TREATMENT MAINTENANCE DURATION OF DUAL THERAPY WITH METFORMIN AND SITAGLIPTIN IN TYPE 2 DIABETES
THE ODYSSEE OBSERVATIONAL STUDY

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ABSTRACT

Sulfonylurea and DPP4 inhibitors are usually prescribed for T2DM patients in combination with metformin. Odyssée, a prospective, real-world, observational study conducted in France in primary care practices, compared the duration of maintenance of treatment without modification (withdrawal, substitution or add-on therapy) in T2DM patients in whom dual therapy with metformin + sitagliptin (MetSita) or metformin + sulfonylurea (MetSU) was initiated, based on physician choice. Patients were not randomized and followed for a period of up to three years.

At baseline, differences between the two arms (MetSita [n = 1874] and MetSU [n = 733]) were modest (mean age: 62.4 *versus* 64.2 years, BMI: 30.3 *versus* 29.6 kg/m2, diabetes duration: 6.4 *versus* 7 years, respectively). HbA1c levels were similar (7.5 *versus* 7.6%).

The median treatment duration for patients in the MetSita group was longer than the MetSU group (median treatment duration 43.2 *versus* 20.2 months, respectively, between-group difference 23 months, log-rank *p*<0.0001). This difference persisted after adjustment for baseline differences with propensity score and application of maximum bias hypothesis for missing data (42.4 *versus* 20.2 months). A similar reduction in HbA1c was noted in both arms (- 0.6%) and the incidence of hypoglycemia (prior to treatment modification) was lower in the MetSita arm (9.7% *versus* 21.0%).

Conducted in real-life conditions, the Odyssée study shows that combined therapy MetSita is maintained without treatment modification longer than combined therapy MetSU. In addition, the study confirms that glycemic efficacy is similar, with a lower incidence of symptomatic hypoglycemia with MetSita compared to MetSU.

INTRODUCTION

Initial treatment of type 2 diabetes mellitus (T2DM) focuses on lifestyle measures related to diet and exercise [1-2]. If these are insufficient to achieve adequate glycemic control, then treatment with oral antidiabetic drugs (OADs) will be necessary. According to the practice guidelines of French health authorities and ADA/EASD guidelines, metformin is the first-line treatment of choice [1-2]. If glycemic control can still not be achieved or maintained over time, then an add-on treatment will be necessary to achieve the glycemia target, ideally an HbA1c level ≤7% [1]. The step-up strategies used after metformin monotherapy most widely used in community medicine in France are either addition of a sulphonylurea (SU 38%) or addition of a dipeptidylpeptidase-4 (DPP4) inhibitor (40%) [3].

Although the efficacy of these treatments is well established in randomized controlled clinical trials, effectiveness in everyday care under real world conditions is less well characterised.

Moreover, since T2DM is a progressive disease, an important therapeutic issue is to ensure that each stage of treatment is as effective as possible to delay escalation of treatment intensity to the next line of treatment as long as possible. Maintaining a patient on an unchanged treatment is a pragmatic outcome criterion which combines notions of both effectiveness and tolerability.

OBJECTIVE

The principal objective of the ODYSSEE study was to compare the duration of maintenance of dual therapy in patients with T2DM treated in primary care between dual therapy with metformin and sitagliptin and dual therapy with metformin and an SU.

PATIENTS AND METHODS

✓Design: comparative effectiveness study

This was an observational, non randomized, prospective, longitudinal, multicenter study performed in France between July 2009 and December 2010. Data were collected by a randomly-selected panel of general practitioners (GPs), who provided patient data at quarterly standard follow-up visits over a period of three years.

Eligibility criteria

- Diagnosis of T2DM,
- Age >18 years,
- Initiation of a *de novo* treatment with metformin and sitagliptin dual therapy or with metformin and SU dual therapy within the previous eight weeks.

