Breaking Barriers With Basal Insulin Biosimilars in Type 2 Diabetes

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Despite increases in the availability and effectiveness of other therapies, insulin remains an essential treatment for approximately 30 million people with type 2 diabetes worldwide. The development of biosimilars has created the potential for significant health care cost savings and may lead to greater access to basal insulin for vast populations. In this review, we discuss evidence demonstrating equipoise between basal insulin biosimilars and the patented analogs they may replace.

Therapeutic management of type 2 diabetes is complex, with some patients requiring only lifestyle management and metformin as first-line therapy and others requiring other antihyperglycemic agents, including insulin therapy (1,2). Approximately 7% of the 405.6 million people with type 2 diabetes, or nearly 30 million people globally, require insulin therapy (3). At 100 years since its discovery, insulin continues to play a key role for glycemic management, as evidenced by international guideline recommendations for basal insulin initiation in people with type 2 diabetes (1,2,4).

Despite high-quality data and guideline recommendations, glycemic control remains inadequate worldwide, which may be a consequence of high cost or, in part, therapeutic inertia, the failure of a health care professional to advance or intensify therapy when indicated (5). Causes of therapeutic inertia can be divided into provider-, patient-, and system-level barriers, which include health care issues (i.e., inadequate health care systems such as low availability of specialist nurses; lack of early diagnosis, management, and psychological support; and poor care plans), medication costs, and limited availability of medications. The full global costs of diabetes in adults are projected to increase from $1.3 trillion in 2015 to $2.4 trillion (baseline scenario increased only with urbanization and population aging), $2.5 trillion (increased in line with previous trends), or $2.1 trillion (with achieved global targets) by 2030 (6). In low- and middle-income countries, a large proportion of these costs are out-of-pocket expenses for patients. An analysis conducted in sub-Saharan Africa estimated out-of-pocket costs of $19.5 billion, or 1.2% of the cumulative gross domestic product; these costs are expected to increase to between $35 billion and $59 billion by 2030 (7).

Biosimilars have been developed to be highly similar to approved biologic medicines, with no clinically meaningful differences related to purity, potency, and safety, and were first approved in the European Union in 2006 and in the United States in 2015 (8). Since then, more than 50 biosimilars have been approved in the European Union, and nearly 30 have been approved in the United States (9). With the need to increase the effectiveness of health systems while optimizing the use of available resources, it makes sense to spend less, and biosimilars offer an opportunity to provide insulins with proven benefit at lower cost. It is the opinion and hope of the authors that the entrance to the market of biosimilars will lead to an insulin cost–savings "price war."

Biosimilars: Definition

According to the U.S. Food and Drug Administration (FDA), a biosimilar is "highly similar to, and has no clinically meaningful differences in safety, purity, and potency (safety and effectiveness) from an existing

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FDA-approved reference product (RP)" (10). According to the European Medicines Agency (EMA), a biosimilar is a biological medicine highly similar to another already-approved biological medicine (the "reference medicine") (11). On 23 March 2020, the FDA moved insulin to its biologic regulatory framework, which means that currently marketed insulins are now labeled as biologics, and biosimilar and interchangeable insulins can be developed and approved in the United States (12).

In Europe, when a biosimilar is considered to be interchangeable, pharmacists have the ability to automatically switch between the RP and the biosimilar without obtaining consent from prescribers (13). This ability could have important clinical implications resulting from improper attribution of adverse events to specific products (particularly if people switch products often). In Europe, no centrally adopted interchangeability or substitution criteria exist; therefore, local authorities develop criteria, which may be different from one country to another (13). In the United States, interchangeability allows for the substitution of the biosimilar for the RP without intervention by the prescribing health care provider (14).

Criteria for approval of a biosimilar require a quality assessment; demonstration of similarity in physicochemical and biological characterization, including receptor binding, metabolic potency, and mitogenicity; pharmacokinetic/pharmacodynamic (PK/PD) profiles in phase 1 studies; and assessment of safety end points in phase 3 clinical trials, with an emphasis on immunogenicity (13). Requirements for biosimilar insulin, according to the EMA, include preclinical studies focused on in vitro receptor binding and in vitro biological activity and clinical studies, including phase 1 PK/PD and phase 3 studies (13).

This article focuses on recently approved insulin biosimilars. Below, we provide expert opinions and insights on the use of basal insulin in type 2 diabetes in the context of new international recommendations. It includes a comparison of basal insulins, a summary of the introduction of biosimilar basal insulins, and a description of the appropriate patient profile for long-acting insulin therapy.

