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Review article

Strategies for clinical trials in type 1 diabetes

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ABSTRACT

During the past one to two decades, substantial progress has been made in our understanding of the immunopathology of type 1 diabetes (T1D) and the potential for immune interventions that can alter the natural history of the disease. This progress has resulted from the use of standardized study designs, endpoints, and, to a certain extent, mechanistic analyses in intervention trials in the setting of new-onset T1D. To date, most of these trials have involved single-agent interventions but, increasingly, future trials will test therapeutic combinations that are based on a compelling scientific rationale and testable mechanistic hypotheses. These increasingly complex trials will benefit from novel trial designs (such as factorial or adaptive designs), enhanced clinical endpoints that more directly assess islet pathology (such as β-cell death assays and islet or pancreatic imaging), improved responder analyses, and sophisticated mechanistic assays that provide deep phenotyping of lymphocyte subsets, gene expression profiling, in vitro T cell functional assessments, and antigen-specific responses. With this developing armamentarium of enhanced trial designs, endpoints, and clinical and mechanistic response analyses, we can expect substantial progress in better understanding the breakdown in immunologic tolerance in T1D and how to restore it to achieve significant and long-lasting preservation of islet function.

1. Introduction

Type 1 diabetes (T1D) is characterized by a progressive loss of β-cell function resulting in absolute insulin deficiency. Although the precise etiology remains obscure, the pathogenesis comprises an organ-specific autoimmune process in genetically susceptible individuals involving activated innate immunity and dysregulated humeral and cellular adaptive immune responses [1,2].

The endocrine deficiency in T1D is treated with insulin replacement therapy, which substantially reduces morbidity and mortality. However, despite modern intensive diabetes management—including the use of insulin pumps, continuous glucose monitoring, sensor-augmented insulin pumps, or closed-loop pump-sensor systems ("artificial pancreas") – normal or near-normal glycemic control (as measured by glycated hemoglobin (HbA1c) < 5.7%) cannot be achieved [3,4]. Even when glycemic control is "good" by current standards (HbA1c < 6.9%), patients with T1D, including children, have a 2-fold greater mortality than their nondiabetic peers [5].

There are currently no disease-modifying interventions for T1D. The restoration of immunologic tolerance is of considerable interest as a means to arrest and possibly reverse the autoimmune destruction of β cells in the pancreas [6]. During the past three decades, substantial efforts have been made to evaluate immunosuppressive and immunomodulatory agents in the clinic [7]. Most T1D trials have been conducted in patients with established or newly diagnosed disease, and this population will be the focus of this review.

2. Targets for immune intervention in T1D

A review of targets for immune intervention and a systematic analysis of the results of intervention trials to date is beyond the scope of this report, and the reader is referred to recent reviews [1,6,7]. Recent decades have witnessed enormous strides in the development of powerful immunomodulatory drugs, most notably fusion proteins and monoclonal antibodies that target specific receptors on B and T cells and a range of cytokines [8]. Many autoimmune disease can now be treated successfully, with evidence of disease modification and induction of remission. However, disease-modifying interventions in T1D have lagged, partly because of inaccessibility of the target organ and partly because the autoimmune process is silent, starting years or decades before diagnosis [9]. Nevertheless, over the past 1–2 decades substantial progress has been made in the design and conduct of intervention trials in T1D [7].

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3. Clinical trial designs in T1D

3.1. Standard trial design

During the past decade, new-onset intervention trials have generally conformed to a common formula, with similar inclusion/exclusion criteria, endpoints, and duration [10,11]. As shown in Fig. 1, these trials are phase 2 proof-of-concept studies with enrolment goals of 60–80 subjects; patients are randomized within 100 days of T1D diagnosis, are autoantibody positive, with a peak C-peptide response of >0.2 pmol/mL during a mixed meal tolerance test (MMTT), and ages in the range 6–45 years. Eligible patients are randomized 2:1, drug to placebo, in a double-blind, placebo-controlled, 2-arm design. The primary endpoint is the change from baseline in the 2- or 4-h mean C-peptide area under the curve (AUC) following an MMTT at 12 or 24 months.

This design has served the community well and has generally provided credible evidence for the presence, or absence, of a signal of efficacy. Nevertheless, this approach has room for improvement: (a) the process is slow, generally 3–5 years from protocol development to completion of the primary analyses; (b) there are a limited number of expert sites and eligible patients, reducing the number of trials that can be conducted; (c) the selection of interventions has often been driven by pragmatic considerations and not by a compelling scientific rationale; and (d) there was often no a priori, testable mechanistic hypothesis and mechanistic insights into success or failure have been limited.

