CASE REPORT

Healthy donor faecal transplant for corticosteroid non-responsive severe alcoholic hepatitis

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SUMMARY

Patients with severe alcoholic hepatitis (SAH) have high mortality in the presence of steroid unresponsiveness in the absence of clear treatment recommendations. Liver transplantation is the curative option in such cases but is controversial in the wake of severe infections, post-transplant recidivism and long waiting on deceased donor listing. Animal and human studies have shed light on the beneficial effects of gut microbiota modulation in alcoholic liver disease. We present the first report of faecal microbiota transplantation (FMT) in a steroid non-responder in whom, clinical, biochemical and liver disease severity scores improved post-FMT and demonstrate distinct bacterial population changes pre-FMT and post-FMT. Healthy donor FMT could be safe and efficacious in SAH not responding to corticosteroid treatment, as a bridge to liver transplantation (LT) or in candidates who are unwilling or not ideal for LT for improvement in short-term transplant free survival. Larger controlled studies are required for confirmation.

BACKGROUND

Patients with severe alcoholic hepatitis (SAH) (defined as patients with clinical and biochemical features of AH with discriminant function (DF) >32 or model for end-stage liver disease (MELD) ≥21 or presence of hepatic encephalopathy (HE) ≥2) are treated with corticosteroids (CS; prednisolone, at a dose of 40 mg per day) as per current guideline recommendations.¹ The Lille model score is used to evaluate response to CS therapy at day 7. Patients with Lille score >0.45 are considered non-responders. Mathurin *et al* demonstrated that complete responders (Lille score ≤0.16), partial responders (Lille score 0.16–0.56) and null responders (Lille score ≥0.56) had 28-day survival rates of 91%, 79% and 53%, respectively.²

There is no established therapeutic alternative for non-responders. Controversial 'salvage' liver transplantation could be used in very selected patients. Other modalities of treatment such as extracorporeal liver support devices, anti-inflammatory therapy, granulocytapheresis, antioxidant therapy, nutritional therapy and complementary and alternative medications do not improve survival benefit and are currently not recommended in the treatment of SAH.³ Gut microbiota and dysbiosis (the pathogenic modification of gut microbiome in the presence of alcohol intake) has been found to play a central role in development and progression of SAH. In mice model, Llopis *et al* demonstrated that

individual susceptibility to alcoholic liver disease (ALD) was substantially driven by intestinal microbiota (IM) and that IM manipulation could help prevent and manage ALD.⁴ Ferrere *et al* confirmed that manipulation of IM prevented alcohol-induced liver injury in mice and IM manipulation be considered as a new therapeutic target in ALD.⁵ A small pilot study on faecal microbiota transplantation (FMT) in patients with SAH who were ineligible for steroid treatment (due to various contraindications) demonstrated significant survival benefit, in the short and long term in comparison to historical controls with similar disease severity profile.⁶ There is no report on the use of FMT in patients with SAH who are CS treatment failures. Here, we present a case of steroid non-responsive SAH successfully salvaged with FMT and shed light on dynamic changes in gut microbiota at baseline and post-treatment using state of the art metagenomic analysis.

CASE PRESENTATION

A 38-year-old man consuming 110 to 140 g of alcohol since the last 10 years, with the last intake of alcohol 4 weeks back was admitted to our Liver Unit with complaints of progressive non-cholestatic jaundice accompanied by fever, new onset abdominal distension for 1 week and alteration in mental status for 2 days. He did not suffer from diabetes mellitus, systemic hypertension, hypothyroidism or cardiac or pancreatic diseases. There was no history of recent travel, consumption of over the counter or complementary and alternative medications. There was no family history of liver disease. Clinical examination revealed a deep icterus with grade 2 ascites and flapping tremors, oriented to person, but not to place and time. Blood investigations revealed haemoglobin 10.2 (normal 12 to 15 g/dL), total leucocyte count 18.2 (4.00 to 10.0 × 10⁹/L), platelet count 190 (150–450 × 10⁹/L), total bilirubin 24.8 (normal 0.3–1.0 mg/dL), direct bilirubin 16.4 (0.0–0.2 mg/dL), aspartate aminotransferase 202 (<37 U/L), alanine aminotransferase 92 (<41 U/L), γ-glutamyl transferase 234 (5–61 U/L), alkaline phosphatase 98 (35–129 U/L), albumin 2.2 (3.5–5.0 g/dL) and international normalised ratio (INR) 2.52 (0.9–1.2). Renal function tests were normal. Tests for acute viral hepatitis A, E and hepatitis B, C and HIV were negative. Tests for antinuclear antibody, antismooth muscle antibody, antiliver kidney microsomal antibody-1 and antiliver soluble antigen were negative. The serum total IgG was within normal limits. Arterial ammonia at baseline

