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Use of Immunosuppressants in the Treatment of Chronic Dermatological Diseases

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A B S T R A C T

Introduction: Chronic dermatological diseases represent significant challenges for patients and physicians due to their inflammatory and recurrent nature. Treatment of these conditions often requires the use of immunosuppressants, which act by modulating the immune response to reduce inflammation and control symptoms. However, their prolonged use may be associated with adverse effects, requiring strict monitoring to ensure the safety and efficacy of the treatment.

Methodology: To understand the efficacy of immunosuppressants in the treatment of these diseases, a literature review was performed, analysing scientific articles, medical guidelines and clinical studies published in databases such as PubMed, SciELO and Embase. The mechanisms of action of the main immunosuppressants were evaluated, in addition to the clinical impacts and recommendations for the safe management of patients.

Results: Studies indicate that immunosuppressants provide significant improvement in dermatological symptoms, reducing skin inflammation and preventing systemic complications. However, the results also point to adverse effects, such as opportunistic infections, liver toxicity and increased risk of neoplasia, especially in patients requiring prolonged immunosuppressive therapies. In addition, new therapeutic approaches, such as JAK and monoclonal antibodies, present greater specificity in modulating the immune response and a lower incidence of serious side effects.

Discussion: The use of immunosuppressants in the treatment of chronic dermatological diseases is essential for controlling inflammation and improving the quality of life of patients. However, the literature reinforces the need for careful monitoring, with periodic exams to assess the liver, kidney and hematologic function of patients undergoing treatment. In addition, the evolution of medical research has led to the development of safer and more effective therapies, allowing a more personalised approach adapted to the individual characteristics of each patient.

Conclusion: Treatment with immunosuppressants remains a fundamental strategy for the management of chronic dermatological diseases, ensuring greater control of symptoms and reducing the negative impacts of these conditions on the lives of patients. However, the challenges related to adverse effects require rigorous medical monitoring and the search for safer therapeutic alternatives. Continuous research in the area of immunomodulation has been essential to improve treatment options, allowing advances in the personalisation of therapies and patient safety.

KEYWORDS: Immunosuppressants, Psoriasis, Severe Atopic Dermatitis, Systemic Lupus Erythematosus, Pyoderma Gangrenosum.

Introduction

Immunosuppressants (IS) play a key role in the treatment of chronic dermatological diseases (CDD), especially those of autoimmune and inflammatory origin, such as psoriasis (Ps), systemic lupus erythematosus (SLE), severe atopic dermatitis (SAD), and pyoderma gangrenosum (PG). These medications act by reducing the body's exacerbated immune response, preventing skin damage, and improving patients' quality of life (QoL) (Franceschi, Darrigade, Sanchez-Pena, Legrain-Lifermann, & Milpied, 2022).

The mechanism of action of IS may vary depending on the type of medication used. T-cell activation inhibitors, such as cyclosporine (CsA)

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and tacrolimus, block the enzyme calcineurin, preventing the activation of T lymphocytes and reducing the release of inflammatory cytokines, such as interleukin-2 (IL-2). This results in a reduced inflammatory response and relief of dermatological symptoms (Barry, AlRajhi, & Aljerian, 2022).

Another important group is cytotoxic agents, such as azathioprine (AZA) and cyclophosphamide (CTX), which interfere with cell replication by inhibiting the synthesis of DNA and RNA in immune cells. In this way, they reduce the activity of the immune system, preventing tissue destruction in autoimmune diseases. Methotrexate (MTX), an antimetabolite, acts by inhibiting the enzyme dihydrofolate reductase, essential for nucleotide synthesis, preventing cell proliferation and controlling inflammation (Montagnon et al., 2020).

Systemic corticosteroids, such as prednisone and methylprednisolone, are also widely used in the management of CDD. Its potent anti-inflammatory and immunosuppressive action occurs through the inhibition of the production of inflammatory cytokines and the blocking of the expression of the Major Histocompatibility Complex (MHC-II), reducing immune activation (Ravi, Trinidad, Spaccarelli, & Kaffenberger, 2022).

In addition to traditional IS, monoclonal antibodies (mAb) emerge as an innovative and highly specific alternative. Drugs such as tumour necrosis factor (TNF) inhibitors and interleukins IL-17 and IL-23 block proteins involved in inflammation, providing a more targeted and effective treatment (Kridin, Damiani, & Cohen, 2021).

The use of IS has been essential for the control of CDD, providing significant improvement in symptoms, reduction of inflammation and prevention of complications. However, its prolonged use requires strict monitoring, as it can increase the risk of opportunistic infections, liver toxicity and haematological alterations (Ergun, 2021).

