Journal of Molecular Medicine (2021) 99:303–310
https://doi.org/10.1007/s00109-020-02027-1

JMolMed

COMMENTARY

# An update to "novel therapeutic approaches for treatment of COVID-19"

Nikoo Hossein-khannazer[1,2] · Bahare Shokoohian[3,4] · Anastasia Shpichka[5,6,7] · Hamid Asadzadeh Aghdaei[8] · Peter Timashev[5,6,7,9] · Massoud Vosough[3]

Received: 13 November 2020 / Revised: 10 December 2020 / Accepted: 14 December 2020 / Published online: 3 January 2021


Although the exact mechanism of pathogenesis in COVID-19 is not fully understood, cytokine storm following viral infection plays an important role in the initiation and progression of disease. SARS-CoV-2 infection induces over-activation of the immune system and massive production of inflammatory cytokines. Therefore, it is necessary to develop new strategies to modulate inflammatory responses [1]. Despite many efforts to improve therapeutic protocols for COVID-19, there is no specific approved treatment or preventable vaccine for this disease [2, 3]. However, intensive research has been conducted to both prevent and treat COVID-19. This commentary is an update for our recent paper in "Journal of Molecular Medicine, June 2020" and highlights the recent achievements in terms of preventive and therapeutic approaches in COVID-19 [4].

## Development of SARS-CoV-2 preventive vaccines

- mRNA-1273 (Moderna TX, Inc.) is an mRNA vaccine that is composed of synthetic mRNA expressing the prefusion-stabilized SARS-CoV-2 spike trimer (mRNA-1273) [5, 6]. The efficacy and immunogenicity of Moderna vaccine investigated in a phase III clinical trial (NCT04470427). Moderna has announced its primary efficacy analysis (95%) and recently applied to the FDA (USA) for emergency use authorization.
- ChAdOx1 nCOV-19 is another vaccine under evaluation in phase II/III clinical trials. This vaccine has been developed by Oxford University and produced due to the technology in which an adeno-viral vector encodes SARS-CoV-2 S protein (NCT04400838) [7]. The pre-clinical investigations showed that ChAdOx1 nCOV-19 was immunogenic in vaccinated mice and rhesus macaques and triggered robust humoral and cell-mediated responses [8]. Its safety and immunogenicity were evaluated in a phase II/III trial in a prime-boost regimen in young and old adults. In 14 days after receiving the boost dose, > 99% of participants had neutralizing antibodies [9].
- BNT162b2 is a COVID-19 RNA vaccine candidate that has been announced by BioNTech/Pfizer. This vaccine encodes the receptor-binding domain (RBD) of the

✉ Peter Timashev
timashev.peter@gmail.com

✉ Massoud Vosough
masvos@Royaninstitute.org

1 Department of Immunology, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

2 Gastroenterology and Liver Diseases Research Center, Research Institute for Gastroenterology and Liver Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran

3 Department of Regenerative Medicine, Cell Science Research Center, Royan Institute for Stem Cell Biology and Technology, ACECR, Tehran Iran

4 Department of Medical Biotechnology, School of Advanced Technologies in Medicine, Tehran University of Medical Sciences, Tehran, Iran

5 Institute for Regenerative Medicine, Sechenov University, Moscow, Russia

6 Chemistry Department, Lomonosov Moscow State University, Moscow, Russia

7 World-Class Research Center "Digital biodesign and personalized healthcare", Sechenov University, Moscow, Russia

8 Department of Molecular Biology, Basic and Molecular Epidemiology of Gastrointestinal Disorders Research Center, Research Institute for Gastroenterology and Liver Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran

9 Department of Polymers and Composites, NN Semenov Institute of Chemical Physics, Moscow, Russia

SARS-CoV-2 spike protein. Data from a phase III clinical trial showed vaccine efficiency over 95% [12, 13].

- CoronaVac is inactivated SARS-CoV-2 manufactured by Sinovac Life Sciences (Beijing, China). Its safety, tolerability, and immunogenicity have been approved in healthy adults aged 18–59 years in a phase I/II clinical trial [14]; and now it is under investigation in a phase III clinical trial (NCT04582344).
- Gam-COVID-Vac (Sputnik V) is a combined vector vaccine that consists of recombinant adenovirus type 26 (rAd26) and type 5 (rAd5) vectors. They carry the spike glycoprotein gene. Gam-COVID-Vac has been developed by Gamaleya National Research Center for Epidemiology and Microbiology (Moscow, Russia) [15]. Its safety and immunogenicity was approved in two formulations in a phase I/II clinical trial [15]. And now, the safety and efficiency of this vaccine is under assessment in a phase III clinical trial (NCT04530396).
- Using Ad5 vector to carry the spike glycoprotein gene, CanSino Biologics Inc. (China) has developed a recombinant novel coronavirus vaccine which safety and efficiency has been being evaluated in a phase III clinical trial (NCT04526990).

The progress in vaccine development is critically discussed in the following recently published reviews in detail [10, 11].

## SARS-CoV-2 therapeutic approaches

In our recently published paper entitled "Novel therapeutic approaches for treatment of COVID-19," we grouped novel therapies into passive immunotherapy, cell-based therapies (including immune cell and non-immune cell therapies), monoclonal antibodies, and anti-viral drugs.

