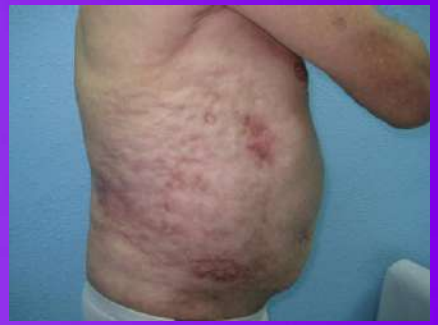
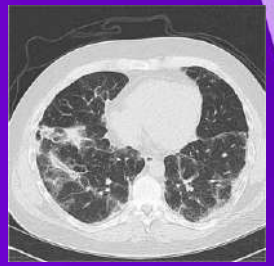
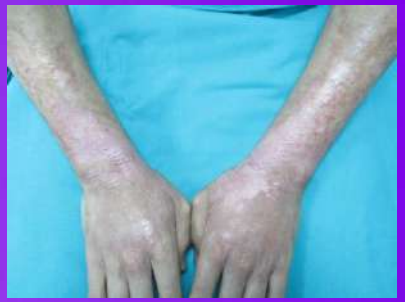
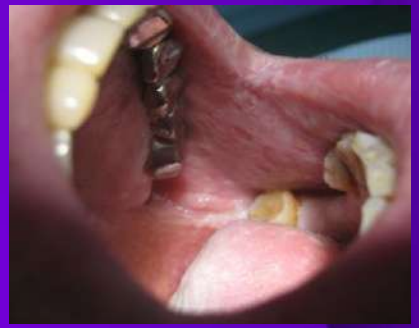
EICR: enfermedad multifactorial. A propósito de un caso









Lucía López Corral

Hospital Universitario de Salamanca

MAT-ES-2400764 V2 Marzo 2024

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Clinical Case with patient permission
all photos will be displayed with patients permission

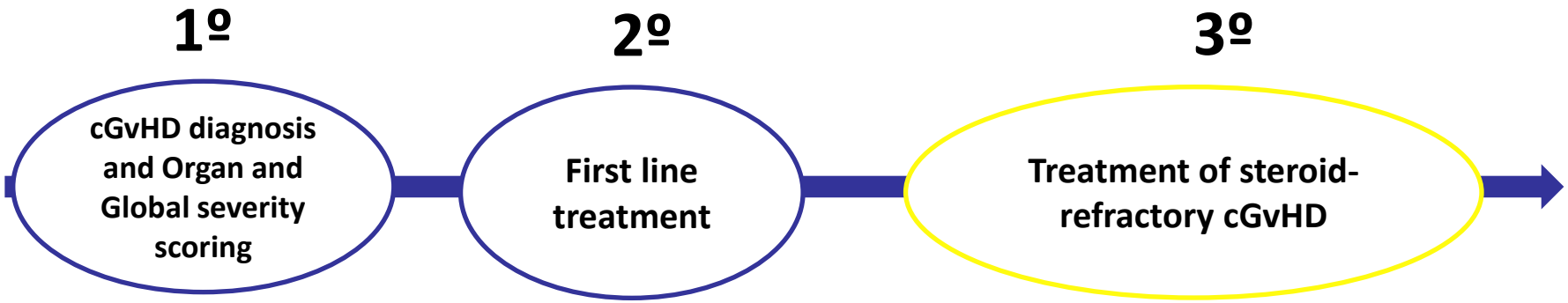
GETH-TC

Disclaimer

- La información proporcionada es esta ponencia tiene finalidad educacional científica y médica y está dirigida a profesionales de la salud.

- Sanofi no recomienda el uso de sus productos de ninguna manera que no sea la descrita en su ficha técnica.

Introduction:



Balance between effective control of cGvHD vs long-term side effects vs the risk to counteract with the protective GVL effect

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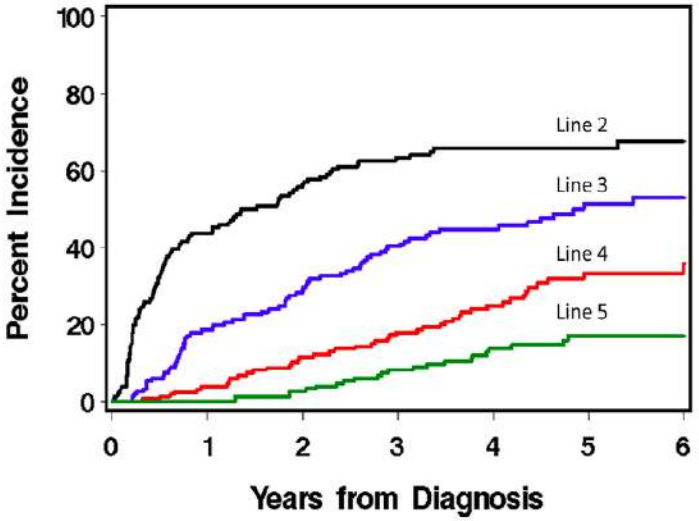
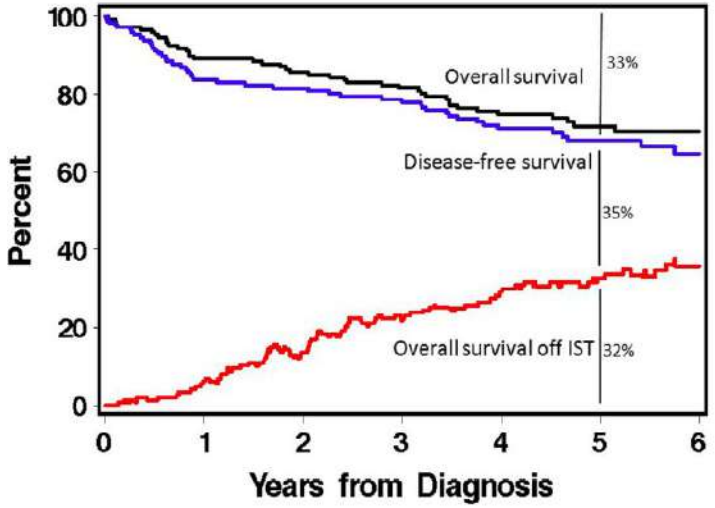
cGvHD remains the leading cause of late non-relapse mortality

Cumulative incidence of starting lines of therapy for chronic GvHD (N=148)



Prevalence of being alive, disease-free, and off immunosuppression (N=148)



Lee S et al. BBMT 2018; 24: 555–562

Clinical case

- 22-year-old male. No relevant medical history. No comorbidities
- April / 2018: asthenia and weight loss in the last month

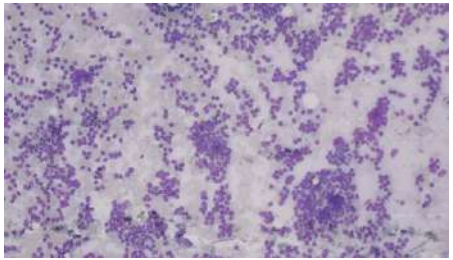
  Hemogram: **Hb: 12 g/dL; Leukocytes 65 x 10^9/L; Platelets: 62 x 10^9/L**

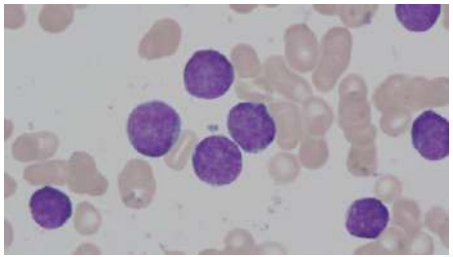
  Biochemistry: **LDH 916 U/L, PCR 5 mg/dL. No other abnormal parameters**

  Coagulation parameters: **D dimeros 2, PT 63%. No other abnormal parameters**

Bone Marrow studies: ALL-B , NOS

- Morphology: 90% blast compatible with ALL-B L2
- Cytometry: 77% blasts, CD34+; CD45+ deb; CD19+; CD10++; CD20+-; cCD79a+; CD22+; CD81+; CD58+; CD24+, CD56c+
- Cytogenetics: normal karyotype and FISH
- Gene mutation analysis: no abnormalities





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Clinical case

Induction / Consolidation / Maintenance therapy: LAL-AR PETHEMA 2011 (05-11 / 2018)

CR with negative MRD 10-4 by FC

First relapse 05/2020: Refractory to FlagIda

CR with negative MRD 10^{-4} after Blinatumumab x 2

Allogeneic stem cell transplantation:

- **HLA-matched related donor**
- **Growth factor-mobilized blood stem cells**
- **GvHD prophylaxis: tacrolimus plus methotrexate**
- **Myeloablative conditioning regimen: Cy + TBI**
- **Infusion date: 03/09/2020**

Engraftment and early toxicity after allo-HSCT

- **Engraftment:** day +14
- **Discharged:** day +17
- **BM aspirate (day +21):** CR with negative MRD. Complete Chimerism

Day +50:

- **Acute GvHD overall clinical grade II:**
  - Skin grade I
  - Upper gut grade I
  - Resolved after treatment with topical steroid and oral beclomethasone and budesonide.

✓ Started tacrolimus reduction on day +180.

✓ **Day + 275: tacrolimus infratherapeutic levels**

Arthralgias and cramps

Signs and symptoms of chronic GvHD:

ORGAN OR SITE	DIAGNOSTIC *(Sufficient to establish the diagnosis of chronic GVHD)*	DISTINCTIVE* *(Seen in chronic GVHD, but insufficient alone to establish a diagnosis)*	OTHER FEATURES OR UNCLASSIFIED ENTITIES**	COMMON*** *(Seen with both acute and chronic GVHD)*
Muscles, Fascia, Joints	• Fasciitis • Joint stiffness or contractures secondary to fasciitis or sclerosis	• Myositis or polymyositis††	• Edema • **Muscle cramps** • **Arthralgia or arthritis**	
Hematopoietic and Immune			• Thrombocytopenia • Eosinophilia • Lymphopenia • Hypo- or hyper-gammaglobulinemia • Autoantibodies (AIHA, ITP) • Raynaud's phenomenon	

** Can be acknowledged as part of the chronic GvHD manifestations if diagnosis is confirmed.

He does NOT currently meet chronic GvHD criteria

Jagasia MH, Greinix HT, Arora M, Williams KM, Wolff D, Cowen EW, Palmer J, Weisdorf D, Treister NS, Cheng GS, Kerr H, Stratton P, Duarte RF, McDonald GB, Inamoto Y, Vigorito A, Arai S, Datiles MB, Jacobsohn D, Heller T, Kitko CL, Mitchell SA, Martin PJ, Shulman H, Wu RS, Cutler CS, Vogelsang GB, Lee SJ, Pavletic SZ, Flowers ME. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group report. Biol Blood Marrow Transplant. 2015 Mar;21(3):389-401.e1. doi: 10.1016/j.bbmt.2014.12.001. Epub 2014 Dec 18. PMID: 25529383; PMCID: PMC4329079.

Chronic GvHD history after allo-HSCT

✓ **Day + 275: tacrolimus infratherapeutic levels**

Arthralgias and cramps

- **Anamnesis and thorough physical examination**
- **Perform respiratory function tests**
- **Rule out hydroelectrolytic abnormalities**
- **Increase water intake (daily tonic –quinine-)**
- **Tacrolimus tapering is stopped**

Close follow-up and screening for any potential manifestation of cGvHD

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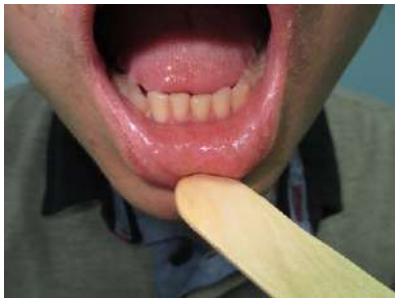
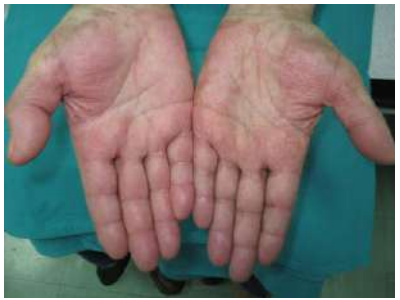
Chronic GvHD history after allo-HSCT

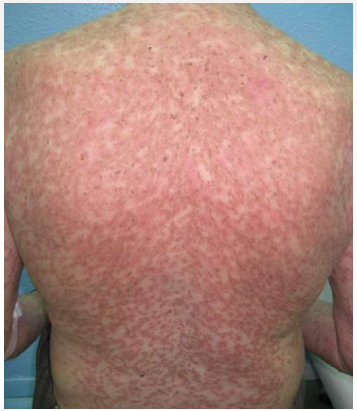
- **Day +350:**
  - ***Eosinophilia*** **(500-580 / µL)**
  - ***Mouth:*** **Asymptomatic lichenoid features**
  - ***Ocular involvement:*** **new onset of dry eyes and blepharitis.**

Ophthalmologist exam: mild keratoconjunctivitis sicca by slit lamp exam. Schirmer´s test value: 9 mm.

