What is Chronic GvHD?

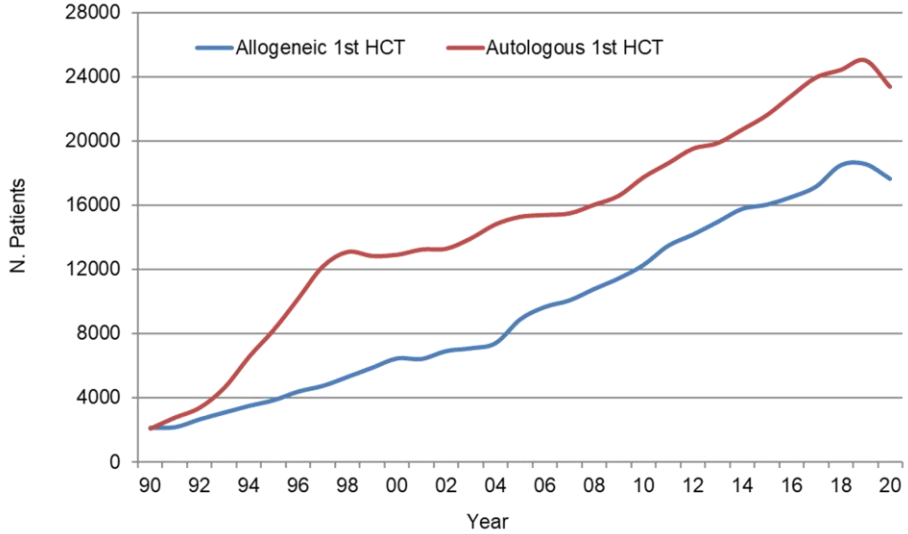
John Murray
Christie Hospital Manchester
17th May 2024

Disclosures

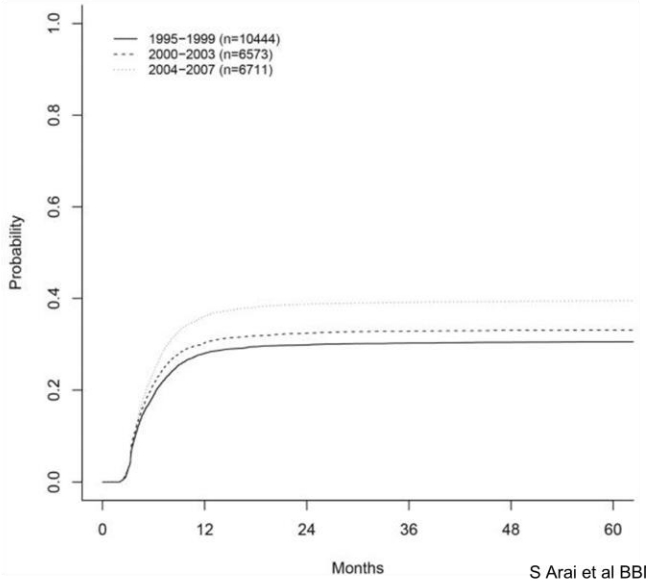
- Non-paid speaker (Sanofi) today

Extent of problem

- 33% of adult allo-SCT and 16% of paediatric allo-SCT.
- Incidence modelling suggests approx 1000 mild, 1500 moderate, 1000 severe cases across Europe.
- Estimate 200-400 patients likely to be suffering cGvHD in UK.



Passweg, et al. BMT. 2022.



S Arai et al BBMT 2015.

Certain characteristics increase a patient's risk for cGVHD

INTEN

An estimated **52%** of patients progress from aGVHD to cGVHD.[1]

Patients aged ≥18 years receiving a bone marrow or cord blood graft had a 5-fold increased risk of developing cGVHD compared with younger patients.[2,a]

- The risk of developing cGVHD was tenfold in patients aged ≥18 years receiving a peripheral blood graft compared with younger patients

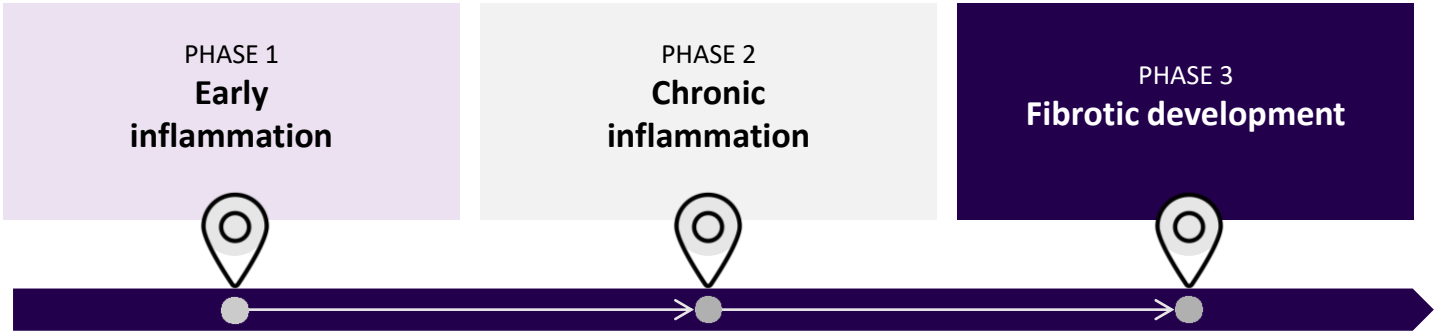
Common risk factors for developing cGVHD[3-6]
Prior aGVHD[3,6]
Older age of recipient or donor[3,6]
Peripheral blood HCT vs bone marrow HSCT[4-6]
Female donors in male recipients[3,4,6]
HLA disparity between recipient and donor[3-6]
Diagnosis of chronic myeloid leukaemia[6]
High-intensity conditioning regimen[4]
Alloimmunization of the donor (eg, history of pregnancy, transfusion)[3]
Administration of donor lymphocyte infusions[3]
Previous splenectomy[5]
CMV seropositivity (donor and/or recipient)[4,5]
Epstein-Barr virus donor seropositivity[4]

aGVHD, acute graft-versus-host disease; alloHSCT, allogeneic haematopoietic stem cell transplant; cGVHD, chronic graft-versus-host disease; CMV, cytomegalovirus; dUCB, double umbilical cord blood; HCT, hematopoietic cell transplant; HLA, human leukocyte antigen; MSD, matched sibling donor; sUCB, single umbilical cord blood. [a]From a study evaluating risk factors for patients with cGVHD undergoing MSD (n=469), dUCB (n=416) or sUCB (n=295) alloHCTs between 2000 and 2012.[2]

