Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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"Cytokine storm", not only in COVID-19 patients. Mini-review

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ABSTRACT

Cytokine storm is a form of uncontrolled systemic inflammatory reaction activated by a variety of factors and leading to a harmful homeostatic process, even to patient's death. Triggers that start the reaction are infection, systemic diseases and rarely anaphylaxis. Cytokine storm is frequently mentioned in connection to medical interventions such as transplantation or administration of drugs.

Presented mini-review would like to show current possibilities how to fight or even stop such a life-threatening, immune-mediated process in order to save lives, not only in COVID-19 patients.

Early identification of rising state and multilevel course of treatment is imperative. The most widely used molecule for systemic treatment remains tocilizumab. Except for anti IL-6 treatment, contemporary research opens the possibilities for combination of pharmaceutical, non-pharmaceutical and adjunctive treatment in a successful fight with consequences of cytokine storm.

Further work is needed to discover the exact signaling pathways that lead to cytokine storm and to determine how these effector molecules and/or combination of processes can help to resolve this frequently fatal episode of inflammation. It is a huge need for all scientists and clinicians to establish a physiological rational for new therapeutic targets that might lead to more personalized medicine approaches.

1. Introduction

Although to date, "cytokine storm" is mainly connected to COVID-19, many hypothesis concerning treatment modalities have been rising in the last fifteen years. It seems to be important to put together knowledge about known immunological mechanisms and the contemporary medicaments (except for antimicrobial drugs without immunomodulatory effect) which are potent to modulate immunologic answer even to fight against such a harmful process. A recent PubMed search for cytokine storm or cytokine release syndrome yielded 1102 and 1817 hits respectively; over 100 articles/year were within the past five years.

Cytokine release syndrome (CRS) or "cytokine storm" is a form of uncontrolled systemic inflammatory reaction that can be triggered by a variety of factors. It starts fairly quickly in cases of severe (mainly respiratory) infections, in other types of massive immune activation such as severe courses of some systemic diseases (RA, SLE), rarely anaphylaxis. It can be frequently mentioned in connection to medical interventions such as transplantation [1] or administration of certain drugs (monoclonal antibodies, adoptive T-cell therapies) [2]. Subtle CRS may occur following immunization against rubella, human papillomavirus, or hepatitis B [3].

The term "cytokine release syndrome" appeared in the early '90 s, when the anti T-cell antibody muromonab-CD3 was introduced as an immunosuppressive treatment for solid organ transplantation [4]. Yet, Vegh et al. as early as in 1975 observed that by administering polyclonal antibodies the possibility of systemic anaphylactic reactions and other side effects may be present [5]. Presumably they supposed a cytokine-storm like reaction which has different phenotypes from the classical type-I or complement-mediated reaction. At that time such biomarkers as tryptase, IL-6, bradykinin etc. were not known or were on the early stages of immunological research [6].

Except for anti-thymocyte globulin [7,8], CRS has been described after administration of several antibody-based therapies such as rituximab [9], alemtuzumab [10], muromomab [4], theralizumab [11], nivolumab [12], obinutuzumab [13], brentuximab [14]. Anticancer non-protein-based treatment with oxaliplatin [15] and IMiDs (lenalidomide) [16] can activate cytokine storm as well. Furthermore, CRS was reported in stem cell transplantation and graft-versus-host disease. As mentioned above, cytokine storm is also a proposed pathomechanism of severe viral infections due to massive T cell stimulation. It is supposed to be combined with all influenza epidemics since Spanish flu in 1919 through dengue, Ebola to corona virus infection in 2020 [17]. CRS has

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been observed also in surgical patients with severe bacterial infections or in patients with inhalation injury [18].

Such broad spectrum of etiological factors leading to clinical and laboratory manifestation of CRS like hypotension, hypoxia, fever, fatigue, myalgias, malaise, nausea, hypoxia, coagulopathy, capillary leakage, tachycardia, tachypnea, hemophagocytic lymphohistiocytosis/macrophage activation syndrome, organ toxicity, pulmonary edema, pneumonitis, and renal insufficiency support the basic scientific postulate: cytokine storm results from excessive pro-inflammatory stimuli, inadequate regulation of inflammation, immune cells or both [19]. Not only pro-inflammatory cytokines, but also anti-inflammatory cytokines appear in circulating blood, such as IL-10 and transforming growth factor-beta (TGF-beta). Cytokines work in counterbalance mode, as demonstrated on typical example: products of the Th2 immune response suppress the Th1 immune response and vice versa [20]. In a case of robust activation of immune balance, without the ability to resolve the inflammation, the collateral damage to surrounding cells can be catastrophic, resulting in septic shock, multiple organ dysfunction, immunosuppression and even death [21]. If the inflammatory response is properly regulated, regulatory mechanisms prevent the body from being damaged by systemic inflammation caused by sudden activation of cytokine release. Such inflammation can be resolved effectively, with little or no long-term damage to the host [22].

If CRS is primarily caused by environmental case, there is a strong request to allow restoration of homeostasis. Offending microbe, allergen, or cytotoxic agent when possible, should be eliminated. Antimicrobial treatment is indicated in any form of cytokine storm if contributing pathogen is suspected. Even though simultaneous antimicrobial treatment is not the topic of presented contribution, many of contemporary molecules have, except for their antimicrobial potency, also anti-inflammatory and immunomodulatory effect.

Canna and Behrens [19] propose a conceptual model of various cytokine release syndromes based on the nature of mechanisms of inflammation. Careful assessment of host and environmental factors strengthen the idea of rational therapeutic approach. In a case of host dependent mechanism of inflammation, they emphasize the use of cytotoxic agents while in a case of environmentally induced inflammation (infection) antimicrobials are predominately indicated. Data about cytokine storm in human anaphylaxis or other severe allergic (drug) reactions are scarce [23]. Even if all forms of cytokine release syndrome induced by environmental or host factors arrive at their final common pathway, the critical point is to understand and specify the exact mechanism directing more precise mode of treatment.

