IN THE NAME OF GOD

MESENCHYMAL STROMAL CELL THERAPY (MSC – DESTRO CELL) IN PEDIATRIC HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT) (MSC & R-CS-GVHD)

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Mesenchymal Stromal Cell
DESTRO CELL (Decidual part of plasenta)

مدیرعامل محترم شرکت زیست بازساختی تسکین

موضوع: ورود داروی Placenta derived Stromal mesanchymal cells (decidua), Injection suspention به فهرست دارویی ایران

با سلام و احترام؛

عطف به نامه شماره ۶۶۵۲۲۶۸۸/د مورخ ۱۴۰۳/۰۴/۰۹ از سوی رئیس محترم اداره خون و فرآورده های بیولوژیک مبنی بر ارائه مستندات آن شرکت جهت ورود داروی Placenta derived Stromal mesenchymal cells (decidua), Injection suspension به فهرست دارویی ایران به اطلاع می‌رساند موضوع در جلسه شماره ۵۲۰ مورخ ۱۴۰۳/۰۵/۱۷ کارگروه بررسی و تدوین فهرست دارویی ایران مطرح و با افزوده شدن داروی مذکور به فهرست به شکل ذیل موافقت گردید.

بدیهی است تولید/واردات داروی مذکور، منوط به اخذ مجوزهای جداگانه از این سازمان می‌باشد.

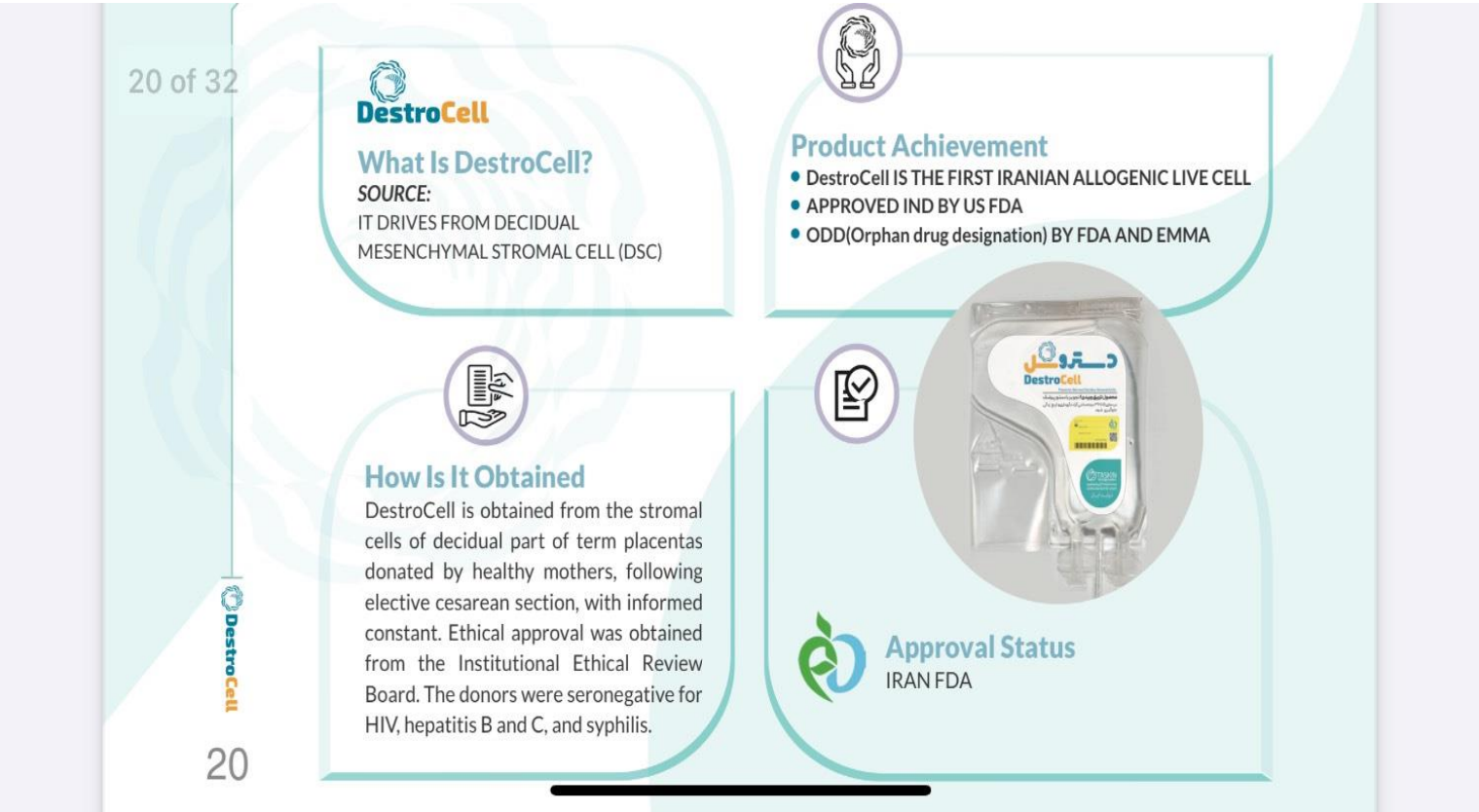
نام دارو	شکل دارو	قدرت دارو	کاربرد
Placenta derived Stromal mesenchymal cells (decidua)	Injection suspension	at least 2 × 10^8 hMSCs /mL	GvHD

لازم به ذکر است مطابق با ضابطه ثبت فرآورده‌های بافت سلول و ژن درمانی به شماره REG-DPNA-BIO-005 مورخ ۱۴۰۳/۰۴/۰۲، آن شرکت حداکثر تا زمان یک سال از تاریخ جلسه کارگروه موظف به ارسال مطالعه ارزیابی اقتصادی جهت تعیین سقف قیمت هزینه اثربخشی فرآورده می‌باشد.

دکتر نازیلا یوسفی
دبیر کارگروه بررسی و
تدوین فهرست دارویی کشور

Destro Cell :Stromal cell of decidual part of plasenta donated by healthy mother.

https;//taskinbr.com/en/.



Short case presentation: 5 patients

P1- Juvenile Metachromatic leukodystrophy, J- MLD : ND disease (MSC Intra tecal IT), NO HSCT

HSCT & MSC for GVHD

- **P2- Primary Immune Deficiency, SCID ;(MSC- IV)**
- **P3- Primary Immune Deficiency , kabuki syndrome(MSC-IV)**
- **P4- Chronic Granulomatosis Disease - CGD (MSC- IV)**
- **P 5- AML Non M3(3th Haplo HSCT)(MSC- IV)**

Case 1: Juvenile Metachromatic Leukodystrophy ;(J-MLD)

(2019)

- Male , 4 y old , Juvenile - MLD
- Symptomatic clinically & MRI involvement , no indication for HSCT
- Request of Neurologist & Parents: MSC therapy (BM)
- MSC ; Intrathecal(IT) cell therapy : 1 x 106 / kg
- Side effects : Fever , headache, LP & CSF analysis :WBC 10-12 , increased L, Glu & pr; Nl . Ab therapy & Supportive care .CSF culture neg .Discharge with good condition.
- No repeat MSC, due to Covid pandemia.

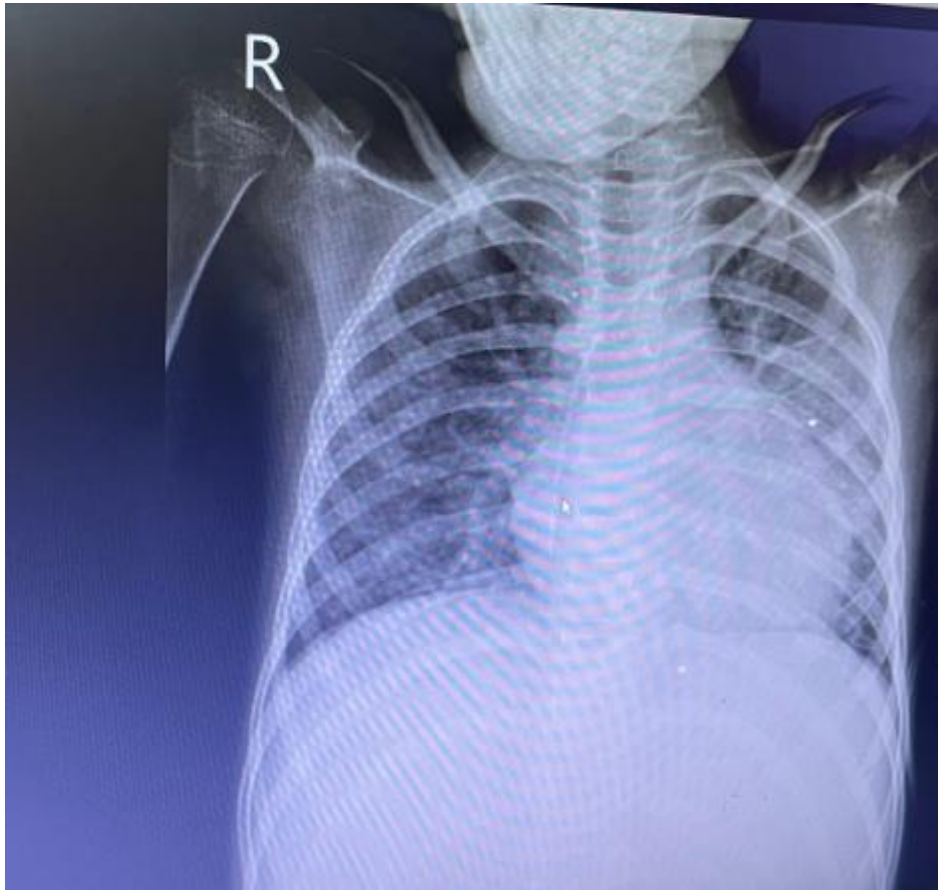
Case 2 : PID – SCID. (1403)