In recent years, new immunomodulatory therapies, including Janus Kinase (JAK) inhibitors, have been developed to offer safer and more effective alternatives. These advances enable more personalised treatment, ensuring greater safety and better QoL for patients (Maverakis et al., 2020).

CsA, for example, is widely used in the management of severe Ps and atopic dermatitis resistant to conventional treatments. Its immunomodulatory effect reduces skin inflammation, providing symptom relief and improving skin appearance. AZA, on the other hand, is frequently prescribed for diseases such as SLE and PG, due to its ability to inhibit the proliferation of immune cells involved in the inflammatory response (Orfaly, Reese, Friedman, Latour, & Ortega-Loayza, 2022).

Despite the benefits, prolonged use of IS requires strict monitoring, as it may increase the risk of infections, skin neoplasias, and systemic adverse effects. Patients using these medications should have regular dermatological follow-up to avoid complications and adjust therapy as necessary (Xu et al., 2020).

In addition, studies indicate that immunosuppressed individuals are more predisposed to skin infections, such as cellulitis, erysipelas, and boils, due to the reduced ability of the immune system to fight infectious agents. Therefore, preventive measures, such as adequate sun protection and skin care, are essential to minimise risks and ensure safe and effective treatment (Alexander et al., 2020).

Advances in research on IS have allowed the development of new immunomodulatory therapies, such as JAKs, which offer promising alternatives for the control of CDD. These new approaches seek to balance treatment efficacy with the reduction of adverse effects, providing greater safety for patients (Seegräber et al., 2020).

Studies indicate that Ps is one of the most commonly treated dermatological diseases with IS, affecting approximately 2% to 3% of the world population. The need to control chronic inflammation and exacerbated immune response means that medications such as CsA, MTX, and AZA are widely prescribed for patients with severe forms of the disease (Wollenberg et al., 2022).

In addition to Ps, other autoimmune and inflammatory conditions, such as cutaneous lupus and PG, also have a high prevalence of IS use. CDD, for example, affects approximately 10% to 20% of children and 2% to 5% of adults, and refractory cases often require IS to control symptoms (Kage, Zarnowski, Simon, & Treudler, 2020).

Despite the therapeutic benefits, prolonged use of these medications requires strict monitoring, as it can increase the risk of skin infections, neoplasia, and systemic adverse effects. Immunosuppressed patients are more predisposed to bacterial and fungal infections, making regular dermatological monitoring essential (Kage, Zarnowski, Simon, & Treudler, 2020).

The prognosis for the use of IS in the treatment of CDD in the coming years points to significant advances both in Brazil and worldwide. With the development of new immunomodulatory therapies and the increasing adoption of immunobiologicals, an improvement in the efficacy of treatments and a reduction in adverse effects associated with conventional therapies are expected (Suaini, Tan, Loo, & Tham, 2021).

Research on IS has evolved rapidly, with emphasis on interleukin (IL) inhibitors and mAbs, which offer greater specificity in modulating the immune response. Studies indicate that JAKs have shown efficacy in controlling diseases, reducing the need for traditional IS (Wollenberg et al., 2022).

In Brazil, the trend follows the global scenario, with an increase in the prescription of immunobiologicals for CDD. The availability of these medications in the Unified Health System (UHS) has been expanded, allowing more patients to have access to innovative treatments (Orfaly, Reese, Friedman, Latour, & Ortega-Loayza, 2022).

However, challenges persist, such as the high cost of immunobiologicals and the need for rigorous monitoring to avoid complications, such as opportunistic infections. National research has focused on the safety of prolonged use of IS, seeking strategies to minimise adverse effects and improve patients' QoL.

Despite the advances, the use of IS still faces challenges, such as the need for continuous monitoring to avoid systemic complications and the search for alternatives that are less aggressive to the immune system.