The clinical picture of cytokine storm slightly varies in its several forms, but generally manifests as "overlap syndrome" laboratory manifesting in decreasing cell counts, decreasing ESR, increased ferritin level, NK dysfunction, and hemophagocytosis [19]. Although the primary cause of CRS is crucial to understand for restoring immunologic balance, the main focus in treatment should be directed towards final common pathway. At that level, influence on all pro-inflammatory and anti-inflammatory humoral and/or cellular compounds might have been considered. When activating intense inflammatory pathways through immune cells, endothelium, bone marrow, liver and kidney, a vicious circle of harmful processes can lead to death. Immunopathology could also be associated with extensive microthrombosis mostly in lungs, thus ischemic/reperfusion injury contributes to broadening of immune mediated inflammation [24]. Therefore, multilevel treatment opportunities should be a challenge (Fig. 1).

Clinical picture of CRS or cytokine storm strikes suddenly and the main goal, after starting intensive care treatment and targeting the elimination environmental trigger (if possible), is to administer potential drugs capable of controlling cytokine production and its harmful effect. Excessive cytokine production by immunomodulatory drugs has its place on top of contemporary research. From web portal "ClinicalTrials.gov" 27 studies under key words cytokine release syndrome and 32 studies under cytokine storm were analyzed (last accessed 26 August 2020). Out of those trials, not all deal with immunomodulators. Studies involved in the text are summarized in Table 1. Three studies are completed, two of them have already been published [25,26].

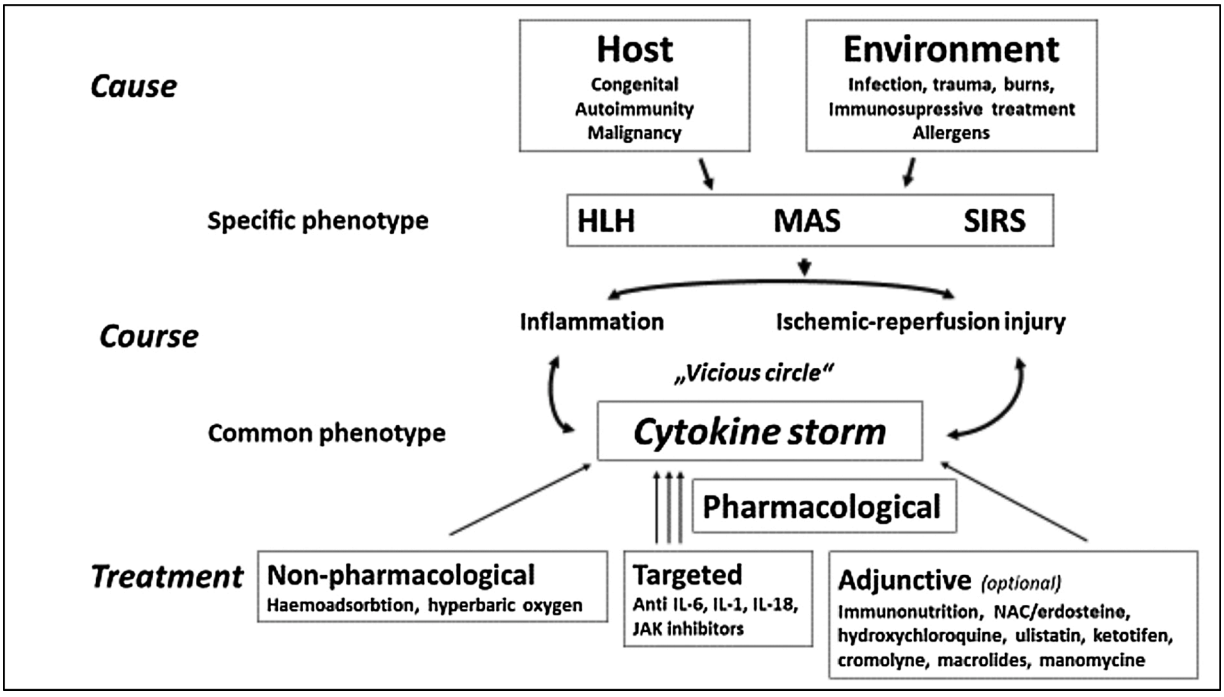

Fig. 1. Vicious circle of cytokine storm in a view of causes, course and treatment. (HLH - hemophagocytic lymphohistiocytosis, MAS - macrophage activation syndrome, SIRS - systemic inflammatory response syndrome, NAC – N-acetylcysteine).

Table 1
Summary of cited clinical trials.

