*HLA-C*06:02* genotype is a predictive biomarker of biologic treatment response in psoriasis

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Abstract

Background: Biologic therapies can be highly effective for the treatment of severe psoriasis but response for individual patients can vary according to drug. Predictive biomarkers to guide treatment selection could improve patient outcomes and treatment cost-effectiveness.

Objective: We sought to test whether *HLA-C*06:02*, the primary genetic susceptibility allele for psoriasis, predisposes patients to respond differently to the two most commonly prescribed biologics for psoriasis, adalimumab (anti-TNFα) and ustekinumab (anti-IL12/23).

Methods: The study utilises a national psoriasis registry that includes longitudinal treatment and response observations and detailed clinical data. HLA alleles were imputed from genome-wide genotype data for 1,326 patients for whom PASI90 response status (90% reduction in psoriasis area and severity index) was observed after 3, 6 or 12 months of treatment. We developed regression models of PASI90 response, examining the interaction between *HLA-C*06:02* and drug type (adalimumab or ustekinumab) while accounting for potentially confounding clinical variables.

Results: *HLA-C*06:02* negative patients were significantly more likely to respond to adalimumab than ustekinumab at all time-points (most strongly at 6m: odds ratio (OR) = 2.95, $P = 5.85\times10^{-7}$) and the difference was greater in *HLA-C*06:02* negative patients with psoriatic arthritis (PsA; OR = 5.98, $P = 6.89\times10^{-5}$). Biologic naive patients that were *HLA-C*06:02* positive and PsA negative demonstrated significantly poorer response to adalimumab at 12m (OR = 0.31, $P = 3.42\times10^{-4}$). Results from HLA-wide analyses were consistent with *HLA-C*06:02* itself being the primary effect allele. We found no evidence for genetic interaction between *HLA-C*06:02* and *ERAP1*.

Conclusion: This large observational study suggests that reference to *HLA-C*06:02* status could offer substantial clinical benefit when selecting treatments for severe psoriasis.

Clinical Implications

*HLA-C*06:02* is associated with differential response to adalimumab and ustekinumab in psoriasis patients. Together with psoriatic arthritis status, *HLA-C*06:02* status could inform optimal selection of first-line biologic therapy.

Capsule Summary

In a large observational study, psoriasis patients lacking the susceptibility allele *HLA-C*06:02* demonstrate significantly better response to adalimumab than ustekinumab. The effect is stronger than at other HLA alleles and varies with psoriatic arthritis status.

Key words: psoriasis, psoriatic arthritis, biologic therapy, genetics, pharmacogenetics, treatment response, HLA, adalimumab, ustekinumab, skin disease

Abbreviations used:

BAD	British Association of Dermatologists
BADBIR	BAD Biologic and Immunomodulators Register
BSTOP	Biomarkers of Systemic Treatment Outcomes in Psoriasis
GxE	gene-environment interaction
HLA	human leukocyte antigen
IL	interleukin
MHC	major histocompatibility complex
OR	odds ratio
PASI	psoriasis area and severity index
PsA	psoriatic arthritis
TNF	tumor necrosis factor

Introduction

Psoriasis is a chronic immune-mediated skin disease with a prevalence of up to 3% in developed nations[1]. It is responsible for a high global burden of disability[2] and the economic impact, in the United States alone, runs into the tens of billions of dollars[3]. Psoriasis is caused by a complex interplay of genetic and environmental factors not yet fully understood[4, 5], and molecular genetic studies have identified more than 60 genomic loci at which variation confers risk of the disease in European populations[6, 7].

In recent years the clinical management of psoriasis has been revolutionised by a series of highly effective monoclonal antibody therapies[8]. The most widely adopted of these biologics include adalimumab, which targets TNFα, and ustekinumab, which targets the p40 subunit common to IL-12 and IL-23 and thus inhibits downstream IL-17 signalling. Clinical trials demonstrate that 71% of moderate to severe psoriasis patients achieve a 75% reduction in psoriasis area and severity index (PASI75 response) after 16 weeks of adalimumab treatment, with 45% achieving the superior PASI90 response that is consistent with being "clear" or "nearly clear" of disease[9]. Similarly, ustekinumab induces a PASI75 response within 12 weeks for 67% of patients, and PASI90 response for 39% across dosing groups[10]. British Association of Dermatologists (BAD) guidelines recommend that in the absence of relevant contraindications both drugs should be considered equally as first-line biologic therapy for psoriasis, unless active psoriatic arthritis (PsA) is present in which case adalimumab is preferred[11]. Both drugs are indicated more widely for other immune-mediated inflammatory diseases[12].

Since individuals can respond differently to different biologics, there is great potential to improve patient outcomes and optimise use of these expensive therapies[13] through the identification of biomarkers that can inform which therapies are most likely to be efficacious. The MHC class I allele *HLA-C*06:02* is a promising candidate biomarker. *HLA-C*06:02* is the genetic variant that makes the largest contribution to psoriasis susceptibility: it accounts for more than 6% of variance in disease risk[14] and each copy of the *HLA-C*06:02* allele carried increases an individual's risk of psoriasis five-fold[15]. Its effect is modified by an interaction with genetic variants in the gene *ERAP1*, which encodes a peptide-trimming protein involved in MHC antigen presentation[15]. *HLA-C*06:02* status has also been reported to be associated with differences in clinical presentation of psoriasis, with *HLA-C*06:02* positive patients experiencing earlier onset, differences in lesion severity and distribution, higher incidence of the Koebner phenomenon and increased likelihood of exacerbation due to streptococcal throat infection[16-18]. These differences hint at distinct pathophysiologies and differential response to treatment might therefore be expected. Some evidence has recently accumulated in support of this, with several studies reporting better response

to ustekinumab among *HLA-C*06:02* positive patients than among *HLA-C*06:02* negative patients[19-21]. The relationship between *HLA-C*06:02* and response to anti-TNF agents is unclear[22].

With the aim of improving outcomes in individuals with moderate to severe psoriasis we therefore sought to test the hypothesis that *HLA-C*06:02* status is an effective predictive biomarker of response that could be used to inform treatment selection between the two most commonly used biologics, adalimumab and ustekinumab. As such, we have undertaken a retrospective evaluation of *HLA-C*06:02* as a predictive biomarker in a large prospective observational study of biologic interventions in the UK psoriasis population. Our primary definition of positive treatment response is achievement of PASI90, as it correlates with the clinically important status of "clear" or "nearly clear" of psoriasis[23]. We consider response at three, six and twelve months after treatment initiation. We consider secondary outcomes of PASI75 and PASI100 response.

Methods

Patient population

The study was conducted in accordance with the 2008 Declaration of Helsinki and in the spirit of the 1996 International Conference on Harmonisation in Good Clinical Practice. Ethical approval for this study was granted by The South East London REC 2 Ethics Committee (11/H0802/7). Written informed consent was obtained from all subjects prior to enrolment.

All participants are adults (>16 years) enrolled in the Biomarkers of Systemic Treatment Outcomes in Psoriasis study (BSTOP; https://www.kcl.ac.uk/lsm/research/divisions/gmm/departments/dermatology/Research/stru/groups/bstop/index.aspx) and the British Association of Dermatologists Biologic and Immunomodulators Register (BADBIR; www.badbir.org). BSTOP is a prospective observational study across 60 UK dermatology centres that includes biological sample collection. It aims to establish clinically relevant markers of outcomes to systemic therapies in severe psoriasis (study protocol: https://www.kcl.ac.uk/ContensisManagedLinks/BSTOP-Protocol-Version-5.pdf). BADBIR is a pharmacovigilance register that has recruited >16,000 psoriasis patients undertaking systemic conventional or biological therapy in the UK and Ireland. It seeks to assess the long-term safety of biologic treatments for psoriasis. Enrolment criteria for the biologic arm for both BSTOP and BADBIR include diagnosis and prescription of systemic therapy by a dermatologist.

Clinical data

Detailed clinical data are recorded by BSTOP and BADBIR at registration and at regular follow-up assessments during the course of routine clinical care. These data include demographics, psoriasis

area and severity index (PASI) assessments of disease severity, treatment details, adverse events and comorbidities. Clinical data were extracted on 1st July 2017. Data derived from BSTOP and BADBIR were merged, and processes were established to identify and resolve inconsistencies between data sources in collaboration with local clinical teams. For a minority of patients appropriate assumptions were employed to demarcate periods of treatment: treatment was considered ongoing where treatment episodes for the same biologic were separated by less than 90 days[24]; missing treatment end dates were imputed based on the start date of subsequent biologic treatment, allowing a 28 day washout period; and patients were considered to be continuing treatment at the data extract date where no end date was recorded. Age of psoriasis onset was inferred from the recorded year of onset. Patients were assumed to be positive for psoriatic arthritis (PsA) if reported at BADBIR registration or at any subsequent follow-up prior to the data extract date (92.8% diagnosed by a rheumatologist).

Genotype data and HLA imputation

DNA was isolated from blood using standard methods. Genotyping was performed using Illumina HumanOmniExpressExome-8 v1.2 and v1.3 BeadChips followed by quality control using standard tools[25-28] and procedures as detailed in **Supplementary Methods**. The final dataset was limited to patients of European ancestry. Classical HLA alleles were imputed using SNP2HLA (v1.0.3), based on the T1DGC reference panel[29]. We excluded poorly imputed alleles ($R^2 < 0.9$) and alleles with frequency <0.01, giving a total of 142 distinct 2- and 4-digit imputed alleles.

Data integration and definition of response

Patients with both genotype data and response data for the first course of treatment for either drug (adalimumab or ustekinumab) were considered for analysis. Patients were required to have a baseline PASI score (up to six months prior to treatment initiation) of >10, and a response PASI score recorded sufficiently close to at least one response time-point (±30 days from 3m; ±60 days from 6m and 12m time-points) while still on treatment. 101 patients with eligible records for both treatments were randomly assigned to the adalimumab or ustekinumab groups (50/51 patients respectively), with their other record being excluded from the analysis. This did not materially impact results (**Table E18**). The final integrated dataset included observations for 1,326 patients.

For each patient observed at each response time-point, PASI90 response was achieved if the response PASI score represented a reduction of 90% or more relative to baseline PASI. Secondary responses of PASI75 and PASI100 were defined similarly.

Statistical modelling

All statistical models were implemented in R[27, 30]. Associations between patient characteristics and drug type were established via regression modelling (linear regression for continuous characteristics; logistic regression for binary characteristics) with drug type (adalimumab vs ustekinumab) as the sole explanatory variable. Associations with *HLA-C*06:02* were established using regression models based on imputed *HLA-C*06:02* dosage with five ancestry PC covariates based on 108,319 independent SNPs genome-wide[26, 31, 32].

At each response time-point, multivariable logistic regression modelling was employed with binary PASI90 response as the dependent variable (PASI75/PASI100 for secondary outcomes) and baseline PASI as a covariate. Drug type and *HLA-C*06:02* dosage were included as main effects and as a drug × *HLA-C*06:02* interaction term: a statistically significant non-zero interaction effect would implicate *HLA-C*06:02* as a predictive biomarker. To generate the full multivariable model accounting for potential clinical confounders, main effect and interaction covariate terms were added based on correlations with *HLA-C*06:02* or drug (**Table 1**). For variables significantly correlated with *HLA-C*06:02* (age of onset, baseline PASI, disease duration and PsA), an interaction term with drug was included, and for variables significantly correlated with drug (PsA and biologic naive status) an interaction term with *HLA-C*06:02* was included. The full model is described in **Supplementary Methods**. Missing observations for age of onset or PsA status covariates were replaced by mean-imputed values derived from *HLA-C*06:02*-positive and negative subgroups. Models of response were fitted within *HLA-C*06:02*- and PsA-defined subgroups; these included a term for drug type and a covariate term for baseline PASI only.

To confirm that our full multivariable model adequately controlled for potential confounding via covariates influencing treatment selection, we repeated the regression analysis with inverse probability of treatment weighting using the propensity score[33]. Weighted regression was implemented using the 'survey' package in R[34]. See **Supplementary Methods** for full details.

HLA-wide analysis was performed for 142 2- and 4-digit alleles having a frequency >1% in our full genotyped cohort of 3,320 patients. The full interaction model was fitted based on imputed dosage for each allele in turn, substituting the *HLA-C*06:02* main effect and interaction terms. Conditional analysis was performed by including main effect and interaction terms for both *HLA-C*06:02* and the alternative alleles.

ERAP1 interaction analysis was based on the genotyped variant rs27524[15]. Psoriasis susceptibility epistasis was confirmed via case-only association testing in the full cohort of 3,320 patients, treating *HLA-C*06:02* status as a binary trait. To test for interaction with respect to adalimumab and ustekinumab response, the full GxE interaction model was supplemented with a

main effect term for rs27524 genotype, first-order interaction terms rs27524 genotype × *HLA-C*06:02* dosage and rs27524 genotype × drug, and second-order interaction term rs27524 genotype × *HLA-C*06:02* dosage × drug. Power analysis for the *ERAP1* interaction test conducted in the *HLA-C*06:02*-negative subgroup was conducted using the method of Demidenko (https://www.dartmouth.edu/~eugened/power-samplesize.php)[35]. Assumptions of the method required rs27524 genotype be collapsed to a binary variable (for the purposes of power estimation only); estimates are therefore approximate.

Results

Results section 1: A prospective observational data resource facilitating predictive genetic biomarker identification in psoriasis

To assess the ability of *HLA-C*06:02* to predict different rates of response to adalimumab and ustekinumab we considered 3,320 patients enrolled in the Biomarkers of Systemic Treatment Outcomes in Psoriasis (BSTOP) study and the British Association of Dermatologists Biologic and Immunomodulators Register (BADBIR) for whom genotype data were available (**Methods**). 53.4% of these patients were *HLA-C*06:02* positive (carrying at least one copy of the allele), with 46.6% being *HLA-C*06:02* negative. After applying eligibility criteria to ensure that valid baseline and response PASI scores were available, 1,326 participants were included in the final analyses (**Figure 1**).

Participant baseline characteristics are summarised in **Table 1**. Since our investigation concerns the relationship between *HLA-C*06:02* and drug used for treatment (adalimumab or ustekinumab), we sought to identify clinical variables correlated with either of these. We found a strong association between age of psoriasis onset and imputed *HLA-C*06:02* dosage (i.e. a probability-weighted estimate of the number of copies of *HLA-C*06:02* that a patient carries; $P = 9.38\times10^{-22}$), as expected[17]. *HLA-C*06:02* was also associated with baseline PASI score and with duration of disease at treatment initiation ($P = 0.031$ and $P = 3.61\times10^{-9}$ respectively). The relationship between *HLA-C*06:02* and the presence of PsA is complex[36], but we observed a statistically significant correlation ($P = 8.44\times10^{-3}$) that persisted even after controlling for age of psoriasis onset ($P_{adjusted} = 3.98\times10^{-3}$). PsA was also significantly associated with drug type ($P = 0.017$), likely reflecting a tendency towards prescription of anti-TNF therapy for patients with PsA due to its beneficial effect on joint disease[37]. We observed an unexpected association between *HLA-C*06:02* and methotrexate co-therapy at the start of biologic treatment ($P = 0.027$). Co-therapy is common in patients with PsA, and indeed the association disappears when controlling for PsA status ($P_{adjusted} = 0.097$). Finally previous exposure to biologics (biologic naive vs biologic exposed) was

strongly correlated with drug type ($P = 2.12\times10^{-32}$), reflecting the frequent use of adalimumab as a first-line biologic in this patient population[37]; it was not associated with *HLA-C*06:02* genotype ($P = 0.411$).

The observed rate of PASI90 response to adalimumab (41.9% at 3m; 49.5% at 6m) was consistent with that reported in clinical trials (45% at 16 weeks)[9], while the observed ustekinumab rate (28.2% at 3m) was lower than the corresponding trial rate (39% at 12 weeks)[10] (**Table 2**). Observed response rates by *HLA-C*06:02* status and for PASI75 and PASI100 outcomes are given in **Table E1**.

Results section 2:* HLA-C*06:02 *is an effective biomarker that could inform treatment selection

We investigated the extent to which *HLA-C*06:02* genotype is predictive of different rates of PASI90 response for adalimumab compared to ustekinumab. Formally, for each time-point (3m, 6m and 12m after treatment initiation) we fitted a logistic regression model for PASI90 response that included an interaction term between imputed *HLA-C*06:02* dosage and drug type (adalimumab and ustekinumab) (**Methods**). These are effectively gene-environment interaction models (GxE), where a statistically significant non-zero interaction term indicates that *HLA-C*06:02* can stratify response.

