biomedicines

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Review

Biologics in covid 19 so far "scoping review"

Milton Arias [1], Rosa-Helena Bustos*[1] and Henry Oliveros [2,*]

[1] Department of Clinical Pharmacology, Evidence-Based Therapeutics Group, Faculty of Medicine, Universidad de La Sabana and Clínica Universidad de La Sabana, Chía 140013, Colombia; milton.arias@unisabana.edu.co; rosa.bustos@unisabana.edu.co

[2] Department of Epidemiology, Health Research Group, Faculty of Medicine, Universidad de La Sabana, Chía 140013, Colombia; henry.oliveros@unisabana.edu.co

* Correspondence: rosa.bustos@unisabana.edu.co

Abstract: This scoping review aimed to evaluate the available evidence of the use of Biologics as treatment candidates for the treatment of severe and advanced COVID–19 disease; what are the rationale for their use, which are the most studied, and what kind of efficacy measures are described. A search through Cochrane, Embase, Pubmed, Medline, medrxiv.org and Google scholar was performed, on the use of biologic interventions in the COVID–19/ SARS-COV-2 infection, viral pneumonia, and sepsis, until July 31, 2021. Throughout the research, we identified 4260 records of which 84 were selected for qualitative analysis. Amongst the results, we identified 5 popular targets of use: IL6 and IL1 inhibitors, Janus Kinase inhibitors, interferons, and mesenchymal stem cells treatment. None of them offered conclusive evidence of their efficacy with consistency and statistical significance; however, Il6 and IL1 inhibitors, as well as interferons show encouraging data in terms of increased survival and favorable clinical course that require further studies with better methodology standardization.

Keywords: SARS-COV-2; COVID–19; Biologics, Biopharmaceuticals, Interleukin inhibitors, Interferon treatment, Janus Kinase inhibitors, Mesenchymal stem cells

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1. Introduction

At the end of 2019, a cluster of patients with pneumonia is identified in the city of Wuhan in the Hubei province in China. The behavior of the disease resulted in a fast-spreading epidemic throughout the country. In a short period of time, sustained human-to - human transmission is confirmed, leading to the recognition that the disease had pandemic potential (1). In February of 2020 the world health organization (WHO), acknowledge the disease as "coronavirus disease 2019" (COVID–19) and the virus that is purified as etiologic agent as "severe acute respiratory syndrome coronavirus 2" (SARS-COV-2) (2).

This pandemic has claimed over 4.7 million fatalities since its beginning (3). The proportion of cases/ deaths are related to the fact that COVID–19 mostly presents itself as a self-limited mild respiratory disease (80% of cases) (4), yet the cumulative number of affected patients determine a large mortality. The comprehension of the common pathophysiological model, in the case of severe COVID-19 disease, suggests that findings such as diffuse alveolar damage, inflammatory infiltrates, and microvascular thrombosis are related to a hyper inflammation, product of the host response to the virus (5). Furthermore if we consider the evidence recorded since the RECOVERY Collaborative Group study (6), regarding the control of inflammatory response with corticosteroids as an effective intervention we should ask ourselves about other drug interventions that can target the host inflammatory response with certain degree of specificity.

Three clinical phases can be categorized according to severity: onset of the disease, pulmonary phase, and hyper inflammation phase. The first stage of the disease is usually characterized by mild symptoms similar to those of seasonal influenza (2). In this stage, it is considered that the virus contacts the respiratory epithelial tissues as a predilection site of entry. Concerning this phenomenon, the first contact mechanism between the virion and the cell is through the Viral crown. The virus has certain structural proteins called "spikes" that protrude from the membrane of the virion; this gives it the characteristic appearance of a crown, in electron microscopy, which is reflected in the name of the virus. These spikes are transmembrane trimeric glycoproteins that are composed of two functional subunits S1 and S2 (7,8). It is these glycoproteins that determine the diversity of coronaviruses in terms of the tropism towards their hosts and specific tissues in an organism.

SARS-CoV-2 in this aspect shows an affinity for angiotensin-converting enzyme 2 (ACE 2) using it as a functional receptor, however, it is not the only mediator involved in the binding of the virus to the host cell. In the most recognized model, the way of entry of the virus is through endocytosis. Once inside, the virion, must fuse its membrane with the endosome and thus release its RNA; for this purpose, it uses the transmembrane protease serine 2 (TMPS2) or the L-cathepsin that cleaves the spike into the S1 and S2 subunits. The S1 subunit ensures the stability of the anchorage to the membrane whereas splitting of S2 requires a second cleavage at S2 ' to generate a conformational change to consolidate the fusion (2,8).

Although this is the most accepted model, in fact, the particularity of this virus compared to other coronaviruses is the type of cleavage sequence "reverse-phase protein array (RPPA)" at the S1 / S2 site, which is susceptible to furin (9). Considering the ubiquity of furin, it is not surprising that this virus is highly pathogenic. While its tropism for the angiotensin-converting enzyme explains its ease of entry through respiratory epithelia, heart, ileum, kidney, and bladder (10), its ability to compromise in other systems and its impact on the reticuloendothelial system may have to do with its RPPA cleavage sequence.

Once inside, the virus must proceed to make use of the nuclear and ribosomal machinery to achieve the replication of its RNA and biosynthesis of structural and non-structural proteins. Considering that the structural components correspond to the membrane, envelope, nucleocapsid, and spikes, non-structural proteins and their interaction with the cellular machinery are of interest as possible therapeutic targets. The evidence regarding cell interactions is extrapolated from the lessons learned in the study of SARS and MERS as close relatives of SARS-CoV-2. In this sense, it is derived that the RNA of our coronavirus consists of 11 open reading frames, which encode 16 non-structural proteins (NSP) that encompass most of the mechanisms implied in the pulmonary phase (11–19). Considering this fact, we will not expand in the function of each NSP and will proceed with the characteristic phase of the critically ill, the hyper inflammation phase.

The hyper inflammation phase axis is the interaction of the virus with the immune system, the primary contact to establish is with the innate immune system; In this category, the pulmonary epithelium mainly has macrophages, which can appear in the apical epithelium, also, dendritic cells are usually found in the sub-epithelium. The immediate predictable consequence is phagocytosis of apoptotic epithelial cells extrapolating models related to influenza viruses (20). Koichi Yuki et al. suggest another kind of approach to this issue, implying that the coronavirus has the potential for direct infection in dendritic cells by replacing its ACE2 receptor with the specific adhesion molecule of dendritic cells

(non-integrin trapping molecule 3) (8). The chain of events continues with the presentation of the pathogen to the T cells of the immune system; This event results in the release of chemotactic that promote the massive recruitment of other lymphocytes. It is possible that the lymphopenia observed in patients with hyperinflammation is related to this fact (21,22).

The presence of multiple inflammatory cytokines has been identified in the severely ill COVID-19 patient. Interleukin 1 (IL) -1, IL-6, IL-10, granulocyte colony-stimulating factor (GCSF), monocytic chemoattractant protein 1 (MQP1), macrophage inflammatory protein (MIP) 1α, and tumor necrosis factor (TNF) -α are relevant (22,23). In the study by Yonggang Zhou et al. Both the cytokine storm and the distribution of the lymphocyte subpopulations, or at least the expression of the flow cytometry, are evaluated. The presence of CD69, CD38, and CD44 are highlighted, demonstrating the recruitment of both T CD8 $^{+}$ and T CD4 $^{+}$. In turn, it is worth noting the increased expression of control receptors Tm3 and PD-1 in both subpopulations of T cells, displaying depletion of cell populations (22). It can be suggested that lymphocyte depletion may perpetuate a poor immune response to the pathogen, all this favored by the mentioned cytokine storm microenvironment.