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Table 1 Clinical and investigational parameters of the patient from baseline, until end of 1 month posthealthy donor FMT

Investigations	Start of steroids	Day 8 after 7 days of steroids (baseline, 3 days before FMT)	Day 8 after 7 days of FMT	One month after FMT
Grade of ascites	2	2	2	1
Grade of HE	2	2	1	0
Haemoglobin (g/dL)	10.2	9.8	9.6	10.1
Total leucocyte counts (x 10 ⁹ /L)	18.2	16.9	12.7	9.6
Platelet counts (x 10 ⁹ /L)	190	126	134	156
Total bilirubin (mg/dL)	24.8	34.4	25.2	5.4
Direct bilirubin (mg/dL)	16.4	20.6	14.7	2.3
Albumin	2.2	2.4	2.6	2.9
Aspartate aminotransferase (IU/L)	202	198	187	97
Alanine aminotransferase (IU/L)	92	81	74	56
Alkaline phosphatase (IU/L)	98	109	169	76
Gamma glutamyl transpeptidase (IU/L)	234	188	142	98
Prothrombin time (seconds)	29.8	32.7	29.5	19.8
International normalised ratio	2.52	2.76	2.49	1.68
Blood urea (mg/dL)	14	22	19	16
Creatinine (mg/dL)	0.8	1.1	1.0	1.1
Sodium (mmol/L)	134	132	137	133
Potassium (mmol/L)	3.8	4.1	3.7	4.1
Arterial ammonia (μmol/L)	204	197	114	64
Child-Pugh score	14	14	14	9
Model for end-stage liver disease	29	32	29	20
Discriminant function	109.9	132.84	108.92	44.5

FMT, faecal microbiota transplantation; HE, hepatic encephalopathy.

was 204 (<47 μmol/L). Imaging was suggestive of cirrhosis with portal hypertension, and chest X-rays did not reveal consolidation. CT of the brain did not reveal bleed or infarct. Blood, urine and ascites cultures were sterile. A transjugular liver biopsy revealed mixed microvesicular and macrovesicular steatosis with hepatocyte ballooning, neutrophilic lobular inflammation and Mallory-Denk bodies associated with substantial perisinusoidal fibrosis extending up to the portal tracts without central-portal or portal-portal bridging fibrosis or nodule formation. The Child-Pugh score was 14 (class C), MELD score 29 and discriminant function 109.9. Prednisolone at 40 mg per day was started with sepsis screening performed every third day. Hepatic encephalopathy (HE) improved from the fourth day onwards with improvement in appetite. However, on the eighth day of admission and sixth day of steroid treatment, flapping tremors reappeared. Sepsis screening was negative for active infections. After completion of 7 days of corticosteroids, liver function tests revealed total bilirubin of 34.4 mg/dL, prothrombin time 32.4 s and INR 2.76. The discriminant function on the eighth day was 132.84 and Lille score was 0.961 suggestive of null response. Given worsening liver severity indices and clinical status, the family was counselled regarding liver transplantation as the curative treatment of choice. However, the family was not willing for the same, given risk of recidivism, severe infections, lack of a living donor and long waiting time on the deceased donor listing. In the absence of other definitive options, healthy donor FMT was offered as salvage therapy.

The family identified the patient's sister as the potential stool donor. She underwent screening with routine laboratory tests including haemogram, fasting blood sugar, liver function tests, lipid profile, stool routine and microscopy for cysts, parasites, ova stool for occult blood, stool cultures, hepatitis B surface