Searching terms "COVID-19" and "treatment" using https://clinicaltrials.gov/ resulted in more than 2200 clinical trials (October 29, 2020). Among these clinical trials, over 200 studies were related to cell-based therapies. They included mesenchymal stromal cell (MSC) therapies and adoptive T cell and natural killer (NK) cell therapies. Other studies applied monoclonal antibodies and nano-medicine to treat COVID-19 patients (Table 1) (Figs. 1 and 2).

### Mesenchymal stromal cells in COVID-19 treatment

- Due to the immunomodulatory effects of MSCs [16, 17], clinical trials using MSCs from various sources including the umbilical cord, adipose tissue, and bone marrow have been registered for the treatment of acute respiratory distress syndrome (ARDS) caused by COVID-19 (NCT04341610, NCT04366063). Primary results showed that this strategy was safe and effective. The MSC therapy improved lung function, downregulated inflammatory cytokines, increased anti-inflammatory ones, and decreased mortality rate [18–20]. MSCs exert their anti-inflammatory properties through direct cell-cell contact, paracrine effects, and their extracellular vesicles such as exosomes [21, 22]. It seems that application of MSCs and their exosomes could be a promising approach for the management of respiratory complications in COVID-19.

### Adoptive T cells in COVID-19 treatment

- Some studies reported lymphopenia and functional exhaustion due to the over-activation of the immune system during infection [23]. COVID-19 specific T and $T_{CD8+}$ cells play an important role in the virus clearance by producing inflammatory cytokines and their cytotoxicity effects [24]. Moreover, virus-specific memory T cells were isolated from the serum of the recovered patients [25–27]. Based on this evidence, recent clinical trials designed and used the adoptive T cells in severe COVID-19 patients. Using this treatment protocol, HLA-matched T cells from fully recovered patients were transfused into newly infected individuals. This approach may help patients who are at the risk of requiring mechanical ventilation (NCT04457726, NCT04401410, and NCT04406064).

### Exosomes derived from adoptive T cells in COVID-19 treatment

- In addition, another clinical trial used COVID-19-specific T cell-derived exosomes (CSTC-Exo) for the treatment of early infected patients in order to boost the IFN-γ production. Compared to the cells, CSTC-Exo does not need HLA-matching, and their administration route is an aerosol inhalation (NCT04389385). If it meets the endpoints, it could be a suitable alternative as an off-the-shelf product.
- Since regulatory T cells (Treg) are known as major anti-inflammatory T cell subsets, Treg cell therapy may be a novel regenerative and anti-inflammatory treatment strategy for COVID-19. Infusion of cord blood-derived Treg cells (CK0802) may improve the ARDS symptoms in these patients (NCT04468971). RAPA-501-ALLO is a hybrid Treg/Th2 off-the-shelf reprogrammed Treg cell product produced by the healthy donors. RAPA-501-ALLO could have a dual advantage by modulating Th1 and Th17 subpopulations and inhibiting the massive production of inflammatory cytokines, as well as regenerating the damaged alveolar tissues [28]. This product may be a useful therapeutic option for the treatment of severe COVID-19 (NCT04482699).