A significant interaction term was observed in basic models that considered only *HLA-C*06:02* dosage and drug (**Table E2**). However, we took two further steps to ensure that these findings were not primarily driven by the effect of confounding clinical variables reported in **Table 1**. First, we developed multivariable regression models to test for drug × *HLA-C*06:02* interaction that included appropriate main effect and interaction covariate terms (**Methods**). We observed statistically significant non-zero effects at all time-points for the drug × *HLA-C*06:02* interaction term (**Table 2**). The strongest evidence for interaction was observed at the 6m time-point where sample numbers were largest ($P = 3.76\times10^{-5}$). A significant interaction effect was also observed for the secondary outcome of PASI75, and for all but the earliest time-point (3m) for PASI100 (**Table E3**).

Second, we employed a propensity-score-weighted approach to adjust for potential confounding via covariates influencing treatment selection (full details in **Supplementary Methods**). We observed that all covariates were well balanced between adalimumab and ustekinumab groups after weighting (**Table E4**, **Figure E1**). The drug × *HLA-C*06:02* interaction terms remained significant at all time-points in the weighted models, at very similar levels of significance to the full unweighted multivariable models (**Table E5**). As such we are confident that our full unweighted model adequately controls for confounding, and all subsequent analyses were based on unweighted models.

To elucidate the observed drug × *HLA-C*06:02* interaction effect, we examined the effect that drug type exerts on probability of response within two subgroups of patients: *HLA-C*06:02* negative (zero copies of the allele) and *HLA-C*06:02* positive (one or two copies; pooled due to the small number of patients that carry two copies). At all time-points, drug type was associated with PASI90 response among *HLA-C*06:02* negative patients (better response to adalimumab; $OR_{6m} = 2.95$, $P_{6m} = 5.85\times10^{-7}$), but not among *HLA-C*06:02* positive patients (**Table 3**, **Figure 2A**). This trend was also observed for the secondary PASI75 and PASI100 outcomes (**Table E6**, **Figure E2**).

We performed separate multivariate regression analyses within adalimumab and ustekinumab groups, including covariate main effects only. These confirmed that while there is some effect size heterogeneity across time-points, *HLA-C*06:02* is associated with response to both drugs individually. It is associated with better response to ustekinumab (PASI90 $OR_{6m} = 1.72$, $P_{6m} = 0.018$), consistent with previous reports[19-21], and poorer response to adalimumab (PASI90 $OR_{6m} = 0.54$, $P_{6m} = 1.67\times10^{-4}$), which has not previously been established (**Table E7, Figure E3**). The opposite effect directions give rise to the observed drug × *HLA-C*06:02* interaction.

Nominally significant interactions are observed between PsA and drug at 12m, and between PsA and *HLA-C*06:02* genotype at 3m (**Table 2**). We tested the effect of drug type on PASI90 response within patient subgroups characterised by both *HLA-C*06:02* status (positive/negative) and PsA status (presence/absence) (**Table 3**, **Figure 2B**). In *HLA-C*06:02* negative patients, the effect of drug type on likelihood of PASI90 response was stronger at all time-points among patients with PsA ($OR_{6m} = 5.98$, $P_{6m} = 6.89\times10^{-5}$) than among patients without PsA ($OR_{6m} = 2.32$, $P_{6m} = 1.41\times10^{-3}$; not significant at 12m). Conversely, among *HLA-C*06:02* positive patients the only significant difference in PASI90 response by drug comprised a weak association in the *HLA-C*06:02* positive and PsA negative group at 12m, where adalimumab demonstrated poorer rates of response than ustekinumab (OR = 0.56, P = 0.018). The same trends held true in general for PASI75 and PASI100 outcomes (**Table E8**).

We note that biologic naive status has a stronger direct effect than drug type on the likelihood of achieving PASI90 response (**Table E9**). However, **Table 2** shows clearly that in the full model *HLA-C*06:02* has a significant GxE interaction with drug and not with biologic naive status. The different relative response rates to adalimumab and ustekinumab among *HLA-C*06:02* positive and negative patients are therefore likely to be drug-specific and not explained by these two groups having different propensities to respond to biologic therapy when accounting for previous biologic exposure. Fitting the multivariable GxE models in biologic naive patients only (925 of 1,326 patients) confirmed a drug × *HLA-C*06:02* interaction effect of similar magnitude to the main analysis (**Tables E10 and E11**, **Figure E4a**). Interestingly, the aforementioned poorer response to adalimumab than

ustekinumab at 12m in *HLA-C*06:02* positive and PsA negative patients is much more striking in this biologic naive group ($OR_{12m} = 0.31$, $P_{12m} = 3.42\times10^{-4}$) (**Table E11**, **Figure E4b**). When considering biologic experienced patients only the drug × *HLA-C*06:02* interaction effect does not achieve statistical significance at any time-point, potentially due to much smaller sample sizes (**Tables E10 and E11**). Nevertheless, the same general trend is observed: the subgroup with the biggest difference in response rates are *HLA-C*06:02* negative and PsA positive patients (better response to adalimumab), while *HLA-C*06:02* positive and PsA negative patients see marginally better response to ustekinumab (**Figure E5**).

Finally, our data show a trend suggesting that ustekinumab may be more effective than adalimumab at inducing PASI90 response among the subgroup of *HLA-C*06:02* positive patients homozygous for the allele, regardless of PsA status (**Figure E6**). This suggests an additive genetic effect of *HLA-C*06:02* on differential treatment response. Larger sample sizes are required to fully investigate the significance of this observation and its implications for clinical practice.

Results section 3: Among all HLA alleles,* HLA-C*06:02 *displays the strongest evidence for being a predictive biomarker

While *HLA-C*06:02* has been established as the allele most highly associated with psoriasis susceptibility, it is possible that distinct *HLA-C* alleles or alleles of other class I or class II MHC genes might elicit an enhanced anti-drug immune response to one of the drugs and consequently better predict differential treatment response. We therefore repeated our analysis for all 142 2- and 4-digit HLA alleles that were imputed with high confidence (**Methods**), using the same full GxE model as for *HLA-C*06:02* (**Table E12**). We confirmed that *HLA-C*06:02* displays the strongest evidence for a drug × HLA allele interaction for 6m PASI90 response, demonstrating statistical significance at a Bonferroni-corrected p-value threshold of 1.17×10^{-4} (based on 426 tests: 142 alleles × 3 time-points) (**Figure 3**). Results at other time-points were not inconsistent with this, no HLA alleles achieving significance at the Bonferroni-corrected threshold (**Table E12**). A similar pattern was also observed for the secondary PASI75 and PASI100 outcomes (**Table E12**, **Figure E7**). These findings suggest that *HLA-C*06:02* is likely to be the primary effect allele contributing to biologic response, but due to the extensive linkage disequilibrium across this region larger samples will be necessary to fully investigate the role of other HLA alleles.

To identify potential independent secondary predictive biomarkers in the HLA region, we also report the most associated 2- and 4-digit HLA alleles after conditioning on *HLA-C*06:02* (main and interaction terms) (**Table E13**). No alleles achieved p-values below the Bonferroni-corrected significance threshold of 1.17×10^{-4}. The smallest p-values were observed for other *HLA-C* alleles and

for *HLA-B* alleles; we found little evidence to support independent secondary predictive biomarkers at MHC class II genes. Note that full results for all HLA alleles are provided in **Table E14**.

Results section 4: No evidence observed for an interaction with* ERAP1 *genotype

Variants such as rs27524 in *ERAP1* exhibit an epistatic effect on psoriasis susceptibility through interaction with *HLA-C*06:02*, with each copy of the risk allele amplifying the increase in disease risk that positive *HLA-C*06:02* status confers[15]. Case-only analysis in our full cohort of 3,320 patients supports this interaction: rs27524 is strongly associated with *HLA-C*06:02* status (OR = 1.35, $P = 5.91 \times 10^{-9}$).

We sought to establish whether a similar effect is observed for differential response to adalimumab versus ustekinumab. We found no evidence for epistasis based on two complementary approaches: a full model including the second-order interaction term rs27524 genotype × *HLA-C*06:02* dosage × drug (effectively a gene-gene-environment (GxGxE) model; **Table E15**), and a simple GxE model within the subgroup of 622 *HLA-C*06:02* negative patients (in which differential response by drug was previously observed) that included the interaction term rs27524 genotype × drug (**Table E16**). When removing the (non-significant) second-order interaction term from the GxGxE model, significant p-values are observed for *HLA-C*06:02* dosage × drug, as expected, but for neither interaction term involving the *ERAP1* variant (**Table E17**).

We estimate that our sample sizes provide 80% power to detect interactions between *ERAP1* and drug in the *HLA-C*06:02* negative subgroup when interaction effect sizes (beta regression parameters) are larger than 1.62, 1.28 and 1.37 at 3m, 6m and 12m respectively. Since such effects were not observed we find no evidence to suggest that an interaction between *ERAP1* and *HLA-C*06:02* could provide a more effective predictive biomarker than *HLA-C*06:02* alone. A similar conclusion holds when considering the secondary outcomes, PASI75 and PASI100 (**Tables E15, E16 and E17**).

Discussion

This study constitutes the largest investigation to date into the pharmacogenetics of biologic response in psoriasis, and the first to utilise jointly generated clinical and genetic data on different drugs to identify a predictive biomarker with potential clinical utility. We report that the *HLA-C*06:02* allele effectively stratifies psoriasis patients into groups with different profiles of response to the two most frequently prescribed biologics, adalimumab and ustekinumab.

While the scale of our clinical data resource makes it highly representative of the UK psoriasis population[38, 39], limitations include the heterogeneous nature of the response data, which

lack a structured series of PASI observations at fixed time-points. This limits more formal longitudinal analyses. Similarly, baseline PASI scores are defined pragmatically. They can precede treatment by up to six months and may have been recorded during alternative treatment, although we took steps to minimise any resulting bias (**Methods**). Adverse drug reactions, not investigated here, represent another important consideration when selecting treatment. Independent replication will be important, although our findings concord with previous studies that consider adalimumab and ustekinumab separately[19-22].

Our results demonstrate that *HLA-C*06:02* negative psoriasis patients are significantly more likely to respond to adalimumab than to ustekinumab, but that there is no significant benefit to adalimumab over ustekinumab in *HLA-C*06:02* positive patients.

We also find that the effect of *HLA-C*06:02* is modulated by the presence or absence of comorbid PsA, with adalimumab conferring the greatest benefit over ustekinumab in patients that are *HLA-C*06:02* negative and PsA positive (31.9% of all patients with PsA status available). Interestingly, these findings demonstrate the effectiveness of adalimumab at treating psoriatic skin disease only. Further investigation of the ability of HLA genes to predict combined skin and joint response for PsA positive psoriasis patients is therefore warranted – ideally via longitudinal studies that collect separate validated objective measurements for both skin and joint involvement.

Through HLA imputation we estimated that 46.6% of severe psoriasis patients are *HLA-C*06:02* negative. While treatment selection should always be considered on a case-by-case basis[11], our results suggest that a default strategy of ascertaining *HLA-C*06:02* status and administering adalimumab as first-line biologic to *HLA-C*06:02* negative patients may be an effective approach. Of the 53.4% of patients that are *HLA-C*06:02* positive, **Table 1** suggests that more than three-quarters will not have active PsA. This group may benefit from ustekinumab as a default first-line treatment over the longer term (**Figure E4**), particularly in light of its longer dosing intervals and better persistence relative to adalimumab[40]. Our findings are not conclusive for patients that are *HLA-C*06:02* positive and PsA positive. Since adalimumab is already the recommended first-line biologic in the UK when PsA is present[11], our recommendations primarily impact the 71.8% of patients without active PsA (**Table 1**). *HLA-C*06:02*-informed treatment selection could therefore offer improved likelihood of PASI90 response through the first 12 months of treatment for 35.9% of all severe psoriasis patients, compared to random assignment to adalimumab or ustekinumab. We acknowledge that random assignment does not reflect current clinical practice in this patient population[37]. However, current UK guidelines do not favour either adalimumab or ustekinumab in the absence of PsA[11], and prescribing practices evolve over time and vary by region. We also note

that our recommendations will have health economic implications as adalimumab biosimilars emerge.

The results presented here support the notion that *HLA-C*06:02* positive and *HLA-C*06:02* negative plaque psoriasis represent biologically distinct pathologies, or endotypes. Differences in presentation have long been recognised[16]. However, we suggest that with the implications for clinical decision-making raised by our findings, *HLA-C*06:02* status represents a more relevant stratification of psoriasis patients than the primarily age-of-onset delimited type I/type II distinction[41].

It is widely accepted that *HLA-C*06:02* is the genetic allele that makes by far the largest individual contribution to the risk of developing psoriasis[42-44]. Intriguingly, our HLA-wide analysis suggests that this allele is also mechanistically relevant to biologic response among patients (**Figure 3**, **Table E12**). As such, it is unlikely that *HLA-C*06:02* should generalise as a predictive biomarker for biologic response in other immune-mediated inflammatory diseases. Conversely, these findings may shed important light on the complex pathogenic mechanisms underlying psoriasis. The difference in response to the two drugs among *HLA-C*06:02* negative patients suggests that aberrant signalling of immune pathways downstream of TNFα, adalimumab's target molecule, may play a more prominent role in the development and maintenance of psoriatic lesions for these individuals than for *HLA-C*06:02* positive patients.

Further investigation of the genetic, transcriptomic and immunological differences between *HLA-C*06:02* positive and negative patients could offer vital insights into the pathophysiology of psoriasis and mechanisms of treatment response. Much larger sample sizes will be required to provide sufficient statistical power to accurately quantify the effect of *HLA-C*06:02* and refine the contributions of other HLA alleles. More generally, genome-wide analyses have the potential to uncover genetic contributions to treatment response beyond the HLA region. The genotype data utilised in this study will contribute to such efforts, and results are eagerly anticipated. With respect to clinical application, the potential impact of our findings on patient outcomes is substantial, but it will be important to validate our findings more formally in an appropriately structured prospective clinical trial setting. The design of such a trial should also formally account for PsA status and the clinical factors most likely to confound observational studies, such as previous biologic exposure.

In summary, we show that *HLA-C*06:02* status is a predictive biomarker that influences response to adalimumab and ustekinumab. Ascertainment of *HLA-C*06:02* genotype is straightforward, and our results could have substantial clinical relevance when selecting between two of the most commonly used biologic treatments for psoriasis.

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Table 1 –Summary statistics for baseline characteristics and potential confounding clinical variables

Negative *HLA-C*06:02* status: no copies of the allele; positive status: one or two copies of the allele; PASI: Psoriasis Area and Severity Index. P-values indicated are derived from regression modelling (linear/logistic regression for continuous/binary characteristics respectively); in particular, the *HLA-C*06:02* p-values are based on imputed *HLA-C*06:02* dosage after controlling for five ancestry principal components.

	All patients	**By drug**			**By HLA-C*06:02 status**		
		Adalimumab	Ustekinumab	P	Negative	Positive	P
N	1,326	839	487		622	704	
Baseline PASI score (mean ± SD)	16.7 ± 6.4	16.8 ± 6.5	16.6 ± 6.3	0.551	17.1 ± 6.6	16.4 ± 6.3	0.031
Age of disease onset (mean ± SD) [a]	21.8 ± 12.6	21.4 ± 12.2	22.4 ± 13.2	0.173	25.6 ± 12.8	18.5 ± 11.4	9.38×10^{-22}
Disease duration at treatment start (years; mean ± SD) [a]	23.3 ± 12.6	22.8 ± 12.1	24.0 ± 13.4	0.121	20.7 ± 11.5	25.5 ± 13.1	3.61×10^{-9}
Psoriatic arthritis (%) [b]	28.2	30.5	24.2	0.017	32.3	24.6	8.44×10^{-3} [c]
Biologic naïve (%)	69.8	81.5	49.5	2.12×10^{-32}	69.3	70.2	0.411
Methotrexate co-therapy at treatment start (%)	11.3	12.4	9.4	0.103	13.7	9.2	0.027 [d]

[a] Based on 1,177 patients (89%) with age of disease onset recorded; [b] Based on 1,275 patients (96%) with PsA status recorded; [c] $P = 3.98\times10^{-3}$ when controlling for age of onset; [d] P = 0.097 when controlling for presence of PsA

Table 2 – *HLA-C*06:02* is a predictive biomarker of PASI90 response to adalimumab or ustekinumab after accounting for potential confounding variables

Results are presented for the model interaction terms only. Results for other model terms are not shown; in particular main effect terms are not unambiguously interpretable in the presence of an interaction term. **Table 3** further elucidates the effects of *HLA-C*06:02* and PsA status.

