



Delaying the Onset of Type 1 Diabetes with Teplizumab: A Narrative Review of Autoantibody Screening and Who Would Actually Be Treated

Hugo Delacroix^{1*}, Merel Hoekstra² and Pavol Bartos³

¹Department of Clinical Immunology, Rhone Valley Institute of Metabolic Medicine, Lyon, France

²Department of Paediatric Endocrinology, Frisian University Medical Centre, Groningen, Netherlands

³Department of Public Health, Vltava Institute of Endocrinology, Prague, Czech Republic

*Correspondence to: Hugo Delacroix, Department of Clinical Immunology, Rhone Valley Institute of Metabolic Medicine, Lyon, France

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Abstract

Type 1 diabetes has an asymptomatic phase that can be detected years before insulin is required, and a single 14-day course of an anti-CD3 antibody has been shown to postpone the clinical diagnosis. In a randomised trial of 76 relatives of people with type 1 diabetes, all of whom had two or more islet autoantibodies and dysglycaemia, 43 per cent of those given teplizumab progressed to clinical diabetes against 72 per cent given placebo, and the median delay in diagnosis was two years. At the close of the trial 57 per cent of the treated group remained free of diabetes against 28 per cent of the placebo group. The result is genuine and was sufficient for regulatory approval, but two problems sit alongside it. Published correspondence noted that the survival curves converge after the first year, so a median delay of two years does not describe a uniform two-year postponement for everyone treated. And the drug can only be given to people identified in the asymptomatic phase, which requires autoantibody screening of populations in whom the great majority screened will never be eligible. This review sets out what the trial established, what it did not, and what the screening requirement implies.

Keywords: Type 1 diabetes; Teplizumab; Islet autoantibodies; Population screening; Disease staging

Introduction

Type 1 diabetes is a T-cell-mediated destruction of pancreatic beta cells, and its clinical presentation is the end of a process that began years earlier [1,2]. A staging framework now describes that process: stage 1 is two or more islet autoantibodies with normal glucose tolerance, stage 2 adds dysglycaemia while the person remains asymptomatic, and stage 3 is clinical diabetes requiring insulin (Figure 3) [3,4].

The clinical significance of stage 2 is that progression from it is close to inevitable. Individuals with two or more autoantibodies and dysglycaemia are described as having a lifetime risk of clinical diagnosis approaching 100 per cent [5,6]. That makes stage 2 an unusually well-defined target for an intervention intended to delay rather than treat [7]. Seroconversion risk itself declines exponentially with age in

childhood [25], and consensus guidelines now formalise the staging for paediatric practice [28].

Teplizumab is a humanised monoclonal antibody binding the CD3 epsilon chain of the T cell receptor. Earlier work in recently diagnosed patients showed preservation of beta cell function [8,9,10,30], and comparisons across trials place that effect in context [33]. This review examines what happened when it was given before diagnosis, and what would be required to use it.

Material and Methods

Search strategy: PubMed and the archives of the major diabetes, immunology and general medical journals were searched for studies of immunotherapy in presymptomatic type 1 diabetes. Search terms combined teplizumab, anti-CD3 and type 1 diabetes with prevention, stage 2, islet autoantibodies, screening and delay. Reference lists of consensus staging documents [3,4] were screened by hand for primary sources.

Eligibility: Studies were included if they reported outcomes of immunotherapy in autoantibody-positive individuals without clinical diabetes, characterised progression from a defined stage, or described population screening programmes for islet autoantibodies. Published correspondence disputing a trial result is cited alongside that trial and identified as such.

Data extraction and handling: Design, sample size, entry criteria, follow-up duration and the reported estimate were extracted as published. Median follow-up is reported alongside every time-to-event figure, because the principal outcome in this field is a delay measured against a censored curve and its interpretation depends on how long participants were observed. No pooling or re-analysis was performed. Figures 1 to 6 and Tables 1 to 3 reproduce published values only. This is a narrative synthesis and was not registered as a systematic review.

