USE OF REGULAR U-500 INSULIN IN TYPE 2 DIABETES TREATMENT WITH PUMP THERAPY : a three center french experience in 52 patients with long term follow up

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INTRODUCTION

Insulin therapy intensification by insulin pump is helpful in insulin resistant type 2 diabetes. The use of concentrated insulin may help improving glycemic control but few studies on pump use are available and most concern multiple daily injections (MDI). The latter demonstrated a mean HbA1c decrease ranging between 1 to 1,8% after switch from U-100 to U-500 MDI [1-3] . U-500 regular insulin (500 U/ml, Eli Lilly, USA) use with MDI was associated to weight gain and increased hypoglycemia ocurrence [1-3]. We report on the utilization of regular insulin U500 in pump device over a 5-year period.

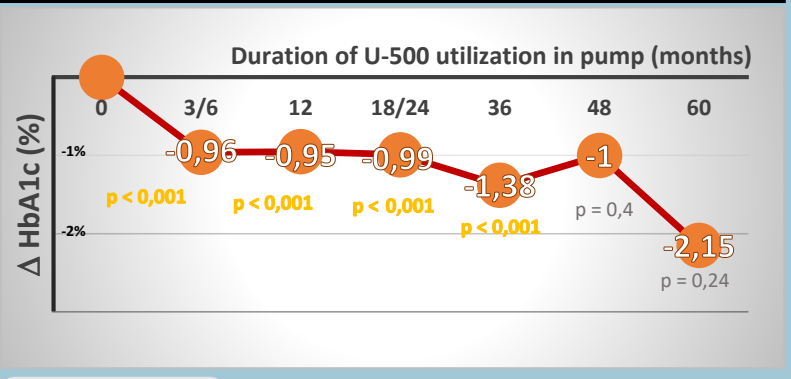
METHODS

Patients on pump therapy with U-100 insulin rapid acting analogs were recruited in two circumstances : HbA1c > 8% and/or insulin dose >100 UI/d. After U-500 therapy initiation, follow up was performed at 1 week, 3, 6, 12, 18, 24 months, then annually for HbA1c, total daily dose (TDD), body weight, incidence of hypoglycemia, treatment drop off.

Baseline characteristics of the Cohort	n = 52
Men (%)	28 (53,8)
Age (years)	62,9 ± 8,8
Duration of diabetes (years)	19,4 ± 8,2
Duration of insulin treatment (years)	13 ± 7
Duration of insulin pump therapy (years)	3,6 ± 2,8
Cardiovascular risk factors	
Hypertension (%)	49 (94,2)
Dyslipidaemia (%)	47 (90,4)
Smokers (%)	20 (38,5)
Obstructive sleep apnea (%)	28 (53,9)
Weight (kg)	109,5 ± 15,6
BMI (kg/m²)	39,1 ± 5,8
Glycated haemoglobin (%)	8,88 ± 1,34
Patients with HbA1c ≤ 8%	17 (32,7)
Diabetic complications	
Cardiologic (%)	25 (48,1)
Vascular (%)	21 (40,4)
Retinopathy (%)	17 (32,7)
Nephropathy (%)	29 (55,8)
Peripheral Neuropathy (%)	32 (61,5)
Associated antidiabetic drugs	39 (75)
Metformin (%)	36 (69,2)
GLP-1 Agonists (%)	20 (38,5)
Both (%)	17 (32,7)
DPP-4 Inhibitors (%)	0 (0)
Other (%)	0 (0)
Total daily insulin dose (UI/day)	199,4 ± 58,5
Total long-acting insulin dose (UI/day)	112,8 ± 38,8
Total rapid-acting insulin dose (UI/day)	86,6 ± 45,1
Total daily insulin dose (UI/kg/day)	1,88 ± 0,74
Hypoglycemia	
Severe (%)	0 (0)
No severe (%)	10 (19,2)
Day (%)	2 (3,8)
Night (%)	8 (15,4)
Lipid Profile	
CT (g/L)	1,69 ± 0,45
HDL (g/L)	0,40 ± 0,12
LDL (g/L)	0,9 ± 0,38
TG (g/L)	2,62 ± 0,88
STATINE therapy (%)	41 (78,8)
FIBRATE therapy (%)	4 (7,8)
Liver	
Hepatic cytolysis (%)	19 (36,5)
Cholestasis (%)	23 (44,2)

RESULTS

After switch from U-100 to U-500, mean HbA1c decreased dramatically after 3-6 months with a durable efficacy on follow-up (mean : 20 ± 15 months, maximum : 60 months).



HbA1c ≤ 8%
- Significant increase during the first year (U-100 : 32,7%, U-500: 45,5%-54,5%, (p<0.05))

BODY WEIGHT
- No significant increase during the trial period

INSULIN TDD
- TDD per day increased by +20 to +50 UI (+11 to +25%) (p= 0,01 to 0,03)
- Significant decrease of long-acting insulin dose (- 3 to -7 % per day, p=0,009 to 0,02)

HYPOGLYCEMIA During hospitalisation or declared
- **SEVERE** : only one episode during the trial
- **NON SEVERE** : significant increase with U500, daytime and night occurrence in 48 to 77% patients vs 21% with U-100 during previous 24 months (p<0.05)

CONTINUOUS GLUCOSE MONITORING
- No significant difference between U-500 and U-100 regarding time < 70 mg/dl during 6-day recordings performed at each time of the study (n=29/52)

METABOLISM
- **LIPID PROFILE** : no significant difference
- **LIVER CYTOLYSIS/CHOLESTASIS :** no significant difference

ADVERSE EVENT
- 1 death, from unknown origin, at 1 month
- No severe adverse event
- 2 patients developped abscesses on injection point
- No device related adverse events

DISCUSSION

Our results are in accordance with Lane et al. who reported U-500 utilization in a pump device. In this 1-year prospective trial which involved 21 T2D adults, U-500 utilization resulted in a decrease in HbA1c by 1,23%[4]. In 2013, a retrospective analysis of 59 T2D adults switching from U-100 to U-500 demonstrated a decrease of HbA1c by 1%, (maintained over 60 months in 15 patients)[5]. No significant increase in hypoglycemia nor weight gain were observed in these 2 studies[4,5].

CONCLUSION

When insulin resistant type 2 diabetes remains uncontrolled on pump therapy delivering U-100 rapid-acting analog, U-500 regular insulin may durably improve glycemic control. Declarative hypoglycemia occured at higher frequency with U-500 vs U-100, but CGM recordings performed in a subset of patients found no difference in time recorded with glucose < 70 mg/dl. Body weight remained stable during the study period. Pump therapy using U500 regular insulin is an option in T2D patients failing to respond to pump therapy with U100 rapid acting analog or in T2D patients with very high insulin requirements.

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