

Impact of HLA-DQA1*05 Genotype in Immunogenicity and Failure to Treatment with Tumour Necrosis Factor-alpha Antagonists in Inflammatory Bowel Disease: A Systematic Review and Meta-analysis

Leticia Rodríguez-Alcolado,^{a,b,*} Elena Grueso-Navarro,^{a,*} Ángel Arias,^{c,d,e}
Alfredo J. Lucendo,^{a,c,d,f,t} Emilio J. Laserna-Mendieta^{a,c,d,t}

^aDepartment of Gastroenterology, Hospital General de Tomelloso, Tomelloso, Spain

^bDepartment of Public Health, Universidad de Alcalá, Alcalá de Henares, Spain

^cCentro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas [CIBERehd], Madrid, Spain

^dInstituto de Investigación Sanitaria de Castilla-La Mancha [IDISCAM], Toledo, Spain

^eResearch Unit, Hospital General Mancha Centro, Alcázar de San Juan, Spain

^fInstituto de Investigación Sanitaria La Princesa, Madrid, Spain

Corresponding author: Dr Alfredo J Lucendo. Department of Gastroenterology. Hospital General de Tomelloso. Vereda de Socuéllamos s/n, 13700 Tomelloso, Ciudad Real, Spain. Fax: 0034926525870; Email: ajlucendo@hotmail.com

*Both authors should be considered as first authors.

†Both authors should be considered as senior authors.

Abstract

Background: HLA-DQA1*05 carriage has been associated with an increased risk of immunogenicity in patients with immune-mediated inflammatory diseases treated with tumour necrosis factor-alpha [TNF- α] antagonists. Results have shown an inconsistent association with a loss of response [LOR] in patients with inflammatory bowel disease [IBD], which could be modified when using proactive optimisation and association with immunomodulatory drugs.

Aims: To define the association of HLA-DQA1*05 on anti-drug antibody development and loss of response [LOR] to anti-TNF- α in IBD.

Methods: We searched MEDLINE, EMBASE, and SCOPUS, for the period up to August 2023, to identify studies reporting the risk of immunogenicity and/or LOR in IBD patients with HLA-DQA1*05 genotype.

Results: A total of 24 studies comprising 12 papers, 11 abstracts and one research letter, with a total of 5727 IBD patients, were included. In a meta-analysis of 10 studies [2984 patients; 41.9% with HLA-DQA1*05 genotype], HLA-DQA1*05 carriers had higher risk of immunogenicity compared with non-carriers (risk ratio, 1.54; 95% confidence interval [CI], 1.23 – 1.94; $I^2 = 62\%$) [low certainty evidence]. Lack of therapeutic drug monitoring [TDM] increased immunogenicity in the presence of risk human leukocyte antigen [HLA] [risk ratio 1.97; 95% CI, 1.35 – 2.88; $I^2 = 66\%$], whereas proactive TDM revoked this association [very low certainty of evidence]. A meta-analysis of six studies [765 patients] found that risk for secondary LOR was higher among HLA-DQA1*05 carriers [hazard ratio 2.21; 95% CI, 1.69 – 2.88; $I^2 = 0\%$] [very low certainty evidence], although definition and time to assessment varied widely among studies.

Conclusion: HLA-DQA1*05 carriage may be associated with an increased risk of immunogenicity and secondary LOR in IBD patients treated with TNF- α antagonists.

Key Words: Biologics; Crohn's disease; HLA-DQA1*05; inflammatory bowel disease; pharmacogenomics; ulcerative colitis

1. Introduction

Inflammatory bowel diseases [IBD], mainly comprising Crohn's disease [CD] and ulcerative colitis [UC], are chronic inflammatory conditions that primarily affect the gastrointestinal tract. Since they may involve other organs, they are considered systemic diseases. With a steady increase in prevalence in developed and newly industrialised countries,¹ IBD represents an important health problem: it affects patients of productive age; is associated with significant morbidity and disability²; and is costly due to long-term and often expensive treatments.³ In moderate and severe forms of the disease,

treatment is usually based on immunosuppressant and/or biologic drugs aimed at reducing gut inflammation by attenuating the activity of the immune system.

Tumour necrosis factor-alpha [TNF α] antagonists were the first biologic agents used in IBD, and are currently the most widely used biologics for treating IBD patients, as well as being effective in other immune-mediated inflammatory diseases [IMIDs]. However, a proportion of patients do not respond to induction with anti-TNF α drugs [primary non-responders] and others can lose response during maintenance [secondary non-responders].⁴ The latter is predicted by low drug concentrations,⁵ mediated in part by the development

of neutralising antidrug antibodies [ADAs], also referred to as immunogenicity.⁶ Combining immunomodulator [IMM] therapy was found to mitigate the risk of developing ADA.⁵ Immunogenicity to biologic therapies is a major concern, and the identification of patients at increased risk of immunogenicity to TNF α antagonist has been the subject of intense research in recent years. The implications for the choice of IBD treatment, the adoption of disease monitoring strategies, or the potential to ameliorate immunogenicity through combination with IMMs, has produced an abundant body of literature. This is particularly after the association of the human leukocyte antigen [HLA] allele group HLA-DQA1*05 with the development of ADA to TNF α antagonists.⁷ Carrying the HLA-DQA1*05 genotype has been associated with increased formation of ADA in patients treated with infliximab and adalimumab for IBD and other IMIDs.⁸ However, conflicting results have been provided on the effect of HLA-DQA1*05 and the risk for secondary loss of response [LOR],^{9,10} treatment persistence,^{11,12} and the effect of therapeutic drug monitoring,^{13,14} and these areas need to be analysed.

We conducted a systematic review and meta-analysis to evaluate the association between HLA-DQA1*05 carriage and the risk of immunogenicity to TNF α antagonists in patients with IBD. The effect of HLA-DQA1*05 on primary non-response [PNR], secondary LOR, treatment discontinuation [defined either as time to cessation, or proportion of patients who stopped treatment], and adverse events were also assessed, whenever possible. The Grading of Recommendations, Assessment, Development and Evaluations [GRADE] framework was used to critically appraise certainty of evidence.¹⁵

2. Methods

We used Preferred Reporting Items for Systematic Reviews and Meta-Analysis [PRISMA] methodology for conducting this systematic review,¹⁶ registered in the International Platform of Registered Systematic Review and Meta-Analysis Protocols [<https://inplasy.com>] as INPLASY202320076. No funding was received for the review.

2.1. Selection criteria

We included any study that met the following inclusion criteria: [1] patients: paediatric or adult patients with IBD who were treated with the anti-TNF α drugs infliximab, adalimumab, or golimumab; [2] exposure: carriage of at least one copy of HLA-DQA1*05; [3] comparator: not carrying HLA-DQA1*05; [4] outcomes: development of ADA to anti-TNF α drugs, and failure [defined either as PNR, secondary LOR, treatment discontinuation, or adverse events] to anti-TNF α therapy.

Inclusion criteria incorporated observational studies [both retrospective and prospective designs] and randomised controlled trials with adult, paediatric, or mixed populations. Abstracts were included and no restrictions were placed on language of publication. Documents identified through the reading of the selected articles and communications were also included. We excluded review articles, systematic reviews, clinical guidelines, book chapters, letters to the editor, and editorials with no original data. Studies lacking information on the desired outcomes [immunogenicity, treatment failure, or both]; studies not carried out on humans; and those providing duplicated information [ie, abstracts repeatedly presented to

different congresses, or abstracts that were subsequently published as a full paper] were also excluded.

2.2. Search strategy

A systematic literature search was performed in duplicate [by AA and AJL] in three databases [PubMed, EMBASE, and Scopus] for the period from database inception up to January 2023. The search terms were: ([Infliximab/therapeutic use] OR [Adalimumab/pharmacology/therapeutic use] OR [Tumour Necrosis Factor Inhibitors/therapeutic use] OR [Tumour Necrosis Factor-alpha/genetics/therapeutic use]; OR [adalimumab] OR [TNF inhibitor or anti-TNF]; OR [TNF inhibitors]; OR [TNF-alpha] OR [infliximab]); AND ([dqa1 05*] OR [HLA-DQ alpha-Chains/genetics] OR [HLA-DQA1*]; OR [HLA-DQ alpha-Chains]; OR [HLA-DQA1 antigen]).

The results of the full search were merged into a single list, where duplicate records were identified and removed. Two researchers [LRA, EGN] independently performed the screening of the unified list, reviewing the title and abstract of every publication, and excluding irrelevant studies. Where disagreement occurred, consensus was reached through discussion with a third researcher [EJLM]. In cases of non-English text articles, Google Translate was first used to determine eligibility, followed by a professional translation service if eligible; however, this was not needed.

Literature searches were repeated on August 29, 2023, to retrieve the most recent documents and provide updated results.

2.3. Data extraction

Full text and supplementary data of the selected articles were retrieved and studied by two researchers [LRA, EGN], who independently extracted relevant information using a standardised data extraction form, followed by a cross-check of the results. Disagreements between reviewers were resolved through discussion with a third researcher [EJLM]. The extracted data included: the last name of first author, publication year, country of origin, type of publication, time of follow-up, study design, number of patients, age and sex [% males] of patients, type of IBD included, outcomes measured and their definitions, therapeutic drug monitoring [TDM] strategy [if any], type of anti-TNF α used and line of treatment [first- or second-line], HLA or single nucleotide polymorphism [SNP] determination and by which method, use of concomitant IMMs, prevalence of HLA-DQA1*05 carriage, and rate of failure to treatment and immunogenicity according to HLA-DQA1*05 carriage.

2.4. Risk of bias assessment

Retrieved documents were evaluated in duplicate [AJL and AA] for risk of bias using the Robins-E tool [Risk of Bias in Non-Randomized Studies—of Exposure].¹⁷ A study was considered to be at low risk of bias if each of the bias items could be categorised as low-risk. However, studies were judged as having a high risk of bias if any of the items were deemed high-risk.

2.5. Outcomes assessed

Outcomes of interest included: a) the risk of immunogenicity [defined as ADA development according to method for assessment] in patients with HLA-DQA1*05 genotype; b) clinical impact of carrying HLA-DQA1*05 in anti-TNF α drug failure

[defined either as PNR, LOR, treatment discontinuation, or development of adverse events]. Curiously, two studies reported results for failure and/or immunogenicity not for patients but calculated for events per each treatment.^{9,18}

2.6. Synthesis methods

To summarise the findings of the review on the immunogenicity outcome, a meta-analysis was carried out, including the raw number of patients with ADA development according to HLA-DQA1*05 carriage. For two studies,^{7,19} these data could not be obtained directly from the paper so authors were contacted, but only one response was received.⁷

Heterogeneity between studies was assessed by means of a chi square test [Cochran Q statistic] and quantified with the I^2 statistic. If $p < 0.05$ and/or $I^2 > 50\%$, there was significant heterogeneity and a random effects model was used. Generally, I^2 was used to evaluate the level of heterogeneity, assigning the categories low, moderate, and high to I^2 values of 25%, 50%, and 75%, respectively.²⁰

For immunogenicity outcomes, a random effects meta-analysis was performed. Results were expressed as pooled Mantel-Haenszel risk ratios [RRs] with 95% confidence interval [95% CI] and forest plot graph. A sensitivity analysis by excluding studies with high risk of bias was performed. Publication bias was evaluated with the aid of a funnel plot, the asymmetry of which was assessed through Egger tests.²¹

For secondary endpoints, descriptive summaries and data tables were created for anti-TNF α drug failure, to address the high variability of definitions and outcomes used [Supplementary Table S1]. When summary data were not available for each intervention group, an overall estimate of the effect of each study was obtained, after extraction of hazard ratios data and meta-analyses using the generic inverse variance method.

