THE ODYSSEE STUDY: PREVENTION OF DYSBIOsis COMPLICATIONS WITH AUTOLOGous FECAL MICROBIOTA TRANSFER (FMT) IN ACUTE MYELOID LEUKEMIA (AML) PATIENTS UNDERGOING INTENSIVE TREATMENT: RESULTS OF A PROSPECTIVE MULTICENTER TRIAL

INTRODUCTION AND OBJECTIVE

AML standard intensive chemotherapy (IC) combined with wide-spectrum antibiotics dramatically altered composition of the gut microbiota, leading to dysbiosis, promoting a pathological condition with uncontrolled local immune responses, systemic inflammation and increased incidence of comorbidities and complications.

Proof-of-concept study to evaluate the use of microbiota-based drug during AML induction treatment to restore the gut microbiota diversity, and thereby ultimately controlling complications to improve outcomes in AML.

STUDY DESIGN AND PATIENTS

- Single arm phase III multicenter trial (NCT02935523)
- Treatment: 2 doses of 150ml auto-FMT biotrophic drug by rectal enema

STUDY MAIN OBJECTIVES

- Primary: Impact of auto-FMT on recovery of microbiota diversity and correction of dysbiosis
- 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 (7+3 or equivalent)
- Leukemia risk category (ELN2010)
- F: 5 (25%); M: 15 (75%)

Key Exclusion Criteria

- Antibiotics 2 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

- 63 AML patients aged between 24 and 69 years old (median: 58) were screened.
- 25 patients fulfilling all inclusion criteria were treated (FAS population; 20 were included in the per-protocol (PP) population. Results from the PP population are presented.

- Age, years, median (range): 50 (24-68)
- Gender, n (%): F: 5 (25%); M: 15 (75%)
- Induction chemotherapy (IC): Ara-C + Daunorubicin: 7 (35%); Ara-C + Idarubicin: 12 (60%)
- Other: 1 (5%)
- FLT3/ITD Mutation: Yes: 14 (87.5%); No: 2 (12.50%); ND: 4 (25%)
- NPM1 Mutation: Yes: 11 (55%); No: 9 (45%)

METHODS AND RESULTS

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 diluant under GMP conditions and stored frozen until administration in MaaT Pharma’s integrated MaaT Microbiome Restoration Biotechnolog (MMSB) platform. After recovery from apalasia and before the second course of chemotherapy, two faeces were administered as enema 24h apart (D30 and 30)

Microbiome analysis: QKap fast DNA stool for DNA extraction; sequencing on the Hiseq 2500 x2 (150bp), 40 million reads/sample. RafSeq2015 for phylogenetic analysis.

Antibiotic resistance gene carriage (ABR copycount) was evaluated through matching of readouts on the MEGARES database.

METHODOLOGIC RESULTS

CONCLUSIONS

First prospective trial testing the safety and efficacy of microbiota-based drug in AML patients receiving intensive induction chemotherapy.

- Primary endpoint reached, establishing the capacity of this biotrophic drug to restore a diverse microbiota with high levels of similarity to baseline, as well as reducing antibiotic resistance gene carriage and intestinal inflammation.

- Ecological data from AML patients that did not receive microbiota-based drugs could be of interest to reinforce the observed efficacy of the product in restoring gut microbiota diversity.

- A randomized controlled trial with repeated one administrations during the different phases of AML treatment is currently planned to further evaluate the impact of dose-derived microbiota-based drugs on clinical outcomes such as infection-related complications, sequelae to the gastrointestinal tract, GVHD occurrence after hematopoietic stem cell transplantation and long-term survival. Indeed, the development of strategies to modulate the gut microbiota may improve overall disease management.

- Product well tolerated
- No SAE reported within 30 days after dosing
- 1 Suspected Unexpected Serious Adverse Reaction was doubtfully reported 93 days after second dosing, sequelae with digestive leaving with E. coli conta-
- 1-year survival: 84% with 4 deaths among 25 patients (FAS population), none of which were related to the product: 2 multiple organ failures, 1 heart attack and 1 grade IV resistant GVHD. Median time to death from the 2nd dosing was 182.5 days (113-225 days)

- Safety Summary

DISCLOSURE

None of the authors had a conflict of interest.

REFERENCES