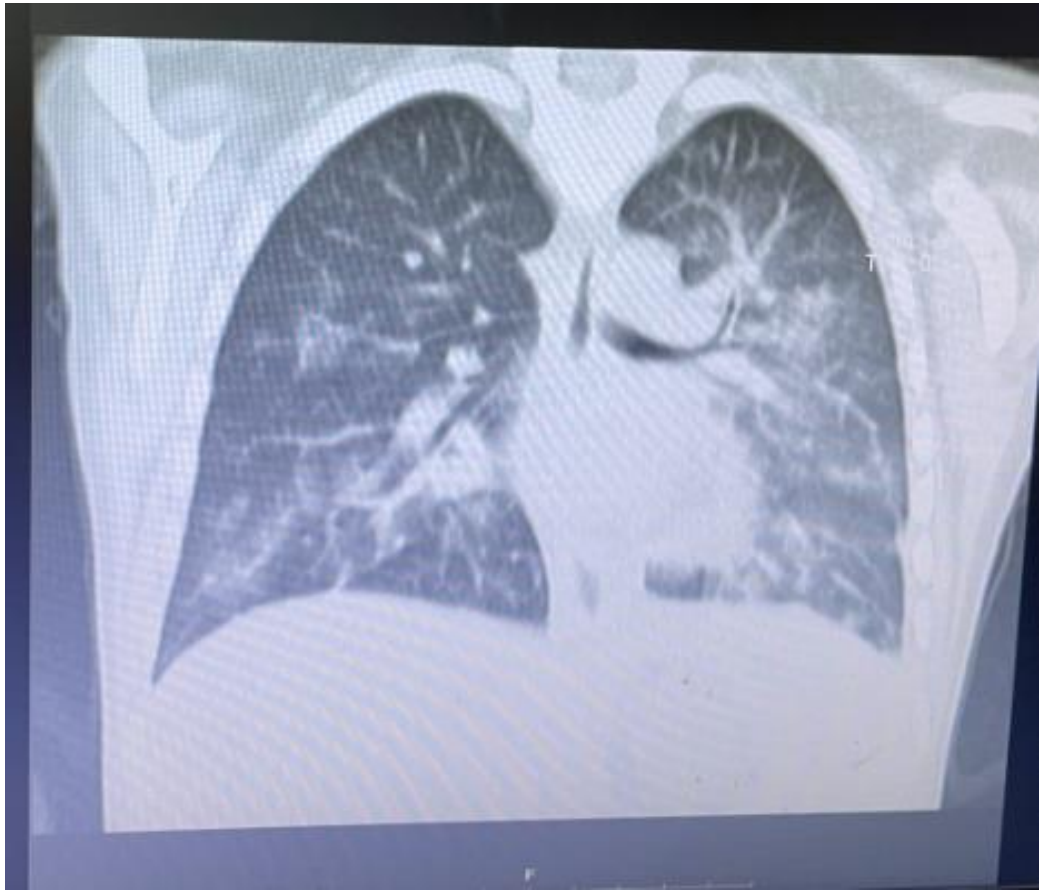
- 4/1403: 7 y old F , SCID , Allo HSCT , Full - MRD , Father , PB ,RIC, Engrafted day + 14 . Chimer : 100%
- Complications ; CMV reactivation then CMV disease (Retinopathy & GI) , EBV pos , stage 3-4 GI GVHD (Abdo pain . Diarrhea , Bloody).
- Treat : Gancyclo , Foscarnet ,Rituximab , & CS , Cyclospurine , Tacrolimus , IVIG ,Ruxolotinib Endoscopy : GVHD + CMV pos
- MSC 1x 106 / kg. 8 -12 / h after infusion , decreased of 02 sat , clinically stable , no fever , no dyspnea . CXR & Chest CT : abnormal.
- MSC side effect ? (Trapping of MSC in lung) or infection….? Add methyl pred , Recovery. No repeat MSC.
- Death > 1 y (5.1404) after HSCT due to COVID 19 &refractory CMV-D

Case 2 : After MSC therapy

CXR 21. 9. 1403

CHEST CT : 22. 9. 1403





Safety and side effects of Using Placenta-Derived Decidual stromal cells for graft-versus-host Disease and hemorrhagic cystitis .Arjang Baygan…… Behnam Sadeghi,….Original research . 2017 . Sweden.

- **Because DSCs and MSCs first home to the lung (, pulmonary embolism should be looked for.**
- **The adverse reaction with reduced oxygen saturation during DSC infusion**, may be due to **congestion with DSCs** i the lung, rather than embolism formation. n
- In study : No increase in pulmonary embolism after DSC infusion.
- **Pulmonary embolism** report; after infusion with **adipose-derived MSCs**

Case 3: PID , Kabuki Syndrome. 1404

- 9y old boy ; Vitiligo , sever neutropenia , anemia , mild IBD?&Mild DD
- ALLO HSCT , full match grand father (MRD) , PB .RIC
- Engrafted & chimerism : 100 %
- Complications : Stage 2-3 skin GVHD day + 20, then GI GVHD day, diarrhea & massive GI bleeding several times (Day + 30- +35) HSCT , CMV reactivation;.... Endoscopy: GVHD & CMV PCR neg
- Treat : CS , Cyclosporine , Ruxolutinib, Gancyclo , Foscarnet ,... , IVIG , Vedolizumab x3 , no response ..... & many times diff - Blood proudcts ....
- MSC x 6 times 1x 106 / kg , Good partial response .
- Discharge on day + 120 , CMV neg.
- F- up, on Ruxolitinib , on pred tapering Chimer : 100%

Case 4 : CGD.(1404)

- **A 10 y old male , CGD, Allo HSCT , MURD , 10 /10 , PB. 32kg . Chimerism 100%**
- **Complication: Pulmonary infection , Skin GVHD stage 2-3 , then GI GVHD stage 4 (diarrhea& GI bleeding) , CMV Reacti…, CH - BK pos & Severe Tubular Nephropathy (low K & Ca)**
- **Treat : CS , Cyclospurine , Ruxolitinib , IVIG , Gancyclo vir , Vedulizumab. Endoscop y : GVHD, CMV PCR neg , HBP pos**
- **MSC x 4 times : 1x106 / kg , Good partial response but again start moderate diarrhea (no bloody), Vedulizumab x 3 .**
- **Now 5 mo after HSCT , partial recovery for GI GVHD , on treatment & supportive care. Taper of CS & Ruxolitinb ,CMV neg, Tubolopathy pathy is improving.**
- **BW : 23 kg Chimer : 100% Now 2 times more MSC**
-

Case 5: AML Non M3. (1405)

- 1404:A 7 Y old male , AML non m3 , Haplo T cell deplet HSCT , Father x 2 times , PB . primary rejection , chimer zero.
- 1405 : 3th HSCT ,Haplo , Mother, T cell deplet , PB, chimerism 100 %
- Complications ; Day + 20 HSCT : stage 3-4 GI GVHD & (diarrhea , some times bloody , nausea , vomit) & symptomatic HC- BK & CMV reactivation
- Treatment : CS , Cyclosporine, Ruxolitinib , Ganciclovir , IVIG , Vedulizumab x 2 till now .
- MSC x 3 times . Each time 1x106 / kg.
- Good partial response. F-UP out patient . CMV neg , BK pos but no symptoms (urine neg for RBc).

patient	1	2	3	4	5
Diagnosis	J MLD	PID/SCID	PID/KABUKI SYNDROME	PID/ CGD	AML NON M3
HSCT	NO HSCT	YES; ALLO HSCT MRD . FATHER, PB Chimer; 100% 1 tim e decrease to 49 % add 1 booster	YES: ALLO HSCT MRD . GRAND FATHER . PB Chimer : 100%	YES :ALLO HSCT MURD 10/10 , PB Chimer: 100%	YES: HAPLO HSCT Father 2 times (PGF) . (1404) ق۳ 3th haplo HSCT mother , chimer 100% (1405 .)
Reason for MSC therapy	TISSURE REGENERATION	1- GI GVHD stage 3-4 2- CMV Reactivation & DISEASE (RETINIPOPATHY & GI GVHD) CMV refractory to treat R CS GVHD Endoscopy : GVHD & CMV Yes	1 Skin GVHD Day + 20 2- GI GVHD stage 4 Day + 30-35 2- CMV Reactivation R CS GVHD Endoscopy: GVHD Yes	1- Chest infection 2-Skin GVHD stage 3 3-GI GVHD Stage 4 4- Hemorrhagic cystitis (BK) 5- Electrolyte imbalance 6- HC BK R CS GVHD Endoscopy : GVHD Yes& HBP	1- GI GVHD stage 3-4 2- H c - BK reactivation 3- CMV reavctivation R CS GVHD No endosvopy

