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REVIEW

Current treatment of Psoriasis triggered by Cytokine Storm and future immunomodulation strategies

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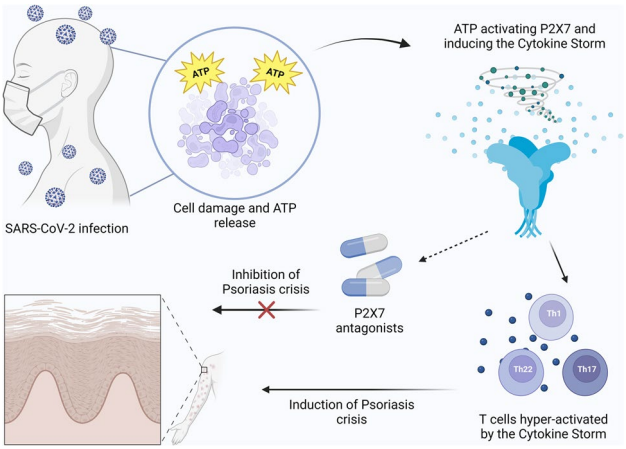
Abstract

Psoriasis is a chronic condition caused by an inflammation mediated mainly by cytokines and T cells. In COVID-19, the same type of imbalance is common, generating the Cytokine Storm and promoting a worsening in the skin conditions of patients with autoimmune disorders, such as Psoriasis. In this context, one of the main mediators of immune responses presented by SARS-CoV-2 infected patients is the Purinergic System. This immunological resource is capable of stimulating the hyperinflammatory state presented by infected individuals, mainly by the activity of the P2X7 receptor, culminating in the Cytokine Storm and consequently in the Psoriasis crisis. Currently, different drugs are used for patients with Psoriasis, such as immunosuppressants and small molecules; however, the safety of these drugs in infected patients has not been analyzed yet. In this context, studies are being developed to evaluate the possible administration of these traditional drugs to COVID-19 patients with Psoriasis crisis. Along with that, researchers must evaluate the potential of administrating P2X7 antagonists to these patients as well, improving both the systemic and the dermatological prognostics of patients, by reducing the Cytokine Storm and its general effects, but also avoiding the provocation of Psoriasis crisis.

Graphical Abstract



Keywords Psoriasis · COVID-19 · Cytokine Storm · Purinergic · Immunomodulation

Introduction

Psoriasis is a chronic inflammatory condition that has as its most known manifestation the development of skin alterations, with the formation of erythematous plaques, caused by an excessive and disorganized proliferation of keratinocytes and a lymphocytic infiltration to the dermis, and with the dilation of blood vessels of the dermis [1, 2]. Along with that, other types of responses to this autoimmune disorder are related to alterations in nails and joints, affecting those structures considerably as well [2].

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Moreover, Psoriasis can be divided into different groups according to the characteristics of the manifestations of the disease, with Psoriasis vulgaris being the most common of them, presenting the classical clinical manifestations [3]. Nowadays, the current treatments for this condition include the possible use of a large range of drugs, such as immunomodulators and chemotherapeutic agents that count with many important adverse effects, such as nephrotoxicity, hepatotoxicity, and teratogenicity [2]. Concerning the triggers of Psoriasis, the possible causes for its initiation include infections, physical trauma, the use of certain medications, the use of cigarettes, and alcohol abuse [1].

In the context of infections, a new possibility of trigger or cause for the exacerbation of Psoriasis deserves to be highlighted, the infection by SARS-CoV-2. Recently, case reports and other studies indicated that patients with COVID-19 presented deterioration in their skin conditions related to autoimmune disorders, with Psoriasis included [4–7]. According to a review evaluating the impact of COVID-19 in skin diseases, from the 14 reports of dermatological conditions exacerbated by SARS-CoV-2 infection that were found in scientific literature, 9 were cases of Psoriasis exacerbation [8], demonstrating an important link between these conditions.

Furthermore, in an observational study with children infected by COVID-19, the virus was indicated as a microorganism to be added in the list of viral agents capable of inducing Psoriasis flares, for its effects on the exacerbation of the disease [9]. However, there still is a lack of precise epidemiologic data regarding the impact of COVID-19 in Psoriasis patients and the risk for Psoriasis exacerbation in infected individuals [9].

Among the leading hypotheses for establishing a relationship between this dysfunction and the virus, considering the immune and inflammatory aspects of Psoriasis, is related to the development of the Cytokine Storm. Within this context, the Cytokine Storm caused by SARS-CoV-2 represents a hyperinflammatory condition generated by immune dysregulation, which causes an intense release of cytokines by infected individuals [10]. Therefore, this theory indicates that the immunological response present in the Cytokine Storm might be capable of mimicking the immune pattern present in patients with Psoriasis, leading to the triggering or worsening of the condition.

In light of that, once the validity of this relationship is successfully verified, the modulation of this pathway will represent a potential new therapeutic target for the treatment of Psoriasis in COVID-19 and post-COVID-19 patients, and one of the main possibilities to be explored is the effects of purinergic signaling modulation in this inflammatory cascade. The Purinergic System is enrolled in many immune responses and inflammatory conditions, being demonstrably linked with autoimmune diseases and suggested as a target against dysfunctions caused by Cytokine Storm in multiple studies [11–14].

Hence, an evaluation of the current treatments against Psoriasis for COVID-19 patients and the possibility of purinergic modulation based on the association between Psoriasis and the Cytokine Storm must be developed, aiming at improving the management of COVID-19 patients who had their skin conditions affected by SARS-CoV-2 infection.

