REVIEW ARTICLES

The efficacy of triazavirin (riamilovir)-based treatment for coronavirus disease 2019 (COVID-19) in clinical trials and preliminary practical experiences

Účinnosť liečby COVID-19 založenej na triazaviríne (riamilovire) v klinických skúšaniach a predbežné praktické skúsenosti

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Summary

Coronavirus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS--CoV-2) has plagued the human population as 2019 turned into 2020, when first cases were confirmed to be infected with the pathogen in Wuhan City, the largest mega-city and capital of Hubei Province in Central China. Since this time, many pharmacotherapeutic modalities were suggested and used to treat the patients suffering from COVID-19. **Triazavirin** (**TZV**; **riamilovir**) is a synthetic non-toxic broad-spectrum antiviral drug belonging into an **azolotriazine** class. Several hypotheses and suggestions based on the knowledge about morphology, structure of virion, genome, replication cycle and functions of particular proteins within SARS-CoV-2 as well as *in silico* analyzes were published aiming to employ **TZV** for the treatment of COVID-19. Results and conclusions from a well--known randomized controlled trial registered under the Registration No. ChiCTR2000030001, which was carried out in China in 2020, indicated not only the anti-SARS--CoV-2 efficacy of given aza analogue of **guanine** but also some limitations of these outcomes in the context of their general interpretability and applicability. Thus, a primary aim of this review article was to provide more complex view on pharmacotherapeutic interventions based on **TZV** against COVID-19/SARS-CoV-2. The focus was on relevant results and conclusions from clinical trials as well as practical experiences with given antiviral agent considering not only real benefits of chosen therapeutic strategies but also several obstacles connected with them.

Key words: SARS-CoV-2 • COVID-19 • triazavirin • riamilovir • clinical trials • practical experiences

Súhrn

Ochorenie COVID-19 (coronavirus disease 2019; COVID-19), zapríčinené koronavírusom 2, spôsobujúcim ťažký akútny respiračný syndróm (Severe Acute Respiratory Syndrome Coronavirus 2; SARS-CoV-2), sužuje ľudskú populáciu od prelomu rokov 2019 a 2020, kedy boli vo Wu-chane, v najväčšej metropole a hlavnom meste provincie Chu-pej v strednej Číne, potvrdené prvé prípady infikovania sa týmto patogénom. Od tohto obdobia bolo v liečbe pacientov s COVID-19 navrhnutých a využitých mnoho farmakoterapeutických modalít. **Triazavirín** (**TZV**; **riamilovir**) je syntetické netoxické antiviroticky širokospektrálne účinkujúce liečivo patriace do skupiny **azolotriazínov**. V kontexte vedomostí o morfológii, štruktúre viriónu, genóme, replikačnom cycle a funkciách jednotlivých proteínov v SARS-CoV-2 a aj v súlade s vykonanými analýzami *in silico* bolo publikovaných niekoľko hypotéz a návrhov so zámerom využiť **TZV** v liečbe COVID-19. Výsledky a závery vyplývajúce z dobre známeho randomizovaného klinického skúšania, evidovaného pod registrač-

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ným číslom ChiCTR2000030001, ktoré bolo realizované v Číne v roku 2020, však indikovali nielen efektívne anti-SARS-CoV-2-pôsobenie tohto azaanalógu **guanínu**, ale aj niektoré obmedzenia v kontexte všeobecnej interpretovateľnosti a uplatniteľnosti formulovaných výstupov. Primárny zámer tejto prehľadovej publikácie spočíval preto v načrtnutí komplexnejšieho pohľadu na farmakoterapeutické intervencie proti COVID-19/-SARS-CoV-2, ktoré sú založené na využití **TZV**. Pozornosť bola sústredená na relevantné výsledky a závery z klinických skúšaní a praktické skúsenosti definujúce nielen reálne benefity zvolených terapeutických stratégií, ktoré zahŕňajú zmienené antivirotikum, ale aj niekoľko úskalí s nimi spojených.
Kľúčové slová: SARS-CoV-2 • COVID-19 • triazavirín • riamilovir • klinické skúšania • praktické skúsenosti