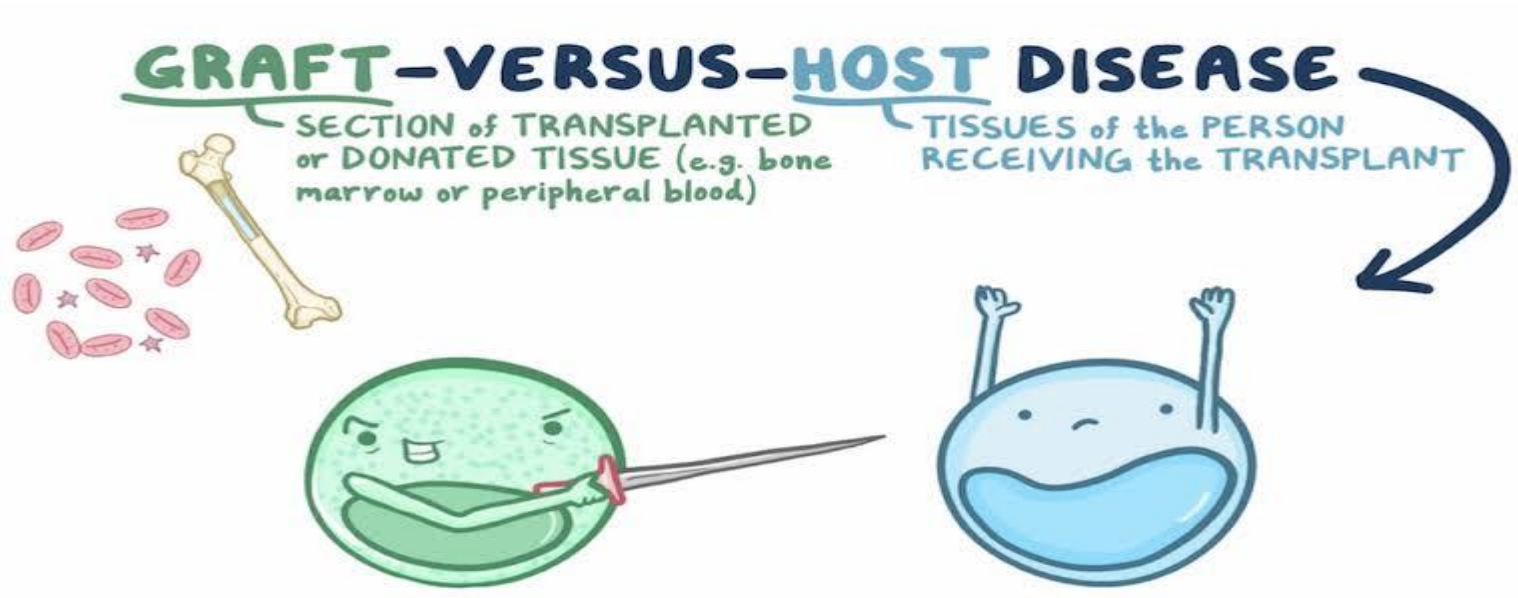
MSC type	BM MSC	Destrocell (Second line)	Destrocell (SL)	Destrocell (SL)	Destrocell (SL)
MSC times	1	1	6	4	3
Response	Mild	PR	VGPR	GPR	VGPR
Side effects	Fever , mild headache , transient	Decreased o2 sat	No	No	No
OUT COME	???	Death > 1 y after HSCT due to Covid 19 & CMV pos Blood and GI	Live	Live	Live

HSCT & Complications

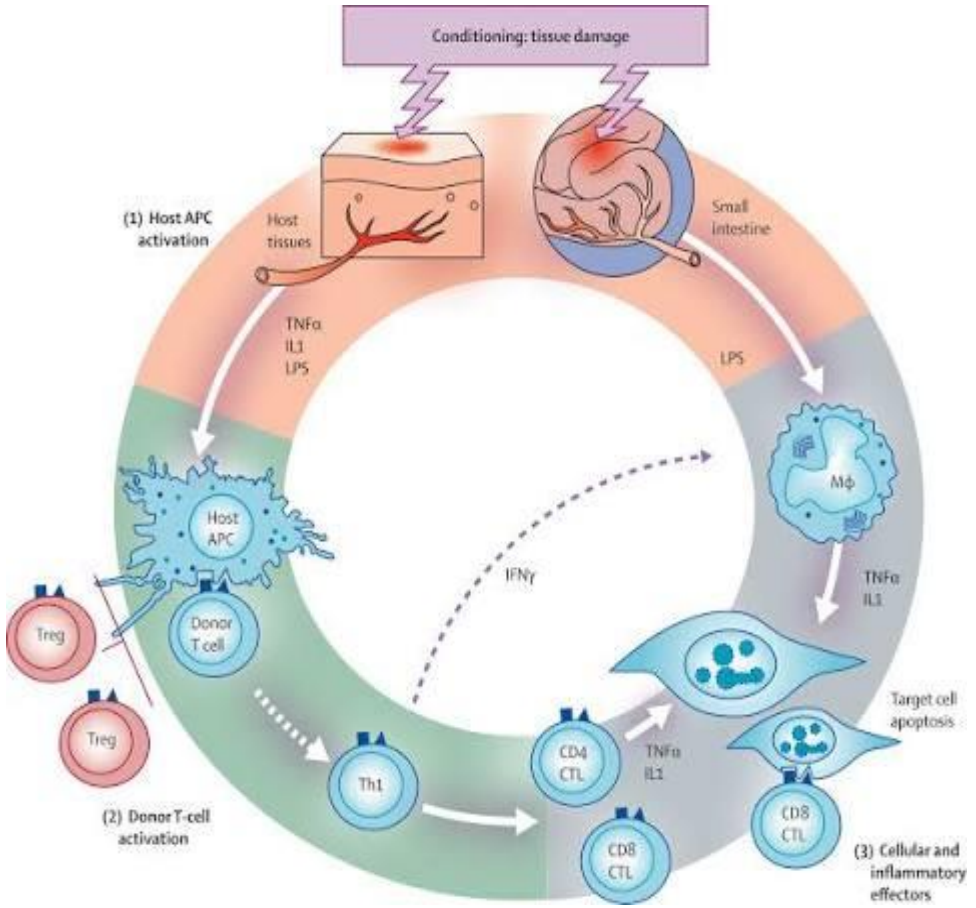
- *Infections
- *** GVHD : Graft versus host disease (GVHD)
- Graft Failure(GF)
- Poor graft function
- Veno occlusive disease (VOD)
- Hemorrhagic cystitis (HC)
- Thrombotic micro angiopathy (TMA)

Graft-versus-host disease (GVHD)

- **(GVHD) is a multisystemic, inflammatory and/or fibrotic disease significantly contributing to morbidity & non-relapse mortality after (allo-HSCT).**



Graft-versus-host disease- GVHD

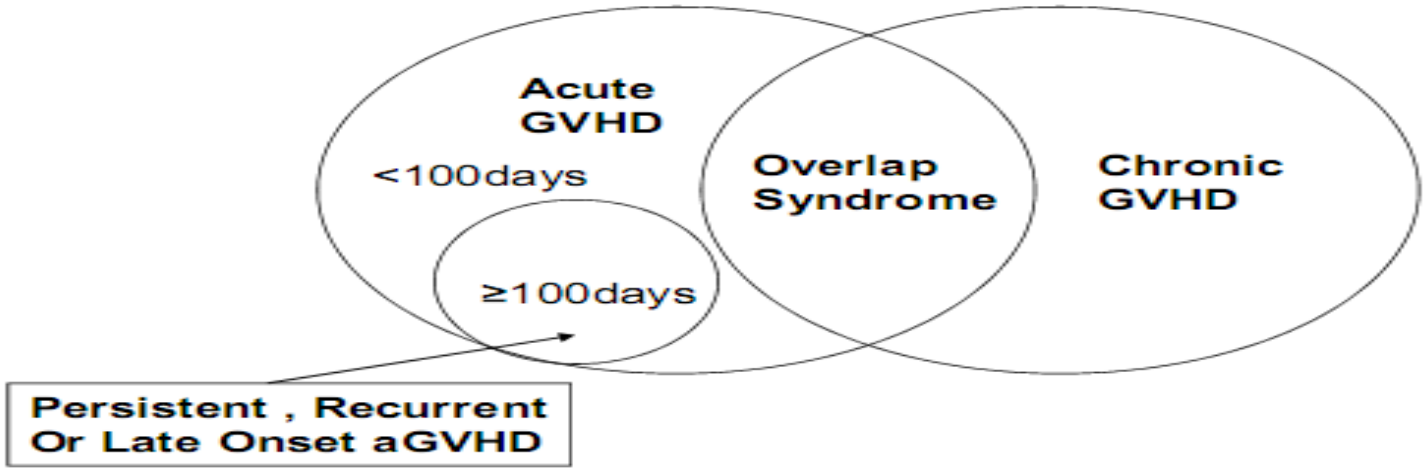


- Damaged host tissue→ cytokines (TNFα, IL1)→ stimulate APCs→ recognition of host Ag by donor T cell
- Donor T cell activated→ cytokines (IFNγ, IL2)→ induce CTL, NKC, phagocytes
- Phagocytes release more cytokines→ cell lysis/apoptosis→ tissue destruction

