"Inhalation Low Dose Radionuclide Therapy in Treatment COVID-19"

NCT: 04724538

Ethical committee approval:

The study was approved by research ethical committee in A. Tsyb Medical Radiological Research Centre - Branch of the National Medical Research Radiological Centre of The Ministry of Health of the Russian Federation (Protocol № 510).

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1. Relevance.

Radiation therapy (RT) was used to treat pneumonia in the first half of the 20th century. The literature contains data on the treatment of more than 800 cases of bacterial, viral, atypical pneumonia using low doses of ionizing radiation. The data are presented in Table 1.

Table 1.

Authors	Type of pneuminia	Number of patients	Treated cases
Musser and Edsall (1905)	Unresolved pneumonia	1	1
Edsall and Pemberton (1907)	Unresolved pneumonia	2	2
Quimby and Quimby (1916)	Unresolved pneumonia	12	11
Krost (1925)	Unresolved pneumonia	12	11
Fried (1926)	Post-operative pneumonia	40	32
Fried (1928)	Post-operative pneumonia	57	N/A
Merritt and McPeak (1930)	Unresolved pneumonia	7	6
Powell (1936, 1938, 1939)	Lobar pneumonia and bronchopneumonia	231	215
Scott (1939)	Lobar pneumonia	138	111
Solis-Cohen and Levine (1939)	Lobar pneumonia	42	40
Settle (1941)	Lobar pneumonia	34	32
Rousseau et al. (1942)	Lobar pneumonia	104	98
Rousseau et al. (1942)	Viral pneumonia	29	22
Correll and Cowan (1943)	Acute atypical pneumonia (not pneumococcal)	23	22
Correll and Cowan, (1943)	Unresolved pneumonia	9	7
Oppenheimer (1943)	Interstital pneumonia (children)	36	33
Oppenheimer (1943)	Virus pneumonia	56	45
Torbett, 1936 (see Abstract of Discussion in Powell (1936))	N/A	30	29
Total		863	717

The researchers applied different radiation regimes based on the results of the treatment of inflammatory diseases such as carbuncle and arthritis. The range of total focal doses during irradiation of the lungs was 50–100 roentgens in air (up to 0.9 Gy).

Oppenheimer (1943) concluded that radiation in the early stages of the disease (days 2-5) led to the best treatment results, while radiation after 14 days of illness was successful in only 50% of cases.

It should be emphasized that the last clinical study on this issue was carried out in 1946. Most studies lack control groups or are poorly organized. There is no dose control, poor methodological support, no information on the spread of doses on the target, etc., which in modern conditions would not allow these studies to be considered legitimate.

A possible mechanism of radiation exposure in the case of pneumonia that does not respond to antibiotic therapy may be as follows:

The inflammatory response is a complex pathophysiological mechanism implemented by a cascade of intercellular interaction through immune responses. Recent laboratory studies have shown that single doses of

radiation in the range of 0.3–0.7 Gy can be effective in influencing the pathophysiology of inflammation, which means they have an anti-inflammatory effect. The anti-inflammatory effect of low-dose radiation therapy (LDRT) is realized at all stages of the inflammatory process.

LDRT affects the production of biologically active substances in all leukocyte fractions, inducing the production of anti-inflammatory cytokines: transforming growth factor beta (TGF-ß1), interleukin-10 (IL-10 and interleukin 4), and a decrease in the production of inflammatory cytokines, in particular interleukin -6 (IL-6), 12 (IL-12) and colony stimulating factors (CSF); and also there is a massive decrease in the release of L-selectin from leukocytes.

Ionizing radiation is able to reduce inflammation through various mechanisms, including the induction of apoptosis in immune cells, the secretion of anti-inflammatory factors, and a decrease in macrophage function [1]. With regard to the use of low-dose radiation therapy for pneumonia associated with SARS-CoV-2 in patients with high levels of IL-6, the role of radiation therapy in the monocyte-macrophage vector may be very relevant.

Recent studies show that LDRT polarizes macrophages towards a m2-like phenotype in a rheumatoid arthritis (RA) model. In this study, LDRT in a single dose of 0.5 g influenced the M1 / M2 balance towards the “anti-inflammatory” m2 phenotype when co-cultivating fibroblast-like synoviocytes and bone marrow macrophages in an experimental model of RA. Thus, LDRT may play an important role in RA-like hyperinflammation through the reduction of IL-6-producing IL-1 and TNF-alpha target cells. Thus, localized radiation therapy at very low doses would modify the inflammatory environment in the lungs of patients with SARS-CoV-2-associated pneumonia, accompanied by hyperproduction of interleukin 6 [2].

In the light of tissue macrophages, it is necessary to highlight the classic immune response, in which macrophages, under the action of proinflammatory cytokines, release inducible nitric oxide synthase (iNOS), catalytic formation of nitric oxide (NO) occurs, when interacting with superoxide, reactive oxygen species (ROI) are formed, leading to lipid peroxidation and destruction of cell membranes, and as a consequence, the development of an extracellular pathway of macrophage inflammation.

Thus, LDRT affects the primary link of this cascade of pathophysiological reactions, namely, inducible nitric oxide synthase (iNOS), thereby reducing its synthesis and slowing down the inflammatory response

In addition, irradiation with single doses not exceeding 1 Gy leads to a change in the endothelium itself in the area of inflammation and to a change in the nature of its interaction with leukocytes. There is a decrease in the adhesion of mononuclear blood cells to endothelial cells due to a decrease in the expression of E-selectin (a receptor for carbohydrate ligands of leukocytes) and induction of apoptosis on the surface of endothelial cells.

As noted above, before 1940s, were obtained results in 850 patients (with viral and interstitial pneumonia) showing an easier course of the disease, amelioration of symptoms and recovery. A decrease in mutation frequency by 20% was found under the action of X-ray radiation. However, the wrong conclusion was made that it would not be as dangerous even at high doses, as it could be assumed from the standard linear

dose-effect relationship. In the light of modern knowledge, it is obvious that in this case we are talking precisely about "getting" into the effects of hormesis, induced radioresistance or adaptive response, when a similar decrease in the biological response in the dose range of 0.3–0.8 Gy was obtained, for example, by cell survival , frequency of chromosome aberrations, micronuclei, output of gamma foci.