- Lichen planus-like eruption: erythematous/violaceous falt-topped papules with surface reticulations and shiny appearance







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Chronic GvHD history after allo-HSCT

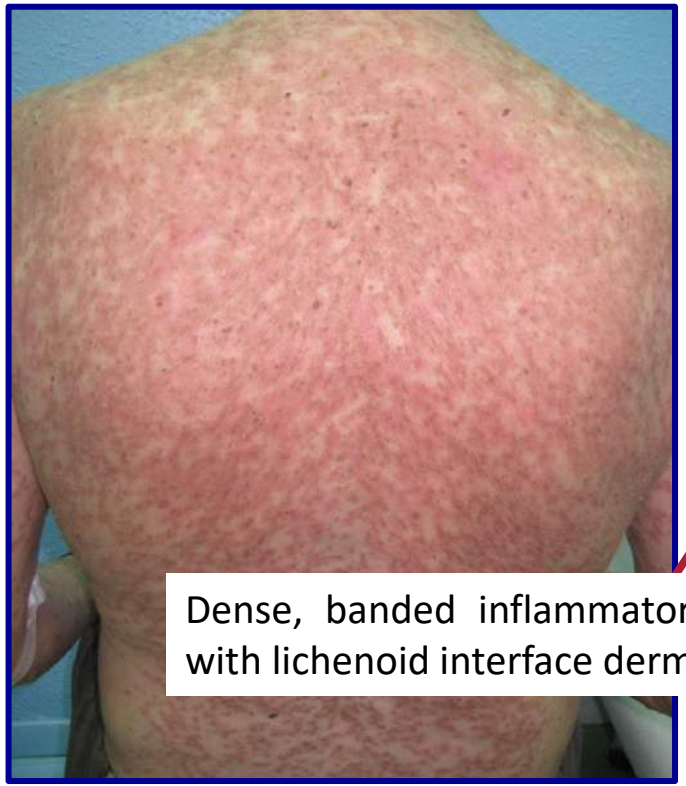
Table 1. Signs and symptoms of chronic GVHD

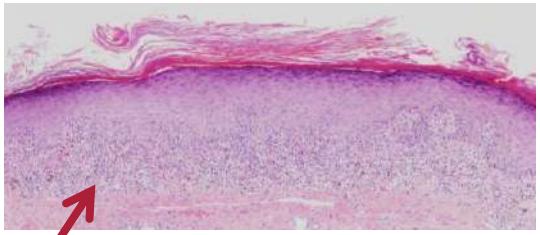
ORGAN OR SITE	DIAGNOSTIC *(Sufficient to establish the diagnosis of chronic GVHD)*	DISTINCTIVE* *(Seen in chronic GVHD, but insufficient alone to establish a diagnosis)*	OTHER FEATURES OR UNCLASSIFIED ENTITIES**	COMMON*** *(Seen with both acute and chronic GVHD)*
Skin	• Poikiloderma • Lichen planus-like features • Sclerotic features • Morphea-like features • Lichen sclerosus-like features	• Depigmentation • Papulosquamous lesions	• Sweat impairment • Ichthyosis • Keratosis pilaris • Hypopigmentation • Hyperpigmentation	• Erythema • Maculopapular rash • Pruritus
Nails		• Dystrophy • Longitudinal ridging, splitting or brittle features • Onycholysis • Pterygium unguis • Nail loss (usually symmetric, affects most nails)		
Scalp and Body Hair		• New onset of scarring or non-scarring scalp alopecia, (after recovery from chemoradiotherapy) • Loss of body hair • Scaling	• Thinning scalp hair, typically patchy, coarse or dull (not explained by endocrine or other causes), • Premature gray hair	
Mouth	• Lichen planus-like changes	• Xerostomia • Mucoceles • Mucosal atrophy • Ulcers • Pseudomembranes		• Gingivitis • Mucositis • Erythema • Pain
Eyes		• New onset dry, gritty, or painful eyes • Cicatricial conjunctivitis • Keratoconjunctivitis sicca • Confluent areas of punctate keratopathy	• Photophobia • Periorbital hyperpigmentation • Blepharitis (erythema of the eye lids with edema)	

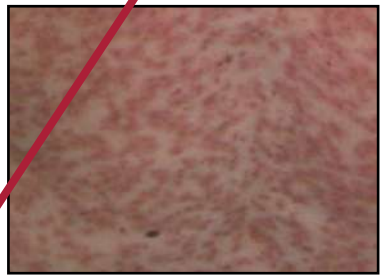
Our patient currently meets chronic GvHD criteria

Jagasia MH, Greinix HT, Arora M, Williams KM, Wolff D, Cowen EW, Palmer J, Weisdorf D, Treister NS, Cheng GS, Kerr H, Stratton P, Duarte RF, McDonald GB, Inamoto Y, Vigorito A, Arai S, Datiles MB, Jacobsohn D, Heller T, Kitko CL, Mitchell SA, Martin PJ, Shulman H, Wu RS, Cutler CS, Vogelsang GB, Lee SJ, Pavletic SZ, Flowers ME. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group report. Biol Blood Marrow Transplant. 2015 Mar;21(3):389-401.e1. doi: 10.1016/j.bbmt.2014.12.001. Epub 2014 Dec 18. PMID: 25529383; PMCID: PMC4329079.

Lichen planus-like eruption:

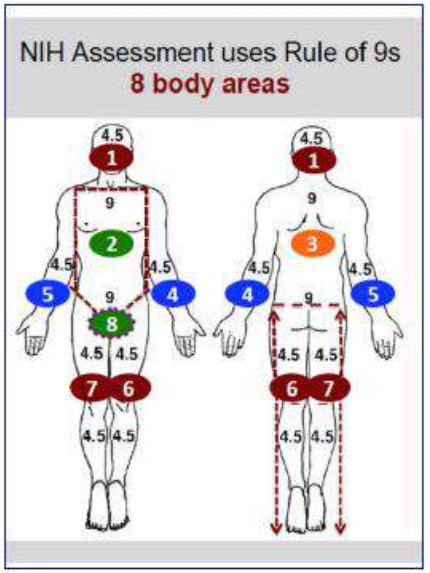






Dense, banded inflammatory lymphocyte infiltrate with lichenoid interface dermatitis

Body surface area (BSA)



BSA 35% →

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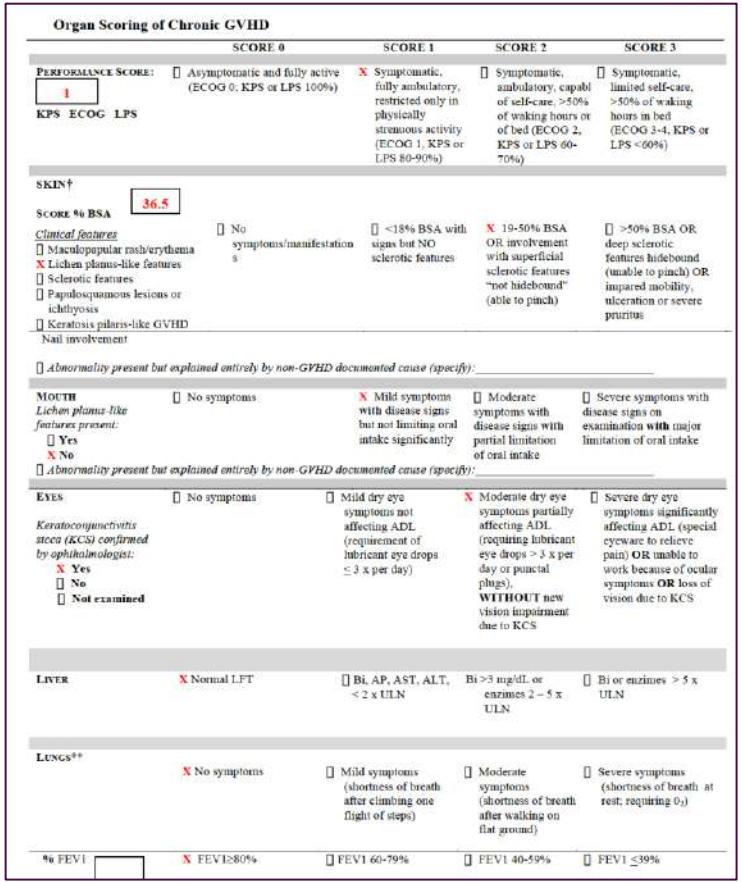
Organ and Global Scoring of Chronic GvHD:

NIH Global Severity of Chronic GvHD

- **Mild cGvHD:** 1 or 2 organs involved with no more than score 1 plus lung score 0
- **Moderate cGvHD:**
  - 3 or more organs involved with no more than score 1 OR
  - At least 1 organ (not lung) with a score of 2 OR
  - Lung score 1
- **Severe cGvHD:**
  - At least 1 organ with a score of 3 OR
  - Lung score of 2 or 3



Organ Scoring of Chronic GVHD

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
PERFORMANCE SCORE: 1 KPS ECOG LPS	☐ Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	X Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%)	☐ Symptomatic, ambulatory, capabl of self-care, >50% of waking hours or of bed (ECOG 2, KPS or LPS 60-70%)	☐ Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%)
SKIN† SCORE % BSA 36.5 *Clinical features* ☐ Maculopapular rash/erythema X Lichen planus-like features ☐ Sclerotic features ☐ Papulosquamous lesions or ichthyosis ☐ Keratosis pilaris-like GVHD Nail involvement	☐ No symptoms/manifestations	☐ <18% BSA with signs but NO sclerotic features	X 19-50% BSA OR involvement with superficial sclerotic features "not hidebound" (able to pinch)	☐ >50% BSA OR deep sclerotic features hidebound (unable to pinch) OR impared mobility, ulceration or severe pruritus
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
MOUTH *Lichen planus-like features present:* ☐ Yes X No	☐ No symptoms	X Mild symptoms with disease signs but not limiting oral intake significantly	☐ Moderate symptoms with disease signs with partial limitation of oral intake	☐ Severe symptoms with disease signs on examination with major limitation of oral intake
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
EYES *Keratoconjunctivitis sicca (KCS) confirmed by ophthalmologist:* X Yes ☐ No ☐ Not examined	☐ No symptoms	☐ Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤ 3 x per day)	X Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops > 3 x per day or punctal plugs), WITHOUT new vision impairment due to KCS	☐ Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) OR unable to work because of ocular symptoms OR loss of vision due to KCS
LIVER	X Normal LFT	☐ Bi, AP, AST, ALT, < 2 x ULN	Bi >3 mg/dL or enzimes 2 – 5 x ULN	☐ Bi or enzimes > 5 x ULN
LUNGS††	X No symptoms	☐ Mild symptoms (shortness of breath after climbing one flight of steps)	☐ Moderate symptoms (shortness of breath after walking on flat ground)	☐ Severe symptoms (shortness of breath at rest; requiring O_2)
% FEV1	X FEV1≥80%	☐ FEV1 60-79%	☐ FEV1 40-59%	☐ FEV1 ≤39%

Jagasia MH, Greinix HT, Arora M, Williams KM, Wolff D, Cowen EW, Palmer J, Weisdorf D, Treister NS, Cheng GS, Kerr H, Stratton P, Duarte RF, McDonald GB, Inamoto Y, Vigorito A, Arai S, Datiles MB, Jacobsohn D, Heller T, Kitko CL, Mitchell SA, Martin PJ, Shulman H, Wu RS, Cutler CS, Vogelsang GB, Lee SJ, Pavletic SZ, Flowers ME. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group report. Biol Blood Marrow Transplant. 2015 Mar;21(3):389-401.e1. doi: 10.1016/j.bbmt.2014.12.001. Epub 2014 Dec 18. PMID: 25529383; PMCID: PMC4329079.

Day +350: Quiescent moderate chronic GvHD with:

- ***Ocular involvement score 2***
- ***Mouth score 1***
- ***Skin score (liquenoide) 2***
- ***Eosinophilia*** **(500-1000 / µL)**

cGvHD: first line treatment

- **EICRc moderado de bajo riesgo: prednisona 1 mg/kg/día con descenso a días alternos (IB)**
- **EICRc moderado riesgo intermedio / alto o severo: prednisona + inhib calcineur (IIC)**

Ensayos fase I / III en primera línea (+- MMF, talidomida, azatioprina, hidroxicloroquina, entospletinib, rituximab, ibrutinib, itacitinib…) no han mostrado superioridad respecto al esteroide en monoterapia

Guía clínica EICRc GETH-TC 2021

Treatment of moderate Chronic GvHD:

Day + 350: Moderate chronic GvHD:

(*Ocular/oral involvement score 2; Skin (lichenoid involvement) score 2*

Systemic AND topical treatment

- **Prednisona 1 mg/kg/day (x 2 weeks followed by a taper to reach and alternate day regimen) and increased tacrolimus**
- **Intensification of topical treatment:**
  - **Skin:**
    - **Clobetasol propionate cream 0.5 mg/g (clovate®) twice a day x 2 weeks, once a day thereafter. Topical CNI FK506 (protopic® 0.1%) was added**
  - **Oral involvement: triamcinolone 0.1% alternating with topical FK506 (protopic® 0.1%)**
  - **Ocular involvement:**
    - **Increase of ocular surface moisture (artificial lubricant tears, viscous eye drops and autologous serum eye drops)**
    - **Decrease inflamation: topical 0.02% tacrolimus ointment**

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Treatment of moderate Chronic GvHD:

Ancilliary therapy and Supportive care

- **Antibiotic prophylaxis** to prevent pneumocystis pneumonia (cotrimoxazole) and antiviral prophylaxis (acyclovir)
- **Bone density test (hip and spine):** T > 1.5 DE
- Daily intake of **vitamin D 1000 UI** and **calcium 1500 mg** was recommended
- **Pulmonary function tests** were performed

Comprehensive monitoring for cGvHD progression (including pulmonary function tests) is essential

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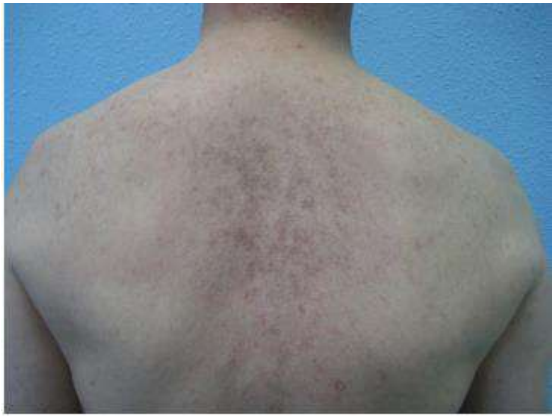
3 months after first line treatment… (day + 440)

