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Distinct biological profiles associated with the risk of short-term relapse and mid/long-term relapse in Crohn's disease patients stopping infliximab

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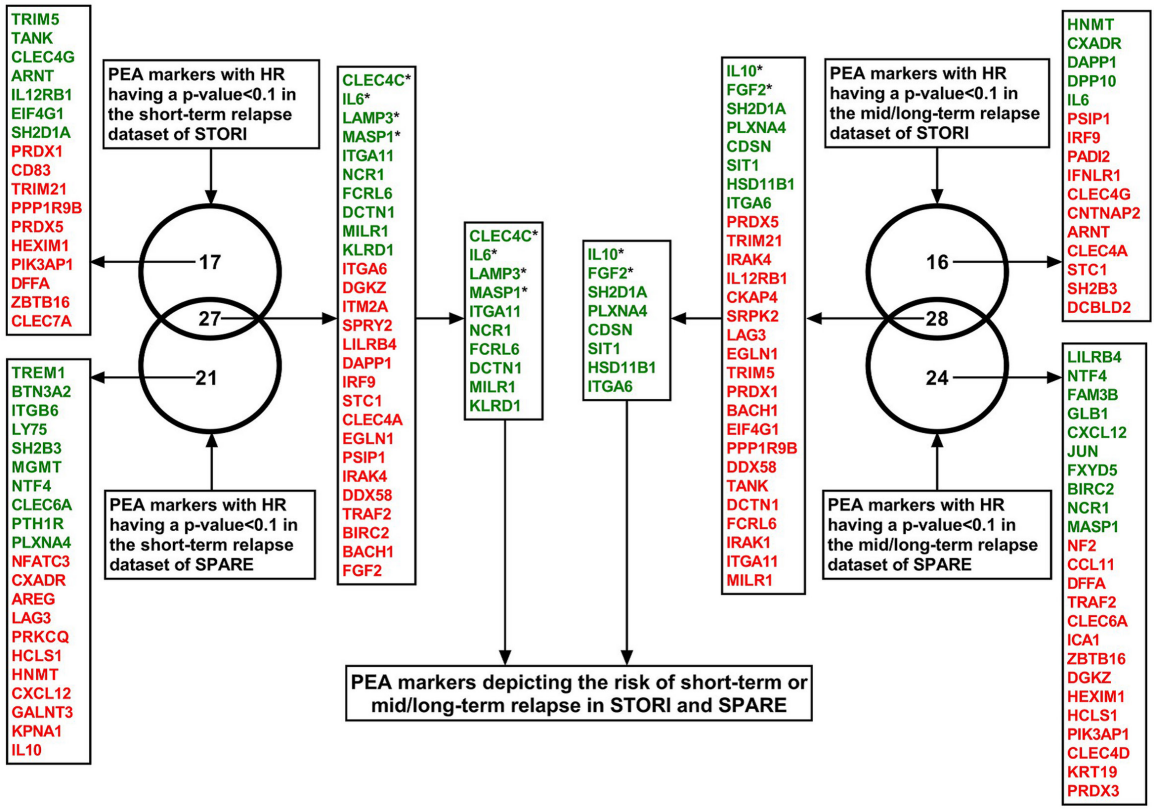
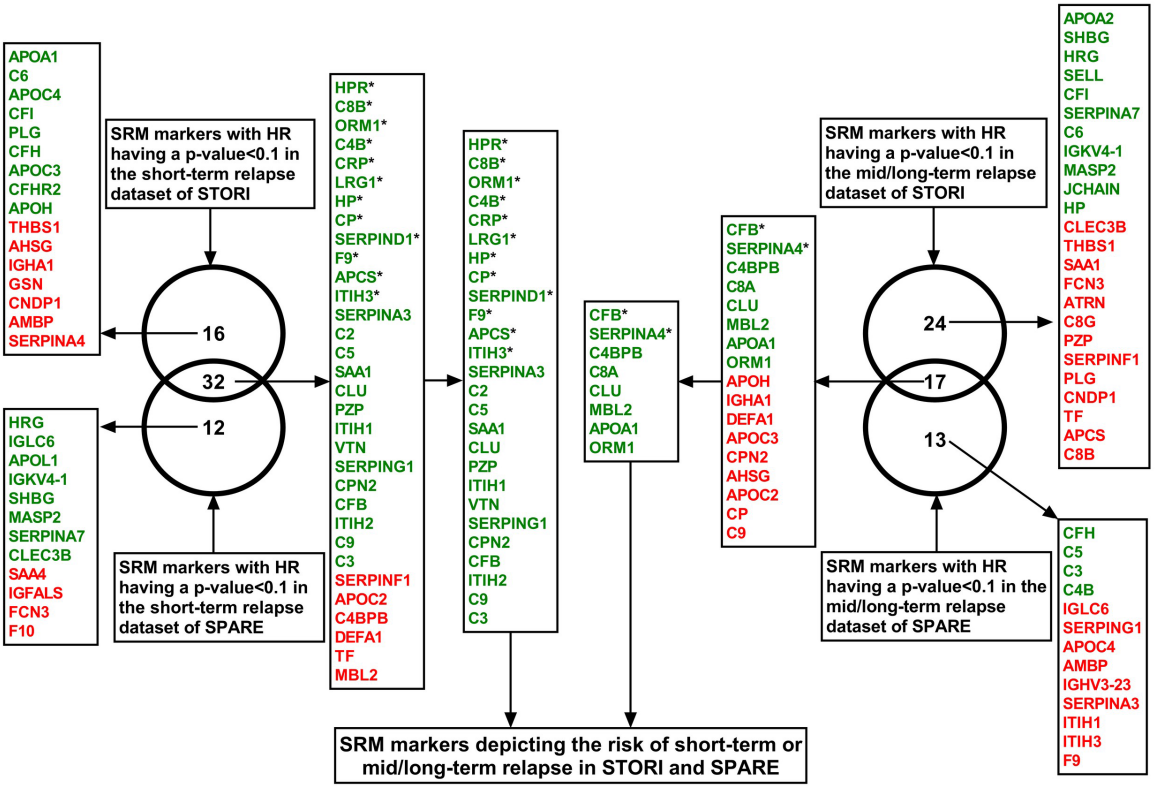
Background: In Crohn's disease (CD) patients stopping infliximab (IFX), the risk of short-term relapse (<6 months) and mid/long-term (>6 months) relapse were associated with distinct biological profiles (STORI trial). Herein, we aim to test the external validity of this finding in an independent trial (SPARE).

