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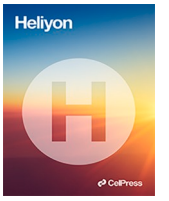

Research article

Adherence and recommended optimal treatment to Azvudine application for the treatment of outpatient COVID-19 patients: A real-world retrospective study

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ABSTRACT

Background: Azvudine was approved for the treatment of coronavirus disease 2019 (COVID-19) in China and has been widely used since the outbreak in December 2022. However, real-world research on the adherence of Azvudine is lacking. Additionally, limited research exists on determining the optimal duration for Azvudine treatment.

Methods: We studied adult patients with COVID-19 who got Azvudine or supportive treatment at an outpatient department between December 19, 2022 and January 5, 2023. The enrolled patients were divided into two groups: the Azvudine group, which received Azvudine, and the control group, which only received supportive care. We recorded their information and analyzed it using descriptive statistics. The primary outcome of this study was the compliance of outpatients with Azvudine, and the secondary outcome of this study was the optimal duration of Azvudine. Inverse probability weighting (IPW) was used to address the imbalance between groups when comparing the optimal duration of Azvudine, and Cox regression to evaluate the effect of Azvudine on the 28-day disease progression rate.

Results: We enrolled a total of 882 patients, of which 382 received Azvudine. Among the patients, 94.0 % (359) had good compliance, and non-compliance was primarily attributed to dosage errors. Azvudine appeared to have a beneficial therapeutic effect when administered for at least 7 days.

Conclusions: Outpatients have relatively good compliance with Azvudine, and optimal therapeutic effects were observed with the recommended duration of at least 7 days.

1. Introduction

The global pandemic of COVID-19 has posed tremendous challenges to healthcare systems of various countries. Since the onset of

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COVID-19, the Chinese government has implemented a series of effective measures to control the pandemic. As the virulence of the strains weakened, China significantly relaxed its prevention and control strategies in December 2022, leading to the spread of the Omicron variant in major Chinese cities [1]. During this period, 85 % of people in mainland China were infected with symptomatic COVID-19 [2].

Antivirals are considered one of the most effective strategies to deal with the COVID-19 pandemic and reduce hospitalization, critical illness, and death [3–5]. Azvudine, known as FNC or 2′-deoxy-2′-β-fluoro-4′-azidocytidine, is the first oral medication developed in China to fight against COVID-19. It was approved in China in July 2022 and has been widely used during this pandemic [6]. Azvudine is a prodrug that can be converted into active triphosphate within cells by cellular kinases, and effectively inhibits the in vivo replication of SARS-CoV-2 by inhibiting viral RNA-dependent RNA polymerase [7]. Studies indicated that Azvudine might cure COVID-19 patients through the thymus-homing feature and immunity promotion [6,7].

Previous studies have suggested that it might reduce viral load and shorten the time of the nucleic acid negative conversion (NANC) in mild and common cases [8,9]. Many clinical trials have studied the effectiveness and safety of Azvudine, and also discovered that it could accelerate the elimination of the virus and consequently reduce the treatment time, as well as the mortality of individuals [8,10]. And a recent study showed that Azvudine treatment showed substantial clinical benefits in hospitalized COVID-19 patients compared with Nirmatrelvir-Ritonavir [11]. Due to the emergency authorization of this drug by the Chinese government, there is currently limited research on its duration. It is unclear as the instructions and guidelines only mention a treatment duration of no more than 14 days [12,13]. Therefore, we assessed patient compliance and the optimal duration of Azvudine use.

2. Materials and methods

2.1. Study design

This retrospective study included outpatients who tested positive for SARS-CoV-2 and received COVID-19 treatment at the fever clinic and emergency department of a tertiary hospital. The study period extended from December 19, 2022 to January 5, 2023. Inclusion criteria included adult outpatients with mild to moderate disease, as defined by the WHO severity scale [14]. The patients were required to have a follow-up period of at least 28 days. The enrolled patients were divided into two groups: the Azvudine group, which received Azvudine, and the control group, which only received supportive care.