Introduction

Triazavirin (**TZV**), also known as **riamilovir** (CAS Registry Number: 123606-06-4), belongs into a nitro substituted [1,2,4]-triazolo[5,1-*c*][1,2,4]triazines class – the drug is considered an aza analogue of **guanine**[1, 2]. **TZV** crystallizes as a dihydrate, i.e., 2-methylthio-6--nitro-1,2,4-triazolo[5,1-*c*] [1,2,4]triazin-7-one sodium salt dihydrate (Fig. 1) as proven by the *X*-ray diffraction analysis[3]. The aspects related to chemical (structural), preclinical and clinical development of this molecule, its ability to fight *in vitro* and/or *in vivo* different RNA and DNA viruses, namely various strains of the Influenza A virus (Influenza Virus A, *Orthomyxoviridae*), i.e., swine flu (H1N1, or H3N2), avian influenza (H5N1, H5N2, H9N2, or highly pathogenic H7N3 strain), Influenza B virus (Influenza Virus B, *Orthomyxoviridae*), Respiratory Syncytial Virus (Orthopneumovirus, *Pneumoviridae*), Tick-Borne Encephalitis Virus (known also as the Forest-Spring Encephalitis Virus; Flavivirus, *Flaviviridae*), West Nile Virus (Flavivirus, *Flaviviridae*), Rift Valley Fever Virus (Phlebovirus, *Bunyaviridae*), and Herpes viruses (Simplexviruses, *Herpesviridae*), as well as pharmacokinetic and toxicological properties of considered aza analogue were very briefly summarized in review articles[2, 4], for example.

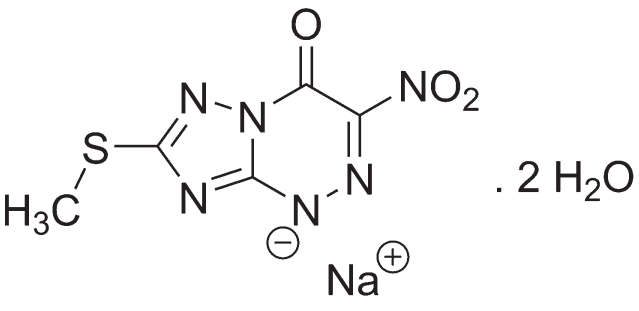

Fig. 1 Chemical structure of ***triazavirin (TZV; riamilovir)***

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2; previously 2019-nCoV) is an oval enveloped linear positive-sense single-stranded RNA *β*-coronavirus (subgenus Sarbecovirus, genus *β*-Coronavirus) with a diameter of around 60–140 nm. The pathogen is classified into the subfamily *Coronavirinae* and family *Coronaviridae*, which, in turn, comprises the order *Nidovirales*[5]. The virus caused a well-known highly transmissible coronavirus disease 2019 (COVID-19), which has plagued the human population from December 2019 and spread very fast all over the world[6].

TZV was proposed (hypothesized) to be included in practical protocols as an active agent for the treatment of COVID-19[4, 7]. Simultaneously, several molecular docking analyses/*in silico* simulations were carried out to investigate eventual interactions (interferences) of **TZV** with relevant biological targets – structural, or non-structural proteins within SARS-CoV-2, for example. In this regard, various scientific papers outlined certain possibilities and some of them can be mentioned[8–12]. The aim of a current review article was to provide more detailed information considering (ongoing) clinical trials as well as real practical experiences with **TZV** as the treatment modality for COVID-19.

Several clinical trials designed for COVID-19 and practical experiences with the treatment of this highly infectious disease using triazavirin

Before discussing several therapeutic modalities employing **TZV** for COVID-19, fundamental differences between the terms *efficacy* (studies) and *effectiveness* (studies) might be very briefly explained. The *efficacy* and *effectiveness* studies are both important when evaluating interventions, however, they serve distinct purposes and have different designs. Placebo--controlled randomized controlled trial (RCT) design is an ideal platform for *efficacy* evaluation – the RCT minimizes bias *via* multiple mechanisms, such as standardization of the intervention and double blinding. RCTs generally eliminate issues of access (intervention is provided free), provider recommendation, and patient acceptance and adherence[13].