All calculations were made with StatsDirect statistical software version 2.7.9 [StatsDirect, Cheshire, UK] and Review Manager [Cochrane Collaboration].

2.7. Subgroup analysis

For testing how sensitive our results were to changes in the study methods or data used in the review, subgroup analyses were planned according to type of publication [full paper or abstract], type of disease [CD or UC], anti-TNF α agent used [infliximab or adalimumab], patients' age [adult or paediatric series], type of assay for ADA measurement [tolerant or sensitive], TDM [proactive or no TDM mentioned], and risk of bias in source documents.

2.8. Certainty of evidence

We ascertained certainty of evidence for the primary outcomes using the GRADE approach.¹⁵ This specifies certainty for a body of evidence for each outcome as high, moderate, low, and very low, by considering five domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias.²²

3. Results

3.1. Results of the systematic literature search

The search retrieved 245 non-duplicated documents. After screening titles and abstracts, 28 studies were reviewed in detail with full reading, and 13 discarded. Six additional studies

were identified by reference tracking, and three more added from the final database search. Thus 24 studies, reporting on 23 individual patient cohorts, were finally included in the systematic review [Figure 1].

3.2. Main characteristics of the included studies

The main data extracted from the selected studies are shown in Table 1 and Table 2. Table 1 details data on study design, patient demographics, IBD type, and treatment details [anti-TNF α drug with or without concomitant IMMs]; Table 2 focuses on outcome assessed, determination techniques and prevalence of HLA-DQA1*05, method for measurement of ADA, line of anti-TNF α treatment, and main conclusions of each individual study.

Of the 24 studies, 12 were full research papers,^{7,9,11,13,19,24,27,32-34,36,37} 11 abstracts,^{10,12,18,23,25,26,28-31,35} and one a research letter.¹⁴ The same cohort of patients was used in the two studies by Colman *et al.* [the full paper did not include data previously reported in an abstract].^{13,25} Most cohorts reported on mixed IBD populations; seven cohorts included CD patients^{7,10,11,19,25,34,37} and one UC patients,²⁸ exclusively. One cohort did not differentiate IBD variants.²⁹ Overall, patients with CD predominated in mixed cohorts.

As for study design, 15 were retrospective cohorts, six were prospective, and data in one study were derived from a randomised controlled trial. The remaining study had no information on study design. Most of the studies [13 cohorts] included adult or mixed patients, with two studies reporting results in paediatric populations predominantly. Eight studies did not provide information about their targeted population. Fifteen cohorts were recruited in European countries, five were American cohorts, two came from China, and one from Japan. Follow-up length to outcome assessment varied greatly among cohorts, from a median of 10 months to 13 years.

Overall, the 23 patient cohorts provided data from 5727 individual patients with IBD [including 4349 with CD, 1129 with UC, 41 with IBD-unclassified, and 208 in whom IBD type was not specified]. Data on HLA-DQA1*05 were provided in all but 31 patients with IBD.

The overall risk of bias evaluated for the 24 individual studies revealed that eight presented a high or very high risk, 14 had an intermediate risk of bias [because concerns on some item were raised], and only two studies were judged as low risk of bias [Figure 2A]. The poor control of potential confounding factors in IBD patients which were not measured, the selection of participants onto the study, and the selection of the reported results were the main domains for risk of bias [Figure 2B].

3.3. Type of TNF α antagonist and concomitant therapy

Among anti-TNF α drugs, infliximab and adalimumab were preferred, with infliximab being the most preferred. Only two cohorts used golimumab, in 33 patients overall.^{26,32} Specifically, 12 cohorts used exclusively infliximab,^{11,12,14,19,25,28,29,34-38} and adalimumab was only used exclusively in one cohort.¹⁰ Nine cohorts included patients treated with both infliximab and adalimumab,^{7,9,18,24,26,27,30-32} Details on the drug used were not provided in a further study.²³ Despite two cohorts also including 138 patients treated with vedolizumab and ustekinumab,^{9,30} only results for patients treated with infliximab and adalimumab were reported and included in this systematic review.

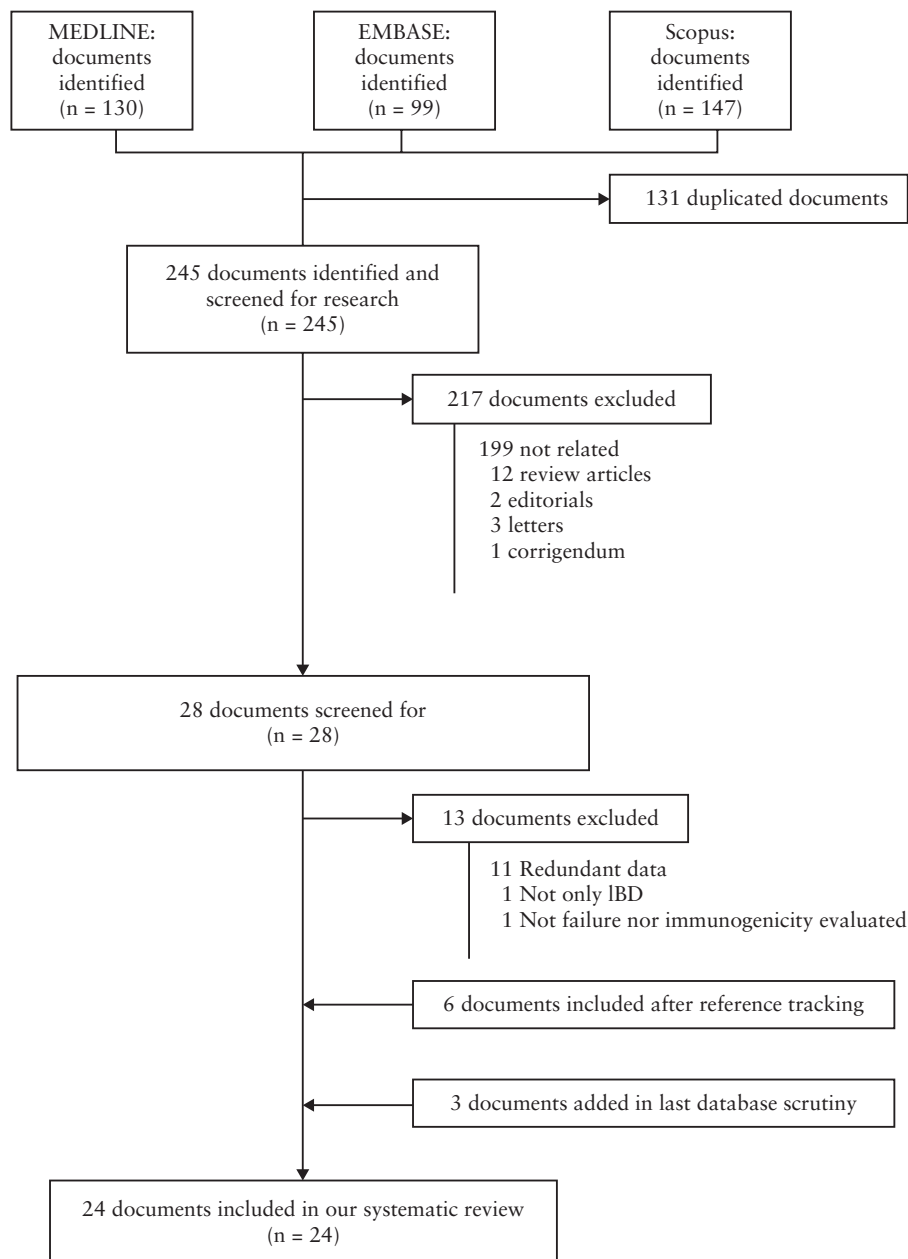


Figure 1 Study selection flowchart.

The use of IMM drugs varied widely among individual studies, from 4%²⁵ to 91%.³⁶ The percentage of patients under concomitant immunosuppressant therapy was not reported in six cohorts^{10,12,29-31,35} and no patients were under combined therapy in the remaining study.³⁷

3.4. Determination of HLA and frequency of HLA-DQA1*05 carriage

HLA-DQA1*05 genotyping was mostly undertaken by analysing the rs2097432 single nucleotide polymorphism [SNP] using different methods [direct genotyping or SNP arrays] in nine cohorts,^{7,14,19,24,30,33,34,36,37} and more complex methods based on polymerase chain reaction, either by sequence specific oligonucleotide [PCR-SSO] or by sequence specific priming [PCR-SSP], were used in five^{18,25,27,31,32} and one cohort,⁹ respectively. One study used both methods,¹¹ another

study used HLA imputation from whole genome sequencing,²⁶ with no details being provided by the remaining [all abstract] six studies.

The frequency of HLA-DQA1*05 carriage was relatively homogeneous among patient cohorts, with most studies reporting 35–50% [range 20–64%].

3.5. Risk of immunogenicity to anti-TNF α drugs

Among the 11 patient cohorts (3027 patients; prevalence of HLA-DQA1*05, 41.9% [range, 37%–58%]) where this outcome was assessed, an association between HLA-DQA1*05 carriage and ADA formation was found in five studies^{7,18,28,36,37} [1829 patients] and 5 more [879 patients] found no association.^{13,14,19,24,25,31} One of the studies identified that HLA-DQA1*05 was associated with immunogenicity for adalimumab exclusively, but not for infliximab.³⁰

Table 1 Main characteristics of the included studies re: type of study, patient demographics, type of inflammatory bowel disease, and type of treatment.

