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Dermatologic Treatment of Cutaneous Graft Versus Host Disease

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Contents

Abstract

Cutaneous involvement in graft versus host disease (GVHD) after allogeneic hematopoietic cell transplant can be separated into acute GVHD (aGVHD), lichenoid chronic GVHD (cGVHD) and sclerodermatous cGVHD. It seems clear that these syndromes result from different mechanisms and entail different treatment approaches. Standard treatment of cutaneous aGVHD involves the intensification of immunosuppressive therapy with adequate topical supportive management. In skin-limited disease, phototherapy has shown promising results. In cutaneous cGVHD, the combination of corticosteroids and cyclosporine (ciclosporin) is the recommended therapy, and other immunosuppressants may be added depending on whether lichenoid or sclerodermatous lesions are present. High response rates to phototherapy have been found in lichenoid disease, while sclerodermatous disease responds better to etretinate or extracorporeal photochemotherapy. Localized cutaneous cGVHD may be treated with topical corticosteroids alone. Few reports on the effect of treatments in GVHD clearly describe the cutaneous involvement and the influence of the treatment on the skin. Therefore, dermatologists should be deeply involved in the diagnosis and treatment of GVHD, and good dermatologic grading systems should be developed. Theses changes will increase our knowledge of cutaneous GVHD, and relevant data in the evaluation of the effect of therapy in the disease will be obtained.

Graft versus host disease (GVHD) is the primary complication of allogeneic hematopoietic cell transplant (AHCT). Clinically significant disease occurs in 50% of patients.[1] Although it is a systemic disease, one of the main target organs is the skin, so dermatologists should be involved in all stages of the condition.[1,2]

Many systemic treatments have been tried in order to prevent or suppress GVHD. Nowadays, immunosuppressive systemic treatment is the basis of therapy; topical treatment has received little consideration. It seems clear to the specialists involved in the treatment of GVHD that cutaneous care should be one of the main concerns in the management of these patients. This has been recently reviewed by Ryan,[3] who clearly indicates that skin-care protocols should include prevention of injury and infection, hydration, provision of barrier, and promotion of healing. On the other hand, topical therapeutic treatment of GVHD has rarely been evaluated, so most of our review will be based on personal experience.

The high incidence of GVHD after AHCT has led to different strategies being sought in order to lower morbidity and mortality. Interventions have been directed at three different phases: conditioning (before AHCT), prophylaxis (after AHCT) and, finally, treatment if GVHD appears.[4] Conditioning and prophylaxis are well standardized and subjected to continuing revision. It is clear that conditioning and prophylactic treatments do have an influence on the incidence of acute and chronic GVHD,[4,5] but this area is beyond the scope of the dermatologist.

In this review, we consider only the third phase, treatment of GVHD, emphasizing the results obtained on cutaneous lesions. Nevertheless, there are some problems regarding the classification and grading of cutaneous GVHD that make this revision a difficult task. These problems are dealt with before describing treatment results.

1. Classification and Grading Systems for Cutaneous Graft Versus Host Disease (GVHD)

Classically, GVHD has been divided into acute GVHD (aGVHD), which occurs within the first 3 months following transplantation, and chronic GVHD (cGVHD), which includes all the manifestations that develop after day 100 following AHCT. Following this classification, cutaneous aGVHD has been defined as any cutaneous manifestation that appears in the first 100 days after AHCT and cutaneous cGVHD when the lesions appear after that limit.[2] This classification has been seriously challenged by different findings: cutaneous lesions of aGVHD have been found after day 100[6] or chronic lichenoid or sclerodermatous lesions can appear before this limit.[2,7] Moreover, Horn et al.[8] found histologic findings of aGVHD after day 100 and of lichenoid cGVHD before day 100, and concluded that the days after AHCT do not differentiate both syndromes. These findings together with the hypothesis that these two syndromes appear to result from different mechanisms[9] suggest that cutaneous aGVHD and cGVHD cannot be reliably classified with that time limit and that good clinical and histologic descriptions should be used.

Moreover, two very different syndromes may appear as manifestations of cGVHD – lichenoid and sclerodermatous – and this division is not taken into account in the classification. These two

syndromes have very different clinical, histologic and evolutional characteristics and responses to treatment.[10,11] In fact, only 40% of patients with sclerodermatous GVHD had a previous lichenoid eruption.[11] It appears that both types of cutaneous cGVHD occur independently[11-13] and may be qualitatively different immunopathologic processes.[10] Several reports have found that lichenoid GVHD histology is a poor prognostic factor[8,10] while sclerodermatous histology is not,[10] although Akpek et al.[14] did not find that cutaneous histology of cGVHD had any prognostic value. Even response to treatment is different in both groups.[15,16] The confounding factor is the non-dermatologic manifestations of cGVHD. The systemic involvement of cGVHD has been poorly correlated with the cutaneous lesions, as most non-dermatologists gather the findings of both types of cutaneous disease together.[17-19] This problem has been stated by other authors as well.[20] No good severity grading system has been designed for lichenoid or sclerodermatous cGVHD,[2,20] as the actual system is based on only two grades of skin involvement (localized and generalized) with no description of the type of lesions or histologic findings (table I).[1] Due to these limitations, most studies on cGVHD cannot be considered useful from the dermatologic point of view.