Our patient maintains topical treatment + prednisone 20 mg/48h + tacrolimus

- ***Ocular involvement score 2*** → ***Subjective and objective improvement (score 1)***
- ***Mouth score 1*** → ***Normal oral mucosa (score 0)***
- ***Skin score 2*** → ***Residual hyperpigmentation, nail dystrophy***



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Comprehensive monitoring for cGvHD progression (including pulmonary function tests) is essential

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3 months after first line treatment… (day + 440)

Our patient maintains topical treatment + prednisone 20 mg/48h + tacrolimus

FORM A

Current Patient Weight: _____ **Today's Date:** _____ **MR#/Name:** _____

CHRONIC GVHD ACTIVITY ASSESSMENT- CLINICIAN

Health Care Provider Global Ratings:

0=none
1= mild
2=moderate
3=severe

Where would you rate the severity of this patient's chronic GvHD symptoms on the following scale, where 0 is cGVHD symptoms that are not at all severe and 10 is the most severe cGVHD symptoms possible:

0 1 2 3 4 5 6 7 8 9 10

cGvHD symptoms not at all severe — Most severe cGvHD symptoms possible

Over the <<time>> would you say that this patient's cGvHD is

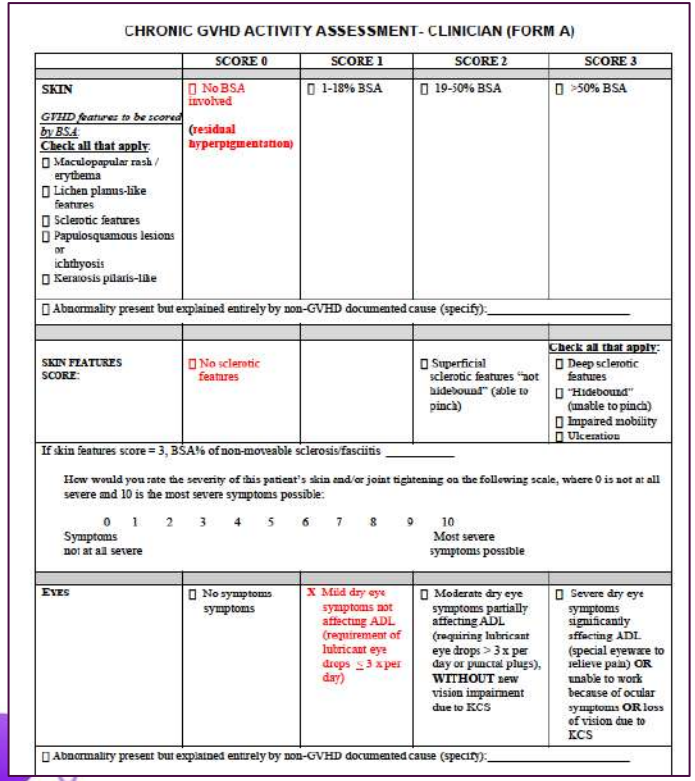
+3= Very much better
+2= Moderately better
+1= A little better
0= About the same
-1=A little worse
-2=Moderately worse
-3=Very much worse

Mouth

Erythema	None	0	Mild erythema or moderate erythema (<25%)	1	Moderate (≥25%) or Severe erythema (<25%)	2	Severe erythema (≥25%)	3
Lichenoid	None	0	Lichen-like changes (<25%)	1	Lichen-like changes (25-50%)	2	Lichen-like changes (>50%)	3
Ulcers	None	0			Ulcers involving (≤20%)	3	Severe ulcerations (>20%)	6
							Total score for all mucosal changes	0

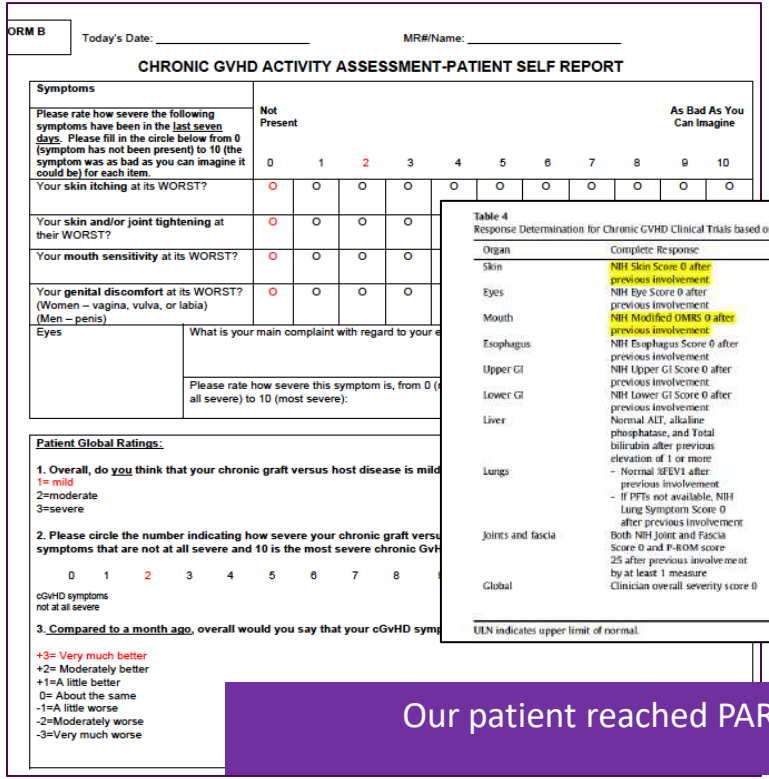
Lee SJ,. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: IV. The 2014 Response Criteria Working Group report. Biol Blood Marrow Transplant. 2015 Jun;21(6):984-99. doi: 10.1016/j.bbmt.2015.02.025. Epub 2015 Mar 19. PMID: 25796139; PMCID: PMC4744804

3 months after first line treatment… (day + 440)



CHRONIC GVHD ACTIVITY ASSESSMENT- CLINICIAN (FORM A)

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
SKIN *GVHD features to be scored by BSA:* **Check all that apply:** ☐ Maculopapular rash / erythema ☐ Lichen planus-like features ☐ Sclerotic features ☐ Papulosquamous lesions or ichthyosis ☐ Keratosis pilaris-like	☐ No BSA involved **(residual hyperpigmentation)**	☐ 1-18% BSA	☐ 19-50% BSA	☐ >50% BSA
☐ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____				
SKIN FEATURES SCORE:	☐ No sclerotic features		☐ Superficial sclerotic features "not hidebound" (able to pinch)	**Check all that apply:** ☐ Deep sclerotic features ☐ "Hidebound" (unable to pinch) ☐ Impaired mobility ☐ Ulceration
If skin features score = 3, BSA% of non-moveable sclerosis/fasciitis _____				
How would you rate the severity of this patient's skin and/or joint tightening on the following scale, where 0 is not at all severe and 10 is the most severe symptoms possible: 0 1 2 3 4 5 6 7 8 9 10 Symptoms not at all severe — Most severe symptoms possible				
EYES	☐ No symptoms symptoms	X Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤ 3 x per day)	☐ Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops > 3 x per day or punctal plugs), **WITHOUT** new vision impairment due to KCS	☐ Severe dry eye symptoms significantly affecting ADL (special eyewear to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision due to KCS
☐ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____				



ORM B Today's Date: _____ MR#/Name: _____

CHRONIC GVHD ACTIVITY ASSESSMENT-PATIENT SELF REPORT

Symptoms Please rate how severe the following symptoms have been in the last seven days. Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
Your **skin itching** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
Your **skin and/or joint tightening** at their WORST?	O	O	O	O							
Your **mouth sensitivity** at its WORST?	O	O	O	O							
Your **genital discomfort** at its WORST? (Women – vagina, vulva, or labia) (Men – penis)	O	O	O	O							
Eyes	What is your main complaint with regard to your e										
	Please rate how severe this symptom is, from 0 (all severe) to 10 (most severe):										

Patient Global Ratings:

1. Overall, do you think that your chronic graft versus host disease is mild
1= mild
2=moderate
3=severe

2. Please circle the number indicating how severe your chronic graft versu symptoms that are not at all severe and 10 is the most severe chronic GvH

0 1 2 3 4 5 6 7 8

cGvHD symptoms not at all severe

3. Compared to a month ago, overall would you say that your cGvHD symp

+3= Very much better
+2= Moderately better
+1=A little better
0= About the same
-1=A little worse
-2=Moderately worse
-3=Very much worse

Table 4
Response Determination for Chronic GVHD Clinical Trials based on Clinician Assessments

Organ	Complete Response	Partial Response	Progression
Skin	NIH Skin Score 0 after previous involvement	Decrease in NIH Skin Score by 1 or more points	Increase in NIH Skin Score by 1 or more points, except 0 to 1
Eyes	NIH Eye Score 0 after previous involvement	Decrease in NIH Eye Score by 1 or more points	Increase in NIH Eye Score by 1 or more points, except 0 to 1
Mouth	NIH Modified OMRS 0 after previous involvement	Decrease in NIH Modified OMRS of 2 or more points	Increase in NIH Modified OMRS of 2 or more points
Esophagus	NIH Esophagus Score 0 after previous involvement	Decrease in NIH Esophagus Score by 1 or more points	Increase in NIH Esophagus Score by 1 or more points, except 0 to 1
Upper GI	NIH Upper GI Score 0 after previous involvement	Decrease in NIH Upper GI Score by 1 or more points	Increase in NIH Upper GI Score by 1 or more points, except 0 to 1
Lower GI	NIH Lower GI Score 0 after previous involvement	Decrease in NIH Lower GI Score by 1 or more points	Increase in NIH Lower GI Score by 1 or more points, except from 0 to 1
Liver	Normal ALT, alkaline phosphatase, and Total bilirubin after previous elevation of 1 or more	Decrease by 50%	Increase by 2 × ULN
Lungs	– Normal $FEV1 after previous involvement – If PFTs not available, NIH Lung Symptom Score 0 after previous involvement	– Increase by 10% predicted absolute value of $FEV1 – If PFTs not available, decrease in NIH Lung Symptom Score by 1 or more points	– Decrease by 10% predicted absolute value of $FEV1 – If PFTs not available, increase in NIH Lung Symptom Score by 1 or more points, except 0 to 1
Joints and fascia	Both NIH Joint and Fascia Score 0 and P-ROM score 25 after previous involvement by at least 1 measure	Decrease in NIH Joint and Fascia Score by 1 or more points or increase in P-ROM score by 1 point for any site	Increase in NIH Joint and Fascia Score by 1 or more points or decrease in P-ROM score by 1 point for any site
Global	Clinician overall severity score 0	Clinician overall severity score decreases by 2 or more points on a 0-10 scale	Clinician overall severity score increases by 2 or more points on a 0-10 scale

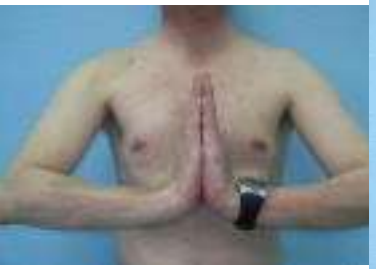
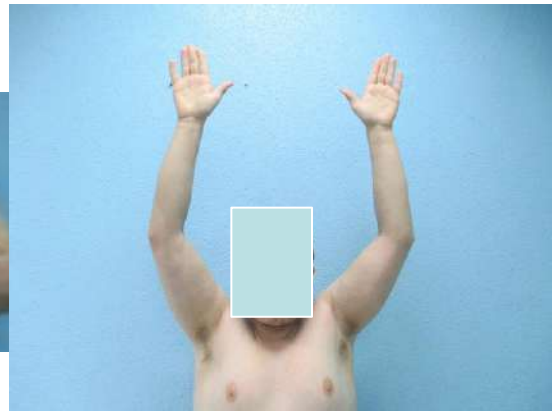
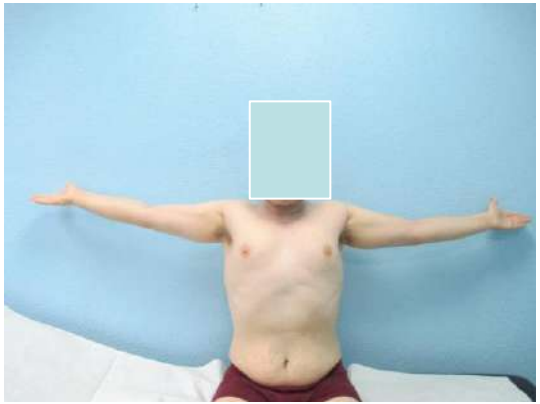
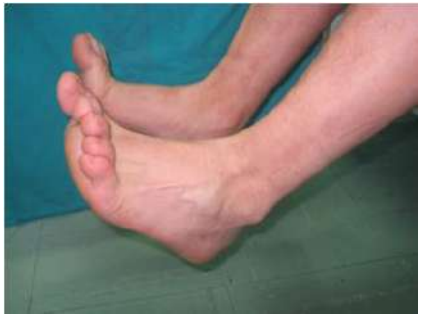
ULN indicates upper limit of normal.

