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ORIGINAL PAPER

Clinical experience with exenatide in predominantly Asian and Pacific Islander patients with type 2 diabetes

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Abstract Exenatide is a new injectable medication for the treatment of hyperglycemia in type 2 diabetes. Due to limited information of exenatide use in Asians and Pacific Islanders (API), we retrospectively reviewed API patients' responses to exenatide treatment and compared the efficacy and safety of treatment to Caucasian patients. A total of 92 patients (70 API, 21 Caucasians, and 1 Hispanic) with type 2 diabetes were treated with exenatide. In all patients, there was a significant decrease in A1c level, BMI, and weight after 6 months of exenatide treatment (A1c from 8.63 ± 1.46 to 8.23 ± 1.46; $P = 0.03$, BMI from 34.54 ± 7.07 to 32.14 ± 6.41; $P < 0.01$, and weight from 215.24 ± 52.04 to 202.50 ± 49.90; $P < 0.01$ at 95% CI, $N = 51$). However, differences in mean change of A1c level, BMI, and weight between API and Caucasian patients were not observed at 3 and 6 months of treatment. Side effects and discontinuation of exenatide treatment between API and Caucasian patients were similar. In conclusion, exenatide is an effective anti-hyperglycemic agent in API patients with responses similar to that observed for Caucasian patients.

Keywords Exenatide · Asian and Pacific Islander patients · Clinical Experience

Introduction

Exenatide is a new anti-diabetic agent for the treatment of hyperglycemia in patients with type 2 diabetes. It is considered an "incretin mimetic" because it is a functional analog of Glucagon-like Peptide-1 (GLP-1) [1]. Exenatide is a 39 amino acid peptide that binds to the GLP-1 receptor and enhances insulin secretion, suppresses glucagon secretion, and slows gastric emptying [2–4]. Exenatide also stimulates CNS GLP-1 receptors and induces satiety, which may result in decreased weight [5].

Although large controlled clinical trials have clearly shown the efficacy of exenatide, the majority of patients were Caucasians, African-Americans, and Hispanics [6–8]. There is limited information of exenatide treatment in Asian and Pacific Islander (API) patients with type 2 diabetes. In this study, we retrospectively reviewed charts of patients who received exenatide treatment and characterized the clinical response between Asian and Pacific Islanders and compared their response to Caucasians. The effect on glycemic control, BMI, and weight as well as side effects of the medication was examined.

Research design and methods

This study is a retrospective medical records review of patients who initiated exenatide treatment between June 2005 and January 2007. Exenatide was prescribed by a single practitioner in a University-based Diabetes Clinic who followed strict FDA indication of combination therapy with sulfonylurea and/or metformin. Other non-sulfonylurea and non-metformin therapies, such as insulin or thiazolidinediones, were discontinued after starting exenatide. Although exenatide with TZD therapy was allowed after January 2007, inclusion of these patients would have changed the characteristics of the initial cohort and the medication adjustment after starting exenatide. This incretin mimetic is yet to be indicated with insulin therapy.

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Exenatide was initiated with 5 micrograms twice a day for a month, followed by 10 micrograms twice a day. A1c level, BMI, and weight were obtained within a month prior to exenatide initiation and discontinuation of other oral anti-diabetic (OAD) medications and insulin, and at 3 months, 6 months, and longer after exenatide treatment. Clinical charts were reviewed and data was analyzed for significance using paired *t*-test with SPSS version14.0 to compare before and after treatment differences and between API and Caucasian patients. Significance of means was calculated using Effect-size calculator software. Differences in side effects and discontinuation rate between groups were calculated by Fisher's exact test. The overall response to treatment by all patients was also analyzed based on previous treatment with OAD medications and insulin before starting exenatide.