1. Mawardi H et al. Oral Dis. 2019;25(4):931-948. doi:10.1111/odi.12936 **2.** Lazaryan A et al. Biol Blood Marrow Transplant. 2016;22(1):134-140. doi:10.1016/j.bbmt.2015.09.008 **3.** Stewart BL et al. Blood. 2004;104(12):3501-3506. doi:10.1182/blood-2004-01-0200 **4.** Cooke KR et al. Biol Blood Marrow Transplant. 2017;23(2):211-234. doi:10.1016/j.bbmt.2016.09.023 **5.** Hymes SR et al. J Am Acad Dermatol. 2012;66(4):515.e1-515.e18. doi:10.1016/j.jaad.2011.11.960 6. Zeiser R, Blazar BR. N Engl J Med. 2017;377(26):2565-2579. doi:10.1056/NEJMra1703472

cGvHD pathogenesis

Three phases of the pathophysiology of cGVHD[1]

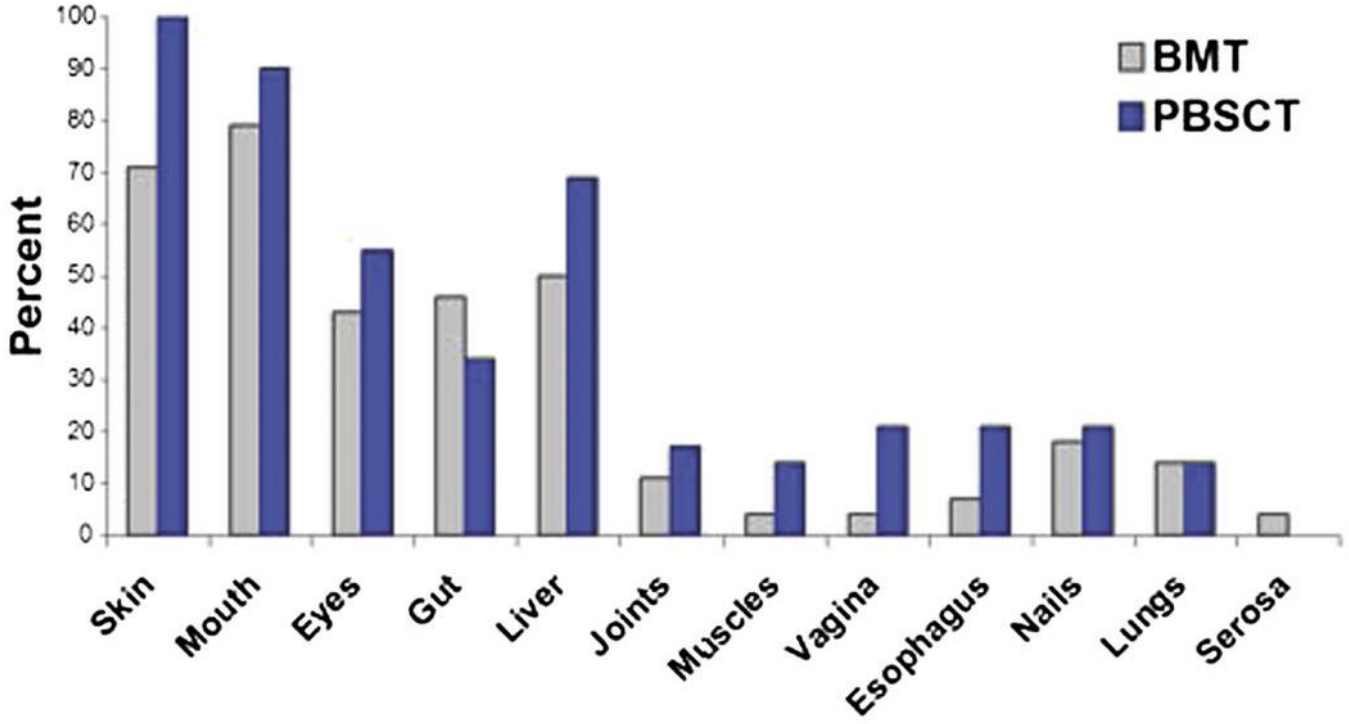


There is a complex relationship between the inflammatory and fibrotic processes in cGVHD; however, both processes actively contribute to the pathology and progression of the disease.[1,2,3]

cGVHD, chronic graft-versus-host disease.