First author, year	Country	Type of publication	Follow-up in months, median [IQR]	Cohort design	No. of patients	Type of IBD	Age of patients in years, median [IQR]	Population of study	Male [%]	Type of anti-TNF α drug	Concomitant use of IMM
Aleman Gonzalez, 2022 ²³	UK	Abstract	12	Prospective	76	CD [56.6%] UC [42.1%] IBD-U [1.3%]	No info	No info	No info	No info	44.0%
Angulo McGrath, 2021 ¹²	Spain	Abstract	35 [58]	Retrospective	88	CD [71.6%] UC [28.4%]	39.0 [20.0]	No info	52.3%	IFX	Yes, but no data
Bangma, 2020 ²⁴	The Netherlands	Full paper	No info	Prospective	376	CD [73.9%] UC [22.6%] IBD-U [3.5%]	47.0 [21.0]	No info	34.6%	IFX [75.5%] ADL [24.5%]	47.3%
Colman, 2021 ^{13,25}	USA	Full paper and abstract	12	Prospective	78 [51 with HLA data]	CD	12.0 [10.0-15.0]	Mixed [paediatric dominance]	64.7% ^a	IFX	3.9% ^a
Davis Gonzalez, 2022 ⁹	Spain	Full paper	108-156 ^b	Retrospective	150	CD [72.0%] UC [28.0%]	No info	Adults	60.7%	IFX [42.9%] ADL [35.9%] Other [21.2%] ^c	CD: 35.2% UC: 43.0%
Doherty, 2023 ²⁶	Ireland	Abstract	65.8	Retrospective	877	CD [69.9%] UC [30.1%]	No info	No info	48.6%	IFX [34.3%] ADL [62.4%] Golimumab [0.3%]	22.5%
Fuentes Valenzuela, 2023 ²⁷	Spain	Full paper	17 [8-31]	Retrospective	112	CD [80.4%] UC [19.3%]	HLA-DQA1*05:- 40.3 [25.3-49.7] HLA-DQA1*05+:- 37.6 [25.3-47.1]	Mixed	58.0%	IFX ADL	35.7%
Gonzalez, 2021 ²⁸	UK	Abstract	15 [9-29]	Retrospective	94	UC	No info	No info	No info	IFX	52.2%
Gu, 2022 ¹⁸	USA	Abstract	11 [1-204]	Retrospective	129	CD [83.7%] UC [14.7%] IBD-U [1.6%]	No info	No info	No info	IFX ADL	29.9%
Guardiola, 2019 ²⁹	Spain	Abstract	56 ^d	Retrospective	64	CD [80.4%] UC [31.2%]	No info	No info	No info	IFX	No info
Guardiola Capon, 2020 ¹⁰	Spain	Abstract	51 [35-74]	Retrospective	53	CD	No info	No info	No info	ADL	Yes, but no data
Hu, 2021 ¹⁹	China	Full paper	20 [13-30]	Retrospective	62 [58 with HLA data]	CD	12.4 [10.0-14.35]	Pediatric	62.9%	IFX	14.5%
Ioannou, 2021 ³⁰	USA	Abstract	No info	Retrospective	610	CD [64.9%] UC [32.8%] IBD-U [2.3%]	HLA-DQA1*05:- 39.0 [17.0-83.0] HLA-DQA1*05+:- 40.0 [22.0-82.0]	Adults	52.6%	IFX [55.7%] ADL [26.9%] Other [17.4%] ^c	No info
Laserna Mendieta, 2023 ¹¹	Spain	Full paper	116 [96-145]	Prospective	131	CD	36.4 [27.7-46]	Adults	50.4%	IFX	51.9%

Table 1. Continued

First author, year	Country	Type of publication	Follow-up in months, median [IQR]	Cohort design	No. of patients	Type of IBD	Age of patients in years, median [IQR]	Population of study	Male [%]	Type of anti-TNF α drug	Concomitant use of IMM
Lopez Blanco, 2022 ³¹	Spain	Abstract	No info	Retrospective	208	IBD	No info	No info	No info	IFX ADL	No info
Pascual Oliver, 2023 ³²	Spain	Full paper	24 [11–66]	Retrospective	199	CD [80.9%] UC [19.1%]	41.8 \pm 15.5 ^d	No info	50.8%	IFX [60.8%] ADL [36.2%] Golimumab [3%]	59.8%
Salvador Martin, 2023 ³³	Spain	Full paper	108	Ambispective	340	CD [70.5%] UC [27.4%] IBD-U [2.1%]	12.2 [4.1]	Paediatric	60.3%	IFX [67.1%] ADL [32.9%]	87.6%
Sazonovs, 2020 ⁷	UK	Full paper	36	Prospective	1240	CD	IFX: 31.3 ^e [21.2–46.0] ADL: 37.6 ^e [28.7–50.3]	Mixed	47.3%	IFX [59.8%] ADL [40.2%]	IFX: 60.4% ADL: 50.6%
Shimoda, 2023 ³⁴	Japan	Full paper	No info	Retrospective	189	CD	No info	No info	71.4%	IFX	16.4%
Spencer, 2022 ¹⁴	USA	Research letter	12	Prospective	186	CD [70.4%] UC [27.4%] IBD-U [2.2%]	17.0 [14.0–20.0]	Mixed	52.2%	IFX	9.7%
Suris Marin, 2021 ³⁵	Spain	Abstract	>6	Retrospective	99	CD [65.7%] UC [34.3%]	No info	No info	No info	IFX	Yes, but no data
Wilson, 2019 ³⁶	Canada	Full paper	36 [22–55]	Retrospective	262	CD [58.0%] UC [42.0%]	39.7 ^d [18.0–79.0]	Adults	48.1%	IFX	90.5%
Zhu, 2023 ³⁷	China	Full paper	10 [5–17]	No info	104	CD	30.0 [24.0–37.0]	Adults	73.1%	IFX	No

ADL, adalimumab; CD, Crohn's disease; HLA, human leukocyte antigens; HLA-DQA1*05, non-carrier of HLA-DQA1*05; IBD, inflammatory bowel disease; IFX, infliximab; IMM, immune-mediated inflammatory disease; IMM, immunomodulatory drugs; IQR, interquartile range; no info, no information; TNF, tumour necrosis factor; UC, ulcerative colitis; IBD-U, inflammatory bowel disease unclassified.

^aThe data correspond to the 51 patients with results for HLA.

^bThe reported result is the range.

^cOther treatments were vedolizumab and ustekinumab.

^dThe reported result is the mean.

^eNot reported if it is mean or median.

Table 2 Main characteristics of the included studies: measured outcome, definitions of failure and immunogenicity to anti-TNF α treatment, determination and prevalence of HLA-DQA1*05, and relevant conclusions.

First author, year	Outcome	Failure definition	Measure of immunogenicity	Therapeutic drug monitoring	Line of treatment with anti-TNF α	Determination of HLA	Prevalence of HLA	Main outcome for failure [HLA +/-]	Immunogenicity outcome [HLA +/-]
Aleman Gonzalez, 2022 ²³	Failure	TD	NA	No info	No info	No info	46.7%	No difference according to HLA carriage $p = 0.3$	NA
Angulo McGrath, 2021 ¹²	Failure	LOR	NA	No info	No info	No info	42.0%	HLA + had increased probability of LOR Multivariate: HR = 2.32, 95% CI 1.07–5.02, $p = 0.03$	NA
Bangma, 2020 ²⁴	Immunogenicity	NA	Radio-immunoassay, Drug-tolerant Cut-off: ≥ 12 AU/mL	No info	No info	SNP WGS and genome-wide genotyping array	39.6%	NA	No difference according to HLA carriage HLA+: 27%, HLA-: 20% OR = 1.65, 95% CI 0.95–2.85, $p = 0.075$
Colman, 2021 ^{13,25}	Failure Immunogenicity	LOR	ECLIA, Drug tolerant Cut-off [ng/mL]: low [22–200], medium [201–1000], high [>1000]	Proactive	1st line: 100%	PCR-SSO	49.0%	No difference according to HLA carriage HLA+: 24%, HLA-: 46%, $p = 0.17$	No difference according to HLA carriage HLA+: 60.0%, HLA-: 69.2%, $p = 0.69$
Davis Gonzalez, 2022 ²⁹	Failure ^a	PNR, LOR, TD, AE	NA	No info	First-line CD: 41.1% ^b First-line UC: 45.2% ^b	PCR-SSP	CD: 41.0% UC: 38.0%	No difference according to HLA carriage $p > 0.30$ for the 4 outcomes assessed	NA
Doherty, 2023 ²⁶	Failure	TD	NA	No info	1st line: 100%	HLA imputation	38.1%	HLA + had increased probability of shorter TD but only for homozygous carriers $p = 0.007$	NA
Fuentes Valenzuela, 2023 ²⁷	Failure	PNR, LOR, TD, AE	NA	Proactive	First-line: 92.9% Second-line: 7.1%	PCR-SSO	CD: 42.2% UC: 63.6%	HLA + had decreased probability of TD HLA+: 15.4%, HLA-: 38.3% HR = 0.31, 95% CI 0.12–0.81, $p = 0.02$	NA
Gonzalez, 2021 ²⁸	Failure Immunogenicity	TD	No info	No info	No info	No info	39.1%	No difference according to HLA carriage HR = 2.36, 95% CI = 0.89–6.25, $p = 0.06$	HLA + had increased probability of ADA formation HLA+: 59%, HLA-: 24%, $p = 0.002$ HR = 4.54, 95% CI = 1.73–11.89

Table 2. Continued

First author, year	Outcome	Failure definition	Measure of immunogenicity	Therapeutic drug monitoring	Line of treatment with anti-TNF α	Determination of HLA	Prevalence of HLA	Main outcome for failure [HLA +/-]	Immunogenicity outcome [HLA +/-]
Gu, 2022 ¹⁸	Failure ^a Immunogenicity	TD	No info	No info	No info	PCR-SSO	42.9%	No difference according to HLA carriage $p = 0.89$	HLA + had increased probability of ADA formation HLA+: 27.0%, HLA-: 10.7%, $p = 0.01$
Guardiola, 2019 ²⁹	Failure	LOR	NA	No info	No info	No info	31.0%	HLA + had increased probability of LOR Multivariate: HR = 3.5, 95% CI 1.6-7.5, $p = 0.002$	NA
Guardiola Capon, 2020 ¹⁰	Failure	LOR	NA	No info	No info	No info	45.0%	HLA + had increased probability of LOR Multivariate HR = 2.74, 95% CI 1.2-6.2, $p = 0.02$	NA
Hu, 2021 ¹⁹	Immunogenicity	NA	Time to ADA detection by IC assay Cut-off ≥ 30 ng/mL	Reactive	First-line: 100%	SNP genotyping	No info	NA	No difference according to HLA carriage No statistical data provided
Ioannou, 2021 ³⁰	Immunogenicity	NA	Cut-off: ≥ 10 AU/mL	No info	No info	SNP WGS	IFX: 41.9% ADL: 50.9%	NA	HLA + had increased probability of ADA formation, but only for ADL IFX: HLA+: 32.2%, HLA-: 25.6%, $p = 0.28$ ADL: HLA+: 41.5%, HLA-: 15.7%, $p = 0.004$
Laserna Mendieta, 2023 ¹¹	Failure	TD	NA	Reactive	First-line: 90.8% Second-line: 9.2%	PCR-SSO & SNP genotyping	PCR-SSO: 40.5% SNP: 38.2%	No difference according to HLA carriage PCR-SSO: HLA+: 52.8%, HLA-: 47.4%, $p = 0.544$ SNP: HLA+: 52.0%, HLA-: 48.1%, $p = 0.668$	NA
Lopez Blanco, 2022 ³¹	Immunogenicity	NA	ELISA Cut-off ≥ 10 AU/mL	No info	No info	PCR-SSO	57.7%	NA	No difference according to HLA carriage HLA+: 11.6%, HLA-: 10.2%
Pascual Oliver, 2023 ³²	Failure	PNR, LOR, AE	NA	No [specified that proactive approach was not followed]	First-line: 100%	PCR-SSO	42.4%	No difference according to HLA carriage $p > 0.30$ for the three outcomes assessed	NA