The pathophysiology of Psoriasis, the role of COVID-19 and the Cytokine Storm

The immunology of Psoriasis

Psoriasis is an autoimmune disease, triggered by many conditions, that manifests in individuals with a genetic predisposition to it due to the alteration in the expression of specific genes [1]. This condition has several dermatological manifestation patterns, with the formation of plaques in Psoriasis vulgaris, the development of pustules in pustular Psoriasis, inverse Psoriasis presenting in the folds of the skin, and guttate Psoriasis presenting small erythematous plaques, often triggered by group-A streptococcal infections in children [3]. Among those patterns, the most frequently presented by patients is Psoriasis vulgaris, plaque-type Psoriasis, with erythematous scaly plaques mostly seen on the trunk and extensor surfaces of the limbs [3]. Moreover, this condition usually presents the Koebner effect, where the lesions are activated by trauma or injury [15].

Furthermore, this disease is also responsible for the impairment of joints and the development of inflammatory processes in other organs besides the skin, demonstrating an association of its exacerbation to intense inflammatory responses [3]. In this regard, Psoriasis is frequently related to other health conditions, such as diabetes, hypertension, and obesity, indicating a bidirectional link between the dermatological condition and several comorbidities [2]. In this sense, according to studies, Psoriasis is a T cell-mediated inflammatory disorder, combining environmental factors and genetics to be developed [1].

Initially, the beginning of the Psoriasis crisis occurs due to the activation of immune responses to damage, to the initiation of apoptosis, and to the release of cytokines, both present in the context of infections [2, 15]. This response consists of the release of antimicrobial peptides, produced by keratinocytes, neutrophils, and macrophages, a group constituted by defensins, the S100 proteins family, and LL37 (cathelicidin), along with the release of other proinflammatory cytokines [2]. Usually, this activity is triggered by the action of antigen-presenting cells (APCs), which recognize antigens and release alert peptides, activating the mentioned cells and the release of their mediators [1].

Initially, after the activation of keratinocytes and immune cells caused by some type of trauma, their released mediators tend to connect to the DNA of damaged cells, activating Toll-like receptor 9 (TLR9) of plasmacytoid dendritic cells (DCs), initiating their responses [1, 2, 16]. In this regard, Psoriasis patients tend to overexpress antimicrobial peptides, producing an increased immune activation and inflammatory response, with cathelicidin especially formatting complexes with self-genetic material and inducing autoimmune responses [3]. When activated, plasmacytoid DCs begin producing IFN-α and IFN-β, activating myeloid DCs, capable of releasing I IFN, which, along with TNFα, IL-6, and IL-1β, promotes local myeloid DCs activation and interaction with T naïve cells, inducing an inflammatory response from the adaptative immunity [1, 3, 16]. The T cell differentiation is executed by the stimuli of the TNF-α, INF-γ, IL-17, IL-23, and IL-12 mediators, leading to the activation of Th1 and Th17 cells [3, 17]. Additionally, TNF-α, IL-23, IL-12, and IL-6 are also responsible for keratinocyte proliferation and recruitment of neutrophils to sites of inflammation, increasing the onset of immune response [1].

T cells, in turn, can act from different pathways to contribute for the development of Psoriasis. Firstly, the activation of those cells leads to the release of further mediators, responsible for stimulating epidermal hyperproliferation and alteration of epidermal differentiation, prejudicing the execution of apoptosis, with Th17 cells being closely related to those processes and mediating these activities through the release of IL-17, IL-21, and IL-22 [1, 18]. Additionally, the release of IL-17 and IL-22 can cause the hyperplasia of keratinocytes, micro abscess formation, and neutrophil recruitment [18], contributing for the formation of lesions.

Also, the Th17 cells, induced by IL-23, along with tissue residential T cells and the natural killers (NK) stimulate the liberation of IL-17 [1]. Despite the protective role of IL-17 against some cutaneous infections, when in higher concentrations, it induces chronic inflammation and autoimmune diseases, and it is highly expressed in the serum of Psoriasis patients, with IL-17A, IL-17C, and IL-17F—three of the five subtypes of IL-17 family—being up to eightfold in psoriatic lesions [1, 19]. Regarding that, this cytokine is responsible for promoting the release of other mediators, inducing further production of antimicrobial peptides, stimulating coagulation, and promoting even joint damage and is also expressed by other cells than Th17, such as some T CD8 + cells, natural killer cells, and myeloid cells, for example [1, 19].

Moreover, the intense proliferation of keratinocytes induces even more inflammation, since it generates the release of more cytokines and chemokines, exacerbating the psoriatic condition, and leading to a cycle of inflammation mediated by the TNF-α/IL-23/IL-17 axis [3, 17]. In this sense, the innate and adaptative immunity are both widely present in the pathophysiology of this condition, with myeloid DCs producing IL-23 and representing part of the role of innate immunity and Th17 producing IL-17 representing the role of adaptative immunity. Therefore, this indicates the complete immune activation present in this disease, along with the complexity enrolled in its pathophysiology [20].

More recently, studies have also demonstrated the participation of IL-20 and IL-8 in the development of Psoriasis. Despite being less mentioned, these interleukins are capable of inducing Psoriasis activities, with IL-20 acting in the growth and differentiation of keratinocytes, and in the production of immunological mediators, and with IL-8 contributing to chemotaxis and angiogenesis, and representing a marker for disease severity [21]. On the other hand, the production of IL-10, mainly released due to the activity of regulatory B cells (Breg), tends to act in reducing inflammatory conditions. However, in Psoriasis patients, Breg activity is reduced, compromising the release of such cytokine and its anti-inflammatory role [1].