All of these studies were carried out by scientists independently of each other, when they were not aware of the results obtained by other research groups. Multicenter studies were not carried out at that time; after the publication of the first results, the researchers did not return to this topic. Therefore, it is not possible to establish the effectiveness of this type of treatment, as well as to assess the risks and manifestation of long-term effects.

Within 1941-1946 several animal studies were conducted to evaluate the ability of ionizing radiation as a potential treatment for bacterial and viral pneumonia. In these studies, a guinea pig and a dog were used to assess the effect of radiation therapy on bacterial pneumonia, while a cat and mouse were used to assess viral pneumonia. The guinea pig study provided a histological comparison of lung tissue between control and treatment groups. Radiation therapy was more effective than previously performed after bacterial exposure (6, 12 and 24 hours).

In general, just a few studies on animal models (mice, guinea pigs, cats, dogs) were carried out, the results were not as unambiguous as at human exposure. It should be noted that in experiments on mice (viral pneumonia caused by the swine flu virus), it was shown that radiation exposure at a dose of 5 R (~ 0.05 Gy) 48 hours before infection of animals did not lead to an effect, while exposure at the same dose 5 R 24 h after infection led to a decrease in mortality (according to the results of two repeated experiments).

Although each experiment had significant limitations, they demonstrate a systematic trend indicating that X-ray exposure can reduce the effects of viral-induced pneumonias, affecting primarily the target cells of pro-inflammatory cytokines and thereby preventing their hyperproduction.

The main question is the choice of the optimal target of exposure in the case of viral pneumonia treatment, i.e.to expose on a locally inflamed area or to carry out a total exposure. The main observation was that low dose X-ray irradiation reproducibly mediates the anti-inflammatory effect.

Thus, the problem of radiation therapy for pneumonia requires serious experimental study, taking into account the characteristics of radiation, the choice of the object of study (type of animals), dose or dose range, emphasizes the need for careful planning of the experiment, compliance with controlled reproducible conditions on samples of sufficient volume.

2. The novelty of the method and (or) its difference from known similar methods.

The proposed therapeutic approach differs from the generally accepted treatment standard by the additional introduction of radiation therapy into the algorithm, namely, radionuclide therapy. In contrast to the previously used technique of external beam therapy, this study will use a different dose delivery mechanism by

inhalation of an ultrafine aerosol of carbon nanoparticles labeled with ^{99m}Tc (UFCNPA, ^{99m}Tc) obtained from the TechnegasPlus generator.

3. A brief description of the known and potential risks to study patients, if any.

UFCNPA, ^{99m}Tc remains a safe drug for ventilation research because it does not have any potentially fatal or adverse results, reactions, consequences or complications that are associated with it, and has been used in clinical practice for more than three decades and can be used safely and successfully in patients.

Adverse effects associated with the use of UFCNPA, ^{99m}Tc, were mainly reported prior to the early 1990s. Notably, among these effects was transient hypoxia caused by an average 8.5% decrease in oxygen saturation during inhalation of UFCNPA, ^{99m}Tc. Given the fact that, prior to publication of this study, a significant number of ventilation studies had already been carried out without any adverse effects, the authors concluded that a temporary decrease in oxygen saturation does not appear to pose a risk to patients.

Currently, more than 2,500 Technegas generators are in use in 51 countries, where nearly 200,000 diagnostic examinations are performed annually. Since 1986, more than 2 million injections of UFCNPA, ^{99m}Tc have been performed for ventilation lung scintigraphy, including in young children, the disabled, the elderly and patients on mechanical ventilation, without any reports of adverse effects and side effects [3, 4, 5].

The global incidence of adverse reactions to radiopharmaceuticals used in diagnostics is generally very low, reported to be approximately 2-3 persons per 100,000 or even less (ie 1.3 per 100,000) [6].

Dangers when using the TechnegasPlus Medical Generator:

- Dangers that could arise from lack of maintenance. The identified situations can lead to unnecessary additional exposure of the operator and / or patient with a small dose of radiation. Radiation can be spread through the air due to worn or damaged O-rings, lack of protective filtration, for example, when a filter is not installed. The identified hazards were eliminated thanks to design solutions and, in addition, by the regulation of periodic maintenance of the device.
- Dangers that could arise from the use of the generator by unqualified or untrained operators. The identified hazards have resulted in unwanted airborne contamination of the operator and patient. This risk has been mitigated by the development of an operating system that has simple controls with a display for prompting when an automatic procedure requires operator intervention. The education, training and experience of prospective operators, nuclear medicine technologists and physicians were taken into account.

- The operator can make a mistake and use the wrong grade of argon, isotope or crucible dampener. The use of a lower grade of argon (and / or wetting agent) may result in higher pertechnetate levels in the production

of UFCNPA, ^{99m}Tc. Although the hazardous situation of using the wrong isotope has not been encountered, it is unknown whether other isotopes will bind to carbon using the supplied "gas."

• Recorded accidents of damage to the main switch may result in a risk of electric shock to the operator, but the product will be suspended promptly. Damage to the lead acrylic shield can result in poor shielding, potentially increasing the risk of operator's exposure.

• Damage to the mechanical integrity of the argon cylinder regulator is a potential hazard. This product was not manufactured by Cyclomedica but was purchased from another manufacturer. Damage to the regulator was possible due to careless or incorrect operation. Physical damage can cause pressure build-up due to release from the gas cylinder and debris flying from the regulator. The correct handling and storage of gas cylinders is the responsibility of the user and the manufacturer acknowledges that institutions have their own rules for the safety of gas cylinders, which are outside the manufacturer's control.

• Potential radiation hazards caused by the operation of the device, in particular air pollution.

