

Treating COVID-19: Review of Drug Hypersensitivity Reactions

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■ Abstract

The disease caused by the new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), ie, coronavirus disease 2019 (COVID-19), has become a global pandemic since it was first reported in Wuhan, China in December 2019. Its severe clinical manifestations, which often necessitate admission to intensive care units, and high mortality rate represent a therapeutic challenge for the medical community. To date, no drugs have been approved for its treatment, and various therapeutic options are being assayed to address the pathophysiological processes underlying the clinical manifestations experienced by patients. New and old drugs administered as monotherapy or in combination to immunologically compromised patients may favor the development of adverse drug reactions, including drug hypersensitivity reactions, which must be identified and managed accordingly. Given the lack of herd immunity and the high rate of viral contagion, new cases are expected to emerge in the coming months. Thus, the probability of more adverse reactions or even new clinical manifestations may increase in parallel. Allergists must receive updated information on these treatments, as well as on the management of possible drug hypersensitivity reactions.

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 a fármacos.

Introduction

The novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported in Wuhan, China in December 2019 and has become a pandemic in only a few months [1]. Community transmission rates are high, and the spectrum of disease ranges from severe respiratory illness and death from its complications (particularly in the elderly and in people with comorbidities) to an asymptomatic course [1,2].

Once the disease manifests, supportive measures are initiated, although a systematic disease-modifying therapeutic approach remains empirical. Currently, there is no evidence from randomized controlled trials (RCTs) that any potential therapy could be superior to another, and many drugs are for compassionate or off-label use depending on experience, availability, and data from published case reports or short communications [3]. Pharmacotherapy targeting the virus seems to be useful when applied early in the course of the disease, although its usefulness in advanced stages may be doubtful [4,5]. Conversely, anti-inflammatory and immunosuppressive therapy applied too early can be dangerous [6], although it may prove useful in advanced stages owing to the damage caused by an amplified immune response and cytokine release (cytokine storm) [7]. Therefore, Siddiqi and Mehra [8] proposed a 3-stage classification system based on distinct clinical findings, response to therapy, and clinical outcome (Figure 1).

While a considerable effort has been made to flatten the curve of new contagions, the global pandemic is expected to continue. As more people are exposed to various treatments,

we might expect to see a rise in the number of drug-related adverse effects, some of which have an immunological basis.

In this narrative review, we summarize current knowledge on the main immunological adverse drug reactions (ADRs) related to the drugs used to treat COVID-19 in order to identify them early and comprehensively address their management.

Our review is based on a search of the PubMed and Medline databases, search engines (including bibliographic references from 1966 to the present), SIETES (www.sietes.org, an information system on developments in clinical and therapeutic pharmacology), the clinical resource UptoDate (<https://www.uptodate.com>), and the Medinteract Drug Interactions Database (<https://www.medinteract.net/>).

Antiviral Drugs

Lopinavir/Ritonavir

Lopinavir/ritonavir is an approved combination oral antiretroviral treatment of the family of HIV protease inhibitors that acts on the CYP3A isoform of cytochrome P450.

Mechanism of action: Lopinavir has antiviral activity. Inhibition of HIV protease prevents cleavage of the gag-pol polyprotein, leading to the production of an immature, noninfectious virus. Lopinavir is active in vitro 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: Since clinical studies in SARS have reported reduced mortality and intubation rates for lopinavir in combination with other antiviral agents, it has been considered for COVID-19 [9,10].