	PASI90 response		
	3 months	**6 months**	**12 months**
n adalimumab	401	586	514
adalimumab responders	168 (41.9%)	290 (49.5%)	257 (50.0%)
n ustekinumab	245	325	298
ustekinumab responders	69 (28.2%)	130 (40.0%)	139 (46.6%)
n total	646	911	812
Drug × BL PASI interaction			
Effect size (beta)	-0.045	0.038	-0.010
95% CI	(-0.109, 0.018)	(-0.008, 0.084)	(-0.062, 0.043)
P-value	0.162	0.108	0.724
Drug × Age of Onset interaction			
Effect size (beta)	0.009	-0.003	-0.001
95% CI	(-0.026, 0.044)	(-0.031, 0.026)	(-0.030, 0.028)
P-value	0.605	0.861	0.932
Drug × Disease Duration interaction			
Effect size (beta)	0.024	-0.014	0.001
95% CI	(-0.009, 0.058)	(-0.043, 0.014)	(-0.028, 0.031)
P-value	0.156	0.329	0.928
Drug × PsA interaction			
Effect size (beta)	-0.102	0.491	0.934
95% CI	(-1.000, 0.795)	(-0.209, 1.191)	(0.215, 1.654)
P-value	0.823	0.169	0.011
HLA-C*06:02 × PsA interaction			
Effect size (beta)	-0.926	-0.175	0.327
95% CI	(-1.649, -0.203)	(-0.725, 0.374)	(-0.261, 0.916)
P-value	0.012	0.531	0.276
HLA-C*06:02 × Biologic Naive interaction			
Effect size (beta)	-0.326	0.101	0.152
95% CI	(-1.079, 0.427)	(-0.495, 0.696)	(-0.464, 0.768)
P-value	0.396	0.741	0.629
Drug × HLA-C*06:02 interaction			
Effect size (beta)	-0.901	-1.198	-0.921
95% CI	(-1.641, -0.161)	(-1.768, -0.628)	(-1.503, -0.340)
P-value	0.017	3.76×10^{-5}	1.90×10^{-3}

Table 3 – Association of drug type with PASI90 response by *HLA-C*06:02* status and presence of concomitant psoriatic arthritis

PsA: psoriatic arthritis (concomitant with psoriasis – see **Methods** for PsA definition; note that PsA subgroup numbers sum to less than "All" numbers, due to a minority of patients without PsA status recorded).

	All			Subgroup without PsA			Subgroup with PsA		
	3 months	**6 months**	**12 months**	**3 months**	**6 months**	**12 months**	**3 months**	**6 months**	**12 months**
HLA-C*06:02 *Negative*									
n adalimumab	195	265	243	124	159	160	66	100	79
adalimumab responders	80 (41.0%)	154 (58.1%)	133 (54.7%)	47 (37.9%)	87 (54.7%)	86 (53.8%)	33 (50.0%)	62 (62.0%)	44 (55.7%)
n ustekinumab	113	153	137	83	109	93	26	38	39
ustekinumab responders	20 (17.7%)	50 (32.7%)	55 (40.1%)	16 (19.3%)	39 (35.8%)	43 (46.2%)	3 (11.5%)	8 (21.1%)	9 (23.1%)
n total	308	418	380	207	268	253	92	138	118
Drug: adalimumab vs ustekinumab									
Odds ratio	3.271	2.950	1.860	2.586	2.316	1.430	7.423	5.977	4.076
95% CI	(1.846, 5.795)	(1.930, 4.510)	(1.207, 2.867)	(1.330, 5.027)	(1.383, 3.878)	(0.845, 2.420)	(1.984, 27.769)	(2.478, 14.417)	(1.707, 9.733)
P-value	4.91×10^{-5}	5.85×10^{-7}	4.94×10^{-3}	5.10×10^{-3}	1.41×10^{-3}	0.182	2.90×10^{-3}	6.89×10^{-5}	1.55×10^{-3}
HLA-C*06:02 *Positive*									
n adalimumab	206	321	271	150	231	198	47	82	65
adalimumab responders	88 (42.7%)	136 (42.4%)	124 (45.8%)	69 (46.0%)	99 (42.9%)	84 (42.4%)	17 (36.2%)	33 (40.2%)	36 (55.4%)
n ustekinumab	132	172	161	91	128	115	35	37	41
ustekinumab responders	49 (37.1%)	80 (46.5%)	84 (52.2%)	35 (38.5%)	60 (46.9%)	63 (54.8%)	12 (34.3%)	15 (40.5%)	19 (46.3%)
n total	338	493	432	241	359	313	82	119	106
Drug: adalimumab vs ustekinumab									
Odds ratio	1.266	0.841	0.738	1.366	0.846	0.565	1.057	0.978	1.461
95% CI	(0.806, 1.987)	(0.579, 1.221)	(0.495, 1.102)	(0.801, 2.329)	(0.548, 1.307)	(0.351, 0.907)	(0.417, 2.680)	(0.442, 2.166)	(0.657, 3.251)
P-value	0.306	0.362	0.137	0.252	0.451	0.018	0.907	0.957	0.353

Figure Legends

Figure 1 – Flow diagram of study eligibility

BADBIR: British Association of Dermatologists Biologic and Immunomodulators Register; BSTOP: Biomarkers of Systemic Treatment Outcomes in Psoriasis; PASI: Psoriasis Area and Severity Index.

Figure 2 – Differential effect of adalimumab and ustekinumab depends on *HLA-C*06:02* status and can be further discriminated by presence of concomitant psoriatic arthritis

Proportion of patients achieving PASI90 response: (**A**) by *HLA-C*06:02* status (negative: no copies of the allele; positive: one or two copies of the allele); (**B**) by *HLA-C*06:02* status and PsA status. Displayed 95% confidence intervals are derived from the Bayesian credible interval using the Jeffreys prior. PsA: psoriatic arthritis (concomitant with psoriasis – see **Methods** for PsA definition).

Figure 3 – GxE interaction p-values for PASI90 response across common 2- and 4-digit HLA alleles

Top panel: GxE interaction p-value by HLA allele; bottom panel: GxE interaction p-value by HLA allele after conditioning on *HLA-C*06:02* main effect and interaction terms; y-axis: $-\log_{10}$(p-value); dark red dashed line: Bonferroni-corrected significance threshold of 1.17×10^{-4}; grey dashed line: nominal significance threshold of 0.05. Time-points are represented by different shaped points. Note that the x-axis represents HLA allele as a categorical variable ordered lexicographically, and does not represent scaled chromosome position. In each panel the most significantly associated allele at each time-point is labelled and highlighted by a grey circle. For ease of identification *HLA-C*06:02* p-values for the three time-points are joined by a dotted green line; there are no *HLA-C*06:02* p-values for the conditional tests.

BADBIR/BSTOP patients with genotype data
3,320

Exposed to biologic therapy
2,596

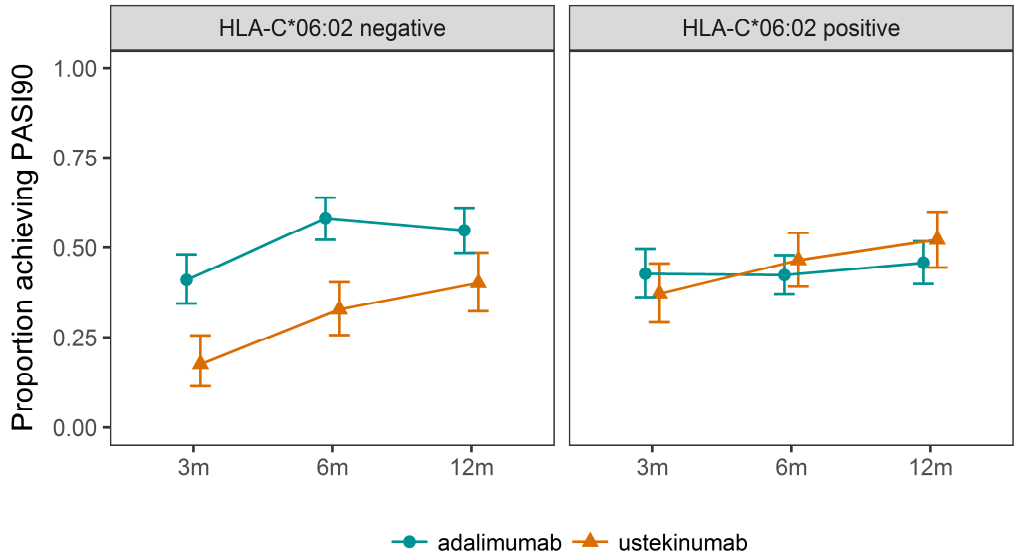
Exposed to adalimumab or ustekinumab
2,319

Response data (PASI score) available for first course of adalimumab or ustekinumab
1,981

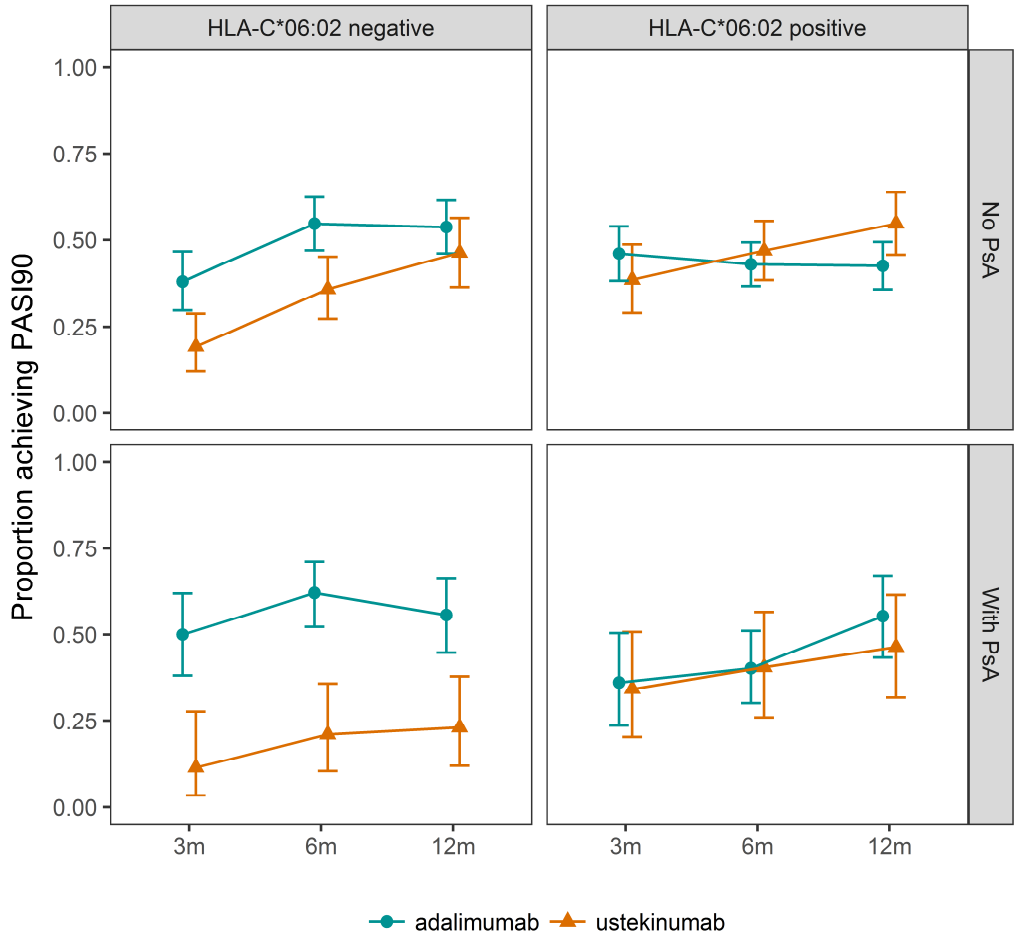
Baseline PASI score available and > 10
1,326

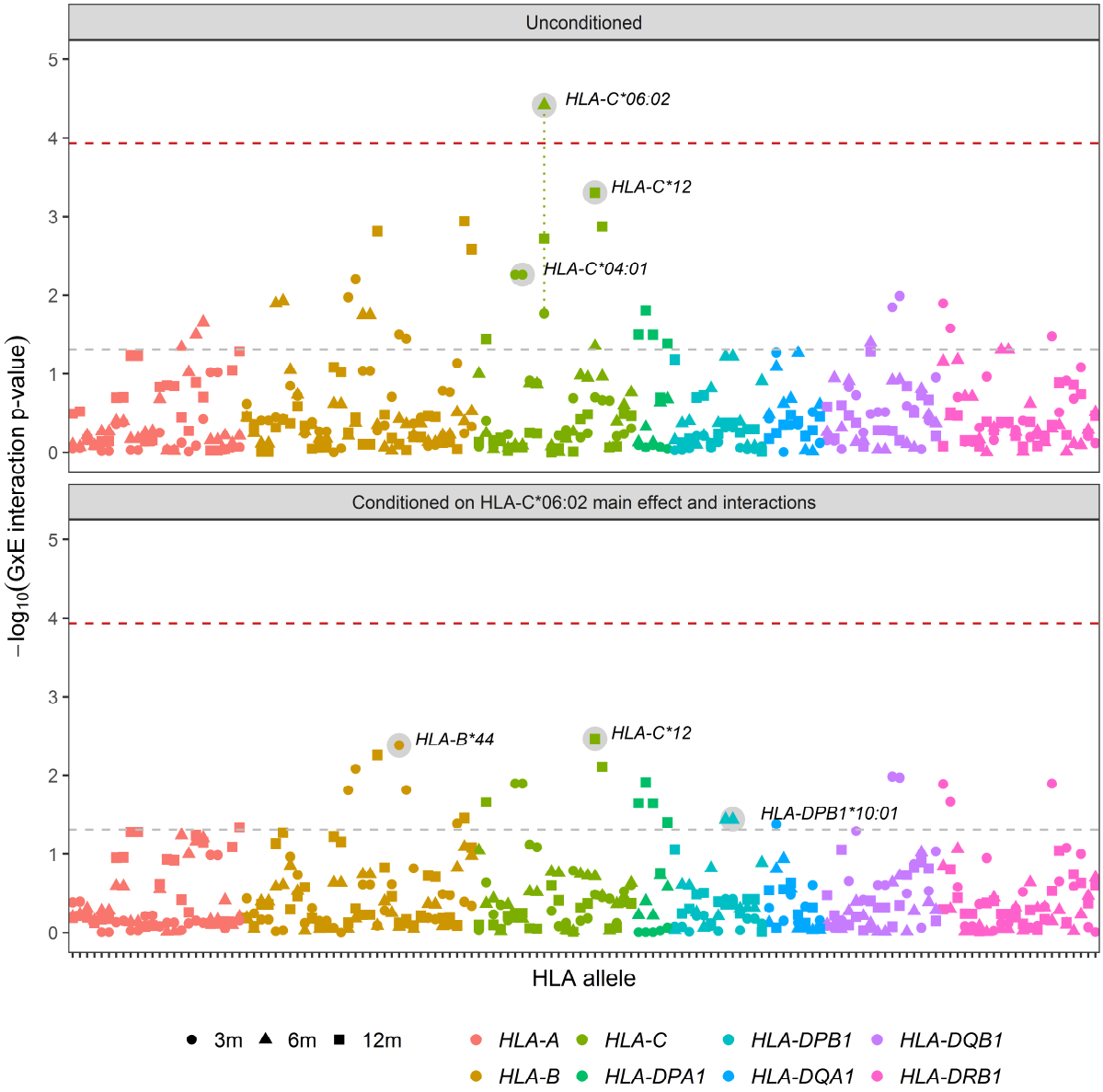
Response data at 3m	Response data at 6m	Response data at 12m
646	**911**	**812**