Lymphocytic infiltration and the depletion of T cells is not the only problem that occurs in this microenvironment, it has been reported that, in patients with severe lung injury, there is a correlation with the cellular population predominance of macrophages and neutrophils in the pulmonary epithelium. (24). To achieve this phenomenon, the immune response must use both interferon (IFN) γ and granulocytic-macrophage colony-stimulating factor (GMCEF). In this scenario, the host uses abnormal CD4 T cells that express both mediators (22).

Now that we highlighted the relevance of the inflammatory response in the patient in the pulmonary (severe) phase and in the hyper inflammation (advanced) phase, knowing that most specific drugs in these type of targets are the biological ones. We aimed to answer the following question in this review: ¿What interventions with biological drugs have been studied in adult patients with confirmed SARS-COV-2 infection, in severe or advanced stage of compromise and what is their efficacy in clinical practice according to the evidence available to date?

2. Materials and Methods

2.1. Search Eligibility Criteria and Search Strategy,

We performed scoping review of the literature concerning the use of biological drugs in the context of patients infected with SARS-COV-2. The PICO components sought information regarding adult patients with confirmed SARS-COV-2 infection, preferring severe or advanced stage of compromise. The selected intervention was the use of biologics according to the regulatory definition adopted by the "U.S. Food and drug administration" (FDA) prior to the modification"Consolidated Appropriations Act, 2020" that was implemented in December 20, 2019. This as a modification to the norm contemplated in the act: "Biologics Price Competition and Innovation Act of 2009 (BPCI Act) "implemented that year. We chose this definition, taking into account that is aligned with the objective of analyzing the therapies with greater specificity that can bring a benefit to the critically ill patient with COVID-19. Considering that the modification of the end of 2019 allows the inclusion of any chemically synthesized polypeptide and not exclusively of synthesis mediated by cells, tissues or microorganisms.

Regarding the outcomes for the search, we prioritized any record depicting overall mortality due to SARS-COV-2 and fatality rates regardless of the nature of primary or secondary outcomes. We also considered time to discharge, risk of mechanical ventilation and surrogate biomarkers of efficacy.

We performed a search of the relevant bibliographic references through the following databases: Cochrane, Embase, Pubmed, Medline, medrxiv.org and Google scholar. The search was performed with the following mesh terms: "COVID-19", "SARS-CoV-2", "Biological Products", "Interleukin 6 Receptor Antagonist Protein", "Interleukin 1 Receptor Antagonist Protein", "Janus Kinase Inhibitors", "Mesenchymal Stem Cells", "Mesenchymal Stem Cell Transplantation". We used these terms as exact phrases and a combination of subject headings according to databases syntax. We also performed a search with the most relevant drug names as mesh terms to complement the preliminary findings with the following terms : "Tocilizumab", "Siltuximab", "sarilumab", "Anakinra", "Canakinumab", "Ruxolitinib", "Baricitinib", "Interferons" and "Mesenchymal Stem Cells". The record data was also expanded through the relevant references of selected literature on first search. No restriction in language was applied, and the research was performed from it´s inception until July 31, 2021 (specific sintax adaptation on appendix 1).

2.2. Study Selection, and Data Extraction

Once the search was carried out, two independent researchers made a preliminary selection of the studies. The selection was based on the titles and abstracts, taking into account the inclusion and exclusion criteria. If the researchers for the selection of a publication reached no consensus, the decision rested in the criteria of a third evaluator.

In a second stage, we applied the following inclusion criteria:
Full text studies, review articles, observational studies, meta-analysis, or clinical trials investigating the use of a biological drugs with the intention of reducing mortality in patients infected by SARS-COV-2; studies investigating the use of a biological drug with the intention of reducing the stay in the intensive care unit; studies investigating efficacy biomarker outcomes in severe or advanced COVID–19 patients.
We also applied the following exclusion criteria: Studies that do not use biological drugs. studies that refer exclusively to anticoagulation methods as an exclusive intervention, even if it is done with drugs that are included in the biological category; studies related to vaccination even if it is done with drugs that are included in the biological category; case report studies or series of cases studies and studies performed in other populations outside adults

Finally, we performed a descriptive analysis of the literature found in the research and synthetized in the adjunct table. In this table, we included all the studies except meta-analysis, since we chose to list the included studies in each compilation article as raw data. The meta-analysis was referenced and described in the result section in each target. In addition, in order to avoid publication, bias we performed an additional search of unpublished and gray literature in the specified databases for this purpose like medrxiv.org and Google scholar.

3. Results

The process of selection and the number of articles selected was performed as described in the following chart (Figure 1).

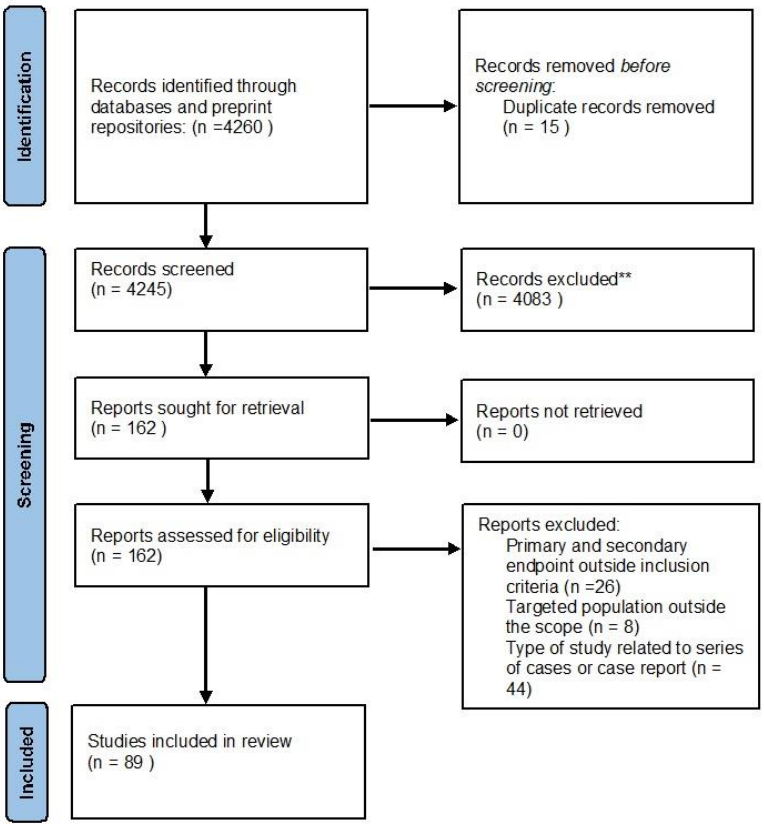

Figure 1. Flowchart of selected studies

** *Articles outside the scope of the review i.e. covid population epidemiological characteristics, contagiousness of different strains of covid and vaccination effects, covid anticoagulation, Chinese herbal products efficacy. etc.*

3.1. Interleukin 6 inhibitors

Interleukin 6 (IL-6) is one of the most popular targets regarding the abundance of evidence generated since 2020. It is comprehensible since there is availability of candidates that do not require further drug development and the pathophysiological involvement can affect one of the axis of direct lung injury. Since 2020, the evidence strongly suggests that the levels of IL-6 correlates with viral load and prognosis in critically ill patients (25). It is also associated with the presumption that the particular mode of apoptosis in the SARS-CoV-2 infection is pyroptosis, explaining the massive release of IL-1β, IL-2, IL-6, TNF-α, MCP1 and the attrition of CD4 and CD8 T cells (26).

