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SUCCESSFUL AND SAFE TREATMENT OF INTESTINAL GRAFT-VERSUS-HOST DISEASE (GVHD) WITH POOLED-DONOR FULL-ECOSYSTEM MICROBIOTA BIOTHERAPEUTICS

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INTRODUCTION

Intestinal Graft-versus-Host Disease (GvHD) following allogeneic Hematopoietic Stem Cell Transplantation (allo-HSCT) leads to a high mortality rate and reduced life-expectancy. Failure to respond to steroids is met by the absence of further therapeutic options, leading to an unmet medical need.

- Reduced gut microbiota diversity is associated to impaired immune functions and reduced overall survival in GvHD
- High gut microbiota diversity appeared to be protective. It is therefore unlikely that microbiome alterations during and after HSCT are devoid of functional implications
- The chemotherapy-related damage to the gastrointestinal (GI) tract seems to condition the development of GvHD

Strong rationale to postulate that the restoration of the gut microbiota by fecal microbiota transfer (FMT) may play a crucial role in addressing the course of GvHD by modulating the immune system

Here we report about the use of a next-gen FMT, a standardized, pooled-donor, high-richness, full-ecosystem microbiota biotherapeutic solution administered by enema (MaaT013), used to treat 8 patients with GI-predominant aGvHD

METHODS

MaaT013 microbiota full-ecosystem biotherapeutic solution:

- Provided as a pharmaceutical preparation to hospitals by its developer, "MaaT Pharma" as part of a compassionate use program
- Prepared under **Good Manufacturing Practices**
- Characterized by a **highly consistent richness** of 455 +/- 3% Operational Taxonomic Units (OTUs) and **an inverse Simpson index greater than 20**
- Batch release specifications based on potency (viability), identity (diversity), and purity (microbiological safety testing following regulatory guidelines, and maintaining a low proportion of proinflammatory species), ensuring the desired consistency between batches
- 150 mL bags, administered by enema (n=7) or nasogastric tube (n=1)
- Each dose administered one week apart from each other. Total doses administered: 21
- Gastrointestinal GvHD response (GI response) was evaluated 7 days after each administration and 28 days after the first dose.

PATIENT CHARACTERISTICS

All patients received antibioprophylaxis before and during the administration of the MaaT013 enema biotherapeutic.

Patient ID	1	2	3	4	5	6	7	8
Gender	F	F	M	M	M	F	M	F
Age at the time of FMT	67	49	52	67	73	71	38	72
Hematologic Malignancy	PMF	AML	MDS	MDS	NHL-AITL	MDS	CMML	MDS
Type of donor	MUD	MUD	MUD	MUD	MUD	MUD	Haplo-identical	Haplo-identical
Stem cells origin	PBSC	PBSC	PBSC	PBSC	PBSC	PBSC	PBSC	PBSC
Conditioning regiment	Fludarabin Busulfan	Fludarabin Busulfan	Fludarabin Busulfan	Fludarabin Busulfan	Fludarabin Busulfan	Fludarabin Busulfan	Thiotepa Busulfan Fludarabin	Baltimore
ATG	Yes	Yes	Yes	Yes	Yes	Yes	No	No
PT-CY	No	No	No	No	No	No	Yes	Yes
GVHD prophylaxis	CSA, MTX	CSA	CSA, MMF	CSA, MMF	CSA	CSA	CSA, MMF	CSA, MMF
Treatments for GVHD	CS, Ruxolitinib, Etanercept	CS, Ruxolitinib	CS, Ruxolitinib	CS, MTX, CSA, Vedolizumab Ibrutinib	CS, MTX, ECP, Ruxolitinib	CS, MTX, ECP	CS	CS, Ruxolitinib
Indication	SR-GI-aGVHD overlap syndrom	SD-GI-aGVHD late onset	SR-GI-aGVHD overlap syndrom	SR-GI-aGVHD	SD-GI-aGVHD overlap syndrom	SR-GI-aGVHD	SD-GI-GVHD late onset	SR-GI-aGVHD CMV colitis *E. coli* sepsis

M: Male; F: Female; PMF: Primary myelofibrosis; AML: Acute Myeloid Leukemia; MDS: Myelodysplastic syndrome; NHL-AITL: Non-Hodgkin Lymphoma- Angioimmunoblastic T-cell Lymphoma; CMML: Chronic Myelo Monocytic Leukemia; MUD: Matched-Unrelated Donor; PBSC: Peripheral Blood Stem Cells; PT-CY: Post-Transplantation Cyclophosphamide; CSA: Ciclosporin A; MTX: Methotrexate; MMF: Mycophenolate Mofetil; ECP: Extracorporeal Photophoresis; CS: Corticosteroids; SR: Steroid-Resistant; SD: Steroid-Dependant; GI: Gastrointestinal; aGVHD: acute Graft-versus-Host Disease; CMV: Cytomegalovirus