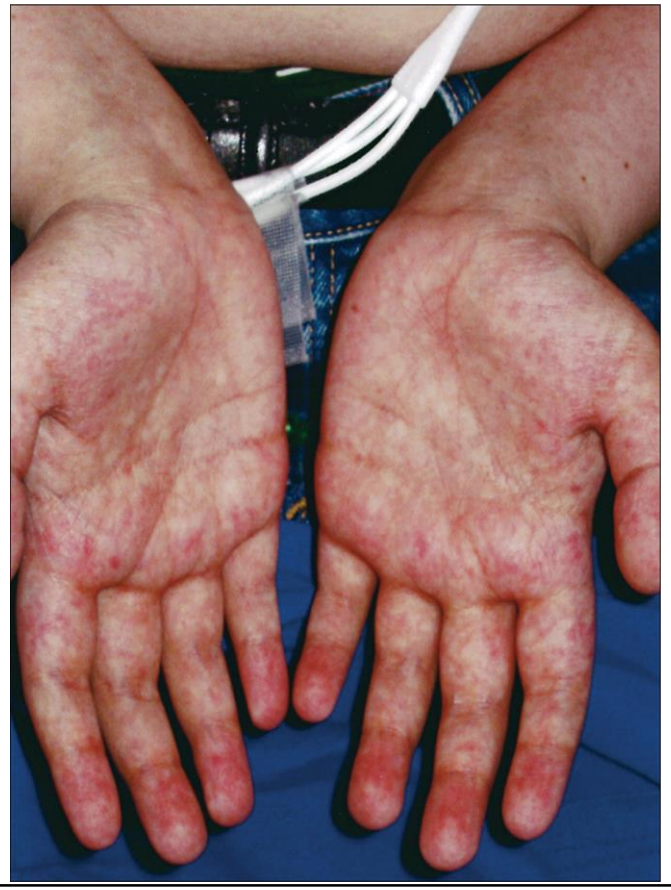
Classifictaion GVHD : Acute & Chronic

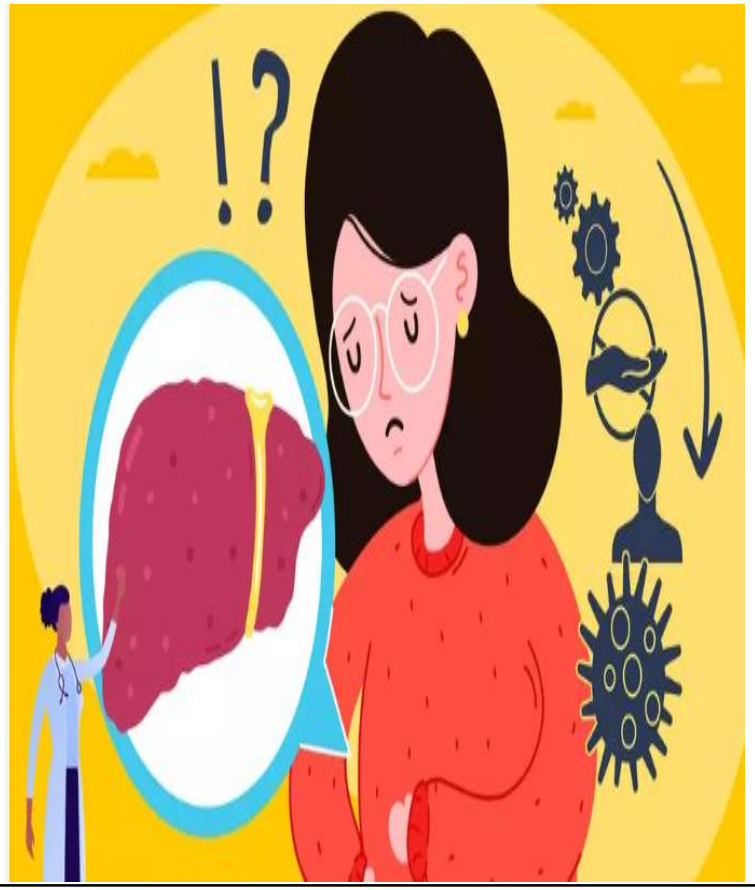
(aGVHD) is a reaction of transplanted donor immune effector cells against epithelial structures of the host, occurring **within 100 days after** HSCT .

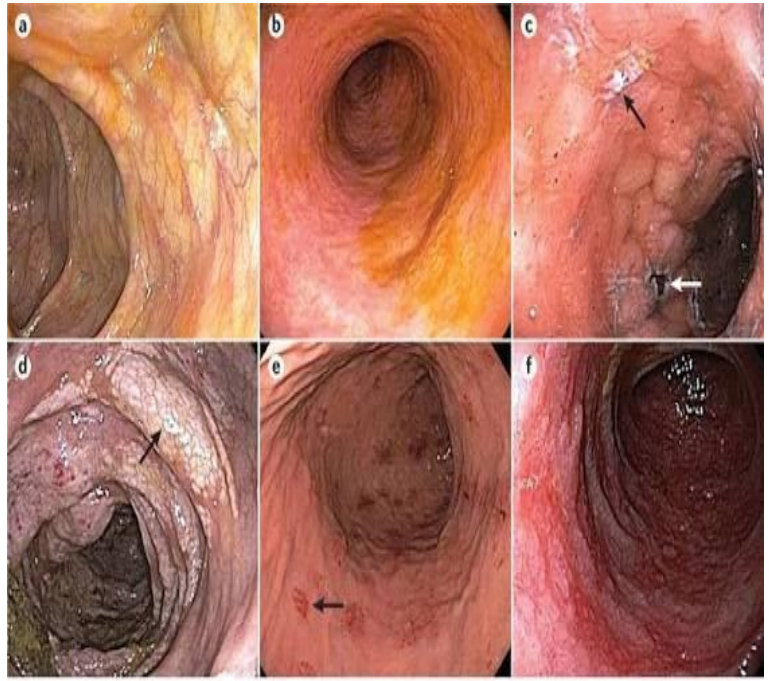
Risk of developing GVHD : degree of match donor /recipient, graft type, T cell depletion/ repletion, conditioning regimen, GVHD prophylaxis, and age of the patient/donor

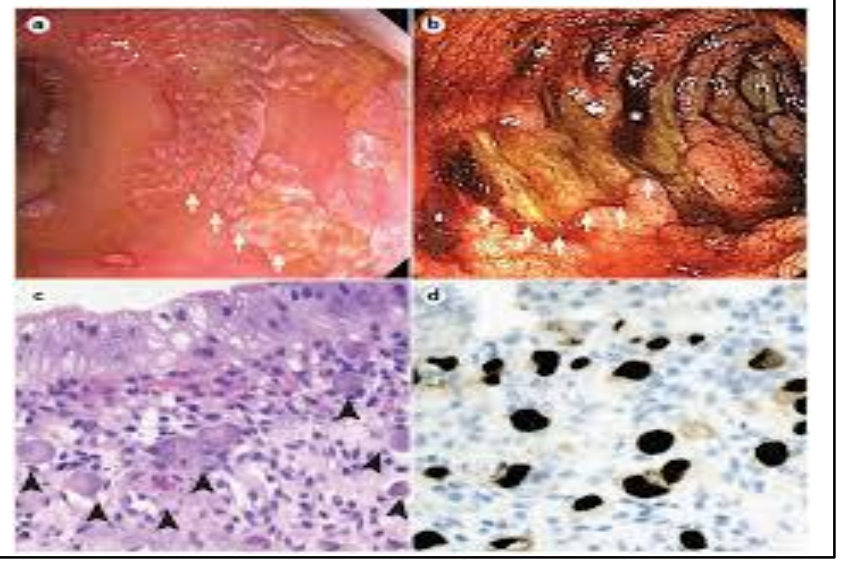


ACUTE GVHD
Skin , liver & GI
(40-60%) Allo HACT









Skin GVHD day + 35, MURD 10/10 Allo HSCT(Chimer 100%)

Primary Immune Deficiency

(DOCK 11) , x lined , immune dyregulation

Chronic GVHD.c GVHD

- T-cell allo-reactivity-

- directed against recipient antigens.

