Prevention of dysbiosis complications with autologous fecal microbiota transplantation (auto-FMT) in AML patients undergoing intensive treatment (ODYSSEE study): First results of a prospective multicenter trial

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INTRODUCTION

- The microbiota plays an important role in human health and disease, in particular in shaping the global immune cell repertoires, thereby altering host susceptibility to inflammation and infection at sites of colonization.
- Many cancer drugs lead to an inflammatory conditions such as mucositis, associated with gut barrier deterioration and bacterial translocation. As these drugs also cause neutropenia, bacterial translocation across the gut mucosa can cause severe systemic infections that will require antibiotics. Intensive treatments of Acute Myeloid Leukemia (AML) are known to negatively impact gut microbiota composition, measured by a deep shutdown of diversity indices (eg. Simpson), also called **dysbiosis**.
- Therefore, development of strategies to manipulate the gut microbiota may minimize treatment-related complications and potentially improve outcomes.
- We propose to use autologous transplantation of fecal microbiota to AML patients treated with intensive chemotherapy and antibiotics in order to restore the balance of their intestinal microbiome.

STUDY DESIGN and PATIENTS

- Single arm phase I/II multicenter trial (NCT02928523)
- Treatment: 2 doses of 150mL auto-FMT by rectal enema

STUDY OBJECTIVES

- Primary: Recovery of microbiota diversity and correction of dysbiosis after auto-FMT
- Secondary:
  - ✓ Safety and feasibility of auto-FMT
  - ✓ Impact of auto-FMT on several patient-related outcomes (clinical status, immune status and recovery)
  - ✓ Exploratory assessment of a dysbiosis biosignature

Key Inclusion Criteria

- ≥ 18 and ≤ 75 years old
- *de novo* diagnosis of **AML**
- Intensive chemotherapy ("3+7" or equivalent)

Key Exclusion Criteria

- Antibiotics ≥ 4 days at V1
- Detection of resistant or pathogenic bacteria, parasites, viruses in faeces at V1
- Severe colitis or digestive disorders within 3 months before V1

Demographics and Baseline Characteristics

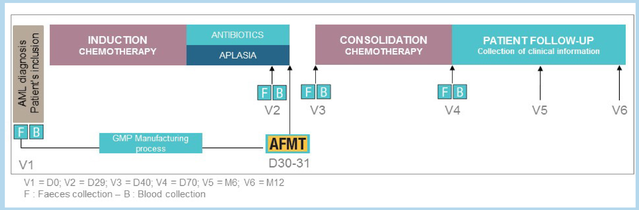
- **35 AML** eligible screened patients
- 9 patients fulfilling all inclusion criteria inclusion and treated with auto-FMT; presented in this interim analysis

Age, yrs; median (range)	47 (32-67)
Gender, n (%)	F: 0 (0%); M: 9 (100%)

Disclosure
The trial was funded by MaaT Pharma whose product was tested in this protocol.
LB and EP are MaaT Pharma employees.
MM and JD are scientific co-founders of MaaT Pharma.

METHODS - STUDY FLOW CHART

- Faeces were collected at the time of patient's admission and AML diagnosis. After rigorous screening according to standard recommendations, faeces were conditioned, processed with a patented diluent under GMP conditions and stored frozen until transplantation. After recovery from aplasia and before the second course of chemotherapy, two autologous inocula of 150mL were administered as enema 24h apart (D30 and 31).
- The current interim results concern the 9 patients who were able to proceed auto-FMT after intensive induction chemotherapy



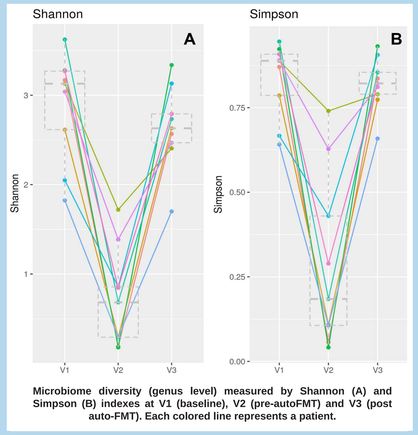
***Inoculum manufactured under GMP conditions**

- The microbiome diversity and richness were measured at baseline V1 (prior to induction chemotherapy), V2 (after induction chemotherapy, aplasia completion and antibiotics discontinuation) and V3 (before consolidation chemotherapy, ie around 10 days post auto-FMT). Microbiome restoration was assessed at the genus and species level, on the basis of metagenomic results obtained for the 3 sequential samples. Illumina TruSeq Nano Prep kit was used for sequence-library preparation and samples were sequenced on HiSeq 2500 2x125bp, 40 million reads/sample.

RESULTS

Microbiome Summary

- ✓ Huge impact of chemotherapy/ antibiotics on microbiome diversity at genus level (idem species level, data not shown)
- ✓ Total recovery of microbiota diversity after auto-FMT
- ✓ Significant increase of the antibiotic resistance gene copynumbers after chemotherapy / antibiotics, returned to baseline after auto-FMT

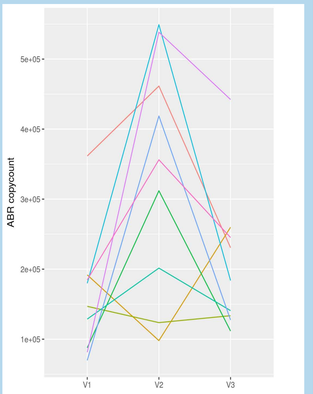


Microbiome diversity (genus level) measured by Shannon (A) and Simpson (B) indexes at V1 (baseline), V2 (pre-autoFMT) and V3 (post auto-FMT). Each colored line represents a patient.

Index	Visits	Mean	Coefficient (comparison to V1)	IC95%	P-value (comparison to V1) Linear mixed-effects model
Simpson	V1	0.837	0,837	0.727; 0.947	0.000
	V2	0.287	-0.549	-0.699; -0.399	< 0.001 **
	V3	0.820	-0.017	-0.017; 0.133	0.830
Shannon	V1	2.889	2.889	2.505; 3.272	0.000
	V2	0.717	-2.172	-2.669; -1.676	< 0.001 **
	V3	2.640	-0.249	-0.745; 0.248	0.304
ABR copycount (log transformed)	V1	5.149	5.149	4.984; 5.314	0.000
	V2	5.466	0.317	0.094; 0.540	< 0.01 *
	V3	5.278	0.130	-0.093; 0.352	0.234

Safety Summary

- ✓ Auto-FMT well tolerated
- ✓ 1 serious adverse event post-FMT reported (*E. coli* infection resolved after appropriate antibiotherapy)



Antibiotics resistance total copycount measured at V1 (baseline), V2 (pre-autoFMT) and V3 (post auto-FMT). Each colored line represents a patient.

CONCLUSIONS

This first multicenter prospective trial reached its primary endpoint in all analyzed cases thus far, and established the capacity of auto-FMT to correct dysbiosis and restore a normal microbiota in AML patients receiving intensive induction chemotherapy and wide-spectrum antibiotics.
Clinical, biochemical and immune parameters of this interim analysis are currently being analyzed and suggest correlation with the dysbiosis correction. The apparent modulation of the immune system through microbiota restoration is a promising venture in the treatment of AML patients warranting further investigations. Data and in particular clinical information from all patients will be soon available, and will allow a better understanding of the impact of auto-FMT on patient-related outcomes. Indeed, the development of strategies to modulate the gut microbiota may improve the overall disease management and thereby the clinical outcomes such as infection-related complications, sequelae to the gastrointestinal tract as well as other co morbidity factors in order to improve the overall mortality of the disease.