Treating COVID-19: Review of drug hypersensitivity reactions

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.18176/jiaci.0588

Abstract

The disease caused by the new Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), Coronavirus Disease 2019 (COVID-19), has expanded as a global pandemic since its beginning in Wuhan, China, in December 2019. Its severe clinical manifestations associated with the need for admission into Intensive Care Units and high mortality rate represent a therapeutic challenge for the medical community. Currently, there is no drug approved for its treatment and different therapeutic options are being essayed to address pathophysiological processes underlying the clinical manifestations experienced by patients. New and old drugs, whether as a single treatment or in combination, in immunologically compromised patients may favour the development of adverse drug reactions (ADR), including drug hypersensitivity, which must be identified and managed accordingly. Given the lack of community immunity and the high rate of virus contagion, it is expected that new cases will emerge in the upcoming months. Thus, the probability of more adverse reactions or even new clinical manifestations may increase in the near future. Allergists must be updated on these treatments as well as on the management of possible drug hypersensitivity reactions (DHR).

Key words: COVID-19, COVID-19 drug treatment, SARS-CoV-2, Adverse drug reaction, Drug hypersensitivity, Drug allergy.

Resumen

La enfermedad causada por el nuevo *Severe Acute Respiratory Syndrome Coronavirus-2* (SARS-CoV-2), *Coronavirus Disease 2019* (COVID-19), se ha expandido en forma de pandemia global desde su inicio en Wuhan (China) en diciembre de 2019. La aparición de formas clínicas graves asociadas a la necesidad de ingreso en unidades de Cuidados Intensivos, con un alto índice de letalidad, ha supuesto un reto terapéutico para la comunidad médica. Actualmente no hay ningún fármaco aprobado para su tratamiento y se están ensayando diversas opciones terapéuticas para abordar los procesos fisiopatológicos responsables de las manifestaciones clínicas que experimentan los pacientes. Tanto el uso de viejos como de nuevos principios activos como tratamiento único o en combinación, en pacientes inmunológicamente comprometidos, puede favorecer la aparición de efectos adversos, entre ellos reacciones de hipersensibilidad de mecanismo inmunológico, que habrá que saber identificar y manejar correctamente. Es de prever que, en los próximos meses, dada la falta de inmunidad comunitaria y el elevado índice de contagiosidad del virus, sigan surgiendo nuevos casos y, con ello, la probabilidad de que aparezcan más reacciones adversas o incluso nuevas manifestaciones clínicas. Es importante que los alergólogos estén al día de las opciones terapéuticas que se están utilizando, así como de sus posibles reacciones adversas, inclusive reacciones de hipersensibilidad y cómo manejarlas.

Palabras clave: COVID-19, Tratamiento COVID-19, SARS-CoV-2, Reacciones adversas, Hipersensibilidad fármacos, Alergia fármacos.

doi: 10.18176/jiaci.0588

The novel “coronavirus disease 2019” (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) began in Wuhan, China, in December 2019 and has exhibited a pattern of pandemic spread in only a few months [1]. Community transmission is high and the spectrum of disease ranges from severe respiratory illness and fatality from its complications (particularly in the elderly and in people with comorbidities) to an asymptomatic course [1,2].

Once the disease is manifested supportive measures are initiated, but a systematic disease modifying therapeutic approach remains empirical. Currently, there is no evidence from randomized controlled trials (RCT) that any potential therapy could be superior than the other and many drugs are for compassionate or off-label use depending on experience, availability and published case-reports or short communications [3]. It appears that pharmacotherapy targeted against the virus can be useful when applied early in the course of the disease, but its usefulness in advanced stages may be doubtful [4,5]. On the other hand, anti-inflammatory and immunosuppressive therapy applied too early can be dangerous [6] but, in contrast, may be of interest at advanced stages due to the damage caused by an amplified immune response and cytokine release (cytokine storm [CS]) [7]. Taking this into consideration, Siddiqi *et al.* have proposed a 3-stage classification system which corresponds with distinct clinical findings, response to therapy and clinical outcome (Figure 1) [8].

Although a lot of effort has been made to flatten the curve of new contagions, this global pandemic spread is expected to continue expanding. As more people are exposed to different treatments this will probably be associated with a rise in the number of drug-related adverse effects, some of which have an immunological basis.

This is not a systematic review but rather a narrative review that summarizes current knowledge regarding mainly the immunological adverse drug reactions (ADR) related

doi: 10.18176/jiaci.0588

to the drugs used for COVID-19, in order to identify them early and address their management in a comprehensive manner.

For this review, we have used a selection of the bibliography identified through the PubMed-Medline databases and search engines (which includes bibliographic references from 1966 to the present), SIETES (www.sietes.org, an information system on developments in clinical and therapeutic pharmacology), the UptoDate clinical resource (https://www.uptodate.com), and the Medinteract Drug Interactions Database. (https://www.medinteract.net/).

Antivirals

Lopinavir/Ritonavir

Lopinavir/Ritonavir is an approved oral antiretroviral combination treatment of the family of the human immunodeficiency virus (HIV) protease inhibitors, acting on the CYP3A isoform of cytochrome P450.

Mechanism of action: Lopinavir provides the antiviral activity. Inhibition of HIV protease prevents cleavage of the *gag-pol* polyprotein leading to the production of an immature, non-infectious virus. *In vitro* activity has been demonstrated for lopinavir against SARS-CoV, the virus that causes SARS in humans [9]. Ritonavir is a pharmacokinetic enhancer used to increase the plasma half-life of lopinavir.

Rationale: As clinical studies in SARS were associated with reduced mortality and intubation rates in combination with other antiviral agents, it has been considered for COVID-19 [9,10].