In the initial search, we identified 3051 results of which 43 were selected through the inclusion criteria and relevance; Three particular systematic reviews highlight amongst the available data. Shao-Huan Lan et. al, developed research regarding the effects of tocilizumab in either mortality, intensive care unit admission or requirement of mechanical ventilation. They managed to analyze seven studies from a 358 studies selection, after the data base research and filtering through inclusion criteria (27). In their results, they included the studies of Capra et al; Colaneri et al; Klopfenstein et al; Quartuccio et al; Ramaswamy et al; Roumier et al and Wadud et al quoted in the table below (28–34). According to presented data, the reported studies could not conclude a risk reduction in the

overall intervention with tocilizumab independent of the dose. Taking into account that most of the studies where retrospective in nature, the overall mortality rate for patients with tocilizumab ranged from 3.2 % to 38.6 % with considerable heterogeneity in the data. Understanding that the authors considered a mean mortality of 24.1% in the control groups, the pooled result did not achieve statistical significance regardless of a pre-established threshold of p= 0.1.

Cortegiani et al. performed a similar review including records regarding the use of tocilizumab in viral pneumonia caused by SARS-CoV-2 or sepsis without any restriction in language or methodology. They identified 2071 articles from which 31 were selected according to relevance (35). Considering the amount of evidence, we will refer to the overall analysis of the database included in this study; the details of the studies can be found in the adjunct table. Summing all the population included in all the clinical data 5776 patients were analyzed in this review, regarding the characteristics of the studies, the first thing to mention is the fact that 14 studies didn't have comparator, making the quoted results a descriptive outcome (34-56)(58). Of the remaining 16 studies 14 suggested tocilizumab improved outcomes related to mortality/ ICU admission, nevertheless, some of the quoted studies revealed effect disappearance in the adjusted analysis as in the case of Martinez et. Al (41). Not all the differences noticed in the studies achieved statistical significance either. Also is worth noticing that the studies with the largest samples, ranging from 1221 to 1229 individuals, showed mixed results when considering lethality rates, although the design was not intended for comparison in the case of Perrone et. Al. (43). Another noticeable tendency in this review was that the studies with the lager samples included very few patients receiving the IL-6 inhibitor compared to the proportion of patients who did not receive the intervention. Finally, a valuable analysis of Cortegiani et al. added a risk of bias in the mentioned data base using the TheROBINS-I tool (Risk of Bias in Non-randomized Studies of Interventions). This allowed judging 13 of the studies with comparator as of poor quality(35).

Fasihul A Khan included a broader perspective regarding the intervention on this pharmacological target they included the aforementioned studies sample but also managed to include the few studies performed with other drugs that attack this same axis (59). In this review we didn't manage to find other studies than those cited in this article with Siltuximab n = 1 nor Sarilumab n= 3 (60–63). Concerning the results, these studies show point estimators that favors the biologic with the same characteristics found in previous studies: observational cohorts with a disproportioned population comparing intervention vs assigned controls, given the limitations of compassionate use. Two of the Sarilumab studies are descriptive of mortality and most of them have small samples. The Gordon et al study reflects the tendency with a total population sample n = 803 with 353 patients assigned to tocilizumab, 48 to sarilumab and 402 to control (62).

Finally, in our research we found that a great deal of the available evidence was addressed in the previous systematic reviews, however, new evidence has emerged since then. Regarding these other studies, it is noteworthy that evidence is beginning to accumulate with prospective clinical trials, some of them randomized. Jacopo Sabbatinelli et al, Olivier et al, Carlo Salvarani et al, Reza et al, Veiga et al, Stone et al, Farzaneh et al, Salama et al, Molinero et al and RECOVERY Collaborative Group. They have all addressed the question of Interleukin 6 inhibitor and the outcomes on severe or critical COVID- 19 patients (64–73); amongst them 4 studies found clinical results that favors the intervention groups with Tocilizumab while 2 are descriptive with no comparator and 3 showed no difference with the intervention. Strangely, the quoted study of Salama et al revealed different results amongst the composite end point of death /mechanical ventilation favoring tocili-

zumab in contrast with death of any cause favoring placebo. From these studies is of paramount importance the RECOVERY study not only regarding the size of the sample but the particular methodology of randomization and the careful consideration regarding the stratified analysis. The results favoring tocilizumab group are even more compelling if we consider the IL-6 inhibitor as an intervention before mechanical ventilation. A single randomized trial used Sarilumab as intervention outside the scope of the aforementioned reviews favoring the use of the biologic without statistical significance (74).

3.2. Interleukin 1 inhibitors

Having addressed (IL-6) as one of the important mediators in direct lung injury we cannot forget interleukin 1 (IL-1) as one of the principal actors in the same axis mediating the pyroptosis process mentioned before, even more, considering it´s similitudes with the macrophage activation syndrome that complicates bacterial sepsis. Data in this environment is partially encouraging (75).

Concerning the data obtained in the initial search, we got 508 hits with the quoted search terms, and selected 18 articles after comprehensive evaluation of the inclusion criteria.

The first record to be highlighted is a meta-analysis performed by Kyriazopoulou et al, recording the available data in the use of Anakinra. The aggregate data showed a pooled population of 1185 patients from 9 selected studies, with a preliminary search of 209 articles (76). Of these studies, most of them used observational cohort methodology either prospective or retrospective. The first thing to notice is the consistency of the data with point estimators favoring the intervention with Anakinra witnessing less objective heterogeneity in the data than that observed in the interventions with (IL-6) inhibitor, comparing with the study of Shao-Huan Lan et. Al (27). Never the less, from the cited studies, some of them don't reach statistical significance i.e. Balkhair et al, Kooistra et al and The CORIMUNO19 Collaborative group (77–79). Furthermore, is worth noticing that even if the overall effect is favoring the biologic, the magnitude of the effect is moderatly variable (80–85). The pooled data used in the systematic review of Kyriazopoulou et al finally estimates an odds ratio (OR) for mortality of 0·37 (95% CI 0·27–0·51; I^2 31%) without signs of publication bias in the forest plot (76).

Out of the scope of the aforementioned systematic review we selected several other studies, one study only presented descriptive results with a small sample in a retrospective manner (86), the rest of them presented association measures regarding death realated endpoints. In these observational studies, we see the same phenomena in the association estimators favoring the use of anakinra, emphasizing that two of them didn't achieve statistical significance (87,88). The last one revealed a significant odds ratio: 3.2 for the use of Anakinra as a survival predictor (89). It is necessary to address the only other randomized trial made by Kyriazopoulou et al that is not recorded in their previous metanalysis(90). This particular clinical trial preselected severe pneumonia SARS-COV-2 patients according to soluble urokinase plasminogen receptor plasma levels and randomized (double blinded) for standard care group and Anakinra intervention. The results were deemed significant with a sample of 606 and a Risk of death at day 28 hazard ratio = 0.45, 95% CI 0.21–0.98, P = 0.045.