3.2. Alternative trial designs

Current T1D intervention trials are inefficient with respect to speed, the ability to evaluate multiple interventions (including novel combinations), dose optimization, and addressing mechanistic hypotheses. Some of these issues can be addressed by using alternative trial designs.

3.2.1. Factorial designs

Factorial designs are well suited to exploring novel drug combinations while limiting total enrolment [12]. Consider the following example: alefacept can induce partial remission but the effect begins to wane in the 2nd year [13]. One hypothesis is that the induction of tolerance is incomplete but might be augmented by an agent that blocks costimulation (e.g., abatacept [14]) or by an agent that blocks TNFα, an inflammatory cytokine (e.g., etanercept [15]), or the combination of all three. With a 2 × 2 factorial design, there are four treatment groups. One group would receive alefacept alone; one would receive alefacept plus abatacept; one alefacept plus etanercept; and one alefacept plus abatacept plus etanercept. For analyzing the effect of abatacept, the response rate for the two arms which received abatacept are compared to the response rate for the two arms which did not receive abatacept. Analyzing the effect of etanercept is similar. The factorial design has efficiency advantages because each drug is evaluated by comparing outcomes for all patients receiving that drug to outcomes for all patients not receiving that drug [16]. Thus, in the example above, a 2 × 2 factorial design will require only two thirds the number of patients as a 3-arm trial (alefacept vs. alefacept plus abatacept vs. alefacept plus etanercept).

A potential concern with factorial designs is that there could be interactions among the drugs [17]. That is, the effect of abatacept may differ depending on whether or not etanercept is administered. However, that can be a strength because factorial designs are effective at screening for combinations that are synergistic for response [16]. A more important concern is the absence of a placebo group. There is variability from trial to trial in the rate of C-peptide decline in the placebo group, which is partly a function of age, time since diagnosis, and residual islet function at baseline [18]. This concern is lessened when the core drug (in this case alefacept) is known to have an effect and the primary question in the trial is whether that effect can be enhanced by a second drug. If a placebo group is considered essential, then this can be achieved by evaluating only 2 drugs [17], for example alefacept and abatacept, and the four groups are: alefacept alone, abatacept alone, alefacept plus abatacept, and placebo.

3.2.2. Adaptive designs

Adaptive designs can accelerate the evaluation of novel drug combinations, the sequencing of drug combinations, and dose optimization. A key feature of adaptive designs is that they include prospectively planned opportunities to modify specified aspects of the trial, such as treatment group assignment and overall enrolment [19]. Adaptive designs rely on the use of biomarkers that drive decisions on planned trial modifications and therefore are suitable for interventions with known mechanisms of action.

An example of where an adaptive design may be useful is in the development of low-dose IL-2 as a tolerogenic intervention (Fig. 2). While IL-2 promotes both Teff and Treg cells [20], Tregs are exquisitely dependent on IL-2 for growth and stability, and therefore low-dose IL-2 may selectively stimulate and expand Tregs [21]. However, the IL-2/Rapa trial gave mixed results: Tregs were robustly expanded and activated and yet islet function transiently declined, possibly because of unintended expansion of NK cells and eosinophils [22]. The dose used in the IL-2/Rapa trial was probably not low enough. A recent trial explored doses that were even lower [23], but further dose optimization is required to find a dose that selectively targets Tregs with no activation of effector cells.

The ITN has proposed an adaptive trial design for dose optimization using the continual reassessment method [10]. In this design

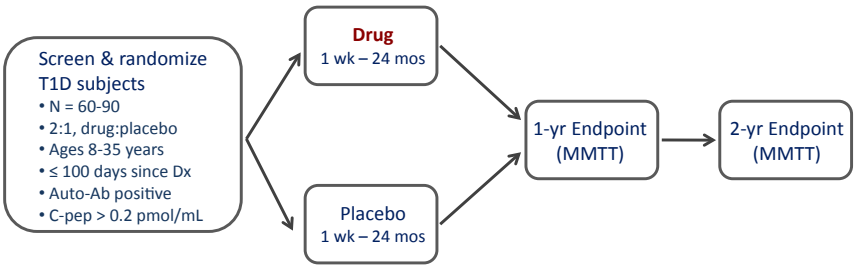

Fig. 1. The standard study design for proof-of-concept trials of novel interventions in new-onset T1D. This is a randomized, placebo-controlled, double-blind phase 2 design, with 2:1 randomization (drug to placebo). Key inclusion criteria are shown. The primary endpoint, generally at 1 year, is the change from baseline in C-peptide area under the curve (AUC) following a mixed-meal tolerance test (MMTT). Secondary endpoints and continued safety follow-up usually extend to 2 years. Reprinted with permission from Ehlers & Nepom [10].