Therefore, to make a diagnosis of acute or chronic cutaneous GVHD, clinical and histologic data, not days after AHCT, should be the mainstay. In this regard, we classify cutaneous GVHD into three main groups:[11]

1. Cutaneous aGVHD: an acute erythematous exanthema with different grades of epidermal damage. Viral and pharmacologic rashes should be excluded. The severity is graded from I to IV using clinical and histologic data (table II).[1,2]

Table I. Grading of chronic graft versus host disease (cGVHD)

Limited cGVHD
Localized skin involvement
and/or
Hepatic dysfunction resulting from cGVHD
Extensive cGVHD
Generalized skin involvement
or
Localized skin involvement and/or hepatic dysfunction caused by cGVHD
plus:
liver histology showing chronic aggressive hepatitis, bridging necrosis, or cirrhosis; *or*
ocular involvement: Shirmer's test less than 5mm wetting; *or*
histologic evidence of minor salivary gland or oral mucosal involvement; *or*
involvement of any other target organ

2. Lichenoid cGVHD: lichen planus-like lesions that involve any cutaneous surface, excluding the mucosa. Histologic findings are also similar to lichen planus.
3. Sclerodermatous cGVHD: scleroderma or morphea-like lesions with collagen homogenization. We further classified this stage into disseminated and localized disease, both presenting with different systemic manifestations.[11]

It is important that dermatologists be involved in the diagnosis of these patients to help in the classification and increase our knowledge of GVHD.

2. Cutaneous Acute GVHD (aGVHD)

aGVHD is still a major obstacle in AHCT and the first priority is prevention. Many prophylactic regimens have been used,[21-25] but, in spite of them, the incidence of aGVHD remains high, between 6% and 90%.[26] The skin is the most common organ involved with AHCT[2] and is a predictor of poor response.[27] Although patients with multiorgan involvement have been found to have survival rates similar to those of patients with aGVHD limited to the skin,[28] other authors have found better responses in aGVHD limited to skin involvement.[29,30]

The pathophysiology of GVHD has been divided into three phases.[5] In the first, the conditioning regimen causes damage to the intestinal mucosa and liver, which leads to activation of host cells and release of inflammatory cytokines.[31] These cytokines upregulate major histocompatibility complex antigens, thus enhancing their recognition by donor T cells. In the second phase, donor T-cells become activated and proliferate in response to host antigens,[32] fueled by the inflammatory cytokines. In the third phase, activated monocytes secrete interleukin (IL)-1 and tumor necrosis factor (TNF)-α, which leads to tissue damage. In addition, cytotoxic T-cells and natural killer cells cause more damage.[5]

Standard treatment of aGVHD involves the intensification of immunosuppressive therapy.[33] If the disease progresses after 3 days, there is no change after 7 days or an incomplete response is achieved after 14 days of first-line therapy, second-line or salvage therapy should be initiated (table III). This salvage therapy is added to the immunosuppressive treatment until an improvement in clinical status allows the tapering and discontinuation of the immunosuppressive drugs.

2.1 Immunosuppressants

The main approach to aGVHD treatment is to increase immunosuppressant therapy.[33] Historically, corticosteroids and antithymocyte globulin (ATG) have been the most commonly used drugs.[53-56] Nowadays, systemic corticosteroids remain as the

Table II. Grading of acute graft versus host disease

Parameter	Stage			
	i	ii	iii	iv
Organ injury				
Skin	Maculopapular rash involving 25% of body surface	Maculopapular rash involving 25–50% of body surface	Generalized erythroderma	Toxic epidermal necrolysis appearance
Liver bilirubin levels, μmol/L (mg/dL)	34–51 (2–3)	51–101 (3–6)	101–256 (6–15)	>256 (>15)
Gastrointestinal tract	Diarrhea, 500–1000 mL/day	Diarrhea, 1000–1500 mL/day	Diarrhea, >1500 mL/day	Severe abdominal pain or ileus
Skin histology	Focal or diffuse vacuolar alteration of the basal cell layer	Eosinophilic degeneration (dyskeratosis) of epidermal or follicular keratinocytes	Subepidermal cleft or microvesicle formation	Complete dermoepidermal separation
Clinical grade				
Skin	1 or 2+	1–3+	2–3+	2–4+
Liver	0	1	2–3+	2–4+
Gastrointestinal tract	0	1	2–3+	2–4+

main treatment,[33,57] alone or in combination with ATG, cyclosporine (ciclosporin) or monoclonal antibodies (mAbs).[4,58,59]

2.1.1 Systemic Corticosteroids

Systemic corticosteroids (methylprednisolone 2 or 2.5 mg/kg/day) show an overall response rate of 50–70% with 30–60% of complete remissions.[28,33,34] A randomized trial found that high-dose methylprednisolone (10 mg/kg/day) has the same rate of response and survival as a low-dose (2 mg/kg/day) regimen.[60] Once control is achieved, the dose is tapered over 3–5 months, although one randomized trial did not find any difference between fast or slow tapering regimens in the rates of aGVHD flare, infection or survival.[61] Response rates are slightly better in patients with only skin involvement (84% vs 70%),[28] and some authors have found that patients with cutaneous plus gastrointestinal involvement respond less often.[34] Other authors have found better response rates in skin lesions than other organs.[62]

