Necesidades no cubiertas. ¿Lo tenemos todo bajo control?

15/11/2023

Anabelle Chinea
Unidad de TPH y TC
H.U Ramón y Cajal

MAT-ES-2302932-V2-2023

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- ETIOPATOGENIA Y MANIFESTACIONES CLINICAS
- DIAGNÓSTICO Y EPIDEMIOLOGÍA
- BIOMARCADORES
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- **ETIOPATOGENIA Y MANIFESTACIONES CLINICAS**
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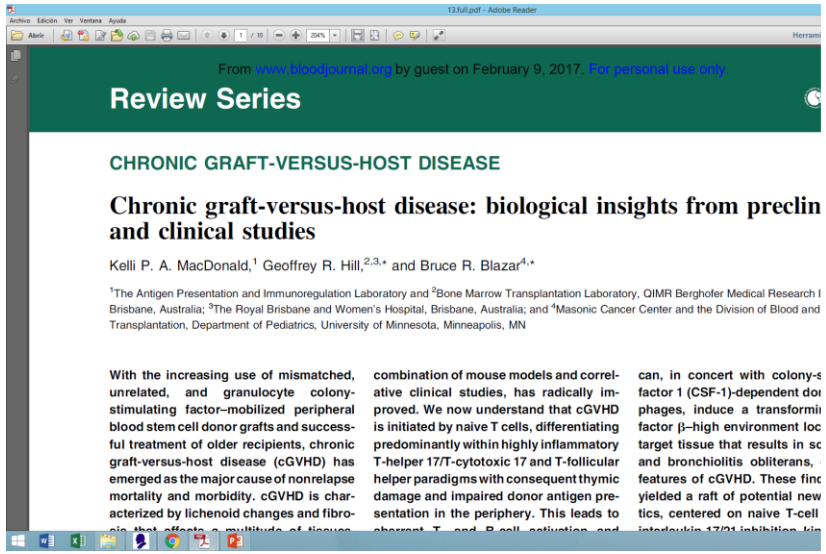
Etiopatogenia



Review Series

CHRONIC GRAFT-VERSUS-HOST DISEASE

Chronic graft-versus-host disease: biological insights from preclin and clinical studies

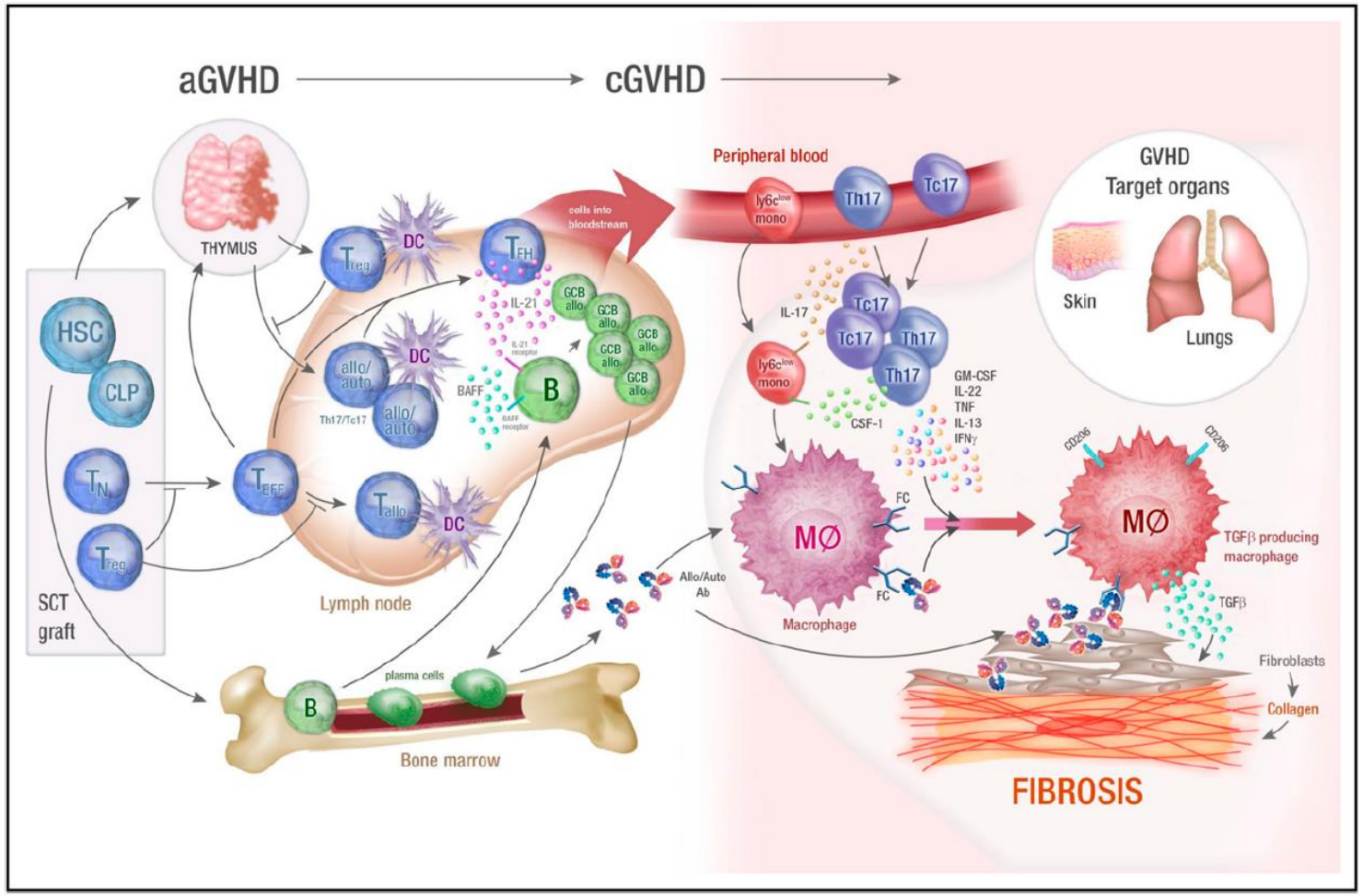
Kelli P. A. MacDonald,[1] Geoffrey R. Hill,[2,3,*] and Bruce R. Blazar[4,*]

[1]The Antigen Presentation and Immunoregulation Laboratory and [2]Bone Marrow Transplantation Laboratory, QIMR Berghofer Medical Research I Brisbane, Australia; [3]The Royal Brisbane and Women's Hospital, Brisbane, Australia; and [4]Masonic Cancer Center and the Division of Blood and Transplantation, Department of Pediatrics, University of Minnesota, Minneapolis, MN

With the increasing use of mismatched, unrelated, and granulocyte colony-stimulating factor–mobilized peripheral blood stem cell donor grafts and successful treatment of older recipients, chronic graft-versus-host disease (cGVHD) has emerged as the major cause of nonrelapse mortality and morbidity. cGVHD is characterized by lichenoid changes and fibro-

combination of mouse models and correlative clinical studies, has radically improved. We now understand that cGVHD is initiated by naive T cells, differentiating predominantly within highly inflammatory T-helper 17/T-cytotoxic 17 and T-follicular helper paradigms with consequent thymic damage and impaired donor antigen presentation in the periphery. This leads to

can, in concert with colony-s factor 1 (CSF-1)-dependent do phages, induce a transformi factor β–high environment loc target tissue that results in sc and bronchiolitis obliterans, features of cGVHD. These finc yielded a raft of potential new tics, centered on naive T-cell



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Etiopatogenia

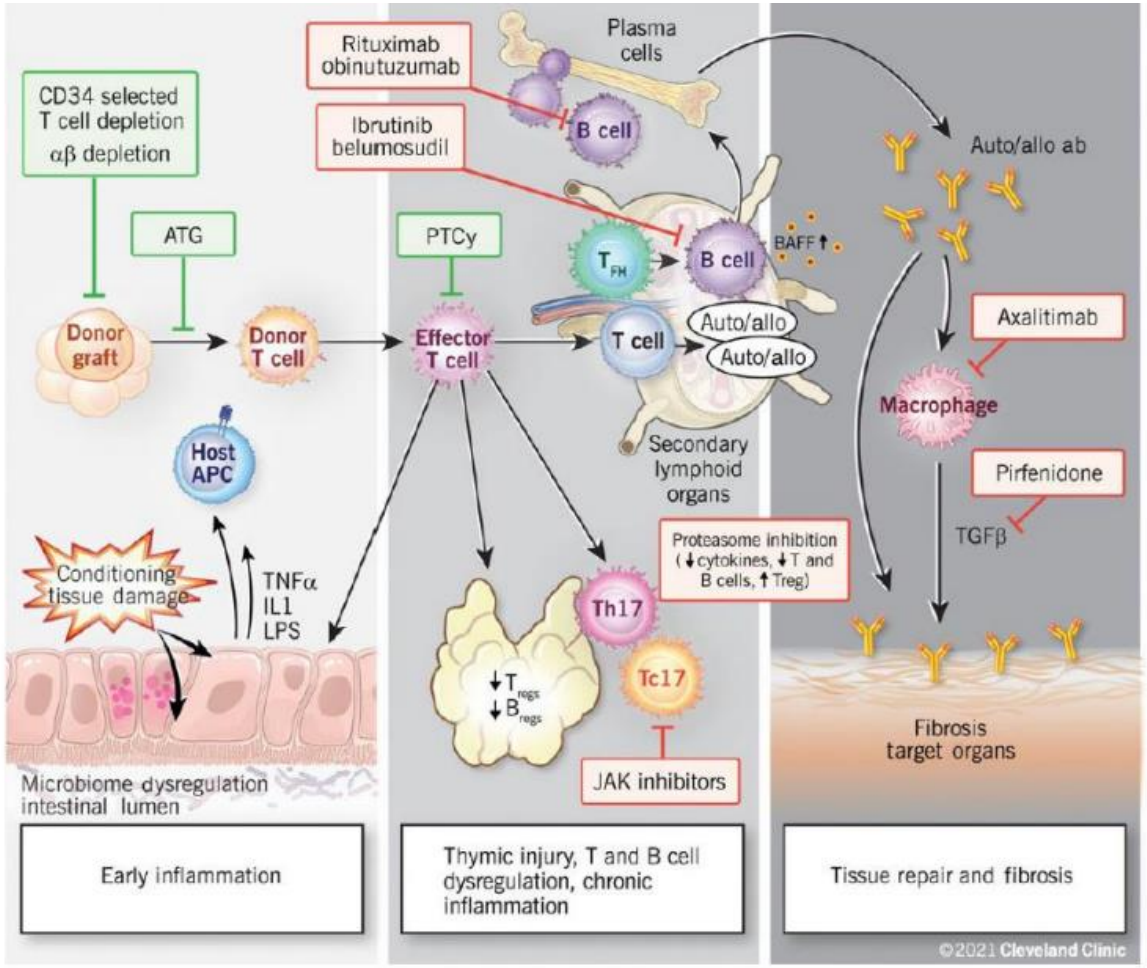
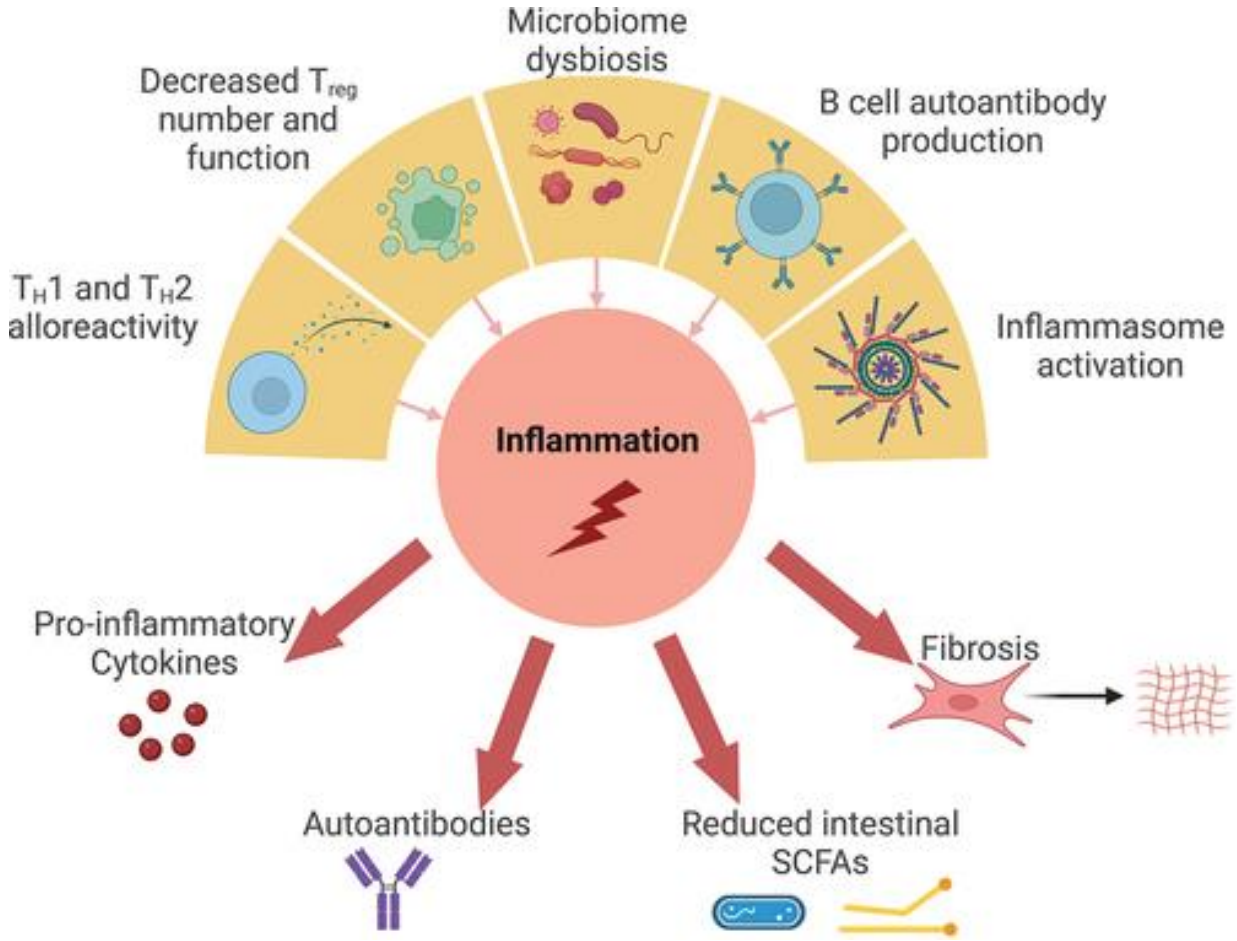


Figure 1. Proposed biologic phases of chronic GVHD. A few novel therapeutic approaches targeting biologic pathways are highlighted. Reproduced with permission from the Cleveland Clinic Center for Medical Art and Photography.

