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Title

Host-Directed Therapies for COVID-19

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Abstract (94 words)

Purpose of review: SARS-CoV-2 induced hyperinflammation is a major cause of death or end organ dysfunction in COVID-19 patients. We review adjunct host-directed therapies (HDTs) for COVID-19 management.

Recent findings: Safety and preliminary mortality benefit of the use of umbilical cord-derived mesenchymal stem cells (MSCs) as HDT for COVID-19 have been shown in Phase 1,2 and 3 trials. Trials of anti-interleukin-6 receptor antibodies show varying results. Repurposed drugs, monoclonal antibodies targeting specific cytokines acting on different aspects of the pro-and anti-inflammatory cascades are under evaluation.

Summary: A range of HDTs show promise for reducing mortality and improving long term disability in patients with severe COVID-19

Keywords: COVID-19; Host-directed Therapies, MSCs, Interleukins, SARS-CoV-2

Introduction

The novel Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) manifests a spectrum of clinical manifestations (1) from asymptomatic, mild, moderate, to severe or critical multi-organ disease and death. As of 25 January 2021, there have been 97,464,094 confirmed cases of COVID-19, including 2,112,689 deaths (2.1% case fatality rate), reported to the WHO from all continents (2). Management outcomes are determined by a range of pathogen (SARS-CoV-2) and host factors including comorbidities (3), innate and adaptive cellular immune responses (4,5) Apart from reducing the death rate, an important clinical management need today, is to prevent long term functional disability (6). Many patients who survive severe COVID-19 develop end organ tissue damage due to excessive inflammation, including deleterious cytokine responses (5) with consequential fibrosis leading to long term functional disability (6). Host-Directed Therapies (HDTs) for tackling the aberrant host immune and inflammatory responses is an area of growing interest for more holistic treatment of patients with severe COVID-19 disease (7).

Host-directed therapies for COVID-19

The inflammatory and immune profiles in response to SARS-CoV-2 infection influence pathogenesis and clinical expression of COVID-19. Studies of immunological and inflammatory profiles in mild and severe cases of COVID-19 show that Lymphopenia, selective loss of CD4+ T cells, CD8+ T cells and NK cells, excessive T-cell activation, high expression of T-cell inhibitory molecules, excess cytokine responses are more prominent in severe cases than in those with mild disease. CD8+ T cells in patients with severe disease express high levels of cytotoxic molecules (4,5). The aberrant activation and dysregulation of CD8+ T cells occur in patients with severe COVID-19 disease, an effect that might be for pathogenesis of SARS-CoV-2 infection and indicate that immune-based targets and host-directed therapeutic interventions may be important in management of severe COVID-19 patients. A range of HDTs with different mechanisms of action have been considered as adjunct treatment for COVID-19 (**Figure 1**). Of over 1,000 COVID-19 related phase 1, 2 and 3 treatment trials registered on clinical trials.gov website nearly 100 are on a range of HDTS such as biologics, repurposed drugs, traditional remedies, nutricients, and cellular therapies (Ref:https://clinicaltrials.gov/ct2/results?cond=covid19&term=treatment&cntry=&state=&city=&dist=&Search=Search). We review data from trials of Mesenchymal stem cells (MSCs) and monoclonal antibody trials and discuss the importance of advancing host-directed

therapies (HDTs) for improving long term management outcomes and functional recovery.

Mesenchymal stem cell therapy for COVID-19

Mesenchymal stem cells (MSC) are non-hematopoietic cells with immune modulatory, regenerative, and differentiation properties. Use of MSC therapy can inhibit cell mediated immune-inflammatory responses induced by the influenza virus in animal models and clinical trials (8,9,10). The safety and potential efficacy of MSC have also been evaluated in the patients with acute respiratory distress syndrome (ARDS). Several trials are evaluating their use in COVID-19 patients. Currently, the ClinicalTrials.gov and the WHO Clinical Trials Registry Platform (WHO ICTRP) report a combined 28 trials exploring the potential of MSCs or their products for treatment of COVID-19 (7). Since infusion of millions of cells into COVID-19 patients who have a hypercoagulable state may induce further thrombotic events, careful evaluation of the safety of infusions of MSCs in phase 1 and 2 trails was required.