Higher doses of systemic corticosteroids (up to 50 mg/kg/day)[63] have been used as salvage therapy, but, as results are poor, other second-line alternatives for these patients have been investigated.[64]

2.1.2 Cyclosporine

Cyclosporine is primarily used in the prophylaxis of aGVHD. Once prophylaxis fails, the only treatment would be to increase the dose of cyclosporine, but there does not appear to be a clear dose response, and renal damage appears frequently at escalating doses.[65]

2.1.3 Antithymocyte Globulin

ATG (5–30 mg/day of horse ATG or 1–5 mg/kg of rabbit ATG, for 5 days) has been used as first-line therapy,[66] but recent randomized studies suggest that ATG is not useful in this setting as outcomes are not better for the combination of ATG/prednisone versus prednisone alone (79% vs 71% responses, respectively, in patients with cutaneous aGVHD).[28] This is further emphasized due to the associated increased risk of infection with ATG treatment.[28,67]

ATG has been primarily used in corticosteroid-refractory aGVHD, but conflicting results have been published in this setting. Overall, response rates up to 79% have been observed,[30,33,35,36,54,62] and patients with skin aGHVD (with or without other organ involvement) responded most frequently,[36] although survival rates were not improved.[30] Nevertheless, the survival rate was as low as 5–10% in some series owing to an increased risk of infection.[35,36,54,64,68] This has led some authors to discourage the use of ATG.[35,64,68] On the other hand, other authors have not seen a lower survival rate and have recommended ATG therapy.[30,69]

2.1.4 Tacrolimus

Tacrolimus (0.03–0.05 mg/kg/day intravenously or 0.12–0.15 mg/kg/day orally, adjusted by blood concentration) has been included as an option in prophylaxis of GVHD instead of cyclosporine, although previously it has been used as treatment of aGVHD, both as first- and second-line therapy.[70] Response rates have been variable from 10% to 56%.[37,38] However, tacrolimus is usually accompanied by adverse effects, the most common being

Table III. Systemic treatment of cutaneous acute graft versus host disease (aGVHD)

Treatment	Additional immunosuppressants	Stage	No. of patients	No. of cutaneous aGVHD[a]	No. of skin only	Results in cutaneous aGVHD	Notes	Reference
Corticosteroids	Yes	First-line		359 443	ND	55% responses	No difference to other organs	34
	CsA	First-line	46	ND	21	71% CR/PR	Multiorgan disease had similar survival rates to GVHD limited to the skin	28
ATG	CS, CsA	First-line	50	ND	29	79% CR/PR	ATG added no benefit	28
	Yes	CS resistant	58	43	7	79% improved	10% survivors (three skin only)	35
	ND	CS resistant	69	ND	ND	51% improved	Survival rate very poor	33
	Yes	CS resistant	29	29	0	72% improved	10% survivors	36
	Yes	CS resistant	79	64	ND	61% CR/PR	Most frequently responses in skin GVHD	30
Tacrolimus	Yes	Refractory	23	9	ND	Two improved	2% survivors	37
	Yes	First-/second-line	18	9	ND	Five improved	Better response than liver	38
Mycophenolate	Yes	Second-line	6	6	3	Four improved	Two alive in CR	39
mofetil	Yes	First-line	17	15	5	93% improved	Better response than other organs	40
Daclizumab	Yes	First-/second-line	43	35	16	54% CR	Better response than other organs	29
	Yes	CS resistant	12	12	2	58% improved	High incidence of infections	41
Basiliximab	CS	CS resistant	17	15	5	80% improved	No difference to other organs	42
Infliximab	CS, T	T resistant	32	12	ND	86% CR	Better responses than liver	43
IL-1 receptor antagonist	ND	CS resistant	17	14	ND	21% CR, 36% PR	Skin and gut the most responsive	44
Anti-CD2	ND	CS resistant	20	15	ND	47% CR, 40% PR	Skin and gut the most responsive	45
Anti-CD147	ND	CS resistant	59	32	ND	20–52% CR (dose dependent)	Better response than other organs	46
PUVA	Yes	CS resistant	103	103	ND	50% responses	92% developed chronic GVHD	47
	CS	CS resistant	20	20	13	70% responses	92% responses in patients with disease restricted to the skin	48
UVB narrowband	ND	CS resistant	10	10	ND	70% CR, 30% PR	No adverse effects	49
Extracorporeal photopheresis	ND	Second-line	76	59	ND	83% improved (67% CR)	Retrospective analysis of studies	50
	Yes	CS resistant	9	9	3	Eight responses (6 CR)	Children	51
		CS resistant	21	21	8	62% CR, 19% PR	No gut or aGVHD grade IV responses	52

a Results are related to the group of patients with cutaneous GVHD with or without other organ involvement.

