Influence of HLA-DQA1*05 allele in the response to anti-TNFα drugs in inflammatory bowel diseases

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Review question / Objective: Do patients with inflammatory bowel disease and treated with any anti-TNFα drug who had the HLA-DQA1*05 allele (in heterozygosis or homozygosis) have lower response or persistence to those drugs than patients without HLA-DQA1*05 allele?

Condition being studied: Inflammatory bowel diseases (IBD), which includes Crohn’s disease (CD) and ulcerative colitis (UC), is a chronic inflammatory condition that may affect any part of the digestive tract (CD) or be limited to the colon (UC). While the specific aetiology of IBD remains unknown, it is believed to involve a complex impairment in the immunity of the gut mucosa due to a combination of several genetic and environmental factors, being the microbiota one of the latest that more attraction has received in recent years. Symptoms of IBD (such as abdominal pain, diarrhoea, fever, tiredness or rectal bleeding) may be either constant or alternate between periods of limited disease activity and flares with remarkable presence of symptoms. As IBD is associated with significant morbidity and disability, pharmacological treatment is required in most cases, especially in CD, aimed at reducing the inflammatory response and attenuating the activity of the immune system. In the moderate and severe forms of the disease, therapy is usually based on immunosuppressant and/or biological drugs. Among the latest, anti-TNFα drugs (infliximab or adalimumab) are normally chosen as the initial biological therapy.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 16 February 2023 and was last updated on 16 February 2023 (registration number INPLASY202320076).
Rationale: The search for clinical variables and biomarkers that could predict the response to anti-TNFα drugs (infliximab and adalimumab, mainly) in advance has not yielded desirable results so far and there are no guidelines recommendations as yet. Among potential tools able to predict the response, genetic variations have attracted special attention and several studies have analysed single-nucleotide polymorphisms (SNPs) as potential markers. One of them, HLA-DQA1*05 (or rs2097432), has recently been associated with an increased risk of immunogenicity to anti-TNFα drugs in inflammatory bowel diseases. Whether this could lead to loss of response to these drugs remains controversial, with some studies supporting this hypothesis while others described that immunosuppressive treatment or avoidance of sub-therapeutic levels of the drugs could lead to the same outcome independently of HLA-DQA1*05 carriage.

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METHODS

Search strategy: Source documents will be retrieved from PubMed, Scopus and EMBASE. End date is 31th January 2023. Appropriate documents identified through the reading of the selected articles and communications, will be also included. Study designs will include prospective and retrospective observational studies, cohort studies and clinical trial. Any document providing original data will be considered. The search terms will be: ((((Infliximab/therapeutic use) or (Adalimumab/pharmacology/therapeutic use) or (Tumor Necrosis Factor Inhibitors/therapeutic use) or (Tumor 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))).

Participant or population: Patients with inflammatory bowel disease and treated with any anti-TNFα drug who had their HLA-DQA1*05 carriage status evaluated.

Intervention: Exposure: having the HLA-DQA1*05 allele in heterozygosis or homozygosis.

Comparator: Patients not having the HLA-DQA1*05 allele.

Study designs to be included: Observational studies (both retrospective and prospective designs), cohort studies and randomized controlled trials.

Eligibility criteria: Any study who analysed the response to or persistence of anti-TNFα drugs according to the HLA-DQA1*05 carriage status.

Information sources: Online repository databases will be the main source. Contact with authors will take place if a selected article or communication could not be
obtained. Only published documents will be considered for this systematic review.

**Main outcome(s):** To analyse the relationship between HLA-DQA1*05 presence and the risk of failing to anti-TNFα drugs and shorter persistence compared to the absence of this allele.

**Additional outcome(s):**
- To determine if the HLA-DQA1*05 effect is different in infliximab and adalimumab.
- To analyse if the HLA-DQA1*05 effect is dependent on age and/or type of IBD.
- To evaluate the influence of HLA-DQA1*05 in the generation of anti-drug antibodies.
- To study if concomitant treatment with immunosuppression influences the HLA-DQA1*05 effect on response/persistence.

**Data management:** Articles and communications retrieved from the search will be reviewed by two independent investigators for selection, with discrepancies solved by the principal investigator. The same procedure will be applied for the extraction of the data of interest from the selected documents. Each investigator will use an Excel file to manage these records.

**Quality assessment / Risk of bias analysis:** The ROBINS-I tool will be employed to evaluate the quality and risk of bias of the observational studies included. Randomized control trials, if any, will be appraised with the aid of the ROB-2 tool.

**Strategy of data synthesis:** The main results will be the number (or percentage) of articles/communications included that support the hypothesis that HLA-DQA1*05 has an effect on response/persistence of anti-TNFα drugs. When possible, the data will be combined and calculations made (for example, mean percentage of patients failing to anti-TNFα drugs or mean time until failure in patients with or without HLA-DQA1*05 allele).

**Subgroup analysis:** When possible and as described in point 19 (additional outcomes), the following sub-groups will be considered when reporting data: age (children/adults), type of IBD (Crohn’s disease/ulcerative colitis), type of drug (infliximab/adalimumab) and concomitant treatment with immunosuppressive drugs (yes/no).

**Sensitivity analysis:** Sensitivity analysis will be performed to assess the consistency of our results by excluding the effect of outlayer studies.

**Language restriction:** No restrictions about language will be applied.

**Country(ies) involved:** Spain.

**Keywords:** Tumor Necrosis Factor Inhibitors; infliximab; adalimumab; HLA-DQ alpha-chains; HLA-DQA1*05; inflammatory bowel diseases; Crohn’s disease; ulcerative colitis.

**Dissemination plans:** Publication of results in a research journal in the Gastroenterology field.

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