1. Zeiser R, Blazar BR. *N Engl J Med*. 2017;377(26):2565-2579. doi:10.1056/NEJMra1703472 **2.** Jagasia MH et al. *Biol Blood Marrow Transplant*. 2015;21(3):389-401.e1. doi:10.1016/j.bbmt.2014.12.001 **3.** Cooke KR et al. *Biol Blood Marrow Transplant*. 2017;23(2):211-234. doi:10.1016/j.bbmt.2016.09.023

Distribution of affected organs



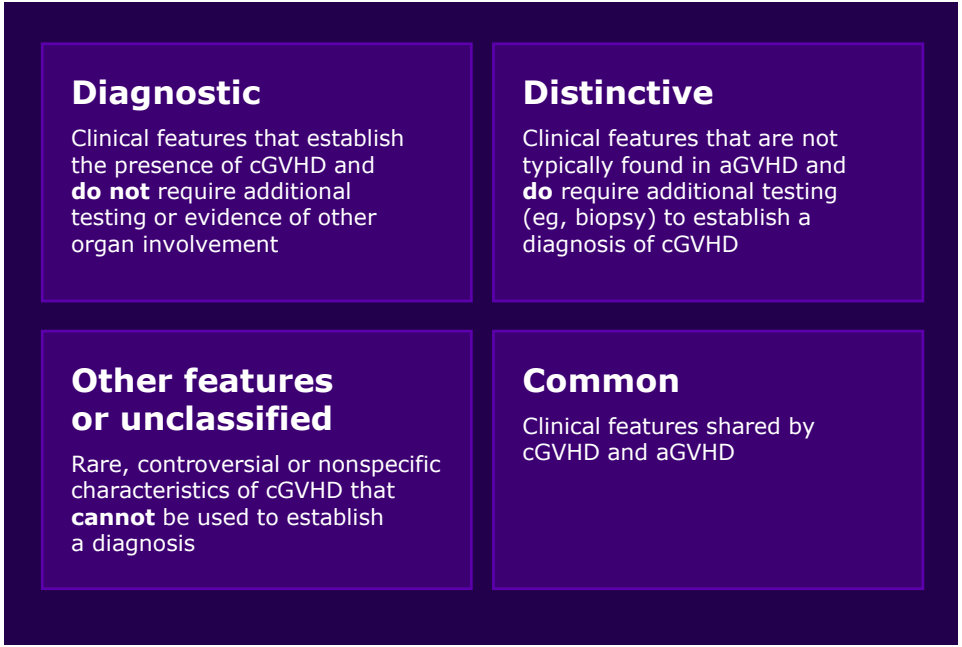
Mary E. D. Flowers Blood, 2015.

cGVHD classification – 2014 NIH criteria

NIH categorizes clinical features as

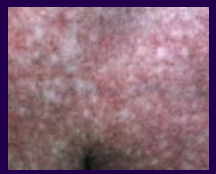
- Diagnostic
- Distinctive
- Other features or unclassified manifestations
- Common

A diagnosis of cGVHD requires the presence of ≥1 diagnostic features OR ≥1 distinctive features plus additional testing (eg, biopsy, laboratory tests, evaluation by a specialist, radiographic imaging)



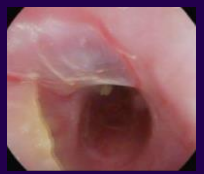
aGVHD, acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease; NIH, National Institutes of Health. Jagasia MH et al. *Biol Blood Marrow Transplant*. 2015;21(3):389-401.e1. doi:10.1016/j.bbmt.2014.12.001

Chronic GVHD has heterogeneous organ involvement and variable disease manifestations[1]

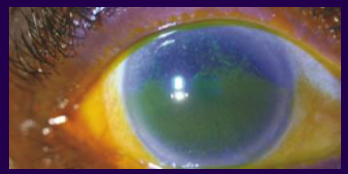


Poikiloderma[2]

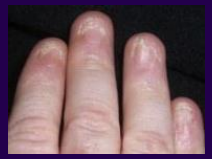
Papulosquamous lesions[3]



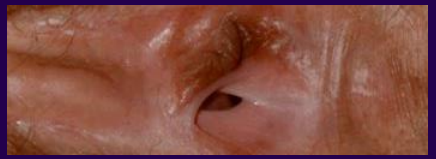
Altered mucosa of the esophagus[4]



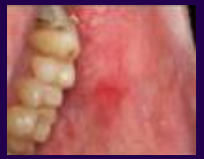
KCS[5]



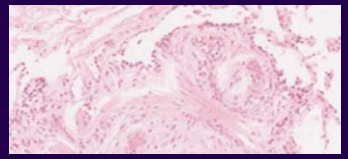
Nail dystrophy[6]



Labial fusion and resorption[7]



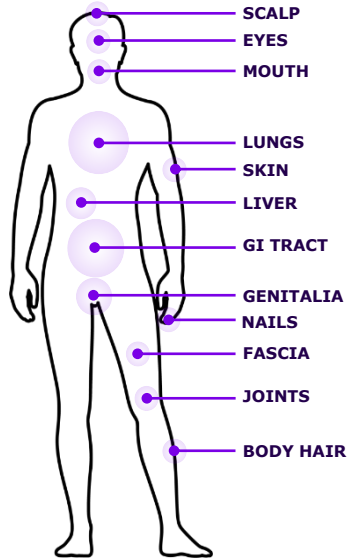
Lichen planus–like changes[8]



Partial obstruction of bronchioles in BOS[9]

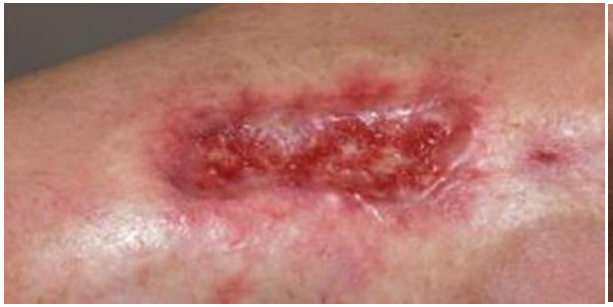
Source: Zeiser et al, Pavletic et al, Jang et al, Nassiri et al, Huang et al, Norian et al, Margaix-Muñoz et al, Dudek et al