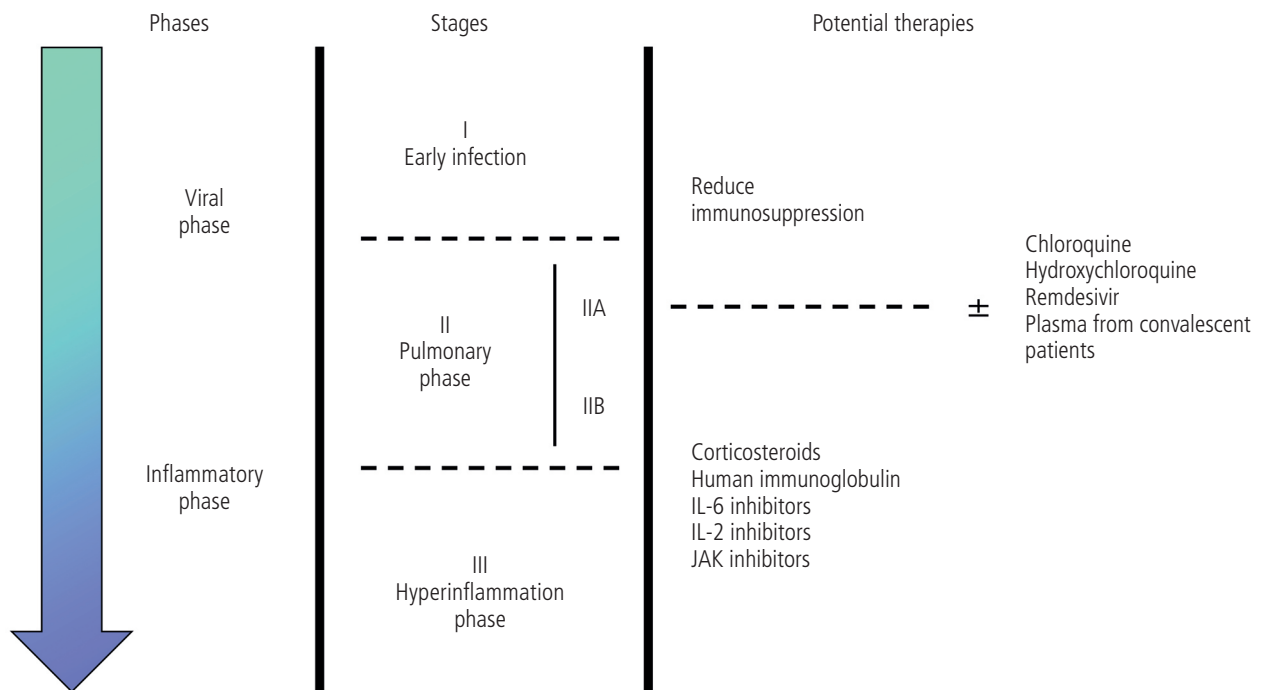


Figure 1. Proposed phases of COVID-19 disease progression and potential therapeutic targets. Adapted from Siddiqi et al [8]. IL indicates interleukin; JAK, Janus kinase.

Table 1. Excipients Present in Commercial Preparations and Possible Inducers of Hypersensitivity Reactions (Adapted from Kang et al [11])

Excipient	Drug (Route of Administration)
Cremophor EL (Polyoxyl 35 hydrogenated castor oil)	Cyclosporine (intravenous)
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 (intravenous)
Cremophor RH 40 (Polyoxyl 40 hydrogenated castor oil)	Lopinavir/ritonavir (oral, solution)
Polysorbate 80	Cyclosporine (oral, capsule) Lopinavir/ritonavir (oral, tablet) Tocilizumab (intravenous) Anakinra (subcutaneous)

Drug hypersensitivity reactions (DHRs): Given the significant drug-drug interactions and potential ADRs, a careful review of concomitant medications and both clinical and analytical monitoring are required when this drug is used. Hypersensitivity and nonspecific mediator release have been reported for the excipients of the commercial formula (Table 1) [11] and for the drug itself. It should be noted that most cases are reported in HIV-infected patients, who are more prone than the general population to drug-related rash, and that published cases of hypersensitivity reactions by protease inhibitors are anecdotal, with reactions to other antiretrovirals, such as reverse transcriptase inhibitors (abacavir, nevirapine, efavirenz) being much more frequent [12]. Mild skin reactions such as maculopapular rash have been reported 7-10 days after ingestion [13], and a DHR has been demonstrated in vitro using the Cellular Antigen Stimulation Test in a case of pruritic rash [12]. More severe skin reactions have also been described: a case of acute generalized exanthematous pustulosis (AGEP) 24 hours after the first dose in a patient who received prophylaxis after occupational exposure [14], and a case of Stevens-Johnson-like syndrome associated with 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: Remdesivir is a nucleotide analog that mimics adenosine, one of the building blocks of the RNA in the viral genome, and therefore interferes with viral RNA polymerization.

