Lung function in children and adolescents with juvenile idiopathic arthritis during long-term treatment with methotrexate: a retrospective study

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Abstract

Objectives

Methotrexate may cause severe adverse pulmonary side-effects in adults with rheumatoid arthritis. Our aim was to examine the long-term effect of MTX on lung function in patients with juvenile idiopathic arthritis (JIA).

Methods

We retrospectively reviewed the charts of all 68 patients with JIA treated with MTX at our centre over a 14-year period. Results of annual pulmonary function tests (PFT) were compared using paired t-tests adjusted by Bonferroni correction and by linear regression analysis.

Results

The patients in our study had taken MTX for a median of 6.7 years with a median cumulative dose of 3219 mg. In a subgroup of 37 patients PFT had been performed before the onset of MTX. In this subgroup there was a significant decrease of mean mid-expiratory flow (MMEF) after 3 years (-14.0%, p<0.001) of MTX. Diffusion capacity of the lung for carbon monoxide (DLCO) was reduced after the third year (-12.4%, p=0.001). In the total group there was a decrease in MMEF between years 3 and 4 after MTX onset (-13.5%, p=0.001). Forced expiratory volume (FEV1) showed a slight rise between years 4 and 5 (+5.5%, p=0.003). All other parameters remained without significant changes. There was no correlation of PFT results and cumulative MTX dose or JIA subtype. None of our patients developed clinically relevant lung disease.

Conclusion

In summary we found some declines of MMEF and DLCO during long-term treatment with MTX. Overall our data confirm the relative safety of long-term MTX treatment in patients with JIA. We conclude that further data on the development of pulmonary function in patients receiving MTX therapy would be helpful.

Key words

juvenile idiopathic arthritis, methotrexate, pulmonary function

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Introduction

Following the first successful placebo-controlled trial in juvenile idiopathic arthritis (JIA) (1), methotrexate (MTX) became the standard first-line treatment of severe cases of JIA (2). JIA is divided into subtypes of oligo- and polyarticular arthritis, enthesitis-related arthritis, juvenile psoriatic arthritis and the systemic form of JIA.

MTX has been shown to have a good effect on disease activity in JIA as well as in rheumatoid arthritis. While it may be used safely in most patients (3), it may lead to considerable adverse drug effects (4), especially hepatic (5), haematologic (6) and pulmonary problems (7). Regarding the lungs methotrexate-induced pneumonitis (MIP) is feared as a serious complication with a lethality of up to 17% in adults (8). In long-term users interstitial lung disease and fibrosis have been reported to be caused by MTX (9), and decreased results in pulmonary function tests (PFT) have been described in several studies (10-11). Although a clear distinction between possible disease effects and adverse drug events was not always possible, most authors conclude that MTX given long-term may affect lung function in adults (8, 11).

In children and adolescents pulmonary adverse drug events of MTX have rarely been examined despite its common use in diseases such as JIA. Few studies exist most of which only searched for adverse events at a single point in time, and the development over more than one year has never been studied (12-14).

The aim of this retrospective study was to assess the effects of MTX on lung function of children and adolescents with JIA over several years.

Patients and methods

Patients

Results from lung function tests of 68 patients (45 females, 23 males) with JIA treated in the paediatric rheumatology clinic of Hannover Medical School between January 1st 1993 and July 31st 2007 were analysed.

Inclusion criteria were a diagnosis of JIA, treatment with MTX for at least nine months and records documenting at least two pulmonary function tests with a time interval of at least 9 months. Patients were at least 6 years old at the time of their first PFT. None of our patients had a concurrent lung disease such as asthma.

A subgroup of 37 children underwent PFT before the onset of MTX therapy. The others were either too young to perform PFT at onset of MTX therapy (26 children), or they were referred to our centre after MTX therapy had been initiated elsewhere. Among our JIA patients 33 (48.6%) had oligoarthritis, 19 (28.0%) rheumatoid factor (RF)-negative polyarthritis, 5 (7.3%) each had systemic arthritis, enthesitis-related arthritis, and psoriatic arthritis, and 1 patient had RF-positive polyarthritis.

