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Original Research

Combination therapy with once-weekly glucagon like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes: a case series

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Abstract

Background: National treatment guidelines recommend glucagon-like peptide receptor agonists (GLP-1 RAs) as add-on therapy to oral agents. However, GLP-1 RAs in combination with dipeptidyl peptidase-4 (DPP-4) inhibitors is not recommended due to a lack of evidence.

Objective: This case series aims to describe the efficacy and safety of once-weekly GLP-1 RAs administered concomitantly with DPP-4 inhibitors in patients with type 2 diabetes.

Methods: A retrospective chart review of electronic medical records at a free health clinic was conducted between July 2014 and September 2016. Patients 18 years and older with type 2 diabetes were included if they received concomitant DPP-4 inhibitor and once-weekly GLP-1 RA therapy with at least one glycated hemoglobin A1c (HbA1c) measurement within three to six months of starting the combination. The primary and secondary outcomes included change in HbA1c and weight, and patient reported adverse events.

Results: Out of forty-three patients that received combination DPP-4 inhibitor plus GLP-1 RA therapy, only eighteen received once-weekly GLP-1 RA. At 3 months, the median (IQR) HbA1c and weight change was -0.8% (-4.3 to 2%) and -0.4kg (-4.2 to 5.8 kg) respectively. No patients reached an HbA1c below 7% and only three patients (17%) reached a HbA1c less than 8%. Patient reported adverse effects included gastrointestinal disturbances (28%), hypoglycemic symptoms (17%), and injection site reactions (0.6%).

Conclusions: Concomitant use of once-weekly GLP-1 RAs and DPP-4 inhibitors provides only modest improvement in glycemic control with minimal weight loss benefits, which is similar to monotherapy with either agent. The combination is unlikely to provide synergistic effects and is not cost effective. These data support the current recommendations against use of combined incretin therapy.

Keywords

Diabetes Mellitus, Type 2; Drug Combinations; Glucagon-Like Peptide 1; Dipeptidyl-Peptidase IV Inhibitors; Hypoglycemic Agents; Blood Glucose; Body Weight; Retrospective Studies; United States

INTRODUCTION

Newer therapeutic options, the dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1 RAs), minimize hypoglycemia without inducing weight gain.[1-3] These agents target an incretin defect or reduced levels of GLP-1 commonly found in patients with type 2 diabetes.[4] DPP-4 inhibitors decrease serum DPP-4 enzyme activity responsible for degradation of GLP-1 by more than 80% and thereby restore GLP-1 to physiologic levels.[5,6] The GLP-1 RAs produce supraphysiologic concentrations of GLP-1 resulting in potent reductions in weight and hemoglobin A1c (HbA1c). Lower GLP-1 concentrations generated by DPP-4 inhibitors exchange better tolerability for decreased efficacy.[5-8] The GLP-1 raising effects of DPP-4 inhibitors and GLP-1 RAs lead to glucose dependent insulin release and post prandial glucagon inhibition. Additionally, GLP-1 RAs also increase satiety and decrease gastric emptying in a dose related manner.[5,7-8] This likely explains the gastrointestinal disturbances (nausea, vomiting, and abdominal pain) and weight loss benefits associated with GLP-1 RAs.[8] Based on their mechanisms, concomitant GLP-1 RA and DPP-4 inhibitor therapy (combination therapy) has potential for a synergistic effect by increasing GLP-1 levels above what is observed by monotherapy with either class. An equally valid and concerning theory for elevated GLP-1 levels with combination therapy is the potential for increased adverse effects.