Rationale: This drug was initially developed for the Ebola virus outbreak, but it is a promising potential therapy for COVID-19 owing to its broad spectrum and potent in

vitro activity against several novel coronaviruses, including SARS-CoV-2 [16]. While remdesivir is not currently approved, various clinical trials are ongoing to evaluate its safety and antiviral activity in patients with moderate-to-severe COVID-19 (including 5 clinical trials in Spain).

DHRs: One case of maculopapular rash with elevated aminotransferases was recently reported [17].

Desensitization protocols: No desensitization protocols have been reported.

Azithromycin

Azithromycin is an azalide. Azalides are a subclass of macrolide antibiotics.

Mechanism of action: Azithromycin works by inhibiting the synthesis of RNA-dependent bacterial proteins, 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 recent years, the antiviral effects of macrolides have attracted considerable attention against rhinovirus, influenza, and the Zika and Ebola viruses [18].

DHRs: Macrolides are generally well tolerated, and allergy to them is infrequent (0.4% to 3%) [19]. However, some cases of immediate hypersensitivity (including urticaria, angioedema, and anaphylaxis) and delayed hypersensitivity (fixed drug eruptions [FDE] and severe cutaneous adverse reactions [SCARs]) have been described with macrolides [20-22]. SCARs with azithromycin include drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome [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, experience with azithromycin has been reported. The Spanish Society of Allergology and Clinical Immunology proposes to carry out prick testing at 10 mg/mL and intradermal testing at 0.01 mg/mL [29]. Patch testing (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 infrequent, although 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 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

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

Mechanism of action: Regarding its immunomodulatory effects, chloroquine/hydroxychloroquine (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 acts at 2 key steps that are required for cell entry by coronaviruses: inhibition of receptor binding (interfering with the glycosylation of angiotensin-converting enzyme 2, 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].

DHRs: CQ/HCQ are relatively well tolerated, although both can cause serious adverse effects such as prolongation of the QTc interval, gastrointestinal symptoms, and hypoglycemia. As for immunological reactions, both mild skin eruptions (maculopapular rash, urticaria) and SCARs (toxic epidermal necrolysis [TEN] SJS, AGEP, DRESS syndrome), including erythema multiforme, have been reported [34-39]. CQ/HCQ has also been associated with photosensitivity [33].

Allergological study: Patch tests with CQ/HCQ (30% pet) 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] found that prick tests with the undiluted drug yielded negative results. In cases of anaphylaxis, dilution up to 1/10 000 has been advised [40]. If skin tests are negative, the risk-benefit ratio should be evaluated before proceeding with a DPT.

Desensitization protocols: Several slow desensitization protocols have been published [41], with increasing doses at 24-hour intervals and lasting from 4 days [42] to 36 days [43] to achieve the full dose. A case of rapid desensitization to HCQ (less than 24 hours) was recently 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 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 response with cytokine release [45]. Although tocilizumab has shown promising results in some studies [46], the lack of a comparator group warrants caution when interpreting the results. Several RCTs with tocilizumab are ongoing in patients with severe COVID-19.

DHRs: Immediate DHRs (urticaria, anaphylaxis) and delayed DHRs (including urticaria, maculopapular rash, vasculitis, AGEP, SJS, and DRESS syndrome) can occur after taking tocilizumab [47-51]. Non-IgE-mediated alpha reactions related to cytokine release have also been reported [49]. It is

important to take hypersensitivity to excipients into account (Table 1) [11].

Allergological study: Skin 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 the results of skin tests are negative, a DPT can be performed after evaluating the risk-benefit ratio. Switching to the subcutaneous route can be considered [49].