Study title	Status	Identification number	Location	Phase*
Cytokine Adsorption in Severe COVID-19 Pneumonia Requiring Extracorporeal Membrane Oxygenation (CYCOV)	R	NCT04324528	Freiburg, Germany	
Cytokine Adsorption in Patients With Severe COVID-19 Pneumonia Requiring Extracorporeal Membrane Oxygenation (CYCOV-II)	IP	NCT04385771	Freiburg, Germany	
Early Haemadsorption in Major Burns	IP	NCT04195126	Pecs, Hungary	
Adsorbtion of Cytokines Early in Septic Shock: the ACESS Study	C	NCT02288975	Szeged, Hungary	
Cytokine Adsorption in Post-cardiac Arrest Syndrome in Patients Requiring Extracorporeal Cardiopulmonary Resuscitation (CYTER)	R	NCT03685383	Freiburg, Germany	
Extracorporeal Cytokine Adsorption as Additive Treatment of CAR-T Associated Cytokine Release Syndrome (CRS) (CYTORELEASE)	IP	NCT04048434	Hannover, Germany	
Effects of Endotoxin Absorption and Cytokine Removal Hemofilter on Severe Septic Shock	R	NCT03974386	Taipei, Taiwan	
Safety and Efficacy of Hyperbaric Oxygen for ARDS in Patients With COVID-19 (COVID-19-HBO)	R	NCT04327505	Gelsenkirchen, Regensburg, Germany*** Blekinge, Sweden	Phase 2/3
Efficacy and Safety of Tocilizumab in the Treatment of SARS-Cov-2 Related Pneumonia (TOSCA)	R	NCT04332913	L'Aquila, Italy	
Tocilizumab for Cytokine Release Syndrome Prophylaxis in Haploidentical Transplantation	R	NCT03533101	Monterrey, Mexico	**
Study of the Tocilizumab Optimization Timing for CART19 Associated Cytokine Release Syndrome	IP	NCT02906371	Philadelphia (PA), US	
Phase 3 Randomized, Double-blind, Placebo-controlled Multi-center Study to Assess the Efficacy and Safety of Ruxolitinib in Patients With COVID-19 Associated Cytokine Storm (RUXCOVID) (RUXCOVID)	R	NCT04362137	Multicentric (62 centers) worldwide	Phase 3
Ruxolitinib for the Treatment of Acute Respiratory Distress Syndrome in Patients With COVID-19 Infection (RESPIRE)	IP	NCT04361903	Pisa, Italy	
Treatment of SARS Caused by COVID-19 With Ruxolitinib	R	NCT04334044	Huixquilucan, Mexico	Phase 1/2
Baricitinib in Symptomatic Patients Infected by COVID-19: an Open-label, Pilot Study. (BARI-COVID)	IP	NCT04320277	Prato, Italy	Phase 2/3
Baricitinib Therapy in COVID-19	C	NCT04358614	Prato, Italy	Phase 2/3
Effects of Free Fatty Acids and 3-hydroxybutyrate on Protein, Glucose, Lipid Metabolism and Intracellular Signals	C	NCT01752348	Aarhus C, Denmark	
Prevention and Treatment With Calcifediol of COVID-19 Induced Acute Respiratory Syndrome (COVIDIOL)	IP	NCT04366908	Córdoba, Spain	Phase 2
The Effect of D3 on Selected Cytokines Involved in Cytokine Storm in the Covid-19 Uninfected Jordanian People	IP	NCT04476745	Amman, Jordan	
A Study to Evaluate OP-101 (Dendrimer N-acetyl-cysteine) in Severe Coronavirus Disease 2019 (COVID-19) Patients (PRANA)	R	NCT04458298	Multicentric (5 centers), US	Phase 2

(* – if applicable, ** – active, but recruitment interrupted in 2018, *** – only Swedish center started to recruit, IP – in preparation, R – recruited, C – completed).

2. Management of cytokine storm

2.1. Haemoadsorbtion

Seven of these studies are focused on using haemoadsorbtion in CRS management caused by SARS-CoV-2 (NCT04324528, NCT04385771), in severe burns (NCT04195126), septic shock (NCT02288975), cardiac arrest (NCT03685383) and after CAR-T cell therapy (NCT04048434). Haemoadsorbtion can lead to a reduction of the circulating pro- and anti-inflammatory cytokines and thus improve the course of the disease and the outcome of patients. One of them (NCT03974386) recruits patients with sepsis to establish influence of environmentally induced inflammation caused by gram-negative bacterial endotoxin as the main trigger for systemic inflammatory reaction. Endotoxin binds to Toll-like receptor 4 (TLR4) and so induces a cytokine storm. The amount of endotoxin is associated with shock, insufficient intestinal perfusion, and poor prognosis. Therefore, haemoadsorbtion can antagonize the action of endotoxin reducing the cytokine storm and inflammatory response to

improve the prognosis of sepsis.

2.2. Hyperbaric oxygen

One study (NCT04327505) is focused on efficacy of hyperbaric oxygen which significantly reduces inflammatory cytokines. It is expected to be effective in the treatment of cytokine storm in viral infections (SARS-CoV-2). It is possible to suppose that a clinical effect of hyperbaric oxygen is caused by immunological factors. The effect on monocytes may be the basis for reduced levels of circulating pro-inflammatory cytokines under stress conditions [27]. Apparently, hyperbaric oxygen could influence inflammation following environmental triggers (injury, sepsis) [28], but its effects on increased morbidity and mortality associated with aberrant inflammatory responses are largely unknown. Additional research is needed to estimate the effect of such treatment.

2.3. Targeted (immunomodulatory) treatment

Although immunomodulatory therapy is not routinely recommended, majority of clinical trials on CRS are focused on direct influencing highly elevated pro-inflammatory cytokines (interleukin IL-1, IL-2, IL-6, IL-7, IL-10, IL-18, TNF-α, indirectly by modulation of INF-γ production or by interfering NF-κB through JAK inhibitors. If possible, it is critical to intervene prior to the initiation of CRS and severe respiratory distress mainly in patients at high risk of worsening. To increase the chances of survival of such patients, the compassionate use of available drugs is required, based on literature data and current experience of many clinicians. Patients with cytokine release syndrome secondary to viral etiology, show increased production of pro-inflammatory cytokines similar to that found in patients who develop CRS secondary to CAR-T cell therapy [29,30].

2.3.1. Anti TNF-α

The most common clinically used group of biological drugs are TNF-α blockers, but their role in treatment of cytokine storm remains unclear. Although TNF-α inhibiting agents have been reported to be effective in cytokine dysbalance, other report worsening during treatment with TNF-α inhibiting agents, the published results have been conflicting [31].

