Attachment 1: Measuring Therapeutic Response in Chronic Graft-versus-Host Disease

Literature Review of Various Response Criteria Used in Chronic Graft-versus-Host Disease Trials (by Gorgun Akpek).

Response Criteria	Definition	Reference
Complete response (CR)	Resolution of all manifestations of chronic GvHD.	Couriel DR, Saliba R, Escalón MP, et al. Sirolimus in combination with tacrolimus and corticosteroids for the treatment of resistant chronic graft-*versus*-host disease. *Br J Haematol*. 2005;130:409-417.
PR was defined as at least a 50% improvement of clinical manifestations without a CR.	PR was defined for each organ as follows: Skin: For lichenoid rashes, a minimum reduction in the body surface area involved by 50%. For sclerodermatous involvement, any improvement in the skin score or range of motion, with an improvement in Zubrod performance status by 1. Ocular GvHD: Subjective improvement and reduction in the frequency of artificial tear administration by 50% or improvement in Schirmer's test for one or both eyes. Oral GvHD: 50% improvement in the mucosal area involved with lichenoid and/or ulcerative changes. GI and liver: 50% decrease in the volume of diarrhea, bilirubin level, or alkaline phosphatase level.	
Stable disease or NR	No change in GvHD.	
Progressive disease	Any worsening while on treatment or steroid taper.	
Mixed response	Patients with a CR or PR in one organ and simultaneous NR or PD in another	

Response Criteria	Definition	Reference
Complete Response (CR) Partial Response (PR) Stable Disease Progression (P) Overall outcome (Effective or ineffective)	Four response categories were used for each system. No specific definition of these categories was given except for thrombocytopenia. The contribution of ECP was considered: 1) determinant (++) when CR was observed in all organs involved after the start of ECP and when the dose of immunosuppressants could be reduced by at least 50% with respect to initial therapy; 2) ineffective (-) when progression was observed in one of the organs involved, when it was necessary to increase the dose of immunosuppressants, or when CR was not observed in any organ and immunosuppressants were not reduced by more than 50%; 3) good (+) in all other cases. Overall outcome was scored 0 when ECP was ineffective and 1 when ECP was determinant or good.	Rubegni P, Cuccia A, Sbano P, et al. Role of extracorporeal photochemotherapy in patients with refractory chronic graft-*versus*-host disease. *Br J Haematol.* 2005;130:271-275.
Resolution Improvement Stable disease Progression Ability to taper immunosuppression	Defined retrospectively for each organ/system. No specific definition.	Giaccone L, Martin P, Carpenter P, et al. Safety and potential efficacy of low-dose methotrexate for treatment of chronic graft-versus-host disease. *Bone Marrow Transplant*. 2005;36:337-341.
Partial response Stable disease No response (or progressive disease)	50% or greater improvement No significant change Progression on treatment	Foss FM, DiVenuti GM, Chin K, et al. Prospective study of extracorporeal photopheresis in steroid-refractory or steroid-resistant extensive chronic graft-versus-host disease: analysis of response and survival incorporating prognostic factors. *Bone Marrow Transplant*. 2005;35:1187-1193.

Response Criteria	Definition	Reference
Complete remission Partial remission Stable disease Progressive disease Ability to decrease prednisone	Defined retrospectively for each organ/system. No specific definition.	Lopez F, Parker P, Nademanee A, et al. Efficacy of mycophenolate mofetil in the treatment of chronic graft-versus-host disease. *Biol Blood Marrow Transplant*. 2005;11:307-313.
Clinical response Discontinuation of immunosuppressive medication Ability to taper systemic immunosuppressive medication No response	Improvement in signs and symptoms of cGvHD Progressive cGvHD	Johnston LJ, Brown J, Shizuru JA, et al. Rapamycin (sirolimus) for treatment of chronic graft-versus-host disease. *Biol Blood Marrow Transplant*. 2005;11:47-55.
Resolution of chronic GvHD Time to discontinuation of immunosuppressive treatment: Time to death not related to recurrent malignancy	Resolution of all cGvHD signs Follow-up was censored at death or recurrent malignancy, whichever occurred first. Follow-up was censored at the onset of recurrent malignancy.	Stewart BL, Storer B, Storek J, et al. Duration of immunosuppressive treatment for chronic graft-versus-host disease. *Blood*. 2004;104:3501-3506.
Marked improvement No response Incomplete response	The clinical outcome was based on the subjective feelings of the patient and the macroscopically visible changes of the skin and oral cavity 1 week before treatment and 8 to 12 weeks after therapy.	Canninga-van Dijk MR, van der Straaten HM, Fijnheer R, Sanders CJ, van den Tweel JG, Verdonck LF. Anti-CD20 monoclonal antibody treatment in 6 patients with therapy-refractory chronic graft-versus-host disease *Blood*. 2004;104:2603-2606.