Results

The trial: A phase 2 randomised, placebo-controlled, double-blind trial enrolled 76 relatives of people with type 1 diabetes who had at least two confirmed islet autoantibodies and abnormal glucose tolerance on oral testing. Forty-four were assigned to a single 14-day course of teplizumab and 32 to placebo. Participants were aged between 8 and 49 years, and 55 of the 76, or 72 per cent, were under 18 (Figure 4) [5,11]. Median follow-up was 745 days, with more than three years of observation in 57 participants [12].

The cohort composition matters for interpretation. Every participant was a relative of someone with type 1 diabetes and had reached stage 2 on formal testing, so the trial describes a population already identified by an established screening programme rather than one encountered in ordinary practice [5,11].

Table 3: Principal studies reviewed, with the finding as reported by the original investigators

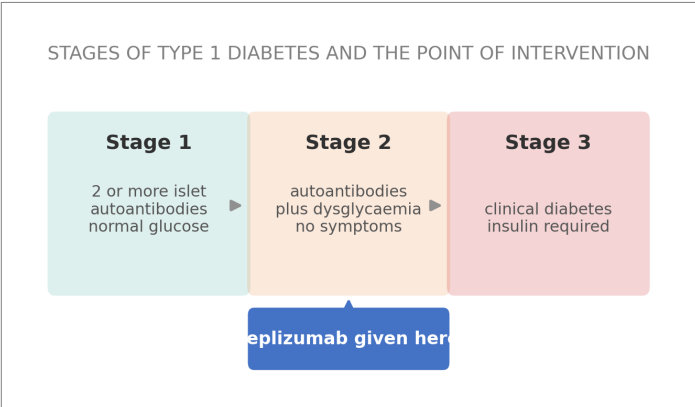


Figure 3: Stages of type 1 diabetes and the point at which teplizumab is given [3,4]

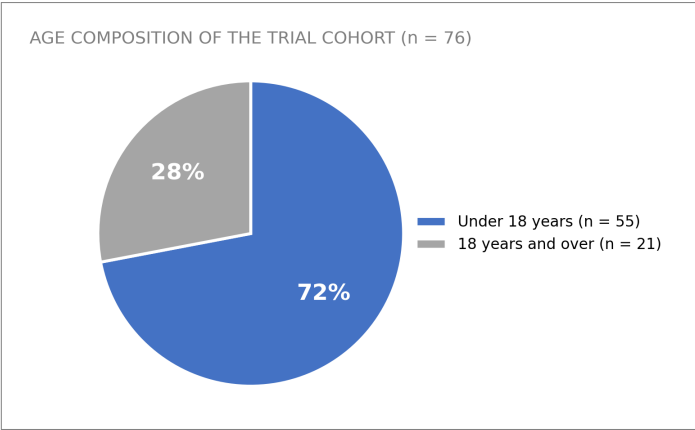


Figure 4: Age composition of the trial cohort [5,11]

The principal result: Clinical type 1 diabetes was diagnosed in 19 of 44 participants given teplizumab, 43 per cent, against 23 of 32 given placebo, 72 per cent (Figure 1). The median time from randomisation to diagnosis was 48.4 months in the teplizumab group against 24.4 months in the placebo group, a median delay of 24 months (Figure 5) [5,11]. At the conclusion of the trial the proportion remaining free of diabetes was 57 per cent in the teplizumab group against 28 per cent on placebo, double the rate (Figure 2) [11,12].

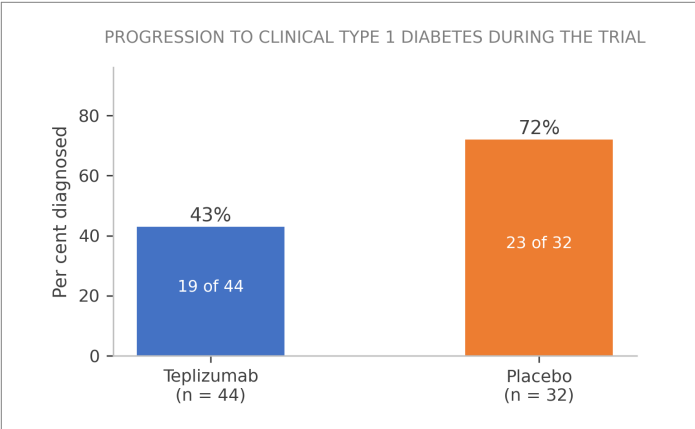


Figure 1: Progression to clinical type 1 diabetes during the trial [5,11]

The two ways of expressing that result answer different questions. The proportion diagnosed describes what happened during the observation period; the proportion still free of

diabetes at the close describes where the groups stood when counting stopped, and both depend on how long participants were followed [11,12].