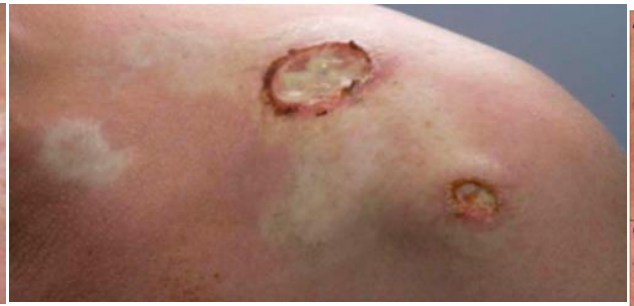
Commonly affected areas[1]

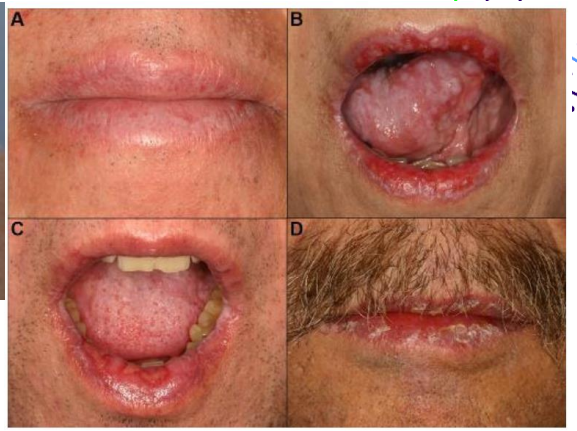


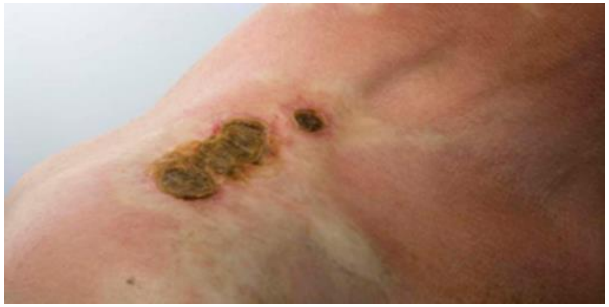
BOS, bronchiolitis obliterans syndrome; GI, gastrointestinal; GVHD, graft-versus-host disease; KCS, keratoconjunctivitis sicca.

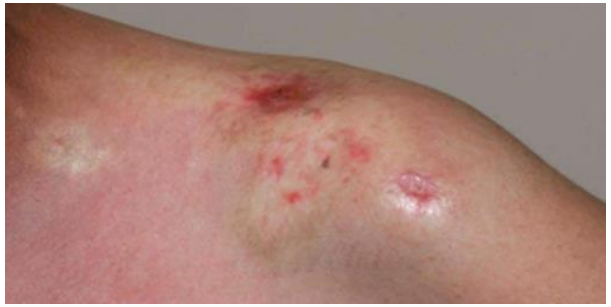
1. Zeiser R, Blazar BR. *N Engl J Med*. 2017;377(26):2565-2579. doi:10.1056/NEJMra1703472 **2.** Pavletic SZ et al. *Bone Marrow Transplant*. 2006;38(10):645-651. doi:10.1038/sj.bmt.1705490 **3.** Jang S et al. *Ann Dermatol*. 2016;28(1):90-93. doi:10.5021/ad.2016.28.1.90 **4.** Khan ZA et al. *Indian J Gastroenterol*. 2021;40(1):91-93. doi:10.1007/s12664-020-01119-7 **5.** Nassiri N et al. *J Ophthalmic Vis Res*. 2013;8(4):351-358. **6.** Huang J et al. *Biol Blood Marrow Transplant*. 2014;20(2):S171-S172. doi:10.1016/j.bbmt.2013.12.278 **7.** Norian JM et al. *Obstet Gynecol*. 2008;112(2 Pt 2):437-439. doi:10.1097/01.AOG.0000299876.18200.8d **8.** Margaix-Muñoz M et al. *J Clin Exp Dent*. 2015;7(1):e138-e145. doi:10.4317/jced.51975 **9.** Dudek AZ et al. *Biol Blood Marrow Transplant*. 2003;9(10):657-666. doi:10.1016/s1083-8791(03)00242-8.

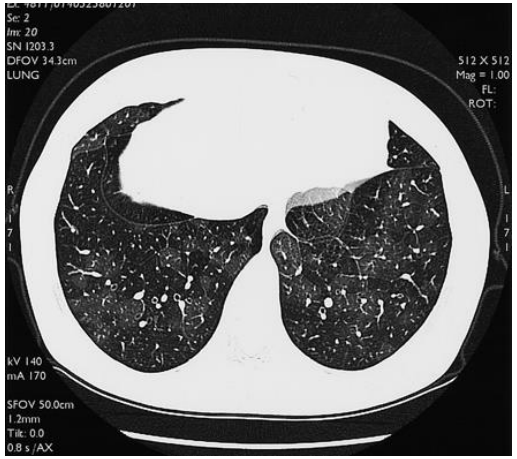


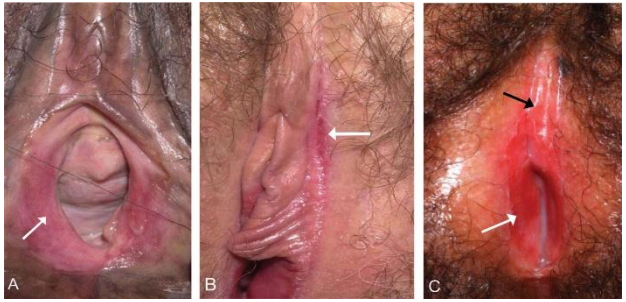


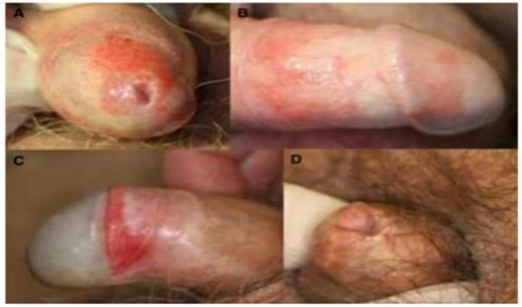












Images provided by the speaker

The 2014 NIH cGVHD consensus criteria also guide assessment of the severity of cGVHD