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

Etiopatogenia



Effects of immune system cells in GvHD and corresponding therapeutic strategies Maryam Jadid Tavaf, Mahboobeh Ebrahimi Verkiani, Fateme Poorhoseini Hanzaii, Mina Soufi Zomorrod.h ttps://doi.org/10.5045/br.2023.2022192 Blood Res 2023;58:2-12.

Manifestaciones clínicas

- PIEL.
- BOCA.
- GENITALES.
- GI.
- PULMÓN.
- MUSCULOESQUELÉTICO:
  - Fascitis.
  - Miositis.

Category	Number of Organs	Maximum Severity
Mild	≤2	1 (0 for lung)
Moderate (a)	≥3	1 (0 for lung)
Moderate (b)	Any	2 (1 for lung)
Severe	Any	3 (2 for lung)

Guía EICR GETH 2022

1. Filipovich. Biol Blood Marrow Transplant. 2005;11:945. 2. Jagasia. Biol Blood Marrow Transplant. 2015;21:389.

Manifestaciones clínicas

Estadio	Piel (solo el eritema activo)	Hígado	GI alto	GI bajo
0	No	<2 mg/dL	No síntomas Náuseas/vómitos o anorexia intermitentes	Adultos: <500 ml/día o <3 episodios/día Niños: <10 ml/kg/día o <4 episodios/día
1	*Rash* maculopapular <25% SC	2-3 mg/dL	Náuseas/vómitos o anorexia persistentes	Adultos: 500-999 ml/día o 3-4 episodios/día Niños: 10-19,9 ml/kg/día o 4-6 episodios/día
2	*Rash* maculopapular 25-50% SC	3,1-6 mg/dL	-	Adultos: 1.000-1.500 ml/día o 5-7 episodios/día Niños: 20-30 ml/kg/día o 7-10 episodios/día
3	*Rash* maculopapular >50% SC	6,1-15 mg/dL	-	Adultos: >1.500 ml/día o >7 episodios/día Niños: > 30 ml/kg/día o >10 episodios/día
4	Eritrodermia generalizada (>50% SC) **más** ampollas y descamación en >5% SC	>15 mg/dL	-	Dolor abdominal grave con/sin íleo, o heces sanguinolentas independientemente de su volumen

GI: gastrointestinal; SC: superficie corporal.

Grado I
Piel estadio 1-2
Grado II
Piel estadio 3 o hígado estadio 1 o intestino estadio 1*
Grado III
Hígado estadio 2-3 o intestino estadio 2-4
Grado IV
Piel estadio 4 o hígado estadio 4

*Las náuseas persistentes con evidencia histológica de EICR, pero sin diarrea, deben incluirse como EICR gastrointestinal en estadio 1.
EICR: enfermedad injerto contra receptor.

Guía EICR GETH 2022

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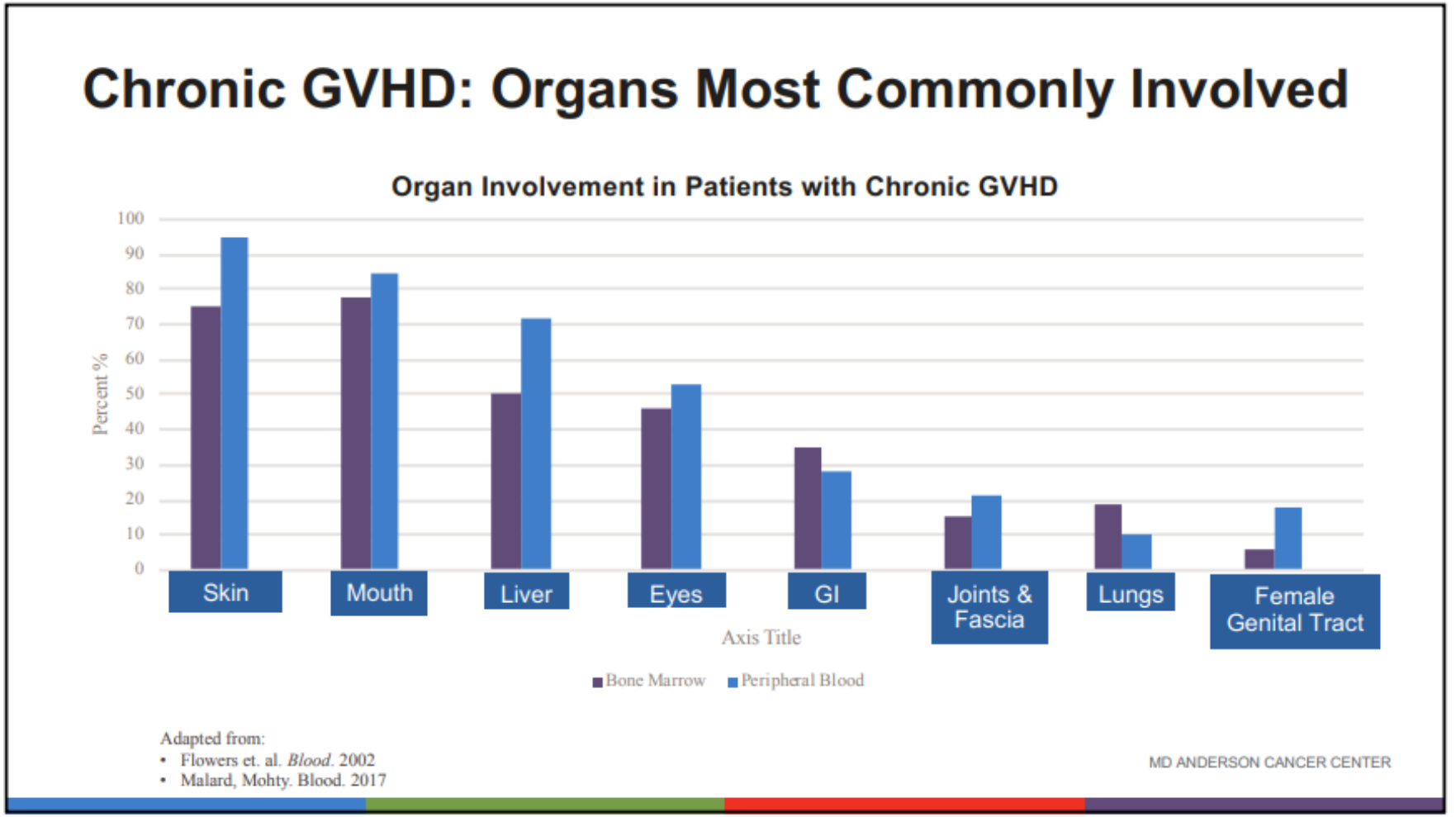
Manifestaciones clínicas



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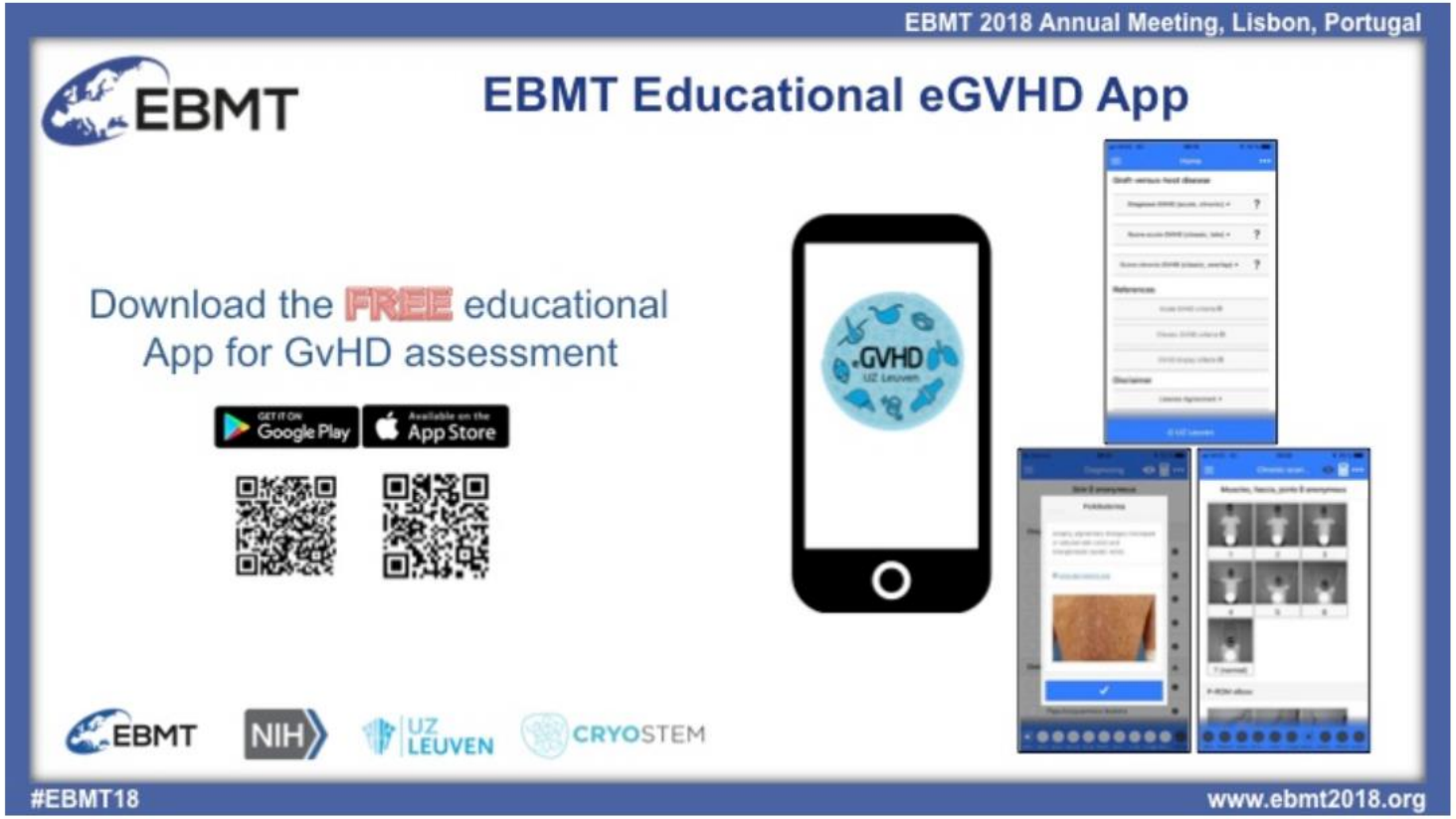
Manifestaciones clínicas y estadiaje.
Criterios de respuesta



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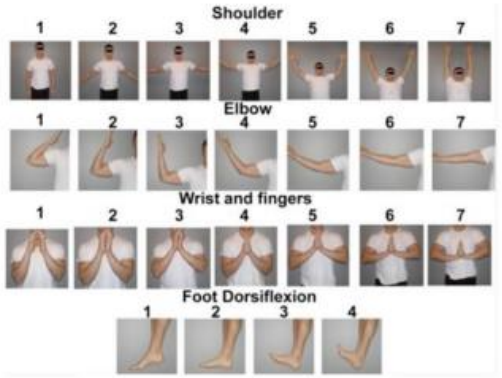
Diagnóstico. Gradación.