Recent data from a phase 1 trials demonstrated that intravenous transfusions of human umbilical cord (UC)-MSCs in patients with moderate and severe COVID-19 were safe and well tolerated (NCT04252118) (9,10). A phase 2 randomized, double-blind, placebo-controlled trial performed at 2 medical centers in Wuhan, China, evaluated further the safety and efficacy of intravenous treatment with UC-MSCs in severe COVID-19 patients with lung damage (11). 100 patients were recruited to receive either UC-MSCs (n=65) or placebo (n=35). The patients receiving UC-MSCs exhibited a trend of numerical improvement in whole lung lesion size from baseline to day 28 compared with the placebo cases. UC-MSCs administration significantly reduced the proportions of consolidation lesion size from baseline to day 28 compared with the placebo (median difference: -15.45%, 95% CI -30.82%, -0.39%, P= .043). The 6-minute walk test showed an increased distance in patients treated with UC-MSCs (difference: 27.00 m, 95% CI 0.00, 57.00, P= .057). A total of three doses of 4×10^7 UC-MSCs were transfused and no MSC-related predefined haemodynamic or respiratory adverse events were observed. No patient died during inpatient stay or the follow-up period and thus effects on mortality could not be concluded. These data suggested that UC-MSC therapy was well tolerated and very safe. Phase 3 trials in severely ill patients are required to evaluate effect of MSC infusion on mortality and long term pulmonary damage. Several ongoing clinical trials (some with higher dose of MSCs) are being conducted in China, Ireland, America, and Europe, more safety data are expected soon (12,13)

Monoclonal antibody therapy trials

A recent systematic review and meta-analysis of COVID-19 studies (14) where interleukin-6 (IL-6) concentrations were recorded analyzed data from 1,245 patients with severe disease. Comparator groups included trials in sepsis (n=5320), cytokine release syndrome (n=72), and acute respiratory distress syndrome (ARDS) unrelated to COVID-19 (n=2767). In severe COVID-19 patients the pooled mean serum IL-6 concentration was 36·7 pg/mL, nearly 100 times higher than patients with cytokine release syndrome, 27 times higher than sepsis patients 12 times higher than patients with acute respiratory distress syndrome unrelated to COVID-19. Many questions remain about the immune features of COVID-19 and the potential role of anti-cytokine and immune-modulating treatments in patients with the disease.

Studies of IL-6 antagonists

The cytokine storm that is well described in patients with severe COVID-19 has led to retrospective analyses and clinical trials of the use of anti-cytokine therapies, particularly interleukin-6 antagonists such as Tocilizumab and Sarilumab (15-18). A retrospective analyses of 112 consecutive hospitalized COVID-19 patients (15) (fifty treated with tocilizumab and 62 treated with the standard of care without tocilizumab (control group), concluded that tocilizumab was effective in the treatment of medium to severe forms of COVID-19 pneumonia, reducing the risk of mortality due to multi-organ failure. Rajendrum et al (16) performed a retrospective, observational, multicenter, cohort study using propensity score matching based on ICU admission source, C-reactive protein, Sequential Organ Failure Assessment score, vasopressor use, age, race, weight, and mechanical ventilation. 102 patients received tocilizumab and were compared to 342 who did not receive tocilizumab and the study concluded that ocilizumab use was associated with a significant decrease in ICU mortality in critically ill COVID-19 patients.