ATG = antithymocyte globulin; **CR** = complete response; **CS** = corticosteroids; **CsA** = cyclosporine (ciclosporin); **GVHD** = graft versus host disease; **IL-1** = interleukin-1; **ND** = not described; **PR** = partial response; **PUVA** = psoralen plus UVA; **T** = tacrolimus; **UVB** = UVB irradiation.

renal toxicity in up to half the patients, nausea in 25%, and neurologic toxicity.[37,38]

2.1.5 Mycophenolate Mofetil

Mycophenolate mofetil 1–2 g/day is increasingly used in prophylaxis and as first-line therapy of aGVHD. Response rates in cutaneous disease range from 67%[39] to 93%.[40,71] Adverse-effects were hematologic (leucopenia, thrombocytopenia or anemia) and gastrointestinal, but none was severe or treatment limiting.

2.1.6 Anti-Interleukin (IL)-2 Receptor Therapies

Anti-IL-2 receptor antibodies have been tried as first-line therapy. BT-563 has shown no benefit in survival or response when added to standard therapy.[72] Daclizumab, a humanized anti-IL-2 receptor antibody, has shown encouraging results that await further studies.[29] As second-line therapy, daclizumab showed promising results in one report (54% complete responses in cutaneous aGVHD, with 63% complete responses in disease limited to the skin),[29] but another found a high infection rate with similar activity.[41]

Basiliximab, a chimeric IL-2 receptor antagonist, has been used in 15 patients at 20 mg/day for 1 or 2 days and repeated weekly. The study reported nine complete and three partial responses and no relevant adverse effects.[42] Presence of gastrointestinal or hepatic GVHD did not negatively affect the response.

2.1.7 Other Treatments

Infliximab was used in 12 patients, of whom 86% showed a complete response.[43] Recombinant IL-1 receptor achieved a 57% response in 14 patients.[44] Similarly, an 87% response rate was obtained with anti-CD2 in 15 patients.[45] Anti-CD147 achieved a 52% complete response in 27 patients treated with high doses.[46] Sirolimus (rapamycin) has also been tried with some activity in cutaneous disease but considerable toxicity.[73] Pentostatin has achieved a 67% response rate in 15 patients, mostly in the skin and gut.[33]

2.2 Phototherapy

2.2.1 Psoralen plus UVA (PUVA) Photochemotherapy

Several case reports and short series have suggested the value of psoralen plus UVA (PUVA) therapy as a second- or third-line treatment in corticosteroid-resistant cases. Recently two extensive series have supported the utility of PUVA in skin grade II–IV aGVHD.[47,48]

Wiesmann et al.,[48] in a study of 20 patients treated with prednisone and PUVA, found a 92% response rate in patients with localized skin disease while only a 33% response was achieved in patients with disease affecting other organs. Other authors have found similar absence of response in patients with systemic aGVHD.[74] The recent series of Furlong et al.,[47] involving 103 patients with corticosteroid-resistant aGVHD, confirms previous findings. Treatment allowed reductions in corticosteroid doses and 50% of patients did not require additional therapy, but remarkably, 13% of patients showed progressive or new aGVHD and 92% of patients developed extensive cGVHD. This evolution has been confirmed by another study.[74]

Treatment schedules are similar to those used in other cutaneous diseases. Two hours after oral administration of 8-methoxypsoralen (0.4–0.9 mg/kg of bodyweight), UVA irradiation was started. These treatments were given three or four times per week over a minimum of 4 weeks, with a maximum dose of 8 J/cm^2.[48,74,75] Reported adverse effects included phototoxicity (erythema or tenderness of the skin) in 10–40% of patients due to UVA, and nausea and vomiting in 10% of patients, related to psoralen intake. Continued surveillance of patients, however, will be needed to determine the long-term risk of skin cancers after the use of PUVA for the treatment of GVHD.

Fewer adverse effects have been observed with psoralen bath plus UVA photochemotherapy, but few patients have been reported.[76]

2.2.2 UVB Phototherapy

UVB phototherapy is less effective than PUVA therapy, thus requiring a higher number of treatment sessions in most clinical settings.[49] Nevertheless, a novel improved form of UVB – narrowband UVB, using the 311–312nm band – can be applied with beneficial effects in patients with aGVHD limited to the skin.[49] Grundmann-Kollmann et al.[49] have recently published a study that observed a 70% complete response rate in ten cases of grade II–III aGVHD resistant to standard immunosuppressive treatment. Patients were treated with five sessions per week of narrowband UVB with a mean cumulative dose of 12.2 J/cm^2 and an average of 17.8 irradiations. No adverse effects, with the exception of mild erythema, were observed and in all patients, immunosuppressive medication could be reduced. The main concern of UVB is carcinogenesis, especially in this group of immunosuppressed patients, but it can only be evaluated after long-term follow-up.