**Table 1** SARS-CoV-2 therapeutic approaches

| Therapeutic approach | Number of studies | CT number | Status | Phase | The product used |
|---|---|---|---|---|---|
| MSC | 65 | NCT04366063 | Recruiting | II/III | MSC, MSC + MSC-EVs |
| | | NCT04333368 | Recruiting | I/II | UC-MSC |
| | | NCT04461925 | Recruiting | I/II | Placenta-derived MSC/UC-MSC |
| | | NCT04486001 | Not yet recruiting | I | Allogenic AD-MSC |
| | | NCT04348435 | Enrolling by invitation | II | AD-MSC |
| | | NCT04473170 | Completed | II | Peripheral blood stem cells |
| | | NCT04445454 | Recruiting | II | BM-MSC |
| | | NCT04349631 | Enrolling by invitation | II | Autologous AD-MSC |
| | | NCT04525378 | Recruiting | I | MSC |
| | | NCT04392778 | Recruiting | I/II | MSC |
| | | NCT04573270 | Completed | I | UC-MSC |
| | | NCT04447833 | Recruiting | I | Allogenic BM-MSC |
| | | NCT04437823 | Recruiting | II | UC-MSC |
| | | NCT04288102 | Completed | II | UC-MSC |
| | | NCT04252118 | Recruiting | I | MSC |
| | | NCT04273646 | Not yet recruiting | - | UC-MSC |
| | | NCT04331613 | Recruiting | I/II | CAStem; regulatory cells from (hESCs) |
| | | NCT04537351 | Recruiting | I/II | CYP-001(MSC from iPS) |
| | | NCT04313322 | Recruiting | I | Wj-MSC |
| | | NCT04299152 | Recruiting | II | BM-MSC |
| | | NCT04400032 | Enrolling by invitation | I | Olfactory mucosa-derived MSCs |
| | | NCT04382547 | Not yet recruiting | I/II | Cord-blood MSC |
| | | NCT04345601 | Recruiting | I | Cord-blood MSC |
| | | NCT04565665 | Recruiting | I | MSC |
| | | NCT04361942 | Not yet recruiting | II | AD-MSC |
| | | NCT04527224 | Recruiting | II | UC-MSC |
| | | NCT04366271 | Recruiting | II | UC-MSC |
| | | NCT04339660 | Active, not recruiting | I/II | WJ-MSC |
| | | NCT04456361 | Not yet recruiting | I | WJ-MSC |
| | | NCT04390152 | Not yet recruiting | I/II | MSC |
| | | NCT04535856 | Recruiting | I | UC-MSC |
| | | NCT04457609 | Not yet recruiting | I | BM-MSC |
| | | NCT04346368 | Active, not recruiting | I/II | UC-MSC |
| | | NCT04371601 | Active, not recruiting | I | AD-MSC |
| | | NCT04362189 | Not yet recruiting | II | MSC |
| | | NCT04467047 | Not yet recruiting | I | AD-MSC |
| | | NCT04348461 | Recruiting | II | MSC |
| | | NCT04416139 | Recruiting | II | DP-MSC |
| | | NCT04336254 | Not yet recruiting | I/II | UC-MSC |
| | | NCT04452097 | Not yet recruiting | I | AD-MSC |
| | | NCT04428801 | Recruiting | II | WJ-MSC |
| | | NCT04390139 | Recruiting | I/II | AD-MSC |
| | | NCT04366323 | Active, not recruiting | I/II | hCT-MSC |
| | | NCT04355728 | Recruiting | I/II | UC-MSC |
| | | NCT04399889 | Not yet recruiting | I/II | UC-LSC |
| | | NCT04429763 | Recruiting | II | UC-MSC |
| | | NCT04494386 | Recruiting | I/II | UC-MSC |
| | | NCT04269525 | Not yet recruiting | II | Remestemcel-L |
| | | NCT04490486 | Recruiting | I | BM-MSC |
| | | NCT04371393 | Not yet recruiting | III | BM-MSC |
| | | NCT04377334 | Recruiting | II | Autologous AD-MSC |
| | | NCT04397796 | Not yet recruiting | I | placental mesenchymal-like adherent stromal cells |
| | | NCT04352803 | Recruiting | I | DP-MSC |
| | | NCT04389450 | Not yet recruiting | II | MSC |
| | | NCT04302519 | Recruiting | I | MSC |
| | | NCT04466098 | Not yet recruiting | II | NestaCell® |
| | | NCT04522986 | Not yet recruiting | I | UC-MSC |
| | | NCT04315987 | Not yet recruiting | II | MSCs or MSCs RNA-engineered |
| | | NCT04398303 | Not yet recruiting | I/II | UC-MSC |
| | | NCT04524962 | Recruiting | I/II | MultiStem; BM-MSC |
| | | NCT03042143 | Recruiting | | |
| | | NCT04367077 | Available | | |
| | | NCT04338347 | | | |
| | | NCT04451291 | | | |
| | | NCT04445220 | | | |
| T cell | 7 | NCT04351659 | Recruiting | I | Convalescent donor |
| | | NCT04457726 | Recruiting | I/II | Convalescent donors |
| | | NCT04482699 | Not yet recruiting | I/II | RAPA-501-ALLO (allogeneic hybrid TREG/Th2 Cells) |
| | | NCT04389385 | Active, not recruiting | I | T cell-derived exosomes |
| | | NCT04406064 | Not yet recruiting | II | Viral-specific T cells |
| | | NCT04401410 | Not yet recruiting | I | Specific T cell |
| | | NCT04468971 | Recruiting | I | cord blood-derived T regulatory cells |
| NK cell | 5 | NCT04324996 | Recruiting | I/II | NKG2D-ACE2 CAR-NK |
| | | NCT04365101 | Recruiting | I/II | CYNK-001(human placental) |
| | | NCT04280224 | Recruiting | I | NK |
| | | NCT04344548 | Not yet recruiting | I/II | Allogeneic NK cell transfer |
| | | NCT04363346 | Recruiting | I | NK cell derived from an iPSC |

