HLA-DQA1*05 Genetic Test for Risk of Immunogenicity (Formation of Anti-Infliximab or Anti-Adalimumab Antibodies)

Introduction

HLA-DQA1*05 Variant Associated With Immunogenicity Risk for Anti-Infliximab (IFX)/Anti-Adalimumab (ADL) Antibodies [167680] is a genetic test on whole blood to identify carriers of the human leukocyte antigen (HLA) allele group, HLA-DQA1*05.

TNF inhibitors and Immunogenicity

Tumor Necrosis Factor-α (TNF) inhibitors, including infliximab (IFX) and adalimumab (ADL), were the first biologics to treat inflammatory bowel disease (IBD) and remain widely used for IBD and other immune-mediated inflammatory diseases (IMID). Even though TNF inhibitors can be highly effective, patient response is often variable and longevity may be suboptimal. As many as 40% to 50% of patients experience a secondary loss of response (LOR), largely due to the development of anti-drug antibodies (immunogenicity).[1] In a cohort of more than 125,000 patient samples, immunogenicity to IFX and ADL occurred in 30%.[2]

Levels of biologic drug and anti-drug antibodies (ADAb) are inversely related. As they rise in titer, ADAb start to negatively impact pharmacodynamically active drug by blocking drug binding to TNF target and/or by increasing drug clearance. Increasing drug (either by increasing dose and/or shortening the dosing interval) with or without the use of a co-immunomodulator (IMM), has been shown to mitigate the risk of developing ADAb as well as to reverse some low-to-intermediate titer ADAb (reversible immunogenicity) with restoration of clinical response.[3] In the setting of high titer ADAb, active drug is diminished to very low or nil, and loss of clinical response and drug failure more likely result.[3]

The HLA-DQA1*05 Allele Group

Recently, the first genetic human leukocyte antigen (HLA) locus associated with immunogenicity to TNF inhibitors was identified.[4] The HLA-DQA1 locus codes for part of the HLA Class II complex (antigen-binding DQαβ heterodimer) that functions to display foreign peptides on antigen-presenting cells to trigger the immune response. The particular allele group, HLA-DQA1*05, has been associated with the development of anti-infliximab and anti-adalimumab antibodies where HLA-DQA1*05 carriage (i.e., a positive result on this test) occurs with a frequency of about 40% in European and North American populations.[1,4]

Patients who carry HLA-DQA1*05, either one or two copies, have a 75% higher risk of anti-IFX or anti-ADL antibodies compared with non-carriers (relative risk or risk ratio (RR) for carriers 1.75, (95% confidence interval (CI), 1.37-2.25) and a 2.24-fold higher risk of secondary LOR (95% CI, 1.67-3.00) as demonstrated by a recent systematic review and meta-analysis of 13 studies including 3,756 patients for a median follow-up of 12 months.[1] Of note, HLA-DQA1*05 noncarrier patients still developed immunogenicity, albeit at a lower incidence (20% noncarriers vs. 35% carriers within 12 months).[1]

This RR for immunogenicity was determined based on nine studies of 2,824 inflammatory bowel disease (IBD) patients on infliximab (IFX) or adalimumab (ADL) and a smaller number (n=570) with rheumatoid arthritis, ankylosing spondylitis, or psoriasis/psoriatric arthritis. The vast majority of studied patients (n=3,310) were on IFX or ADL with only 84 on etanercept (ETN).[1]

Two other meta-analyses confirmed very similar RR that focused on only adult and pediatric IBD patients.[5,6] Among 2,984 patients in 10 studies, Rodriquez-Alcolado et al. found carriers had RR of 1.54 for immunogenicity compared with non-carriers. LOR was evaluated in 765 patients across six studies where carriers were 2.21-fold more likely to lose response.[5] Bergstein et al. reported RR for immunogenicity of 1.63 based on 1,947 patients in six studies and RR for LOR of 1.84 in 2,099 patients in eight studies.[6]