One randomized controlled trial that evaluated combination therapy found the addition of exenatide to sitagliptin provided a slightly larger HbA1c reduction compared to switching from sitagliptin to exenatide (-0.68% vs. -0.38%) with no clinically significant differences in weight loss.[9] However, once-weekly GLP-1 RAs in combination with DPP-4 inhibitors have not been prospectively evaluated in a randomized controlled trial. Once-weekly agents produce less fluctuations in GLP-1 and may provide better tolerance and efficacy when combined

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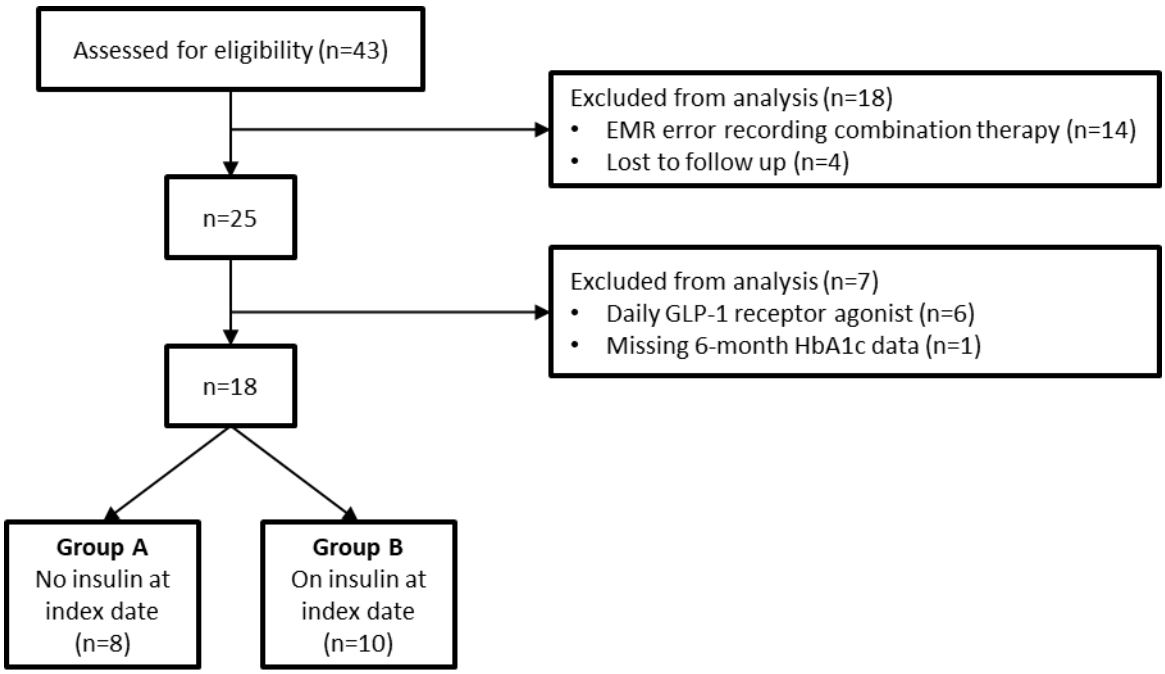

Figure 1. Patient flow

with DPP-4 inhibitors compared to daily GLP-1 RAs. Case reports with combination therapy present appreciably different outcomes ranging from improved glycemic control to acute pancreatitis.[10,11] Recently, the investigation of liraglutide plus sitagliptin demonstrated intensified GLP-1 levels without any increase in C-peptide and insulin.[13] The modest data available suggests little benefit of combination therapy.[9-12]

The American Diabetes Association (ADA) and American Association of Clinical Endocrinologists recommend GLP-1 RAs as add-on therapy to oral agents and in combination with insulin. Both guidelines recommended against combination therapy (DPP4-inhibitor and GLP-1 RA) due to the paucity of evidence with this strategy.[1,2] However, sometimes clinicians can find themselves in unique situations that fall outside of guideline recommendations. Providers at free clinics are usually very limited in their drug choices having to consider cost before any other benefits. Furthermore, brand-only products new to the market, including fixed-dose combinations of metformin plus DPP-4 inhibitors and GLP-1 RAs, are commonly prescribed in free clinics through patient assistance programs at no cost. Given the lack of data on once-weekly GLP-1 RA in combination with DPP-4 inhibitors and the cost limitation, providers at a free clinic were prescribing the combination hoping for additional HbA1c lowering and weight loss effects. Our case series aims to describe the safety of once-weekly GLP-1 RAs administered concomitantly with DPP-4 inhibitors and confirm that the combination does not provide synergistic effects.

