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The protective effect of rheumatic disease agents in COVID-19



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A B S T R A C T

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Several immunosuppressive therapies have been investigated as potential treatments for patients with severe and critical coronavirus disease 2019 (COVID-19). Notable examples include corticosteroids, interleukin 6 (IL-6), interleukin 1 (IL-1), Janus kinase (JAK), and tumor necrosis factor alpha (TNF- α) inhibitors. The aim of this narrative review is to analyze the mechanistic rationale and available evidence for these selected anti-rheumatic drugs for the treatment of COVID-19. Currently, only corticosteroids have consistently proven to be effective in decreasing mortality and are recommended in clinical guidelines for the treatment of severe and critical COVID-19. Multiple randomized controlled trials (RCTs) are ongoing to determine the role of other immunosuppressants.

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Introduction

The severe acute respiratory coronavirus 2 (SARS-CoV-2), discovered in late 2019, is the etiologic agent of the pandemic coronavirus disease 2019 (COVID-19) [1]. The disease course of COVID-19 ranges from asymptomatic or mild upper respiratory symptoms to the acute respiratory distress syndrome (ARDS) [2]. In severe COVID-19 cases, the host immune response is thought to play a role in the pathophysiological mechanisms that lead to ARDS and multisystem organ failure (MSOF). Features of exuberant immune activation have been described and critical cases may resemble macrophage

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activation syndrome (MAS), also known as secondary hemophagocytic lymphohistiocytosis (sHLH). Such “cytokine storm” syndromes typically present with elevated levels of serum ferritin and d-dimer, lymphopenia (including low natural killer (NK) and cytotoxic T cells), and elevated pro-inflammatory cytokines, including interleukin-6 (IL-6), interleukin-1 (IL-1), tumor necrosis factor alpha (TNF- α), and interleukin-8 (IL-8) [3,4].

In an effort to curb inappropriate immune activation, several immunosuppressive therapies have been investigated as potential treatments for cases of severe COVID-19, including corticosteroids, IL-6, IL-1, Janus kinase (JAK), and TNF- α inhibitors [5–9].

Many of these agents have been investigated for septic shock, including steroids, TNF inhibitors, and IL-1 inhibitors [10–12]. In addition, targeted therapies have been used in hyperinflammatory conditions, such as adult onset Still’s disease and chimeric antigen receptor (CAR) T cell-induced cytokine release syndrome (CRS). Finally, though they have not been studied for hyperinflammatory conditions, JAK inhibitors are used in the treatment of autoimmune diseases, and it has been speculated that may inhibit AAK1, which could theoretically impair SARS-CoV-2 entry into human cells [8].

The aim of this narrative review is to analyze the mechanistic rationale and available evidence for selected anti-rheumatic drugs for the treatment of COVID-19. The data for this review were obtained from searches of Medline/PubMed as well manual searches of the coronavirus resource sites and collections of *The Lancet*, *New England Journal of Medicine*, *Journal of the American Medical Association*, *British Medical Journal*, and *Annals of Internal Medicine*. We prioritized peer-reviewed publications, systematic reviews with meta-analyses and randomized controlled trials (RCTs). Additionally, we summarized the ongoing active RCTs on phases 3–4 to reflect the current research efforts related to these drugs.

Corticosteroids

Corticosteroids have been widely used for rheumatologic diseases, hyperinflammatory conditions, and in patients with MSOF. These lipophilic molecules activate cytoplasmic receptors that in turn translocate to the nucleus and alter several genes implicated in the inflammatory response. As nonselective immunosuppressive agents, they modify the expression of pro-inflammatory cytokines (IL-1, IL-2, IL-6, TNF- α and interferon- γ [IFN- γ]), inhibit leukocyte migration to tissues, and upregulate anti-inflammatory genes [13]. Given their broad availability and wide ranging effects, corticosteroids have been investigated as treatments for dysregulated immune responses in severe sepsis, septic shock, bacterial pneumonia, and ARDS. On balance, RCTs have been equivocal or have suggested a small benefit. Notably, in a large RCT hydrocortisone decreased respiratory mortality in severe bacterial pneumonia [14] and in another fludrocortisone decreased mortality in septic shock [10]. Others have been equivocal, demonstrating no benefit in 90-day mortality for hydrocortisone [15] and only marginal improvement in outcomes with respect to ARDS [16,17]. A high-quality systematic review and meta-analysis found that the use of corticosteroids may result in a small reduction in mortality in patients with sepsis [18]. Beside sepsis, corticosteroids are also used as a first-line therapy in hyperinflammatory conditions, including sHLH, adult onset Still’s disease (AOSD), and CRS, among others [19–21].

