INTRODUCTION

Tenvir (Tenofovir or T705) is most promising antiviral drug against SARS-COV2 viral infection in post-soviet countries. COVID-19 (Corona virus disease), Wuhan, China, 2019 became pandemic scale headache for global health care system in early 2020 [1]. Virus Strain, Variant B.1.1.1, Sampled from Kazakhstan has about 30K bp genome [2-3], divided into three main groups from 5'-UTR start, it has ORF1a and ORF1b which contain 16 non-structural proteins (NSPs) that are responsible for proteins synthesis, among them RNA dependent RNA-polymerase (RdRp) the non-structural protein 12 (NSP12) located in the genome overview of SARS-COV-2, Wuhan-Hu-1 strain, December 2019, from 5'-UTR to 3'-UTR with four main antiviral sites: a) ORF1a (NSP3 and NSP5 for instance) – innate immune system induction – interferon activity-viral replication. b) ORF1b (NSP12 -RNA dependent RNA polymerase and NSP13 for instance) – nucleotide analogs in our case purine-analogs -Tenvir (Tenofovir)- RdRP inhibitor –is used primarily against HIV-infection before COVID19 pandemics occurred c) structural proteins, especially, spike protein is main target for vaccination strategies worldwide to induce adaptive immunity-IgGs that neutralize viruses and virions effectively d) the accessory proteins (ORF8a and ORF8ab for instance) help to suppress the host interferon cellular activity during innate immunity encounter, these ORF8s are located close and dense to structural proteins, spike protein recognition by naturally and synthetically derived monoclonal antibodies neutralize the accessory proteins activity too [6].

Diagram 1. Genome of the first Wuhan strain sequenced in March 2020

Source: https://doi.org/10.3390/pathogens9050331

Tenvir (Tenofovir)

Tenofovir belongs both for anti-HIV drugs and Anthepa-
Tenofovir represents the reverse transcriptase inhibitors or nucleoside reverse transcriptase inhibitors (NRTIs) are structural analogues of nucleosides, adenosine monophosphate which competitively inhibit the reverse transcriptase by causing the chain termination after they got involved into viral DNA. This viral DNA-incorporation causes so-called 'lethal mutagenesis'. Tenofovir is also used as antiviral drug against chronic hepatitis B virus) reverse transcriptase by competing with natural substrate for in cooperation with growing viral DNA-strand causing as virally inhibit the reverse transcription by causing the chain termination and synthesis of viral DNA. Tenofovir is yet another nucleotide analogue that was initially designed to inhibit the HIV (human immunogenicity virus reverse transcriptase by interfering the ATP-Polymerization in the growing nucleic acid chain [7,8]. Tenofovir was initially designed to inhibit the HIV (human immunogenicity virus reverse transcriptase by interfering the ATP-Polymerization in the growing nucleic acid chain [7,8]. Tenofovir was also assumed to be effective against COVID-19 as it showed immune incooperation and transcription of viral RNA. Tenofovir was selected to study antiviral activity against the SARS-CoV-2 virus. Before determining the antiviral activity, a working dose was established that did not cause toxicity in cell culture.

2.5. Gene sequencing

Viral RNA and DNA are isolated using a set of QIAamp virus RNA and trizol reagents according to the manufacturer’s instructions. The RNA is eluted with water, 2 times 40 µl each. Given the fact that the full genome of the SARS-CoV-2 virus includes about 30 thousand nucleotides, a set of primers is used to amplify the full genome for sequencing. PCR is performed using a set of single-stage RT-PCR elevated III systems. Cleaning of PCR products is carried out using the Ampure kit according to the manufacturer’s instructions. The purity of PCR products is checked by electrophoretic analysis. PCR sequencing products were obtained using the BigDye® Terminator v3.1 cyclic sequencing kit. The purification of the sequencing reaction was carried out with the Clean Seq Kit. The sequencing is carried out on 16 capillaries sequencers of the genetic analyzer 3130xl (Applied Biosystems; K&Laborgeraete, Germany; Thermal cycler TC-512, Techne; thermal boards DryBlockHeater, Techne; thermal cycler GeneAmp PCR System 9600, Applied Biosystems; thermal cycler TC-512, Techne; thermal boards DryBlockHeater, Techne; shakers, vortexes Genie 2 Shaker, Col-Parmer; automatic micropipettes, Eppendorf; apparatus for electrophoresis of nucleic acids GI000, equipment for phylogenetic analysis.