On the other hand, *effectiveness* studies examine interventions under circumstances that are more closely related to real-world practice, with more heterogeneous patient populations, less-standardized treatment protocols, and delivery in routine clinical settings. The RCT design may be also used in these studies; however, the intervention is more often compared to usual care, rather than placebo[13].

In general, *efficacy* research maximizes the likelihood of observing an intervention effect, while *effectiveness* research better accounts for external patient-, provider-, and system-level factors that may moderate an intervention's effect in clinical practice[13].

Website and online database of National Library of Medicine/National Center for Biotechnology

Information[14] contains information about only two ongoing clinical trials till the end of August 2022, and several characteristics of the trials can be found in Table 1.

The RCT, registered under a Registration No. NCT04581915 (PHRU CoV01) and officially titled *A Pragmatic, Individually Randomised, Double-Blind, Placebo-Controlled Trial of Triazavirin (TZV) for the Treatment of Mild-Moderate SARS-CoV-2 Infection A Phase II and III Clinical Trial*, started on September 8, 2020, and was terminated on April 20, 2021 (Table 1).

The trial concluded that, in addition to standard of care therapy, the treatment with 250 mg of **TZV** administered *per os* three times daily for five days (i.e., 3 × 250 mg of **TZV**/day for five days) reduced a composite outcome – death, Intensive Care Unit admission, or mechanical ventilation, or prolonged duration of admission – by ≥ 29% when compared to the composite outcome in hospitalised patients with a mild-moderate laboratory proven COVID-19 receiving standard of care therapy only.

The randomized parallel double blinded trial, registered under a Registration No. NCT04973462 and officially titled *Evaluation of The Efficacy of Triazavirin Versus Oseltamivir in Egyptian Patients Infected With COVID-19 (COVID-19)*, started later on August 1, 2021 (study completion: December 30, 2021), and should compare the efficacy and safety (side effects and/or adverse effects) of **TZV** and **oseltamivir** as the treatment for COVID-19 in Egyptian patients in military hospitals (Table 1).

The so-called **TZV** group of patients took standard treatment for COVID-19 plus 3 × 250 mg of **TZV**/day for seven days. The so-called **oseltamivir** group of patients took standard treatment for COVID-19 plus 2 × 75 mg of **oseltamivir**/day for seven days. However, no results from given ongoing trial have been posted yet.

Chinese Clinical Trial Registry[15] provides a recruiting randomized double-blinded, placebo-controlled trial registered under a Registration No. ChiCTR2000030001. The RCT, officially titled *The Efficacy and Safety of Triazavirin for 2019 Novel Coronary Pneumonia (COVID-19): A Multicenter, Randomized, Double Blinded, Placebo-Controlled Trial*, was initiated on February 14, 2020, and completed on May 31, 2020 (Table 1). The details concerning given RCT were already published in[16, 17].

The participants (patients) with a mild or "ordinary" condition took standard therapy plus 250 mg of **TZV** administered *per os* three times a day, for seven consecutive days (3 × 250 mg of **TZV**/day for seven days), while participants (patients) with a severe or critical condition took standard therapy plus 250 mg of **TZV** administered *per os* four times a day for seven consecutive days (4 × 250 mg of **TZV**/day for seven days). Total number of patients (*n*) included in "both groups" was 120.

The placebo group of patients (*n* = 120) received the same standard therapy plus placebo (3 × 250 mg of placebo/day for seven days in mild or ordinary cases, and 4 × 250 mg of placebo/day for seven days in severe or critically severe cases)[16, 17].