**Table 1** (continued)

| Therapeutic approach | Number of studies | CT number | Status | Phase | The product used |
|---|---|---|---|---|---|
| CD34+ cells | 1 | NCT04522817 | Not yet recruiting | I | Peripheral blood-derived autologous CD34+ cells |
| Acellular product | 1 | NCT04384445 | Recruiting | I/II | Zofin; human amniotic fluid (HAF) |
| Monoclonal antibody | 80 | NCT04413838 | Not yet recruiting | II | Nivolumab |
| | | NCT04268537 | Not yet recruiting | II | PD-1 blocking antibody |
| | | NCT04464395 | Recruiting | I | monoclonal antibody targeting the CD73 |
| | | NCT04334044 | Recruiting | I/II | Ruxolitinib is an inhibitor of JAK1/2 |
| | | NCT04390464 | Recruiting | IV | Ravulizumab/Baricitinib |
| | | NCT04331665 | Not yet recruiting | - | Ruxolitinib |
| | | NCT04439006 | Recruiting | II | Ibrutinib |
| | | NCT04346277 | Available | - | IC14, against human CD14 |
| | | NCT04441918 | Recruiting | I | Anti-SARS-CoV-2 |
| | | NCT04354766 | Recruiting | - | Anti-SARS-CoV-2 |
| | | NCT04425629 | Recruiting | I/II | Anti-Spike (S) |
| | | NCT04426695 | Recruiting | I/II | Anti-Spike (S) |
| | | NCT04483375 | Recruiting | I | Anti-SARS-CoV-2 |
| | | NCT04409509 | Recruiting | II | Garadacimab; anti-factor XIIa |
| | | NCT04391309 | Not yet recruiting | II | Antibody to CD14 |
| | | NCT04351152 | Recruiting | III | Lenzilumab; anti GM-CSF |
| | | NCT04341116 | Recruiting | I/II | Anti GM-CSF |
| | | NCT04519437 | Recruiting | I | Anti-Spike (S) |
| | | NCT04432298 | Recruiting | II | Pamrevlumab; anti-Connective tissue growth factor |
| | | NCT04545060 | Recruiting | II/III | Anti-SARS-CoV-2 |
| | | NCT04452318 | Recruiting | III | Anti-Spike (S) |
| | | NCT04429529 | Active, not recruiting | I | Anti-SARS-CoV-2 |
| | | NCT04324021 | Recruiting | II/III | Emapalumab/anakinra |
| | | NCT04561076 | Not yet recruiting | I | Anti-Spike (S) |
| | | NCT04351243 | Recruiting | II | Gimsilumab; Anti GM-CSF |
| | | NCT04343651 | Active, not recruiting | II | Leronlimab; Anti-CCR5 |
| | | NCT04386239 | Not yet recruiting | I | Sarilumab; Anti-IL-6 |
| | | NCT04357808 | Recruiting | II | Sarilumab; Anti-IL-6 |
| | | NCT04305106 | Recruiting | - | Bevacizumab; Anti-VEGF |
| | | NCT04570397 | Not yet recruiting | III | Ravulizumab; Anti- Complement component 5 |
| | | NCT04435184 | Recruiting | II | Crizanlizumab; anti-P-selectin |
| | | NCT04377750 | Recruiting | IV | Tocilizumab; anti-IL-6R |
| | | NCT04516564 | Recruiting | I | AK119; anti-CD73 |
| | | NCT04519424 | Not yet recruiting | II | CSL324; anti-GCSF |
| | | NCT04447469 | Recruiting | II/III | Mavrilimumab; anti-GM-CSF-Rα |
| | | NCT04397497 | Not yet recruiting | II | Mavrilimumab; anti-GM-CSF-Rα |
| | | NCT04454398 | Recruiting | I | Anti-Spike (S) |
| | | NCT04476979 | Recruiting | II | Tocilizumab; anti-IL-6R |
| | | NCT04347239 | Recruiting | II | Leronlimab; anti-complement component 5 |
| | | NCT04324073 | Active, not recruiting | II/III | Sarilumab; anti-IL-6 |
| | | NCT04365153 | Active, not recruiting | II | Canakinumab; anti-IL-1-β |
| | | NCT04322773 | Recruiting | II | Tocilizumab; anti-IL-6R |
| | | NCT04331808 | Active, not recruiting | II | Tocilizumab; anti-IL-6R |
| | | NCT04355494 | Available | - | Eculizumab; anti-complement component 5 |
| | | NCT04369469 | Recruiting | III | Ravulizumab; anti-complement component 5 |
| | | NCT04445272 | Recruiting | II | Tocilizumab |
| | | NCT04479358 | Recruiting | II | Tocilizumab |
| | | NCT04317092 | Recruiting | II | Tocilizumab |
| | | NCT04345445 | Not yet recruiting | III | Tocilizumab |
| | | NCT04412772 | Recruiting | III | Tocilizumab |
| | | NCT04331795 | Recruiting | II | Tocilizumab |
| | | NCT04377659 | Recruiting | II | Tocilizumab |
| | | NCT04412291 | Recruiting | II | Tocilizumab/anakinra |
| | | NCT04359667 | Not yet recruiting | II | Tocilizumab |
| | | NCT04335071 | Recruiting | II | Tocilizumab |
| | | NCT04372186 | Active, not recruiting | III | Tocilizumab |
| | | NCT04356937 | Active, not recruiting | III | Tocilizumab |
| | | NCT04320615 | Completed | III | Tocilizumab |
| | | NCT04377503 | Not yet recruiting | II | Tocilizumab |
| | | NCT04363736 | Completed | II | Tocilizumab |
| | | NCT04363853 | Recruiting | II | Tocilizumab |
| | | NCT04361032 | Not yet recruiting | III | Tocilizumab |
| | | NCT04409262 | Recruiting | III | Tocilizumab |
| | | NCT04424056 | Not yet recruiting | III | Anakinra, Tocilizumab, Ruxolitinib |
| | | NCT04332913 | Recruiting | - | Tocilizumab |
| | | NCT04335305 | Recruiting | II | Tocilizumab, Pembrolizumab |
| | | NCT04560205 | Recruiting | I | Tocilizumab |
| | | NCT04306705 | Recruiting | - | Tocilizumab |
| | | NCT04310228 | Recruiting | - | Tocilizumab |
| | | NCT04315480 | Active, not recruiting | II | Tocilizumab |
| | | NCT04339712 | Recruiting | II | Anakinra, Tocilizumab |
| | | NCT04519385 | Completed | - | Tocilizumab |
| | | NCT04423042 | Not yet recruiting | III | Tocilizumab |
| | | NCT04492501 | Completed | - | Tocilizumab |
| | | NCT04380519 | Completed | II/III | Olokizumab |