Lastly regarding other less popular IL-1 inhibitors, no studies were found using rilonacept and 4 studies were selected with the use of Canakinumab. Three of them were observational with descriptive outcomes. Lorenza Landi et al described overall survival rate with no comparator (91), while Katia et al described reduction in oxygen consumption compared with standard treatment and Generali et al referred a survival rate comparison

(92,93). Although the raw proportion of survival and the reduction in oxygen consumption is statistically significant, the dosage used on interventions are very variable and the samples are relatively small. This leads us to the final piece of evidence in this matter with the only randomized trial found in the effect of Canakinumab and mortality/ clinical deterioration measures: Roberto Caricchio et reported a non-significant mortality risk reduction with Canakinumab with an odds ratio of 0.67 (95%CI, 0.30 to 1.50) regardless of a population sample of 454 patients.

Jannus kinase (JAK) inhibitors

Jannus kinase inhibitors are members of the big family of tyrosine kinase proteins. They perform several functions in intracellular signaling that can be overlooked as no related to the mentioned covid physiopathology, however, as their family name implies, they mediate intracellular signaling through phosphorylation. This is related specially to cytokine proliferation, cell survival, apoptosis, migration and growth factor transduction signaling (94,95). The purpose of addressing this signal pathway, that is usually used in other pathologies (like the infection hemophagocytic lymphohistiocytosis), is to inhibit the cytokine derangement similar to what observed in SARS-COV-2 (96).

About the data of the preliminary search, 390 studies were obtained, which only identified studies with clinical data about Ruxolitinib and Baricitinib; seven studies were selected. From this data we must start with the only systematic review concerning this issue. Lucas Walz et al evaluated a pool of 14 studies (97); nevertheless, they included interferon modulation as part of this signal pathway. From this pooled data, only two studies used Ruxolitinib and one of them is a case series which we chose to exclude. Yang Cao et al presented a multicenter, single-blind, randomized controlled trial with a small population in a single center. They reported cumulative incidence of death as secondary outcome without a single fatality on the Ruxolitinib group and 14.3% deaths in the control group at day 28% (no association measures were derived) (96).

We managed to find a single additional record (outside Lucas review) apropos the use of ruxolitinib in SARS-COV-2 severely ill patients. D'Alessio et al compared the use of ruxolitinib in two scenarios, survival rate of ruxolitinib in mechanical ventilated and no mechanical ventilated patients, without considering a placebo group (98).

Regarding Baricitinib the aforementioned review discloses 3 studies observational studies that mainly reveal descriptive raw incidence values. From the obtained data, all differences were significant even though the nature of the studies limit inferences concerning the systematic use of the drug (99–101). One of the cited studies refers of a pilot considering the benefits in biomarkers differences as surrogate outcomes to suggest larger studies (101). Finally, only one other study was identified outside the ones used by Walz: Rodriguez-Garcia et al performed a prospective observational study evaluating Requirement of supplemental oxygen at discharge finding an OR: 0.18; 95% CI: 0.08, 0.43; P<0.00. No considerations speaking of mortality are described (102).

3.3. Interferons

The value of interferons intertwining with the pathology of the lung injury in SARS-COV-2 infection, radiate from classical signaling pathways described for the most well-defined type I interferons (IFNs). From the known variety, IFNα and IFNβ are the most studied, describing functions in cell antimicrobial states through limiting the spread of infectious

pathogens (particularly true for viruses). They interact with the innate immune system, modulating the production of cytokines, promoting antigen presentation and natural killer cell functions while restraining pro-inflammatory pathways. They interact with the adaptive immune system by promoting the development of antigen-specific T and B cell responses deriving in immunological memory (103). It is of particular interest the fact that IFNs interact with the JAK 1 axis to reach specific genome sequences for transcription, since this pathway encodes in several types of proteins that restrain pathogens via the inhibition of viral transcription, translation and replication, the degradation of viral nucleic acids and the alteration of cellular lipid metabolism (104).

In this review, we encountered 206 articles in the preliminary search with a selection of nine records for analysis. The aforementioned Lucas Walz et al. included several interferon studies in his analysis of the clinical relevance of JAK inhibitors; some of the used records were specific of pediatric populations or were epidemiological descriptions of cured patient's data that deemed to be out of the scope of this review (97). Still, of the remaining data we found 5 articles related to group 1 IFNs to be relevant, 3 observational studies and 2 clinical trials (105–109). While Monfared et al performed a clinical trial with mortality primary end point, Hung et al described nasopharyngeal swaps negativization as a surrogate outcome of resolution of the disease. Both trials favored the use of IFNs on these circumstances, given the significance of the differences (105,107). In the analysis of Walz, the pooled data, also supported the fact that interferon reduced the mortality probability (OR, 0.19; 95% CI, 0.04–0.85); p=0.03, N=1906. This including the other observational data regardless of the descriptive nature of the incidences in these records, without standardization or control in the disease stage of the intervention, nor the regimes of dosage among centers.

Beyond the noted bibliography, we found only three other studies that complied with the inclusion criteria and were not addressed in other meta-analysis or reviews. 2 of the studies referred to group 1 IFNs and one study addressed group 3 IFNs. Zhou et al described clearance of real time polymerase chain reaction (RT-PCR) for SARS-CoV-2 as a surrogate of disease improvement to prevent severe pneumonia. They found accelerated viral clearance from the upper respiratory tract in patients who received IFN-a2b treatment (20.4 days, p = 0.002) mean difference of 7 days with control group (110). Rahmani et al completed a randomized clinical trial with a sample of 80 patients considering the mortality outcome as secondary outcome. Time to clinical improvement was the primary one depicting significant differences HR=2.30; 95% CI: 1.33–3.39 for a mean difference in two days for resolution(111). Finally, the only study to portrait the effects of another group of interferon in the COVID–19 patients was the one performed by Feld and colleagues. Decline in SARS-CoV-2 RNA was the main outcome, reporting greater reduction in those treated with peginterferon lambda than placebo from day 3 onwards, with a difference of 2·42 log copies per mL at day 7 (p=0·0041) (112).

3.4. Mesenchymal stem cells

Mesenchymal stem cells are also known as mesenchymal stromal cells. The use of these cells is widely known in certain inflammatory diseases, also as part of allogenic adoptive transfer therapy and even in graft vs host disease. This might be related to their properties of tissue repair and low immunogenicity. These cells tend to present surface markers such as CD44, CD90 and CD105 but also they are characterized by the absence of hematopoietic markers, such as CD34, CD45 and HLA-DR. those characteristics have consequences in cell recognition and may contribute to the anti-inflammatory properties (113).

In the other hand even if we can't pinpoint the exact interaction of this pharmacological intervention in the context of SARS-COV-2 infection, and even if we think of this rationale as insufficient, there is already evidence of its use on other viral driven lung injuries like A/H5N1 acute lung injury (114). From the available preeliminary data, we managed to find 105 articles from whom we selected 7 According to the inclusion criteria.

