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AVANCES EN DIABETES TIPO 1

Genetic Markers of Immunotherapy Response in Type 1 Diabetes

Marcadores genéticos de respuesta a inmunoterapia en la diabetes de tipo 1

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Abstract

Introduction. Type 1 diabetes (T1D) is biologically heterogeneous with respect to genetic susceptibility, immune phenotype, and metabolic trajectory, contributing to variable responses in prevention and recent-onset intervention trials. Genetic information offers two complementary applications in interventional studies: enrichment of trial populations through eligibility criteria and identification of treatment-response modifiers through treatment×genotype interactions.

Methods. This narrative review focuses on interventional clinical trials in T1D prevention or recent-onset disease that incorporated genetic markers either as eligibility criteria or as modifiers of therapeutic efficacy. Priority was given to genetically selected designs and studies reporting formal treatment × genotype interaction analyses, with emphasis on primary and secondary prevention trials.

Results. In primary prevention, the Primary Oral Insulin Trial (POInT) did not reduce the overall primary endpoint but reported an interaction at the *INS* locus, with signals of benefit in genetically susceptible genotypes and potential adverse signals in non-susceptible genotypes. In secondary prevention, a pharmacogenetic analysis within the TrialNet Oral Insulin Prevention Trial (TN07) identified *GLIS3* variation, specific human leukocyte antigen (HLA)-DR4 haplotypes, and genetic risk scores associated with therapeutic benefit within metabolically enriched subgroups. In stage 2 prevention, teplizumab delayed progression to clinical T1D and demonstrated exploratory evidence of greater efficacy among HLA-DR3–negative and HLA-DR4–positive participants.

Conclusions. The available evidence supports a stepwise framework for translating genetic response markers into trial design, including prospective stratification, genetic enrichment, and, when supported by consistent validation, genotype-restricted trials.

Key words: type 1 diabetes, prevention, disease modifying therapies, immunotherapy, pharmacogenetics, genetics, genetic risk scores.

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Introduction

Type 1 diabetes (T1D) progresses through presymptomatic stages characterized by islet autoimmunity and subsequent dysglycemia, with substantial interindividual variability in progression rate and beta cell decline[1]. This heterogeneity likely contributes to differential responses to immunomodulatory and antigen-specific therapies, particularly in prevention and recent-onset trials[2].

Genetic susceptibility is dominated by human leukocyte antigen (HLA) class II haplotypes, notably DR3-DQ2 and DR4-DQ8, and complemented by

non-HLA loci influencing immune regulation, antigen tolerance, and beta cell biology[3]. These determinants provide a biologically grounded framework for therapeutic stratification.

A conceptual distinction is necessary between genetic response markers and genetic eligibility criteria. Genetic response markers are typically identified through treatment × genotype interaction analyses and generate hypotheses regarding differential benefit or potential harm. Genetic eligibility criteria represent prospective operational decisions restricting enrollment based on sufficiently robust and validated evidence. Translation from response marker to eligibility criterion generally follows a staged pathway, from prospective stratification to genetic enrichment and ultimately, genotype-restricted trial design when supported by consistent mechanistic and clinical validation.

Methods

A narrative review was conducted of interventional clinical trials in T1D, including primary prevention, secondary prevention (stage 1 or stage 2), and recent-onset disease (stage 3). Trials were included if genetics was explicitly used as a criterion for inclusion or enrichment, or if treatment × genotype interactions were reported in primary publications or associated analyses. Observational studies were excluded.

Priority was given to trials with documented genetic eligibility criteria, predefined genetic stratification, or formal statistical testing of treatment×genotype interactions. Trials using explicit genetic eligibility criteria are summarized in table 1, and trials reporting genetic modifiers of therapeutic response are summarized in table 2.

Results

Primary prevention

The Primary Oral Insulin Trial (POInT) evaluated high-dose daily oral insulin in infants selected for elevated genetic risk of islet autoimmunity[4]. Genetic screening was integral to trial design, increasing event rates and statistical efficiency (Table 1). Although the composite primary endpoint of multiple islet autoantibodies or T1D was not reduced overall, POInT reported a treatment×genotype interaction at *INS* rs1004446[4] (Table 2). Signals suggested benefit in genetically susceptible *INS* genotypes and potential adverse signals in non-susceptible genotypes for selected outcomes.

Other primary prevention trials, including rial to Reduce Insulin-Dependent Diabetes Mellitus in the Genetically at Risk (TRIGR)[5], Finnish Dietary Intervention Trial for the Prevention of Type 1 Diabetes (FINDIA)[6],

Table 1. Interventional trials in type 1 diabetes with explicit use of genetics as an eligibility criterion.

Trial	Stage	Intervention	Genetic Eligibility Criterion	Primary Endpoint	Overall Result	Reference: PMID
POInT (Primary Oral Insulin Trial)	Primary prevention (infants)	High-dose oral insulin	Genetic screening for elevated risk of islet autoimmunity (>10%)	≥2 islet autoantibodies or T1D	No overall benefit; *INS* interaction signal	41237794
TRIGR (Trial to Reduce Insulin-Dependent Diabetes Mellitus in the Genetically at Risk)	Primary prevention	Extensively hydrolyzed formula vs conventional formula	HLA susceptibility	Incidence of T1D	No reduction in T1D	29297078
FINDIA (Finnish Dietary Intervention Trial for the Prevention of Type 1 Diabetes)	Primary prevention	Formula without bovine insulin	HLA susceptibility	Islet autoantibodies	Genetically selected cohort; no clear prevention of T1D	22393174
BABYDIET	Primary prevention	Delayed gluten introduction	High genetic risk (including HLA)	Development of islet autoantibodies	Feasible and safe; no substantial risk reduction	21515839
DIPP Nasal Insulin (Type 1 Diabetes Prediction and Prevention Study)	Secondary prevention	Intranasal insulin	HLA risk plus autoantibody positivity	Development of T1D	No prevention of T1D	18814906
DIAGNODE-3	Recent-onset (stage 3)	Intralymphatic glutamic acid decarboxylase (GAD)-alum plus vitamin D	HLA-DR3-DQ2 required	C-peptide preservation / glycemic control	HLA-restricted precision trial	36316084

Table 2. Genetic markers associated with therapeutic response in interventional type 1 diabetes trials.