Puntuación	0	1	2	3
ESTADO GENERAL ECOG (KPS):	☐ Asintomático y totalmente activo (ECOG: 0, KPS: 100%)	☐ Sintomático, ambulatorio, limitación actividad física extenuante (ECOG: 1, KPS: 80 – 90%)	☐ Sintomático, ambulatorio, se vale por sí mismo, deambula >50% del tiempo (ECOG: 2, KPS: 60 – 70%)	☐ Sintomático, dificultad para su propio cuidado, >50% en sillón-cama (ECOG 3 – 4, KPS <60%)
PIEL Puntuación % SC: Marcar todo lo que aplique: ☐ Rash maculopapular / Eritema ☐ Liquen plano-*like* ☐ Esclerosis ☐ Lesiones pápulo-escamosas o ictiosis ☐ Queratosis pilaris-*like*	☐ No afectación	☐ 1 – 18% SC ★	☐ 19 – 50% SC	☐ >50% SC
Puntuación por manifestaciones cutáneas EICR	☐ No lesiones escleróticas		☐ Esclerosis superficial (se puede pellizcar)	Marcar todo lo que proceda: ☐ Esclerosis profunda ☐ Esclerosis con fijación ósea ☐ Movilidad limitada ☐ Ulceración
Otras manifestaciones no incluidas: ☐ Hiperpigmentación ☐ Hipopigmentación ☐ Poiquilodermia ☐ Prurito grave o generalizado ☐ Afectación ungueal ☐ Afectación capilar ☐ Alteración explicada por completo por causa de no EICR (especifique):_____				

Puntuación	0	1	2	3
BOCA Liquen plano-*like* presente: ☐ Si ☐ No	☐ No síntomas	☐ Síntomas leves que no dificultan ingesta	☐ Síntomas moderados que si limitan parcialmente la ingesta ★	☐ Síntomas graves con limitación grave de la ingesta
☐ Alteración explicada por completo por causa de no EICR (especifique): _____				
OJOS KCS confirmada por oftalmólogo: ☐ Si ☐ No ☐ No explorado	☐ No síntomas	☐ Sequedad ocular leve que no afecta actividad cotidiana (colirio lubricante <3 veces al día)	☐ Sequedad ocular moderada que afecta algo a la actividad cotidiana (requiere colirio lubricante >3 veces al día o tapones lacrimales), SIN pérdida agudeza visual por KCS	☐ Sequedad ocular grave que afecta la actividad cotidiana (dolor) o incapacidad laboral por síntomas oculares o pérdida de visión por KCS
☐ Alteración explicada por completo por causa de no EICR (especifique): _____				
TRACTO GI Marque todo lo que aplique ☐ Membrana esofágica/ Estenosis alta o tercio medio esófago ☐ Disfagia ☐ Anorexia ☐ Náusea ☐ Vómitos ☐ Diarrea ☐ Pérdida de peso ≥5% ☐ Imposibilidad alimentación	☐ No síntomas	☐ Síntomas sin pérdida de peso (<5%) ★	☐ Síntomas que ocasionan pérdida 5 – 15% peso o diarrea moderada sin interferencia significativa con actividades vida diaria	☐ Síntomas con pérdida >15% peso, que requiera suplemen- tos nutricional - calórico adicionales o dilatación esofágica o diarrea grave que interfiere de forma significativa en vida diaria
☐ Alteración explicada por completo por causa de no EICR (especifique): _____				
HÍGADO	☐ Función hepática normal y ALT o FA <3 x VN	☐ Bilirrubina total normal con ALT 3 – 5 x VN o FA ≥3 x VN	☐ Bilirrubina total elevada pero <3 mg/dl o FA >5 x VN	☐ Bilirrubina total elevada pero >3 mg/dl
☐ Alteración explicada por completo por causa de no EICR (especifique): _____				
PULMÓN Puntuación de síntomas	☐ No síntomas	☐ Síntomas leves (taquipnea tras subir un tramo de escalera)	☐ Síntomas moderados (taquipnea al andar en suelo llano)	☐ Síntomas graves (taquipnea de reposo; necesidad O_2)
Puntuación pulmón FEV1%: ☐ No realizado	☐ FEV1 ≥80%	☐ FEV1 60 – 79%	☐ FEV1 40 – 59%	☐ FEV1 <39%
☐ Alteración explicada por completo por causa de no EICR (especifique): _____				

Puntuación	0	1	2	3
APARATO LOCOMOTOR Puntuación P-ROM (ver anejo) Hombro (1 – 7): _____ Codo (1 – 7): _____ Muñeca/Dedos (1 – 7): _ Cadera (1 – 4): _____	☐ No síntomas	☐ Rigidez leve en brazos o piernas. Rango de movimiento normal o reducción leve y no afectación de actividades de vida diaria	☐ Rigidez en brazos o piernas o contracturas en articulaciones, fascitis, reducción moderada del Rango de movimiento y no afectación de actividades de vida diaria	
☐ Alteración explicada por completo por causa de no EICR (especifique): _____				
TRACTO GENITAL ☐ No explorado Actualmente sexualmente activo: ☐ Si ☐ No	☐ No signos	☐ Signos leves y mujeres con o sin molestias en la exploración	☐ Signos moderados y pueden tener molestias en la exploración	☐ Signos graves y pueden con o sin molestias en la exploración
☐ Alteración explicada por completo por causa de no EICR (especifique): _____				
Otras alteraciones, datos clínicos o complicaciones relacionadas con EICRc. Señale todas las que correspondan y asigne una puntuación de gravedad (0-3) en base al impacto funcional (Nada: 0; Leve: 1; Moderado: 2; Grave: 3)				
☐ Ascitis (serositis): _____ ☐ Derrame pericárdico: _____ ☐ Derrame pleural: _____ ☐ Síndrome nefrótico: _____		☐ Miastenia *Gravis*: _____ ☐ Neuropatía periférica: _____ ☐ Polimiositis: _____ ☐ Pérdida peso >5% sin síntomas GI: ___		☐ Eosinofilia >500/mcl: _____ ☐ Plaquetas <100.000/mcl: _____ ☐ Otros (especificar): _____
GRAVEDAD GLOBAL	☐ No EICRc	☐ Leve	☐ Moderado	☐ Grave

Escala fotográfica para evaluar rango de movimiento (P-ROM)



Jagasia MH, Greinix HT, Arora M, et al. 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; 21: 389–40

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Diagnóstico. Gradación.

Table S2: NIH Global Severity of chronic GVHD

(according to [1])

NIH Global Severity of chronic GVHD	Criteria
Mild chronic GVHD	1 or 2 Organs involved with no more than score 1 plus Lung score 0
Moderate chronic GVHD	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 chronic GVHD	At least 1 organ with a score of 3 OR Lung score of 2 or 3

The individual scores from 0 to 3 are shown in detail in the 2014 NIH consensus publication[1]. In this scoring system, the 8 organ systems skin, mouth, eyes, gastrointestinal tract, liver, lungs, genital tract and fasciae/joints are scored.

Jagasia MH, Greinix HT, Arora M, et al. 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; 21: 389–40

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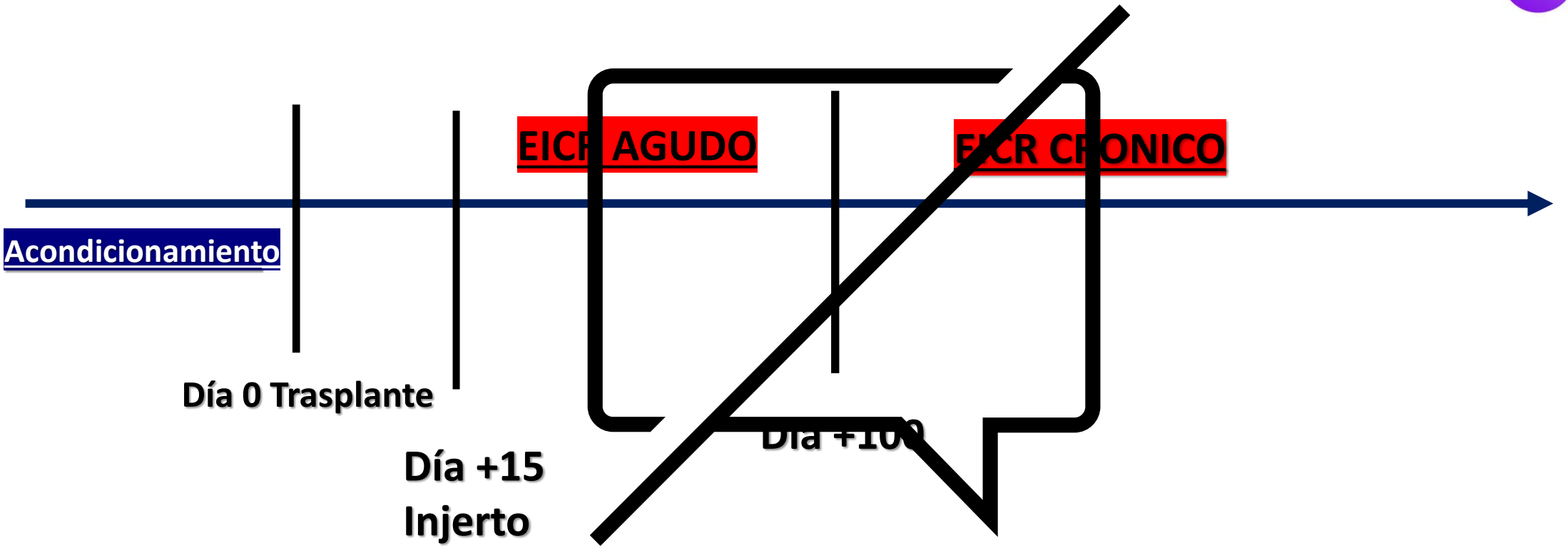
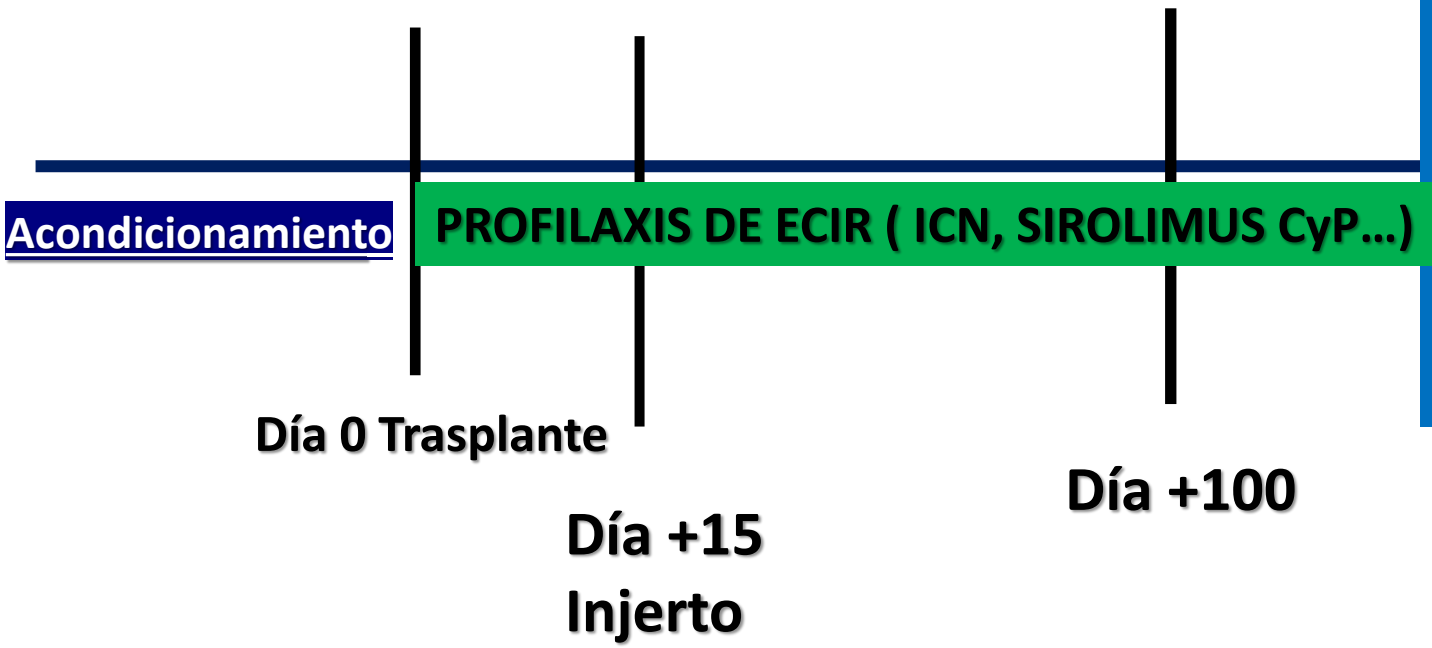
Diagnóstico:



Jagasia MH, Greinix HT, Arora M, et al. 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; 21: 389–40

Diagnóstico:

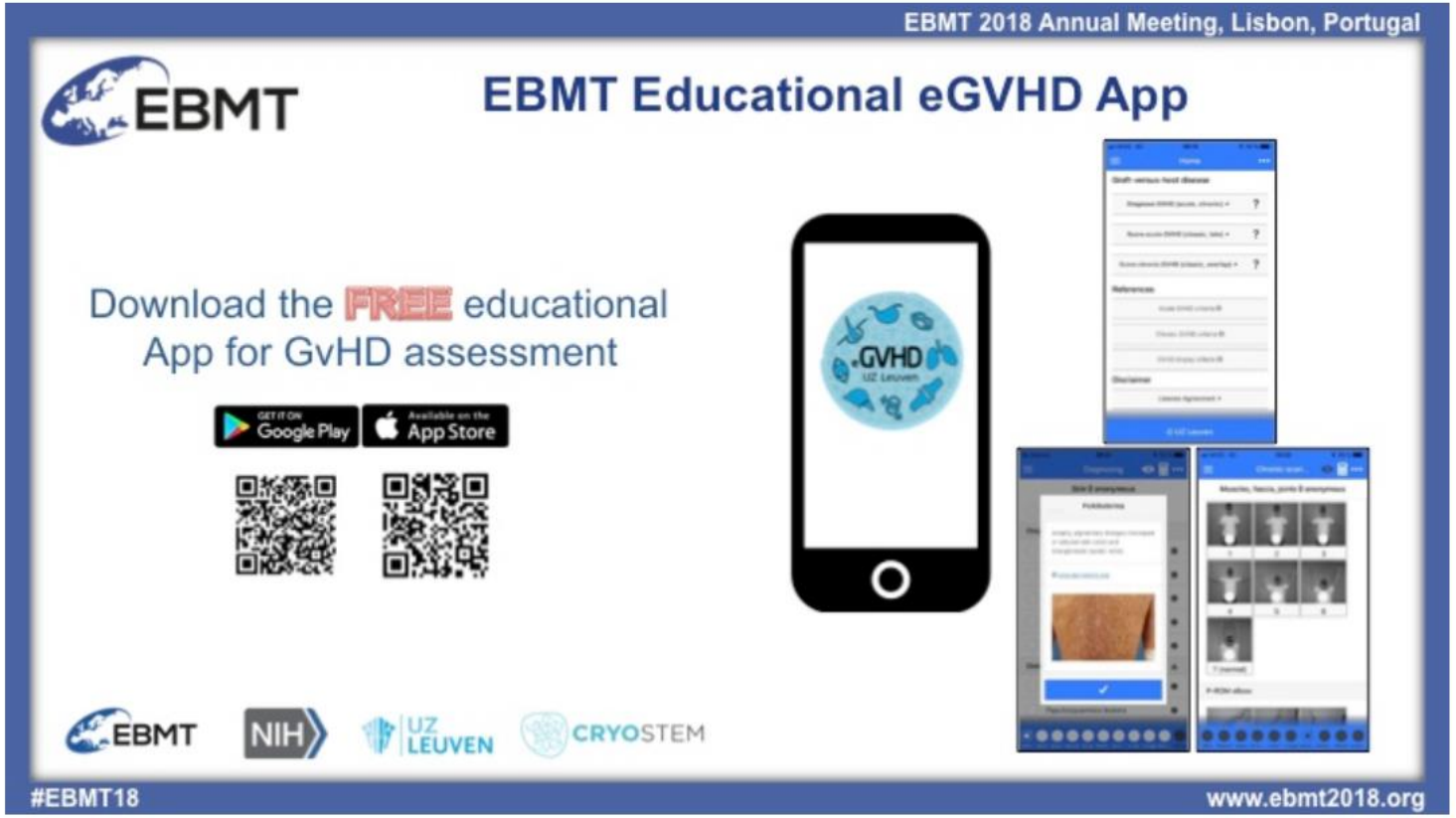


EICR CRONICO:

- Mediana de inicio. 5-6 meses
- 90% inicio en el primer año.
- Aparición poco frecuente después de los 2 años.

Hamilton BK, Hematology Am Soc Educ Program, Dec 2021

Diagnóstico



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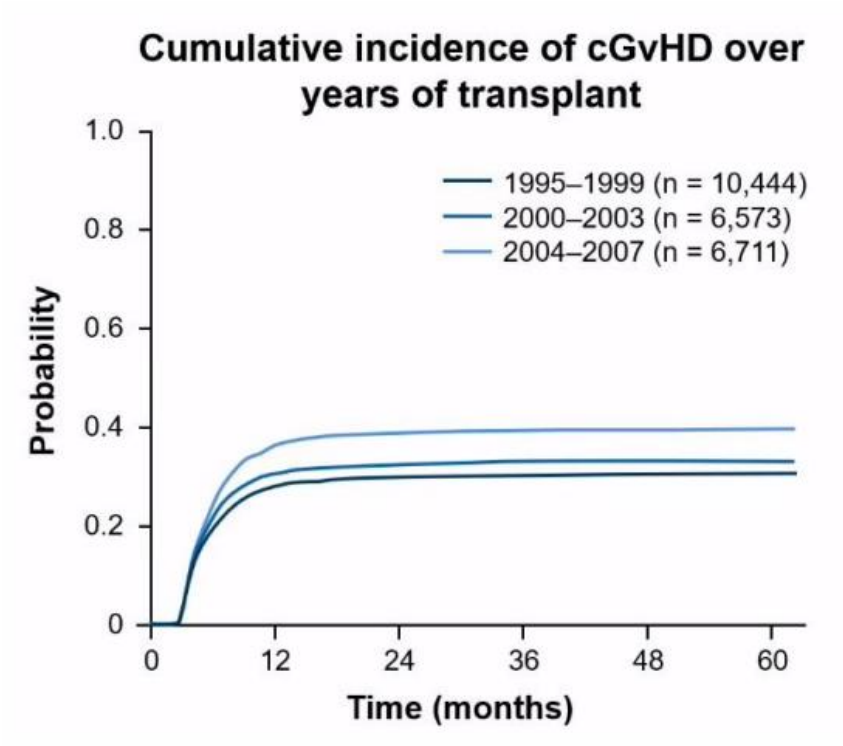
Epidemiología

- 30-70% lo presentarán en algún grado.
- Incidencia creciente:
  - Pacientes más mayores.
  - Sangre periférica como fuente de progenitores.
  - Aumento de supervivencia.
  - ¿PTCy? ☐ Tendencia al descenso de dosis



Arial S, et al. Biol Blood Marrow Transplant 2015;21:266-74

Factores de riesgo

- **Episodio previo de EICRa .**
- **Sangre periférica como fuente de progenitores**
- **Donante mujer/Receptor varón.**
- **Disparidad HLA .**
- **Edad del receptor.**
- **Enfermedad de base.**

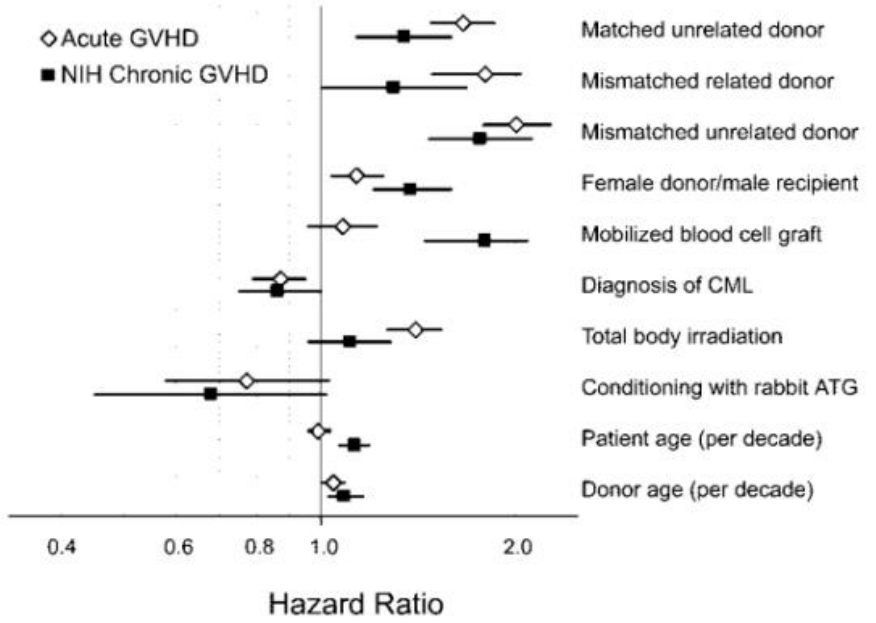


Figure 2. Multivariate risk factor profiles for grades 2-4 acute GVHD and NIH chronic GVHD. Hazard ratio and 95% CI for each risk factor are shown. The analysis included 2355 grades 2-4 acute GVHD events and 1022 NIH chronic GVHD events. Hazard ratios are relative to patients without the risk factor.

Flowers ME et al. Blood. 2011 Mar 17;117(11):3214-9

Pronóstico

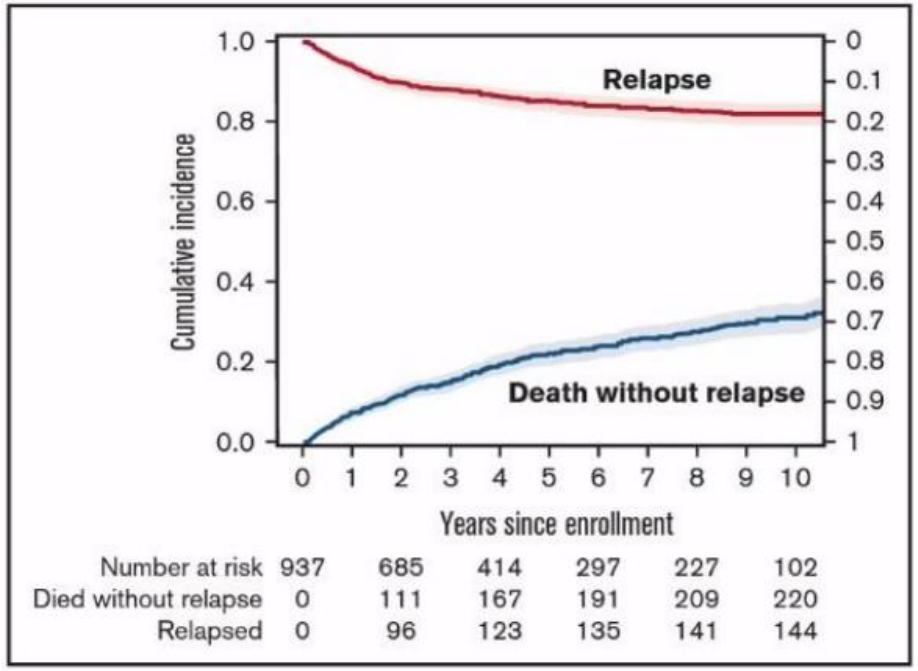


Figure 1. The cumulative incidence of NRM among patients diagnosed with cGVHD. Relapse shown as a competing risk.

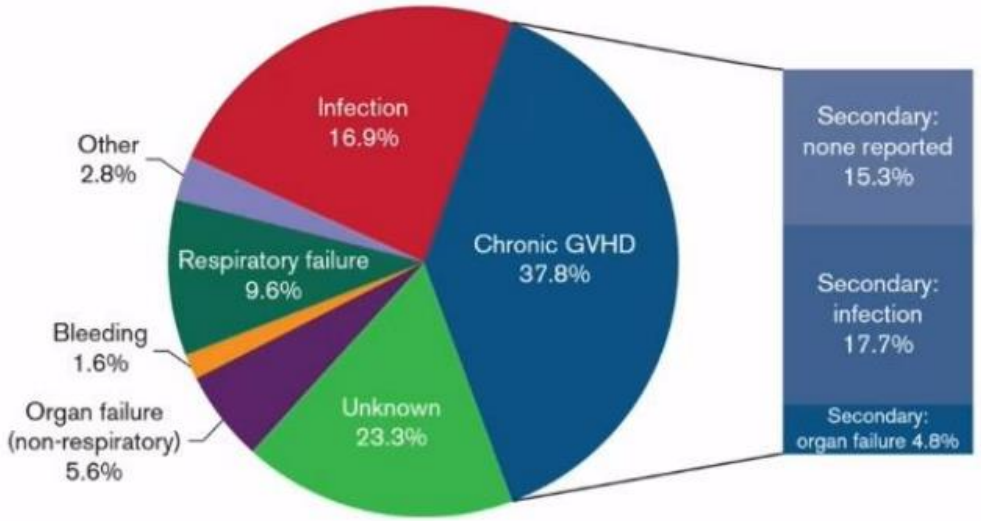


Figure 2. Reported primary causes of death for cases of NRM.

DeFilipp Z, et al. Blood Adv. 2021 Oct 26;5(20):4278-4284.

Biomarcadores

Biomarker definitions as per NIH BEST Resource [3]

Biomarker Subtype	Definition
Diagnostic	An assay used to confirm the presence of the disease
Predictive	An assay used to identify individuals who are more likely than similar individuals without the biomarker to experience a favorable or unfavorable effect from exposure to a specific medical product (before treatment is received)
Response	An assay used to show that a biological response has occurred in an individual who has been exposed to a medical product (after treatment is received)
Prognostic	An assay used to identify likelihood of a clinical event, disease recurrence or progression in patients who have the disease
Risk	An assay that indicates the potential for developing the disease in individuals who do not have clinically apparent disease

Current Definitions and Clinical Implications of Biomarkers in Graft Versus Host Disease Alan Bidgoli, Transplant Cell Ther. 2022 October ;

Biomarcadores

Table 5.