2.2.3 Extracorporeal Photopheresis

Extracorporeal photopheresis (ECP) is a therapy based on the biologic effects of PUVA on peripheral blood mononuclear cells collected by apheresis, and reinfused into the patients. ECP has shown efficacy in corticosteroid-resistant cutaneous and hepatic grade II–III aGVHD.[52,77] Treatment is not effective for intestinal or cutaneous grade IV aGVHD.[52] Greinix et al.[52] found that 62% of patients with cutaneous GVHD and 67% of patients with hepatic GVHD achieved a complete response after 3 months of

therapy. Mixed results have been published by other authors.[51,78] The ECP procedure was performed using a photopheresis system for 3.5 hours on 2 consecutive days (one cycle) at 1- to 2-week intervals until improvement, and thereafter every 2–4 weeks until maximal response was achieved. Then, ECP was tapered on an individual basis. ECP is usually very well tolerated, with very few adverse effects; a marked decrease in hemoglobin levels and leukocyte and platelet counts are frequent with no increase in infectious events.[52] In a recent analysis of GVHD cases treated with ECP, Dall'Amico and Messina[50] found improvement of cutaneous lesions in 83% of aGVHD patients, complete remission in 67%, and hepatic and intestinal remissions in 38% and 54% respectively. Mean survival was 53% and only 8 of the 59 surviving patients developed cGVHD. No long-term adverse effects were described.

2.3 Topical Treatment

The skin involvement in mild aGVHD could be treated with emollients and topical corticosteroids,[1] but usually patients required systemic treatment due to the involvement of other organs. In this regard, topical treatment could be seen as an adjuvant or complement to immunosuppressive treatment.[28,34] Nevertheless, if the patient is severely immunocompromised, topical corticosteroids should be used with caution owing to the risk of infection.

Meticulous cutaneous hygiene and liberal application of emollients should be recommended to all patients. Adequate use of topical antiseptics should be sought to avoid cutaneous irritation and help to prevent skin infections. Supportive topical treatment will vary depending on the severity of disease. Grade III and IV cutaneous aGVHD patients need the same care as severely burned patients, taking into account their severe immunosuppression.

3. Cutaneous Chronic GVHD (cGVHD)

cGVHD occurs in approximately 60–80% of long-term survivors of AHCT, and it is frequently (but not regularly) preceded by the acute form.[11,79,80] The skin is affected in more than 90% of patients.[1,2]

Pathogenically, cGVHD seems to be the result of autoreactive T cells, from donor-derived stem cells. Donor lymphocytes mature in the host thymus and some host-reactive T cells escape from the elimination mechanisms, resulting in persistent alloreactive and autoreactive T-cell clones.[79] These immune dysregulations result in immunodeficiency and autoimmunity.[81] Most patients have evidence of B cell dysregulation with high prevalence of autoantibodies.[9]

cGVHD should be treated. Sullivan et al.[82] reported that 76% of the patients treated with immunosuppressive combination therapy were free of disease compared with 23% of inadequately treated patients and 18% of nontreated patients. In the treatment of cGVHD, different agents have been tried,[79,83] alone or in combination, leading to a reduction in the frequency of skin sclerosis and ulcers.[84] It has been found that patients with *de novo* cGVHD (who have never had aGVHD) or quiescent cGVHD (after an interval of response to treatment for aGVHD) are more likely to respond to therapy than patients with progressive cGVHD (evolved from active aGVHD).[9]

Standard treatment in most groups includes the combination of prednisone and other immunosuppressants, such as cyclosporine. Failure of first-line therapy is usually defined as no improvement of cGVHD after 2–3 months of previous treatment or as a progression of cGVHD after 4–8 weeks. Second-line treatments are usually added to the immunosuppressive therapy until a partial or complete response allows the tapering or discontinuation of immunosuppressive treatment.

Although most reports mix patients with lichenoid and sclerodermatous GVHD, we will try to analyze both diseases independently (table IV). Nevertheless, we will start with a review of treatments for cGVHD that makes no mention of whether lichenoid or sclerodermatous patients were treated. Therefore, the conclusions should be confirmed in appropriated groups of patients with cutaneous cGVHD.

3.1 Non-Defined Cutaneous cGVHD

3.1.1 Immunosuppressants

For cGVHD, with no indication of lichenoid or sclerodermatous involvement, a combination of corticosteroids and immunosuppressants is recommended.[2] In a randomized study, Sullivan et al.[99] found that the combination of prednisone (1 mg/kg) and azathioprine (1.5 mg/kg) caused an increase in mortality due to infection compared with prednisone alone, with similar response rates (64% and 62%, respectively). Azathioprine has been avoided in most studies.[100] In another study by Sullivan et al.,[101] the combination of alternate-day prednisone (1 mg/kg) and cyclosporine (6 mg/kg) improved survival over prednisone alone (51% and 26%) and had a better response rate (56% and 32%, respectively). Currently, most centers use this combination as 'standard' therapy,[84,102] sometimes starting with daily doses of prednisone (1 mg/kg) and cyclosporine (10 mg/kg) and changing to alternate-day therapy after 2 weeks.[100] At Johns Hopkins University,[33] patients are evaluated every 3 months, and therapy is continued 3 months after maximal response.