Methods

Pulmonary function tests

Pulmonary function was tested using a Viasys Masterscreen Bodyplethysmograph (formerly E. Jaeger, Germany). Spirometry was performed by an experienced technician according to international recommendations (15) for spirometry, manoeuvers were accepted if they were visually acceptable and reproducible even if forced exspiratory time was shorter than 6 seconds. The following parameters were stored when manoeuvers met quality control criteria: vital capacity (VC), forced exspiratory volume (FEV1), maximal exspiratory flow at 25% of vital capacity (MEF_{25}), mean mid-exspiratory flow (MMEF), diffusion capacity of the lung for carbon monoxide (DLCO), and thoracic gas volume (TGV). DLCO was corrected for actual haemoglobin levels.

The results are expressed as percentages predicted based on the equations summarised by Quanjer and Stocks (16).

Statistics

Data were stored in Excel tables (Microsoft Inc.); statistical analysis was performed using SPSS (version 18). Since it was not possible to perform repeated measurement analysis because of missing values in our retrospective study, paired *t*-tests were used to compare data before and during MTX therapy, as well as to compare values with the respective previous year's values. Because of the multitude of *t*-tests, significance levels were adjusted by

Bonferroni correction to rule out accidental significances. Thus, significance levels were divided by the number of tests performed reducing the original significance level of 0.05 to 0.0071 and 0.0038, respectively, depending on the subgroup and the number of tests calculated in an analysis**.**

A series of linear regression analyses was used to assess the association between cumulative MTX dose and final PFT results under therapy. Finally, the association between JIA subtype and lung function was assessed using ANOVA (analysis of variance).

Results

Data for MTX treatment

Sixty-eight children were included in the study. All were treated with weekly oral or subcutaneous doses of methotrexate. In the last 6 months prior to discontinuing the therapy, MTX was reduced to dosing every other week. Single doses varied between 2.5 mg and 30 mg, representing 10–20 mg/m^2 body surface area per week. Further data on duration of MTX therapy and cumulative doses are shown in Table I.

Subgroup with PFT before starting MTX

In the subgroup of 37 children in whom PFT were performed prior to starting MTX, a reduction of maximum mid-expiratory flow (MMEF) was found two (-10.9%; 95% CI=-4.4/-17.3; p=0.002) and three years (-14.0%, 95% CI=-3.1/-7.6 p<0.001) after beginning MTX treatment. DLCO was reduced after 3 years by 12.4% (95% CI=-8.7/16.1; p=0.001) compared to baseline (Fig. 1). Vital capacity (VC), thoracic gas volume (TGV), maximal expiratory flow at 25% of vital capacity (MEF_{25}) and forced expiratory volume in one second (FEV1) showed no significant changes.

Total group

The subgroup of 31 children without a PFT before MTX onset had their first PFT a median of 28 months after onset of MTX, with a range from 12 to 93 months.

Only 50 patients were capable of performing all pulmonary function tests. While spirometry was successful in all 68 patients, body plethysmography was only completed more than once in 50 of the 68 patients.

In the total group we compared the lung function values with the respective previous year´s values. Diffusion capacity (DLCO) fell from year 3 to year 4 (-13.5%; 95% CI =-7.2/-19.9; p=0.001) of MTX therapy (Fig. 2). Exspiratory flows MMEF and MEF_{25} showed no significant changes. FEV1 rose comparing fourth and fifth year (+5.5%; 95 % CI = 2.1/8.9; p=0.003). VC and TGV did not change significantly.

Last lung function values

Only one patient had a reduced DLCO (<70%) at the end of the observation period, a 17-year-old girl with no clinical signs of a lung disease. She had smoked 20 cigarettes a day for more than one year. Further data are presented in Table II.

