Selected Summaries

Prednisone versus tamoxifen in patients with idiopathic retroperitoneal fibrosis

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SUMMARY

Idiopathic retroperitoneal fibrosis (IRF) is an uncommon condition and has no established medical treatment. Most patients are treated with a combination of steroids and tamoxifen with surgery for ureteric obstruction. This prospective open-label study, done between October 2000 and June 2006, enrolled 40 patients, 18–85 years of age with newly diagnosed IRF to compare the efficacy of prednisone and tamoxifen as maintenance therapy. Following diagnosis, all patients received induction therapy with prednisone 1 mg/kg/day for 1 month. Thirty-six patients who achieved complete remission (defined as symptom remission and near normalization of erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP] values) were randomized to two equal groups for maintenance therapy. One group received prednisone 0.5 mg/kg/day tapered gradually over a period of 8 months while the second group received tamoxifen 0.5 mg/kg/day (maximum 40 mg/day) for 8 months after withdrawal of the induction phase prednisone over 2 weeks. Following completion of maintenance therapy (8 months) the patients were followed up for another 18 months. Clinical examination and routine laboratory tests were done every 1–2 months for the duration of the study and every 3–6 months thereafter till completion of the study. CT or MRI was done at baseline and repeated at months 4, 8 and every 6–12 months thereafter.

The relapse rate at the end of the 8-month study period constituted the primary end-point. Change in renal functions, ESR, CRP, size of the IRF mass on imaging and relapse during follow-up were the secondary end-points.

Of the 36 patients, one in the prednisone and seven in the tamoxifen group relapsed during the first 8 months (Difference: 33%; 95% CI : 58%–8%; p=0.0408). Cushingoid features, weight gain and hypercholesterolaemia were significantly higher in the prednisone group (p=0.01, 0.02 and 0.0408, respectively). The relapse rate during the follow-up period was similar in both the groups. The cumulative overall probability of relapse was more common in the tamoxifen group. The authors concluded that prednisone was more effective than tamoxifen as a maintenance agent in preventing relapses in IRF and should be considered as the first-line treatment for patients newly diagnosed with IRF.

COMMENT

The estimated incidence of retroperitoneal fibrosis is 1.8 cases per 100 000 people and the idiopathic variety (IRF) is the commonest.[1] IRF appears to be autoimmune in nature but no specific immunological markers have been identified.[2] Clinical manifestations of the disease are non-specific and the diagnosis is often delayed till renal failure sets in. Imaging studies demonstrating a mass or plaque surrounding the retroperitoneal structures is a *sine qua non* of diagnosis but cases where imaging is equivocal also occur. Surgical ureterolyis as well as medical treatment with steroids are the mainstay of treatment with the best outcome observed in patients receiving both treatments.[2–4] Prednisone is the most commonly used drug with an initial dose of 60 mg on alternate days for 2 months followed by tapering of the dose to 5 mg/day, often continued for 2 years.[5] The side-effects of prednisone had led to the use of a number of other agents such as cyclophosphamide, methotrexate, azathioprine, colchicine or mycophenolate mofetil with varying outcomes.[2]

This is the first randomized trial looking at the efficacy of prednisone and tamoxifen as maintenance therapy in newly diagnosed IRF.[1] It is difficult to enrol patients in a prospective study for IRF due to the rarity of the condition and this is one of the largest studies to date. However, it leaves a number of questions unanswered, some of which the authors readily list as limitations of their study. We disagree with the statement that this provides evidence for a short induction phase of high-dose steroids since the study was not designed to answer this. The high-dose induction could have been one of the reasons for the high adverse effects recorded and the withdrawal of two patients from the study. The decision to continue maintenance therapy for 8 months was also arbitrary.

Hydronephrosis progressing to renal failure, the commonest and potentially most devastating complication of IRF, occurs in nearly 75% of patients.[6] In this report 27 patients presented with ureteric obstruction, more often bilateral and nearly 50% with acute renal failure. Relieving ureteric obstruction is the first step in managing IRF and the authors achieved this using ureteral stenting, nephrostomy or ureterolysis. Medical treatment is begun after achieving renal drainage. In many situations stents are not useful and a nephrostomy is required. Nephrostomy tubes are plagued by displacement, blockage and infection, especially in the background of immunosuppression. Surgical ureterolysis may be a better alternative to percutaneous drainage as it provides an opportunity to obtain tissue for histology, relieves mechanical obstruction and avoids prolonged use of tubes.