2.3.2. Anti IL-6

Tocilizumab remains the most commonly used therapy for systemic treatment of CRS. Multiple studies confirmed the correlation of peak IL-6 levels with the severity of CRS leading to the approval of tocilizumab for treatment of CRS concurrent with the approval of tisagenlecleucel, CAR T-cell therapy in non-Hodgkin lymphomas (DLBCL) [32]. Tocilizumab, IL-6 receptor-targeted monoclonal antibody has been effectively used to treat CRS in several scenarios. Since April 2020, newly opened clinical trial “Efficacy and safety of tocilizumab in the treatment of SARS-Cov-2 related pneumonia (TOSCA)” (NCT04332913) might show a rationale for those patients who develop CRS, blocking the complications caused by high levels of IL-6, and possibly preventing the development of a multi-organ failure. Two other studies recruit patients with the aim to influence CRS in hematopoietic stem cell transplantation (haplo-HSCT) (NCT03533101) and in CAR-T cell therapy pediatric patients with CD19 expressing relapsed and refractory B-cell acute lymphoblastic leukemia (NCT02906371). Other molecule which could manage CRS is siltuximab, a murine chimeric moAb which is an IL-6 antagonist. According to a survey published by special interest group of American Society for Blood and Marrow Transplantation Pharmacy, siltuximab should be considered for cases of tocilizumab-refractory CRS. The liable favour of siltuximab is its direct binding to IL-6 whereas tocilizumab binds to IL-6R which may result in increased IL-6 levels [33].

2.3.3. Anti IL-1

Perspective pathway in immunomodulatory approaches is to modulate levels of IL-1 by using anakinra or canakinumab. It is well established that an over-expression of interleukin-1 is one of the hallmarks in CRS, probably through activation of nuclear factor transcription and activator protein 1. Environmental trigger binds to TLRs which activate the formation of pro-IL-1 and activation of the inflammasome [34]. Inflammasome activation is important for the regulation of both the innate and adaptive immune mechanisms paving the way for specific immune responses. After the inflammasome activation, IL-1β is subsequently produced, which mediates the inflammation and thus contributes to cytokine storm. Shakoory et al. in 2016 [35] reported that IL-1R blockade with anakinra is associated with higher survival rate of septic patients presenting signs of cytokine storm. The safety and wide therapeutic margin of anakinra and the central role of IL-1 in the cytokine storm merit reconsideration of this therapeutic agent as a potential treatment option for CRS. This cytokine is not consistently elevated in patients with severe CRS [36], so an aspect of personalized medicine approaches should be considered. Canakinumab is a monoclonal antibody directed against IL-1β [37]. Although canakinumab is an effective treatment in SJIA, it does not appear to have a significant effect on reducing the cytokine storm.

2.3.4. Anti IL-18

IL-18 has a strong pro-inflammatory activity so inhibition of the pro-inflammatory cascade triggered by IL-18 can be a therapeutic target not only for the treatment of inflammatory diseases but also for cytokine storm. Gabay et al. published the results in open-label, multicenter study of tadekinig-α, recombinant human interleukin-18 binding protein (IL-18BP) in adult-onset Still’s disease (Phase II). They concluded that IL-18 inhibition might offer another possibility of therapy within the scope of anti-cytokine treatment such as NLRC4-related macrophage activation syndrome, the etiological factor leading to clinical manifestation of CRS [38].

2.3.5. JAK inhibitors

The Janus kinases (JAKs) transduce cytokine-induced signals from specific receptors that bind a broad array of cytokines, including those involved in almost all forms of CRS. Based on their essential roles in transmitting, the JAKs might become a target for pharmacologic manipulation not only in inflammatory diseases (rheumatoid arthritis, ulcerative colitis) and in myeloproliferative disorders (myelofibrosis, polycytaemia vera) but also in the management of cytokine storm. There are several antibody-based TH17 blockades (anti IL-17, anti IL-17R and anti IL-12/23p40) available; however, the antibody-based treatment is expensive and has only a narrow spectrum of effects [39]. Therefore, treatment by JAK inhibitors is tested to restrict the pro-inflammatory function of existing TH17 cells. Treatment with the JAK1/2 inhibitor ruxolitinib significantly reduced the symptoms of disease and prolonged survival time in experimental murine model. Ruxolitinib diminished pro-inflammatory cytokine production, mitigating the cytokine-driven hyperinflammation that occurs in various cytokine release syndromes [40]. This experimental work supports the integration of JAK inhibitors such as ruxolitinib into clinical trials as a novel strategy to counteract pathological cytokine-driven tissue inflammation [41]. Since April 2020, three new, currently recruiting clinical trials are available on ClinicalTrial.gov (accessed 26 August 2020) focusing on treatment COVID-19 associated cytokine storm with ruxolitinib as monotherapy (NCT04362137, NCT04361903, NCT04334044 - see Table 1). Except for ruxolitinib, even baricitinib and fedratinib are potent and selective JAK inhibitors approved for indications in rheumatology and hematology. All three are powerful anti-inflammatory drugs that, as JAK–STAT signaling inhibitors, are likely to be effective against the consequences of the elevated levels of cytokines in various forms of CRS, not excluding viral etiology (COVID-19). Although the three candidates have similar JAK inhibitor potencies, Stebbing et al. [42] suggests, due to a high affinity for AAK1, baricitinib as the best of the group, especially given its once-daily oral dosing and acceptable side-effect profile. Two Italian

studies (NCT04320277, NCT04358614) are registered for clinical testing of baricitinib and its effect on reduction of cytokine release. The second one is focused on reduction of ICU patient admission with COVID-19 associated moderate pneumonia. The last of three above mentioned JAK2 inhibitors which are used to restrict the pro-inflammatory function of existing TH17 cells is fedratinib. Fedratinib is approved in U.S. for myeloproliferative neoplasms. Wu and Yang [39] found that fedratinib treatment decreased in vitro the expression of IL-17 by murine TH17 cells. He supposed fedratinib suppresses TH17 associated cytokine pathways (including the effect of IL-6 on cells) and so could prevent the harmful effect of TH17 associated cytokine storm. A recent study has been published (phase I) for itacitinib, selective JAK-1 inhibitor in GVHD [43]. At that stage, no information concerning cytokine release syndrome has been obtained.