**Table 1** (continued)

| Therapeutic approach | Number of studies | CT number | Status | Phase | The product used |
|---|---|---|---|---|---|
| | | NCT04330638 | Recruiting | III | Anakinra, Tocilizumab, Siltuximab |
| | | NCT04486521 | Recruiting | - | Tocilizumab |
| Nanoparticle | 6 | NCT04378244 | Not yet recruiting | I | DeltaRex-G; mimic RNA virus SARS-CoV-2 by binding to viral receptors in human cells and may serve as a decoy |
| | | NCT04517162 | Recruiting | I | |
| | | NCT04385095 | Recruiting | II | |
| | | NCT04276987 | Completed | I | Polymerized-type I collagen |
| | | NCT04491240 | Enrolling by invitation | I/II | Inhaled IFN-β |
| | | NCT04493242 | Not yet recruiting | II | MSCs-derived exosomes |
| | | | | | MSCs-derived exosomes |
| | | | | | BM-derived MSC |
| Polyclonal antibody | 1 | NCT04453384 | Recruiting | II | Swine glyco-humanized polyclonal antibody |

## NK cells in COVID-19 treatment

- NK cells are an essential part of the innate immune system and play an important role in mediating virus-induced immune responses. So, interventional therapies using NK cells have been developed for the COVID-19 treatment. Recently, the adoptive transfer of allogenic NK cells has been developed to boost the antiviral immune responses and clearance of the infected cells in COVID-19 patients (NCT04344548, NCT04280224). NKG2D-ACE2 CAR-NK is an off-the-shelf product that has been investigated in a phase I/II clinical trial (NCT04324996). These cells simultaneously target ACE2 (the main receptor for SARS-CoV-2) [29] and NKG2D on the infected cells and removed them. Therefore, they could inhibit the SARS-CoV-2 infection through ACE2 blockade.

## Monoclonal antibodies in COVID-19 treatment

- It has been shown that monoclonal antibodies could be a promising treatment approach for COVID-19. Monoclonal antibodies against inflammatory cytokines such as anti-IL-1 receptor, IL-6 antagonist, anti-TNF-α,