Our patient reached PARTIAL RESPONSE

Lee SJ,. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: IV. The 2014 Response Criteria Working Group report. Biol Blood Marrow Transplant. 2015 Jun;21(6):984-99. doi: 10.1016/j.bbmt.2015.02.025. Epub 2015 Mar 19. PMID: 25796139; PMCID: PMC4744804

4 months after first line treatment… (day + 470)

- **Our patient maintains topical treatment and prednisone 10 mg/48 h**
- cGvHD with ocular involvement (score 1)
- **Arthralgias and eosinophilia 1200 /microL**
- **Mild tighness of arms and legs not affecting ADL.**

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The dose of prednisone was increased two levels
Physiotherapy and close monitoring for early detection of sclerosis

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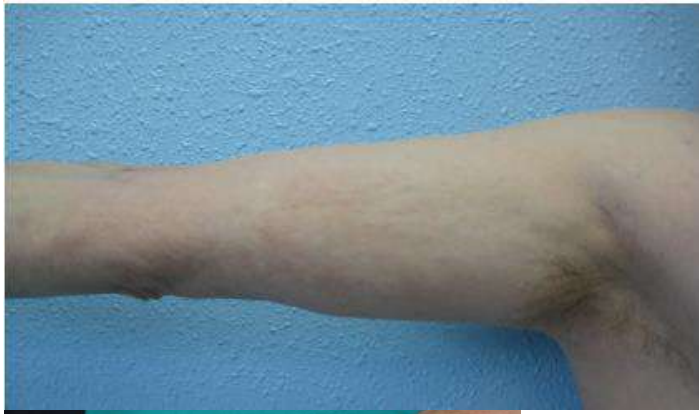
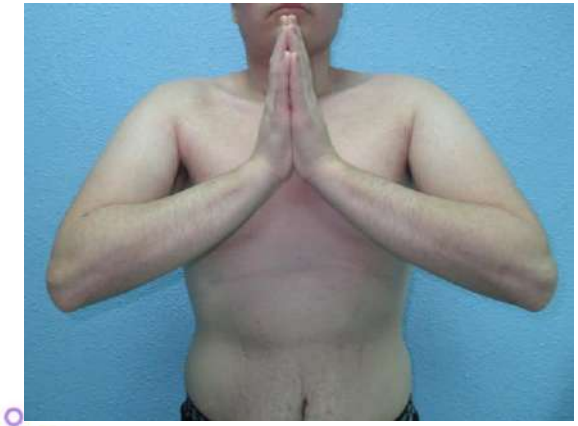
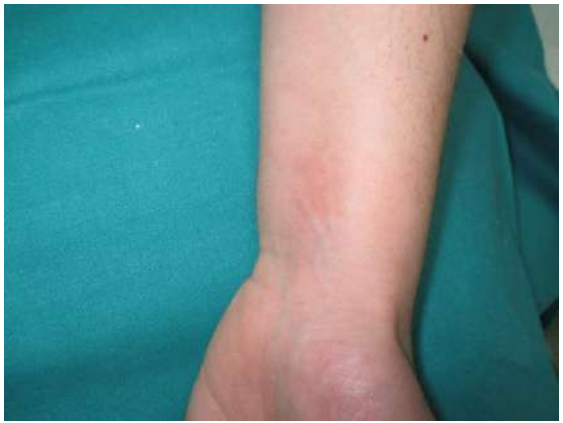
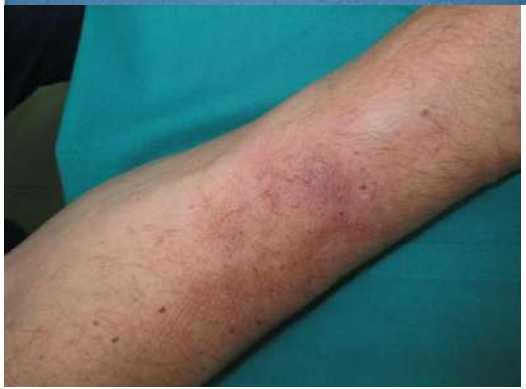
6 months after first line treatment… (day + 530)

Our patient maintains topical treatment and prednisone 20 mg/48 h
cGvHD with ocular and liver involvement (score 1)
Progressive worsening of the tighness of arms and legs









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Organ and Global Scoring of cGvHD:

Organ Scoring of Chronic GVHD

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
PERFORMANCE SCORE: 1 KPS ECOG LPS	☐ Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	X Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%)	☐ Symptomatic, ambulatory, capabl of self-care, >50% of waking hours or of bed (ECOG 2, KPS or LPS 60-70%)	☐ Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%)
SKIN† Score % BSA 18 *Clinical features:* ☐ Maculopapular rash/erythema ☐ Lichen planus-like features X Sclerotic features ☐ Papulosquamous lesions or ichthyosis ☐ Keratosis pilaris-like GVHD X Nail involvement	☐ No symptoms/manifestations	☐ <18% BSA with signs but NO sclerotic features	☐ 19-50% BSA OR involvement with superficial sclerotic features "not hidebound" (able to pinch)	X >50% BSA OR deep sclerotic features hidebound (unable to pinch) OR impared mobility, ulceration or severe pruritus
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):* ___				
MOUTH *Lichen planus-like features present:* ☐ Yes X No	☐ No symptoms	X Mild symptoms with disease signs but not limiting oral intake significantly	☐ Moderate symptoms with disease signs with partial limitation of oral intake	☐ Severe symptoms with disease signs on examination with major limitation of oral intake
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):* ___				
EYES *Keratoconjunctivitis sicca (KCS) confirmed by ophthalmologist:* X Yes ☐ No ☐ Not examined	☐ No symptoms	X Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤ 3 x per day)	Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops > 3 x per day or punctal plugs) WITHOUT new vision impairment due to KCS	☐ Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) OR unable to work because of ocular symptoms OR loss of vision due to KCS
LIVER	Normal LFT	X Bi, AP, AST, ALT, < 2 x ULN	Bi >3 mg/dL or enzimes 2 – 5 x ULN	☐ Bi or enzimes > 5 x ULN
LUNGS**	X No symptoms	☐ Mild symptoms (shortness of breath after climbing one flight of steps)	☐ Moderate symptoms (shortness of breath after walking on flat ground)	☐ Severe symptoms (shortness of breath at rest; requiring 0_2)
% FEV1 ___	X FEV1≥80%	☐ FEV1 60-79%	☐ FEV1 40-59%	☐ FEV1 ≤39%

Figure 1. Organ scoring of chronic GVHD (continued)

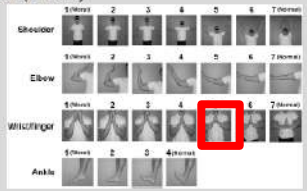
	SCORE 0	SCORE 1	SCORE 2	SCORE 3
JOINTS AND FASCIA P-ROM score *(see below)* Shoulder (1-7): 7 Elbow (1-7): 7 Wrist/finger (1-7): 5 Ankle (1-4): 4	☐ No symptoms	☐ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) AND not affecting ADL	X Tightness of arms or legs OR joint contractures, erythema thought due to fasciitis, moderate decrease ROM AND mild to moderate limitation of ADL	☐ Contractures WITH significant decrease of ROM *AND* significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):* ___				
GENITAL TRACT *(See Supplemental figure‡)* ☐ Not examined *Currently sexually active* ☐ Yes ☐ No	☐ No signs	☐ Mild signs‡ and females with or without discomfort on exam	☐ Moderate signs‡ and may have symptoms with discomfort on exam	☐ Severe signs‡ with or without symptoms
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):* ___				

Other indicators, clinical features or complications related to chronic GVHD (check all that apply and assign a score to severity (0-3) based on functional impact where applicable none – 0,mild -1, moderate -2, severe – 3)

☐ Ascites (serositis)___	☐ Myasthenia Gravis___	
☐ Pericardial Effusion___	☐ Peripheral Neuropathy___	X Eosinophilia > 500/µl___
☐ Pleural Effusion(s)___	☐ Polymyositis___	☐ Platelets <100,000/µl___
☐ Nephrotic syndrome___	☐ Weight loss>5%* without GI symptoms___	☐ Others (specify):___

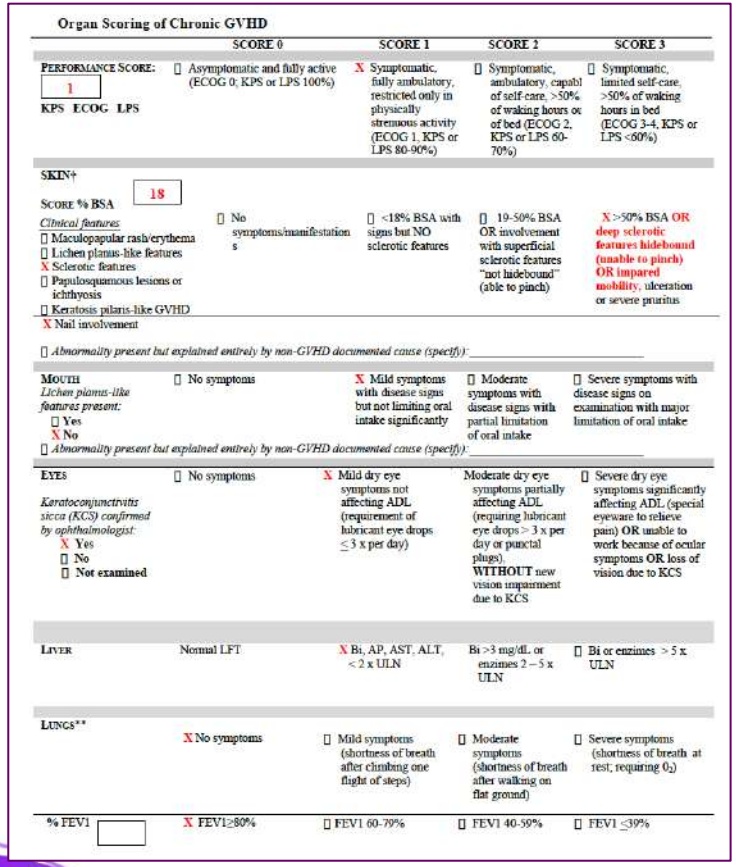
Overall GVHD Severity *(Opinion of the evaluator)* ☐ No GVHD ☐ Mild ☐ Moderate X Severe

Photographic Range of Motion (P-ROM)



Jagasia MH, Greinix HT, Arora M, Williams KM, Wolff D, Cowen EW, Palmer J, Weisdorf D, Treister NS, Cheng GS, Kerr H, Stratton P, Duarte RF, McDonald GB, Inamoto Y, Vigorito A, Arai S, Datiles MB, Jacobsohn D, Heller T, Kitko CL, Mitchell SA, Martin PJ, Shulman H, Wu RS, Cutler CS, Vogelsang GB, Lee SJ, Pavletic SZ, Flowers ME. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group report. Biol Blood Marrow Transplant. 2015 Mar;21(3):389-401.e1. doi: 10.1016/j.bbmt.2014.12.001. Epub 2014 Dec 18. PMID: 25529383; PMCID: PMC4329079.

Organ and Global Scoring of cGvHD:



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SKIN† SCORE % BSA 18 *Clinical features:* ☐ Maculopapular rash/erythema ☐ Lichen planus-like features X Sclerotic features ☐ Papulosquamous lesions or ichthyosis ☐ Keratosis pilaris-like GVHD X Nail involvement	☐ No symptoms/manifestation s	☐ <18% BSA with signs but NO sclerotic features	☐ 19-50% BSA OR involvement with superficial sclerotic features "not hidebound" (able to pinch)	X >50% BSA OR deep sclerotic features hidebound (unable to pinch) OR impared mobility, ulceration or severe pruritus
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% FEV1	X FEV1≥80%	☐ FEV1 60-79%	☐ FEV1 40-59%	☐ FEV1 ≤39%

Severe cGvHD with deep sclerotic features and fascial involvement

NIH Global Severity of Chronic GvHD

- **Mild cGvHD: 1 or 2 organs involved with no more than score 1 plus lung score 0**
- **Moderate cGvHD:**
  - **3 or more organs involved with no more than score 1 OR**
  - **at least 1 organ (not lung) with a score of 2 OR**
- **Severe cGvHD:**
  - **at least 1 organ with a score of 3 OR**
  - **lung score of 2 or 3**
  - **lung score 1**

Jagasia MH, Greinix HT, Arora M, Williams KM, Wolff D, Cowen EW, Palmer J, Weisdorf D, Treister NS, Cheng GS, Kerr H, Stratton P, Duarte RF, McDonald GB, Inamoto Y, Vigorito A, Arai S, Datiles MB, Jacobsohn D, Heller T, Kitko CL, Mitchell SA, Martin PJ, Shulman H, Wu RS, Cutler CS, Vogelsang GB, Lee SJ, Pavletic SZ, Flowers ME. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group report. Biol Blood Marrow Transplant. 2015 Mar;21(3):389-401.e1. doi: 10.1016/j.bbmt.2014.12.001. Epub 2014 Dec 18. PMID: 25529383; PMCID: PMC4329079.

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6 months after first line treatment… (day + 530)

Severe cGvHD with deep sclerotic features and fascial involvement developed during steroid treatment

Definition of inadequate response to steroids:

- **Steroid refractoriness or resistance**
  - cGvHD progression while on prednisone at >= 1 mg/kg/day for 1-2 weeks
  - Stable GvHD disease while on > = 0.5 mg/kg/day of prednisone for 1-2 months
  - Inability to taper prednisone below 0.5 mg/kg/day
- **Steroid dependence:** inability to taper prednisone below 0.25 mg/kg/day in at least two unsuccessful attempts separated by at least 8 weeks
- **Steroid intolerance:** Emergence of unacceptable toxicity due to the use of corticosteroids

EBMT-NIH-IBMTR Task Force (con matización del grupo Consenus Conference on Clinical Practice in cGvHD
Schoemans et al. BMT 2018, Martin PJ, BBMT 2015; Wolff BBMT 2011)

Second line and beyond treatment options

Agent	Reco	Evid.	comments	Agent	Reco	Evid	comments
Steroids	B	III-1	Important, spare steroids due to side effect profile	IL-2	C-2	III-1	best results in mucocutaneous and liver involv.
ECP	C-1	II	spares steroids, use in steroid dependent overlap	Bortezomib	C-2	III-1	effective in mucocutaneous cGVHD, neuropathy
Ruxolitinib	C-1	II	risk for infections, cytopenia, use in overlap	Ixazomib	C-2	III-1	effective in mucocutaneous cGVHD, GI tox
mTOR -I.	C-1	III-1	increased risk for TAM in combination with CNI	Hydroxychlor.	C-2	III-2	best results in mucocutaneous and liver involv.
CNI	C-1	III-1	spares steroids, renal toxicity, use in overlap	MSC	C-3	III-1	preliminary data demonstrate efficacy
MMF	C-1	III-1	risk for viral reactivation, spares steroids	Pomalidomide	C-2	III-1	best results in sclerosis, risk flare early after Tx
Ibrutinib	C-1	III-1	B cell driven disease, risk for infections & bleeding	Axatilimab	C-2	III-2	Best results in sclerotic disease, only in clinical trials
Belumosudil	C-1	III-1	efficacy in classic cGVHD, lack of approval by EMA	Tocilizumab	C-3	III-3	best results in sclerotic mucocutaneous cGVHD
MTX	C-2	III-1	best results in mucocutaeous cGVHD	Reg. T cells	C-3	III-1	currently explored in a number of trials
Imatinib	C-2	II	sclerotic skin lesions and mild and moderate BO	Abatacept	C-3	III-2	preliminary data show efficacy in lung disease
Rituximab	C-2	II	effective if applied early in B cell driven disease, infections	Retinoids	C-3	III-2	effective in sclerotic skin lesion
TLI	C-2	III-2	best results in fasciitis or mucocutaneous cGVHD	Cyclophosph.	C-3	III-3	either low dose or pulse, most effective in GN
Pulse steroids	C-2	III-2	rapid control of symptoms	FAM	C-1	III-1	As add on in BOS, single in mild early BOS

Some of the mentioned drugs may not be approved for cGvHD treatment
Please, always refer to the label of the product in your country.