2.4. Adjunctive treatment

Solitary trials registered on Clinical trial.gov are focused on adjunctive treatment. One study is being prepared for using immunonutrition (n3- fatty acids and antioxidant vitamins in extraordinary doses) on modulation of cytokine production. Such specific nutrients are capable to modulate the host immune response and ameliorate the cytokine storm (NCT01752348). Two others evaluate the effect of vitamin D on selected cytokines involved in cytokine storm in the Covid-19 (NCT04366908, NCT04476745).

Reactive oxygen species may be involved in signal transduction pathways that stimulate production of pro-inflammatory cytokines through the activation of transcription factors (NF-kB). The decrease in oxidative stress by widely used antioxidants (N-acetylcysteine and erdosteine) encourages us to use them in the treatment of cytokine storm. N-acetylcysteine (NAC) serves as a prodrug to L-cysteine and L-cysteine is a precursor to the naturally occurring antioxidant molecule – glutathione. NAC, a modified form of the amino acid cysteine inhibits the production of pro-inflammatory molecules (e.g., IL-6, CCL5, CXCL8, and CXCL10) in H5N1-infected lung cells and reduces migration of monocyte in experimental model. With its anti-inflammatory effects, it may also be effective for the treatment of cytokine storm induced by severe influenza [44]. Similar encouraging results were observed in experimental model even with erdosteine [45,46]. However, current clinical evidence indicates the administration of antioxidants has a limited effect on cytokine storm and further clinical studies would still be needed [47]. The study (NCT04458298) with OP-101 (dendrimer N-acetyl-cysteine) actually recruits severe COVID-19 patients with the aim to determine the effect of OP-101 in reducing pro-inflammatory cytokines.

Not far from alleviating effect of previously mentioned antioxidants on CRS in animal models, similar protection on excessive release of pro-inflammatory cytokines by use of sodium cromoglycate was published by Han et al. [48]. Sodium cromoglycate or ketotifen generally used to treat allergic diseases, significantly inhibit degranulation and the acute release of histamine and inflammatory mediators from mast cells. Han observed that sodium cromoglycate protects mice effectively from death after viral infection by alleviating inflammatory injury via its function as an inhibitor of mast cell degranulation. Other experimental study evaluated mast cell degranulation after cromoglycate and ketotifen in rat liver resulting in decreased levels IL-6 and TNF-α [49].

Unclear results come from publications focusing on ameliorating effect of (hydroxy)chloroquine over cytokine storm in COVID-19 patients [50]. Similar unexplicit results were published by He et al. in metaanalysis upon clinical evidence that even though ulinastatin, a serine protease inhibitor, suppresses pro-inflammatory cytokine elevation and upregulates the release of anti-inflammatory mediators. Because of the poor quality of the evaluated trials and the small cohorts, their findings should be interpreted cautiously [51]. Even macrolides have long been recognised to modulate immune- and anti-inflammatory actions. They suppress the “cytokine storm” in selected patients, yet the confirmation of their effect in larger series is still awaited [52].

Based on promising results in preclinical models by adjunctive immunomodulatory treatment, novel innovative approaches will emerge. Additional research is clearly needed to fully understand the mechanisms of intensive rise of cytokine storm and search for appropriate treatment options. Some preclinical studies are encouraging. Decreased production of pro-inflammatory cytokines IL-6 and IL-1 in cell cultures of human monocytes was observed after incubation with manomycin A, a polyketide antibiotic, with known potent anti-inflammatory and immunomodulatory effect [53]. Indeed, antimicrobials with immunomodulatory effect, such as manumycin A might have potential clinical importance and should be evaluated in further not only experimental studies. Other experimental studies show that PPAR-g agonist (pioglitazone) reduces pro-inflammatory cytokine production and increases the survival of influenza infected mice by 20–40% [54]. PPAR-g (pioglitazone, rosiglitazone) influence the transcription of the upstream inflammatory genes and so could prevent the cytokine storm in the cases of viral infections thus becoming an attractive target for immunomodulatory therapy [55].

3. Conclusion

Cytokine release syndrome is a sudden onset of almost life-threatening clinical symptomatology which can occur within diverse external or internal conditions. Early identification of rising state and multilevel course of treatment is imperative. Strictly immunologic approach is necessary mainly when considering immunomodulatory treatment. At present, the most widely used molecule for systemic treatment of CRS remains tocilizumab. Its FDA and EMA approval for the treatment of cytokine storm after CAR-T cell therapy gives us a promise for the future. The only exact knowledge about immunologic processes gives us possibilities for combination of pharmaceutical and non-pharmaceutical and adjunctive treatment in successful fight with consequences of CRS. Further work is needed to cut off the signaling pathways that lead to “cytokine storm” and to determine how these effector molecules can be most effectively targeted to help resolve this frequently fatal episode of inflammation. It is a huge need for all scientists and clinicians to establish a physiological rational for new therapeutic targets and understanding of exact genetics as well as epigenetic factors that might lead to more personalized medicine approaches.

Declaration of Competing Interest

The author declares no commercial or financial conflict of interest.