Corticosteroids have been used off label for COVID-19 since the beginning of the pandemic, and multiple observational studies have been published to date. Early observational data were largely conflicting, with suggestions of decreased mortality in patients with COVID-19-induced ARDS [22,23], increased mortality or intensive care unit (ICU) admission [24–26], and prolonged viral shedding. Such discrepancies led to recommendations against the routine use of corticosteroids in World Health Organization (WHO) guidelines [27] and cautious endorsement of selective use by critical care societies [28] and infectious disease societies [29].

More recently, robust clinical evidence in favor of corticosteroid use among patients with severe COVID-19 has emerged. First, the adaptive RECOVERY trial from the United Kingdom demonstrated that the use of 6 mg of dexamethasone daily resulted in a decrease in 28-day mortality among patients who required mechanical ventilation (rate ratio, 0.64; 95% CI, 0.51–0.81) or supplemental oxygen (rate ratio, 0.82; 95% CI, 0.72–0.94). It should be noted that dexamethasone showed no benefit – and possible harm – among those patients who did not require respiratory support (rate ratio, 1.19; 95% CI, 0.91–1.55) [5].

Further evidence supporting the conclusions of the RECOVERY trial has since emerged. These include other multicenter randomized clinical trials (DEXA-COVID-19 [16], CoDEX [30], CAPE COVID [31], REMAP-CAP [32] and GLUCOVID [33], Steroids Sari, and COVID STEROID) that evaluated different corticosteroid regimens within different populations. In a systematic review and meta-analysis, this body of evidence suggests a benefit with regard to 28-day all-cause mortality (odds ratio (OR) 0.66; 95% CI, 0.53–0.82; $P < 0.001$) that is maintained across multiple subgroups of patients, including older and younger patients, men and women, and different durations of symptoms. Furthermore, this new evidence has confirmed that the protective effect is a class effect rather than one limited to dexamethasone. In light of these data, corticosteroid use has become the standard of care in severe and critical COVID-19 [34].

Despite these encouraging data, reasons for caution remain. First, corticosteroids are not a panacea or cure, and many patients who receive them will still suffer ARDS, MSOF, and death. The trials have followed patients for a short period of time, therefore, the long-term effects of steroids on mortality and functional outcomes have not been defined. Second, the long-term effects of glucocorticoid use, such as weight gain, hyperglycemia, and bone fragility, were not assessed in time-limited clinical trials. Such adverse events are expected to be minimal given a short course of glucocorticoid therapy, but care should be taken to minimize unnecessary exposure. Third, supraphysiologic baseline glucocorticoid use (prednisone > 10 mg/day) increased the risk of hospitalization of COVID-19 patients [9] highlighting the need for robust immunity early in COVID-19 infection to control viral spread. Finally, no data support the use of glucocorticoids in asymptomatic or mild disease.

Interleukin-6 inhibitors

A strong rationale for investigating IL-6 inhibitors also exists. IL-6 exerts pleiotropic effects in adaptive and innate immune cells. IL-6 plays a central role in promoting the secretion of other cytokines and growth factors – vascular endothelial growth factor and interleukin-8, for instance – and has been implicated in cytokine storm syndromes [3]. In fact, the IL-6 inhibitor tocilizumab, a humanized monoclonal antibody directed against the IL-6 receptor, is approved by the Federal Drug Administration (FDA) for the treatment of systemic juvenile idiopathic arthritis (SJIA) and CRS induced by CAR T cell therapy [35]. The hyperinflammatory phenotype of COVID-19 resembles CRS, and elevated IL-6 levels have been observed in severe COVID-19 [36], which are associated with a worse prognosis [4,37].