Desensitization protocols: Desensitization to tocilizumab has been reported, both in immediate and in delayed reactions [53-55]. Demir et al [56] described 65 rapid drug desensitizations with tocilizumab in 3 patients, with only 1 episode of anaphylaxis during the fifth desensitization cycle. However, after modifying the protocol, this patient was able to continue the protocol uneventfully.

Sarilumab

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

Mechanism of action: The same as that of tocilizumab.

Rationale: Several phase 2-3 clinical trials have evaluated the efficacy of sarilumab in patients with severe COVID-19 [3].

DHRs: One published article reported mild-to-moderate rashes in 4 patients treated with sarilumab, although the reaction did not require treatment to be stopped [57]. Injection site reactions have also been reported [58].

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

Anakinra

Anakinra is a recombinant nonglycosylated form of the human IL-1 receptor antagonist (IL-1R α).

Mechanism of action: The IL-1 family is a group of proinflammatory cytokines, with IL-1 α and IL-1 β 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-1 α and IL-1 β by competitively inhibiting their binding to the type I receptor [59].

Rationale: In a recent study, continuous intravenous infusion of anakinra resulted in rapid serologic and subsequent clinical improvement in adult patients with macrophage activation syndrome [60], suggesting that this agent could be an option for treatment of patients with severe COVID-19 who experience a cytokine storm.

DHRs: Local reactions consisting of inflammation, erythema, itching, and pain are frequent with anakinra owing to the large amount of protein in the solution, which produces mast cell degranulation [61]. It is possible to prevent both immediate local reactions (application of ice locally before and after the injection and ensuring that the liquid is at room temperature prior to administration) and late local reactions (alternative injection sites and application of local topical corticosteroids). Case reports show that systemic allergic reactions to anakinra range from mild-to-moderate rash to anaphylaxis [62-65]. Anakinra contains polysorbate 80 as an excipient; this may also cause DHR [66-68].

Allergological study: One article reported a positive skin prick test with undiluted drug [63], and another described a

positive intradermal test result at the 1/10 concentration [64]. If skin tests are negative, the risk-benefit ratio should be evaluated before proceeding with a DPT.

Desensitization protocols: The few published case reports of successful rapid subcutaneous desensitizations advise starting with a dilution of 1/1000 [65] and increasing 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 signal involving STAT proteins, it ultimately modulates the expression of genes associated with inflammation in immune cells by means of an anti-inflammatory effect.

Rationale: 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-associated protein kinase 1 [69]. Clinical trials are underway to assess its effectiveness.

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

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

Cyclosporine

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

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

Rationale: Cyclosporine has been shown to inhibit the replication of several coronaviruses in vitro at noncytotoxic concentrations and independently of its immunosuppressive effect [71,72]. It also reduces cell proliferation and the concomitant production of cytokines.

DHRs: Cases of hypersensitivity/nonspecific release of mediators associated with excipients in the formula have been reported (Table 1) [11]. Polyoxyethylated castor oil (Cremophor EL) is a nonionic surfactant that is extracted from the seeds of *Ricinus communis* and used as a vehicle in hydrophobic medications such as cyclosporine. It can cause itching, erythematous rash, urticaria, angioedema, facial flushing, bronchospasm, dyspnea, nausea, vomiting, and anaphylaxis following infusion. The probable pathophysiological mechanisms underlying this reaction include IgE-mediated immune response, complement activity, histamine release by basophils or mast cells, and IgG antibody formation [73]. Assuming that Cremophor EL is the culprit agent in hypersensitivity to intravenous cyclosporine, corn oil-based soft gelatin capsules, which contain polyoxyethylated glycolized glycerides, would be a safe alternative in cases of hypersensitivity to other forms of cyclosporine [74].

This observation has been confirmed elsewhere [11,75-77]. Finally, the basophil activation test (BAT) can be used as a diagnostic tool for both cyclosporine- and excipient-induced hypersensitivity [73,75].

Allergological study: Cyclosporine and Cremophor EL have been tested at 1/1000 to 1/1 for prick testing and at 1/1000 and 1/100 for intradermal testing [73,74]. If the results of skin tests are negative, the risk-benefit ratio should be evaluated before proceeding with a DPT.