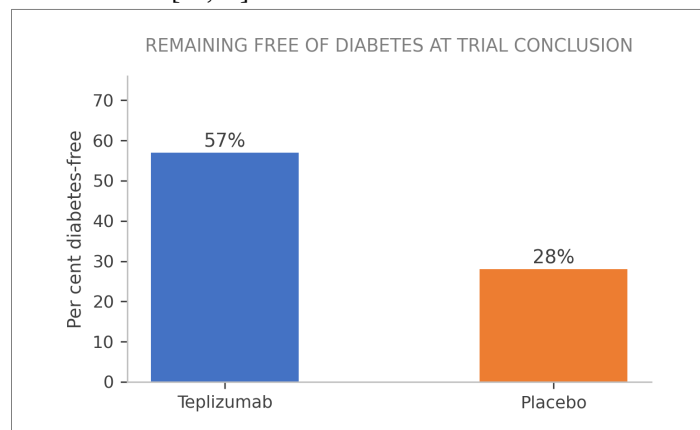


Figure 2: Proportion remaining free of diabetes at trial conclusion [11,12]

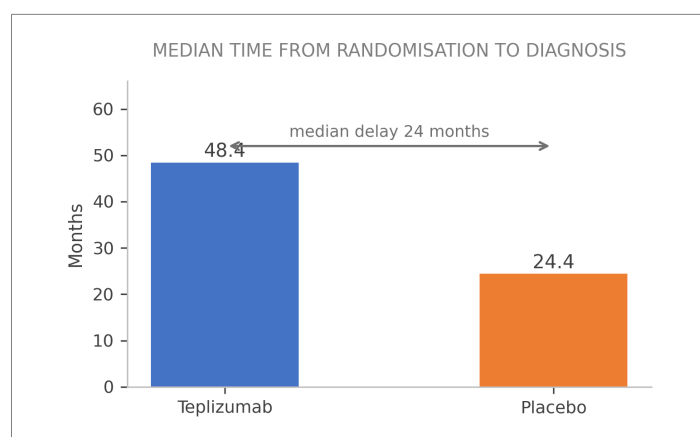


Figure 5: Median time from randomisation to diagnosis in each group [5,11]

The published objection: Correspondence in the same journal argued that the Kaplan-Meier estimates show the separation between the groups to be concentrated early. From roughly one year after treatment the proportion of participants developing diabetes was reported as greater in the teplizumab group than in the control group, which the correspondents took to indicate that the delay is brief rather than durable [13]. This is a dispute about the shape of the curve rather than about whether the primary endpoint was met, and it deserves to be reported alongside the headline figure.

Longer-term and regulatory position: Extended follow-up and subsequent analyses describe preservation of beta cell function and a median delay in progression to stage 3 of two to three years, with the explicit qualification that not all treated individuals respond [14,15]. The drug was approved in 2022 to delay onset of stage 3 disease in people aged 8 years and over with stage 2 disease [14,16]. Treatment causes a transient fall in lymphocyte count, and reported infection rates have been similar to controls [14,17].

Outcome	Teplizumab	Placebo
Number randomised	44	32
Progressed to clinical diabetes	43% (19)	72% (23)
Diabetes-free at trial close	57%	28%
Median time to diagnosis	48.4 months	24.4 months
Median delay	24 months	—

Table 1: Principal outcomes of the randomised trial as reported by the original investigators [5,11,12]

The screening requirement: Treatment presupposes identification during the asymptomatic phase, and that is the harder problem (Figure 6). The trial recruited relatives through an established screening programme, but restricting screening to relatives will not identify most future cases, because the majority of people who develop type 1 diabetes have no affected first-degree relative [18,19]. Population screening programmes have therefore been established: the Fr1da study in Bavaria has screened almost 200,000 children aged 1 to 21 years for islet autoantibodies [20,21]. Comparative analysis has examined whether progression risk in the trial population generalises to such a European screened cohort [20]. General-population screening has been reviewed as a strategy in its own right [29,31], and long-running birth cohorts continue to refine risk prediction [27].