Salama C et al (17) evaluated the safety and efficacy of the anti-interleukin-6 receptor antibody tocilizumab in ethnic minority patients hospitalized with Covid-19 pneumonia randomly assigning 2:1 ratio patients who were not receiving mechanical ventilation to receive standard care plus one or two doses of either tocilizumab. The primary outcome was mechanical ventilation or death by day 28. 249 patients were in the tocilizumab group and 128 patients in the placebo group (56.0% were Hispanic or Latino, 14.9% were Black, 12.7% were American Indian or Alaska Native, 12.7% were

non-Hispanic White, and 3.7% were of other or unknown race or ethnic group). The cumulative percentage of patients who had received mechanical ventilation or who had died by day 28 was 12.0% in the tocilizumab group and 19.3% in the placebo group. The conclusion of the study was that hospitalized patients with Covid-19 pneumonia who were not receiving mechanical ventilation, tocilizumab reduced the likelihood of progression to the composite outcome of mechanical ventilation or death, but it did not improve survival.

Stone JH et al (18) performed a randomized, double-blind, placebo-controlled trial of standard care plus a single dose of either tocilizumab (8 mg per kilogram of body weight) or placebo. The primary outcome was intubation or death, assessed in a time-to-event analysis. The secondary efficacy outcomes were clinical worsening and discontinuation of supplemental oxygen among patients who had been receiving it at baseline, both assessed in time-to-event analyses. Enrolling 243 patients; (45% of the patients were Hispanic or Latino) the study concluded that Tocilizumab was not effective for preventing intubation or death in moderately ill hospitalized patients with Covid-19. Some benefit or harm could not be ruled out because the confidence intervals for efficacy comparisons were wide.

VARIABLES TO CONSIDER IN DESIGNING HDT TRIALS

There are several variables to consider when selecting HDT interventions for management of COVID-19 patients. Ongoing trials of MSC therapy in COVID-19 patients are different in design, have different sources of MSCs, different dose administration schedules, selection of patients and primary outcomes highlighting the need for standardizing protocols through a global consortium network (8). There is an urgent need for reaching global consensus on advancing HDTs for COVID-19 and other infectious diseases.

The genetic background of the individual undergoing treatment. COVID-19 may exhibit a different clinical presentation, based on a different MHC or ethnic backgrounds (19), inherent defects in the type I interferon response patterns, the route of administration of HDTs. SARS-CoV-2 specific T-cells have been identified in healthy (SARS-Cov-2-negative) individuals that exhibit a different epitope focus as compared to individuals after a COVID-19 infection. HDTs may therefore work differently in individuals with pre-existing innate immune responses and they will imprint and shape the long-term immune memory response. T-cells can be the source of overt ‘non-productive’ inflammation in the lung of patients with COVID-19, and may contribute to long-term protective immune responses. Access of HDTs (drugs or cells into the CNS) also

needs to be considered, particularly if ‘Neuro-COVID’, a recently coined term for patients with considerable neurological symptoms is to be treated who show a curtailed interferon response.

Nearly all components of immune system are affected by age along with other risk co-morbidity factors it represents a key risk factor for increased COVID-19 mortality. According to the Leiden Longevity Study, expression levels of the gene encoding IL-7R (Il7R) decreases with chronological age. IL-7R expression is higher in both the nonagenarians and middle-aged individuals, pointing to higher Il7R expression levels in ‘healthy’ and immune-fit individuals. A multi-center study with recombinant Interleukin-7 that aims to increase immune fitness, replenish the lymphocyte pool, increase SARS-CoV-2 specific T-cell responses and to decrease TGF-beta production is currently underway.

Author declarations:

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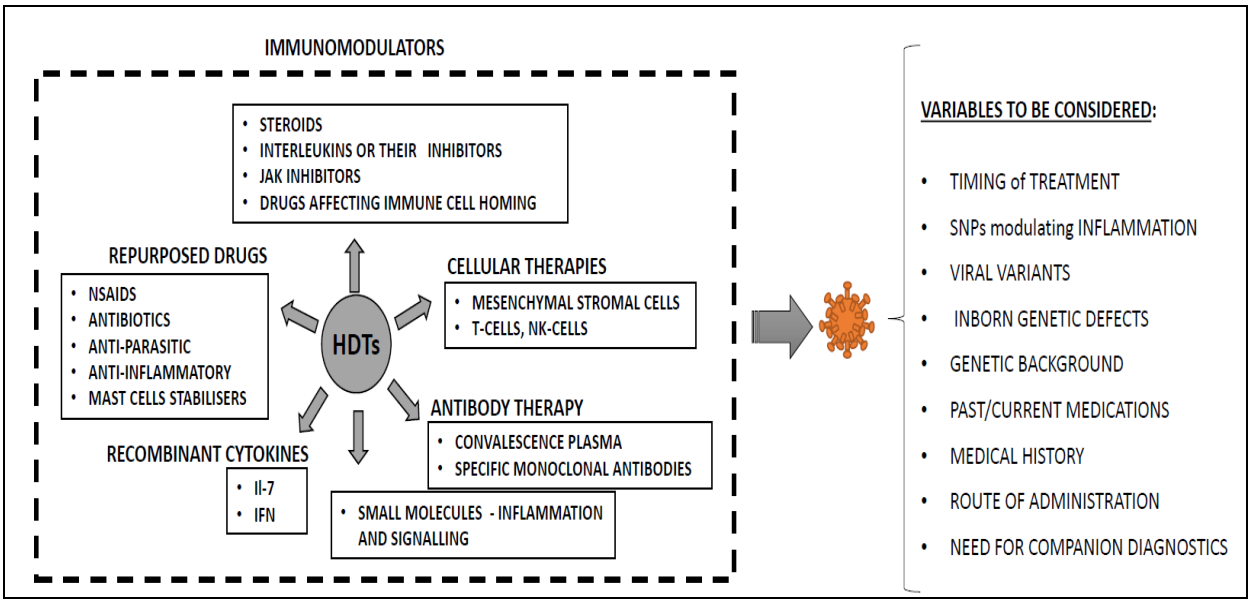
Figure 1 – **Host directed therapy categories.**



REFERENCES

1. Huang C, Wang Y, Li X. Clinical features of patients infected with 2019 coronavirus in Wuhan, China. Lancet. 2020 doi: 10.1016/S0140-6736(20)30183-5. published online Jan 24.

2. World Health Organization. COVID-19 Dashbaord: https://covid19.who.int/- accessed 25th January, 2021

3. Richardson S, Hirsch JS, Narasimhan M, et al. Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. JAMA. 2020. doi: 10.1001/jama.2020.677), innate and adaptive cellular immune responses

4. Li G, Fan Y, Lai Y. Coronavirus infections and immune responses. J Med Virol. 2020 doi: 10.1002/jmv.25685. published online Jan 25.

5. **Song JW, Zhang C, Fan X, Meng FP, Xu Z, Xia P, Cao WJ, Yang T, Dai XP, Wang SY, Xu RN, Jiang TJ, Li WG, Zhang DW, Zhao P, Shi M, Agrati C, Ippolito G, Maeurer M, Zumla A, Wang FS, Zhang JY. Immunological and inflammatory profiles in mild and severe cases of COVID-19. Nat Commun. 2020 Jul 8;11(1):3410. doi: 10.1038/s41467-020-17240-2. PMID: 32641700; PMCID: PMC7343781.

**Sentinel study describing immunological profiles across the COVID-19 clinical spectrum

6. Heiss R, Grodzki DM, Horger W, Uder M, Nagel AM, Bickelhaupt S. High-performance low field MRI enables visualization of persistent pulmonary damage after COVID-19. Magn Reson Imaging. 2021 Feb;76:49-51. doi: 10.1016/j.mri.2020.11.004. Epub 2020 Nov 18. PMID: 33220447; PMCID: PMC7673210.

7. Zumla A, Hui DS, Azhar EI, Memish ZA, Maeurer M. Reducing mortality from 2019-nCoV: host-directed therapies should be an option. Lancet. 2020 Feb 22;395(10224):e35-e36. doi: 10.1016/S0140-6736(20)30305-6. Epub 2020 Feb 5. PMID: 32035018; PMCID: PMC7133595.