- Chronic GVHD is classified into mild, moderate or severe, based on a global score
- The global score takes into consideration the involvement and severity of 8 organs or sites
  - Skin
  - Mouth
  - Eyes
  - GI tract
  - Liver
  - Lungs
  - Joints and fascia
  - Genital tract
- Each organ or site score ranges from 0 (no involvement) to 3 (severe impairment)

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

Key points:

1. In skin: higher of the two scores to be used for calculating global severity.
2. In lung: FEV1 is used instead of clinical score for calculating global severity.
3. If the entire abnormality in an organ is noted to be unequivocally explained by a non-GVHD documented cause, that organ is not included for calculation of the global severity.
4. If the abnormality in an organ is attributed to multifactorial causes (GVHD plus other causes) the scored organ will be used for calculation of the global severity regardless of the contributing causes (no downgrading of organ severity score).

Source: Jagasia et al.

cGVHD, chronic graft-versus-host disease; FEV_1, forced expiratory volume in 1 second; GI, gastrointestinal; NIH, National Institutes of Health.

Jagasia MH et al. *Biol Blood Marrow Transplant*. 2015;21(3):389-401.e1. doi:10.1016/j.bbmt.2014.12.001

Data capture - eGVHD

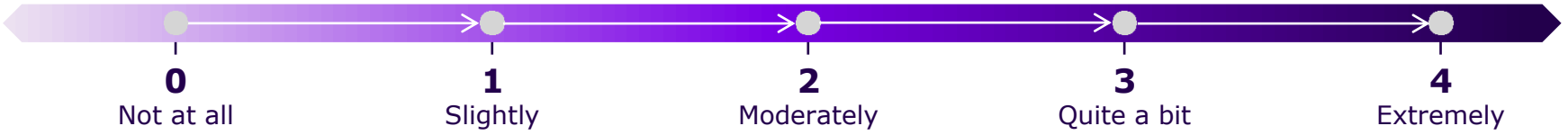
The eGVHD app is developed by the UZ Leuven (Belgium) in collaboration with the EBMT (European Bone Marrow Transplantation Society) Transplantation Complications Working Party and the National Institute of Health (Bethesda, USA). It is an electronic tool designed as an algorithm-driven application, to help clinicians apply the internationally recognized criteria for the assessment of graft versus host disease (GVHD).

This app is not owned by Sanofi and therefore are not responsible for the content.

Data capture – Lee Symptom Scale (LSS)[1]

Consists of 7 subscales with a total of 30 items rated on a 5-point Likert scale[1]

Clinically meaningful improvement is indicated by a 6- to 7-point reduction in LSS score.[1,2]



cGVHD, chronic graft-versus-host disease; LSS, Lee Symptom Scale.

1. Lee SJ et al. *Biol Blood Marrow Transplant*. 2002;8(8):444-452. doi:10.1053/bbmt.2002.v8.pm12234170 **2.** Teh C et al. *Biol Blood Marrow Transplant*. 2020;26(3):562-567. doi:10.1016/j.bbmt.2019.11.020

As a serious posttransplant complication, cGVHD impacts many aspects of patients' lives[1]

Patients with cGVHD face physical, functional and psychosocial deficits that **result in poor QOL and an inability to return to work**[1]

Worse overall QoL/physical functioning[6]

Self-reported symptoms of depression significantly associated with lower overall survival[6]

Development of fibrosis-related signs and symptoms, such as those in the joints or lungs, can lead to **chronic disability and significant morbidity**[2-4]

Approximately

1 out of 3

patients with moderate to severe cGVHD had clinically **significant psychological distress**, including depression or anxiety.[5,a]

cGVHD, chronic graft-versus-host disease; QOL, quality of life.

[a]From a 2018 study evaluating psychological distress in patients with cGVHD (n=53).[7]

Lee SJ. *Blood*. 2017;129(1):30-37. doi:10.1182/blood-2016-07-686642 **2.** Martires KJ et al. *Blood*. 2011;118(15):4250-4257. doi:10.1182/blood-2011-04-350249 **3.** Baird K et al. *Biol Blood Marrow Transplant*. 2013;19(4):632-639. doi:10.1016/j.bbmt.2013.01.013. **4.** Au BKC et al. *Biol Blood Marrow Transplant*. 2011;17(7):1072-1078. doi:10.1016/j.bbmt.2010.11.018 **5.** Waldman L et al. *J Clin Oncol*. 2018;36(15)(suppl):e22137. doi:10.1200/JCO.2018.36.15_suppl.e22137 **6.** El-Jawahri et al., Biol Blood Marrow Transplant 2018, 2285–2292

A continuing problem

- Health care providers concentrate on medical aspects
- Not always well assessed or appreciated
- Patient does not always volunteer information
- Fear of stigmatisation
- Do not want to feel ungrateful
- Should be happy to be alive

Speaker's point of view

PRO clinical trials

Current Hematologic Malignancy Reports (2019) 14:22–30
https://doi.org/10.1007/s11899-019-0494-x

STEM CELL TRANSPLANTATION (R MAZIARZ, SECTION EDITOR)