Drug hypersensitivity reactions (DHR): Given the significant drug-drug interactions and potential ADR, careful review of concomitant medications and both clinical and analytical monitoring are required when this drug is used. Some cases of

doi: 10.18176/jiaci.0588

hypersensitivity/nonspecific mediator release have been described for the excipients of the commercial formula (see Table I) [11] and by the drug itself. It should be noted that the majority of cases are described in HIV-infected patients, more prone than the general population to experience drug-related rashes, and that published cases of hypersensitivity reactions by protease inhibitors are anecdotal, being much more frequent with other antiretrovirals like reverse transcriptase inhibitors (abacavir, nevirapine, efavirenz) [12]. Mild skin reactions like maculopapular rashes have been described 7-10 days after their onset [13], and a DHR has been demonstrated *in vitro* by the Cellular Antigen Stimulation Test in a case of pruritic rash [12]. More severe skin reactions have also been described: one acute generalized exanthematous pustulosis (AGEP) 24 hours after the first dose in a patient treated for prophylaxis after occupational exposure [14], and a case of Stevens-Johnson-like syndrome associated to myeloid, hepatic, and renal toxicity after the first dose [15].

Allergological study: No *in vivo* tests have been reported.

Desensitization protocols: No desensitization protocols have been found.

Remdesivir

Mechanism of action: It is a nucleotide analog that mimics adenosine, one of the building blocks of any RNA virus' genome and so interferes with virus RNA polymerization.

Rationale: This drug was initially developed for the Ebola virus outbreak, but it is a promising potential therapy for COVID-19 due to its broad-spectrum and potent *in vitro* activity against several novel coronavirus, including SARS-CoV-2 [16]. Remdesivir is not currently approved but different clinical trials are ongoing to evaluate its safety and

doi: 10.18176/jiaci.0588

antiviral activity in patients with mild to severe COVID-19 (including five clinical trials in Spain).

DHR: One case of maculopapular rash with elevated aminotransferases has recently been reported [17].

Desensitization protocols: No desensitization protocols have been described.

Azithromycin

Azithromycin is an azalid, a subclass of macrolide antibiotics.

Mechanism of action: It works by inhibiting the synthesis of RNA-dependent bacterial proteins by binding to the 50s subunit of the ribosome and inhibiting translocation of the peptides.

Rationale: Azithromycin is thought to have antiviral and anti-inflammatory activity and may work synergistically with other antiviral treatments. In the past years, the antiviral effects of macrolides have attracted considerable attention against Rhinovirus, Influenza, Zika and Ebola viruses [18].

DHR: Macrolides are generally well tolerated and allergy to them is infrequent (occurring from 0.4% to 3%) [19]. However, some cases of both immediate hypersensitivity (including urticaria, angioedema and anaphylaxis), and delayed hypersensitivity (fixed drug eruptions [FDE] and severe cutaneous adverse reactions [SCAR]) have been described with macrolides. [20-22]. SCAR reactions with azithromycin include drug reaction with eosinophilia and systemic symptoms syndrome (DRESS) [23], AGEP [24], Stevens-Johnson syndrome (SJS) [25,26] and vasculitis [27].

Organ-specific reactions with hepatic involvement have also been described [28]. The long half-life of azithromycin could explain why hypersensitivity reactions are especially delayed.

Allergological study: Diagnostic procedures include a detailed clinical history, skin tests and provocation tests. Despite being highly irritative drugs for skin testing, some experience does exist with azithromycin. The Spanish Society of Allergology and Clinical Immunology (SEAIC) proposes to carry out prick-test at 10 mg/mL and intradermal test at 0.01 mg/ml [29]. Patch test (20% pet) [29] can be an option for delayed reactions, although its sensitivity is low. If skin tests are negative, the risk-benefit ratio should be evaluated before proceeding with a drug provocation test (DPT). Cross-reactivity between different macrolides seems to be low, but it is necessary to confirm tolerance to another drug in cases of confirmed allergy to azithromycin [30].

Desensitization protocols: There are very few published reports of macrolide desensitization, one of them involved a patient diagnosed with mast cell activation syndrome who was successfully desensitized to azithromycin following a 14-step protocol, achieving a total dose of 528.45 mg in 24 hours [31].

Chloroquine/Hydroxychloroquine (CQ, HCQ)

Hydroxychloroquine is a 4-aminoquinoline similar to chloroquine with antimalarial and immunomodulatory effects.

Mechanism of action: Regarding its immunomodulatory effects, CQ/HCQ can attenuate cytokine production and inhibit autophagy and lysosomal activity in host cells [32]. *In vitro*, CQ/HCQ possesses antiviral activity against RNA and DNA viruses [33].

Rationale: CQ/HCQ act at two key steps that are required for cell entry by coronaviruses: inhibition of receptor binding (interfering with the glycosylation of

doi: 10.18176/jiaci.0588

angiotensin-converting enzyme 2 (ACE2), the cellular receptor of SARS-CoV-2) and inhibition of membrane fusion (CQ/HCQ concentrate in lysosomes, increasing their pH and preventing viral protease activity) [32].

DHR: CQ/HCQ are relatively well tolerated, but both can cause serious adverse effects such as QTc prolongation, gastrointestinal symptoms or hypoglycaemia. Relating to immunological reactions, both mild skin eruptions (maculopapular rash, urticaria), and SCAR (toxic epidermal necrolysis [TEN] SJS, AGEP, DRESS), including erythema multiforme have been described [34-39]. Photosensitivity is another ADR related to CQ/HCQ [33].

Allergological study: Patch tests with CQ/HCQ at 30% petrolatum have been reported in delayed reactions with both negative and positive results [34,36,37,39]. In cases of immediate reactions, Soria *et al.* [34] performed prick-tests with the undiluted drug with negative results. In case of anaphylaxis, dilution up to 1/10,000 has been advised [40]. If cutaneous tests are negative, the risk-benefit ratio should be evaluated before proceeding with a DPT.

Desensitization protocols: Several slow desensitization protocols are published [41], with increasing doses at 24-hour intervals and lasting from 4 [42] to 36 days [43] to achieve full dose. Recently, one case of rapid desensitization (less than 24 hours) to HCQ has been published [44].

Anticytokine or immunomodulatory agents

Tocilizumab

Tocilizumab is a humanized monoclonal antibody interleukin (IL)-6 receptor antagonist.

