HLA-DQA1*05 is associated with immunogenicity to anti-TNF therapy in biologic-naive patients with Crohn's disease

Short title:
HLA-DQA1*05 is associated with immunogenicity to anti-TNF therapy

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Abbreviations:
TNF, Tumor Necrosis Factor; HLA, Human Leucocyte Antigen; HR, Hazard ratio; PANTS, Personalising Anti-TNF Therapy in Crohn's disease; HRC, Haplotype Reference Consortium; MHC, Major Histocompatibility Complex; UC, ulcerative colitis; IBD-U, inflammatory bowel disease type-unclassified; AIC, Akaike information criterion

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Abstract

Background & Aims

Anti-tumor necrosis factor (anti-TNF) therapies are the most widely used biologic drugs for treating immune-mediated diseases. Nonetheless, repeated administration can induce the formation of anti-drug antibodies. The ability to identify patients at increased risk of immunogenicity would facilitate the choice of anti-TNF treatment and the use of preventative strategies.

Methods

We performed a genome-wide association study to identify variants associated with time to immunogenicity in a discovery cohort of 1240 biologic-naïve Crohn's disease patients starting infliximab or adalimumab. Immunogenicity was defined as an anti-drug antibody titer ≥10 AU/ml using a drug tolerant ELISA assay. Replication of significant association signals was sought in a cohort of 178 patients with inflammatory bowel disease.

Results

The Human Leukocyte Antigen (HLA) allele, HLA-DQA1*05, carried by approximately 40% of Europeans, significantly increased the rate of immunogenicity (hazard ratio [HR], 1.90; 95% CI, 1.60-2.25; P=5.88×10^{-13}). The highest rates of immunogenicity, 92% at 1 year, were observed in patients treated with infliximab monotherapy who carried HLA-DQA1*05; conversely the lowest rates of immunogenicity, 10% at 1 year, were observed in patients treated with adalimumab combination therapy who did not carry HLA-DQA1*05. We confirmed this finding in the replication cohort (HR, 2.00; 95% CI, 1.35 to 2.98; P=6.60×10^{-4}). This association was consistent for patients treated with adalimumab (HR, 1.89; 95% CI, 1.32-2.70) and infliximab (HR, 1.92; 95% CI, 1.57-2.33), and for patients treated with anti-

TNF therapy alone (HR, 1.75; 95% CI, 1.37-2.22) or in combination with an immunomodulator (HR, 2.01; 95% CI, 1.57-2.58).

Conclusions

We report the first genome-wide significant association with immunogenicity to biologic drugs. A randomized controlled biomarker trial is required to investigate whether pre-treatment genetic testing for HLA-DQA1*05 improves clinical outcomes by directing the choice of anti-TNF and the use of combination therapy.

Keywords

PANTS, GWAS, loss of response, drug persistence, anti-drug antibody

Trial registration number

ClinicalTrials.gov identifier: NCT03088449

Background

Anti-tumor necrosis factor (anti-TNF) therapies are the most widely used biologics for treating immune-mediated diseases, and in 2018, accounted for a global expenditure in excess of $23.5 billion.[1] Repeated administration often induces the formation of anti-drug antibodies (immunogenicity) leading to treatment failure.[2]

Immunogenicity is more common in patients treated with infliximab (a murine-human chimeric monoclonal antibody) than adalimumab (a fully human monoclonal antibody) and is a major cause of low anti-TNF drug level, infusion reactions, and non-remission in patients with Crohn's disease.[2,3] Combination immunomodulator therapy reduces the risk of immunogenicity to both adalimumab and infliximab, and for infliximab, improves treatment outcomes.[2,4–6] Despite these benefits, many patients are still treated with anti-TNF monotherapy because of concerns about the increased risk of adverse drug reactions, opportunistic infections, and malignancies associated with combination therapy with immunomodulators.[7–9]

The ability to identify patients at increased risk of immunogenicity may influence the choice of anti-TNF treatment and the use of preventative strategies, including combination therapy with immunomodulators. However, our understanding of the cellular and molecular mechanisms underpinning immunogenicity to biologics is limited. Retrospective candidate gene studies have suggested variants in *FCGR3A*[10] and *HLA-DRB1*[11,12] increase susceptibility to immunogenicity to anti-TNF therapy. These associations did not achieve genome-wide significance and are yet to be independently replicated. Here, we report the first genetic locus robustly associated with immunogenicity to anti-TNF therapies.