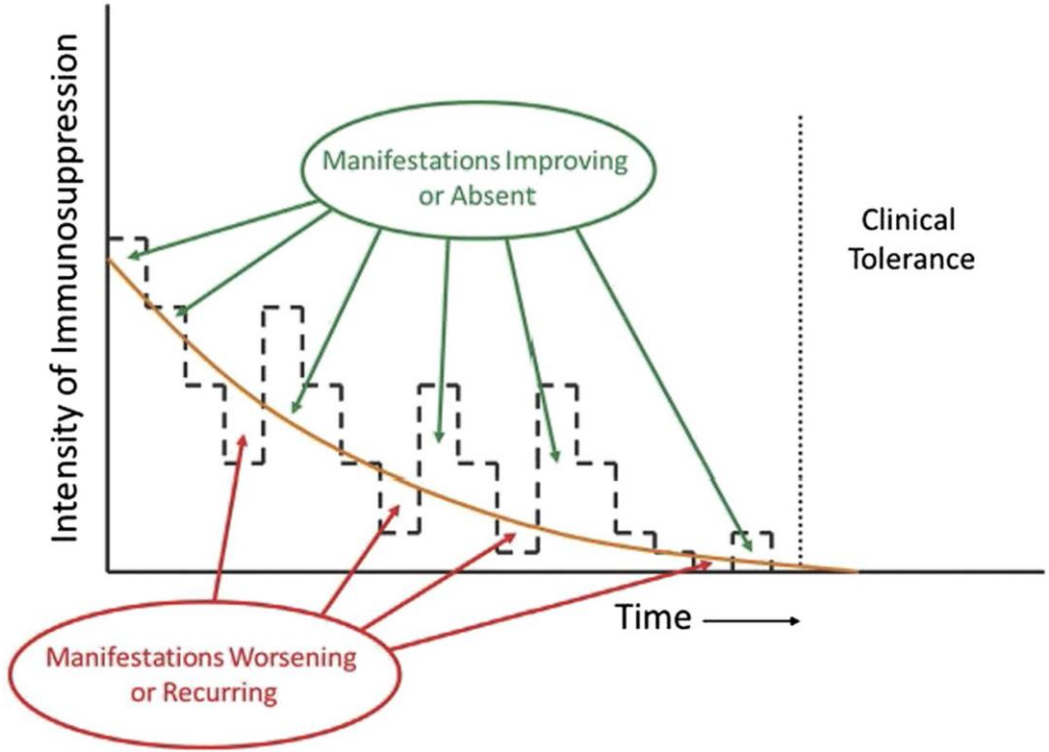
Graft Versus Host Disease Clinical Trials: Is it Time for Patients Centered Outcomes to Be the Primary Objective?

Bronwen E. Shaw[1]

Conclusions:

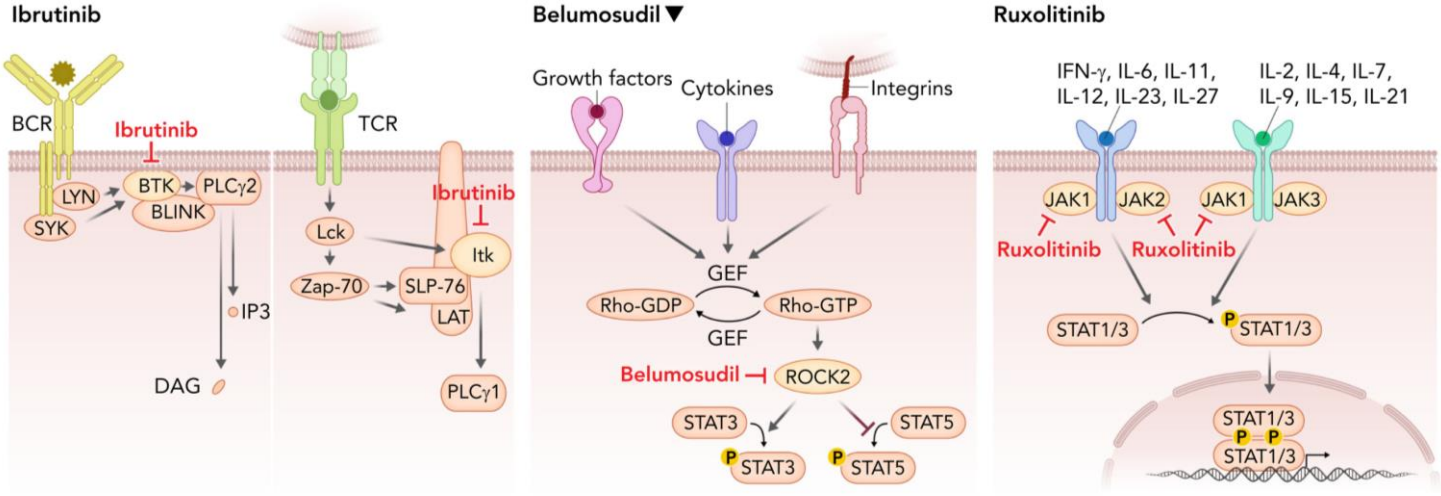
- Consensus recommendations for PRO inclusion in cGVHD clinical trials have yet to be consistently applied
- Validated PRO measure for aGVHD is needed
- Development of composite endpoints (PRO, clinician assessment, laboratory or functional measures) for all GVHD clinical trials required
- Trials now have PRO built in

Treatment goal



Mary E. D. Flowers Blood, 2015.

Targeted therapies in cGVHD



Treatment effects in cGVHD

- ↓ Cell survival
- ↓ Cell proliferation
- ↓ Autoantibody production
- ↓ Cytokine production IL-9, IL-17A, IL-2

- ↓ Cytokine production
- ↓ Proliferation
- ↓ Th17 cells
- ↓ Follicular helper T cells
- ↑ Treg cells
- ↓ Collagen/extracellular matrix production

- ↓ Cytokine production
- ↓ Proliferation
- ↓ Th17 cells
- ↑ Treg cells
- ↓ Collagen/extracellular matrix production

