acyclovir in herpesvirus infections *in vitro* and *in vivo* (Akahoshi et al., 2017; Daikoku et al., 2018; Ida et al., 1999; Shiraki, Ogino, Yamanishi, & Takahashi, 1983).

Table 1
Summary of toxicity of favipiravir and antiviral drugs for early rat embryogenesis.

Group	Dose (mg/kg/day)	Rat/Human AUC ratio [§]	Mortality of embryo/fetus				Anomaly of fetus	
			Mean pre-implantation loss rate (%)	Mean number of surviving fetuses	Mean number of premature deaths	Mean post-implantation loss rate (%)	Rate of fetuses with abnormalities (%)	External malformation
Vehicle control	0	N/A	13.8	11.8	1.1	8.4	0	
Favipiravir	10	0.12	4.0	13.6	0.6	4.3	0	
	30	0.37	5.7	6.8*	7.9**	55.5**	0	
Ribavirin	30	0.14	10.0	8.8	4.4*	36.1*	14.7*	
	100	0.41	7.2	0.6**	12.6**	95.0**	62.5	
Valacyclovir	100	1.1	9.7	13.4	0.3	2.1	0	
	200	2.3	6.9	14.5	0.8	5.1	0.9	
	400	4.9	5.9	9.4	6.1*	39.3*	2.0	

Administration period: 0–7 days gestation (until implantation).

Caesarean section on the 20th day of gestation to observe the endometrium and foetation.

§, Human AUC was based on the following dose: favipiravir, 1600 mg × 2/day (loading dose for influenza patients); ribavirin, 400 mg × 2/day (dose for 60–80 kg patients); valacyclovir, 1000 mg × 3/day (dose for zoster patients).

Statistically significant difference from the vehicle control: **p* < 0.05; ***p* < 0.01.

The table is provided with permission by Fujifilm Toyama Chemical Co., Ltd. (Toyama-Chemical-Co.-Ltd, 2014).

2.3. Favipiravir suppresses production of tumor necrosis factor- α in influenza virus-infected cells and mice

Viral RNA produced in influenza-infected cells is recognized by Toll-like receptor (TLR)-3 or TLR-7/8, which induces various cytokines, such as interleukin (IL)-1 and 6, tumor necrosis factor (TNF)- α , and interferons (IFNs) (Guillot et al., 2005; Kurokawa, Brown, Kagawa, & Shiraki, 2003; Poux et al., 2019). These cytokines and IFNs are responsible for inducing influenza symptoms (Kurokawa, Imakita, Kumeda, & Shiraki, 1996). Favipiravir has been shown to significantly suppress the production of TNF- α in influenza virus-infected cells and mice compared to oseltamivir (Tanaka et al., 2017). TNF- α is induced and diminished first among cytokines in macrophage-like P388D1 cells and animals (Kurokawa et al., 2003). Further, reduction of viral RNA synthesis by favipiravir terminates TLR-mediated TNF- α production first among various cytokines.

2.4. Embryotoxicity of viral RdRp inhibitors, ribavirin and favipiravir

Since early embryonic deaths and teratogenicity have been observed in viral RdRp inhibitor animal studies, favipiravir and ribavirin should

not be administered to pregnant or possibly pregnant women. Ribavirin has anti-RNA viral activity and has been used for the treatment of parainfluenza virus infections (Sidwell et al., 1975), respiratory syncytial virus infection (Krillov, 2002), and chronic hepatitis C (Awad et al., 2010). The Ribavirin Pregnancy Registry has prospectively reported 464 pregnant women exposed to ribavirin, and preliminary findings do not suggest clear signs of human teratogenicity (Sinclair et al., 2017).

Ribavirin induced congenital abnormalities of the limbs, ribs, eyes, and central nervous system as well as fetal death when administered to pregnant hamsters (Kilham & Ferm, 1977). Ribavirin inhibits both DNA and RNA synthesis and has an increased risk of causing malformation in fetuses compared to cytosine arabinoside (Kochhar, 1990).

Shiraki and Toyama Chemical Co. Ltd. compared early embryo lethality and teratogenicity in animals treated with antivirals. Ribavirin inhibits both RNA and DNA synthesis, whereas favipiravir selectively inhibits RNA synthesis. Toxicity studies were performed based on the area under the curve (AUC) in the “early embryogenesis” and “embryo-fetal development” tests. Favipiravir and ribavirin increased post-implantation mortality and reduced the number of living embryo/fetuses at lower rat/human AUC ratios (Table 1). Ribavirin showed fetal anomalies at lower rat/human AUC ratios (Table 2).

Table 2
Summary of embryo-fetal developmental toxicity of favipiravir and antiviral drugs.

Group	Dose (mg/kg/day)	Rat/Human AUC ratio [§]	Mortality of embryo/fetus		Anomaly of fetus			
			Mean number of live fetuses	Post-implantation loss (%)	Rate of fetuses with abnormalities (%)			
					External malformation	Visceral malformation	Skeletal malformation	Skeletal variation
Vehicle control	0	N/A	12.6	5.5	0	1.7	0	6.0
Favipiravir	30	0.37	13.8	7.2	0	4.1	0	6.8
	60	0.87	–	–	–	–	–	Supernumerary of lumbar vertebra
Ribavirin	100	1.6	12.9	3.8	2.2	18.8	4.4	32.1
	3	0.014	13.7	2.1	0	8.0	0	36.7**
Valacyclovir	10	0.041	11.5	21.3	3.3	31.8**	29.5**	85.1**
	200	2.3	14.1	3.1	0	12.3	0	19.6
	400	4.9	10.4*	29.3**	2.5	29.3**	0	57.7**

Administration period: 7 to 17 days of gestation (organogenesis period).

Caesarean section on the 20th day of gestation to observe the endometrium and foetation.

§, Human AUC was based on the following dose: favipiravir, 1600 mg × 2/day (loading dose for influenza patients); ribavirin, 400 mg × 2/day (dose for 60–80 kg patients); valacyclovir, 1000 mg × 3/day (dose for zoster patients).

–, numerical data were not presented since the dose of 60 mg/kg was applied in another study.

Statistically significant difference from the vehicle control: **p* < 0.05; ***p* < 0.01.

The table is provided with permission by Fujifilm Toyama Chemical Co., Ltd. (Toyama-Chemical-Co.-Ltd, 2014).

Table 3
Statistical comparisons of semen parameters change from baseline.

Semen parameter	Test days	Least squares mean		Difference ^a	95% confidence interval for difference			
		Favipiravir	Placebo					
Sperm concentration (10 ⁶ /mL)	60	10.26	(57)	17.91	(55)	-7.65	-41.83	26.53
	90	47.38	(57)	28.03	(54)	19.35	-14.93	53.63
Sperm motility (%)	60	-1.72	(57)	-1.13	(55)	-0.59	-4.02	2.84
	90	-2.65	(57)	-3.12	(54)	0.48	-2.97	3.92
Normal sperm morphology (%)	60	-0.44	(57)	-0.26	(55)	-0.17	-1.17	0.83
	90	-1.86	(57)	-1.89	(54)	0.02	-0.98	1.03
Total sperm count (10 ⁶ /mL)	60	-14.83	(57)	-46.96	(55)	32.13	-73.19	137.44
	90	44.61	(57)	36.76	(54)	7.85	-97.75	113.44
Total motile sperm count (10 ⁶ /mL)	60	-18.18	(57)	-49.32	(55)	31.15	-55.55	117.84
	90	35.67	(57)	7.07	(54)	28.60	-58.31	115.52

Total sperm count = sperm count in semen sample + sperm count in first post-ejaculate urine sample

Dosage and administration: 1200 mg twice daily on the 1st day, 800 mg twice daily on the 2nd to 5th days

The test days is the number of days after the end of administration

Number of subjects in parentheses

The table is provided with permission by Fujifilm Toyama Chemical Co., Ltd. (Toyama-Chemical-Co.-Ltd, 2014).

^a Difference in Least Squares Mean (Favipiravir–Placebo)

2.5. Possible mechanism of RdRp inhibitors on impaired early embryogenesis

In contrast to valacyclovir, favipiravir and ribavirin were more toxic in early embryogenesis than in the embryo–fetal development stage (Tables 1 and 2). Since telomerase reverse transcriptase (TERT) expression is a characteristic event during early embryogenesis, the possibility of TERT-mediated disorders has been examined in the literatures.

Telomeres protect the ends of chromosomes with repetitive sequences and shorten the lagging strand by 50–150 bases during each cell division until termination by gradual loss of telomeric sequences, called senescence (Hayflick & Moorhead, 1961; Olovnikov, 1973). TERT extends telomeres in fertilized eggs to early embryos (at the time of implantation) to restore the telomere length consumed during development (Ozturk, Sozen, & Demir, 2014; Turner, Wong, Rai, & Hartshorne, 2010). TERT exhibits RdRp activity and produces small interfering RNA, resulting in RNA silencing (Maida et al., 2009). MicroRNAs function as post-translational developmental regulators from gametogenesis to embryogenesis (Bernstein, Caudy, Hammond, & Hannon, 2001; Salas-Huetos et al., 2019). Although there are no experimental data on the interaction between anti-RdRp agents and TERT, we hypothesized that favipiravir and ribavirin impair miRNA function through TERT RdRp activity during embryogenesis, resulting in embryotoxicity and teratogenicity. Contraception is indicated during and up to 14 days for favipiravir and 6 months for ribavirin after the end of treatment.

2.6. Effect of favipiravir and ribavirin on spermatogenesis

The effects of favipiravir on sperm disorders were not observed in the favipiravir or placebo group in clinical trials (Table 3). Testicular toxicity in monkeys was not observed even at 6.3 and 1.2 times the maximum human exposure for 2 and 6 weeks, respectively (PMDA, 2014; Toyama-Chemical-Co.-Ltd, 2014). In contrast to ribavirin, favipiravir did not impair human spermatogenesis (Hofer et al., 2010). Abstinence should be practiced during and 10 to 14 days after administration to avoid the effects of residual drugs in the semen on early embryogenesis.

2.7. Adverse reactions in clinical studies

The major side effects of favipiravir included increased blood uric acid in 24 (4.79%) patients and diarrhea in 24 (4.79%) patients in a clinical study involving 501 patients with influenza (Fujifilm, 2019). In an observational study, favipiravir was administered to 2970 patients with COVID-19 pneumonia, and the adverse reactions are shown in

Table 4 (Doi, et al., 2020). The major adverse reactions were elevated uric acid levels in 17.6% (524/2970) patients and liver dysfunction in 8.1% (240/2970) patients. However, liver dysfunction might be a result of COVID-19 itself because the incidence rate of liver dysfunction did not differ between the favipiravir and control groups (Cai et al., 2020; Chen et al., 2020; Singh, Barkate, Patil, Rangwala, & Pendse, 2020).