Guideline Recommendations for Basal Insulin Initiation in Type 2 Diabetes

International guidelines have been published regarding basal insulin initiation in patients with type 2 diabetes (1,2,15). At some point in the natural history of the disease, many people with diabetes become relatively insulin deficient, which is an early indication for insulin therapy. It has been demonstrated that lowering A1C to ≤7% through the use of insulin or other therapies reduces the risk of microvascular disease (16). Furthermore, randomized, controlled trials have shown significant reductions in cardiovascular events among people with type 2 diabetes treated with a sodium–glucose cotransporter 2 inhibitor (e.g., empagliflozin, canagliflozin, or dapagliflozin) or a glucagon-like peptide 1 (GLP-1) receptor agonist (e.g., liraglutide, semaglutide, dulaglutide, or efpeglenatide) (2,17).

In the past decade, there has been a large shift in the breadth of choices of therapy for type 2 diabetes, particularly in economies that can afford more expensive therapeutic options. Results from a systematic review and meta-analysis of 453 trials investigating 21 antidiabetic interventions from nine drug classes revealed that various insulin regimens and specific GLP-1 receptor agonists added to metformin therapy produced the greatest reductions in A1C (17). The option to use a GLP-1 receptor agonist in combination with a basal insulin makes early use of insulin more attractive by reducing hypoglycemia and weight gain compared with insulin when used alone. According to recommendations by the American Diabetes Association (ADA), insulin therapy should be initiated for patients who present with blood glucose levels ≥300 mg/dL (2).

NPH insulin may require up to three injections daily to achieve 24-hour coverage (Table 1) (18). The first-generation basal insulin analogs detemir and glargine 100 units/mL (U100) require injections at the same time each day. Second-generation basal insulin analogs include insulin degludec 100 and 200 units/mL and insulin glargine 300 units/mL (U300) (18). These insulins have a lower variation in glucose-lowering effect within and between days and a reduced risk of hypoglycemic events, as well as an extended duration of action with low peak-to-trough ratios that enable flexibility in dose timing.

Although data are unclear whether the second-generation basal insulin analogs are advantageous for reducing hypoglycemic risk, they provide treatment options for patients requiring insulin therapy who may be vulnerable to or fearful of hypoglycemia (18). Results from the DEVOTE 7 study, which was designed to evaluate the risk of cardiovascular events and severe hypoglycemia in patients with type 2 diabetes who are ≥65 years of age and treated with insulin degludec or glargine U100, demonstrated a reduced risk of severe hypoglycemia with insulin degludec regardless of age (19).

TABLE 1 Properties of Basal Insulins (18)

Product	Onset of Action, hours	Median Time to Reach Peak Serum Concentration, hours	Recommended Injection Timing	Duration of Action at Steady State, hours
NPH	2	4*	One to three times daily	12
Detemir	1–2	6–8	Once daily in the evening or twice daily in the morning and evening	<24
Glargine U100	1–2	8–12	Same time of day	24
Insulin degludec	1	9	Any time of day†	>42
Glargine U300	≤6	12–16	Same time of day‡	<36

*Mean value reported. †With a minimum of 8 hours and a maximum of 40 hours between consecutive doses. ‡±3 hours.

The International Hypoglycemia Study Group (IHSG) has defined three clinically relevant levels of hypoglycemia to be used in clinical trials. They argue that level 1 (glucose ≤3.9 mmol/L [≤70.2 mg/dL]) does not need to be reported routinely in clinical trials, level 2 (<3.0 mmol/L [≤54 mg/dL]) is sufficiently low to indicate serious and clinically important hypoglycemia, and level 3 (severe hypoglycemia as previously defined by the ADA) reflected severe cognitive impairment that requires external assistance for recovery (20). Hypoglycemia, defined using the IHSG level 2 low glucose definition (21), has been validated in a post hoc analysis of the SWITCH 1, SWITCH 2, and DEVOTE trials, which demonstrated the ability to discriminate between basal insulins. This analysis also demonstrated a similarly low rate of hypoglycemia with different treatments, demonstrating that the level 2 definition highlights hypoglycemia that is more common than severe episodes (level 3) and may still cause serious consequences such as cognitive impairment and cardiac arrythmias. Notably, insulin degludec was shown to have less hypoglycemia than insulin glargine at the hypoglycemia levels specified (21). This classification of hypoglycemia is now being adopted in many clinical studies involving new treatments for diabetes and has been endorsed by many organizations including the European Association for the Study of Diabetes, the ADA, the International Society for Pediatric and Adolescent Diabetes, and the EMA (20,22,23).