Methods

The Personalising Anti-TNF Therapy in Crohn's disease (PANTS) study is a UK-wide, multicenter, prospective observational cohort reporting the treatment failure rates of the anti-TNF drugs infliximab (originator, Remicade [Merck Sharp & Dohme, UK] and biosimilar, CT-P13 [Celltrion, South Korea]), and adalimumab (Humira [Abbvie, USA]) in 1610 anti-TNF-naïve patients with Crohn's disease.[2]

At inclusion, subjects were aged six years or over and had active luminal Crohn's disease involving the colon and/or small intestine. Choice of anti-TNF drug and use of concomitant immunomodulator therapy was at the discretion of the treating physician as part of usual care. Patients were initially studied for 12 months or until drug withdrawal. In the first year, study visits were scheduled at first dose, post-induction (weeks 12-14), weeks 30, 54, and at treatment failure. For infliximab-treated patients, additional visits occurred at each infusion. After 12 months, patients were invited to continue follow-up for a further two years. Drug persistence was defined as the duration of time from initiation of anti-TNF therapy to exit from the study due to treatment failure. Patients who exited the study for other reasons, declined to participate in the two-year extension, or were lost to follow-up were censored at the time of last drug dose or study visit.

At each visit, serum infliximab or adalimumab drug and anti-drug antibody levels were analyzed using total antibody enzyme linked immunosorbent assays.[13] See the Supplementary Appendix for a detailed description of drug and anti-drug antibody testing. The total antibody, unlike the more commonly reported free antibody assay, includes a drug-antibody disassociation step that allows the assessment of anti-drug antibodies in the

presence of drug. We defined immunogenicity as an anti-drug antibody concentration of ≥10 AU/mL, irrespective of drug level, at one or more time points.

DNA was extracted from pre-treatment blood samples from 1524 individuals in the PANTS cohort and genotyping undertaken using the Illumina CoreExome microarray. See the Supplementary Appendix for a detailed description of the genetic analyses. We excluded individuals of non-European ancestry (identified using principal component analysis), one individual from each related pair (defined as a pi-hat>0.187), and those with an outlying number of missing or heterozygous genotypes. 1323 individuals remained in the study following quality control, of which 1240 had drug and anti-drug antibody level data available (Figure S2 in the Supplementary Appendix). With its case-control design, our study has more than 80% power to detect genome-wide significant evidence of association ($\alpha = 5\times10^{-8}$) to variants with a minor allele frequency greater than 22% and a relative risk more than 1.4 (Figure S3 in the Supplemental Appendix).[14] Baseline demographics for these patients are shown in Table S1 in the Supplementary Appendix.

Variants with a genotype call rate of <95%, or with significant evidence of deviation from Hardy-Weinberg equilibrium ($P<1\times10^{-10}$) were excluded. Single nucleotide polymorphisms were imputed via the Sanger Imputation Service using the Haplotype Reference Consortium (HRC) panel, and 7 578 947 variants with an information content metric (INFO) score $\geq$ 0.4 were subsequently taken forward for analysis.[15] Human leukocyte antigen (HLA) types were imputed at 2-, and 4-digit resolution for the following loci: *HLA-A*, *HLA-C*, *HLA-B*, *HLA-DRB1*, *HLA-DQA1*, *HLA-DQB1*, and *HLA-DPB1*. Long-read sequencing of these HLA alleles was undertaken to assess the accuracy of our imputation.

We assembled an independent cohort to replicate significant findings from the discovery cohort. This comprised 107 Crohn's disease, 64 ulcerative colitis (UC), and 7 inflammatory bowel disease type-unclassified (IBD-U) patients with cross-sectional drug and anti-drug antibody levels measured as part of routine clinical practice. The samples were genotyped using either the Illumina CoreExome array (N=164)[16] or the Affymetrix 500k array (N=14).[17] Quality control and imputation methods were the same as in the discovery cohort.

Statistical analysis

Rates of immunogenicity were estimated using the Kaplan-Meier method. Clinical outcomes and genetic association tests with time to anti-drug antibody development were performed using multivariable Cox proportional hazards regression: sex, drug type (infliximab or adalimumab), immunomodulator use, and the first within-sample principal component, were included as covariates (See Table S3 in the Supplementary Appendix). Patients who did not develop immunogenicity during the study were censored at the point of last observation. Post-hoc sensitivity analyses were undertaken to test our genetic findings with immunogenicity, firstly, at progressively higher antibody thresholds; secondly, to simulate a free-antibody assay and thirdly, excluding patients with a single anti-drug antibody level $\geq$ 10 AU/ml and subsequent negative anti-drug antibodies <10 AU/ml.