3. Innate and adaptive immunity against viral infection and anti-viral therapies

3.1. Effect of antivirals on infected cells and the fate of infected cells

Understanding the mechanism of immune response and onset of major symptoms of common viral infections has led to the development of an appropriate treatment strategy for COVID-19. Viral progeny are released within 10–12 h of SARS-CoV-2, influenza virus, and herpes simplex virus (HSV) infection and 14 h of varicella-zoster virus (VZV) infection

Table 4.
Adverse events associated with favipiravir in Fujita Health University (Doi, et al., 2020)

Total number of patients	2970	100%
Number of patients with adverse events	826	28.5%
Number of adverse events	1005	
Hyperuricemia / increased uric acid level	524	17.6%
Liver dysfunction / elevation of hepatic enzymes	240	8.1%
Rash/ toxicoderma	56	1.9%
Renal dysfunction / increased creatinine level	25	0.8%
Diarrhea / loose stool	20	0.7%
Fever	19	0.6%
Vomiting / nausea	16	0.5%
Gout	9	0.3%
Rhabdomyolysis / increased CK value	5	0.2%
Hyperkalemia	5	0.2%
Bradycardia	4	0.1%
Itching	4	0.1%
Leukopenia	4	0.1%
Abnormal coagulation test	4	0.1%
Thrombocytopenia	3	0.1%
Anorexia	3	0.1%
Exacerbation of pneumonia	3	0.1%
Dizzy	2	0.1%
Lymphocytopenia	2	0.1%
Exacerbation of the underlying disease	2	0.1%
Hypernatremia	2	0.1%
Hyperbilirubinemia	2	0.1%
Thromboembolism	2	0.1%
Seizures	2	0.1%
High blood sugar	2	0.1%
Malaise	2	0.1%
Abdominal pain / epigastric discomfort	2	0.1%

(Bar-On, Flamholz, Phillips, & Milo, 2020; Harcourt et al., 2020; Shiraki & Daikoku, 2020; K. Shiraki et al., 2020). Acyclovir inhibit viral replication, but infected cells in the late phase continue to express synthesized viral antigens, regardless of antiviral agents (K. Shiraki et al., 2020).

Fig. 1 shows the susceptibility of VZV-infected cells to acyclovir (A) and the cluster (plaque) of infected cells (B) in the cultured cells. Fig. 1A shows the change in susceptibility of VZV-infected cells to acyclovir from 0 to 18 h after infection. The half-maximal effective concentration (EC_{50}) of infected cells is below C_{max} (red dashed line) of oral valacyclovir in newly infected cells (0–4 h), but it is above C_{max} after >9 h after infection. The infected cells (yellow) surrounding the plaque are susceptible to acyclovir (Fig. 1B). However, the infected cells (brown) in the center completed viral DNA synthesis within 12 h and, therefore, are resistant to acyclovir with high EC_{50} values and are not eliminated. These cells continue to produce viral proteins and particles (Fig. 1A and B) and are the target of immune responses and augment inflammation after initiation of antiviral therapy until they become apparently normal.

VZV and HSV cause eruptions and vesicles on the skin through adaptive CMI; however, the skin becomes apparently normal over time with no erosions or ulcers due to extensive cell necrosis. Despite showing strong cytolytic activity in cell cultures, VZV-infected cells became apparently normal morphology with losing antigen expression but retaining viral DNA by antigenic modulation (Joseph & Oldstone, 1975; Shiraki et al., 2011). Erythema multiforme occurs 1–3 weeks after recovery of HSV skin lesions, and HSV DNA is detected in the cells of erythema multiforme lesions (Miura, Smith, Burnett, & Aurelian, 1992). The infected cells in HSV lesions are converted to apparently normal cells, leaving HSV genome in the cells until development of erythema multiforme. Nasopharyngeal epithelial cells are infected with influenza virus, but they

neither die nor generate erosion in the nasopharyngeal mucosa and revert to normal epithelial cells during recovery.

VZV, HSV, and influenza virus-infected cells die in culture, but they survive without leaving skin or mucous membrane defects, returning to apparently normal cells in the skin and mucosa. The infected cells with antigen expression after peak of virus production become targets of adaptive CMI and stimulate the immune system for a few days until they revert to normal cells without viral antigen expression.

3.2. Role of innate immunity and adaptive immunity in viral infection

In HSV and VZV infection, the prodromal stage before the onset of skin lesions is formed by innate immunity, and skin lesions are formed by antigen specific adaptive CMI (Morizane et al., 2005). The Langerhans cells, which play a central role in the innate immunity of the skin, are impaired by ultraviolet light sunburn, which in turn impairs innate immunity (Aberer, Schuler, Stingl, Honigsman, & Wolff, 1981). Impairment of innate immunity by sunburn enables viral spread and replication in the prodromal phase, and adaptive CMI against HSV and VZV results in broader, denser, and more severe skin lesions called “photodistribution” (Fig. 2) (Gilchrist & Baden, 1974). Innate immunity suppresses viral replication and spread in the prodrome. Adaptive CMI generates eruptions and vesicles on areas of HSV and VZV replication, known as delayed-type hypersensitivity (DTH), through T cell responses, including CD4 and CD8 lymphocytes (Morizane et al., 2005). Severely immunocompromised patients, such as children with leukemia who lack CMI, either have a longer incubation period of 3–4 weeks or do not present with skin rashes throughout the course of varicella, indicating that skin lesions are caused by adaptive CMI. VZV spreads more widely in immunocompromised patients and some

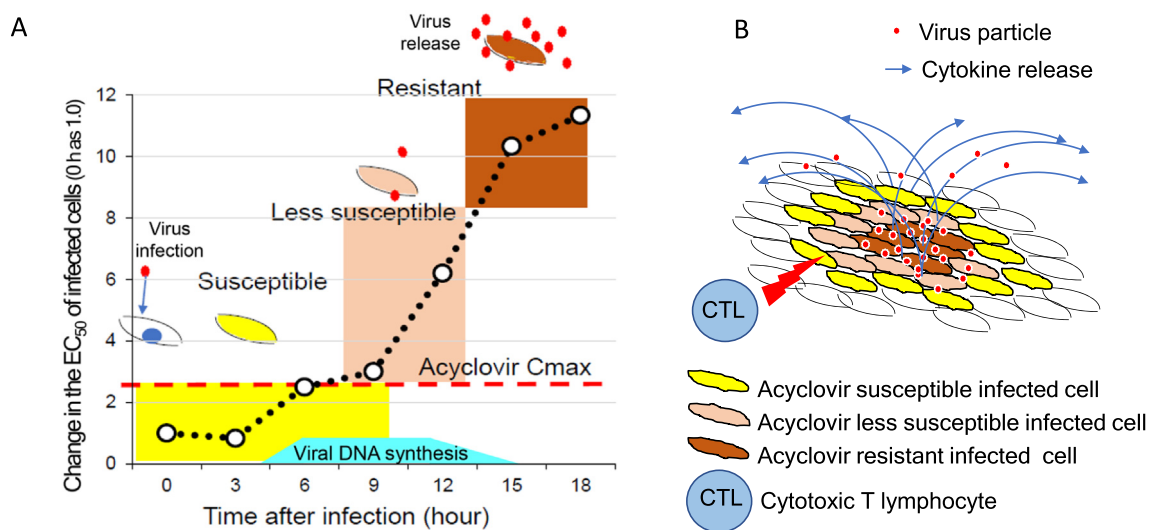


Fig. 1. Susceptibility of infected cells to antiviral agent and plaque distribution of infected cells.

Change in susceptibility of infected cells to acyclovir from 0 to 18 h after infection and schematic illustration of the plaque consisting of infected cells that are susceptible (yellow), less susceptible (beige), and resistant (brown) to antivirals. A. The susceptibility of varicella-zoster virus (VZV)-infected cells to acyclovir was assessed at 0, 3, 6, 9, 12, 15, and 18 h after infection, and the increase in their EC_{50} values at each time point was expressed with respect to considering 1 at 0 h after infection (K. Shiraki et al., 2020). VZV-infected cells were observed to be acyclovir-susceptible until 4–6 h of infection when viral DNA synthesis began, and then the EC_{50} values gradually increased from a level of being susceptible (yellow) to resistant (brown) at a concentration above the C_{max} of oral valacyclovir. B. VZV infection spread from the initially infected cells in the center to the periphery, and these cells form the plaque while infecting the next cell in 14 h. The infected cells in the periphery of the plaque consisted of cells immediately after the infection and were susceptible to acyclovir, as shown in yellow colour in the panel A. However, the cells in the center were resistant to acyclovir due to the time lapse after infection, as shown in brown colour. Acyclovir susceptibility in the plaque is shown by acyclovir-resistant cells in the center (brown), less susceptible infected cells (beige) in the middle, and susceptible infected cells (yellow) in the periphery, depending on the time lapse after infection. The authors obtained permission from the Antiviral Research to reuse this figure (Shiraki et al., 2020).

Infected cells in the center died in culture, but they do not cause tissue loss or defects due to death and reverse to apparently normal cells in the skin of patients with herpes zoster. The infected cells colored in yellow in the periphery will not produce viral proteins, and those colored beige and brown in the center are resistant to acyclovir and produce viral proteins and particles until they reverse to apparently normal cells regardless of the presence of acyclovir. These beige and brown-colored infected cells are the major targets of CMI that causes inflammation.

Coronavirus-infected cells produce cytokines, such as interleukin (IL)-1, IL-6, IL-8, and tumor necrosis factor (TNF)- α via the Toll-like receptor (TLR) pathway for augmenting inflammation in coronavirus disease 2019 (COVID-19) pneumonia (Deinhardt-Emmer et al., 2021; Funk et al., 2012).

