Verapamil: a promising therapeutic option in diabetes mellitus type 1?

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Introduction

Type 1A diabetes mellitus (DMT1 in the following text) is caused by the autoimmune destruction of the insulin-producing beta cells in the islets of Langerhans [1, 2]. This destruction is determined by genetic susceptibility, such as the presence of HLA-DQα/β, HLA-DR, preproinsulin, PTPN22 gene, CTLA-4, interferon-induced helicase, IL2 receptor (CD25), lectin-like gene (KIAA0035), and ERBB3e [3-8]. It is usually triggered by environmental agents, such as perinatal factors (maternal age over 25 years, preeclampsia, neonatal respiratory disease, and jaundice), viruses (Coxsackie virus, enteroviruses), dietary factors (cow’s milk), exposure to nitrates, and treatment with checkpoint inhibitors [9-14].

Despite significant improvements in insulin therapy, DMT1 remains a therapeutic challenge. Therefore, the slowing down of pancreatic beta cell (PβC) loss may be of great value. With that said, the author summarizes the available evidence on such therapeutic options.

The use of verapamil in DMT1

Verapamil, a non-dihydropyridine calcium channel blocker primarily used to treat tachyarrhythmias, has been observed to inhibit thioredoxin-interacting protein (TXNIP), which may prevent PβC loss [15]. TXNIP inhibits thioredoxin, which is part of an antioxidant system, and induces oxidative stress, making PβC highly susceptible [16]. PβC TXNIP expression is strongly induced by glucose, and as there is hyperglycemia in DMT1, this expression is extremely high in diabetes, promoting further apoptosis of PβC and consequent reduction in insulin production, which closes the vicious circle.

Animal studies have shown that verapamil can prevent PβC apoptosis [17, 18].

Results of an observational study (REGARDS) showed that verapamil can significantly decrease fasting plasma glucose (P = 0.039), which was correlated with a 1% reduction in glycated hemoglobin [19]. Another observational study demonstrated that the use of verapamil in patients with no prior diabetes was associated with a lower incidence of type 2 diabetes compared to other calcium channel blockers [20]. Furthermore, an exploratory study using global DMT1 serum proteomics analysis identified chromogranin A (CHGA), an important DMT1-autoantigen, as the top protein altered by verapamil. Verapamil normalized CHGA serum levels and reversed DMT1-induced elevations in circulating proinflammatory T-follicular-helper cell markers [21].

The results of a phase 2 clinical trial indicated that verapamil treatment in adult patients with recent-onset DMT1 was associated with improved endogenous PβC function, as measured by mixed-meal-stimulated C-peptide area under the curve. Additionally, verapamil treatment was linked to a lower increase in insulin requirements, fewer hypoglycemic events, and better on-target glycemic control [22]. Two larger ongoing studies, Ver-A-TID and GLVer, are investigating the potential clinical benefits of verapamil in DMT1 [21].

Conclusion

The discovery of drugs that can slow down or even stop the loss of PβC may be of great value, as even a small amount of preserved endogenous insulin can lead to more beneficial clinical outcomes. Such therapeutic options may also be associated with lower exogenous insulin demands and potentially less severe and/or less frequent complications associated with DMT1, such as diabetic nephropathy, retinopathy, neuropathy, prolongation of complications-free period, and increased quality of life. These improved outcomes would also be associated with significant pharmaco-economic benefits.

Available scientific data suggest that verapamil may have such characteristics, as it has been shown to inhibit TXNIP and protect PβC from oxidative stress. Additionally, it normalizes CHGA serum levels and reverses DMT1-induced elevations in circulating proinflammatory T-cell markers, all of which may be associated with a slowdown of PβC loss and better control of the disease. Although clinical data are limited to a relatively small number of patients, the addition of verapamil to DMT1 therapy may be associated with a lower increase in insulin requirements, less frequent episodes of hypoglycemia, and better glycemic control.

However, larger ongoing studies are expected to be published, and these will hopefully reveal more about the clinical significance of verapamil as an additional treatment option in type 1 diabetes mellitus.

References


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The author confirms sole responsibility for the literature research and manuscript preparation.

Competing interests
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Abbreviations
DMT1, type 1A diabetes mellitus; PβC, pancreatic beta cell; TXNIP, thioredoxin-interacting protein; CHGA, chromogranin A.

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