✓Treatment

In this study, two groups of patients defined by the treatment regimen prescribed by the investigator at inclusion were compared:

- Patients receiving dual therapy with metformin and sitagliptin (MetSita Group),
- Patients receiving dual therapy with metformin and an SU (MetSU Group).

✓Data collected

- Demographic data,
- Lifestyle variables,
- Diabetes and treatment history,
- Cardiovascular and metabolic comorbidity,
- Diabetic complications,
- Fasting plasma glucose (FPG) and HbA1c,
- Sitagliptin prescription regimen and co-prescriptions,
- Treatment modifications (add-on, discontinuations, switches or dose changes).

The study was designed to collect adverse event information in line with real-world treatment, and not systematically. The study protocol specified that the following categories of adverse events be reported:

- Serious or unexpected adverse events that were considered related to a medicinal product
- Adverse events that accompanied changes in diabetes medications
- Adverse events that accompanied patient withdrawal from the study
- Adverse events could also be reported spontaneously by investigators.

✓Primary outcome criterion

- The treatment maintenance duration (expressed as [dual therapy initiation date – date of treatment modification]) of the initial dual therapy (MetSita or MetSU), defined as number of days.
- Any discontinuation of a drug, switch between drugs or addition of a new drug was considered as a strict change in initial dual therapy (*ie* a treatment modification) defining the end of the dual therapy. Changes in dose were not considered to be treatment modifications.

✓Statistical analysis

- The primary endpoint (median of treatment maintenance duration) was compared between the MetSita and MetSU groups using Kaplan-Meier survival analysis and a logrank test; all premature treatment discontinuations without documented treatment modification were censored.
- A multivariate Cox model was implemented to identify variables other than treatment group potentially associated with the primary endpoint. The variables entered into the Cox model were age, gender, duration of diabetes, comorbidities, prior treatment, HbA1c and FPG at inclusion, number of follow-up visits and physician characteristics.
- Because patients were not randomized to treatment, the primary outcome variable was adjusted by a propensity score matching in order to limit potential bias due to imbalance between the two groups. This score was derived from multiple logistic regression analysis of the variables entered into the Cox model, with the exception of FPG at inclusion (considered less informative for glycemic status than HbA1c) and the number of follow-up visits (not a baseline variable).

✓Sensitivity analysis

- Missing data imputation according to a maximum bias hypothesis: patients lost to follow-up in the MetSita group considered as having discontinued medication, those in the MetSU group considered as not having discontinued.
- Multiple missing data imputation using a Markov chain Monte Carlo method
- Exclusion of patients previously treated with metformin + SU/ glinide dual therapy

RESULTS

Participants

Overall, 1 569 GPs agreed to participate in the study, of whom 705 included at least one patient fulfilling the eligibility criteria. The representativeness of the GPs was assessed with respect to the 2009 CNAM (*Caisse Nationale d'Assurance Maladie*) database and the representativeness of the patients with respect to the 2009-2010 LPD (Longitudinal Patient Data) database. All differences in age, gender and geographical distribution observed were trivial and of little clinical significance.

Of the 4031 patients recruited, 578 failed to fulfil the eligibility criteria. This was due to inconsistencies in the reported data for 369 patients, to lack of information on the initial treatment prescribed for 184 and to infringement of the inclusion criteria for 25 (Figure I).

Of the remaining 3453 eligible patients, 1874 received a dual therapy with metformin and sitagliptin (MetSita Group) and 733 a dual therapy with metformin and an SU (MetSU Group). The principal study analysis was conducted in these two groups of patients. In addition, 846 patients were treated with sitagliptin in an other regimen; data concerning these patients are not presented.