Modified according to Wolff 2011/2019 and NCCN 2023 guidelines

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FDA regulatory approval landscape for cGvHD in 2024

Agent	Year	Age	Therapy lines	ORR	CR	AEs	Study design Open label
Ibrutinib	2017	≥18	≥1	67%	21%	Bleeding AFib	Phase 2, N=42
Belumosudil	2021	≥12	≥2	75%	6%	GI LFT	Phase 2, N=65
Ruxolitinib	2021	≥12	1-2	76%	7%	Anemia PLTs	Phase 3, N=329

Ibrutinib y Belumosudil no están actualmente aprobados por la EMA para el tratamiento de la EICRc

D Miklos Blood 2017
Cutler et al. Blood. 2021 and EBMT 2022
Zeiser R et al New Engl J Med. 2021

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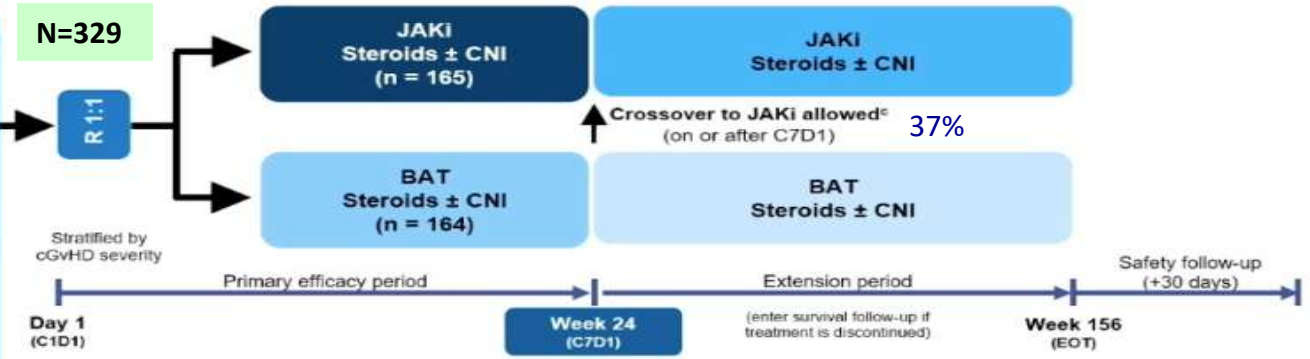
Steroid-refractory cGvHD: Ruxolitinib

REACH3: Prospective, phase 3 randomized, open-label, multicenter study investigating the efficacy of RUX as add-on theraphy to corticosteroid therapy for the treatment of patients with steroid-refractory or steroid-dependent cGvHD

Eligibility

- Age ≥ 12 years
- SR/D cGvHD (moderate or severe), defined as:
  - Lack of response or disease progression after prednisone ≥ 1 mg/kg/day[a] for ≥ 1 week ***or***
  - Disease persistence without improvement with prednisone > 0.5 mg/kg/day or 1 mg/kg/every other day[a] for ≥ 4 weeks ***or***
  - Increase in prednisone dose to > 0.25 mg/kg/day[a] after 2 unsuccessful attempts to taper the dose
- Evident myeloid and platelet engraftment[b]



Primary endpoint: ORR (CR + PR) at Week 24 using NIH consensus criteria for response[2]

Key secondary endpoints:

- FFS
- mLSS response at Week 24

[a] Or prednisone equivalent. [b] Absolute neutrophil count > 1 x 10^9/L and platelet count > 25 x 10^9/L [c] On or after C7D1, patients randomized to BAT who progressed, had a mixed or unchanged response, developed toxicity to BAT, or experienced a cGvHD flare could crossover from BAT to JAKi.
BAT, best available treatment; C, cycle; CNI, calcineurin inhibitor; CR, complete response; D, day; EOT, end of treatment; mLSS, modified Lee Symptom Scale; PR, partial response;

1. Zeiser R, et al. Abstract presented at ASH 2020; abstract 77.
2. Lee SJ, et al. Biol Blood Marrow Transplant. 2015;21:984-99.

Zeiser R et al New Engl J Med. 2021
Lee SJ et al Biol Blood Marrow Trasplant. 2015

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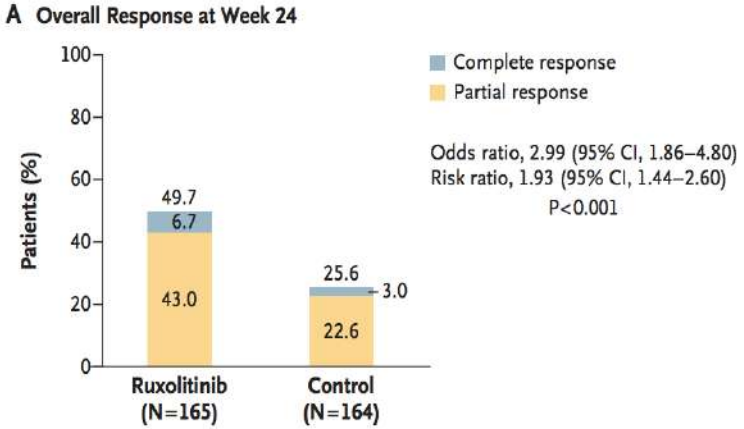
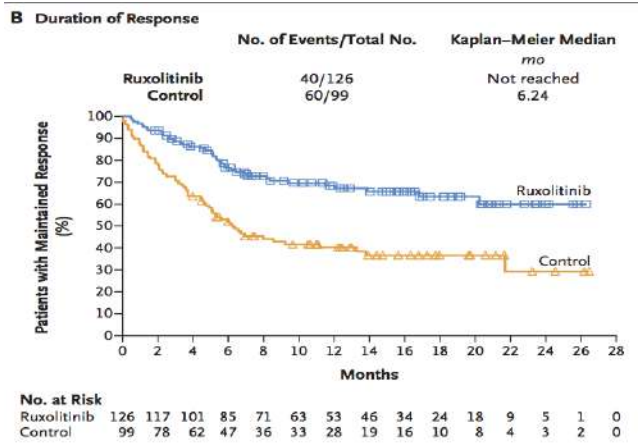
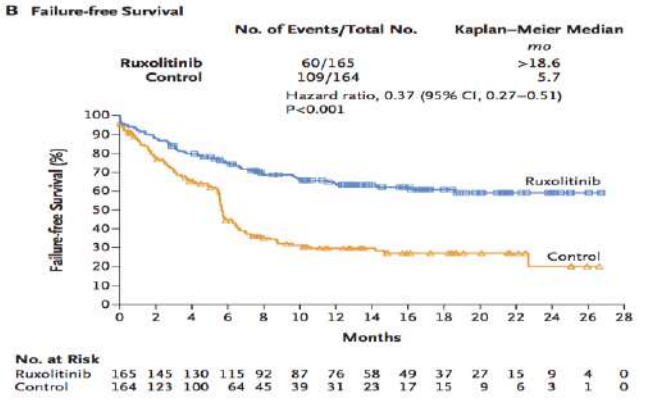




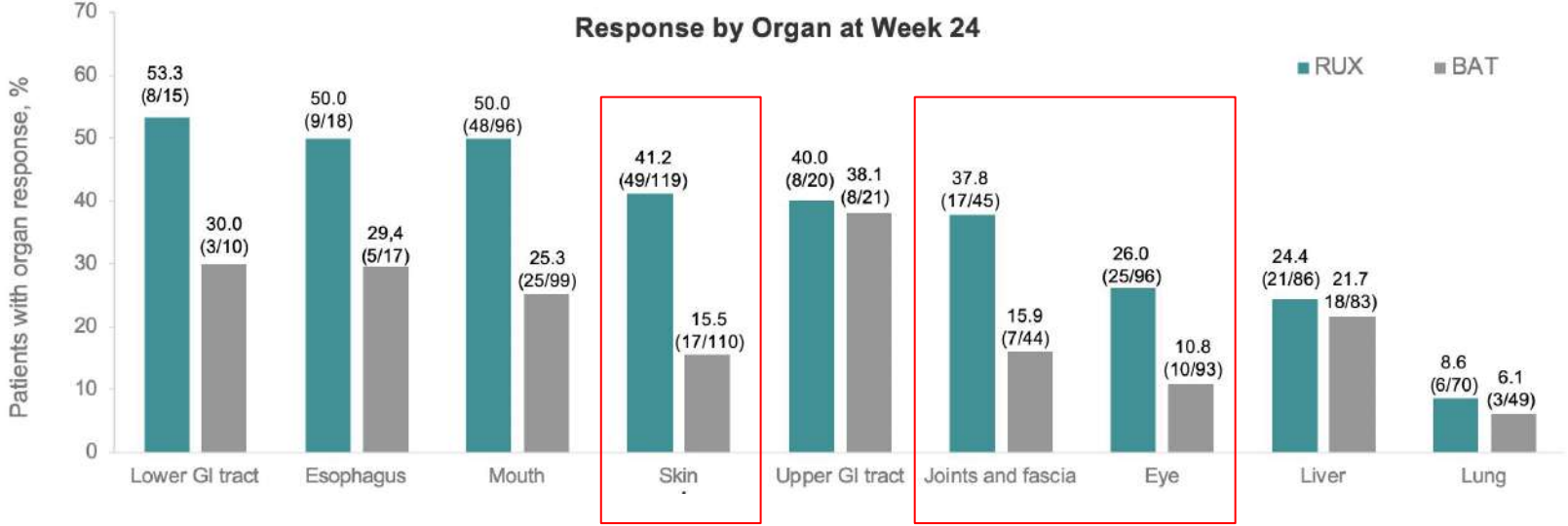


OOR at 24 week was higher with Ruxo vs BAT in all subgroups of patient an disease characteristics at baseline

Best ORR at any time: **76.4% vs 60.4%**

Zeiser R et al New Engl J Med. 2021

REACH3: SR cGvHD Response to Ruxolitinib according to the Presentation



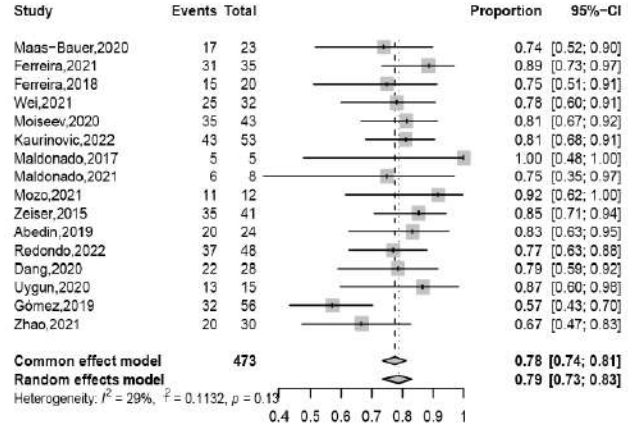
Adverse Events	Ruxolitinib (N=165)		BAT (N=158)	
	Any grade	Gr≥3	Any grade	Gr≥3
Cytopenias				
Anemia	29%	13%	13%	8%
Thrombocytopenia	21%	15%	15%	10%
Neutropenia	11%	9%	5%	4%
Pyrexia	16%	2%	10%	1%
Hypertension	16%	5%	13%	7%
Serum creatinine ↑	14%	0%	4%	1%
ALT ↑	15%	4%	4%	0%
CMV reactivation	6%	1%	8%	0%

Zeiser R et al New Engl J Med. 2021

Efficacy and safety of Ruxolitinib in chronic GVHD: a meta-analysis

N= 1580

C



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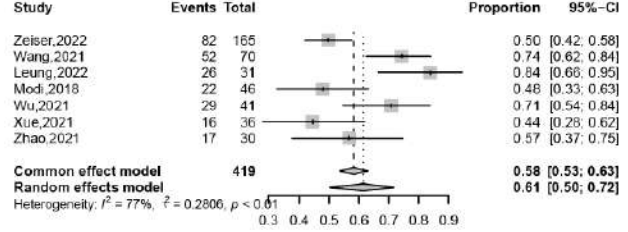


Fan et al. Front. Immunol. 2022

SR cGvHD Response to Ruxolitinib according to the Presentation

Subgroup	ORR		CRR	
	Cumulative incidence (%)	95%CI	Cumulative incidence (%)	95%CI
SR-cGVHD				
Skin	73.2	58.7–87.7	30.1	18.2–42.0
Gut	69.2	50.9–87.5	25.7	2.4–48.9
Liver	65.7	45.0–86.3	32.7	15.8–49.6
Mouth	76.5	61.5–91.5	34.0	24.7–43.3
Eyes	61.1	38.7–83.5	16.7	2.4–31.0
Lung	47.3	29.8–64.9	11.1	1.2–21.0
Joints and fascia	67.4	46.4–88.3	11.9	0.0–23.8
Esophagus	50.0	NA	0.0	NA