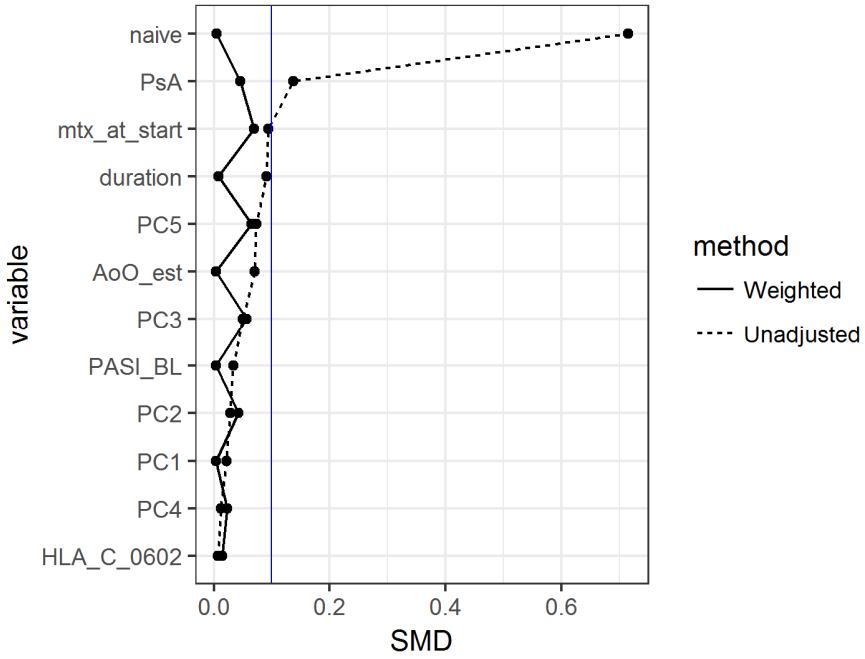
A

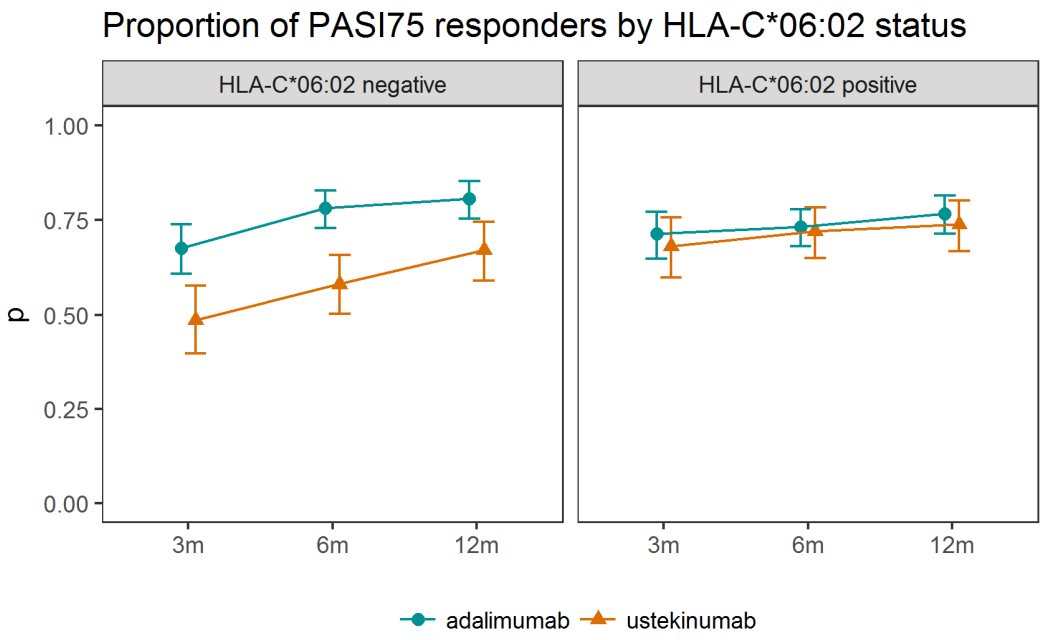

HLA-C*06:02 negative
HLA-C*06:02 positive
Proportion achieving PASI90
1.00
0.75
0.50
0.25
0.00
3m
6m
12m
adalimumab
ustekinumab

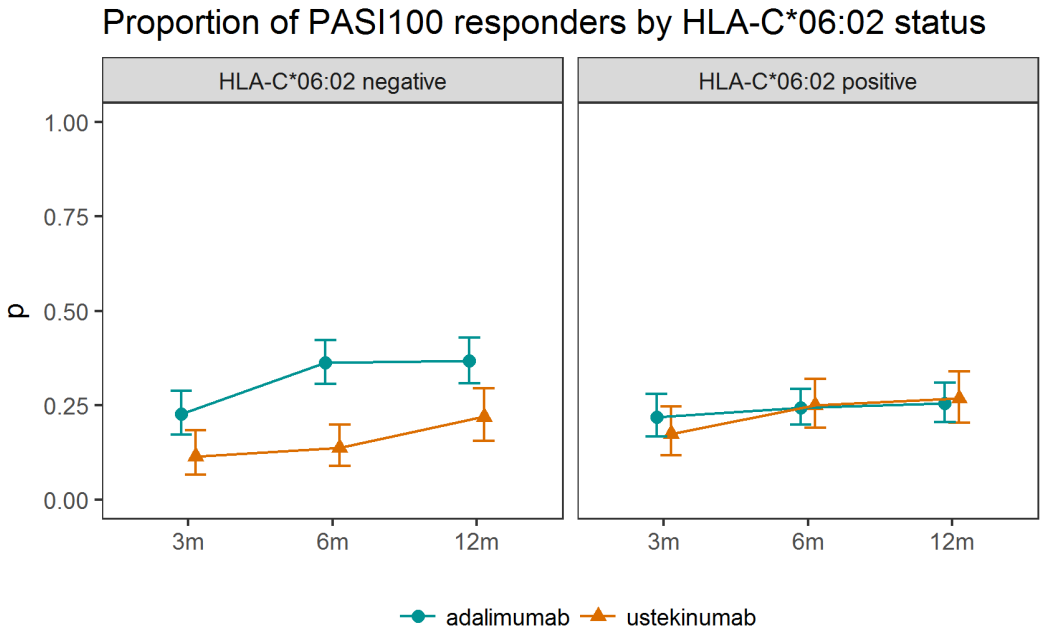
B

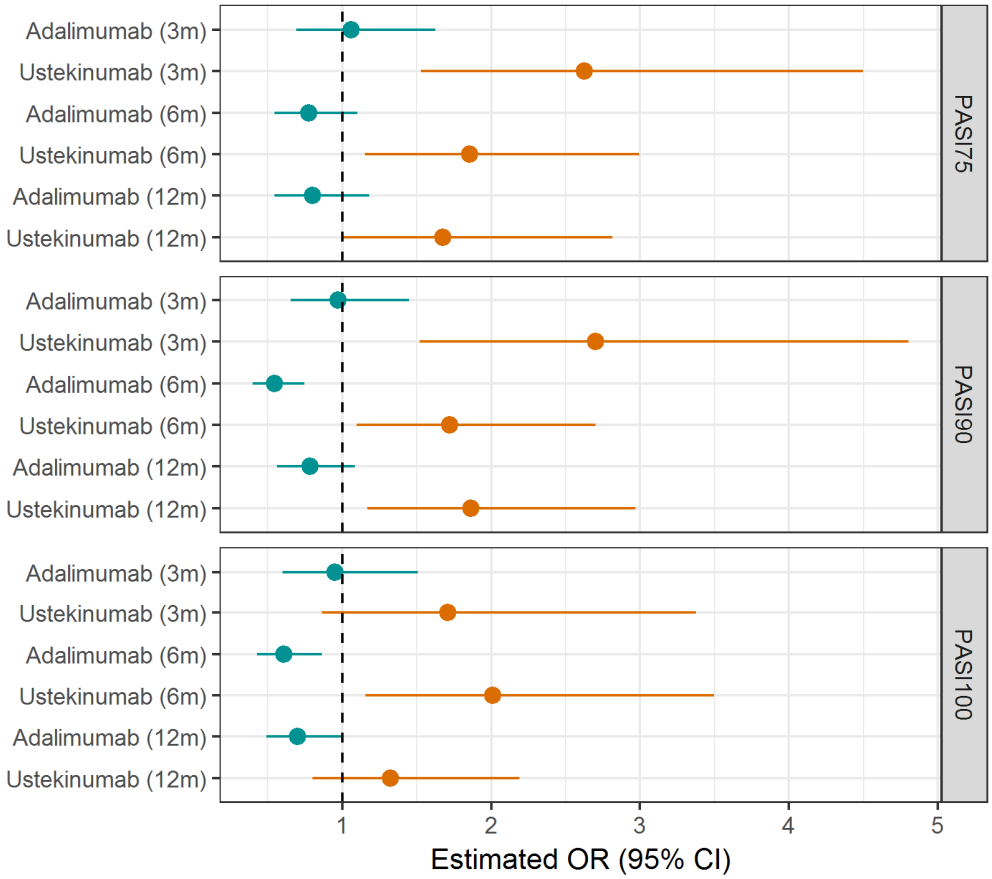

HLA-C*06:02 negative
HLA-C*06:02 positive
No PsA
With PsA
Proportion achieving PASI90
1.00
0.75
0.50
0.25
0.00
3m
6m
12m
adalimumab
ustekinumab


Unconditioned
HLA-C*06:02
HLA-C*12
HLA-C*04:01
Conditioned on HLA-C*06:02 main effect and interactions
HLA-B*44
HLA-C*12
HLA-DPB1*10:01
−log10(GxE interaction p-value)
HLA allele
3m
6m
12m
HLA-A
HLA-C
HLA-DPB1
HLA-DQB1
HLA-B
HLA-DPA1
HLA-DQA1
HLA-DRB1

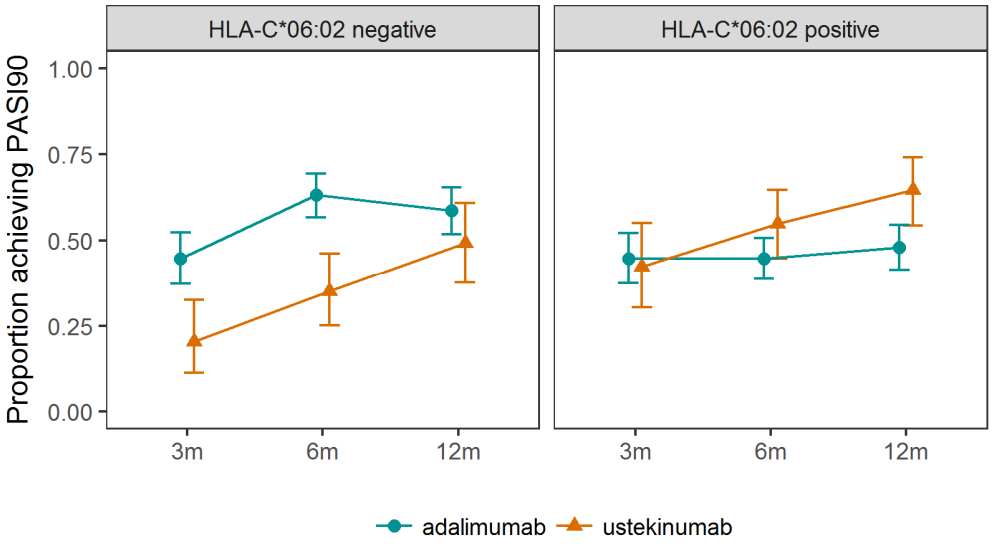



Proportion of PASI75 responders by HLA-C*06:02 status
HLA-C*06:02 negative
HLA-C*06:02 positive
p
1.00
0.75
0.50
0.25
0.00
3m
6m
12m
adalimumab
ustekinumab

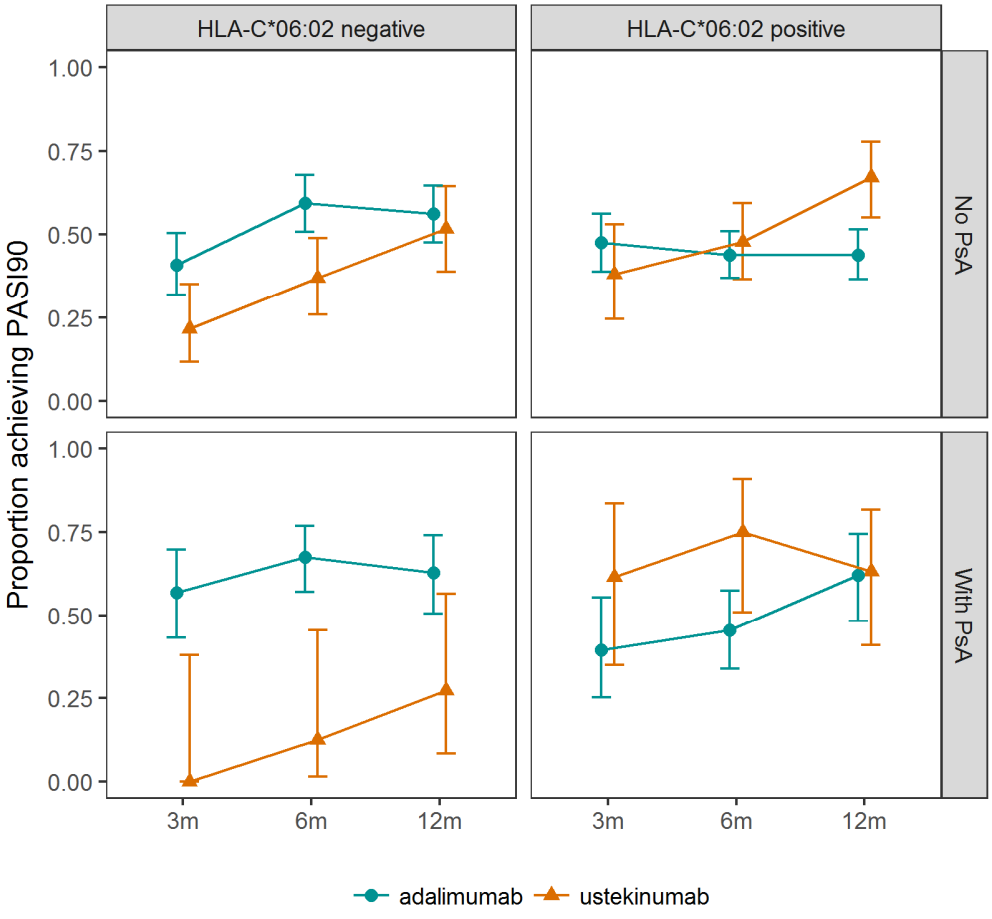

Proportion of PASI100 responders by HLA-C*06:02 status
HLA-C*06:02 negative
HLA-C*06:02 positive
p
1.00
0.75
0.50
0.25
0.00
3m
6m
12m
adalimumab
ustekinumab



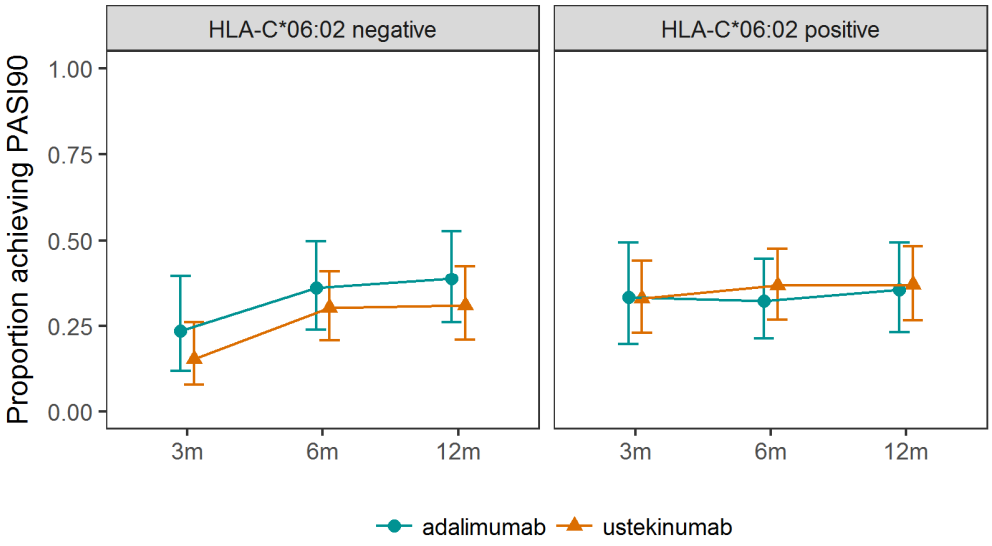
A


HLA-C*06:02 negative
HLA-C*06:02 positive
Proportion achieving PASI90
1.00
0.75
0.50
0.25
0.00
3m
6m
12m
adalimumab
ustekinumab