2.7. Comparative and phylogenetic analysis of the nucleotide sequence of genes

The available complete genomes of the SARS-CoV-2 virus downloaded from the GenBank are used for the complete analysis. Phylogenetic trees were created using the maximum similarity method on the CLC Genomics Server 12.0 using the «neighbor Joining» method and the Jukes-Cantor model with gamma distribution 1.0 and 100 replications to assign confidence levels to branches. The MEGA 7.0 application is also used for phylogenetic analysis.

2.8. Determination of cytotoxicity of Tenvir (Tenofovir) for cell culture

Tenvir (Tenofovir) was selected to study antiviral activity against the SARS-CoV-2 virus. Before determining the antiviral activity, a working dose was established that did not cause toxicity in cell culture.

2.9. CCK8 test for cell-viability in Tenvir of concentration 50ng/ml-200 µg/ml

The CCK-8 (KK-8) enables sensitive colorimetric analyses to determine the viability of cells in the analysis of cell proliferation and cytotoxicity. The dojindo-tetrazole salt, WST-8, soluble in water, is restored in the cells by the activity of dehydrogenase, forming a yellow formazan dye, soluble in a medium for tissue culture. The amount of the dye formazan is measured as a result of the activity of dehydrogenases in cells, is directly proportional to the number of living cells. Three steps: Step 1: Add 10 Pl of Cell Counting Kit-8 to each well in a 96 well microplate. Step 2: Place in a CO2 incubator for 1-4 hours to react. Step 3: Measure the absorbance at 450 nm with a microplate reader.

2.10. COVID19 Antigen count of GenSure-kit from a specimen swab: TID50

Equipment
- oligonucleotide synthesizer Synthesizer H-16, K&Laborgerate, Germany; thermal cycler GeneAmp PCR System 9600, Applied Biosystems; thermal cycler TC-512, Techne; thermal boards DryBlockHeater, Techne; shakers, vortexes Genie 2 Shaker, Col-Parmer; automatic micropipettes, Eppendorf; apparatus for electrophoresis of nucleic acids GI000.
**Table 1. The TID50 (viral load) scheme count (viral load pattern)**

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Concentration</th>
<th>Crossoverreactivity (YES/NO)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza A (H1N1, H3N2)</td>
<td>1.0 x 10^7 TCID50/mL</td>
<td>NO</td>
</tr>
<tr>
<td>Avian Influenza (H5N1, H7N9)</td>
<td>1.7 x 10^5 TCID50/mL</td>
<td>NO</td>
</tr>
<tr>
<td>Influenza B (Victoria, Yamagata)</td>
<td>2.5 x 10^5 TCID50/mL</td>
<td>NO</td>
</tr>
<tr>
<td>Respiratory Syncytial Virus</td>
<td>3.8 x 10^5 TCID50/mL</td>
<td>NO</td>
</tr>
<tr>
<td>Rhinovirus</td>
<td>1.4 x 10^5 TCID50/mL</td>
<td>NO</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>1.8 x 10^5 TCID50/mL</td>
<td>NO</td>
</tr>
<tr>
<td>Measles</td>
<td>1.0 x 10^5 TCID50/mL</td>
<td>NO</td>
</tr>
<tr>
<td>Human coronavirus</td>
<td>1.0 x 10^5 TCID50/mL</td>
<td>NO</td>
</tr>
<tr>
<td>(OCA1.29E, NL63)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronavirus, MERS</td>
<td>1.2 x 10^4 TCID50/mL</td>
<td>NO</td>
</tr>
<tr>
<td>Mycoplasma pneumoniae</td>
<td>1.0 x 10^4 CFU/ml</td>
<td>NO</td>
</tr>
</tbody>
</table>

