

[https://doi.org/10.24245/rev\\_hematol.v26i1.3](https://doi.org/10.24245/rev_hematol.v26i1.3)

## Graft-versus-host disease: A focus on skin.

### Enfermedad de injerto contra huésped: enfoque en la piel

Zulia Guzmán Martínez,<sup>1,3</sup> Anahí Morales Pedraza,<sup>1,3</sup> Alia Guadalupe Ordoñez Ayala,<sup>1,3</sup> Sonia Chávez Álvarez,<sup>2</sup> Perla R Colunga Pedraza<sup>1</sup>

#### Abstract

**BACKGROUND:** Graft-versus-host disease (GVHD) remains a significant complication of allogeneic hematopoietic stem cell transplantation, with cutaneous manifestations being the most prevalent and early presenting. Both acute and chronic forms of cutaneous GVHD impose substantial morbidity and mortality risks.

**OBJECTIVE:** To provide a comprehensive overview of graft-versus-host disease's pathophysiology, clinical presentation, differential diagnosis, and therapeutic approaches, highlighting its impact on patient outcomes and quality of life.

**METHODOLOGY:** A bibliographic search in PubMed was done using the terms "cutaneous graft versus host disease", "acute cutaneous graft versus host disease", "chronic cutaneous graft versus host disease", "acute GVHD", "chronic GVHD", "diagnosis" and "treatment". The articles were selected based on the most recent published ones, text availability, citation frequency, and relevance.

**RESULTS:** While acute cutaneous GVHD often presents with a characteristic rash, chronic GVHD exhibits a diverse clinical spectrum. Accurate diagnosis can be challenging and frequently necessitates histopathological confirmation. Management requires a multidisciplinary approach, incorporating pharmacological, phototherapeutic, and emerging immunomodulatory interventions. Given the complexity of the disease, personalized treatment plans, regular monitoring, and ongoing research are essential to optimize patient outcomes.

**CONCLUSIONS:** Cutaneous graft-versus-host disease remains a common and challenging complication of allogeneic bone marrow and hematopoietic cell transplantation.

**KEYWORDS:** Graft-versus-host disease; Allogeneic hematopoietic stem cell transplantation; Dermatology.

#### Resumen

**ANTECEDENTES:** La enfermedad de injerto contra huésped (EICH) es una complicación significativa del trasplante alogénico de células madre hematopoyéticas, cuyas manifestaciones cutáneas son las más prevalentes y tempranas. La forma aguda y crónica de la enfermedad implican riesgos sustanciales de morbilidad y mortalidad.

**OBJETIVO:** Proporcionar una descripción general completa de la fisiopatología, manifestación clínica, diagnóstico diferencial y enfoques terapéuticos de la enfermedad de injerto contra huésped, con insistencia en su repercusión en los resultados de los pacientes y la calidad de vida.

**METODOLOGÍA:** Búsqueda bibliográfica en PubMed utilizando los términos "cutaneous graft versus host disease", "acute cutaneous graft versus host disease", "chronic cutaneous graft versus host disease", "acute GVHD", "chronic GVHD", "diagnosis" y "treatment". Los artículos se seleccionaron en función de los publicados más recientemente, la disponibilidad del texto, la frecuencia de citas y la relevancia.

<sup>1</sup> Hematology Service, Hospital Universitario Dr. José Eleuterio González.

<sup>2</sup> Dermatology Service, Hospital Universitario Dr. José Eleuterio González.

<sup>3</sup> Facultad de Medicina. Universidad Autónoma de Nuevo León, Monterrey, Nuevo León, México.

<https://doi.org/0000-0002-9937-439X>

**Received:** April 1st, 2024

**Accepted:** Novembre 29, 2024

#### Correspondence

Perla Rocío Colunga Pedraza  
alrep\_rcp@hotmail.com

**This article must be quoted:** Guzmán-Martínez Z, Morales-Pedraza A, Ordoñez-Ayala AG, Chávez-Álvarez S, Colunga-Pedraza PR. Graft-versus-host disease: A focus on skin. Hematol Mex 2025; 1: 1-14.

**RESULTADOS:** Mientras que la enfermedad de injerto contra huésped aguda suele manifestarse con una erupción característica, la forma crónica exhibe un espectro clínico diverso. El diagnóstico preciso puede ser desafiante y con frecuencia requiere confirmación histopatológica. El tratamiento requiere un enfoque multidisciplinario que incluya intervenciones farmacológicas, fototerapéuticas y nuevas inmunomoduladoras. Debido a la complejidad de la enfermedad, los planes de tratamiento personalizados, la vigilancia regular y la investigación en curso son decisivos para optimizar los resultados de los pacientes.