Psoriasis

Ps is an immune-mediated inflammatory disease with autoimmune pathogenic features that affects the skin and joints. The worldwide prevalence of Ps is 2–3%, which tends to be lower in some regions of Asia and Africa but higher in Scandinavian populations (Parisi et al., 2013; Gibbs, 1996; Danielsen, Olsen, Wilsgaard, & Furberg, 2013). Known environmental triggers and associations include streptococcal infections, physical trauma (e.g., tattoos, surgical incisions), certain medications (e.g., antidepressants, antihypertensives, anticytokine therapy), smoking, as well as alcohol abuse, respectively (Raychaudhuri, Jiang, & Raychaudhuri 2008; Abel et al., 1986; Perera, Di Meglio, & Nestle, 2012). Ps is characterised by excessive proliferation and aberrant differentiation of keratinocytes, resulting clinically in erythematous scaly plaques of variable sizes. Ps was initially considered a variant of leprosy until 1841, when von Hebra (Schön, & Boehncke, 2005) identified it as a separate disease entity. Patients with Ps typically present with demarcated chronic erythematous plaques covered by silvery-white scales mainly on the knees, elbows, scalp, umbilicus, and lower back (Owen, Chalmers, O'Sullivan, & Griffiths, 2000). The disease is frequently associated with psoriatic arthritis, metabolic syndrome, cardiovascular problems, diabetes mellitus, and other comorbidities. Patients with Ps are at increased risk for chronic inflammatory bowel disease and chronic renal disorders. In addition, the prevalence of depression, anxiety, and suicide has increased (Nestle, Kaplan, & Barker, 2009). Taken together, different factors contribute to the development of Ps, causing adverse effects on patients' QoL and disease burden.

Ps is a complex genetic disease that is triggered by multiple risk factors involving a variety of processes, such as inflammation, antigen presentation, cell signalling, and transcriptional regulation (Muhr, Zeitvogel, Heitland, Werfel, & Wittmann, 2011). The hallmark of Ps is sustained inflammation that leads to uncontrolled keratinocyte proliferation and dysfunctional differentiation. Ps plaque formation is thought to be a combination of inflammation in the epidermal layers resulting from the interaction of keratinocytes with many different cell types in the skin. Histological studies often show dramatic changes in psoriatic skin characterised by deep thickening of the epidermis (acanthosis), hyperkeratosis, and parakeratosis (Tian et al., 2012; Suárez-Fariñas, Li, Fuentes-Duculan, Hayden, Brodmerkel, & Krueger, 2012). There is a genetic predisposition to Ps, and several psoriasis susceptibility loci (PSORs) have been identified and appear to be involved in the pathogenesis of the disease. Among a variety of risk factors that promote the development of Ps, HLA-C*06:02 is a predominant risk gene. T-cell hybridoma studies with a unique T-cell receptor (Vα3S1/Vβ13S1) have demonstrated that T cells detect the ADAMTS-like protein 5, a melanocyte-derived autoantigen, in an HLA-C*06:02-restricted manner

(Arakawa et al., 2015). Several reports have also suggested an important role of the nervous system in the pathogenesis of Ps. The latter appears to be co-responsible for the symmetric distribution of the plaque in the body, and interactions between immunomodulatory networks and peripheral sensory nerves have been described (Ostrowski, Belkadi, Loyd, Diaconu, & Ward, 2011; Farber, Nickoloff, Recht, & Fraki, 1986; Farber, Lanigan, & Boer, 1990). Clinical data also suggest that surgical denervation of psoriatic lesions or local anaesthesia not only decreases local sensitivity but also leads to a reduction in regional inflammation (Farber, Lanigan, & Boer, 1990). In this context, emotional stress may also be linked to the onset and/or exacerbation of Ps (Seville, 1977).

ISs play an essential role in the treatment of Ps, especially in moderate to severe cases that do not respond to topical therapies or phototherapy. These medications act by regulating the body's immune response, reducing the chronic inflammation that characterises the disease (Orfaly, Reese, Friedman, Latour, & Ortega-Loayza, 2022).

Among the main ISs used in the management of Ps, MTX, CsA, and AZA stand out. MTX is widely used due to its effectiveness in reducing skin lesions and improving joint symptoms in patients with psoriatic arthritis. CsA, in turn, blocks the activation of T cells, providing rapid relief of symptoms and reducing inflammation (Xu et al., 2020).

The use of these medications can provide benefits such as reducing skin lesions, improving QoL and controlling psoriatic arthritis. However, treatment with IS requires strict monitoring, as it can increase the risk of opportunistic infections, liver toxicity, and renal alterations (Alexander et al., 2020).

In recent years, immunobiologics have gained prominence as an alternative to traditional IS. These drugs act more specifically, blocking proteins involved in inflammation, such as TNF and interleukins IL-17 and IL-23 (Langan, Irvine, & Weidinger, 2020).

The treatment of Ps should be individualised, considering the severity of the disease, the patient's history, and the response to previous therapies (Seegräber et al., 2020).