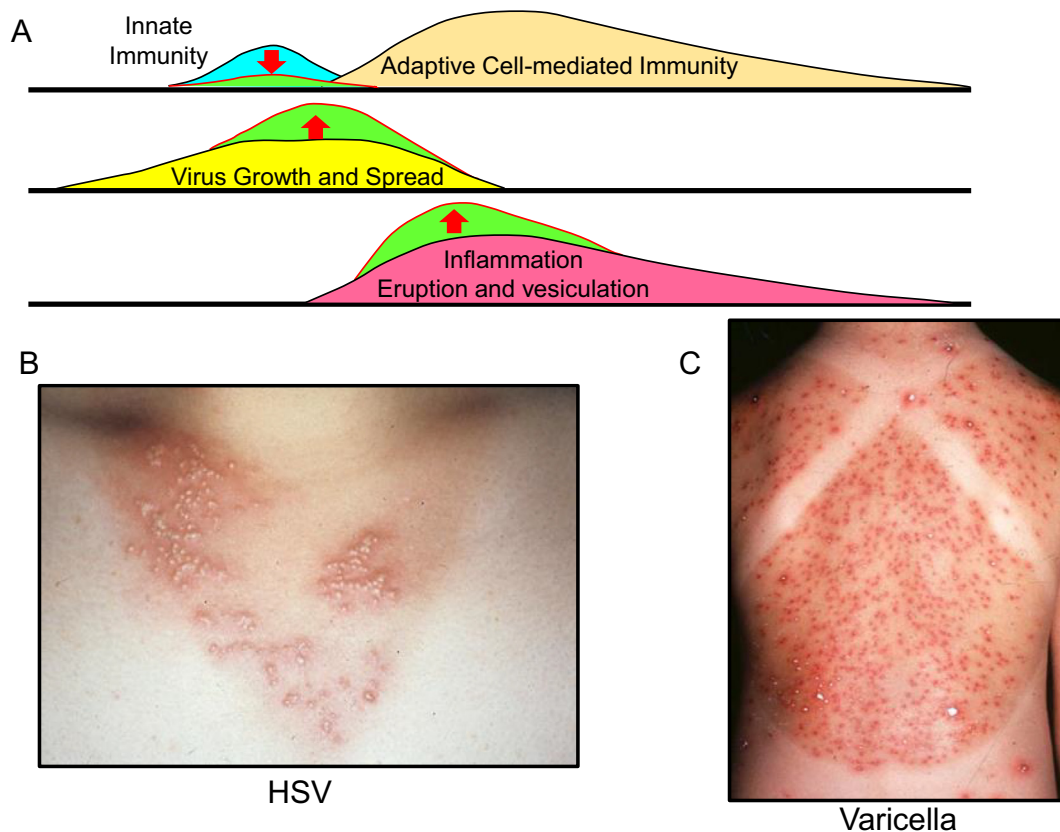


Fig. 2. Importance of innate immunity visualized by photodistribution of herpetic skin lesion and varicella. A: Mechanism of Photodistribution. Red arrows indicate the photodistribution. Innate immunity is impaired and suppressed, leading to enhanced viral growth and spread, which resulted in widespread and high-density skin lesions in the sunburned skin as shown in the shaded skin as shown in the photographs. Sunburn impairs the function of the Langerhans cells, thereby impairing innate immunity, which allows the replication and spread of viral infection in the prodrome of herpes simplex virus (HSV) infection and varicella. Sunburn causes broader, denser, and severer skin lesions in the sunburned area (photodistribution) than in the shaded area. The extent of viral lesions is determined by viral replicated area before the induction of adaptive immunity and innate immunity plays a critical role by suppressing viral spread and the broadness and density of viral skin lesions in the prodrome, as indicated by photodistribution in the photographs of HSV infection and varicella. B: Photodistribution by HSV. A young woman (20–29 years old) developed vesicles that were densely distributed in the anterior cervical area after sun exposure two days ago. C: Photodistribution by varicella-zoster virus (VZV). An 8-year-old girl was diagnosed with varicella with fever and vesicles three days after sea bathing. The skin covered by the suspender of the swimsuit in the upper back and the swimsuit in the lower back was protected from sunburn and had mild distribution density of eruptions of varicella. In contrast, sunburn impaired the innate immunity leading to enhanced viral growth and spread and caused higher density and severer eruptions of varicella in the sunburned skin than in the shaded skin. The photographs are provided by Dr. Yasumoto.

older people than in healthy patients due to the longer incubation period, resulting in a wide range of severe HZ manifestations (Dworkin, et al., 2007). Photodistribution shows the significance of suppressing viral spread and growth by innate immunity in the prodrome, and the severity of skin lesions is determined by the extent of viral infection before the onset of adaptive CMI.

Typical adaptive inflammation caused by DTH is known as a type IV hypersensitivity reaction presenting as the positive tuberculin test, contact dermatitis, and urushiol-induced dermatitis. Inflammation presents as redness and swelling within 5–6 h in a limited area, increases in size and peaks during 48–72 h, and takes a week to disappear. As inflammation due to DTH peaks 3 days after contact with the antigen, inflammation in HZ exacerbates 3–5 days after onset due to continuous stimulation and augmentation by infected cells and lasts for 3 weeks (Fig. 3).

4. Optimal timing of antiviral administration against various viral infections

4.1. Optimal treatment of COVID-19 based on established antiviral therapies for other viral infections

Fig. 4 shows the pathophysiology and timing of initiation of established antiviral treatment for influenza, varicella and HZ, recurrent

herpes, and CMV pneumonia. Since innate immunity suppresses viral growth and spread in the prodrome and determines the severity of infection, the efficacy of antiviral therapy can be determined by the inhibition of virus growth in the prodrome. Information on antiviral therapies can help understand the optimal therapy for COVID-19.

4.2. Influenza infection

Vigorous replication of influenza virus induces cytokine production mediated by TLR-3, -7, and -8, which recognize viral RNA. The release of these cytokines triggers inflammation in the upper respiratory tract, resulting in influenza-specific symptoms such as fever, sore throat, nasal discharge, and myalgia, which appear within 1–2 days of infection (Betakova, Kostrabova, Lachova, & Turianova, 2017; Y. Gu et al., 2019; Kurokawa et al., 1996; Tsurita et al., 2001). Seasonal influenza has an incubation period of 1–2 days, and the symptoms resolve after 3–7 days in uncomplicated influenza (Carrat et al., 2008; Memoli et al., 2014). Pre-existing immunity to seasonal influenza viruses is crucial to decrease the susceptibility and severity of seasonal influenza (Doyle et al., 1994).

Influenza virus replicates in the nasopharyngeal epithelium. The infected epithelial cells survive and continue to produce viral RNA and antigens until they revert to healthy epithelial cells without epithelial defects. Oseltamivir shortens the duration and severity of influenza

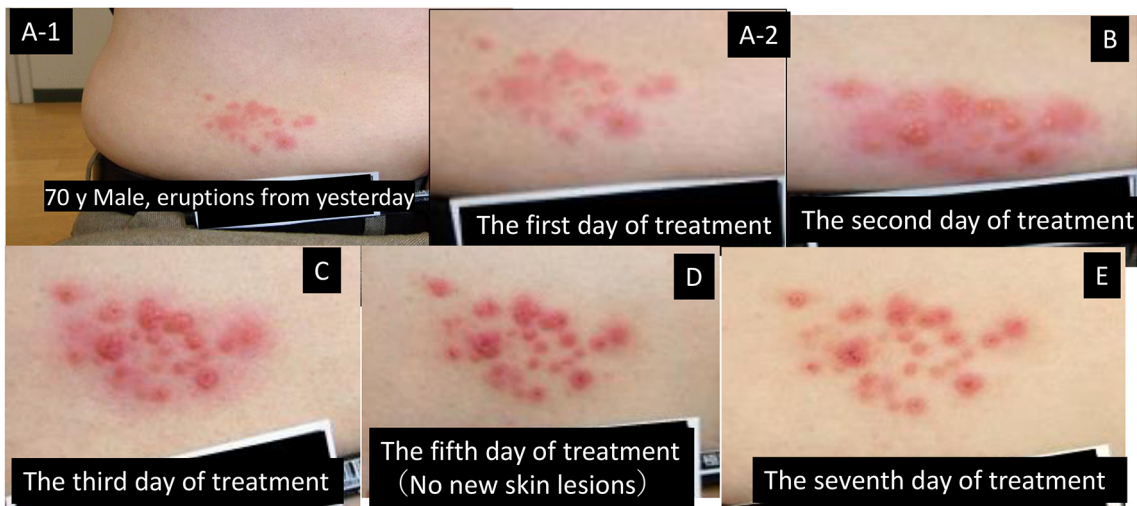


Fig. 3. Recovery process of inflammation and improvement of herpes zoster (HZ) lesions due to adaptive CMI after initiation of antiviral treatment. A 70-year-old male patient noticed a rash on his left waist and consulted a dermatologist the next day. Early treatment with amenamevir, starting the next day after the appearance of the rash, prevented skin lesion enlargement and new lesion formation, and cured the lesions without vesiculation (abortive infection) (Kawashima et al., 2017; Shiraki, 2017). Panels A1 and A2 show a panoramic view and a close view of HZ, respectively, on the first day of initiation of the anti-herpetic drug (amenamevir) therapy. During day 1–5, redness and swelling representing inflammation increased in the center of the eruption, but day 3 onwards, the redness in the peripheral part of the erythema (red halo) gradually disappeared. Panel B shows that redness and swelling increased around the lesions, indicating stimulation of the inflammatory response due to maturation and enhancement of the CMI to varicella-zoster virus (VZV) on the second day after treatment compared with the first day. Panels C and D show the contrasting course of reduction in peripheral inflammation at the red halo areas, while increase at the center of lesions, with the peak inflammatory response on day 5. Urushiol-induced dermatitis peaks on the third day of antigen contact *via* adaptive immunity. Since no new eruption appeared on day 4, antiviral treatment blocked the formation of new lesions and prevented the spread of eruption and formation of vesicles. Redness and swelling representing inflammation exacerbated despite antiviral treatment. Although antiviral drugs prevented the spread of infection, but do not directly reduce the level of inflammation, which makes it difficult to determine the therapeutic effect. Despite effective antiviral treatment, the inflammation exacerbates for 3–5 days as a natural course of adaptive immunity. The photographs are provided by Dr. Toyama.

symptoms, but the symptoms continue for 1 day after treatment (Treanor et al., 2000). Inflammation in influenza is induced by influenza virus-infected cells and cytokines and continues until the mucosal epithelium reverts to normal.

Influenza is treated with anti-influenza drugs within 48 h of the onset of the innate immune response, and the duration of treatment is 5 days. A single dose of baloxavir marboxil, laninamivir, and peramivir is recommended for treatment of influenza (Fig. 4A) (CDC, 2021b).

4.3. Varicella and HZ

Varicella induces CMI against viral replication in the skin and internal organs during the 2-week incubation period and causes papules, vesicles, and crusts due to adaptive CMI (Asano et al., 1993; Grose, 1981; Ku, Besser, Abendroth, Grose, & Arvin, 2005).

Treatment for varicella is initiated within 24 h of onset and continues for 5–7 days (Fig. 4B), and some eruptions do not progress to vesiculation (abortive infection). Seven-day acyclovir treatment during the first half of the incubation period did not reduce the severity of the disease, but rendered it to asymptomatic varicella during the second half (Suga, Yoshikawa, Ozaki, & Asano, 1993). The second half included the prodrome, as shown by photodistribution and efficient suppression of viral growth by acyclovir, which made varicella asymptomatic. Antiviral therapy in the prodrome is the ideal strategy for the conversion of varicella to asymptomatic disease.