Myelosuppression after Ruxolitinib in SR cGvHD

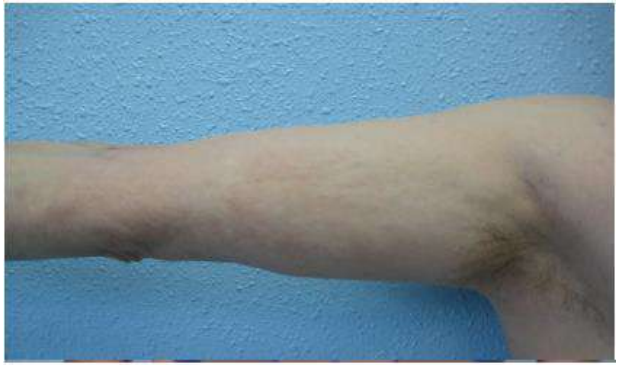
SR-cGVHD						
Cytopenia						
Grades I–IV	28.8	13.0–44.6	28.3	4.8–51.7	NA	NA
Grades III–IV	10.4	0.0–27.9	21.0	0.0–100.0	NA	NA
Anemia						
Grades I–IV	35.1	13.2–57.0	20.7	0.0–57.9	8.3	NA
Grades III–IV	11.2	2.1–20.3	5.0	0.0–15.6	0.0	NA
Leukopenia						
Grades I–IV	22.9	6.2–39.6	11.5	2.6–20.4	8.3	NA
Grades III–IV	8.9	4.7–13.1	9.8	2.3–17.3	0.0	NA
Thrombocytopenia						
Grades I–IV	19.2	6.9–31.6	7.0	0.0–17.6	8.3	NA
Grades III–IV	10.2	3.6–16.8	3.8	0.0–8.3	0.0	NA

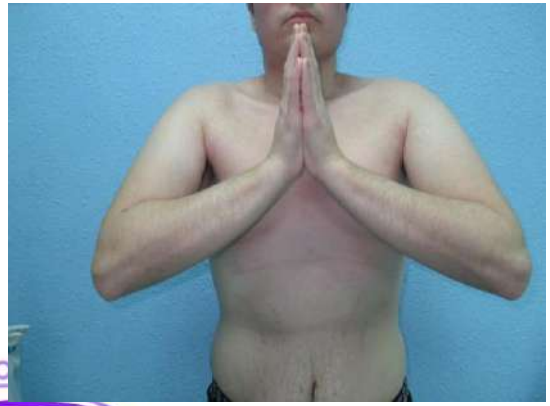
CI, confidence interval; NA, not available; SR-aGVHD, steroid-refractory acute graft-versus-host disease; SR-cGVHD, steroid-refractory chronic graft-versus-host disease.

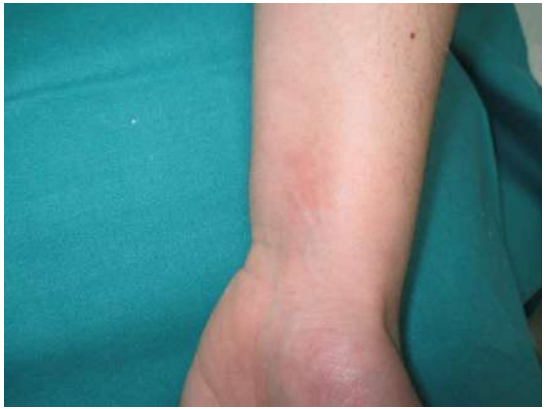
6 months after first line treatment… (day + 530)

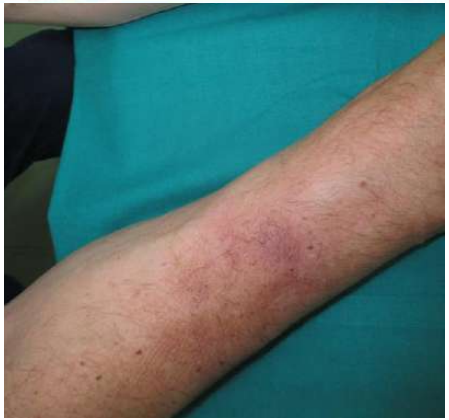
- BSA 18% (sclerotic features with fascial involvement)
- ROM 2 P-ROM (wrist) 5
- Ocular involvement (score 1)

We start treatment with Ruxolitinib
10 mg / 12 h









Photos displayed with patients' permission

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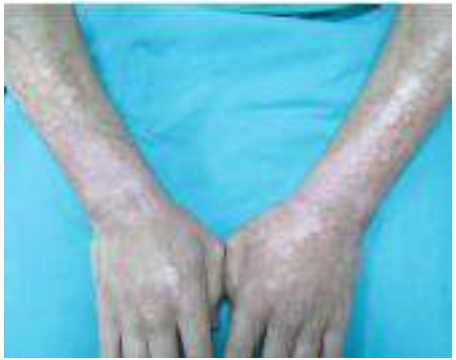
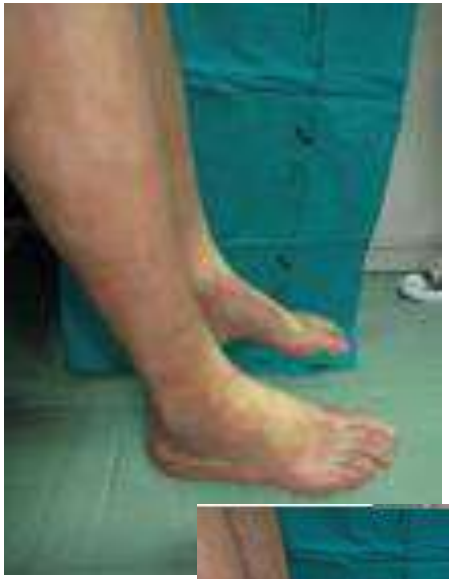
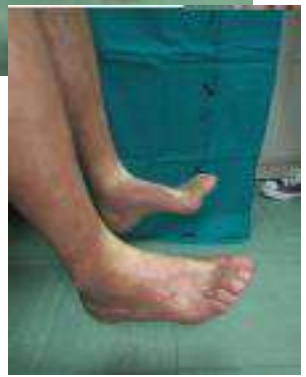
3 months after Ruxolitinib… (day + 620)

BSA 54% (sclerotic features)
ROM 2 P-ROM (wrist) 4 (ankle 2)
Ocular and liver involvement (score 1)







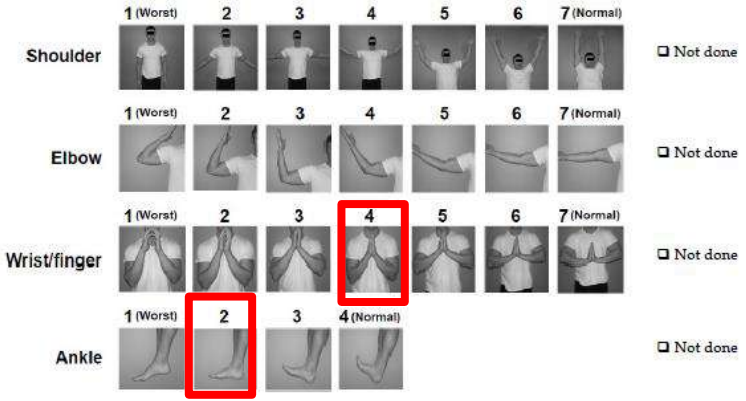
Photos displayed with patients' permission

3 months after Ruxolitinib… (day + 620)

CHRONIC GVHD ACTIVITY ASSESSMENT- CLINICIAN (FORM A)

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
SKIN *GVHD features to be scored by BSA:* **Check all that apply:** ☐ Maculopapular rash / erythema ☐ Lichen planus-like features ☐ Sclerotic features ☐ Papulosquamous lesions or ichthyosis ☐ Keratosis pilaris-like	☐ No BSA involved (residual hyperpigmentation)	☐ 1-18% BSA	☐ 19-50% BSA	X >50% BSA
☐ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____				
SKIN FEATURES SCORE:	☐ No sclerotic features		☐ Superficial sclerotic features "not hidebound" (able to pinch)	**Check all that apply:** X Deep sclerotic features X "Hidebound" (unable to pinch) X Impaired mobility ☐ Ulceration
If skin features score = 3, BSA% of non-moveable sclerosis/fasciitis 54%				
How would you rate the severity of this patient's skin and/or joint tightening on the following scale, where 0 is not at all severe and 10 is the most severe symptoms possible: 0 1 2 3 4 5 6 7 **8** 9 10 Symptoms not at all severe … Most severe symptoms possible				
EYES	☐ No symptoms symptoms	X Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤ 3 x per day)	☐ Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops > 3 x per day or punctal plugs), WITHOUT new vision impairment due to KCS	☐ Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) OR unable to work because of ocular symptoms OR loss of vision due to KCS

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
JOINTS AND FASCIA	☐ No symptoms	☐ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) AND not affecting ADL	X Tightness of arms or legs OR joint contractures, erythema thought due to fasciitis, moderate decrease ROM AND mild to moderate limitation of ADL	☐ Contractures WITH significant decrease of ROM AND significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
☐ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____				



Jagasia MH, Greinix HT, Arora M, Williams KM, Wolff D, Cowen EW, Palmer J, Weisdorf D, Treister NS, Cheng GS, Kerr H, Stratton P, Duarte RF, McDonald GB, Inamoto Y, Vigorito A, Arai S, Datiles MB, Jacobsohn D, Heller T, Kitko CL, Mitchell SA, Martin PJ, Shulman H, Wu RS, Cutler CS, Vogelsang GB, Lee SJ, Pavletic SZ, Flowers ME. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group report. Biol Blood Marrow Transplant. 2015 Mar;21(3):389-401.e1. doi: 10.1016/j.bbmt.2014.12.001. Epub 2014 Dec 18. PMID: 25529383; PMCID: PMC4329079.

3 months after Ruxolitinib… (day + 620)

ORM B

Today's Date: _____ MR#/Name: _____

CHRONIC GVHD ACTIVITY ASSESSMENT-PATIENT SELF REPORT

Symptoms Please rate how severe the following symptoms have been in the last seven days. Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
Your **skin itching** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
Your **skin and/or joint tightening** at their WORST?	O	O	O	O	O	O	O	O	O	O	O
Your **mouth sensitivity** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
Your **genital discomfort** at its WORST? (Women – vagina, vulva, or labia) (Men – penis)	O	O	O	O	O	O	O	O	O	O	O
Eyes	What is your main complaint with regard to your eyes?										
	Please rate how severe this symptom is, from 0 (not at all severe) to 10 (most severe):	0	1	2	3	4	5	6	7	8	9 10

Patient Global Ratings:

1. Overall, do you think that your chronic graft versus host disease is mild, moderate or severe?
1= mild
2=moderate
3=severe

2. Please circle the number indicating how severe your chronic graft versus host disease symptoms are, where 0 is cGvHD symptoms that are not at all severe and 10 is the most severe chronic GvHD symptoms possible.

0 1 2 3 4 5 6 7 8 9 10

cGvHD symptoms not at all severe — Most severe cGvHD symptoms possible

3. Compared to a month ago, overall would you say that your cGvHD symptoms are:

+3= Very much better
+2= Moderately better
+1=A little better
0= About the same
-1=A little worse
-2=Moderately worse
-3=Very much worse

Our patient has PROGRESSION DISEASE

Table 4
Response Determination for Chronic GVHD Clinical Trials based on Clinician Assessments

Organ	Complete Response	Partial Response	Progression
Skin	NIH Skin Score 0 after previous involvement	Decrease in NIH Skin Score by 1 or more points	Increase in NIH Skin Score by 1 or more points, except 0 to 1
Eyes	NIH Eye Score 0 after previous involvement	Decrease in NIH Eye Score by 1 or more points	Increase in NIH Eye Score by 1 or more points, except 0 to 1
Mouth	NIH Modified OMRS 0 after previous involvement	Decrease in NIH Modified OMRS of 2 or more points	Increase in NIH Modified OMRS of 2 or more points
Esophagus	NIH Esophagus Score 0 after previous involvement	Decrease in NIH Esophagus Score by 1 or more points	Increase in NIH Esophagus Score by 1 or more points, except 0 to 1
Upper GI	NIH Upper GI Score 0 after previous involvement	Decrease in NIH Upper GI Score by 1 or more points	Increase in NIH Upper GI Score by 1 or more points, except 0 to 1
Lower GI	NIH Lower GI Score 0 after previous involvement	Decrease in NIH Lower GI Score by 1 or more points	Increase in NIH Lower GI Score by 1 or more points, except from 0 to 1
Liver	Normal ALT, alkaline phosphatase, and Total bilirubin after previous elevation of 1 or more	Decrease by 50%	Increase by 2 × ULN
Lungs	- Normal %FEV1 after previous involvement - If PFTs not available, NIH Lung Symptom Score 0 after previous involvement	- Increase by 10% predicted absolute value of %FEV1 - If PFTs not available, decrease in NIH Lung Symptom Score by 1 or more points	- Decrease by 10% predicted absolute value of %FEV1 - If PFTs not available, increase in NIH Lung Symptom Score by 1 or more points, except 0 to 1
Joints and fascia	Both NIH Joint and Fascia Score 0 and P-ROM score 25 after previous involvement by at least 1 measure	Decrease in NIH Joint and Fascia Score by 1 or more points or increase in P-ROM score by 1 point for any site	Increase in NIH Joint and Fascia Score by 1 or more points or decrease in P-ROM score by 1 point for any site
Global	Clinician overall severity score 0	Clinician overall severity score decreases by 2 or more points on a 0-10 scale	Clinician overall severity score increases by 2 or more points on a 0-10 scale

ULN indicates upper limit of normal.