2.2. Data source

The necessary variables were collected through the hospital's HIS system and follow-up visits, including demographic data (age, gender, etc.), clinical data (symptom score, comorbidities, etc.), medication-related data (dosage, duration), 28-day disease progression rate (COVID-19-related admission or death from any cause), etc.

2.3. Outcomes

2.3.1. Compliance

The primary outcome of this study was the compliance of outpatients with Azvudine, defined as the percentage of individuals whose Azvudine dosage and treatment duration align with the prescription information for Azvudine.

2.3.2. Optimal duration

The secondary outcome of this study was the optimal duration of Azvudine, which refers to the duration of continued Azvudine intake that resulted in improved 28-day disease progression rate, including overall mortality and hospitalization.

2.4. Statistical analysis

Descriptive statistics were used to summarize the demographic and clinical characteristics, presented as the median with interquartile range (IQR) values, and frequencies expressed as a number (%). $\chi 2$ exact methods were used for the analysis of categorical variables, and the Mann-Whitney test was used for the analysis of continuous variables, comparing the baseline characteristics of the two groups. We used the inverse probability weighting (IPW) method to address the imbalance between the Azvudine group and control group. Cox regression was employed to analyze the effect of duration on the 28-day disease progression rate, the results were presented as adjusted hazard ratios (aHR) with their corresponding 95 % confidence intervals (CI), and the log-rank test was used to determine statistical significance. For all analyses, we considered $p < 0.05$ as statistically significant. We conducted all the analyses using R version 4.2.2.

3. Results

3.1. Descriptive characteristics

From December 19, 2022 to January 5, 2023, a total of 1166 consecutive patients with mild to moderate COVID-19 received prescriptions for Azvudine or other symptomatic drugs in the outpatient department of tertiary hospital. A total of 284 patients were

excluded due to lack of information of the time from symptom onset to treatment. Therefore, the present analysis included 882 patients, among whom 382 took Azvudine. The demographic and clinical characteristics of the patients taking Azvudine were shown in Table 1. Of the participants, 54.1 % were male, with a median age of 64 years (interquartile range, IQR: 48–74), and the majority (95.6 %) belonged to the Han nationality. Additionally, 67.5 % of participants were vaccinated against SARS-CoV-2, and the median time from symptom onset to treatment with Azvudine was 6 days (IQR: 3–10). At the time of presentation, the median number of COVID-19 related symptoms was 3 (IQR: 2–5) and 63.0 % of patients had viral pneumonia.

3.2. Compliance to Azvudine in outpatients

The recommended dosage of Azvudine is 5 mg (5 tablets) once a day for up to 14 days for the treatment of COVID-19. A total of 23 (6.0 %) patients did not comply with the recommended dosage or treatment regimen (Table 2). Among all patients, their mean therapeutic dosage was 4.8 ± 0.7 mg per day. Among the 22 participants who did not follow the recommended dosage of Azvudine, their mean dosage was 2.4 ± 1.1 per day. 4 patients switched to correct dose after taking the wrong dose for several days.

Prescriptions are valid for no more than 14 days. Among all patients, the mean duration of their treatment was 5.2 ± 2.7 days, with a maximum of 20 days and a minimum of 1 day. The duration of treatment exceeded the recommended 14 days in 3 patients, which was irrational.

3.3. Optimal duration of Azvudine treatment

To further explore the optimal duration, we analyzed the effect of different treatment duration of Azvudine on the 28-day disease progression rate of COVID-19 infection compared with the control group. The Azvudine group only included 359 patients whose medication met the current recommendations of the Azvudine label, while the control group consisted of 500 patients who received supportive care. There was significant difference in the clinical characteristics in the groups of different duration of Azvudine compared to control group. So IPW was implemented in each comparison. After IPW, baseline characteristics were well-balanced (all $p > 0.05$) (Appendix Table S1 and Table S2).