1) If the PAS is not connected to the device and there is an erroneous output of UFCNPA, ^{99m}Tc, it can lead to air pollution. This will be an operator's error. Correct connection and use of PAS are given in the operating instructions.

2) Erroneous gas output can lead to air pollution. In a), the erroneous release of UFCNPA, ^{99m}Tc by an operator without a PAS connected may result in UFCNPA, ^{99m}Tc being released into airspace. The correct use of UFCNPA, ^{99m}Tc and PAS is prescribed in the Operation Manual.

3) A defective purification filter can lead to air pollution. If an electrostatic filter is present, air pollution can occur due to improper arrangement of the filter media. The design includes the installation of a long-life filter that has passed 100% quality control in accordance with its specifications.

4) The lack of filter can lead to air pollution. The design includes the installation of a filter with a long service life, inaccessible to the user to prevent erroneous removal by the operator.

5) Failure to open the drawer can lead to air contamination - a programming error could allow the drawer to open based on the UFCNPA, ^{99m}Tc production sequence. Failure prevention is provided by the use of insulating elements inside the drawer and by software validation.

6) Incorrect opening of the drawer in post-firing can lead to air pollution. Refer to item 5)

• Potential excessive temperature hazards caused by the operation of the device. The device has been designed in such a way that the heating components are completely hidden so that the operator does not touch hot areas, reducing the hazardous situation to an acceptable level. The Operator's Manual contains warnings identifying the potential hazards of excessive temperatures. The likelihood of harm to the operator can only occur if he uses his hands to contact heated components, not the clamp.

• Hazards of biological contamination of the product or potential patient during operation of the device and its accessories, caused by improper manufacturing, operator, or potential failure conditions. The high firing

temperature (2750 ° C) will destroy any living biological molecules in the crucible. The PAS design includes a sequence of check valves, thereby preventing cross-contamination of the patient and device, and is also single-use, which eliminates any cross-contamination.

- Dangers associated with incorrect output of UFCNPA, ^{99m}Tc, and failures that may affect the quality and yield of the produced UFCNPA, ^{99m}Tc. The product is designed to control the generation of UFCNPA,^{99m}Tc and to prevent generation or injection if the appropriate conditions are not met. Failure conditions mentioned as potential hazards prevent the unit from working.
- Biological hazards of allergenicity, teratogenicity, carcinogenicity and mutagenicity. It was concluded that the likelihood of such a hazard is minimal or zero. Taking into account the use of argon, graphite, technetium (^{99m}Tc), plastic forms of the patient administration system, at the time of the review, any quantitative one might not have been established. There are no known incidents associated with the above hazards. The use of UFCNPA, ^{99m}Tc by patients is not constant, and the operators control the radiation exposure.
- Potential electrical hazards associated with a crucible furnace: liquid spills, accidental damage, and failure conditions. According to the design, the product (crucible furnace) should be located in the lower chamber of TechnegasPlus to reduce the risk of accidental damage, and installation in the drawer section provides good grounding to protect against electric shock. To prevent hazards associated with spillage of liquid, electronic components are covered with insulating material, thus sealing them against any potential short circuits due to liquid. The crucible furnace component is also designed to use DC voltage, which eliminates the risks associated with 240 V AC mains. Testing according to IEC 60601 has been carried out as proof of electrical safety and found to be in compliance with the requirements.

4. Published research results on this issue

Authors Pedro C. Laraa, Javier Burgosa, David Maciasa in the article “Low dose lung radiotherapy for COVID-19 pneumonia. The rationale for a cost-effective anti-inflammatory treatment ”proved that the use of low-dose external radiation therapy (0.5 Gy) promotes the implementation of the anti-inflammatory effect in the affected lung tissue [7].

Low-dose external beam radiation therapy is an affordable method with minimal toxicity and high cost-effectiveness.

In the article "Low dose radiation therapy as a potential life saving treatment for COVID-19-induced acute respiratory distress syndrome (ARDS)" by Gaurav Dhawana, Rachna Kapoorb, Rajiv Dhawanc, et al. recommend to use a low-dose external radiation therapy (0.3-0.5 Gy) in the acute phase of the disease, when there is a surge of cytokines, in order to reduce the likelihood of fulminant and long-term side effects [8].

To date, several pilot articles have been published in which the authors have demonstrated the feasibility and safety of low-dose irradiation in patients with COVID-19 associated with viral pneumonia [9, 10]. In the article "Low-Dose Whole-Lung Radiation for COVID-19 Pneumonia: Planned Day-7 Interim Analysis of a Registered Clinical Trial", the authors irradiated the entire lung volume with a dose of 1.5 Gy per 1 fraction in

five patients with various concomitant diseases, and the presence of severe respiratory distress requiring oxygen support. Within 24 hours after the session, 3 (60%) patients were removed from auxiliary methods of oxygenation, 4 people (80%) achieved CT-confirmed regression of pneumonia, no acute toxicity associated with radiation therapy was noted [9].

5. Goals and objectives of scientific research.

Objective: To determine the possibility, safety and effects of the use of inhaled low-dose radionuclide therapy in the complex treatment of patients with COVID-19 - associated viral pneumonia.

Tasks:

1. To investigate the dosimetric characteristics of the applied technique on anthropometric phantoms to obtain the coefficients of the transition from the rate of counting pulses over the region of interest to the activity contained in this region (in kBq).
2. To determine the accumulated dose in human lungs during internal irradiation of ^{99m}Tc in a group of healthy volunteers.
3. To develop a methodology for the use of inhaled low-dose radionuclide therapy in complex treatment of patients with COVID-19 - associated viral pneumonia.
4. To assess the possibility of using inhaled low-dose radionuclide therapy in the complex treatment of patients with COVID-19 - associated viral pneumonia.

6. Research design

At the first stage of preparation for the study, to obtain the coefficients of the transition from the pulse count rate over the region of interest to the absolute activity of ^{99m}Tc in the region of interest (in kBq), measurements will be made on a human phantom (see Section 7.3.1).

