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PUBTEXTO

Larger Efficacy on Combined Vildagliptin/Metformin (Equmet) and Imeglimin (Twymeeg) By Bis in Die (Bid) Administration

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Abstract

Several oral hypoglycemic agents (OHAs) have been developed for years. They were provided for 1, 2 or 3 times a day, which are quaque die (qd), bis in die (bid), and ter in die (tid). Vildagliptin and metformin (EquMet) and imeglimin (Twymeeg) are administered by bid. Consequently, blood glucose variability shows stable for 24 hours. Various evidence was obtained from Vildagliptin Efficacy in combination with metfoRmIn for early treatment of type 2 diabetes (VERIFY) and Trials of Imeglimin for Efficacy and Safety (TIMES). In VERIFY, relative risk was significantly lower (0.51) in combined vildagliptin/metformin group compared with metformin monotherapy.

Keywords: Bis in die (bid); Vildagliptin and metformin (EquMet); Imeglimin (Twymeeg); Vildagliptin Efficacy in combination with metfoRmIn for early treatment of type 2 diabetes (VERIFY); Trials of Imeglimin for Efficacy and Safety (TIMES)

Commentary

For some decades, various types of oral hypoglycemic agents (OHAs) have been developed into actual practice [1]. Formerly, sulfonyl urea (SU), biguanides, α-GI and glinides were usual OHAs for treating patients with type 2 diabetes (T2D). After that, novel types as DPP4-i, SGLT2i and oral GLP-1RA were produced with effective and safe benefits [2]. The differences would be that former meds were likely to provide a few times a day, and recent meds are often given once a day. Generally, OHAs can be almost classified into some groups as follows: three times a day (ter in die, tid) for α-GI and glinides, twice a day (bis in die, bid) for DPP4-i and biguanides, and once daily (quaque die, qd) for biguanides, DPP4-I and oral GLP-1RA [3]. Number of taking times per day has been gradually decreased due to the compliance and convenience. In recent years, OHAs have been often provided from bid to qd. However, diabetic treatment will be possibly more effective by bid rather than qd.

Authors and co-researchers continued diabetic research and practice for long [4]. We have recently recognized more clinical efficacy of OHAs which are given by bid. They include the combination of DPP4-i and biguanide as vildagliptin and metformin (EquMet) [5]. Furthermore, novel OHA for with dual mechanism has been introduced as imeglimin (Twymeeg) [6,7]. In this article, we present some perspectives about these OHAs associated with related experiences.

As DPP4-i, vildagliptin shows beneficial clinical efficacy by bid, which was found by all-day blood glucose fluctuations [8]. Thus, EquMet is likely to give better glucose variability, which includes vildagliptin and metformin twice a day. Large clinical studies of VERIFY (Vildagliptin Efficacy in combination with metfoRmIn for earlY treatment of type 2 diabetes) were conducted in 254 centers including 34 countries [5]. The protocol consisted 2-week screening period, 3-week metformin-provided period, and administering period for years. The cases were randomly divided to 1:1 ratio to two groups, which were combination therapy and metformin monotherapy groups. Among 4524 applicants, 2001 eligible cases were assigned with combined and monotherapy group (n=998, 1003), respectively. In VERIFY, time to initial and second treatment failure was analyzed. Relative risk was significantly lower in combined group for 5 years with hazard ratio of 0.51. The results showed the importance of early strict treatment by combined therapy.

Effects of vildagliptin twice daily can contribute decreased Mean amplitude of glycemic excursion (MAGE) [8]. Further, vildagliptin could reduce the MAGE at 6 months about -20.1mg/dL of average blood glucose [9]. Compared study was conducted between vildagliptin (bid) and sitagliptin (qd) [10]. The results of both groups were 142mg/dL vs 153mg/dL for mean 24-hour glucose, 110.5mg/dL vs 129.4mg/dL for MAGE, 206mg/dL vs 223mg/dL for highest glucose after supper, 484mg/min/dL vs 898mg/min/dL for 3hr-AUC of blood glucose after breakfast. Consequently, intake of vildagliptin by bid showed more beneficial result.

Concerning clinical efficacy of EquMet, comparative study was performed for monotherapy of metformin and vildagliptin/metformin (EquMet) [11]. They analyzed 8533 cases from 11 RCT reports. As a result, combination therapy showed more effects than monotherapy with mean differences of -0.59 value. For VERIFY study, compared study was also conducted for young-onset diabetes (YOD) and late-onset diabetes (LOD) with the borderline of 40 years old [12]. The result showed reduced risk of time for initial treatment failure (TF) for 48% vs 46% in YOD vs LOD, respectively. Similarly, reduced risk for secondary TF was 48% vs 24% in each group. In particular, treatment-naïve YOD cases (HbA1c 6.5%-7.5%) showed early attainment of glycemic target level with durability in comparison with those in metformin monotherapy.

By the results of VERIFY studies for 5 years, the necessity of earlier combination therapy for better glycemic control was presented [5]. The combined treatment of vildagliptin and metformin showed clinical efficacy with evidence. Such paradigm shift for earlier intensified therapy has been known and recommended by the European Association for the Study of Diabetes (EASD) and American diabetes Association (ADA) [13]. Among VERIFY studies, obtained results from 8 countries in Latin America region were analyzed [4]. For the protocol, primary endpoint was the time period until TF (HbA1c is 7.0% and more) for two consecutive clinical visit 3 months apart. Two groups were early combination (EC) and metformin monotherapy (MET). As a results, TF time period showed 46.4% vs 66.3% in EC and MET, respectively. Therefore, significant decreased risk of time for initial TF was 47% lower between the two groups. Similarly, second TF period was 31% lower in EC group. Consequently, large ratio of cases in EC have maintained successfully durable HbA1c < 7.0%, < 6.5%, and < 6.0%. Similarly, glycemic durability was compared in EC and MET group in Korean VERIFY trial [15]. The initial reduced risk TF was 15% vs 58.7% in EC vs MET, which means 78% risk reduction between the related two groups. T2D cases in the EC group have achieved constantly better HbA1c values. Consequently, EC group showed improved long-term glucose variability.

Both of EquMet and Twymeeg are OHAs for twice daily. This bid administration would be known to show clinical efficacy of improving blood glucose profile for 24 hours [16]. From historical point of view, metformin has been used for T2D as first-line OHA for long [17]. Imeglimin (Twymeeg) shows various additive effects with DPP4-i, biguanides, α-GI, SGLT2i, sulfonyl urea, and glinides from Trials of Imeglimin for Efficacy and Safety (TIMES) 1,2,3 studies [6,7]. Imeglimin contributes stable glucose variability measured by continuous glucose monitoring (CGM) [18]. Further development of research will be required concerning mitochondrial mechanism [19]. There is a possibility that imeglimin will become the first-line OHA in the future [20].

In summary, achieving diabetes remission in earlier period will contribute much for the future QOL and reducing the risk of macrovascular and microvascular complications [21]. Furthermore, such measure will bring the mitigation of burden of diabetes against influences on healthcare systems. Especially, successfully strict glycemic control for earlier diabetic stages will lead to decreasing various impaired dysfunction.

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