Plasma Biomarkers for Chronic GVHD

Name	Study	(n)	Associations/Timepoints in cGVHD *(D0 = HCT date)*	Framework steps completed	Potential clinical implementation
Diagnostic Biomarkers					
sBAFF	Sarantopoulos 2007	104	Increased levels in active cGVHD	Step 1: Discovery	• Improve diagnostic accuracy • Differentiate GVHD vs other complications
	Ahmed 2015	115	Increased levels at 6 and 12 months	Step 1: Previous discovery	
	Kariminia 2016	283	Increased levels around time of diagnosis	Step 1: Previous discovery Step 2: 2 cohorts	
	Rozmus 2019	107	Increased levels around onset of symptoms	Step 1: Previous discovery	
CXCL9	Kitko 2014	320	Increased levels at diagnosis	Step 1: Discovery Step 2: 2 cohorts	
	Kariminia 2016	85	Increased levels in 1 replication cohort	Step 1: Previous discovery Step 2: 2 cohorts	
	Hakim 2016	95	Increased levels and upregulation of gene expression	Step 1: Previous discovery	
CXCL10	Ahmed 2015	115	Increased levels at 6 and 12 months	Step 1: Hypothesis	
	Kariminia 2016	283	Increased levels in both replication cohorts	Step 1: Previous discovery Step 2: 2 cohorts	
	Hakim 2016	95	Increased levels and upregulation of gene expression	Step 1: Hypothesis	
Biomarker panel: ST2, MMP3, CXCL9, OPN	Yu 2016	172	Increased levels at diagnosis	Step 1: Discovery Step 2: 2 cohorts	
MMP3	Liu 2016	112	Increased levels in BOS patients	Step 1: Discovery	
DKK3	Inamoto 2020	186	Increased levels at diagnosis	Step 1: Discovery	
Reg3α	DePriest 2021	289	Increased levels associated with GI-cGVHD	Step 1: Previous discovery Step 2: 2 cohorts	
Predictive Biomarkers					
No validated cGVHD predictive biomarker exists					• Intensify for high risk group • Reduce immunosuppression for low/standard risk group

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Response Biomarkers					
sBAFF	Whittle 2011	46	Increased levels 1 month after ECP predicted response of cutaneous cGVHD	Step 1: Previous discovery	• Monitoring treatment response • Guide GVHD management • Future: Clinical efficacy endpoint
ST2	Dunavin 2018	16	ST2 levels declined after 2-, 4- and 6-months of ECP	Step 1: Previous discovery	
Prognostic Biomarkers					
CXCL9	Giesen 2020	480	Increased levels at symptom onset associated with severe cGVHD	Step 1: Previous discovery	• Anticipate course of disease • Adjust immunosuppression
DKK3	Inamoto 2020	186	Increased levels at diagnosis associated with NRM	Step 1: Discovery	
MMP-9	Inamoto 2021	33	Increased levels at BOS diagnosis associated with OS	Step 1: Discovery	
Reg3α	DePriest 2021	289	Increased levels at GI-cGVHD diagnosis associated with nrm	Step 1: Previous discovery Step 2: 2 cohorts	
Risk Biomarkers					
Biomarker panel: ST2, MMP3, CXCL9, OPN	Yu 2016	172	Levels D+100 associated with cGVHD development	Step 1: Discovery Step 2: 2 cohorts	• Implement preemptive strategies
CXCL9	Abu Zaid 2017	211	Increased levels D+100 or D+180 associated with cGVHD development	Step 1: Previous discovery Step 2: Clinical trial cohorts	
	Dai 2021	287	Increased levels D+28 associated with severe cGVHD development	Step 1: Previous discovery	
CD163	Inamoto 2017	167	Increased levels D+80 associated with de-novo cGVHD	Step 1: Previous discovery	

Current Definitions and Clinical Implications of Biomarkers in Graft Versus Host Disease Alan Bidgoli, Transplant Cell Ther. 2022 October ;

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Biomarcadores

En desarrollo para intentar predecir enfermedad y seguimiento.

Menos explorados que en EICRa por variabilidad.

ST2 y REG3α.

Incorporación de biomarcadores en ensayos clínicos aleatorios y finalmente la práctica clínica.

Requieren validaciones en grandes cohortes.

No aplicabilidad clínica en la mayoría de los centros.

Supondrá ayuda en las decisiones clínicas.

Current Definitions and Clinical Implications of Biomarkers in Graft Versus Host Disease Alan Bidgoli, Transplant Cell Ther. 2022 October ;

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Qué sabemos de EICRc???

Tratamientos de primera línea

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Estrategias de prevención

Table 1. Summary graft-versus-host disease (GVHD) preventative strategies.

GVHD prophylaxis	Outcome
Calcineurin inhibitor (CSA/TAC) plus MTX/MMF (standard GVHD prophylaxis)	Reduces aGVHD and cGVHD
Addition of sirolimus to standard GVHD prophylaxis	Reduces aGVHD but no difference in cGVHD
Addition of abatacept to standard GVHD prophylaxis	Reduces aGVHD
Post-transplant cyclophosphamide	Reduces aGVHD and cGVHD
In vivo TCD using ATG	Reduces aGVHD and cGVHD
In vivo TCD using alemtuzumab	Reduces aGVHD and cGVHD (increased infection and relapse risk compared with ATG)
Ex vivo TCD - CD3+TCRαβ+/CD19+ lymphocyte removal	Reduces aGVHD and cGVHD
Ex vivo TCD - removal of naïve T-lymphocytes	Reduces cGVHD but not aGVHD
Ex vivo TCD - CD34+ selection with infusion of Tregs (regulatory T-lymphocytes) and conventional T-lymphocytes	Reduces aGVHD and cGVHD

aGVHD, acute graft-versus-host disease; ATG, anti-thymocyte globulin; cGVHD, chronic graft-versus-host disease; CSA, ciclosporin; MMF, mycophenolate mofetil; MTX, methotrexate; TAC, tacrolimus; TCD, T-cell depletion.

Recent advances in graft-versus-host disease 1 Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, NE1 7RU, UK 2 Great North Children's Hospital, Newcastle upon Tyne, UK. Faculty Rewius 2023.

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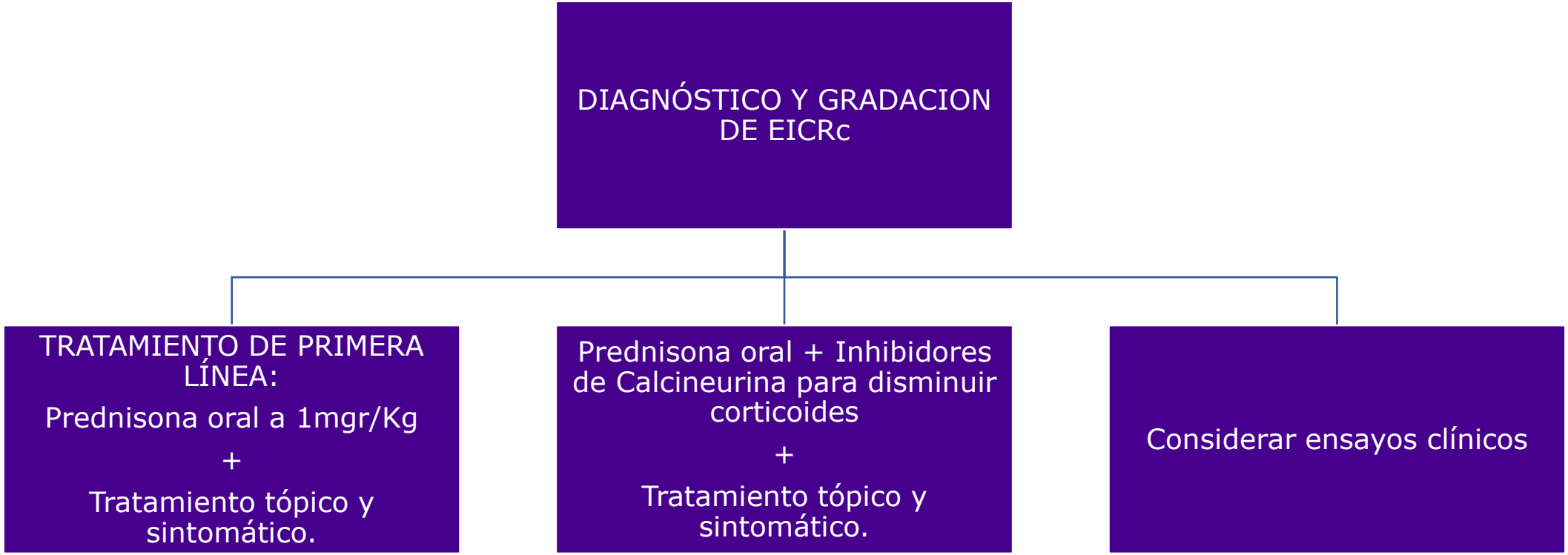
Tratamientos de primera línea



Prophylaxis and management of graft versus host disease after stem-cell transplantation for haematological malignancies: updated consensus recommendations of the European Society for Blood and Marrow Transplantation Olaf Penack et al. Lancet Haematol 2020; 7: e157–67
GUIAS EICRc GETH 2022

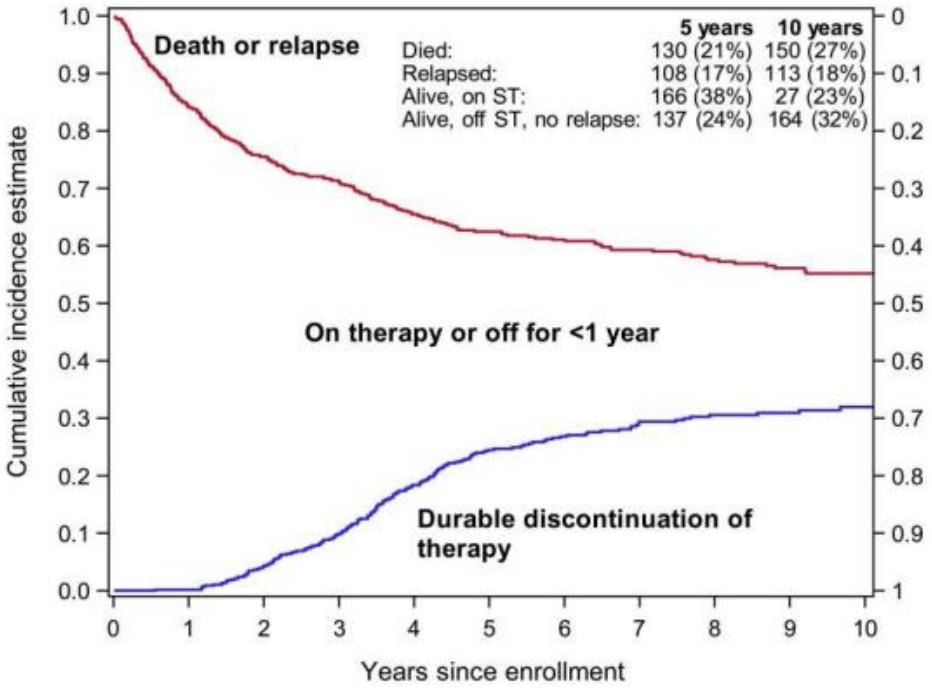
Tratamientos de primera línea.

Fase III.

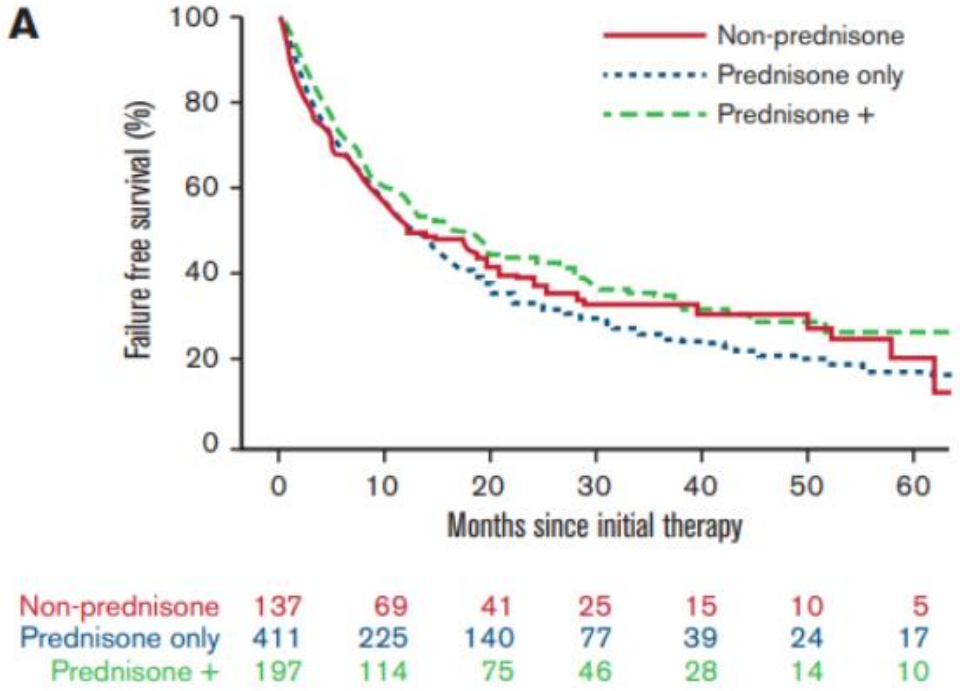
Author	Arms Compared	Double Blind	N	Results
Sullivan[1]	Prednisone ± azathioprine	Yes	179	Decreased survival
Koc, 2002[2]	Prednisone ± CSP	No	287	Limited benefit
Koc, 2000[3]	CSP/prednisone ± thalidomide	Yes	52	Toxicity
Arora[4]	CSP/prednisone ± thalidomide	No	54	No benefit
Martin[5]	CNI/prednisone ± MMF	Yes	151	No benefit
Gilman[6]	CNI/prednisone ± hydroxychloroquine	Yes	54	Terminated early
Carpenter[7]	Sirolimus/prednisone ± CNI	No	151	Terminated early
Miklos[8]	Prednisone ± ibrutinib	Yes	193	No difference in 12-mo ORR

1.Sullivan. Blood. 1988;72:546. 2. Koc. Blood. 2002;100:48. 3. Koc. Blood. 2000;96:3995. 4. Arora. Biol Blood Marrow Transplant. 2001;7:265. 5. Martin. Blood. 2009;113:5074. 6. Gilman. Biol Blood Marrow Transplant. 2012;18:84.
7. Carpenter. Haematologica. 2018;103:1915. 8. Miklos. EHA 2021. Abstr S235.