Systemic Lupus Erythematosus (SLE)

SLE is a chronic, fluctuating, multisystem autoimmune disease with a variety of clinical presentations. Disease severity ranges from mild arthritis and cutaneous symptoms to severe inflammatory pain and organ damage. Abnormal immune function and the formation of antibodies against "self" antigens underlie its pathogenesis. The reported female-to-male ratio is 10:1 (Hopkinson, 1992), and the peak incidence in women occurs in middle age. Although the aetiology of SLE is still unclear, a possible hormonal role (Da Silva, 1995; Ansar Ahmed, Penhale, & Talal, 1985) has been implicated based on the predominance of the disease in women and the immunomodulatory effects of certain hormones.

AZA, which acts by reducing the proliferation of immune cells involved in the inflammatory process, is among the most widely used IS in the management of SLE. Its effectiveness has been proven in controlling disease activity, especially in patients with renal involvement or severe manifestations. CTX, in turn, is frequently prescribed for cases of lupus nephritis, helping to preserve renal function and minimising the need for long-term dialysis. An alternative is mycophenolate mofetil, which has shown good results in lupus nephropathy, being a less toxic option compared to CTX (Seegräber et al., 2020).

In addition to renal involvement, SLE can affect joints, skin and even the central nervous system, requiring therapeutic approaches adapted to each manifestation. MTX is a widely used IS for the control of joint symptoms, helping to reduce inflammation and improve mobility in patients with lupus arthritis (Langan, Irvine, & Weidinger, 2020).

The mainstay of SLE treatment is IS therapy, which consists primarily of corticosteroids (Kimberly, 1988; Chatham & Kimberly, 2001). Doses during maintenance therapy range from low (≤ 10 mg per day) to moderate (< 100 mg per day). Minipulses of IS of 100 to 200 mg/day for 2 to 5 days are given for rapid control of active disease, and bolus doses of 1000 mg IV for 4 days are given for acute lupus nephritis. Other cytotoxic agents, such as CsA and AZA (Donadio & Glassock, 1993; Abu-Shakra & Shoenfeld, 2001), have become standard adjunctive treatment for the more severe manifestations of SLE. In addition, antimalarial agents such as chloroquine and hydroxychloroquine have demonstrated efficacy in symptomatic relief and in controlling the activity of the underlying disease. Treatment of SLE is currently suboptimal due to the adverse effects of corticosteroid therapy, such as hyperglycemia, hypertension, hyperlipidemia, avascular necrosis, osteoporosis, and muscle atrophy. These side effects have a profound impact on the QoL of patients with lupus (Seegräber et al., 2020). Agents such as dehydroepiandrosterone (DHEA), tamoxifen, bromocriptine, mycophenolic acid (MPA), and 2-chloro-2'-deoxyadenosine (2-CDA) have demonstrated positive therapeutic results in human and/or murine models of SLE and have relatively safe side effect profiles. Combination therapy of IS with relatively safe disease-modifying compounds that are additive or synergistic in their therapeutic effects may provide adequate IS, sparing patients from high-dose steroids and their adverse effects (Alexander et al., 2020).

Severe Atopic Dermatitis (SAD)

Atopic dermatitis (AD) is among the most common skin diseases. Its 1-year prevalence in Germany is at least 7% in children (Zietze et al., 2021) and 4–5% in adults (Zietze et al., 2021). Approximately half of patients suffer intermittently from moderate to severe AD, which often cannot be adequately treated by external methods alone, especially in adults (Kage, Zarnowski, Simon, & Treudler, 2020). The high prevalence, chronic course, and disease burden of AD make it a condition of socioeconomic importance (Kage, Zarnowski, Simon, & Treudler, 2020; Wollenberg et al., 2020). Both intense itching and the accompanying stigmatisation lead to marked comorbidity and psychosocial distress (Kage, Zarnowski, Simon, & Treudler, 2020), so optimal treatment is required, by guidelines (Wollenberg et al., 2020).

AD is among the most common skin diseases. Its annual prevalence is at least 7% in childhood and 4–5% in adulthood.

Skin lesions, often accompanied by intense itching, include infiltrative erythema, erythema with scratch erosions, lichenified areas, and pruritic papules and nodules. The childhood nummular variant resembles nummular eczema in adults (Wollenberg et al., 2022). AD significantly impairs QoL (Ring et al., 2019).

Minimal manifestations include dry lip inflammation (cheilitis sicca), inflammatory fissures at the corners of the mouth (perlèche), infranasal erosion, infraauricular lacerations, retroauricular intertrigo, eczema on the fingertips and toes ("atopic winter feet"), eczema on the nipples, and pityriasis alba (Alexander et al., 2020).