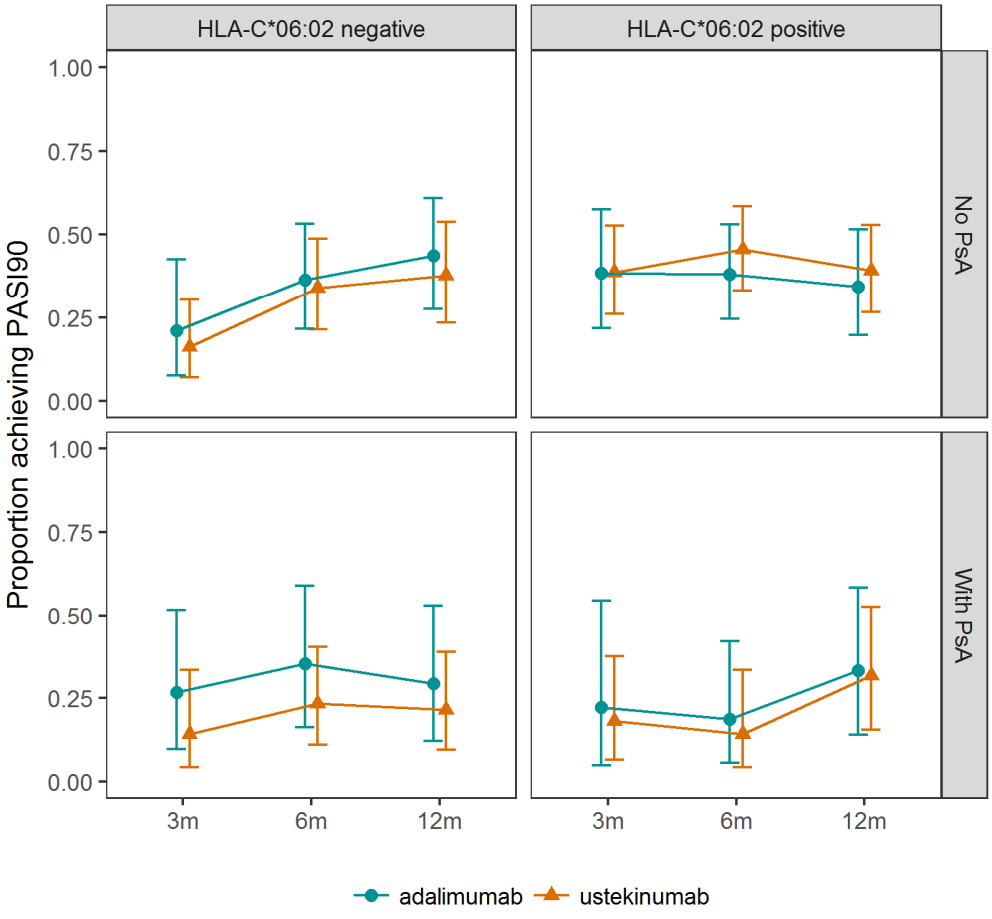
B


HLA-C*06:02 negative
HLA-C*06:02 positive
No PsA
With PsA
Proportion achieving PASI90
1.00
0.75
0.50
0.25
0.00
3m
6m
12m
adalimumab
ustekinumab

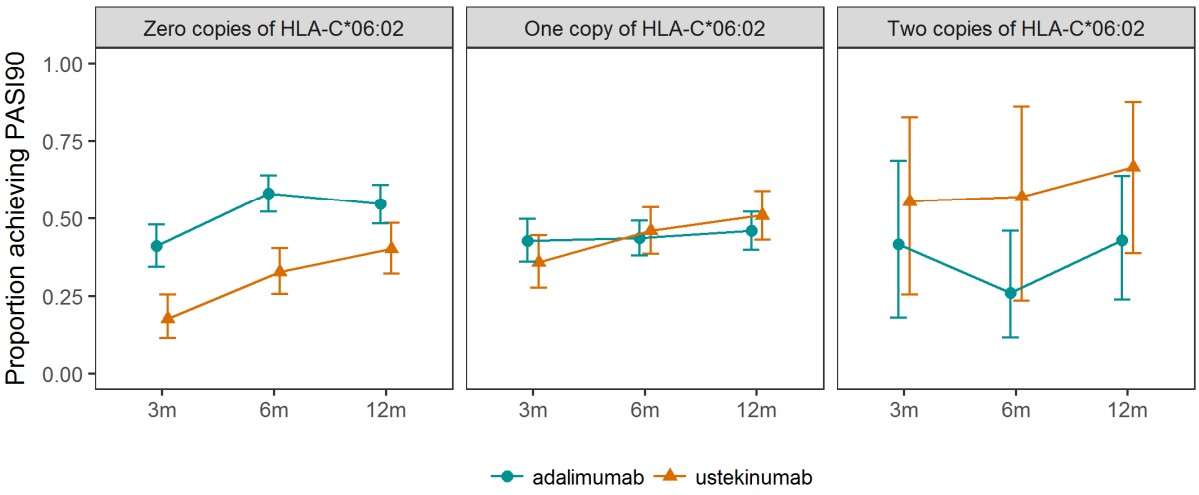
A


HLA-C*06:02 negative
HLA-C*06:02 positive
Proportion achieving PASI90
1.00
0.75
0.50
0.25
0.00
3m
6m
12m
adalimumab
ustekinumab

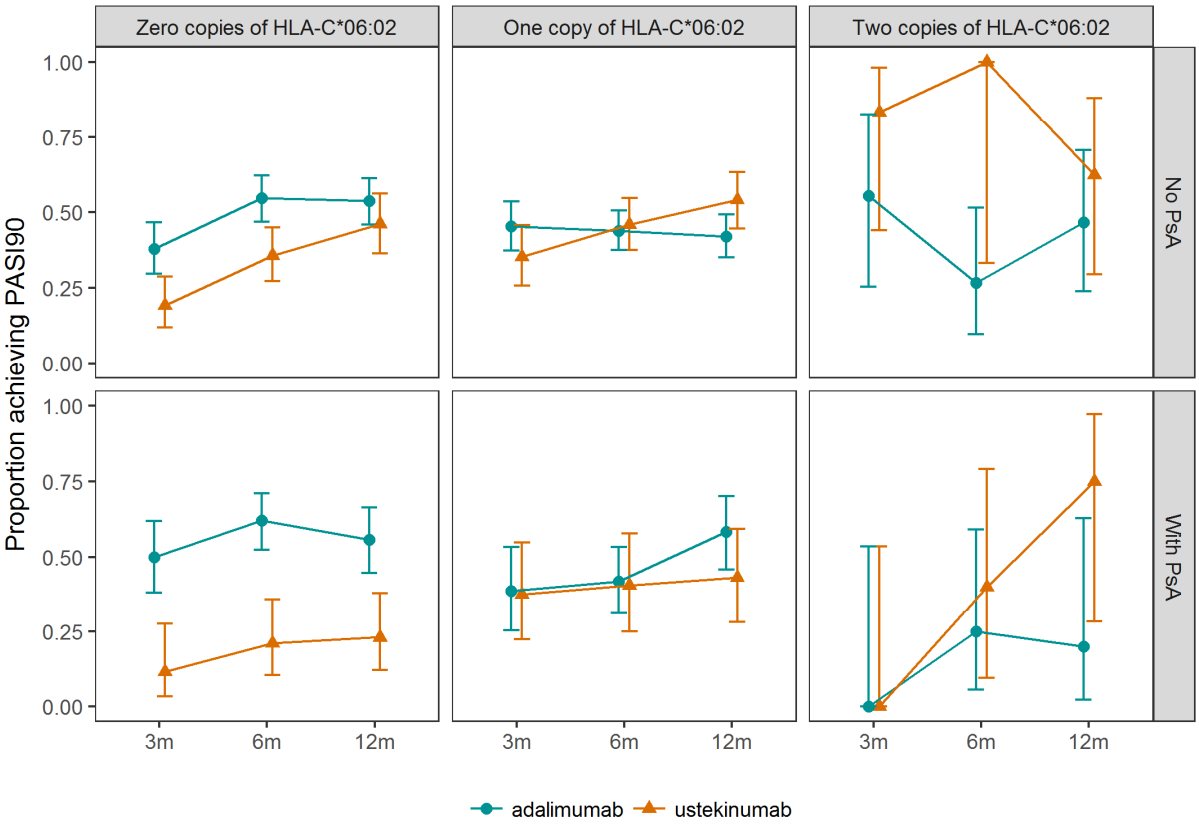
B

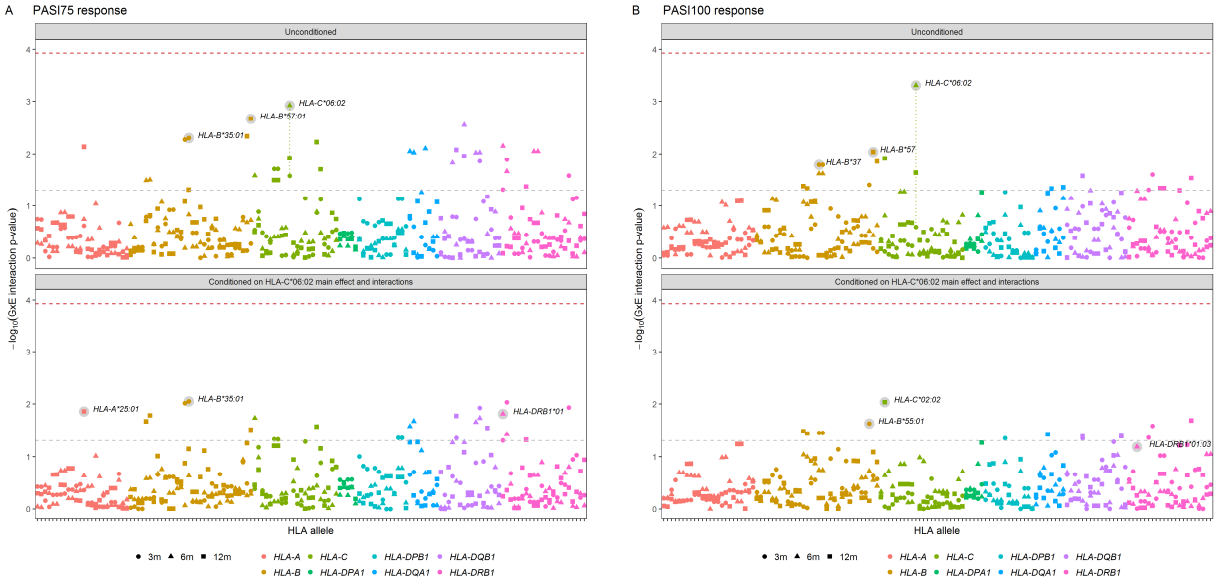

HLA-C*06:02 negative
HLA-C*06:02 positive
No PsA
With PsA
Proportion achieving PASI90
1.00
0.75
0.50
0.25
0.00
3m
6m
12m
adalimumab
ustekinumab

A


Zero copies of HLA-C*06:02
One copy of HLA-C*06:02
Two copies of HLA-C*06:02
Proportion achieving PASI90
1.00
0.75
0.50
0.25
0.00
3m
6m
12m
adalimumab
ustekinumab

B


Zero copies of HLA-C*06:02
One copy of HLA-C*06:02
Two copies of HLA-C*06:02
No PsA
With PsA
Proportion achieving PASI90
1.00
0.75
0.50
0.25
0.00
3m
6m
12m
adalimumab
ustekinumab



Online Repository Materials

*HLA-C*06:02* genotype is a predictive biomarker of biologic treatment response in psoriasis vulgaris

Nick Dand, Michael Duckworth, David Baudry, Alice Russell, Charles J. Curtis, Sang Hyuck Lee, Ian Evans, Kayleigh J. Mason, Ali Alsharqi, Gabrielle Becher, A. David Burden, Richard G. Goodwin, Kevin McKenna, Ruth Murphy, Gayathri K. Perera, Radu Rotarescu, Shyamal Wahie, Andrew Wright, Nick J. Reynolds, Richard B. Warren, Christopher E. M. Griffiths, Catherine H. Smith*, Michael A. Simpson*, and Jonathan N. Barker*, on behalf of the BADBIR study group, the BSTOP study group and the PSORT consortium

Supplementary Methods

Figure E1 – Standardised mean differences in covariates between adalimumab and ustekinumab treatment groups before and after inverse probability of treatment weighting using the propensity score

Covariates ordered by size of SMD before inverse probability of treatment weighting adjustment. Blue line indicates accepted threshold of 0.1 below which covariates are effectively balanced between treatment groups. SMD: standardised mean difference; PsA: psoriatic arthritis; mtx: methotrexate; PC: (ancestry) principal component; AoO_est: estimated age of disease onset (including imputed values; see **Methods**); PASI_BL: baseline PASI.

Figure E2 - Differential effect of adalimumab and ustekinumab depends on *HLA-C*06:02* status

Proportion of patients achieving PASI75 or PASI100 response, by *HLA-C*06:02* status (negative: no copies of the allele; positive: one or two copies of the allele). Displayed 95% confidence intervals are derived from the Bayesian credible interval using the Jeffreys prior.

Figure E3 – Size of *HLA-C*06:02* main effect on PASI75, PASI90 and PASI100 response by drug

OR: odds ratio; CI: confidence interval.

Figure E4 - Differential effect of adalimumab and ustekinumab by *HLA-C*06:02* status and psoriatic arthritis status, in <u>biologic naive</u> patients only

Proportion of biologic naive patients achieving PASI90 response: (**A**) by *HLA-C*06:02* status (negative: no copies of the allele; positive: one or two copies of the allele); (**B**) by *HLA-C*06:02* status and PsA status. Displayed 95% confidence intervals are derived from the Bayesian credible interval using the Jeffreys prior. PsA: psoriatic arthritis (concomitant with psoriasis – see Methods for PsA definition).

Figure E5 - Differential effect of adalimumab and ustekinumab by *HLA-C*06:02* status and psoriatic arthritis status, in <u>biologic experienced</u> patients only

Proportion of biologic experienced patients achieving PASI90 response: (**A**) by *HLA-C*06:02* status (negative: no copies of the allele; positive: one or two copies of the allele); (**B**) by *HLA-C*06:02* status and PsA status. Displayed 95% confidence intervals are derived from the Bayesian credible interval using the Jeffreys prior. PsA: psoriatic arthritis (concomitant with psoriasis – see Methods for PsA definition).

Figure E6 – Cohort analysis suggests that the differential effect of adalimumab and ustekinumab by *HLA-C*06:02* status and psoriatic arthritis status extends to genotype

Proportion of patients achieving PASI90 response: (**A**) by *HLA-C*06:02* genotype; (**B**) by *HLA-C*06:02* genotype and PsA status. Displayed 95% confidence intervals are derived from the Bayesian credible interval using the Jeffreys prior. PsA: psoriatic arthritis (concomitant with psoriasis – see **Methods** for PsA definition).

Figure E7 - GxE interaction p-values for PASI75 and PASI100 response across common 2- and 4-digit HLA alleles

(a) PASI75 response; (b) PASI100 response. Top panel: GxE interaction p-value by HLA allele; bottom panel: GxE interaction p-value by HLA allele after conditioning on *HLA-C*06:02* main effect and interaction terms; y-axis: -log10(p-value); dark red dashed line: Bonferroni-corrected significance threshold of 1.17×10^{-4}; grey dashed line: nominal significance threshold of 0.05. Time-points are represented by different shaped points. Note that the x-axis represents HLA allele as a categorical variable ordered lexicographically, and does not represent scaled chromosome position. In each panel the most significantly associated allele at each time-point is labelled and highlighted by a grey circle. For ease of identification *HLA-C*06:02* p-values for the three time-points are joined by a dotted green line; there are no *HLA-C*06:02* p-values for the conditional tests.

Table E1 – Observed PASI75, PASI90 and PASI100 response rates by drug and *HLA-C*06:02* status

	Adalimumab			**Ustekinumab**		
	*HLA-C*06:02* Positive	*HLA-C*06:02* Negative	Total	*HLA-C*06:02* Positive	*HLA-C*06:02* Negative	Total
3m time-point						
n	206	195	401	132	113	245
PASI75 response	147 (71.4%)	132 (67.7%)	279 (69.6%)	90 (68.2%)	55 (48.7%)	145 (59.2%)
PASI90 response	88 (42.7%)	80 (41.0%)	168 (41.9%)	49 (37.1%)	20 (17.7%)	69 (28.2%)
PASI100 response	45 (21.8%)	44 (22.6%)	89 (22.2%)	23 (17.4%)	13 (11.5%)	36 (14.7%)
6m time-point						
n	321	265	586	172	153	325
PASI75 response	235 (73.2%)	207 (78.1%)	442 (75.4%)	124 (72.1%)	89 (58.2%)	213 (65.5%)
PASI90 response	136 (42.4%)	154 (58.1%)	290 (49.5%)	80 (46.5%)	50 (32.7%)	130 (40.0%)
PASI100 response	78 (24.3%)	96 (36.2%)	174 (29.7%)	43 (25.0%)	21 (13.7%)	64 (19.7%)
12m time-point						
n	271	243	514	161	137	298
PASI75 response	208 (76.8%)	196 (80.7%)	404 (78.6%)	119 (73.9%)	92 (67.2%)	211 (70.8%)
PASI90 response	124 (45.8%)	133 (54.7%)	257 (50.0%)	84 (52.2%)	55 (40.1%)	139 (46.6%)
PASI100 response	69 (25.5%)	89 (36.6%)	158 (30.7%)	43 (26.7%)	30 (21.9%)	73 (24.5%)

Table E2 – Significant interaction of drug and *HLA-C*06:02* genotype in achievement of PASI90 response (uncorrected model)

Based on logistic regression model of PASI90 response that includes baseline PASI and five ancestry principal components as the only covariates (no adjustment for clinical confounders). Results are presented only for the drug × *HLA-C*06:02* interaction term in the GxE model. Results for other model terms are not shown; in particular the terms for *HLA-C*06:02* and drug main effects are not unambiguously interpretable (due to the presence of an interaction term between the two, the value of each main effect term depends on the precise coding of the other).