**Materials, reagents, and solutions**

- Recombinant Taq DNA Polymerase 5000 unit/mL, SIGMA.
- T4 DNA Ligase;
- ProtoScript® II First Strand cDNA Synthesis Kit;
- RNAZap decontamination solution;
- SuperScript IV One-Step RT-PCR System with Platinum Taq DNA Polymerase (Invitrogen, USA) (100 reaction);
- 310 and 31xx Running Buffer, 10X;
- BigDye™ Terminator v3.1 Cycle Sequencing Kit, 100 reactions;
- Reagent for safe staining of agarose gel SYBR Safe;
- 310 and 31xx Running Buffer, 10X;
- Microtubes 0.2 ml with flat cap 1000 pcs/pack Tubes, 0.2 ml, flat cap 1000 pcs Eppendorf;
- UltraPure™ nuclease-free distilled water;
- Reagent for safe staining of agarose gel SYBR Safe;
- 310 and 31xx Running Buffer, 10X;
- Microtubes 0.2 ml with flat cap 1000 pcs/pack Tubes, 0.2 ml, flat cap 1000 pcs Eppendorf;
- Microtubes 0.5 ml with flat cap 1000pcs/pack Tubes, 0.5 ml, flat cap 1000 pcs Eppendorf;

**The vero cells E6**

Vero C1008 [Vero 76, clone E6, Vero E6], from African green monkey kidney, by Sigma Aldrich. Vero cells are derived from the kidney of an African green monkey. These are anchorage-dependent cells that have applications in molecular and cellular biology research. Vero E6 cells enable achieving high titers of severe acute respiratory syndrome coronavirus (SARS-CoV virus) [18]. Split sub-confluent cultures (70-80%) 1:3 to 1:10, i.e., seeding at 1-3 x 10^6 cells/cm^2 using 0.05% trypsin or trypsin/EDTA; 5% CO2; 37°C.

**The culture medium**

DMEM (D6866) + 2 mM L-Glutamine (G7512) + 10% FBS / FCS (F2442); DMEM with 2% bovine serum and 0.1% (1000/ml) antibiotics (Penicillin-Streptomycin) was prepared.

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- Microtubes 0.5 ml with flat cap 1000pcs/pack Tubes, 0.5 ml, flat cap 1000 pcs Eppendorf;

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3.2.1. Phylogenetic analysis of the SARS-CoV-2 strain/human/KAZ/Britain/2021

3.2.2. Phylogenetic analysis of the SARS-CoV-2 strain/human/KAZ/B 1.1/2021

3.2.3. Uploading a genome-wide nucleotide sequence to the GenBank database

The search and development of nucleotide sequence primers was carried out manually on the NCBI website using the GenBank database. The nucleotide sequence of specific primers was selected based on the reference strain MN908947.3. The specificity of the primers was verified with the NCBI Primer BLAST Service. The primers were selected so that each pair of primers overlapped, and their sequence was conservative among all variants of the SARS-CoV-2 virus. As a result, 65 pairs of sequencing primers were selected to develop the complete genome of SARS-CoV-2 virus variants with an overlap of about 100 nucleotide pairs (bp). The estimated amplitude length ranges from 604 to 772 bp.

Table 3. Sequencing primer parameters, the main gene product of SARS-CoV-2/human/KAZ/B1.1/2021 on ORF1ab here is NSP12 that is responsible for RNA dependent RNA polymerase with 2697 bp long as same as Wuhan-Hu-1 strain has 2696 bp [Wuhan-Hu-1 -GenBank MN908947.3].