Key highlights

- This test identifies patients who have a higher risk of developing immunogenicity against TNF inhibitor biologic therapies
- A positive result on this test is associated with a 75% higher risk of developing anti-infliximab or anti-adalimumab antibodies and a 124% greater likelihood of secondary loss of response[1]
- However, increased relative risks are not observed in patients who are dose-optimized using proactive therapeutic drug monitoring (TDM) (*Dose*ASSURE IFX, *Dose*ASSURE ADL)[1,3,7]

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Table 1. HLA-DQA1*05 Genotype and Immunogenicity to TNF Inhibitors: Findings of 3 Systematic Reviews/Meta-Analyses

Meta-Analysis	Relative Risk (RR) for immunogenicity	Relative Risk (RR) for secondary loss of response	Does Co-IMM abrogate increased RR of carriers?	Does Proactive TDM abrogate increased RR of carriers?	Study details
Solitano et al.[1]	1.75 (95% CI, 1.37-2.25)	2.24 (95% CI, 1.67-3.00)	No	Yes	83% IBD 17% Other IMID
Rodriquez-Alcolado et al.[5]	1.59 (95% CI, 1.23-1.94)	2.21 (95% CI, 1.69-2.88)	No	Yes, and lack of TDM increases RR to 1.93 (95% CI, 1.58-2.36)	Pediatric and Adult IBD
Bergstein et al.[6]	1.63 (95% CI, 1.35-1.98)	1.84 (95% CI, 1.53-2.22)	No	Yes, and lack of TDM increases RR to 1.97 (95% CI, 1.35-2.88)	Pediatric and Adult IBD

Use of Co-immunomodulators

The use of concomitant immunosuppressive therapy (co-immunomodulators, (IMM)) such as thiopurines mitigates overall risk of TNF inhibitor immunogenicity. However, increased risk of immunogenicity in HLA-DQA1*05 carriers persisted even after adjusting for concomitant IMM use as reported by two meta-analyses.[1,5]

Use of Proactive Therapeutic Drug Monitoring (TDM) of IFX of ADL

Notably, proactive drug optimization is beneficial in eliminating any increased risk of immunogenicity or loss of response in HLA-DQA1*05 carriers in comparison to noncarriers. When target serum IFX or ADL drug trough concentrations were maintained by routine use of proactive TDM, the presence of the HLA-DQA1*05 allele was associated with neither increased risk of TNF inhibitor immunogenicity (RR 0.74, 95% CI, 0.42-1.31) nor increased risk of loss of response.[1,3,5,7]

Two other meta-analyses demonstrated that the lack of proactive TDM increased immunogenicity in HLA-DQA1*05 carriers (to RR 1.93, 95% CI, 1.58-2.36; to RR 1.97, 95% CI, 1.35-2.88).[5,6]

Potential Implications

Based on a 41% prevalence of HLA-DQA1 carriage, a positive result on this test carries a positive predictive value (PPV) for immunogenicity of 30%.[1] A negative result on this test indicates noncarrier status and does not mean the patient cannot develop anti-IFX or anti-ADL; it only suggests that the patient may be at decreased risk, with a negative predictive value (NPV) for immunogenicity of 80%.[1]

Taken together, these PPV and NPV may be helpful in determining candidates for monotherapy and for tapering concomitant IMM. Patients who are non-carriers may be candidates for monotherapy with a TNF inhibitor alone. In contrast, combination therapy with an IMM and/or proactive TDM may be preferable in carriers.

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Test Name	Test No.
HLA-DQA1*05 Variant Associated With Immunogenicity Risk for Anti-Infliximab (IFX)/Anti-Adalimumab (ADL) Antibodies	167680

Methodology: Next-generation sequencing (NGS)
Note: NGS is a more comprehensive method for determining the DNA sequence for DQA1 allele(s) carried by a patient than testing for single nucleotide polymorphism (SNP), rs2097432

References

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