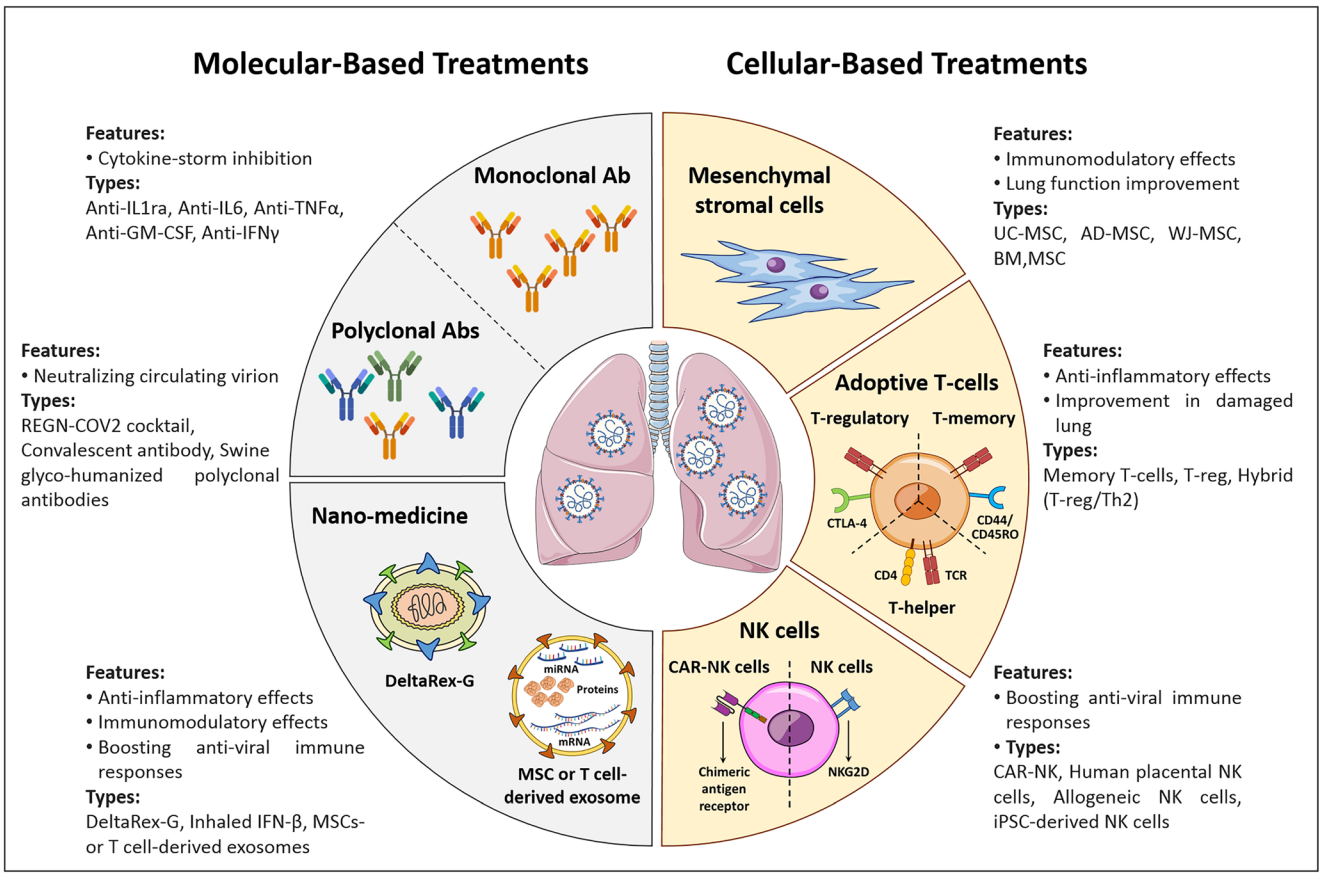
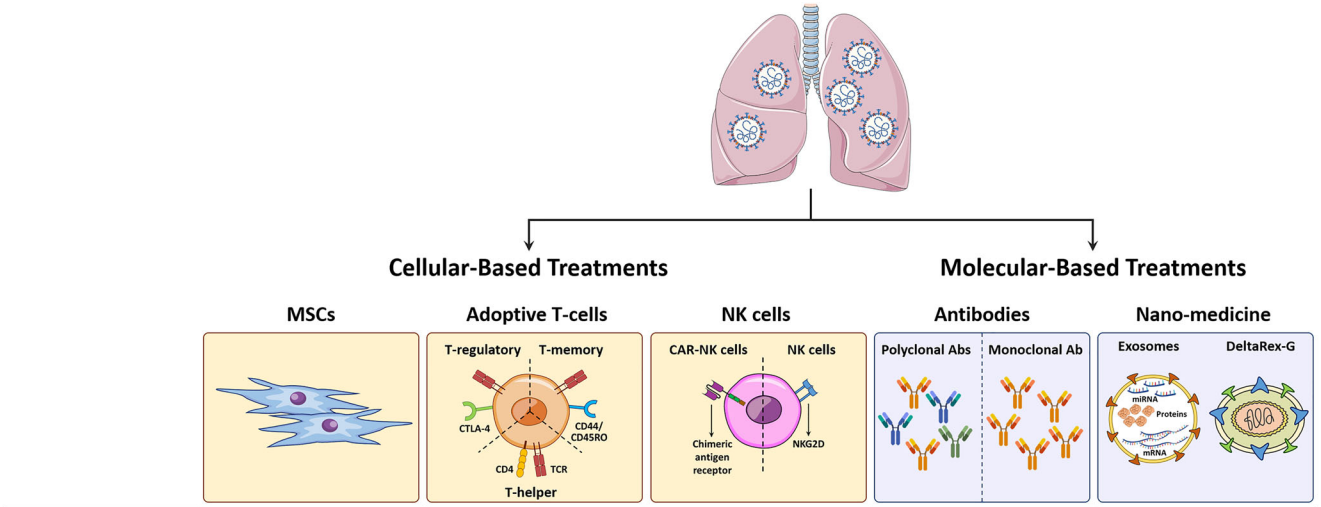



**Fig. 1** Overview of molecular- and cellular-based treatments




| | MSCs | Adoptive T-cells | NK cells | Antibodies | Nano-medicine |
|---|---|---|---|---|---|
| Safety | ✓ | ✓ | ✓ | ✓ | ✓ |
| Efficiency | ✓ | ✓ | ✓ | ✓ | ✓ |
| Boosting anti-viral immune responses | ✗ | ✓ | ✓ | ✗ | ✓ |
| Inflammation alleviation | ✓ | ✓ | ✗ | ✓ | ✓ |
| Lung function improvement | ✓ | ✓ | ✗ | ✗ | ✓ |
| Neutralizing circulating virion | ✗ | ✗ | ✗ | ✓ | ✗ |

**Fig. 2** Comparative analysis of therapeutic approaches to treat COVID-19

anti-GM-CSF, anti-IFN-γ, and C5a inhibitor have been studied in different clinical trials. Over 60 clinical trials have been registered to evaluate the treatment efficiency of Tocilizumab and Olokizumab (anti-IL-6 mAbs) [30–33]. The published studies showed that Tocilizumab (anti-IL-6 mAb) could improve the outcomes in COVID-19 patients and inhibit a cytokine storm [34]. Anakinra (IL-1ra) [35, 36] also showed beneficial effects for the treatment of COVID-19 patients and could decrease the mechanical ventilation need. Moreover, REGN-COV2 has been developed and consists of two neutralizing antibodies (REGN10987 + REGN10933) targeting SARS-CoV-2 spike protein [37, 38].