<table>
<thead>
<tr>
<th>#</th>
<th>Primer orientation</th>
<th>Sequence (5’-&gt;3’)</th>
<th>Start</th>
<th>Stop</th>
<th>Tm (primer) heat (temp)</th>
<th>GC%</th>
<th>Product size(bp)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PP 28</td>
<td>Forward</td>
<td>TGGAAACCACTTGTAAGTTT</td>
<td>12891</td>
<td>12910</td>
<td>56.57</td>
<td>45.00</td>
<td>652</td>
</tr>
<tr>
<td>PP 28</td>
<td>Reverse</td>
<td>AGCCCTGATACGACATCAG</td>
<td>13542</td>
<td>13523</td>
<td>56.52</td>
<td>50.00</td>
<td></td>
</tr>
<tr>
<td>PP 29</td>
<td>Forward</td>
<td>ACCCTGTTGTTTTACACTT</td>
<td>13341</td>
<td>13360</td>
<td>56.86</td>
<td>45.00</td>
<td>706</td>
</tr>
<tr>
<td>PP 29</td>
<td>Reverse</td>
<td>AACAATACCCAGATTTCGCA</td>
<td>14046</td>
<td>14027</td>
<td>56.32</td>
<td>40.00</td>
<td></td>
</tr>
<tr>
<td>PP 30</td>
<td>Forward</td>
<td>TACGCCAATTAGTTGAAAGC</td>
<td>13963</td>
<td>13982</td>
<td>57.93</td>
<td>50.00</td>
<td>639</td>
</tr>
<tr>
<td>PP 30</td>
<td>Reverse</td>
<td>TAGATTACCGAAGACCGGT</td>
<td>14601</td>
<td>14582</td>
<td>56.36</td>
<td>45.00</td>
<td></td>
</tr>
<tr>
<td>PP 31</td>
<td>Forward</td>
<td>CCACCTCAGAGAGACTGGTT</td>
<td>14478</td>
<td>14497</td>
<td>57.04</td>
<td>55.00</td>
<td>713</td>
</tr>
<tr>
<td>PP 31</td>
<td>Reverse</td>
<td>CTCAATGTCGAGCCATTTAT</td>
<td>15190</td>
<td>15171</td>
<td>56.88</td>
<td>50.00</td>
<td></td>
</tr>
<tr>
<td>PP 32</td>
<td>Forward</td>
<td>CCAAGTCACTTGTTAAAAAC</td>
<td>14913</td>
<td>14932</td>
<td>57.03</td>
<td>50.00</td>
<td>644</td>
</tr>
<tr>
<td>PP 32</td>
<td>Reverse</td>
<td>CAAATACGCGTTAGCGTACA</td>
<td>15556</td>
<td>15537</td>
<td>56.71</td>
<td>45.00</td>
<td></td>
</tr>
<tr>
<td>PP 33</td>
<td>Forward</td>
<td>GTTGTGATGTTGTTGACACC</td>
<td>15372</td>
<td>15391</td>
<td>56.98</td>
<td>50.00</td>
<td>659</td>
</tr>
<tr>
<td>PP 34</td>
<td>Forward</td>
<td>ATGTTGACTGAGACTGACA</td>
<td>15834</td>
<td>15853</td>
<td>56.86</td>
<td>50.00</td>
<td>669</td>
</tr>
<tr>
<td>PP35</td>
<td>Forward</td>
<td>TCGTGATGTTATGAAAGCTC</td>
<td>16374</td>
<td>16393</td>
<td>56.80</td>
<td>45.00</td>
<td>712</td>
</tr>
</tbody>
</table>

Table 4. RNA dependent RNA polymerase nucleotide positioning of SARS-CoV-2/human/KAZ/B1.1/2021 on NSP12, almost the same nucleotide position as Wuhan-Hu-1 strain has: 13442 – 16236 [Wuhan-Hu-1 -GenBank MN908947.3].

Gene: ORF1ab

<table>
<thead>
<tr>
<th>5’UTR</th>
<th>Gene product/region</th>
<th>Nucleotide position</th>
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<tbody>
<tr>
<td>106</td>
<td>Non-structural protein NSP 12</td>
<td>14120</td>
</tr>
<tr>
<td>241</td>
<td>Non-structural protein NSP 12</td>
<td>14408</td>
</tr>
<tr>
<td>358</td>
<td>Non-structural protein NSP 12</td>
<td>14676</td>
</tr>
<tr>
<td>15017</td>
<td>Non-structural protein NSP 12</td>
<td>15017</td>
</tr>
<tr>
<td>15279</td>
<td>Non-structural protein NSP12</td>
<td>15279</td>
</tr>
<tr>
<td>16176</td>
<td>Non-structural protein NSP12</td>
<td>16176</td>
</tr>
</tbody>
</table>

Figure 2. Electron microscopy of the SARS-CoV-2 virus. Uv. 120,000, on the microscope Jeol Jem 100 XC, (provided by Kozhabergenov N.S.)

