Cochrane Database of Systematic Reviews - - Cochrane Review

Drug treatments for managing cystic fibrosisâ€•related diabetes

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Study design (if review, criteria of inclusion for studies)

Randomized controlled trials comparing all methods of diabetes therapy in people with diagnosed cystic fibrosis-related diabetes

List of included studies (4)

Ballmann; Grover 2008; Moran 2001; Moran 2009

Participants

Participants of all ages with CF (a positive diagnostic test for CF that may include sweat, nasal epithelial and genotype testing) associated with pulmonary or gastrointestinal disease or both. Diabetes from this cohort will be further established by oral glucose tolerance testing, A1C data, two fasting or random blood sugars as defined by ADA standards (ADA 2004). The CF Foundation Guidelines (USA) related to a diagnosis during pulmonary exacerbations and in those with CF requiring feeding tubes may also be additionally used in establishing diagnostic criteria for CFRD.

Interventions

Different insulin regimens and regimens of oral diabetic medications. Studies where insulin regimens plus either an oral medication or placebo are compared. Different classes of these therapeutic agents, as well as strategies to reduce side effects and harm in using these agents. Insulin preparations: 1. short-acting insulin (with duration of action typically lasting two to four hours); 2. intermediate-acting insulin (action to 12 hours); 3. long-acting insulin (duration of actions approaching 24 hours). Post hoc change Oral anti-diabetic agents: 1. sulphonyureas and related agents; 2. biguanides and related agents; 3. glitazones and related agents; 4. other agents that specifically manage hyperglycaemia

Outcome measures

Primary outcomes 1. Biochemical measures of glycaemic control, ie HbA1c, fasting and two-hour post-meal serum blood sugar values 2. Pulmonary function (eg forced expiratory volume (FEV1) and forced vital capacity (FVC)) 3. Assessment of nutritional status (eg body mass index (BMI)) Secondary outcomes: Prevalence of microvascular and macrovascular disease; Rate of pulmonary exacerbations; Complications of therapeutic management (hypoglycemia, liver toxicity, metabolic effects on acid-base status); Clinical status: six-minute walk test, health-related quality of life (HRQoL) instrument (eg the Cystic Fibrosis Questionnaire-Revised (CFQ-R) (Quittner 2009)), mortality

Main results

The searches identified 29 trials (45 references). Four included trials provide results: one shortâ€•term singleâ€•center crossâ€•over trial (seven adults) comparing insulin with oral repaglinide and no medication in adults with CFRD and normal fasting glucose; one longâ€•term multicenter trial (61 adults with CFRD) comparing insulin with oral repaglinide and placebo; one longâ€•term multicenter trial (67 adults) comparing insulin with oral repaglinide; and one 12â€•week singleâ€•center crossâ€•over trial (20 adults) comparing the longâ€•acting insulin glargine to shortâ€•term neutral protamine Hagedorn insulin. Two ongoing trials of newly approved incretin mimics have been noted for possible future inclusion. Downgrading of the quality of the evidence was mainly due to risks of bias across all domains, but particularly due to concerns surrounding allocation concealment and selective reporting. There were also some concerns due to imprecision from small sample sizes and low event rates. Finally, there may be some bias due to the amounts of insulin and repaglinide given not being comparable. Data from one trial comparing insulin to placebo (39 participants) did not show any difference between groups for the primary outcomes of blood glucose levels (very lowâ€•quality evidence), lung function (lowâ€•quality evidence) or nutritional status (lowâ€•quality evidence). Similarly, no differences between groups were seen for the secondary outcomes of number of hypoglycemic episodes (lowâ€•quality evidence), secondary infection complications or quality of life (QoL). These results were mirrored in the narrative reports for the second trial in this comparison (seven participants). Data from the oneâ€•year trial comparing repaglinide to placebo (38 participants), showed no differences between groups for the primary outcomes of blood glucose levels (very lowâ€•quality evidence), lung function (lowâ€•quality evidence) and nutritional status (lowâ€•quality evidence). Also, no differences were seen between groups for the secondary outcomes of number of hypoglycemic episodes (lowâ€•quality evidence), secondary infection complications or QoL. These findings were mirrored in the narrative reports for the second trial (n = 7) in this comparison. Three trials compared insulin to repaglinide (119 participants). Data from one trial (n = 67) showed no difference in blood glucose levels at either 12 months (highâ€•quality evidence) or 24 months; narrative reports from one trial (45 participants) reported no difference between groups, but the second trial (7 participants) reported a beneficial effect of insulin over repaglinide. Two trials (112

participants) found no difference between insulin and repaglinide in lung function or nutritional status (moderateâ€•quality evidence). Two trials (56 participants) reported no difference in the number of hypoglycemic episodes (lowâ€•quality evidence). One trial (45 participants) reported no difference between groups in secondary infections and cystic fibrosis QoL. The single trial comparing glargine to neutral protamine Hagedorn insulin did not report directly on the review's primary outcomes, but did report no differences between groups in postâ€•prandial glucose values and weight; neither group reported infectious complications. There was no difference in episodes of hypoglycemia (very lowâ€•quality evidence) and while there was no difference reported in QoL, all participants opted to continue treatment with glargine after the trial was completed. Mortality was not reported by any trial in any comparison, but death was not given as a reason for withdrawal in any trial.

Authors' conclusions

There is insufficient evidence that corrector monotherapy has clinically important effects in pwCF with F508del/F508del. Both dual therapies (lumacaftorâ€•ivacaftor, tezacaftorâ€•ivacaftor) result in similar improvements in QoL and respiratory function with lower pulmonary exacerbation rates. Lumacaftorâ€•ivacaftor was associated with an increase in early transient shortness of breath and longerâ€•term increases in blood pressure (not observed for tezacaftorâ€•ivacaftor). Tezacaftorâ€•ivacaftor has a better safety profile, although data are lacking in children under 12 years. In this population, lumacaftorâ€•ivacaftor had an important impact on respiratory function with no apparent immediate safety concerns; but this should be balanced against the blood pressure increase and shortness of breath seen in longerâ€•term adult data when considering lumacaftorâ€•ivacaftor. There is highâ€•quality evidence of clinical efficacy with probably little or no difference in AEs for triple (elexacaftorâ€•tezacaftorâ€•ivacaftor) therapy in pwCF with one or two F508del variants aged 12 years or older. Further RCTs are required in children (under 12 years) and those with more severe respiratory function.

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See also

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Keywords

Diabetes Mellitus; Gastrointestinal Diseases; Hypoglycemic Agents; Insulin; Oral; Pancreatic Diseases; pharmacological_intervention;