METHODS

To investigate the effect of concomitant prescriptions of DPP-4 inhibitors with GLP-1 RA products, we conducted a retrospective chart review of electronic medical records (EMR) at Crossover Healthcare Ministry, a free health clinic in Richmond, Virginia. Collected data from the EMR included patients seen in clinic between July 2014 and September 2016. An index date was identified for each case based on the first date the patient started combination therapy. Patients 18 years and older with type 2 diabetes were included if they received concomitant DPP-4 inhibitor and once-weekly GLP-1 RA with at least one HbA1c measurement within six months from index date. The local institutional review board approved the study protocol.

Cases were divided into two groups: 1) Group A patients received metformin, DPP-4 inhibitor + sulfonylurea prior to the index date, and 2) Group B patients were prescribed insulin therapy + other oral agents prior to the index date. Independent evaluation of cases was performed in an unblinded fashion by the first and second authors. The primary outcomes were change in HbA1c and weight from baseline to the next available HbA1c and weight within 3-6 months. Secondary outcomes included patient reported adverse events documented in the EMR, number of patients requiring insulin initiation in Group A, and change in insulin dose for Group B. Wilcoxon Signed Ranks Test was used to measure the change in A1c and weight from baseline to 3 months and 6 months.

RESULTS

Forty-three patients were identified as receiving combination therapy. Of those, 18 met inclusion criteria for the case series (Figure-1). Eight patients on oral treatment for type 2 diabetes were assigned to Group A and ten patients on insulin therapy were assigned to Group B.

Group A: Oral Therapy

Group A cases were generally young and obese with a median baseline HbA1c of 10.2% (Table 1). Treatment for cases pre-index date was predominantly triple therapy

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Table 1. Patient demographics

Baseline Characteristics	Group A (n=8)	Group B (n=10)	Combined (n=18)
Age (years); Median (IQR)	43.5 (41-54.3)	52.5 (47.0-56.5)	51.0 (41.5-56.5)
Hemoglobin A1C (%);Median (IQR)	10.2 (8.9-10.9)	10.8 (10.4-12.1)	10.6 (9.8-11.6)
Weight (kg); Median (IQR)	84.6 (80.0-106.2)	89.3 (80.4-94.8)	86.3 (79.3-95.5)
BMI (kg/m2); Median (IQR)	34.6 (31.1- 41.9)	33.6 (31.1-36.5)	34.1 (31.0-36.9)
Gender; n (%)			
Female	6 (75)	9 (90)	15 (83)
Male			
Race; n (%)			
White	1 (12)	1 (10)	2 (11)
African American			
Hispanic/Latin	7 (88)	3 (30)	10 (55)
Middle Eastern	0	3 (30)	3 (17)
Medications; n (%)			
DPP-4 inhibitors			
Sitagliptin	7 (88)	10 (100)	17 (94)
Saxagliptin	1 (12)	0	1 (6)
GLP-1 RAs			
Albiglutide	6 (75)	6 (60)	12 (67)
Exenatide ER	2 (25)	4 (40)	6 (33)
Metformin	8 (100)	9 (90)	17 (94)
Sulfonylurea	7 (88)	0	7 (39)
Insulin			
Basal	N/A	4 (40)	4 (22)
Basal + Bolus	N/A	4 (40)	4 (22)
Biphasic	N/A	2 (20)	2 (11)

(87.5%). At the index date, a once-weekly GLP-1 RA was added to all cases increasing their regimen to triple or quadruple non-insulin therapy.