Response Criteria	Definition	Reference
Complete Response Partial response Steroid-sparing response	Complete resolution of all active skin involvement with or without residual clinically inactive skin lesions Improvement in skin rash and/or skin involvement on at least 50% of the body surface area A steroid-sparing response (SS) was a 50% or more decrease in the systemic corticosteroid requirement between the beginning and end of ECP therapy Overall and cGvHD-related mortality	Apisarnthanarax N, Donato M, Körbling M, et al. Extracorporeal photopheresis therapy in the management of steroid-refractory or steroid-dependent cutaneous chronic graft-versus-host disease after allogeneic stem cell transplantation: feasibility and results. *Bone Marrow Transplant*. 2003;31:459-465.
Improvement or stabilization in skin manifestations and overall disease activity	Skin evaluation by the modified scleroderma skin scoring method whereby 22 body areas are palpated and scored	Bisaccia E, Palangio M, Gonzalez J, Adler KR, Rowley SD, Goldberg SL. Treating refractory chronic graft-versus-host disease with extracorporeal photochemotherapy. *Bone Marrow Transplant*. 2003;31:291-294.
Skin score: 0 = normal; 1 = thickened; 2 = thickened, unable to move; and 3 = thickened, unable to pinch (with a possible maximum score of 66).	Weekly evaluation of clinical status	Schwartz J, Gonzalez J, Palangio M, Klainer AS, Bisaccia E. Extracorporeal photochemotherapy in progressive systemic sclerosis: a follow-up study. *Int J Dermatol.* 1997;36:380-385.
Complete response Partial response	Complete resolution of the conjunctival hyperemia with either total resolution of the conjunctival neovascularization or presence of inactive, nonvascular, conjunctival scarring 50% reduction in conjunctival hyperemia with no progression of the conjunctival neovascularization	Robinson MR, Lee SS, Rubin BI, et al. Topical corticosteroid therapy for cicatricial conjunctivitis associated with chronic graft-versus-host disease. *Bone Marrow Transplant*. 2004;33:1031-1035.
Response No response	Ongoing resolution or improvement	Ratanatharathorn V, Ayash L, Reynolds C, et al. Treatment of chronic graft-versus-host disease with anti-CD20 chimeric monoclonal antibody. *Biol Blood Marrow Transplant*. 2003;9:505-511.

Response Criteria	Definition	Reference
Complete response	Complete resolution of clinical signs, no new organ involvement, and normal performance status	Kulkarni S, Powles R, Sirohi B, et al. Thalidomide after allogeneic haematopoietic stem cell transplantation: activity in chronic but not in acute graft-versus-host disease. *Bone Marrow Transplant*. 2003;32:165-170.
Partial response	Improvement in the performance status of at least two orders and at least 50% resolution of signs and symptoms of disease	
No response	No response (NR) was defined as lack of improvement within three months or progression of disease on therapy.	
No response	No change in the oral GvHD signs	Elad S, Or R, Resnick I, Shapira MY. Topical tacrolimus—a novel treatment alternative for cutaneous chronic graft-versus-host disease *Transpl Int*. 2003;16:665-670.
Mild response	A limited reduction of the involved surface (25% IA) or early healing of ulcerated lesions or mild decrease in lesions' thickness	
Moderate response	A reduction of the involved surface (50% IA) or moderate decrease in lesions' thickness or a reduction of the erythema severity	
Good response	A marked reduction of the involved surface (75% IA) and marked reduction in lesions' thickness and a marked reduction of the erythema severity	
Complete response	A complete resolution of the oral GvHD	

Response Criteria	Definition	Reference
Complaints score	Patients were asked to grade their symptoms relating to dry eye by using a complaint sheet.	Ogawa Y, Okamoto S, Mori T, et al. Autologous serum eye drops for the treatment of severe dry eye in patients with chronic graft-versus-host disease. *Bone Marrow Transplant*. 2003;31:579-583.
Corneal sensitivity scores	Corneal sensitivity was measured using a Cochet-Bonnet esthesiometer.	
Fluorescein scores	Fluorescein staining was also rated from 0 to 9, but only in the cornea.	
Rose Bengal scores	The degree of the rose bengal staining was recorded at each of the temporal and nasal conjunctiva and the cornea and was quantified on a scale of 0–3 points; thus, the total score of rose bengal staining was rated from 0 to 9.	
Tear break-up time	Tear break-up time was measured, and three readings were taken.	
Value of Schirmer’s test	Schirmer’s test was performed with nasal stimulation.	
30-item symptom scale with seven subscales	The symptom scale correlated highly with patients' self-assessed mild, moderate, and severe cGvHD manifestations in cross-sectional analysis.	Lee S, Cook EF, Soiffer R, Antin JH. Development and validation of a scale to measure symptoms of chronic graft-versus-host disease. *Biol Blood Marrow Transplant*. 2002;8:444-452.
Either the SF-36 or the FACT-BMT plus cGvHD-specific symptom scale	To measure the impact of cGvHD on patients’ quality of life	