Finally, the hyperkeratosis stimulated by the immunological response causes the formation and maintenance of erythematous plaques—with the maintenance of the lesions made by the intense influence of the tissue residential T cells—along with other typical manifestations of Psoriasis, such as nail alterations for example [1, 17]. Furthermore, regulatory T cells (Treg) can be found in the lesions of Psoriasis patients; however, their functionality is reduced and they are present in fewer quantities than the ideal [22–24]. Hence, with both Breg and Treg being impaired in this disease, another feature of Psoriasis to be considered beyond the excessive pro-inflammatory manifestations is the reduction of anti-inflammatory activities, contributing to the prolonged installation of the hyperinflammatory state [18, 25].

Furthermore, the infiltration of multiple other immune cells can be found in Psoriasis lesions, such as mast cells, and excessive vascularity can also be present [26]. Regarding that, the Vascular Endothelial Growth Factor (VEGF) is responsible for the excessive vascularization of the dermis and, therefore, is being linked to the characteristic keratinocyte hyperplasia manifested by the disease [26, 27]. In this sense, Auspitz's sign frequently can be seen with the removal of the scale plaques, related to the increase in the vascularization of the affected inflamed skin [17, 28]. Also, another lesion caused by the immune imbalance present in Psoriasis is the formation of sterile pustules, composing the frame of skin damage caused by this autoimmune disease [17].

On the other hand, infections can also trigger Psoriasis by another immunological pathway: molecular mimicry [29]. Scientific literature has indicated that the presence of homologous proteins between microorganisms and human tissues can generate an autoimmune response responsible for triggering Psoriasis after the infection [29, 30]. Concerning that,

infections caused by a few microorganisms were already linked to the development of Psoriasis, such as infections by *Clostridioides difficile* and streptococcal infections [29, 30]. In these cases, keratin in the dermis was found to be confounded with bacterial peptides, leading to adaptative immunity responses present in Psoriasis; thus, triggering the T cell activities previously elucidated and the disease itself [29, 30].

Therefore, Psoriasis is an immune-mediated condition, which can be triggered by different microorganisms and by traumas. Furthermore, it is mediated by both innate and adaptative immunity, being closely linked with T cell dysfunctional activity and a hyperinflammatory state established by the actions of immune cells and several pro-inflammatory molecules. As a result from these dysfunctions, the dermis is affected by keratinocyte metabolic abnormalities and the formation of lesions, mainly seen as plaques.

Cytokine Storm as a trigger for Psoriasis

With the COVID-19 pandemic, several studies and case reports have reported the worsening of Psoriasis patients' conditions and suggested an association between Psoriasis exacerbation and SARS-CoV-2 infection, indicating that the virus can induce the worsening of this disease [31–34]. Epidemiological data regarding the incidence of this phenomenon is not fully developed yet; however, research shows that both Psoriasis and COVID-19 are capable of negatively influencing each other's outcomes, meaning that Psoriasis patients infected by the virus tend to develop both a severe SARS-CoV-2 infection and a worsening of Psoriasis [35, 36].

Considering that, a few hypotheses have been raised regarding the explanation for this link, most associating the immune responses to the virus with the pathophysiology of Psoriasis [35]. Nonetheless, some studies also suggest the influence of social isolation stress due to the infection as a possible trigger for Psoriasis exacerbation, as this disease is known for being associated with psychological conditions [35, 37]. Thus, researchers conclude that both the psychological effect of quarantine and immunological responses might be responsible for the negative effects of COVID-19 on Psoriasis [35]. Furthermore, additionally to that, SARS-CoV-2 infection occurs via the virus binding to the angiotensin-converting enzyme type 2 (ACE2) receptors. In this sense, individuals with Psoriasis have higher levels of ACE2, indicating another possible association between these conditions [37].

However, SARS-CoV-2 infection is provenly associated with an increased risk for the development of different autoimmune conditions, indicating a pattern of viral influence over autoimmune disorders; in this regard, COVID-19 patients present higher C-reactive protein and ferritin levels, which demonstrate the intense inflammatory state imposed by the infection [38, 39], possibly capable of triggering Psoriasis worsening. Therefore, COVID-19 must affect Psoriasis by modifying immunologic responses and inflammatory parameters, although its role is not totally known yet.

Aiming at explaining this association through immunological pathways, many studies turned to the analysis of the Cytokine Storm occurrence in patients infected with the virus. In this sense, in a general form, the Cytokine Storm represents an immune response to a harmful agent in the organism [10]. In physiological conditions, immune responses are balanced by pro- and anti-inflammatory mediators; however, what was seen in SARS-CoV-2 patients was an insufficiency of anti-inflammatory activities, leading to a hyperinflammatory state characterized by the excessive liberation of inflammatory cytokines, thus called Cytokine Storm [10].

Moreover, studies demonstrated that the Cytokine Storm is not an exclusive feature of the body's response to COVID-19, but is also present in other infections, sepsis, and autoimmune conditions, the group to which Psoriasis belongs [1, 10]. Despite the clear existence of a link between a worsening in skin conditions of Psoriasis patients and the infection by the virus, there is no final explanation for the reason for this relationship [1, 10]. Nonetheless, the Cytokine Storm is capable of inducing a hyperinflammatory state, a key condition for the development of inflammatory conditions, such as Psoriasis [39, 40]. Hence, we hypothesize that the Cytokine Storm is related to the worsening of Psoriasis by individuals infected by COVID-19.