**CONCLUSIONES:** La enfermedad de injerto contra huésped cutánea sigue siendo una complicación común y desafiante del trasplante alogénico de médula ósea y de células hematopoyéticas.

**PALABRAS CLAVE:** Enfermedad de injerto contra huésped; trasplante alogénico de células madre hematopoyéticas; dermatología.

## INTRODUCTION

Graft-versus-host disease (GVHD) is a significant complication arising from allogeneic bone marrow, the most common cause of GVHD, and hematopoietic cell transplantation (HCT).<sup>1</sup> The skin emerges as the most frequently affected organ, trailed by the oral mucosa, liver, eyes, and gastrointestinal tract; however, any organ or system could be impacted. Also, it confers substantial risk for morbidity, mortality, and diminished quality of life.<sup>2</sup> The condition arises due to the interplay between immunocompetent T cells from the donor and recipient tissues identified as foreign antigens by the donor cells.<sup>3</sup>

Graft-versus-host disease is traditionally divided into two categories: acute and chronic, with symptoms occurring within and after 100 days after HSCT.<sup>4</sup> Recently, a new classification for both has been introduced. Acute GVHD (aGVHD) is categorized in four subcategories: “classic” if it develops within 100 days of HSCT, “persistent” if it continues beyond 100 days, “recurrent” if it resolves but reappears after 100 days, and “late-onset” if appears after 100 days.<sup>5</sup> Chronic GVHD

(cGVHD) is divided into two subcategories: classic disease, characterized by only cGVHD clinical features without any aGVHD features, and overlap disease, including acute and chronic GVHD manifestations.<sup>6</sup>

The incidence of GVHD in patients who received HCT ranges from 40% to 60%.<sup>7</sup> Among these individuals, the incidence of aGVHD ranges from about 30% to 50% of individuals who undergo transplantation, even with implementing GVHD prophylaxis protocols.<sup>8</sup> Regarding cGVHD, it develops in 30% to 70% of individuals undergoing HCT.

GVHD is a systemic condition that can affect the liver, gastrointestinal tract, and skin.<sup>9</sup> The skin is the most frequently affected organ, and thus, it is important to review the cutaneous manifestations.

Determining a differential diagnosis holds great importance since cutaneous GVHD can clinically mimic dermatological and autoimmune disorders.<sup>10</sup> Recognizing and differentiating cutaneous symptoms of both aGVHD and cGVHD

is essential for a correct diagnosis and the proper treatment.

This review focuses specifically on the cutaneous manifestations of GVHD, encompassing both acute and chronic forms. It aims to provide a comprehensive overview of their pathophysiology, clinical presentation, differential diagnosis, and therapeutic approaches, highlighting their impact on patient outcomes and quality of life.

## METHODOLOGY

The search strategy used was a PubMed search using the terms “cutaneous graft *versus* host disease”, “acute cutaneous graft *versus* host disease,” “chronic cutaneous graft *versus* host disease,” “acute GVHD,” “chronic GVHD,” “diagnosis” and “treatment.” The articles were selected based on the most recent published ones, text availability, citation frequency, and relevance.

## RESULTS

### Basic pathophysiology

GVHD results from an interaction between immunocompetent T cells in the donated tissue that recognize the host's cells as foreign and mount an immune response against them.<sup>11</sup>

### *Pathophysiology of cutaneous aGVHD*

In aGVHD, the chain of events begins when donor-derived T-cells, primed by host antigen-presenting cells (APCs), encounter host tissue damaged by the conditioning regimen for HSCT or other recent cytotoxic therapies.<sup>12</sup> Both T cells and innate immune cells, such as neutrophils and monocytes, contribute to inflammation through mechanisms such as ROS production and the release of proinflammatory signals via pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs)

from injured cells.<sup>13</sup> The PAMPs and DAMPs stimulate the activation of host APCs and pro-inflammatory cytokine release, amplifying and differentiating the immune response. Ultimately, the process culminates in activating cellular effector cells (donor-derived CD8+ T cells and natural killer [NK] cells), which target cutaneous structures and induce the apoptosis of epidermal stem cells.<sup>12</sup>