Desensitization protocols: One successful slow oral cyclosporine desensitization protocol has been reported (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 interferons [79].

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

DHRs: Cases of hypersensitivity/nonspecific release of mediators caused both by excipients of the drug (Table 1) and by the drug itself have been reported [11]. The intravenous form of tacrolimus contains polyoxyethylated castor oil, which can induce various ADRs, 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 demonstrated with positive patch test results at 2.5% in alcohol [81]. Recently, a case of contact urticaria by a tacrolimus-containing ointment [82] and a case of symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) with oral tacrolimus [83] were published.

While tacrolimus is a macrolide drug, its chemical structure differs substantially from that of macrolide antibiotics. A case report describing cross-sensitivity between tacrolimus and macrolides was found, although the patient had been diagnosed with allergy to clarithromycin without an allergy work-up [84]. On the other hand, in a retrospective review of 8 patients with reported macrolide allergy (not confirmed), all of them tolerated tacrolimus (including 3 patients with an anaphylactic-type reaction) [85]. Exposure to tacrolimus was recently associated with posttransplantation 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 the bacteria *Streptomyces avermitilis*.

Mechanism of action: Ivermectin binds to the chlorine channels of nerve and muscle cells in invertebrate

microorganisms, causing paralysis and death of the parasite. Ivermectin has also been proven to be active against various viruses in vitro.

Rationale: Ivermectin was recently reported to be 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]. Therefore, well conducted clinical trials are required.

DHR: The main adverse events are pruritus and rash, which usually appear during the first days of treatment [89-91]. A few case reports of ivermectin-associated SCARS (TEN, SJS, and DRESS syndrome) have been published [92-94]. There is 1 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 that of bradykinin. It has been 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. It 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 respiratory epithelial cells through the ECA2 receptor [96]. ECA2 is responsible for the catabolism of des-Arg9-bradykinin, and a decrease in its activity implies an increase in bradykinin levels [97,98]. The pulmonary edema present in the early stages of pneumonia in COVID-19 could therefore be caused by local activation of the bradykinin receptors located in the endothelial cells [99], which would result in vasodilation and increased vascular permeability leading to pulmonary edema and inflammation.

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

DHRs: The most common adverse effects are injection site reactions, which are generally mild in severity and transient in nature [101-104].

Desensitization protocols: No desensitization protocols have been published.

Corticosteroids

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

Rationale: Corticosteroids decrease 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