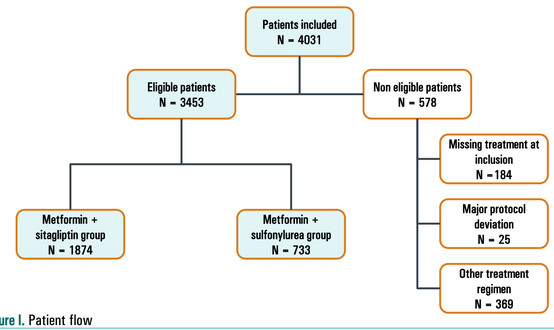

Figure I. Patient flow

Out of the 3 453 eligible patients, 1 084 (31.4%) patients discontinued the study before the end of the 36-month follow-up period stipulated by the protocol, most frequently within the first six months of the study. This proportion did not differ between the two treatment groups (31.9% for the MetSita group and 30.4% for the MetSU group).

Demographic and clinical characteristics of patients at inclusion

- The characteristics of the study population are presented in Table I.
- At baseline, differences between the two arms (MetSita [n = 1874] and MetSU [n = 733]) were modest (mean age: 62.4 (SD = 10.8) vs 64.2 (SD = 11.5) years, BMI: 30.3 (SD = 5.2) vs 29.6 (SD = 5.4) kg/m², diabetes duration: 6.4 (SD = 5.9) vs 7 (SD = 5.6) years, respectively). HbA1c levels were similar (7.5 vs 7.6%).

	MetSita Group (N = 1874)	MetSU Group * (N = 733)	*p*
Age (years; mean ± SD)	62.4 ± 10.8 [N = 1866]	64.2 ± 11.5 [N = 733]	*< 0.001*
Gender (men; %)	1108 (59.4%) [N = 1866]	422 (57.6%) [N = 733]	*0.400*
BMI (kg/m² ; mean ± SD)	30.3 ± 5.2 [N = 1738]	29.6 ± 5.4 [N = 686]	*0.004*
Time since diagnosis (years; mean ± SD)	6.4 ± 5.9 [N = 1702]	7.0 ± 5.6 [N = 644]	*0.049*
HbA1c (%)	N = 1735	N = 678	
Mean ± SD	7.5 ± 1.0	7.6 ± 1.0	*0.092*
< 6.5 %	180 (10.4%)	74 (10.9%)	*0.541*
[6.5-7] %	396 (22.8%)	139 (20.5%)	
[7-8] %	736 (42.4%)	280 (41.3%)	
[8-9] %	282 (16.3%)	124 (18.3%)	
> 9 %	141 (8.1%)	61 (9.0%)	
FPG (g/L ; mean ± SD)	1.55 ± 0.38 [N = 1348]	1.53 ± 0.40 [N = 512]	*0.218*
24 h microalbuminuria (mg)	N = 420	N = 185	
Mean ± SD	25.2 ± 61.8	26.4 ± 45.3	*0.047*
≥ 30 mg/24 h	76 (18.1%)	36 (19.5%)	*0.626*
Creatinine clearance < 60 ml/min (%)	196 (13.3%) [N = 470]	109 (19.3%) [N = 564]	*<0.001*
Documented comorbidities			
Hypertension (%)	1274 (68.5%)	501 (68.4%)	*0.999*
Dyslipidemia (%)	1253 (67.4%)	455 (62.2%)	*0.026*
Hepatic disorders (%)	88 (4.7%)	24 (3.3%)	*0.077*
Renal impairment (%)	36 (1.9%)	31 (4.2%)	*0.004*
Retinopathy (%)	71 (4.0%)	45 (6.4%)	*0.039*
Previous therapy; n (%)			
None	100 (5.4%)	48 (6.7%)	
OAD monotherapy	1210 (65.3%)	415 (57.6%)	
OAD dual therapy	464 (25.0%)	235 (32.6%)	
OAD triple therapy	30 (1.6%)	8 (1.1%)	*< 0.001*
OAD and GLP-1 analogue	38 (2.1%)	8 (1.1%)	
OAD and insulin	4 (0.2%)	4 (0.6%)	
Insulin only	2 (0.1%)	1 (0.1%)	
Other	5 (0.3%)	1 (0.1%)	

Table I. Demographic and clinical characteristics of patients at inclusion

*54% of the patients in the SU group were taking gliclazide, 24 % taking glibenclamide and 21.6% taking glimepiride

Primary outcome

Duration of maintenance of initial dual therapy

In the primary efficacy analysis, the median treatment maintenance duration was:

- 43.2 months [95%CI: 41.4 - non-evaluable] in the MetSita group
- 20.2 months [95%CI: 17.0 - 25.1] in the MetSU group

This difference was statistically significant (logrank test, $p < 0.0001$). Kaplan-Meier survival curves for treatment persistence are presented in Figure II.

