

■ Satellite Symposium

Management of obesity including Xenical

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Obesity (BMI >30 kg/m²) is now such a prevalent condition, particularly in industrialized countries, that the WHO has officially declared it a "pandemic". In many European countries the prevalence of obesity is about 15% of the adult population and in US 20-25% of all adults are obese. In many parts of the world obesity is doubling every five to ten years, and projection suggests that this pandemic will create huge health burdens. These relate not only to the cost associated with management of obesity, but also to associated comorbidities, including glucose metabolism disorders, hypertension and hyperlipidemia, which may ultimately lead to Type 2 diabetes and cardiovascular disorders.

Treatment of obesity is primarily based upon lifestyle changes with dietary induced energy restriction (mainly based on dietary fat reduction) and increased physical activity to obtain a negative energy balance of about 600-800 kcal/day. However, the relatively minor treatment success by this lifestyle intervention used alone on the amount of weight loss and weight loss maintenance (more than 85% return to initial body weight after three years follow-up) has reemphasized the interest in new, effective, and well tolerated anti-obesity drugs to ensure more rational and successful management strategies. Moreover, it has been established that health benefits (reduction in risk factors

and decline in morbidity) can be achieved in most obese patients by a moderate reduction in body weight (reduction of 5-15%).

The current available anti-obesity agents reduce weight by appetite suppression, acting on neurotransmitter release in the central nervous system. However, an entirely new approach to the pharmacological management of obesity is the development of an agent (Xenical) which acts locally within the gastrointestinal tract, partially inhibiting the uptake of dietary fat (by about 30%) by blocking the activity of the gastric and pancreatic lipase. Several randomized trials have now been published where it has been found that Xenical, combined with moderate dietary restriction (particular of fat intake), significantly enhanced weight loss during periods up to 2 years. After 1 year the mean extra weight loss is about 3.5-4.0 kg (corresponding to 3.5-4.0% reduction of body weight) in the Xenical treated obese subjects compared to placebo. More than double as many patients treated with Xenical obtained relevant weight losses $\geq 5\%$ as compared with placebo (52% versus 22%). Xenical has beneficial effects on lipids, blood pressure and glucose homeostasis. In particular, Xenical has additional effects in reducing LDL-cholesterol and triglycerides besides its effect on body weight resulting in improved LDL/HDL-ratio and a significantly improved cardiovascular risk profile.

Weight loss is the best treatment for obesity-related Type 2 diabetes and several investigations have now been performed with Xenical in these patients. The Xenical-induced extra weight loss resulted in improved glucose regulation with a reduction of glycosylated haemoglobin (HbA1c) by 0.3-0.5 % after treatment for 1 year of obese Type 2 patients and this improved diabetes regulation was obtained even though Xenical treatment was associated with reduced anti-diabetic treatment as compared with placebo.

Adverse effects of Xenical are mostly related to gastrointestinal (GI) problems and can be anticipated from the known action of Xenical with increasing fat content in the stool. The most common adverse effects are flatus with discharge, oily spot-

ting, fecal urgency, fatty/oily stools, and fecal incontinence. These GI events generally occur early during treatment, are mild to moderate in intensity and are generally transient and can be reduced by maintaining a low fat diet. In randomized studies Xenical treatment is not associated with enhanced frequency of withdrawal indicating that the adverse effects are mild and generally acceptable. In conclusion lifestyle interventions are important in the treatment of obesity but if they are used alone the success rate is rather minor. Addition of a well tolerated anti-obesity drug such as Xenical to lifestyle modifications seems to improve both the absolute weight loss as well as weight loss maintenance and improves several of the risk factors and comorbidities associated with obesity.