Observational data have lent support to this proposed potential benefit. The largest published study of which we are aware evaluated 544 patients with severe COVID-19 [38]. After adjustment for sex, age, and disease severity, receiving the IL-6 inhibitor tocilizumab was associated with a reduction in mortality (adjusted hazard ratio (HR) 0.61, 95% CI 0.40–0.92). A smaller study that compared treatment with glucocorticoids with or without tocilizumab to age and sex-matched historical controls also suggested a reduction in mortality (HR: 0.35; 95% CI 0.19–0.65). A large body of small observational studies without comparator groups has been largely unrevealing and should not be used to draw inferences with regard to tocilizumab [6,39–45]. Observational data assessing the IL-6 receptor antagonist sarilumab have been similarly flawed and inadequate for evaluating its potential efficacy [46,47].

More importantly, large RCTs assessing the effect of IL-6 inhibition of severe COVID-19 have recently been completed. In a July 29th press release regarding the results of the phase 3 global RCT COVACTA, tocilizumab, did not achieve its primary endpoint of improvement in clinical status ($p = 0.36$; OR = 1.19 [0.81–1.76]) or the secondary endpoint of decrease in mortality at week 4 (19.7% mortality in experimental group vs 19.4% in control group). However, in a more recent press release of the phase 3 RCT EMPACTA, tocilizumab decreased the probability of progression to mechanical ventilation or death ($p = 0.348$; HR = 0.56 [0.32, 0.97]), but there were no statistical differences in mortality alone [48]. Peer-reviewed publication of both trials is pending [49]. Similarly, preliminary findings from an adaptive phase 2/3 trial of the IL-6 receptor antagonist sarilumab have been discouraging and enrollment has been stopped [50].

In Table 1, we summarized the active trials assessing tocilizumab, sarilumab, and other IL-6 agents (siltuximab [51] and olokizumab), which are expected to be published in the near future. Current guidelines recommend against the use of IL-6 inhibitors outside of clinical trials [52].

Table 1

Ongoing phase 3 or 4, currently recruiting randomized clinical trials of IL-6 inhibitors.

Drug	Study title	Design	ClinicalTrials.gov Identifier
Tocilizumab	A Randomized, Controlled Clinical Trial of the Safety and Efficacy of Tocilizumab for the Treatment of Severe COVID-19 (ARCHITECTS)	Double-blinded, placebo-controlled RCT	NCT04412772
Remdesivir + Tocilizumab (RDV + TCZ)	A Phase III, Randomized, Double-Blind, Multicenter Study to Evaluate the Efficacy and Safety of Remdesivir Plus Tocilizumab Compared With Remdesivir Plus Placebo in Hospitalized Patients With Severe COVID-19 Pneumonia (REMDACTA)	Double-blinded, placebo-controlled RCT	NCT04409262
Tocilizumab	The Use of Tocilizumab in the Management of Patients Who Have Severe COVID-19 With Suspected Pulmonary Hyperinflammation	Open label RCT	NCT04377750
Tocilizumab Siltuximab	A Prospective, Randomized, Factorial Design, Interventional Study to Compare the Safety and Efficacy of Combinations of Blockade of Interleukin-6 Pathway and Interleukin-1 Pathway to Best Standard of Care in Improving Oxygenation and Short- and Long-term Outcome of COVID-19 Patients With Acute Hypoxic Respiratory Failure and Systemic Cytokine Release Syndrome (COV-AID)	Open label RCT	NCT04330638
Tocilizumab	Randomized Evaluation of COVID-19 Therapy (RECOVERY Tocilizumab arm)	Open label RCT	NCT04381936
Tocilizumab Sarilumab	Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP)	Open label RCT	NCT02735707
Olokizumab	An International, Multicenter, Randomized, Double-blind, Adaptive Placebo-controlled Study of the Efficacy and Safety of a Single Administration of Olokizumab and RPH-104 With Standard Therapy in Patients With Severe SARS-CoV-2 Infection (COVID-19)	Double-blinded placebo-controlled RCT	NCT04380519

Abbreviations: IL-6, interleukin 6; RCT, randomized controlled trial; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Interleukin-1 inhibitors

The earliest suggestions of immunosuppression in COVID-19 considered IL-1 antagonists [53]. IL-1 is secreted after viral activation of Toll-like receptors in macrophages, monocytes, and dendritic cells, and leads to the formation of the inflammasome. There are two main forms of IL-1: IL-1 α and IL-1 β .