Table 2. Continued

First author, year	Outcome	Failure definition	Measure of immunogenicity	Therapeutic drug monitoring	Line of treatment with anti-TNF α	Determination of HLA	Prevalence of HLA	Main outcome for failure [HLA +/-]	Immunogenicity outcome [HLA +/-]
Salvador Martín, 2023 ³³	Failure	TD	NA	No info	First-line: 93.5% Second-line: 6.5%	SNP genotyping	CD: 45.8% UC: 40.8% IFX: 43.0% ADL: 48.2%	HLA + had increased probability of TD only for CD and ADL CD, Multivariate: HR = 2.07, 95% CI 1.07–3.99, <i>p</i> = 0.030 UC, Multivariate: HR = 1.40, 95% CI, 0.68–2.89, <i>p</i> = 0.358 IFX, Multivariate: HR = 1.44, 95% CI 0.79–2.62, <i>p</i> = 0.237 ADL, Multivariate: HR = 2.32, 95% CI 1.02–5.26, <i>p</i> = 0.044	NA
Sazonovs, 2020 ⁷	Failure Immunogenicity	TD	ELISA, Drug tolerant cut-off: >10 AU/mL	Proactive	First-line: 100%	SNP genotyping/ HLA imputation	39.0%	HLA + had increased probability of TD only for ADL in monotherapy No statistical data provided	HLA + had increased probability of ADA formation IFX: HR = 1.92, 95% CI, 1.57–2.33 ADL: HR = 1.89, 95% CI, 1.32–2.70
Shimoda, 2023 ³⁴	Failure	TD	NA	No info	First-line: 100%	SNP array genotyping	19.6%	HLA + had increased probability of TD Multivariate: HR = 2.23, 95% CI 1.10–4.51, <i>p</i> = 0.026	NA
Spencer, 2022 ¹⁴	Failure Immunogenicity	TD	Homogeneous mobility shift assay, Drug-tolerant Cut-off: $\geq 1.19 \mu\text{g/mL}$	Proactive	First-line: 77.9% Second-line: 23.1%	SNP Risk immune test	45.6%	No difference according to HLA carriage <i>p</i> = 0.58	No difference according to HLA carriage HLA+: 10.6%, HLA-: 13.8% HR = 0.7, 95% CI 0.2–2.0, <i>p</i> = 0.55
Suris Marin, 2021 ³⁵	Failure	LOR, TD	NA	No info	No info	No info	39.4%	HLA + had increased probability of LOR Multivariate: HR = 1.90, 95% CI 1.14–3.31, <i>p</i> = 0.015	NA
Wilson, 2019 ³⁶	Failure Immunogenicity	LOR, TD, AE	ELISA, Drug-sensitive Cut-off: no info	No info	No info	SNP allelic discrimination	40.1%	HLA + had increased probability of LOR and TD LOR: HR = 2.34, 95% CI 1.41–3.88, <i>p</i> = 0.001 TD: HR = 2.27, 95% CI 1.46–3.43, <i>p</i> = 2.5 $\times 10^{-4}$	HLA + had increased probability of ADA formation HLA+: 25.7%, HLA-: 4.5%, HR = 7.29, 95% CI 2.97–17.19, <i>p</i> = 1.5 $\times 10^{-5}$

Table 2. Continued

First author, year	Outcome	Failure definition	Measure of immunogenicity	Therapeutic drug monitoring	Line of treatment with anti-TNF α	Determination of HLA	Prevalence of HLA	Main outcome for failure [HLA +/-]	Immunogenicity outcome [HLA +/-]
Zhu, 2023 ³⁷	Immunogenicity	NA	ELISA, Drug-tolerant Cut-off: titres of 1:20 and \geq 1:60 were considered low- and high-titre, respectively.	Proactive	First-line: 94.2% Second-line: 5.8% ^c	SNP genotyping	36.5%	NA	HLA + had increased probability of ADA formation HLA+: 71.1%, HLA-: 43.9%, $p = 0.01$ OR = 2.94, 95% CI 1.19–7.3, $p = 0.02$

ADA, anti-drug antibodies; ADL, adalimumab; AE, adverse events; AU, arbitrary units; CD, Crohn's disease; HLA, human leukocyte antigens; HLA-, non-carrier of HLA-DQA1*05; HLA+, carrier of HLA-DQA1*05; HR, hazard ratio; IC, immunochromatography; IFX, infliximab; OR, odds ratio; PCR-SSO, polymerase chain reaction-sequence specific oligonucleotide; PCR-SSP, polymerase chain reaction-sequence specific primer; PNR, primary non-response; SNP, single nucleotide polymorphism, LOR, secondary loss of response; TD, treatment discontinuation; UC, ulcerative colitis; WGS, whole-genome sequencing; wPCDAL, weighted Paediatric Crohn's Disease Activity Index.

^aThe outcomes were measured for events per each treatment, and not for patients as in the remaining included studies.

^bThe data correspond to number of biologic treatments.

^cHad received IFX previously.

The definition of immunogenicity was highly dependent on the method/assay and cut-off point used, and this was greatly variable among studies, with some providing incomplete or no information about the procedure for ADA determination [Supplementary Table S2]. At least five different methodologies were employed [electrochemiluminescence immunoassay or ECLIA, enzyme-linked immunosorbent assay or ELISA, radioimmunoassay, homogeneous mobility shift assay, and immunochromatography], and several papers included incomplete descriptions of the assay^{19,30,31,36} [missed information about cut-off point, drug-tolerant or -sensitive type] or provided no information at all.^{18,28}

To evaluate the effect of HLA-DQA1*05 carriage on immunogenicity, a meta-analysis was performed using raw data from source studies [Figure 3A]. One study that did not support association between HLA-DQA1*05 and immunogenicity was not included in the meta-analysis as the required data were neither found in the paper nor provided by the authors.¹⁹ Thus, 10 studies were included in the final analysis, with three caveats: only data from patients treated with infliximab and adalimumab were retrieved from the abstract by Ioannou *et al.*,³⁰ data in the study by Gu *et al.* referred to events per treatment [instead per patient],¹⁸ and the data received from Sazonovs included 1237 of the 1240 patients reported in the initial cohort, in whom the HLA status was determined.⁷ Overall results showed that the presence of HLA-DQA1*05 genotype was associated with a 54% higher risk of immunogenicity, compared with non-carriers, in patients with IBD treated with TNF α antagonists (risk ratio [RR], 1.54; 95% confidence interval, 1.23–1.94) and with considerable heterogeneity [$I^2 = 67\%$]. Regarding subgroup analyses, the significant association between HLA-DQA1*05 carriage and immunogenicity was maintained in studies that included only adult patients and were published both as full articles and as abstracts, and in those that determined ADAs using drug tolerant assays. Exposure to both infliximab and adalimumab was significantly associated with ADA formation among HLA-DQA1*05 carriers when both drugs were evaluated separately [Table 3]. No meta-analyses were done for patients with UC, paediatric patients, or for drug-sensitive assays, as only one study per each subgroup was found.

Sensitivity analyses, excluding studies with a high risk of bias, maintained an association between HLA-DQA1*05 and ADA formation [$n = 6$ studies], but without statistical significance [$p = 0.06$].

No significant publication bias was found in the funnel plot analysis [Figure 3B] and Egger bias test [$p = 0.52$]. GRADE assessment found a low certainty of evidence for the impact of HLA DQA1*05 carriage on development of ADA to TNF α antagonists [Table 4].

3.6. Therapeutic drug monitoring

Proactive TDM was performed in five cohorts^{7,13,14,25,27,37} and reactive TDM was performed in two studies.^{11,19} One study stated that proactive TDM was not performed, and no mention of reactive TDM was found.³² No data were provided in the remaining studies; therefore it was assumed that TDM was not performed. A meta-analysis of studies with proactive TDM abrogated the effect of HLA-DQA1*05 on ADA production [risk ratio, 1.24; 95% confidence interval,

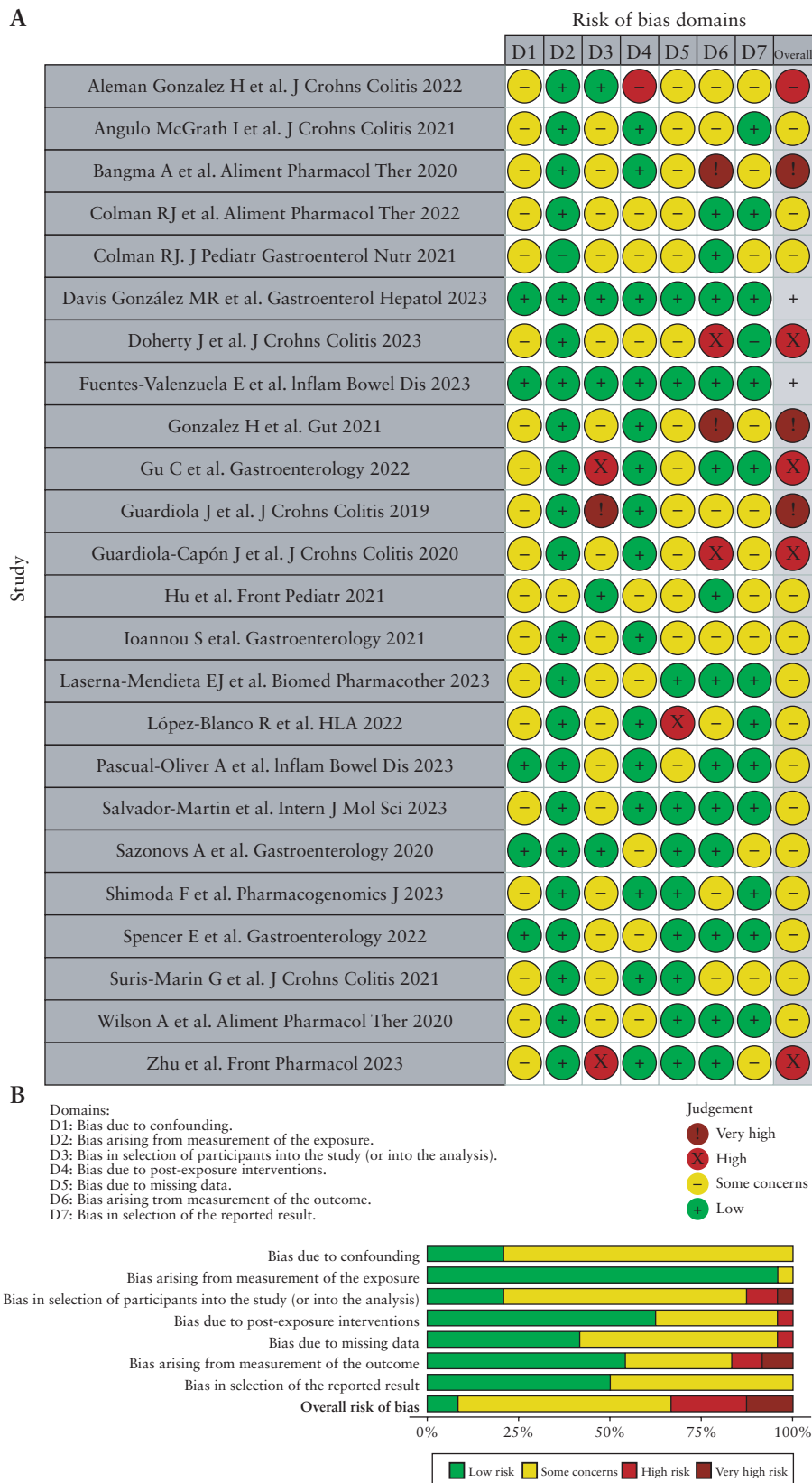


Figure 2 Risk of bias of studies included in the systematic review according to the Cochrane ROBINS-E tool. A, 'Traffic light' plots of the domain-level judgments for each individual result. B, Weighted bar plots of the distribution of risk of bias judgements within each bias domain.