Tacrolimus 0.12 mg/kg combined with prednisone has been used as salvage therapy in patients that do not respond to predni-

Table IV. Systemic treatment of cutaneous chronic graft versus host disease (cGVHD)

Drugs	Additional immunosuppressants	Stage	No. of patients	Type of cutaneous cGVHD	No. of cutaneous cGVHD[a]	No. of skin only	Results in cutaneous cGVHD	Notes	Reference
Prednisone azathioprine	No	First-line	9	SG	9	2	Eight CR	No severe adverse effects	11
Prednisone CsA	No	First-line	27	ND	21	ND	93% responded	Skin predictor of more frequent responses	85
Prednisone tacrolimus	No	Refractory	39	LG/SG	28/9	3	21% improved (13% CR)	Skin better than lung	86
	No	Refractory	31	ND	6	ND	Three responses	Better response than liver or lung	38
Mycofenolate mofetil	Yes	First-line	13	ND	ND	4	Nine remissions	No difference to other organs	39
	Yes	Refractory	15	LG/SG	7/7	3/2	Five/one CR	Children	16
Mycofenolate mofetil tacrolimus	No	Refractory	26	LG/SG	4/19	ND	46% responded	No difference to multiorgan disease	87
Thalidomide	CS-CsA	First-line	27	ND	16	ND	93% responded	Thalidomide added no benefit	85
	Yes	Refractory	37	ND	30	ND	43% responded	Severe rash in four patients	88
	Yes	Refractory	80	ND	ND	9	11% responded	No responses in skin only or liver and skin disease	15
Etanercept	Yes	Refractory	10	ND	6	1	Four responses	Three alive	89
Ketotifen	No	Refractory	8	ND	8	1	Six responses	Two total leukoderma	90
Clofazimine	Yes	Refractory	22	LG/SG/LSG	6/6/4	ND	56% PR	Similar efficacy in LG/SG	91
Hydroxychloroquine	Yes	Refractory	40	LG/SG/LSG/ND	4/4/4/5	1/0/1/2	1/1/0/3 CR+PR	Better than lung	92
PUVA	Yes	Refractory	6	LG/SG	5/1	ND	Three/one responded	Two alive	74
	Yes	Refractory	40	LG/SG/LSG/ND	20/2/2/11	11/2/2/0	16/0/2/7 CR+PR	No response of sclerodermatous lesions	93
Extracorporeal photochemotherapy		Refractory	204	ND	160	ND	76% improvement (35% CR)	Retrospective analysis of studies	50
	Yes	Refractory	15	LG/SG/LSG	3/7/5	2/2/0	100% responses (80% CR)	93% survival	77
	Yes	Refractory	10	SG	10	0	70% PR	Low incidence of infections	94
	Yes	Refractory	8	SG	7	1	Three PR	No significant adverse effects	95
	Yes	Refractory	6	SG	6	1	Four PR	Early response: 3–8 weeks	96
	Yes	Refractory	14	ND	12	3	Ten responses (five CR)	Children	51
	Yes	Refractory	32	LG/SG	15/17	4/5	56% responses, 22% CR	Similar responses in skin only and systemic disease	97
Etretinate	Yes	Refractory	32	SG	32	4	74% of responses	Skin breakdown and ulcers	98

a Results are related to the group of patients with cutaneous GVHD with or without other organ involvement.

CR = complete response; **CsA** = cyclosporine (ciclosporin); **CS-CsA** = corticosteroid plus CsA; **LG** = lichenoid; **GVHD** = graft versus host disease; **LSG** = mixed lichenoid sclerodermatous GVHD; **ND** = not described; **PR** = partial response; **PUVA** = psoralen plus UVA; **SG** = sclerodermatous GVHD.

sone/cyclosporine.[86] Response rates to tacrolimus range from 13%[86] to 50%,[38] with a higher rate of response in the skin.

Several studies with mycophenolate mofetil 1–2 mg/day (combined with other immunosuppressants) have been reported, with responses ranging from 46% to 71%.[39,87,103,104] Adverse effects include gastrointestinal symptoms, liver toxicity and infections with no influence on patients' survival. Ongoing studies combining mycophenolate mofetil and tacrolimus have found a corticosteroid-sparing effect in half the patients.[100]

3.1.2 Thalidomide

Chao et al.[105] showed that thalidomide used as prophylaxis for cGVHD is associated with an increased rate of cGVHD and mortality compared with placebo. Moreover, in a randomized study with thalidomide as a first-line therapy for cGVHD, no differences were found between thalidomide/prednisone/cyclosporine and prednisone/cyclosporine.[85] Adverse effects were frequent but no increase in mortality was found. Skin involvement was a predictor of good response, with 93% responders. In refractory cGVHD, a 43% response rate, with few adverse effects, has been found.[88] Nevertheless, another randomized placebo-controlled study using thalidomide as first-line therapy was terminated when 92% of patients in the thalidomide group abandoned the study, and no assessment of efficacy could be made.[106]

3.1.3 Other Drugs

There have been recent trials with etanercept[89] and infliximab[43] with good responses but involving a limited number of patients. Daclizumab has been used with no clear response.[41] Ketotifen 6 mg/day improved the skin in six of the eight refractory patients treated.[90] Pentostatin has also been studied, with an overall response rate of 65% in a study involving 17 patients.[33]

3.1.4 Extracorporeal Photochemotherapy

Dall'Amico and Messina[50] reviewed 204 cases of cGVHD treated with ECP and found a 76% response in patients with cutaneous lesions (35% complete responses), 48% response in patients with liver involvement, and 39% in patients with lung disease. The overall survival rate was 79%.