Influence of cumulative MTX dose on lung function

To determine whether there was a correlation between cumulative MTX dose and changes in PFTs, we analysed the respective lung function value at the end of the observation period and the total dose of MTX received. These multiple regression analyses showed no significant association. A higher dose of MTX was not associated with reduced lung function, only slightly higher values were observed.

Correlation between subtype of JIA and PFT results

The individual analysis of JIA subtypes showed no significant changes in PFT

Table I. Data for methotrexate treatment.

	Range	Median
Age at onset of MTX (years)	2.1–15.5	5.4
Duration of therapy (years)	0.8–14.3	6.7
Number of PFTs performed by each patient	2–12	4
Cumulative dose of MTX (mg)	400–12890	3219

MTX: Methotrexate; PFT: pulmonary function testing.

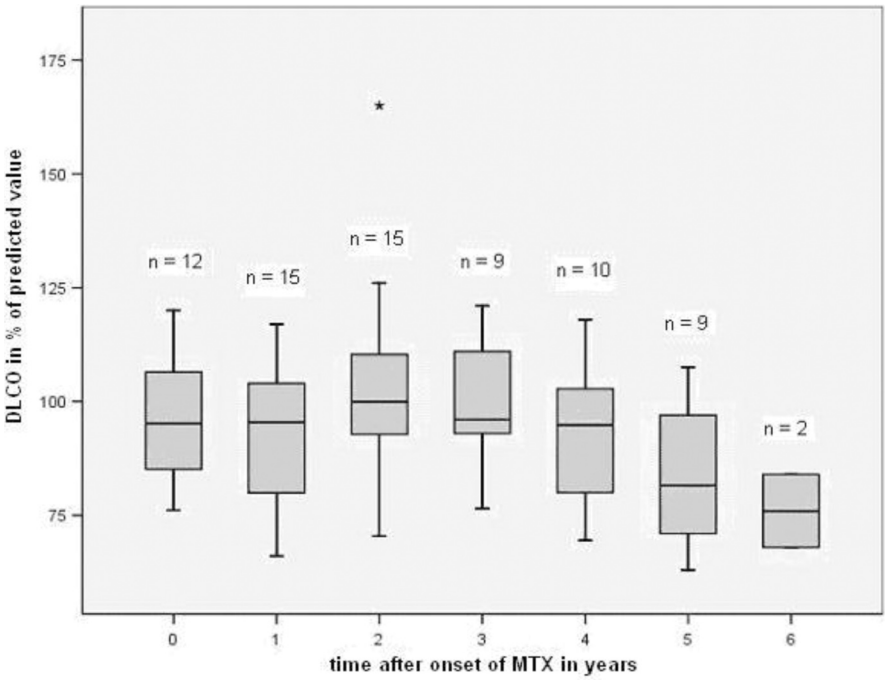

Fig. 1. Development of DLCO for the subgroup of children with PFT before MTX onset.
(Box plot: Box equals mean 50% of the values, line in the box is the median value, upper and lower whisker equal the 1.5th of the interquartile range, star is an outlier).
MTX: Methotrexate; DLCO: diffusion capacity of the lung for carbon monoxide.