At the second stage of preparation for the study to determine the accumulated absorbed dose in the lungs of a volunteer under internal irradiation of ^{99m}Tc after inhalation of UFCNPA, ^{99m}Tc obtained from the TechnegasPlus generator into the crucible of which an activity equal to 833MBq is loaded, a group of 5 volunteers without clinical and radiological signs of pneumonia will be preliminarily formed. For this purpose, at the initial stage, patients from this group will undergo: thermometry and physical examination, as well as X-ray CT of the thoracic organs. In addition, given the importance of immunological criteria in the pathogenesis of Covid-19, it is advisable to assess the immune status and the level of blood cytokines (pro-inflammatory cytokines: TNFa, IL-6, IL-12 TNF-a4; anti-inflammatory cytokines IL-4, IL-10, TGFb).

In the absence of signs of pneumonia, patients in this group will undergo a single inhalation procedure, followed by a planar scintigraphy on a gamma camera at set intervals (see Item 7.3.2), and an assessment of the cytokine profile 3 hours after the procedure. The modes and geometry of measurements will strictly correspond to the modes and geometry of measurements on the phantom.

The study will enroll women and men aged 18 and over, hospitalized with a diagnosis of moderate new coronavirus infection (COVID-19) and receiving standard therapy.

Classification of COVID-19 by severity [11]:

Average, defined by the presence of at least one of the following signs:

- Fever above 38 ° C;
- NPV more than 22 / min;
- Shortness of breath during physical exertion;
- Pneumonia (susceptible to CT of the lungs);
- SpO2 <95%;
- CRP of blood serum more than 10 mg / l;

It is planned to include at least 10 patients in the protocol of a scientific prospective study.

All patients should undergo:

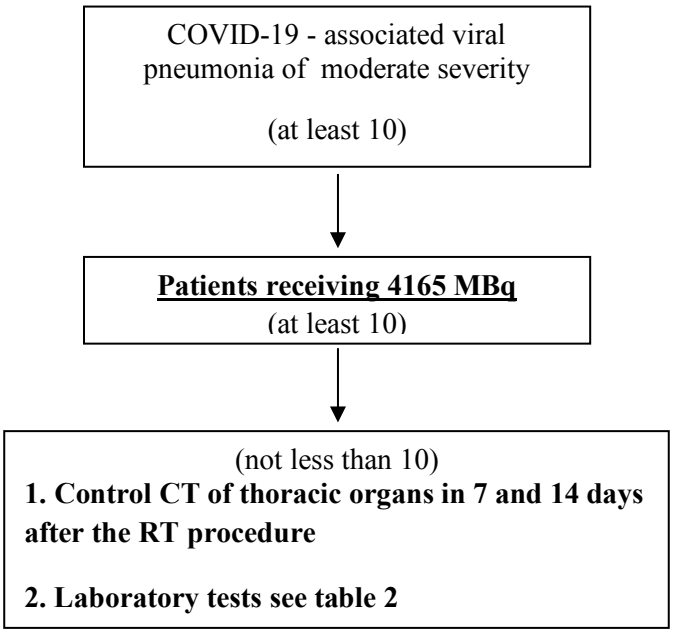
- laboratory test for confirmation of COVID-19 (PCR detection of SARS cov2 RNA);
- X-ray computed tomography of the thoracic organs, in which the presence of viral pneumonia is confirmed;
- the levels of cytokines in blood plasma were determined (TNFa, IL-6, IL-12 TNF-aE, IL-4, IL-10, TGFb, interferon-γ-inducible protein (IP-10), monocyte chemoattractant protein 1 (MCP-1)
- an assessment of the immune status was carried out,
- biochemical indicators (levels of immunoglobulins and CEC) and indicators of the blood coagulation system (hemostasiogram) were evaluated;
- the levels of pathogen-specific immunoglobulins A, M, G were assessed (one of the factors in predicting the severity of the course of the disease);
- output dosimetric control in accordance with the norms of NRB-99/2009 (SanPiN 2.6.1.2523-09).

Traditionally, in LDRT, the level of single doses with an anti-inflammatory effect ranges from 0.5 Gy to 1.0 Gy, and total doses - from 3 Gy to 6 Gy. With another method of dose administration, namely, by inhalation of UFCNPA, ^{99m}Tc, this range can be changed, therefore, the lower level is 10 cGy, and the upper one is 50 cGy.

Based on the dose coefficients, Table 1, presented in the ICRP Publication 128, in the lungs of a standard adult, in accordance with the standard kinetics model of the RFP UFCNPA, ^{99m}Tc, with inhalation of the drug activities of 833 MBq and 4165 MBq, average lung doses will be created internal irradiation equal to 0.1 Gy (10 cGy) and 0.5 Gy (50 cGy), respectively [12].**Table 1.**

Age	Adult	15 years	10 years	5 years	1 year
Dose cGy / MBq	0,012	0,016	0,022	0,033	0,063

Radionuclide therapy will be carried out no later than one day after CT of the thoracic organs by inhalation of UFCNPA, ^{99m}Tc, carbon nanoparticles with ^{99m}Tc radionuclide attached to them (physical half-life 6.04 hours), by loading the TechnegasPlus 4165 MBq generator into the crucible.



Patients will be transported by specially designated ambulance vehicles using personal protective equipment (goggles, disposable gloves, FFP2 or FFP3 respirator, type 1 anti-plague suit, shoe covers) by the driver and accompanying medical worker. All transported persons are provided with a medical mask. After delivery, the vehicles are disinfected in a specially equipped place on the territory of a medical organization that receives COVID-19 patients (suspected).

Personal protective equipment (goggles, disposable gloves, respirator of the appropriate protection class, type 1 anti-plague suit, shoe covers) will also be used to protect personnel.

At the end of the radionuclide therapy session, all surfaces in the room are treated with disinfectants with a virucidal effect, medical waste is collected in special containers for class B waste and disposed of, air disinfection is provided with bactericidal irradiators.