In this sense, studies suggest that the immune response caused by the Cytokine Storm is capable of inducing the production of many types of inflammatory mediators, with the cytokines upregulated in the infection being the same ones upregulated in individuals with Psoriasis, explaining the relationship between these dysfunctions and how the cascade triggered by COVID-19 can also trigger Psoriasis exacerbation simultaneously [41]. Initially, SARS-CoV-2 infection is able to trigger an innate response from the immunological system, which is responsible for the first dysregulated inflammatory response [42]. This response is mediated by the activity of neutrophils, macrophages, and other immune cells, along with the release of several cytokines and chemokines [42].

In this context, some of the central cytokines elevated in Cytokine Storm in common with Psoriasis and studied for therapeutic reduction against the viral infection are TNF-α, IL-8, IL-12, and IL-17 [43, 44]. In addition, a study developed by Patrick et al. (2021) found that the main immune pathways stimulated by COVID-19 infection are TNF and IL-17 pathways, the same ones upregulated in Psoriasis patients [7]. As mentioned, the elevation in these cytokines triggered by an infection can induce an

inflammatory condition and the Psoriasis crisis [2]. Therefore, the development of the Cytokine Storm by SARS-CoV-2 has significant potential for causing the development and worsening of Psoriasis.

Furthermore, the Cytokine Storm also promotes an intense activation of T cells—major promoters of Psoriasis crisis—through the excessive release of cytokines, which stimulate T cell differentiation and activity [1, 43, 45]. Among these cytokines, IL-1, IL-10, IL-12, IL-18, and IL-33 are the primary responsible for stimulating T cell differentiation and activity, along with the action of chemokines in SARS-CoV-2 infected [46]. In this sense, the level of activation of T cells in patients with exacerbated immune responses is so elevated that many of them also presented T cell lymphopenia in posterior stages of infection, due to cell exhaustion, demonstrating the intense activation of this immune resource and stimulating T cell reproduction [43, 47].

Additionally, studies also suggest a heterogeneity in T cell activation in COVID-19 patients, demonstrating a dysregulated adaptative immune response in individuals; thus, the virus is capable of inducing T cell abnormal behavior, variable in each patient, which can imply different immunophenotypes and manifestations of the infection, impairing an effective clinical care [48]. Nonetheless, research also suggests that T cells specific for SARS-CoV-2 spike protein can present a Th1 cell pro-inflammatory profile, contributing for cytokine release and recruitment of other immune cells, consequently, maintaining the inflammatory state [49, 50]. Hence, the triggering of these cells' inflammatory response by the Cytokine Storm and the dysfunctionality of T cells in this scenario also represents a possible link between the Psoriasis crisis and the COVID-19 infection, when considering the relevance of T cells in Psoriasis pathophysiology.

Moreover, studies also suggest that the infection by this virus is capable of inducing a rise in the activity of genes related to different dermatological conditions, with Psoriasis included [7]. Apparently, the induction of an intense immune response due to the viral infection stimulates the transcription of genes related to immunological mechanisms, such as the activity of nuclear factor kappa B signaling, and the IL-17 pathway, for example [7]. Also, some genes stimulated by SARS-CoV-2 are directly related to skin barrier activities and signaling in injury or infection, demonstrating that the immune responses to the virus can reach the skin and its immune cells [7]. As mentioned, Psoriasis has an important genetic component, besides being stimulated by immune and inflammatory conditions [1]. Hence, the alterations in gene expressions induced by the COVID-19 immune response can trigger inflammatory mechanisms related to Psoriasis and the infection itself but also promote the stimulation of genes linked to Psoriasis alone [7].

Therefore, the immune response generated by SARS-CoV-2 infection, when deregulated, can cause a Cytokine Storm, which affects normal inflammatory responses increasing its physiological mechanism activities and turning it into a pathological condition [10]. Once this disbalance happens, multiple immune tools are mobilized against the virus; however, this hyperinflammatory response can induce the same apparatus enrolled in Psoriasis worsening and skin damage, such as T cell activity, genetic activation, and cytokines release, explaining the association between these conditions [7] (Fig. 1).

Moreover, Psoriasis is already known to be triggered by a few infectious conditions, such as streptococcal infection, for example, and hyperinflammatory states, suggesting that what is seen in the COVID-19 scenario is not an unusual response [37]. Regarding that, as mentioned, molecular mimicry associated with Psoriasis development is a phenomenon already described in the literature, and studies have demonstrated that SARS-CoV-2 is capable of causing immune cross-reactivity, a similar process in which autoimmune responses can be triggered [36, 51]. Therefore, this immune mistake triggered by the COVID-19 infection is another possible pathway for developing intense immune responses and inflammation, resulting in Psoriasis exacerbation.

Thus, in order to reduce the skin damage caused by SARS-CoV-2 infection, more must be understood about both the cytokine storm and molecular mimicry, along with the development of further research related to the control of the immune response to the virus.

Current management of Psoriasis in COVID-19 patients and the potential of purinergic modulation

Current knowledge in therapy for Psoriasis in COVID-19-infected patients

Given the exacerbation of the Psoriasis crisis due to SARS-CoV-2 infection, physicians worldwide had to evaluate the management of the infected patients who developed this condition. In this sense, some therapies earlier considered ideal, became uncertain, considering the pandemic scenario and the danger represented by COVID-19 [39]. Therefore, the options for treatment for these patients must be analyzed and chosen carefully.