	PASI90 response		
	3 months	**6 months**	**12 months**
n adalimumab	401	586	514
n ustekinumab	245	325	298
n total	646	911	812
Drug × *HLA-C*06:02* interaction			
Effect size (beta)	-0.894	-1.221	-0.859
95% CI	(-1.535, -0.253)	(-1.739, -0.702)	(-1.382, -0.337)
P-value	6.25×10^{-3}	3.94×10^{-6}	1.27×10^{-3}

Table E3 – Significant interaction of drug and *HLA-C*06:02* status in achievement of PASI75 and PASI100 response when accounting for potential confounding variables

	PASI75 response			PASI100 response		
	3 months	**6 months**	**12 months**	**3 months**	**6 months**	**12 months**
n adalimumab	401	586	514	401	586	514
n ustekinumab	245	325	298	245	325	298
n total	646	911	812	646	911	812
Drug × BL PASI interaction						
Effect size (beta)	-0.032	0.033	-0.061	-0.021	0.051	0.025
95% CI	(-0.101, 0.037)	(-0.018, 0.084)	(-0.125, 0.004)	(-0.095, 0.053)	(-0.003, 0.105)	(-0.029, 0.079)
P-value	0.365	0.208	0.065	0.583	0.063	0.364
Drug × Age of Onset interaction						
Effect size (beta)	0.008	-0.001	-0.003	0.019	0.012	-0.015
95% CI	(-0.026, 0.043)	(-0.032, 0.031)	(-0.038, 0.033)	(-0.024, 0.062)	(-0.022, 0.046)	(-0.046, 0.016)
P-value	0.634	0.969	0.886	0.390	0.488	0.351
Drug × Disease Duration interaction						
Effect size (beta)	0.028	-0.003	-0.008	0.030	0.011	-0.007
95% CI	(-0.006, 0.061)	(-0.034, 0.028)	(-0.041, 0.025)	(-0.010, 0.071)	(-0.023, 0.046)	(-0.040, 0.025)
P-value	0.105	0.851	0.639	0.143	0.519	0.662
Drug × PsA interaction						
Effect size (beta)	-0.443	0.836	0.924	-0.725	0.234	0.854
95% CI	(-1.267, 0.381)	(0.114, 1.557)	(0.139, 1.709)	(-1.777, 0.327)	(-0.611, 1.079)	(0.042, 1.666)
P-value	0.292	0.023	0.021	0.177	0.587	0.039
***HLA-C*06:02* × PsA interaction**						
Effect size (beta)	-0.782	0.022	0.248	-0.743	-0.262	0.107
95% CI	(-1.488, -0.077)	(-0.566, 0.611)	(-0.424, 0.920)	(-1.588, 0.103)	(-0.885, 0.362)	(-0.530, 0.744)
P-value	0.030	0.941	0.470	0.085	0.411	0.743

***HLA-C*06:02* × Biologic Naive interaction**						
Effect size (beta)	-0.184	0.387	0.412	-0.372	-0.048	-0.029
95% CI	(-0.909, 0.541)	(-0.229, 1.003)	(-0.260, 1.083)	(-1.264, 0.519)	(-0.788, 0.692)	(-0.718, 0.661)
P-value	0.619	0.218	0.230	0.413	0.899	0.935
Drug × *HLA-C*06:02* interaction						
Effect size (beta)	-0.832	-1.026	-0.854	-0.504	-1.199	-0.724
95% CI	(-1.568, -0.097)	(-1.648, -0.405)	(-1.521, -0.187)	(-1.377, 0.369)	(-1.874, -0.524)	(-1.349, -0.100)
P-value	0.026	1.21×10^{-3}	0.012	0.258	5.00×10^{-4}	0.023

Table E4 – Distribution of covariates between adalimumab and ustekinumab treatment groups before and after inverse probability of treatment weighting using the propensity score

SMD: standardised mean difference.

	Pre-weighting			Post-weighting		
	Adalimumab (mean (sd))	**Ustekinumab (mean (sd))**	**SMD**	**Adalimumab (mean (sd))**	**Ustekinumab (mean (sd))**	**SMD**
n	487	839		1309.66	1332.66	
Baseline PASI	16.60 (6.27)	16.81 (6.50)	0.034	16.62 (6.33)	16.65 (6.36)	0.004
Biologic naive	0.49 (0.50)	0.82 (0.39)	0.715	0.69 (0.46)	0.69 (0.46)	0.005
Age of psoriasis onset	22.38 (12.44)	21.53 (11.63)	0.071	21.77 (11.98)	21.82 (11.83)	0.004
Disease duration at treatment start	23.91 (12.50)	22.82 (11.51)	0.091	23.40 (12.31)	23.30 (11.71)	0.009
Psoriatic arthritis	0.24 (0.42)	0.30 (0.45)	0.138	0.25 (0.42)	0.27 (0.44)	0.046
Methotrexate co-therapy at treatment start	0.09 (0.29)	0.12 (0.33)	0.095	0.09 (0.29)	0.12 (0.32)	0.069
*HLA-C*06:02* dosage	0.57 (0.56)	0.56 (0.57)	0.007	0.58 (0.56)	0.57 (0.56)	0.015
PC1	-0.00 (0.02)	-0.00 (0.02)	0.022	-0.00 (0.02)	-0.00 (0.02)	0.004
PC2	-0.00 (0.02)	0.00 (0.02)	0.029	-0.00 (0.02)	0.00 (0.02)	0.043
PC3	-0.00 (0.02)	0.00 (0.02)	0.050	-0.00 (0.02)	0.00 (0.02)	0.057
PC4	-0.00 (0.02)	-0.00 (0.02)	0.012	0.00 (0.02)	-0.00 (0.02)	0.024
PC5	0.00 (0.02)	-0.00 (0.02)	0.073	-0.00 (0.02)	-0.00 (0.02)	0.065

Table E5 – Significant interaction of drug and *HLA-C*06:02* status in achievement of PASI75, PASI90 and PASI100 response based on inverse probability of treatment weighting using the propensity score

	PASI75 response			PASI90 response			PASI100 response		
Interaction term	3 months	6 months	12 months	3 months	6 months	12 months	3 months	6 months	12 months
Drug × BL PASI									
Effect size (beta)	-0.025	0.038	-0.075	-0.067	0.047	-0.022	-0.030	0.052	0.012
95% CI	(-0.105, 0.055)	(-0.028, 0.105)	(-0.149, -0.001)	(-0.137, 0.003)	(-0.006, 0.100)	(-0.080, 0.035)	(-0.097, 0.037)	(-0.001, 0.105)	(-0.045, 0.069)
P-value	0.542	0.258	0.049	0.062	0.082	0.441	0.379	0.056	0.683
Drug × Age of Onset									
Effect size (beta)	0.006	-0.008	0.003	0.010	-0.008	0.006	0.031	0.011	0.000
95% CI	(-0.030, 0.043)	(-0.042, 0.026)	(-0.037, 0.042)	(-0.027, 0.047)	(-0.037, 0.021)	(-0.026, 0.037)	(-0.014, 0.077)	(-0.026, 0.048)	(-0.036, 0.036)
P-value	0.733	0.649	0.896	0.591	0.595	0.722	0.177	0.561	0.986
Drug × Disease Duration									
Effect size (beta)	0.028	0.000	0.003	0.021	-0.019	0.005	0.034	0.015	0.005
95% CI	(-0.008, 0.063)	(-0.032, 0.033)	(-0.032, 0.038)	(-0.016, 0.057)	(-0.049, 0.011)	(-0.027, 0.038)	(-0.011, 0.079)	(-0.024, 0.054)	(-0.032, 0.042)
P-value	0.131	0.987	0.851	0.270	0.205	0.747	0.141	0.458	0.788
Drug × PsA									
Effect size (beta)	-0.719	0.602	0.846	-0.310	0.128	0.912	-1.082	-0.258	0.588
95% CI	(-1.555, 0.117)	(-0.132, 1.336)	(0.008, 1.685)	(-1.240, 0.620)	(-0.589, 0.846)	(0.150, 1.673)	(-2.133, -0.030)	(-1.156, 0.640)	(-0.266, 1.442)
P-value	0.092	0.108	0.048	0.513	0.726	0.019	0.044	0.573	0.178
***HLA-C*06:02* × PsA**									
Effect size (beta)	-0.431	0.073	0.126	-0.774	-0.055	0.394	-0.409	-0.203	0.062
95% CI	(-1.156, 0.293)	(-0.572, 0.718)	(-0.593, 0.846)	(-1.492, -0.057)	(-0.672, 0.562)	(-0.233, 1.021)	(-1.230, 0.411)	(-0.906, 0.499)	(-0.619, 0.744)
P-value	0.244	0.825	0.731	0.035	0.862	0.218	0.329	0.571	0.858

***HLA-C*06:02* × Biologic Naive**									
Effect size (beta)	-0.134	0.426	0.372	-0.347	0.070	0.173	-0.320	-0.124	-0.114
95% CI	(-0.825, 0.558)	(-0.212, 1.064)	(-0.302, 1.045)	(-1.085, 0.391)	(-0.528, 0.668)	(-0.457, 0.803)	(-1.207, 0.566)	(-0.871, 0.623)	(-0.827, 0.599)
P-value	0.705	0.191	0.280	0.357	0.818	0.591	0.479	0.744	0.754
Drug × *HLA-C*06:02*									
Effect size (beta)	-0.818	-1.205	-0.946	-0.893	-1.237	-0.988	-0.396	-1.217	-0.694
95% CI	(-1.535, -0.100)	(-1.860, -0.551)	(-1.607, -0.285)	(-1.616, -0.171)	(-1.818, -0.656)	(-1.585, -0.391)	(-1.284, 0.492)	(-1.911, -0.524)	(-1.326, -0.063)
P-value	0.026	3.24×10^{-4}	5.16×10^{-3}	0.016	3.32×10^{-5}	1.23×10^{-3}	0.382	6.05×10^{-4}	0.032

Table E6 – Association of drug type with PASI75 and PASI100 response by *HLA-C*06:02* status

	PASI75 response			PASI100 response		
	3 months	**6 months**	**12 months**	**3 months**	**6 months**	**12 months**
***HLA-C*06:02* Negative**						
n adalimumab	195	265	243	195	265	243
n ustekinumab	113	153	137	113	153	137
n total	308	418	380	308	418	380
Drug: adalimumab vs ustekinumab						
Odds ratio	2.206	2.583	2.069	2.215	3.595	2.063
95% CI	(1.357, 3.585)	(1.671, 3.991)	(1.280, 3.346)	(1.133, 4.329)	(2.125, 6.082)	(1.274, 3.339)
P-value	1.41×10^{-3}	1.93×10^{-5}	3.02×10^{-3}	0.020	1.84×10^{-6}	3.23×10^{-3}
***HLA-C*06:02* Positive**						
n adalimumab	206	321	271	206	321	271
n ustekinumab	132	172	161	132	172	161
n total	338	493	432	338	493	432
Drug: adalimumab vs ustekinumab						
Odds ratio	1.171	1.055	1.146	1.325	0.963	0.931
95% CI	(0.726, 1.890)	(0.697, 1.598)	(0.728, 1.803)	(0.758, 2.315)	(0.627, 1.479)	(0.597, 1.451)
P-value	0.517	0.799	0.557	0.323	0.862	0.752

Table E7 – *HLA-C*06:02* genotype associates with response to either drug

Statistics relate to *HLA-C*06:02* dosage term in separate multivariable models for response to adalimumab and ustekinumab. Other model covariates (ancestry PCs 1-5, baseline PASI, age of psoriasis onset, presence of psoriatic arthritis, biologic naive status, disease duration at treatment start and methotrexate co-therapy up to the response measurement date) not shown.

	Adalimumab			**Ustekinumab**		
	3 months	**6 months**	**12 months**	**3 months**	**6 months**	**12 months**
n	401	586	514	245	325	298
***HLA-C*06:02* main effect: PASI75 response**						
Effect size (OR)	1.059	0.775	0.802	2.624	1.856	1.675
95% CI	(0.690, 1.625)	(0.544, 1.104)	(0.543, 1.183)	(1.530, 4.499)	(1.151, 2.993)	(0.997, 2.813)
P-value	0.793	0.158	0.266	4.53×10^{-4}	0.011	0.051
***HLA-C*06:02* main effect: PASI90 response**						
Effect size (OR)	0.972	0.544	0.782	2.702	1.722	1.864
95% CI	(0.653, 1.447)	(0.397, 0.747)	(0.563, 1.085)	(1.520, 4.804)	(1.098, 2.699)	(1.170, 2.970)
P-value	0.889	1.67×10^{-4}	0.141	7.07×10^{-4}	0.018	8.83×10^{-3}
***HLA-C*06:02* main effect: PASI100 response**						
Effect size (OR)	0.952	0.608	0.700	1.707	2.011	1.325
95% CI	(0.601, 1.507)	(0.429, 0.863)	(0.490, 1.001)	(0.863, 3.374)	(1.157, 3.496)	(0.802, 2.189)
P-value	0.834	5.35×10^{-3}	0.051	0.124	0.013	0.272

Table E8 – Association of drug type with PASI75 and PASI100 response by *HLA-C*06:02* and psoriatic arthritis status

	PASI75 response			PASI100 response		
	3 months	**6 months**	**12 months**	**3 months**	**6 months**	**12 months**
HLA-C*06:02 *Negative without PsA*						
n adalimumab	124	159	160	124	159	160
n ustekinumab	83	109	93	83	109	93
n total	207	268	253	207	268	253
Drug: adalimumab vs ustekinumab						
Odds ratio	1.754	2.025	1.714	1.933	2.590	1.555
95% CI	(0.984, 3.125)	(1.178, 3.482)	(0.936, 3.139)	(0.877, 4.260)	(1.387, 4.838)	(0.882, 2.743)
P-value	0.057	0.011	0.081	0.102	2.83×10^{-3}	0.128
HLA-C*06:02 *Negative with PsA*						
n adalimumab	66	100	79	66	100	79
n ustekinumab	26	38	39	26	38	39
n total	92	138	118	92	138	118
Drug: adalimumab vs ustekinumab						
Odds ratio	5.329	4.841	3.281	4.142	8.866	4.436
95% CI	(1.946, 14.593)	(2.171, 10.793)	(1.419, 7.590)	(0.876, 19.583)	(2.550, 30.821)	(1.560, 12.614)
P-value	1.13×10^{-3}	1.16×10^{-4}	5.48×10^{-3}	0.073	5.98×10^{-4}	5.21×10^{-3}
HLA-C*06:02 *Positive without PsA*						
n adalimumab	150	231	198	150	231	198
n ustekinumab	91	128	115	91	128	115
n total	241	359	313	241	359	313
Drug: adalimumab vs ustekinumab						
Odds ratio	1.800	0.867	0.816	1.867	0.980	0.766
95% CI	(1.002, 3.236)	(0.529, 1.420)	(0.470, 1.418)	(0.947, 3.677)	(0.591, 1.624)	(0.454, 1.290)
P-value	0.049	0.571	0.471	0.071	0.937	0.315

HLA-C*06:02 *Positive with PsA*						
n adalimumab	47	82	65	47	82	65
n ustekinumab	35	37	41	35	37	41
n total	82	119	106	82	119	106
Drug: adalimumab vs ustekinumab						
Odds ratio	0.422	1.767	2.331	0.585	0.919	1.576
95% CI	(0.162, 1.097)	(0.771, 4.049)	(0.963, 5.644)	(0.189, 1.808)	(0.380, 2.220)	(0.634, 3.919)
P-value	0.077	0.178	0.061	0.351	0.851	0.327

Table E9 – Joint association of drug and biologic naive status with response

Results based on simple model that includes drug and biologic naive status terms, fitted using the full cohort of 1,326 patients (controlling for baseline PASI; no other covariate terms and in particular no interaction terms).