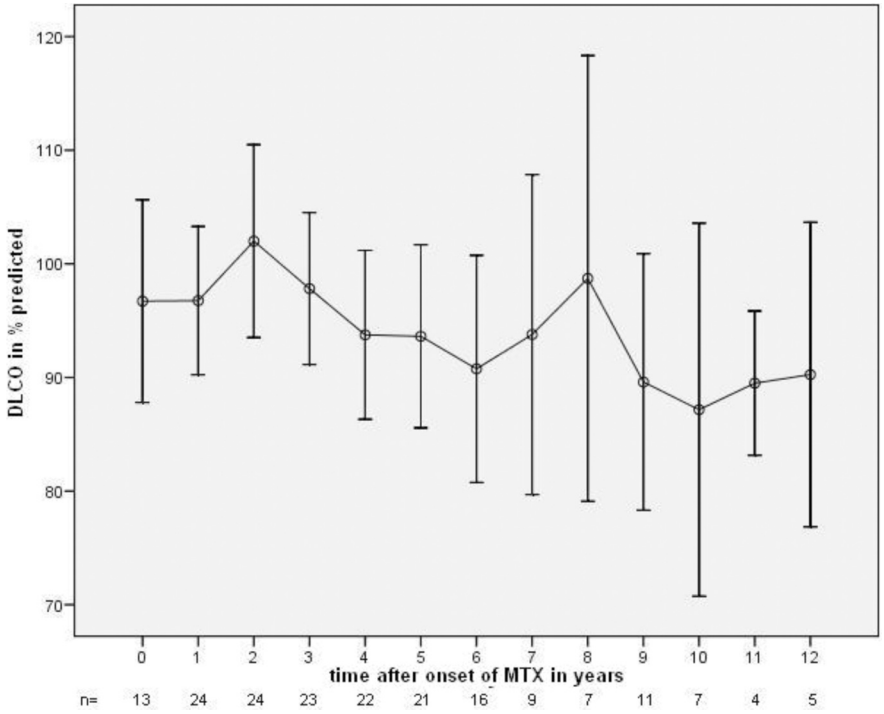

Fig. 2. Development of DLCO for the whole group (n=68). The circles represent mean values (±1 standard deviation). MTX: methotrexate; DLCO: diffusion capacity of the lung for carbon monoxide.

Table II. Last measured lung function values after / under MTX treatment.

Lung function parameter	Lower limit of normal value	n.	Number of patients with value below lower limit
DLCO	<70%	58	1 (1.7%)
VC	<80%	68	5 (7.4%)
MEF_{25}	<55%	68	8 (11.8%)
MMEF	<65%	68	7 (10.3%)
FEV_1	<80%	68	0
TGV	<80%	67	3 (4.5%)
FRC	<80%	58	2 (3.4%)

DLCO: Diffusion capacity of the lung for carbon monoxide; VC: vital capacity; MEF_{25}: maximal exspiratory flow at 25% of vital capacity; MMEF: mean mid-exspiratory flow; FEV_1: forced exspiratory volume; TGV: thoracic gas volume; FRC: functional residual capacity.

results for a certain subtype after use of Bonferroni correction.

Clinical impression

None of our patients developed clinically apparent pulmonary disease during our observation period.

Discussion

The present data are reassuring as we found no clinically relevant pulmonary disease among our patients with JIA after several years of MTX therapy. This stands in contrast to the literature for adults with RA, in whom longitudinal studies showed significantly reduced FVC, FEV1, TLC and FRC after two years of MTX treatment leading to the recommendation of annual PFTs (10, 17). About half of the adults with pulmonary side-effects had pulmonary relapses upon reexposure to MTX, and a few patients died (8). Lung damage included fibrosis, thickening of bronchial walls and bronchiectasia (18-22). Overall mainly acute pulmonary complications under MTX were described with less evidence for chronic pulmonary side-effects. Pulmonary complications in adults can be life-threatening (23). As an acute complication MTX induced pneumonitis (MIP) has been described leading to dyspnea, coughing, fever and restrictive ventilatory dysfunction due to a massive interstitial infiltration by lymphocytes and giant cells (8). Air trapping, the pulmonary retention of gas after expiration was observed in a study of Dayton *et al*. (24). Concerning JIA, very limited data could be found: MIP appears to be very rare in childhood, only two cases were reported known to us (25-26). Acute pulmonary complications were not observed in our study.