Despite small numbers in the present study, some conclusions can be drawn. High-dose induction therapy is useful in achieving initial disease remission, steroids as maintenance therapy are associated with more side-effects but fewer relapses compared to tamoxifen and a large number of patients relapse after cessation of either therapy. Some questions regarding management of IRF still remain: Does medical treatment alone suffice? Can we predict the subgroup of patients who will have worsening renal failure needing intervention? Can early ureterolysis reduce the intensity and duration of medical treatment and relapses? It is unlikely that any single centre study will accrue sufficient patients to answer these questions. Till then, the strategy of renal decompression, steroid induction and maintenance seems to be the best option.

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Poor folate status: A predictor of persistent diarrhoea in young children?

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SUMMARY

Data from a primary zinc supplementation trial in an urban slum of Dakshinpuri, New Delhi, were used to perform a cohort analysis to study the association between the status of folate/cobalamin and diarrhoeal morbidity in children. Of the initial 3802 children surveyed, 2482 were included in the trial, which met the sample size requirement. For the current analysis, 2296 children who had results for at least one vitamin parameter were included. At baseline, four parameters were measured—plasma folate, plasma cobalamin, plasma MMA and plasma tHcy—among others, using standardized microbiological assays. The cut-off for deficiency state was taken as less than 25th percentile for folate/cobalamin, and more than 75th percentile for MMA/tHcy. Diarrhoea was defined as more than or equal to three episodes of loose watery stools in a 24-hour period, and recovery as the first day of a 72-hour period without diarrhoea. Acute diarrhoea was for a duration of <7 days, prolonged for 7–13 days, and persistent for ≥14 days. The follow-up was done weekly for 4 months and data collected for the preceding 7 days, i.e. every child was visited 17 times. Each week was denoted as a period. Most baseline characteristics among the low and high folate/cobalamin children were comparable except for age, breastfeeding status and levels of other vitamin parameters.

In a total of 250 310 days of follow-up, there were 4596 child-periods of acute diarrhoea, 633 child-periods of prolonged diarrhoea, and 117 child-periods of persistent diarrhoea. Using generalized estimating equations (GEE) in stepwise logistic regression manner, the risk factors identified for acute and persistent diarrhoea were younger age, enrolment in the months of February to May, and self-reported diarrhoea 24 hours before inclusion. The protective effect of breastfeeding for persistent diarrhoea was decreased when plasma folate was added to the regression. GEE logistic regression was used to estimate associations between the vitamin parameters and diarrhoea. Acute diarrhoea was significantly associated with only high tHcy level (adjusted OR 1.14; 95% CI 1.04–1.24; p=0.006). For prolonged diarrhoea, there was no significant association with any parameter. Persistent diarrhoea was significantly associated with low folate level (adjusted OR 1.77; 95% CI 1.14–2.75; p=0.010). There was also interaction between low cobalamin and breastfeeding status for acute diarrhoea; adjusted OR for breastfed children was 1.01 (95% CI 0.92–1.12), whereas in non-breastfed children it was 1.48 (95% CI 1.17–1.87), p value for interaction was 0.003. There was interaction between sex and folate status for persistent diarrhoea; adjusted OR for boys was 2.51 (95% CI 1.47–4.28) whereas in girls it was 1.03 (95% CI 0.53–2.01), p value for interaction was 0.03. Generalized additive models showed a linear relationship between log odds of persistent diarrhoea and folate concentration <20 nm/L in boys.

The biological plausibility given for the association between low folate and persistent diarrhoea is that folate is necessary for regeneration of intestinal epithelial cells and recovery from infection, and hence, its deficiency is associated with severity rather than the incidence of diarrhoea. The authors concluded that poor folate status was an independent predictor of persistent diarrhoea in this cohort of children.

COMMENT

Persistent diarrhoea is an episode of diarrhoea of presumed infectious aetiology, which starts acutely but lasts for >14 days, and excludes chronic or recurrent diarrhoeal disorders such as tropical sprue, gluten-sensitive enteropathy or other hereditary disorders.[1] It is more common in malnourished infants and young children.[2] The major consequences of persistent diarrhoea are growth faltering, worsening of malnutrition and death during subsequent diarrhoeal or non-diarrhoeal illness.[2] It has been reported that 3%–20% of acute diarrhoeal episodes in children in developing countries are persistent.[3]

This study examined an association between folate/cobalamin and diarrhoea in children. However, the analysis was conducted as part of a zinc supplementation trial with its own primary objectives.[4] Hence, the results need to be viewed with caution. A participation rate <60% raises questions on the representativeness of the study group. Had this been a primary objective, the age group included might have been beyond the 6–30 month range.