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SUPPLEMENT ARTICLE

New Developments in Influenza Polymerase Inhibitors

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Influenza RNA polymerase is a critical enzyme responsible for viral replication and is highly conserved across different influenza virus strains, making it an ideal target for antivirals. Novel inhibitors targeting its 3 subunits (polymerase basic protein 1, polymerase basic protein 2, and polymerase acidic protein) have been developed and have demonstrated efficacy in clinical trials. The cap-dependent endonuclease inhibitor baloxavir is now widely available and several other polymerase inhibitors are undergoing regulatory review. This review discusses new developments in influenza RNA polymerase inhibitors, including their mechanisms of action, pharmacokinetics, efficacy in preclinical and clinical studies, and the emergence of resistant variants. These new agents offer expanded treatment options, including antiviral combinations, and contribute to enhanced strategies for controlling influenza virus infections.

Keywords. influenza polymerase inhibitors; antiviral agents; baloxavir; pharmacokinetics; antiviral resistance.

Despite the availability of vaccines and antiviral drugs, the evolution of influenza viruses, characterized by antigenic drift and shift, continually challenges efforts to prevent illnesses and treat infected individuals. The currently available antivirals, matrix protein 2 (M2) inhibitors and neuraminidase inhibitors (NAIs), may become ineffective due to the emergence and spread of resistant variants. The M2 inhibitors amantadine and rimantadine, once widely used, are no longer recommended due to the global prevalence of resistant seasonal influenza A strains [1]. Although the influenza viruses currently in circulation are generally sensitive to NAIs (oseltamivir, zanamivir, peramivir, and laninamivir), oseltamivir-resistant A(H1N1) viruses circulated globally during the 2008–2009 season [2]. These events raise concerns about the risk of widespread antiviral resistance, even in the absence of drug pressure. Consequently, there is an urgent need for novel therapeutic strategies capable of effectively combating a broad range of influenza strains, including those resistant to existing treatments.

Influenza polymerase inhibitors have emerged as an especially promising new class of antiviral agents, which target the viral RNA polymerase complex that is critical for viral replication [3] (Figure 1). To date, 3 classes of such inhibitors have been developed, including polymerase acidic protein (PA) cap-dependent endonuclease (CEN) inhibitors, polymerase basic protein 2 (PB2) cap-binding domain inhibitors, and polymerase basic protein 1 (PB1) RNA synthesis inhibitors (Table 1). The polymerase complex genes are among the most highly conserved genes of influenza viruses, making the polymerase an ideal target for antivirals [4]. Indeed, most of these drugs inhibit a wide range of influenza virus strains, including those resistant to adamantanes and NAIs. Many also exhibit synergistic antiviral effects when combined with antivirals such as oseltamivir and peramivir in preclinical models.

This overview addresses new developments in influenza polymerase inhibitors, including their mechanisms of action, pharmacokinetics (PK), efficacy in preclinical and clinical studies, and the emergence of resistant variants. We also summarize the completed and ongoing clinical trials of these agents (Supplementary Tables 1–9).

PA CAP-DEPENDENT ENDONUCLEASE INHIBITORS

Baloxavir Marboxil

Baloxavir marboxil (BXM, formerly S-033188) is a prodrug of baloxavir acid (BXA), designed to improve absorption by adding a phenolic hydroxyl group (Figure 2). Upon oral administration, it is rapidly hydrolyzed by arylacetamide deacetylase to BXA, which binds to the CEN and inhibits the cleavage of host pre–messenger RNAs (mRNAs), thereby inhibiting viral

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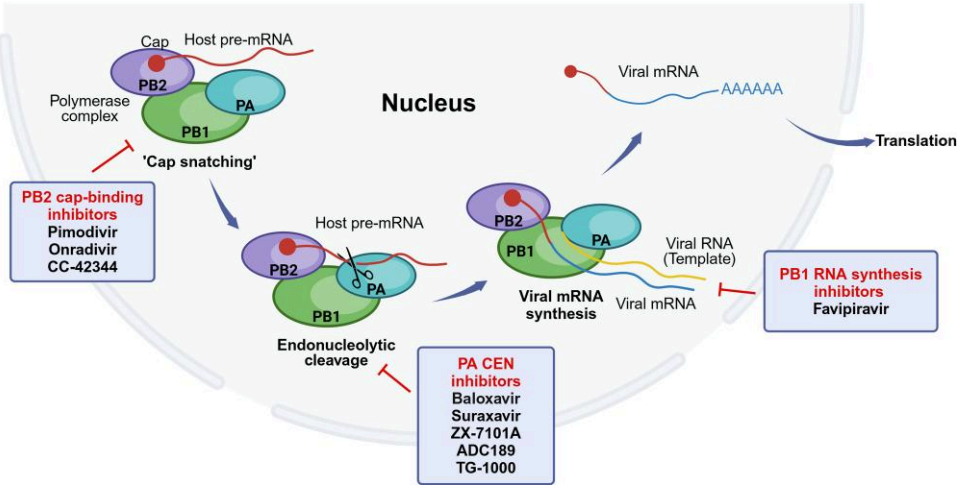

Figure 1. Transcription mechanism of influenza RNA polymerase and related inhibitors. The influenza RNA polymerase consists of 3 subunits in influenza A and B viruses: polymerase basic protein 1 (PB1), polymerase basic protein 2 (PB2), and polymerase acidic protein (PA). Transcription of the viral genome RNA (vRNA) to messenger RNA (mRNA) is initiated by a unique mechanism known as cap-snatching. During the process, the PB2 subunit binds to the 5′ capped ends of host pre-mRNAs in the nucleus, and the cap-dependent endonuclease (CEN) of the PA subunit cleaves these capped pre-mRNAs approximately 10–13 nucleotides downstream of the cap, generating short capped RNA fragments that act as primers for viral mRNA synthesis. Subsequently, the PB1 subunit uses the vRNA template to synthesize complementary viral mRNA, which is then exported to the cytoplasm for translation. Image created in BioRender.com, with permission.

Table 1. Overview of Influenza Polymerase Inhibitors

Feature	Baloxavir Marboxil	Suraxavir Marboxil	ZX-7101A	ADC189	TG-1000	Pimodivir	Onradivir	Favipiravir
Alternative designation (trade name)	S-033188 (Xofluza)	GP681	N/A	N/A	N/A	JNJ-63623872, VX-787	ZSP1273	T-705
Active form	Baloxavir acid	GP1707D07	ZX-7101	N/A	TG-0527	N/A	N/A	Favipiravir-RTP
Target protein	PA	PA	PA	PA	PA	PB2	PB2	PB1
Target viruses[a]	A, B, C	A, B	A, B	A, B	A, B	A	A	A, B, C, D
Current status	Approved in multiple countries	Approved for marketing in China	Approved for marketing in China	NDA	NDA	Phase 3 clinical trials halted	Approved for marketing in China	Approved in Japan and China
Usual treatment regimen	Single oral dose	Single oral dose	Single oral dose	Single oral dose	Single oral dose	BID oral dose for 5 d	QD oral dose for 5 d	BID oral dose for 5 d
Activity against M2 inhibitor–resistant viruses	Yes	N/A	Yes	Yes	Yes	Yes	N/A	Yes
Activity against NAI-resistant viruses	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Emergence of variants with reduced susceptibility during clinical use	Yes	Yes	Yes	Yes	N/A	Yes	Yes	No

Abbreviations: BID: twice daily; M2, matrix protein 2; N/A, not available; NAI, neuraminidase inhibitor; NDA, New Drug Application; PA, polymerase acidic protein; PB, polymerase basic protein; QD, once daily; RTP, ribofuranosyl-5′-triphosphate.