All work on packaging ^{99m}Tc, preparation of UFCNPA, ^{99m}Tc, inhalation of UFCNPA, ^{99m}Tc will be carried out in accordance with the norms of Radiation Standards-99/2009 (SanPiN 2.6.1.2523-09).

7. Technique for obtaining and introducing ultradispersed aerosol of carbon nanoparticles labeled with ^{99m}Tc, biodistribution, dosimetry

7.1 Methodology for obtaining and introducing UFCNPA, ^{99m}Tc

It is necessary to connect an argon gas cylinder to the TechnegasPlus generator and open the gas cylinder, connect the TechnegasPlus generator to the mains, turn on the TechnegasPlus generator and open the drawer. Remove the charcoal crucible from its packaging and place it on a watch glass. Before adding sodium pertechnetate, ^{99m}Tc (Na99mTcO4), it is necessary to moisten the crucible using absolute or 95% ethyl alcohol,

then the moistened crucible must be placed in the contacts of the drawer section. Next, the crucible must be filled with sodium pertechnetate, ^{99m}Tc (Na99mTcO4) with a volume of 0.1 to 0.3 ml with the required specific activity and close the drawer section. Start a slow heating cycle at the end of which, if necessary, you can refill the crucible with sodium pertechnetate, ^{99m}Tc (Na99mTcO4) to increase the specific activity, and repeat the slow heating cycle. Upon reaching the required specific activity, start the firing cycle, which consists in a short-term increase in temperature to 2700 ° C in an argon atmosphere, after which UFCNPA, ^{99m}Tc is ready for use within 10 minutes. After that, it is necessary to close the gas cylinder and disconnect it from the TechnegasPlus generator, turn off the TechnegasPlus generator and disconnect it from the mains.

For best results, ^{99m}Tc-labeled carbon ultrafine aerosol must be administered to the patient as soon as possible after being generated, and certainly within the 10 minutes allowed. The ^{99m}Tc-labeled carbon ultrafine aerosol is introduced to the patient through a series of deep and slow breaths with a 5 second delay of each breath through a special system of tubes and filters with a check valve. Before and during the inhalation of the ^{99m}Tc-labeled carbon ultrafine aerosol, all patients and volunteers will be tested for the degree of blood oxygen saturation (pulse oximetry).

7.2 Biodistribution UFCNPA, ^{99m}Tc

More than 96% of UFCNPA, ^{99m}Tc accumulates in the lung parenchyma within 6-48 hours after the end of inhalation. The bladder accumulates about 3-4% of the injected activity. The accumulation of the radiopharmaceutical in the parenchyma of the liver and spleen is not observed [13, 14].

7.3 Dosimetry

7.3.1. Measurements using a human phantom.

Measurements on a human phantom are carried out to obtain the coefficients of transition from the pulse count rate over the region of interest, obtained from planar scintigraphy in the "whole body" mode in the anterior and posterior direct projections (in imp./min), to the absolute activity of ^{99m}Tc in the region of interest (in kBq).

The measurements are made with the use of unified prefabricated human anthropometric phantoms UF-02T with different body manufactured by RADEK STC [15]. They are available at A. Tsyb MRRC.

Phantoms consist of rectangular polyethylene blocks weighing 1.0 kg and 0.5 kg. In the thoracic region of the phantom, there are phantoms of human lungs made of tissue-equivalent material with a density of 0.26 g / cm3 and a mass from 400 g to 1100 g, depending on the body weight of the phantom [16]. The phantoms of the lungs have through channels to accommodate sealed tubes with known ^{99m}Tc (kBq) activity, obtained from the ^{99mTc} generator immediately before measurements. Measurements using planar scintigraphy with the following scanning parameters: low energy high resolution (LEHR) collimators, 140 keV photopeak (^{99m}Tc), discriminator window width ± 7.5%, tabletop speed 16 cm / min, matrix 256 × 1024, are carried out and

recorded in strict compliance with the modes and geometry of measurements used in the corresponding measurements of patients and with the delineation of regions of interest.

According to the results of measurements on phantoms, the values of the transition coefficients from the counting rate of pulses in the region of interest (lungs) obtained from planar scintigraphy in the "whole body" mode in the anterior and posterior direct projections (in imp./min.) To the absolute activity of ^{99m}Tc in areas of interest (in kBq) - depending on the person's body weight. These coefficients are then used to determine the absolute activity of ^{99m}Tc in the lungs of patients with different body weights.

7.3.2 Determination of the accumulated absorbed dose in the lungs of volunteers under internal irradiation with ^{99m}Tc.

After inhalation of UFCNPA, ^{99m}Tc, each volunteer undergoes planar scintigraphy in the "whole body" mode in the anterior and posterior direct projections with contouring of the areas of interest (lungs, whole body, abdominal region) and recording the results of measurements over the regions of interest with the following scanning parameters: low collimators energy high resolution (LEHR), photopeak 140 keV (^{99m}Tc), discriminator window width ± 7.5%, table deck speed 16 cm / min, matrix 256 × 1024. Measurements are carried out and recorded in strict accordance with the modes and geometry of measurements used in the corresponding measurements of phantoms. The body weight, height and age of the volunteer are recorded. The activity of the RFP for inhalation, loaded into the crucible of the TechnegasPlus generator, equal to 833 MBq, is recorded. The time interval between the preparation of the RFP for inhalation and the beginning of inhalation, as well as the duration of inhalation and the number of breaths / exhales, are recorded. The number of impulses recorded over the areas of interest is recorded. Scintigraphy is performed at the following times after inhalation: 10 minutes, 1 hour, 3 hours, 6 hours, 8 hours, 24 hours. The exact time and duration are recorded. Based on the results of scintigraphy, the functions of retention and removal of the drug from the areas of interest are described. The values of the measurement results, expressed in pulses above the zones of interest, are converted into activity values, expressed in kBq, using the coefficients of the transition from the pulse count rate over the region of interest to the absolute activity of ^{99m}Tc in the region of interest obtained from the data of phantom measurements (see clause 7.3. one). The time integrals of these functions are the values of the accumulated activity (kBq × h). The calculation of the accumulated absorbed doses in the lungs and organs of a volunteer from internal irradiation of ^{99m}Tc is carried out according to the methodology of the Medical Internal Dose Committee [17], taking into account the results of measurements of the accumulated activity of ^{99m}Tc and using databases containing the values of the specific absorbed energy fractions of quantum and corpuscular energy calculated by the Monte Carlo method radiation in organs and tissues of a person of different sex and age [18-33].