When binding to the IL-1 receptor type 1 (IL-1R1), IL-1 β , released by monocytes, macrophages, and neutrophils, has a protagonist role in viral infections, mediating neutrophil recruitment and inflammation, fever, and severe respiratory problems [54,55]. Moreover, this IL-1/Inflammasome signaling pathway is involved in lung dysfunction in influenza-induced chronic obstructive lung disease exacerbations [56] and for the pathology seen in fulminant viral hepatitis [57]. This pathophysiologic rationale has been supported by studies of cells infected with SARS-CoV, which found high secretion of IL-1 β by immune cells, thus potentially leading to lung damage and increased disease severity [58].

The majority of studies to date have assessed the recombinant version of the human IL-1 receptor antagonist protein, anakinra. Anakinra is approved by the FDA for the treatment of autoinflammatory conditions, such as cryopyrin-associated periodic syndromes (CAPS), and was recently approved for AOSD [59]. Moreover, it has been widely used off-label for sHLH [59]. Small case series have suggested potential efficacy for anakinra in moderate to severe COVID-19 [7,60–64].

Larger cohort studies have also been published. Most notably, in a cohort study that included 52 anakinra-treated patients and 44 historical controls, anakinra use was associated with a lower risk of mechanical ventilation or death (HR 0.22 95% CI 0.10–0.49). However, a high percentage of patients in both groups were receiving other agents [65]. In another retrospective cohort, which compared 29 patients (with moderate COVID-19 requiring non-invasive ventilation) treated with high-dose intravenous anakinra and seven patients with low-dose subcutaneous anakinra to a standard treatment control group, only high-dose anakinra was associated with a higher survival rate at 21 days (90% vs 50% survival rate, HR: 0.20; CI 95% 0.04–0.63). It should be noted that 24% of patients treated with high doses of anakinra developed adverse effects that required discontinuation of the drug, including bacteremia and elevations in liver enzymes [7]. In a meta-analysis of both studies, anakinra was associated with a significantly lower risk of mortality (pooled HR: 0.2; CI 0.1–0.4) [66]. Table 2 summarizes the ongoing actively recruiting, phase 3 or 4 clinical trials using anakinra.

Rilonacept and canakinumab are other IL-1 antagonists. Rilonacept is a soluble decoy factor that binds directly to IL-1 α and IL-1 β , while canakinumab is a human anti-IL-1 β antibody. Both are also approved for the treatment of CAPS, and canakinumab is also approved for SJIA and other periodic fever syndromes [67]. There is one retrospective analysis of 10 patients with COVID-19 pneumonia, acute hypoxemic respiratory failure, and elevated C-reactive protein (CRP), who were treated subcutaneously with a single dose of canakinumab. This study observed that canakinumab administration was associated with a rapid decrease of CRP levels and an improvement in oxygenation, but such observational studies require further validation [68]. Currently, there are no registered clinical trials evaluating rilonacept and there is one actively recruiting phase 3 evaluating canakinumab. IL-1 inhibitor use should remain in the context of clinical trials until more robust evidence is available.

Janus kinase inhibitors

Cytokine-mediated activation of the JAK-STAT (Janus-kinases-signal transducer and activator of transcription proteins) pathway is critical in the immune response, and JAK inhibitors have also been considered for COVID-19. As with IL-1 and IL-6 inhibitors, it has been hypothesized that inhibition of the JAK-STAT pathway could lead to decrease of cytokine-mediated inflammation [4]. At the same time, inhibition of the interferon pathway by JAK-STAT inhibitors may be counterproductive, as IFN signaling may be necessary to clear viral infections [69]. In addition to immunomodulatory effects, JAK inhibitors may inhibit the AP2-associated protein kinase 1 (AAK1). Both kinases are key regulators of clathrin-mediated endocytosis, a mechanism used by COVID-19 to enter and infect cells. Therefore, inhibition of these kinases may also interrupt viral entry to target cells and intracellular assembly of the virus [8,70].