In this sense, usually, the use of topical treatment has been the main choice for individuals with mild Psoriasis; however, for those with moderate to severe Psoriasis and/or with the simultaneous presence of Arthritic Psoriasis, systemic treatment is also indicated [52]. The topical treatment generally is composed of corticosteroids, vitamin D analogs, calcineurin inhibitors, and keratolytics, not imposing

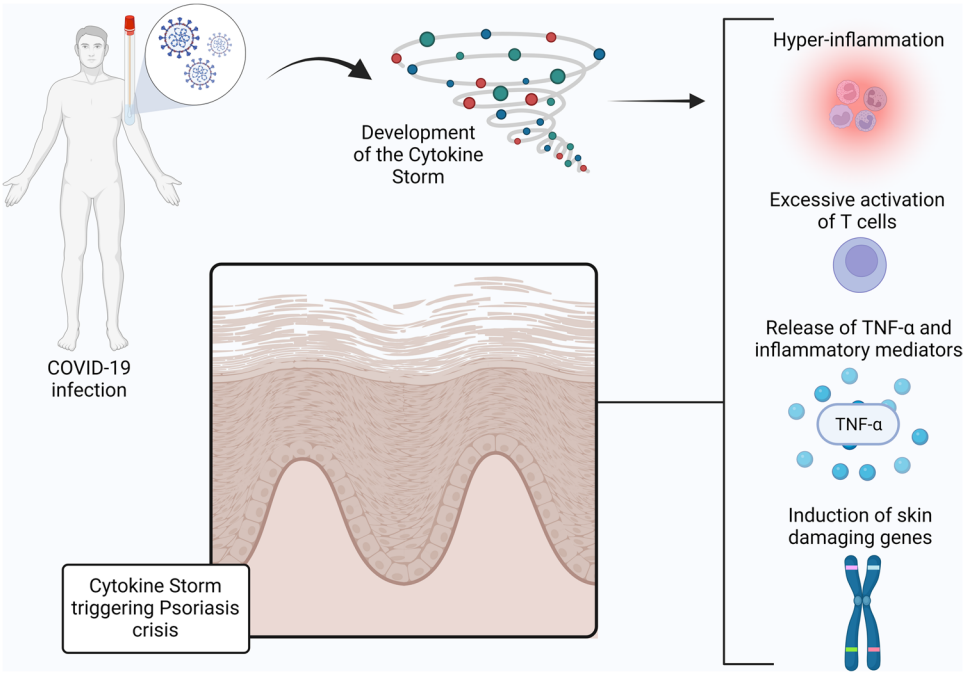

Fig. 1 The association between the COVID-19-triggered Cytokine Storm and the development of the Psoriasis crisis. Multiple individuals infected by COVID-19 presented the development of a Cytokine Storm, triggering numerous immune responses and a hyperinflammatory state capable of inducing a Psoriasis crisis. Moreover, this condition causes excessive activation of T cells; the liberation of more inflammatory mediators, such as the ones involved in the TNF-α cascade; and the induction of genes related to skin damage. All these altered immune and genetic mechanisms are active in Psoriasis; therefore, these features can induce the Psoriasis crisis

a significative impact in systemic alteration, except for the prolonged use of corticosteroids, which can generate adverse effects [52].

On the other hand, systemic therapy with biologics or oral drugs targets the alteration of immune responses, therefore being discouraged by multiple dermatology societies during the COVID-19 pandemic [39]. The current biologics prescripts approved by the FDA for the treatment of Psoriasis are the anti-TNF-α, anti-IL-17, anti-IL-12/23, and anti-IL-23 [52, 53]. With the emergence of SARS-CoV-2, different studies suggested a protective or dangerous effect when maintaining or introducing these therapies for patients infected by the virus, with no conclusive evidence related to the effects of biologics for patients with COVID-19 [39].

Concerning oral systemic therapy, immunomodulators such as Methotrexate, Acitretin, Apremilast, and Cyclosporine are medications approved by the FDA for Psoriasis [52, 53] (Table 1). In the COVID-19 pandemic scenario, these medications also had to be reevaluated for infected patients, with Methotrexate and Cyclosporine being associated with an increased risk of infection and Cyclosporine linked with a slightly increased risk for pneumonia contraction [39]. Moreover, some of the main side effects of Cyclosporine are related to hypertension and renal dysfunction, leading patients to an elevated vulnerability to SARS-CoV-2 [39].

However, Acitretin apparently presented anti-inflammatory effects for infected patients without increasing the risk of a respiratory infection, since it does not present immunosuppressive effects [39]. Therefore, despite the few studies related to the use of this drug for Psoriasis during COVID-19 infection, it shows promising results.

Nonetheless, due to the lack of evidence regarding the effects of systemic medications on patients with the Coronavirus, their administration was initially discouraged as well [39]. Moreover, health professionals were also advised to share the available options of treatments and their risks with patients for a common decision and also to evaluate the individual condition of each patient [39]. Thus, the lack of research and the absence of a proper guideline for these circumstances might lead to doubts and insecurities in the prescription of these drugs in infected patients.

Table 1 FDA-approved oral systemic drugs currently used in the treatment of Psoriasis

Drug	Mechanism	Activity	Safety in COVID-19 infected
Methotrexate	Dihydrofolate reductase inhibitor	Immunosuppressant	Unknown
Apremilast	Phosphodiesterase-4 inhibitor	Immunosuppressant	Unknown
Acitretin	Retinoid	Anti-inflammatory	Unknown
Cyclosporine	Calcineurin inhibitor	Immunosuppressant	Unknown

Considering the uncertainty present in the sphere of the currently used drugs for patients with simultaneous Psoriasis and COVID-19, there is a need for consideration of other types of drugs and therapies that do not offer harm or doubts in the context of infection. In this sense, numerous studies have indicated the benefits of controlling the Cytokine Storm in patients infected by SARS-CoV-2 [10]. Along with that, considering that this pathway might also be responsible for the Psoriasis crisis in infected patients, drugs used for the modulation of this condition could present double benefits, when controlling the Cytokine Storm and at the same time treating Psoriasis, offering great potential.