8. Selection and exclusion of patients participating in scientific research

8.1 Criteria for the inclusion of patients in the protocol:

1. The presence of a signed informed consent form (IC) for participation in the study (signed by the subject or his legal representative);

2. Men and non-pregnant women aged 18 years and older, at the time of signing the IP, with the presence of early laboratory signs of a cytokine storm in accordance with the interim guidelines for the prevention, diagnosis and treatment of new coronavirus infection (Covid-19): increased serum ferritin levels blood> 600 ng / ml or a combination of two of the following indicators: a decrease in the number of blood platelets ≤ 180 * 109 / l, leukocytes ≤ 3.0 * 109 / l, lymphopenia or a rapid decrease in the number of platelets and / or leukocytes (within 24 hours) more than doubled against the background of persistent high inflammatory activity, increased activity of AST, serum triglycerides> 156 mg / dL; decrease in blood fibrinogen (≤ 360 mg / dL) [30].

Men and non-pregnant women over the age of 65 years with or without the early laboratory signs of a cytokine storm indicated above.

3. A positive laboratory test result for the presence of SARS-CoV-2 RNA using nucleic acid amplification methods at the time of signing the IP;

4. Admission in a hospital with a radiographically confirmed diagnosis of pneumonia;

8.2 Exclusion criteria

1. Severe/ extremely severe course of COVID-19 illness, determined by the presence of any of the following signs:

• Acute respiratory failure with the need for invasive respiratory support (tracheal intubation);

• septic shock;

• Multiple organ failure;

2. Life forecast - less than 24 hours, according to the researcher;

3. Forecast of stay in the research center less than 48 hours;

4. The use of another non-standard therapy regimen for the treatment of COVID-19;

5. Established diagnosis of active tuberculosis;

6. Pregnancy or breastfeeding period;

7. Significant diseases or laboratory abnormalities that, in the opinion of the investigator, may increase the risks of participating in the study.

8.3 Criteria for excluding patients from research:

Research subjects will be excluded from further participation in the research in the following cases:

• Revealing, after inclusion of the subject in the study, gross violations of the inclusion / exclusion criteria;

• Withdrawal by the research subject of his consent to participate in the research (despite the fact that the subject has the right not to report the reasons for the withdrawal of the IP, the researcher should make every

possible effort to clarify the reasons for the subject's refusal to participate, for example: the subject does not have an effect from therapy; toxicity / intolerance, etc.);

• Loss to follow-up (this refers to repeated missed visits and inability to contact the subject in other ways. The investigator should make every possible effort to contact the subject and obtain more specific reasons for discontinuing participation, for example: the subject does not feel that the therapy is effective) ; toxicity / intolerance, etc.);

• Termination of the study as decided by local ethics committees or regulatory authorities.

9. Methods and terms of assessment, registration, accounting and analysis of performance indicators.

X-ray CT of the thoracic organs, detailed clinical and biochemical blood tests (ALT, AST, bilirubin, glucose, albumin, creatinine, LDH, CPK, troponin, lactate, ferritin, C-reactive protein, electrolytes), IL-6, NT-proBNP, coagulogram (APTT, prothrombin time, D-dimer), immunogram.

Terms: 1) the evaluation of the clinical results of treatment is carried out during the entire observation period for a limited period of hospitalization of the patient, on the 7th and 14th days after irradiation.

2) laboratory parameters assessment - during the in-patient period, in accordance with clinical need, but at least 4 times: before the start of RT, in 1, 3, 7 days after irradiation, and before the patient's discharge, cytokine levels - after 3 hours and after 10-12 hours from the procedure.

Table 2.

Methods of assessment	Terms
X-ray CT of thoracic organs	Before treatment, on 7th and 14th days after radionuclide therapy, or according to indications
Complete blood count (detailed)	- before treatment - on 1st and 3rd days after irradiation, then, according to indications, once every 2-3 days
ALT, AST, bilirubin, glucose, albumin, creatinine, LDH, lactate, electrolytes	- - before treatment - on the1st and 3rd days after irradiation, then, according to indications, once every 2-3 days
CPK, troponin, C-reactive protein, IL-6, NT-proBNP, ferritin, procalcitonin	- before treatment - on the1^{st,}, 3rd и 7th days after treatment after irradiation, then, according to indications,
Coagulogram (APTT, prothrombin time, D-dimer)	- before treatment - on the 1st,, 3rd и 7th days after treatment after irradiation, then, according to indications,
Immunogram	- before treatment - on the 1st,, 3rd и 7th days after treatment after irradiation, then, according to indications,
Antibodies to SARS cov2 A, M, G	- before treatment - on the 7th day after treatment after irradiation, then, according to indications,
Cytokine profile	before treatment, 3 hours after the procedure, 12 hours after the procedure, on the 3rd and 7th days after irradiation

10. Statistical Analysis Plan

Laboratory indicators were evaluated in accordance with the GLP criteria and with the laboratory standards for them . The assessment of biochemical parameters, the levels of circulating immune complexes and the antibody response to the SARS-cov2 pathogen was carried out on an automatic analyzer AU 480 (Becman Coulter) . The hemostasis parameters were evaluated using an ALC Elit PRO automatic analyzer and a TAG 5000 thromboelastograph. The evaluation of immunological parameters was carried out in the direct immunofluorescence reaction with the detection of the results by 6-parameter flow cytometry on the FACS Canto II. Flow cytometry data were processed in the FCS3.0 and Kaluza software applications (Becman Coulter).