Response Criteria	Definition	Reference
Transplantation-related mortality at five years from cGvHD treatment Overall mortality Survival without recurrent malignancy Recurrent malignancy Secondary therapy Discontinuation of all immunosuppressive therapy in the absence of recurrent malignancy		Koc S, Leisenring W, Flowers ME, et al. Therapy for chronic graft-versus-host disease: a randomized trial comparing cyclosporine plus prednisone versus prednisone alone. *Blood*. 2002;100:48-51.
Response 1) Major response 2) Minor response 3) No response	Evaluated by reduction of clinical signs and symptoms of skin, joint, liver, mouth, eye, and other cGvHD involvement by clinical criteria Resolution or improvement in all of the cGvHD manifestations Improvement in one or more sites while no change in the other sites of cGvHD No change or progressive worsening of cGvHD	Akpek G, Lee SM, Anders V, Vogelsang GB. A high-dose pulse steroid regimen for controlling active chronic graft-versus-host disease. *Biol Blood Marrow Transplant*. 2001;7:495-502.
Complete response (CR) Partial Response (PR) Flare No response	Resolution of all signs and symptoms of cGvHD Improvement in one organ and no worsening in others PR or CR followed by worsening to severity less than baseline Progression to worse than a baseline or no improvement after six months of therapy	Arora M, Wagner JE, Davies SM, et al. Randomized clinical trial of thalidomide, cyclosporine, and prednisone versus cyclosporine and prednisone as initial therapy for chronic graft-versus-host disease. *Biol Blood Marrow Transplant*. 2001;7:265-273.

Response Criteria	Definition	Reference
A complete response (CR) Partial response (PR) No response (NR) or refractory to treatment	Resolution of all clinical manifestations of cGvHD without signs of activity on skin biopsies Greater than 50% improvement in cGvHD symptoms in all affected organs, but not a complete response Progression of cGvHD after 3 months of treatment or new organ involvement developed during immunosuppressive therapy	Gaziev D, Lucarelli G, Polchi P, et al. A three or more drug combination as effective therapy for moderate or severe chronic graft-versus-host disease. *Bone Marrow Transplant*. 2001;27:45-51.
Complete response Partial response No response	No evidence of GvHD affecting any organ or system Improvement in one or more involved organs, without evidence of progression in any involved organ No improvement in one or more involved organs, or progression of chronic GvHD on therapy Patients whose best response was transient (not maintained for at least six months or to last contact) or those who died within three months of commencing cGvHD treatment were considered non-responders.	Browne PV, Weisdorf DJ, DeFor T, et al. Response to thalidomide therapy in refractory chronic graft-versus-host disease. *Bone Marrow Transplant*. 2000;26:865-869.
Complete response Partial response	No specific definition. All responders tolerated a >50% reduction in their steroid dose while receiving HCQ.	Gilman AL, Chan KW, Mogul A, et al. Hydroxychloroquine for the treatment of chronic graft-versus-host disease. *Biol Blood Marrow Transplant*. 2000;6:327-334.
Objective response Stable disease Progression	No specific definition	Mookerjee B, Altomonte V, Vogelsang G. Salvage therapy for refractory chronic graft-versus-host disease with mycophenolate mofetil and tacrolimus. *Bone Marrow Transplant*. 1999;24:517-520.