Mechanism of action: IL-6 is a proinflammatory cytokine involved in various physiological processes such as activation of T lymphocytes, induction of

doi: 10.18176/jiaci.0588

immunoglobulins and acute-phase proteins and stimulation of hemopoiesis. IL-6 has been implicated in the pathogenesis of inflammatory diseases, osteoporosis, and malignancies.

Rationale: Studies conducted in patients who died of SARS and Middle East Respiratory Syndrome (MERS) suggest that mortality is associated with an amplified immune system response with cytokine release [45]. Although tocilizumab has had promising results in some studies [46], the lack of a comparator group warrants caution with these results. Several RCTs of tocilizumab are underway in patients with severe COVID-19.

DHR: Immediate (urticaria, anaphylaxis) and delayed DHR (including urticaria, maculopapular rash, vasculitis, AGEP, SJS and DRESS) can occur secondary to the use of tocilizumab [47-51]. There are also some cases of type alpha reactions not IgE-mediated related to cytokine release [49]. Hypersensitivity to excipients must also be considered (Table I) [11].

Allergological study: Cutaneous testing with tocilizumab is usually performed at 20 mg/ml for the prick-test and 0.2 mg/ml [29], 20 mg/ml [52] or 2 mg/ml [49,53] for the intradermal test. If skin tests are negative, a DPT can be performed after evaluating the risk-benefit ratio and switching to a subcutaneous route can be considered [49].

Desensitization protocols: There are some published case reports of tocilizumab desensitization, both in immediate and delayed reactions [53-55]. Demir *et al.* [56] described 65 rapid drug desensitizations with tocilizumab in 3 patients with only one anaphylaxis during the 5th desensitization cycle. However, after modifying the protocol, this patient continued the tocilizumab desensitization protocol uneventfully.

doi: 10.18176/jiaci.0588

Sarilumab

Sarilumab is a human monoclonal antibody against the IL-6 receptor.

Mechanism of action: The same as tocilizumab.

Rationale: There are several phase II-III clinical trials evaluating its efficacy in patients with severe COVID-19 [3].

DHR: One published article reporting mild/moderate rashes in four patients treated with sarilumab was found and the reaction did not force the ending of the treatment [57]. Local reactions at injection site have also been reported [58].

Desensitization protocols: To date, no desensitization protocols have been reported.

Anakinra

Anakinra is a recombinant nonglycosilate form of the human IL-1 receptor antagonist (IL-1Ra).

Mechanism of action: The IL-1 family is a group of proinflammatory cytokines, with IL-1α and IL-1β having the greatest inflammatory effect. Through the expression of integrins in leukocytes and endothelial cells, they regulate and initiate the inflammatory response [59]. Anakinra neutralizes the biological activity of IL-1α and IL-1β by competitively inhibiting its binding to the type I receptor [59].

Rationale: In a recent study, continuous infusion of IV anakinra resulted in rapid serologic and subsequent clinical improvement in adult patients with macrophage activation syndrome [60], suggesting it could be an option in the subgroup of patients with severe COVID-19 who have a CS presentation.

DHR: Local reactions consisting of inflammation, erythema, itching and pain are frequent with anakinra due to the large amount of protein solution that produces mast cell degranulation [61]. It is possible to prevent both immediate (application of ice

doi: 10.18176/jiaci.0588

locally before and after the injection and ensuring that the liquid is at room temperature prior to administration) and late local reactions (alternate injection sites and application of local topical corticosteroids). There are some case reports of systemic allergic reactions to anakinra, from mild/moderate rashes to anaphylaxis [62-65]. Anakinra contains polysorbate 80 as excipient that may also cause DHR [66-68].

Allergological study: One article was found describing a positive skin prick-test with undiluted drug [63] and another describing a positive intradermal test at 1/10 concentration [64]. If cutaneous tests are negative, the risk-benefit ratio should be evaluated before proceeding with a DPT.

Desensitization protocols: There are few published case reports of successful rapid subcutaneous desensitizations, starting with a dilution of 1/1000 [65] to 1/100 [64].

Baricitinib

Baricitinib is a selective and reversible inhibitor of Janus kinase (JAK) types 1 and 2.

Mechanism of action: Baricitinib reversibly inhibits JAK1/JAK2 and through a transduction pathway signals involving STAT proteins, it ultimately modulates the expression of genes associated with inflammation in immune cells with an anti-inflammatory effect.

Rationale: The inhibition of JAK1/JAK2 could therefore have a potential role in reducing systemic inflammation and lung damage. This drug may also reduce receptor-mediated SARS-CoV-2 endocytosis by inhibiting the adaptor protein-2 complex (AP2)-associated protein kinase 1 [69]. There are some clinical trials underway to assess its effectiveness.

DHR: There is a reported case of palmoplantar pustulosis-like eruption due to baricitinib [70].

doi: 10.18176/jiaci.0588

Desensitization protocols: To date, no desensitization protocols have been described.

Cyclosporine

Cyclosporine is an immunosuppressant peptide isolated from the fungus *Tolyplocadium inflatum*.

Mechanism of action: Cyclosporine binds to the cyclophilin protein of T lymphocytes forming a complex that, in turn, inhibits the activity of calcineurin, thus preventing the transcription of multiple genes related to inflammatory cytokines. It also acts on the mitochondria, inhibiting their apoptosis.

Rationale: Cyclosporine has been shown to inhibit the replication of several coronaviruses *in vitro* at non-cytotoxic concentrations and independently of its immunosuppressive effect [71,72], and to reduce cell proliferation and the concomitant production of cytokines.