The Akaike information criterion (AIC) was used to compare non-nested models to assess if the mode of inheritance was dominant or additive, and to determine whether HLA allele group, specific HLA alleles, or amino acid sequence best explained the association. The fixed effects Q statistic was used to perform tests of heterogeneity of effect; this test is an

extension of Cochran's Q-test and examines whether the observed effect size variability is larger than expected by chance. Interaction tests of the differential effects of drug type (infliximab vs adalimumab and Remicade vs CT-P13) and combination therapy (immunomodulator vs no immunomodulator) conditional on the genotype were performed. Mann-Whitney U tests were used to compare serum levels of anti-drug antibodies at week 54 stratified by anti-TNF drug and immunomodulator use.

Ethics

The South West Research Ethics committee approved the study (REC reference: 12/SW/0323) in January, 2013. Patients were included after providing informed, written consent. The protocol is available online (www.ibdresearch.co.uk).

Results

Within the first 12 months, 44% of patients developed anti-drug antibodies (95% CI, 0.41 to 0.48), and 62% of patients did so within 36 months (95% CI, 0.57 to 0.67). After correcting for immunomodulator use, the rate of immunogenicity was greater in patients treated with infliximab (N=742) than adalimumab (N=498) (hazard ratio (HR), 3.21; 95% CI, 2.61 to 3.95; $P=1.18\times10^{-28}$). In a model including drug-type as a covariate, rates of immunogenicity were greater in patients treated with anti-TNF monotherapy (N=544) compared to combination therapy with immunomodulators (N=696), (HR, 2.30; 95% CI, 1.94 to 2.75; $P<6.10\times10^{-21}$).

A locus within the HLA region is associated with time to immunogenicity

We identified a genome-wide significant association on chromosome 6 with time to development of immunogenicity, with the most associated SNP, rs2097432 (b38_pos: 6:32622994; HR, 1.70; 95% CI, 1.48 to 1.94; $P=4.24\times10^{-13}$), falling within the major histocompatibility complex (MHC) region (Fig. 1 and Figure S4-5 in the Supplementary Appendix). We replicated this association in our independent cohort of 178 patients with IBD (HR, 1.69; 95% CI, 1.26 to 2.28; P=8.80×10-4). A variant on chromosome 11, rs12721026 (b38_pos: 11:116835452; HR, 0.46; 95% CI, 0.33 to 0.63; $P=4.76\times10^{-8}$) also reached genome-wide significance in our discovery analysis, though the association was not replicated in our independent cohort (HR, 0.85; 95% CI, 0.49 to 1.44; P=0.51).

Fine-mapping of the signal in the HLA region

At the HLA allele group level (2-digit resolution), only HLA-DQA1*05 achieved genome-wide significance (HR, 1.90; 95% CI, 1.60 to 2.25; $P=5.88\times10^{-13}$) (Fig. 2). At the specific allele level (4-digit resolution), no single allele reached genome-wide significance. The two most common HLA-DQA1*05 subtype alleles, HLA-DQA1*05:01 (HR, 1.57; 95% CI, 1.33 to 1.85; $P=4.24\times10^{-7}$) and HLA-DQA1*05:05 (HR, 1.48; 95% CI, 1.24 to 1.78; $P=5.54\times10^{-5}$), had similar effects on time to immunogenicity and a model containing these two 4-digit alleles was virtually indistinguishable from a model including only HLA-DQA1*05 ($AIC_{05}=6659.07$ versus $AIC_{05:01\&05:05}=6659.50$). We did not identify any amino acids that better fit the data than HLA-DQA1*05. We observed >99% concordance between imputed and sequenced HLA genotypes at *HLA-DQA1* (Table S4 in the Supplementary Appendix).

To formally assess the inheritance pattern of HLA-DQA1*05 mediated immunogenicity, we compared the fit of additive and dominant models and found that the dominant model gave a better fit (AIC_{DOM}=6652.12 vs AIC_{ADD}=6659.07), and stronger association signal for HLA-DQA1*05 (HR, 1.90; 95% CI, 1.60 to 2.25; P=5.88×10^{-13}) (Fig. 3 and Table S2 in the Supplementary Appendix). We also looked for non-additive effects across all other HLA alleles, but the model assuming a dominant effect for HLA-DQA1*05 remained the best fit to the data. The HLA-DQA1*05 association was confirmed in our replication cohort (entire cohort (HR, 2.00; 95% CI, 1.35 to 2.98; P=6.60×10^{-4}), Crohn's disease-only subset (HR=2.26, 95% CI: 1.33 to 3.84, p=0.003), and UC-only subset of the replication cohort (HR=2.02, 95% CI: 1.08-3.79 p=0.03), again with a better fit for the dominant model (AIC_{DOM}=942.51 vs AIC_{ADD}=944.81). After conditioning on HLA-DQA1*05 we did not identify any secondary signals of association with time to immunogenicity within the MHC region (Figure S6 in the Supplementary Appendix).