[a]Seasonal influenza.

mRNA formation. Currently, BXM is available in >80 countries for the treatment of acute influenza A and B infections.

Preclinical Studies

In cell culture, BXA effectively inhibited the replication of influenza A and B and zoonotic influenza viruses at nanomolar concentrations, including those resistant to adamantanes and NAIs [5, 6] (Table 1). BXA is also inhibitory for influenza C and D viruses [7, 8]. In murine models with influenza A or B infection, BXM demonstrated superior antiviral effects compared to oseltamivir, and combination therapy with oseltamivir yielded a synergistic effect [9, 10]. No toxicity has been detected in preclinical studies at exposure levels well above those expected in humans [11].

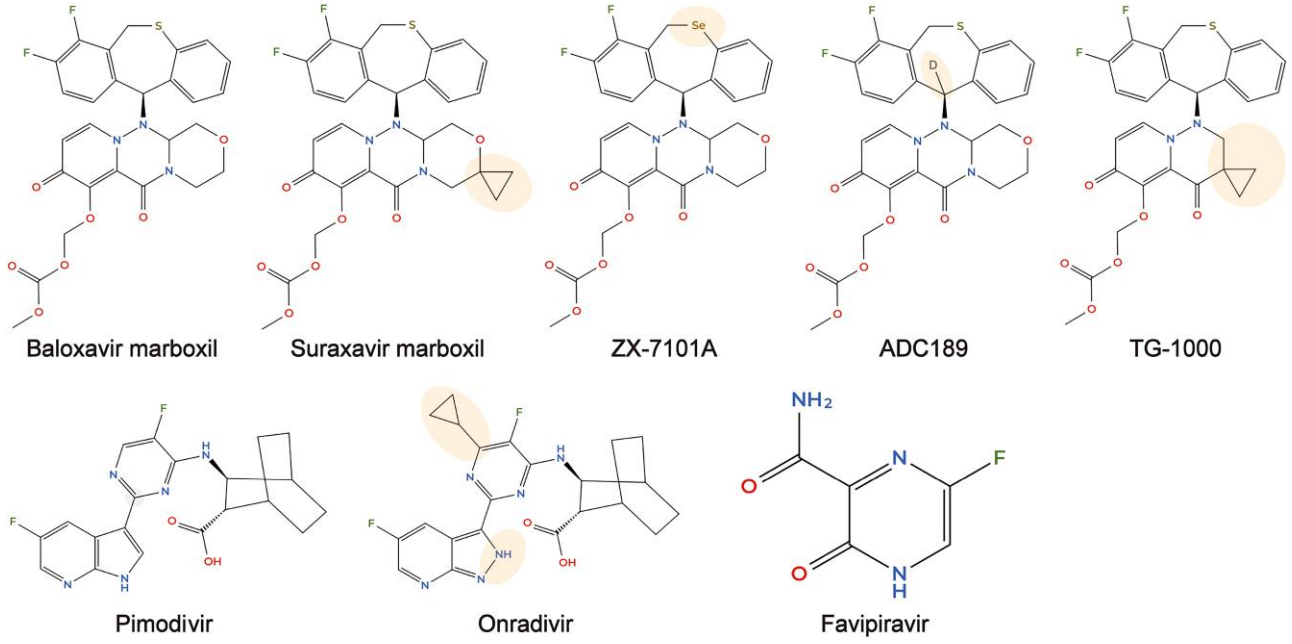

Figure 2. Chemical structures of influenza polymerase inhibitors, with brown ellipses highlighting the structural differences of each drug compared to its first-in-class agents, baloxavir marboxil or pimodivir. Images created in MolView (https://app.molview.com/).

Pharmacokinetics

Because of BXA's prolonged plasma terminal elimination half-life ($T_{1/2elim}$; 49–91 hours), the usual treatment regimen for BXM is a single dose of 40 mg for patients weighing 20–80 kg and 80 mg for those weighing >80 kg [12]. BXM can be taken with or without food, although ingestion with food decreases overall exposure. However, it should not be co-administered with dairy products or polyvalent cation-containing substances due to potential reductions in plasma concentrations caused by food effects or formation of chelate with polyvalent cations [12]. After administrated, BXA reaches its maximum concentration (C_{max}) within 4 hours, and binds to plasma protein at >90%, with a volume of distribution of 1180 L [12]. The drug is primarily eliminated via the UGT1A3 metabolism pathway and excreted in the feces and urine [13]. The effect of severe renal or hepatic impairment on BXA pharmacokinetics has not been evaluated. Additional information is summarized in Supplementary Table 10.

Clinical Efficacy

A dose-ranging phase 2 trial of 400 adults with uncomplicated influenza A(H1N1)pdm09 demonstrated that the median time to alleviation of influenza symptoms (TTAS) was 23.4 to 28.2 hours shorter in the BXM groups compared to the placebo group [14]. Reductions in influenza virus titers were significantly more rapid in all BXM groups [14]. Subsequently, a phase 3 trial (CAPSTONE-1) recruited 1436 otherwise healthy adolescents and adults with uncomplicated influenza, most of whom were infected with influenza A(H3N2) [14]. BXM significantly reduced the median TTAS compared to placebo (53.7 vs 80.2 hours) but not to oseltamivir (53.5 vs 53.8 hours) [14]. Additionally, BXM was associated with significantly more rapid declines in infectious virus titers than placebo and oseltamivir. A phase 3 trial in high-risk outpatients (CAPSTONE-2) enrolled 2184 participants [15]. In all patients and in those infected with A(H3N2) virus, the median time to improvement of influenza symptoms in the BXM group was significantly shorter than that in the placebo group (73.2 vs 102.3 hours, and 75.4 vs 100.4 hours, respectively), and was similar to that in the oseltamivir group [15]. For patients with influenza B virus infection, BXM was superior to both placebo and oseltamivir (74.6 vs 100.6 vs 101.6 hours) [15]. The incidence of influenza-associated complications in BXM recipients (3%) was lower compared to placebo (10%) and was similar to that in oseltamivir recipients (5%) [15]. A meta-analysis of 21 randomized controlled trials further concluded that BXM and NAIs were superior to placebo in alleviating influenza symptoms and reducing complications in patients with uncomplicated influenza [16].

Multiple pediatric trials of BXM have also been performed. The miniSTONE-2 trial enrolling children aged 1–12 years found that the median TTAS was similar between the BXM and oseltamivir groups (138.1 vs 150.0 hours) [17]. In an open-label trial enrolling children aged <1 year (miniSTONE-1), the TTAS was approximately 7 days, generally consistent with profiles in children aged 1–12 years, and no safety signals were identified [18]. Currently, the drug is approved for children aged ≥1 year in Japan and the European Union, but only for children aged ≥5 years in the United States and China.

