OFR-9

AN RCT OF AUTOLOGOUS STEM-CELL TRANSPLANTATION IN TREATMENT REFRACTORY CROHN’S DISEASE (LOW-INTENSITY THERAPY EVALUATION): ASTICLITE

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Introduction

Reports of benefit from HSCT were tempered by the ASTIC trial which failed its ambitious primary endpoint and reported high toxicity. Subsequent reports suggest that HSCT achieves complete mucosal healing in 50%, and that toxicity relates to the cyclophosphamide dose.

Design

A UK multi-site RCT comparing low intensity HSCT with standard of care (SOC) in patients with active CD at endoscopy (SESCD ulcer score ≥ 2) refractory to 2 biologic classes. Planned recruitment was 99 patients randomised 2:1 to HSCT versus SOC. The primary endpoint was centrally read endoscopic remission (SESCD ulcer subscore of 0) without requirement for surgery or death at week 48.

Results

The trial was halted due to unexpected SAE after 23 patients (13 HSCT, 10 SOC) had been randomised. The coronavirus pandemic prevented some outcome assessments. Patients had advanced disease: mean (SD) CD duration 13.9 (7) years; CDAI at baseline 337.5 (182.4) with 20 (91%) having undergone surgery and 9 (43%) having a stoma. All patients contributed to the safety analysis. The primary outcome using central reading was available for 7/10 HSCT and 6/9 SOC patients. Absence of endoscopic ulceration without surgery or death was reported in 3/7 (43%) HSCT patients compared to 0/9 (0%) SOC patients. Centrally read SESCD (mean SD) was 11.8 (8.7) and 10.1 (5.7) at baseline compared to 2.8 (2.9) and 18.7 (9.1) at week 48 in the HSCT and SOC groups respectively. Clinical remission (CDAI <150) occurred in 57% and 0% of patients in the HSCT and SOC groups at week 48. SAE were more frequent after HSCT (39 in 13 (100%) patients) than SOC (15 in 4 (40%) patients).

Importantly, 10 SUSARs were reported in 6 HSCT patients including 3 cases of delayed renal failure due to thrombotic microangiopathy (TMA). Two patients in the HSCT arm died.

Conclusion

HSCT using a low intensity regimen results in meaningful reduction in endoscopic disease activity with some patients experiencing resolution of ulceration. However, the incidence of serious adverse events makes the regimen used in this trial unsuitable for future clinical use.

This project (15/178/09) is funded by the Efficacy and Mechanism Evaluation (EME) Programme, an MRC and NIHR partnership. The views expressed in this publication are those of the author(s) and not necessarily those of the MRC, NIHR or the Department of Health and Social Care.

10.1136/gutjnl-2021-BSG.6

OFR-10

ADMISSION MODEL FOR INTENSIFICATION OF THERAPY IN ACUTE SEVERE COLITIS (ADMIT-ASC)

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10.1136/gutjnl-2021-BSG.7

Introduction

Acute severe colitis (ASC) is an important cause of morbidity and mortality in UC, requiring hospitalisation and often colectomy. Accepted management is protocolised response assessment at Day 3 of IV steroid treatment. If steroid non-responders could be identified at all earlier stage, intensification may be possible prior to Day 3. It is also unclear whether ASC outcomes have changed over the past 25 years and we aimed to examine this.

Methods

We examined ASC cohorts across 3 continents to produce an accurate predictor of steroid response. All patients received protocolised treatment including first-line IV corticosteroids, and endoscopic (UCEIS) scoring. Factors associated with rescue therapy, colectomy during admission, and the following year, and a composite measure of steroid response were identified by logistic regression in 131 adult ASC admissions in Oxford, UK, between 2015-9.
Epigenetic alterations in IBD: defining filgotinib efficacy in patients with ulcerative colitis

Results We report 137 differentially methylated positions (DMP) in whole blood in IBD, including VMP1/MIR21 (p=9.11×10^-15) and RPS6KA2 (6.43×10^-13); with consistency seen across Scandinavia and UK. Cell of origin analysis preferentially implicated the monoocyte lineage. Dysregulated loci demonstrated strong genetic influence, notably VMP1 (p=1.53×10^-15). Age acceleration is seen in IBD (coefficient 0.94, p=2.2×10^-14). Several immuno-active genes demonstrated highly significant correlations between methylation and gene expression in IBD, in particular OSM: IBD r= -0.32, p=0.77. Multi-omic integration of methylene, genome and transcriptome also identified specific pathways that associate with immune activation, response and regulation at disease inception. At follow up, a signature of 3 DMPs (TAPI, TESP1, RPTOR) associated with treatment escalation to biological agents or surgery (hazard ratio of 5.19 (CI:2.14-12.56, logrank p=9.70×10^-4).

Conclusion This study highlights the stability of the IBD-specific circulating methylome across regions with shared ancestry. Through integrative multi-omic analyses we identify key pro-inflammatory genes that are upregulated in IBD at inception. Furthermore, differential methylation within certain genes such as TAPI associate with disease course over time.

OMO-2 Filgotinib efficacy in patients with ulcerative colitis by line of therapy: phase 2B/3 selection results

INTRODUCTION Filgotinib (FIL) is a once-daily, oral, Janus kinase 1 preferential inhibitor. We assessed the efficacy of FIL in biologic (bio)-naïve and bio-experienced patients with UC, and in bio-experienced patients with failure of 1 or ≥2 biologics or 1 or 2 mechanisms of action (MoAs).

METHODS SELECTION (NCT02914522) was a phase 2b/3 double-blind, randomised, placebo-controlled trial comprising two induction studies and a maintenance study. Adults (18–75 years) with moderately to severely active UC were randomised 2:2:1 to FIL 200 mg, FIL 100 mg or placebo (PBO) once daily for 11 weeks in Induction Study A (bio-naïve) and B (bio-experienced). Patients in either clinical remission or Mayo Clinic Score (MCS) response at week 10 (responders) could enter the Maintenance Study. Responders who received induction FIL were re-randomised 2:1 to continue their induction regimen or PBO through week 58. Responders who received induction PBO continued PBO. We assessed clinical remission and MCS response at weeks 10 and 58 in bio-naïve patients and bio-experienced patients with failure of 1 or ≥2 biologics and 1 or 2 MoAs (TNF antagonists and vedolizumab). All p values for subgroup analyses are nominal.

Results Week 10 clinical remission was achieved by a significantly higher proportion of bio-naïve and -experienced patients treated with FIL 200 mg than PBO. A higher proportion of bio-experienced patients with 1 biologic or MoA failure treated with FIL 200 mg than PBO achieved clinical remission.