0.93 – 1.64; $I^2 = 64\%$]. However, summary estimates of the six studies that did not mention performing any type of TDM, increased the chances of developing immunogenicity in the

presence of risk HLA on meta-analysis [risk ratio, 1.97; 95% confidence interval, 1.35 – 2.88; $I^2 = 66\%$] [very low certainty evidence].

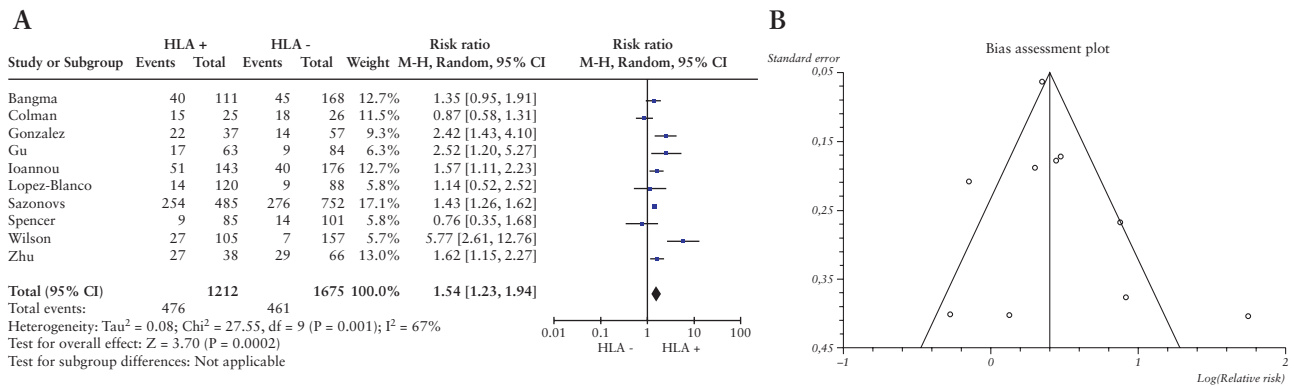


Figure 3 A, Forest plot comparing the risk of immunogenicity to TNF α antagonists [defined as positive serum anti-drug antibodies] in IBD patient carriers of HLA-DQA1*05 versus non-carriers. B, Begg funnel plot of studies risk of immunogenicity to TNF α antagonists in IBD patients with HLA DQA1*05. TNF, tumour necrosis factor; IBD, inflammatory bowel disease.

Table 3 Subgroup analyses comparing risk of immunogenicity [anti-drug antibodies formation] with anti-tumour necrosis factor-alpha drugs according to HLA-DQA1*05 carriage.

Subgroup analysis	Number of cohorts	Risk ratio [95% confidence interval]	I ²	p-value
Patient population				
Adult patients only	3	2.17 [1.22 – 3.85]	80%	0.008
Crohn's disease patients only	3	1.31 [0.98 – 1.74]	67%	0.06
Type of TNF α antagonist				
Infliximab exclusively	7	1.50 [1.10 – 2.05]	77%	0.01
Adalimumab exclusively	2	1.85 [1.18 – 2.90]	39%	0.008
Publication type				
Abstracts	4	1.81 [1.33 – 2.47]	23%	<0.001
Full papers	6	1.42 [1.04 – 1.94]	76%	0.03
Type of drug measurement assay				
Drug-tolerant assays	5	1.28 [1.04 – 1.59]	51%	0.02
Excluding high-risk bias studies				
Low/intermediate risk of bias	6	1.41 [0.98 – 2.01]	76%	0.06
Therapeutic drug monitoring				
Proactive	4	1.24 [0.93 – 1.64]	64%	0.15
No TDM strategy mentioned	6	1.97 [1.35 – 2.88]	66%	<0.001

TDM, therapeutic drug monitoring; I², statistical inconsistency.

3.7. HLA-DQA1*05 carriage and risk of treatment failure with TNF α antagonists

Eighteen cohort studies (4308 patients, median prevalence of HLA-DQA1*05, 39.7% [range, 20–64%]) overall reported risk of failure to anti-TNF α therapy, which was defined heterogeneously among studies [Supplementary Table S1], and consisted mainly of: a) PNR [defined as treatment cessation before 14–16 weeks after initiation of biologic drugs],^{7,9,26,32} b) secondary LOR [defined by the appearance of IBD-related symptoms, or symptoms or test evidence of disease activity leading to the suspension of treatment, a change in treatment or to dose escalation, hospitalisation or surgery, throughout follow-up of variable length],^{9,10,12,13,25,26,29,32,35,36} or c) time to discontinuation.^{7,11,14,18,23,26–28,32,33,36} Adverse events to anti-TNF α were considered as failure in four studies.^{9,26,32,36}

Six studies [755 patients] supported the hypothesis of higher risk of failure [in any of its definitions] in HLA-DQA1*05 carriers [very low certainty evidence, Table 4], and nine studies

[1096 patients] did not find such association. One of these nine studies even found HLA-DQA1*05 genotype protected against treatment cessation with TNF α antagonists when proactive TDM was carried out.²⁷ Two studies found higher risk of treatment discontinuation exclusively in patients carrying HLA-DQA1*05 who were exposed to adalimumab monotherapy,⁷ and in patients with CD or treated with adalimumab.³³ Additionally, another study found only higher risk of treatment discontinuation for homozygous HLA-DQA1*05 carriers.²⁶

Three studies evaluated the effect of HLA-DQA1*05 carrier status on primary non-response to anti-TNF α treatment, without demonstrating significant differences between carriers and non-carriers in the meta-analysis of individual data [risk ratio, 0.88; 95% confidence interval, 0.55 – 1.41; I² = 0%; p = 0.61]. No difference in adverse events to TNF α antagonist were noted according to HLA-DQA1*05 status in the two studies that assessed separately this outcome^{9,27} [risk ratio, 1.55; 95% confidence interval, 0.64 – 3.75; I² = 53%].

Overall, six cohort studies' expressed risk of secondary LOR to TNF α antagonist, according to HLA-DQA1*05 carriage, by hazard ratios [HR] with 95% confidence intervals^{10,12,29,32,35,36}; On meta-analysis, presence of HLA-DQA1*05 was associated with an increased risk of secondary LOR [HR, 2.21; 95% confidence interval, 1.69–2.88] with no inconsistency [$I^2 = 0\%$] [very low certainty evidence] [Figure 4A and Table 4]. In subgroup analyses, this association was maintained for patients with CD, for both infliximab and adalimumab, in abstracts and in full papers, and was not affected by risk of bias [Table 5].

Data on HR for anti-TNF α therapy discontinuation according to HLA-DQA1*05 carrying status were provided by six studies overall,^{27,28,33–36} the summary estimate also providing a significant increased risk among HLA-DQA1*05 carriers [HR, 1.72; 95% confidence interval, 1.10–2.70; $I^2 = 68\%$] [very low certainty evidence] [Figure 4B and Table 4]. In subgroup analyses, this association remained significant for adult CD patients, those treated with infliximab, and for studies published as abstracts; but lost statistical significance for full papers and in the sensitivity analysis according to risk of bias [Table 5].

3.7. Concomitant immunosuppressive treatment

The risks of immunogenicity or loss of response associated with the concomitant use of IMM drugs were not reported at the level of individual patients, so we sought to compare risk differences between cohorts of patients with a predominant association of IMM (>70% of patients) and with predominant anti-TNF α monotherapy (<30% patients associating IMM). Only four studies measured some of these results,^{12,13,17,37} with anti-TNF α monotherapy predominating in three of them, thus preventing a comparative summary of the results [very low certainty evidence, Table 4]. Specifically, the association between immunogenicity to anti-TNF α therapy according to IMM exposure and HLA-DQA1*05 carrier status was evaluated in two studies, with opposite results.^{7,18} Gu *et al.* found no differences among monotherapy or in combination therapy and expressed results as patients' proportions.¹⁸ In contrast, Sazonovs *et al.* found a 92% risk of ADA formation at 1 year in HLA-DQA1*05 carriers treated with infliximab monotherapy, but only 10% in patients treated with adalimumab combined with IMM who did not carry HLA-DQA1*05.⁷ Three additional studies evaluated treatment failure outcomes [in some of its definitions] according to IMM exposure and HLA-DQA1*05 carrier status; whereas no association was found in the first³² [results showed as *p*-values exclusively], the other two studies found improved outcomes among patients who combined IMM and anti-TNF α drugs: Davis-Gonzalez *et al.* found that time to adalimumab discontinuation was shorter in HLA-DQA1*05 carriers under anti-TNF α exclusively compared with combination therapy [HR = 2.8; 95% CI = 1.1–6.9; vs HR = 1.5; 95% CI = 0.34–5.5].⁹ For their part, Sazonovs *et al.* observed that HLA-DQA1*05 carriage was associated with lower drug persistence only in patients treated with adalimumab in monotherapy.⁷

4. Discussion

This systematic review and meta-analysis of 23 patient cohorts [reported in 24 studies], and overall involving 5727 patients with IBD treated with TNF α antagonists, is the first and

most exhaustive assessment of the risk of immunogenicity linked to HLA-DQA1*05 genotype. Previous studies had shown a higher risk of developing ADA in HLA-DQA1*05 carriers, which was associated with higher risk of loss of clinical response to TNF α antagonists in individual patient cohorts. These studies were recently summarised in two meta-analyses^{8,39}: the first focused on IBD³⁸ but only included 14 studies, six of which evaluated immunogenicity and eight LOR, and presented some inconsistencies in the data regarding original sources.^{7,14,27} The second focused on IMID instead of IBD, and also included patients with rheumatoid arthritis, ankylosing spondylitis, and psoriasis.⁸ The authors summarised results of 13 studies only by combining risk ratios for immunogenicity and secondary LOR in meta-analysis, rather than data of events per each HLA-DQA1*05 carriage at individual patient level.

Our results support the finding that among IBD patients, carrying HLA-DQA1*05 increased the risk of developing ADA by 54% compared with non-carriers, with a low certainty of evidence, according to GRADE assessment. This result had an impact on the risk of secondary LOR, as shown after results of six studies were combined on meta-analysis. Likewise, risk of anti-TNF α treatment discontinuation was also higher among HLA-DQA1*05 carriers. However, these latter results were obtained from a limited number of studies, some of which were affected by methodological inconsistencies when combining heterogeneous clinical variables [association of IMMs, line of treatment in which anti-TNF α therapy was used, length of follow-up until LOR or treatment cessation or, in particular, the definition of secondary LOR itself]. All of these contributed to a very low certainty evidence in GRADE assessment overall.