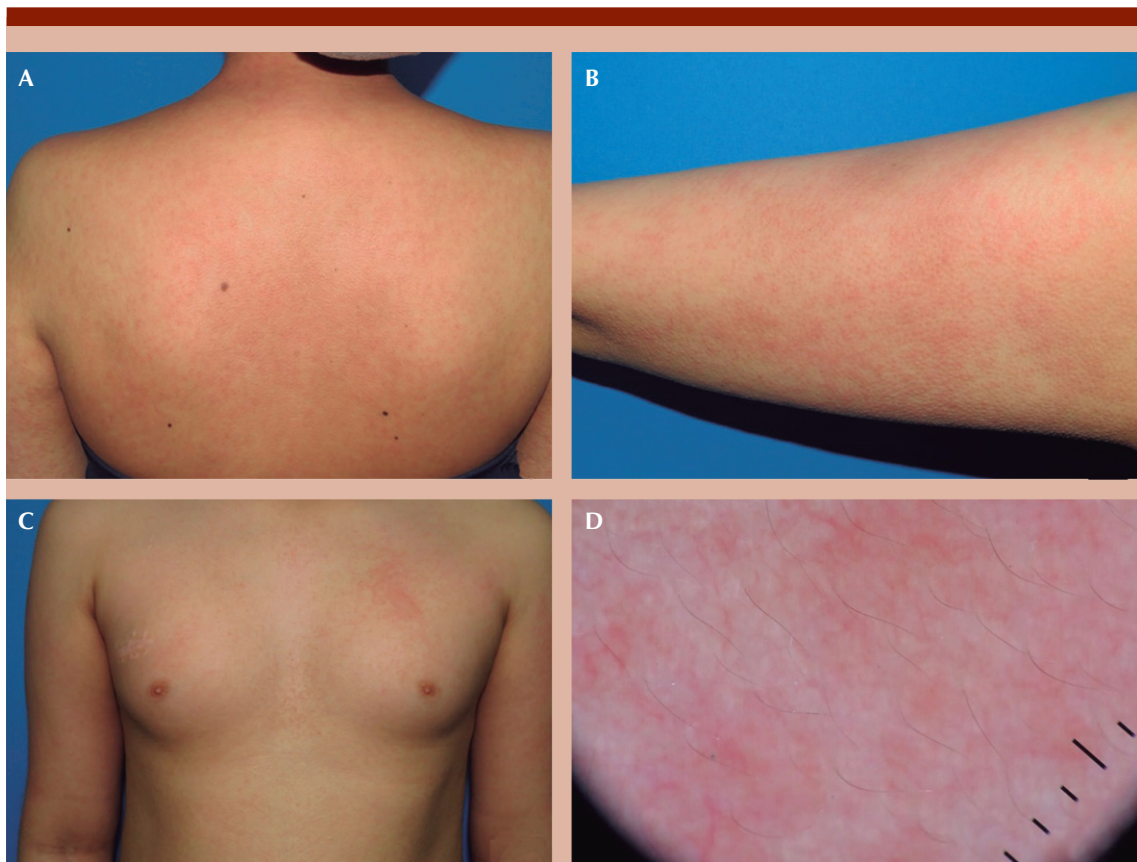
### *Pathophysiology of cutaneous cGVHD*

While the pathophysiology of cGVHD shares some processes of aGVHD, such as the dysregulated alloimmune response of T cells and cytokines release, the overall understanding of cGVHD seems more complex, reflecting its diversity in clinical presentation.<sup>12,14</sup> Understanding the cGVHD pathogenesis requires differentiating the GVHD variants and their main mechanisms, such as inflammation, allo/autoimmune-mediated, and mechanisms resulting in skin fibrosis.<sup>13</sup> Some of the mechanisms involved include the ineffective thymus elimination of autoreactive T cells and the production of both auto-reactive and alloreactive T cells, as well as the dysregulation of B lymphocytes and its secretion of autoantibodies and alloantibodies and involvement of innate immune effectors like macrophages, dendritic cells, and neutrophils.<sup>14,15</sup>

### Cutaneous manifestations

#### *Acute GVHD (aGVHD)*

About 30% to 50% of individuals who undergo transplantation experience aGVHD.<sup>14</sup> Initially, the skin is the most affected organ in GVHD.<sup>13</sup> Symptoms generally emerge within 1-3 weeks post-HTC, with pruritus being the initial manifestation, followed by a pruritic maculopapular rash that begins on the trunk and then spreads throughout the skin. Subsequently, the condition may develop vesicles and bullae or advance to a generalized erythroderma.<sup>16,17,18</sup> **Figure 1**



**Figure 1.** Clinical manifestations of cutaneous aGVHD. **A & B.** Clinical image in a female patient of a diffuse, disseminated macular erythema on the upper back and arm of a patient which corresponds to an acute phase of graft vs host disease. **C & D.** Disseminated dermatosis in a young male patient with a disseminated erythematous macular rash; upon dermoscopic examination, erythema, and telangiectasias can be observed.