DHR: Cases of hypersensitivity/nonspecific release of mediators have been described related to excipients in the formula (Table I) [11]. Polyoxyethylated castor oil (Cremophor EL) is a non-ionic surfactant which is extracted from seeds of *Ricinus Communis* and is used as a vehicle in hydrophobic medications such as cyclosporine. It may cause itching, erythematous rash, urticaria, angioedema, facial flushing, bronchospasm, dyspnea, nausea, vomiting, and anaphylaxis following drug infusion. IgE-mediated immune response, complement activity, histamine release by basophils or mast cells, and IgG antibody formation are the probable mechanisms thought of as the pathophysiology to this reaction [73]. Assuming Cremophor EL as the culprit agent in hypersensitivity with IV cyclosporine, corn oil-based soft gelatin capsules, which contain polyoxyethylated glycolyzed glycerides, would be a safe alternative regarding hypersensitivity to other forms of cyclosporine [74]. This has been confirmed in other

doi: 10.18176/jiaci.0588

publications [11,75-77]. Finally, a basophil activation test (BAT) can be used a diagnostic tool for both cyclosporine- or excipient-induced hypersensitivity [73,75].

Allergological study: Cyclosporine and Cremophor EL have been tested at 1/1,000-1/1 for prick-test and at 1/1,000 and 1/100 for intradermal test [73,74]. If cutaneous tests are negative, the risk-benefit ratio should be evaluated before proceeding with a DPT.

Desensitization protocols: There is one report of satisfactory slow oral cyclosporine desensitization protocol (11 days) [78].

Tacrolimus

Tacrolimus is a macrolide immunosuppressant produced by the bacteria *Streptomyces tsukubaensis.*

Mechanism of action: Tacrolimus inhibits signal transduction pathways in T lymphocytes and prevents transcription of multiple proinflammatory cytokine-related genes (IL-2), as well as type 1 IFNs [79].

Rationale: Clinical trials are currently underway in severe SARS-Cov-2 pneumonia based on tacrolimus' ability to counteract excessive inflammation caused by the associated CS syndrome [7].

DHR: Cases of hypersensitivity/nonspecific release of mediators have been described by both excipients of the drug (Table I) [11] and by the drug itself. The IV form of tacrolimus contains polyoxyethylated castor oil which can induce different ADR including anaphylaxis (see cyclosporine). If the excipient is the culprit agent of the ADR, patients may tolerate oral tacrolimus which lacks this excipient [80]. Allergic contact dermatitis to tacrolimus has been described with positive patch-test at 2.5% in alcohol [81]. Recently, one case of contact urticaria by a tacrolimus-containing ointment

doi: 10.18176/jiaci.0588

[82] and one of symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) with oral tacrolimus [83] have been published.

While tacrolimus is a macrolide drug, the chemical structure substantially differs from that of macrolide antibiotics. A case-report describing cross-sensitivity between tacrolimus and macrolides was found, although the patient had been diagnosed of allergy to clarithromycin without an allergic evaluation [84]. On the other hand, in a retrospective review of eight patients with reported macrolide allergy (not definitively confirmed) all of them tolerated tacrolimus (including three patients with an anaphylactic-type reaction) [85]. Recently, tacrolimus exposure has been associated with post transplantation food allergy in a large cohort from a pediatric tertiary care center [86].

Desensitization protocols: No desensitization protocols have been found.

Miscellaneous

Ivermectin

Ivermectin is an antiparasitic agent isolated from the fermented broth of *Streptomyces avermitilis bacteria*.

Mechanism of action: Ivermectin binds to chlorine channels of nerve and muscle cells in invertebrate microorganisms causing paralysis and death of the parasite. In addition, antiviral activity has been found *in vitro* on various viruses.

Rationale: Recently, ivermectin has been reported as a potent inhibitor of SARS-Cov-2 replication *in vitro* [87]. However, available evidence suggests that levels of ivermectin with meaningful activity against SARS-CoV-2 would not be achieved without potentially toxic increases in ivermectin dosing levels in humans [88]. So, well conducted clinical trials are required.

doi: 10.18176/jiaci.0588

DHR: Pruritus and rashes are described as adverse effects that usually appear the first days of treatment [89-91]. A few case-reports have been found of ivermectin-associated SCARS: TEN, SJS and DRESS [92-94]. There is one published case of FDE following ivermectin [95]. No allergological studies were performed in these cases.

Desensitization protocols: To date, no desensitization protocols have been published.

Icatibant

Icatibant is a synthetic decapeptide with a structure similar to bradykinin (BK), approved for use in the treatment of acute angioedema attacks in patients with hereditary C1-inhibitor deficiency.

Mechanism of action: Bradykinin is a direct end-product of the kallikrein-kinin system which binds to the bradykinin type 2 receptors (BK2) on the vascular endothelium. Icatibant acts as a specific antagonist of BK2 receptors.

Rationale: The SARS-CoV-2 virus enters the respiratory epithelial cell through the ECA2 receptor [96]. ECA2 is responsible for the catabolism of des-Arg9-bradykinin, a decrease in its activity implies an increase in the levels of bradykinin [97,98]. The pulmonary edema, present in the early stages of pneumonia in COVID-19, could therefore be caused by a local activation of the bradykinin receptors located in the endothelial cells [99] that would result in vasodilation and increased vascular permeability leading to pulmonary edema and inflammation.

Finally, icatibant has been identified in a theoretical computational model as a possible inhibitor of the SARS-CoV-2 protease M, a key enzyme in the coronavirus replication [100]. The proposed timing of treatment with icatibant in COVID-19 is depicted in Figure 2.

doi: 10.18176/jiaci.0588

DHR: The most common adverse effects are injection-site reactions that are of generally mild severity and transient in nature [101-104].

Desensitization protocols: No desensitization protocols have been published yet.

Corticosteroids

Corticosteroids are a class of steroid hormones produced in the adrenal cortex. Glucocorticoids (GC) have anti-inflammatory, immunosuppressive and antiproliferative effects.