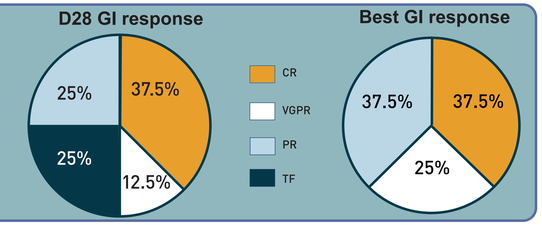
RESULTS

EFFICACY

CR : Complete Response
VGPR : Very Good Partial Response
PR : Partial Response
TF : Treatment Failure

	D28 GI response	Best GI response
CR	3	3
VGPR	1	2
PR	2	3
TF	2	0

Patients still alive at last follow-up (median survival : 231 days)



PATIENT ID	1	2	3	4	5	6	7	8
Indication	SR-GI-aGVHD overlap syndrome	SD-GI-aGVHD late onset	SR-GI-aGVHD overlap syndrome	SR-GI-aGVHD	SD-GI-aGVHD overlap syndrome	SR-GI-aGVHD	SD-GI-aGVHD late onset	SR-GI-aGVHD CMV colitis *E. coli* sepsis
No. of MaaT013 doses	1	3	3	3	3	3	3	2
Route of administration	Nasogastric tube	Enema	Enema	Enema	Enema	Enema	Enema	Enema
GI staging (MAGIC criteria) before administration	Stage 1	Stage 2	Stage 0	Stage 4	Stage 3	Stage 3	Stage 4	Stage 4
GI response at D28	PR	CR	VGPR	TF	CR	PR	CR	TF
Best GI response	VGPR at M3	CR	VGPR	Transient VGPR	CR	PR	CR	Transient PR
Status	Alive Mild skin and GI cGVHD	Alive CR of GVHD No immunosuppressive drugs since 4 months	Dead	Dead	Alive Local mouth cGVHD Diarrhea relapse 3 months later	Dead	Alive Molecular relapse of HM	Dead
Cause of death	N/A	N/A	Infectious pneumopathy	GVHD	N/A	GVHD and HM relapse	N/A	GVHD CMV colitis *E.coli* sepsis
Follow-up duration (days) from first dose until last visit, or death	413	301	176	28	231	39	197	15
Safety	Bacteremia with *E. coli, E. faecium* and *B. vulgatus* 1-day post administration *E. coli* septic arthritis 3-days after dosing, resolved with antibiotics	No AE / SAE reported	No AE / SAE reported	Severe abdominal pain and MOF 48h post dosing. Causal relationship to MaaT013 was not assessable	No AE / SAE reported	Transient abdominal pain with rectal bleeding 3 days post dosing Sepsis 1-day post dosing resolved with antibiotherapy. No germ identified in cultures	Staphylococcus bacteremia and *K. pneumonia* cystitis 6 days post dosing treated with antibiotics	*E. coli* septicemia, CMV reactivation and GI hemorrhage

HM: Hematologic Malignancy; AE: Adverse event; SAE: Serious Adverse Event; MOF: Multiple Organ Failure; TF : Treatement Failure

SAFETY

- 1 potentially related sepsis. No pathogen identified in blood cultures, full recovery of the patient with antibiotics.
- 3 bacteremias, all resolved with appropriate antibiotherapy.
- 1 *E. coli* septic arthritis.
  The *E. coli* strain was isolated from blood and sequenced to compare with the genomic signatures of MaaT013 used. The strain detection and comparison tool, which is limited by the detection thresholds of the method, revealed that the *E. coli* strain had been present in the patient's faeces before administration of MaaT013, and not in MaaT013; suggesting that this particular strain was neither in the product nor transmitted by it.

CONCLUSION

We report for the first time the treatment of 8 patients with steroid-dependent or steroid-refractory intestinal aGvHD using a full-ecosystem, standardized, pooled-donor, high-richness microbiota biotherapeutic suspension (MaaT013) .

- All patients, who had previously failed in previous lines (1 to 5 lines, median: 2.5), experienced at least a partial response following administration of MaaT013.
- 3 out of 8 patients attained a complete response following treatment and are still alive with a median follow-up of 231 days. A total of 4 patients out of 8 are still alive at last follow-up (median follow-up: 266 days)
- The off-the-shelf MaaT013 product showed a reasonably safe and effective profile in these immunocompromised patients with severe medical conditions, warranting further exploration of the full-ecosystem microbiota restoration approach.

DISCLOSURES

FM: Astellas, JAZZ pharmaceutical, Sanofi, Keocyte, Janssen, Therakos/Mallinckrodt (Honoraria). **EP**, **RC**: MaaT Pharma (employment). **PC**: Daiichi Sankyo, Incyte, Jazz Pharmaceuticals (honoraria). **DB**: Jazz Pharmaceuticals, Sanofi, Molmed, Pierre Fabre (Honoraria). **MM**: Jazz Pharmaceuticals, Janssen, Sanofi (Consultancy, Honoraria, and Speakers Bureau), Roche (Research Funding), BMS, Celgene, Amgen, Takeda, Pfizer, Novartis (Honoraria)