Over the follow-up period, 621 patients (33.1%) in the MetSita group and 341 patients (46.5%) in the MetSU group underwent a strict change in initial dual therapy.

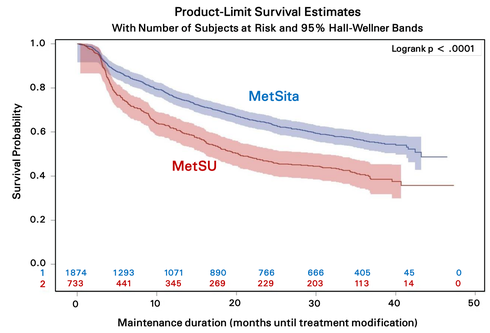

Figure II. Treatment maintenance duration until treatment modification.

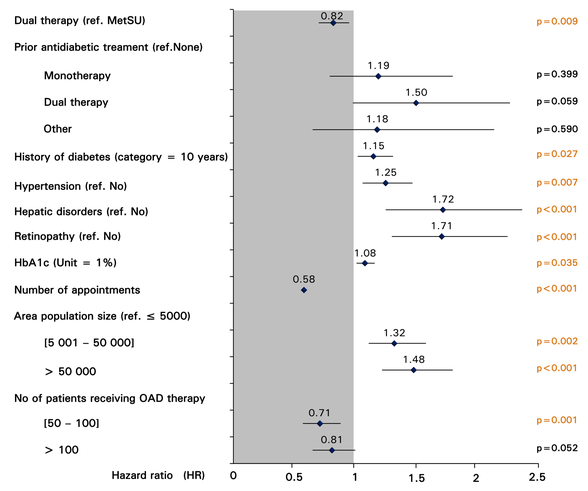

Figure III. Multivariate Cox Model

Sensitivity analyses

When missing data for the primary endpoint were assigned according to the maximum bias hypothesis, the difference in time to treatment change between the MetSita and MetSU groups was similar to that observed in the principal analysis and remained statistically significant (42.4 months [37.8 - non-evaluable] *vs* 20.2 months [17.0 - 25.1]; p <0.0001).

Primary outcome adjusted through the multiple imputation of missing data or exclusion of patients previously treated by dual therapy with metformin and an SU or a glinide did not change the principal finding of the study.

Reasons for treatment modification

The principal reason for changing treatment was inadequate efficacy in both groups, accounting for around two-thirds of documented cases (Table II). Poor tolerability accounted for 12% of treatment changes overall. The proportion of patients whose treatment was changed due to the occurrence of hypoglycemia was higher in the MetSU group (13.5%) than in the MetSita group (4.2%).

The reasons for modification of the initial dual therapy are presented in Table II.

	MetSita Group (N = 1874)	MetSU Group (N = 733)
Reasons for strict treatment change	N = 433	N = 215
Insufficient efficacy	301 (69.5%)	138 (64.2%)
Poor tolerability	57 (13.2 %)	25 (11.6%)
Hypoglycemia	18 (4.2 %)	29 (13.5 %)
Other treatment event	7 (1.6 %)	6 (2.8 %)
Patient decision	19 (4.4 %)	10 (4.7 %)
Other	54 (12.5 %)	38 (17.7 %)

Table II. Reasons for strict treatment modification

Effectiveness

Changes in HbA1c level up to the modification of the initial dual therapy are presented in Figure IV.