Inflammatory lesions caused by adaptive CMI in moderate HZ improves after 3 weeks. Anti-herpetic drugs such as acyclovir, famciclovir, valacyclovir, and amenamevir are used within 3 days of onset for 7 days (Shiraki, 2017, 2018; Shiraki, Takemoto, & Daikoku, 2021). These therapeutics are very effective in preventing the appearance of new rashes and the spread of existing rashes, but they cannot alleviate inflammation. Anti-herpetic drugs accelerate viral clearance, prevent new rash formation, decrease pain, and cause disappearance of crusting. However, these drugs do not significantly accelerate rash healing (Balfour Jr. et al., 1983; Kawashima et al., 2017). Inflammatory conditions of

skin lesions, indicated by redness, swelling, and vesiculation, worsen during 3–5 days, regardless of initiation of anti-herpetic drug treatment, indicating the ineffectiveness of antivirals in alleviating inflammation (Fig. 3).

Although the combination of acyclovir and prednisolone accelerated rash healing and pain reduction in HZ, it could not decrease the time taken for the complete healing of conditions associated with more adverse events (Wood et al., 1994). Anti-herpetic drugs in combination with prednisolone are generally reserved for complicated HZ, such as Ramsay Hunt syndrome, to alleviate inflammation (Albrecht, 2020).

Anti-inflammatory steroids reduce inflammation caused by urushiol-induced or contact dermatitis without shortening the duration of inflammation. Similarly, antiviral drugs against HZ prevent the appearance of new skin lesions and inhibit the progression to vesiculation without reducing the duration or inflammation, even with the use of prednisolone (Balfour Jr. et al., 1983; Wood et al., 1988).

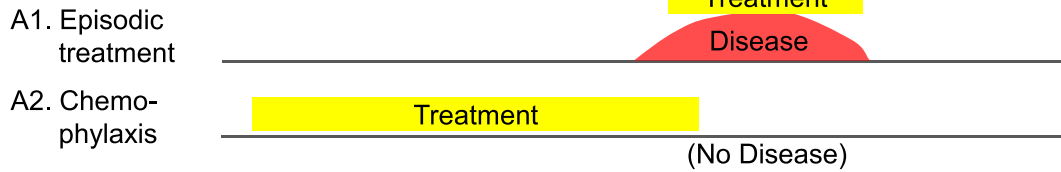
4.4. Recurrent herpes

HSV causes recurrent orofacial and genital lesions that typically occur within 1 week (Fig. 4C). Prodrugs offer simplified twice-a-day dosing (Patel et al., 2015; Patel et al., 2017). Oral anti-herpetic drugs initiated within 24 h of onset and continued for a period of 5 days are effective in reducing the severity and duration of recurrent lesions by a median of 1–2 days. Short-course therapies of 1–3 days have shown similar efficacy. Initiation of treatment in the prodrome created by innate immunity is effective in preventing the appearance of genital lesions in approximately one-third of patients. Thus, prodromal treatment improves patient quality of life without vesiculation or ulcers in the face or genitalia.

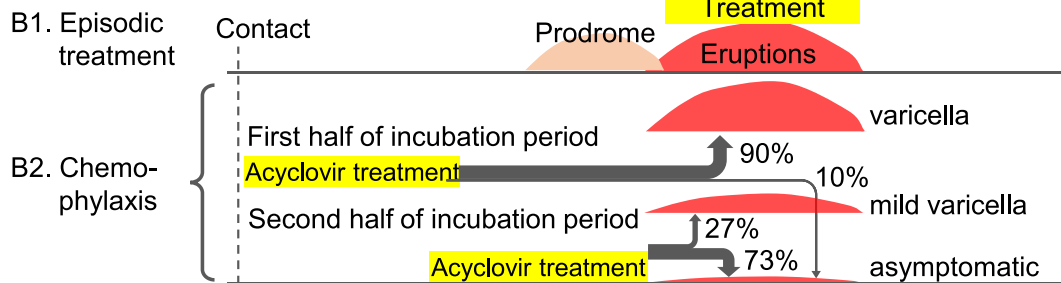
4.5. CMV pneumonia

CMV causes CMV pneumonia in immunocompromised hosts, particularly transplant recipients. Since CMV pneumonia is not observed in

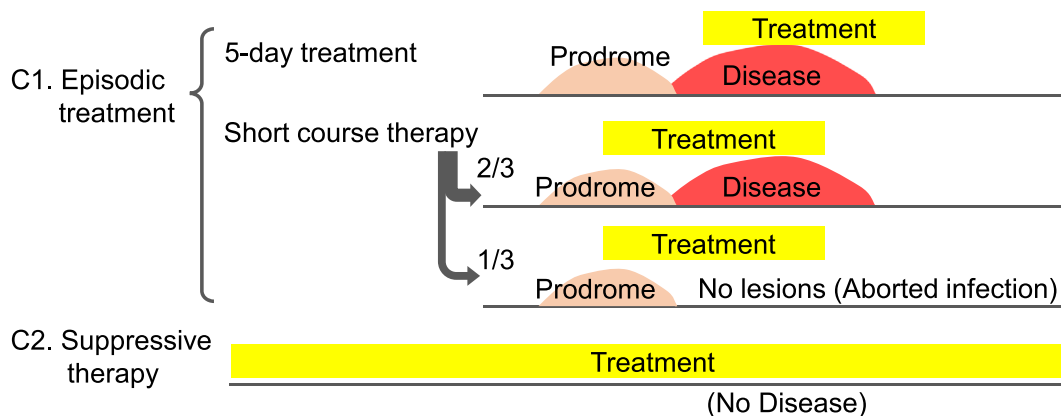
A. Influenza



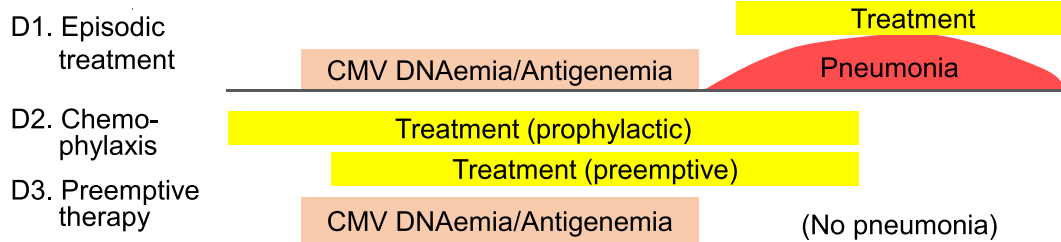
B. Varicella



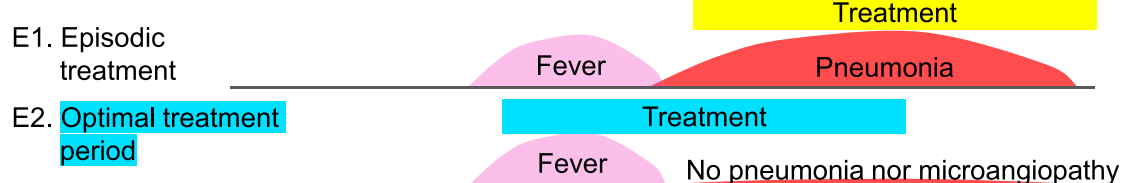
C. Recurrent genital herpes



D. CMV pneumonia



E. COVID-19 pneumonia



severely immunocompromised patients, it is caused by adaptive CMI against virus-infected cells.

During the 1980s, ganciclovir was used for the treatment of refractory CMV pneumonia by transplant physicians; however, the drug offered no immediate effect. During ganciclovir treatment for ≥ 3 weeks, pneumonia was occasionally exacerbated even after treatment

initiation. Thus, CMV pneumonia treatment was changed to CMV pneumonia prophylactic treatment. Guidelines have been established to initiate prophylactic treatment with ganciclovir or letermovir, when CMV DNAemia or antigenemia is observed (Chemaly et al., 2014; Ljungman et al., 2019; Razonable & Humar, 2019). The introduction of these standard procedures eliminates the risk of refractory CMV pneumonia in

transplant recipients (Fig. 4D). Prevention has become the standard treatment for CMV pneumonia. This experience can be used for the COVID-19 treatment strategy from treatment to prevention of COVID-19 pneumonia and microangiopathy.

4.6. Comparison of antiviral therapy against influenza and HSV and VZV skin lesions

Seasonal influenza causes symptoms such as fever because cytokines and interferons, produced by innate immunity, suppress the growth of the virus and aid in resolution of the infection (Fig. 4A). The overall incidence of oseltamivir-resistant virus infection was 10 of 182 (5.5%) and 9 of 50 (18%), in two previous studies, after five days of oseltamivir treatment among children (Kiso et al., 2004; Whitley et al., 2001). The emergence of baloxavir-resistant mutants occurred in 2.2% and 9.7% of baloxavir recipients in phase 2 and phase 3 trials, respectively (Hayden et al., 2018). Resistant viruses appear during antiviral therapy. In contrast, no virus exhibited reduced susceptibility to favipiravir in 57 pairs of influenza viruses in phase 3 clinical trials (Takashita et al., 2016). Virus secretion continues and may be accompanied by pneumonia in immunocompromised patients.

In HSV and VZV infections, the virus rapidly proliferates and spreads during prodrome, and the adaptive CMI forms skin lesions and resolves (Fig. 4B and C). Antiviral drugs are administered for 5–7 days, starting from the appearance of skin lesions in the late prodrome and beginning of adaptive CMI. In immunocompromised patients, chronic skin lesions with viral replication persist despite the use of antiviral drugs due to the lack of sufficient CMI to eliminate the virus. Therefore, if skin lesions in a patient with immunodeficiency do not improve after 2 weeks of antiviral therapy due to persistent viral growth, the emergence of drug-resistant strains should be considered (Shiraki et al., 2021). Since acyclovir and famciclovir require activation by thymidine kinase, the spread of resistant viruses is limited in mixed infection with wild strains and resistant viruses are not isolated during uncomplicated treatment, in contrast to influenza (Okuda et al., 2004; Ozaki, Nishimura, Kajita, Ida, & Shiraki, 1998). Although HSV isolates from genital lesions were all susceptible to acyclovir, the frequency of guanosine-string mutations was significantly less frequent in isolates from patients naïve to acyclovir than in those who experienced episodic or suppressive therapy, when examined as viral clones (Daikoku et al., 2016). The virus strain in chronic active viral lesions in immunocompromised hosts is replaced with resistant strains, and lesions do not improve and gradually spread during antiviral treatment. It has been reported that chronic lesions are improved by antiviral drugs with different mechanisms of action (Onaka, Shiraki, & Yonezawa, 2021; Shiraki et al., 2021).