Generally, cutaneous aGVHD manifests as a mild erythema resembling sunburn or as a morbilliform eruption that may be difficult to distinguish from a drug-induced rash. However, in severe cases, it presents as generalized erythema, blisters, and erosions, with lesions that may exhibit similarities to Stevens-Johnson syndrome or toxic epidermal necrolysis.<sup>5,13,16,17</sup>

The emergence of bullae or a positive Nikolsky sign signals the initiation of a more advanced stage of the disease, marked by widespread

loss of the outer skin layer. Additionally, various epithelial surfaces, such as the eyes and mucous membranes, may also undergo extensive involvement.<sup>17</sup>

The current aGVHD classification considers the three principal organs affected (skin, liver, gastrointestinal tract) and their manifestations to stage the disease correctly, from stage I to IV. Dermatological lesions are assessed based on the total body surface area (BSA) percentage affected and the degree of blister or cyst formation.<sup>19</sup> **Table 1**

**Table 1.** Clinical staging of acute graft-versus-host disease

| Stage        | Skin   | Liver                      | Gut  |
|--------------|--|----------------------------|--|
| 1            | Less than 25 percent body surface area (BSA) involvement | Bilirubin, 2 to < 3 mg/dL  | Diarrhea, > 500 to 1000 mL/d, nausea and vomiting  |
| 2            | 25 to 50 percent BSA involvement                         | Bilirubin, 3 to < 6 mg/dL  | Diarrhea, > 1000 to 1500 mL/d, nausea and vomiting |
| 3            | Greater than 50 percent BSA involvement                  | Bilirubin, 6 to < 15 mg/dL | Diarrhea, > 1500 mL/d, nausea and vomiting         |
| 4            | Erythroderma with bullae                                 | Bilirubin, > 15 mg/dL      | Severe abdominal pain with or without ileus        |
| <b>Grade</b> |  |                            |  |
| I            | Stage 1-2  |                            |  |
| II           | Stage 3  |                            |  |
| III          | Stage 1-3  |                            |  |
| IV           | Stage 4  |                            |  |

Adapted from Przepiorka et al.<sup>43</sup>**Chronic GVHD (cGVHD)**

Among cGVHD patients, 75% experience cutaneous manifestations, leading to discomfort, restricted mobility, and elevated susceptibility to wound infections, according to Yoo Jung Kim et al.<sup>20</sup>

Cutaneous cGVHD varies widely in its presentation and often mimics autoimmune disorders.<sup>13</sup> Clinical diagnostic features encompass poikiloderma, lichen planus-like lesions, morphea-like-sclerosis, and fasciitis/deep sclerotic features.<sup>17</sup>

Atrophy, pigmentary alterations, and telangiectasias characterize poikilodermatous lesions. It typically impacts the face, lateral neck, and trunk<sup>21</sup> (**Figure 2**). Lesions resembling lichen planus exhibit erythematous-violet lichenoid papules and plaques, appearing early in the disease. These manifestations are primarily observed over the dorsal surfaces of the hands, on the forearms, trunk, and around the eyes.<sup>16,21</sup>

**Figure 2.** Clinical manifestations of cutaneous cGVHD. Diffuse hyperpigmentation in a patient with chronic GVHD.



Sclerotic lesions typically emerge at a later stage in the progression of the disease. According to a study involving 977 transplanted patients (HTC), 20% developed sclerotic lesions corresponding to cGVHD.<sup>2</sup> The disease manifestation varies based on the depth of tissue affected. It may appear as lesions resembling lichen sclerosus, morphea-like plaques, or in a deeper plane resembling eosinophilic fasciitis. Lichen sclerosus-like lesions are more common in the neck and upper to mid-trunk, while morphea-like lesions typically affect the lower trunk. Eosinophilic fasciitis is predominantly observed in the extremities, except for sparing the hands and feet.<sup>22,23</sup>

Alopecia or nail dystrophy may also be consequential outcomes.<sup>16</sup> Nails may show brittleness, splitting, longitudinal ridging, or onychia.<sup>23</sup> The hair shaft may become thinner, coarse, dull, and with premature graying. The alopecia identified in these patients can be sclerotic or non-scarring. Acquired *pili torti* has also been described.<sup>24</sup>

Although it is not common, mucosal involvement may occur, particularly affecting oral and vaginal mucosa. Oral cGVHD presents as erythema, xerostomia, ulcers, and lichenoid lesions that appear as characteristic white reticular plaques. Perioral sclerosis can lead to limited mouth opening, while salivary gland dysfunction results in candidiasis infection.<sup>23</sup> Women can also experience symptoms such as dryness, vulvodynia, pruritus, or dyspareunia, and the physical examination reveals vaginal stenosis and lichen planus-like lesions.