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References

[1] P.P. Wadia, A.R. Tambur, Yin and yang of cytokine regulation in solid organ graft rejection and tolerance, Clin Lab Med. 28 (3) (2008) 469–479, https://doi.org/10.1016/j.cll.2008.08.001, vii-viii.
[2] F. Kroschinsky, F. Stölzel, S. von Bonin, G. Beutel, M. Kochanek, et al., Intensive Care in Hematological and Oncological Patients (iCHOP) Collaborative Group. New drugs, new toxicities: severe side effects of modern targeted and immunotherapy of cancer and their management, Crit Care. 21 (1) (2017) 89, https://doi.org/10.1186/s13054-017-1678-1.
[3] K. Stratton, A. Ford, E. Rusch, E. Wright Clayton (Eds.), Adverse effects of vaccines: Evidence and causality, IOM (Institute of Medicine), The National Academies Press, Washington, 2012.
[4] L. Chatenoud, C. Ferran, A. Reuter, C. Legendre, Y. Gevaert, et al., Systemic reaction to the anti-T-cell monoclonal antibody OKT3 in relation to serum levels of tumor necrosis factor and interferon-gamma [corrected], N Engl J Med 320 (1989) 1420–1421.
[5] P. Végh, E. Erdös, E. Balogh, T. Jánossy, T.G. Kováts, A comparative study on the local inflammatory and immunosuppressive activities of anti-mouse anti-lymphocyte sera, Clin Exp Immunol. 19 (2) (1975) 387–391.

[6] A. Sala-Cunill, M. Guilarte, V. Cardona, Phenotypes, endotypes and biomarkers in anaphylaxis: current insights, Curr Opin Allergy Clin Immunol. 18 (5) (2018) 370–376, https://doi.org/10.1097/ACI.0000000000000472.

[7] X. Feng, P. Scheinberg, A. Biancotto, O. Rios, S. Donaldson, et al., In vivo effects of horse and rabbit antithymocyte globulin in patients with severe aplastic anemia, Haematologica 99 (9) (2014) 1433–1440, https://doi.org/10.3324/haematol.2014.106542.

[8] R. Pihusch, E. Holler, D. Mühlbayer, P. Göhring, O. Stötzer, et al., The impact of antithymocyte globulin on short-term toxicity after allogeneic stem cell transplantation, Bone Marrow Transplant. 30 (6) (2002) 347–354, https://doi.org/10.1038/sj.bmt.1703640.

[9] M. Williams, T. Khalid, S. Hughes, D. Bonney, R. Wynn, Rituximab-induced Cytokine Storm in the Absence of Overt Lymphoproliferative Disease, J Pediatr Hematol Oncol. 38 (1) (2016) e29–31, https://doi.org/10.1097/MPH.0000000000000485.

[10] M.G. Wing, T. Moreau, J. Greenwood, R.M. Smith, G. Hale, et al., Mechanism of first-dose cytokine-release syndrome by CAMPATH 1-H: involvement of CD16 (FcgammaRIII) and CD11a/CD18 (LFA-1) on NK cells, J Clin Invest. 98 (12) (1996) 2819–2826, https://doi.org/10.1172/JCI119110.

[11] G.P. Sandilands, M. Wilson, C. Huser, L. Jolly, W.A. Sands, et al., Were monocytes responsible for initiating the cytokine storm in the TGN1412 clinical trial tragedy? Clin Exp Immunol. 162 (3) (2010) 516–527, https://doi.org/10.1111/j.1365-2249.2010.04264.x.

[12] L. Zhao, Y. Yang, W. Li, T. Li, Q. Gao, Nivolumab-induced cytokine-release syndrome in relapsed/refractory Hodgkin's lymphoma: a case report and literature review, Immunotherapy 10 (11) (2018) 913–917, https://doi.org/10.2217/imt-2018-0025.

[13] C.L. Freeman, F. Morschhauser, L. Sehn, M. Dixon, R. Houghton, et al., Cytokine release in patients with CLL treated with obinutuzumab and possible relationship with infusion-related reactions, Blood 126 (24) (2015) 2646–2649, https://doi.org/10.1182/blood-2015-09-670802.

[14] S.K. Alig, M. Dreyling, B. Seppi, B. Aulinger, L. Witkowski, et al., Severe cytokine release syndrome after the first dose of Brentuximab Vedotin in a patient with relapsed systemic anaplastic large cell lymphoma (sALCL): a case report and review of literature, Eur J Haematol. 94 (6) (2015) 554–557, https://doi.org/10.1111/ejh.12396.

[15] G. Tonini, D. Santini, B. Vincenzi, D. Borzomati, G. Dicuonzo, et al., Oxaliplatin may induce cytokine-release syndrome in colorectal cancer patients, J Biol Regul Homeost Agents. 16 (2) (2002) 105–109.

[16] N. Nakamura, N. Kanemura, Y. Shibata, T. Matsumoto, R. Mabuchi, et al., Lenalidomide-induced cytokine release syndrome in a patient with multiple myeloma, Leuk Lymphoma 55 (7) (2014) 1691–1693, https://doi.org/10.3109/10428194.2013.853300.

[17] A. Shimabukuro-Vornhagen, P. Gödel, M. Subklewe, H.J. Stemmler, H.A. Schlößer, et al., Cytokine release syndrome, J Immunother Cancer. 6 (1) (2018) 56, https://doi.org/10.1186/s40425-018-0343-9.

[18] N. Aikawa, S. Fujishima, Y. Shinozawa, S. Hori, Cytokine-mediated biological response to severe infections in surgical patients, Nihon Geka Gakkai Zasshi 97 (12) (1996) 1054–1059.

[19] S.W. Canna, E.M. Behrens, Making sense of the cytokine storm: a conceptual framework for understanding, diagnosing, and treating hemophagocytic syndromes, Pediatr Clin North Am. 59 (2) (2012) 329–344, https://doi.org/10.1016/j.pcl.2012.03.002.

[20] F. Chung, Anti-inflammatory cytokines in asthma and allergy: interleukin-10, interleukin-12, interferon-gamma, Mediators Inflamm. 10 (2) (2001) 51–59, https://doi.org/10.1080/09629350120054518.