Jagasia MH, Greinix HT, Arora M, Williams KM, Wolff D, Cowen EW, Palmer J, Weisdorf D, Treister NS, Cheng GS, Kerr H, Stratton P, Duarte RF, McDonald GB, Inamoto Y, Vigorito A, Arai S, Datiles MB, Jacobsohn D, Heller T, Kitko CL, Mitchell SA, Martin PJ, Shulman H, Wu RS, Cutler CS, Vogelsang GB, Lee SJ, Pavletic SZ, Flowers ME. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group report. Biol Blood Marrow Transplant. 2015 Mar;21(3):389-401.e1. doi: 10.1016/j.bbmt.2014.12.001. Epub 2014 Dec 18. PMID: 25529383; PMCID: PMC4329079.

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GETH-TC

Severe cGvHD with progressive deep sclerotic features, fascial involvement and impaired movility developed during ruxolitinib treatment

BSA 54% (sclerotic features with fascial involvement)

ROM 2 P-ROM (wrist) 4 (ankle) 2

Ocular involvement (score 1)

- Wait for Ruxo response?
- Add ECP?
- Ibrutinib?
- Belumosudil?
- Axatilimab?
- Other options?

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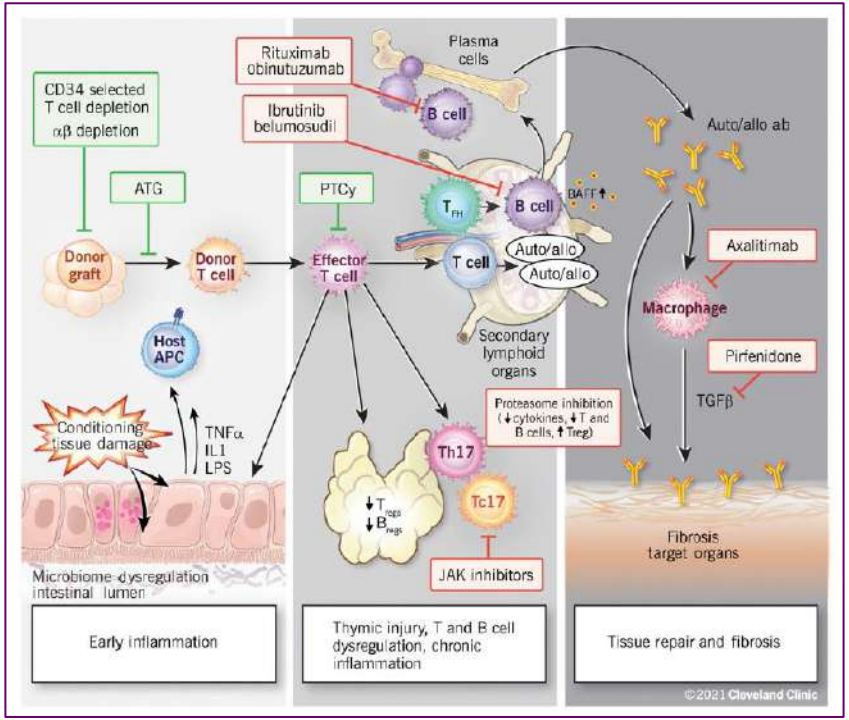
Challenge: Beyond 2nd line / specific features



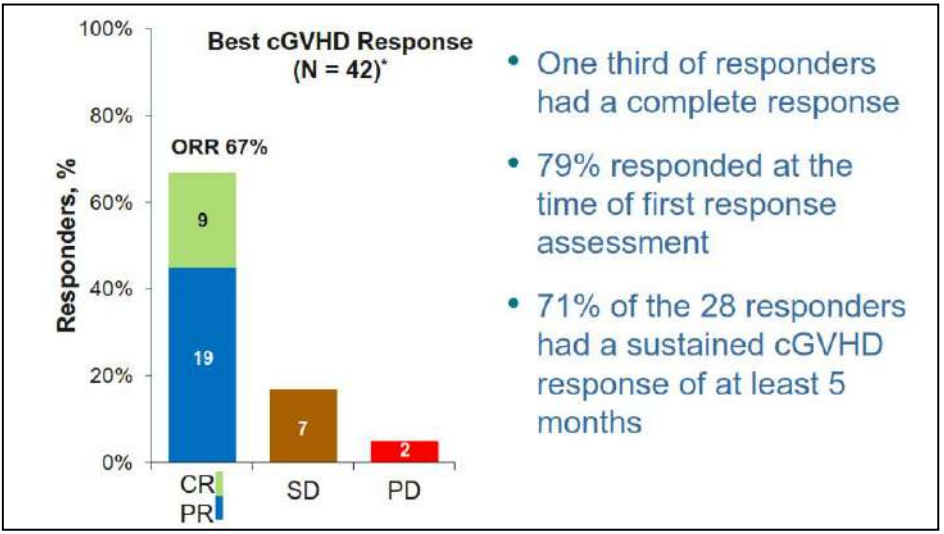
*"Focus of novel cGVHD treatment has thus shifted form the use of **broad, long-term IS** toward the investigation of **immunomodulatory agents that target pathways** relevant to the pathophysiology of the disease"*

Hamilton BK, Hematology Am Soc Hematol Educ Program. 2021 Dec 10;2021(1):648-654

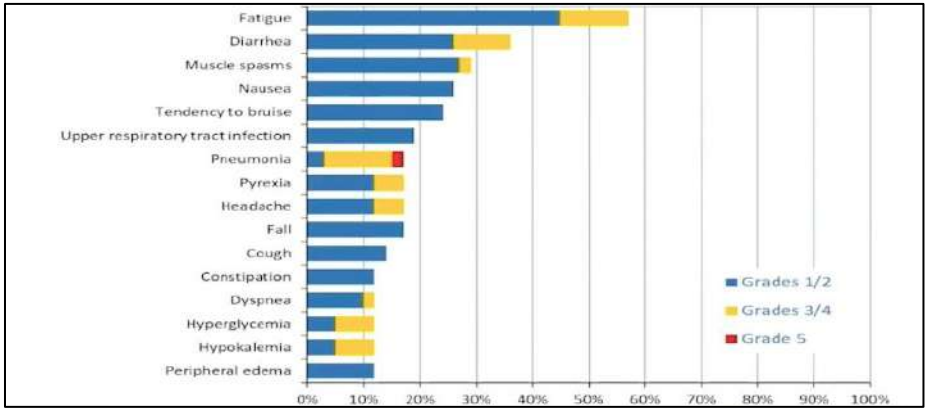
Steroid-refractory cGvHD: Ibrutinib*

Multicenter open-label phase II trial of ibrutinib in cGVHF after failure to steroids

N= 42



- One third of responders had a complete response
- 79% responded at the time of first response assessment
- 71% of the 28 responders had a sustained cGVHD response of at least 5 months



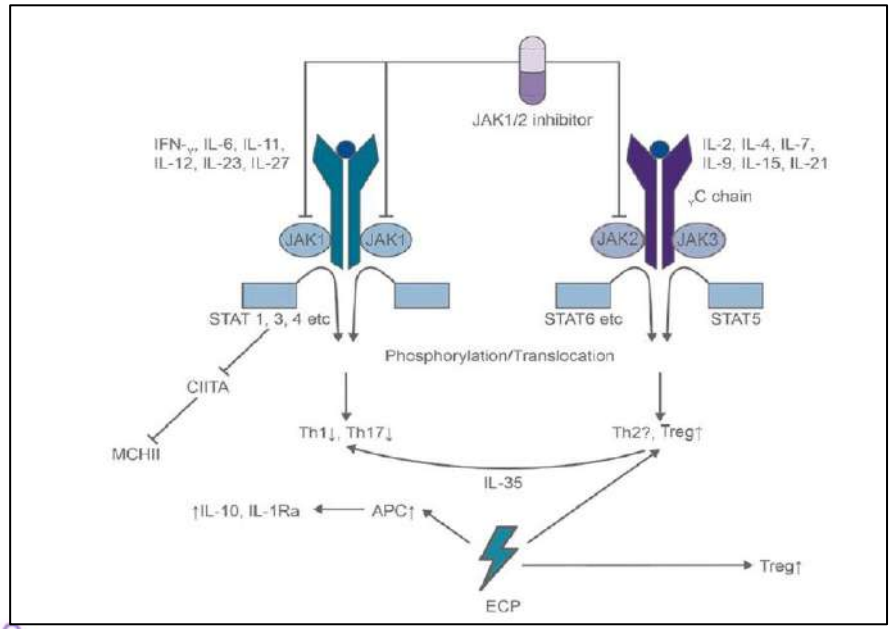
D Miklos Blood 2017

*Ibrutinib is not currently approved by EMA for cGvHD treatment

Waller et al, BBMT 2019: Longer FU (26 months): sustained responses >44 weeks in 16 of 29 (55%) responders

Steroid-refractory cGvHD: Ruxo and ECP combination

Complementary mechanism of action of ECP plus Ruxo:



Ruxolitinib–ECP combination treatment for refractory severe cGvHD

Retrospective study
N= 23 patients
ORR: 74% (9% CR)
OS at 24 months: 75%
Newly diagnosed ytopenia: 22%
CMV reactivation: 26%

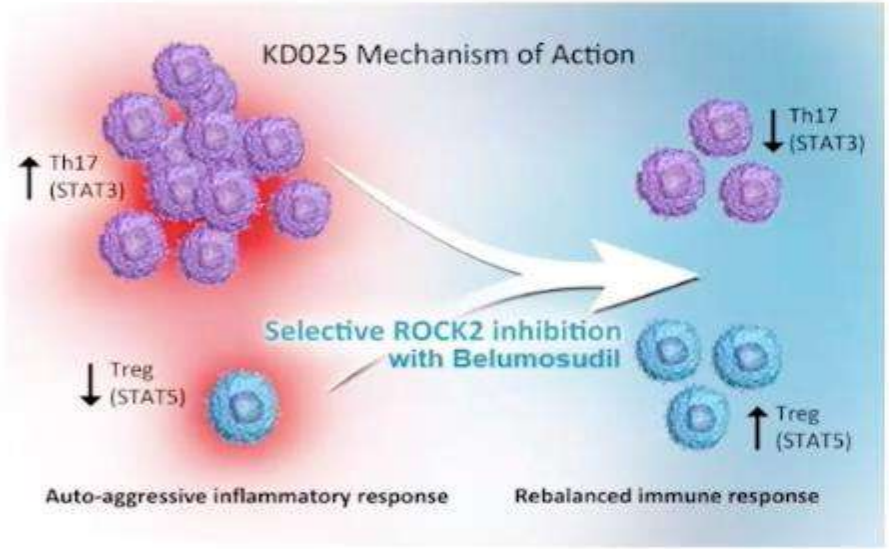
Needs validation in a prospective trial!

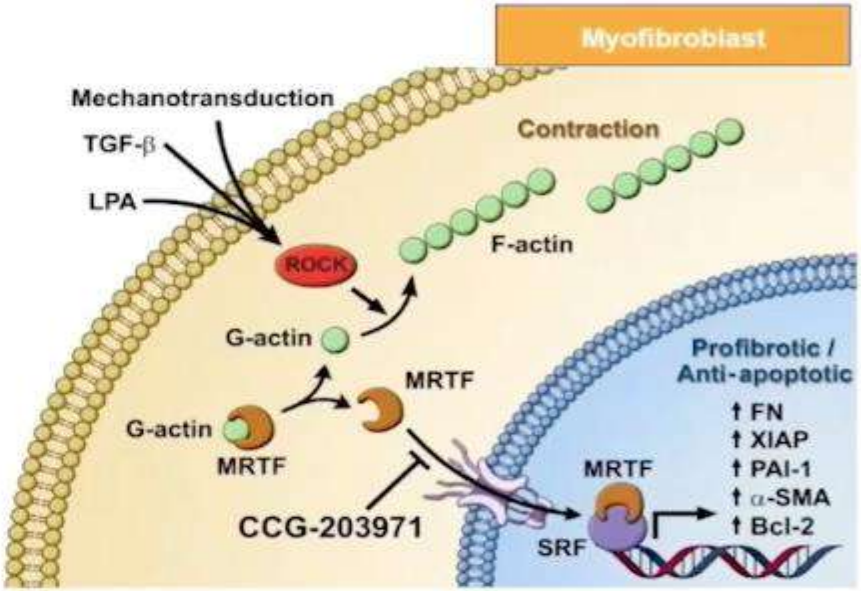
Maas-Bauer K et al, BMT 2021; Greinix e tal, STC 2023

Steroid-refractory cGvHD: Belumosudil*

ROCK2 plays a key role in Immune Diseases

Kd025 (belumosudil): is a selective inhibitor of ROCK2 inhibitor with a a novel mechanism of action that targets both inflammation and fibrosis in cGvHD



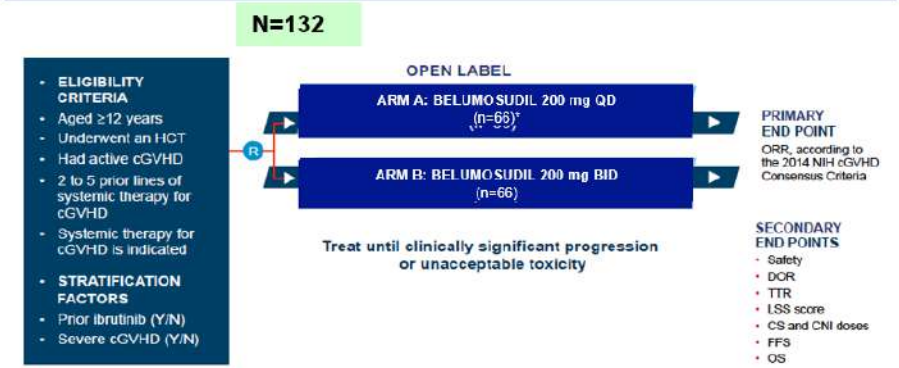


*Belumosudil is not currently approved by EMA

Zanin—Zhorova A, et al. Clin Inmunol. 2021
Riches DWH, et al. Am J Pathol. 2015

Belumosudil for chronic graft-versus-host disease after 2 or more prior lines of therapy: the ROCKstar Study

The ROCKstar Study: Design and End Points



*In the PI, one non-GVHD patient in the 200mg QD arm was omitted from the primary analysis (N=65).