The so-called atopic stigmata are typical, non-pathological skin signs that indicate atopic diathesis. These include dry skin, hyperlinearity of the palms and soles, double infraorbital eyelid crease, periorbital halo formation, facial pallor, thinning of the lateral portion of the eyebrow, and white dermographism (Xu et al., 2020).

AD is a global problem and one of the most common skin diseases, even in low-income countries (Suaini, Tan, Loo, & Tham, 2021). In highly pigmented skin, the characteristic erythema appears grey ("ashy") rather than red as in Caucasians (Schmid-Grendelmeier et al., 2019). Formal catalogues of diagnostic criteria have been incorporated into international guidelines (Wollenberg et al., 2018). Age-related rash in typical locations, pruritus as the main symptom, and a tendency toward IgE-mediated sensitisation and disease in the patient's personal or family history are the main criteria (Wollenberg et al., 2022).

Differential diagnosis includes other skin conditions such as infections (e.g., scabies), other forms of eczema (allergic contact dermatitis, toxic irritant eczema, seborrheic eczema), and, in infants, seborrheic dermatitis.

Skin infections are the most common type of complication of AD. Only a few pathogens are responsible for the lesions. Staphylococcus aureus is the most common pathogen; it causes colonisation and infection (Kong et al., 2012). Severe infections are treated systemically, milder ones with topical antiseptic agents. Continuous long-term prophylaxis with emollients containing antiseptics or topical antibiotics is not recommended (Wollenberg et al., 2022). Antibacterially coated silver textiles are of highly variable quality (Gieler et al., 2017). Colonisation with Malassezia species is important in the head and neck variant of atopic dermatitis; topical antifungal therapy may be considered (Wollenberg et al., 2022; Schmid-Grendelmeier & Crameri, 2006; Alexander et al., 2020; Eyerich et al., 2011).

Disseminated herpes simplex virus infection, known as eczema herpeticum, is a dermatologic emergency. If clinically suspected, this potentially life-threatening condition should be treated promptly with systemically administered acyclovir (Wollenberg, 2012). The risk of developing eczema herpeticum is multiplied in patients with untreated CDD and those with the IgE-associated (extrinsic) subtype (Seegräber et al., 2020). Disseminated coxsackievirus infection (eczema coxsackium) may have a similar course on the skin (Neri et al., 2016). Other viral

dermatoses, such as molluscum contagiosum or common warts (verruca vulgaris), can occur in a widespread form in patients with AD (eczema moluscatum, eczema verrucatum). Pseudomonas aeruginosa infections play only a minor role among the complications of AD.

AD arises in the context of a hereditary predisposition (diathesis) and is precipitated by environmental and lifestyle factors (Langan, Irvine, & Weidinger, 2020). Well-documented associated factors include living in an urban environment and regions with low ultraviolet exposure and dry climate, a "Western" diet, small family size, high educational level, and frequent antibiotic exposure during pregnancy and the first year of life, but the effects of these factors are small (Kage, Zarnowski, Simon, & Treudler, 2020). More than 30 genomic regions show robust associations with AD. They mainly contain genes with known roles in epidermal structure and function, or immunological mechanisms (Kong et al., 2012). Loss-of-function null mutations in the pro-filaggrin (FLG) gene result in a lack of functional filaggrin peptides in the outer epidermis, leading to a complex skin barrier defect. Approximately 10% of the population carries a single FLG mutation and presents with generalised dry skin, palmar hyperlinearity and a threefold increased risk of atopic dermatitis (Gieler et al., 2017). The cytokine gene cluster, in which genetic variants and epigenetic mechanisms influence the expression of the type 2 cytokines IL-4, IL-5 and IL-13, is another risk locus (Alexander et al., 2020; Wollenberg, 2012). Skin barrier dysfunction and predominantly T-cell-mediated cutaneous inflammation are the central molecular and immunological mechanisms of AD (Seegräber et al., 2020).

Skin barrier dysfunction is characterised by reduced skin microbiome diversity and frequent colonisation by Staphylococcus aureus, in addition to dryness, altered lipid composition, and increased epidermal permeability. Pro-inflammatory, skin barrier-destabilising, and pruritogenic mediators are present at higher levels in eczematous lesions. Due to the predominance of type 2 cytokines, this is considered a type 2 inflammation.

Pyoderma Gangrenosum (PG)

PG is an ulcerative inflammatory skin disease classified within the group of neutrophilic dermatoses. It is a rare disease with a prevalence of 5.8 cases per 100,000 adults (Xu et al., 2020; Orfaly, Reese, Friedman, Latour, & Ortega-Loayza, 2022).