Rationale: They are focused on decreasing the host inflammatory response in the lungs, which, if not stopped, may lead to acute lung injury and SARS. However, this benefit may be eclipsed because possible adverse effects have been defined, including delayed virus clearance and increased risk of secondary infection. Observational studies and systematic reviews have indicated inconclusive clinical evidence on the effects of GC therapy for viral pneumonias such as SARS and MERS [105,106]. Nevertheless, recently, the investigators of the Randomised Evaluation of COVid-19 thERapY (RECOVERY) Trial which enrolled over 11,500 patients infected with COVID-19 in the United Kingdom stated that dexamethasone reduced deaths by one-third in ventilated patients and one-fifth in other patients receiving oxygen only [107]. These results are to be published shortly given the public health importance they withhold.

DHR: According to their chronology they are classified as immediate, appearing within a few minutes/hours of GC administration (incidence estimated between 0.1-0.3%) and delayed, appearing 24-48 hours after administration or even later (incidence estimated between 0.3-6%) [108].

Immediate DHR usually occur following systemic GC (except intraarticular administration where there could be a delayed reaction) which clinically manifest as

doi: 10.18176/jiaci.0588

pruritus, rash, urticaria, angioedema, rhinoconjunctivitis, broncospasm, anaphylaxis, hypotension, vascular collapse and death [108-110]. Immediate DHR are more frequent with hydrocortisone, methylprednisolone or a specific salt (succinate) but may also be due to the excipients (carboxymethyl cellulose, benzyl alcohol, propylene glycol, polyethylene glycol, polysorbate 80 or parabens) [108,111]. Reactions to GC administered systemically are more frequent in asthmatics with hypersensitivity to aspirin, transplant patients or patients with nephritis, hemodynamically unstable patients or those with rheumatologic diseases [108,112].

Delayed DHR are usually due to topical GC occurring mostly in atopic patients, patients with contact dermatitis, ulcers, stasis dermatitis and other previous dermatological disorders [113]. Worsening of such disorders as well as bronchospasm or pain in the nasal or oral mucosa after nasal or bronchial application may also appear. Delayed DHR may also manifest after systemic GC ranging from rash, eczema, blistering or purpura to SDRIFE, FDE, SJS, AGEP [114].

Table II shows the main differences between GC immediate and delayed DHR.

Allergological study: Diagnostic procedure includes cutaneous testing and drug provocation tests. The patch-test has been proven to be useful for the study of delayed reactions mediated by a type IV hypersensitivity mechanism. In general, GC are tested at 0.1% - 1% concentration. In addition to the usual readings at 48h-96h, it is important to make a reading on the seventh day, as the GC's own anti-inflammatory effect may delay a positive response [115]. A repeated open application test can be an option if patch-tests are negative [116]. It consists of topically applying the GC twice daily, in the anterior part of the forearm, for 7 days. For the prick-test and intradermal test, commercial preparations are used. Although assays for *in vitro* testing for GC hypersensitivity are primarily research tools and are not commercially available,

doi: 10.18176/jiaci.0588

specific IgE and BATs have been noted to be positive in some cases [117,118]. It is also important to test the excipients, if possible [111]. If cutaneous tests are negative, the risk-benefit ratio should be evaluated before proceeding with a DPT.

Regarding cross-reactivity, certain patterns have been described in delayed contact reactions:

- According to the Coopman classification [113], classes C and D1 produce fewer allergic reactions and have little cross-reactivity, while classes A, B2 and budesonide produce more allergic reactions and have greater intra-group and between-group cross-reactivity.
- According to the Baeck classification [119], which distinguishes between non-C16-methyl GC, most non-halogenated (group 1), GC with C16/C17 structure cis ketal diol, most halogenated (group 2) and GC with substitution C16-methyl and the majority halogenated (group 3), we could distinguish two patient profiles: allergic only to group 1 (able to tolerate groups 2 and 3), and potentially allergic to any GC (a systematic and individualized evaluation would be necessary to find a therapeutic alternative).

In immediate reactions, these cross-reactivity patterns are not applicable. A systematic and individualized evaluation will be necessary to find a therapeutic alternative [114]. Some studies have shown cross-reactivity between hydrocortisone, methylprednisolone and prednisolone, which have a C21 esterification in common and recommend, as an alternative, halogenated GCs such as betamethasone and dexamethasone [120].

Desensitization protocols: Two case-reports were found regarding this topic; One describes a case of desensitization to hydrocortisone prior to the administration of radiological contrast medium in a patient allergic to GC and iodinated contrasts [121].

doi: 10.18176/jiaci.0588

The other describes a case of desensitization to methylprednisolone hemisuccinate, but with subsequent tolerance to another methylprednisolone salt [122].

Heparins

Heparins are important anticoagulants used in the prophylaxis and treatment of thromboembolic disorders. They include unfractionated heparins (UFHs) and low-molecular-weight heparins (LMWHs) [123,124].

Mechanism of action: The anticoagulant effect of heparin is mediated through its interaction with antithrombin III that, in turn, accelerates its ability to inactivate the coagulation enzymes: factor IIa, Xa and IXa.

Rationale: Severe COVID-19 is commonly complicated with coagulopathy and disseminated intravascular coagulation [125-127]. All COVID-19 hospitalized patients should receive prophylactic heparin to prevent venous thromboembolism [128].

DHR: Delayed DHR to subcutaneously injected heparin is the most commonly reported reaction [129-131], LMWHs being the most frequently involved [132]. Itchy erythematous or eczematous plaques develop around injection sites. The usual latency for development of characteristic lesions during ongoing therapy is 7 to 10 days; in case of prior sensitization and re-exposure, skin lesions appear within 1 to 3 days [133]. Less frequently, in cases with continuation of subcutaneous injections despite local reaction, a generalized eczema or exanthema with accentuation around injection sites may be observed [134]. Female sex, older age and longer exposure to heparins seem to be risk factors for heparin allergy [135].

Other immune reactions during ongoing anticoagulation with heparins may present as heparin-induced thrombocytopenia, a classic type II reaction induced by polyclonal antibodies [132] and type III Arthus reaction, resulting from antigen-antibody

doi: 10.18176/jiaci.0588

complexes characterized by inflammation, erythematous induration and edema at the injection site, which can result in subsequent hemorrhage and necrosis [136]. In rare cases, DRESS [137], SJS [138] and IgE-mediated urticaria or anaphylaxis have been described [124,139-144].