In a recent meta-analysis of JAK inhibitors and interferon, five studies evaluating JAK inhibitors were promising (3 baricitinib and 2 ruxolitinib). Overall, JAK inhibitor or INF treatment was associated with lower odds of mortality (OR, 0.12; 95% CI, 0.03–0.39; $p = 0.0005$), lower odds of ICU admission, (0.05; 95% CI, 0.01–0.26; $p = 0.0005$) and higher odds for discharge (OR, 22.76; 95% CI, 10.68–48.54; $p < 0.00001$) [71]. However, this meta-analysis has not been peer-reviewed and there was high heterogeneity among the studies, including differences in therapies, patient characteristics, and the study type.

Table 2

Ongoing phase 3 or 4, currently recruiting randomized clinical trials of IL-1 Inhibitors.

Drug	Title	Design	ClinicalTrials.gov Identifier
Anakinra	Efficacy and Safety of ANakinra During Adult "COVID-19" With Aggravating Respiratory Symptoms: a Multicenter Open-label Controlled Randomized Trial (ANACONDA)	Open label RCT	NCT04364009
Anakinra	Clinical Trial of the Use of Anakinra in Cytokine Storm Syndrome Secondary to Covid-19. A Phase 2/3, Randomized, Open-label, Parallel Group, 2-arm, Multicenter Study Investigating the Efficacy and Safety of Intravenous Administrations of Anakinra, an Interleukin-1(IL-1) Receptor Antagonist, Added to Standard of Care, Versus Standard of Care, in Reducing Hyper-inflammation and Respiratory Distress in Patients With SARS- CoV-2 Infection (ANA-COVID-GEAS)	Open label RCT	NCT04443881
Anakinra	A Phase 2/3, Randomized, Open-label, Parallel Group, 3-arm, Multicenter Study Investigating the Efficacy and Safety of Intravenous Administrations of Emapalumab, an Anti-interferon Gamma (Anti-IFN γ) Monoclonal Antibody, and Anakinra, an Interleukin-1(IL-1) Receptor Antagonist, Versus Standard of Care, in Reducing Hyper-inflammation and Respiratory Distress in Patients With SARS-CoV-2 Infection	Open label RCT	NCT04324021
Anakinra	A Prospective, Randomized, Factorial Design, Interventional Study to Compare the Safety and Efficacy of Combinations of Blockade of Interleukin-6 Pathway and Interleukin-1 Pathway to Best Standard of Care in Improving Oxygenation and Short- and Long-term Outcome of COVID-19 Patients With Acute Hypoxic Respiratory Failure and Systemic Cytokine Release Syndrome	Open label RCT	NCT04330638
Anakinra	Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community- Acquired Pneumonia (REMAP-CAP)	Open label RCT	NCT02735707
Canakinumab	Phase 3 Multicenter, Randomized, Double-blind, Placebo-controlled Study to Assess the Efficacy and Safety of Canakinumab on Cytokine Release Syndrome in Patients With COVID-19-induced Pneumonia (CAN-COVID)	Double-blinded placebo-controlled RCT	NCT04362813

Abbreviations: IL-1, interleukin 1; RCT, randomized controlled trial; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Individual results from two small RCTs with ruxolitinib in the setting of severe COVID-19 also found some improvement in clinical outcomes [72,73]. Recently, a press release of the Adaptive COVID-19 Treatment Trial-2 study noted a small benefit with respect to baricitinib in combination with remdesivir, which reduced median recovery time by one day. Results regarding mortality and safety are pending [74]. Currently, there are no late phase trials for tofacitinib. Results from ongoing clinical trials are needed to make a recommendation regarding the use of these drugs (Table 3).