The FLAGSTONE trial randomized 366 hospitalized patients with severe influenza to receive BXM plus standard-of-care (SoC) NAIs or placebo plus NAIs [19]. The results revealed no significant differences in median time to clinical improvement (97.5 vs 100.2 hours) or median time to discharge between the 2 groups, though BXM was associated with shorter median time to cessation of viral shedding [19]. Additionally, despite numerically lower mortality in the BXM group (2% vs 6%), the small number of events limits definitive conclusions. Larger, ongoing trials by RECOVERY and REMAP-CAP investigators, known for their successes in improving coronavirus disease 2019 management, are assessing treatments for patients hospitalized with seasonal influenza, including BXM alone and in combination with oseltamivir [20, 21] (see Waite et al in this supplement [22]).

BXM also demonstrates efficacy in prophylaxis. In the BLOCKSTONE trial, 752 Japanese household contacts (HHCs) with influenza A were randomized to receive BXM or placebo to access its efficacy in postexposure prophylaxis (PEP) [23]. The percentage of HHCs developing clinical influenza was significantly lower in the BXM group (1.9% vs 13.6%), regardless of underlying risk factors, vaccination status, and age category of the index patients (IPs) or infecting influenza A virus subtypes [23]. A network meta-analysis concluded that BXM exhibits comparable effectiveness to NAIs in influenza PEP [24]. In the CENTERSTONE trial, 1457 IPs were randomized to take BXM or placebo to assess the efficacy of BXM treatment in reducing transmission of influenza to HHCs [25, 26]. Among 2681 HHCs, the transmission of laboratory-confirmed influenza was significantly reduced at day 5 (adjusted odds ratio, 0.68 [95.38% confidence interval, .50–.93]) in the BXM group compared to the placebo group [26]. Influenza virus transmission resulting in symptoms by day 5 also tended to be lower with BXM. Although the preexposure prophylaxis efficacy of BXM has been demonstrated in mice, its effectiveness in humans remains unassessed [27]. In conclusion, BXM shows efficacy in PEP and preventing influenza virus transmission.

Safety and Adverse Events

Clinical trials have found no important differences between the BXM, oseltamivir, and placebo groups in the incidence of adverse events (AEs) [14, 17, 19, 23, 28]. In influenza subjects receiving BXM, AEs reported in at least 1% of adults and adolescents include diarrhea, bronchitis, nausea, sinusitis, and headache, and AEs reported in at least 5% of pediatric subjects include vomiting and diarrhea [12]. AEs of uncertain association reported during postmarketing use include disorder involved immune system, skin and subcutaneous tissue, gastrointestinal tract, and psychic system [12]. Although no developmental effects were observed in rats or rabbits receiving BXM, adequate and well-controlled studies in pregnant women are lacking [12]. Consequently, the use of BXM is not currently recommended during pregnancy.

Treatment-Associated Resistance

Treatment-emergent PA I38X-substituted viruses were detected in 2.2%, 9.7%, and 5% of BXM recipients in the phase 2, CAPSTONE-1, and CAPSTONE-2 trials, respectively [14, 15]. These substitutions emerged 3–9 days after treatment, occurring more often in A(H3N2) than A(H1N1), and were rare in influenza B virus infections [14, 15, 29]. These substitutions significantly reduced BXM susceptibility in vitro and had an impact on clinical virological outcomes (Table 2) [15, 29, 38]. In the FLAGSTONE trial conducted in hospitalized patients, a lower incidence of treatment-emergent PA I38X-substituted (2%) was observed in patients receiving BXM plus oseltamivir [19], consistent with the findings in a mouse model [39]. These results suggest that the combination reduces BXM resistance due to the synergistic effects of the 2 drugs [9]. Notably, the rate of PA I38X substitutions are higher in young children, raising concerns about the drug's suitability as monotherapy for pediatric treatment. In the miniSTONE-2 trial in which A(H3N2) infections predominated, the rates were 31.3% in children aged 1–5 years and 14.6% in children aged 5–12 years [17]. In another analysis of 2 pediatric studies conducted in Japan, the rates were 25% and 13%, respectively [28]. The PebbleSTONE trial is currently recruiting patients aged 1–12 years to evaluate the development of treatment-emergent BXM-resistant influenza viruses in children https://clinicaltrials.gov/study/NCT06094010.

Nationwide monitoring of BXM susceptibility was initiated in the 2017–2018 influenza season in Japan, where BXM has been most frequently used compared to other countries [40]. When incorporating the surveillance data from 2017 to 2025, BXM resistance was reported in 15 of 2194 A(H1N1)pdm09 (0.7%), 49 of 2169 A(H3N2) (2.3%), and 0 of 898 influenza B viruses (0%) [40]. The World Health Organization (WHO) Collaborating Centers have also reported data on BXM susceptibility from 2017 to 2020, with an arbitrary cutoff ≥3-fold increase from the median half-maximal effective concentration (EC_{50}) used for reporting viruses with reduced susceptibility to BXM. PA substitutions potentially associated with reduced susceptibility were detected in 101 of 45 121 viruses (0.2%), including PA I38T/F/M/S/L/V/K, E23G/K, A37T/A, E199G, M34I/V, L28P, and K34R/Q [41, 42]. Viruses with mixed substitutions at PA I38 and A37 were also identified [42]. A higher incidence of substitutions was observed in children [42–44].

Preclinical studies in ferrets confirmed that the PA I38T virus could transmit by respiratory droplets, despite somewhat lower fitness relative to the wild-type virus [45, 46]. In the BLOCKSTONE and CENTERSTONE trials, no transmission of resistant variants was documented [23, 26]. However, PA I38X variants have also been detected in individuals without BXM treatment. During the 2018–2019 influenza season in Japan, PA I38T-substituted influenza A viruses were first reported to be isolated from children without prior BXM exposure [47–50], including 3 infected by influenza A(H1N1)pdm09 and 5 infected by

Table 2. Antiviral Efficacy of Influenza Polymerase Inhibitors In Vitro and In Vivo