Little is known about cross-reactivity between heparins so, tolerance must always be demonstrated [124]. Tolerance does not seem to depend on molecular weight [145]. Tolerance to fondaparinux is well known in patients who react to LMWHs [146] and data in the literature show that patients with delayed DHR to heparins tolerate intravenous heparin application [132,147,148].

Allergological study: For immediate reactions, sensitivity and specificity of skin tests have yet to be determined [149] so, according to some authors [149,150], a BAT could be a useful *in vitro* diagnostic technique to study possible sensitization to heparins. Prick-tests using the original undiluted drug are not necessary in patients with delayed hypersensitivity reactions, and patch-testing with the undiluted drug can be omitted because of reduced sensitivity [132]. Intradermal testing with drug concentrations ranging from 1/1000 to 1/10 are recommended [151,29]. If cutaneous tests are negative, the risk-benefit ratio should be evaluated before proceeding with a DPT.

Desensitization protocols: Quite a few desensitization protocols have been reported [143,144,152-154]. One reports heparin desensitization before cardiopulmonary bypass by gradually increasing the dose of heparin IV, starting with 100 units in 1 L of saline over 24h [144]. Another describes a successful 3-hour desensitization protocol after an anaphylactic shock due to heparin comprising IV administration of diluted heparin, gradually increasing doses (0.1 to 5000 units) at 15-minute intervals [143].

doi: 10.18176/jiaci.0588

Please refer to Table III for a summary of all DHR and Table IV for detailed concentrations for prick and patch tests mentioned in this revision and other possible options.

Other adverse reactions

Although our focus has been DHR, these therapies can be responsible for other ADR, some of which may be potentially severe. Gastrointestinal effects, severe infections, QT prolongation and other electrocardiogram alterations, drug interactions, hematological and metabolic disorders or nephrotoxicity are the main serious adverse reactions reported.

Limits

This review has some limitations. Firstly, the number of articles published in the last few weeks and the speed in which they are being published implies that the recommendations and even the drugs used to treat the disease are constantly being modified, so it is probable that some will not appear in this review. Secondly, this is not a systematic review but rather a narrative review. The described DHR appear in the databases reviewed, but some may not have been reported or published. Finally, considering the type of reactions that are the subject of this review, there are only two suspicions of DHR registered in the Pharmacovigilance Program on the *Hospital Universitari de Bellvitge* since 2007, one with cyclosporine and the other with azithromycin [155].

doi: 10.18176/jiaci.0588

Final thoughts about COVID-19 and drug hypersensitivity

A new disease implies new therapeutic challenges, but to date, no treatment has definitively been shown to improve the prognosis of COVID-19 patients. At present, most of the published work consists of small observational studies or case series, without randomization or control groups. Some drugs have shown *in vitro* activity, but their potential clinical benefits are unclear. On the other hand, the use of any medication relies on the assumption that the benefits outweigh associated risks, and augmented toxicity with combination therapy requires a careful evaluation of the risk-benefit ratio.

Multiple RCT are currently underway and are expected to provide further therapeutic evidence in the near future, and as far as the mechanisms of action of the virus become better known, new lines of treatment are expected to emerge. Figure 2 illustrates the targeted treatments proposed and the timing in which they should be administered [99].

It is expected that new therapeutic options, new indications and a greater number of possible COVID-19 patients undergoing these drugs will generate more ADR. It seems that these drugs have poor immunogenicity, but it remains to be seen what will happen in the future with increased use. As allergists, we must keep to date on the possible spectrum of hypersensitivity reactions with these treatments in order to adequately and promptly assist the possible inter-consultations generated regarding this topic.

Funding sources:

None

Conflicts of interest:

None

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FIGURES

Figure 1. Proposed phases of COVID-19 disease progression and potential therapeutic targets. Adapted from Siddiqi HK et al. [8]. IL: interleukin; JAK: janus kinase

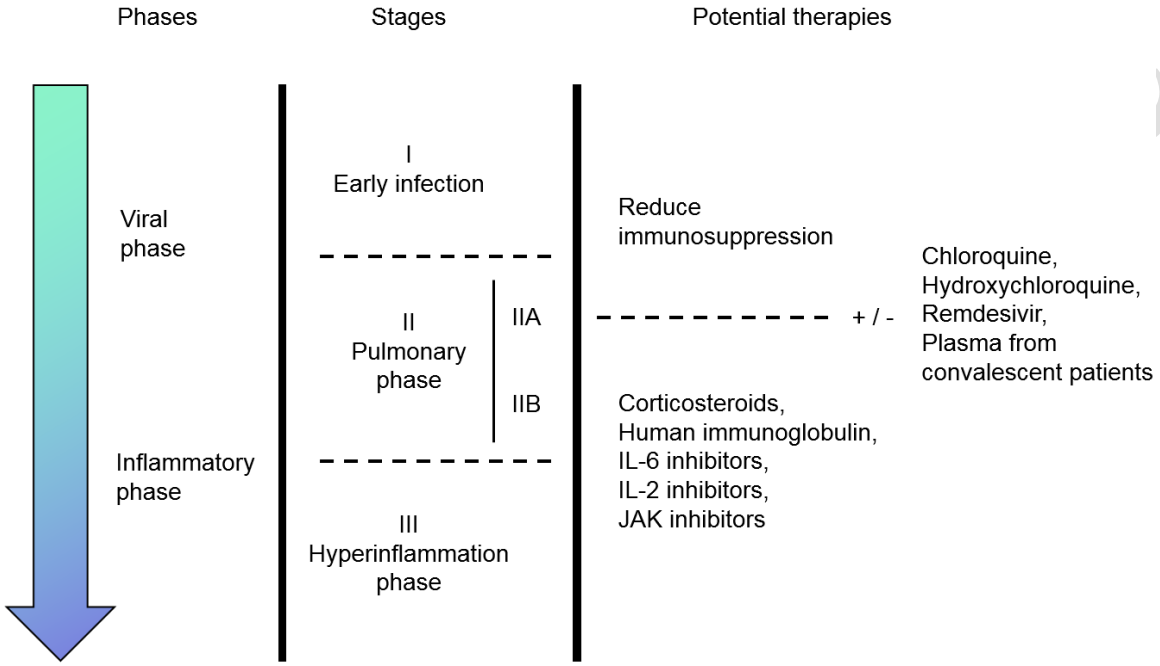

Figure 2. COVID-19 proposed targeted treatments and the timing of administration. Adapted from Van der Veerdonk F et al. [99]. B1/B2: Bradykinin receptor 1/2; CT: Computed tomography; IgG: Immunoglobulin G

