

Development of oedema is associated with an improved glycaemic response in patients initiating thiazolidinediones: a MASTERMIND study

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Background/Aim: Oedema is a common and serious side effect of thiazolidinedione therapy. A stratified medicines approach would aim to give thiazolidinediones to patients likely to have a good glycaemic response but to not develop oedema. We investigated whether oedema was associated with glycaemic response to thiazolidinedione therapy.

Methods: We retrospectively studied 11,459 patients initiating a thiazolidinedione from UK primary care data (Clinical Practice Research Datalink), and identified medical records of new oedema in the subsequent twelve months. Response was defined as change in HbA1c at twelve months and was adjusted for baseline HbA1c, baseline BMI, gender and compliance (medication possession ratio). In secondary analyses we restricted oedema classification to patients with concomitant weight gain. As a comparison the same analysis was performed in 13,089 patients initiating a sulfonylurea.

Results: The 5% of patients with recorded oedema on thiazolidinediones had a mean (CI) 2.2 (1.1-3.2)mmol/mol greater fall in HbA1c ($p<0.001$) compared to thiazolidinedione patients without oedema. This improved response increased when oedema was associated with weight gain, with a 2.5 (1.1-4)mmol/mol greater HbA1c fall when weight gain $>3\text{kg}$ (<0.001) and a 3.6 (1.8-5.4)mmol/mol greater fall when weight gain $>5\text{kg}$ (<0.001). Oedema was recorded in 3.7% of sulfonylurea patients and was not associated with response (HbA1c fall difference 1 (-0.5-2.5)mmol/mol, $p=0.2$), even when associated with weight gain $>3\text{kg}$ ($p=0.19$).

Conclusion: Patients with Type 2 diabetes who develop oedema on initiating thiazolidinediones have an improved glycaemic response, and more severe oedema may be associated with greater reductions in HbA1c. An association between oedema and glycaemic response was not observed in patients initiating sulfonylureas. This supports glycaemic lowering and fluid retention being mediated by a common pathway of thiazolidinedione drug action.