Concentrated glargine U300 has a reduced redissolution rate after subcutaneous injection and provides flatter and more prolonged PK/PD profiles than glargine U100 (24). The EDITION trials were designed to assess the safety and efficacy of glargine U300 versus glargine U100 in different patient populations (24–27). In patients with type 1 or type 2 diabetes, A1C decreased similarly between treatment groups (24–27). In patients with type 2 diabetes, glargine U300 was associated with a lower risk of hypoglycemia in insulin-naive patients and a lower risk of nocturnal hypoglycemia in patients using basal insulin and oral antihyperglycemic agents or on a basal-bolus regimen compared with patients treated with glargine U100 (24–26). Results from the BRIGHT study in insulin-naive patients with type 2 diabetes demonstrate similar improvements in glycemic control and hypoglycemia incidence rates between glargine U300 and insulin degludec, suggesting that agent selection should be determined by access and cost in addition to clinical evaluation (28). These benefits may be dependent on the study design and patient selection.

Biosimilar Insulins for Type 2 Diabetes

Before March 2020, similar insulin products (e.g., Basaglar [Eli Lilly]) were approved in the United States by an abbreviated FDA process known as the 505(b)(2) pathway and were termed "follow-on biologics"; now, they are regulated through the 351(k) pathway, which was designed specifically for biosimilars. As of 23 March 2020, the FDA has classified insulin and other biologics, including chorionic gonadotropin, pancrelipase, menotropins, follitropin alfa, and human growth hormone (somatropin), as biological products instead of drugs for regulatory purposes (29).

The first biosimilar insulin, Abasaglar, was approved in the European Union in 2014; in the United States, the first biosimilar insulin (Basaglar, originally approved as a follow-on biologic) was approved in 2016 (13). Approved biosimilar insulins in the European Union and the United States are listed in Table 2 (30–33).

TABLE 2 Approved Biosimilar Insulins (30–33)

Reference Products	Biosimilars (Year Approved)	Action
Insulin glargine	Basaglar*/Abasaglar† (2015/2014) Lusduna† (2017) Semglee (2020)	Long-acting
Insulin lispro	Admelog* (2017)	Short-acting
Insulin aspart	Insulin aspart Sanofi (2020) Sar-Asp† (2020) Kixelle† (2021)	

*Products approved in the United States before 23 March 2020 were termed "follow-on biologics." †Approved in the European Union.

Use of Biosimilar Long-Acting Insulins

Abasaglar/Basaglar was the first biosimilar insulin to be approved in the European Union and in Japan that is similar to Lantus (insulin glargine) (34). In vitro and in vivo experiments revealed no meaningful differences between Abasaglar and insulin glargine. ELEMENT 2 (once-daily Abasaglar [$n = 376$] or insulin glargine [$n = 380$]) was a phase 3, randomized, 24-week study of patients with type 2 diabetes who were insulin-naive and using at least two oral antihyperglycemic medications (35). Both treatment groups exhibited significant decreases in average A1C from baseline, and, importantly, Abasaglar met the prespecified noninferiority criteria for change in A1C from baseline. No treatment differences were observed in the proportion of patients reaching an A1C <7%, insulin dose, or fasting plasma glucose (FPG) levels at 24 weeks (35). Additionally, both groups exhibited similar adverse events, weight change, hypoglycemia, and insulin antibodies.

Semglee (Mylan Pharmaceuticals) is an approved interchangeable biosimilar of insulin glargine that has been FDA-approved for the treatment of type 1 diabetes in adults and children and type 2 diabetes in adults. It is the second biosimilar (or follow-on biologic) insulin glargine product available in the United States; Basaglar (also a follow-on biologic of insulin glargine) was the first available, but it is not approved as an interchangeable biosimilar (36).

The INSTRIDE 2 study included 560 patients with type 2 diabetes and was designed to compare Semglee and insulin glargine (37,38). Results from this study demonstrated a similar decrease in A1C from baseline to 24 weeks between Semglee and insulin glargine (i.e., Semglee met criteria for noninferiority), with a similar safety profile, including overall and nocturnal hypoglycemia incidence and a similar immunogenicity profile. Semglee and Abasaglar are compared with insulin glargine in Table 3 (35,38).