Although the presence of ADA was associated in some studies with LOR, hypersensitivity reactions, and adverse events,⁴⁰ it is not clear which ADA concentrations were needed to manifest these results. Low ADA levels can be transient, and dose escalation and/or adding an IMM are effective strategies to maintain drug response in most patients.^{41,42} Drug-tolerant assays detect positive ADA in a higher number patients compared with drug-sensitive ones, so the former could measure transient ADA with little or no impact on drug effectiveness; their usefulness may therefore be limited in predicting PNR risk during induction⁴³; and some experts do not recommend them, stating that detection of ADA at higher concentrations by drug-sensitive assays do associate with loss of response.⁴⁴ In accord with this, relatively high ADA concentrations against infliximab were established in some studies to find clinical impact.^{45,46} A cut-off point of 8 $\mu\text{g/mL}$ for ADA against infliximab was defined in the TAXIT trial,⁴⁷ which was later proved as equivalent to 400 ng/mL in some ELISA assays that measure the same ADA type,⁴⁸ and was therefore much more elevated than the cut-off points used in the majority of studies included in this systematic review. This partially explains the differences found between immunogenicity and LOR for HLA-DQA1*05, as the concentrations of ADA detected in most studies may have no impact on drug effectiveness.

Assays for measuring ADA do not have a universal calibrator, and consequently differences among them have been reported.⁴⁹ Studies comparing different assays found relevant differences for ADA against both infliximab and adalimumab, especially for borderline positive concentrations.^{50–52} Therefore, differences found in the association of

Table 4 Grade ASSESSMENT for HLA-DQA1*05 carriage compared with HLA-DQA1*05 non carriage for immunogenicity and effectiveness of TNF α antagonists in patients with IBD.

Certainty assessment		No. of patients		Effect		Certainty		Importance			
No. of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HLA-DQA1*05 carriage	Anti-TNF α mono-therapy	Relative [95% CI]	Absolute [95% CI]		
In IBD patients treated with anti-TNFα, does carrying HLA-DQA1*05 compared with not carrying HLA-DQA1*05 increase the risk of immunogenicity? [assessed with: anti-drug antibodies]											
10	Observational studies	Serious ^a	Serious ^b	Not serious	All plausible residual confounding factors would reduce the demonstrated effect	476/1250 [38.1%]	461/1734 [26.6%]	RR 1.55 [1.23–1.95]	146 more per 1000 [from 61 more to 253 more]	⊕⊕○○ Low	IM-PORTANT
In IBD patients treated with anti-TNFα, does carrying HLA-DQA1*05 compared with not carrying HLA-DQA1*05 increase the risk of secondary loss of response to treatment? [assessed with: clinical variables]											
6	Observational studies	Not serious	Not serious ^d	Serious ^e	Extremely serious ^f All plausible residual confounding factors would reduce the demonstrated effect	178/440 [40.5%]	Not pooled	HR 2.21 [1.69–2.68]	See comment	⊕○○○ Very low	CRITICAL
Certainty assessment											
No. of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No. of patients carrying HLA-DQA1*05 genotype		Relative [95% CI]	Absolute [95% CI]	Certainty	Importance
3	Observational studies	Not serious	Serious [*]	Not serious	Publication bias strongly suspected All plausible residual confounding factors would suggest spurious effect, whereas no effect was observed ^h	27/105 [25.7%]	24/110 [21.8%]	RR 1.18 [0.73–1.91]	See comment	⊕○○○ Very low	IMPORTANT
In IBD patients carrying HLA-DQA1*05 and treated with anti-TNFα drugs, does associating immunomodulatory drugs [>70% of patients with combination therapy in patient cohorts] compared with monotherapy [<30% patients in anti-TNF-alpha monotherapy] reduce the risk of immunogenicity? [assessed with: antitumor antibodies]											
3	Observational studies	Not serious	Very serious ⁱ	Very serious ^j	All plausible residual confounding factors would reduce the demonstrated effect	50/105 [47.6%]	11/110 [10%]	RR 4.76 [2.63–8.64]	See comment	⊕○○○ Very low	CRITICAL

Table 4. Continued

Certainty assessment		No. of patients carrying HLA-DQA1*05 genotype		Effect		Certainty		Importance				
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Anti-TNF α and pro-active TDM	Anti-TNF α no TDM	Relative [95% CI]	Absolute [95% CI]		
In IBD patients carrying HLA-DQA1*05 and treated with anti-TNF-alpha drugs, does proactive drug monitoring reduce the risk of immunogenicity? [assessed with: antidrug antibodies]?												
10	Observational studies	Serious ^k	Serious ^l	Not serious	Serious ^m	All plausible residual confounding factors would suggest spurious effect, while no effect was observed	305/633 [48.2%]	164/605 [27.1%]	RR 1.78 [1.52–2.07]	See comment	⊕○○○ Very low	IMPORTANT
In IBD patients carrying HLA-DQA1*05 and treated with anti-TNFα drugs, does proactive drug monitoring reduce the risk of treatment failure? [assessed with: clinical criteria]?												
6	Observational studies	Not serious	Not serious ⁿ	Very serious ^o	Serious ^l	All plausible residual confounding factors would reduce the demonstrated effect	69/267 [25.8%]	109/173 [63%]	RR 0.41 [0.32–0.52]	See comment	⊕○○○ Very low	CRITICAL

CI, confidence interval; HR, hazard ratio; IMM, immunomodulatory drugs; RR, risk ratio; TDM, therapeutic drug monitoring.

^aNo study was evaluated as a low risk of bias; two studies were rated as at high risk of bias.

^bInconsistency in Hensell-Mantel random meta-analysis was 67%.

^cTreatment length until the detection of anti-drug antibodies varied widely among studies, as did the methods used for this, and positivity thresholds considered.

^dInconsistency in Hensell-Mantel random meta-analysis was 75% in the full series of patients when summary data for each intervention group were combined, rather than the overall estimate of the effect of each study expressed as hazard ratio.

^eFailure to therapy was defined heterogeneously in the different studies, and included: a) primary lack of response; b) secondary loss of response [considered as the appearance of IBD-related symptoms, or discontinuation of anti-TNF α therapy or d) adverse events to TNF α antagonists.

^fThe different studies presented extremely variable criteria to define treatment failure, measured also at very variable times. It cannot be excluded that some results do not faithfully reflect the outcome measure.

^gTreatment length until the detection of anti-drug antibodies varied widely among studies, as did the methods used for this, and positivity thresholds considered.

^hTwo studies found no impact of combining immunomodulators with anti-TNF-alpha in immunogenicity; the remaining suggested that combination therapy reduced the risk of anti-drug antibodies.

ⁱDefinition of treatment failure included lack of response after two anti-TNF-alpha infusions, need of systemic corticosteroids, primary lack of response and secondary loss or response.

^jDue to the use of various definitions of failure, which cannot be combined with each other.

^kOne study was considered to have a high risk of bias; the remainder were assessed as at undetermined risk of bias.

^lInconsistency in Hensell-Mantel random meta-analysis would be 64%.

^mTreatment length before anti-drug antibody measure, methods for detection and positivity thresholds varied greatly among studies.

ⁿInconsistency in an Hensell-Mantel random meta-analysis would be 75%.

^oDefinition of failure to therapy varied widely among studies, and included symptoms persistent after two infusions, need of systemic corticosteroids, treatment discontinuation, or change to other biologic agent.

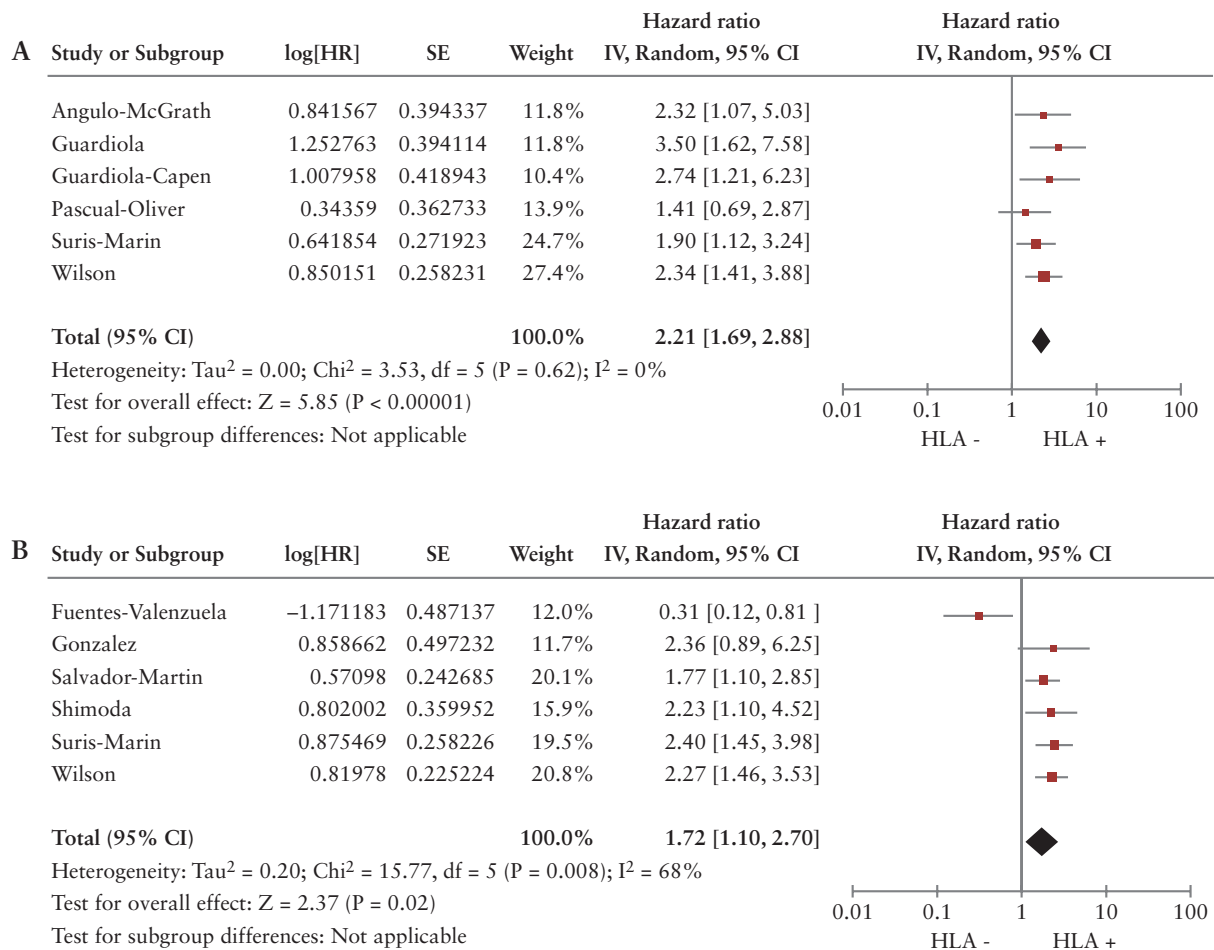


Figure 4 A, Forest plot using hazard ratios to compare the risk of secondary loss of response to TNF α antagonists [defined heterogeneously according to clinical variables] in IBD patient carriers of HLA-DQA1*05 versus non-carriers. B, Forest plot using hazard ratios to compare the risk of anti-TNF α treatment discontinuation in IBD patient carriers of HLA-DQA1*05 versus non-carriers. TNF, tumour necrosis factor; IBD, inflammatory bowel disease.

immunogenicity with HLA-DQA1*05 could be explained by the high variability of the assays used across the studies.