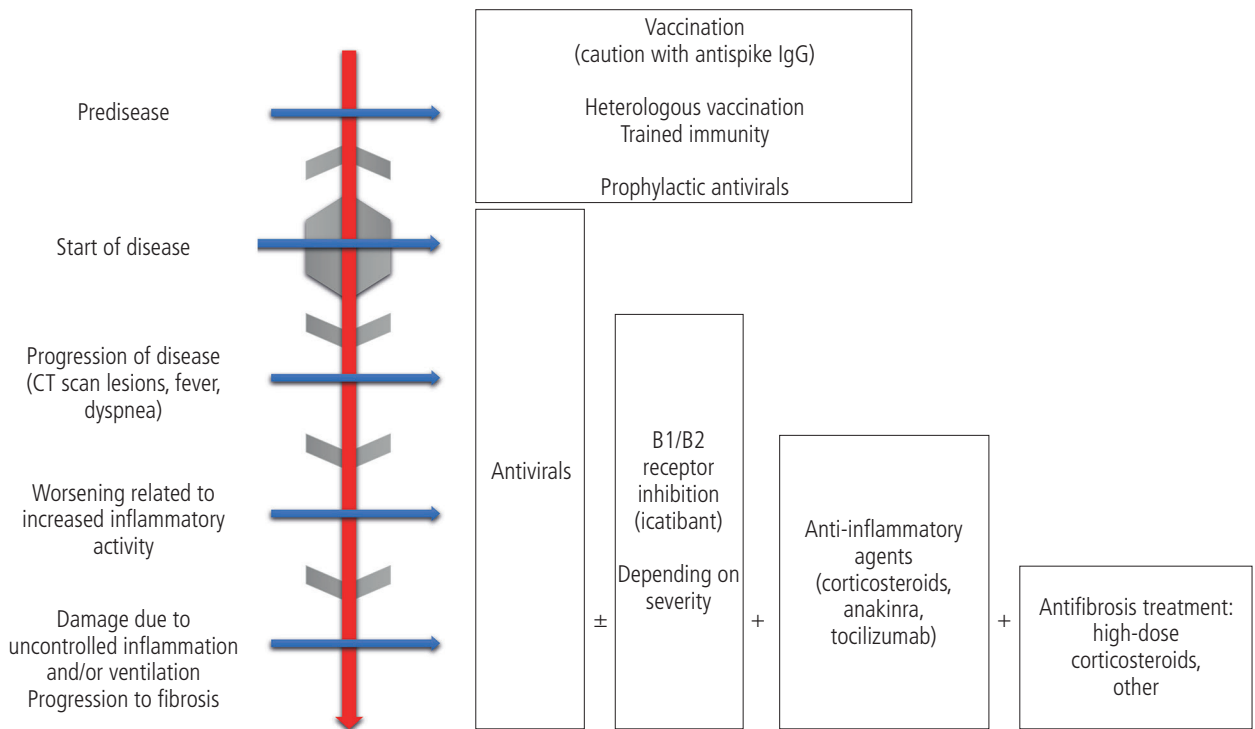


Figure 2. Proposed targeted treatments for COVID-19 and timing of administration. Adapted from Van der Veerdonk F et al. [99]. B1/B2 indicates bradykinin receptor 1/2; CT, computed tomography; IgG, immunoglobulin G.

by possible adverse effects, including delayed viral clearance and increased risk of secondary infection. Observational studies and systematic reviews report inconclusive clinical evidence on the effects of corticosteroid therapy for viral pneumonia such as that induced by SARS and MERS [105,106]. Nevertheless, 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, recently 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 their importance for public health.

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

Immediate DHRs usually occur following systemic therapy (except for intra-articular administration, where there could be a delayed reaction) and manifest clinically as pruritus, rash, urticaria, angioedema, rhinoconjunctivitis, bronchospasm, anaphylaxis, hypotension, vascular collapse, and death [108-110]. Immediate DHRs are more frequent with hydrocortisone, methylprednisolone, or a specific salt (succinate), although

they may also be due to the excipients (carboxymethyl cellulose, benzyl alcohol, propylene glycol, polyethylene glycol, polysorbate 80, or parabens) [108,111]. Reactions to systemic therapy are more frequent in asthmatics with hypersensitivity to aspirin, transplant recipients, patients with nephritis, hemodynamically unstable patients, and patients with rheumatic diseases [108,112].

Delayed DHRs are usually due to topical corticosteroids and mainly affect atopic patients and patients with contact dermatitis, ulcers, stasis dermatitis, and other previous dermatological disorders [113]. Worsening of such disorders, as well as bronchospasm and pain in the nasal or oral mucosa after nasal or bronchial application, may also appear. Furthermore, delayed DHRs can manifest after systemic therapy and range from rash, eczema, blistering, and purpura to SDRIFE, FDE, SJS, and AGEP [114].

Table 2 shows the main differences between immediate and delayed DHRs induced by corticosteroids.