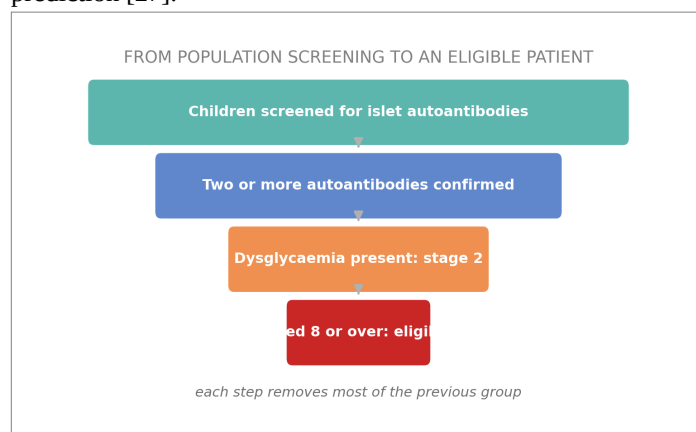


Figure 6: Attrition from population screening to an eligible patient [18,20,21]

Stage	Definition	Clinical status
Stage 1	Two or more islet autoantibodies, normal glucose	Asymptomatic
Stage 2	Autoantibodies plus dysglycaemia	Asymptomatic; near-certain progression
Stage 3	Clinical diabetes	Insulin required

Table 2: Staging of type 1 diabetes used to define eligibility [3,4]

Study or source	Design	Principal reported finding
Herold et al. 2019 [5]	Phase 2 RCT, n = 76	Median delay of 24 months to diagnosis
TrialNet TN-10 [11,12]	Trial reporting and repository	57% vs 28% diabetes-free at trial close
NEJM correspondence [13]	Published critique	Curves converge after year one; delay may be brief
Regulatory review 2022 [14,16]	Approval documentation	Median delay 2-3 years; not all individuals respond

Study or source	Design	Principal reported finding
Fr1da study [20,21]	Population screening, Bavaria	Almost 200,000 children screened for autoantibodies
Ziegler et al. [18,19]	Cohort analyses of autoantibody risk	Progression risk by antibody number and age

What is known about who responds: Extended analyses report that treatment preserves beta cell function and stabilises C-peptide in antibody-positive high-risk individuals, and that the effect is heterogeneous [15,30]. No pre-treatment marker currently predicts which individuals will gain a long delay and which will progress on schedule, and identifying one would change the calculation considerably, because it would allow the drug to be offered to those most likely to benefit rather than to everyone reaching stage 2 [14,15].

Screening at scale: Public health screening in Bavaria has reported the yield of testing children for islet autoantibodies, and follow-on work has examined how progression risk differs by the number of antibodies detected and by age at seroconversion [20,21,25]. A consistent finding across birth cohorts is that seroconversion risk peaks in early childhood and declines thereafter, which bears directly on when screening should be offered and how often it should be repeated [25,27]. Children identified through screening have been reported to present with milder metabolic disturbance at clinical diagnosis, which is a benefit of screening that does not depend on any drug being available [24].

Discussion

The trial result is real and it is a first: no previous intervention had postponed the clinical onset of type 1 diabetes [5,7]. For a disease diagnosed largely in children, two additional years without insulin is not a trivial gain, given what long-term exposure to the disease carries with it [34], and the doubling of the diabetes-free proportion at trial close is a substantial effect from a single 14-day course [11,12].

The published objection should nevertheless be taken seriously rather than noted and set aside. If the survival curves converge after the first year, then the median delay of 24 months describes the midpoint of a distribution in which some participants gained a great deal and others gained little or nothing [13]. That is compatible with the later observation that not all treated individuals respond [14]. A patient asking what the drug will do for them specifically cannot be told two years; the honest answer is that the average is two years and the variance around it is wide and not yet predictable.

