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Editorial

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Insulin Analogs: Non-inferior and Expensive

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Introduction

The tremendous rise in the cost of insulin has been due mostly to the high cost of synthetic insulin analogs [1]. The onset and duration of action of insulin analogs are more predictable than human insulin. For this reason, patients generally prefer to use analogs, but head-to-head comparisons of analogs to human insulin have not shown major net differences in clinical outcomes [2].

The first rapid acting insulin analog, Humalog, was introduced by Eli Lilly in the US in 1997. To compete with Humalog, Novo Nordisk introduced NovoLog in 2000. Both Lilly and Novo Nordisk have kept the commitment they had made to the US Food and Drug Administration (FDA) to continue to market their low-cost human insulin products, Humulin and Novolin respectively [2]. The first long-acting analog, Lantus, was introduced in 2000 by Hoechst which later became part of the company now called Sanofi. Today all three manufacturers offer a range of insulin products, except that Sanofi has never marketed low-cost human insulin in the US.

March 23, 2020 marked a turning point in the regulation of insulin products by the FDA. Insulin products are now considered to be biologics not drugs [3]. It was hoped that this change would spur price competition. Two new insulin products were approved soon after, Lyumjev on June 15, 2020 and Semglee on June 11, 2020. Each of these illustrates different aspects of how the insulin market has changed over the years.

Humalog is Eli Lilly's original brand of the rapid acting insulin analog, lispro. Lyumjev is a new formulation of lispro with an onset of action several minutes sooner than Humalog. Studies in type 1 and type 2 diabetes showed that Lyumjev was "non-inferior" to Humalog, but not better. The slightly faster absorption with Lyumjev did not translate into better glycemic control than with Humalog. Whether cost conscious patients will want to use Lyumjev over Humalog or Lilly's own generic lispro remains to be determined.

Semglee is a version of the highly successful long-acting analog, insulin glargine. Insulin glargine was introduced in 2000 and marketed by Sanofi as Lantus. Following the expiration of Sanofi's patent protection, Lilly marketed its own brand of glargine, Basaglar, to compete with Lantus. Sanofi countered by marketing a reformulation of glargine known as Toujeo. Toujeo has three times the concentration of glargine, but its reduced bioavailability means that patients need to use more drug to get the same effect.

The FDA has required manufacturers to show that a new insulin product is non-inferior to an existing insulin product with respect to lowering HbA1c in patients with diabetes. Given that analogs were so expensive, the public could well have believed that these new products were better than the older ones. This was not necessarily the case. "Non-inferior" is statistical jargon within the FDA to be mean effective enough to be approved.

Approvals were based on the prespecified criteria that the 95% confidence interval for the difference in change in HbA1c must be 0.4% units or less. This approach originated in 2004 when the FDA needed to compare an extended-release metformin (Fortamet) given once daily to immediate release metformin given twice daily. A difference of 0.4 % units was thought to be small enough to be offset by the more convenient dosing. The same criteria were applied to approval of insulin detemir (Levemir) in 2005, and to all subsequent insulin products [2].

Any reduction in HbA1c without hypoglycemia is clinically important. The non-inferiority margin of 0.4% was a pragmatic choice to be consistent with the standard that FDA uses to approve generic drugs. A tighter margin could have required that many more patients be studied.

Trials comparing new insulin products to existing insulin products have been performed in accordance with the dosing regimens in the labels of the existing insulin products. But in ordinary practice, physicians are not required to prescribe insulin exactly as labeled. Insulin glargine is labeled to be used once daily, but its activity does not always last a full 24 hours [2]. For this reason, splitting the dose of glargine has been advocated for patients whose hyperglycemia is not adequately controlled on a once daily dose [4]. For a true comparison to insulin glargine, trials of ultra-long-acting insulin analogs should allow patients to split the dose of glargine [5].

Clinical trials do not necessarily capture differences among individual patients, nor allow individual patients to accommodate different situations. In real life, patients adjust their insulin dosing according to meals and physical activity. The nature of randomized clinical trials does not accommodate all the variability that exists among patients. An analog may be important for some patients' lifestyle but not others. Still, other than the small advantage of degludec (Tresiba) over once daily glargine (Lantus) with respect to hypoglycemia, there is little evidence that one insulin product is better than another. They were all approved based on being non-inferior to each other or to human insulin [2].

NPH human insulin is a cost-effective way to treat patients with type 2 diabetes. Switching back to NPH human insulin from analogs has little effect on glycemic control in patients with type 2 diabetes [5-7]. The convenience and predictability of analogs may make them better choices for some patients with type 1 diabetes. But the difference is not nearly great enough to mean life or death. As recently noted by the American Diabetes Association, recombinant human insulin can be purchased at Walmart without a prescription for $25 per 1000 units [9]. Patients reported to have died because of rationing their insulin [10] are victims of misinformation. Switching from analogs to human insulin would have been infinitely preferable to rationing.

Going forward, the FDA and other regulatory agencies should base approvability on a broader measure of glucose control than simply change in HbA1c. Of particular importance is metric that captures hypoglycemia in addition to improvement in hyperglycemia [11-13]. Until that happens, we will never know that a new insulin product is better than older insulin products, just that it is non-inferior.

Acknowledgements

None.

Conflict of Interest

None..

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