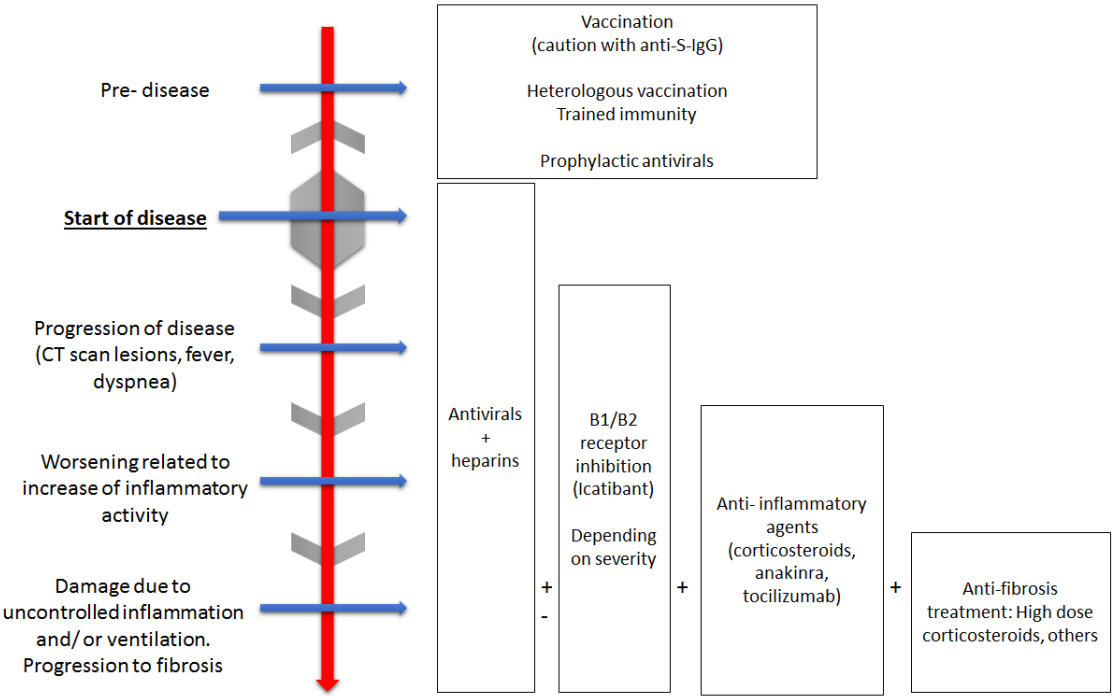

Table 1. Excipients present in commercial preparations and possible inducers of hypersensitivity reactions. Adapted from Kang SY et al. [11]. IV: Intravenous; SC: Subcutaneous

Excipient	Drug (route of administration)
Cremophor EL (Polyoxyl 35 hydrogenated castor oil)	**Cyclosporine** (IV)
Cremophor RH 40 (Polyoxyl 40 hydrogenated castor oil)	**Cyclosporine** (Oral, capsule and solution) **Lopinavir/Ritonavir** (Oral, solution)
Cremophor RH 60 (Polyoxyl 60 hydrogenated castor oil)	**Tacrolimus** (IV)
Cremophor RH 40 (Polyoxyl 40 hydrogenated castor oil)	**Lopinavir/Ritonavir** (Oral, solution)
Polisorbate 80	**Cyclosporine** (Oral, capsule) **Lopinavir/Ritonavir** (Oral, tablet) **Tocilizumab** (IV) **Anakinra** (SC)

Table 2. Differential diagnosis of immediate and delayed hypersensitivity reactions to corticosteroids. Adapted from Rosado-Ingelmo [108]. AGEP: Acute generalized exanthematous pustulosis; FDE: Fixed drug eruption; GC: Glucocorticoids; SDRIFE: Symmetrical drug-related intertriginous and flexural exanthema; SJS: Stevens Johnson syndrome

	Immediate hypersensitivity	**Delayed hypersensitivity**
Frequency	Rare	Contact dermatitis: common
Main route of sensitization	Intravenous	Cutaneous
Latency period	Minutes after the exposition	Hours or days after exposure
Clinical presentation	Urticaria, angioedema, pruritus, rhinoconjunctivitis, bronchospasm, anaphylaxis, etc.	Worsening of previous skin pathology, rash, eczema, contact dermatitis, etc. Occasionally after systemic administration: rash, purpura, SDRIFE, FDE, SJS, AGEP, etc.
Molecules more frequently implicated	Hydrocortisone (ester succinate) Methylprednisolone	Budesonide Hydrocortisone Methylprednisolone Dermatitis is more frequent with GC of groups A, B and D2 of the Coopman classification Topical non-fluorinated GC induce more allergic contact reactions than fluorinated ones
***In vivo* diagnostic tests**	Prick test Intradermal test Drug provocation test	Patch test Intradermal test (delayed reading) ROAT Drug provocation test
Cross-reactivity patterns	Uncertain Hydrocortisone – Methylprednisolone (¿?)	According to Baeck's classification: • Profile 1: allergy only to group 1 • Profile 2: potential allergy to all / various corticosteroids
Alternatives	Individualized assessment of sensitization / tolerance profile. Betamethasone, dexamethasone, and deflazacort are usually well tolerated	Profile 1 patients: molecules of groups 2 and 3. Patients with profile 2: individualized assessment of the sensitization / tolerance profile

doi: 10.18176/jiaci.0588

Table 3. Summary of all DHR for each drug included in this revision

AGEP: Acute generalized exanthematous pustulosis; DRESS: Drug reaction with eosinophilia and systemic symptoms; EM: Erythema multiforme; FDE: Fixed drug eruption; MPE: Maculopapular eruption; NR: Not reported up to date; SDRIFE = Symmetrical drug-related intertriginous and flexural exanthema; SJS: Stevens Johnson syndrome; TEN: Toxic epidermal necrolysis