Statistical data processing was carried out using the SPSS 2020 program for Windows. The statistical analysis included an estimate of the average values for the sample size, the average value, the minimum and maximum values, the standard deviation, the sum, and the standard error of the average.

To determine the reliability of the differences in the indicators, a T-test for independent variables was used, where for each variable being compared, the sample size, the average value, the standard deviation and the standard error of the average value were compared. For the difference between the means: the average value, standard error, and confidence interval is assumed to be 95%, the significance of the differences is considered reliable at $p<0.05$ and highly reliable at $p< 0.0001$. The Levin's criterion of equality of variances and the t-criterion of equality of averages for both the combined and separate variances are used.

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Appendix 1

Informed consent of the patient to participate in the scientific study

"Study of the safety and effects of inhaled low-dose radionuclide therapy in the complex treatment of patients with COVID - 19 – associated viral pneumonia"

Place of study: A. Tsyb Medical Radiological Research Centre - Branch of the National Medical Research Radiological Centre of The Ministry of Health of the Russian

Address of the healthcare institution: 4 Koroleva str., Obninsk, Kaluga Region, 249036, Russian Federation.

Information about the study:

It is known that the coronavirus infection (Covid-19) is a pandemic of unprecedented scale. The number of patients infected worldwide is increasing exponentially. And although the mortality of the disease depends on many factors, one of the main causes of death is pneumonia, which causes respiratory failure, which is resistant to artificial lung ventilation. Infection of epithelial cells of the respiratory tract with coronavirus (SARS-CoV-2) causes a severe inflammatory form of programmed cell death, which in some cases triggers a cascade of difficult-to-control reactions, the so-called cytokine storm. It is reliably known that radiation therapy in low doses (up to 100-150 sGr) has a pronounced anti-inflammatory effect, and previously this method was successfully used for the treatment of bacterial and viral pneumonia, before the widespread use of antimicrobial agents. Preliminary data from the current international phase 1-2 studies also demonstrate the safety and effectiveness of radiation therapy for coronavirus pneumonia.

You are invited to participate in a scientific study in which patients with pneumonia developed as a result of Covid-19 infection, who do not need oxygen support, will be exposed to a single dose of the entire lung volume by loading 833MBk to 4165MBk of sodium pertechnetate into the crucible of the TechnegasPlus generator, followed by inhalation by the patient of an ultrafine aerosol of ^{99m}Tc-labeled carbon nanoparticles (physical half-life of 6.04 hours) obtained from the generator TechnegasPlus. The study will evaluate the effectiveness and safety of radiation treatment, according to clinical and serological indicators, both during hospitalization and after the end of treatment, at time intervals determined by the protocol.

Possible benefits from your participation in this study. Participation in this study means that you will be under the supervision of a research physician who will be in contact with you to try to prevent or influence the side effects of the underlying disease/treatment. The purpose of this study is to explore the possibility of improving the safety and effectiveness of treatment for your disease.

Cost. The study is free of charge for the patient.

The right to withdraw from the study. Your participation in this scientific research is voluntary. You can decide to stop participating in the study at any time. This will not entail any penalties. Your decision to stop participating in the study will not in any way affect the order of medical care provided to you and the attitude of the doctors of the research center towards you. For its part, the research doctor also has the right to terminate your participation in the study in cases where it is in your best interests, namely: if you do not properly follow the instructions. If you are considering or have decided to terminate your participation in the study ahead of time, it is advisable to inform the research doctor. If you decide to terminate your participation in the study early, the research physician may ask you to visit the research center to conduct a final examination and record safety indicators, as well as recommendations for your subsequent treatment.

Privacy. All necessary measures will be taken to protect personal information and ensure the confidentiality of records, but complete confidentiality will not be guaranteed. The results of the study can be published in medical literature or journals and presented at scientific conferences, as well as used for educational purposes. However, no personal information will be disclosed in materials intended for training or presentation to a wide range of people. Your medical records relating to the study will be kept in accordance with the law. One copy of this document will be kept at the research center along with the research records. The second copy will be kept by you.

Thus, having read all the information provided to me by the research physician,

I, the undersigned_____
(Patient's full name)
in an accessible and understandable form, I am informed about the purpose of the study and the method of conducting the proposed option of radionuclide therapy for the entire volume of **the lungs for pneumonia caused by SARS-CoV-2 infection (Covid-19, coronavirus-19)**, as well as about other possible treatment options for this disease/condition; the benefits, complications and side effects known at the time of the study, which may occur during and after radiation treatment.

I voluntarily give my consent to participate in the study. I am aware that I can withdraw from this study at any time.

I confirm that I have carefully read and understood all the information provided to me about the study and the proposed treatment method. I was given time to carefully study the "Informed Consent to Participate in Scientific Research " form and the information about the scientific research. I had the opportunity to ask the research doctor questions and find out everything that was not clear about my participation in this study. All my questions have been answered fully, and I am satisfied with them. I am informed:

- about the full diagnosis of the disease, about all the circumstances related to my illness;

- about possible methods and treatment options, about the need, purpose and expected results of the upcoming course of radiation therapy, about the risk associated with treatment when performing this scientific study;

- that it is impossible to accurately predict the outcome and toxicity of treatment, in addition, the results are delayed in time;

- about possible complications during and after treatment;

- that full guarantees regarding the results of therapy during and after the end of the proposed treatment option were not provided to me;

- that during the preparation and conduct of scientific research, unforeseen emergency circumstances and complications may arise, in which I will not be able to consent to the necessary emergency actions. In this case, the course of treatment can be changed by doctors at their discretion;

- that during the proposed treatment option, the use of alcohol and narcotic drugs is strictly prohibited, as well as the unauthorized use of medicines, biological additives or other means that are not allowed for use in the Russian Federation without the consent of the doctor. I am also informed that if this clause is violated, the special treatment will be immediately terminated without my consent.;

I am fully informed that, in the interests of my health and well-being, I must adhere to the recommendations of my doctor, and that withholding any information regarding my past or present health status or taking any medications may adversely affect my health.