Ezelin is under development by Kalbe Farma in Indonesia as a biosimilar for insulin glargine (39). In a randomized, multicenter, open-label, 24-week study, 133 insulin-naive patients with type 2 diabetes and an A1C >7.0% received Ezelin or insulin glargine. A similar proportion of patients had changes in insulin autoantibodies from baseline (1.7 vs. 1.6%). Similar glucose control was observed via change in A1C, FPG, and 2-hour postprandial plasma glucose with Ezelin (−2.0%, −3.74 mmol/L [–67.32 mg/dL], and −4.25 mmol/L [–76.5 mg/dL], respectively) and insulin glargine (−1.7%, −3.23 mmol/L [–58.14 mg/dL], and −3.89 mmol/L [–70.02 mg/dL], respectively). There were also a similar number of documented hypoglycemia events with Ezelin or insulin glargine (six vs. five events).

In the future, biosimilar insulin development may come to be viewed as a natural progression that will follow the introduction of innovative insulins that are already in the pipeline of many companies. Such development

TABLE 3 Efficacy of Semglee and Abasaglar Compared With Reference Insulin Glargine (35,38)

Study Characteristics/Findings	INSTRIDE 2 Trial	ELEMENT 2 Trial
Population	Type 2 diabetes (n = 560)	Type 2 diabetes (n = 756)
Study length, weeks	24	24
Treatment	Semglee	Abasaglar
Mean change in A1C from baseline to week 24, %	−0.60 with Semglee versus −0.66 with reference insulin glargine	−1.29 with Abasaglar versus −1.34% with reference insulin glargine
Hypoglycemia rate (total), %	22.5 versus 19.9	21.3 versus 22.3
Immunogenicity, %	25.4 versus 27.0	15 versus 11

could bring additional benefits by making these innovations more accessible to millions of people with diabetes worldwide on the basis of lower cost, but with guaranteed efficacy and safety.

Interchangeability (substitution at the pharmacy) might make using biosimilar insulin more straightforward by facilitating the substitution process. Advantages of interchangeability include the ease of changing to a less expensive product; reduced medical provider time to approve substitutions and, in turn, reduced time spent at the pharmacy waiting for approval of substitutions; and more seamless movement to the lower-cost insulin, which leads to lower costs for the health care system. Furthermore, this strategy demonstrates to providers and patients alike that the health care system approves of the safety and efficacy of the biosimilar products. Concerns with interchangeability include the potential inappropriate use by patients or caregivers based on different products' degree of similiarity to the RP. As a result, FDA guidance has required data supporting the performance testing and appropriate use of the delivery device as part of the interchangeable product that is proposed (40). To approve a biosimilar insulin as interchangeable, the FDA has issued the following requirements:

- That the biological product is biosimilar to the RP
- That it has the same clinical result as the RP in any patient
- That, for products administered more than once, safety risks or the risk of diminished efficacy of alternating or switching between using the biosimilar and the RP is no greater than the risks of using the RP without alternating or switching (14)

Semglee (insulin glargine-yfgn) received landmark approval from the FDA as interchangeable with reference insulin glargine in July 2021, making it the first insulin glargine biosimilar to be approved as interchangeable (41).

Financial Considerations

The use of biosimilar insulin may contribute to potential cost savings without compromising safety or efficacy. Compared with insulin glargine, the wholesale acquisition cost of Basaglar is ∼22% cheaper, and Semglee is 64% cheaper in the United States (33). Despite the price reduction of Semglee, it is important to note that payer contracts and different insurance types may result in another product being cheaper for individual patients. In Europe, Semglee offers a 20% National Health Service cost savings compared with insulin glargine (MIMS listing £29.99 vs. £34.75) (42,43). From October 2015 to December 2018, insulin glargine biosimilars contributed to cost savings of £900,000 in England (44). However, because of the low uptake of insulin glargine biosimilars in primary care, only 3.42% of the potential savings was achieved. In Spain, the use of biosimilar insulin glargine contributed to €110.54 million in savings during the period from 2009 to 2019 (45). Results from this Spanish retrospective analysis also demonstrate that the savings from insulin biosimilar use do not appear to contribute to increased utilization, which could be a limitation to the potential cost savings realized with these products. It is possible that biologics, because they are made from living cells, have an increased level of complexity in production that limits the ability to reduce the price. This is in contrast to generics, which are small molecules that can be synthesized in the laboratory.