Figure 3. Electropherogram of results of RT-PCR genes of ORF1ab variant B. Virus SARS-CoV-2 As it can be seen from Figure 1, the developed primers make it possible to generate specific PCR products. Electrophoretic analysis yielded products with molecular weights between 604 and 772 bp, from the ORF1ab gene. The length of the amplicon absolutely corresponds to the length of the synthesized primers.

Table 4. RNA dependent RNA polymerase nucleotide positioning of SARS-CoV-2/human/KAZ/B1.1/2021 on NSP12, almost the same nucleotide position as Wuhan-Hu-1 strain has: 13442 – 16236 [Wuhan-Hu-1 -GenBank MN908947.3].

Gene: ORF1ab

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<td>Non-structural protein NSP 12</td>
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</tr>
<tr>
<td>15279</td>
<td>Non-structural protein NSP12</td>
<td>15279</td>
</tr>
<tr>
<td>16176</td>
<td>Non-structural protein NSP12</td>
<td>16176</td>
</tr>
</tbody>
</table>

Figure 4. Phylogenetic analysis of the SARS-CoV-2 strain/human/KAZ/Britain/2021 [2].
3.3.2. CCK8 test for cell-viability in Tenofovir in concentration of 50µg/ml

3.3.3 Antiviral activity

The study of the antiviral activity of the drugs was carried out in a culture of Vero cells infected with the SARS-CoV-2 virus, variant B, based on the coefficient of inhibition of the cytopathic activity of the virus and virus reproduction. After 24 hours of incubation after infection of cells (at a dose of 10 CPD50) with a, when drugs were added in a concentration range of 50 μg/ml, the cytopathic effect of the virus was detected to varying degrees. The results of viral suppression are presented in Table 5.

Discussion

The Tenvir – antiviral drug is a purine analog that was well established since 2003 MERS-epidemics, furthermore they have been recommended themselves as effective pharmaceutical therapy against chronic diseases caused by long term viral infections like HIV, turning soon into AIDS, or Hepatitis B/C lifelong viral load control. Cellular toxicity depends on the name of the virus strain was uploaded to the NCBI database under registration number ON692359.1 dated June 07, 2022, and OP084305.1 dated October 20, 2022. The obtained sequences were analyzed using the Pangolin COVID-19 database (https://pangolin.cog-uk.io), as a result of which it was established that they belong to lines B.1.1.7 and 1.1 (Graph 3 and Graph 4, respectively)

The analysis of the nucleotide sequence of the whole genome showed that the strains isolated in the Almaty region are 100% similar to SARS CoV-2/human/KAZ/2021 and SARS-CoV-2/human/KAZ/1.1/2021 and have 99.80% and 99.82% of the total similarity. identity with the reference strain SARS-CoV-2, the Wuhan-Hu-1 isolate belonging to the B-line (see table, as well as graph 3 and graph 4)

3.3.1. Determination of cytotoxicity of drugs for cell culture

The cytotoxicity results showed that Tenvir at a dosage of 50 μg is non-toxic to cell culture and will be used to study the inhibition of antiviral activity. Also, with an increase in the dosage of the Tenvir drug, alkalization of the medium and detachment of cells from the surface are observed.

3.3.2. CCK8 test for cell-viability in Tenofovir in concentration of 50µg/ml

**Table 4. Analysis of the nucleotide sequence of the entire genome of SARS-CoV-2 viruses isolated in the Almaty region in the Republic of Kazakhstan**

