10.7861/clinmed.22-4-s22

Predicting outcomes for Crohn's disease using a molecular biomarker: profile trial

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Introduction

Crohn's disease (CD) and ulcerative colitis (UC), the two major forms of inflammatory bowel disease (IBD), collectively affect 0.8% of the population in the UK.[1] IBD can have a profound health and socio-economic impact on patients, typically affecting educational achievement, relationships and employment.[1] However, the course of IBD varies substantially between individuals and accurate prognostic markers have historically not been available to guide clinical practice.[3] It has, therefore, become widely recognised that no single treatment strategy would be optimal for all patients.[4] Accordingly, there has been an aspiration for a more personalised approach in IBD, being named one of the key research priorities by a research priority-setting partnership group, which included patients, clinicians and other key stakeholders.[5,6]

Previously, our group has described a transcriptional signature detectable within peripheral blood CD8 T-cells at diagnosis, identifying two subgroups of patients, correlating with subsequent disease course.[7,8] We have sought to develop a biomarker that could re-capitulate the previously identified prognostic CD8 subgroups and then assess whether such a biomarker could improve clinical outcomes by appropriately matching therapy to disease course for individual patients.

Methods

From a training cohort of 69 newly diagnosed IBD patients, we simultaneously obtained a whole-blood PAXgene® RNA tube and peripheral-blood CD8 T-cell sample. Gene expression in both samples was measured by microarray. Statistical modelling was used to identify a transcriptional classifier in whole-blood gene expression data re-capitulating the CD8 findings and optimised into a multi-gene qPCR assay with independent validation in a second, independent cohort of 123 newly diagnosed patients.

The PROFILE trial has incorporated this classifier to compare relative efficacy of 'top-down' and 'accelerated step-up' therapy between biomarker-defined subgroups of 400 patients with newly diagnosed Crohn's disease.[9] PROFILE is assessing outcomes that have consistently been reported as important to patients: clinical remission and avoidance/reduction of steroids and surgery, as well as quality of life. Alongside the trial, a formal health economic analysis is being conducted, as well as a national evaluation by the National Institute for Health and Care Excellence (NICE). If clinical utility is demonstrated, then it is anticipated that this biomarker-stratified approach could be implemented into routine clinical care.

Results

Following application of statistical learning methods described, a 17-gene qPCR assay was developed and optimised. In the validation cohort, 123 patients could be classified into two distinct subgroups: IBD^{hi} (high risk) and IBD^{lo} (lower risk). Irrespective of the underlying diagnosis, IBD^{hi} patients experienced significantly more aggressive disease than IBD^{lo} patients, with earlier need for treatment escalation (hazard ratio 2.65 (CD) and 3.12 (UC)).[10] Subsequently, this biomarker has been used to stratify therapy in the PROFILE trial (395 enrolled), where recruitment has completed and follow-up due for completion in December 2022.

Conclusion

We have developed, optimised and validated a whole-blood qPCR classifier that predicts disease course from diagnosis in patients with IBD. This classifier is currently being assessed in the PROFILE trial, the first biomarker-stratified trial in gastroenterology and, if clinical utility of a stratified treatment approach is demonstrated, this would represent a major step towards personalised therapy in IBD. ■

Funding statement

This trial is funded by the Wellcome Trust via an investment in PredictImmune (200448/Z/16/Z).

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