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Carriage of the HLA-DQA1*05 allele is associated with a high risk of loss of response to adalimumab in patients with Crohn's disease

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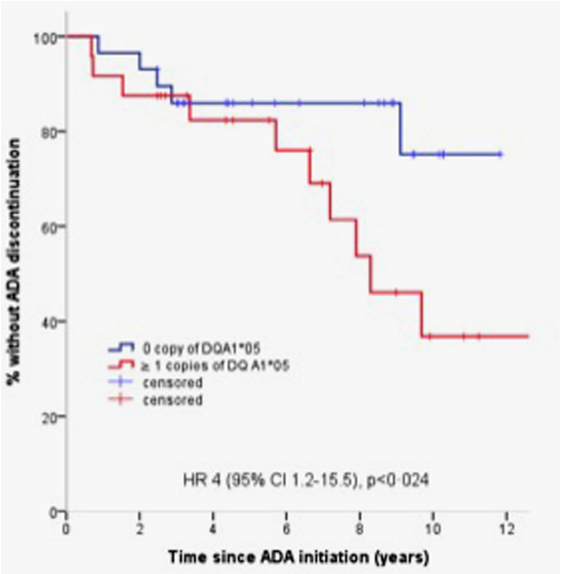
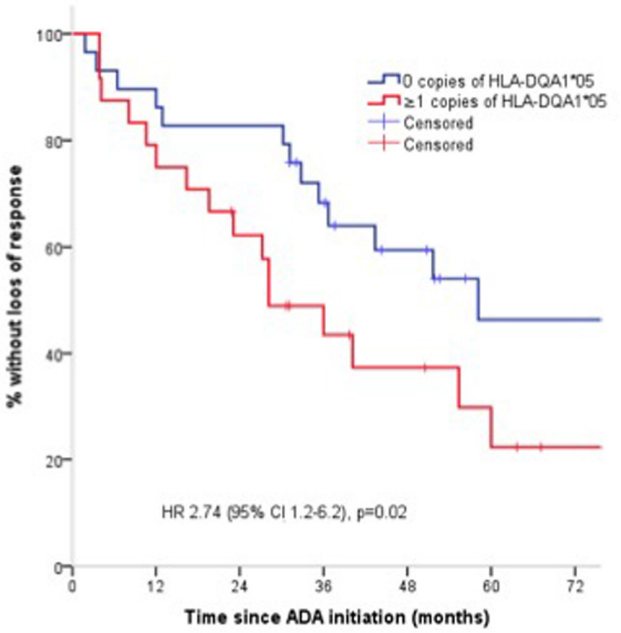
Background: Loss of response (LOR) to tumour necrosis factor antagonists (anti-TNF) occurs in up to 50% of patients with inflammatory bowel disease (IBD). The ability to predict which patients are likely to lose response would allow therapies to be tailored to the patient's characteristics. Immunogenicity is a common cause of LOR. Recently, a GWAS performed using the PANTS cohort demonstrated that carriage of one or more HLA-DQA1*05 alleles confers an increased risk of immunogenicity to anti-TNF therapy (Sazonovs et al. Gastroenterology 2019). We found that HLA-DQA1*05 carriage also identified patients at increased risk of clinical LOR to infliximab (Guardiola et al. ECCO 2019). The aim of our study was to know if carriage of a HLA-DQA1*05 allele is also associated with secondary LOR to adalimumab (ADA) in patients with Crohn's disease (CD).
Methods: This is a retrospective cohort study from a prospectively maintained data base. Patients were included if they had achieved response to ADA. LOR was defined as recurrence or worsening of IBD-related symptoms that required a change or intensification in treatment, hospitalisation or surgery. Independent predictors of LOR were identified using univariate and multivariable Cox proportional hazard regression.
Results: We included 53 patients with Crohn's disease, followed up to LOR (n = 31, 58%) or a median of 51 months (IQR 35–74). Forty-five per cent were carriers of an HLA-QA1*05 allele. HLA-DQA1*05 carriage was associated with LOR both, upon univariate analysis (HR 2.1 (95% CI 1.1–4.3), p = 0.04) and upon multivariate analysis, after adjusting for immunomodulators use, smoking status and BMI (HR 2.74 (95% CI 1.2–6.2), p = 0.02) (Figure 1). The cumulative persistence rates of ADA after adjusting for immunomodulators use was significantly lower in HLA-DQA1*05 carriers compared with non-carriers (HR 4 (95% CI 1.2–15.5), p = 0.02) (Figure 2).





Conclusion: HLA-DQA1*05 carriage is frequent and it is associated with a marked increase in the risk of LOR to ADA. HLA-DQA1*05 may become a clinically meaningful genetic marker that could allow for treatment to be tailored according to the risk of LOR, which is a step towards personalised medicine.

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Association of histologic-endoscopic mucosal healing after ustekinumab induction or maintenance therapy with 2-year outcomes in the UNIFI Phase 3 study in ulcerative colitis

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Background: Ustekinumab (UST) is an effective therapy for moderate-to-severe ulcerative colitis (UC). Histological and endoscopic improvement of mucosa after induction are associated with clinical remission and steroid-free clinical remission at maintenance Week 44. The association of histological-endoscopic mucosal healing after UST induction or maintenance therapy with 2-year outcomes in moderate-to-severe UC is not known.
Methods: In the UNIFI study of UST in moderate-to-severe UC, histological-endoscopic mucosal healing was defined as achieving both endoscopic improvement (Mayo endoscopy subscore ≤1) and histological improvement (i.e., neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue; based on the Geboes score). Associations of mucosal improvement after induction (irrespective of treatment) or UST maintenance with long-term efficacy of UST, disease severity, inflammation level,