	PASI75 response			PASI90 response			PASI100 response		
	3 months	**6 months**	**12 months**	**3 months**	**6 months**	**12 months**	**3 months**	**6 months**	**12 months**
n adalimumab	401	586	514	401	586	514	401	586	514
n ustekinumab	245	325	298	245	325	298	245	325	298
n total	646	911	812	646	911	812	646	911	812
Drug: adalimumab vs ustekinumab									
Effect size (beta)	0.262	0.311	0.218	0.442	0.204	-0.097	0.405	0.329	0.162
95% CI	(-0.104, 0.627)	(-0.002, 0.625)	(-0.129, 0.566)	(0.070, 0.813)	(-0.088, 0.496)	(-0.407, 0.214)	(-0.051, 0.860)	(-0.012, 0.671)	(-0.177, 0.501)
P-value	0.160	0.052	0.218	0.020	0.171	0.541	0.082	0.058	0.350
Biologic naive status									
Effect size (beta)	0.535	0.572	0.691	0.483	0.650	0.806	0.276	0.834	0.562
95% CI	(0.158, 0.911)	(0.249, 0.895)	(0.337, 1.045)	(0.087, 0.880)	(0.337, 0.963)	(0.472, 1.141)	(-0.207, 0.759)	(0.441, 1.227)	(0.184, 0.939)
P-value	5.38×10^{-3}	5.23×10^{-4}	1.32×10^{-4}	0.017	4.80×10^{-5}	2.29×10^{-6}	0.263	3.14×10^{-5}	3.54×10^{-3}

Table E10 – Significant interaction of drug and *HLA-C*06:02* status in achievement of PASI90 response in biologic naive and biologic experienced subgroups

	PASI 90 response					
	Biologic naive			Biologic experienced		
	3 months	6 months	12 months	3 months	6 months	12 months
n adalimumab	331	477	417	70	109	97
adalimumab responders	148 (44.7%)	253 (53.0%)	221 (53.0%)	20 (28.6%)	37 (33.9%)	36 (37.1%)
n ustekinumab	113	170	157	132	155	141
ustekinumab responders	36 (31.9%)	78 (45.9%)	91 (58.0%)	33 (25.0%)	52 (33.5%)	48 (34.0%)
n total	444	647	574	202	264	238
Drug × BL PASI interaction						
Effect size (beta)	-0.091	0.047	-0.056	-0.002	0.064	0.045
95% CI	(-0.179, -0.003)	(-0.007, 0.102)	(-0.138, 0.026)	(-0.137, 0.132)	(-0.035, 0.164)	(-0.056, 0.147)
P-value	0.042	0.088	0.182	0.972	0.203	0.380
Drug × Age of Onset interaction						
Effect size (beta)	0.007	-0.013	0.005	0.028	0.012	-0.002
95% CI	(-0.040, 0.054)	(-0.048, 0.022)	(-0.031, 0.041)	(-0.047, 0.103)	(-0.047, 0.071)	(-0.064, 0.061)
P-value	0.766	0.469	0.799	0.463	0.697	0.962
Drug × Disease Duration interaction						
Effect size (beta)	-0.002	-0.025	0.003	0.049	0.000	0.002
95% CI	(-0.049, 0.045)	(-0.061, 0.012)	(-0.035, 0.040)	(-0.019, 0.118)	(-0.059, 0.059)	(-0.055, 0.059)
P-value	0.935	0.182	0.890	0.157	0.992	0.949
Drug × PsA interaction						
Effect size (beta)	-0.424	-0.027	1.419	-0.172	0.350	-0.136
95% CI	(-1.803, 0.954)	(-1.050, 0.996)	(0.375, 2.462)	(-1.902, 1.559)	(-0.991, 1.690)	(-1.423, 1.151)
P-value	0.546	0.959	7.71×10^{-3}	0.846	0.609	0.836

***HLA-C*06:02* × PsA interaction**						
Effect size (beta)	-0.834	0.088	0.349	-1.377	-1.031	0.298
95% CI	(-1.728, 0.059)	(-0.581, 0.757)	(-0.381, 1.079)	(-2.735, -0.019)	(-2.235, 0.174)	(-0.787, 1.383)
P-value	0.067	0.796	0.349	0.047	0.093	0.590
Drug × *HLA-C*06:02* interaction						
Effect size (beta)	-0.655	-1.479	-0.963	-1.010	-1.038	-0.940
95% CI	(-1.594, 0.284)	(-2.189, -0.768)	(-1.673, -0.253)	(-2.484, 0.464)	(-2.224, 0.148)	(-2.071, 0.190)
P-value	0.171	4.58×10^{-5}	7.87×10^{-3}	0.179	0.086	0.103

Table E11 – Association of drug type with PASI90 response by *HLA-C*06:02* and psoriatic arthritis status in biologic naive and biologic experienced subgroups

N/A confidence interval for *HLA-C*06:02* negative and biologic naive patients with PsA at 3m is due to zero (of five) observed responders to ustekinumab.

	All			Subgroup without PsA			Subgroup with PsA		
	3 months	**6 months**	**12 months**	**3 months**	**6 months**	**12 months**	**3 months**	**6 months**	**12 months**
HLA-C*06:02 *Negative and biologic naive*									
n adalimumab	161	215	194	105	126	128	51	83	62
n ustekinumab	54	77	69	46	65	56	5	8	11
n total	215	292	263	151	191	184	56	91	73
Drug: adalimumab vs ustekinumab									
Odds ratio	3.047	3.119	1.406	2.463	2.482	1.142	3.60×10^{7}	14.452	4.418
95% CI	(1.444, 6.427)	(1.802, 5.400)	(0.805, 2.458)	(1.093, 5.550)	(1.322, 4.662)	(0.601, 2.172)	N/A	(1.680, 124.3)	(1.056, 18.492)
P-value	3.45×10^{-3}	4.84×10^{-5}	0.231	0.030	4.70×10^{-3}	0.684	0.992	0.015	0.042
HLA-C*06:02 *Positive and biologic naive*									
n adalimumab	170	262	223	124	189	166	38	66	50
n ustekinumab	59	93	88	42	71	64	13	16	19
n total	229	355	311	166	260	230	51	82	69
Drug: adalimumab vs ustekinumab									
Odds ratio	1.154	0.669	0.470	1.514	0.857	0.314	0.469	0.282	1.008
95% CI	(0.629, 2.116)	(0.415, 1.077)	(0.278, 0.796)	(0.736, 3.117)	(0.495, 1.482)	(0.167, 0.592)	(0.125, 1.766)	(0.082, 0.967)	(0.332, 3.061)
P-value	0.644	0.098	4.93×10^{-3}	0.260	0.580	3.42×10^{-4}	0.263	0.044	0.989
HLA-C*06:02 *Negative and biologic experienced*									
n adalimumab	34	50	49	19	33	32	15	17	17
n ustekinumab	59	76	68	37	44	37	21	30	28
n total	93	126	117	56	77	69	36	47	45

Drug: adalimumab vs ustekinumab									
Odds ratio	1.817	1.570	1.773	1.495	1.381	1.831	2.233	1.810	1.466
95% CI	(0.618, 5.347)	(0.708, 3.479)	(0.781, 4.025)	(0.356, 6.288)	(0.505, 3.773)	(0.626, 5.355)	(0.412, 12.103)	(0.473, 6.929)	(0.359, 5.985)
P-value	0.278	0.267	0.171	0.583	0.529	0.269	0.351	0.386	0.594
HLA-C*06:02 *Positive and biologic experienced*									
n adalimumab	36	59	48	26	42	32	9	16	15
n ustekinumab	73	79	73	49	57	51	22	21	22
n total	109	138	121	75	99	83	31	37	37
Drug: adalimumab vs ustekinumab									
Odds ratio	1.010	0.769	0.921	0.996	0.693	0.801	1.290	1.076	0.785
95% CI	(0.432, 2.365)	(0.373, 1.588)	(0.430, 1.976)	(0.373, 2.656)	(0.303, 1.582)	(0.318, 2.018)	(0.182, 9.133)	(0.167, 6.938)	(0.168, 3.672)
P-value	0.981	0.478	0.833	0.993	0.384	0.638	0.799	0.939	0.759

Table E12 – HLA alleles with strongest evidence for interaction with drug

Based on full GxE model including clinical covariates and interaction terms. The ten most strongly associated HLA alleles are reported for each combination of outcome (PASI75, PASI90, PASI100) and time-point. "Interaction p-value": p-value of HLA allele dosage × Drug interaction term; "Conditional on *HLA-C*06:02*": the p-value for the same interaction term in a model that also includes *HLA-C*06:02* main effect and interaction terms. *: P < 0.05; **: P < 0.005; **: P < 1.17×10^{-4} (Bonferroni multiple testing threshold for 142 alleles × 3 time-points = 426 tests). Table entries for *HLA-C*06:02* are highlighted in bold underlined font; note that *HLA-C*06:02* is not among the top ten alleles for PASI100 response at 3m.

	PASI75 response			**PASI90 response**			**PASI100 response**		
	Allele	Interaction p-value	Conditional on *HLA-C*06:02*	Allele	Interaction p-value	Conditional on *HLA-C*06:02*	Allele	Interaction p-value	Conditional on *HLA-C*06:02*
3 months	*HLA-B*35:01*	$^{**}4.96\times10^{-3}$	$^{*}8.92\times10^{-3}$	*HLA-C*04*	$^{*}5.45\times10^{-3}$	*0.013	*HLA-B*37*	*0.016	*0.036
	*HLA-B*35*	$^{*}5.32\times10^{-3}$	$^{*}9.65\times10^{-3}$	*HLA-C*04:01*	$^{*}5.45\times10^{-3}$	*0.013	*HLA-B*37:01*	*0.016	*0.036
	*HLA-DRB1*01:01*	*0.013	$^{*}9.25\times10^{-3}$	*HLA-B*35:01*	$^{*}6.20\times10^{-3}$	*0.008	*HLA-DRB1*04:01*	*0.025	*0.026
	*HLA-DQB1*05:01*	*0.014	*0.012	*HLA-DQB1*05:01*	*0.010	*0.011	*HLA-B*55:01*	*0.039	*0.024
	*HLA-C*04*	*0.019	*0.047	*HLA-B*35*	*0.011	*0.015	*HLA-DRB1*04*	*0.049	*0.044
	*HLA-C*04:01*	*0.019	*0.047	*HLA-DRB1*01*	*0.013	*0.013	*HLA-DPB1*04:02*	0.054	*0.045
	*HLA-DRB1*13:02*	*0.026	*0.012	*HLA-DQB1*05*	*0.014	*0.010	*HLA-DQB1*06*	0.086	0.052
	HLA-C*06:02	***0.026**	N/A	***HLA-C*06:02***	***0.017**	N/A	*HLA-DRB1*13*	0.089	0.060
	*HLA-DRB1*01*	*0.048	*0.050	*HLA-DRB1*01:01*	*0.026	*0.022	*HLA-DQB1*03:01*	0.103	*0.045
	*HLA-DRB1*14:01*	0.070	0.094	*HLA-B*44*	*0.032	**0.004	*HLA-DQA1*03:01*	0.112	0.083
	Allele	Interaction p-value	Conditional on *HLA-C*06:02*	Allele	Interaction p-value	Conditional on *HLA-C*06:02*	Allele	Interaction p-value	Conditional on *HLA-C*06:02*
	HLA-C*06:02	$^{**}\mathbf{1.21\times10^{-3}}$	N/A	***HLA-C*06:02***	$^{***}\mathbf{3.76\times10^{-5}}$	N/A	***HLA-C*06:02***	$^{**}\mathbf{5.00\times10^{-4}}$	N/A
	*HLA-DQB1*03:03*	$^{**}2.84\times10^{-3}$	0.054	*HLA-B*13:02*	*0.012	0.249	*HLA-B*37*	*0.024	0.181
	*HLA-DRB1*01*	$^{*}7.08\times10^{-3}$	*0.015	*HLA-B*13*	*0.013	0.264	*HLA-B*37:01*	*0.024	0.182
	HLA-	$^{*}7.85\times10^{-3}$	0.205	*HLA-B*37*	*0.018	0.181	*HLA-*	0.051	0.562

	*DQA1*02:01*						*DQB1*03:03*		
6 months	*HLA-DRB1*07*	*8.86×10^{-3}	0.225	*HLA-B*37:01*	*0.018	0.181	*HLA-DRB1*01:03*	0.052	0.066
	*HLA-DQA1*01*	*8.87×10^{-3}	*0.027	*HLA-A*30:01*	*0.022	0.063	*HLA-C*04:01*	0.054	0.139
	*HLA-DRB1*07:01*	*8.87×10^{-3}	0.225	*HLA-A*30*	*0.032	0.069	*HLA-C*04*	0.054	0.139
	*HLA-DQA1*01:01*	*9.38×10^{-3}	*0.021	*HLA-DQB1*03:03*	*0.040	0.766	*HLA-DQA1*05:01*	0.072	0.429
	*HLA-DQB1*05:01*	*9.39×10^{-3}	*0.019	*HLA-C*12*	*0.045	0.192	*HLA-DQB1*02:01*	0.072	0.451
	*HLA-DQB1*05*	*9.54×10^{-3}	*0.022	*HLA-A*29*	*0.046	0.058	*HLA-B*13*	0.075	0.635
	Allele	Interaction p-value	Conditional on *HLA-C*06:02*	Allele	Interaction p-value	Conditional on *HLA-C*06:02*	Allele	Interaction p-value	Conditional on *HLA-C*06:02*
12 months	*HLA-B*57:01*	**2.17×10^{-3}	*0.031	*HLA-C*12*	**4.95×10^{-4}	**3.45×10^{-3}	*HLA-B*57*	*9.11×10^{-3}	0.082
	*HLA-B*57*	**4.65×10^{-3}	0.056	*HLA-B*57*	**1.14×10^{-3}	*0.035	*HLA-C*02:02*	*0.012	*9.24×10^{-3}
	*HLA-C*12*	*5.95×10^{-3}	*0.027	*HLA-C*12:03*	**1.33×10^{-3}	*7.79×10^{-3}	*HLA-B*57:01*	*0.014	0.126
	*HLA-A*25:01*	*7.31×10^{-3}	*0.014	*HLA-B*39*	**1.53×10^{-3}	*5.54×10^{-3}	***HLA-C*06:02***	***0.023**	N/A
	*HLA-DQB1*03:01*	*8.38×10^{-3}	*0.017	***HLA-C*06:02***	****1.90×10^{-3}**	N/A	*HLA-DQB1*03:01*	*0.027	*0.042
	*HLA-DQB1*03:03*	*0.011	0.083	*HLA-B*57:01*	**2.59×10^{-3}	0.083	*HLA-DRB1*13:01*	*0.029	*0.021
	HLA-C*06:02	***0.012**	N/A	*HLA-DPA1*01:03*	*0.016	*0.012	*HLA-B*27*	*0.042	*0.033
	*HLA-C*12:03*	*0.020	0.070	*HLA-DPA1*01*	*0.032	*0.023	*HLA-DQA1*05:01*	*0.044	0.147
	*HLA-C*04:01*	*0.032	0.063	*HLA-DPA1*02*	*0.032	*0.023	*HLA-DRB1*07*	*0.046	0.212
	*HLA-C*04*	*0.032	0.063	*HLA-C*02:02*	*0.036	*0.022	*HLA-DRB1*07:01*	*0.046	0.212

Table E13 – HLA alleles with strongest evidence for interaction with drug independently of *HLA-C*06:02*

Based on full GxE model including clinical covariates and interaction terms, plus *HLA-C*06:02* main effect and interaction terms. The ten most strongly associated HLA alleles are reported for each combination of outcome (PASI75, PASI90, PASI100) and time-point. *: P < 0.05; **: P < 0.005; no tests achieved P < 1.17×10^{-4} (Bonferroni multiple testing threshold for 142 alleles × 3 time-points = 426 tests).