3.2 Lichenoid cGVHD

Lichenoid cGVHD presents with lesions similar to lichen planus and other lichenoid eruptions. Histologic findings are also similar.[1,2]

3.2.1 Immunosuppressants

For generalized disease, a combination of corticosteroids and immunosuppressants is recommended.[2] Mycophenolate mofetil has produced good response rates[39] with up to 70% of patients exhibiting complete remission in lichenoid cGVHD.[16]

3.2.2 Thalidomide

High-dose thalidomide (200–800 mg/day) has been useful in several case reports and small series, but its beneficial effect remains difficult to evaluate.[2] A recent study has found an 11% response rate in patients with cutaneous cGVHD other than sclerodermatous disease.[15] Thalidomide treatment has frequent adverse effects, including sedation, constipation and bowel discomfort, sensory neuropathy, granulocytopenia and cutaneous lesions of GVHD.[15]

3.2.3 PUVA

PUVA therapy has been found useful in lichenoid GVHD incompletely controlled by systemic treatments.[107,108] Complete or partial remissions were obtained in 82% of 22 patients[93] and 100% of five[107] patients with lichenoid lesions. Related GVHD death rates have been reported as high in several series,[74,93] suggesting that PUVA lacks any systemic effect. Another remarkable adverse effect is the evolution to sclerodermatous GVHD, which occurred in 3 of 22 patients in one series[93] and two of four patients in another.[108] Results with psoralen bath plus UVA were disappointing in some cases[109] and encouraging in others.[110]

3.2.4 Extracorporeal Photochemotherapy

ECP (2 consecutive days at 2-week intervals) for lichenoid lesions had some success in two trials, one of eight patients (75% complete and 25% partial responses)[77] and the other involving 15 patients (27% complete and 27% partial responses).[97] The only severe adverse effects reported were catheter infection, fluid overload and thrombosis.

3.2.5 Other Treatments

Clofazimine 300 mg/day for 90 days followed by 100 mg/day has been used in ten lichenoid patients, with six partial responses.[91] Adverse effects were mild. Red-brown hyperpigmentation of the skin and conjunctiva appeared in 55% of the patients.

In eight patients with lichenoid lesions, hydroxychloroquine 800 mg/day achieved one partial response,[92] although taking all 17 patients with cutaneous cGVHD into account, 29% achieved partial or complete responses with few adverse effects. Broadband UVB phototherapy[74,111] or pentostatin[112] have been useful in some cases.

3.2.6 Topical Treatment

Topical medium- to high-potency corticosteroids are used on localized, mild disease, sometimes with good results. It may also be reasonable to treat these lesions with drugs used in lichen planus. One recent report used tacrolimus to treat eczematous lesions in patients with cutaneous cGVHD,[113] with partial responses in 18 patients. Nevertheless, all required increased doses

of oral corticosteroids or other systemic treatment due to progression of the disease.

3.3 Sclerodermatous cGVHD

In sclerodermatous cGVHD, morphea-like or lichen sclerosis-like lesions appear.[1,2] They usually start on the trunk and become generalized in a few weeks, often resulting in joint contractures. In some cases, sclerosis appears in areas of previous injury.[11] Extensive sclerodermatous cGVHD should be treated. Untreated patients, who developed contractures, did not subsequently show evidence of spontaneous improvement of skin disease, and became crippled.[114] As in other stages of GVHD, optimal systemic treatment is the goal of therapy.

3.3.1 Immunosuppressants

Following the rationale described previously, most authors use alternating cyclosporine 12 mg/kg/day and corticosteroids 1 mg/kg/day as their main treatment.[80] Our group has recently confirmed the efficacy of the prednisone 1 mg/kg and azathioprine 1.5 mg/kg treatment combination. We achieved eight complete responses in nine patients and did not observe any significant adverse effect.[11] This combination therapy was also shown to be effective in a report of Sullivan et al.,[99] but it entailed a high risk of death from infectious diseases. We believe the reason for this apparent contradiction is that we used this combination in sclerodermatous GVHD[11] while Sullivan et al.[99] used it in cGVHD, with or without skin involvement. This highlights the value of good dermatologic descriptions and classifications in patients with cGVHD. We consider that, under proper surveillance, it could be a valuable approach until better treatments appear.

Responses rates from 14%[16] to 69%[39] in sclerodermatous cutaneous cGVHD with mycophenolate mofetil have been achieved in small series.

Aggressive treatments with three (cyclosporine, methylprednisolone, azathioprine) to five (cyclosporine, methylprednisolone, azathioprine, cyclophosphamide and methotrexate) drugs have controlled sclerodermatous GVHD both as initial (94% complete responses) and as salvage therapy, with an overall response of 77% in 45 patients under 16 years of age.[115] Treatment-related complications appeared in 20% of patients.

3.3.2 Thalidomide

Responses to thalidomide treatment have been seen in patients with GVHD.[116] We have treated two patients with no evidence of any benefit in cutaneous lesions of sclerodermatous GVHD.[11] A recent report[15] found only one patient with sclerodermatous GVHD showing a partial response out of 41 patients with cutaneous lesions of cGVHD,[15] and the authors concluded that thalidomide cannot be used in sclerodermatous GVHD. Moreover, 14 of the 27 patients included in a study with etretinate had been previously unresponsive to thalidomide treatment.[98]

3.3.3 Etretinate

A recent paper has found a very good response to etretinate of sclerodermatous GVHD nonresponsive to other treatments.[98] Of 27 evaluable patients, they obtained improvement in 74%, from which two patients have had a complete response. The most important adverse effects were skin breakdown and/or ulceration.

