Efficacy and safety evaluation of Azvudine in the treatment of COVID-19 based on four phase III clinical trials.

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Abstract

Azvudine was included into the Guidelines for the Diagnosis and Treatment of Coronavirus Disease 2019 (version ninth) issued by the National Health Commission and National Administration of Traditional Chinese Medicine announced on August 9, 2022. Numerous domestic public hospitals introduced Azvudine to copy with the current omicron wave of the COVID-19 pandemic by the end of 2022. In the study, we comprehensively evaluated the efficacy and safety of Azvudine using the clinical data from four phase III clinical trials.

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Abstract

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Keywords: Azvudine; efficacy; safety; COVID-19; phase III clinical trial.

To the editor:

Azvudine as a synthetic nucleoside analog was used to treat adult patients with plasma HIV-1 RNA more than 100,000 copies/ml through combination of another nucleoside reverse transcriptase inhibitor (NRTI) or non-nucleoside reverse transcriptase inhibitor (NNRTI). Azvudine inhibits RNA-dependent RNA polymerase (RdRp) after phosphorylation, leading to discontinuation of DNA chain synthesis in viruses.[1] Azvudine (Henan Sincere Biotechnology Co., Ltd., Pingdingshan, Henan Province, China) was approved by the National Medical Products Administration (NMPA, Beijing, China) for the treatment adult HIV-1-infected patients on July 21, 2021. Moderate coronavirus disease 2019 (COVID-19) was added into the indications of Azvudine to resist the COVID-19 omicron wave, and this application was conditionally approved by NMPA on July 25, 2022. The National Health Commission and National Administration of Traditional Chinese Medicine announced on August 9, 2022 that Azvudine was included into the Guidelines for the Diagnosis and Treatment of Coronavirus Disease 2019 (version ninth). The recommended oral dose of Azvudine for the treatment of moderate COVID-19 is 5 mg once daily, and the duration of Azvudine treatment should not exceed 14 days.[2]

By the end of 2022, numerous domestic public hospitals introduced Azvudine to copy with the current omicron wave of the COVID-19 pandemic. 113 community hospitals admitted Azvudine as a prescription drug in the treatment of COVID-19 on January 3rd, 2023. However, most of clinician are unclear about the efficacy and safety of Azvudine. Here, we comprehensively evaluated it using the clinical data from four phase III clinical trials.

The three phase III clinical trials were carried out in China, Russia, and Brazil. In China, the phase III clinical trial was registered in the Chinese Clinical Trial Registry (ChiCTR2000032769; registration date: May 9, 2020; website:*https://www.chictr.org.cn/showproj.aspx?proj=53368*), and the clinical trial was simultaneously registered in the International Clinical Trials Registry Platform (NCT04425772; registration date: May 9, 2020;*https://trialsearch.who.int/Trial2.aspx?TrialID=NCT04425772*). The randomized, double-blinded, parallel-controlled clinical trial was carried out in Beijing Ditan Hospital affiliated to Capital Medical University (Beijing, China) from June 2020 to March 2022. The sponsor was Henan Sincere Biotechnology Co., Ltd.. A total of 348 COVID-19 patients were enrolled in the study, and the patients were randomly assigned to the Azvudine group or control group with a 1:1 ratio. The patients in the Azvudine group received oral Azvudine tablets (5 mg once daily) plus standard treatment, and the patients in the control group received Azvudine dummy tablets (placebo) and standard treatment. The duration of treatment in both the two groups was less than 14 days. The primary efficacy outcome was the change (reduction) in viral load from baseline on day 7 and 14. Among the patients with viral load [?] 3log10 copies/ml, the reduction in viral load from baseline on day 3, 5, and 7 in the Azvudine group was higher than that in the placebo group. However, only the difference in the reduction in viral load from baseline on day 5 between the Azvudine group and placebo group was statistically significant (Figure 1). The result was similar to that in the patients with viral load [?] 4log10 copies/ml. In addition, 341 subjects were involved in safety analysis. 62 subjects experienced 119 adverse events (AEs) in the Azvudine group, while 76 subjects experienced 175 AEs in the placebo group. Most of AEs were evaluated as grade 1 or grade 2 according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 of the National Cancer Institute. One patient experienced an AE evaluated as grade 3 in the Azvudine group, and 3 AEs evaluated as grade 3. No AE evaluated as grade 4 or serious AE occurred. There was no significant difference in the incidence or severity of AE between the Azvudine group and placebo group.[3]