		Baloxavir Marboxil [5, 14]	Suraxavir Marboxil [30]	ZX-7101A [31,32]	ADC189 [64]	Pimodivir [33,34]	Onradivir [35]	Favipiravir [36,37]
In vitro								
EC_{50}	Influenza A(H1N1)pdm09	0.20–1.80 nM	0.41–2.33 nM	4.13 nM	N/A	1.8–2.8 nM	0.02±0.003 nM	0.83–22.5 μM
	Influenza A(H3N2)	0.35–1.90 nM	0.31±0.02 nM	1.03 nM	N/A	0.65–2.1 nM	0.01±0.0002 nM	0.45–0.6 μM
	Influenza B	3.30–13.00 nM	3.09±0.07 nM	N/A	N/A	N/A	>1 nM	0.57–5.3 μM
	HPAI	H5N1: 1.6±1.6 nM H5N2: 0.96 ±0.55 nM, H5N6: 0.73±0.53 nM H7N9: 0.80 ±0.36 nM, H9N2: 0.79–0.96 nM[a]	N/A	H7N9: 4.39 nM	N/A	H5N1: <1.5 nM	H5N6: 0.25 nM H7N9: 0.63–0.78 nM	H5N1: 1.3–5.2 μM H7N9: 8.9 μM
In adults and adolescents with uncomplicated influenza[b]								
Reduction of viral load by day 1	Infectious viral titer (compared to placebo)	−4.8 vs −1.3 $\log_{10}$ $TCID_{50}$/mL, $P < .05$	−2.7vs −1.6 $\log_{10}$ $TCID_{50}$/mL, $P < .05$	N/A	−1.5 vs −0.8 $\log_{10}$ $TCID_{50}$/mL, $P < .0001$	N/A	−0.87 vs −0.72 $\log_{10}$ $TCID_{50}$/mL, $P = .017$	US316: −0.8 vs −1.3 $\log_{10}$ $TCID_{50}$/mL; US317: −1.1 vs −1.7 h $\log_{10}$ $TCID_{50}$/mL
	Viral RNA load (compared to placebo)	~−1.7 vs −0.5 $\log_{10}$ virus particles/mL, $P < .005$	−2.2 vs −1.3 $\log_{10}$ copies/mL, $P < .05$	N/A	−2.3 vs −1.0 $\log_{10}$ virus copies/mL, $P < .0001$	N/A	−1.22 vs −0.69 $\log_{10}$ copies/mL, $P < .0001$	N/A
	Infectious viral titer (compared to oseltamivir)	−4.8 vs −2.8 $\log_{10}$ $TCID_{50}$/mL, $P < .05$	N/A	N/A	N/A	N/A	−0.87 vs −0.66 $\log_{10}$ $TCID_{50}$/mL, $P = .002$	N/A
	Viral RNA load (compared to oseltamivir)	~−1.6 vs −1.0 $\log_{10}$ virus particles/mL, $P < .05$	N/A	N/A	N/A	N/A	−1.22 vs −0.70 $\log_{10}$ copies/mL, $P < .0001$	N/A
Duration of virus detection	Infectious virus (compared to placebo)	24 vs 96 h, ↓75%, $P < .001$	22.0 vs. 46.9 h, ↓53%, $P < .001$	23.1/22.7 vs 24.9 h, ↓7.2/8.8%, $P < .001$[c]	22.0 vs 25.5 h, ↓14%, $P < .0001$	N/A	19.75 vs 23.20 h, ↓15%, $P < .0001$	US316: 47.5 vs 70.7 h, ↓75%, $P = .001$; US317: 47.7 vs 71.7 h, ↓33%, $P < .001$
	Viral RNA (compared to placebo)	N/A	N/A	43.2/41.4 vs 90.7 h, ↓52/54%, $P < .001$[c]	49.2 vs 101.7 h, ↓52%, $P < .0001$	↓18%	68.65 vs 88.62 h, $P < .0001$	US316: 100.1 vs 98.2 h; US317: 96.8 vs >120 h
	Infectious virus (compared to oseltamivir)	24 vs 72 h, $P < .001$	N/A	N/A	N/A	N/A	19.75 vs 22.44 h, $P < .0001$	N/A
	Viral RNA (compared to oseltamivir)	N/A	N/A	N/A	N/A	N/A	68.65 vs 86.03 h, $P < .0001$	N/A
Emergence of variants with reduced susceptibility		PA/I38T/M, 36/370 (9.7%)	PA/I38T, 3/351 (< 1%)	PA/I38T, 5/122 (4.1%)	PA/I38T/M, 16/389 (4.1%)	S337P, K376N/R, S324K/N/R, N510K, and T378S, 6/28 (21.4%)	PB2/S324R, N510T, M475I/I554del, I674M, A174D, K376Q, G74E, 8/419 (1.9%)	N/A

Table 2. Continued

		Baloxavir Marboxil [5, 14]	Suraxavir Marboxil [30]	ZX-7101A [31,32]	ADC189 [64]	Pimodivir [33,34]	Onradivir [35]	Favipiravir [36,37]
Fold change in susceptibility of influenza virus	Influenza A	I38T: 20–391 I38M: 4–29	A(H1N1): ~20	N/A	33–142	A(H1N1)	S337P: >372 K376R: 90 K376K/R: 9.4 S324K/N/R, N510K: 69 S324N: 45–60 S324S/N: 127 T378S: 240	N/A
	Influenza B	I38T: 5–15 I38M: 2–8	A(H3N2): ~10					
Impact on clinical and virological outcomes (compared to recipients without mutations)		Longer TTAS and sustained cessation of virus shedding	N/A	Delayed clearance of viral RNA	Longer TTAS	N/A	N/A	N/A

Abbreviations: EC_{50}, half-maximal effective concentration; HPAI, highly pathogenic avian influenza; N/A, not available; PA, polymerase acidic protein; PB, polymerase basic protein; $TCID_{50}$, 50% tissue culture infective dose; TTAS, time to alleviation of influenza symptoms.

[a]These data of baloxavir are 90% effective concentration.

[b]The data for baloxavir, suraxavir, ZX-7101A, ADC189, and TG-1000, onradivir, and favipiravir are derived from phase 3 trials, while the data for pimodivir are obtained from a phase 2b trial. Though the data for suraxavir are derived from a trial enrolling patients aged >5 years, approximately 95% of the participants are >12 years old. The data for ZX-7101A, pimodivir, onradivir, and favipiravir are derived from trials on adults.

[c]The values are presented as 40 group/80 mg group vs placebo group.

A(H3N2) [40]. Subsequently, a PA E23K mutant influenza A(H1N1)pdm09 virus with reduced susceptibility to BXM was also detected from a child without BXM treatment [40, 51]. In 2023, a community cluster of PA E199G mutant influenza A(H3N2) was detected in Japan, in which none of the 3 patients had received BXM before specimen collection [52]. These findings suggest that human-to-human transmission of BXM-resistant viruses is possible.

Although viruses with BXM-associated PA substitutions are uncommonly detected in circulating seasonal viruses, continuous monitoring and strategies to mitigate resistance remain crucial (see Takashita et al in this supplement [53]).

Suraxavir Marboxil

Suraxavir marboxil, also known as GP681, is a prodrug of GP1707D07, which selectively inhibits the CEN of influenza A and B viruses. The structural difference between suraxavir and BXM lies in the replacement of the morpholine ring with a 4-Oxa-7-azaspiro[2.5]octane moiety (Figure 2). Phase 1–3 clinical studies have been completed with positive results in adults and adolescents with uncomplicated influenza A and B [30, 54, 55], and the novel drug has been approved for marketing by the National Medical Products Administration (NMPA) of China.

Preclinical Studies

Suraxavir demonstrates potent antiviral activity against influenza A and B viruses in preclinical studies. In vitro, GP1707D07 exhibited nanomolar antiviral activity, comparable to that of BXM [30] (Table 2). GP1707D07 was also effective against oseltamivir- and pimodivir-resistant viruses. However, it showed a significant EC_{50} value increase against the BXM-resistant influenza A(H1N1)pdm09 virus carrying PA I38T substitution, indicating cross-resistance with BXM. In murine models, the antiviral efficacy of suraxavir was comparable to BXM and superior to oseltamivir [30].