Immunogenicity and secondary LOR to TNF α antagonists have been linked to several pharmacogenetic factors besides HLA-DQA1*05. Among these, other HLA variants have been shown to determine immunogenicity risk, including the HLA-DQ2 molecule, which determined even greater immunogenicity risk than HLA-DQA1*05 in patients with IBD and several other IMIDs.³⁸ HLADRB1*03 also increased risk of immunogenicity in patients with IBD treated with infliximab,⁵³ as well as in patients with rheumatoid arthritis or hidradenitis suppurativa treated with adalimumab.⁵⁴ In addition, several single nucleotide polymorphisms [SNPs] have been described as influencing responses to TNF α antagonists, mostly located in genes involved in the nuclear factor kappa light-chain enhancer of activated B cells [NF- κ B] pathway, TNF α downstream signalling, release of inflammatory mediators, transport of organic molecules/drugs, and autophagy.^{11,55,56}

The ability of IMM treatment to reduce the formation of anti-infliximab antibodies has been known for decades,⁵⁷ and the concomitant use of IMMs is recommended in clinical guidelines as it has proved superior to either biologic or IMM monotherapy.⁵⁸ Our systematic review could not demonstrate the advantage of combination therapy to reduce immunogenicity among HLA-DQA1*05 carriers, due to limitations in the

design of source studies and the poor systematisation of their data. We did however find some clues about the potential benefit of the combination with IMM: combination therapy is more common among IBD patients treated with TNF α antagonists than among those with other IMIDs, which could explain the 75% higher risk of immunogenicity in IMID patients⁸ compared with the 54% in IBD we found.

Research has also shown proactive/reactive TDM could be helpful in managing the risk of developing immunogenicity among HLA-DQA1*05 carriers, since secondary LOR and treatment discontinuation were not higher in these compared with non-carriers, when TDM was performed.^{7,11,13,14,25,27} Our meta-analysis confirmed this fact for immunogenicity and proactive TDM, and documented an increased risk of ADA formation in studies that did not mention any TDM modality.

Among the strengths of our study is, first, the exhaustive systematic search undertaken, which allowed us to retrieve more documents than any other previous systematic review. The rigorous evaluation of clinical and methodological aspects that were overlooked in previous studies [such as the wide variability in the definition of anti-TNF α treatment failure, or the differences in the techniques for determining HLA-DQA1*05 carrier status], application of GRADE to critically appraise the body of evidence, and our approach in evaluating the risk of immunogenicity associated with HLA-DQA1*05

Table 5 Risks of secondary loss of clinical response to anti-tumour necrosis factor- α drugs and treatment discontinuation in inflammatory bowel disease patients carrying HLA-DQA1*05 versus non-carriers. Overall data and subgroup analysis results are provided.

Subgroup analysis	Number of cohorts	Hazard ratio [95% confidence interval]	I ²	p-value
Secondary loss of response [overall]	6	2.21 [1.69 – 2.88]	0%	<0.001
Patient population				
Crohn's disease patients only	2	1.79 [0.81 – 3.95]	52%	0.15
Type of TNF- α antagonist				
Infliximab exclusively	5	2.01 [1.36 – 2.97]	44%	<0.001
Adalimumab exclusively	2	2.46 [1.42 – 4.28]	0%	0.001
Publication type				
Abstracts	4	2.39 [1.69 – 3.37]	0%	<0.001
Full papers	2	1.94 [1.20 – 3.13]	23%	0.007
Risk of bias				
Studies with low/moderate risk of bias	4	2.00 [1.48 – 2.70]	0%	<0.001
Studies with high risk of bias	2	3.12 [1.78 – 5.48]	0%	<0.001
Treatment discontinuation [overall]	6	1.72 [1.10 – 2.70]	68%	0.002
Patient population				
Adult patients only	2	1.84 [1.15 – 2.93]	44%	0.01
Crohn's disease patients only	2	2.14 [1.32 – 3.47]	0%	0.002
Type of TNF- α antagonist				
Infliximab exclusively	5	2.11 [1.63 – 2.74]	0%	<0.001
Publication type				
Full papers	4	1.43 [0.74 – 2.77]	79%	0.29
Abstracts	2	2.39 [1.53 – 3.75]	0%	<0.001
Risk of bias				
Excluding high-risk bias studies	5	1.64 [0.98 – 2.72]	74%	0.06

I², statistic inconsistency.

exclusively in IBD patients, are further strengths. Our approach led to the exclusion of two studies aimed at assessing immunogenicity which were included in previous research.^{8,39} They were excluded because results were provided for IMID overall, with no chance of individualising IBD patients. In addition, two sub-analyses were discarded as they reported on a previous cohort [PANTS]⁵ used by Sazonov *et al.*⁷ They reported HLA-DQA1:05:05 as associated with higher risk of ADA generation for infliximab and adalimumab, whereas HLA-DQA1:05:01 only conferred higher risk for infliximab.^{59,60} with underpowering of the PANTS study to support this finding.⁶¹ Therefore, the level of discrimination of HLA-DQA1:05 classes may also be a factor in explaining discrepancies between the studies.

We must also acknowledge some limitations of our study. First, our synthesis was performed at study level, and all the complex patient variables that might explain anti-TNF α effectiveness and drug clearance could not be explored. Second, clinical and analytical differences in definitions of treatment failure [including LOR and treatment discontinuation] were meta-analysed by combining the overall estimate of the effect of each study, rather than of summary data for each intervention group. Results from different studies reflected the clinical practice at different points and settings and the evolving impact of measuring anti-TNF α trough levels, ADA, and HLA-DQA1*05 carrier status on clinical decisions and consequences, therefore limiting the certainty of evidence derived from our results. Third, differences in: the resolution of techniques used to determine HLA-DQA1*05 carrier status,

to measure ADA, the thresholds to define positivity and the tolerance to drug of the different assays for ADA measurement, prevented us from obtaining a solid conclusion from our results. Fourth, our results were mostly obtained from cohorts of Caucasian origin or ancestry, and are not necessarily applicable to other ethnicities with different distribution of HLA-DQA1*05 carriage.⁶² Finally, the risk of bias that affected most source studies means our results need to be taken with caution, and points to the need for new studies, ideally randomised controlled trials, able to control the multiple variables and confounding factors that determine the effectiveness of anti-TNF α therapy.

In conclusion, this systematic review and meta-analysis of 24 studies with data from 5727 patients with IBD, documents that HLA-DQA1*05 carriage seems to be associated with increased risk of immunogenicity overall, which could have determined increased risks of secondary LOR and anti-TNF α discontinuation. Evidence on the benefit of proactive TDM was also suggested. However, the potential benefit of associating IMMs with TNF α antagonists to reverse the increased risk of ADA development in patients with IBD and who carry HLA-DQA1*05 genotype, requires further studies with improved designs.

Funding

No funding was received for the review. EJM is a recipient of a Juan Rodes grant [JR19/00005] from the Instituto de Salud Carlos III [ISCIII], Spanish Ministry of Health—Social

Services and Equality, which is partly funded by the European Social Fund [period 2014-2020]. LR-A is a recipient of a predoctoral contract for Health Research Training—PFIS grant [FI22/00013] from the Instituto de Salud Carlos III [ISCIII], Spanish Ministry of Health—Social Services and Equality, which is partly funded by the European Social Fund.

Conflict of Interest

The authors declare that there are no conflicts of interest.

CRedit Authorship Contributions

Study concept and supervision: AJL, EJM. Study design: AJL, AA. Data collection: LR-A, EG-N, EJM. Data analysis: AA, EJM, AJL. Drafting of manuscript: AJL, EJM. Data interpretation, review of results and revision of manuscript: all authors.

Acknowledgements

We are grateful to Melanie Radcliff for English language revision.

Data Availability

All relevant data generated or analysed during this study are included in this article and its [supplementary data](#). Further enquires can be directed to the corresponding author.

Supplementary Data

Supplementary data are available at [ECCO-JCC](#) online.

References

- Ng SC, Shi HY, Hamidi N, *et al.* Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet* 2017;390:2769–78.
- Kaplan GG. The global burden of IBD: from 2015 to 2025. *Nat Rev Gastroenterol Hepatol* 2015;12:720–7.
- Burisch J, Zhao M, Odes S, *et al.* The cost of inflammatory bowel disease in high-income settings: a Lancet Gastroenterology & Hepatology Commission. *Lancet Gastroenterol Hepatol* 2023;8:458–92.
- Wong U, Cross RK. Primary and secondary nonresponse to infliximab: mechanisms and countermeasures. *Expert Opin Drug Metab Toxicol* 2017;13:1039–46.
- Kennedy NA, Heap GA, Green HD, *et al.*; UK Inflammatory Bowel Disease Pharmacogenetics Study Group. Predictors of anti-TNF treatment failure in anti-TNF-naive patients with active luminal Crohn's disease: a prospective, multicentre, cohort study. *Lancet Gastroenterol Hepatol* 2019;4:341–53.
- Garcês S, Demengeot J, Benito-Garcia E. The immunogenicity of anti-TNF therapy in immune-mediated inflammatory diseases: a systematic review of the literature with a meta-analysis. *Ann Rheum Dis* 2013;72:1947–55.
- Sazonovs A, Kennedy NA, Moutsianas L, *et al.*; PANTS Consortium. HLA-DQA1*05 carriage associated with development of anti-drug antibodies to infliximab and adalimumab in patients with Crohn's disease. *Gastroenterology* 2020;158:189–99.
- Solitano V, Facciorusso A, McGovern DPB, *et al.* HLA-DQA1*05 genotype and immunogenicity to tumour necrosis factor- α antagonists: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2023;21:3019–29.e5.
- Davis González MR, Ballester MP, Romero-González E, *et al.* Biological treatment interruption in inflammatory bowel disease: motivation and predictive factors. *Gastroenterol Hepatol* 2022;46:671–81.
- Guardiola Capón J, Serra K, Rodríguez-Alonso L, *et al.* Carriage of the HLA-DQA1*05 allele is associated with a high risk of loss of response to adalimumab in patients with Crohn's disease. *J Crohns Colitis* 2020;14:S574.
- Laserna-Mendieta EJ, Salvador-Martín S, Arias A, *et al.* Single nucleotide polymorphisms in ADAM17, IL23R and SLCO1C1 genes protect against infliximab failure in adults with Crohn's disease. *Biomed Pharmacother* 2023;159:114225.
- Angulo McGrath I, Bracho González M, Ocaña Ledesma A, *et al.* HLA-DQA1*05 allele and its association with the secondary loss of response to infliximab in patients with Inflammatory Bowel Disease. *United Eur Gastroenterol J* 2021;9:433.
- Colman RJ, Xiong Y, Mizuno T, *et al.* Antibodies-to-infliximab accelerate clearance while dose intensification reverses immunogenicity and recaptures clinical response in paediatric Crohn's disease. *Aliment Pharmacol Ther* 2022;55:593–603.
- Spencer EA, Stachelski J, Dervieux T, Dubinsky MC. Failure to achieve target drug concentrations during induction and not HLA-DQA1*05 carriage is associated with antidrug antibody formation in patients with inflammatory bowel disease. *Gastroenterology* 2022;162:1746–8.e3.
- Santesso N, Glenton C, Dahm P, *et al.*; GRADE Working Group. GRADE guidelines 26: informative statements to communicate the findings of systematic reviews of interventions. *J Clin Epidemiol* 2020;119:126–35.
- Page MJ, McKenzie JE, Bossuyt PM, *et al.* The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71.
- ROBINS-E Development Group. *Risk of Bias in Non-randomized Studies of Exposure [ROBINS-E]*. Launch version, June 1, 2022. <https://www.riskofbias.info/welcome/robins-e-tool>
- Gu C, Nasser M, Pabla BS, *et al.* HLA-DQA1*05 is associated with higher rates of antibody formation and lower serum drug levels in inflammatory bowel disease patients treated with anti-TNF agents. *Gastroenterology* 2022;162:S809–10.
- Hu W, Feng Y, Ye Z, *et al.* The association between genetic variants, pharmacokinetics, and infliximab efficacy in pediatric patients with Crohn's disease in China. *Front Pediatr* 2021;9:744599.
- Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557–60.
- Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple graphical test. *BMJ* 1997;315:629–34.
- Schünemann HJ, Higgins JPT, Vist GE, *et al.* Completing 'summary of findings' tables and grading the certainty of the evidence. In: Higgins JPT, Thomas J, Chandler J, *et al.*, editors. *Cochrane Handbook for Systematic Reviews of Interventions*. 2nd edn. Chichester (UK): Wiley-Blackwell; 2019: 375–402.
- Aleman Gonzalez H, Ramachandran S, Whitehead E, *et al.* Incorporating HLADQA1*05 in pre-biologic screening in IBD patients initiating biologic therapies. *J Crohns Colitis* 2022;16:i342.
- Bangma A, Voskuil MD, Uniken Venema WTC, *et al.* Predicted efficacy of a pharmacogenetic passport for inflammatory bowel disease. *Aliment Pharmacol Ther* 2020;51:1105–15.
- Colman R, Hyams JS, Noe J, *et al.* No association between HLA-DQA1*05 and the rate of immunogenicity in an intensive PK sampled Crohn's disease cohort. *J Pediatr Gastroenterol Nutr* 2021;73:S67–8.
- Doherty J, Ryan A, Quinn E, *et al.* P607 HLA-DQA1*05 allele carriage and anti-TNF therapy persistence in inflammatory bowel disease. *J Crohns Colitis* 2023;17:i734–5.
- Fuentes-Valenzuela E, García-Alonso FJ, Maroto-Martín C, *et al.* Influence of HLADQA1*05 genotype in adults with inflammatory bowel disease and anti-TNF treatment with proactive therapeutic