In both study arms, a reduction in HbA1c level was observed during the first six months of treatment (about -0.6%), which was maintained up to the end of the observation period.

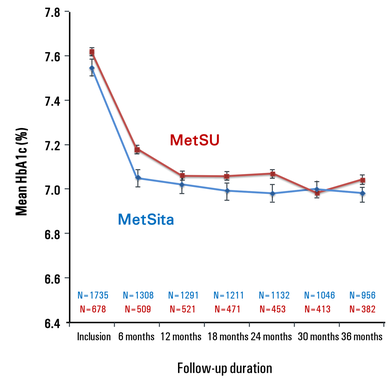

Figure IV. HbA1c level variation up to strict modification of the initial treatment

The proportion of patients achieving an HbA1c level <7% at least once during the follow-up period was 64.8% in the MetSita group and 58.8% in the MetSU group until strict change in treatment.

Occurrence of hypoglycemia

The proportion of patients reporting at least one symptomatic hypoglycemia episode during the follow-up period until strict change in treatment was lower among patients in the MetSita arm (9.7%) than among those in the MetSU arm (21%) (Figure V).

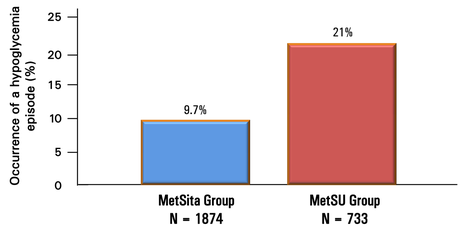

Figure V. Occurrence of a hypoglycemia episode

Weight and renal function

Variations in body weight during follow-up were minor and of a similar scale in the two patient groups.

The number of patients with documented microalbuminuria was limited, and the number of patients with at least one abnormal measure was low in both patient groups. The proportion of patients presenting at least one creatinine clearance measure <60 mg/ml was lower in the MetSita group than in the MetSU group (20.8% vs 25.6%; p <0.0006).

Safety

130 (6.9%) and 58 (7.9%) patients reported a total of 159 and 79 adverse events (AEs) during follow-up in the MetSita and MetSU group, respectively. According to the investigating physicians, 60 AEs potentially related to treatment occurred in 52 (2.8%) patients in the MetSita group, and 24 AEs potentially related to treatment occurred in 20 (2.7%) patients in the MetSU group.

DISCUSSION

The results of the ODYSSEE study, carried out in everyday primary care and involving 3453 patients starting a dual therapy with MetSita or MetSU between July 2009 and December 2010, showed that:

- Dual therapy with MetSita was maintained without treatment modification (defined as any add-on therapy, withdrawal or substitution) longer than dual therapy with MetSU.
- The median duration of treatment maintenance was 43.2 months in the MetSita group *versus* 20.2 months in the MetSU group.
- An HbA1c level decrease of 0.6% up to treatment modification occurred in both treatment groups.
- Symptomatic hypoglycemia occurred in 9.7% of patients in the MetSita group compared to 21% of patients in the MetSU group.

Follow-up data for the biochemical variables should be interpreted with caution given the extent of missing data. Nevertheless, the data on effectiveness with respect to HbA1c level and occurrence of symptomatic hypoglycemia obtained in this naturalistic real-life observational study are comparable to those described previously during the clinical development program for sitagliptin.

Conflicts of interest

Pr. Valensi, Pr de Pouvourville and Dr Dallongeville have received honoraria, consultancy fees, or speaker's fees from MSD France. Dr Kempf is an employee of CSD, the CRO responsible for operational management of the study. N. Benard, Dr C.Moisan, C. Chanut Vogel are employees of MSD France.

References

[1] *ANSM/HAS. Recommandation de bonne pratique : Strategie medicamenteuse du controle glycemique du diabete de type 2. 2013.* [2] *ADA/EASD guidelines 2012. Diabetes Care June 2012 vol. 35 no. 6 1364-1379.* [3] *Source Thales, donnees annuelles de prescription (annual data prescription). July 2013.*

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