Amongst the selected studies, we managed to find a single meta-analysis. Wenchun Qu et al. reviewed the available data concerning the use of mesenchymal stromal cells, regardless of the origin (marrow, adipose tissue, or umbilical cord), and evaluated the impact on mortality on adults with acute respiratory distress syndrome (ARDS). They encompass several literatures that addresses ARDS, however only a single bibliography was related directly with COVID–19 patients. They use indirect evidence to analyze the plausibility of use in critically ill COVID–19 patients. Even more, some of the records used in the review, reference to case reports or series of cases. Despite this, it´s worth evaluating the conclusions of the pooled data: regarding the secondary outcome of mortality rate, the data seemed to favor treatment with mesenchymal cells without achieving significance: OR 0.63, 95% confidence interval 0.21-1.93. The primary outcome was safety related without reporting any serious adverse events (115).

Regarding the other selected records, only two were observational studies and 4 of the registries were clinical trials, some of them with randomization and masking. Overall, the studies in this topic tend to have the smallest of samples compared with the above-mentioned pharmacological targets. The consequent analysis derives into mostly descriptive outcomes, regardless of methodology. The incidence of mortality and related outcomes is limited in the small samples. There are studies that in spite of having placebo group as control, did not present a single fatality in either group. All these factors were taken into account in the study design, since most of the outcomes related to either radiological evolution, biomarker evolution or pulmonary function tests after a predetermined time lapse(116–120). The characteristics of the studies can be found in the adjunct table.

Lastly, we must highlight a mesenchymal stem cell derived compound used in a single clinical trial performed by Sengupta et al. In this trial, the authors attempted to use exosomes derived from bone marrow mesenchymal stem cells as immunomodulatory mediators that could avoid the possibility of infusional reactions and allergic responses (121). The limitations of the study are the same as in the cluster of records mentioned above, never the less it opens the possibility to another method of implementing this particular pharmacological target.

Table 1. Biotherapeutics in Covid-19 patients

Drug	Therapeutic target	n	Study type	Dose	Clinical Outcome	Ref
Tocilizumab	Il 6	85	Retrospective observational study	400 mg i.v. once (n = 33), 324 mg s.c. once (n = 27), 800 mg i.v. (n = 2)	Survival rate increase favoring tocilizumab hazard ratio for death: 0.035; 95% confidence interval [CI], 0.004 to 0.347; p = 0.004	28
Tocilizumab	Il 6	112	Retrospective observational study	8 mg/kg i.v. and repeated after 12 h (n = 21)	ICU admission and mortality favors tocilizumab OR 0.78; 95% CI between 0.06 and 9.34; p = 0.84	29
Tocilizumab	Il 6	45	Retrospective case–control study	1 or 2 doses (n = 20)	Combined primary endpoint (death and/or ICU admission) was higher in the control group than in the Tocilizumab group (72% vs 25%, p= 0.002)	30
Tocilizumab	Il 6	111	Retrospective observational study	8 mg/kg i.v. once (n = 42)	Fatality rate and levels of inflammatory markers increase in tocilizumab group 4 of 42 cases died with no fatalities in standard care group	31
Tocilizumab	Il 6	86	Retrospective case–control study	400 mg fixed dose or 8 mg/kg (n = 21) once or twice	Death rates decrease in tocilizumab group RR 0.472; 95% CI 0.449-0.497	32
Tocilizumab	Il 6	59	Retrospective case–control study	8 mg/kg at discretion of the treating physicians,	Death, invasive ventilation reduction in tocilizumab group OR: 0.25 95%CI [0.05-0.95], p =0.04	33
Tocilizumab	Il 6	94	Retrospective case–control study	N/A (n = 44)	Survival rate in tocilizumab group 61.36 % versus 48 % in the control group, p < 0.00001	34
Tocilizumab	Il 6	25	Retrospective observational study	median total dose 5.7 mg/kg	36% of patients were discharged alive from ICU by day 14 with no comparator	36
Tocilizumab	Il 6	65	Prospective observational study	400 mg fixed dose and 24-hour 400 mg depending on clinical deterioration	At day 28 (16%) of the tocilizumab group died, compared to 33% of standard treatment group (p = 0.150).	37

Tocilizumab	Il 6	544	Multicentered retrospective observational study	Tocilizumab 8 mg/kg (up to 800 mg) twice	hazard ratio of death/ mechanical ventilation favors tocilizumab adjusted (hazard ratio 0·61, 95% CI 0·40-0·92; p = 0·020)	38
Tocilizumab	Il 6	51	Retrospective observational study	Tocilizumab 8 mg/kg and received (up to 400 mg)	death/ clinical improvement at 21 days in treated vs. Control favors control 76.5% (95% CI: 57.3-95.6) vs.79.4% (95% CI: 56.0-100)	39
Tocilizumab	Il 6	15	Retrospective observational study	80–600 mg per time according to clinical worsening	Laboratory data and clinical course with no comparator; 20% of the patients died	40
Tocilizumab	Il 6	51	Prospective nonrandomized study	fixed first dose of 400 mg followed by 400 mg after 12 h	Mortality and clinical course with no comparator 30-day mortality: 27%.	41
Tocilizumab	Il 6	153	Prospective observational study	Tocilizumab 8 mg/kg i.v. (up to 800 mg); second dose if elevated body mass	87% survival at day 14 with no comparator	42
Tocilizumab	Il 6	63	Prospective observational study	Tocilizumab i.v. 8 mg/kg	11% Mortality at day 14 no comparator	43
Tocilizumab	Il 6	100	Prospective observational study	Tocilizumab 8 mg/kg (up to 800 mg) twice	Clinical outcome at day 10: 77% improved or stabilized and 23%worsened no comparator	58
Tocilizumab	Il 6	21	Retrospective observational study	Tocilizumab 4- 8 mg/kg (up to 800 mg) twice	Mean discharge day 15.1 without comparator	45
Tocilizumab	Il 6	89	Retrospective observational study	Tocilizumab 400 mg single dose	Descriptive deaths, mechanical ventilation and discharged with no comparator; 63/72 not mechanically ventilated patients were discharged	44
Tocilizumab	Il 6	186	Retrospective observational study	Tocilizumab single dose of 400–600 mg	51 patients were intubated or dead at day 15 with no comparator.	46
Tocilizumab	Il 6	547	Retrospective observational study	Tocilizumab: 400 mg some with a second dose of 800 mg	The unadjusted 30-day mortality favored tocilizumab (HR, 0.76, 95% CI,0.57–1.00)	47