<table>
<thead>
<tr>
<th>№</th>
<th>Variant</th>
<th>Strain</th>
<th>Country</th>
<th>Date</th>
<th>Genome identity%</th>
<th>GenBank</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>B</td>
<td>SARS-CoV-2 isolate Wuhan-Hu-1</td>
<td>PRC</td>
<td>18.03.2020</td>
<td>Ref.</td>
<td>MN908947.3</td>
</tr>
<tr>
<td>2</td>
<td>B.1.1.7</td>
<td>SARS-CoV-2/human/KAZ/2021</td>
<td>Kazakhstan</td>
<td>07.06.2022</td>
<td>99.80%</td>
<td>ON092359.1</td>
</tr>
<tr>
<td>3</td>
<td>B.1.1</td>
<td>SARS-CoV-2/human/KAZ/2021</td>
<td>Kazakhstan</td>
<td>20.10.2022</td>
<td>99.82%</td>
<td>OP084305.1</td>
</tr>
</tbody>
</table>

Tenvir also shows high toxicity rates (cell layers are clearly torn even at minimum concentration) because only relatively few concentrations are recommended to achieve therapeutic effect.
many factors, not only increasing drug concentration for in- stance, but also how long a drug can suppress the viral replication with significant side effects factor. Thumb rule – the lower daily concentration is prescribed the less damage it brings during pharma dynamics both in-vivo and in-vitro. The importance of detecting ORF1ab products represent a great interest to fight current viral infections and develop future an- tiviral strategies using purine-analogs medication to increase the positive income among infected patients.

**CONCLUSION**

Tenvir is now most effective anti-viral orally administered drug at concentration range of 50 μg/ml. The viral infection, particularly, the SARS-CO2 has many ways to invade the host cell, first due to high variability of mutation of spike protein (viral structural protein) that could be coupled by sys- tematic vaccination – B-cells production – immunoglobulins (active immunity). The second strategy is to use purine-anal- ogus that seriously inhibits the viral replication, thereby, stop- ping the viral load development. Purine-analogs also causes so called ‘‘lethal shock’’ phenomenon where viral extinction via already well known and established drugs that were already used against other diseases based on virus onogenesis. The purine analogs could be used not only as main treatment strat- egy but also as option or in combination with others, further- more, dexamethasone increases the survival rates in severe cases of COVID-19 infection, especially, in pneumonia comp- lication [14]. This study is still important because it shows that traditional antiviral drugs is effective in vitro against new and local SARS-CO2-variants and shows high conserva-

<table>
<thead>
<tr>
<th>Drug</th>
<th>Concentration mg/ml</th>
<th>Virus accumulation lg, PFU/ml</th>
<th>Suppression of reproduction virus, lg</th>
<th>Inhibition coefficient, Percent %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenvir</td>
<td>50</td>
<td>5.03±0.15</td>
<td>2.13</td>
<td>99,31</td>
</tr>
</tbody>
</table>

**REFERENCES**

Абстракт
COVID-19 стал настоящей мишенью для лекарств во всем мире из-за масштабов пандемии в 2020 году. С вирусными инфекциями, как правило, трудно справиться, особенно если вирусная нагрузка и скорость распространения срежсильно превосходят иммунную реакцию, как врожденную, так и адаптивную. Таким образом, лишь относительно небольшое количество препаратов применялось клинически для остановки либо на ранних стадиях репродукции вируса, например, с помощью Тенвир (Тенофовира), либо вакцинации для получения коллективного иммунитета в конкретной популяции. Ни один из препаратов на основе интерферона не продемонстрировал явного медицинского эффекта в медицинских исследованиях и во время протоколов госпитализации в связи с пандемией. Однако аналоги пуринов, такие как Тенвир и другие, показали устойчивые показатели выживаемости и выздоровления среди пациентов, инфицированных вирусом SARS-COV-2, на средней и тяжелой стадиях пневмонии, вызванной этим вирусом. Во данной статье представлены результаты испытаний in vitro препарата Тенвир на штамме вируса Вариант B.1.1, отобранного из Казахстана, а также молекулярно-генетическая характеристика NSP12 (неструктурного белка 12), расположенной в регионе ORF1b генома SARS-COV 2. Тенвир или тенофовир широко использовались против ВИЧ-инфекции, и это исследование показывает достаточный эффект на распространение вируса благодаря свойствам ингибирования RdRP in vitro.

Ключевые слова: COVID-19, NSP-12, РНК-зависимая РНК-полимераза (RdRP), аналоги пуринов, ОТ-ПЦР, ген-продукт.