Sensitivity analyses showed that the effect size of HLA-DQA1*05 carriage on immunogenicity was similar across subgroups (Fig. 4A and 4B): firstly, when the threshold for defining immunogenicity was increased from 10AU/mL to $\geq$ 150 AU/mL. Secondly, when we simulated a drug-sensitive instead of a drug-tolerant assay, where immunogenicity was defined as an anti-drug antibody titer ≥10 AU/ml without detectable drug (HR, 1.57; 95% CI, 1.23-2.01; P = 3.66×10^{-4}). Thirdly, when we removed patients with a one-off transient anti-drug antibody level ≥10 AU/ml (HR, 1.94; 95% CI, 1.62-2.32; P = 8.46×10^{-13}).

The effect of HLA-DQA1*05 across drug and treatment regimes

While immunogenicity rates were lower with adalimumab-treated compared to infliximab-treated patients, we did not detect a significant difference in the effect of HLA-DQA1*05 on the immunogenicity rate for these two drugs (HR, 1.89; 95% CI, 1.32-2.70 in adalimumab-, HR, 1.92; 95% CI, 1.57-2.33 in infliximab-treated patients; P_{het}=0.91) (Fig. 5). We also found no significant evidence for heterogeneity of effect of HLA-DQA1*05 on immunogenicity between patients treated with the infliximab originator, Remicade, and its biosimilar CT-P13 (P_{het}=0.23) (Figure S7 in the Supplementary Appendix). Likewise, we did not detect any significant heterogeneity of effect of HLA-DQA1*05 carriage on immunogenicity for individuals on monotherapy (HR, 1.75; 95% CI, 1.37-2.22) versus combination therapy (HR, 2.01; 95% CI, 1.57-2.58) with immunomodulators (P_{het}=0.14). In addition, we did not identify any significant interactions between HLA-DQA1*05 and the clinical covariates (drug type: p=0.83; mono- vs combination therapy: p=0.71; Remicade vs CT-P13: p=0.59).

The highest rates of immunogenicity, 92% at 1 year, were observed in patients treated with infliximab monotherapy who carried HLA-DQA1*05 (Fig. 6A). Conversely, the lowest rates of immunogenicity, 10% at 1 year, were observed in patients treated with adalimumab combination therapy who did not carry HLA-DQA1*05 (Fig 6B). Our final model, which includes HLA-DQA1*05 status, sex, drug, and immunomodulator usage, explained 18% of the variance in immunogenicity to anti-TNF in our cohort.

Having demonstrated that HLA-DQA1*05 was associated with time to immunogenicity, we sought associations with anti-drug antibody titers after one year of treatment and

subsequent non-persistence on drug. Carriage of HLA-DQA1*05 was associated with higher maximal anti-drug antibody titers ($P_{infliximab} = 8\times10^{-10}$; $P_{adalimumab} = 0.002$). We observed lower drug persistence rates to year three in patients treated with an anti-TNF drug without an immunomodulator (Fig. 7A and 7B); the optimal model here used the interaction between immunomodulator use and HLA-DQA1*05 (DQA1*05: HR, 1.40; 95% CI 1.08-1.80; P=0.011, immunomodulator use: HR, 0.74; 95% CI, 0.58-0.94, P=0.014, interaction between DQA1*05 and immunomodulator use: HR, 0.65; 95% CI, 0.45-0.95; P=0.026).

Discussion

Immunogenicity to biologic therapies is a major concern for patients, regulatory authorities, and the pharmaceutical industry. We report the first genome-wide significant association with immunogenicity to anti-TNF therapy using the largest prospective cohort study of infliximab and adalimumab in Crohn's disease. We have demonstrated that carriage of one or more HLA-DQA1*05 alleles confers an almost two-fold risk of immunogenicity to anti-TNF therapy, irrespective of concomitant immunomodulator use or drug type (infliximab [Remicade or CT-P13], or adalimumab). Fine-mapping and confirmatory sequencing of the HLA identified that the specific alleles HLA-DQA1*05:01 and HLA-DQA1*05:05 mediated most of this risk. Carriage of HLA-DQA1*05 was associated with higher anti-drug antibody levels and lower drug persistence rates, although further studies are needed to more accurately quantify the relationship between HLA-DQA1*05 and the risk of anti-TNF treatment failure.

