

Cap-dependent endonuclease inhibitors for adult patients with influenza: the use of baloxavir marboxil

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Abstract: Baloxavir marboxil (BXM) is a novel anti-influenza agent that developed in Japan and inhibit the cap endonuclease specifically, and suggested the more clinical effectiveness in influenza. BXM reduces viral shedding more than do neuraminidase inhibitors (NAIs), and its clinical efficacy is equivalent to that of NAIs but is superior to that of NAIs in the case of type B influenza. BXM does not demonstrate any issues with safety, and treatment with BXM reduces the incidences of complicating sinusitis and bronchitis. Prophylactic administration of BXM inhibits intrafamilial transmission of influenza although low susceptible viruses with a PA/I38X substitution are isolated with a certain frequency following administration of BXM. Finally, In influenza treatment for patients aged 12–19 years and for adult outpatients, BXM can be used with the same recommendation level as oseltamivir.

Keywords: Influenza virus, Clinical efficacy, Complications, Post-exposure preventive effects, Viral shedding

1. Introduction

Baloxavir marboxil (BXM) exerts an excellent antiviral effect by inhibiting influenza virus mRNA transcription at an early stage (Figure 1)[1, 2]. However, during treatment in some cases, a variant is isolated in which isoleucine, the 38th amino acid of cap-dependent endonuclease and the molecular target of baloxavir, which resides in the PA subunit of RNA polymerase and is essential for viral mRNA transcription, is substituted with another amino acid such as methionine, threonine, or aspartic acid (this variant, which is indicated to have low susceptibility, is hereafter referred to as “PA/I38X”); therefore, in Japan, the use of BXM have been involved uncertain recommendations[3, 4].

The world is currently experiencing an influenza epidemic for the first time in three seasons after COVID-19 pandemic, including Japan; in week 44 of 2023, more than 20 cases per sentinel site were reported. From fall to winter in 2023-2024 season, an increasing number of patients require early diagnosis and rapid treatment. The present mini review introduces Japanese views for the world on the use of BXM with reference to published clinical and epidemiological findings.

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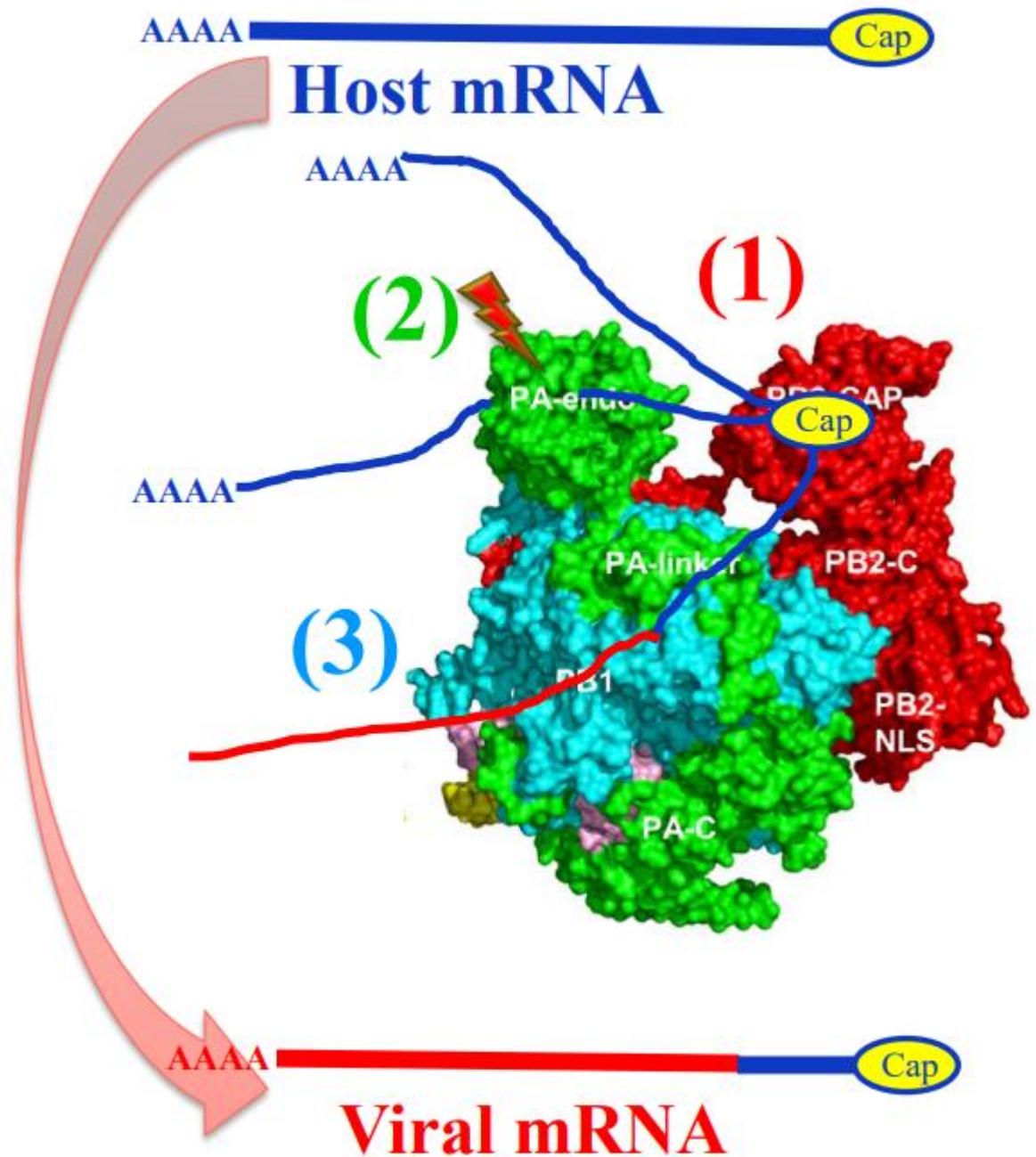