Diagnosis

The skin-related signs of aGVHD lack specificity for diagnostic purposes. The primary considerations for distinguishing a skin rash in post-transplant patients encompass viral exanthem, adverse drug reactions, cutaneous eruptions associated with lymphocyte recovery,

septicemia, and chemotherapy-induced acral erythema.<sup>25</sup> When assessing a patient with a morbilliform rash and history of HSCT, the presence of concurrent liver and GI signs and symptoms, such as elevated bilirubin and liver enzymes, nausea, vomiting, abdominal pain, and diarrhea, provides support for a diagnosis of aGVHD.<sup>26</sup>

There has been debate surrounding the effectiveness of skin biopsy in diagnosing aGVHD.<sup>16,27</sup> Characteristic histopathologic features on aGVHD include interface dermatitis, vacuolar degeneration of the basal layers, dyskeratosis, and a superficial perivascular infiltrate.<sup>27</sup> Similar alterations may occur in the upper regions of eccrine and follicular structures. Distinguishing aGVHD histologically from viral exanthem and the eruption associated with lymphocyte recovery can pose a challenge.<sup>23</sup> **Table 2**

Meanwhile, histological findings of cGVHD mirror the diverse clinical manifestations of the condition. Lichen planus-like lesions manifest as satellitosis and vacuolization of the epidermal basal layer, similar to aGVHD histology. Other lesions like lichen sclerosus-like, morphea-like, and fasciitis features may exhibit thickening, homogenization, and collagen compaction in the papillary dermis, reticular dermis, or fascial tissue, respectively.<sup>23</sup>

In line with the NIH Consensus on Chronic Graft-versus-Host Disease, diagnosing mandates

**Table 2.** Histopathological staging of acute graft-versus-host disease

| Grade | Histopathologic features  |
|-------|---|
| 0     | Normal epidermis  |
| 1     | Focal or diffuse vacuolar alteration of the basal cell layer              |
| 2     | Grade 1 plus dyskeratotic squamous cell in epidermis and/or hair follicle |
| 3     | Grade 2 plus subepidermal vesicle formation                               |

Adapted from Lerner et al.<sup>28</sup>

identifying clinical features or signs indicative of cGVHD. This identification should be supported by biopsy and laboratory or radiologic tests, all conducted within the same organ or another. It is crucial to eliminate potential alternative diagnoses during the diagnostic evaluation. **Table 3**

In the initial stages of the disease, the histopathological characteristics of cGVHD closely resemble those observed in aGVHD. These features include surface-level interface dermatitis lymphocyte infiltration arranged in a lichenoid pattern, with or without the presence of satellitosis. Additionally, a vacuolar change in the basilar layer is evident. In advanced sclerotic disease, dermal fibrosis emerges, accompanied by vacuolar interface alterations.<sup>21,28</sup>

It's worth mentioning that although histopathology is the "gold standard" of diagnosis in skin diseases, the diagnosis of cutaneous GVHD requires further standardization due to its complex presentation.<sup>29</sup>

### Treatment

The management of GVHD requires a collaborative approach involving oncologists, hematologists, and primary care physicians. Before initiating any treatment strategy, it is crucial to assess the diagnosis of GVHD and determine the severity of the disease. It is essential to distinguish classic cGVHD from late aGVHD and overlap syndrome. In instances where the overlap syndrome exhibits predominant characteristics of aGVHD and late aGVHD, treatment should follow the protocol established for aGVHD.

Initially, patients should receive antihistamines, balanced nutrition, and the application of topical emollients for the skin, mucous membranes, and eyes.<sup>15,21</sup>

### Systemic steroid therapy

No other treatments have shown such efficacy as systemic steroids in patients with moderate to

**Table 3.** Differential diagnosis of skin lesions related to hematologic transplant

| Skin lesion                              | Differential diagnosis  |
|--|---|
| <b>Acute graft-versus-host disease</b>   |   |
| Exanthema                                | Drug reactions<br>Viral exanthemas  |
| Bullae and desquamation                  | Stevens-Johnson syndrome<br>Toxic epidermal necrolysis  |
| <b>Chronic graft-versus-host disease</b> |   |
| Lichen planus-like                       | Idiopathic lichen planus<br>Psoriasis<br>Cutaneous lupus erythematosus<br>Drug-induced lichenoid reaction<br>Pityriasis rosea<br>Tinea corporis |
| Superficial sclerosis                    | Chronic radiation dermatitis<br>Morphea<br>Lichen sclerosis   |
| Deep sclerosis/fasciitis-like            | Systemic sclerosis<br>Lipodermatosclerosis<br>Eosinophilic fasciitis  |