In Russia, the phase III clinical trial was approved by the Russian Ministry of Health (*http://www.minzdravsoc.ru*) in January 2021, and was initiated in June 2021. The results of the two phase III clinical trial performed in China and Russia were disclosed in detail by Fujie Zhang on the 17th National Infectious Diseases Conference, which was hosted by the Chinese Medical Association in Anhui, China.[3] Fujie Zhang, as a chief physician in the Beijing Ditan Hospital affiliated to Capital Medical University, was also the principal investigator (PI) in the Chinese phase III clinical trial. In addition, the results of the phase III clinical trial performed in Russia were recorded into the package insert of Azvudine manufactured by Henan Sincere Biotechnology Co., Ltd. using Chinese language. A total of 314 patients with moderate COVID-19 were enrolled as the full analysis set (FAS) in the study, and the patients were randomly assigned

to the Azvudine group or control group with a 1:1 ratio. The primary efficacy outcome was the median time to improvement in clinical condition and the proportion of improvement in clinical condition on day 7. 279 patients were eligible according to inclusion and exclusion criteria, and were included into the per protocol set (PPS), which consisted of 141 subjects in the Azvudine group and 138 subjects in the control group. The mean baseline age was 48 years. 39% and 61% of subjects aged 18 ˜ 45 years and 45 ˜ 65 years (including 45 years), respectively. Male subjects and female subjects accounted for 43% and 57%, respectively. There was no significant difference in the demographic or clinical characteristics between the Azvudine group and control group. As shown in Table 1, Azvudine significantly elevated the proportion of improvement in clinical condition and reduced the median time to improvement in clinical condition compared to placebo in both FAS and PPS. With regard to the safety, 62 patients underwent 119 AEs in the Azvudine group, and 76 patients underwent 175 AEs in the placebo group. Most of the AEs were determined as grade 1 or grade 2 according to CTCAE version 4.03. Only one serious AE occurred in the placebo group, and no serious AE occurred in the Azvudine group. There was no statistically significant difference in the frequency or severity of AEs between the Azvudine group and placebo group.[3]

In Brazil, two phase III clinical trials for Azvudine were registered in the International Clinical Trials Registry Platform (NCT05033145 and NCT04668235). Of which, one was performed in patients with mild COVID-19, and the other one was performed in patients with moderate COVID-19. The results were detailedly disclosed in the preprints published on the Research Square platform (*https://www.researchsquare.com*), and showed that Azvudine significantly reduced the time of nucleic acid negative conversion (NANC) as well as the viral load of the patients compared to placebo.[4,5]

Taken together, Azvudine could decrease the time of NANC, viral load, and median time to improvement in clinical condition, and increase the proportion of improvement in clinical condition on day 7 in the patients with COVID-19. In addition, Azvudine exhibited good safety and well tolerance as compared to placebo. In summary, Azvudine was effective and well-tolerated in the treatment of mild and moderate COVID-1.

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Abbreviations

NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; NMPA, National Medical Products Administration; RdRp, RNA-dependent RNA polymerase; COVID-19, coronavirus disease 2019; AE, adverse events; CTCAE, Common Terminology Criteria for Adverse Events; PI, principal investigator; FAS, full analysis set; PPS, per protocol set; NANC, nucleic acid negative conversion.

Statements

Ethics approval statement

NA.

Patient consent statement

NA.

Permission to reproduce material from other sources

NA.

Data availabilitystatement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Conflict of interest disclosure

The authors declare that they have no competing interests.

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Authors' contributions

NA.

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Table 1. The median time to improvement in clinical condition and the proportion of improvement in clinical condition on day 7 after administration of Azvudine and placebo.

Parameters	Full analysis set	Full analysis set	Per protocol set	Per protocol set
	Azvudine	Placebo	Azvudine	Placebo
N (missing)	157 (0)	157 (0)	141 (0)	138 (0)
Endpoint (%)	138 (87.90)	136 (86.62%)	137 (97.16%)	136 (98.55%)
Censoring (%)	19 (12.10)	21 (13.38%)	4 (2.84%)	2 (1.45%)
Improvement	57 (36.31%)	15 (9.55%)	57 (40.43%)	15 (10.87%)
No Improvement	100 (63.69%)	142 (90.45%)	84 (59.57%)	123 (89.13%)
P value	< 0.001	< 0.001	< 0.001	< 0.001
Mean time	10.00	13.00	10.00	13.00
P value	< 0.001	< 0.001	< 0.001	< 0.001

Note:

1. The clinical data were obtained from the package insert of Azvudine manufactured by Henan Sincere Biotechnology Co., Ltd..

2. The missing values in the primary efficacy outcome was imputed using a worst value method.

3. Clinical condition was determined according to the WHO Ordinary Clinical Progression Scale (Jun/2020), Score 4 to 10. The data was acquired according to the WHO score between day 1 and day 31.

4. The time to improvement in clinical condition was calculated in terms of the first time improvement in clinical condition emerged, which was determined by a decrease of [?] 2 in the WHO score. The patients without any improvement in clinical condition by the end of the study were denoted as censoring patients. The last time that the WHO scare was determined was used to calculate the censoring time.

Figure legends

Figure 1. The change (reduction) in viral load from baseline on day 3 and day 5 in patients with mild to moderate COVID-19 treated with Azvudine or placebo. (A) Patients with viral load [?] 3log10 copies/ml. (B) Patients with viral load [?] 4log10 copies/ml. The P values indicated the differences in the change (reduction) in viral load from baseline on day 5 between the Azvudine group and placebo group.