Pharmacokinetics

The currently recommended dose for suraxavir is 40 mg. It displays linear pharmacokinetic characteristics and has a prolonged $T_{1/2elim}$ of 72–136 hours [30]. The mean blood concentration remains above the in vitro 90% effective concentration (EC_{90}) by day 5 (8.8 vs 6.9 ng/mL) [30]. A negative correlation exists between mean concentration in 24 hours and body weight, but dose adjustments based on weight are not currently recommended [30].

Clinical Efficacy

The phase 2 study in China enrolled adults with uncomplicated acute influenza (influenza A: 0.5% and influenza B: 99.5%) and randomized them to receive a single oral dose of suraxavir (20 or 40 mg) or placebo [55]. The median TTAS was significantly

shorter in both suraxavir groups compared with the placebo group (50 and 46.1 vs 82.3 hours). The subsequent phase 3 trial enrolled patients aged >5 years with uncomplicated acute influenza, including 39.4% with influenza A(H1N1), 59.1% with influenza A(H3N2), and 0.4% with influenza B [30]. The median TTAS was significantly shorter in the suraxavir group compared to the placebo group (42.0 vs 63.0 hours), with a reduction comparable to that observed for BXM [14, 30]. A subgroup analysis revealed significantly shorter TTAS in both adults (median difference, 17.5 hours) and adolescents/children (median difference, 26.0 hours). Suraxavir was also associated with significantly more rapid decrease in viral load by day 1 after administration and a shorter median time to viral RNA clearance (Table 2) [30]. Overall, single-dose suraxavir outperformed placebo in treating uncomplicated influenza. Several subsequent trials are ongoing, aiming to evaluate suraxavir treatment in high-risk patients with uncomplicated influenza and in children with uncomplicated influenza, as well as for PEP in HHCs [56–58].

Safety and Adverse Events

In the phase 3 trial, the incidence of AEs was similar between the suraxavir and placebo groups [30]. Among participants receiving suraxavir, the primary AEs included diarrhea (6.1%) and transient electrocardiographic abnormalities (sinus arrhythmia 4.8%, sinus bradycardia 2.5%), which were primarily classified as mild to moderate based on the Common Terminology Criteria for Adverse Events (CTCAE) grade and did not require treatment. Compared with adults, children are more likely to experience these AEs.

Treatment-Associated Resistance

In the phase 3 trial, 3 participants in the suraxavir group developed viruses with the PA I38T substitution, including 1 (0.7%) with influenza A(H1N1)pdm09 and 2 (0.9%) with A(H3N2) [30]. The substitution was associated with decreased sensitivity to suraxavir (Table 2). Compared to the BXM trials, suraxavir-associated substitutions have been detected less commonly. However, this conclusion should be interpreted cautiously due to the limited number of samples tested.

ZX-7101A

ZX-7101A is the prodrug of a novel CEN inhibitor, ZX-7101, that demonstrates broad-spectrum antiviral activity against influenza A, influenza B, and highly pathogenic avian influenza (HPAI) viruses in vitro. The structural difference between ZX-7101A and BXM is the replacement of the sulphur atom with selenium (Figure 2). The phase 1–3 trials have been completed and indicate that the drug is an effective and safe treatment for adults with uncomplicated influenza. ZX-7101A has been approved for marketing by the NMPA of China.

Preclinical Studies

ZX-7101 exhibited potent activity against many influenza A subtypes, influenza B, and HPAI A(H7N9) viruses (Table 2) [31]. ZX-7101A also demonstrated therapeutic efficacy in mice infected by influenza A(H1N1), including preventing death, decreasing viral RNA loads in lungs, and alleviating pulmonary damage [31]. One study in ferret models indicated that ZX-7101A exhibited superior antiviral efficacy compared to BXM [59].

Pharmacokinetics

The findings in the phase 1 study support 40 mg and 80 mg as single-dose regimens of ZX-7101A for adults, though the optimal dose has not been determined [59, 60]. Upon administration, ZX-7101A is rapidly metabolized into the active form, ZX-7101, which reaches C_{max} within approximately 3–4 hours [59]. ZX-7101A can be taken with or without food, though C_{max} decreases significantly when administered after a high-fat meal [59]. The $T_{1/2elim}$ of ZX-7101A ranges from 83.0 to 125.6 hours, which is longer than that of BXM [13, 59].

Clinical Efficacy

In a phase 2 trial, 177 adults with uncomplicated influenza were randomized to receive 40 mg or 80 mg ZX-7101A, or a placebo [61]. Compared to the placebo group, the median TTAS was significantly shorter in both ZX-7101A groups (40 mg/80 mg: 34.7/45.8 hours) compared with 63.6 hours in the placebo group [32]. Additionally, the ZX-7101A groups exhibited a faster decline in viral load and a shorter viral shedding duration. In a subsequent phase 3 trial enrolling 723 subjects, ZX-7101A demonstrated superiority over placebo in alleviating influenza symptoms (40 mg/80 mg: 48.4/39.4 hours, placebo: 62.9 hours) and reducing the median time of viral clearance (Table 2) [32]. Subgroup analysis revealed that the efficacy of ZX-7101A was superior in females, nonsmokers, subjects with A(H1N1) infections, participants with higher influenza symptom score (≥12), and subjects with earlier drug administration (≤24 hours) [32]. Further trials on the safety and efficacy of ZX-7101A in adolescents aged 12–18 years and children aged 5–11 years with influenza are ongoing [62, 63].

Safety and Adverse Events

In the phase 3 trial, the incidence of treatment-related AEs was similar in the ZX-7101A and placebo groups (8.1% vs 7.9%) [32]. AEs in the ZX-7101A group were predominantly classified as mild or moderate according to the CTCAE grade, with the most common ones being neutropenia and leukopenia [32].

Treatment-Associated Resistance

Virus with a PA I38T substitution was detected in 1 patient (5.9%) in the phase 2 trial and 5 patients (4.1%) in the phase 3 trial [32]. The variant was associated with delayed clearance

of viral RNA but not with prolonged TTAS [32]. Additionally, an in vitro drug resistance analysis identified an E18G substitution in an A(H1N1) P15 virus, which significantly reduced susceptibility to ZX-7101A [31]. However, this substitution has not been detected in patients to date.

ADC189

ADC189 is a novel CEN inhibitor in advanced clinical development. The structural difference between ADC189 and BXM is the replacement of the hydrogen atom with deuterium (Figure 2). In preclinical studies, ADC189 exhibited antiviral activity against influenza A, B, and HPAI viruses in vitro (Table 2). The single-dose regimen is 45 mg for individuals weighing 20–80 kg and 90 mg for those weighing >80 kg. After administration, the plasma ADC189 concentration remains above the EC_{90} for influenza B for up to 7 days, and above the EC_{90} for influenza A for up to 14 days. A phase 2 trial involving adults with influenza indicated that a single oral dose of 45 mg ADC189 had effects similar to those of other CEN inhibitors in terms of improving symptom relief and reducing viral load [65]. Subsequently, a phase 3 trial of adults and adolescents with uncomplicated influenza showed that ADC189 was associated with significantly shorter time to illness alleviation compared to placebo (50.0 vs 68.1 hours) [64]. The incidence of AEs was comparable between the two groups (35.0% vs 40.9%). An additional trial to assess the safety and efficacy of ADC189 in children aged 2–11 years with influenza is ongoing [65].