Methods: The SPARE trial has included 211 CD patients (from 64 sites in Europe and Australia) in steroid-free remission >6 months, receiving a combined therapy (IFX and immunosuppressant (IS)) >8 months and who were then randomised in three arms: continuing combo, stopping IFX or stopping IS. The arm stopping IFX was used to externally validate our findings generated in the STORI trial. To this end, the measurement of 161 proteins obtained in the baseline serum of STORI was repeated in SPARE (arm stopping IFX) with the same technologies: selected reaction monitoring (SRM, 69 proteins measured in 67 patients) or proximity extension assay (PEA, 92 proteins measured in 63 patients). Associations between serum protein levels and time to relapse (HR: hazard ratio and its associated statistics) were determined by using univariable Cox model in the stratified (relapse <6 or >6 months) and non-stratified cohort.

Results: The blood proteins depicting the risk of short-term or mid/long-term relapse in STORI and SPARE were selected as shown Fig. 1 (SRM) and Fig. 2 (PEA). The representation of those markers in volcano plots clearly confirmed that short-term and mid/long-term relapsers present distinct biological profiles (Fig. 3-4). This is also corroborated by the fact that only ORM1 was selected as a marker of short-term and mid/long-term relapse (Fig. 1-2). In STORI and SPARE, the risk of short-term relapse was associated (p-value<0.05) with a high serum level of inflammatory markers (IL6, CRP, HPR, ORM1, LRG1, HP, CP, APCS, ITIH3), complement components (C8B, C4B), blood coagulation proteins (F9, SERPIND1), markers of dendritic cells (LAMP3, CLEC4C) and a low serum level of a complement component (MASP1) (Fig. 1-2-3). In STORI and SPARE, the risk of mid/long-term relapse was associated (p-value<0.05) with a high serum level of a complement component



Hazard ratio (HR) with the same direction in STORI and SPARE
HR with an opposite direction in STORI and SPARE
*p-value <0.05 in STORI and SPARE