Response Criteria	Definition	Reference
Objective cutaneous improvement	Skin scores were assessed clinically according to the following protocol: (1) *Erythematous and lichenoid eruptions*: area skin score: percentage of body surface or cm diameter of isolated lesions. Grading of erythema: 0: no lesions, 1: erythema or lichenoid lesions, 2: both erythema and lichenoid lesions. (2) *Sclerodermatous lesions*: modified Rodman area score. 0: normal skin thickness, 1: thickened, 2: thickened and fixed, 3: hidebound, unable to pinch. (3) *Mucosal involvement*: 0: absent, 1: present. (4) *Lung involvement:* Pulmonary function tests (5) *Liver involvement:* Liver function tests	Child FJ, Ratnavel R, Watkins P, et al. Extracorporeal photopheresis (ECP) in the treatment of chronic graft-versus-host disease (GvHD). *Bone Marrow Transplant*. 1999;23: 881-887.
Clinical improvement No response Progression	Softening of the skin, flattening of cutaneous lesions, increased range of motion, and improved performance status	Marcellus DC, Altomonte VL, Farmer ER, et al. Etretinate therapy for refractory sclerodermatous chronic graft-versus-host disease. *Blood*. 1999;93:66-70.
Complete response Partial response Reduction of other immunosuppressive medications	No specific definition	Lee SJ, Wegner SA, McGarigle CJ, Bierer BE, Antin JH. Treatment of chronic graft-versus-host disease with clofazimine. *Blood*. 1997;89:2298-2302.

Response Criteria	Definition	Reference
Complete response	Complete resolution of all symptoms and signs of cGvHD	Vogelsang GB, Wolff D, Altomonte V, et al. Treatment of chronic graft-versus-host disease with ultraviolet irradiation and psoralen (PUVA). *Bone Marrow Transplant*. 1996;17:1061-1067.
Partial response	Complete resolution of cutaneous GvHD but persistence of other systemic manifestations or at least a 50% improvement in GvHD	
No response	No improvement	
Response*	Only patients with sustained responses to therapy without reprogression were included among the responders.	Parker PM, Chao N, Nademanee A, et al. Thalidomide as salvage therapy for chronic graft-versus-host disease. *Blood*. 1995;86:3604-3609
1) Complete response	Complete disappearance of all clinical manifestations of cGvHD	
2) Partial response	A 50% improvement in objective parameters of cGvHD manifestations (extent of skin involvement, total bilirubin, pulmonary function tests [PIT] in bronchiolitis obliterans with organizing pneumonia [BOOP])	
3) No response	Progression of cGvHD after one month of therapy or failure to improve after three months of thalidomide therapy	
*A response in oral cGvHD required symptomatic improvement as well as physician assessment of comparative improvement.		
Clinical response	Resolution of symptoms of chronic GvHD and withdrawal of other immunosuppressive therapy	Cole CH, Rogers PC, Pritchard S, Phillips G, Chan KW. Thalidomide in the management of chronic graft-versus-host disease in children following bone marrow transplantation. *Bone Marrow Transplant*. 1994;14:937-942.

Response Criteria	Definition	Reference
Complete	Resolution of all chronic GvHD manifestations	Vogelsang GB, Farmer ER, Hess AD, et al. Thalidomide for the treatment of chronic graft-versus-host disease. *N Engl J Med*. 1992;326:1055-1058.
Partial	>50% but less than complete organ responses	
No response	<50% response	
Progression	Worsening while on therapy	
Response	Percent decrease from baseline in liver function tests	Fried RH, Murakami CS, Fisher LD, Willson RA, Sullivan KM, McDonald GB. Ursodeoxycholic acid treatment of refractory chronic graft-versus-host disease of the liver. *Ann Intern Med*. 1992;116:624-629.
Clear response		Heney D, Norfolk DR, Wheeldon J, Bailey CC, Lewis IJ, Barnard DL. Thalidomide treatment for chronic graft-versus-host disease. *Br J Haematol*. 1991;78:23-27.
Partial response		
Good response*		Sullivan KM, Witherspoon RP, Storb R, et al. Alternating-day cyclosporine and prednisone for treatment of high-risk chronic graft-v-host disease. *Blood*. 1988;72:555-561.
Discontinuation of all immunosuppressive therapy	Major improvement of cGvHD symptoms and signs	
Fair response	Minor improvement of cGvHD symptoms and signs	
No response	Worsening cGvHD symptoms and signs	

*Also, the following end points were evaluated:
- Toxicity
- Karnofsky performance status
- Actuarial survival at 4 years

Response Criteria	Definition	Reference
Good response*		
Discontinuation of all immunosuppressive therapy	Major improvement of cGvHD symptoms and signs	Sullivan KM, Shulman HM, Storb R, et al. Chronic graft-versus-host disease in 52 patients: adverse natural course and successful treatment with combination immunosuppression. *Blood*. 1981;57:267-276.
Fair response	Minor improvement of cGvHD symptoms and signs	
No response	Worsening cGvHD symptoms and signs	
*Also, the following end points were evaluated: - Survival with or without disability - GvHD-free survival - Disability rate - Improvement in Karnofsky performance status		