

Basaglar: A Hypersensitivity Reaction

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Introduction

The human insulin molecule is composed of a specific sequence of amino acids built in such a way that any change or modification will affect its primary, secondary, or tertiary structure, which in turn can affect the safety and efficacy of the therapeutic protein. As patents on currently available basal insulins begin to expire, biosimilar products will emerge and quickly replace many of these products owing to their favorable pricing profiles. However, biosimilar products are not 100% identical to their reference products because of their complex manufacturing processes from living cells or organisms (1). For that reason, the regulatory requirements for biosimilars are more complex than for generic molecules. The Biologics Price Competition and Innovation Act of 2009, passed as part of the Patient Protection and Affordable Care Act, allows biosimilar products to be approved by the U.S. Food and Drug Administration (FDA) via an abbreviated pathway (2). Biosimilars must demonstrate no clinically meaningful differences from their reference products in safety, purity, and potency, but they do not have to complete a therapeutic equivalence study. Yet, a major concern with biosimilars is the risk of immunogenicity resulting from variations in manufacturing, and thus clinical studies must be conducted before FDA approval to evaluate potential differences in the incidence and severity of immune responses (3). However, such FDA approval stud-

ies may not be sufficient, and post-marketing monitoring of biosimilars is essential for patient safety.

Hypersensitivity reactions to insulin analogs are rare, with only one published case report of a reaction caused by a biosimilar product in China (4). In 2016, Basaglar was the first “follow-on” insulin glargine approved for use in the United States, with an amino acid sequence identical to that of insulin glargine (Lantus) (5). In Europe, this agent is referred to as a “biosimilar,” but because of varying regulatory approval pathways in the United States, insulin products cannot currently be called “biosimilar,” but rather are referred to as “follow-on” products. This terminology is expected to change, with such insulins transitioning to “biosimilars” by 2020 under the Public Health Services Act. Here, we report the first case of a post-marketing hypersensitivity reaction to the follow-on (biosimilar) insulin glargine Basaglar in Brooklyn, N.Y.

Case Presentation

A frail 77-year-old woman with type 2 diabetes, hypertension, asthma, hypothyroidism, hyperlipidemia, and fibromyalgia was to be transitioned from Lantus to Basaglar therapy because of changes in her insurance plan's preferred insulin brand. She had been diagnosed with diabetes 8 years earlier and had been on insulin therapy for 13 months. Before the patient's transition to Basaglar, her A1C was slightly above goal at 8.3%, and

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her average fasting blood glucose was 146 mg/dL (range 86–222 mg/dL). She was adhering to Lantus 45 units daily, glulisine 6 units twice daily with meals, metformin 500 mg twice daily, and sitagliptin 25 mg daily. She had no known allergies and had not been started on any new medications in the past 3 months.

The patient was advised to begin her Basaglar therapy once she completed using all of her Lantus pens. She reported that she injected herself with Basaglar 45 units on a Thursday morning and within 1 hour developed a diffuse hive-like rash and pruritus, along with shortness of breath and chest tightness, which eventually caused her to fall in her home. The next day, she re-challenged herself with Basaglar but injected a lower dose of 20 units. The same symptoms occurred. She returned to the clinic for an unscheduled appointment early the next week, with signs of diffuse hives still visible on her body. She reported that she had not taken any basal insulin for the past 2 days but had continued to take all of her other medications as prescribed. The patient has always been compliant and has denied missed doses at each clinic visit.

An emergent prior authorization request and phone call were made to the patient's insurance company for approval of Lantus therapy. However, it took 7 days for the insurance company to complete the prior autho-

rization. As a result, the patient had an average fasting blood glucose of 443 mg/dL during that 7-day period. Until now the patient had no documented local or systemic allergic response to insulin glargine.

Questions

1. Do batch-to-batch variations in the manufacturing of biosimilar or "follow on" products lead to clinical differences?
2. Should post-marketing monitoring via pharmacovigilance programs be mandatory within the United States?
3. Can care be compromised when patients are switched from their insulin product to their insurance plan's preferred biosimilar insulin product?

Commentary

To our knowledge, this is the first case report in the United States of a hypersensitivity reaction to a follow-on (biosimilar) insulin in which the allergy was not shared with the original (reference) insulin molecule. This may suggest intrinsic differences in drug formulations and manufacturing processes of biosimilar insulin glargine that could lead to adverse events and clinical limitations. A previous post-marketing case report by Garcia-Nares et al. (4) described a patient who developed a hypersensitivity reaction to a different biosimilar of insulin glargine approved in China. That patient developed bron-

chial spasms, and immunology tests revealed abnormal basophil degranulation within the biosimilar molecule that was not found in the reference glargine molecule.