- T-cell auto-reactivity.

- B-cell dys regulation.

- Skin, Ocular , Gastrointestinal, Hepatic , Lung ,…

GVHD TREATMENT in HSCT

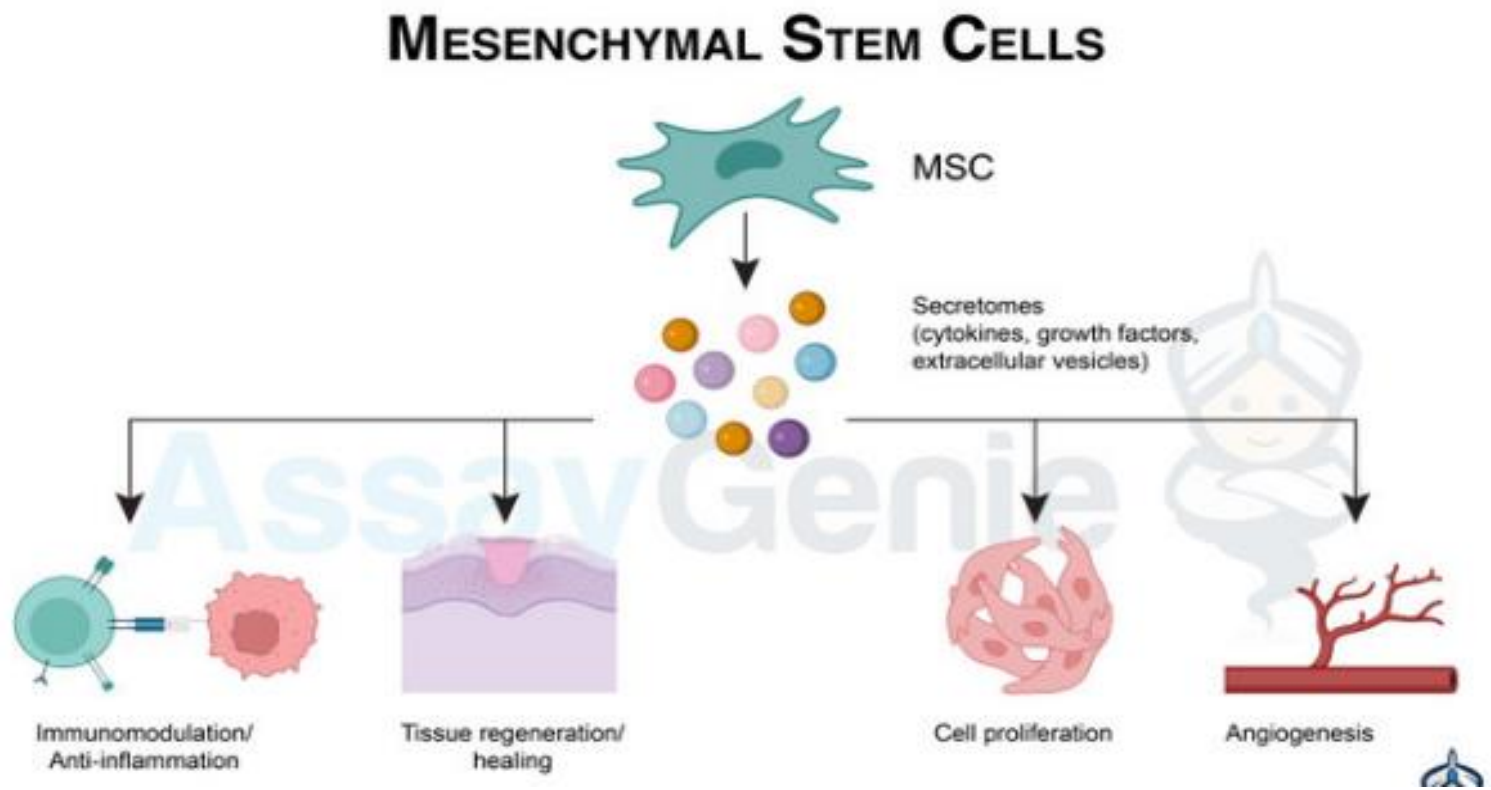
- (GVHD) is a complication that significantly affects **mortality and morbidity**
- **GVHD NEED : PREVENTION & TREATMENT**
- **Cortico Steroids (CS);** gold standard GVHD treatment;**(anti-lymphocyte & anti inflammatory)**
- **1/2 of GVHD cases ; non-responsiveness to CS**
- **Despite new developments in the field of GVHD ,MMF , JAK inhibitors, extracorporeal photopheresis, sirolimus…., no clear which treatment agent will be used as the first choice in the second-line setting.**
  - **Survival rates ,only 5% in grade 4 GVHD of patients**

Mesenchymal STEM Cell (MSC)

Mesenchymal Stromal Cell (MSC)

First Identified by Alexander Friedenstein in the late 1960.

Pharmacological application in humans was first investigated in 1990

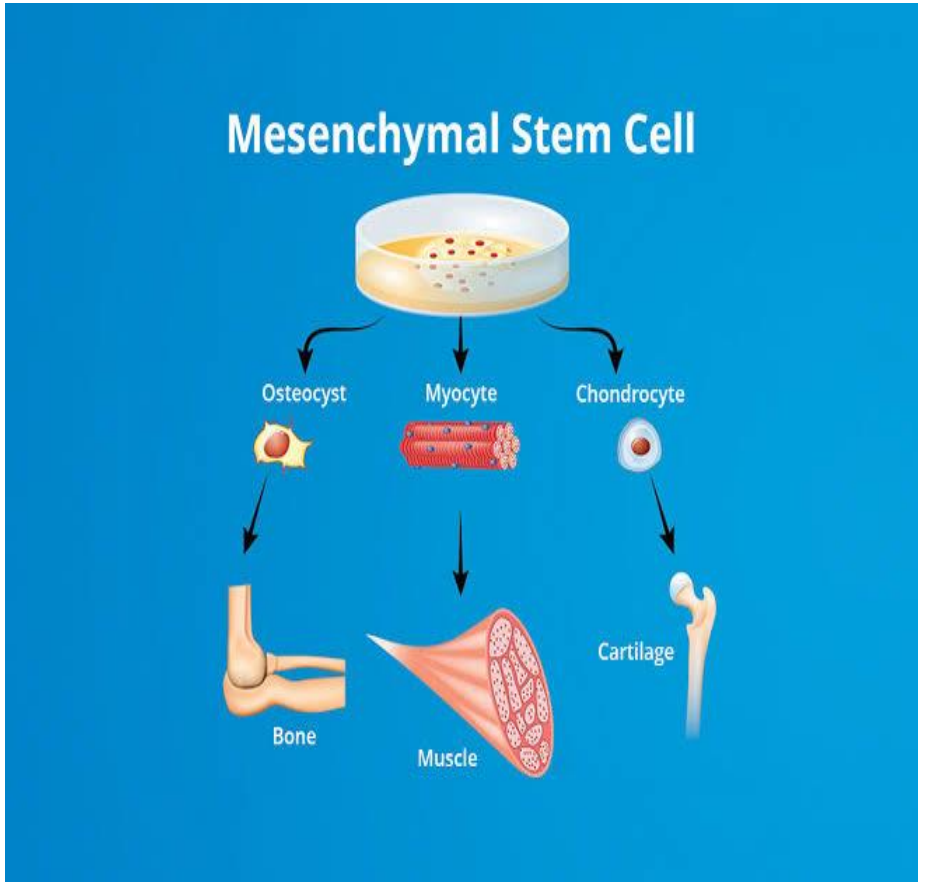


Mesenchymal stromal Cell .MSC

- Non-hematopoietic stem cells
- Self-renewing ,multi potential
- Sources : adult & fetal tissue ;adult bone marrow (BM), umbilical cord blood (UCB) or adipose tissue
- Down-express MHC Class 1 molecules,