Purinergic modulation in the control of the Cytokine Storm and treatment of Psoriasis

In virtue of the need for precise drugs against Psoriasis triggered by COVID-19 in infected patients, that do not prejudice the organism in relation to the infection, new strategies deserve attention, such as the control of the Cytokine Storm. In this sense, as mentioned, the Cytokine Storm is capable of inducing the development of Psoriasis and, at the same time, causing severe consequences to the human body related to the viral infection and due to the excessive inflammatory response generated [4, 6, 10]. Thus, targeting the control of this pathway against Psoriasis and SARS-CoV-2 simultaneously would offer multiple benefits to infected individuals.

Considering that, a few drugs have been analyzed to reduce the Cytokine Storm and the T cell immune response. Among them, treatments with specific cytokine inhibitors have been suggested, focusing on the administration of corticosteroids, cyclosporine, or etoposide [54]. The drugs evaluated were already effective for other Cytokine Storms caused by different diseases and presented a cytokine or chemokine as an inhibition target [54, 55]. Moreover, inhibitors of pathways responsible for cytokine release were also analyzed as a therapy against the Cytokine Storm. In this regard, inhibitors of the JAK pathway presented positive results, reducing ICU hospitalizations and mortality [54, 56].

In addition to that, other possible anti-inflammatory treatments were considered against the Cytokine Storm. Concerning that, glucocorticoids present an immunosuppressive effect and reduce inflammatory condition, hence were evaluated [54]. Currently, these drugs are considered for the therapy of Cytokine Storms; however, the moment of administration and the patients' conditions can influence its effects [57, 58]. Additionally to glucocorticoids, chemotherapeutics are currently considered for the treatment of cytokine storms, as well [58]. However, there still is a lack of a safe protocol for the treatment of this condition with less toxic drugs [58]; thus, other compounds must be analyzed to combat the Cytokine Storm and potentially reduce the exacerbation of COVID-19-triggered Psoriasis.

In light of that, the Purinergic System has been studied as a possible way to control the Cytokine Storm and Psoriasis. This system is composed of a range of receptors present in multiple cells and tissues of the organism, located in different regions and systems—such as the central nervous system and cardiovascular system for example—and capable of influencing several physiological and pathological processes [12]. Furthermore, these receptors are divided into P1 and P2 families and are activated by extracellular nucleotides, such as adenosine triphosphate (ATP) and its derivatives [12]. During conditions that impose cell damage, such as inflammations, hypoxia, apoptosis, necrosis, and further pathological conditions, ATP is released, serving as a damage-associated molecular pattern (DAMP), leading to the activation of purinoreceptors [59, 60].

The purinergic receptors activated in pathological spheres are capable of mediating many immune responses enrolled in conditions such as neurodegenerations, carcinogenesis, and autoimmune diseases, also acting in systemic hyperinflammation, as seen in the COVID-19 Cytokine Storm [14, 61, 62]. In this regard, the main purinoreceptor enrolled in the development of inflammatory responses is the P2X7, present in multiple immune cells and responsible for the release of most pro-inflammatory cytokines [12]. Moreover, this receptor is also responsible for the activation of the NLRP3 inflammasome, another immune structure related to the installation of intense inflammation and already linked to chronic inflammatory dysfunctions [63].

Once the P2X7 receptor (P2X7R) and the inflammasome are activated, they induce the liberation of the mediators IL-1, IL-2, IL-6, IL-18, IL-1β, IL-1α, and TNF-α, leading to the hyperinflammatory state present in the Cytokine Storm [12]. It is important to highlight that the P2X7R is present in the keratinized epithelium, therefore being able to induce inflammation directly from the site of formation of Psoriasis plaques as well [59]. Hence, this purinergic-mediated immune imbalance and inflammation can generate the full phenomena seen in the Cytokine Storm [14].

Moreover, the association between purinergic signaling and Psoriasis has already been a significant theme for scientific research. According to studies, the inflammasome has a vital role in the development of Psoriasis [63]. Its activity in the blood of Psoriasis patients is significantly superior, indicating the relevance of systemic inflammation in the development of this condition, along with the importance of purinergic signaling influence in the exacerbation of the disease [63]. Furthermore, apparently adenosine (Ado) availability is associated with the proliferation of keratinocytes, suggesting that Ado and ATP balance can also affect the main cellular structures enrolled in Psoriasis development [64].

Furthermore, studies have also reported an upregulation of P2X7 activities in lesions of Psoriasis patients and

healthy skin of chronic Psoriasis patients previously to the disease exacerbation, indicating a clear association between its activities and the worsening of patients' conditions [63, 65, 66]. Along with that, research suggests that when stimulated by ATP, P2X7 activity is able to induce intense proinflammatory activity, specifically in the skin tissue as well [67]. Additionally, when mediating the development of this inflammatory state, the receptor is also responsible for inducing the activity of Th17 cells, which are enrolled in the development of cutaneous inflammatory response [67]. Finally, studies also suggest that these receptors are upregulated in the presence of certain inflammatory cytokines, hence exacerbating Psoriasis when already under inflammatory states [59]. Considering that the same purinergic apparatus mobilized by Psoriasis can be stimulated by infections and inflammatory conditions, such as COVID-19, the modulation of this signaling becomes of scientific interest.