Tocilizumab	Il 6	60	Nonrandomized prospective observational study	Tocilizumab 400 mg single dose according to clinical response re-dosing possibility	Bacterial and fungal infections	48
Tocilizumab	Il 6	1229	Multicentered retrospective observational study	Tocilizumab median dose 600 mg, second dosing according to clinical response	Tocilizumab associated with higher risk of death (HR 1.53,95% CI 1.20-1.96, p = 0.001)	49
Tocilizumab	Il 6	171	Retrospective observational study	Tocilizumab 400 mg/24 for patients with ≤75 kg and 600 mg/24 for patients with >75 kg with second and third dosing according to clinical response	Description of frequency for composite ICU admission or death favoring Tocilizumab (10.3% vs. 195 27.6%, *p* = 0.005)	50
Tocilizumab	Il 6	1221	Multicentered phase 2 clinical trial	Tocilizumab 8 mg/kg and second dose according to clinical response	Lower lethality rates at 14 and 30 days (15.6%and 20.0%) among the treated with tocilizumab	51
Tocilizumab	Il 6	145	Multicentered retrospective observational study	Tocilizumab 400 - 800 mg single dose	Descriptive study of mortality with no comparator 43.8% of the population discharged and 29.3% died	52
Tocilizumab	Il 6	86	Multicentered retrospective observational study	Tocilizumab 400 - 800 mg single dose	In hospital mortality with tocilizumab: 27% of patients with no comparator	53
Tocilizumab	Il 6	246	Retrospective observational study	Tocilizumab 400 mg single dose	Composite of all-cause mortality and invasive mechanical ventilation favoring tocilizumab (HR = 0.49 (95% CI 0.3–0.81), *p* e = 0.005)	54
Tocilizumab	Il 6	82	Prospective and retrospective observational	Tocilizumab 400 mg single dose with second dose according to clinical response; 600 mg if > 75 kg	Mortality at 7 days of tocilizumab start; 26.8 % of all patients died (no comparator)	55
Tocilizumab	Il 6	154	Single center retrospective observational	Tocilizumab 8 mg/kg single dose	Survival probability post intubation favoring tocilizumab in 3 models: model A HR 0.54 (95% CI 0.29, 1.00)	56

Tocilizumab	Il 6	94	Single center retrospective observational	(preprint) does not show administered dose yet	length of stay favoring control group, ventilation and survival rates favoring control tocilizumab (61.36 vs 48% of all patients)	57
Tocilizumab	Il 6	29	single center prospective clinical trial	Tocilizumab 8 mg/kg single dose	Classified as responders or non-responders (secondary analysis described correlation with miR-146a marker) 55.17% of patients where responders	64
Tocilizumab	Il 6	129	Prospective multicenter randomized clinical trial	Tocilizumab 8 mg/kg two doses	Risk of mechanical ventilation or death at day 28 favored tocilizumab HR 0.58 (90% CrI, 0.30 to 1.09).	65
Tocilizumab	Il 6	126	Prospective randomized clinical trial	Tocilizumab 8mg/kg up to a maximum of 800mg	Clinical worsening ratio showed worst outcome in tocilizumab group (risk ratio, 1.05; 95%CI, 0.59-1.86).	66
Tocilizumab	Il 6	126	Prospective nonrandomized clinical trial	Tocilizumab 324 mg - 486 mg according to body weight single dose	Mortality rates with no comparator: by day 14 of the study, 4.65% (4/86) of severe patients and 50.00% (20/40) of critical patients died.	67
Tocilizumab	Il 6	42	Prospective nonrandomized clinical trial	Tocilizumab 400 mg single dose	mortality rates with no comparator: 35 patients (83.33%) showed clinical improvement by day 28	68
Tocilizumab	Il 6	418	Matched cohort study	Tocilizumab up to 3 doses ranging from 400 mg to 600 mg according to clinical evaluation	Inspired oxygen fraction / saturation 48 h post treatment showed no difference, logistic regression did not show an effect of tocilizumab on mortality (OR 0.99; p = 0.990).	69
Tocilizumab	Il 6	389	Randomized clinical trial	Tocilizumab 8 mg/kg one or two doses according to response	Death / mechanical ventilation at day 28 HR: 0.56 CI, -0.33 – 0.97 Death from any cause at day 28: weighted difference, 2 percentage points favoring placebo CI, -5.2 – 7.8	70

Tocilizumab	Il 6	129	Randomized clinical trial	Tocilizumab 8mg/kg up to a maximum of 800mg	Death / mechanical ventilation at day 15 (odds ratio 1.54, 95% confidence interval 0.66 to 3.66; P=0.32)	71
Tocilizumab	Il 6	243	Randomized clinical trial	Tocilizumab 8mg/kg up to a maximum of 800mg	Death / intubation at day 14 HR: 0.83 (95% [CI], 0.38 to 1.81; P = 0.6)	72
Tocilizumab	Il 6	4116	Randomized clinical trial	800 mg if weight >90 kg; 600 mg if weight >65 and ⩽90 kg; 400 mg if weight >40 and ⩽65 kg; and 8 mg/kg if weight ⩽40 kg	Invasive mechanical ventilation or death (35% vs 42%; risk ratio 0·84; 95% CI 0·77–0·92; p<0·0001) favors tocilizumab	73
Siltuximab	IL 6	218	Observational cohort study	Siltuximab 2 doses 11 mg/kg	30-day mortality rate favors Siltuximab (HR 0.462, 95% CI 0.221– 0·965); p=0·0399).	60
Sarilumab	Il 6	28	Observational cohort study	Sarilumab 400 mg single dose	Clinical improvement and lethality rate showed no differences; 61% of patients treated with sarilumab experienced clinical improvement and 7% died	61
Sarilumab	Il 6	803	Prospective nonrandomized clinical trial	Sarilumab 400 mg single dose	Descriptive Hospital mortality: 28.0% (98/350) for tocilizumab, 22.2% (10/45) for sarilumab and 35.8% (142/397) for control.	62
Sarilumab	Il 6	53	Prospective nonrandomized clinical trial	Sarilumab 400 mg two doses	Descriptive with Sarilumab no comparator; global resolution rate of 83.0% (89.7% in medical wards and 64.3% in ICU) and an overall mortality rate of 5.7%.	63
Sarilumab	Il 6	457	Randomized clinical trial	Sarilumab 200 - 400 mg single dose	All cause mortality at day 29: Risk difference - 5.5%; 95% CI,–20.2 to 8.7; relative risk reduction 13.3%)	74

Anakinra	IL 1	22	Observational cohort study	Anakinra 300 mg for two 5 days tapered to 200 mg for 2 days	Descriptive outcomes regarding mechanical ventilation, death, and mean days to discharge (mean days in control group 9.5 and 5 days in Anakinra group)	80
Anakinra	IL 1	96	Observational cohort study with historical controls	Anakinra 100 mg twice a day for 72 h, then 100 mg daily for 7 days	Composite endpoint of admission to the ICU for invasive mechanical ventilation or death (HR 0.22 [95% CI 0·10–0·49]; *p* =0·0002)	81
Anakinra	IL 1	153	Randomized control trial	Anakinra 400 mg/day on days 1–3 then 200 mg on day 4, and 100 mg once on day 5	Patient death or need of mechanical ventilation HR 0.97; 90% CrI 0·62 to 1.52	79
Anakinra	IL 1	120	Observational cohort study	High dose anakinra non specified	Adjusted risk of death comparing anakinra group with control HR, 0.18, 95% CI, 0.07-0.50, *p=o*.001,	82
Anakinra	IL 1	392	Observational cohort study with historical controls	Anakinra 10 mg/kg/ day until clinical benefit	Anakinra group with reduced mortality risk (hazard ratio [HR] 0.450, 95% CI 0.204–0.990, *p* =0.047)	83
Anakinra	IL 1	128	Observational cohort study	Anakinra 100 mg every 8 hours for 3 days, with tapering	Mortality reduction favoring anakinra adjusted [HR] = 0.26; *p* < .001	84
Anakinra	IL 1	21	Observational prospective cohort	Anakinra300 mg initial dose following 100 mg every 6 hours	In the anakinra group, 28-day mortality was 19% vs. 18% in the control group (*p* = 0.87).	78
Anakinra	IL 1	130	Observational prospective cohort	Anakinra 100 mg once daily for 10 days	Reduction in 30-day mortality with anakinra (hazard ratio 0.49; 95% CI 0.25–0.97)	85
Anakinra	IL 1	69	Observational cohort study with historical controls	Anakinra 100 mg twice daily for 3 days, followed by 100 mg daily for a maximum of 7 days	hospital death occurred in 13 (29%) of the anakinra-treated group and 11 (46%) of the historical cohort (*p* = 0.082).	77
Anakinra	IL 1	93	Observational retrospective Cohort studies	Anakinra minimum use of 100 mg every 12 hours (depending on	Survival rate of anakinra vs Tocilizumab: HR 0.46, 95% confidence interval 0.18–1.20	87