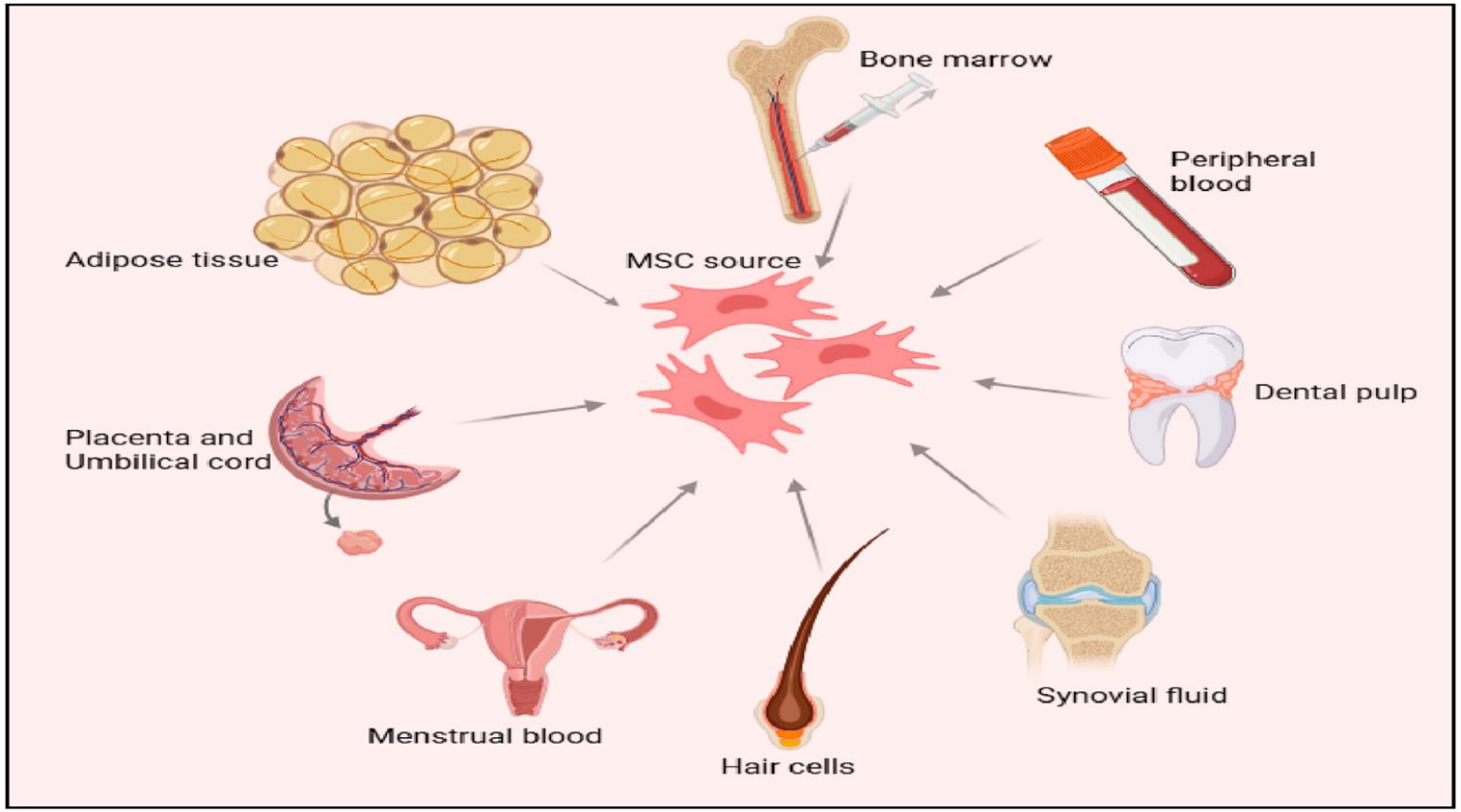
- Do not contain MHC Class II molecules ,

-A barrier to immune rejection, facilitates their application even without donor-recipient HLA compatibility,



Sources of Mesenchymal Stem Cells (MSCs)

Jai Chand Patel .2025.US



Mesenchymal stromal Cell (MSC):

- **3 minimum criteria ,2006 ; by "International Society for Cellular Therapy" (ISCT.**

1)MSCs must **adhere to plastic surfaces** when cultured *in vitro*.

2) MSCs ; express surface antigens **CD73, CD90, and CD105** , **lacking** the expression of "**CD45, CD34,** CD14 or CD11b, CD79a or CD19, and HLA-DR".

3) (MSCs) capacity to **differentiate into mesodermal lineages, such as adipocytes, chondrocytes, and osteoblasts**, under *in vitro* culture conditions

Application of Mesenchymal Stem Cells in Graft-Versus-Host Disease as a Regenerative Therapy. Neslihan Mandacı Şanlı and Aysu Timuroğlu.2025

- **MSC :Immune modulatory, low immunogenicity**

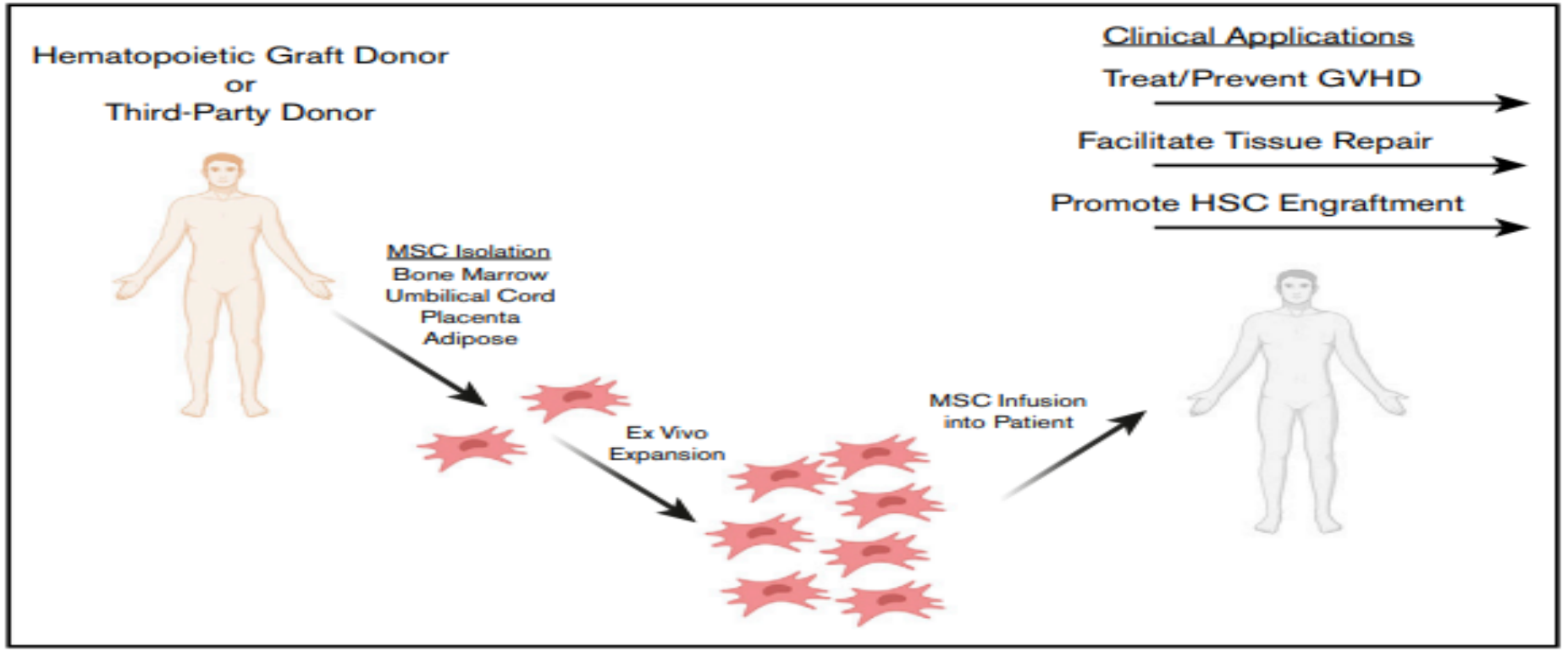
- **Homing properties;** are able to migrate to the damaged area and help **tissue repair by releasing bioactive substances**, Angiogenic, Anti-Inflammatory, Anti Apoptotic, Anti-Fibrotic, & Anti-Oxidant effects.

- **In the BM niche ;support Hematopoiesis &Engraftment**

- **Potential clinical applications of MSCs as adjunct cell therapies in HCT.** **Acute GVHD are better than in chronic GVHD**