In addition to that, studies suggest that the hydrolysis of ATP into Ado can reduce P2X7R activities and induce the activities of the P1 family of receptors in Psoriasis patients [68]. These receptors tend to act through anti-inflammatory pathways, reducing the intense immune response present in this disorder and positively affecting Psoriasis patients [68]. Regarding that, A3A receptors (A3AR) are the central P1 receptors enrolled in purinergic anti-inflammatory responses for Psoriasis patients, with their agonists already going under clinical trials for serving as a therapy in this condition [68].

Hence, purinergic influence in Psoriasis exacerbation and development is already known, with P1 receptors being previously explored by scientists for their anti-inflammatory effects. However, the relevance of promoting ATP hydrolysis and inhibiting P2X7R activities, especially in COVID-19 infected, must receive further attention, since it can promote both benefits in the response to the infection and to the reduction of Psoriasis manifestations.

In this sense, aiming at avoiding the Cytokine Storm through the modulation of purinergic activities, numerous studies have been developed. Initially, Di Virgilio and team (2020) have indicated the need to study P2X7R antagonists to reduce inflammation and ameliorate the Cytokine Storm conditions in COVID-19-infected patients [69]. Along with that, Simões and collaborators (2021) have also suggested the negative modulation of this receptor as a treatment for the Cytokine Storm, indicating once again the inflammatory role of P2X7R and its actions in the immune imbalance [13].

Corroborating these theories, Whitehead et al. (2022) developed tests with mice, demonstrating that the negative modulation of P2X7R and its gene deletion can reduce inflammatory processes in infections in animal models [70]. Also, according to studies, the blockage of P2X7R is capable of not only reducing pro-inflammatory activities but inducing anti-inflammatory actions as well, such as the induction of Treg cells [14]. Moreover, in mice models exposed to toxic compounds, the deactivation of this receptor has shown results in diminishing inflammation and fibrosis, demonstrating a potential better prognosis in inflammatory scenarios with blocked P2X7R [69, 71, 72]. In addition to that, the blockage of P2X7 has also demonstrated effects over skin cells, such as melanocytes, reducing their ATP-mediated production of melanin, thus indicating the influence of the receptor in the epidermis cells [73]. Therefore, the blockage of this receptor can be explored as a pharmacological target in SARS-CoV-2 and Psoriasis context, influencing systemic and local responses.

Considering the extensive data indicating the promising actions of P2X7R modulation, different drugs are being analyzed with this objective (Fig. 2). Initially, researchers have indicated the actions of Lidocaine—frequently used for regional anesthesia and nerve blocks—as a partial antagonist of P2X7R in the COVID-19 scenario, with clinical trials being developed to evaluate the activity of this drug in the Cytokine Storm [74, 75]. According to a study with an infected cell line, the use of this drug in combination with dexamethasone modulates the release of TNFα and IL-1β, NF-κB pathway, and inflammasome activation, stimulating anti-inflammatory activity and reducing the severity of the immune response to the virus [76].

Moreover, Colchicine—usually used for treating Gout—has also been analyzed as a possible drug for the control of the Cytokine Storm [12, 77]. This drug, already used in other chronic inflammatory conditions, might be capable of blocking P2X7R activities avoiding chemotaxis and intense inflammatory responses [12]. However, there are few studies presenting the effects of the drug in COVID-19 infection; hence, a recently published systematic review has suggested that this drug still must not be used for SARS-CoV-2 patients, due to the lack of definitive data regarding its positive effects [78]. Nevertheless, the same study suggests that the drug can reduce all-cause mortality and hospitalization, demonstrating Colchicine's potential [78].

Furthermore, studies with AZD-9056, a P2X7R antagonist, have promoted interesting hypotheses. Firstly, analyzed against Rheumatoid Arthritis, this drug did not present promising results via oral administration [79]. However, studies evaluating the potential of the drug, also via oral administration, but in Crohn's disease found significant improvement in the conditions of patients under the intervention [80]. Hence, it was hypothesized that the differences between the tissues affected, with Crohn's disease injuring oral and gastrointestinal mucosa and the presence of mucosa-associated lymphoid tissue in the region, would allow a better spreading of the drug and local action [14]. Therefore, these patients presented lower C-reactive protein levels and a decrease in disease activity when compared to individuals who received a placebo,

