Low-dose methotrexate for advanced pulmonary disease in patients with cystic fibrosis

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Abstract

Inflammation is a hallmark in the pathogenesis of pulmonary destruction in cystic fibrosis (CF). There is no proven effective systemic anti-inflammatory treatment for CF patients with advanced pulmonary disease. Methotrexate (MTX) is known as an effective anti-inflammatory treatment in asthma and in juvenile rheumatoid arthritis. The question was: Is an improvement in pulmonary function achievable with low-dose MTX in patients with cystic fibrosis and advanced pulmonary disease?

Methods: We treated five CF patients with advanced pulmonary disease, who deteriorated in spite of intensive conventional therapy on an individual basis with low-dose MTX. FEV1% and immunoglobulin G (IgG) serum levels were followed from the year before to the year after starting with MTX. Results: In the year before starting with MTX, FEV1% decreased (median: 9% FEV1; range: 2–15% FEV1; \( P < 0.005 \)) after starting with MTX, FEV1% increased (median: 10% FEV1; range: 9–15% FEV1; \( P < 0.05 \)). IgG changed (median: 2 g/l; range: 0.2 to 6.3 g/l) in the first year with MTX. Conclusion: These preliminary data suggest a beneficial effect of MTX even in advanced pulmonary disease in CF patients and support the need for a controlled prospective study.

Keywords methotrexate; cystic fibrosis; treatment.

INTRODUCTION

Cystic fibrosis (CF) is the most frequent lethal autosomal recessive inherited disease among Caucasians. Inflammation is a hallmark in the pathogenesis of pulmonary destruction in CF. Anti-inflammatory treatment was recognised as a potentially important therapeutic tool (1,2). A slower decrease of FEV1% was demonstrated in a long-term study (2) with high-dose ibuprofen. This effect was most pronounced in children younger than 13 years with mild lung disease. There were also beneficial effects of alternate-day systemic steroids (1), but they are unsuitable for long-term treatment because of the side-effects (3). Patients with CF and advanced lung disease may also profit from systemic immunosuppression. The drug one wants to use should have a proven anti-inflammatory effect and long-term experience regarding adverse effects must be available to estimate the potential benefit/risk relation. Methotrexate (MTX) is well known as an effective anti-inflammatory drug even in children and there is also some experience with long-term treatment (i.e. juvenile rheumatoid arthritis (4), asthma(5)). The adverse effects of low-dose MTX are tolerable (6). In CF patients who deteriorated in spite of intensive conventional therapy, we used MTX as an add-on therapy. The question was: Is a pulmonary improvement with low-dose MTX achievable in patients with CF and advanced pulmonary disease.

METHODS

Retrospectively the clinical data of five chronically Pseudomonas aeruginosa infected patients with CF (details see Table I) and advanced pulmonary disease who were treated on an individual basis with oral MTX were summarised. MTX doses ranged from 10 to 20 mg/m² orally once every week. All patients were treated with intravenous antibiotics routinely every 3 months and on exacerbations. Systemic steroids (1), ibuprofen (2), azithromycin (7) or colchicine (8) were not part of the treatment regimes. There were no changes in the use of rhDNase or inhaled steroids during the observation period. The
patients thorax X-ray scores (9) ranged from 18 to 25 points indicating severe pulmonary damage. FEV1% predicted and immunoglobulin G (IgG) serum levels were followed from the year before to the year after starting with MTX. The change in FEV1% was the primary outcome parameter. IgG was used as a systemic marker of chronic inflammation. The best value in the year before, the value when starting MTX and the best value in the following year was taken. We used the best annual values to exclude actual reversible decreases in pulmonary function or immune responses. Paired t-test was used to compare data with/without MTX and \( P < 0.05 \) was considered significant.

RESULTS
In the year before starting with MTX, FEV1% decreased (median: 10.5%; range 9–15% FEV1; \( P < 0.005 \)). In the year after starting MTX, FEV1% increased (median: 9% FEV1; range: 2–15% FEV1; \( P < 0.05 \)). In patient number 4, the FEV1 was not measurable when MTX was started (see Table 1). IgG levels decreased in the year after starting with MTX in four out of five patients (see Table 1). The most relevant improvement of FEV1% and IgG was seen in patient number 5 who had the best pulmonary function at the time when MTX was started and she was treated with the highest dose of MTX compared to the other four patients. No severe side-effects were observed. One patient reported some nausea on the day when MTX was taken during the week.

DISCUSSION
With the use of MTX, an improvement of pulmonary function and a trend to a reduction of IgG were observed in a highly selected group of patients with CF. All conventional therapeutic options were used before MTX was added to the treatment regime on an individual basis. As with other indications (i.e. juvenile rheumatoid arthritis (4), asthma (5)) there were responder and non-responder to low-dose MTX. In three out of four patients, the clinical improvement (increased FEV1%) was accompanied by decreased IgG levels. At this time, we cannot speculate on a cause/effect relation regarding the higher dose of MTX in patient number 5 and the more pronounced clinical response compared to the other patients. In accordance with the effect of ibuprofen (2), it might be possible that a relative milder pulmonary destruction allowed more improvement. In a subgroup analysis of patients with steroid-resistant asthma who were treated with MTX those responded more with a steroid-sparing effect, whose long-term steroid doses were low (5). We are aware of the limitations (retrospective nature and small number of patients) of this first report of MTX in CF. Nevertheless, these preliminary data suggest a beneficial effect of MTX even in advanced pulmonary disease in CF patients and supports the need for a controlled prospective study.

REFERENCES