The larger practical difficulty is upstream. Teplizumab acts at stage 2, which is asymptomatic by definition, so it can only be given to someone who has been screened [3,4]. Screening relatives is efficient in the sense that risk is concentrated in that group, but it will miss most future cases, because most people who develop the disease have no affected first-degree relative [18,19]. Population screening addresses that and brings its own

arithmetic: almost 200,000 children screened in Bavaria to identify the small number who reach stage 2 [20,21].

That arithmetic is what should be examined before this is described as a preventive strategy. Each step of the funnel removes most of the previous group, and the great majority of children screened will be autoantibody-negative and derive no benefit from having been tested. Against that sit the harms rarely quantified in the trial literature: telling parents that a well child carries antibodies predicting a disease that cannot yet be prevented, only postponed [22,23]. Trial networks have argued that co-ordinated infrastructure is the limiting factor in bringing such therapies into use [26,32]. Screening programmes report that children diagnosed through screening present with milder metabolic disturbance, which is a genuine benefit independent of any drug [21,24].

The reasonable summary is that an effective disease-modifying therapy now exists for a condition that had none, that its magnitude in the individual is less certain than the median suggests, and that the constraint on its use is not the drug but the infrastructure required to find the people who could receive it.

There is a further asymmetry worth naming. The trial population was recruited through a long-established research network among families already engaged with type 1 diabetes research [26,32]. Those families are not typical: they know the disease, they have watched a relative live with it, and their willingness to enrol a well child in an immunotherapy trial reflects that. Extending the same offer to families identified through population screening, who have no experience of the condition, is a different conversation, and nothing in the trial literature describes how it goes [22,23,29].

Finally, the comparison that will matter clinically is not teplizumab against placebo but teplizumab against what happens to a screen-detected child under surveillance alone. Screening itself brings earlier diagnosis, milder presentation and avoidance of ketoacidosis at onset [21,24]. A trial arm receiving structured monitoring without immunotherapy would isolate the drug effect from the benefit of simply being watched, and that comparison has not been made [29,31].

One further point concerns what the delay is for. Two years without insulin in a child is valuable in itself, but the stronger argument is that the delay buys time during which other interventions may arrive, and that beta cell mass preserved is beta cell mass available to any future therapy [15,30,33]. That argument is reasonable and it is speculative, and it should be presented as such rather than as part of the trial result. The trial measured time to diagnosis; it did not measure what happens afterwards, and long-term follow-up of treated individuals is still accumulating [14,15].

It is also worth stating what the disease costs over a lifetime, because that is the quantity a two-year delay is set against. Decades of follow-up from the landmark intervention trials

establish that glycaemic exposure accumulates into microvascular and macrovascular complications, and that the burden begins at diagnosis [34]. Postponing that starting point is therefore not simply postponing an inconvenience, which is the strongest version of the case for treatment and does not depend on any claim about durability [7,31].

Study limitations

The limitations belong to the underlying literature. The pivotal trial randomised 76 participants, which is small for a time-to-event endpoint, and the confidence around the median delay is correspondingly wide [5]. Median follow-up was 745 days against an outcome measured in years, so later divergence or convergence is poorly characterised [12,13]. The cohort was predominantly paediatric and entirely composed of relatives of affected individuals, so generalisation to screen-detected cases without family history rests on modelling rather than direct evidence [11,20]. The reported convergence of the survival curves after one year is contested and unresolved [13]. Responder and non-responder status cannot currently be predicted before treatment [14]. Long-term safety beyond the trial period is not established. And the screening programmes that would supply eligible patients are concentrated in a small number of well-resourced European and North American settings [20,21].

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Conclusion

A single 14-day course of teplizumab postponed clinical type 1 diabetes by a median of two years in relatives who had already reached stage 2, and doubled the proportion still free of diabetes when the trial closed. That is a genuine first and it justified approval. Two qualifications belong with it. The survival curves have been argued to converge after the first year, so the median describes an average across people who benefited very differently, and the drug cannot be given to anyone who has not first been found by screening in an asymptomatic phase. The scientific problem of delaying this disease now has a partial answer; the logistical problem of identifying who to treat does not.

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Conflict of Interest

The authors declare no competing interests.

Ethics Statement

This article reviews previously published studies only. No new patient data were collected and no participants were recruited, so ethical approval was not required.

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