PG negatively impacts QoL and carries a mortality risk three times higher than that of the general population (Langan, Groves, Card, & Gulliford, 2012). The classic clinical presentation is very painful skin ulcers with a predilection for the lower extremities in approximately 80% of cases (Orfaly, Reese, Friedman, Latour, & Ortega-Loayza, 2022; Binus, Qureshi, Li, & Winterfield, 2011; Bennett et al., 2000). When the lower extremities are involved, it is particularly important to fully evaluate other causes of skin ulceration. For example, venous and arterial status should be assessed, and frequent evaluation for infection is necessary. In addition, skin biopsy can rule out many other differential diagnoses. However, any hairy skin on the body has the potential to develop PG. Less common presentations, including bullous, verrucous, and pustular variants, have been described (Maverakis et al., 2020). Other ulcerative variants include peristomal PG. In the early acute inflammatory stage of classic PG, patients often present with an erythematous papule or pustule that rapidly develops into a painful skin ulceration or multiple ulcerations with gunmetal-grey borders and violaceous erythema. Once the acute inflammation has subsided, large wounds may also present without classic or distinctive features, making diagnosis even more challenging (Maverakis et al., 2020). The phenomenon of pathergy has been reported in up to 30% of patients with PG and describes the formation of new ulcers after minor trauma (e.g., needlestick injury). This is sometimes a clinical clue to the diagnosis of PG; however, it is not specific for PG and has been described in other patients with autoinflammatory or neutrophilic conditions (Ergun, 2021).

PG remains a diagnostic challenge as it is a rare disease with several clinical mimics. With a misdiagnosis rate of up to 39%, it is considered the prototype for misdiagnosis among other skin ulcerations where the initial diagnosis was PG (Weenig, Davis, Dahl, & Su, 2002). The most common clinical mimics are venous leg ulcers, vasculitis, vasculopathies, and factitious ulcers. Recent efforts by clinical researchers, including experts worldwide, have supported the implementation of diagnostic frameworks to improve this critical issue in clinical practice.

PG is frequently associated with other inflammatory disorders, such as inflammatory bowel disease and rheumatoid arthritis (Kridin, Cohen, & Amber, 2018; Kridin, Damiani, & Cohen, 2021; Sawka, Zhou, Latour, Friedman, & Ortega-Loayza, 2021). It is also important to note that PG does not reflect the clinical course of the underlying disease, and it is not uncommon for patients with PG to have well-controlled diabetes mellitus or vice versa (Sawka, Zhou, Latour, Friedman, & Ortega-Loayza, 2021). Some patients also have underlying hematologic disorders (monoclonal gammopathy of unknown significance) or malignancies (leukaemias or other neoplasms) (Montagnon et al., 2020; Gupta & Ortega-Loayza, 2019). Although these comorbidities are clinical clues in the diagnosis and investigation of PG, they appear to have a more preponderant role in the prognosis and/or selection of an appropriate therapeutic approach (Ravi, Trinidad, Spaccarelli, & Kaffenberger, 2022). In addition to medical treatment to control the associated comorbidity and the inflammation inherent to PG with local pharmacological therapy and/or systemic therapy, wound care and pain control also need to be addressed throughout the treatment.

The occurrence of PG after the use of medications has been repeatedly reported in the literature. Although the underlying pathomechanisms are not clearly known, it must be assumed that a dysregulated inflammatory reaction with disturbed migration and activation of neutrophil granulocytes also occurs as a result of medications in genetically predisposed individuals. Keratinocyte apoptosis and alteration of epigenetic mechanisms may also play a role (Wu, Patel, & Ortega-Loayza, 2017).

A direct assessment of the causal relationship between drug intake and the induction of a PG is not always easy, and reports of drug reintroduction are rare. Most often, these are descriptions of single patients. Many of these patients had an underlying disease, such as (hematological) neoplasia or a chronic inflammatory disease (Wang, French, Shear, Amiri, & Alavi, 2018). Therefore, it is not always possible to say with certainty whether the drug was the trigger for the PG or whether the disease would have occurred even without the drug. Another important aspect is the temporal relationship between the initiation of drug therapy and the occurrence of PG. Very different time frames have been described (Barry, AlRajhi, & Aljerian, 2022; Aggarwal, 2020). For example, if a large proportion of the world population received appropriate vaccines during the COVID-19 pandemic, the temporal context would include patients with PG (Franceschi, Darrigade, Sanchez-Pena, Legrain-Lifermann, & Milpied, 2022). It is then only possible to determine whether clustering has occurred by analysing large patient populations. In the context of rare PG, however, these are exclusively individual case descriptions, which in principle could also be random. However, other immune-mediated clinical diseases have also been found significantly more frequently in association with COVID-19 vaccines, so a connection could certainly exist (Gambichler et al., 2022).