- drug monitoring: a retrospective cohort study. *Inflamm Bowel Dis* 2023;29:1586–93.
28. Gonzalez H, Ramachandran S, Pattinson A, et al. Association of anti-infliximab antibodies and HLA-DQA1*05 variant in ulcerative colitis: a retrospective single centre study. *Gut* 2021;70:A32–3.
 29. Guardiola J, Rodriguez Alonso L, Santacana E, et al. Carriage of the HLA-DQA1*05 allele is associated with a high risk of loss of response to infliximab in patients with inflammatory bowel disease. *J Crohns Colitis* 2019;13:S435–6.
 30. Ioannou S, Beecham AH, Gomez L, et al. Hispanic IBD patients with HLA-DQA1*05 have higher rates of anti-TNF immunogenicity compared with non-carriers. *Gastroenterology* 2021;160:S72.
 31. López-Blanco R, Mendez-López I-M, Recio-Romero R, et al. HLA-DQA1*05 and development of antidrug antibodies in anti-TNF treated patients with inflammatory bowel disease. *HLA* 2022;99:539–40. doi:10.1111/tan.14606
 32. Pascual-Oliver A, Casas-Deza D, Cuarán C, et al. HLA-DQA1*05 was not associated with primary nonresponse or loss of response to first anti-TNF in real-world inflammatory bowel disease patients. *Inflamm Bowel Dis* 2023;izad130. doi:10.1093/ibd/izad130
 33. Salvador-Martín S, Zapata-Cobo P, Velasco M, et al. Association between HLA DNA Variants and Long-Term Response to Anti-TNF Drugs in a Spanish Pediatric Inflammatory Bowel Disease Cohort. *Int J Mol Sci* 2023;24:1797. doi:10.3390/ijms24021797
 34. Shimoda F, Naito T, Kakuta Y, et al; NCBN Controls WGS Consortium. HLA-DQA1*05 and upstream variants of PPARGC1B are associated with infliximab persistence in Japanese Crohn's disease patients. *Pharmacogenomics J* 2023;23:141–8. doi:10.1038/s41397-023-00312-z
 35. Suris Marin G, Santacana E, Padullés N, et al. Impact of the HLA-DQ1*05 allele on the initial response to infliximab in patients with Inflammatory Bowel Disease. *J Crohns Colitis* 2021;15:S301–2.
 36. Wilson A, Peel C, Wang Q, Pananos AD, Kim RB. *HLADQA1*05* genotype predicts anti-drug antibody formation and loss of response during infliximab therapy for inflammatory bowel disease. *Aliment Pharmacol Ther* 2020;51:356–63.
 37. Zhu K, Ding X, Chen Z, et al. Association between genetic variants and development of antibodies to infliximab: a cross-sectional study in Chinese patients with Crohn's disease. *Front Pharmacol* 2023;14:1096816.
 38. Brun MK, Bjørlykke KH, Viken MK, et al. HLA-DQ2 is associated with anti-drug antibody formation to infliximab in patients with immune-mediated inflammatory diseases. *J Intern Med* 2023;293:648–55.
 39. Bergstein S, Spencer EA. DOP72 HLA-DQA1*05 associates with immunogenicity and loss of response to anti-TNF therapy in the IBD population: a meta-analysis. *J Crohns Colitis* 2023;17:148–50.
 40. Boehncke W-H, Brembilla NC, Brembilla NC. Immunogenicity of biologic therapies: causes and consequences. *Expert Rev Clin Immunol* 2018;14:513–23.
 41. Vande Casteele N, Gils A, Singh S, et al. Antibody response to infliximab and its impact on pharmacokinetics can be transient. *Am J Gastroenterol* 2013;108:962–71.
 42. Stallhofer J, Guse J, Kesselmeier M, et al. Immunomodulator comedication promotes the reversal of anti-drug antibody-mediated loss of response to anti-TNF therapy in inflammatory bowel disease. *Int J Colorectal Dis* 2023;38:54.
 43. Barrau M, Duprat M, Veyrard P, et al. A systematic review on the interest of drug-tolerant assay in the monitoring of inflammatory bowel disease. *J Crohns Colitis* 2023;17:633–43.
 44. Mitrev N, Vande Casteele N, Seow CH, et al.; IBD Sydney Organisation and the Australian Inflammatory Bowel Diseases Consensus Working Group. Review article: consensus statements on therapeutic drug monitoring of anti-tumour necrosis factor therapy in inflammatory bowel diseases. *Aliment Pharmacol Ther* 2017;46:1037–53.
 45. Baert F, Noman M, Vermeire S, et al. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. *N Engl J Med* 2003;348:601–8.
 46. West TA, Sam M, Toong C. Comparison of three commercially available ELISA assays for anti-infliximab antibodies. *Pathology [Phila]* 2021;53:508–14.
 47. Vande Casteele N, Ferrante M, Van Assche G, et al. Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease. *Gastroenterology* 2015;148:1320–9.e3.
 48. Imbrechts M, Van Stappen T, Compennolle G, Tops S, Gils A. Anti-infliximab antibodies: How to compare old and new data? *J Pharm Biomed Anal* 2020;177:112842.
 49. Prado MS, Bendtzen K, Andrade LEC. Biological anti-TNF drugs: immunogenicity underlying treatment failure and adverse events. *Expert Opin Drug Metab Toxicol* 2017;13:985–95.
 50. Afonso J, Lopes S, Gonçalves R, et al.; on behalf Portuguese IBD Study Group [GEDII]. Detection of anti-infliximab antibodies is impacted by antibody titer, infliximab level and IgG4 antibodies: a systematic comparison of three different assays. *Therap Adv Gastroenterol* 2016;9:781–94.
 51. Laserna-Mendieta EJ, Salvador-Martín S, Marín-Jiménez I, et al. Comparison of a new rapid method for determination of serum anti-adalimumab and anti-infliximab antibodies with two established ELISA kits. *J Pharm Biomed Anal* 2021;198:114003.
 52. Berger AE, Gleizes A, Waeckel L, et al. Validation study of a new random-access chemiluminescence immunoassay Analyzer i-TRACK10® to monitor infliximab and adalimumab serum trough levels and anti-drug antibodies. *Int J Mol Sci* 2022;23:9561.
 53. Billiet T, Vande Casteele N, Van Stappen T, et al. Immunogenicity to infliximab is associated with HLA-DRB1. *Gut* 2015;64:1344–5.
 54. Liu M, Degner J, Davis JW, et al. Identification of HLA-DRB1 association to adalimumab immunogenicity. *PLoS One* 2018;13:e0195325.
 55. Prieto-Pérez R, Almoguera B, Cabaleiro T, Hakonarson H, Abad-Santos F. Association between genetic polymorphisms and response to anti-TNFs in patients with inflammatory bowel disease. *Int J Mol Sci* 2016;17:225.
 56. Lauro R, Mannino F, Irrera N, et al. Pharmacogenetics of biological agents used in inflammatory bowel disease: a systematic review. *Biomedicine* 2021;9:1748.
 57. Farrell RJ, Alsahli M, Jeen Y-T, Falchuk KR, Peppercorn MA, Michetti P. Intravenous hydrocortisone premedication reduces antibodies to infliximab in Crohn's disease: a randomized controlled trial. *Gastroenterology* 2003;124:917–24.
 58. Colombel JF, Sandborn WJ, Reinisch W, et al.; SONIC Study Group. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med* 2010;362:1383–95.
 59. Powell Doherty RD, Liao H, Satsangi JJ, Ternette N. Extended analysis identifies drug-specific association of 2 distinct HLA Class II haplotypes for development of immunogenicity to adalimumab and infliximab. *Gastroenterology* 2020;159:784–7.
 60. Hässler S, Bachelet D, Duhaze J, et al.; ABIRISK consortium. Clinicogenomic factors of biotherapy immunogenicity in autoimmune disease: a prospective multicohort study of the ABIRISK consortium. *PLoS Med* 2020;17:e1003348.
 61. Sazonovs A, Ahmad T, Anderson CA. Underpowered PANTS: a response to the conclusions of “extended analysis identifies drug-specific association of two distinct HLA class II haplotypes for development of immunogenicity to adalimumab and infliximab”. *Gastroenterology* 2021;160:470–1.
 62. Fernandez Vina MA, Hollenbach JA, Lyke KE, et al. Tracking human migrations by the analysis of the distribution of HLA alleles, lineages and haplotypes in closed and open populations. *Philos Trans R Soc Lond B Biol Sci* 2012;367:820–9.