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

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Background

Intestinal graft-versus-host disease (GvHD), following allogeneic hematopoietic stem cell transplantation (allo-HSCT), comes with a high mortality rate and a reduced life-expectancy. In this context, failure to respond to steroid therapy is associated with an absence of further therapeutic options, thereby representing 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 fuctional implications

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

Here we report on the use of a next-gen FMT product “MaaT013”, a standardized, pooled-donor, high-richness microbiota biotherapeutic, used to treat 11 patients with intestinal aGvHD as part of a compassionate use program.

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=10) or nasogastric tube (n=1)
- Each dose administered one week apart from each other. Total doses administered: 29 (median: 3)
- Gastrointestinal GvHD response (GI response) was evaluated 7 days after each administration and 28 days after the first dose

Patients characteristics

Patients received antibioprophylaxis before and during administration of the MaaT013 enema biotherapeutic

Patient ID	PATIENT 1	PATIENT 2	PATIENT 3	PATIENT 4	PATIENT 5	PATIENT 6	PATIENT 7	PATIENT 8	PATIENT 9	PATIENT 10	PATIENT 11
Gender	F	F	M	M	M	F	M	F	M	F	M
Age at the time of dosing	67	49	52	67	73	71	38	72	52	43	50
Hematologic malignancy	PMF	AML	MDS	MDS	NHL-AITL	MDS	CMML	MDS	AML	MDS	PTCL
Type of donor	MUD	MUD	MUD	MUD	MUD	MUD	Haplo-identical	Haplo-identical	MUD	Haplo-identical	MUD
Stem cells origin	PBSC	PBSC	PBSC	PBSC	PBSC	PBSC	PBSC	PBSC	PBSC	PBSC	PBSC
Conditioning regimen	Fludarabin Busulfan	Fludarabin Busulfan	Fludarabin Busulfan	Fludarabin Busulfan	Fludarabin Busulfan	Fludarabin Busulfan	Thiotepa Busulfan Fludarabin	Baltimore	Fludarabin Aracytin TBI	Fludarabin Busulfan	unknown
ATG	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
PT-CY	No	No	No	No	No	No	Yes	Yes	Yes	No	No
GvHD prophylaxis	CSA, MTX	CSA	CSA, MMF	CSA, MMF	CSA	CSA	CSA, MMF	CSA, MMF	CSA, MMF	CSA	CSA
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	CS	CS, Ruxolitinib	CS, Ruxolitinib, Etanercept
Indication	SR-aGVHD late onset	SD-aGVHD late onset	SR-aGVHD overlap syndrom	SR-aGVHD	SD-aGVHD overlap syndrom	SR-aGVHD	SD-aGVHD late onset	SR-aGVHD *CMV colitis* *E. coli sepsis*	SR-aGVHD	SR-aGVHD overlap syndrom	SR-aGVHD

M: Male; F: Female; PMF: Primary myelofibrosis; AML: Acute Myeloid Leukemia; MDS: Myelodysplastic syndrom; NHL-AITL: Non-Hodgkin Lymphoma- Angioimmunoblastic T-cell Lymphoma; CMML: Chronic Myelo Monocytic Leukemia; PTCL: Peripheral-T-cell Lymphoma; 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; aGVHD: acute Graft-versus-Host Disease; CMV: Cytomegalovirus

Results

HM: Hematologic Malignancy; AE: Adverse event; SAE: Serious Adverse Event; MOF: Multiple Organ Failure, IS: Immunosuppressive

Patient ID	PATIENT 1	PATIENT 2	PATIENT 3	PATIENT 4	PATIENT 5	PATIENT 6	PATIENT 7	PATIENT 8	PATIENT 9	PATIENT 10	PATIENT 11
Indication	SR-aGVHD late onset	SD-aGVHD late onset	SR-aGVHD overlap syndrom	SR-aGVHD	SD-aGVHD overlap syndrom	SR-aGVHD	SD-aGVHD late onset	SR-aGVHD *CMV colitis* *E. coli sepsis*	SR-aGVHD	SR-aGVHD overlap syndrom	SR-aGVHD
Nb of FMT	1	3	3	3	3	3	3	2	3	3	2
Route of administration	Nasogastric tube	Enema	Enema	Enema	Enema	Enema	Enema	Enema	Enema	Enema	Enema
GI staging (MAGIC criteria) before FMT	Stage 1	Stage 2	Stage 0	Stage 4	Stage 3	Stage 3	Stage 4	Stage 4	Stage 4	Stage 2	Stage 4
GI response at D28 post-dosing	PR	CR	VGPR	TF	CR	PR	CR	TF	CR	CR	VGPR
Best GI response	VGPR at M3	CR	VGPR	Transient VGPR	CR	PR	CR	Transient PR	CR	CR	VGPR
Status	Alive Mild skin and GI cGVHD	Alive CR of GVHD No IS drugs since 4 months	Dead	Dead	Alive Local mouth cGVHD Diarrhea relapse 3 months later	Dead	Alive Molecular relapse of HM	Dead	Alive	Alive	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*	N/A	N/A	Chronic pulmonary GVHD
Follow-up duration (days) from firsts dosing until last visit or death	413	301	176	28	231	39	197	15	55	49	47
Safety	Bacteremia with *E. coli, E. faecium* and *B. vulgatus* 1 day post-dosing *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	No AE / SAE reported	No AE / SAE reported	No AE / SAE reported

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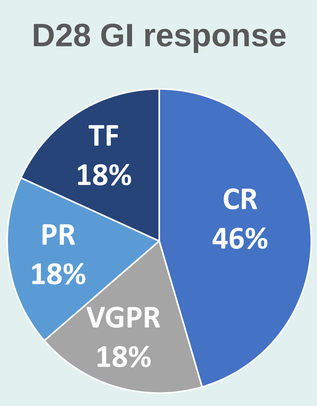

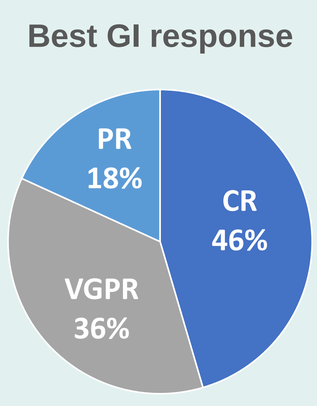

Response	D28 GI response	Best GI response
CR	5	5
VGPR	2	4
PR	2	2
TF	2	0

CR: Complete Response; VGPR: Very Good Partial Response; PR: Partial Response; TF: Treatment 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 genomic signatures of MaaT013 used. The strain detection and comparison tool, which is limited by the detection threshold 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 herein report the treatment of 11 patients with steroid-dependent or steroid-refractory intestinal aGVHD using a full ecosystem, standardized, pooled-donor, high-richness biotherapeutic.

- All patients experienced at least a partial response following dosing
- 5/11 patients attained a complete response following treatment and are still alive with a median follow-up of 197 days.
- The off-the-shelf MaaT013 product is shown to be safe and effective in these immunocompromised patients with severe conditions, warranting further exploration of the full ecosystem microbiota restoration approach