3.3.4 PUVA

PUVA therapy has been shown to fail in the treatment of sclerodermatous GVHD,[93,107] inducing more sclerosis in some patients.[2] Recently, several short series have been published showing partial and complete responses to psoralen bath plus UVA[76,109,110] and some case reports showed response to UVA1 therapy.[110,117,118]

3.3.5 Extracorporeal Photochemotherapy

ECP has been reported as useful in five of eight children with sclerodermatous GVHD.[95,119] Greinix et al.[77] used it in 12 adult patients and found 75% of complete and 25% of partial responses, but in other reports only 70% partial responses in ten patients,[94] and 18% complete and 41% partial responses out of 17 patients[97] were obtained. Other reports found that cutaneous lesions rarely disappear completely.[120] Supporters of the technique affirm that treatment should be longer than 6 months and performed on 2 consecutive days every 2 weeks to obtain good results.[77,119,120]

A recent analysis of ECP in sclerodermatous cGVHD found partial or complete responses in 100% of eight patients with T-cell clonality and no responses in the four patients with no clonality.[121] If these results are confirmed, T-cell receptor-γ gene rearrangement analysis may prove of use in predicting responses to ECP.

3.3.6 Other Treatments

One partial response was obtained in eight patients with sclerodermatous lesions treated with hydroxychloroquine.[92] In ten patients treated with clofazimine, a 60% response rate was achieved.[91] Pentostatin,[112] intravenous lidocaine (lignocaine),[122] low-dose total lymphoid irradiation[123] and UVB phototherapy[111] have also been used.

3.3.7 Topical Treatment

Treatment has been tried with heat, massage and stretching exercises with some functional improvement.[124] High-potency topical corticosteroids are the main agent used to treat localized forms of sclerodermatous GVHD.[2,11] Topical treatment has been tried with halofuginone, an alkaloid known to specifically inhibit collagen type α1 (I) gene expression and collagen synthesis. At least one patient has responded to this topical therapy.[125]

Complications of sclerodermatous GVHD, like ulcers or phimosis should be treated.[126] Ulcers require topical care with hydrocolloid occlusive dressings and it is possible that topical corticosteroids will help. Phimosis has been treated with high-potency topical corticosteroids.[2]

Some authors believe that aggressive occupational therapy and physical therapy with paraffin baths early in the treatment might prevent the development of severe skin contractures.[124] In any case, we agree that patients may improve their quality of life using physical therapy in their daily lives.[78,93]

Topical cutaneous care should be emphasized in cGVHD, as it is a long-lasting disease.[2,100] Emollients, sunscreens, and mild soaps should be used.[93]

4. Conclusions

Many factors influence survival in patients with GVHD, for example, conditioning regimens, modifications in blood transfusion support, and monitoring and treatment of infections.[84,126] These confounding factors may be relevant when analyzing the effects of treatments in different cohorts.[11] On the other hand, it is clear that further stratification should be included in the analysis of responses to treatment in GVHD. It seems important to differentiate the responses of patients by the organs involved (e.g. skin, gastrointestinal tract), and in cGVHD the different responses of lichenoid and sclerodermatous forms. Furthermore, a good grading system for cutaneous involvement in the chronic phases should be developed to allow comparisons between different series. Nevertheless, some conclusions can be drawn.

4.1 aGVHD

Unless involved in a clinical trial, it is better to use systemic corticosteroids together with another immunosuppressant (cyclosporine, tacrolimus or mycophenolate mofetil) as first-line therapy for aGVHD. PUVA or ECP have shown promising results in skin-limited aGVHD. Adequate topical supportive treatment is needed.

4.2 cGVHD

Optimal systemic immunosuppressive treatment is the mainstay of therapy in systemic disease. Corticosteroids and cyclosporine should be recommended as first-line therapy for cGVHD, although other immunosuppressants can be taken into account (e.g. mycophenolate mofetil and azathioprine) depending on the type of cutaneous involvement.

In predominantly cutaneous involvement, other therapies may be tried. In lichenoid GVHD, best results have been found with phototherapy (PUVA, UVB or ECP), although high death rates and evolution to sclerodermatous GVHD should be taken into account. In sclerodermatous GVHD, etretinate and ECP have achieved better response rates.

4.3 Topical Care

Topical care is very important in the treatment of GVHD. Although there are no studies on the effect of skin-care protocols in the evolution of the disease, there are indirect data showing that correct care improves the prognosis. Case reports and small series show improvement of GVHD using topical and systemic treatments. In the acute phase, optimal systemic treatment is the goal of therapy and topical corticosteroids should be considered with caution. In chronic limited forms, topical therapy may have an effect by itself. In more disseminated chronic forms, topical therapy may be used as an adjuvant to proper systemic treatment.

Nevertheless, well controlled clinical trials with a good dermatologic grading system are needed and dermatologists should be deeply involved in the treatment of patients with GVHD.

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