Allergological study: The diagnostic procedure includes skin testing and DPTs. Patch testing has been proven to be useful for the study of delayed reactions mediated by a type IV hypersensitivity mechanism. In general, corticosteroids are tested at concentrations ranging from 0.1% to 1%. In addition to the usual readings at 48-96 hours,

Table 2. Differential Diagnosis of Immediate and Delayed Hypersensitivity Reactions to Corticosteroids (Adapted from Rosado-Ingelmo [108])

	Immediate Hypersensitivity	Delayed Hypersensitivity
Frequency	Rare	Contact dermatitis: common
Main route of sensitization	Intravenous	Cutaneous
Latency period	Minutes after exposure	Hours or days after exposure
Clinical presentation	Urticaria, angioedema, pruritus, rhinoconjunctivitis, bronchospasm, and anaphylaxis	Worsening of previous skin condition, rash, eczema, and contact dermatitis Occasionally after systemic administration: rash, purpura, SDRIFE, FDE, SJS, and AGEP
Drugs most frequently implicated	Hydrocortisone (ester succinate) Methylprednisolone	Budesonide Hydrocortisone Methylprednisolone Dermatitis is more frequent with corticosteroids from groups A, B, and D2 of the Coopman classification Topical nonfluorinated corticosteroids induce more allergic contact reactions than fluorinated corticosteroids
In vivo diagnostic tests	Prick test Intradermal test Drug provocation test	Patch test Intradermal test (delayed reading) Repeat open application test Drug provocation test
Cross-reactivity patterns	Uncertain Hydrocortisone – Methylprednisolone (?)	According to the Baeck 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: groups 2 and 3 • Profile 2: individualized assessment of the sensitization/tolerance profile

Abbreviations: AGEP, acute generalized exanthematous pustulosis; FDE, fixed drug eruption; SDRIFE, symmetrical drug-related intertriginous and flexural exanthema; SJS, Stevens-Johnson syndrome.

it is important to take a reading on the seventh day, as the anti-inflammatory effect of the drug itself may delay a positive response [115]. A repeated open application test can be an option if patch test results are negative [116]. This consists of twice-daily topical application on the anterior aspect of the forearm for 7 days. Commercial preparations are used for the prick test and intradermal test. Although assays for in vitro testing for hypersensitivity to corticosteroids are primarily research tools and are not commercially available, 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 skin test results 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, as follows:

- According to the Coopman classification [113], classes C and D1 produce fewer allergic reactions and have little cross-reactivity, whereas classes A, B2, and budesonide produce more allergic reactions and have greater intragroup and intergroup cross-reactivity.
- According to the Baeck classification [119], which distinguishes between non-C16-methyl molecules, most nonhalogenated corticosteroids (group 1) with a C16/C17 cis ketal/diol structure, most halogenated corticosteroids (group 2) and agents with C16-methyl substitution, and most halogenated agents (group 3), we can distinguish 2 patient profiles: allergic only to group 1 (able to tolerate groups 2 and 3) and potentially allergic to any corticosteroid (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 is necessary to find a therapeutic alternative [114]. Some studies have shown cross-reactivity between hydrocortisone, methylprednisolone, and prednisolone, which have C21 esterification in common, and recommend, as an alternative, halogenated agents such as betamethasone and dexamethasone [120].

Desensitization protocols: This topic is addressed in 2 case reports. One describes a case of desensitization to hydrocortisone prior to the administration of radiological contrast medium in a patient allergic to corticosteroids and iodinated contrasts [121]. The other describes a case of desensitization to methylprednisolone hemisuccinate in a patient who subsequently tolerated another methylprednisolone salt [122].

Heparins

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

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

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

DHRs: Delayed DHR to subcutaneously injected heparin is the most commonly reported reaction [129-131], with LMWHs being the most frequently involved [132]. Itchy erythematous or eczematous plaques develop around the injection site. The usual latency for development of characteristic lesions during ongoing therapy is 7 to 10 days; in cases 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 reactions, generalized eczema or exanthema with accentuation around the injection site 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 complexes and characterized by inflammation, erythematous induration, and edema at the injection site, which can result in subsequent hemorrhage and necrosis [136]. In rare cases, DRESS syndrome [137], SJS [138], and IgE-mediated urticaria and anaphylaxis have been described [124,139-144].

As little is known about cross-reactivity between heparins, 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 [132,147,148].