Despite of the lack of statistical significance due to a limited sample size, i.e., relatively low number of participants/patients (*n* = 240), it could be expected that **TZV** might benefit COVID-19 patients by controlling symptoms and reducing frequent usage of concomitant therapies for vital organ supports. In more detail, the patients within a group treated with **TZV** used less frequent concomitant therapies for respiratory, cardiac, renal, hepatic, or coagulation supports. However, further research has to be carried out involving larger sample sizes to assess these outcomes[16, 17].

The findings and conclusions from RCTs of antivirals for COVID-19, which were summarized and published by Okoli et al. (2022), indicated no evidence for efficacy of chosen antiviral drugs or their combinations[18], i.e., **TZV** (250 mg of **TZV**/day for seven days), **baloxavir-marboxil** (80 mg of **baloxavir-marboxil**/day for two-three days), **remdesivir** (100 mg of **remdesivir**/day for ten days), and **lopinavir** (400 mg of **lopinavir**/day for 14 days)/**ritonavir** (100 mg of **ritonavir**/day for 14 days) combination, compared to placebo/(or even) no treatment, or with another antiviral for all efficacy outcomes.

The **lopinavir**/**ritonavir** combination significantly increased diarrhea, nausea, and vomiting compared to placebo/no treatment and other antivirals, and was ranked worst for these outcomes, while **TZV**, **baloxavir-marboxil**, and **remdesivir** ranked best, respectively[18].

Okoli et al. (2022) systematically searched for literature up to September 2020, and included English-language papers aiming at primary studies – RCTs, or primary studies – not RCTs among hospitalised COVID-19 patients[18]. Thus, the authors did not take into consideration the observations and conclusions

*Table 1. List of main (well-known) terminated and ongoing (interventional) clinical trials employing **TZV** as the treatment for COVID-19 according to National Library of Medicine/National Center for Biotechnology Information[14] and Chinese Clinical Trial Registry[15] databases till August 31, 2022*

Identifier (Registration No.)	Recruiting Status	Phase	Country of Recruitment	Enrollment
NCT04581915 (PHRU CoV01)	Terminated	3	South Africa	74
NCT04973462	Recruiting	4	Egypt	80
ChiCTR2000030001	Recruiting	3	China	240

published previously in several scientific papers written in other languages than English in their analyses.

In fact, appropriate adjustment of the amount of **TZV** administered *per* day as well as appropriate adjustment of the length of COVID-19 therapy might be beneficial. Sabitov et al. (2020) reported in a primary study – not RCT[19] that the average time required to complete resolution of symptoms during the treatment in a group of the patients (n = 100) with a moderate COVID-19 was 6–7 days. The patients received 3 × 250 mg of **TZV**/day for ten days as antiviral monotherapy.

The body temperature of the majority of those patients (75%) returned to normal on day 4 of the treatment. In addition, computerized tomography scans showed improvement in the lungs of these patients. No serious adverse events were noted when using **TZV**[19].

Sabitov et al. (2021) also investigated the efficacy, safety, and tolerability of **TZV** in patients with a mild COVID-19 within a randomized open-label study. This primary study – RCT[20] involved the patients (n = 120) with clinical and epidemiological manifestations of the SARS-CoV-2 infection and its laboratory confirmation with a Polymerase Chain Reaction (PCR) test. The patients received 750 mg of **TZV** *per* day for seven days (3 × 250 mg of **TZV**/day for seven days) as the monotherapy. The authors[20] concluded that **TZV** showed high efficacy, safety and good tolerability and they recommended given aza analogue of **guanine** as a first-line drug for the treatment of COVID-19.

Kasyanenko et al. (2020) focused on clinical outcomes regarding the treatment of patients (n = 59) with a moderate PCR-confirmed COVID-19. One group of those patients (so-called **TZV** group; n = 29) was treated with 1250 mg of **TZV** off-label *per* day for five days (5 × 250 mg of **TZV**/day for five days), comparison group consisted of the patients (n = 30), to whom **ribavirin** and **umifenovir** in a combination was administered (4 × 200 mg of each antiviral drug/day for five days).

