**SUPPLEMENTARY MATERIAL TO:**

Suitability and Usefulness of a Flexible Dosing Timing of Oral Semaglutide to Maximize Benefit in Clinical Practice: an Expert Panel


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Although there are no data from RCTs or observational studies, clinical practice has highlighted how strategies for modifying the administration time can overcome the encountered challenges. The following clinical experiences, derived from 4 different Italian clinical centers, clarify how practical approaches could help improving the management of treatment with oral semaglutide. These clinical experiences come from 4 different Italian clinical centers (Table).

Case 1 was a 65-year-old man taking metformin (2550 mg/day) and sitagliptin (100 mg/day). His clinical parameters were as follows: BMI 30.2 kg/m$^2$, waist circumference 103 cm, LDL cholesterol 142 mg/dl, presence of hypertension, no previous cardiovascular event, HbA1c 10.3%. During this visit, sitagliptin was suspended and treatment with oral semaglutide was initiated. After 3 months of treatment with 7 mg of semaglutide (at a dosage of 3 mg in the first month and 7 mg in the following two months), HbA1c noticeably decreased from 10.3 to 8.2% with reduction in body weight (-5 kg), without tolerability issues. Therefore, the dosage of the medication was escalated to 14 mg/day. After further 3 months, HbA1c levels only slightly decreased from 8.2 to 8.0% without additional weight loss. The patient reported problems in treatment adherence due to the onset of side effects. In particular, difficulties in respecting the pre-breakfast assumption of the medication were reported. After a comprehensive evaluation of clinical and lifestyle needs and after mutual agreement with the patient, he was advised to take the medication 30 minutes before dinner to ensure an adequate fasting period after the previous meal, thereby guaranteeing an empty stomach. Six months later, tolerability was improved, adherence increased resulting in improved metabolic control (HbA1c reduction from 8.0% to 6.7%) and additional weight loss (-4.5 kg).

Case 2 was a 70-year-old man taking metformin (1500 mg/day) with HbA1c of 7.8%. His clinical parameters were as follows: BMI 29 kg/m$^2$, waist circumference 105 cm, LDL cholesterol 58 mg/dl, presence of hypertension and dyslipidemia, previous minor stroke. Oral semaglutide 3 mg was added before breakfast, but the patient reported dyspeptic disorders. Shifting the administration to before dinner resulted in the patient no longer experiencing GI disturbances and significantly improved adherence to the therapy. Improvements in HbA1c (-0.8%), body weight (-3 kg), and systolic blood pressure (-3 mm Hg) were observed after 6 months of treatment.

Case 3 was a 63-year-old woman taking metformin (1000 mg/day) with history of obesity, hypertension, depression, mixed dyslipidemia (total cholesterol 313 mg/dl, LDL cholesterol 219 mg/dl, HDL cholesterol 58 mg/dl, triglycerides 178 mg/dl) and at high cardiovascular risk. Treatment was implemented with addition of oral semaglutide, to be dose escalated according to the label. After experiencing two weeks of nausea alongside the use of semaglutide 14 mg/day before breakfast, the administration was moved to 30 minutes before dinner and the patient reported an overall sense of wellbeing, demonstrated motivation, and dedicated to controlling her diet. Remarkable reductions in HbA1c (-0.9%), body weight (-4 kg), and waist circumference (-8 cm) were observed at which time point?

Case 4 was a 48-year-old woman taking metformin (1500 mg/day) with HbA1c levels of 8.7% and BMI of 29.6 kg/m$^2$. Diabetes treatment was modified by adding oral semaglutide before breakfast. The agent, at initial dosage of 3 mg was not well tolerated and, before escalating to the 7 mg, the drug assumption was rescheduled to before lunch. This adjustment resulted in improved tolerability, adherence, and efficacy. Significant reductions in HbA1c (-2.2%) and body weight (-9 kg) were obtained, showing that initiating oral semaglutide therapy in an early stage of the disease could be an optimal approach for managing weight and glycemic levels, even in patients without overt obesity.

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All the cases presented GI intolerance after the initiation of oral semaglutide taken before breakfast, leading to a substantial decrease in adherence with consequent loss of efficacy. Following the recommendation to shift the administration time from morning to pre-dinner or pre-lunch, always checking for an adequate fasting period that guarantees an empty stomach condition, a marked improvement in both treatment adherence and tolerability was observed. Therefore, understanding possible reasons for suboptimal response to therapy is pivotal for tailored treatment approaches and optimization of therapeutic outcomes, ultimately contributing to enhanced adherence leading to improved efficacy and patient well-being.

An alternative time of drug intake may be considered as a valid strategy for gaining tolerability without penalizing the effectiveness on metabolic control and body weight.

**Table** Case Reports on the use of a flexible dosing timing of oral semaglutide.

| **Characteristic** | **Case 1** | **Case 2** | **Case 3** | **Case 4** |
|---|---|---|---|---|
| **Baseline** | | | | |
| Gender | M | M | F | F |
| Age | 65 years | 70 years | 63 years | 48 years |
| Diabetes duration | 72 months | 60 months | 3 months | 9 months |
| BMI | 30.2 kg/m$^2$ | 29 kg/m$^2$ | 30 kg/m$^2$ | 29.6 kg/m$^2$ |
| Body Weight | 87.5 kg | 78 kg | 96 kg | 83 kg |
| Waist circumference | 103 cm | 105 cm | 110 cm | 103 cm |
| Lifestyle | Non-sedentary work activity, but no physical activity | Sedentary | Modest physical activity, High-fat diet | No physical activity |
| Diabetes treatment before oral semaglutide | Metformin 850 mg x 3/day; sitagliptin 100 mg/day | Metformin 750 mg x 2/day | Metformin 1000 mg x 2/day | Metformin 500 mg x 3/day |
| Baseline HbA1c | 10.3% | 7.8% | 7.6% | 8.7% |
| Oral Semaglutide prescription | In the morning<br>3 mg titrated to 7 mg and 14 mg | In the morning<br>3 mg titrated to 7 mg | In the morning<br>14 mg | In the morning<br>3 mg titrated to 7 mg |
| | | | | |
| **Follow-up** | 12 months | 6 months | 4 months | 12 months |
| HbA1c | 6.7% | 7.0% | 6.7% | 6.5% |
| Weight reduction | -9.5 kg | -3 kg | -4 kg | -9 kg |
| Tolerability | After 6 months from semaglutide initiation, the patient experienced nausea. | Patient reported dyspeptic disorders. | Patient reported nausea in the first 2 weeks of use of semaglutide 14 mg/day before breakfast. | Patient reported nausea and diarrhea in the first month of use of semaglutide 3 mg/day before breakfast. |
| Clinical decision | Shift of administration from before breakfast to before dinner | Shift of administration from before breakfast to before dinner | Shift of administration from before breakfast to before dinner | Shift of administration from before breakfast to before lunch |
| Outcomes | • Resolution of tolerability issues.<br>• Increasing of adherence.<br>• Achievement of metabolic control.<br>• Substantial reduction in body weight. | • Removal of digestive disturbances.<br>• Increasing of adherence.<br>• Improvement in healthy eating.<br>• Slightly decrease in HbA1c. | • Resolution of nausea.<br>• Feeling of general well-being.<br>• Improvement in HbA1c levels.<br>• Reduction of body weight. | • Increased tolerability resulting in guaranteed adherence and effectiveness.<br>• Substantial improvement in HbA1c, body weight and LDL-cholesterol. |

BMI, body mass index; HbA1c, glycated hemoglobin; LDL, low-density lipoprotein.