When the duration of Azvudine was less than 7 days, there was no statistically significant difference in 28-day disease progression rate compared to the control group (aHR: 0.292, CI: 0.081–1.056, $p = 0.060$, Table 3). However, when the duration of Azvudine treatment reached 7 days, a statistically significant reduction in the 28-day disease progression rate was observed compared to the control group (aHR: 0.184, CI: 0.058–0.581, $p = 0.004$).

4. Discussion

At present, the effectiveness of Azvudine in treating COVID-19 has been reported, and it has been widely used in China. However, there is no study on the adherence of this drug. Furthermore, due to its emergency approval, there is a lack of research on specific details regarding the treatment duration. In our study, we included 882 outpatients, out of which 382 patients utilized Azvudine. We conducted an analysis focusing on the adherence to Azvudine among these patients in real-world settings. At the same time, we used real-world data to analyze the optimal duration of Azvudine.

In this study, we found that the compliance of outpatients with Azvudine reached 94.0 %. This finding indicates that many patients

Table 1
Baseline characteristics of the Azvudine group.

Characteristic	Azvudine (N = 382)
Gender, male, n[a] (%)	207 (54.1)
Age, median (IQR[b])	64 (48–74)
Age ≥60 years, n (%)	220 (57.5)
Obesity, n (%)	163 (42.6)
BMI, median (IQR)	24.2 (22.0–27.1)
Vaccination against SARS-CoV-2, n (%)	258 (67.5)
Minorities, n (%)	17 (4.4)
Number of patients with comorbidities, n (%)	213 (55.7)
Comorbidities	
Smoke, n (%)	39 (10.2)
Hypertension, n (%)	157 (41.0)
Diabetes, n (%)	88 (23.0)
Cardiovascular diseases, n (%)	79 (20.6)
Lung disease, n (%)	31 (8.1)
Immunodeficiency, n (%)	17 (4.4)
Renal disease, n (%)	7 (1.8)
Time from symptom onset to treatment, days, median (IQR)	6 (3–10)
Number of symptoms at presentation, median (IQR)	3 (2–5)
Viral pneumonia at presentation, n (%)	241 (63.0)

[a] n = number.
[b] IQR = interquartile range.

Table 2
Use of Azvudine.

Characteristic	Azvudine (N = 382)
dosage of Azvudine	
Dosage (mg), mean (SD[a])	4.8 (0.7)
Rational dosage, n (%)	364 (95.3)
Irrational dosage (mg), mean (SD)	2.4 (1.1)
Irrational dosage, n (%)	22 (5.8)
1 mg qd, n (%)	11 (2.9)
2 mg qd, n (%)	4 (1.0)
3 mg qd, n (%)	8 (2.1)
4 mg qd, n (%)	2 (0.5)
Duration of Azvudine	
Duration, days, mean (SD)	5.2 (2.7)
<7 d, n (%)	222 (58.1)
7–14 d, n (%)	157 (41.1)
>14 d, n (%)	3 (0.79)

[a] SD: Standard deviation, d: day.

Table 3
The effects of different courses of Azvudine on 28-day disease progression in outpatients with COVID-19.

Days of continuous use of Azvudine	HR[a](HR$_{025}$-HR$_{975}$)	p-Value	Adjusted HR (HR$_{025}$-HR$_{975}$)	Adjusted p-Value
≤ 3d	0.343 (0.045–2.611)	0.302	0.212 (0.027–1.651)	0.139
≤ 4d	0.280 (0.037–2.132)	0.219	0.192 (0.025–1.491)	0.117
≤ 5d	0.355 (0.081–1.562)	0.171	0.211 (0.046–0.962)	0.044
≤ 6d	0.504 (0.145–1.755)	0.282	0.292 (0.081–1.056)	0.060
≤ 7d	0.405 (0.133–1.232)	0.111	0.184 (0.058–0.581)	0.004
≤ 14d	0.394 (0.130–1.197)	0.100	0.178 (0.056–0.566)	0.003

[a] HR = hazard ratio.

were able to apply the indicated dosage and treatment. Of the patients who did not use the medication correctly according to recommendations, part of the error was attributed to inadequate doses, especially when patients arbitrarily changed the medication dosage. This might have been linked to patients' insufficient knowledge about Azvudine and casual use. Healthcare providers should educate patients on the correct dosage and duration of Azvudine. Compared to other effective antiviral drugs, such as Paxlovid, the Greek study found that compliance was 97.5 %, which was attributed to patients voluntarily stopping treatment two or three days after starting treatment due to significant clinical improvement (doctors recommended 5 days of treatment) [15].