Results

Baseline characteristic of patients

The 92 patients included 46 men and 46 women, with ages ranging from 27 to 80 years and a mean age of 56.5 years (mean age of APIs was 56.39 ± 11.17 years, mean age of Caucasians was 56.94 ± 10.26). The self-reported ethnicities of patients were 58 Asians (36 Japanese, 17 Filipino, 3 Chinese, and 2 Mixed-Asian; total of 60.87%), 12 Hawaiians and Pacific Islanders (13.04%), 21 Caucasians or Mixed-Caucasians (21.74%) and 1 Hispanic (1.09%).

The previous anti-diabetic treatment regimen of patients is listed in Table 1. There were 56 of 92 patients treated with oral anti-diabetic medications (60.87%), and 36 of 92 patients (39.13%) treated with insulin, with or without oral anti-diabetic medications. The previous treatment characteristics of 91 API and Caucasian patients are also presented in Table 1. The majority of patients previously treated with insulin (34 out of 36 patients) were taking insulin glargine with an average daily dose of 49.92 ± 26.07 units/day (45.90 ± 28.11 in APIs, 51.50 ± 24.26 in Caucasians).

Effect of exenatide on glycemic control and weight in all patients treated

A total of 78 patients received exenatide treatment for at least 3 months with 51 patients receiving treatment for more than 6 months. There was no significant improvement in A1c level for patients completing treatment for 3 months (Fig. 1a), however, the A1c level significantly decreased in patients treated for 6 months (Fig. 1d). Exenatide treatment for 3 months resulted in a non-significant decrease in A1C level from 8.27 ± 1.28 to 7.98 ± 1.32 ($P = 0.09$ at 95% CI, $N = 46$) in patients previously treated with OAD medications, which was not statistically significant. Three month treatment with exenatide in patients previously treated with insulin showed an increase in A1C levels 9.14 ± 1.41 to 9.32 ± 1.99 ($P = 0.28$ at 95% CI, $N = 32$), which was also not significant (Fig. 1b, c). After 6 months of exenatide treatment, there was a non-significant decrease in A1c level in patients who were previously treated with oral anti-diabetic agents (8.35 ± 1.41 to 7.88 ± 1.33; $P = 0.06$ at 95% CI, $N = 30$), and previously treated with insulin (9.02 ± 1.47 to 8.73 ± 1.53; $P = 0.16$ at 95% CI, $N = 21$) (Fig. 1e, f).

Table 1 Previous diabetes treatment regimen among Asian and Pacific Islander (API) and Caucasian patients

Oral anti-diabetic (OAD) agents	All patients $N = 92$ (%) $N = 56$ (61)	APIs $N = 70$ (%) $N = 40$ (57)	Caucasian $N = 21$ (%) $N = 15$ (70)
None	1 (1)	1 (1)	0
Sulfonylurea	4 (4)	3 (4)	1 (4)
Metformin	4 (4)	2 (3)	2 (10)
Thiazolidinedione (TZD)	1 (1)	1 (1)	0
Sulfonylurea + Metformin	18 (20)	11 (16)	7 (33)
Sulfonylurea + TZD	2 (2)	1 (1)	1 (4)
Metformin + TZD	8 (8)	5 (7)	2 (10)
Sulfonylurea + Metformin + TZD	18 (20)	16 (23)	2 (10)
Insulin Treatment	$N = 36$ (39)	$N = 30$ (43)	$N = 6$ (30)
Insulin only	1 (1)	1 (1)	0
Insulin + 1 OAD Agent	9 (10)	7 (10)	2 (10)
Insulin + 2 OAD Agents	17 (18)	15 (21)	2 (10)
Insulin + 3 OAD Agents	9 (10)	7 (10)	2 (10)