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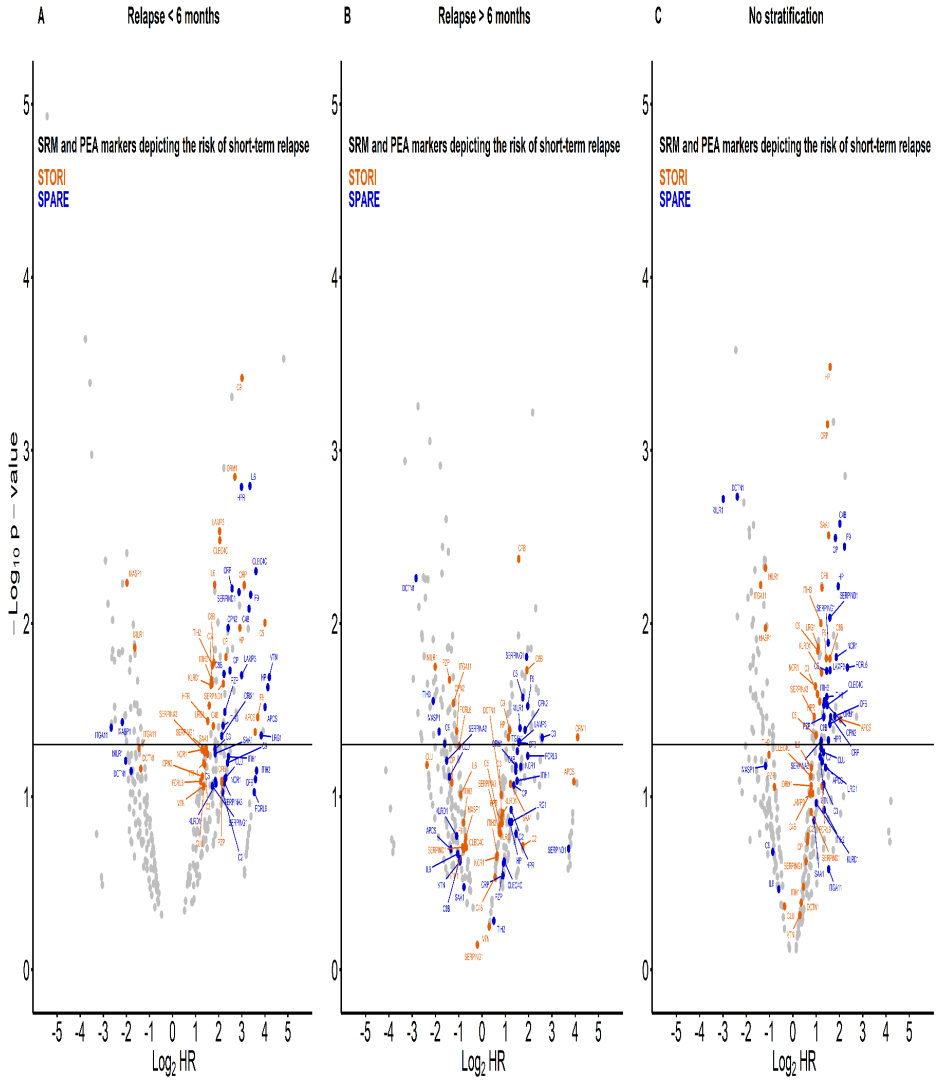

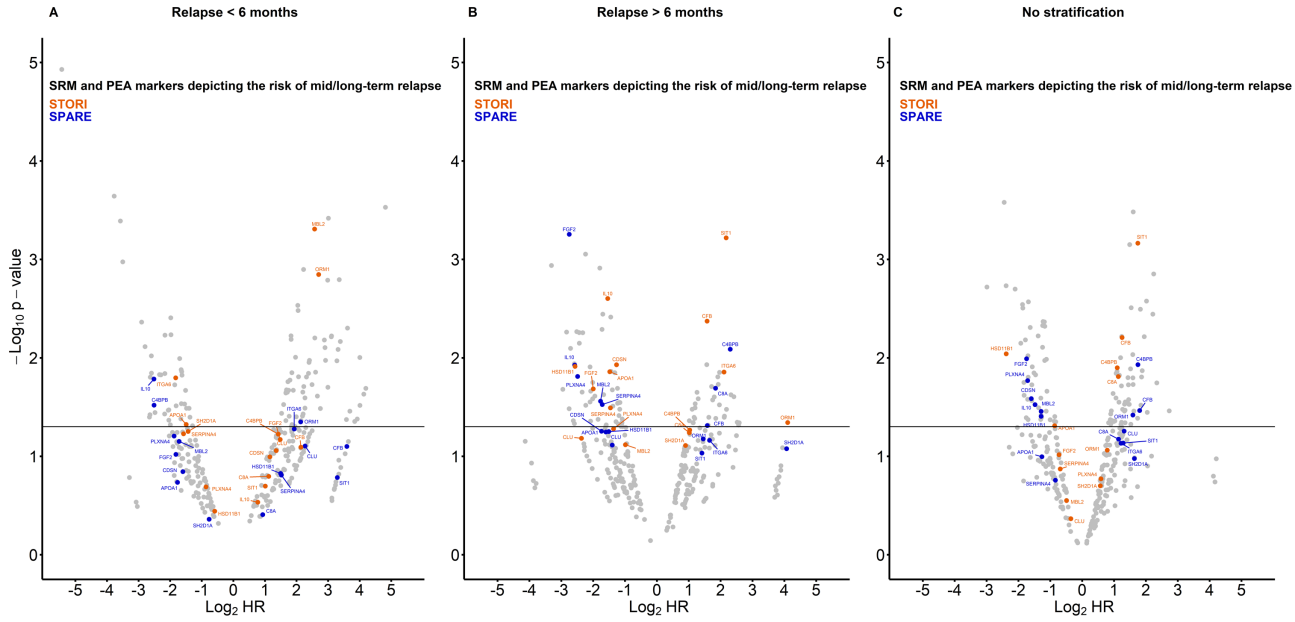

(CFB) and a low serum level of a protease inhibitor (SERPINA4), a growth factor (FGF2), an anti-inflammatory cytokine (IL10) (Fig. 1-2-4). For other proteins, STORI and SPARE showed convergent tendencies (p-value<0.01; Fig. 1-2-3-4) or differences (Fig. 1-2).

Conclusion: We confirm that, after stopping IFX in CD patients, the risk of short-term and mid/long-term relapse are associated with distinct biological profiles. The risk of short-term relapse is deeply associated with residual inflammation while the biological picture depicting the risk of mid/long-term relapse seems less clear.