Adapted from Zeiser and Lee, Blood 2022

What do we know

- Chronic GVHD is a complex and heterogeneous multiorgan disease known to have both inflammatory and fibrotic components that can result in variable disease manifestations[1,2]
  - **Chronic GVHD can affect almost any organ, but most commonly affects the skin, mouth and eyes, resulting in oral lesions, dry or gritty eyes that can cause great discomfort, hair loss and severe skin erythema (rash)[3]**
  - **It is important to note that, even at the time of diagnosis, patients can have involvement in many organs, including the lungs and others with symptoms associated with poor survival[4,5]**
- Chronic GVHD is classified as mild, moderate or severe on a global score that takes into consideration the involvement of 8 organs or sites[3]
- The LSS score measures the effect of cGVHD on a patient's functioning and well-being over the past month[6]
- Treatment goals for cGVHD include symptom relief, disease control and prevention of damage and disability[3,6,7]
- Considerable unmet need and high morbidity, with variable treatment options across the world
- Clinical trial data is needed to optimise therapies moving forward
- Corticosteroids are the mainstay of therapy for cGVHD in both pediatric and adult patients; however, most patients will require subsequent lines of therapy[8-10]
  - **There is no clear choice among these options for additional lines of therapy[8]**

cGVHD, chronic graft-versus-host disease; LSS, Lee Symptom Scale; NIH, National Institutes of Health.

1. Zeiser R, Blazar BR. *N Engl J Med*. 2017;377(26):2565-2579. doi:10.1056/NEJMra1703472 **2.** MacDonald KPA et al. *Blood*. 2017;129(1):13-21. doi:10.1182/blood-2016-06-686618. **3**. Jagasia MH et al. *Biol Blood Marrow Transplant*. 2015;21(3):389-401.e1. doi:10.1016/j.bbmt.2014.12.001 **4**. Arora M, Cutler CS, Jagasia MH, Pidala J, Chai X, Martin PJ, et al. Late Acute and Chronic Graft-versus-Host Disease after Allogeneic Hematopoietic Cell Transplantation. Biology of blood and marrow transplantation: Journal of the American Society for Blood and Marrow Transplantation. 2016;22(3):449-55. **5.** Mawardi H, Hashmi SK, Elad S, Aljurf M, Treister N. Chronic graft-versus-host disease: Current management paradigm and future perspectives. Oral Dis. 2019;25(4):931-48. **6.** Lee SJ et al. *Biol Blood Marrow Transplant*. 2002;8(8):444-452. doi:10.1053/bbmt.2002.v8.pm12234170. **7.** Dignan FL et al. *Br J Haematol*. 2012;158(1):46-61. doi:10.1111/j.1365-2141.2012.09128.x **8.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Hematopoietic Cell Transplantation (HCT). V.1.2023. © National Comprehensive Cancer Network, Inc. 2023. All rights reserved. Accessed April 6, 2023. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. **9.** Sobkowiak-Sobierajska A et al. *Front Pediatr*. 2022;10:808103. doi:10.3389/fped.2022.808103 **10.** Flowers MED, Martin PJ. *Blood*. 2015;125(4):606-615. doi:10.1182/blood-2014-08-551994.

Prescribing Information: REZUROCK (belumosudil) ▼ 200mg film-coated tablets (Licence valid in GB only)

Therapy should be initiated and supervised by physicians experienced in the management of chronic GVHD.
Please refer to the Summary of Product Characteristics (SmPC) before prescribing.

Presentation: Each film-coated tablet contains belumosudil mesilate, equivalent to 200mg belumosudil.
Indication: Rezurock is indicated for the treatment of patients aged 12 years and older with chronic graft-versus- host disease (chronic GVHD) who have received at least two prior lines of systemic therapy.
Dosage and Administration: The recommended dose of Rezurock is 200mg administered orally once daily at approximately the same time with a meal. The film-coated tablet should not be broken, crushed or chewed. Treatment should continue until disease progression or unacceptable toxicity. A complete blood cell count and liver function test must be performed before initiating therapy with Rezurock. Perform liver function tests at least monthly throughout treatment. Dose modification due to hepatotoxicity and other adverse reactions: For Grade 3 alanine aminotransferase (ALT) or aspartate aminotransferase (AST) (>5 – 20 × upper limit of normal (ULN)) or Grade 2 bilirubin (>1.5 – 3 × ULN) or other Grade 3 adverse reactions, hold Rezurock until recovery to ≤Grade 1, then resume Rezurock at the recommended dose at physician's discretion. For Grade 4 ALT or AST (>20 × ULN) or Grade ≥3 bilirubin (>3 × ULN) or other Grade 4 adverse reactions, permanently discontinue Rezurock. Dose modification due to drug interactions: *Strong CYP3A Inducers:* Increase the dosage of Rezurock to 200mg twice daily when co-administered with strong CYP3A inducers. *Proton Pump Inhibitors:* Increase the dosage of Rezurock to 200mg twice daily when co- administered with proton pump inhibitors. Delayed or missed dose: If a dose is missed or delayed for <12 hours after the scheduled dose, the dose should be taken as soon as possible on the same day with a return to the normal schedule the following day. If a dose is missed or delayed for >12 hours after the scheduled dose, the dose should be taken at the usual time the following day. If a patient vomits following the intake of a dose, the next dose should be taken at the usual time the following day. Patients should not take extra doses to make up the missed dose.
Special Populations: Hepatic impairment: Dose modification is not recommended when administering belumosudil to patients with mild or moderate hepatic impairment (Child-Pugh A and B). Belumosudil is not recommended in patients with severe hepatic impairment. The safety and efficacy of belumosudil in severe (Child-Pugh C) hepatic impairment has not been evaluated. For patients with pre-existing severe hepatic impairment (Child-Pugh C), consider the risks and potential benefits before initiating treatment with belumosudil. Monitor patients frequently for adverse reactions.
Renal impairment: No dose modification of Rezurock is required in patients with mild or moderate renal impairment (creatine clearance ≥30 mL/min). No data are available for patients with severe renal impairment (creatine clearance<30 mL/min) or for patients with end-stage renal disease on dialysis. Use with caution. Elderly patients (≥65 years): No additional dose adjustments are recommended for elderly patients. Paediatric population: The posology is the same in adults and adolescents aged 12 – 18 years. The safety and efficacy of Rezurock in children and adolescents aged below 12 years of age have not been established. No data are available.
Contraindications: Pregnancy. Hypersensitivity to the active substance or to any of the excipients.
Precautions and Warnings: Female patients of childbearing potential and male patients with female partners of childbearing potential: Women of childbearing potential (WOCBP) should be advised to avoid becoming pregnant while they or their male partner are taking belumosudil and of the potential risk to a fetus. WOCBP should be advised to have a pregnancy test prior to starting treatment with belumosudil. WOCBP and male patients with female partners of childbearing potential must use a highly effective method of contraception during treatment with belumosudil and for at least one week after the last dose of belumosudil. Hepatotoxicity: Increases in liver function tests were observed in clinical studies with belumosudil and generally occurred early during treatment with the incidence decreasing thereafter. Liver function tests should be performed prior to the initiation of treatment with belumosudil and monitored at least monthly during treatment with belumosudil and the dose should be adjusted for ≥Grade 2 toxicities. Sodium: This product is essentially sodium free. **Interactions:** Effect of CYP3A inhibitors on belumosudil: The co-administration of multiple doses of itraconazole did not alter exposure to belumosudil to any clinically relevant extent. Effect of CYP3A inducers on belumosudil: The co- administration of multiple doses of rifampin decreased belumosudil Cmax by 59% and AUC by 72%. The co- administration of strong CYP3A4 inducers with belumosudil may decrease belumosudil exposure. Increase the dose of belumosudil to 200mg twice daily. The co-administration of moderate CYP3A4 inducers e.g., efavirenz is predicted to have a reduced effect on belumosudil as compared to strong CYP3A4 inducers. The co-administration of moderate CYP3A4 inducers with belumosudil may decrease belumosudil exposure. No dose adjustment is recommended. Effect of proton pump inhibitors on belumosudil: The co-administration of multiple doses of rabeprazole decreased belumosudil Cmax by 87% and AUC by 80%. The co-administration of multiple doses of omeprazole decreased belumosudil Cmax by 68% and AUC by 47%. The co-administration of proton pump inhibitors with belumosudil may decrease belumosudil exposure. Increase the dose of belumosudil to 200mg twice daily. Effect of other gastric acid reducing agents on belumosudil: The co-administration of belumosudil with gastric acid reducing agents other than proton pump inhibitors may decrease belumosudil exposure. No dose adjustment is recommended, however belumosudil and the gastric acid reducing agent should be taken 12 hours apart. In vitro studies: *Effect of belumosudil on CYP3A substrates:* The co- administration of belumosudil is predicted to increase midazolam Cmax and AUC approximately 1.3- and 1.5-fold, respectively. No dose adjustment is recommended.