Adapted from Canninga-van Dijk et al.<sup>49</sup>

severe cases of aGVHD or cGVHD, establishing them as the first-line therapy in these cases.<sup>15,30</sup>

For severe cases of aGVHD with a grade of 2 or higher, the primary approach involves systemic steroid treatment. Methylprednisolone or an equivalent, starting at 1 mg/kg/day for grade 2 and 2 mg/kg/day for grade 3-4 disease, is recommended as the initial treatment. Once the condition is under control, a rapid tapering of the steroid dosage is advised to minimize potential medication side effects. Reported cases indicate complete remission in 30-60% of patients.<sup>16</sup>

If the aGVHD is unresponsive to 3–14 days of steroid treatment, it is defined as steroid-refractory.<sup>31</sup> The steroid-refractory aGVHD has a poor prognosis, and the central part of patients experience organ failure or infection.<sup>32</sup>

In the management of moderate to severe cGVHD, standard treatment includes prednisone or prednisolone administered at 1 mg/kg/day for 2-4 weeks before initiating the tapering process.<sup>16</sup>

However, it is important to consider that the use of systemic steroids increases the risk of infections.<sup>33</sup> In addition, suppressing the immunologic response may increase the risk of leukemia relapse.<sup>14</sup> Due to the adverse effects associated with long-term use of steroids, steroids-sparing agents and other therapies must be utilized.

### ***Skin-targeted therapy***

#### ***General measures***

Patients with cutaneous GVHD typically experience dehydrated skin; thus, consistent lubrication plays a crucial role in preserving the skin barrier integrity, relieving itchiness and preventing skin cracking.<sup>34,35</sup> Ointments and creams are recommended over lotions due to their longer-lasting hydration effects.<sup>35</sup>

Exposure to sunlight induces a GVHD flare, in addition to the inherent risk of cutaneous malignancies in transplanted patients, making the use of high protection, wide-spectrum sunscreen, and appropriate clothing (long sleeves, broad-brimmed hats) essential.<sup>15,35</sup>

### ***Topical steroids***

The initial treatment approach will consist of a topical steroid for locally restricted forms of grade 1 or 2 cutaneous aGVHD and for cGVHD, particularly in cases with ichthyotic, papulosquamous, lichen planus-like, and lichen sclerosus-like manifestations. They can also offer benefits for focal morphea-like and other forms of sclerotic cGVHD.<sup>13,36</sup>

Topical steroids exert various effects on the skin, such as reducing inflammatory cells in the epidermis, suppressing dendritic cell responses, inhibiting the synthesis of pro-inflammatory factors, and limiting the production and cross-linking of collagen. In certain situations, intralesional steroids may be considered as well.<sup>36</sup>

The selection of a topical steroid, vehicle, and prescribed regimen can vary significantly and depends on each patient's situation. These may be the anatomical region, the skin level affected (epidermis, dermis, subcutaneous), and the anticipated compliance of the patient. As a general guideline, for areas with thinner skin (such as the face, neck, axillae, and groin), it is advisable to use a low-potency topical steroid, such as hydrocortisone 2.5%, fluocinolone 0.01%, or triamcinolone 0.025%. The scalp, however, is an exception to this recommendation, where higher-potency steroids may be employed when necessary. Additionally, steroid solutions or oils can facilitate the application on the scalp.<sup>16</sup>

In the treatment of lichen sclerosis and sclerotic forms of cGVHD, considering higher potency grade 1 (such as clobetasol propionate 0.05%)



or grade 2 (like fluocinonide 0.05%) topical steroids as initial interventions are recommended, especially when dealing with active or progressing lesions. Typically, these topical steroids are applied twice daily. While ointments are more effective, many patients find creams more convenient. In such cases, a cream can be applied daily for practicality with clothing, and an ointment can be used at night for better occlusion. Applying topical steroids under occlusion using plastic wrap can enhance efficacy for focal sclerotic disease.<sup>20</sup>

Caution is crucial, especially in prolonged or high-potency topical steroid application, particularly on large body surface areas or when used under occlusion, as this elevates the risk of local and potentially systemic side effects.<sup>15</sup> Alternative agents, including other topical agents or systemic treatments, should be considered.<sup>36</sup>

### *Immunoregulators*

*Tacrolimus.* The use of topical tacrolimus ointment as a steroid-sparing agent is well-established. It reduces cytokine expression in the skin. Topical tacrolimus has also shown promise in enhancing the appearance and symptoms of sclerotic and non-sclerotic cutaneous GVHD lesions.<sup>37</sup>