				clinical condition and comorbidities)		
Anakinra	IL 1	27	Observational retrospective Cohort studies	Anakinra 100 mg every 6 h for at least 3 days, tapering until 7 days	Descriptive of only 9 treated patients with matched cohort of tocilizumab treated patients (9 survivals)	86
Anakinra	IL 1	120	Prospective nonrandomized clinical trial	100mg anakinra daily for 5 days	Patient mortality without significant difference OR of 0.9 (95%CI [0.80–1.01], $p = 0.067$)	88
Anakinra	IL 1	606	Multicentered, double blind, randomized, clinical trial	100 mg anakinra daily for7 - 10 days	Risk of death at day 28 hazard ratio = 0.45, 95% CI 0.21–0.98, $p = 0.045$	90
Anakinra	IL 1	112	Observational cohort study with matched controls	100 mg four times a day, if managed in a regular ward, or 200 mg three times daily if managed in the intensive care unit,	Anakinra as a survival predictor at day 28 odds ratio: 3.2; 95% confidence interval, 1.47–7.17	89
Canakinumab	IL 1	88	Observational prospective cohort	Canakinumab 300 mg single dose	Descriptive outcome with no comparator, overall survival at 1 month was 79.5% (95% CI 68.7–90.3)	91
Canakinumab	IL 1	34	Observational prospective cohort	Canakinumab 300 mg single dose	descriptive oxygen support requirement at 3 time points: reduction in oxygen flow in patients treated with canakinumab (−28.6% at T1 vs. T0 and −40.0% at T2 vs. T1).	92
Canakinumab	IL 1	454	Randomized Clinical trial	Canakinumab 450 - 750 mg single dose	Non-significant mortality risk reduction with Canakinumab odds ratio of 0.67 (95%CI, 0.30 to 1.50)	94
Canakinumab	IL 1	48	Prospective case control	Canakinumab 150 mg at day 1 and day 7	Descriptive outcome, survival at 60 days was 90.0% (95% CI 71.9–96.7) in patients treated with canakinumab and 73.3% (95% CI 43.6–89.1)	93

Ruxolitinib	Jak 1 and 2	43	Randomized single blinded Clinical trial	Ruxolitinib 5 mg twice a day	Cumulative incidence of death favors ruxolitinib,14.3% overall mortality at day 28 in control group; no patients died in the ruxolitinib group	96
Ruxolitinib	Jak 1 and 2	75	Non-randomized clinical trial	Ruxolitinib 5 mg twice a day	Comparison of outcomes in survival rate of ruxolitinib in mechanical ventilated and no mechanical ventilated without placebo group	98
Baricitinib	Jak 1 and 2	20	Observational longitudinal trial	Baricitinib 4 mg twice daily for 2 days, followed by 4 mg per day for the remaining 7 days.	Descriptive outcome of incidence baricitinib- treated patients (5%) mortality compared with (45%) of 56 patients in the non–baricitinib-treated group ($p < 0.001$)	99
Baricitinib	Jak 1 and 2	191	Retrospective Cohort	Baricitinib 4 mg/day for 2 weeks	Descriptive 2-week case fatality rate was lower in the baricitinib-arm compared with controls [0% (0/113) vs 6.4% (5/78) (p -value: 0.010; 95%CI 0.0000–0.4569)]	100
Baricitinib	Jak 1 and 2	24	Prospective Cohort	Baricitinib 4 mg/day for 2 weeks	Pilot study that only address biomarkers difference	101
Baricitinib	Jak 1 and 2	387	Prospective observational study	Low dose regime: loading dose of 4mg the first day and then 2mg daily; high dose regime: 4mg daily each	Requirement of supplemental oxygen at discharge favors baricitinib OR: 0.18; 95% CI: 0.08, 0.43; p <0.001	102
Interferon β-1a	interferon β-1a	81	Randomized Clinical trial	12 million IU/ml three times a week for two weeks	Mortality reduction in interferon group at day 28 (OR, 6.65; 95% CI, 1.67 to 26.45) adjusted for confounders.	105
Interferon β-1b	interferon β-1b	256	Retrospective cohort	250 mcg on alternate days	Descriptive outcome mortality rate was 24.6% (63/256). Twenty-two patients (20.8%) in the interferon group and 41 (27.3%) in the control group (p =0.229)	106

Interferon β-1b	interferon β-1b	127	Randomized Clinical trial	three doses of 8 million IU on alternate days	Combination group of interferon was independent risk factor for nasopharyngeal swaps negativization HR 4.27 [95% CI 1.82–10·02], p=0.0010; no deaths in either group	107
Interferon α-2b	interferon α-2b	814	Multicenter prospective observational study	3 million IU 3 times per week, for 2 weeks	Descriptive outcome: The overall case fatality rate was 2.95% of the infected population. The case fatality rate for patients treated with IFN-a2b was 0.92 ($p < 0.01$)	108
Interferon α-2b	interferon α-2b	446	Retrospective multicenter cohort study	Different regimes in each center (non-specified)	IFN therapy is univariably associated with lower mortality (odds ratio [OR] = 0.18, $p = 0.029$)	109
Interferon α-2b	interferon α-2b	77	Prospective observational study	5 mIU in inhaled aerosol each day	Accelerated viral clearance from the upper respiratory tract in patients who received IFN-a2b treatment (20.4 days, p = 0.002) mean difference of 7 days with control group	110
Interferon β-1b	interferon β-1b	80	Randomized clinical trial	250 µg on alternate days	All-cause 28-day mortality was 6.06% and 18.18% in the IFN and control groups respectively ($p = 0.12$)	111
Peginterferon lambda	interferon lambda	60	Randomized Clinical trial	180 mcg single dose	Favors faster viral clearance with pegylated interferon 2.42 log copies per mL at day 7 (p =0·0041)	112
Mesenchymal stem cells	Mesenchymal stem cells	200	Meta analysis	variable according to study and type of mesenchymal stem cells	favor treatment with mesenchymal cells without achieving significance: OR 0.63, 95% confidence interval 0.21-1.93	115
Mesenchymal stem cells	Mesenchymal stem cells	10	Nonrandomized pilot clinical trial	1 × 10 ^ 6 cells per kilogram of weight single transplantation	Descriptive outcome favoring treatment group: none of the patients in the mesenchymal stem cell group died	116