Tratamientos de primera línea



Chen GL, et al. Haematologica; 108:483-89



Pidala et al. Blood advances. 2021 5;22:4549-59

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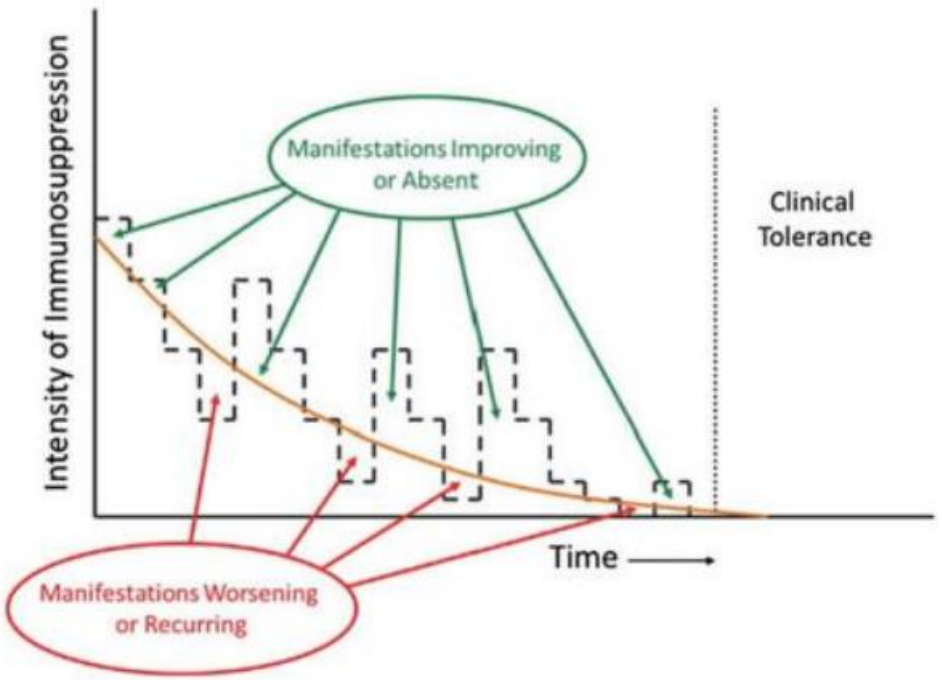
Tratamientos de primera línea

Response	Ibrutinib-Prednisone (n = 95)	Placebo-Prednisone (n = 98)
Response at 48 weeks, No. (%)	39 (41)	36 (37)
CR	9 (9)	6 (6)
PR	30 (32)	30 (31)
SD	4 (4)	2 (2)
PD	23 (24)	34 (35)
cGVHD flare	1 (1)	3 (3)
Not evaluable[a]	28 (30)	23 (23)



Flowers ME et al. Blood. 2015 Jan 22;125(4):606-15.

Criterios de respuesta

- Reevaluar a las 2-4 semanas.
  - Respuesta completa.
  - Respuesta parcial: mejoría en al menos un órgano sin progresión en otro.
  - No respuesta/progresión.
    - Enfermedad estable.
    - Respuesta mixta.
    - Progresión

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.

Lee S. et al. Biol Blood Marrow Transplant. Jun 2015

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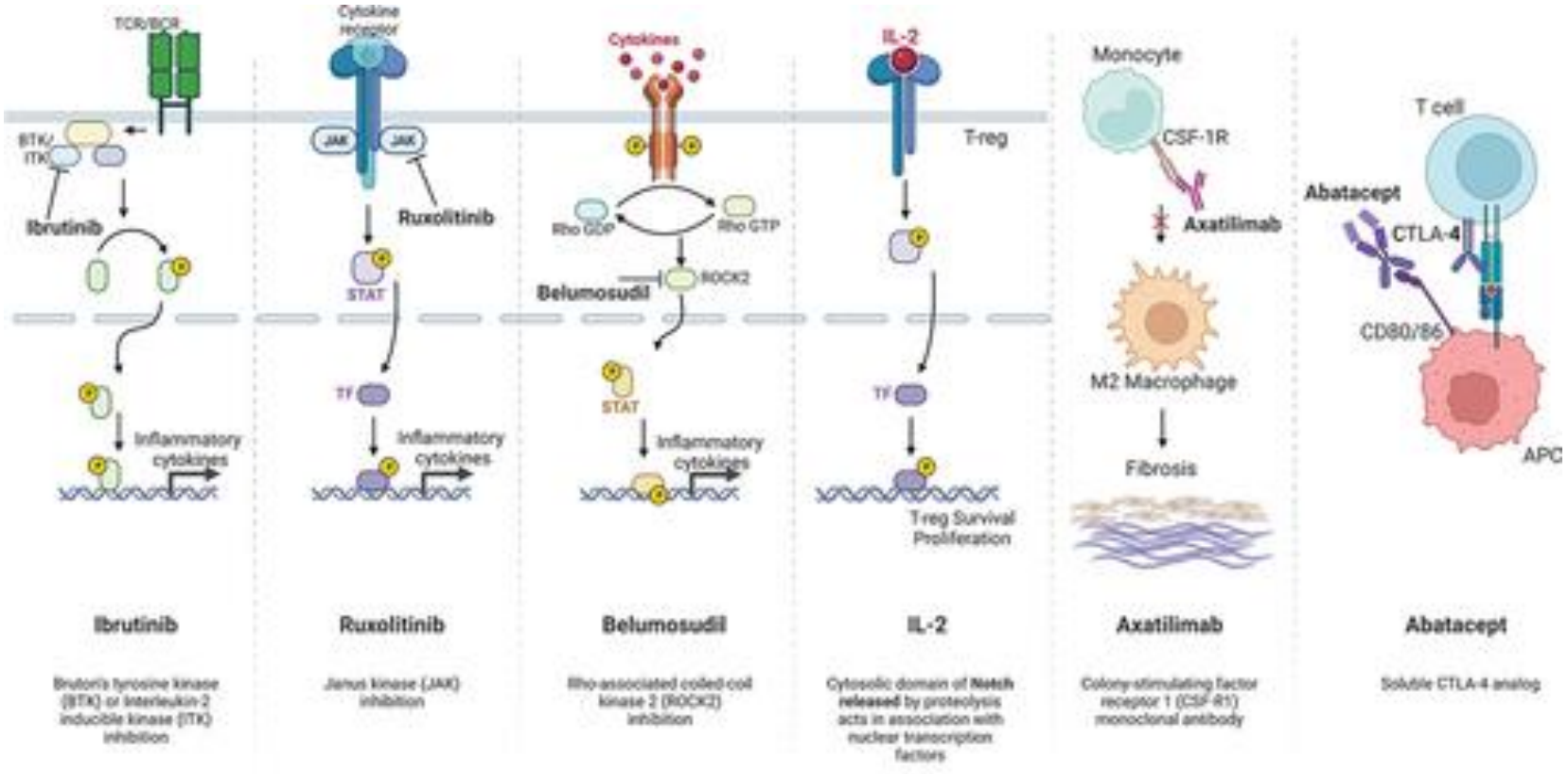
Tratamientos de segunda línea



Effects of immune system cells in GvHD and corresponding therapeutic strategies Maryam Jadid Tavaf, Mahboobeh Ebrahimi Verkiani, Fateme Poorhoseini Hanzaii, Mina Soufi Zomorrod.h ttps://doi.org/10.5045/br.2023.2022192 Blood Res 2023;58:2-12.

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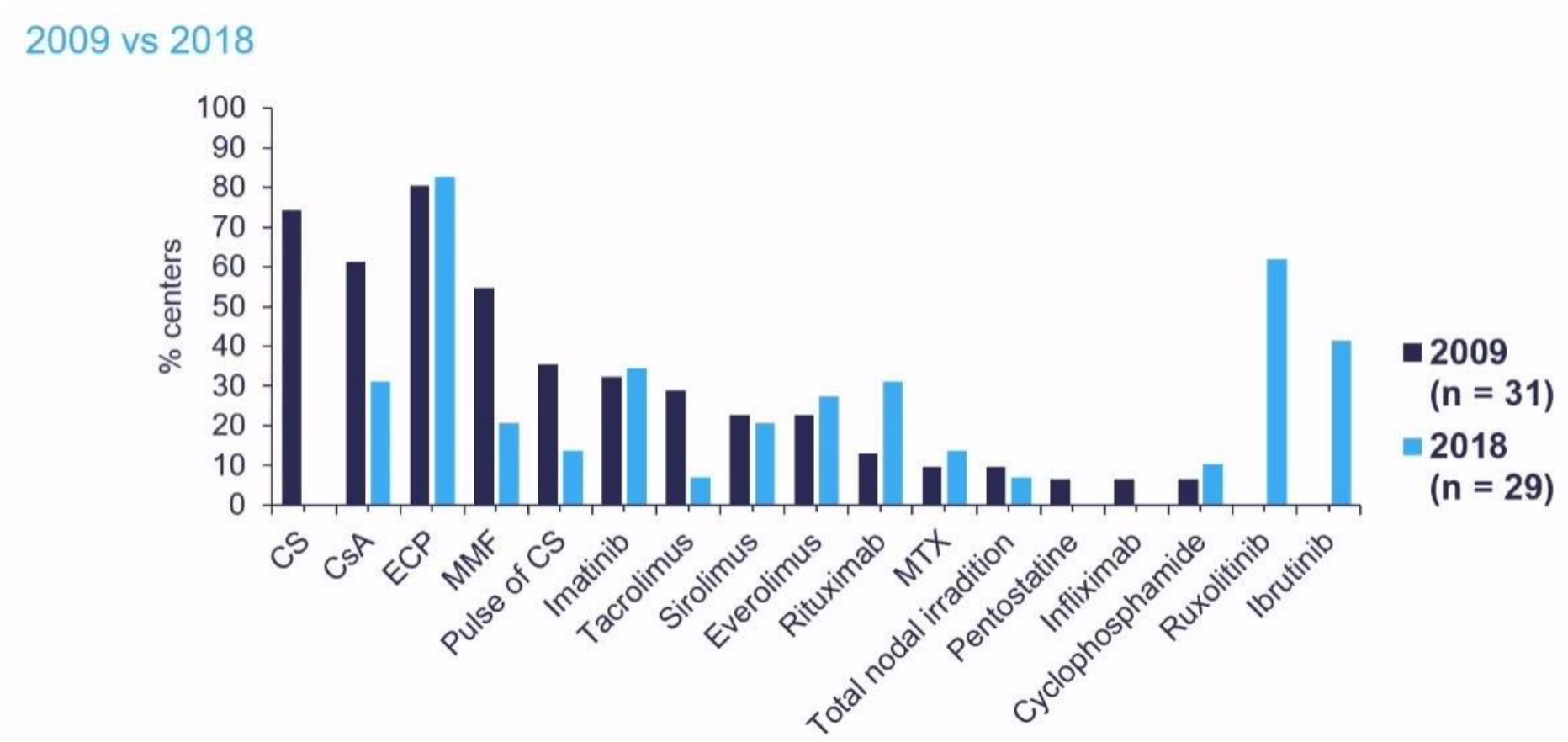
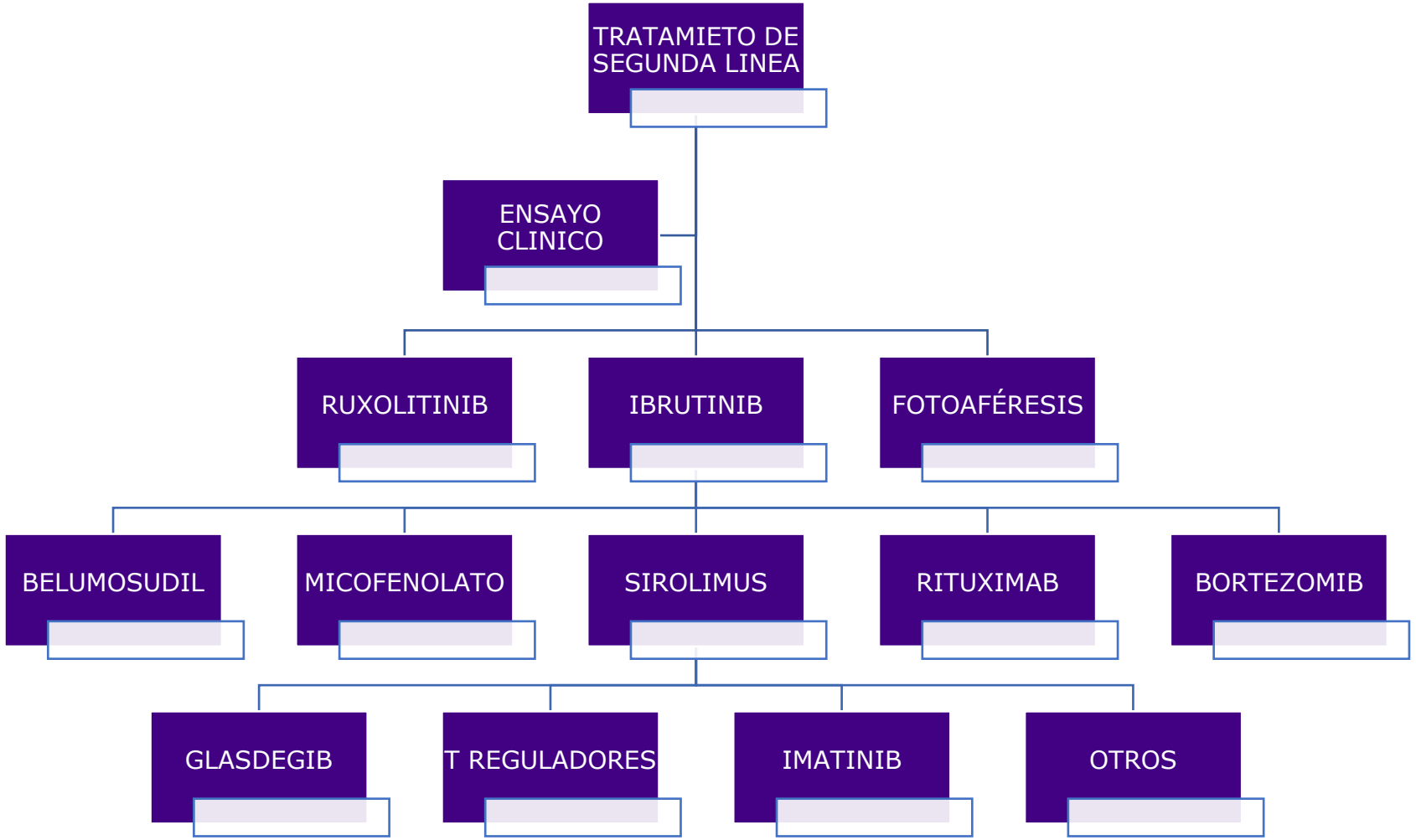
Tratamientos de segunda línea