Patients in Group A experienced a moderate HbA1c and weight reduction at 3 months after starting combination therapy. The median (interquartile range [IQR]) HbA1c and weight changes were -0.9% (-2.3 – -0.3%) and -0.8 kg (-1.7 – 0.6 kg) respectively (Table 2). All patients' HbA1c improved; however, no patients reached an HbA1c less than 7%. Additionally, insulin therapy was initiated for 2 patients (25%). Insulin detemir was initiated and titrated in patient 1 to a total daily dose (TDD) of 28 units, which notably contributed to the patient's HbA1c decrease of 2.1%. Patient 5 only experienced a 0.3% HbA1c reduction after albiglutide was switched to insulin isophane and titrated to a total daily dose of 30 units.

Group B: Insulin Therapy

Group B cases were generally middle-aged, obese, and female (90%) (Table 1) with a baseline median (IQR) HbA1c of 10.8% (10.4-12.1%). A once-weekly GLP-1 RA was added to insulin and sitagliptin + other oral agents at index date for 80% of patients. The remaining two patients (1 and 10) were started on sitagliptin and a GLP-1 RA simultaneously.

The median (IQR) HbA1c and weight change in 3 months was -0.8% (-2.5 – (-0.3)%) and +0.2 kg (-1.0 – 1.1 kg) respectively (Table 2). Most patients' HbA1c improved between 0.1% to 3%, except patient 7 who experienced a 2% increase. Metformin therapy changes at index date impacted results for patients 1 and 3. Patient 1 stopped metformin and experienced only a 0.1% reduction in HbA1c, while patient 3 started metformin and observed a considerable reduction of 1.3%. No patient reached an HbA1c less than 7%. Regarding weight, five patients gained between 0.5 to 5.8 kg, three lost between 0.7 to 3.8 kg, and one experienced no change.

At index date, 80% of patients were treated with basal insulin, half of which were also prescribed bolus insulin, and the remaining two used biphasic insulin (Table 3). Dose increases for insulin occurred for 80% of cases despite combination therapy and insulin treatment. Likewise, the median HbA1c reduction of 0.8% was the same for patients treated with basal or basal-bolus strategies. However, the biphasic insulin subgroup experienced a larger reduction (1.4%) compared to the other insulin subgroups. The median weight change was also comparable among the insulin regimens ranging between -0.4 – 0.8 kg.

Combined Data

The combined demographics of the groups reflect a relatively young, diverse, obese, and poorly controlled population (Table 1). Combination therapy most frequently included sitagliptin (94%) and albiglutide (67%). The remaining cases received saxagliptin (0.06%) and exenatide extended release (ER) (33%).

Combined analysis of groups A and B showed a median (IQR) HbA1c change of -0.8% (-2.5 – (-0.3)%) at 3 months. No patients reached a HbA1c below 7% and only 3 cases (17%) reached a HbA1c less than 8%. Furthermore, insulin initiation or addition occurred in 56% of patients. Median (IQR) weight change at 3 months was only -0.4 kg (-1.4 – 1.2 kg), but was highly impacted by Group A patients, all of whom experienced weight loss. Unlike Group A, only three patients in Group B lost weight over 3 months.

Adverse effects were mild and included gastrointestinal disturbances (28%), hypoglycemic symptoms (17%), and injection site reactions (0.6%). The single reported injection site reaction occurred with exenatide ER. No patients elected to discontinue GLP-1 RA or DPP-4 inhibitor therapy due to intolerable adverse effects.