4.7. Summary of antiviral treatment and optimal treatment for COVID-19

An optimal window to initiate antiviral therapy in influenza, varicella, HZ, recurrent herpes, and CMV pneumonia has been established, as shown in Fig. 4. When antiviral treatment is initiated in the prodrome of the innate immunity phase of varicella, recurrent herpes, and CMV

pneumonia, treatment effectively prevents the onset of major symptoms.

Coronavirus infection induces IFNs, chemokines, and cytokines in primary cultures of human alveolar epithelial cells and alveolar macrophages, similar to influenza (Deinhardt-Emmer et al., 2021; Funk et al., 2012; Mazaleuskaya, Veltrop, Ikpeze, Martin-Garcia, & Navas-Martin, 2012). COVID-19 has an incubation period of 5 days for fever and influenza-like symptoms; pneumonia occurs 4–5 days after disease onset. COVID-19 pneumonia is caused by adaptive CMI, including CD4 and CD8 lymphocytes, with a strong inflammatory cytokine response (Ackermann et al., 2020; Frisoni et al., 2021; Song et al., 2020). The time interval after infection and infiltrated cellular response indicate that COVID-19 pneumonia is caused by adaptive CMI, similar to the major symptoms of HSV, VZV, and CMV infections.

The prodromal stage of innate immunity alleviates major symptoms; is a crucial stage that determines severity of infection, as shown by photodistribution; and is the optimal time for antiviral therapy. Varicella can be prevented by initiating antiviral therapy in the prodrome, and in recurrent herpes, antiviral drugs in the prodrome can prevent the formation of blisters. CMV pneumonia can be prevented by prophylactic or preemptive treatment.

In Ebola virus-infected mice, all mice who received favipiravir treatment from 6 days after infection survived, but those who received treatment from 8 days after infection died (Oestereich et al., 2014). A 2-day delay is fatal for lethal infections. Favipiravir successfully prevented Ebola virus transmission when administered immediately after percutaneous needlestick exposure (Jacobs et al., 2015). The use of anti-human immunodeficiency virus drugs and hepatitis B immunoglobulins immediately after percutaneous exposure to human immunodeficiency virus and hepatitis B virus, respectively, is a standard practice to prevent infection (Marrazzo et al., 2014; Puro et al., 2005).

Antiviral therapy for COVID-19 should start with fever caused by innate immunity and blocks the viral spread and damage to the epithelial cells, the airway, endothelial cells, and nerve cells for smell and taste, indicating that optimal COVID-19 therapy is prevention of pneumonia and microangiopathy and not treatment of pneumonia, as shown in Fig. 5.

5. Clinical aspect of COVID-19 and pneumonia

5.1. Clinical characteristics of COVID-19

SARS-CoV-2, an enveloped positive-sense RNA virus, infects cells via the angiotensin-converting enzyme 2 receptor, and the viral spike protein is a key target for viral neutralization (P. Zhou et al., 2020). The incubation period of SARS-CoV-2 is approximately 2–14 days, and the median incubation period is 4–6 days, with 5%–10% of individuals developing symptoms after ≥ 14 days of exposure (Backer, Klinkenberg, & Wallinga, 2020; Bi et al., 2020; Li et al., 2020). Presymptomatic transmission of SARS-CoV-2 occurs 1–3 days before onset (Cheng et al., 2020; Wei et al., 2020; WHO, 2020a). The presence of underlying diseases, including hypertension, diabetes mellitus, cardiovascular diseases,

Fig. 4. Antiviral therapy for various viral infections. A. Influenza (CDC, 2021a): Influenza is treated within 48 h of the onset with anti-influenza drugs administered for five days (oseltamivir or zanamivir) or once (baloxavir marboxil or laninamivir). Influenza infection is prevented by chemoprophylaxis of single dose of baloxavir marboxil or laninamivir, or once daily administration of oseltamivir or zanamivir. B. Varicella: Varicella is treated with anti-herpetic drug within 24 h of the onset. Varicella is highly contagious, and is responsible for approximately 80% of infections within the family. After exposure to varicella patients, individuals were prophylactically treated with acyclovir during the first and second halves of the incubation period, and infection was confirmed by increase in antibody level (Suga et al., 1993). Prophylactic acyclovir administration during the second half of the incubation period including the prodrome was effective in converting chickenpox infection to asymptomatic infection. C. Recurrent herpes (Patel et al., 2015; Patel et al., 2017): Episodic treatment shortens the disease course duration by a median of 1–2 days, making short course therapy with prodrugs sufficient. Treatment during the prodromal stage leads to an abortive infection that does not cause herpetic lesions in the one-third of patients, avoiding the occurrence of unpleasant lesions and symptoms that stay for a week. Suppressive therapy suppresses the recurrence of herpes and includes daily administration of anti-herpes drugs. D. Cytomegalovirus (CMV) pneumonia in transplant recipients (Chemaly et al., 2014; Ljungman et al., 2019; Razonable & Humar, 2019): CMV pneumonia is prevented prophylactically using ganciclovir and letermovir or preemptively using ganciclovir as a standard treatment, thus successfully avoiding the treatment of refractory CMV pneumonia experienced in the 1980s. CMV pneumonia is treated with ganciclovir for at least three weeks, occasionally leaving sequelae of infection. E. COVID-19 pneumonia: Current application of favipiravir is the treatment of COVID-19 pneumonia. As antiviral treatment shown in A to D, particularly CMV pneumonia in transplant recipients, strongly suggests the treatment with favipiravir should be initiated immediately after the diagnosis of COVID-19 infection to avoid development of refractory COVID-19 pneumonia and complications due to microangiopathy.

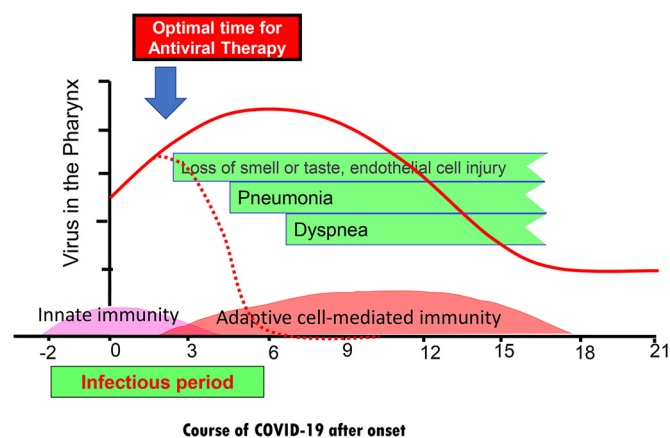


Fig. 5. Optimal treatment for COVID-19. Antiviral treatment should be started in the prodromal phase, which is produced by innate immunity, fever, or influenza like symptoms to block the spread of the virus into the respiratory tract, endothelium, and neurons, resulting in preventing pneumonia and other complications.

chronic pulmonary diseases, obesity, and malignancy, and age > 60 years has been identified as risk factors for severe illness (ChinaCDC, T. N. C. P. E. R. E. T., CCDC, 2020; Stokes et al., 2020).

Fever and cough are the most common symptoms in hospitalized patients. Loss of smell and taste was observed in 1754 (73.1%) and 1136 (60.5%) patients, respectively, among 2013 European patients (Lechien et al., 2020). Fever, cough, loss of smell and taste, and malaise are the initial symptoms associated with COVID-19. The relatively high frequency of anosmia and ageusia may help distinguish COVID-19 from other acute febrile illnesses.

COVID-19 causes cardiovascular and nervous system complications and coagulation abnormalities in addition to pneumonia (Bhatnagar et al., 2021). Autopsy findings in fatal COVID-19 have revealed wide dissemination of the virus in the brain, heart, kidneys, and other organs, indicating that SARS-CoV-2 causes infection outside the pulmonary system (Bhatnagar et al., 2021; Puelles et al., 2020). Arrhythmias and other cardiovascular symptoms are associated with electrocardiographic abnormalities, myocarditis, ischemia, and cardiomyopathy (Abrams et al., 2020; Madjid, Safavi-Naeini, Solomon, & Vardeny, 2020). The most frequent neurological manifestations in a previous study were myalgia (44.8%), headache (37.7%), encephalopathy (31.8%), dizziness (29.7%), dysgeusia (15.9%), and anosmia (11.4%) (Liotta et al., 2020). Nervous system symptoms in patients with severe infection results in acute cerebrovascular diseases, impaired consciousness, and skeletal muscle injury (Mao et al., 2020). Thromboembolic complications cause pulmonary embolism during pneumonia and stroke in patients with underlying diseases (S. X. Gu et al., 2021; Merkle et al., 2020). Thus, COVID-19 may lead to systemic complications involving the pulmonary, cardiovascular, and nervous systems as well as sensory disorders (Ellul et al., 2020; Rogers et al., 2020; Zubair et al., 2020).

5.2. Clinical characteristics of COVID-19 in children

Most children infected with SARS-CoV-2 consistently present a milder course and have better outcomes than adults worldwide. During the initial 3 months of the pandemic (between January and March 2020), 44 COVID-19-related deaths were reported in 42,846 confirmed cases in children aged 0–19 years (0–14 in the USA) were reported (Bhopal, Bagaria, & Bhopal, 2020). COVID-19 is generally less severe in children than adults in seven countries collectively (the USA, the UK, Italy, Germany, Spain, France, and Korea) (Bialek et al., 2020; Dong et al., 2020; Viner et al., 2021). Moreover, the incidence rate of clinical symptoms of fever, cough, or shortness of breath during COVID-19

was lower in children than in adults (73% vs. 93%). Further, the rates of hospitalization and ICU admission was estimated to be 5.7%–20% and 0.58%–2.0%, respectively (Bialek et al., 2020). Concomitant medical issues ranging from rash to severe Kawasaki-like disease have been sporadically reported in Western countries, but there are few such reports in Eastern countries (Verdoni et al., 2020). COVID-19 is milder in children than in adults, and although the reason is unclear, the expression and function of the angiotensin-converting enzyme 2 and immune response are speculated to play important roles (Bunyavanich, Do, & Vicencio, 2020; Felsenstein & Hedrich, 2020; Williams et al., 2020).