## Nano-medicine in COVID-19 treatment

- Using nano-medicine including aerosol inhalations of therapeutic agents attracts lots of attention. Recent studies have investigated the efficiency and safety of the MSC-derived exosome (NCT04491240, NCT04276987) and interferon beta inhalation (NCT04385095).

Now, most of the mentioned studies are ongoing. The growing number of clinical trials in this field could provide more validated designs and higher quality data. In this context, the increase in international collaborations to provide larger number of patients will be helpful to obtain more definite results [39]. Identifying the exact mechanisms of the COVID-19 immunopathogenesis will ensure the development of more effective therapies.

**Funding** This work was supported by Royan Institute and the Russian Foundation for Basic Research (N. 20-04-60063).

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interests.

## References

1. Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP (2020) The trinity of COVID-19: Immunity, inflammation and intervention. Nat Rev Immunol 20(6):363–374
2. Touma M (2020) COVID-19: Molecular diagnostics overview. J Mol Med (Berl) 98(7):947–954

3. Khoshdel-Rad N, Zahmatkesh E, Shpichka A, Timashev P, Vosough M (2020) Outbreak of chronic renal failure: Will this be a delayed heritage of COVID-19? J Nephrol 2:1–3
4. Hossein-Khannazer N, Shokoohian B, Shpichka A, Aghdaei HA, Timashev P, Vosough M (2020) Novel therapeutic approaches for treatment of COVID-19. J Mol Med (Berl) 98(6):789–803
5. Corbett KS, Edwards DK, Leist SR et al (2020) SARS-CoV-2 mRNA vaccine design enabled by prototype pathogen preparedness. Nature 586:567–571
6. Anderson EJ et al (2020) Safety and immunogenicity of SARS-CoV-2 mRNA-1273 vaccine in older adults. N Engl J Med 383: 2427–2438
7. Sharpe HR, Gilbride C, Allen E, Belij-Rammerstorfer S, Bissett C, Ewer K, Lambe T (2020) The early landscape of coronavirus disease 2019 vaccine development in the UK and rest of the world. Immunology. 160(3):223–232
8. van Doremalen N, Lambe T, Spencer A, Belij-Rammerstorfer S, Purushotham JN, Port JR, Avanzato V, Bushmaker T, Flaxman A, Ulaszewska M et al (2020) ChAdOx1 nCoV-19 vaccination prevents SARS-CoV-2 pneumonia in rhesus macaques. bioRxiv [Preprint] 2020.05.13.093195. Update in: Nature. 2020 Jul 30. https://doi.org/10.1101/2020.05.13.093195
9. Ramasamy MN, Minassian AM, Ewer KJ, Flaxman AL, Folegatti PM, Owens DR, Voysey M, Aley PK, Angus B, Babbage G et al (2021) Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): A single-blind, randomised, controlled, phase 2/3 trial. Lancet 396(10267):1979–1993 Erratum in: Lancet. 2021 Dec 19;396(10267):1978
10. Poland GA, Ovsyannikova IG, Kennedy RB (2020) SARS-CoV-2 immunity: Review and applications to phase 3 vaccine candidates. Lancet 396:1595–1606
11. Krammer F (2020) SARS-CoV-2 vaccines in development. Nature 586(7830):516–527
12. Walsh EE, Frenck R, Falsey AR, Kitchin N, Absalon J, Gurtman A, Lockhart S, Neuzil K, Mulligan MJ, Bailey R et al (2020) RNA-based COVID-19 vaccine BNT162b2 selected for a pivotal efficacy study. medRxiv:2020.08.17.20176651. https://doi.org/10.1101/2020.08.17.20176651
13. Dong Y et al (2020) A systematic review of SARS-CoV-2 vaccine candidates. Signal Transduct Target Ther 5(1):1–14
14. Zhang Y et al (2020) Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18–59 years: A randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. Lancet Infect Dis. https://doi.org/10.1016/S1473-3099(20)30843-4
15. Logunov DY, Dolzhikova IV, Zubkova OV, Tukhvatullin AI, Shcheblyakov DV, Dzharullaeva AS, Grousova DM, Erokhova AS, Kovyrshina AV, Botikov AG et al (2020) Safety and immunogenicity of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine in two formulations: two open, non-randomised phase 1/2 studies from Russia. Lancet 396(10255): 887–897
16. Hossein-Khannazer N et al (2019) Study of the immunomodulatory effects of osteogenic differentiated human dental pulp stem cells. Life Sci 216:111–118
17. Hashemi SM, Hassan ZM, Hossein-Khannazer N, Pourfathollah AA, Soudi S (2020) Investigating the route of administration and efficacy of adipose tissuederived mesenchymal stem cells and conditioned medium in type 1 diabetic mice. Inflammopharmacology 28(2):585–601