Reviewing the literature, three studies were found in which topical tacrolimus ointments were administered to 30 patients experiencing cutaneous cGVHD. The first of them, conducted by Choi and Nghiem, published a case series involving 18 patients with cGVHD treated with 0.1% topical tacrolimus ointment. Thirteen of these patients experienced an improvement in pruritus or erythema within “hours to days” of starting the treatment. However, all patients required additional therapies, such as higher doses of corticosteroids, PUVA, or extracorporeal phototherapy. As a result, the authors concluded that topical tacrolimus should be used as an adjunctive treatment.<sup>38</sup>

Elad et al. reported similar results in a study where seven out of ten patients who received 0.03% - 0.1% tacrolimus ointment two to three times a day showed limited improvement in their skin condition. The evaluator observed improvements in the skin within one day of administering tacrolimus.<sup>39</sup>

Olson et al. reported on a case study involving two individuals with erythematous cutaneous cGVHD who underwent treatment with tacrolimus 0.1% ointment and occlusive dressings twice daily. Both patients exhibited general improvement while receiving oral tacrolimus, systemic corticosteroids, and topical corticosteroids. Nonetheless, the authors observed substantial systemic absorption of tacrolimus, resulting in unpredictable serum levels. This ultimately led to the discontinuation of topical tacrolimus for both patients.<sup>40</sup>

### *Phototherapy*

Two segments of the UV spectrum are recognized as useful in treating cutaneous GVHD: UVA (320-400 nm) and UVB (280-230 nm).<sup>19</sup> Specifically, the UV therapy incorporates the combination of psoralen with UVA (PUVA, wavelength 400-315 nm), UVA-1 (340-400 nm), broadband UVB (BBUVB, 315-280 nm), and narrowband UVB (nbUVB, 311 nm).<sup>41</sup>

The depth of skin absorption is determined by the wavelength of radiation, thus indicating that UVA is preferably for sclerodermatous lesions. At the same time, UVB is better for more superficial lesions as lichenoid changes.<sup>35</sup>

The efficacy of this therapy has been demonstrated in both cutaneous acute and chronic GVHD. It is recommended for patients with extensive skin involvement or when the administration of systemic immunosuppression increases the risk of infections and major complications or potentially disrupts the graft-versus-tumor response.<sup>35</sup>

Although this treatment may be helpful in decreasing corticosteroids and other immunoregulators, it has been linked to a higher risk of skin cancer, such as basal cell carcinoma, squamous cell carcinoma, and melanoma.<sup>42</sup> This is especially relevant in this population because of the immunosuppressive medications they use, which is in itself a risk factor for neoplasias.<sup>19</sup>

The optimal doses or frequency of this treatment have yet to be well established. Ballester-Sanchez et al. reported that the psoriasis treatment protocols can be used as a reference. The initial doses depend on the minimal phototoxic dose, eritematogenic dose, and the phototype. The treatment is then individualized according to the patient's response. According to these authors, compared to other diseases, patients with GVHD require smaller initial doses, a more gradual escalation of doses, and more session frequency; the resolution occurs around the 10th session, and the maximum response appears between the 15th and 30th sessions.<sup>42</sup>

There is also the possibility of using psoralen for UVA phototherapy, but clinicians should be aware of its hepatic metabolism; caution should be taken in patients with hepatic GVHD.<sup>43</sup>

#### *Extracorporeal photopheresis*

Extracorporeal photopheresis (ECP) is also a therapeutic option for the treatment of skin-predominant forms of aGVHD and functions as an alternative for patients with no response to the primary treatment options.<sup>13,14</sup> ECP as a second-line treatment can induce a reaction in more than 80% of the patients and long-term survival in at least 50% in both aGVHD and cGVHD cases.<sup>44</sup> This immunomodulatory process involves separating plasma containing white blood cells, then treating them with 8-MOP and exposing them to UVA light irradiation. The treated blood is then returned to the patient.<sup>14</sup> ECP causes lymphocyte apoptosis, leading to a decrease of

effector T cells, and stimulation of regulatory T cells, triggering the release of immunomodulatory cytokines and inhibiting the production of pro-inflammatory cytokines.<sup>14</sup>

In cGVHD, using ECP can result in a significantly higher proportion of the subject achieving partial or complete response of skin manifestation.<sup>13</sup> Also, this treatment emerges as a first-line treatment for people with steroid-resistant GVHD.<sup>14</sup>

