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IMEGLIMIN FOR DIABETES TYPE 2

Keywords: imeglimin, new anti-diabetic agent, tetrahydrotriazine, glimins

SUMMARY OF TECHNOLOGY

Imeglimin is the first drug in a new tetrahydrotriazine-containing class of oral antidiabetic agents, known as glimins with novel mechanism of action that simultaneously targets all three key organs of diabetes namely the pancreas, liver, and muscles. It targets insulin-resistant organs by decreasing excessive hepatic glucose production and increasing muscle glucose uptake and claimed to have potential to restore appropriate glucose-stimulated insulin secretion and protect β-cells from cell death under high glucose conditions. [1,2,3]

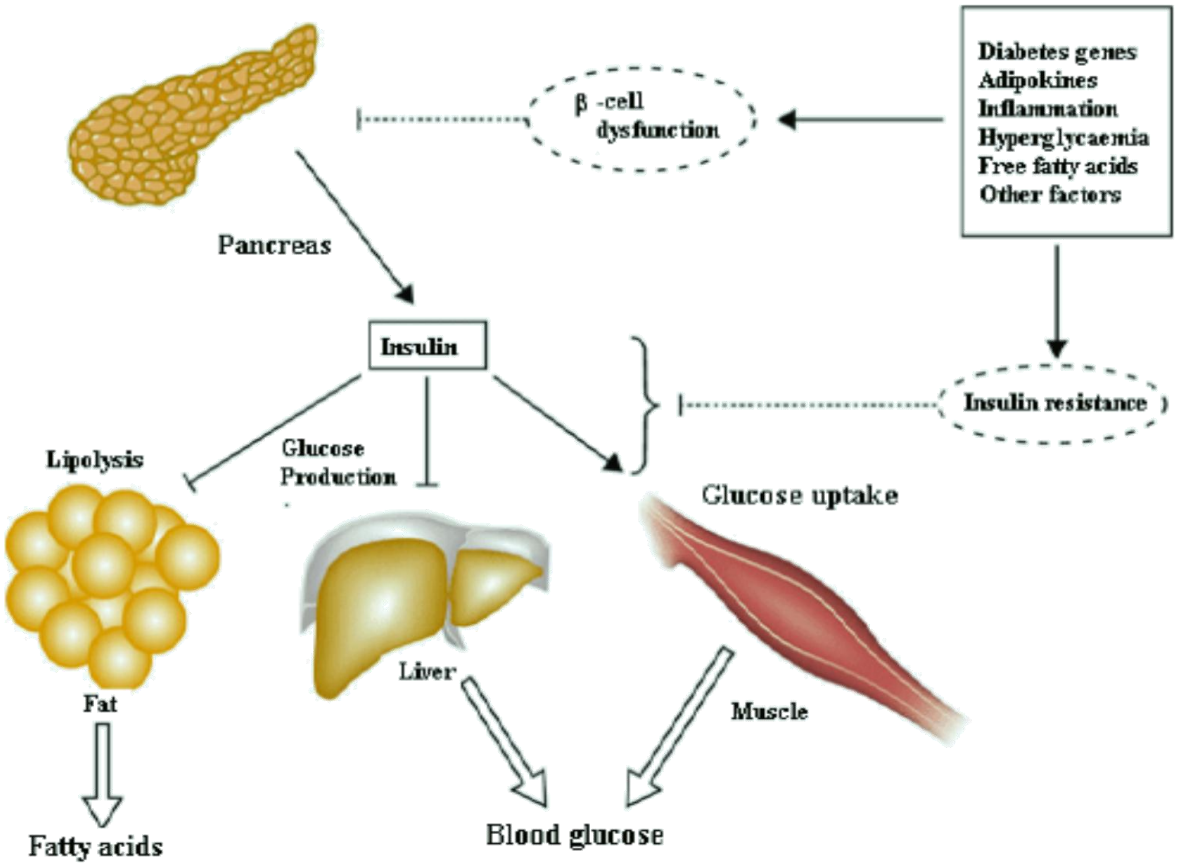

Figure 1: Pathophysiology of hyperglycemia & increased circulating fatty acids in type 2 diabetes.[4]