5.3. Clinical features of COVID-19 and pneumonia

COVID-19 pneumonia appears after 4–6 days and dyspnea on day 8 of onset caused by adaptive CMI (Ackermann et al., 2020; Frisoni et al., 2021; Huang et al., 2020; Song et al., 2020). The pathological pattern of lung injury in COVID-19 pneumonia appears to be similar to that in SARS or Middle East respiratory syndrome pneumonia (Xu et al., 2020). The lungs of patients with COVID-19 have distinctive vascular features of severe endothelial injury associated with the presence of intracellular SARS-CoV-2. Pulmonary histopathology indicated diffuse alveolar damage associated with stronger perivascular T-cell infiltration and prevalent thrombosis with microangiopathy and vascular angiogenesis. These pathological features that are characteristic of COVID-19 are inconsistent with those of equally severe influenza virus infections and cause interstitial pneumonia and microangiopathy (Table 5) (Ackermann et al., 2020; Bhatnagar et al., 2021). T-cell infiltration is more prevalent in COVID-19 pneumonia than in influenza pneumonia, indicating the involvement of a more potent CMI that causes inflammation. Increased levels of IL-6, IL-10, and C-X-C motif chemokine ligand 10; lymphopenia (decreased CD4+ and CD8+ T cells); and decreased IFN- γ expression (in CD4+ T cells) are also associated with severe COVID-19 (Laing et al., 2020; Pedersen & Ho, 2020; Song et al., 2020). Microangiopathy and extensive inflammation in the alveolus cause the impaired pulmonary epithelial function of gas exchange and alveolar capillary thrombosis, and lower oxygen levels to a greater extent than imaging findings of pneumonia. Anti-IL-6 antibody and dexamethasone are effective in suppressing severe inflammation and exacerbation of COVID-19 pneumonia (The REMAP-CAP Investigators, 2021; The WHO Rapid Evidence Appraisal for COVID-19 Therapies Working Group, 2020).

5.4. Asymptomatic pneumonia

COVID-19 spread on the Diamond Princess cruise ship in Tokyo Bay, and infection and clinical symptoms were confirmed for polymerase chain reaction (PCR)-positive individuals at the time of disembarkation (Tabata et al., 2020). Among 104 PCR-positive patients, 33 (32%) were asymptomatic and 71 (68%) were symptomatic, including 43 (41%) with mild and 28 (27%) with severe symptoms at the end of the observation period (Inui et al., 2020; Tabata et al., 2020). Asymptomatic pneumonia cases showed a greater proportion of ground-glass opacity to consolidation

Table 5

Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in COVID-19 pneumonia.

	COVID-19 patients	Influenza patients	Comparison ^a
CD3-positive T cells ^b	26.2 ± 13.1	14.8 ± 10.8	
CD4-positive T cells	13.6 ± 6.0	5.8 ± 2.5	P = 0.004
CD8-positive T cells	5.3 ± 4.3	11.6 ± 4.9	P = 0.008
Neutrophils (CD15 positive)	0.4 ± 0.5	4.8 ± 5.2	P = 0.002
Lung weight (control 1045 ± 91 g)	1681 ± 49	2404 ± 560	P = 0.04
Alveolar capillary microthrombi	159 ± 73	16 ± 16	P = 0.002

Table is created from the report (Ackermann et al., 2020).

^a Comparison between COVID-19 and influenza patients.

^b Number in 20 fields of examination per patient (n = 7).

(83%), while symptomatic cases more frequently showed a greater proportion of consolidation to ground-glass opacity (41%). Fig. 6 shows a pulmonary image of a 73-year-old patient with asymptomatic pneumonia. Pneumonia and alveolar microangiopathy in some patients may progress inconspicuously without dyspnea despite underlying hypoxia at $\text{PaO}_2 < 60$ mmHg and $\text{PaCO}_2 > 39$ mmHg (range, 41–49 mmHg), a condition referred to as “Happy hypoxia,” resulting in poor prognosis (Couzin-Frankel, 2020; Tobin, Laghi, & Jubran, 2020).

5.5. Variant infection

The emergence and rapid spread of SARS-CoV-2 variants of the spike protein is a grave concern for COVID-19 vaccine efficacy, with some variants being more infectious and contagious than earlier forms of the virus (CDC, 2021d; Rambaut et al., 2020, 2021; WHO, 2021c). Variants are divided into three categories—variants of interest, variants of concern (VOC), and variants of high consequence (CDC, 2021d; WHO, 2021c). VOCs show an increase in transmissibility, more severe disease, significant reduction in neutralization by antibodies generated during previous infection or vaccination, and reduced efficacy of vaccines (CDC, 2021a; Hacısuleyman et al., 2021; WHO, 2021b).

The variants have adapted to humans, acquired tropism to the airway epithelium, and spread faster and broader in the airway than the prototype (Bhatnagar et al., 2021; Hou et al., 2020; Laporte et al., 2021; Volz et al., 2021). Since the variants spread broader in the respiratory tract than the prototype during the incubation period of pneumonia from infection, the range of pneumonia expands broader in the variant-infected area in the respiratory tract than in the prototype-infected area. As mentioned in Section 3.2., pneumonia caused by variants is first found in a limited area, and inflammation spreads in the infected area of the lung in 3–5 days, resulting in severe pneumonia. VZV infection in immunocompromised individuals spreads widely with a

long incubation period before CMI and causes widespread severe lesions and pneumonia, as described in Section 3.2, and variants spread widely even in healthy individuals.

6. Therapeutic activity of favipiravir for the treatment of COVID-19

6.1. Pharmacological basis of favipiravir efficacy in COVID-19

The dosage regimen of favipiravir is twice-daily oral administration of 1600 mg on day 1, followed by 600 mg for 4 days in adults to maintain favipiravir blood concentration between 240 and 380 μM for influenza treatment (PMDA, 2014). A similar regimen is recommended for patients with severe fever with thrombocytopenia syndrome, with a loading dose of 1800 mg twice a day on day 1, followed by 800 mg twice a day for 7–14 days (Suemori et al., 2021).

Coronaviruses have the largest genome, with approximately 30 kb, among all RNA viruses, and SARS coronavirus has an enzyme with proofreading function (Smith, Blanc, Surdel, Vignuzzi, & Denison, 2013). The susceptibility of SARS-CoV-2 to favipiravir is indicated by an EC_{50} of 61.88 μM (Wang et al., 2020), an EC_{50} of 110 μM (Zhou et al., 2021), and 118.3 μM in case of cytopathic effect at viral multiplicity of infection of 0.002 and 207.1 μM in the viral replication inhibition assay, respectively (Shannon et al., 2020). These values are lower than the trough value of favipiravir in influenza (Fig. 7), and the maintenance of anti-SARS-CoV-2 concentration suggests its efficacy in COVID-19. Direct inhibition of SARS-CoV-2 replication in endothelial cells prevents microangiopathy in the nervous, cardiovascular, and pulmonary systems (Ackermann et al., 2020; Aid et al., 2020; Bhatnagar et al., 2021; S. X. Gu et al., 2021; Thacker et al., 2021). The advantage of drug repositioning is the availability of information on the drug's efficacy, side effects, and pharmacokinetics. Based on the results of *in vitro* studies, the efficacy of favipiravir has been demonstrated in

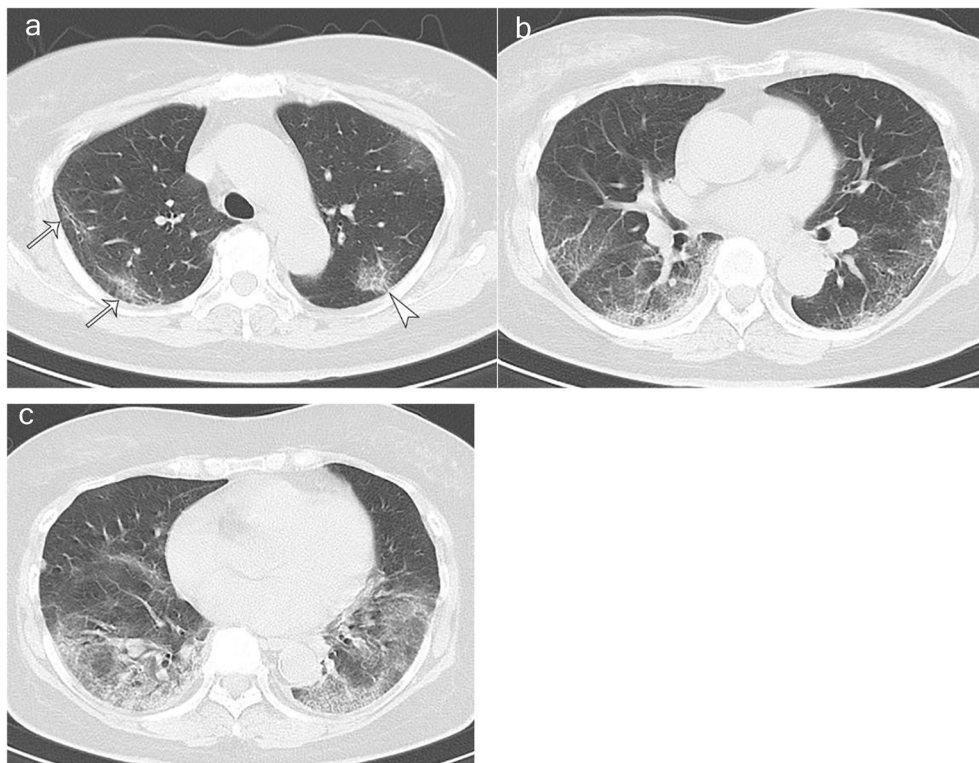


Fig. 6. Chest CT images of a 73-year-old asymptomatic woman with COVID 19 pneumonia. (a) Axial CT images presenting focal peripheral ground-glass opacities with intralobular and smooth interlobular septal thickening are shown in the left (arrowhead) and right upper lobes (arrows). The right upper lobe lesions are accompanied by subpleural curvilinear lines (arrow). (b, c) Diffuse ground-glass (reticular) opacities with consolidation with bronchiectasis and bronchial wall thickening are demonstrated in the left and right lower lobes. The authors obtained permission from the Radiology: Cardiothoracic Imaging to reuse this figure (Inui et al., 2020).

hamsters infected with SARS-CoV-2 and in human clinical trials (Cai et al., 2020; Kaptein et al., 2020; Shinkai et al., 2021).

Favipiravir and acyclovir, which are competitive inhibitors of guanosine triphosphate, have been assessed using the plaque reduction assay because the yield reduction assay is not suitable for competitive inhibitors of nucleosides. Multiplicity of infection at 0.001 and > 1 plaque-forming unit per cell is used in the plaque reduction assay and the yield reduction assay, respectively. Since the ratio of the guanosine analog to viral RNA/DNA should theoretically have similar inhibitory ratios between the two assays to show similar antiviral activity, approximately 100–1000-fold higher concentrations of favipiravir or acyclovir are required in the yield reduction assay than in the plaque reduction assay (Shiraki et al., 1992; Sleeman et al., 2010; Yajima et al., 2017). Choy et al. did not observe any inhibitory effects of 100 μM favipiravir on SARS-CoV-2 in a yield reduction assay, but they have discussed the suitability of assaying the nucleoside analogs in their assay method (Choy et al., 2020). Ohashi et al. (National Institute of Infectious Diseases, Japan) examined a series of favipiravir concentrations up to 64 μM and reported that favipiravir up to 64 μM showed negligible antiviral activity against SARS-CoV-2 in the yield reduction assay (Ohashi et al., 2021), but the concentrations used were below the trough level of favipiravir from pharmacokinetic studies; thus, the efficacy of favipiravir as a repurposed drug could not be adequately explored.