[21] R.V. D'Elia, K. Harrison, P.C. Oyston, R.A. Lukaszewski, G.C. Clark, Targeting the "cytokine storm" for therapeutic benefit, Clin Vaccine Immunol. 20 (3) (2013) 319–327, https://doi.org/10.1128/CVI.00636-12.

[22] K. Asadullah, W. Sterry, H.D. Volk, Interleukin-10 therapy–review of a new approach, Pharmacol Rev. 55 (2) (2003) 241–269, https://doi.org/10.1124/pr.55.2.4.

[23] M. Picard, V.R. Galvão, Current Knowledge and Management of Hypersensitivity Reactions to Monoclonal Antibodies, J Allergy Clin Immunol Pract. 5 (3) (2017) 600–609, https://doi.org/10.1016/j.jaip.2016.12.001.

[24] D. McGonagle, K. Sharif, A. O'Regan, C. Bridgewood, The Role of Cytokines including Interleukin-6 in COVID-19 induced Pneumonia and Macrophage Activation Syndrome-Like Disease, Autoimmun Rev. 19 (6) (2020) 102537, https://doi.org/10.1016/j.autrev.2020.102537.

[25] H.H. Thomsen, N. Rittig, M. Johannsen, A.B. Møller, J.O. Jørgensen, et al., Effects of 3-hydroxybutyrate and free fatty acids on muscle protein kinetics and signaling during LPS-induced inflammation in humans: anticatabolic impact of ketone bodies, Am J Clin Nutr. 108 (4) (2018) 857–867, https://doi.org/10.1093/ajcn/nqy170.

[26] F. Hawchar, I. László, N. Öveges, D. Trásy, Z. Ondrik, Z. Molnar, Extracorporeal cytokine adsorption in septic shock: A proof of concept randomized, controlled pilot study, J Crit Care.49 (2019) 172–178, https://doi.org/10.1016/j.jcrc.2018.11.003.

[27] R.M. Benson, L.M. Minter, B.A. Osborne, E.V. Granowitz, Hyperbaric oxygen inhibits stimulus-induced proinflam-matory cytokine synthesis by human blood-derivedmonocyte-macrophages, Clin Exp Immunol 134 (2003) 57–62.

[28] S.R. Thom, Oxidative stress is fundamental to hyperbaric oxygen therapy, J Appl Physiol. 106 (3) (2009) 988–995, https://doi.org/10.1152/japplphysiol.91004.2008.

[29] J. Garcia Borrega, P. Gödel, M.A. Rüger, Ö.A. Onur, A. Shimabukuro-Vornhagen, et al., In the Eye of the Storm: Immune-mediated Toxicities Associated With CAR-T Cell Therapy, Hemasphere 3 (2) (2019) e191, https://doi.org/10.1097/HS9.0000000000000191.

[30] R.L. Hoiland, S. Stukas, J. Cooper, S. Thiara, L.Y.C. Chen, et al., Amelioration of COVID-19-related cytokine storm syndrome: parallels to chimeric antigen receptor-T cell cytokine release syndrome, Br J Haematol. 190 (3) (2020) e150–e154, https://doi.org/10.1111/bjh.16961.

[31] G.S. Schulert, A.A. Grom, Pathogenesis of macrophage activation syndrome and potential for cytokine- directed therapies, Annu Rev Med. 66 (2015) 145–159, https://doi.org/10.1146/annurev-med-061813-012806.

[32] H. Murthy, M. Iqba, J.C. Chavez, M.A. Kharfan-Dabaja, Cytokine Release Syndrome: Current Perspectives, Immunotargets Ther. 29 (8) (2019) 43–52, https://doi.org/10.2147/ITT.S202015.

[33] Z. Mahmoudjafari, K.G. Hawks, A.A. Hsieh, D. Plesca, K.S. Gatwood, K.A. Culos, American Society for Blood and Marrow Transplantation Pharmacy Special Interest Group Survey on Chimeric Antigen Receptor T Cell Therapy Administrative, Logistic, and Toxicity Management Practices in the United States, Biol Blood Marrow Transplant. 25 (1) (2019) 26–33, https://doi.org/10.1016/j.bbmt.2018.09.024.

[34] B. Russell, C. Moss, G. George, A. Santaolalla, A. Cope, et al., Associations between immune-suppressive and stimulating drugs and novel COVID-19-a systematic review of current evidence, Ecancermedicalscience. 27 (2020) (2020) 14, https://doi.org/10.3332/ecancer.2020.1022, 1022.

[35] B. Shakoory, J.A. Carcillo, W.W. Chatham, R.L. Amdur, H. Zhao, et al., Interleukin-1 Receptor Blockade Is Associated With Reduced Mortality in Sepsis Patients With Features of Macrophage Activation Syndrome: Reanalysis of a Prior Phase III Trial, Crit Care Med. 44 (2) (2016) 275–281, https://doi.org/10.1097/CCM.0000000000001402.

[36] D.T. Teachey, S.F. Lacey, P.A. Shaw, J.J. Melenhorst, S.L. Maude, et al., Identification of Predictive Biomarkers for Cytokine Release Syndrome after Chimeric Antigen Receptor T-cell Therapy for Acute Lymphoblastic Leukemia, Cancer Discov. 6 (6) (2016) 664–679, https://doi.org/10.1158/2159-8290.CD-16-0040.

[37] S. Federici, A. Martini, M. Gattorno, The Central Role of Anti-IL-1 Blockade in the Treatment of Monogenic and Multi-Factorial Autoinflammatory Diseases, Front Immunol. 31 (4) (2013) 351, https://doi.org/10.3389/fimmu.2013.00351.

[38] C. Gabay, B. Fautrel, J. Rech, F. Spertini, E. Feist, et al., Open-label, multicentre, dose- escalating phase II clinical trial on the safety and efficacy of tadekinig alfa (IL-18BP) in adult-onset Still's disease, Ann Rheum Dis. 77 (6) (2018) 840–847, https://doi.org/10.1136/annrheumdis-2017-212608.