Switching to Biosimilar Insulin

The INSTRIDE 3 study included patients from the INSTRIDE 1 study who completed 52 weeks of treatment with insulin glargine and were then randomized to receive reference insulin glargine for 36 weeks or to a treatment-switching sequence (Semglee for weeks 0–12, reference insulin glargine for weeks 12–24, and Semglee for weeks 24–36) to assess efficacy, insulin dose, immunogenicity, and safety (46). The primary end point of mean change in A1C from baseline to week 36 was similar for the reference and treatment-switching sequences (−0.05 vs. −0.06%, respectively). Similar changes in FPG, self-monitored blood glucose, and insulin dose were observed between groups. Additionally, the reference and treatment-switching sequences led to similar immunogenicity and safety profiles, including similar rates of hypoglycemia.

Since the development of biosimilar insulins, guidance documents have been published to help facilitate their use in clinical practice. The International Diabetes Federation (IDF) Europe Region published a position statement on biosimilars for the treatment of patients with diabetes, providing recommendations for clinicians, patients, the pharmaceutical industry, national authorities and health-related services, and IDF Europe member associations (47). This document recommends that people with diabetes should be familiar with all relevant aspects of using a biosimilar insulin to facilitate informed discussions with their clinicians if a suggestion to make a change occurs and that patients should be

sure to report any adverse events related to a biosimilar insulin to allow for appropriate monitoring.

In the United Kingdom, several guidelines have been published. A position statement from Diabetes UK includes recommendations for clinicians, patients, and the pharmaceutical industry (48). Regarding people who are considered to be stable on their therapy, Diabetes UK suggests that "individuals well managed on an existing insulin should not be changed to a biosimilar insulin without good clinical reason, evidence of interchangeability, and informed agreement from the person with diabetes." A comparable key message about the use of biosimilar insulin from a position statement developed by the Association of British Diabetologists advises that people who are stable on their current insulin therapy and who are achieving A1C targets with no episodes of hypoglycemia should not be switched automatically to receive a biosimilar insulin (49). This position statement also highlights the importance of ensuring that the decision to switch a patient to a biosimilar insulin should be made by clinical teams who have appropriate levels of experience, expertise, and training. It is also necessary to ensure that each patient receives a clear account of the rationale for changing insulins and is involved in and agrees with the decision. Additional U.K. guidelines have been published online that provide a flowchart that health care professionals can use for guidance regarding the introduction of biosimilar basal insulin (50). The flowchart provides information on switching patients who are currently stable on their insulin regimen and patients who require further treatment optimization. Additional guidance related to biosimilar switch programs is provided, with evidence from the NOR-SWITCH study demonstrating that switching from the infliximab RP to the biosimilar version was safe and effective and, importantly, noninferior to continuing the RP (51).

In Spain, regulatory authorities do not encourage switching to biosimilar insulin; however, biosimilar use is highly encouraged as a first step in patients initiating insulin therapy. The decision to switch to a biosimilar should include the patient, but he or she must understand and accept the process of change, which is quite different from biosimilars used in hospital treatments. Therefore, the health care team should help to reinforce this education. Variable penetrance is important in different markets, as patients do become attached to their insulin and device. For some, it may be cost that drives this issue, as the savings may allow different markets to use newer therapies in combination, which can reduce the side effects of insulin therapy (i.e., hypoglycemia and weight gain) in those whose β-cell delivery is sufficiently impaired to require insulin therapy in combination.

Interchangeability (in the United States) will facilitate the use of biosimilar insulin glargine. The data clearly show biosimilarity and safety, and our clinical experience has been consistent with the studies regarding similar efficacy. Therefore, prescribers will likely change to biosimilars increasingly to lower costs.

Conclusion

Basal insulins have a well-established role in the management of type 2 diabetes, alone or in combination with other injectable or oral glucose-lowering medications. The development of biosimilar insulins has provided additional safe and effective options with the potential for cost savings for patients with diabetes. To realize optimal benefits of biosimilar insulins, clinicians and health services must be knowledgeable about their utility. Their use would increase cost savings, which might permit greater access to insulin for people with diabetes who require it. It is imperative for patients to be educated about biosimilars and to be involved in any decision to switch from reference products to biosimilars.

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