Figure 1. Structure of influenza A polymerase bound to the viral RNA promoter and the action mechanism of baloxavir marboxil (BXM). (1) Influenza virus catch the host mRNA that has cap structures at the binding domain comprising subunits PA, PB1 and PB2 subunits, (2) The PA endonuclease cut and snatch the cap structures from the host mRNA (so called 'cap snatching' process), and (3) viral mRNA had the cap structures finally to continue the viral replications in the host cell. BXM specifically inhibit the PA endonuclease and then stop the viral replication without side effects to the host cell.

2. Mini Review

2.1. Clinical efficacy (time to alleviation of symptoms) and antiviral efficacy

In a randomized controlled trial (RCT) conducted with 2,184 patients aged 12–65 years or older with influenza (H3N2 48%, H1N1 7%, B 42%, mixed/unidentified 3%) which

included patients at high risk of severe influenza, treatment with BXM shortened the time to alleviation of symptoms to the same degree as oseltamivir in comparison to a placebo in analysis of all patients and patients with type A (H3N2) influenza. In a sub-analysis of type B viral infection, BXM significantly shortened the time to alleviation of symptoms compared to oseltamivir (median 74.6 hours vs 101.6 hours) [5].

Japanese post-marketing surveillance of 3,094 patients (2,198 patients aged ≥ 12 years) confirmed that BXM rapidly improved clinical symptoms and was safe regardless of age group or virus type [6]. Other Japanese studies have also found that the times to resolution of fever and the improvement of clinical symptoms were faster with BXM than with NAIs [7, 8].

In a meta-analysis [1, 5, 9] of three RCTs conducted with a total of 3,771 patients (including one RCT which included 173 pediatric patients aged < 12 years), compared to oseltamivir, baloxavir shortened the symptomatic period (difference not significant) in addition to significantly reducing post-administration viral titer and RNA volume regardless of age group. In addition, adverse events occurred less frequently along adolescents/adults who were treated with BXM (OR 0.82, 95% CI: 0.69–0.98) [10].

In a network meta-analysis (NMA; a technique which uses relative effect assessment of results from multiple studies to analyze comparisons between two drugs indirectly when direct comparisons are unavailable) of a high-risk group and of a low-risk group of patients without complications, BXM demonstrated a clinical efficacy equivalent to that of oseltamivir and all other NAIs, and it was superior to all NAIs in terms of viral titer reduction in the high-risk group [11].

In an analysis of the therapeutic effects of single-dose treatment with BXM, peramivir, and laninamivir via NMA of 12 RCTs, the times to symptom improvement and resolution of fever were shortest with peramivir and BXM, respectively, while BXM yielded the greatest reduction in viral shedding at 24 and 48 hours [12].

In a recently reported Japanese systematic review and meta-analysis, in two RCTs conducted with outpatients, BXM produced significant reductions in viral titer and RNA volume, a reduction in adverse events, and a trend towards shorter disease duration than did oseltamivir [13].

2.2. Post-exposure preventive effects and inhibition of transmission of viruses with low susceptibility to NAIs

In a multicenter double-blinded study of preventive effects in 752 participants exposed to 545 index cases living in the same households as them, the influenza incidence rate by day 10 post-exposure was 1.9% in the BXM group versus 13.6% in the placebo group, thus demonstrating a marked preventive effect (86% onset prevention effect) [14].

Among 25 patients (median age 13 years, range 1–25 years) in a cluster of influenza cases caused by the A(H1N1)pdm09NA/H275Y variant that continuously occurred during prophylactic administration of oseltamivir in a long-term nursing care pediatric ward, changing to BXM resolved the cluster infection, and 13 of the patients demonstrated rapid resolution of fever [15].

2.3. Inhibition of onset of related complications

In the previously-cited RCT conducted with high-risk patients [5] and a meta-analysis of 21 RCTs [16], BXM significantly inhibited complicating sinusitis and bronchitis compared to a placebo. Hospitalizations and complicating pneumonia also decreased in both analyses, but these differences were not significant.

2.4. PA/I38X substitutions

PA/I38X-substituted strains are unlikely to greatly diminish the clinical efficacy of BXM. However, In an analysis of patients who were treated with baloxavir during the 2018/19 season (n = 81, ages 9–87 years) conducted by the Japan Physicians Association,

PA/I38X substitutions were detected 3–4 days after administration in 6.2% of patients with A/H3N2, but the presence of this substitution did not affect time to resolution of fever [17]. In addition, the spread of PA/I38X-substituted strains has not yet been observed in the community [18].

3. Conclusions

As the above shows, BXM exerts a therapeutic effect equivalent to that of NAIs in cases of type A influenza virus infections among adolescents (age ≥ 12 years) and adults, is highly likely to have a superior therapeutic effect on type B influenza, and demonstrates antiviral activity superior to that of NAIs in all studies examined here. These data suggests that BXM can be recommended at the same level as oseltamivir as a therapeutic for influenza in adolescents (age 12–19 years) and adults.

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