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EDITORIALS

Orlistat: should we worry about liver inflammation?

Events are rare and a causal link unproved; still a useful option for some obese patients

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In a linked paper (doi:10.1136/bmj.f1936), Douglas and colleagues used data from the UK Clinical Practice Research Datalink and Hospital Episodes Statistics to explore the possible association between orlistat use and abnormalities of liver function in 94 695 patients who received orlistat over a 12 year period.[1] Orlistat is an inhibitor of intestinal and pancreatic lipases that was first licensed for the treatment of overweight and obesity in 2008 and became available in the United Kingdom in 2009. It is currently the only prescription drug available for the treatment of obesity and is also available over the counter in a lower strength form, with slightly reduced efficacy. The drug acts within the gastrointestinal tract and less than 1% is absorbed systemically. As a result, circulating concentrations of orlistat are low (<0.02 μmol/L), and at this concentration it has no systemic effects on other lipases.

A meta-analysis of more than 10 000 patients in clinical trials showed a mean placebo subtracted weight loss of 2.9 kg over 12 months of treatment.[2] Weight loss was maintained long term for subjects in one study, as long as four years for some.[3] As with all weight loss drugs, weight regain is common when orlistat is stopped.[4] Other clinically important outcomes associated with orlistat use are improved lipid profile (for example, 0.26 mmol/L reduction in low density lipoprotein cholesterol), lowered blood pressure (about 1.5 mm Hg in systolic and diastolic blood pressure), and a 0.38% reduction in glycated haemoglobin (HbA_{1c}) in patients with diabetes.[2]

Adverse effects that relate to orlistat's mechanism of action include gastrointestinal side effects due to increased faecal fat; these include fatty stools (14% of patients) and faecal incontinence (4% of patients). Small reductions in circulating concentrations of the fat soluble vitamins (A, D, E, K) and β carotene (mostly within the reference ranges) are also seen. These are not thought to be clinically important for most patients, however, especially because relevant markers such as calcium, parathyroid hormone, and international normalised ratio are not altered during treatment. Orlistat may interfere with the absorption of some drugs—notably warfarin, thyroxine, oral contraceptives, anticonvulsants, and ciclosporin. Appropriate precautions such as monitoring of international normalised ratio or thyroid function and institution of additional or alternative contraception are needed in patients taking these agents. Orlistat should not be used in patients taking ciclosporin.[5]

Use of orlistat in the NHS was supported by a National Institute for Health and Care Excellence (then the National Institute for Clinical Excellence) technology appraisal in 2001, which was updated when orlistat was included as a recommended option for the treatment of obesity in the more comprehensive guideline published in 2006.[6] This recommendation was made on the basis of projected reductions in obesity related comorbidity with long term orlistat treatment. The drug was considered clinically and cost effective overall when used within its licensed indications.

Concerns about potential liver toxicity with orlistat were first raised in 2001, and sporadic case reports have appeared in the literature since.[7] The most recent comprehensive review from the European Medicines Agency in 2012 identified a total of 21 reports of severe liver injury worldwide associated with orlistat use between 2007 and 2011. However, in many of these cases an alternative cause could not be excluded, and these have to be put in the context of widespread use of the drug—more than 53 million people worldwide have taken orlistat since its introduction.[8] It seems that if idiosyncratic reactions that cause severe liver injury do occur with orlistat, they are very rare. Obesity itself is also associated with non-alcoholic fatty liver disease, and evidence from case series suggests that orlistat might improve liver function in such patients,[9] although the only randomised trial found no benefit.[10]

Douglas and colleagues found that, although patients who were prescribed orlistat had a higher rate of liver function abnormalities, these abnormalities were as likely to occur in the 90 days before starting the drug as in the period after its initiation. They also found no evidence of a higher rate of severe events of liver impairment in those using orlistat.[1] The study provides reassurance that, although abnormal liver function is common in patients who are obese, it is unlikely to be caused by orlistat. This study would, however, be unlikely to detect very rare idiosyncratic events of severe liver toxicity that, on the available evidence, might be expected to occur in less than one in two million people taking the drug.

Because obesity can have substantial adverse effects on health and quality of life, interventions to support body weight

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reduction are important. These should always incorporate lifestyle and behaviour changes but, for many, lifestyle modification does not result in weight loss, and if it does weight regain is common. Although orlistat has some limitations, about a third of obese and overweight patients who start treatment as an adjunct to lifestyle changes can lose and maintain clinically meaningful weight loss, with associated improvements in disease risk and quality of life.[6] Most of the adverse effects and potential interactions with orlistat are well characterised, and as long as prescribing guidelines are followed (including stopping the drug if a clinically worthwhile weight loss is not achieved), it remains useful for the treatment of obesity, with an overall positive benefit-risk profile.

Competing interests: I have read and understood the BMJ Group policy on declaration of interests and declare the following interests: I have given lectures and acted as consultant for Roche (manufacturers of orlistat) and have also received a research grant for my institution (not related at all to the drug), although my last contact with Roche in relation to orlistat was more than five years ago. I have consulted for Roche and other companies in relation to obesity and diabetes drug development.

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