Wolff D, et al. Bio Blood Marrow Trasplant. 2019;25(7):1450-1455

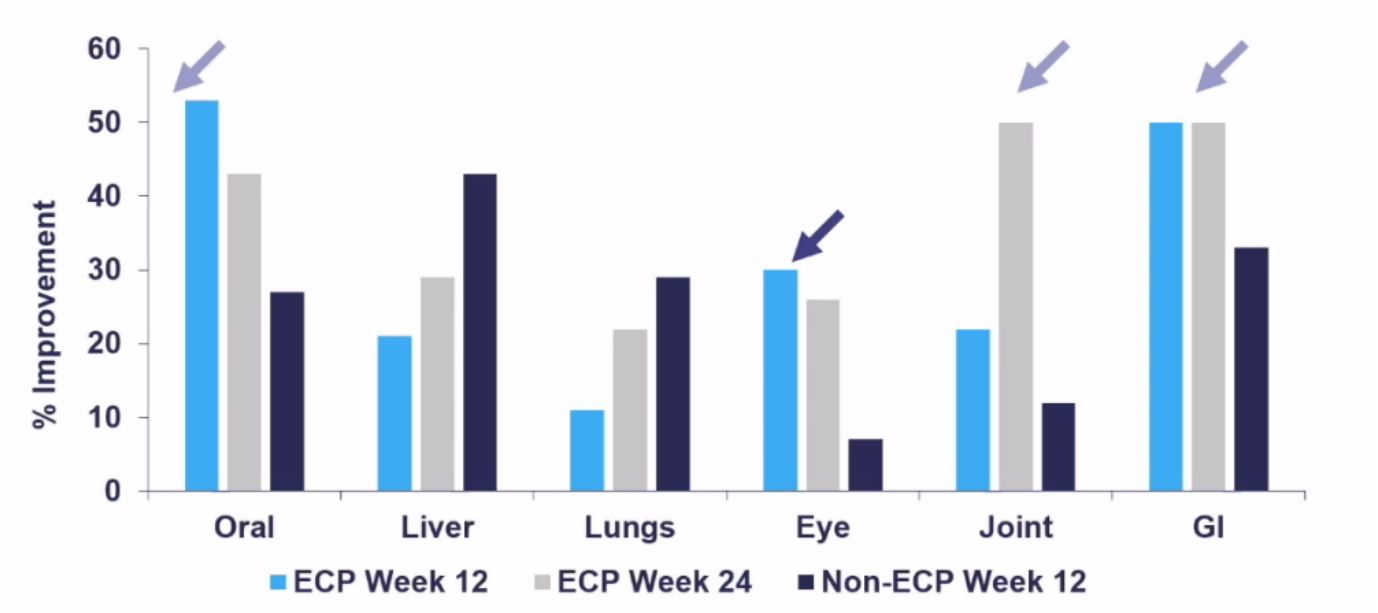
Tratamientos de segunda línea



GUIAS EICRc GETH 2022 NUEVA GUIA EICR 2021 (geth.es)

Las guías pueden recoger productos no comercializados en España

Fotoaféresis



Flowers MED, et al. Blood 2008;112(7):2667-2674

Tasas de respuestas

Table 2. Cutaneous Response to Crossover ECP and Steroid-Sparing

	Weeks after Start of ECP	
	12	24
Number of patients	24*	24*
Cutaneous response		
- Complete and partial response (nonblind clinical investigator assessment), n (%)	7/27† (26)	9/29‡ (31)
- Median percent change in TSS from baseline (blind observer)	−7.9	−25.8
Corticosteroid-sparing effect		
≥50% Reduction in corticosteroid dose, n (%)	4/24 (17)	8/24 (33)
≥50% Reduction in corticosteroid dose and corticosteroid dose < 10 mg/day.	4/24 (17)	6/24 (25)

Table 3. Complete and Partial Response of Extracutaneous Manifestations to Crossover ECP

	Oral Mucosa	Liver	Lungs	Ocular	Joint	GI Tract
Weeks after Start of ECP	Numbers (%)					
12	13/20 (65)	3/6 (50)	3/4 (75)	4/15 (27)	4/11* (36)	1/2 (50)
24	14/20 (70)	3/6 (50)	2/4 (50)	7/15 (47)	5/12 (42)	2/2 (100)

Greinix HT, et al. Biol Blood Marrow Transplant. 2011 Dec;17(12):1775-82.

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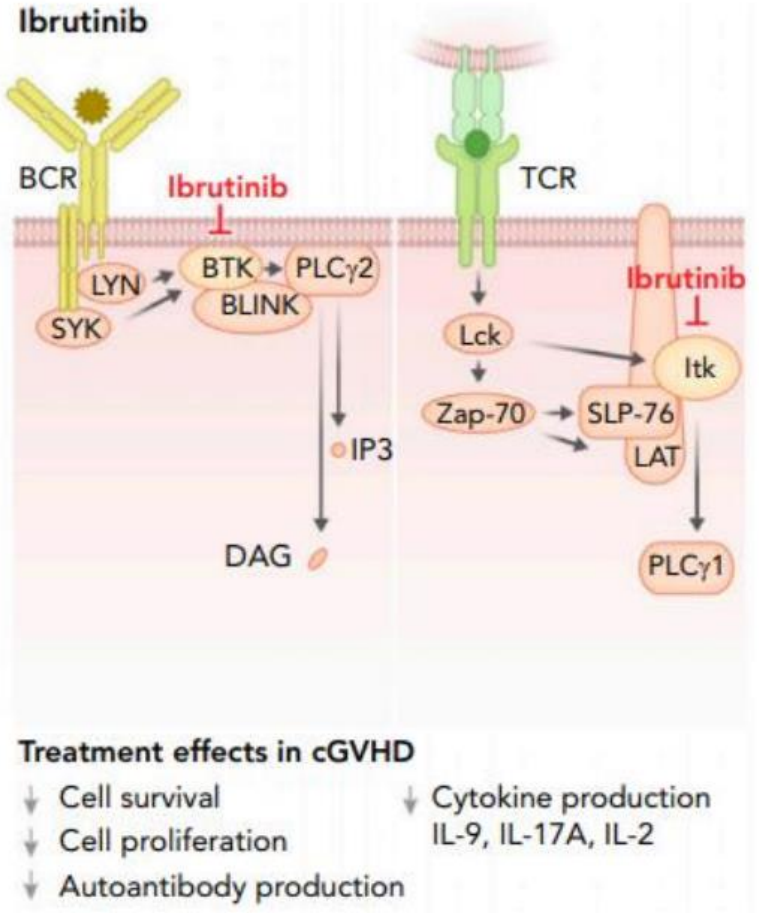
Tasas respuesta. Ibrutinib. Integrate.

Patients with steroid-dependent/refractory cGvHD (> 25% BSA "erythematous rash" or > 4 total mouth score)

→ Ibrutinib 420 mg until cGvHD progression or unacceptable toxicity

Primary endpoint: cGvHD response per NIH 2005 Consensus response criteria



Miklos D, et al. Blood. 2017;130-2243-2250. Zeiser R, Lee SJ. Blood. 2022 Mar 17;139(11):1642-1645.

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Tasas respuesta. Ibrutinib.

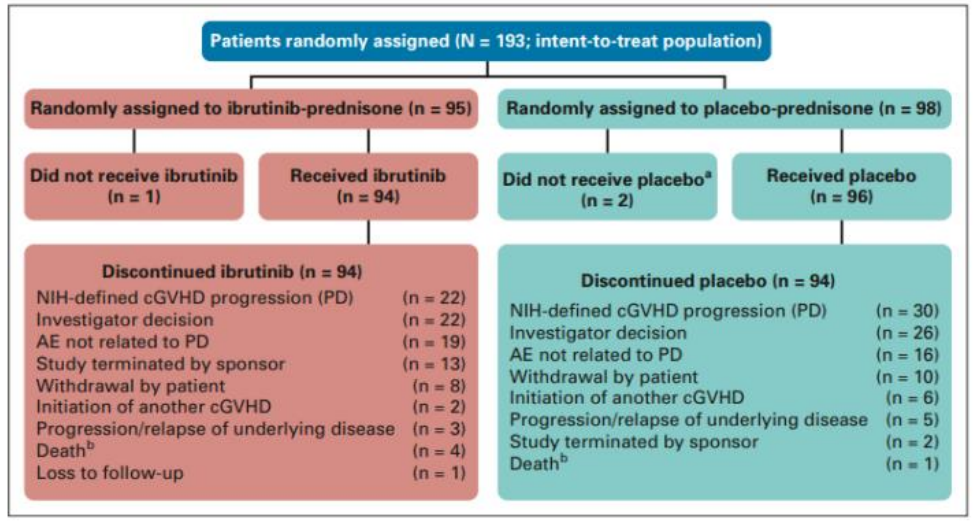
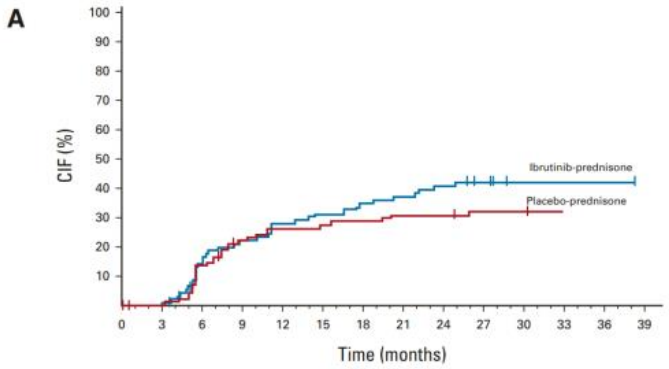
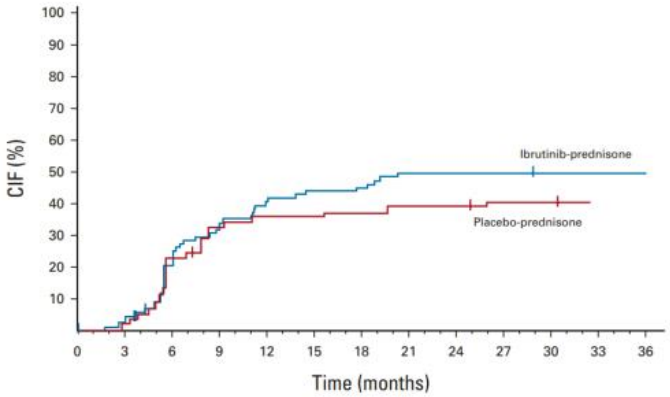


TABLE 2. Response Rates at 48 Weeks (intent-to-treat population)

Response	Ibrutinib-Prednisone (n = 95)	Placebo-Prednisone (n = 98)
Response at 48 weeks, No. (%)	39 (41)	36 (37)
CR	9 (9)	6 (6)
PR	30 (32)	30 (31)
SD	4 (4)	2 (2)
PD	23 (24)	34 (35)
cGVHD flare	1 (1)	3 (3)
Not evaluable[a]	28 (30)	23 (23)
Difference in response rates between the two arms at 48 weeks (95% CI)	0.04 (–0.09 to 0.18)	
P	.54	





Miklos DB, et al. J Clin Oncol. 2023 Apr 1;41(10):1876-1887.