The co- administration of belumosudil may increase exposure of sensitive CYP3A4 substrates with a narrow therapeutic index such as ciclosporin and tacrolimus. No dose adjustment is recommended. *Effect of belumosudil on CYP2C9 substrates*: The co-administration of belumosudil is not expected to have clinically meaningful effect on the exposure of CYP2C9 substrates (such as warfarin). *Effect of belumosudil on CYP2C8 substrates*: The co-administration of belumosudil is not expected to have clinically meaningful effect on the exposure of CYP2C8 substrates that are not an OATP1B1 substrate. *Effect of belumosudil on UGT1A1 substrates*: Belumosudil is a weak inhibitor of UGT1A1, the clinical consequences are not known. *Transporters*: Belumosudil is a substrate of P-gp. Belumosudil inhibits BCRP, P-gp, and OATP1B1. The co-administration of oral BCRP, P-gp and OATP1B1 substrates with belumosudil may increase the concentrations of the substrate drugs (such as digoxin and docetaxel).

Pregnancy: There are no data on the use of belumosudil in pregnant women. Belumosudil can cause fetal harm based on findings from animal studies and its mechanism of action. As a precautionary measure, belumosudil is contraindicated in pregnancy. **Breast-feeding:** It is unknown whether belumosudil or its metabolites are excreted in human milk. No data are available regarding the presence of belumosudil or its metabolites in animal or human milk or its effects on the breast-fed child, or on milk production. A risk to the infant cannot be excluded. Because of the potential for serious adverse reactions in a breast-fed child, breast-feeding should be discontinued during treatment with belumosudil and for at least one week after the last dose. **Fertility:** There are no human data on the effect of belumosudil on fertility. Based on findings from animal studies, belumosudil may impair male and female fertility at dose levels above the recommended clinical dose. The effects on fertility are reversible.

Adverse Reactions: Very common: Nausea, asthenia. Common: upper and lower respiratory tract infections, anaemia, leukopenia, platelet count decreased, decreased appetite, hyperglycaemia, headache, neuropathy peripheral, dizziness, hypertension, dyspnoea, cough, diarrhoea, vomiting, abdominal pain, constipation, AST and ALT increased, gamma-glutamyltransferase increased, pruritus, musculoskeletal pain, muscle spasms, blood alkaline phosphatase increased, blood creatine phosphokinase increased, blood creatinine increased, oedema, pyrexia, weight decreased. *Prescribers should consult the SmPC in relation to other adverse reactions.*

Legal Category: POM

GB List Price and Marketing Authorisation Number:
200mg x 30 tablets (PLGB 04425/0902): £6708.

Marketing Authorisation Holder: Sanofi, 410 Thames Valley Park Drive, Reading, Berkshire, RG6 1PT, UK.

Further information is available from: Medical Information, Sanofi, 410 Thames Valley Park Drive, Reading, Berkshire, RG6 1PT, UK.
uk-medicalinformation@sanofi.com

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Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.
Adverse events should also be reported to the Sanofi drug safety department on Tel: 0800 0902 314. Alternatively, send via email to UK-drugsafety@sanofi.com