I know that it is my duty to inform the doctor of any health problems, allergic reactions, or individual drug intolerance, as well as of any past alcohol or drug abuse, as well as any changes in my condition and medications that I will take in the course of its implementation.

I voluntarily agree that my data obtained in the course of the research will be used for scientific purposes and published, subject to confidentiality rules.

I have read all the paragraphs of this document, as evidenced by my signature below:

_____ _____ ____/_____ 2020

Patient's signature (Legal representative's signature) | Patient's full name (Legal representative's full name)

_____ _____ ____/_____2020

(Research physician's signature) | (Research physician's full name)

With this signature, I confirm that I have received one signed and dated copy of the patient's informed consent to participate in the scientific study

_____ _____ ____/_____2020

Patient's signature | Patient's full name

Appendix 2

Informed consent of a volunteer

to participate in the scientific study

"Study of the safety and effects of inhaled low-dose radionuclide therapy in the complex treatment of patients with COVID - 19 – associated viral pneumonia"

Place of study: A. Tsyb Medical Radiological Research Centre - Branch of the National Medical Research Radiological Centre of The Ministry of Health of the Russian

Address of the healthcare institution: 4 Koroleva str., Obninsk, Kaluga Region, 249036, Russian Federation.

Information about the study:

It is known that the coronavirus infection (Covid-19) is a pandemic of unprecedented scale. The number of patients infected worldwide is increasing exponentially. And although the mortality of the disease depends on many factors, one of the main causes of death is pneumonia, which causes respiratory failure, which is resistant to artificial lung ventilation. Infection of epithelial cells of the respiratory tract with coronavirus (SARS-CoV-2) causes a severe inflammatory form of programmed cell death, which in some cases triggers a cascade of difficult-to-control reactions, the so-called cytokine storm. It is well known that radiation therapy in low doses (up to 100-150 sGr) has a pronounced anti-inflammatory effect, and previously this method was successfully used for the treatment of bacterial and viral pneumonia, before the widespread use of antimicrobial agents. Preliminary data from the current international phase 1-2 studies also demonstrate the safety and effectiveness of radiation therapy for coronavirus pneumonia.

You are invited to participate in a scientific study in which volunteers will be inhaled with an ultrafine aerosol of ^{99m}Tc-labeled carbon nanoparticles (physical half-life 6.04 hours) obtained from the TechnegasPlus generator by loading 833MBk of sodium pertechnetate into the crucible of the TechnegasPlus generator, followed by planar scintigraphy in the "whole body" mode in the anterior and posterior straight projections.

The right to withdraw from the study. Your participation in this scientific research is voluntary. You can decide to stop participating in the study at any time. This will not entail any penalties. Your decision to stop participating in the study will not in any way affect the order of medical care provided to you and the attitude of the doctors of the research center towards you. For its part, the research doctor also has the right to terminate your participation in the study in cases where it is in your best interests, namely: if you do not properly follow the instructions. If you are considering or have decided to terminate your participation in the study ahead of time, it is advisable to inform the research doctor. If you decide to terminate your participation in the study early, the research physician may ask you to visit the research center to conduct a final examination and record safety indicators, as well as recommendations for your subsequent treatment.

Privacy. All necessary measures will be taken to protect personal information and ensure the confidentiality of records, but complete confidentiality will not be guaranteed. The results of the study can be published in medical literature or journals and presented at scientific conferences, as well as used for educational purposes. However, no personal information will be disclosed in materials intended for training or presentation to a wide range of people. Your medical records relating to the study will be kept in accordance with the law. One copy of this document will be kept at the research center along with the research records. The second copy will be kept by you.

Thus, having read all the information provided to me by the research physician,

I, the undersigned_____

(Volunteer's full name)
in an accessible and understandable form, I am informed about the purpose of the study and the method of inhaling an ultrafine aerosol of ^{99m}Tc-labeled carbon nanoparticles obtained from the TechnegasPlus generator, followed by planar scintigraphy in the "whole body" mode in the anterior and posterior straight projections.

I voluntarily give my consent to participate in the study. I am aware that I can withdraw from this study at any time.

I confirm that I have carefully read and understood all the information provided to me about the study. I was given time to carefully study the "Informed Consent to Participate in Scientific Research " form and the information about the scientific research. I had the opportunity to ask the research doctor questions and find out everything that was not clear about my participation in this study. All my questions have been answered fully, and I am satisfied with them. I am informed:

- possible complications during and after the inhalation of an ultrafine aerosol of carbon nanoparticles labeled with ^{99m}Tc, followed by planar scintigraphy in the "whole body" mode in the anterior and posterior straight projections;

- that during the preparation and conduct of scientific research, unforeseen emergency circumstances and complications may arise, in which I will not be able to consent to the necessary emergency actions. In this case, the course of treatment can be changed by doctors at their discretion;

- that during the study it is strictly prohibited to use alcohol and narcotic drugs, as well as the unauthorized use of medicines, biological additives or other means that are not allowed for use in the Russian Federation without the consent of the doctor. I am also informed that if this clause is violated, the special treatment will be immediately terminated without my consent.;

I am fully informed that, in the interests of my health and well-being, I must adhere to the doctor's recommendations, and that withholding any information regarding my past or present health status or taking any medications may adversely affect my health.

I know that it is my duty to inform the doctor of any health problems, allergic reactions, or individual drug intolerance, as well as of any past alcohol or drug abuse, as well as any changes in my condition and medications that I will take in the course of its implementation.

I voluntarily agree that my data obtained in the course of the research will be used for scientific purposes and published, subject to confidentiality rules.

I have read all the paragraphs of this document, as evidenced by my signature below:

_____ _____ ____/_____2020

(Volunteer's Signature) (Volunteer's full name)

_____ _____ _____/_____2020

((Research physician's sSignature) (Research physician's full name)