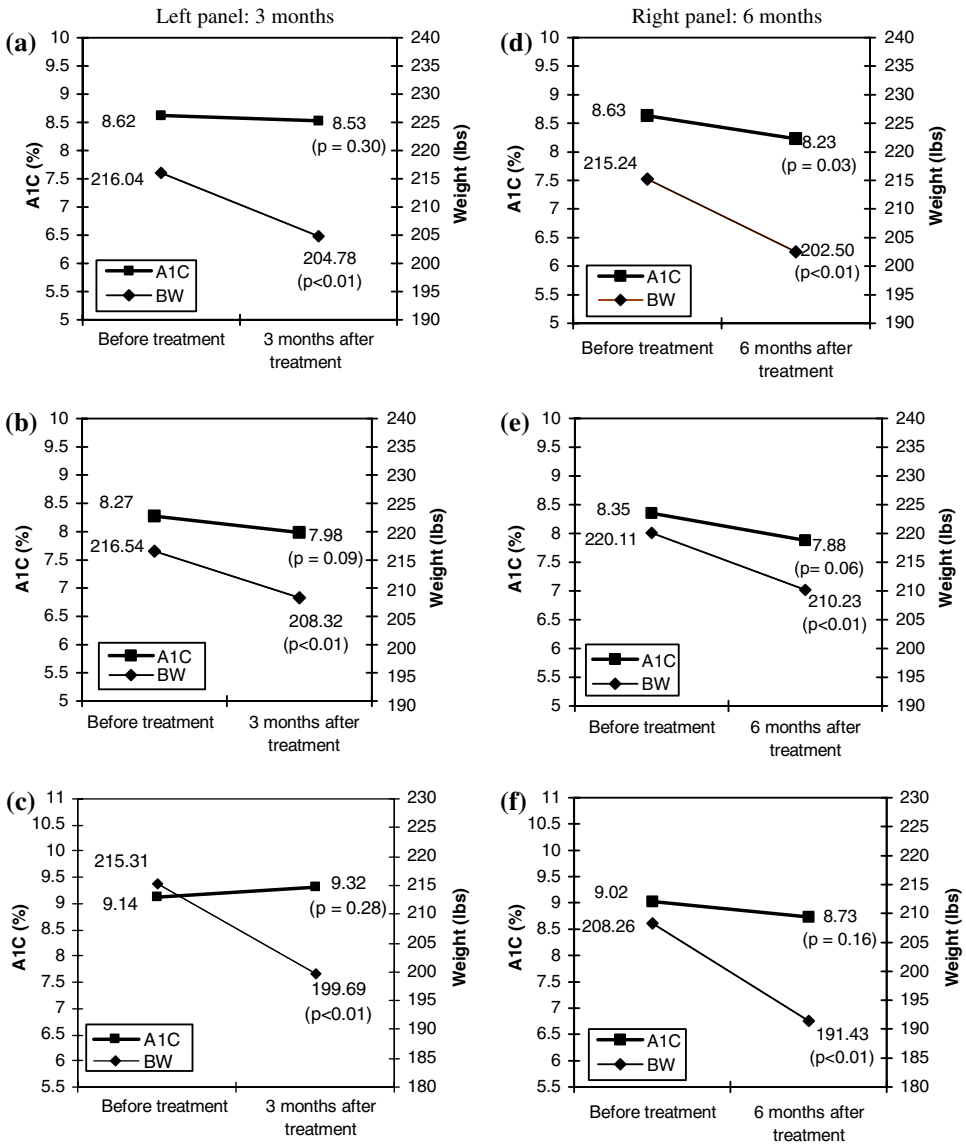

Fig. 1 Changes in A1c level and weight with exenatide treatment. *Left panel*: The effect of exenatide treatment on A1c level and weight after at least 3 months of treatment; (**a**) all patients ($N = 78$); (**b**) patients previously treated with oral diabetes medications ($N = 46$); (**c**) patients previously treated with insulin ($N = 32$). *Right panel*: The effect of exenatide treatment on A1c level and weight after at least 6 months of treatment; (**d**) all patients ($N = 51$); (**e**) patients previously treated with oral diabetes medications ($N = 30$) (**f**) patients previously treated with insulin ($N = 21$)

Weight significantly decreased in all groups treated with exenatide as noted in Fig. 1. Irrespective of previous therapy, exenatide treatment resulted in statistically significant weight loss at 3 or 6 months of treatment. The decrease in weight occurred largely within the first 3 months of treatment with smaller weight reduction, thereafter.