The EC_{50} values of remdesivir, lopinavir, chloroquine, umifenovir, berberine, cyclosporine A, and molnupiravir against SARS-CoV-2 have been reported to be 0.77–0.99, 5.2, 1.13–1.38, 3.5, 10.6, 3, and 3.4 μM , respectively (Cox, Wolf, & Plemper, 2021; Pizzorno et al., 2020; Wang et al., 2020). Although the EC_{50} of favipiravir is higher than that of other repurposed drugs because of the nucleoside precursor, favipiravir is expected to show efficacy at the same dose as that in Ebola virus infection (Bai et al., 2016; Jacobs et al., 2015; Sissoko et al., 2016).

6.2. Structural and sequencing analysis for favipiravir action

We have reported the structural and sequencing analysis of poliovirus and revealed that favipiravir binds to the active site of its RNA

polymerase and the lack of generation of favipiravir-resistant mutants (Daikoku et al., 2018). RNA synthesized in the presence of favipiravir is elongated and favipiravir causes mutation in viral genome in favipiravir-treated cells despite chain termination in various viruses (Arias, Thorne, & Goodfellow, 2014; Baranovich et al., 2013; Delang et al., 2014; Goldhill et al., 2019; Shannon et al., 2020; Vanderlinden et al., 2016). A similar study has investigated the interaction between favipiravir and SARS-CoV-2 (Naydenova et al., 2021; Peng et al., 2021; Shannon et al., 2020).

Structural studies have revealed the structure of the nsp12-nsp7-nsp8 core polymerase complex of SARS-CoV-2 with FTP. They have shown that the nonproductive binding mode of FTP to the catalytic site of SARS-CoV-2 RdRp and little covalent incorporation, making a covalent bondage with the adjacent nucleotide, into the replicating strand result in an inefficient rate of incorporation in primer extension assays, and short RNA is produced due to chain termination (Naydenova et al., 2021; Peng et al., 2021). When the effect of favipiravir on RNA synthesis was analyzed biochemically in various viruses, chain termination was detected and short RNA strands were formed in primer extension assays (Jin et al., 2013; Sangawa et al., 2013; Naydenova et al., 2021; Shannon et al., 2020). FTP is inefficiently incorporated into the replicating strand in primer extension assays, and suppressed completion of RNA replication even when excess concentrations of rNTPs to FTP is added due to the activity of chain termination (Naydenova et al., 2021).

Peng et al. also reported FTP binding in the pre-catalytic states of the SARS-CoV-2 core polymerase complex. Furthermore, based on RNA sequence analysis, chain termination and possible lethal mutagenesis was observed (Peng et al., 2021; Zhao & Zhong, 2021). The RNA synthesis leaked from chain termination continues to elongate and accumulate mismatched mutations in the synthesized viral genome in infected cells.

Favipiravir demonstrated antiviral activity with an EC_{50} of 110 μM , no cell toxicity, and undetectable mutagenic effect on the SARS-CoV-2 genome at the highest concentrations tested (300 μM) and β -d-N4-hydroxycytidine, a metabolite of molnupiravir, showed the EC_{50} of 0.3 μM and the increased mutation rate in a dose-dependent manner between 0.3 and 10 μM (S. Zhou et al., 2021). The authors observed

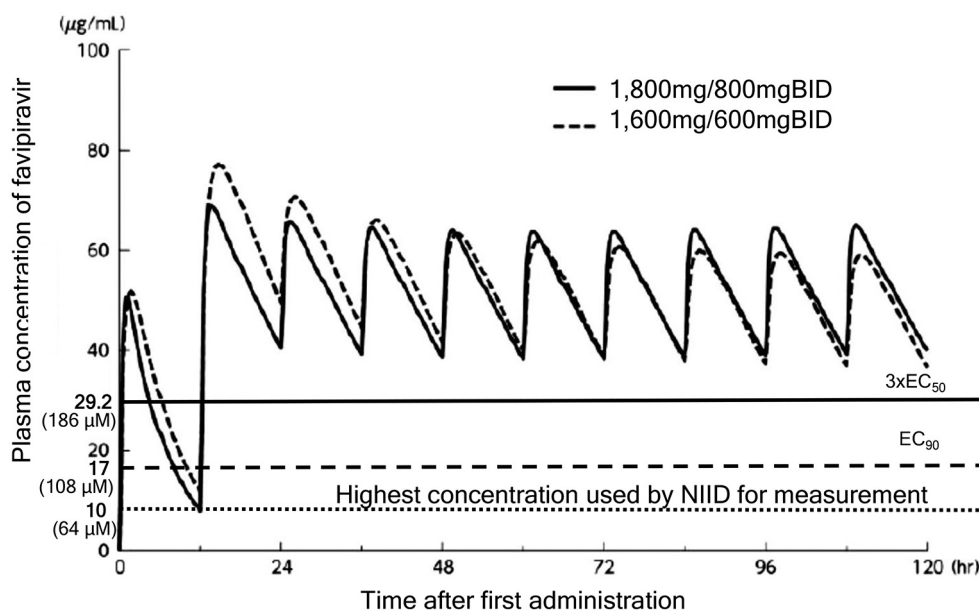


Fig. 7. Pharmacological basis of favipiravir against SARS-CoV-2 and its therapeutic efficacy against COVID-19 infection. Figure shows the time course of plasma concentration of favipiravir after its first administration at the dosage used for influenza treatment (Avigan Tablets 200 mg, Report on the Deliberation Results, Japan, PMDA, 2014). Solid, dashed, and dotted lines indicate the favipiravir concentrations at three times the EC_{50} , EC_{90} , and maximal concentration examined by Ohashi et al. at the National Institute of Infectious Diseases (NIID) of Japan, respectively (Ohashi et al., 2021; Wang et al., 2020). The plasma concentrations of favipiravir were higher than the EC_{90} and $3 \times \text{EC}_{50}$ values for SARS-CoV-2 throughout the day, suggesting the therapeutic potential of favipiravir against COVID-19 infection. 1800 mg/800 mg BID: loading dose of 1800 mg twice a day followed by 800 mg twice a day for six days. 1600 mg/600 mg BID: loading dose of 1600 mg twice a day followed by 600 mg twice a day for six days.

mutations in the hypoxanthine phosphoribosyltransferase gene after 32 days of treatment with β -d-N4-hydroxycytidine and favipiravir in the CHO-K1 cells.

6.3. Clinical trials and case reports of favipiravir for COVID-19

In an open-label non-randomized control study, patients were assigned to either the favipiravir and IFN- α inhalation group ($n = 35$) or lopinavir/ritonavir and IFN- α inhalation group ($n = 45$) (Cai et al., 2020). A significantly shorter viral clearance time was observed in the favipiravir group (day 4) than in the lopinavir/ritonavir group (day 11, $P < 0.001$). The incidence improvement rate according to the chest image was not significant on day 9; however, it significantly increased by day 14, with 91.43% in the favipiravir group and 62.22% in the lopinavir/ritonavir group ($P = 0.004$).

An interim report of an adaptive multicenter, open-label, randomized, phase II/III clinical trial of favipiravir (Avifavir®) versus the standard of care (SOC) in hospitalized patients with moderate COVID-19 pneumonia has been reported (Ivashchenko et al., 2021). Viral clearance was achieved in 25/40 (62.5%) patients treated with favipiravir and in 6/20 (30.0%) patients treated with the SOC ($P = 0.018$) on day 5. The median time to body temperature normalization ($<37^\circ\text{C}$) was 2 days in the favipiravir group and 4 days in the SOC group ($P = 0.007$). By day 15, chest CT findings improved in 36/40 (90.0%) patients treated with favipiravir and 16/20 (80.0%) patients with SOC ($P = 0.283$).

6.4. Favipiravir blocks virus growth for 6 cycles and shortens recovery time by 2.8 days

In a randomized, placebo-controlled, single-blind comparative study conducted in Japan, the time to viral clearance and symptom relief (body temperature, oxygen saturation, and chest image) was examined in 156 patients with non-severe COVID-19 pneumonia (Shinkai et al., 2021). Favipiravir significantly shortened the time to symptom relief from 14.7 days for placebo to 11.9 days ($P = 0.0136$); the adjusted hazard ratio was 1.593 (95% confidence interval 1.024–2.479). As shown in Fig. 8, COVID-19, unlike HZ, is a 3-week illness that combines 5–6 days of viral replication, followed by an inflammation period, due to adaptive immunity of approximately 2 weeks. The shortened time to symptom relief by 2.8 days with favipiravir treatment is defined by shortening of the viral replication period; since one cycle of viral replication is approximately 10 h, shortening of 2.8 days corresponds to the inhibition of 6 viral replication cycles (Shiraki & Kobayashi, 2020). Therefore, favipiravir is expected to show a similar therapeutic potential in COVID-19 to that of an anti-herpetic drug in HZ.

6.5. A multi-center open-label post-marketing clinical study in 940 patients with COVID-19 confirming the efficacy of Avifavir® (favipiravir)

A multicenter, open-label post-marketing clinical study on the efficacy of favipiravir was conducted in 940 hospitalized patients with moderate-to-severe and severe COVID-19, including 470 patients in the favipiravir and standard of supportive care (control) groups (Corritori et al., 2021; Viriom-Inc, 2021). The median duration of onset was 4.9 days for the favipiravir group and 4.7 days for the control group. The median time to virus elimination in the favipiravir and control groups was 8 and 12 days, respectively ($P < 0.001$). The median time to clinical improvement in the favipiravir and control groups was 12 and 15 days, respectively ($P < 0.001$), with a significantly greater number of patients showing clinical improvement in the favipiravir group than in the control group at 7 days ($P = 0.0248$) and 14 days ($P < 0.001$). The favipiravir group showed statistically significant improvement compared to the control group, with 33% faster virological response, 20% shorter time to normalization of clinical symptoms, and 31% lower mortality rate.