TG-1000

TG-1000 is the prodrug of TG-0527, a potent CEN inhibitor. In vitro studies revealed that TG-0527 was active against influenza A and B at nanomolar concentrations (0.35–3.10 nM and 2.75–11.90 nM, respectively) [66]. In murine models, TG-1000 demonstrated superior efficacy in reducing lung viral titers and improving survival rates compared to placebo [66]. The PK of TG-1000 exhibits nonlinear characteristics due to saturation of absorption. TG-1000 is usually administered as a single oral dose of 40 mg for patients weighing 40–80 kg and 80 mg for those weighing >80 kg. The drug is rapidly converted to TG-0527 by hydrolysis, which reaches its C_{max} within about 3.5 hours. In clinical trials, it was administered under a fasting condition due to declines in the area under the curve $(AUC)_{0-\infty}$ and C_{max} when taken with high-fat food [66]. TG-0527 is eliminated primarily through hepatic metabolism, with a $T_{1/2elim}$ of approximately 36 hours [66]. Phase 2 and 3 trials evaluating the efficacy and safety of TG-1000 in adults and adolescents with acute uncomplicated influenza have been completed in China [67]. Preliminary analysis from the phase 3 trial revealed that the median TTAS was significantly shorter in the TG-1000 group compared to the placebo group (60.9 vs 87.9 hours) (unpublished data) [68]. The incidence of AEs was comparable in both groups. The drug has been submitted to the NMPA of China for NDA, indicated for the treatment of uncomplicated influenza A and B infections.

PB2 CAP-BINDING DOMAIN INHIBITORS

Pimodivir

Pimodivir (VX-787, JNJ-63623872) is a cyclohexyl carboxylic acid analogue (Figure 2) [69]. It binds to the PB2 subunit and specifically targets the cap-binding site, thereby inhibiting the "cap-snatching" process required for initiating viral mRNA synthesis in influenza A viruses [33, 69]. Clinical development of pimodivir was halted in 2020 due to its lower-than-expected clinical benefits in hospitalized influenza patients when added to SoC oseltamivir treatment.

Preclinical Studies

In vitro studies demonstrated that pimodivir had antiviral activity against influenza A(H1N1)pdm09 and A(H5N1), as well as NAI- and amantadine-resistant strains (Table 2) [33, 69]. However, no significant antiviral activity was observed for influenza B viruses [11]. In vitro synergistic efficacy was observed when combining pimodivir with NAIs or favipiravir [33]. In mice with lethal A(H5N1) infection, pimodivir outperformed oseltamivir in reducing mortality and reducing lung viral titers.

Pharmacokinetics

The usual oral pimodivir dosing regimen in adults is 600 mg twice daily (BID) for 5 days. Upon administration, pimodivir reaches mean C_{max} of 1590 ng/mL within about 3 hours [70]. Steady-state plasma concentrations of approximately 1500 ng/mL are reached by day 3–4 [34, 71]. Pimodivir is metabolized by CYP3A4 and aldehyde oxidase and predominantly eliminated via feces (~95%) [11]. No dose adjustments are required for patients with renal insufficiency or elderly patients [73]. Other PK information is summarized in Supplementary Table 10.

Clinical Efficacy

In a phase 2a study of 140 volunteers inoculated with influenza A(H3N2) and a phase 2b study (TOPAZ) of 292 adults with uncomplicated influenza A infection (half with H1N1 and half with H3N2), pimodivir demonstrated more rapid alleviation of influenza symptoms. A synergistic effect was observed when combined with oseltamivir [34, 71]. A subsequent phase 3 study of 544 high-risk outpatients with influenza A found that pimodivir plus SoC treatment (85% oseltamivir) demonstrated a significantly shorter median time to resolution compared to placebo plus SoC (92.6 vs 105.1 hours) [73].

A phase 2 study (OPAL) enrolled 95 adults hospitalized with influenza A infection to receive either pimodivir plus oseltamivir or placebo plus oseltamivir; the median TTAS was numerically shorter in the pimodivir plus oseltamivir group compared to oseltamivir alone [74]. However, a phase 3 trial found that pimodivir plus SoC (oseltamivir) showed no added benefit

over placebo plus SoC, with no difference in the Hospital Recovery Scale at day 6 or in the median time to hospital discharge [73].

Safety and Adverse Events

In clinical trials, the most frequently reported treatment-emergent AE is diarrhea, which is usually mild or moderate in severity. Other AEs probably related to pimodivir included nausea, vomiting, elevations in transaminases, and neutrophil count decrease.

Treatment-Associated Resistance

In a phase 2b trial, PB2 substitutions with reduced susceptibility to pimodivir were detected in 9 patients, with 6 (21.4%) in the pimodivir 600 mg group (Table 2), 3 (10%) in the pimodivir 300 mg group, and none in the pimodivir 600 mg plus oseltamivir 75 mg group [34, 74]. In a phase 3 study on high-risk outpatients and hospitalized patients with influenza A infection, treatment-emergent substitutions in PB2 were observed in 2 (1.2%; S324I, and K376R plus N510K) and 4 (2.1%; S324I/N, K376R, and S324G plus K376R) patients, respectively, in the pimodivir plus SoC group [73]. Notably, the incidence of resistant variants was lower in patients receiving the combination of pimodivir and oseltamivir, similar to the findings with BXM and oseltamivir.

Onradivir

Onradivir was developed through structure optimization of pimodivir by introducing a cypropyl into position 6 of the pyrimidine ring and replacing the azazindole with azazindazole (Figure 2). Onradivir attains considerably improved antiviral activity compared to pimodivir [35]. Onradivir has been approved by the NMPA for treatment of adults with uncomplicated influenza in China.

Preclinical Studies

In vitro studies demonstrate that onradivir exhibits stronger antiviral activity against influenza A virus compared to pimodivir (Table 2) [35]. Additionally, onradivir is inhibitory for oseltamivir- and BXM-resistant strains and HPAI viruses. Combinations of onradivir and oseltamivir show in vitro synergy. In mice with influenza A infection, onradivir reduced virus titers in a dose-dependent manner and protected against mortality.

Pharmacokinetics

In the phase 1 and 2 clinical trials of onradivir, a single oral dose of 100–1200 mg was rapidly absorbed, with C_{max} attained within 0.5–2 hours [75, 76]. A high-fat meal has little effect on the drug levels. Onradivir is extensively bound to plasma protein (98.9%–99.9%) and is widely distributed in the human body. The plasma $T_{1/2elim}$ ranges from 12.1 to 35.0 hours, and onradivir is primarily metabolized by UDP-glucuronosyltransferases in the liver, with elimination of the drug or its metabolites through biliary excretion. Onradivir C_{max} and $AUC_{0-\infty}$ are considerably higher in those with mild or moderate hepatic impairment (Child-Pugh class A or B) compared to healthy controls [77], suggesting a need for dose adjustment. Other PK information is summarized in Supplementary Table 10.