POTENTIAL FOR IMPACT

Diabetes mellitus is an important public health problem where the prevalence of diabetes in Malaysia increased by 31.0% within 5 years, from 11.6% (2006) to 15.2% (2011).[5] The overall prevalence of DM in age group above 60 years old increased from 2011 (36.6%) to 2015 (38.3%).[6] Currently, pharmacology therapy for diabetic patients includes multiple medications with synergistic mechanism of action and there is no single agent targets the three primary defects of this widespread disease.[1]

Pacini et al. was explored imeglimin's mechanism of action on beta cells function in a double-blind, randomized, placebo-controlled study which involved 33 patients of Type 2 Diabetic that received either naïve treatment or withdrawn from their previous metformin monotherapy for 2 weeks with average reading A1C of 6.8±0.1%. Patients then, received imeglimin 1500 mg twice daily or placebo for 1 week. After seven days of imeglimin treatment, the results showed significant increased of the insulin secretory response (ISR) to glucose by 112% (p=0.035) in imeglimin group (9.6±2.2 nmol.L^{-1}min) than in the placebo group (4.5±0.7 nmol.L^{-1}min), and beta cell glucose sensitivity was improved by 36% (p=0.034) in imeglimin group (24.6±2.2 pmol $min^{-1}m^{-2}L$ $mmol^{-1}$) compared to placebo (18.1±1.6 pmol $min^{-1}m^{-2}L$ $mmol^{-1}$).[1,7]

The efficacy and safety of imeglimin as add-on therapy in patients with type 2 diabetes inadequately controlled with metformin was studied in a randomised, double-blind and multicenter trial. In this 12-week study, 156 patients were randomised 1:1 to Imeglimin 1500 mg bd or placebo. Results showed that AIC reduced from baseline to 12-week by -0.65% in imeglimin-metformin group & -0.21% in placebo-metformin group (P=0.001). The FPG reduced by -0.91 mg/dL in imeglimin-metformin group but increased 0.36 mg/dL in placebo-metformin group (P<0.001).[8]

The efficacy and safety of imeglimin as add-on therapy in patients with type 2 diabetes inadequately controlled with sitagliptin monotherapy has also been studied in a randomised, double-blind, multicenter for 12-week therapy and 1-week follow-up period with placebo. About 170 patients randomly received 1500 mg bd imeglimin (81 subjects) or placebo (88 subjects) which added to a stable dose of sitagliptin 100 mg qid. Results showed that AIC reduced from baseline to 12-week by -0.6% in imeglimin-sitagliptin group but increased 0.12% in placebo- sitagliptin group (P<0.001). The FPG also reduced by -0.93 mg/L in imeglimin-sitagliptin group & -0.11 mg/dL in placebo-sitagliptin group (P=0.014).[9]

No serious adverse events or cardiovascular events were reported with imeglimin-metformin treated group. In Imeglimin-sitagliptin study, there was no related treatment-emergent adverse events (TEAE) reported in the imeglimin group except one subject in the imeglimin group experienced serious adverse event but not related to treatment (surgery for appendicitis). There were no effect on weight and waist circumference and no hypoglycaemic events reported in combination group.[1,8,9]

Imeglimin has a potential to be well-tolerated and efficacious treatment either as monotherapy or in combination with other antihyperglycaemic agents for type 2 diabetes

mellitus. Patients may receive monotherapy which is more convenient compared to multiple pharmacotherapy for optimal disease management. In terms of price, the cost of this technology is not yet known.[3,9]

EVIDENCE

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Fouqueray P,Pirags V,Diamant M et al. The efficacy and safety of imeglimin as add-on therapy in patients with type 2 diabetes inadequately controlled with sitagliptin monotherapy. Diabetes Care. 2014;37:1924–30.

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Prepared by:

Maria Jaafar
Principal Assistant Director
Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia

Reviewed by:

Dr. Izzuna Mudla bt Mohamed Ghazali
Public Health Physician/Senior Principal Assistant Director
Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia

Dr. Junainah bt Sabirin
Public Health Physician/Deputy Director
Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia

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Horizon Scanning Unit,
MaHTAS,
Medical Development Division,
Ministry of Health, Malaysia,
Email: htamalaysia@moh.gov.my
Web: http://www.moh.gov.my