Drug	Immediate reactions	Non-immediate reactions	Desensitization protocols [Reference]
Lopinavir/Ritonavir	NR	MPE, AGEP, SJS	NR
Remdesivir	NR	MPE	NR
Azithromycin	Urticaria, angioedema, anaphylaxis	MPE, FDE, AGEP, DRESS, SJS, vasculitis, organ-specific reactions	[31]
Chloroquine / Hydroxychloroquine	Urticaria	MPE, AGEP, DRESS, EM, SJS, TEN, photosensitivity	[41-44]
Tocilizumab	Urticaria, anaphylaxis	Urticaria, MPE, AGEP, SJS, DRESS, vasculitis	[53-56]
Sarilumab	NR	Pruritic rash, delayed local reactions	NR
Anakinra	Immediate local reactions, urticaria, angioedema, anaphylaxis	Delayed local reactions	[64,65]
Baricitinib	NR	Palmoplantar pustulosis	NR
Cyclosporine	Urticaria, angioedema, pruritic rash, bronchospasm, anaphylaxis		[78]
Tacrolimus	Urticaria, angioedema, pruritic rash, bronchospasm, anaphylaxis	Allergic contact dermatitis, SDRIFE	NR
Ivermectin	Urticaria, pruritic rash	MPE, TEN, SJS, DRESS, FDE	NR
Icatibant	NR	Local reactions	NR
Corticosteroids	Urticaria, pruritic rash, angioedema, rhinoconjunctivitis, bronchospasm, anaphylaxis	Rash, eczema, allergic contact dermatitis, purpura, worsening of previous cutaneous disorders, SDRIFE, FDE, SJS, AGEP	[121,122]
Heparins	Urticaria, anaphylaxis	Delayed local reactions, generalized eczema or exanthema, DRESS, SJS, heparin induced thrombocytopenia	[143,144,152-154]

Table 4. Concentrations used for skin tests. CQ: chloroquine; HCQ: hydroxychloroquine; IDT: Intradermal test; NR: not reported;*High risk of systemic reactions

Drug class	Drug	Prick-test	IDT	Patch test
Antivirals				
	Lopinavir/Ritonavir	NR	NR	NR
	Remdesivir	NR	NR	NR
	Azythromycin	10 mg/ml [29]	0.01 mg/ml [29] 0.1 mg/ml [156]	20% pet [29,157] 1-5% pet [158]
	Chloroquine/ Hydroxychloroquine	1/10.000 [41] Undiluted [35] 2-20 mg/ml [40]	NR ??	30% pet [35] CQ: 1%-5% aq; 1%-5% pet [157] HCQ: 5% aq [157]; 10% DMSO [39]
Anticytokine / Immunomodulatory agents				
	Tocilizumab	20 mg/ml [49, 159]	0.2 mg/ml [29,159] 2 mg/ml [49,53] 20 mg/ml [52]	NR
	Sarilumab	NR	NR	NR
	Anakinra	Undiluted [64]	1/10 [65]	NR
	Baricitinib	NR	NR	NR
	Cyclosporine	1/1.000-1/1 [73,74]	1/1.000-1/100 [73,74]	NR
	Tacrolimus			2.5% alc [82] 2.5% pet [157]
Corticosteroids				
	Methylprednisolone	40 mg/ml [160] 2-20 mg/ml [161]	0.4-4 mg/ml [160] 0.2-2 mg/ml [161]	1% pet; 1% alc [157]
	Hydrocortisone	100 mg/ml [29]	10 mg/ml [29]	0.5% alc or DMSO; 1% pet [157]
	Triamcinolone	4-40 mg/ml [29]	0.4-4 mg/ml [29]	1% alc; 2% pet [157] 0.25%-1% pet [29]
	Paramethasone	20 mg/ml [29]	0.2-2 mg/ml [29]	2% alc [157]
	Budesonide	0.5 mg/ml [29]	0.005 mg/ml [29]	0.1% pet [157] 0.01-0.1% pet [29]
	Dexamethasone	4 mg/ml [160]	0.04-0.4 mg/ml [160]	0.1% alc [157] 1%-25% pet [29]
	Betamethasone	4 mg/ml [29]	0.4 mg/ml [29]	0.1% alc [157] 1%-5% pet [29]
	Fluticasone	Undiluted [29]	1/100 [29]	0.1% alc [157]
Miscellaneous				
	Ivermectin	NR	NR	NR
	Icatibant	NR	NR	NR
	Heparins	Undiluted [29]	1/100-1/10 [151]	Undiluted [29,161]
Excipients				
	Cremophor EL	1/1.000-1/1 [73,74]	1/1.000-1/100 [73,74] 1-10 mg/ml [29]	
	Carboxymethyl cellulose 1%	5 mg/ml [29] Undiluted [162]	0.05-0.005 mg/ml [29] 1/10 [108]	2% pet [157]
	Povidone	Undiluted [29] 35 mg/ml [108] 100 mg/ml [162]	1/1.000 [29]	5-10% aq or pet; 0.5% alc [157]
	Macrogol (polyethylene glycol high molecular weight)	50%-Undiluted [162]	1/10.000 – 1/100* [162]	1-5% pet [157]
	Polysorbate 80	0.04-0.15mg/ml [29] 20% [162]	1/1.000-1/10 mg/ml [29]	5% aq or pet [157]

doi: 10.18176/jiaci.0588