Among the main ISs used in the management of PG, systemic corticosteroids such as prednisone stand out, which are frequently prescribed to reduce inflammation and alleviate symptoms. However, in more severe or refractory cases, additional immunosuppressive agents are indicated, such as CsA, MTX, and AZA, which act by modulating the immune response and preventing tissue destruction (Wollenberg et al., 2022).

CsA has been widely used due to its effectiveness in reducing inflammation and healing ulcers, being an option for patients who do not respond adequately to corticosteroids. MTX, in turn, is indicated for more resistant cases, especially when associated with other autoimmune diseases. AZA can be used as maintenance therapy to prevent disease recurrences (Wollenberg et al., 2022).

Despite the benefits, prolonged use of IS requires strict monitoring, as it can increase the risk of opportunistic infections, liver toxicity, and hematologic changes.

In recent years, new therapeutic approaches, such as immunobiologicals, have been explored for the treatment of PG. These drugs work by blocking specific proteins involved in inflammation, such as TNF and IL, offering safer and more effective alternatives for patients who do not respond to conventional IS.

The management of PG should be individualised, considering the severity of the disease, the patient's history and the response to previous therapies. The integration of different medical specialities, such as dermatology, rheumatology and gastroenterology, is essential to ensure effective treatment and improve the QoL of patients.

Methodology

A literature review was conducted to provide a scientific and clinical context for the topic. Articles published in dermatological journals and medical guidelines were analysed to provide theoretical support. A search was conducted in recognised databases, such as PubMed, SciELO, and Embase, using specific terms such as immunosuppressants, psoriasis, severe atopic dermatitis, systemic lupus erythematosus, and pyoderma gangrenosum. Inclusion and exclusion criteria were applied to ensure that only relevant and up-to-date studies were considered.

The content of the articles was analysed, evaluating the methodology of the studies, the results presented, and the authors' conclusions. The data were organised systematically, allowing the identification of patterns and trends in the use of immunosuppressants. The results were summarised by categorising the information, highlighting aspects such as mechanisms of action, clinical efficacy, adverse effects, and future perspectives. The discussion of the findings was based on the scientific literature. A critical analysis of the limitations of this study was carried out, considering possible methodological biases and gaps in the research.

Results

Scientific literature highlights that ISs have been widely used in the management of diseases such as Ps, CDD, SLE and PG. Studies indicate that these medications are effective in reducing skin inflammation and improving symptoms, providing better QoL for patients.

However, the results also point to risks associated with prolonged use of these drugs. Immunosuppressed patients are more predisposed to skin infections, such as cellulitis and erysipelas, in addition to an increased risk of developing skin neoplasms, especially in individuals exposed to solar radiation.

In addition, recent research has explored new therapeutic alternatives, such as JAKs and mAbs, which offer greater specificity in modulating the immune response and have a lower incidence of serious adverse effects.

The study reinforces the need for rigorous monitoring of patients undergoing IS treatment, ensuring the safety and efficacy of the therapy. The integration of new immunomodulatory approaches and personalised treatment is are promising trend for the future of dermatology.

Discussion

The use of IS in the treatment of CDD has been widely discussed in the medical literature, especially due to its efficacy in controlling inflammation and modulating the immune response. However, challenges related to adverse effects and patient safety require a careful approach to ensure effective and safe treatment (Wollenberg et al., 2022).

The use of IS in the treatment of Ps has been widely discussed in the medical literature due to its efficacy in modulating the inflammatory response and controlling the symptoms of the disease. As it is a chronic autoimmune condition, it is characterised by hyperproliferation of keratinocytes and exacerbated activation of the immune system, especially T cells and inflammatory cytokines, such as TNF-α, IL-17 and IL-23 (Zietze et al., 2021).

ISs act by reducing this dysregulated immune response, providing relief from symptoms and preventing associated complications, such as psoriatic arthritis. To treat this condition, MTX is one of the most widely used agents due to its ability to inhibit DNA synthesis in immune cells, reducing cell proliferation and inflammation. CsA blocks the activation of T lymphocytes, preventing the release of pro-inflammatory cytokines and rapidly improving skin symptoms, as does AZA, which can be used in certain patients who have contraindications to other ISs (Xu et al., 2020).