Clinical Efficacy

In the dose-ranging phase 2 clinical trial in adults with acute uncomplicated influenza A infection, the median TTAS was 46.9 hours (200 mg BID), 54.9 hours (400 mg BID), and 40.1 hours (600 mg once daily [QD]) in the dose groups compared to 62.9 hours in the placebo group [76]. Consequently, the 600 mg QD dosage was selected for the phase 3 trial. The phase 3 trial enrolled a total of 750 participants and found that the median TTAS was shortened by 24.5 hours with onradivir (38.8 hours) compared to placebo (63.4 hours), and was similar to that of oseltamivir (42.2 hours) [78]. Compared historically to the pimodivir findings, the magnitude of the relative reduction in TTAS was larger (39% vs 13%). Additionally, onradivir significantly shortened the duration of detectable viral RNA and viral RNA load compared to placebo and oseltamivir.

Safety and Adverse Events

Onradivir is safe and generally well tolerated. In the phase 1 trial, 26% subjects experienced at least 1 mild or moderate drug-related AE, most of whom recovered completely within 24–72 hours [75]. The most frequent drug-related AEs were diarrhea (38%–75%), leukocytopenia (19%), and neutropenia (19%). In the phase 2 and 3 trials, the most common treatment-emergent AE was diarrhea, reported in 33%–65% and 49% of participants treated with onradivir, respectively [76]. No serious AEs were observed.

Treatment-Associated Resistance

In the phase 2 trial, I66T/V and N510I substitutions in the PB2 subunit were observed in 3 patients receiving onradivir [76]. The significance of the I66T/V substitution is unclear due to the polymorphism at locus 66, while the N510K substitution was related previously to pimodivir resistance [34]. In the phase 3 trial, the S324R substitution in PB2 was observed in 3 A(H3N2) isolates, but only 2 isolates exhibited resistance to onradivir in vitro [79]. Other substitutions in PB2 causing drug resistance- M475I/I554del, I674M, A174D, K376Q and G74E in A(H3N2) and N510T in A(H1N1)pdm09 viruses- were found once [79, 80]. Further studies on these substitutions and their clinical relevance are required.

CC-42344

CC-42344 is a novel PB2 inhibitor discovered though structure-based drug discovery [79]. It specifically occupies the cap-binding domain of PB2 and interacts with the highly conserved

residues, E361 and K376, on side chains [80], thereby blocking the binding of PB2 to m^7G cap. CC-42344 showed potent in vitro antiviral activity against a wide panel of influenza A strains with a low EC_{50} range of 0.1–9 nM, including seasonal and pandemic strains, as well as strains resistant to oseltamivir and BXM [80]. A completed phase 1 clinical study demonstrated favorable PK and safety profiles of oral CC-42344, and a phase 2a challenge study of oral CC-42344 is now recruiting [81].

Novel formulations for other routes of administration, including inhalation and intravenous, have been developed and showed promising results in preclinical studies. Inhaled CC-42344 demonstrated superior lung exposure, excellent safety, and strong efficacy in human lung epithelial cells infected with the influenza virus [79]. A phase 1 study of inhaled CC-42344 is planned.

PB1 RNA SYNTHESIS INHIBITORS

Favipiravir

Favipiravir (T-705), a pyrazine derivative (Figure 2), was first discovered in Japan through screening for anti–influenza virus compounds [82]. After entering host cells, favipiravir undergoes phosphoribosylation to become the active form, favipiravir ribofuranosyl-5′-triphosphate (favipiravir-RTP) [83]. It performs antiviral activity through 2 kinds of mechanism. First, favipiravir-RTP is a purine analogue and functions as a competitive substrate inhibitor of the viral RNA-dependent RNA polymerase (RdRp). It is incorporated into nascent RNA strand in competition with guanosine triphosphate and adenosine triphosphate, thereby inhibiting RNA elongation [36]. Second, it induces lethal mutagenesis by increasing the frequency of G→A and C→T mutations, resulting in nonviable viral progeny [84].

Favipiravir has been approved in Japan in 2014 and China in 2020 for the treatment of novel or reemerging influenza virus infections when other influenza antiviral drugs are ineffective or insufficiently effective [85].

Preclinical Studies

In cell culture, favipiravir inhibits the replication of seasonal influenza A, B, C, and D viruses, and HPAI A(H5N1) and A(H7N9) viruses, including those resistant to M2 inhibitors and NAIs (Table 2) [8, 36, 86]. In mice infected with influenza A(H5N1) and A(H7N9), favipiravir demonstrated dose-dependent efficacy in reducing lung viral titers and mortality [11]. A synergistic antiviral efficacy was observed between favipiravir and NAIs (oseltamivir and peramivir) [36]. In an immunocompromised nude mouse model with influenza A virus infection, both favipiravir monotherapy and combination therapy with oseltamivir provided extended survival compared to oseltamivir monotherapy [87].

Pharmacokinetics

Favipiravir exhibits high oral bioavailability (>95%), with no important effect of food on its absorption, and reaches its C_{max} within 2 hours after a single dose peroral [11]. It is primarily metabolized by and in turn inhibits aldehyde oxidase in the liver, so that loading doses are used to increase blood concentrations. The inactive oxidative metabolite (T-705M1) is eliminated mainly by renal clearance. The plasma $T_{1/2elim}$ of favipiravir is estimated to be approximately 4 hours. No significant PK interactions have been observed between favipiravir and oseltamivir. However, potential drug–drug interactions with acetaminophen, theophylline, pyrazinamide, and warfarin have been reported (Supplementary Table 10) [11, 88].

Favipiravir exhibits complex, nonlinear, and dose-dependent PK [89, 90], posing a great challenge in determining the optimal dosage. The initially approved dosage regimen in Japan was 1600 mg BID on day 1 and 600 mg BID thereafter (1600 mg/600 mg BID) [89]. However, the plasma concentration in participants in the United States were approximately 50% lower than those in Japan, raising concerns about the effects of body weight and ethnicity on favipiravir PK [90].

In a phase 2 dose-finding study of favipiravir in uncomplicated influenza (US204), patients with minimum plasma concentration (C_{min}) >19.5 μg/mL after the first 24 hours of treatment showed the shortest TTAS (unpublished data) [91, 92]. In another phase 2 study in uncomplicated influenza (US213), compared to the 2400 mg–600 mg–600 mg/600 mg 3 times daily dosage, the 1800 mg/800 mg BID dosage was more reliable in attaining a C_{min} ≥20 μg/mL 24 hours after the first dose (unpublished data). The 1800 mg/800 mg BID dosage was also superior in terms of antiviral efficacy [91, 92]. In 2 phase 3 trials of adults with uncomplicated influenza in the United States (US316 and US317), patients in the favipiravir arm received an 1800 mg/800 mg BID dosage over 5 days. Post hoc analysis revealed significant interindividual variability in favipiravir concentrations, with this dosage regimen failing to reach an average C_{min} >20 mg/L in 41%–43% of participants. In participants with average C_{min} <20 mg/L, the mean ratio of the metabolite T-705M1 to favipiravir was >2-fold higher, suggesting increased metabolism in these individuals [92].