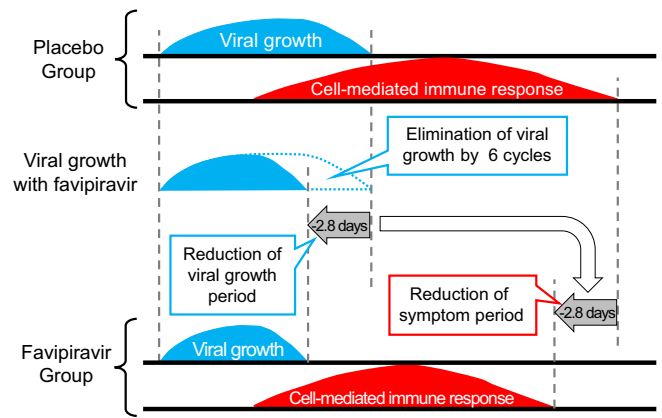


Fig. 8. Avigan® (favipiravir) inhibited 6 cycles of viral replication and reduced time to recovery by 2.8 days in a randomized, placebo-controlled, single-blind comparative study. The primary endpoint was defined as the time to negative RT-PCR assay report and alleviation of symptoms (body temperature, oxygen saturation, and chest images). The median time to alleviation of this primary composite endpoint was 11.9 days in the favipiravir group and 14.7 days in the placebo group, which demonstrates a statistically significant difference ($P = 0.0136$) (Shinkai et al., 2021). The COVID-19 pneumonia is caused by viral proliferation and adaptive immunity, as shown in the clinical course of herpes zoster treated with anti-herpetic agent in Fig. 3. Reduction of time to recovery by 2.8 days indicates a shortened viral replication phase by 6 cycles. Favipiravir showed sufficient efficacy against COVID-19 pneumonia as an antiviral drug. The authors obtained permission from the Japan Medical Journal to use, modify and translate the figure into English (Shiraki & Kobayashi, 2020).

6.6. Summary of clinical studies on efficacy of favipiravir for COVID-19 pneumonia

Many clinical studies on favipiravir treatment for COVID-19 pneumonia have been conducted after the onset of pneumonia, but not before the onset of pneumonia, and this is not an optimal time for initiating treatment for viral infections, as mentioned in Section 4. According to clinical studies, favipiravir administration within 4 days of onset is more desirable than after 4 days of onset (Fuji et al., 2021; Hassanipour et al., 2021), but clinical trials initiating treatment approximately 5 days after onset still showed efficacy in patients with COVID-19 pneumonia (Cai et al., 2020; Ivashchenko et al., 2021; Shinkai et al., 2021). Due to the similarities between COVID-19 pneumonia and HZ in viral replication and inflammatory patterns, antiviral treatment inhibits viral RNA/DNA synthesis, but it does not improve immune-induced inflammation of pneumonia and skin lesions. Although favipiravir has been shown to be effective in the treatment of pneumonia, experience in treating CMV pneumonia indicates the need to initiate treatment early or at least when pneumonia can be prevented.

6.7. Early antiviral treatment for prevention of pneumonia and microangiopathy as an optimal treatment for COVID-19

COVID-19 causes influenza-like symptoms due to innate immunity, and pneumonia is caused by adaptive CMI. As discussed in Section 4, antiviral treatment should be initiated at the optimal window during the prodromal phase of influenza-like fever, where innate immunity suppresses the growth and spread of viral infections. The optimal treatment of COVID-19 with favipiravir requires early treatment immediately after diagnosis, similar to that in acute viral infections of influenza and varicella.

Kidney transplant recipients and patients with chronic renal disease are at a high risk of developing critical COVID-19 due to chronic immunosuppression and comorbidities (Cravedi et al., 2020; Gansevoort & Hilbrands, 2020). A solid organ transplant recipient with chronic kidney disease tested positive on the PCR test on day 2 of fever, and oxygen saturation decreased on day 3 along with high fever, lymphocytopenia, and

a high C-reactive protein level. After initiating favipiravir treatment on day 3, oxygen saturation recovered on day 4, the fever disappeared on day 5, and the PCR test result was negative on day 6 (Sakai et al., 2020). A high-risk patient was diagnosed with COVID-19 shortly after the onset of fever, and favipiravir treatment improved symptoms, similar to that in influenza, and severe pneumonia and complications were avoided.

In Japan, the Japanese Association for Infectious Diseases issued the provisional guidelines in February and May 2020 governing the use of antiviral drugs, stating that “antivirals are to be initiated in patients only after the appearance of hypoxia and the requirement for oxygen supplementation is present” without showing the rationale for starting antiviral therapy after progression of pneumonia (The Japanese Association for Infectious Diseases, 2020). The Ministry of Health, Labor and Welfare referred to the provisional guidelines for the use of antiviral agents including favipiravir, and limited favipiravir to inpatients. Since this policy does not seem to reflect the opinions of experts in viral infections and antiviral therapies, the Japanese Society of Clinical Virology recommended that antiviral agents including favipiravir should be used immediately after onset, similar to that in influenza treatment (The Japanese Society of Clinical Virology, 2020), since antiviral therapy after progression to pneumonia is too late as an effective antiviral therapy.

The Novel Coronavirus Expert Meeting in Japan restricted PCR tests in patients with 4 days of fever until May 2020, and the PCR test system was established nationwide and became available at an early stage of onset in June. In June 2020, Shiraki proposed to Fujifilm Corporation to conduct clinical trials to prevent COVID-19 pneumonia and microangiopathy by early treatment with favipiravir within 3 days of onset. In April 2021, Fujifilm Toyama Chemical Co., Ltd. announced a new clinical trial of early treatment with favipiravir within 3 days of onset (jRCT2041210004).

New COVID-19 therapeutic drugs have been developed, and clinical trials have been conducted at the optimal timing in the early stage of infection before pneumonia as shown in Fig. 5. Molnupiravir, an anti-viral RdRp drug, has exhibited anti-SARS CoV-2 activity *in vitro* and *in vivo*, and oral molnupiravir within 5 days of onset has been shown to reduce the risk of hospitalization or death by approximately 50% compared to the placebo in patients with mild or moderate COVID-19 in a phase 3 study (Fischer et al., 2021; Merck, and Co., I, 2021; Rosenke et al., 2021; Wahl et al., 2021).

AT527, an anti-viral RdRp drug, has exhibited anti-SARS CoV-2 activity both *in vitro* and *in vivo* (Good et al., 2021), and clinical trials have been conducted in patients with onset ≤ 5 days (NCT04709835 and jRCT2031210070).

Moreover, 3CL protease (MPro), a cysteine endoprotease, cleaves coronavirus polyprotein into active viral proteins, resulting in the formation of infectious viruses. Masitinib is a 3CL protease inhibitor that inhibits the processing of polyprotein and replication of SARS CoV-2 *in vitro* and *in vivo* (Drayman et al., 2021), and its clinical trial has been conducted in patients with symptomatic mild-to-moderate COVID-19 with onset ≤ 5 days (NCT05047783). A clinical trial of the 3CL protease inhibitor S-217622 developed in Japan has been conducted in patients with symptomatic mild-to-moderate COVID-19 with onset ≤ 5 days (jRCT2031210350).

PF-07321332/Ritonavir (PAXLOVID®) has shown 89% efficacy by administration 1–3 days after onset (NCT04960202) (Pfizer Inc, 2021). Ritonavir is an antiretroviral drug and may help the increase and maintain PF-07321332 concentrations in patients by inhibiting the cytochrome P-450 CYP3A4 enzyme, which degrades the second protease inhibitor, PF-07321332 (Zeldin & Petruschke, 2004).

7. Need for antiviral therapy even after the spread of COVID-19 vaccines

The efficacy of COVID-19 vaccines has been reported in 95% vaccine recipients, whereas 5% have been reported to have mild infection (FDA,

2020a, 2020b). Promotion of COVID-19 vaccines will end the acute phase of the COVID-19 pandemic (CDC, 2021c; WHO, 2021a). The neutralizing antibody titer achieved by COVID-19 vaccines is higher than that in convalescent patients, and booster immunization is planned to maintain the antibody titer (Anderson et al., 2020). However, COVID-19 vaccines induce neutralizing antibodies and CMI to the spike protein, but they cannot produce mucosal antibodies that are important for infection protection. Therefore, breakthrough infection is unavoidable because mucosal infection cannot be prevented. However, if the vaccine recipients retain a sufficient level of antibody titer, the resultant infection is subclinical or mild. Some breakthrough infections cause symptomatic or mild-to-severe infections, possibly depending on the neutralizing antibody titer to the infecting variant. Thus, the emergence and rapid spread of SARS-CoV-2 variants is concerning in terms of COVID-19 vaccine efficacy.

Antiviral therapy is not necessary if the infection causes subclinical infection, where viral propagation is ultimately limited to the upper respiratory tract. However, if symptoms, such as fever, are associated with upper respiratory tract infection, there is a possibility that the infection may spread outside of the upper respiratory tract and cause pneumonia, microvascular injury, neurological disorder, and sequelae. These infections need to be treated with antivirals early after to prevent spreading of the infection and worsening of the disease and sequelae in vaccinated, re-infected, and variant-infected persons.

8. Conclusions and future perspectives

Favipiravir needs to be administered at a high therapeutic dose due to it being a purine and not a nucleoside analogue, but its conversion to the active form in infected cells with active RNA synthesis enhances the specificity and selectivity of antiviral action. Favipiravir has shown promising therapeutic efficacy against COVID-19 pneumonia. This review describes the optimal time for antiviral COVID-19 treatment based on the experiences of antiviral therapy for influenza, varicella, HZ, recurrent herpes, and CMV pneumonia and many clinical studies on favipiravir for the treatment of COVID-19 pneumonia. Current antiviral therapy, initiating from the prodromal stage by innate immunity, is essential for the prevention and alleviation of the main symptoms of infection. As the major symptoms of viral infections are caused by adaptive CMI, immunosuppressants and anti-cytokine antibodies are more effective than antiviral drugs in alleviating major inflammatory symptoms.

The most efficacious treatment of COVID-19 pneumonia was found to be similar to the treatment strategy for CMV pneumonia, *i.e.*, prevention instead of treatment. Clinical trials for COVID-19 treatment have shown that antiviral therapy should be initiated within 3 days after symptom onset and during the prodromal stage to achieve maximum effectiveness—this is similar to other viral infection as stated in Section 4.

Regardless of the widespread use of vaccines, antiviral therapy for COVID-19 is required in case of vaccine failure, reinfection, or variant infection. Optimal treatment with antiviral agents, including favipiravir, should be initiated within 3 days of onset to prevent COVID-19 pneumonia, microangiopathy, and neurological complications without any sequelae, as shown in Fig. 5.

Declaration of Competing Interest

K.S. reports the receipt of consulting fee from Maruho Co.,Ltd., lecture fee from Maruho Co.,Ltd., MSD, and Novartis and research funding from Maruho Co.,Ltd., MSD, and Japan Blood Products Organization; all payments to the institution. R.K. is reporting that he is a consultant to Fujifilm Toyama Chemical Co. Ltd. and Chief Medical Officer of AiPharma and did not receive any additional compensation for this study. These funding agencies had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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