Therapy / Trial	Stage	Genetic Marker	Type of Evidence	Direction of Effect	Reference: PMID
Oral insulin / POInT	Primary prevention	*INS* rs1004446	Exploratory treatment×genotype interaction	Benefit in susceptible genotypes; possible adverse signal in non-susceptible genotypes for selected endpoints	41237794
Oral insulin / TrialNet TN07 (Oral Insulin Prevention Trial)	Secondary prevention	*GLIS3* rs7020673	Association with multiplicity correction within metabolic stratum (SS1)	Greater benefit in metabolically enriched SS1 subgroup	41364459
Oral insulin / TrialNet TN07	Secondary prevention	Specific HLA-DR4 haplotype	Nominal association	Greater benefit in SS1 subgroup	41364459
Oral insulin / TrialNet TN07	Secondary prevention	T1D genetic risk score 2 (T1D-GRS2) and type 2 diabetes polygenic risk scores	Exploratory analyses	Greater benefit with higher T1D-GRS2; association with magnitude of effect in defined subgroups	41364459
Teplizumab / TrialNet TN10	Stage 2 prevention	HLA-DR3 negative and HLA-DR4 positive	Exploratory subgroup analyses	Greater delay in progression to clinical T1D	31180194
Oral insulin / TrialNet TN07 (reanalysis)	Secondary prevention	HLA-DR4-DQ8 with or without elevated insulinoma-associated protein 2 autoantibodies (IA-2A)	Exploratory analysis	Signal of delayed progression to stage 3 in defined subgroup	38949847

and BABYDIET[7], incorporated HLA-based eligibility criteria and are summarized in table 1. Although these were dietary interventions rather than classical immunotherapies, they demonstrate operational use of genetic selection in interventional prevention. The Type 1 Diabetes Prediction and Prevention Study (DIPP) nasal insulin trial similarly incorporated HLA-based eligibility with autoantibody positivity[8] (Table 1).

Secondary prevention (stage 1)

The TrialNet Oral Insulin Prevention Trial (TN07) evaluated 7.5 mg/day oral insulin in autoantibody-positive relatives[9]. The overall trial did not demonstrate significant benefit. However, a pharmacogenetic analysis examined genetic modifiers of response within a predefined metabolic risk stratum characterized by reduced first-phase insulin response[10] (Table 2).

Within this metabolically enriched subgroup, *GLIS3* rs7020673 was significantly associated with therapeutic response after correction for multiple testing[10]. A specific HLA-DR4 haplotype showed nominal association. Exploratory analyses also suggested that T1D genetic risk score 2 (T1D-GRS2) and type 2 diabetes polygenic risk scores were associated with magnitude of benefit in defined subgroups[10] (Table 2). A complementary reanalysis focusing on HLA-DR4-DQ8 and elevated insulinoma-associated protein 2 autoantibodies (IA-2A) reported signals of delayed progression in a defined subgroup[11] (Table 2). These findings indicate that pharmacogenetic signals may be more detectable when combined with clinical or metabolic enrichment and suggest that distinct genetic axes, including autoimmune risk, beta cell biology, and metabolic traits, may modulate preventive immunotherapy response.

Stage 2 prevention

Teplizumab, an anti-CD3 monoclonal antibody, delayed progression to clinical T1D in high-risk relatives with stage 2 disease[12]. Exploratory subgroup analyses suggested greater efficacy among HLA-DR3–negative and HLA-DR4–positive participants[12] (Table 2). Although hypothesis-generating, this represents one of the clearest examples of potential HLA-modulated efficacy in a non–antigen-specific immunotherapy.

Recent-onset (stage 3) T1D

Genetic restriction has been more explicitly implemented in antigen-specific strategies. DIAGNODE-3 (a phase 3 trial of intralymphatic glutamic acid decarboxylase[GAD]–alum immunotherapy in recent-onset type 1 diabetes) restricts enrollment to individuals with HLA-DR3-DQ2 for intralymphatic GAD–alum immunotherapy plus vitamin D[13] (Table 1). This design reflects translation from response marker to eligibility restriction within a precision-medicine framework. In contrast, most recent-onset trials of non–antigen-specific therapies have not routinely incorporated germline pharmacogenetics as primary modifiers of efficacy in main publications.

Conclusions

Genetics is already integrated into T1D prevention trial design and, in selected cases, into recent-onset disease. Trials using explicit genetic eligibility criteria are summarized in table 1, and trials reporting genetic modifiers of therapeutic response are summarized in table 2. POInT demonstrates genetic risk enrichment and suggests genotype-dependent heterogeneity of oral insulin response at the *INS* locus[4]. TN07 pharmacogenetic analyses implicate *GLIS3* variants, specific HLA haplotypes, and polygenic risk scores in modulating response within metabolically enriched subgroups[10]. Teplizumab provides proof-of-concept for stage 2 prevention with exploratory evidence of HLA-modulated heterogeneity[12].

Collectively, these findings support prospective validation of genetic treatment-response interactions and their disciplined translation into trial design to advance biologically stratified immunotherapy in T1D.

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Conflicts of interest

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