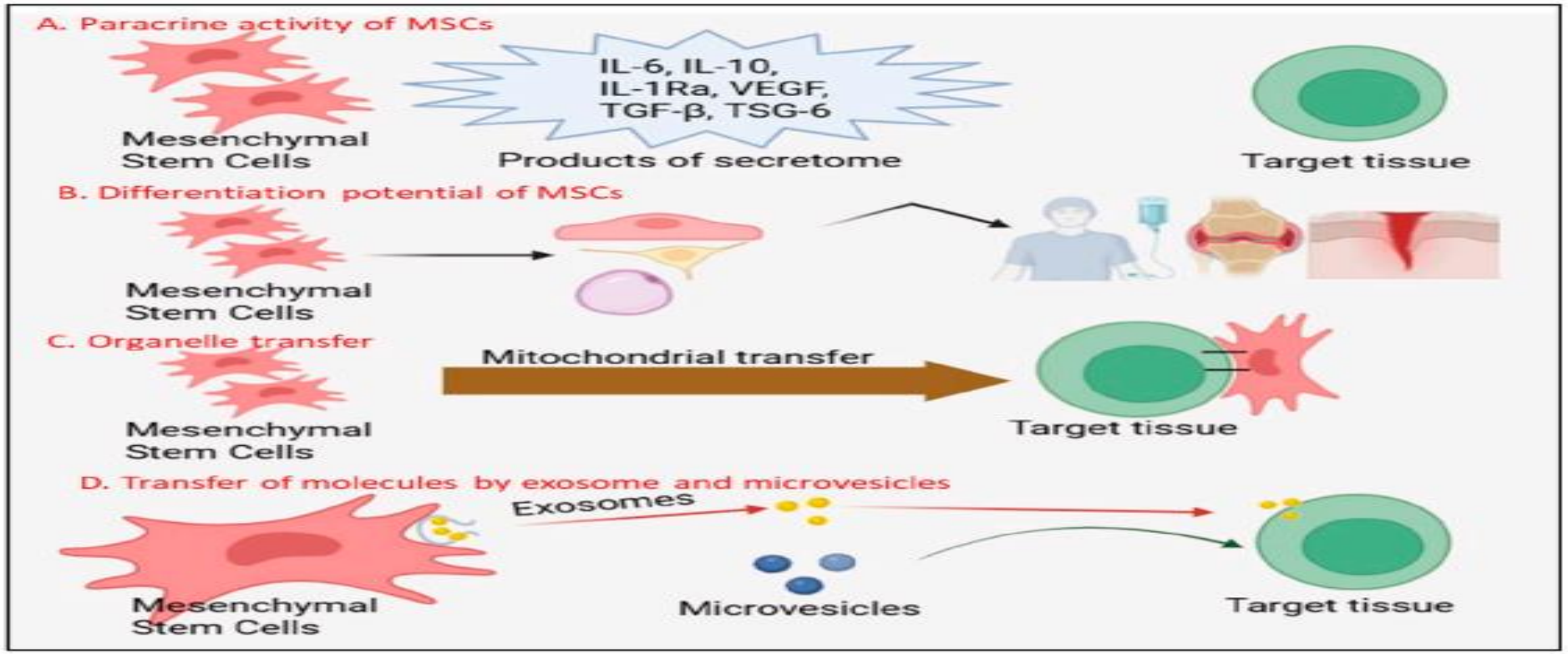
Refrence 2025: 62 study related to GVHD & MSC.

MBURNHAM et al.2020 . Blood advances



Multifunctional Mechanisms of **Mesenchymal Stem Cells (MSCs)** in **Regenerative Therapy**. Jai Chand Patel .**2025.US**

ARDS and Myocardial ischemia……,Efficacy in diseases like (GVHD), Crohn's disease, and COVID-19…….



Review Articles

Treatment of severe acute graft-versus-host disease with third party haploidentical mesenchymal stem cells. Katarina Le Blanc. LANCET. 2004. Sweden

- A 9-year-old boy ALL ,3th remission HSCT ,MURD , female donor
- Resistance -Acute GVHD GI and liver.
- BM- MSC Haploidentical MSC (Mother) , 2 x 106 cells /kg , IV on day +73
- 2th MSC from his mother (1x +106 /kg) on day+ 170
- MSC : Rapid healing effect on the damaged gut epithelium.
- Discharge :day+ 220. Good 1 year after HSCT , BIL T of 8 mmol/L.
- 25/ 1000 allo HSCT , 25 p grade IV acute GVHD.
- 24 patients died , med 2 mo after HSCT (range 0·5–5·5)

Safety and side effects of Using Placenta-Derived Decidual stromal ells for GVHD & hemorrhagic cystitis

Arjang Baygan…… Behnam Sadeghi. .Division of Therapeutic Immunology, Karolinska Institutet, Sweden. 2017

- **Placenta-derived decidual stromal cells (DSCs) ; a novel therapy for acute (GVHD) & hemorrhagic cystitis (HC).**
- DSCs ;more immunosuppressive than MSCs.
- **Adverse events and safety using DSCs ?**
- **44 treated p / 40 controls.**
- **Median dose of infused cells ; 1.5 (range 0.9–2.9) × 106 DSCs/kg.**
- **2 (1–5) doses.** **Total dose of 82 infusions.**

Safety and side effects of Using Placenta-Derived Decidual stromal ells for GVHD & hemorrhagic cystitis .

Arjang Bayqan…… Behnam Sadeghi. .Division of Therapeutic Immunology, Karolinska Institutet, Sweden. 2017

- 3 patients : transient reactions.
- No significant difference in diff factors .
- **Death in HSCT p ,due to GVHD & others ; MSC 2 /7 control**

❑ **1-y survival - DSC p with GVHD : 67%, significantly better than achieved previously at our center.**

❑ **1-y survival 90% -DSC-treated HC group.**

A Phase 3 Randomized Study of Remestemcel-L versus Placebo Added to Second-Line Therapy in Patients with SR - A GVHD .
Partow Kebriaei1. Biol Blood Marrow Transplant. 2020

- Controlled studies **BM derived mesenchymal stem cells (MSCs)** against (aGVHD).
- A multicenter,randomized study ;efficacy of using ex vivo cultured adult human MSC (remestemcel-L) in addition to second-line therapy to treat SR a-GVHD
- **260 p, 6 mo-70 y of age, 2006 -2009**
- Rrandomized 2:1 to receive **8 iv infusions of remestemcel-L or placebo**, given over 4weeks, in addition to second-line therapy according to institutional standards.
- **4 additional Infusions over 4 weeks** were indicated for patients with incomplete response at day 28. **f up : 180 days**

A Phase 3 Randomized Study of Remestemcel-L versus Placebo Added to Second-Line Therapy in Patients with Steroid-Refractory Acute Graft-versus-Host Disease
Partow Kebriaei1. Biol Blood Marrow Transplant. 2020

- Durable complete response (DCR), defined : complete resolution of aGVHD symptoms for any period of at least 28 days after beginning treatment.
- **Remestemcel-L did not meet the primary endpoint of greater DCR in the intent-to-treat population (35% versus 30%; P = .42).**
- **Pediatric patients ;** higher OR with MSCs compared with placebo (64% vs 23%;
- Remestemcel-L was safe and well tolerated
- Results of this study did not demonstrate superior DCR compared with placebo when added to standard of care.

Pérez-Torres Lobato et al. Spain .2024
Single-center, Retrospective study (2016–2023).

30 - P (53.7% boys), age at transplant 11 y (2–19).

MSC indication in pediatric HSCT, Source : BM & Cord ;Wharton's Jelly (WJ)

	Previous treatments	Number of patients *N* (%)	MSCs infusion scheme
aGVHD	GC, ECP, RXL, MMF, infliximab, sirolimus	13 (43.3)	4 infusions on days: +1, +4, +11, +18
cGVHD	GC, ECP, RXL	5 (16.7)	
Graf failure	1–3 previous HSCT	2 (6.7)	2 infusions on days: +1 (co-infusion with HSCT), +15
Poor graft function	Eltrombopag, CD34 boost	6 (20)	2 infusions on days: +1 (co-infusion with CD34 boost), +15
Hemorrhagic cystitis	Cydofovir, intravesical: hyaluroic acid, E-aminocaproic acid/ urokinase	4 (13.3)	3–4 infusions on days: +1, +7, +14, (+18)
All	NA	30	NA

Mesenchymal stromal cells in the treatment of pediatric HSCT related complications (GVHD , hemorrhagic cystitis, graft failure and poor graft function): a single center experience Maria Pérez-Torres Lobato, spain . 2024

- NO adverse- events (OR) ;83% (25/30) 44% (11/25); CR
- OR for GVHD, HC, PGF and GF was 83.3%, 100%, 66.7% and 100%

- 7p Death : respiratory failure , BO, bacterial penumonia, relapse disease ,alveolar hemorrhage

Conclusion:

- The most frequent indication of MSCs : refractory aGVHD (43.3%)

Extended Treatment With Mesenchymal Stromal Cells-Frankfurt am Main in a Pediatric Patient With Steroid-refractory Acute Gastrointestinal Graft-Versus-Host Disease: Case Report and Review of the Literature . Bernd Gruhn.2021

- **MSC-Frankfurt am Main (MSC-FFM, Obnitix),** which is manufactured from **pooled mononuclear bone marrow cells from 8 donors** using a standardized process, :a response rate of 84% in children with steroid-refractory aGVHD.
- A F 13 AML (MSC)Obnitix as a **3th treatment for** GI- aGVHD in a life-threatening situation.
- The patient was initially given a total of 4 Obnitix infusions as per the regulatory approval, with her symptoms **improving from day 9** after the first infusion.
- **Second cycle of 4 Obnitix infusions followed due to persistent severe protein-losing enteropathy : complete remission.**
- **Treatment protocols :case-by-case basis.**