Table 2. Results

	Agents at index date				Baseline		3 months			6 months		
	Biguanide	**GLP-1 RA**	**DPP-4i**	**SU**	**HbA1c (%)**	**Weight (kg)**	**HbA1c (%)**	**Change (%)**	**Weight (kg)**	**Change (kg)**	**HbA1c (%)**	**Weight (kg)**
	Group A											
1*	Metformin 2000mg	Albiglutide 30mg	Sitagliptin 100mg	N/A	12.4	86.9	10.3	- 2.1	88.7	+1.8	--	--
2	Metformin 2000mg	Albiglutide 30mg	Sitagliptin 100mg	Glimepiride 2mg	10.7	77.8	7.8	-2.9	76.4	-1.5	--	--
3	Metformin 2000mg	Exenatide ER 2mg	Sitagliptin 100mg	Glipizide 5mg	11.6	82.3	7.3	-4.3	86.4	+4.2	9.1	90.0
4	Metformin 2000mg	Exenatide ER 2mg	Sitagliptin 100mg	Glimepiride 4mg	9	75.6	7.7	-1.3	75.7	-0.2	7.7	72.7
5*	Metformin 2000mg	Albiglutide 30mg	Sitagliptin 100mg	Glimepiride 4mg	9.8	117.2	9.5	-0.3	113.0	-4.2	--	--
6	Metformin 2000mg	Albiglutide 30mg	Sitagliptin 100mg	Glipizide 20mg	8.6	114.0	8.3	-0.3	113.1	-0.9	8.3	112.3
	Group B											
1*	Stopped at index date	Detemir 62U Aspart 36U	Sitagliptin 100mg	Exenatide ER 2mg	12.3	85.1	12.2	-0.1	86.0	+0.9	--	--
2	Metformin 2000mg	Glargine 120U	Sitagliptin 100mg	Albiglutide 30mg	9	76.9	7.7	-1.3	79.2	+2.3	8	80.1
3	Started Metformin 2000mg at index date	Detemir 32U	Sitagliptin 100mg	Exenatide ER 2mg	11	93.0	8	-3	89.2	-3.8	8.4	91.0
4	Metformin 2000mg	Detemir 35U	Sitagliptin 100mg	Exenatide ER 2mg	10.5	95.0	--	--	100.8	+5.8	10	--
5	Metformin 2000mg	Isophane/ Regular 70/30 240U	Sitagliptin 100mg	Albiglutide 30mg	13.9	78.6	11.4	-2.5	79.7	+1.2	9.1	81.4
6	Metformin 2000mg	Lispro protamine/ Lispro 75/25 80U	Sitagliptin 100mg	Albiglutide 30mg	10.6	60.6	10.3	-0.3	61.1	+0.5	9.4	62.4
7	Metformin 2000mg	Detemir 44U	Sitagliptin 100mg	Albiglutide 30mg	13	85.2	>15	+2	84.2	-1.1	--	--
8	Metformin 1000mg	Glargine 84U Glulisine 56U	Sitagliptin 100mg	Albiglutide 30mg	9.9	95.3	9.1	-0.8	94.6	-0.7	7.9	95.9
9	Metformin 1000mg	Detemir 180U Aspart 84U	Sitagliptin 100mg	Exenatide ER 2mg	10.4	99.5	7.9	-2.5	99.6	0	7.3	100.5
10*	Metformin 1000mg	NPH 110U Aspart 36U	Sitagliptin 100mg	Albiglutide 30mg	11.4	92.8	10.6	-0.8	90.7	-2.1	7.3	88.3
				Median	10.2	84.6	8.4	-0.9	87.6	-0.8	8.3	85
				P25	8.9	80.0	7.8	-2.3	79.2	-1.7	8.0	78.2
				P75	10.9	106.2	9.7	-0.3	104.1	-0.6	8.7	95.6
P value					--	--	--	0.34	--	0.32	--	--

*Indicates insulin was started during 6-month period of combination therapy DPP-4i: dipeptidyl peptidase-4 inhibitor