#### *Emerging treatments for cutaneous GVHD*

Recent advancements in therapeutic approaches are emerging for cutaneous GVHD. Janus Kinases (JAK) pathways participate in signaling cytokines involved in the activation and proliferation of several immune cells.<sup>45</sup> The use of JAK inhibitors like ruxolitinib regulates the immune cells relevant for GVHD, such as dendritic cells, macrophages, and B and T cells. In addition to its systemic use as a JAK inhibitor, topical application of ruxolitinib suppresses IFN- $\gamma$  signaling and T-cell infiltration into the skin.<sup>13</sup> These qualities led to the approval of ruxolitinib for treating corticosteroid-refractory aGVHD in adults and children aged 12 years or older.<sup>46</sup> Recent data also indicates favorable responses in heavily pretreated patients with cGVHD.<sup>13</sup> Since ruxolitinib impairs viral-specific T-cell response, it is important to maintain monitoring for viral reactivation.<sup>13</sup>

Regulatory T cells (Tregs) maintain immunological tolerance and moderate excessive immune responses.<sup>47</sup> Tregs induce cytotoxicity by perforin and granzyme secretion, inhibit functions of effector T cells through inhibitory cytokines release, and interfere with DC activation and antigen presentation. Due to their immunosuppressive properties, adoptive transfer of Tregs can be an approach to control GVHD.<sup>47</sup> Patients diagnosed with GVHD treated with Tregs showed improved symptoms and reduced systemic immunosuppression.<sup>13</sup> Furthermore, instead of treating GVHD after it emerges, clinical trials

proved that adoptive transfer of T regs can prevent GVHD.

Mesenchymal stem cells (MSCs) are involved in activating and recruiting immune-tolerant regulatory T cells, suppressing pro-inflammatory immune cells, and secretion of immunosuppressive soluble factors.<sup>48</sup> MSCs can promote tissue healing by migrating to the sites of host tissue and suppressing alloreactive T-cells.<sup>13</sup> Although these are promising approaches, further research is required to refine them. **Table 4**

## CONCLUSIONS

Cutaneous GVHD remains a common and challenging complication of allogeneic bone marrow and hematopoietic cell transplantation (HCT). Both acute and chronic clinical manifestations are prevalent and substantially impact the quality of life for affected individuals. Managing cutaneous GVHD requires a multidisciplinary approach, focusing on individualized treatment strategies, regular monitoring, and addressing the evolving nature of the disease.

**Table 4.** Treatment modalities for cutaneous GVHD (continued on next page)

|   | Indication   | Mechanism of action   | Considerations   |
|---|--|---|--|
| <b>Systemic</b>                                   |  |   |  |
| Systemic steroids                                 | First-line therapy for severe cases of aGVHD and cGVHD   | Reduce inflammatory cells and inhibit synthesis of pro-inflammatory factors                 | After the initial response, the steroid dosage should be tapered promptly to minimize side effects. Patients who do not respond to steroids have poorer outcomes, and alternative therapies must be considered |
| <b>Topical</b>                                    |  |   |  |
| Emollients and lubricants                         | Restores the skin barrier and mucous membranes   | Decreases transepidermal water loss and provide hydration                                   | Every patient should receive emollients  |
| Sunscreen   | Prevent GVHD flares and protect against UV exposure.   | Mineral components that reflect UV rays, or chemical blockers that absorb them.             | Should be accompanied by physical protection as appropriate clothing   |
| Topical steroids                                  | Initial treatment for localized forms of grade 1/2 aGVHD and specific cases of cGVHD               | Reduces inflammatory cells and inhibits the synthesis of pro-inflammatory factors           | The choice of steroid potency depends on the skin thickness. Topical steroids are not free from side effects and must be used with caution   |
| Topical calcineurin inhibitors (e.g., tacrolimus) | Steroid-sparing agent  | Reduces cytokine expression   | Should be used as an adjunctive therapy, not as monotherapy  |
| Phototherapy                                      | Extensive skin involvement or refractory cases of aGVHD and cGVHD. Side effects of other therapies | Reduces inflammation and decreases skin sclerosis mediating depleting APCs in the skin      | Treatment must be individualized. UVA is preferable for deeper lesions, while UVB is better for superficial lesions  |
| Extracorporeal photopheresis                      | Alternative treatment for patients who do not respond to traditional treatment                     | Reduces inflammatory cells and cytokines after treating patient's plasma with 8-MOP and UVA | Treatment must be individualized   |

**Table 4.** Treatment modalities for cutaneous GVHD (continuation)

|                                  | Indication                 | Mechanism of action  | Considerations                                  |
|----------------------------------|----------------------------|--|---|
| <b>Emerging</b>                  |                            |  |   |
| JAK inhibitor (e.g. ruxolitinib) | Refractory aGVHD and cGVHD | Blocks JAK pathways involved in cytokine activation and immune cells proliferation | Monitor viral reactivation                      |
| Tregs transference               | Refractory aGVHD and cGVHD | Interferes with immune responses   | Clinical trials suggest its use to prevent GVHD |

Source: original work.

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