As Azvudine was granted emergency approval, its optimal duration of treatment has not been thoroughly studied. Based on our research findings, Azvudine appears to have a beneficial therapeutic effect when administered for at least 7 days. While the 5-day duration showed some effectiveness ($p = 0.044$), the p-value was close to the critical value, and the 6-day duration ($p = 0.060$) produced inconsistent results, suggesting instability. However, when the duration of treatment reached 7 days, a significant statistical difference was observed and maintained stability. Therefore, we recommend administering Azvudine for a period of at least 7 days to achieve optimal therapeutic outcomes.

Additionally, we noted in the drug instructions a stipulated duration of use not exceeding 14 days. There is no literature indicating that extending the application of Azvudine beyond 14 days would cause harm to patients, such as an increase in adverse reactions. Moreover, Azvudine was previously approved for long-term treatment of HIV at a 3 mg dosage, suggesting the drug's relative safety for extended use [16]. Nevertheless, as Azvudine exerts its effectiveness by inhibiting viral replication, its efficacy may diminish with usage beyond 14 days. In our study, only three patients continued usage beyond this timeframe, and we did not observe significant adverse events. But the limited sample size precludes more definitive conclusions.

Previous research has found that the incidence of side effects after taking Azvudine was 16.12 %, mainly including dizziness and nausea [7]. Other clinical trials have also found headaches, elevated liver enzymes, and elevated D-dimer [8,10]. While serious adverse reactions associated with Azvudine were rarely reported, it's important to note that the sample size may have contributed to this observation. Physicians should pay close attention to adverse reactions related to Azvudine, and more research on its safety is needed.

In addition to dosage and treatment duration, the details of Azvudine application also focus on the timing of dosing initiation. In our study, the median time from symptom onset to treatment with Azvudine was 6 days (IQR: 3–10). Although an optimal start time could not be obtained, this may suggest clinical benefit in patients beyond 5 days. A retrospective study of COVID-19 patients with comorbidities found that Azvudine showed significant clinical benefit over Paxlovid in patients treated more than 5 days after onset of illness [17].

Our research had several limitations. Firstly, this was a single-center study, so the assessment of adherence and clinical outcomes related to the use of Azvudine were based exclusively on samples from our hospital Additionally, as our hospital is a well-known tertiary hospital in China, the findings may not fully reflect the national level of adherence to this drug. Various medical institutions should focus on providing patient medication education and guidance, especially for new drugs like Azvudine. Secondly, in

terms of the study on the optimal treatment regimen, the retrospective nature of the study design might introduce limitations. Therefore, further studies are needed to validate the results.

5. Conclusions

Outpatients have relatively good compliance with the use of Azvudine. Administering Azvudine for at least 7 days appeared to be necessary to achieve optimal therapeutic outcomes. More high-quality research should be conducted to substantiate this conclusion.

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Ethical approval

This study was approved by the institutional review board of Beijing Chao-Yang Hospital (Ethics Approval: 2023-1-29-1). Due to the study's retrospective design, the requirement for informed consent was waived in accordance with local regulations and policies.

Data availability statement

The datasets generated and/or analyzed during the current study are not publicly available considering the privacy or ethical restrictions but are available from the corresponding author on a reasonable request.

CRediT authorship contribution statement

Hui Yang: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Ying Zhang:** Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Zhaojian Wang:** Investigation. **Man Xu:** Investigation. **Yushu Wang:** Investigation. **Yi Zhang:** Investigation. **Xin Feng:** Writing – review & editing, Methodology. **Zhuoling An:** Writing – review & editing, Supervision, Project administration, Methodology.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e30619.

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