BID, twice a day; DOR, duration of response; FFS, failure-free survival; HCT, hematopoietic cell transplant; LSS, Lee Symptom Scale; NIH, National Institutes of Health; OS, overall survival; QD, every day.

Select Demographics and Baseline Characteristics

Demographics	Overall (N=132)
Median age, y (range)	56 (21-77)
Male, %	57
Median prior lines of systemic therapy, n	3
Median time from cGVHD diagnosis to enrollment, mo	28
NIH moderate cGVHD, n (%)	41 (31)
NIH severe cGVHD,[a] n (%)	89 (67)
Median prednisone dose, mg/kg/d	0.19
≥4 organs involved, n (%)	68 (52)
Prior ibrutinib treatment,[a] n (%)	45 (34)
Prior ruxolitinib treatment, n (%)	38 (29)
Refractory to last prior lines of systemic therapy, n (%)	79 (72)

*Belumosudil is not currently approved by EMA

Cutler et al. Blood. 2021 and EBMT 2022

Challenge: Beyond 2nd line / specific features

CSF-1R y Axatilimab* for Chronic Graft-Versus-Host Disease

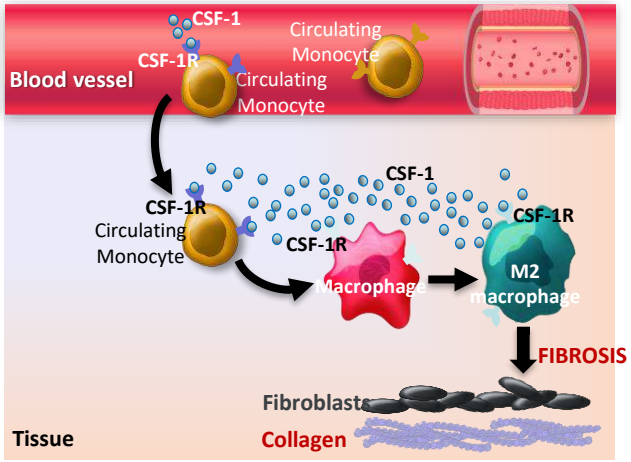


Figure Adopted from MacDonald, K.P.A. et al., *Blood*, 5 (129) 13-21;

AGAVE-201: An Open-label randomized, Phase 2 Study

Key eligibility criteria
- ≥2 years of age
- Allo-HSCT recipients with active cGVHD requiring SIS
- Recurrent or refractory active cGVHD after ≥2 lines of systemic therapy
- Karnovsky PS ≥60 (≥16 years)
- Lansky PS ≥60 (<16 years)
- Concomitant use of corticosteroids, CNI, or mTOR inhibitors was permitted but not required

Stratification factors
- Previous therapy (ibrutinib, ruxolitinib, belumosudil)
- cGVHD severity

Randomization 1:1:1

- 0.3 mg/kg q2w (n=80)
- 1 mg/kg q2w (n=81)
- 3 mg/kg q4w (n=80)

Treatment for up to 2 years

Primary endpoint
- ORR in the first 6 cycles as defined by NIH 2014 Consensus Criteria[4]
  - Endpoint was met if lower bound of 95% CI >30%

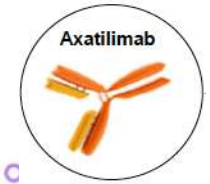
Key secondary endpoints
- Clinically meaningful improvement in mLSS score (≥7-points)
- Organ-specific response rate, DoR, OS
- Safety

Exploratory endpoint
- FFS

The modified Lee Chronic GVHD Symptom Scale

The Lee Chronic GVHD Symptom Scale

Objective: Evaluate the efficacy, safety, and tolerability of axatilimab at 3 dosing regimens in patients (N=241) with recurrent or refractory active cGVHD after ≥2 lines of systemic therapy



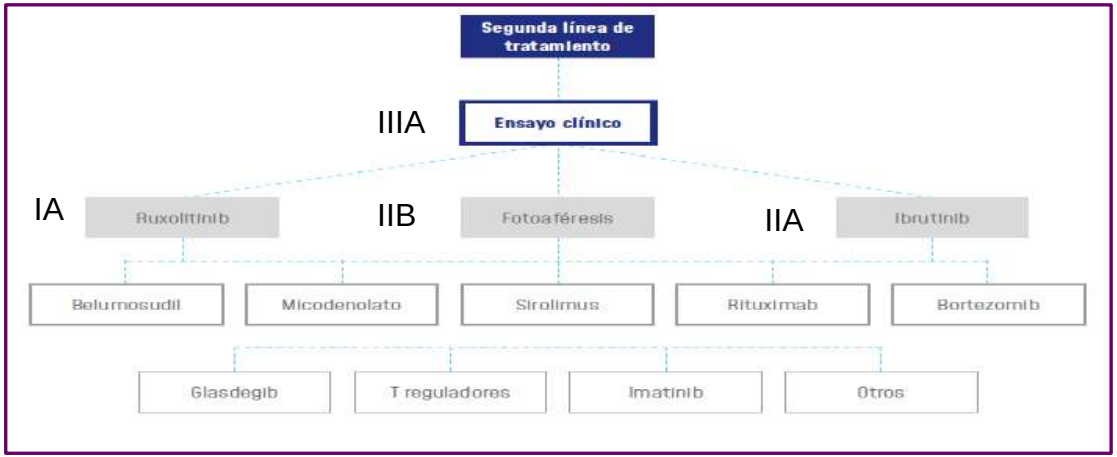
- Axatilimab is a high-affinity, humanized IgG4 monoclonal ab against CSF-1R
- Axatilimab inhibited both CSF-1 and IL-34-induced MCP-1 release from human monocytes
- Axatilimab reduced the viability of Macrophages and Tissue macrophage counts

1. deFilipp Z, et al. TANDEM 2024. Oral presentation 36. 2. Wolff D, et al. ASH 2023. Oral presentation 1. 3. ClinicalTrials.gov. Accessed February 2024. https://clinicaltrials.gov/ct2/show/NCT04710576. 4. Lee SJ, et al. *Biol Blood Marrow Transplant*. 2015;21:984-999.

*Axatilimab is not currently approved neither by FDA nor by EMA for cGvHD treatment

cGvHD: second treatment and beyond

Guías EICR. GETH, 2021.



Updated consensus recommendations EBMT
Penack et al , Lancet Haematol february 2024

Panel 3: Recommendations on cGVHD treatment

New recommendations

- In adults with steroid-refractory chronic graft-versus-host disease (SR-cGVHD), we recommend ruxolitinib (National Comprehensive Cancer Network [NCCN] classification 1)
  - Large beneficial effect on overall response rate and failure-free survival in a randomised trial, a propensity-adjusted retrospective analysis, and three meta-analyses[50-52,61,62]
- In adults with SR-cGVHD, belumosudil is a potential therapeutic option (NCCN classification 2C)
  - Encouraging overall response rates in non-randomised trials showing a low drug induced toxicity profile[63-66]
- In adults with SR-cGVHD, ibrutinib is a potential therapeutic option (NCCN classification 2B)
  - Encouraging overall response rates in non-randomised trials in patients with moderate GVHD burden and an acceptable toxicity profile[67-71]

Ibrutinib and Belumosudil are not currently approved by EMA for cGvHD treatment

Steroid-refractory chronic GVHD:

Factors influencing decisions

- **Relapse risk**: HR of relapse – avoid “overimmunosuppression” and substances which potentially increase relapse risk (e.e. CNI, MMF)
- **Infectious disease history**: some agents are associated with infectious risks. Safety is important driver.
- **Comorbidity**: avoid agents with side effects in already impaired organs (renal insufficiency, pancitopenia …)
- **History of applied agents:** avoid treatment options already failed or associated with inacceptable side effects, flare after stop?
- **Biology of disease**: overlap symptoms present, organ pattern…
- **Compliance**: consider substances given i.v. If pts tend to stop medication, listen to patient´s preferences.
- **Distance to Tx center and availability of treatment**
- **Approval status**: avoid financial toxicity

Steroid-refractory chronic GVHD:

Rules

- **Corticosteroids remain important:** goal is steroid sparing!
- **Do not change more than 1 agent at once:** unless toxicity drives decision
- **Do not combine > 3 systemic agents at the same time**
- **Appropriate response assessment:** apply NIH organ grading + response assessment Evidence outside cGvHD: use evidence derived from corresponding autoimmune diseases and organ transplantation.
- **Adapt prophylaxis + monitoring to the applied treatment:** new infections with unusual pattern should be regarded as toxicity leading to either changed prophylaxis or treatment

Challenges in cGvHD landscape in 2024

- **Disease and clinical course** are now well characterized
- **Complex pathophysiology** is much better understood
- **Many investigational agents** are available for treatment
- Resources are available through **industry colaboration**
- **Regulatory approval** pathway has been established
- **New drugs** have been recently approved for cGvHD treatment

But…

- Initial treatment is still prednisone with / without calcineurin inhibitor
- Best choice of subsequent treatment is still undefined
- No standard approaches to prevention or preemption
- Highly morbid forms of chronic GvHD still exist

Adapted from Paul Martin, lecture to Brazilian BMT Society and Pavletic, lecture to EMBT 2022.

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Challenges in cGvHD landscape: NIH 2020

Ultimate Goal for Upfront Treatment of cGvHD Patients

Instead of **STEROIDS FIT ALL**

- Improved insights into biology of cGvHD
- Availability of targeted therapies relevant to pathophysiology of cGvHD

Administration of the **RIGHT DRUG TO THE RIGHT PATIENT AT THE RIGHT TIME**

DeFilipp Z et al. TCT 2021;27:545

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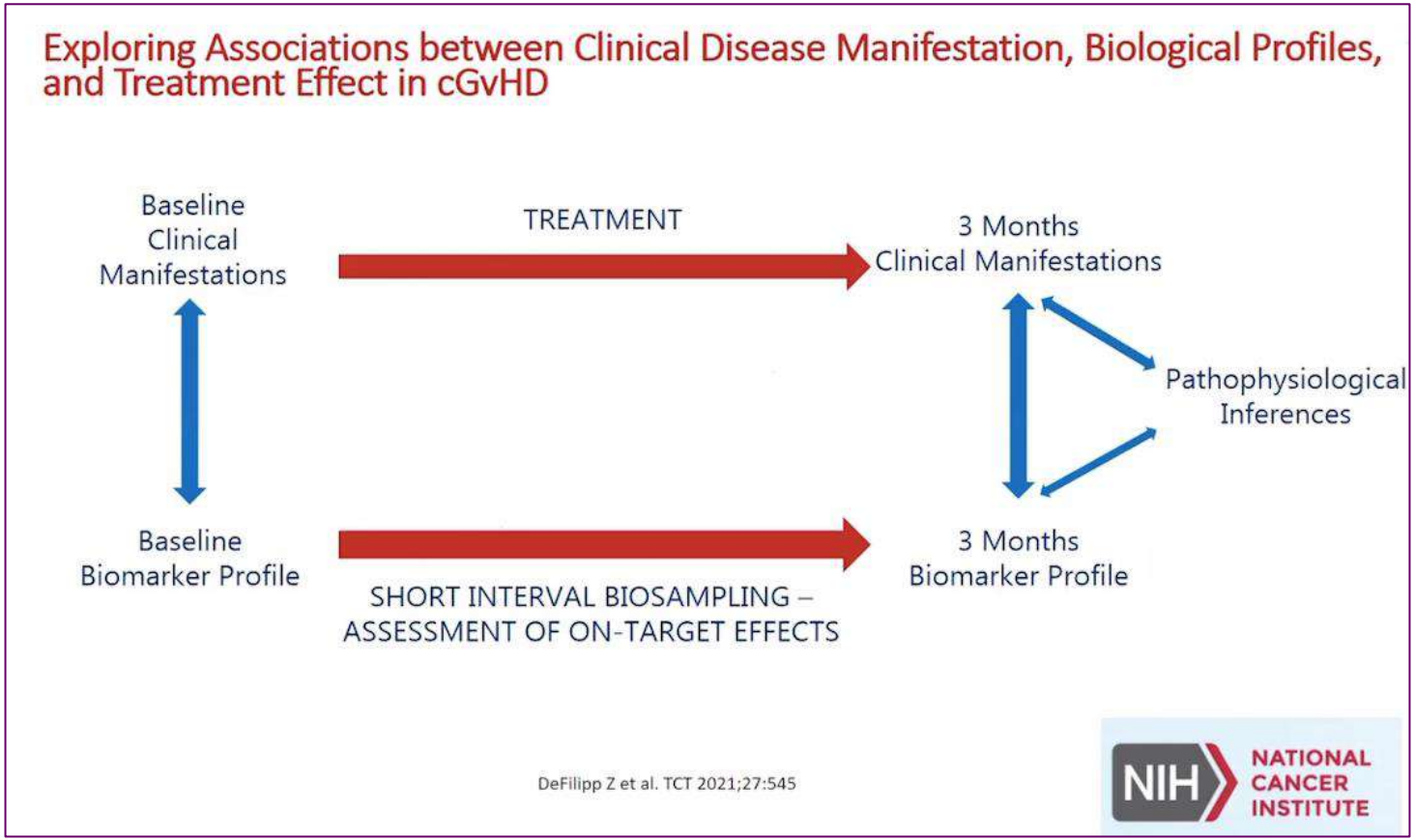
GETH-TC

Challenges in cGvHD landscape: NIH 2020



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Chronic GvHD publications / year

Gracias por vuestra atención