8. Zumla A, Wang FS, Ippolito G, Petrosillo N, Agrati C, Azhar EI, Chang C, El-Kafrawy SA, Osman M, Zitvogel L, Galle PR, Locatelli F, Gorman E, Cordon-Cardo C, O'Kane C, McAuley D, Maeurer M. Reducing mortality and morbidity in patients with severe COVID-19 disease by advancing ongoing trials of Mesenchymal Stromal (stem) Cell (MSC) therapy - Achieving global consensus and visibility for cellular host-directed therapies. Int J Infect Dis. 2020 Jul;96:431-439. doi: 10.1016/j.ijid.2020.05.040. Epub 2020 May 17. PMID: 32425638; PMCID: PMC7231497.

9. **Meng F, Xu R, Wang S, Xu Z, Zhang C, Li Y, Yang T, Shi L, Fu J, Jiang T, Huang L, Zhao P, Yuan X, Fan X, Zhang JY, Song J, Zhang D, Jiao Y, Liu L, Zhou C, Maeurer M, Zumla A, Shi M, Wang FS. Human umbilical cord-derived mesenchymal stem cell therapy in patients with COVID-19: a phase 1 clinical trial. Signal Transduct Target Ther. 2020 Aug 27;5(1):172. doi: 10.1038/s41392-020-00286-5. PMID: 32855385; PMCID: PMC7450163.

** The first ever Phase 1 trial of MSC adjunct therapy in COVID-19 patients which shoed MSC cell infusion is afe

10. Tang L, Jiang Y, Zhu M, et al. Clinical study using mesenchymal stem cells for the treatment of patients with severe COVID-19. Front Med. 2020. doi: 10.1007/s11684-020-0810-9

11.** Lei Shi, Hai Huang, Xuechun Lu, Xiaoyan Yan, Xiaojing Jiang, Ruonan Xu, Siyu Wang, Chao Zhang, Xin Yuan, Zhe Xu, Lei Huang, Jun-Liang Fu, Yuanyuan Li, Yu Zhang, Weiqi Yao, Tianyi Liu, Jinwen Song, Liangliang Sun, Fan Yang, Xin Zhang, Bo Zhang, Ming Shi, Fanping Meng, Yanning Song, Yongpei Yu, Jiqiu Wen, Qi Li, Qing Mao, Markus Maeurer, Alimuddin Zumla, Chen Yao, Wei-Fen Xie, Fu-Sheng Wang. Effect of human umbilical cord-derived mesenchymal stem cells on lung damage in severe COVID-19 patients: a randomised, double-blind, placebo controlled phase 2 trial. *Signal Transduction and Targeted Therapy* 2021 -in press

**The first randomised phase 2 trial evaluating safety, effects on lung lesions resolution and lung function in COVID-19 patients.

12. Payares-Herrera C, Martínez-Muñoz ME, Vallhonrat IL, de Molina RM, Torres MP, Trisan A, de Diego IS, Alonso R, Zafra R, Donaire T, Sánchez R, Rubio JJ, Duarte Palomino RF, Solá CA. Double-blind, randomized, controlled, trial to assess the efficacy of allogenic mesenchymal stromal cells in patients with acute respiratory distress syndrome due to COVID-19 (COVID-AT): A structured summary of a study protocol for a randomised controlled trial. Trials. 2021 Jan 6;22(1):9. doi: 10.1186/s13063-020-04964-1. PMID: 33407777; PMCID: PMC7785778.

13. Gorman E, Shankar-Hari M, Hopkins P, Tunnicliffe WS, Perkins GD, Silversides J, McGuigan P, Jackson C, Boyle R, McFerran J, McDowell C, Campbell C, McFarland M, Smythe J, Thompson J, Williams B, Curley G, Laffey JG, Clarke M, O'Kane C, McAuley DF. Repair of Acute Respiratory Distress Syndrome by Stromal Cell Administration in COVID-19 (REALIST-COVID-19): A structured summary of a study

protocol for a randomised, controlled trial. Trials. 2020 Jun 3;21(1):462. doi: 10.1186/s13063-020-04416-w. PMID: 32493473; PMCID: PMC7267756.