Based on our data in patients with luminal Crohn's disease, all patients treated with an anti-TNF should be prescribed an immunomodulator to lower the risk of immunogenicity. We

hypothesize that for patients who carry HLA-DQA1*05 in whom immunomodulators are contraindicated or not tolerated, clinicians might advise against the use of anti-TNF drugs, particularly infliximab. This is because 90% of patients who carry HLA-DQA1*05 who are treated with infliximab monotherapy have evidence of immunogenicity by week 54. In contrast, patients who do not carry HLA-DQA1*05 might be given the choice between adalimumab or infliximab combination therapy. Patients without the risk allele and a history of adverse drug reactions to thiopurines and/or methotrexate or who are at high risk of opportunistic infections might be spared the additional risks of combination therapy and treated with adalimumab monotherapy. A randomized controlled biomarker trial is required to explore these hypotheses and confirm whether HLA-DQA1*05 testing may help direct treatment choices in order to improve clinical outcomes.

The shared genetic association between HLA-DQA1*05 and immunogenicity to infliximab and adalimumab may explain the widely reported diminishing returns of switching between anti-TNF therapies at the time of loss of response.[18,19] If the immunogenic effect of HLA-DQA1*05 extends to other therapeutic antibodies, then subjects who carry the variant may be candidates for non-antibody modality therapies, such as small molecule drugs.

Allelic variation in the *HLA-DQA1* gene has been linked to aberrant adaptive immune responses. The HLA class II gene *HLA-DQA1* is expressed by antigen presenting cells and encodes the alpha chain of the HLA-DQ heterodimer that forms part of the antigen binding site where epitopes are presented to T-helper cells. Relevant to immunogenicity, carriage of HLA-DQA1*05 has been associated with celiac disease, type 1 diabetes, and protection

against rheumatoid arthritis and pulmonary tuberculosis.[20–24] Several hypotheses have been proposed, but exactly how specific HLA alleles contribute to disease pathogenesis or, in this case, increased immunogenicity, remains unknown.

HLA-DQ1A*05 may serve as a useful biomarker of immunogenicity risk and may impact how the next-generation of anti-TNF drugs are designed to minimize HLA-DQA1*05 mediated immunogenicity. Previous studies have shown that it is possible to map and eliminate potential immunogenic T cell epitopes with the aim of producing safer and more durable biologic drugs.[25,26] However, caution needs to be exercised to ensure protein sequence modifications designed to reduce the risk of immunogenicity to patients carrying HLA-DQA1*05 do not put a different group of patients at risk.

Multiple assays are available to detect anti-drug antibodies and there is no universally accepted, validated threshold to diagnose immunogenicity. We deliberately chose a total, or drug tolerant assay, that permits the measurement of anti-drug antibodies in the presence of drug, in order to minimize the number of false negative patients assigned to the control group. We then validated the manufacturer's positivity threshold in independent experiments in 500 drug-naïve controls and confirmed that the recommend cut-off of 10 AU/mL corresponds to the 99th centile of the anti-drug antibody titer distribution. In support of this threshold we have recently demonstrated that even modestly elevated anti-drug antibodies levels (10-30 Au/ml) at weeks 14 and 54 of treatment are associated with lower drug levels at these time points, and non-remission at week 54.[2] In addition, sensitivity analyses confirmed that the association and effect size between HLA-DQA1*05 and immunogenicity remained at progressively higher diagnostic thresholds for

immunogenicity, when we simulated a free-assay, and when we removed patients with transient antibodies. Finally, HLA-DQA1*05 was associated with the quantitative trait of maximal anti-drug antibody titer.

We acknowledge several important limitations of this study. Firstly, we may have underestimated the contribution of HLA-DQA1*05 to immunogenicity because of the short duration of follow-up in patients who did not continue in the study beyond the first year. Secondly, because we designed a schedule of visits to minimize patients' inconvenience, there were fewer assessments for those treated with adalimumab than infliximab. As a result, we might have underestimated rates of immunogenicity amongst adalimumab-treated patients.