18. Leng Z, Zhu R, Hou W, Feng Y, Yang Y, Han Q, Shan G, Meng F, du D, Wang S et al (2020) Transplantation of ACE2-mesenchymal stem cells improves the outcome of patients with COVID-19 pneumonia. Aging Dis 11(2):216–228
19. Chen X, Shan Y, Wen Y, Sun J, Du H (2020) Mesenchymal stem cell therapy in severe COVID-19: A retrospective study of short-term treatment efficacy and side effects. J Infect 81(4):647–679
20. Ramezankhani R, Solhi R, Memarnejadian A, Nami F, Hashemian SMR, Tricot T, Vosough M, Verfaillie C (2020) Therapeutic modalities and novel approaches in regenerative medicine for COVID-19. Int J Antimicrob Agents 56:106208
21. Xiao K et al (2020) Mesenchymal stem cells: Current clinical progress in ARDS and COVID-19. Stem Cell Res Ther 11(1):1–7
22. Golchin A, Seyedjafari E, Ardeshirylajimi A (2020) Mesenchymal stem cell therapy for COVID-19: Present or future. Stem Cell Rev Rep 16(3):427–433
23. Mathew D, Giles JR, Baxter AE, Oldridge DA, Greenplate AR, Wu JE, Alanio C, Kuri-Cervantes L, Pampena MB, D'Andrea K et al (2020) Deep immune profiling of COVID-19 patients reveals distinct immunotypes with therapeutic implications. Science 369(6508):eabc8511
24. Olwenyi OA, Dyavar SR, Acharya A, Podany AT, Fletcher CV, Ng CL, Reid SP, Byrareddy SN (2020) Immuno-epidemiology and pathophysiology of coronavirus disease 2019 (COVID-19). J Mol Med (Berl) 98(10):1369–1383
25. Chen Z, John Wherry E (2020) T cell responses in patients with COVID-19. Nat Rev Immunol 20(9):529–536
26. De Biasi S et al (2020) Marked T cell activation, senescence, exhaustion and skewing towards TH17 in patients with COVID-19 pneumonia. Nat Commun 11(1):1–17
27. Le Bert N et al (2020) SARS-CoV-2-specific T cell immunity in cases of COVID-19 and SARS, and uninfected controls. Nature 584(7821):457–462
28. Ghosh A, Menon A, Hussain A, Dubey M, Kumar R (2020) A review of mesenchymal stem cell therapy for severe SARS-CoV-2 infection. PUMRJ [Internet]. [cited 21Dec.2020];3(SPECIAL). Available from: http://www.praxisug.com/index.php/Praxis/article/view/104
29. Bellone M, Calvisi SL (2020) ACE polymorphisms and COVID-19-related mortality in Europe. J Mol Med 98(11):1505–1509
30. Luo P, Liu Y, Qiu L, Liu X, Liu D, Li J (2020) Tocilizumab treatment in COVID-19: A single center experience. J Med Virol 92(7):814–818
31. Zhang C et al (2020) The cytokine release syndrome (CRS) of severe COVID-19 and Interleukin-6 receptor (IL-6R) antagonist Tocilizumab may be the key to reduce the mortality. Int J Antimicrob Agents 55:105954
32. Xu X, Han M, Li T, Sun W, Wang D, Fu B, Zhou Y, Zheng X, Yang Y, Li X et al (2020) Effective treatment of severe COVID-19 patients with tocilizumab. Proc Natl Acad Sci 117(20):10970–10975
33. Russell B, Moss C, George G, Santaolalla A, Cope A, Papa S, Van Hemelrijck M (2020) Associations between immune-suppressive and stimulating drugs and novel COVID-19-a systematic review of current evidence. Ecancermedicalscience 14:1022
34. Comentale G, Manzo R, Pilato E (2020) Sars-Cov-2 interference in HEME production: Is it the time for an early predictive biomarker? J Mol Med 98(8):1053–1054
35. Navarro-Millán I, Sattui SE, Lakhanpal A, Zisa D, Siegel CH, Crow MK (2020) Use of anakinra to prevent mechanical ventilation in severe COVID-19: A case series. Arthritis Rheum 72(12):1990–1997
36. Iglesias-Julián E, López-Veloso M, de-la-Torre-Ferrera N, Barraza-Vengoechea JC, Delgado-López PD, Colazo-Burlato M, Ubeira-Iglesias M, Montero-Baladía M, Lorenzo-Martín A, Minguito-de-la-Iglesia J et al (2020) High dose subcutaneous Anakinra to treat acute respiratory distress syndrome secondary to cytokine storm syndrome among severely ill COVID-19 patients. J Autoimmun 115:102537

37. Baum A, Ajithdoss D, Copin R, Zhou A, Lanza K, Negron N, Ni M, Wei Y, Mohammadi K, Musser B et al (2020) REGN-COV2 antibodies prevent and treat SARSCoV-2 infection in rhesus macaques and hamsters. Science 370(6520):1110–1115
38. Matthews DB (2020) A cocktail of antibodies for COVID-19 therapy. Nat Rev Immunol 20(10):591
39. Lythgoe MP, Middleton P (2020) Ongoing clinical trials for the management of the COVID-19 pandemic. Trends Pharmacol Sci 41:363–382