[39] D. Wu, X.O. Yang, TH17 responses in cytokine storm of COVID-19: An emerging target of JAK2 inhibitor Fedratinib, J Microbiol Immunol Infect. 11 (2020), https://doi.org/10.1016/j.jmii.2020.03.005. S1684-1182(20)30065-30067.

[40] A. Ahmed, S.A. Merrill, F. Alsawah, P. Bockenstedt, E. Campagnaro, et al., Ruxolitinib in adult patients with secondary haemophagocytic lymphohistiocytosis: an open-label, single-centre, pilot trial, Lancet Haematol. 6 (12) (2019) e630–e637, https://doi.org/10.1016/S2352-3026(19)30156-5.

[41] R. Das, P. Guan, L. Sprague, K. Verbist, P. Tedrick, et al., Janus kinase inhibition lessens inflammation and ameliorates disease in murine models of hemophagocytic lymphohistiocytosis, Blood. 127 (13) (2016) 1666–1675, https://doi.org/10.1182/blood-2015-12-684399 (2016).

[42] J. Stebbing, A. Phelan, I. Griffin, C. Tucker, O. Oechsle, et al., COVID-19: combining antiviral and anti-inflammatory treatments, Lancet Infect Dis. 20 (4) (2020) 400–402, https://doi.org/10.1016/S1473-3099(20)30132-8.

[43] M.A. Schroeder, H.J. Khoury, M. Jagasia, H. Ali, G.J. Schiller, et al., A phase 1 trial of itacitinib, a selective JAK1 inhibitor, in patients with acute graft-versus-host disease, Blood Adv. 28 (8) (2020) 1656–1669, https://doi.org/10.1182/bloodadvances.2019001043 (2020).

[44] J. Geiler, M. Michaelis, P. Naczk, A. Leutz, K. Langer, et al., N-acetyl-L-cysteine (NAC) inhibits virus replication and expression of pro-inflammatory molecules in A549 cells infected with highly pathogenic H5N1 influenza A virus, Biochem Pharmacol. 79 (3) (2010) 413–420, https://doi.org/10.1016/j.bcp.2009.08.025 (2010).

[45] Y.Y. Jang, J.H. Song, Y.K. Shin, E.S. Han, C.S. Lee, Depressant effects of ambroxol and erdosteine on cytokine synthesis, granule enzyme release, and free radical production in rat alveolar macrophages activated by lipopolysaccharide, Pharmacol Toxicol. 92 (4) (2003) 173–179, https://doi.org/10.1034/j.16000773.2003.920407.x.

[46] R. Demiralay, N. Gürsan, H. Erdem, The effects of erdosteine and N-acetylcysteine on apoptotic and antiapoptotic markers in pulmonary epithelial cells in sepsis, Eurasian J Med. 45 (3) (2013) 167–175, https://doi.org/10.5152/eajm.2013.35.

[47] Q. Liu, Y.H. Zhou, Z.Q. Yang, The cytokine storm of severe influenza and development of immunomodulatory therapy, Cell Mol Immunol. 13 (1) (2016) 3–10, https://doi.org/10.1038/cmi.2015.74.

[48] D. Han, T. Wei, S. Zhang, M. Wang, H. Tian, et al., The therapeutic effects of sodium cromoglycate against influenza A virus H5N1 in mice, Influenza Other Respir Viruses. 10 (1) (2016) 57–66, https://doi.org/10.1111/irv.12334.

[49] N.A. El-Shitany, K. El-Desoky, Cromoglycate, not ketotifen, ameliorated the injured effect of warm ischemia/reperfusion in rat liver: role of mast cell degranulation, oxidative stress, proinflammatory cytokine, and inducible nitric oxide synthase, Drug Des Devel Ther. 16 (9) (2015) 5237–5246, https://doi.org/10.2147/DDDT.S88337.

[50] J. Geleris, Y. Sun, J. Platt, J. Zucker, M. Baldwin, et al., Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19, N Engl J Med. 7 (2020), https://doi.org/10.1056/NEJMoa2012410. NEJMoa2012410.

[51] G. He, Q. Li, W. Li, Y. Ruan, X. Xiong, et al., Effect of ulinastatin on interleukins and pulmonary function in bypass patients: a meta-analysis of randomized controlled trials, Herz. (2018), https://doi.org/10.1007/s00059-018-4732-0.
[52] P. Zarogoulidis, N. Papanas, I. Kioumis, E. Chatzaki, E. Maltezos, K. Zarogoulidis, Macrolides: from in vitro anti-inflammatory and immunomodulatory properties to clinical practice in respiratory diseases, Eur J Clin Pharmacol. 68 (5) (2012) 479–503, https://doi.org/10.1007/s00228-011-1161-x.
[53] E. Cecrdlova, K. Petrickova, L. Kolesar, M. Petricek, A. Sekerkova, et al., Manumycin A downregulates release of proinflammatory cytokines from TNF alpha stimulated human monocytes, Immunol Lett. 169 (2016) 8–14, https://doi.org/10.1016/j.imlet.2015.11.010.
[54] I. Darwish, S. Mubareka, W.C. Liles, Immunomodulatory therapy for severe influenza, Expert Rev Anti Infect Ther. 9 (7) (2011) 807–822, https://doi.org/10.1586/eri.11.56.
[55] C. Ciavarella, I. Motta, S. Valente, G. Pasquinelli, Pharmacological (or Synthetic) and Nutritional Agonists of PPAR-γ as Candidates for Cytokine Storm Modulation in COVID-19 Disease, Molecules 25 (9) (2020) E2076, https://doi.org/10.3390/molecules25092076.