Our genome-wide association study was limited to patients with luminal Crohn's disease of European descent. Given that HLA-DQA1*05 is not associated with IBD risk[27] the percentage of carriers among our patients (39%) was similar to that reported in an independent British population cohort (38%).[28] As such, we hypothesize that HLA-DQA1*05 will make a similar contribution to anti-TNF immunogenicity in other patient populations where the allele is not associated to disease susceptibility (e.g. ankylosing spondylitis, perianal Crohn's disease). Due to the wide variation in the frequency of HLA-DQA1*05 across ethnic groups,[28] further studies are required to assess the contribution of HLA-DQA1*05 to immunogenicity across populations. Whether HLA-DQA1*05 is also associated with immunogenicity to other biologic drugs also needs to be determined.

Conclusion

We report the first genome-wide significant association with immunogenicity to biologic drugs. Carriage of HLA-DQA1*05 almost doubles the rate of anti-TNF anti-drug antibody development, independent of immunomodulator use, for both infliximab and adalimumab. To minimize the risk of immunogenicity, pre-treatment genetic testing for HLA-DQA1*05 may help personalize the choice of anti-TNF and the need for combination therapy with an immunomodulator.

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Figure Captions

Figure 1: **A regional plot of the association results with the MHC region on chromosome 6.** Midpoint positions of the HLA alleles across the MHC region are shown in red on the x-axis. SNPs that passed the genome-wide significance threshold ($P=5\times10^{-8}$) are shown above the red horizontal dashed line with the most significant SNP in red. SNPs correlated with the lead SNP ($r^2>0.05$) are color-coded from purple to yellow. Pairwise genotype correlation (r^2) between SNPs was calculated using genotype data from the non-Finnish European population of the 1000 Genomes Project.

Figure 2: **Effect sizes of the most strongly associated SNP, HLA alleles, and amino acids of time to immunogenicity.** Blue lines represent 95% CIs. Association test P-values are shown in parentheses

Figure 3: Kaplan–Meier estimator showing the rate of anti-drug antibody development, stratified by the number of HLA-DQA1*05 alleles carried. Orange, blue, and red indicate 0, 1, and 2 copies of DQA1*05 allele, respectively. Carriers of one or two copies of the allele have a similar rate of immunogenicity development, and a dominant model is a better fit for the data than an additive model ($AIC_{DOM}=6652.12$ vs $AIC_{ADD}=6659.07$). X-axis truncated at 700 days, due to the low number of observations for longer time periods.

Figure 4:
A Sensitivity analysis of the effect size of DQA1*05 association and time to immunogenicity

B Sensitivity analysis of the significance of DQA1*05 association and time to immunogenicity

In the primary analyses, immunogenicity was defined as an anti-drug antibody concentration ≥10 AU/mL, irrespective of drug concentration (red dot). We repeated the time to immunogenicity analysis varying this definition from ≥5 to ≥200 AU/mL.

Figure 5:
HLA-DQA1*05 has a consistent effect on immunogenicity in different patient subgroups. We repeated the proportional hazard association analysis, separating the full cohort into subgroups by drug and therapy type. Estimated hazard ratios and standard errors between the pairings were compared using a heterogeneity of effects test (P>0.05), suggesting that the effect of DQA1*05 on immunogenicity is not affected by these clinical covariates. Blue lines represent 95% CIs. Association test P-values are shown in parentheses

Figure 6:
A Anti-drug antibody development - infliximab
B Anti-drug antibody development - adalimumab

Kaplan–Meier estimator showing the rate of anti-drug antibody development (A and B), stratified by carriage of HLA-DQA1*05 alleles and treatment regime. Dotted lines indicate patients undergoing anti-TNF monotherapy; solid lines indicate combination therapy with

immunomodulators. Red indicates carriers of the HLA-DQA1*05 allele (1 or 2 copies); blue indicates non-carriers. For both drugs and treatment regimes, immunogenicity rates are higher for HLA-DQA1*05 carriers. The X-axis was truncated at 700 days due to the low number of observations.

Figure 7:
A Drug persistence - infliximab
B Drug persistence – adalimumab

Kaplan–Meier estimator showing the rate of drug persistence (A and B), stratified by carriage of HLA-DQA1*05 alleles and treatment regime. Dotted lines indicate patients undergoing anti-TNF monotherapy; solid lines indicate combination therapy with immunomodulators. Red indicates carriers of the HLA-DQA1*05 allele (1 or 2 copies); blue indicates non-carriers. For both drugs and treatment regimes, drug persistence rates are higher for HLA-DQA1*05 carriers. The X-axis was truncated at 700 days due to the low number of observations.