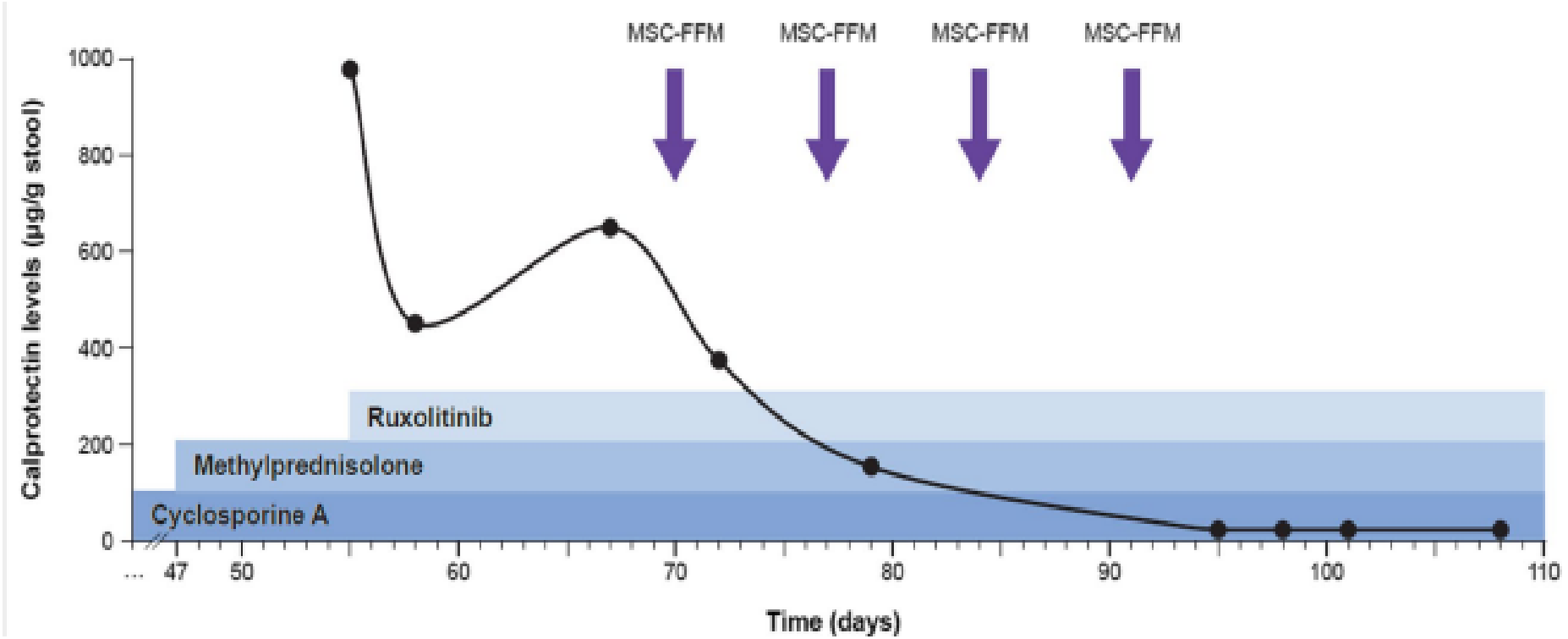
Successful treatment with MSC in a **pediatric patient with SR refractory and ruxolitinib refractory acute GI GVHD** .
Jana Ernst.Annals of Hematology (2025), Germany .

- **A 12-year-old male patient , HR AML , ALLO HSCT**
- **Severe GI aGVHD.**
- **Grgrade IV aGVHD of the intestine, NO improvement under triple IS with CS , cyclosporine A & ruxolitinib.**
- **4 weekly infusions of human allo MSC DRK-BaWü-He-FFM (MSCFFM)**
- Intestinal inflammation finally improved, ,symptoms; normalized intestinal wall thickness **(ultrasonography)** , **decreasing calprotectin levels.**
- Intestinal mucosal healing was further supported by a strict, formula-based modular **diet.**

Annals of Hematology (2025) 104:4237–4243

Diagnosis and evaluation of GVHD : Clinical finding , Imaging (sono , color doppler sono , CT , biomarkers and main one : Biopsy sampling

GI GVHD:Calprotectin levels decreased during treatment with MSC

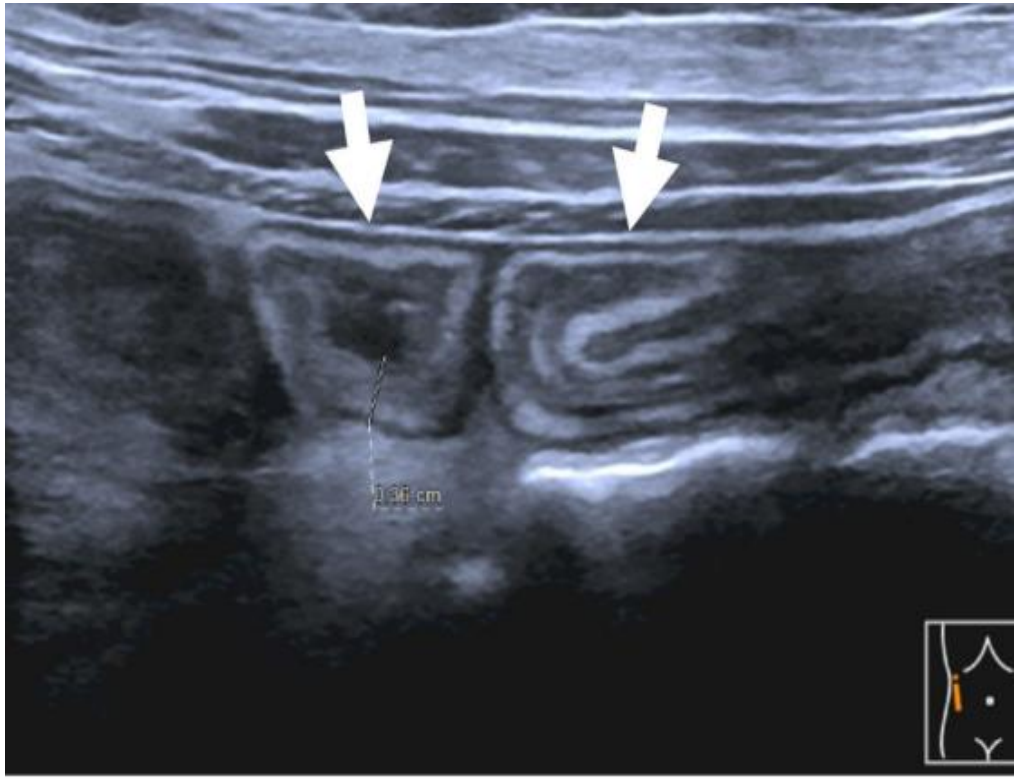


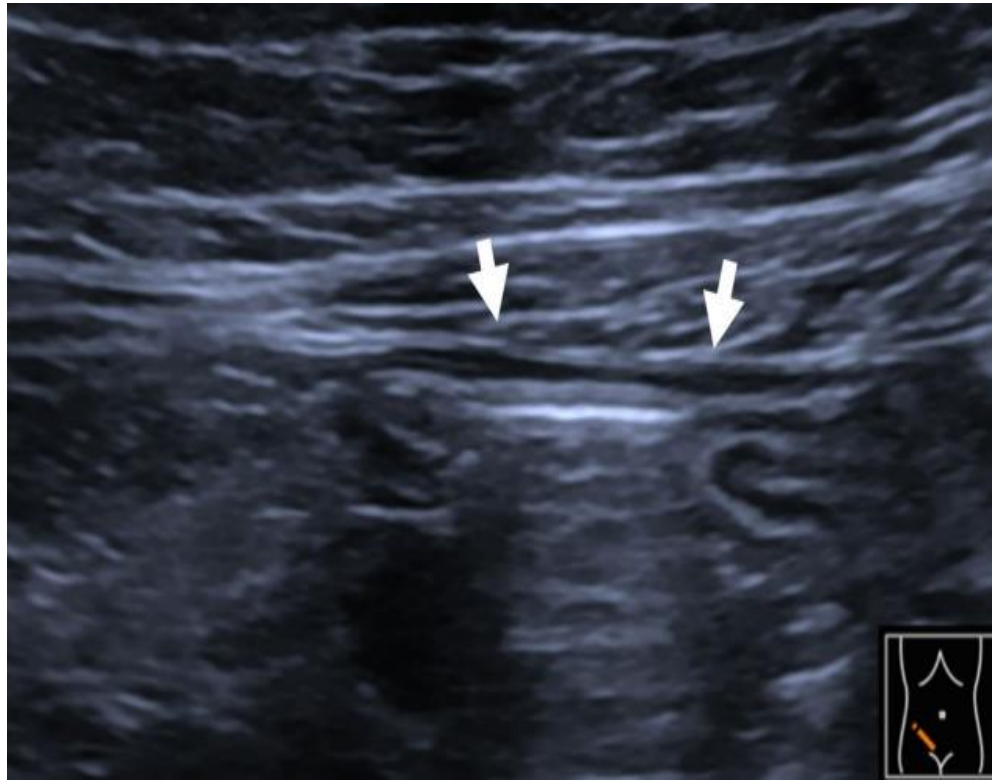
Annals of Hematology (2025) 104:4237–4243

Imaging in GI Acute GVHD:

1-Blurred bowel & thickened wall structure (arrows) in the R middle abdomen

2- NL bowel wall structure





Conclusion

- Preventing GVHD and reducing GVHD-related mortality and morbidity should be an important health strategy.

- The studies indicating that the use of MSCs is effective in the prevention and treatment of GVHD are promising

- More and more comprehensive studies on this subject are needed.

THANK YOU