Its prolonged use requires strict monitoring, as it can lead to significant adverse effects, including liver toxicity, renal dysfunction, hypertension and increased predisposition to opportunistic infections (Maverakis et al., 2020).

In recent years, there have been important advances in the treatment of SAD, including the incorporation of new drugs into the Brazilian public health system, such as oral MTX, as well as immunomodulatory ointments such as tacrolimus and mometasone furoate. These options expand access to effective therapies for patients who cannot use corticosteroids or are resistant to conventional treatments (Ergun, 2021). Systemic IS are indicated for severe cases that do not respond to topical therapies. CsA is often prescribed due to its rapid action in reducing inflammation, providing symptom relief in a few weeks. However, its prolonged use requires strict monitoring due to the risk of adverse effects, such as hypertension and renal dysfunction. MTX, in turn, is an effective alternative for patients who cannot use CsA (Kridin, Damiani, & Cohen, 2021). SLE is a chronic autoimmune disease characterised by widespread inflammation and involvement of multiple organs and systems. The medical literature emphasises that SLE results from an imbalance in the immune response, leading to the production of autoantibodies that attack healthy tissues of the body itself, causing progressive damage (Montagnon et al., 2020).

The disease presents varied clinical manifestations, including fatigue, fever, arthritis, skin lesions, renal impairment, and hematologic changes. The scientific literature highlights that up to 95% of patients with SLE have joint involvement, and many develop lupus nephritis, a serious complication that can lead to renal failure (Sawka, Zhou, Latour, Friedman, & Ortega-Loayza, 2021).

In the management of SLE, IS play a fundamental role in reducing exacerbated immune activity. Medications are widely used to modulate the inflammatory response and minimise organ damage (Gupta & Ortega-Loayza, 2019).

PG is a rare and severe inflammatory dermatosis that is frequently associated with autoimmune diseases, such as inflammatory bowel diseases, rheumatoid arthritis, and hematologic malignancies. The medical literature highlights that PG is a difficult condition to diagnose, as it can be confused with skin infections and other ulcerative diseases. The etiopathogenesis of PG is not yet fully understood, but studies suggest that the disease results from an immune dysfunction, involving a dysregulated inflammatory response mediated by neutrophils. The presence of autoantibodies and proinflammatory cytokines contributes to tissue destruction and ulcer formation 9 Kridin, Cohen, & Amber, 2018).

The treatment of PG is challenging, as there is no standardised protocol for choosing the therapy. Systemic corticosteroids and CsA are often used as first-line treatment due to their ability to reduce inflammation and control lesion progression (Kridin, Damiani, & Cohen, 2021).

Conclusion

The use of IS in the treatment of SAD represents a significant advance in medicine, allowing for the effective control of dermatological diseases. These drugs act by modulating the immune response, reducing inflammation and preventing progressive skin damage, providing an improvement in the QoL of patients. Since they present an effective risk of opportunistic infections, liver toxicity, haematological alterations and skin neoplasias, monitoring treatment becomes essential.

In recent years, new therapeutic approaches, such as JAK and mAb, have been developed to offer safer and more effective alternatives. These innovative therapies seek to reduce the adverse effects of traditional IS and improve the response to treatment.

Therefore, the management of chronic dermatological diseases must be individualised, considering the severity of the condition, the patient's history and the response to previous therapies. The integration of different medical specialities and continuous research is essential to improve therapeutic strategies and ensure greater safety and efficacy in treatment.

Abreviations

AD - Atopic dermatites, **AZA - Azathioprine, CsA - Cyclosporine, CTX - Cyclophosphamide, AT - Atopic Dermatitis, SAD - Severe Atopic Dermatitis, CDD - Chronic Dermatologic Diseases, DHEA - Dehydroepiandrosterone, FLG - Pro-Filaggrin Gene, IL - Interleukins, IS - Immunosuppressants, JAK- Janus-Kinase Inhibitors, SLE- Systemic Lupus Erythematosus, mAb- Monoclonal Antibodies, MHC-II- Major Histocompatibility Complex, MPA - Mycophenolic Acid, MTX- Methotrexate, PG- Pyoderma Gangrenosum, Ps- Psoriasis, PSORs -** several psoriasis susceptibility loci, **QoL - Quality of Life, TNF - Tumor Necrosis Factor Inhibitors, UHS -** Unified Health System, **2-CDA - 2-chloro-2'-deoxyadenosine.**

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