The Use of CD3-Specific Antibodies in Autoimmune Diabetes: A Step Toward the Induction of Immune Tolerance in the Clinic

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Abstract

CD3-specific monoclonal antibodies were the first rodent monoclonals introduced in clinical practice in the mid 1980s as approved immunosuppressants to prevent and treat organ allograft rejection. Since then compelling evidence has been accumulated to suggest that in addition to their immunosuppressive properties, CD3-specific antibodies can also afford inducing immune tolerance especially in the context of ongoing immune responses. Thus, they are highly effective at restoring self-tolerance in overt autoimmunity, a capacity first demonstrated in the experimental setting, which was recently transferred to the clinic with success.

1 Introduction

OKT3, a mouse IgG2a (Kung et al. 1979), was the first monoclonal antibody (MAb) introduced in clinical practice in 1981 to treat and prevent renal allograft rejection (Cosimi et al. 1981a,b; Vigeral et al. 1986; Debure et al. 1988). Amazingly, this...
occurred about 4 years before the complexities of its target molecule, CD3 were discovered (Clevers et al. 1988; Davis and Chien 1999). In addition, due to the tight species-specificity of anti-human CD3 antibodies, which only cross-react with chimpanzees T cells and not those from more commonly used nonhuman primates (i.e., Rhesus or Cynomolgus), conventional in vivo preclinical toxicology data were not available when the first patients were treated with OKT3. In this particular case this was fortunate since the risk was high for this antibody to be excluded because of its T cell mitogenic potential leading to the well described cytokine-mediated “flu-like” syndrome. Several controlled trials were conducted demonstrating the very efficient immunosuppressive properties of OKT3 both to reverse and prevent acute organ allograft rejection episodes (Cosimi et al. 1981a, b; Ortho 1985; Debure et al. 1988), thus explaining that the MAb was licensed both in the USA and Europe for use in transplantation.

Over the last 10 years, as other immunosuppressants developed, the use of OKT3 was almost completely abandoned, essentially because of the aforementioned cytokine releasing potential (Chatenoud et al. 1986, 1989, 1990; Cosimi 1987; Abramowicz et al. 1989; Eason and Cosimi 1999; Chatenoud 2003). In parallel, however, second generation CD3-specific MAbs have been produced by molecular engineering that are humanized (Bolt et al. 1993; Alegre et al. 1994), or even fully human, and Fc mutated. Because of the Fc mutation these antibodies are well tolerated since they express a significantly decreased cytokine releasing potential. In addition, the experimental work conducted in different autoimmunity and transplant models have demonstrated that far beyond their immunosuppressive potential, CD3 MAbs are also unique tools to promote immune tolerance in naive hosts (Hayward and Shreiber 1989; Nicolls et al. 1993; Plain et al. 1999) and, perhaps more impressively and more important in terms of clinical translation, to reestablish self-tolerance in established autoimmunity (Chatenoud et al. 1994, 1997; Belghith et al. 2003; Chatenoud 2003).

It is on this basis that in the early 2000, CD3-specific MAbs were back in the clinic in the context of challenging protocols that mostly aim at testing whether one may translate into patients the tolerogenic potential observed in preclinical models. It is the aim of this review to gather the data showing the reader that this may indeed be the case. Since the most compelling clinical evidence in support of such conclusion presently derives from the experience with CD3-specific MAbs in an autoimmune disease that is insulin-dependent diabetes, it appears important to start with a brief description of the physiopathology of this condition.

2 The Physiopathology of Autoimmune Insulin-Dependent Diabetes

Diabetes mellitus is a clinical syndrome characterized by chronic hyperglycemia. It became apparent by the 70s that this definition included two major physiopathological entities namely, Type 1 (T1D) and Type 2 (T2D) diabetes. Type 1 diabetes is an autoimmune disease causing the progressive and selective destruction of insulin