Pharmacological Research 98 (2015) 31–38

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Review

The rise, fall, and resurgence of immunotherapy in type 1 diabetes

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ARTICLE INFO

Article history:
Received 26 May 2014
Received in revised form 30 June 2014
Accepted 1 July 2014
Available online 6 August 2014

Keywords:
Type 1 diabetes
NOD mice
Immunotherapy
Hematopoietic stem cells
T cells
B cells
Immunosuppression

ABSTRACT

Despite considerable effort to halt or delay destruction of β-cells in autoimmune type 1 diabetes (T1D), success remains elusive. Over the last decade, we have seen a proliferation of knowledge on the pathogenesis of T1D that emerged from studies performed in non-obese diabetic (NOD) mice. However, while results of these preclinical studies appeared to hold great promise and boosted patients' hopes, none of these approaches, once tested in clinical settings, induced remission of autoimmune diabetes in individuals with T1D. The primary obstacles to translation reside in the differences between the human and murine autoimmune responses and in the contribution of many environmental factors associated with the onset of disease. Moreover, inaccurate dosing as well as inappropriate timing and uncertain length of drug exposure have played a central role in the negative outcomes of such therapeutic interventions. In this review, we summarize the most important approaches tested thus far in T1D, beginning with the most successful preclinical studies in NOD mice and ending with the latest disappointing clinical trials in humans. Finally, we highlight recent stem cell-based trials, for which expectations in the scientific community and among individuals with T1D are high.

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http://dx.doi.org/10.1016/j.phrs.2014.07.004
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Introduction

Type 1 diabetes (T1D) is perceived as one of the most relevant autoimmune disorders in children and is characterized by selective and aggressive destruction of insulin-producing β-cells, orchestrated by autoreactive T cells [1]. The global incidence and prevalence of T1D have been increasing worldwide at a rate of nearly 3% per year, with fluctuating geographical distributions that cannot be attributed solely to genetic factors, emphasizing the influence of the environment in T1D [2]. The current therapeutic regimen for T1D relies on insulin administration and on glucose sensing technologies, which result in acceptable glycometabolic control for many individuals, while some individuals still may experience hypoglycemic episodes [1]. While quality of life has improved with the use of novel glucose sensors and pumps and allowed for better management of glycemia control concomitant with a reduction in hypoglycemia risk, the effect of these novel tools on diabetic complications is not completely clear [3,4]. Other alternative treatments, such as islet transplantation or whole pancreas transplantation, have been shown to restore patients' ability to regulate endogenous insulin production but remain limited due to a shortage of donors and the need for chronic immune suppression [5]. Finally, intensive insulin therapy, which is known to slow down the progression of diabetic complications by 35–70% [6], is associated with a high incidence of hypoglycemia [6]. Given the aforementioned issues, development of an alternative therapy is mandatory. A better understanding of the pathogenesis of T1D has emerged from several studies using the NOD mouse [7]. In particular, while prevention studies in NOD mice often do not translate to human because identifying human with T1D early enough is problematic, reversal studies are stringent and have contributed in the past to better design of novel treatments [8]. However, despite the success in preclinical studies in NOD mice, translation of these therapies to humans has failed. Several factors have contributed to this failure: (i) some treatments were not previously tested in NOD mice (e.g. GAD-alum, NBI-6024 [insulin altered peptide ligand], and DiaPep277 [heat-shock protein peptide60 peptide p277]); (ii) the heterogeneity of the disease in humans; (iii) the choice of dosing for intervention has not been optimized; (iv) and the timing of intervention needs to be better explored [2]; indeed earlier intervention may be more effective given the fact that at earlier stage of disease, 20–30% of β-cells are still present [9]. Many variables may explain the difficulty to translate NOD mice studies into effective therapies in T1D individuals. The main differences are related to the drug itself, to the optimal timing and to the dosing [10]. Furthermore, patients heterogeneities, differences in kinetics of the disease and the variable responses of β-cells to stress and injuries, dissimilarities of the innate and adaptative pathways responses that are mainly targeted by therapeutics lead to the failure of most of the approaches [10]. Recently, there has been a large discussion on the role of environmental factors (e.g. the gut microbiota) in the onset of T1D and this may represent a further difference between mice and men [11]. Finally, the translation of preclinical data to clinical trials represent a big challenge as many parameters should be considered such as the choice of endpoint in clinical trials and the proof of concept of efficacy and robustness of the therapy. The need of a post hoc analysis to identify responders and non responders groups may help to design future successful trials.

The evolving concept of immunotherapy in type 1 diabetes

The majority of T1D clinical trials performed thus far have not demonstrated any effect on β-cell function or on exogenous insulin requirement, although some have achieved a transient delay in β-cell destruction with slight preservation of C-peptide [10,12–16]. Thus, investigators have begun to consider the use of more robust approaches. After cyclosporine A, the first immunosuppressive agent tested, which preserved successfully β-cell function, but that induced nephrotoxicity and forced the early termination of the study [17,18], the idea of inducing tolerance to autoantigens was introduced. However, inducing tolerance may not necessarily lead to depletion of autoreactive T and B cells that infiltrate pancreatic islets. The use of T/B cell-targeting drugs was then considered with the goal of reducing the pancreatic islet infiltrate [19–21]. The failure of T/B cell-targeting trials highlighted the unique setting of T1D and its resistance to conventional cell-targeting strategies. Indeed the resolution of autoimmunity may not be the sole answer, particularly if inflamed/injured β-cells continue to undergo cell death or if the disease recurs. Investigators at last began to realize that a very narrow therapeutic window exists before islets can no longer be rescued. Another potential confounding issue that investigators faced was the heterogeneity of the disease in human. Indeed, T1D can be prevented in special circumstance, known as pre-diabetic period, when sufficient and functional β-cell mass is still maintained [22]. The presence of autoantibodies against islets antigens detectable before the onset of the disease can help to distinguish different phases of the disease: antibodies negative abnormal glucose tolerance, antibody positive normoglycemic, new onset and later onset and may be helpful to identify subject at high risk [22]. In a recent study, Sosenko et al. [23] developed a T1D risk score (DPTRS) from DPT-1 trial, that was helpful to stratify high-risk normoglycemic and low risk dysglycemic individuals.

The situation room of preclinical studies

Antigen-specific studies

Antigen-specific approaches are of potential interest in the treatment of autoimmune diabetes, as they target only pathogenic autoreactive T cells and induce immune tolerance toward autoantigens, without affecting the ability of the immune system to counteract infections and cancers [24]. Treatment of overtly diabetic mice with DEF-GAD65, an antigen that induces apoptosis of effector T cells, restored short-term normoglycemia in 72% of treated NOD mice [24]. Long-term normoglycemia was obtained in 80% of mice upon continuous administration of DEF-GAD65, with sustained and increased IL-10 secretion and a decrease in IFN-γ secretion by $CD4^+$ T cells in a GAD65 peptide-specific manner [24]. The potential existence of different autoantigens for mice and humans, however, has halted or slowed progress in preclinical testing of other antigen-specific strategies.

Anti-inflammatory studies

The discovery of an important inflammatory component in autoimmune diabetes has led to an increase of the number of anti-inflammation-based approaches. Anti-inflammatory studies in NOD mice reverted diabetes to a higher extent, by reducing

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