antigen, anti-HCV, HIV 1 and 2, *Clostridium difficile* and venereal disease research laboratory test. A written informed consent was taken from the donor to donate fresh stool sample every day. The donor was advised to follow a normal diet plan for 1 week. Thirty grams of freshly acquired stool was homogenised (within 6 hours) with 100 mL of normal saline in a home blender and filtered thrice through a sterile gauze to remove solid and vegetable matter. In supine position and with head end raised to 45°, 100 mL of the filtered stool was infused through a fluoroscopically placed nasoduodenal tube, under close monitoring, daily for 7 days. Liquid food consumption was allowed after 2 hours of the procedure. Non-absorbable antibiotics were stopped at the time of stool infusions, but disaccharides and albumin infusions, as per the treating physician's discretion, were continued. No other intravenous or oral antibiotics were given in view of a negative sepsis screen. Stool samples were collected before, at the end of 1 week and 1 month after FMT for microbial community analysis as per standard protocols. In brief, microbial DNA was extracted and used for 16S rRNA V3–V7 genome sequencing. Metagenome libraries were constructed, quantified and sequenced in an Illumina MiSeq as per standard published protocols. Greengenes database was used for annotation of sequenced bacterial metagenomes. The 16S amplicon libraries were analysed using QIIME bioinformatics pipeline using the operational taxonomic unit (OTU) approach for microbial analysis. The Shannon Diversity Index was used to define diversity in groups.⁷

OUTCOME AND FOLLOW-UP

From the fifth day of FMT, improvement in the form of general well-being and enhanced appetite was noted. The patient

Figure 1 (A) Bar histogram representation of faecal microbial communities (phyla) in the healthy donor (D0), patient at baseline (P0), patient at day 8 (P8) and 1 month after healthy donor faecal microbiota transplantation (P30). (B) Faecal microbial community (order) representation in the donor, patient at baseline, patient at day 8 and 1 month after faecal transplant. (C) Area bar diagram showing dynamic changes within the bacterial communities from the donor and the patient at baseline to day 8 and 1 month after faecal transplant procedure. (D) The principal coordinate analysis showing distinct variations between microbial communities at baseline in the donor and patient and near similarity between both at the end of 1 month.

developed three episodes of loose, watery stools on the sixth day that was self-limiting and excessive flatulence throughout the procedure that abated after completion of FMT. He was discharged home on the 10th day after FMT. One month after the procedure, he remained well, with significant improvement in hyperbilirubinaemia, coagulation parameters and ascites control without overt hepatic encephalopathy (HE). Clinical and investigational parameters at baseline and subsequently on the 8th and 30th day post-FMT are shown in [table 1](#).

On microbial community analysis, in the healthy donor, at baseline, at phylum level, Actinobacteria and Firmicutes dominated while in the patient Proteobacteria and Bacteroides were noted. After FMT, in the patient at day 8, the relative abundance (RA) of Firmicutes was much higher, which was maintained at the end of 1 month with new representation from Verrucomicrobia and lesser RA of Proteobacteria and Actinobacteria ([figure 1A](#)). At the genus level, at baseline, the healthy donor had RA of *Ruminococcus*, *Faecalibacterium*, *Lachnospira* and *Bifidobacterium* compared with the patient, in whom, an abundance of *Enterococcus*, *Prevotella* and *Bacteroides* were noted. On the 8th day after FMT, *Faecalibacterium*, *Ruminococcus* and new representation from *Catenibacterium* was seen in the patient, in lieu with improvement in clinical and biochemical parameters. One month after FMT, the modified microbial communities persisted with significant improvement in liver disease severity ([figure 1B,C](#)). On principal component analysis ([figure 1D](#)), a statistical analysis technique used to emphasise variation, we found that the patient and donor microbiome profiles were

distinct at baseline but converged to near similarity at the end of 1 month.

DISCUSSION

Patients with SAH and DF >32 or MELD score >20 without contraindications to CS are conventionally treated with prednisolone, but the appropriate duration of treatment remains a subject of controversy. Patients with contraindication to steroids and steroid non-responders have no definitive treatment options. In such patients, when the MELD score is >26, and with good insight into their alcohol use disorder and adequate social support, referral for evaluation for liver transplantation is advocated by some groups as the 90-day mortality rate is very high. But the risk of recidivism and severe infections in such sick patients do not make this a practical option for many. In the study by Philips *et al* in steroid ineligible SAH, resolution of ascites and HE following FMT associated with improved 1 year survival rate compared with historical controls (87.5% compared with 33.3%) was noted.⁶ Bajaj *et al*, in their study on FMT versus standard of care for recurrent HE found that none of the patients in the FMT arm developed overt HE and that FMT increased diversity and beneficial taxa in treated patients.⁸