	PASI75 response		**PASI90 response**		**PASI100 response**	
	Allele	Interaction p-value	Allele	Interaction p-value	Allele	Interaction p-value
3 months	*HLA-B*35:01*	*8.92×10^{-3}	*HLA-B*44*	**4.16×10^{-3}	*HLA-B*55:01*	*0.024
	*HLA-DRB1*01:01*	*9.25×10^{-3}	*HLA-B*35:01*	*8.28×10^{-3}	*HLA-DRB1*04:01*	*0.026
	*HLA-B*35*	*9.65×10^{-3}	*HLA-DQB1*05*	*0.010	*HLA-B*37*	*0.036
	*HLA-DRB1*13:02*	*0.012	*HLA-DQB1*05:01*	*0.011	*HLA-B*37:01*	*0.036
	*HLA-DQB1*05:01*	*0.012	*HLA-C*04:01*	*0.013	*HLA-DRB1*04*	*0.044
	*HLA-DPB1*13*	*0.044	*HLA-C*04*	*0.013	*HLA-DPB1*04:02*	*0.045
	*HLA-DPB1*13:01*	*0.044	*HLA-DRB1*13*	*0.013	*HLA-DQB1*03:01*	*0.045
	*HLA-DQB1*03:01*	*0.045	*HLA-DRB1*01*	*0.013	*HLA-DQB1*06*	0.052
	*HLA-C*04*	*0.047	*HLA-B*44:02*	*0.015	*HLA-DRB1*13*	0.060
	*HLA-C*04:01*	*0.047	*HLA-B*35*	*0.015	*HLA-B*44*	0.073
	Allele	Interaction p-value	Allele	Interaction p-value	Allele	Interaction p-value
6 months	*HLA-DRB1*01*	*0.015	*HLA-DPB1*10:01*	*0.037	*HLA-DRB1*01:03*	0.066
	*HLA-C*01:02*	*0.018	*HLA-DPB1*10*	*0.037	*HLA-DRB1*15:01*	0.090
	*HLA-DQB1*05:01*	*0.019	*HLA-A*29*	0.058	*HLA-DRB1*15*	0.091
	*HLA-DQA1*01:01*	*0.021	*HLA-A*30:01*	0.063	*HLA-B*27*	0.092
	*HLA-DQB1*05*	*0.022	*HLA-A*30*	0.069	*HLA-DQB1*06:02*	0.093
	*HLA-DQA1*01*	*0.027	*HLA-B*57*	0.082	*HLA-B*27:05*	0.102
	*HLA-DRB1*01:01*	*0.038	*HLA-DRB1*01:03*	0.087	*HLA-A*29:02*	0.102
	*HLA-DQB1*03:03*	0.054	*HLA-C*01:02*	0.090	*HLA-C*07*	0.104

	*HLA-DQB1*03*	0.055	*HLA-DQB1*06:02*	0.095	*HLA-A*29*	0.105
	*HLA-DQA1*01:03*	0.077	*HLA-A*29:02*	0.100	*HLA-C*07:01*	0.122
	Allele	Interaction p-value	Allele	Interaction p-value	Allele	Interaction p-value
12 months	*HLA-A*25:01*	*0.014	*HLA-C*12*	**3.45×10^{-3}	*HLA-C*02:02*	*9.24×10^{-3}
	*HLA-B*13:02*	*0.017	*HLA-B*39*	*5.54×10^{-3}	*HLA-DRB1*13:01*	*0.021
	*HLA-DQB1*03:01*	*0.017	*HLA-C*12:03*	*7.79×10^{-3}	*HLA-B*27*	*0.033
	*HLA-B*13*	*0.022	*HLA-DPA1*01:03*	*0.012	*HLA-B*27:05*	*0.037
	*HLA-C*12*	*0.027	*HLA-C*02:02*	*0.022	*HLA-DQA1*01:03*	*0.038
	*HLA-DQB1*06*	*0.029	*HLA-DPA1*01*	*0.023	*HLA-DQB1*06:03*	*0.041
	*HLA-B*57:01*	*0.031	*HLA-DPA1*02*	*0.023	*HLA-DQB1*03:01*	*0.042
	*HLA-DRB1*04:01*	*0.048	*HLA-B*57*	*0.035	*HLA-DPA1*02:02*	0.055
	*HLA-DQA1*01:02*	0.053	*HLA-DPA1*02:02*	*0.040	*HLA-A*31:01*	0.058
	*HLA-DQA1*01*	0.054	*HLA-A*68:01*	*0.046	*HLA-A*31*	0.058

Table E14 – Full drug × HLA allele interaction test results for all HLA alleles

See supplementary data file (Excel workbook)

Table E15 – GxGxE test results for interaction between *HLA-C*06:02* and *ERAP1* variant rs27524

Based on full GxGxE model including the second-order interaction term drug × *HLA-C*06:02* dosage × rs27524 genotype, all lower-order interaction and main-effect terms, and all covariates from the full GxE model. Results shown are for first- and second-order interaction terms between drug, *HLA-C*06:02* dosage and rs27524 genotype only.

	PASI75 response			PASI90 response			PASI100 response		
	3 months	**6 months**	**12 months**	**3 months**	**6 months**	**12 months**	**3 months**	**6 months**	**12 months**
n adalimumab	401	586	514	401	586	514	401	586	514
n ustekinumab	245	325	298	245	325	298	245	325	298
n total	646	911	812	646	911	812	646	911	812
Drug × *HLA-C*06:02* interaction									
Effect size (beta)	-1.201	-0.649	-0.744	-0.634	-1.304	-0.674	-0.419	-1.195	-0.597
95% CI	(-2.274, -0.127)	(-1.559, 0.262)	(-1.713, 0.225)	(-1.700, 0.432)	(-2.140, -0.469)	(-1.499, 0.151)	(-1.722, 0.884)	(-2.182, -0.207)	(-1.513, 0.318)
P-value	0.028	0.163	0.132	0.243	2.22×10^{-3}	0.109	0.528	0.018	0.201
Drug × rs27524 interaction									
Effect size (beta)	-0.751	0.301	-0.101	0.092	-0.017	-0.209	-0.410	-0.234	-0.264
95% CI	(-1.484, -0.019)	(-0.370, 0.972)	(-0.844, 0.642)	(-0.746, 0.929)	(-0.655, 0.622)	(-0.871, 0.453)	(-1.389, 0.569)	(-1.013, 0.545)	(-0.986, 0.458)
P-value	0.044	0.379	0.789	0.830	0.959	0.536	0.412	0.556	0.473
***HLA-C*06:02* × rs27524 interaction**									
Effect size (beta)	-0.422	0.314	0.090	0.078	-0.331	0.053	0.027	-0.109	0.060
95% CI	(-1.177, 0.333)	(-0.370, 0.998)	(-0.636, 0.815)	(-0.723, 0.879)	(-0.985, 0.323)	(-0.597, 0.703)	(-0.904, 0.957)	(-0.902, 0.683)	(-0.648, 0.768)
P-value	0.274	0.368	0.809	0.848	0.321	0.873	0.955	0.787	0.868
Drug × *HLA-C*06:02* × rs27524 interaction									
Effect size (beta)	0.585	-0.506	-0.131	-0.312	0.090	-0.259	0.028	0.013	-0.102
95% CI	(-0.339, 1.509)	(-1.343, 0.332)	(-1.039, 0.777)	(-1.257, 0.632)	(-0.702, 0.883)	(-1.059, 0.540)	(-1.066, 1.122)	(-0.923, 0.949)	(-0.971, 0.767)
P-value	0.215	0.237	0.778	0.517	0.823	0.525	0.960	0.979	0.818

Table E16 – GxE model for drug and *ERAP1* genotype among patients that are *HLA-C*06:02* negative

Based on GxE model for patients that are *HLA-C*06:02* negative only. Results are presented for the model interaction term only. Results for other model terms are not shown; in particular main effect terms are not unambiguously interpretable in the presence of an interaction term.

	PASI75 response			PASI90 response			PASI100 response		
	3 months	**6 months**	**12 months**	**3 months**	**6 months**	**12 months**	**3 months**	**6 months**	**12 months**
HLA-C*06:02 *Negative*									
n adalimumab	195	265	243	195	265	243	195	265	243
n ustekinumab	113	153	137	113	153	137	113	153	137
n total	308	418	380	308	418	380	308	418	380
Drug × rs27524 interaction									
Effect size (beta)	-0.893	0.082	-0.346	0.166	-0.109	-0.319	-0.410	-0.356	-0.314
95% CI	(-1.644, -0.142)	(-0.594, 0.758)	(-1.086, 0.393)	(-0.732, 1.064)	(-0.771, 0.552)	(-0.986, 0.349)	(-1.437, 0.616)	(-1.171, 0.459)	(-1.049, 0.422)
P-value	0.020	0.812	0.359	0.717	0.746	0.350	0.433	0.392	0.403

Table E17 – Test results for *HLA-C*06:02* and *ERAP1* model excluding GxGxE term

Based on model including same main effect and first-order interaction terms as the full GxGxE model, but no second-order interaction term. Results shown are for interaction terms between drug, *HLA-C*06:02* dosage and rs27524 genotype only.

	PASI75 response			PASI90 response			PASI100 response		
	3 months	**6 months**	**12 months**	**3 months**	**6 months**	**12 months**	**3 months**	**6 months**	**12 months**
n adalimumab	401	586	514	401	586	514	401	586	514
n ustekinumab	245	325	298	245	325	298	245	325	298
n total	646	911	812	646	911	812	646	911	812
Drug × *HLA-C*06:02* interaction									
Effect size (beta)	-0.722	-1.051	-0.845	-0.886	-1.235	-0.863	-0.395	-1.185	-0.675
95% CI	(-1.470, 0.025)	(-1.680, -0.422)	(-1.522, -0.167)	(-1.639, -0.133)	(-1.813, -0.657)	(-1.451, -0.275)	(-1.292, 0.502)	(-1.866, -0.504)	(-1.308, -0.043)
P-value	0.058	0.001	0.015	0.021	2.80×10^{-5}	4.01×10^{-3}	0.388	6.45×10^{-4}	0.036
Drug × rs27524 interaction									
Effect size (beta)	-0.440	0.010	-0.177	-0.115	0.037	-0.363	-0.392	-0.226	-0.324
95% CI	(-0.979, 0.098)	(-0.454, 0.473)	(-0.703, 0.349)	(-0.668, 0.439)	(-0.397, 0.470)	(-0.825, 0.098)	(-1.054, 0.270)	(-0.740, 0.287)	(-0.832, 0.183)
P-value	0.109	0.968	0.510	0.685	0.868	0.123	0.246	0.388	0.210
***HLA-C*06:02* × rs27524 interaction**									
Effect size (beta)	-0.030	-0.022	0.007	-0.145	-0.270	-0.118	0.047	-0.100	-0.007
95% CI	(-0.470, 0.409)	(-0.417, 0.372)	(-0.435, 0.448)	(-0.572, 0.281)	(-0.642, 0.102)	(-0.498, 0.263)	(-0.449, 0.543)	(-0.524, 0.323)	(-0.422, 0.407)
P-value	0.892	0.912	0.976	0.504	0.155	0.545	0.853	0.642	0.973

Table E18 – GxE test results for which duplicated patients are excluded from both groups

Results of fitting the simple GxE model including covariate terms for baseline PASI, five ancestry PCs, drug, *HLA-C*06:02* dosage and the drug × *HLA-C*06:02* interaction, after excluding 101 patients that were randomly allocated to adalimumab/ustekinumab groups due to having eligible records for both. Results are comparable to main findings shown in Table E2.

	PASI75 response			**PASI90 response**			**PASI100 response**		
	3 months	**6 months**	**12 months**	**3 months**	**6 months**	**12 months**	**3 months**	**6 months**	**12 months**
n adalimumab	379	548	489	379	548	489	379	548	489
n ustekinumab	216	294	268	216	294	268	216	294	268
n total	595	842	757	595	842	757	595	842	757
Drug × *HLA-C*06:02* interaction									
Effect size (beta)	-0.794	-0.972	-0.846	-1.108	-1.177	-0.813	-0.794	-1.227	-0.804
95% CI	(-1.454, -0.135)	(-1.560, -0.384)	(-1.476, -0.216)	(-1.802, -0.414)	(-1.718, -0.636)	(-1.360, -0.266)	(-1.612, 0.024)	(-1.873, -0.582)	(-1.405, -0.204)
P-value	0.018	1.21×10^{-3}	8.53×10^{-3}	1.75×10^{-3}	2.03×10^{-5}	3.56×10^{-3}	0.057	1.95×10^{-4}	8.68×10^{-3}

Supplementary Methods

Genotype data and HLA imputation

DNA was isolated from blood using standard methods. Genotyping was performed using Illumina HumanOmniExpressExome-8 v1.2 and v1.3 BeadChips. Three rounds of genotype calling were performed using Illumina's GenomeStudio Data Analysis software, based on four different genotyping batches (samples clustered using GenTrain 2.0 algorithm). Genotyping QC was performed using PLINK v1.07[1], KING v1.4[2] and R[3]. Samples were excluded based on call rate (<0.99), mismatch with recorded gender, heterozygosity (±4 s.d. from the mean), relatedness (second degree relative or closer; kinship coefficient > 0.0884), suspected non-European ancestry indicated by principal component analysis (PCA) and residual PCA outlier status (>5 s.d. from the mean for PCs 1-20). Genetic variants were excluded based on call rate (<0.99), low GenomeStudio cluster separation score (<0.4), deviations from Hardy-Weinberg equilibrium ($P < 7.5\times10^{-8}$ based on number of variants tested) and minor allele frequency <1%. To eliminate potential batch effects we checked that there were no allele flips between batches and excluded variants with differential missing rates ($P < 0.01$) and allele frequencies ($P < 10^{-5}$; 7 variants) between batches.

HLA imputation proceeded as follows. First, genotype intensity cluster plots were inspected for 3,141 single nucleotide polymorphisms in the HLA region (all SNPs within the range chr6:29494897-33160425 in the GRCh37/hg19 genome assembly, to correspond to the imputation reference panel described below). Where appropriate, genotypes were manually "rescued" using Evoker (version 2.3)[4]. Classical HLA alleles were imputed using SNP2HLA (v1.0.3), based on the T1DGC reference panel[5]. We excluded poorly imputed alleles (R2 < 0.9) and alleles with frequency <0.01, giving a total of 142 distinct 2- and 4-digit imputed alleles.

Statistical modelling

To generate the full multivariable logistic regression model for response accounting for potential clinical confounders, main effect and interaction covariate terms were added based on correlations with *HLA-C*06:02* or drug (**Table 1**). For variables significantly correlated with *HLA-C*06:02*, an interaction term with drug was included, and vice versa.

The full model included: covariate main effect terms for baseline PASI, ancestry PCs 1-5 derived from 108,319 independent SNPs using KING software[2], age of psoriasis onset, presence of PsA, biologic naive status, disease duration at treatment start, and methotrexate co-therapy up to the response measurement date (binary variable); interaction terms with drug for age of onset,

baseline PASI, disease duration and PsA; and interaction terms with *HLA-C*06:02* dosage for PsA and biologic naive status

Propensity score modelling

To confirm that our full multivariable model adequately controlled for potential confounding via covariates influencing treatment selection, we repeated the regression analysis with inverse probability of treatment weighting (IPTW) using the propensity score[6]. Specifically, we derived a propensity score model to estimate the probability that each patient would have been received treatment with adalimumab rather than ustekinumab. As recommended by Austin[6], we included in the propensity score model all "potential confounders": covariates that were independently associated with PASI90 response. Conservatively, we included all covariates that demonstrated a nominal association with PASI90 response ($P < 0.05$) at any of our three time-points, among adalimumab patients only, ustekinumab patients only, or all patients combined (data not shown). The propensity score model included baseline PASI, ancestry PC 1, age of psoriasis onset, presence of PsA, biologic naive status, disease duration at treatment start and *HLA-C*06:02* dosage. Balance analysis showed that all covariates were well matched between adalimumab and ustekinumab groups after IPTW using the propensity score (**Table E4**, **Figure E1**): all standardised mean differences were below the accepted threshold of 0.1 at which a covariate differences between groups can be considered negligible[6].

IPTW can be incorporated into regression models analogously to survey sampling weights. The full multivariable logistic regression model (described in the previous section) was re-fitted using IPTW derived from the propensity score model using the 'survey' package in R.

References for supplementary methods

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Supplementary Data

HLA-C*06:02 genotype is a predictive biomarker of biologic treatment response in psoriasis vulga

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Table E14 **Full drug × HLA allele interaction test results for all HLA alleles**

"Full model": based on full Gwl model including clinical covariates and interaction terms; "Conditional on HLA-C*06:02": based on a model that also includes HLA-C*06:02 main effect and interaction terms. In each case effect size (beta), standard error and p-value of HLA allele dosage × Drug interaction term are reported.

	PASI75 response												PASI90 response												PASI100 response											
	3m						12m						3m						12m						3m						12m					
	Full model drug × HLA allele interaction			Conditional on HLA-C*06:02			Full model drug × HLA allele interaction			Conditional on HLA-C*06:02			Full model drug × HLA allele interaction			Conditional on HLA-C*06:02			Full model drug × HLA allele interaction			Conditional on HLA-C*06:02			Full model drug × HLA allele interaction			Conditional on HLA-C*06:02			Full model drug × HLA allele interaction			Conditional on HLA-C*06:02		
	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]