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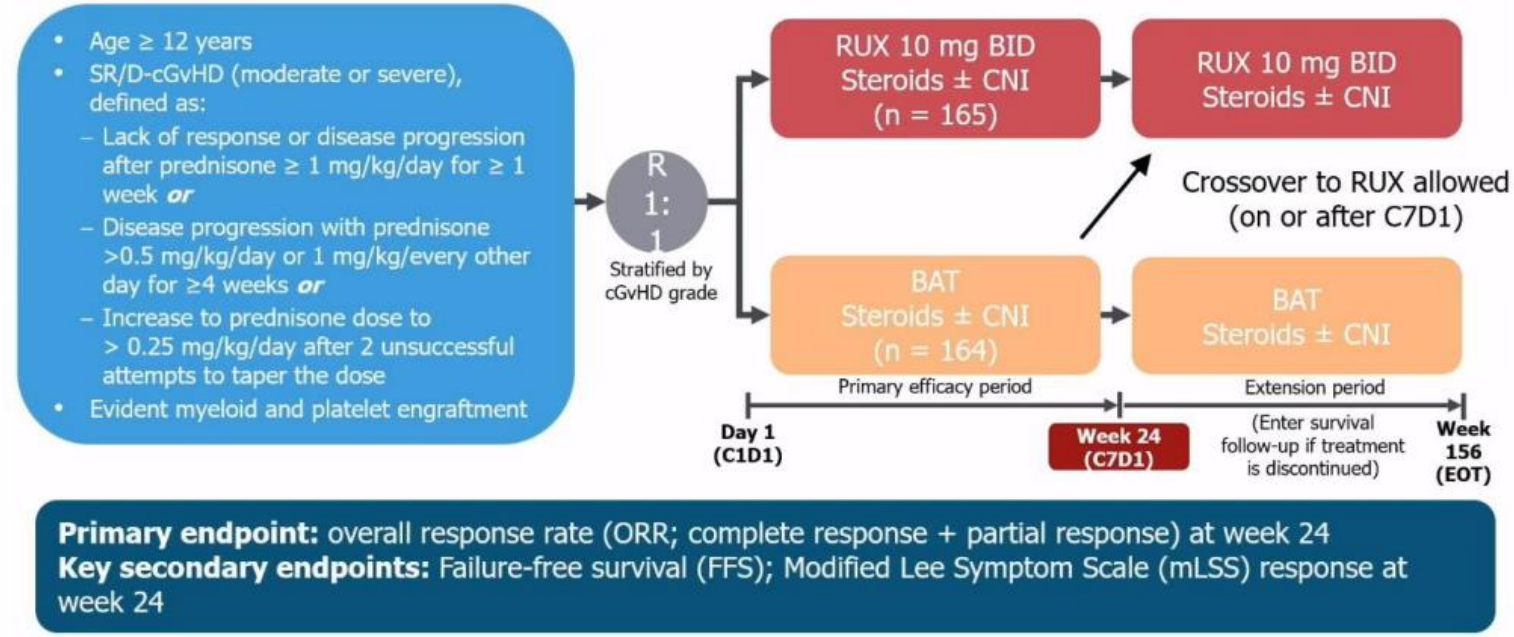
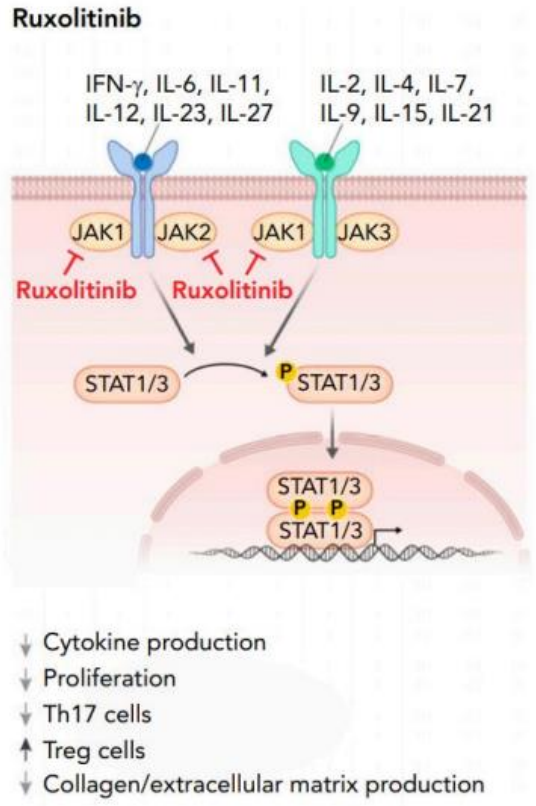
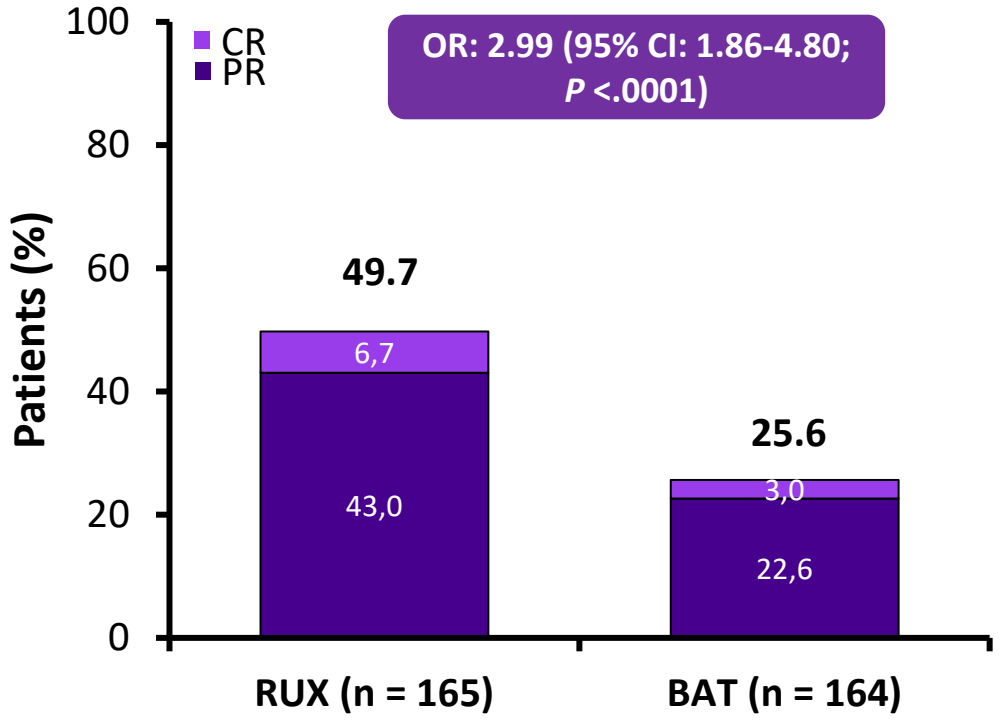
Tratamientos de segunda línea. Ruxolitinib. REACH3.





Zeiser el al. N Engl J Med 385;2021. Zeiser R, Lee SJ. Blood. 2022 Mar 17;139(11):1642-1645.

REACH3



Zeiser. NEJM. 2021;385:228. Ruxolitinib PI.

- ORR was significantly higher with RUX
- **FDA approved ruxolitinib 10 mg BID for treatment of cGVHD after failure of 1-2 prior lines of systemic therapy in adults and pediatric patients 12 yr of age or older (9/22/21)**

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Tratamiento tópico

Diferentes tratamientos tópicos utilizados en los estudios incluidos fueron: dexametasona tópica, budesonida tópica, ácido málico, clobetasol tópico, tacrolimus tópico, triamcinolona.

Table 2: Unstimulated salivary flow rate in comparison.

Topical agent	Baseline	End of study
Malic acid	0.15 ± 0.06 mL/min	0.24± 0.08
Clobetasol	0.19 (0.02-1.6) mL/min	0.30 mL/min
Dexamethasone	0.24 (0.02-0.84) mL/min	No significant difference (p=1.00)

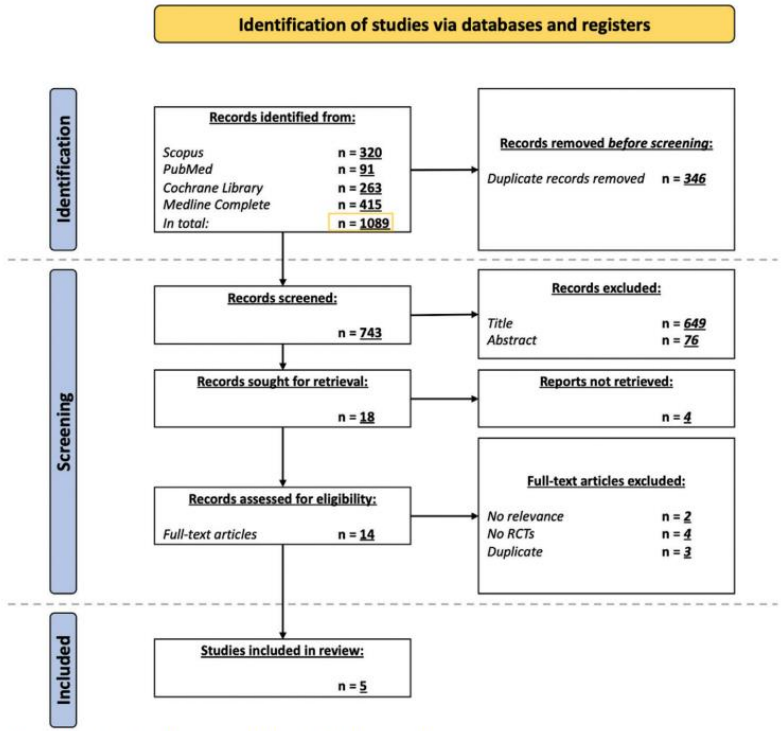

Fig. 1: Flow-chart of the search carried out in the four databases.

Topical treatment of oral chronic graft-versus-host- disease in hematopoietic stem cell transplant recipients: A systematic review Livia Haas , Marta Cruz-Pamplona. J Clin Exp Dent. 2023;15(5):e420-7.

Tratamiento tópico. Importancia equipos multidisciplinares.

- Oftalmología
- Dermatología
- Reumatología
- Ginecología

Calidad de vida

Incluye la exploración del impacto psicosocial, financiero, ocupacional y sexual del trasplante.

Los resultados sugieren que es necesario seguir trabajando para desarrollar y probar intervenciones que puedan preparar mejor a los pacientes para el trasplante y mejorar su capacidad para afrontar los impactos significativos que el trasplante puede tener en sus vidas y las vidas de quienes los rodean.

Mejoría de la percepción de los pacientes.

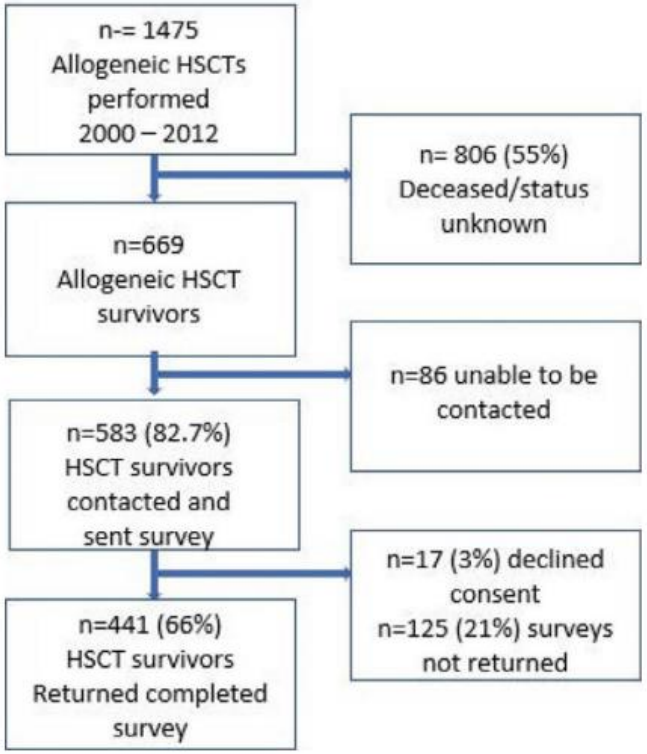

Fig. 1 Study flowchart

Predictors of post traumatic growth in allogeneic hematopoietic stem cell transplantation survivors: a cross-sectional survey. McErlean et al. BMC Psychology (2023) 11:235 https://doi.org/10.1186/s40359-023-01204-4

Calidad de vida

Table 5. *Variables independently associated with QOL and psychopathology (stepwise multiple regression analysis)*

	FACT-BMT				BDI			
	Autologous		Allogeneic		Autologous		Allogeneic	
	beta	t(p)	beta	t(p)	beta	t(p)	beta	t(p)
Psychiatric comorbidity	0.3	4.61 (p<0.001)	−0.38	−3.79 (p<0.001)			−0.44	−5.37 (p<0.001)
Clinical Global Impression							0.23	3.38 (p=0.002)
Beck Depression Inventory	−0.56	−5.62 (p<0.001)	−0.71	−5.04 (p<0.001)				
Spielberger Anxiety Inventory			−0.42	−3.51 (p=0.01)	0.89	8.6 (p<0.001)	0.55	6.86 (p<0.001)
Spielberger Anxiety Inventory "State" scale	−0.31	−3.1 (p=0.004)						

Impact of the type of hematopoietic stem-cell transplant on quality of life and psychopathology Henrietta JANICSÁK. Ideggyogy Sz 2023;76(1–2):025–035. https://doi.org/10.18071/isz.76.0025

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Conclusiones

- Complicación tardía más frecuente tras alotrasplante.
- Amplia manifestaciones clínicas.
- GCs +/- ICN constituyen tratamiento estándar en primera línea.
- Datos que apoyan el uso de Ruxulotinib en segunda línea de tratamiento.
- Importancia comité multidisciplinar.
- Calidad de vida.
- Mejoría en el desarrollo de nuevas terapias.

Gracias a pacientes y familiares

Reunirse es un comienzo, permanecer un progreso, trabajar juntos constituye el éxito.

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Gracias a pacientes y familiares

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