Our patient was a steroid non-responder, a group of patients with SAH with very high mortality and with little recommendations for definitive treatment. The cost and risks associated with curative living donor liver transplantation and prolonged wait list timing on the deceased donor programme is a major deterrent towards patient and family compliance to this treatment

Learning points

- ▶ Patients with severe alcoholic hepatitis (SAH) have high mortality in the presence of steroid non-response or ineligibility towards corticosteroid treatment.
- ▶ There is no definite treatment recommendations for patients with SAH who are steroid non-responders.
- ▶ Liver transplantation is the only definitive/curative option for patients with SAH without response to conventional medical treatment but comes with high risk of severe infections, recidivism post-transplant and long wait times on deceased donor list.
- ▶ Even though our study is a single patient report, with confounding factors, we demonstrate that healthy donor faecal microbiota transplantation (FMT) in SAH not responding to steroid treatment can improve clinical, biochemical and liver disease severity parameters.
- ▶ Healthy donor FMT modulated microbiota beneficially, thereby improving clinical outcomes.
- ▶ Healthy donor FMT could be a safe, efficacious and cost-effective modality of treatment for patients with SAH not responding to conventional management as a bridge to liver transplantation or as a salvage therapy to improve short-term survival in those not willing or are not ideal candidates for liver transplantation. Larger controlled studies are required for confirmation.

modality in a developing country like India. Growth factor therapy and its benefit in steroid unresponsive SAH has been used by some groups; but this needs to be confirmed in large patient population and compared against current standards of care to rationalise recommendations regarding the same.⁷ In patients ineligible for steroid treatment, FMT was shown to be more beneficial than pentoxifylline in improving survival in a small cohort of patients.⁹ Similarly, a larger study considering beneficial effects of FMT in SAH against conventional steroid treatment is ongoing (ClinicalTrials.gov Identifier: NCT03091010). We chose 1 month as our follow-up in view of high short-term mortality associated with CS non-responsive SAH. Long-term effects of FMT in this group of patients, considering high rates of recidivism needs further clarification and close follow-up.

In our patient, post FMT, beneficial microbial modulation occurred from day 8 which persisted at the end of 1 month. We did not find active sepsis anytime before, during or after FMT. Spontaneous improvement in our patient in the wake of high liver disease and alcoholic hepatitis severity scores was unlikely. Active medical intervention is usually warranted in severe cases and a short course of antibiotics prior to FMT could not have produced improvement at 30 days especially in the presence of steroid unresponsiveness. The probable mechanism behind efficacy of FMT in ALD was demonstrated in mice by Ferrere *et al.* They showed that alcohol feeding in sensitive mice disrupted gut homeostasis. Alcohol induced loss of mucin producing goblet cells, diminution in gut barrier function, penetration of bacteria into crypts and translocation into epithelial layer leading to an inflammatory response were effectively reduced with healthy FMT. Bile acid homeostasis was thrown into disarray in the

presence of alcohol with deoxycholic acid component rise affecting mucosal barrier function. This too, was reversed with FMT. We believe that healthy donor FMT decreased alcohol-related liver lesions by modifying microbial communities towards benefiting the host.⁵ The improvement in gut barrier function, decreased leakiness, endotoxaemia and amelioration of dysfunctional microbiota metabolism are central to this effect. We found discrepancies on principal coordinate analysis of the patient microbial communities between day 8 (more towards donor profile) and day 30 (in between donor and patient profiles). This could have been due to durable coexistence of donor and patient microbial communities post-FMT, as was shown in the study by Li *et al.*¹⁰ In their study, they observed an extensive and long-lasting coexistence of donor and recipient strains of the same species, with a considerable amount of strain replacement after FMT.

Through this novel report, we demonstrate the beneficial effects of FMT in a patient with SAH not responding to steroids. Further larger studies on FMT in SAH are warranted, both against conventional treatment and in patients not responding to current treatment modalities. FMT could be safe, beneficial, efficacious and cost-effective in patients who are not immediate candidates for liver transplantation as a bridge therapy and for patients with SAH not willing for or poor candidates for liver transplantation as salvage therapy for improving short-term and long-term transplant-free survival.

Contributors CAP: study concept and design, acquisition of data, analysis; NP and KG: interpretation of data and analysis; PA: critical revision of the manuscript for important intellectual content; all authors finalised manuscript content.

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