Statistically significant decrease in duration of fever, cough, and anosmia (i.e., the loss of ability to detect one or more smells) as well as more rapid elimination of the pathogen from the body were noted in a **TZV** group. Decreased levels of non-specific inflammatory markers in blood serum as well as normal values of liver enzymes were observed in a **TZV** group during the therapy, as opposed to a comparison group. No serious adverse events were noted when using **TZV**, as reported in given primary study – not RCT[21].

Kasyanenko et al. (2021) also evaluated data from 69 health records of patients with a moderate, or severe PCR-confirmed SARS-CoV-2 infection and reported the observed results in a primary study – not RCT[22]. The **TZV** group of these patients (n = 34) was treated with **TZV** off-label (5 × 250 mg of **TZV**/day for five days), comparison group was covered with the patients (n = 35) taking a **ribavirin** and **umifenovir** combination (4 × 200 mg of each antiviral drug/day for five days). The antiviral therapy was initiated within 72 hours from the onset of COVID-19.

Significantly shorter time to clinical improvement as well as increased PCR-negative rate by day 7 were observed in a **TZV** group of patients. Opposed to the treatment of moderate SARS-CoV-2 infection based on an **umifenovir** and **ribavirin** combination, the **TZV**-based regime was associated with significantly shorter time to clinical improvement by day 14 of hospitalisation. Furthermore, PCR-negative rate by day 7 of hospitalisation was significantly more likely in a **TZV** group[22].

In addition, **TZV** was recommended as the prophylaxis when people, who had not previously been infected with SARS-CoV-2 (this fact had been confirmed with negative PCR results for COVID-19), had so-called level 1 contacts with the patients infected with given pathogen. The prophylactic dose was 250 mg of **TZV** *per* day for twenty days (1 × 250 mg of **TZV**/day for twenty days) in the foci of COVID-19[23].

TZV as the prevention against COVID-19 for „specific" collectives – organized groups of young people (18–20 years of age) was recently suggested by Zhogolev et al. (2022). The people included in a **TZV** group (n = 384) took 250 mg of **TZV**/day for 20 days. On the contrary, **TZV** was not administered to a control group of people (n = 392). The incidence rate of COVID-19 for six months of observation in a **TZV** group was 1.8 times lower[24] compared to the same indicator characterizing a control group. Preventive efficiency was set to 43% (χ^2 = 10.931, p < 0.05) with an efficiency index value of 1.8.

Conclusions

The findings and conclusions based on ongoing and finished clinical trials as well as results from several primary studies – practical findings and experiences from research centers, clinical institutions and hospitals indicated that **TZV** might be considered a highly effective and safe small molecule drug for (at least) mild-moderate COVID-19.

In fact, there can also be found several issues, which should be addressed and can not be omitted. The eventual uncertainty in the ratio of potential benefits and risks related to the **TZV**-based treatment(s) could result from relative lack of relevant clinical data. The obstacle might be limited *via* interim guidelines on the treatment for COVID-19, which will reflect the most current experiences with **TZV** and will be regularly updated. Thus, regular updating and publishing the „List of Recommended Drugs" is highly appreciated. Furthermore, relatively unsatisfactory number of participants (patients) was sometimes involved in the trials/studies dealing with **TZV** for COVID-19. For example, in regard to the RCT (Registration No. ChiCTR2000030001) carried out in China, statistically significant improvement in clinical

outcomes for the patients with COVID-19 was not observed (also) due to relatively low number of the participants (patients; *n* = 240) included in the trial. In addition, several scientific papers did not provide the information, which SARS-CoV-2 variant has been regarded as the susceptible one to the activity of **TZV**. One of the possible ways of how to effectively limit given difficulties, will definitely be more extensive international cooperation between relevant institutions.

Finally, the issue connected with real availability of **TZV**-based treatments can also be mentioned – considered pharmacotherapeutic interventions are very notably limited (they are impossible to be currently implemented, in fact) in the European Union countries because given drug has not been officially approved for the therapy of viral infections by relevant authorities yet.

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