14. Leisman DE, Ronner L, Pinotti R, Taylor MD, Sinha P, Calfee CS, Hirayama AV, Mastroiani F, Turtle CJ, Harhay MO, Legrand M, Deutschman CS. Cytokine elevation in severe and critical COVID-19: a rapid systematic review, meta-analysis, and comparison with other inflammatory syndromes. Lancet Respir Med. 2020 Dec;8(12):1233-1244. doi: 10.1016/S2213-2600(20)30404-5. Epub 2020 Oct 16. PMID: 33075298; PMCID: PMC7567529.

15. Castelnovo L, Tamburello A, Lurati A, Zaccara E, Marrazza MG, Olivetti M, Mumoli N, Mastroiacovo D, Colombo D, Ricchiuti E, Vigano' P, Paola F, Mazzone A. Anti-IL6 treatment of serious COVID-19 disease: A monocentric retrospective experience. Medicine (Baltimore). 2021 Jan 8;100(1):e23582. doi: 10.1097/MD.0000000000023582. PMID: 33429732; PMCID: PMC7793456.

16. Rajendram P, Sacha GL, Mehkri O, Wang X, Han X, Vachharajani V, Duggal A. Tocilizumab in Coronavirus Disease 2019-Related Critical Illness: A Propensity Matched Analysis. Crit Care Explor. 2021 Jan 13;3(1):e0327. doi: 10.1097/CCE.0000000000000327. PMID: 33490955; PMCID: PMC7808529.

17. **Salama C, Han J, Yau L, Reiss WG, Kramer B, Neidhart JD, Criner GJ, Kaplan-Lewis E, Baden R, Pandit L, Cameron ML, Garcia-Diaz J, Chávez V, Mekebeb-Reuter M, Lima de Menezes F, Shah R, González-Lara MF, Assman B, Freedman J, Mohan SV. Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia. N Engl J Med. 2021 Jan 7;384(1):20-30. doi: 10.1056/NEJMoa2030340. Epub 2020 Dec 17. PMID: 33332779; PMCID: PMC7781101

**Important phase 3 randomized controlled trial of Tocilizumab .

18. **Stone JH, Frigault MJ, Serling-Boyd NJ, Fernandes AD, Harvey L, Foulkes AS, Horick NK, Healy BC, Shah R, Bensaci AM, Woolley AE, Nikiforow S, Lin N, Sagar M, Schrager H, Huckins DS, Axelrod M, Pincus MD, Fleisher J, Sacks CA, Dougan M, North CM, Halvorsen YD, Thurber TK, Dagher Z, Scherer A, Wallwork RS, Kim AY, Schoenfeld S, Sen P, Neilan TG, Perugino CA, Unizony SH, Collier DS, Matza MA, Yinh JM, Bowman KA, Meyerowitz E, Zafar A, Drobni ZD, Bolster MB, Kohler M, D'Silva KM, Dau J, Lockwood MM, Cubbison C, Weber BN, Mansour MK; BACC Bay Tocilizumab Trial Investigators. Efficacy of Tocilizumab in Patients Hospitalized with Covid-19. N Engl J Med. 2020 Dec 10;383(24):2333-2344. doi:

10.1056/NEJMoa2028836. Epub 2020 Oct 21. PMID: 33085857; PMCID: PMC7646626.

**Important phase 3 randomized controlled trial of Tocilizumab

19. de Sousa E, Ligeiro D, Lérias JR, Zhang C, Agrati C, Osman M, El-Kafrawy SA, Azhar EI, Ippolito G, Wang FS, Zumla A, Maeurer M. Mortality in COVID-19 disease patients: Correlating the association of major histocompatibility complex (MHC) with severe acute respiratory syndrome 2 (SARS-CoV-2) variants. Int J Infect Dis. 2020 Sep;98:454-459. doi: 10.1016/j.ijid.2020.07.016. Epub 2020 Jul 18. PMID: 32693089; PMCID: PMC7368421.