Tumor necrosis factor inhibitors

TNF- α is a key cytokine in the pro-inflammatory host response to COVID-19. Aside from its pathological implication in the COVID-19 complications, TNF- α is critical for promoting viral cell entry. The virus spike protein is able to induce TNF- α release by inducing TNF- α -converting enzyme activity, a process that facilitates viral entry [75]. Thus, TNF- α inhibitors (infliximab, etanercept, adalimumab, golimumab, and certolizumab) have been suggested to have a role in the prevention of SARS-CoV-2 infection and subsequent inflammatory consequences.

Interestingly, data from the COVID-19 Global Rheumatology Alliance showed that patients treated with anti-TNF- α agents for other autoinflammatory and rheumatologic diseases experienced a lower rate of hospitalization (OR, 0.40; 95% CI 0.19–0.81) [9]. Moreover, a decrease in cytokine levels was seen in a small case series of patients with severe COVID-19 treated with infliximab [76]. Other case reports

Table 3
Ongoing phase 3 or 4, currently recruiting randomized clinical trials of JAK inhibitors.

Drug	Title	Design/NCT	ClinicalTrials.gov Identifier
Baricitinib	A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Phase 3 Study of Baricitinib in Patients With COVID-19 Infection (COV-BARRIER)	Double-blinded placebo-controlled RCT	NCT04421027
Baricitinib	mulTi-Arm Therapeutic Study in Pre-ICU Patients Admitted With Covid-19 - Repurposed Drugs (TACTIC-R)	Open label RCT	NCT04390464
Ruxolitinib	A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Assess the Efficacy and Safety of Ruxolitinib in Participants With COVID-19-Associated ARDS Who Require Mechanical Ventilation (RUXCOVID-DEVENT)	Double-blinded placebo-controlled RCT	NCT04377620
Ruxolitinib	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)	Double-blinded placebo-controlled RCT	NCT04362137
Ruxolitinib	Randomized, Double-Blind Clinical Trial of Ruxolitinib in Patients With Acute Respiratory Disorder Syndrome Due to SARS-CoV-2 Infection (RUXO-COVID)	Double-blinded placebo-controlled RCT	NCT04477993

Abbreviations: JAK, Janus kinase; RCT, randomized controlled trial; ICU, intensive care unit.

of patients previously taking anti-TNF- α inhibitors have also suggested a protective effect for COVID-19 pneumonia [77–79]. Currently, there are no active phase 3 or 4 trials for TNF inhibitors. A phase 2 clinical trial of infliximab in the United States is ongoing. Given the paucity of data, TNF inhibitors should not be used in routine COVID-19 care.

Summary

Multiple immunosuppressive medications are under investigation for the treatment of coronavirus disease 2019 (COVID-19). High-quality evidence and clinical practice recommendations support the use of corticosteroids in severe or critical COVID-19. Observational data with interleukin 6 (IL-6) inhibitors have been promising, but recent press releases have had mixed reports and the full peer-reviewed reports have not been published. Similarly, observational studies suggest a benefit from IL-1 and tumor necrosis factor (TNF) inhibitors, but evidence from randomized controlled trials (RCTs) has yet to be published. JAK-STAT inhibitors have emerged as a potential therapeutic option, and a preliminary report from a trial of baricitinib in combination with remdesivir suggests a small benefit. Multiple phase 3 trials are currently ongoing to evaluate these and other immunosuppressive therapies.

Practice points

- Corticosteroids are recommended in current guidelines for severe and critical coronavirus disease 2019 (COVID-19).
- For patients with non-severe COVID-19, immunosuppressive therapy is not recommended.
- There is a paucity of evidence regarding the use of other anti-rheumatic disease therapies, which should be used within the context of ongoing RCTs.

Research agenda

- Evidence from ongoing placebo-controlled clinical trials is needed to determine the role of interleukin 6 (IL-6), interleukin 1 (IL-1), Janus kinase (JAK), and tumor necrosis factor alpha (TNF- α) inhibitors in the prevention or treatment of coronavirus disease 2019 (COVID-19).

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Declaration of competing interest

The authors report no conflicts of interest.

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