Allergological study: For immediate reactions, the sensitivity and specificity of skin tests have yet to be determined [149]; therefore, according to some authors [149,150], the BAT could be a useful in vitro diagnostic technique when investigating possible sensitization to heparins. Prick tests using the original undiluted drug are not necessary in patients with delayed DHRs, 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: Many desensitization protocols have been reported [143,144,152-154]. One involved desensitization to heparin before cardiopulmonary bypass by gradually increasing the dose of intravenous heparin, starting with 100 units in 1 L of saline over 24 hours [144]. Another describes a successful 3-hour desensitization protocol after an anaphylactic shock due to heparin comprising intravenous administration of diluted heparin, with doses gradually increasing (0.1 to 5000 units) at 15-minute intervals [143].

Table 3 provides a summary of DHRs. Table 4 provides detailed concentrations for the prick and patch tests mentioned in this review, as well as other possible options.

Table 3. Summary of all Drug Hypersensitivity Reactions for the Drugs Included in This Review

Drug	Immediate reactions	Nonimmediate 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]

Abbreviations: 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 to date; SDRIFE, symmetrical drug-related intertriginous and flexural exanthema; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

Other Adverse Reactions

Although our review has focused on DHRs, the therapies presented may be responsible for other ADRs, some of which could prove severe. The main serious adverse reactions reported are gastrointestinal effects, severe infections, prolongation of the QT interval and other electrocardiographic abnormalities, drug interactions, hematological and metabolic disorders, and nephrotoxicity.

Limitations

Our review is subject to a series of limitations. Firstly, the number of articles published in the last few weeks and the speed with which they are being published imply that the recommendations and even the drugs used to treat the disease are constantly being modified. Therefore, some may not appear in this review. Secondly, this is not a systematic review, but rather a narrative review. The DHRs described appear in the databases reviewed, although some may not have been reported

or published. Finally, considering the types of reaction that are the subject of this review, only 2 suspicions of DHRs have been registered in the Pharmacovigilance Program of Hospital Universitari de Bellvitge, Barcelona, Spain since 2007: one with cyclosporine and the other with azithromycin [155].

Final Thoughts About COVID-19 and Drug Hypersensitivity

A new disease implies new therapeutic challenges; however, to date, no treatment has been definitively shown to improve the prognosis of patients with COVID-19. At present, most published work consists of small observational studies or case series, with no randomization or control groups. While some drugs have shown in vitro activity, their potential clinical benefits are unclear. Furthermore, the use of any medication relies on the assumption that the benefits outweigh the associated risks, and increased toxicity with combination therapy requires a careful evaluation of the risk-benefit ratio.

Multiple RCTs are currently underway and are expected to provide further therapeutic evidence in the near future. Moreover, 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 time schedule according to which they should be administered [99].

It is expected that new therapeutic options, new indications, and a greater number of possible COVID-19 patients taking these drugs will generate more ADRs. While new drugs seem to have little ability to generate an immune response, it remains to be seen what will happen in the future with increased use. As allergists, we must keep up to date on the possible spectrum of hypersensitivity reactions with these treatments in order

Table 4. Concentrations Used for Skin Tests

Drug class	Drug	Prick Test	Intradermal Test	Patch Test
Antivirals	Lopinavir/ritonavir	NR	NR	NR
	Remdesivir	NR	NR	NR
	Azithromycin	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 Tacrolimus	1/1000 to 1/1 [73,74]	1/1000 to 1/100 [73,74]	NR 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 to 1/10 [151]	Undiluted [29,161]
Excipients	Cremonophor EL	1/1000 to 1/1 [73,74]	1/1000 to 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]	1/1000 [29]	5-10% aq or pet, 0.5% alc [157]
	Macrogol (polyethylene glycol high molecular weight)	50%-Undiluted [162]	1/10 000 to 1/100 [162]a	1-5% pet [157]
	Polysorbate 80	0.04-0.15 mg/mL [29] 20% [162]	1/1000 to 1/10 mg/mL [29]	5% aq or pet [157]

Abbreviations: CQ, chloroquine; DMSO, dimethyl sulfoxide; HCQ, hydroxychloroquine; IDT, intradermal test; NR, not reported.

^aHigh risk of systemic reactions

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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