Comparison of response to exenatide treatment between API and Caucasian patients

Comparison of differences in exenatide treatment between API and Caucasian patients is shown in Table 2. BMI and weight significantly decreased in both groups after 3 and 6 months of exenatide treatment. However, the observed decrease in A1c level was not statistically significant except among Caucasian patients at 3 months of treatment. The API patients had a smaller decrease in A1c level at 3 and 6 months of treatment as compared to Caucasian patients, however the difference in mean A1c change between these two groups was not statistically significant. In addition the BMI and weight changes from baseline of BMI and weight between API and Caucasian patients were similar (Table 3).

Discontinuation and side effects with exenatide treatment

Among the 92 patients, 28 discontinued exenatide treatment (30.43% of the treatment individuals) with 8 patients (28.57%) discontinuing because of significant nausea with or without vomiting. Other reasons for discontinuation were marked pruritis and rash around the injection sites

Table 2 A1C level, BMI and weight before and after at least 3 and 6 months of exenatide treatment in API and Caucasian patients with type 2 diabetes

	3 months of exenatide treatment					
	APIs ($N = 34$)			Caucasian ($N = 12$)		
	Before (mean ± SD)	After (mean ± SD)	Mean	Before (mean ± SD)	After (mean ± SD)	Mean
A1c (%)	8.34 ± 1.36	8.19 ± 1.43	−0.15	8.07 ± 1.01	7.40 ± 0.72	−0.67*
BMI (k/m2)	33.89 ± 7.40	32.39 ± 6.60	−1.50†	37.07 ± 6.27	35.63 ± 6.69	−1.44†
Weight (lbs)	212.49 ± 57.46	204.29 ± 53.40	−8.20†	228.04 ± 46.20	219.75 ± 44.45	−8.29*
	6 months of exenatide treatment					
	APIs ($N = 21$)			Caucasian ($N = 9$)		
A1c (%)	8.58 ± 1.53	8.18 ± 1.42	−0.40	7.80 ± 0.94	7.18 ± 0.73	−0.62
BMI (k/m2)	33.20 ± 8.15	31.28 ± 6.87	−1.91†	36.64 ± 7.17	34.87 ± 7.59	−1.77†
Weight (lbs)	219.98 ± 67.12	210.17 ± 62.47	−9 .81†	220.44 ± 44.54	210.39 ± 44.53	−10.05*

* $P < 0.05$; † $P < 0.01$

Table 3 Between-treatment difference in API and Caucasian patients at 3 and 6 months

	APIs	Caucasian	
	Mean change from baseline at 3 months		Between-treatment differences
HbA1C %	−0.15	−0.67	0.52 (95% CI −1.62–0.91; $P = 0.94$)
BMI	−1.50	−1.44	0.06 (95% CI −0.62–0.70; $P = 0.90$)
Weight (lbs)	−8.20	−8.29	7.09 (95% CI −0.65–0.67; $P = 0.98$)
	Mean change from baseline at 6 months		
HbA1C %	−0.40	−0.62	0.22 (95% CI −1.08–1.52; $P = 0.73$)
BMI	−1.91	−1.77	0.14 (95% CI −1.31–1.60; $P = 0.84$)
Weight (lbs)	−9.81	−10.05	0.07 (95% CI −5.06–5.56; $P = 0.93$)

(4 patients, 14.29%), poor glycemic control (5 patients, 17.86%), insurance issues (4 patients, 14.29%), and fear of needles (3 patients, 10.71%). Five of 28 patients (17.86%) were lost follow up. The discontinuation rate in API patients was 30.00% (21 out of 70 patients) and the discontinuation rate in Caucasian patients was 23.81% (5 out of 21 patients). The difference in the discontinuation rate between API and Caucasian patients was not significant ($P = 0.38$) and the reasons for discontinuation were similar between the groups.