In a phase 2a, dose-escalating study in patients hospitalized with severe influenza, C_{min} of favipiravir at both lower (1600 mg/600 mg BID) and higher (1800 mg/800 mg BID) dosages decreased significantly over time [93]. Modeling predicted that only 18.8% and 42.1% of patients on the lower- and higher-dose regimen, respectively, achieved a C_{min} ≥20 mg/L for >80% of the treatment duration. Simulation analysis suggested that dosing regimens of ≥3600 mg/2600 mg might be required for adequate concentrations [93]. The markedly lower C_{min} levels after several days of dosing raised the concern about increased metabolism in severely ill patients.

Because plasma concentrations vary widely among individuals and are affected adversely by disease severity, further studies are needed to better understand the dosing strategy of favipiravir, including the potential value of intravenous delivery. Data of tissue and intracellular concentrations of the active drug favipiravir-RTP are lacking, which could provide valuable insights for a more accurate pharmacokinetic profile [94].

Clinical Efficacy

Clinical studies have shown varying efficacy of favipiravir in the treatment of uncomplicated influenza. Two large phase 3 international trials enrolled adults with uncomplicated influenza. In US316, favipiravir significantly reduced the TTAS (84.2 vs 98.6 hours). In contrast, in US317, favipiravir did not significantly decrease the median TTAS (77.8 vs 83.9 hours). In both trials, favipiravir was associated with a more rapid decrease in viral titers by day 1 and a shorter time to cessation of virus detection [37]. Post hoc analysis of the 2 trials found that individuals reaching a C_{min} >20 μg/mL threshold had greater reductions in nasopharyngeal viral titers and lower viral titer AUCs [92]. However, in an earlier phase 2a pharmacokinetic study of favipiravir in severely ill patients, no significant association between C_{min} ≥20 mg/L on day 3 and viral load reduction was found [93]. Better understanding of the optimal dosage of oral favipiravir will be crucial for realizing its full effectiveness.

The efficacy of oral favipiravir in the treatment of severe influenza virus infection has not been fully elucidated [95]. A retrospective study enrolled 168 critically ill adult patients to receive favipiravir plus oseltamivir (23.8%) and oseltamivir monotherapy (76.2%) and found that combination therapy was associated with better clinical improvement on day 14 compared to oseltamivir alone (62.5% vs 42.2%). The proportion of patients with undetectable viral RNA on day 10 was also higher in the combination group (67.5% vs 21.9%). However, there was no significant difference in mortality between the 2 treatment groups (17.5% vs 28.1%) [96].

Safety and Adverse Events

Favipiravir is generally well tolerated in clinical studies. However, it is not recommended for patients with hyperuricemia, gout, or severe hepatic impairment due to the asymptomatic increase in serum uric acid and liver enzymes observed in clinical studies [11]. Other common AEs include diarrhea and neutropenia. Due to the risk of early embryonic death and teratogenicity observed in animal studies, favipiravir is contraindicated in women during pregnancy, delivery, and lactation. Men should take effective contraceptive during intercourse and avoid intercourse with pregnant women during treatment and for 7 days afterward [11, 89].

Treatment-Associated Resistance

Data on clinically significant favipiravir-resistant variants remain very limited. To date, despite the occurrence of amino acid substitutions in the PA, PB1, and PB2 subunits, no viruses with reduced in vitro susceptibility to favipiravir have been identified in isolates recovered from treated patients [97, 98].

PROTEIN–PROTEIN INTERACTION INHIBITORS

The subunits of influenza RdRp are stably bound through the PA–PB1 and PB1–PB2 interactions (Figure 1), which are also potential antiviral drug targets. In 2017, a pyrazolidine-3,5-dione derivative (PP7), which impaired the PB1–PB2 interaction, was identified through compound screening and showed inhibitory activity on influenza polymerase [99]. Many PA–PB1 interaction inhibitors belonging to different chemical classes have been identified as well [100]. Protein–protein interaction between influenza polymerase and host proteins also showed therapeutic opportunities. The inhibitors of PB1–RanBP5 interaction, responsible for the nuclear import of PB1, were found to strongly inhibit nuclear localization of PB1 and polymerase activity [101]. However, none of these inhibitors have progressed to clinical trials as yet and more preclinical studies are required to further validate their efficacy and safety.

CONCLUSIONS

In this review, we summarize recent developments in 3 classes of influenza polymerase inhibitors. The CEN inhibitors discussed in this article have shown promising results in completed clinical trials, with all 5 significantly speeding recovery in adults and adolescents with uncomplicated influenza (Supplementary Table 11). Compared to BXM, the other 4 novel inhibitors exhibit comparable antiviral efficacy against a broad spectrum of influenza viruses (Table 2), but direct head-to-head comparisons are lacking in clinical trials, especially with respect to antiviral efficacy and risk of emergence of resistant variants. In addition, the efficacy of these novel CEN inhibitors as monotherapies or in combination with other antivirals in hospitalized patients or children remains largely undetermined. Notably, though BXM is effective in prophylaxis, it cannot replace vaccination due to its short-lived protection, inability to induce immune memory and herd immunity, and potential for resistance development. The PB2 inhibitors exhibit potent antiviral activity against multiple influenza A virus strains but show negligible activity against influenza B viruses (Table 2). The first-in-class drug pimodivir showed some antiviral and clinical efficacy in outpatients with uncomplicated influenza A infection but, when added to oseltamivir, did not provide clinical benefit in hospitalized patients, leading to the cessation of its development. The novel PB2 inhibitor onradivir demonstrates more potent antiviral activity and apparently greater clinical efficacy in adults with uncomplicated influenza compared to pimodivir. The PB1 inhibitor favipiravir is a broad-spectrum antiviral for various

RNA viruses, including influenza. However, it has a complex PK and shows a large interindividual variability in plasma concentrations and inconsistent efficacy in adults with uncomplicated influenza. Currently, it is only recommended in Japan and China for the treatment of novel or reemerging influenza virus infections when other influenza antiviral drugs are ineffective or insufficiently effective.

Despite promising developments, we think that future studies should address the following considerations. First, the efficacy of these novel drugs should be explored in scenarios beyond uncomplicated influenza, including the treatment of children or hospitalized patients with severe influenza, and also in prophylaxis. The outcome measures used in clinical trials of BXM can serve as valuable references (Supplementary Table 11). Second, additional clinical studies are needed to investigate the combined efficacy of novel antivirals with existing treatments, particularly in populations at high risk of drug resistance, such as young children, immunocompromised hosts, and seriously ill patients including those with zoonotic infections. Third, as already being done for BXM and NAIs through the WHO's Global Influenza Surveillance and Response System, antiviral resistance, especially to CEN inhibitors, should be closely monitored in circulating human strains and in zoonotic influenza threats. Finally, novel formulations and routes of administration, such as inhalation or intravenous delivery, should be further explored, especially for drugs like favipiravir, where the efficacy of oral administration is variable because of inadequate drug exposure.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (http://jid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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