** Started combination therapy at the same time

SU: sulfonylurea; P25: percentile 25%; P75: percentile 75%

DISCUSSION

With the prevalence of diabetes and obesity rising, therapeutic strategies that facilitate weight loss, improve glycemic control, and reduce cardiovascular risk should be emphasized.[13] Agents in the GLP-1 RA class meet most or all of these criteria; however, DPP-4 inhibitors do not, but theoretically could potentiate the effects of a GLP-1 RAs. Past studies investigating combination therapy omit once-weekly GLP-1 RAs and solely focused on glycemic and weight outcomes. In the absence of studies for combination therapy with once-weekly GLP-1 RAs, our case series represents the first evidence describing the safety and efficacy of once-weekly GLP-1 RA and DPP-4 inhibitor combination. For a synergistic response to have occurred with combination therapy, a decrease in HbA1c greater than 1.5% would be expected. Given the HbA1c lowering of albiglutide and exenatide ER is 0.6-1.6%, the median HbA1c reduction of 0.8% among cases, likely reflects the effects of the GLP-1 RA initiated and not a synergistic response.[14,15]

We retrospectively evaluated 18 patient cases, 10 of which experienced a HbA1c decrease of 0.5% or more at 3 months. Interestingly, this HbA1c reduction was similar across groups regardless of background insulin therapy. While there were improvements in HbA1c, an indicator of suboptimal response was the need for insulin initiation for 25% of patients in Group A and dose escalation in 80% of patients in Group B.

Weight loss was greater in Group A (-0.8 kg) compared to Group B (+0.2 kg), which is unsurprising given Group B was

treated with insulin. Nevertheless, both groups failed to show any augmented impact on weight loss, which could have possibly been influenced by non-adherence.

For Group B, weight loss was likely negated by the weight gain effects of insulin. Eight out of 10 cases required insulin dose increases in Group B, so this negative effect was experienced by most cases on insulin. Overall, the effect of combination therapy on weight was essentially neutral over 3 months.

Adverse effect reporting relied upon documentation in the EMR, which limits the results of this outcome measure. As expected, the highest incidence of adverse events were gastrointestinal disturbances. However, no patients discontinued treatment due to adverse effects suggesting the combination was generally well tolerated for 3 months. While the results of this retrospective analysis indicate the guidelines are correct in separating the use of these two classes, evidence on the benefits and harms of this combination was not available. This manuscript represents the first study of combination DPP-4 inhibitor and once-weekly GLP-1 RA therapy. Patients were prescribed this combination because of high body mass indexes, poor glycemic control, and medication formularies; however, our results found little benefit, but also little harm in using these classes together.

Our results are limited by retrospective design of a case series and the small sample size studied. Furthermore, no treatment protocols were utilized. Insulin initiation and dose titration potentially confounded HbA1c results, however, most patients underwent small increases. The largest insulin dose increase for one case in Group B was 20 units, while the majority of patients (75%) increased by 10 units or less. This suggests insulin adjustments marginally affected HbA1c results. The retrospective nature also prevents investigators from accounting for non-adherence, which may explain the worsening of glycemic control for a small subset of patients in the case series.

CONCLUSIONS

Our findings support the American Diabetes Association recommendations to avoid combination therapy with GLP-1 RA and DPP-4 inhibitors.[2] Moderate improvements in glycemic control without clinically significant weight loss are the likely outcomes of concomitant GLP-1 RA and DPP-4 inhibitor treatment, regardless of dosing frequency.[9,11] Additionally, the clinical improvements reflect the effects GLP-1 RA and are not potentiated by the combination. While GLP-1 levels were not measured, the results of this case series suggest a plateauing response to supraphysiologic GLP-1 levels above what is already reached with GLP-1 RA treatment. Given the approximate average wholesale price for the DPP-4 inhibitor and GLP-1 RA classes are USD 434 and USD 887 respectively, outcomes from this case series are unlikely to be cost effective.[1] Therefore, we advise clinicians to discontinue DPP-4 inhibitors in patients not meeting glycemic goals before initiating a GLP-1 RA. This approach is further supported in that current American Diabetes Association Guidelines now recommend initiating GLP-1 RA before insulin in most patients.[1] A prospective, randomized controlled trial would be necessary to fully assess the long-term effects of combination therapy, but are unlikely to occur based on the unfavorable results of preliminary data.

CONFLICT OF INTEREST

None declared.

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