The most common side effect was nausea with or without vomiting found in 34 of 92 patients (36.96%). Patients usually experienced nausea during the first few weeks of the treatment. Twenty-three of 70 API patients (32.86%) had nausea as a side effect as compared to 11 out of 21 Caucasian patients (52.38%). The difference in the rate of nausea between Caucasian and API patients was not statistically significant ($P = 0.11$). The second most common side effect was decreased appetite found in 24 patients (26.09%). Other side effects were rash and pruritis (4 patients, 4.35%), and diarrhea (1 patient, 1.09%).

Discussion

This study was undertaken to assess the response of API patients with diabetes to exenatide treatment in a clinical practice. Overall, significant A1c reduction was observed after completing 6 months of treatment with minimal changes at 3 months. The limitation of exenatide use in this clinical experience clearly explains this delay in blood sugar improvement. Availability of new products entices patients to request it, especially when weight loss is promoted. Due to this consideration, 39.13% of the cohort included previous insulin-treated patients and discontinuation of insulin was required for strict observation of FDA indication and for the insurer to cover exenatide. Thus, diabetic patients who were further along with their disease by virtue of insulin use were included, unlike patients in randomized and controlled clinical trials.

Data after 3 and 6 months of treatment in patients previously treated with OAD medications demonstrated a trend to lower A1c level without statistical significance.

This finding is similar to that observed in another clinical experience report [9] which showed non-significant A1c reduction after 12 months of exenatide treatment. Significant A1c reduction after 12 weeks of exenatide treatment in clinical observation have also been reported [10]. In patients previously treated with insulin, A1c level trend upward after 3 months of exenatide treatment and insulin discontinuation. Most of these patients were previously on combination of OAD medications and insulin, and their average dose of insulin was nearly 50 units/day of primarily glargine. It would be expected that stopping insulin treatment and adding exenatide to continuing OADs would result in worsening hyperglycemia. Based on the two insulin comparison clinical trial results [11–13], it may be fair to suggest that 10 mcg of exenatide twice a day is equivalent to 25 units/day of insulin for anti-hyperglycemic effect, and stopping the higher insulin doses used by our patients may explain the worsening glycemia when switched to exenatide. Still, continued treatment to 6 months resulted in improvement in glycemia after the initial increase which could be attributed to exenatide effect and resultant reduction in consumption and weight loss.

BMI and weight significantly decreased in all patients at 3 and 6 months of exenatide therapy irrespective of previous treatment regimen. The average weight loss in our study was 12.74 lbs after at least 6 months of therapy, a more robust weight reduction as compared to results from controlled clinical trials [14, 15]. The greater weight loss in the previous insulin-treated patients is not explained by worsening of glycemic control as the A1c level increased minimally at 3 months and slightly improved at 6 months of exenatide treatment. Still, the discontinuation of TZD and insulin, independent of hyperglycemia probably contributed to this robust reduction as weight loss tapered off after 3 months of treatment.

Among API patients with diabetes, the response to exenatide was similar to that of Caucasian patients at 3 and 6 months of treatment. Due to the small number of patients, differences between previous treatment with OAD medication and insulin groups could not be analyzed between API and Caucasian patients. However, it is noteworthy that there were more 3 OAD medication use among API patients, which resulted in more discontinuation of TZD treatment. This difference in previous treatment before exenatide initiation could mask a clinical response that is different from Caucasian patients. The most common side effect of exenatide treatment was nausea, reported in 34 of 92 patients, however discontinuation occurred in only 8 patients. The overall side effect profile and discontinuation rate were similar among API and Caucasian patients.

In conclusion, exenatide is an effective agent that lowers blood sugar levels and causes weight loss in API patients with diabetes. Efficacy and safety of exenatide in API patients are similar to Caucasian patients. Patients on high dose of insulin (50 units/day) with concomitant OAD medication treatment can expect a transient increase in BS levels when switching to exenatide, but improved glycemia with significant weight loss as therapy is continued. Still, longer observation of exenatide treatment with more API patients could identify unique and interesting responses among this minority population.

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