Mesenchymal stem cells (umbilical cord)	Mesenchymal stem cells	41	Randomized clinical trial	2 × 10 ^ 6 cells per kilogram of weight single transplantation	Descriptive outcome favoring treatment group: none of the patients in the mesenchymal stem cell group died	117
Mesenchymal stem cells (umbilical cord)	Mesenchymal stem cells	18	Nonrandomized clinical trial	three transplantations of 3 × 10 ^ 7 cells per infusion	Descriptive outcome: mechanical ventilation was required in one patient in the treatment group compared with four in the control group	118
Mesenchymal stem cells	Mesenchymal stem cells	25	Retrospective observational study	1 ×10 ^ 6 mononuclear cells per kilogram of weight per infusion every 5 days	No differences comparing Mesenchymal cell treatment and placebo group (inflammatory markers surrogate did not show any differences either)	119
Mesenchymal stem cells	Mesenchymal stem cells	100	Randomized double blind clinical trial	Three transplantations of 4 × 10 ^ 7 cells per infusion	Lung function in 6 min walking test at day 28 favors mesenchymal cell treatment median 420 meters vs 403 meters in control group $p = 0.057$	120
Exosomes Derived from Bone Marrow Mesenchymal Stem Cells	Mesenchymal stem cells	27	Prospective nonrandomized cohort study	15 mL intravenous dose of ExoFlo single dose	Descriptive outcome with no comparator with overall survival rate in the study of 83%.	121

4. Discussion

The use of biologics in the context of COVID–19 implies a deep understanding of the physiopathological pathways of the infection to address more directed axis hoping new alternatives of management to prevent severe or advanced phases of the illness. However, even if we understand the biological plausibility in each scenario of proposed interventions, we must consider the principle that guides epidemiological studies to endorse interventions. This principle is mainly directed to the degree of certainty that the evidence allows. To our knowledge, this is the first compilation study of biologicals in general, in contrast with the existing compilations of studies addressing individual targets. In a general approach to the complied data in this review we must stress the common findings in the limitations these studies share regardless of the pharmacological target.

First is the methodological consistency. In this aspect the studies show great variability in their design. We are not referring to the nature of the study itself but the fact that throughout the evolution of the pandemic what is considered standard care changes continuously. If we evaluate what entails standard care in the earliest publications, in each target, we would find that the concomitant use of antivirals such as lopinavir/ ritonavir and the use of Hydroxychloroquine were considered as standard care. Even if we argue that both control groups and intervention groups were submitted to the same variables, the risk of confounders is there, since we cannot always tell or predict interaction pathways. The multivariate regressions employed in most of the non-descriptive studies can stratify and eliminate some of this burden, however, the standard care in the most recent studies do not entail the same co interventions.

In this line of thought, we also encounter the difficulty of controlling consistency with over added variables, according to the selected population in each study, since not every single one performs regressions models. The fact that most of the studies start with a population with severe phase to hyperinflammatory phase, implies that not only more interventions are added as part of standard care, but the fact that dealing with these populations gives different startup lines, with great variability in prognosis factors that must be either analyzed or controlled per protocol. The sheer amount of possible prognosis markers and scales can explain in some part the heterogeneity in the cited review studies as seen in different conclusions between Shao-Huan Lan et. Al and Cortegiani et al. (27,35), regarding Tocilizumab.

A second broad point is the inherent limitations in each methodological design. While observational, cohorts studies can evaluate multiple outcomes simultaneously and stablish a causal degree of certainty, the control over the multiple variables that can influence the outcome is limited, in contrast to experimental designs. This may sound as an apparent truth, but the volume of observational studies amongst the total of the data extracted may raise some eyebrows regarding of the magnitude of the possibility of unidentified confounding bias. Of course, considering the ethical reservations in the case of a pandemic, this type of study would be popular at the start of the spread, since it does not require experiment with an intervention with a preselected population of intervention. Nevertheless, we cannot ignore the strains it pose on the validity of conclusions.

As a third point we must stress the importance of the variable sample size amongst the studies. Even regarding targets with huge number of studies like Il 6, most of the studies have very small sample sizes individually. This can limit the possibility of reaching conclusions that can be extrapolated outside the study environment. There are even cases

(I.e. JAK kinase inhibitors) that neither group of intervention nor control have fatalities, as we must understand it is possible (with the documented lethality / case rate) if the sample is too small. Being aware of this might favor methodological designs that prefer surrogate outcomes as biomarkers, pulmonary function tests, radiological improvement or pcr clearance. These surrogate markers obviously limit the possibility of wide endorsement use of these pharmacological interventions.

Not only the sample sizes tend to be small, but also the context of compassionate use determines a disproportionate number of patients in either control groups or intervention groups compared to their counterpart. Many of the cited studies were affected since the view of compassionate use can change in each institution. In some cases, the treatment patients were to few compared to the number of controls even in large samples. In other cases, the number of controls were insufficient as the center were the studies where performed, had already implemented the intervention as hospital protocol.

A third point to be addressed is the large amount of evidence that submits pure incidence descriptive outcomes. This type of evidence is valuable in order to support the notion of the need of randomized trials with larger population samples, but; taking into account the development of the pandemic with still relevant number of new deaths, we cannot endorse pharmacological interventions prospects with the analyzed data as a widespread practice. Furthermore, methodological standardization is needed regarding the variability of treatment regimens that differ in each center at each intervention group

Finally, in regard our added limitations in the methodology of our study:

- This descriptive scoping review study does not generate measures of association contrary to systematic reviews performed in individual pharmacological targets.
- The immediate perspective of studies that are still in progress, during the review period, are not included if there are no prepublication manuscripts.
- In this study, the risk of bias was not objectified with predetermined tools per study.

Conclusions

Il 6 inhibitors

This pharmacological target has the most amount of accumulated evidence available. We cannot ignore the fact that even with all the limitations mentioned before, most of the point estimators regarding disease resolution; mortality and mechanical ventilation use, tend to favor the intervention in this target. No generalization can be made regarding the use of these pharmacological alternatives since the heterogeneity of the data is high with several studies without statistical significance and a fair number of studies that show no difference with the intervention. We encourage more data recollection with randomized clinical trials, with larger samples, controlling prognosis factors (i.e. with tools like the Charlson score index). Standardization of treatment regimens is needed to accumulate consistent data.

Il 1 inhibitors

The compiled data shows less heterogeneity compared with the Il 6 inhibitors. Most of the point estimators favor this pharmacological group, without overlooking the fact that some of the data is not statistically significant. The number of records and the small samples suggest the need of larger randomized trials, despite the encouraging results. Standardization of treatment regimens is needed to accumulate consistent data.

JAK inhibitors

Most of the available evidence in this group tend to be descriptive in nature about surrogate outcomes as primary end points, and incidence descriptions. There is too little evidence with small sample sizes. To generate a perspective about this target more data is needed at least with comparators and larger samples regardless of methodology.

Interferons

In this group most of the estimators related to death or disease deterioration showed good responses to the intervention, nevertheless, we must stress that half of the data use surrogate or descriptive outcomes and the availability of records within the criteria gives a very small sample. Regardless of the methodology, more data is needed to conclude in this target.

Mesenchymal stem cells

This biological has the less data available regarding its efficacy with the studies with the smallest of samples. The descriptive nature of biomarkers as surrogate primary end-points is widespread amongst the studies. We speculate that the availability and logistical challenges in this matter may limit the number of studies to be performed in the future. Furthermore, even if the results reflected encouraging data the possibility of widespread use in certain countries may limit its implementation.

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