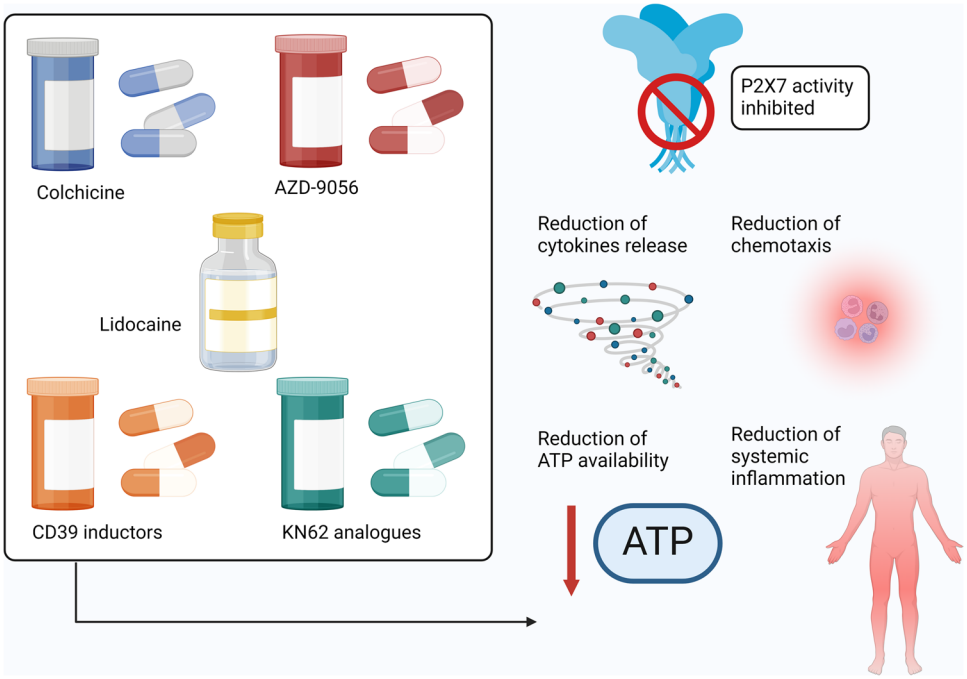

Fig. 2 Promising purinergic modulators in the control of COVID-19 triggered Psoriasis. The main drugs to be studied against Psoriasis crisis in SARS-CoV-2 infected are Colchicine, Lidocaine, AZD-9056, CD39 inductors, and KN62 analogs. These drugs act by inhibiting P2X7R activities, avoiding ATP availability, excessive cytokines release and the Cytokine Storm, chemotaxis of immune cells, and systemic inflammation. All these P2X7-mediated conditions contribute to Psoriasis exacerbation on SARS-CoV-2 infected; hence, their modulation would be beneficial

indicating an anti-inflammatory effect of P2X7R blockage for Crohn's disease patients [80]. In addition to that, as previously mentioned, this substance has influenced skin cells in studies in vitro [73], therefore corroborating the idea of local effect administration. Thus, P2X7R antagonism presents important results in hyperinflammatory states; nonetheless, the choice of administration via of the drug must be carefully evaluated.

Along with that, other molecules have been suggested as P2X7R antagonists and presented positive impacts in inflammatory conditions. Concerning that, analogues of KN62 have been suggested as possible molecules to act blocking P2X7R activities and have presented anti-inflammatory effects, reducing cytokine and chemokine release, in the Cytokine Storm triggered by dengue virus [81, 82]. Additionally, the stimulation of the CD39 enzyme has presented positive effects in inflammatory diseases as well [83]. CD39 is an ectonucleotidase that acts by hydrolyzing ATP into Ado and its derivatives; hence, it can reduce the activity of P2X7R by diminishing the availability of ATP [83]. In mice, the induction of this enzyme reduced septic manifestations, indicating an anti-inflammatory effect in the blockage of P2X7 activity and in CD39 manifestations [83].

Therefore, the control of the P2X7R activity can reduce inflammatory and immune activity in several diseases. Considering the enrollment of this receptor in the installation of a pro-inflammatory environment and in the recruitment of immune cells, the blockage of such structure can contribute both for the reduction of the Cytokine Storm and for diminishing the impacts of this imbalance in Psoriasis.

Future perspectives

Considering the analysis developed so far, the Purinergic System represents a potential target against the Cytokine Storm and, consequently, the Psoriasis crisis. In this sense, different drugs have been evaluated to avoid the immune dysfunction and skin condition of these patients. Initially, considering that Psoriasis already has a therapeutic guideline for non-infected patients, exploring the known drugs is relevant. In this sense, Acitretin has demonstrated safe and effective results until this date; therefore, this drug must be studied to corroborate the present theories related to its security.

In the context of immunomodulation by purinergic activity, considering the role of purinergic receptors in both autoimmune chronic conditions, such as Psoriasis, and the Cytokine Storm, the P2X7R antagonism could offer an amelioration of the two conditions, presenting a possible improvement of the full prognosis of these patients. Moreover, it could also serve as a basis for new possibilities of therapies for non-infected patients with Psoriasis as well since it is based on the reduction of hyperinflammation, the main problem for this group.

Taking that into consideration, both Lidocaine and Colchicine might present relevant results in the Psoriasis triggered by SARS-CoV-2, presenting promising results in the Cytokine Storm and, therefore, reducing the induction of skin damage. Finally, the studies with AZD-9056 have also offered new perspectives related to the modulation of P2X7R in different regions. Considering that the main issue in the tests with this drug was the delivery of the

compound to the site of immune imbalance, and that in the Psoriasis crisis, one of the main manifestations is the formation of plaques, it could potentially serve as a topic drug on skin lesions.

Hence, the evaluation of drugs currently used in the treatment of Psoriasis, along with the analysis of drugs capable of antagonizing P2X7R and reducing the Cytokine Storm, must be developed to improve the management of patients with Psoriasis infected by COVID-19. Furthermore, new discoveries could be useful in non-infected patients as well or have synergic effects, improving the already chosen therapies.

Conclusion

The infection by SARS-CoV-2 is capable of inducing exacerbated immune responses, similar to those present in Psoriasis and capable of triggering Psoriasis crisis. Along with that, the Purinergic System mediates this immunologic response, especially by the activity of P2X7R. Considering that the main therapies suggested for Psoriasis have not been evaluated for COVID-19-infected patients, it is important to analyze its safety for infected and to explore new drugs capable of improving the skin conditions of these patients. Along with that, the development of drugs capable of interfering in the Cytokine Storm cascade induced by purinergic signaling could potentially ameliorate the systemic and dermatological conditions of these patients by reducing hyperinflammation stimulated by the virus.

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Data availability All data is available online.

Declarations

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