Before receiving FDA approval, Basaglar was evaluated in two clinical trials (the ELEMENT 1 trial in type 1 diabetes [6] and the ELEMENT 2 trial in type 2 diabetes [7]) analyzing antibody production and clinical outcomes compared to the reference product (Lantus). A total of 1,291 patients enrolled in these studies received at least one dose of the randomly assigned drug, with 644 patients receiving Basaglar and 647 patients receiving Lantus. In ELEMENT 1, there was no significant difference in insulin antibodies between the two groups, with antibodies detected in 80 patients (30.2%) in the Lantus group and 90 patients (33.7%) in the Basaglar group at week 24, week 52, and the last observation carried forward (LOCF) (6). Likewise, in ELEMENT 2, detectable antibodies were similar among insulin-naïve patients at the same time points. However, in further subgrouping of patients in ELEMENT 2 who had been on Lantus therapy before the study, 29 patients (19.2%) of those randomized to Basaglar had detectable antibodies compared to 11 patients (7.95%) of those in the group receiving Lantus. This difference was statistically significant ($P = 0.006$)

TABLE 1. Proportion of Patients With Detected Antibodies in the ELEMENT 2 Trial

Population	Visit	Basaglar Patients With Detected Antibodies (n [%])	Lantus Patients With Detected Antibodies (n [%])
Full analysis set	Baseline	20 (5.5)	13 (3.6)
	Week 24 overall	56 (15.3)	40 (11.0)
	Week 24 LOCF	30 (8.2)	22 (6.0)
Previous Lantus patients	Baseline	10 (6.6)	6 (4.4)
	Week 24 overall	29 (19.2)	11 (7.9)
	Week 24 LOCF	13 (8.6)	5 (3.6)
Previously insulin-naïve patients	Baseline	10 (4.7)	7 (3.1)
	Week 24 overall	27 (12.6)	29 (12.8)
	Week 24 LOCF	17 (7.9)	17 (7.5)

at week 24, but not with the LOCF (Table 1). However, there were no significant correlations seen between the endpoints of antibody levels and clinical outcomes such as A1C, insulin doses, or hypoglycemia rates (7). The effect of Basaglar immunogenicity remains unknown (8).

Rigorous post-marketing surveillance is crucial to ensuring the safety of these medications, particularly when large insurance companies favor these products, increasing their use within the general population. The FDA has published guidance for pharmacovigilance to ensure safety for biosimilars, but questions exist about the validity of this process and its translation into clinical practice (9).

Before drug approval, most clinical trials enroll a small patient population over a short duration of time. Therefore, postmarketing surveillance is crucial to help identify situations involving high-risk groups, long-term effects, drug-drug interactions, and, as illustrated by this case report, low-frequency reactions. According to a survey conducted by the Biosimilars Forum and SERMO (a global social network organization for physicians) (10), an estimated 76.8% of physicians were aware of the term “biosimilars,” but there was a large knowledge gap of details of biosimilars, such as the FDA approval pathways for biosimilars and safety parameters of these agents. However, education to health care professionals on pharmacovigilance has been shown to decrease this knowledge gap and increase the reporting of adverse drug reactions to ensure the safety of newly approved biosimilar products (11).

Some limitations of this case report deserve acknowledgment. The observational nature is subject to limitation in that we were unable to perform laboratory tests such as measurement of anti-insulin antibodies. Additionally, the first reaction and re-challenge of the patient did not occur in an inpatient setting where her repeated hypersensitivity reaction could be observed.

Clinical Pearls

- Pharmacovigilance programs and health care provider awareness are necessary to determine whether the safety profile of biosimilar products is comparable to that of their reference biologic product.
- Major differences in manufacturing processes can lead to suboptimal clinical outcomes and should be monitored by government regulatory agencies.
- It is unknown at this time whether follow-on (biosimilar) insulins will contribute to better patient care and reduced costs.

Duality of Interest

No potential conflicts of interest relevant to this article were reported.

Author Contributions

E.M.G. researched data and wrote the manuscript. R.F. and G.S. reviewed and edited the manuscript. E.M.G. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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