Pulmonary involvement is rare in JIA. PFT values prior to therapy with MTX in our study were within normal limits making it unlikely that JIA itself led to a reduction in pulmonary function. Graham *et al*. showed no pulmonary side-effects of low-dose MTX therapy in children with JIA (27), another study showed no serious adverse drug effects at all (28)

Schmeling *et al*. performed PFT on 89 children with JIA, 40 of whom were treated with MTX and found reduced DLCO in 2 patients only, one with and one without treatment with MTX. No further abnormalities were seen in that study, and the authors concluded that neither administration of MTX nor JIA affected the lungs in their patients (13). Lung abnormalities in paediatric studies were reported in individual cases, while the larger studies did not show a pulmonary involvement. However, long-term PFTs were not previously studied in children with JIA under MTX treatment.

In our study DLCO showed reductions for some later measurements under MTX treatment. Although the lowest DLCO with a median of 87% was not very low, distinct limitations in diffusion capacity were found. Pelucchi *et al*. described significant reductions in MMEF and DLCO in a group of children with JIA without any difference between a MTX-treated group and a control group. The same study found better PFT results for a group of JIA-children without MTX treatment. The authors explained this with a more severe disease course in the MTX-treated group. Another study confirmed a DLCO decrease and found a reduction in pulmonary exercise capacity not due

to MTX (29). In contrast, the study of Knook *et al*. found increased DLCO values in children with JIA (30).

Our data showed a significant decrease for MMEF in the first years of MTX treatment compared to the initial values. This could argue for an obstructive lesion of the small airways. In contrast, after five years of MTX treatment we observed slowly increasing values, though not reaching significance levels, leading to final results higher than the initial values; all in all, there was no clear trend for these parameters. Pelucchi found similar results considering lowered exspiratory flows, but correlated to a higher index of disease activity, which suggested a disease effect rather than a side-effect of MTX (14). Knook *et al*. explained decreased MEF and FVC as an expression of muscle weakness due to the arthritis rather than direct pulmonary involvement of JIA (30).

FRC showed decreases by the end of our study which did not reach significance after Bonferroni transformation. We only had a small group for these final values which were all above average (>100%) and since a high FRC can be a sign of obstructed peripheral airways (31) the negative trend may be interpreted as an improvement of obstruction. Other values did not show significant changes compared to the initial values.

The paired tests of the whole group comparing the mean PFT values with the previous years' values showed a negative trend of DLCO and significant increases of FEV1 in two measurements which contradicted possible interpretations of obstructive illness.

Interstitial lung changes have been described in the systemic onset subgroup of JIA by Athreya and colleagues (32). Our analysis of possible influence of the subtype of JIA showed lower base values for DLCO in the group of oligoarticular arthritis. However, our subtype groups were small, the finding was not confirmed in later measurements or by another study.

Furthermore, we did not find a relevant correlation between cumulative MTX dose and changes in lung function values. The regression analysis showed no significant correlation, the values were widely spread and showed no comprehensible trend. Schmeling *et al*. and Pelucchi *et al*. also found no correlation between cumulative MTX dose and PFT results, albeit at 2 to 4 times lower total doses of MTX (13-14). Our study is the first to analyse the PFTs of MTX-treated children with JIA over a period of several years. Other studies performed either single PFTs or measured lung function twice over a period of no longer than one year. Our study documented the course of lung function in some children for more than ten years, and as a mean value we achieved more than 5 PFTs in a period of over 4 years.

Table III. Mean lung function values during the first 2 years of MTX treatment.

Time after onset of MTX (years)	VC in % mean / median (n. of patients)	DLCO in % mean / median (n. of patients)	MMEF in % mean / median (n. of patients)	FEV1 in % mean / median (n. of patients)
0	93.8 / 92.7 (37)	97.8 / 97 (13)	114.1 / 110 (31)	107.9 / 107 (37)
1	94.7 / 96 (42)	96.4 / 100.5 (24)	107.9 / 101 (41)	107.4 / 106 (41)
2	97.0 / 97.5 (48)	103.3 / 100 (24)	104.8 / 102 (47)	105 0 / 104 (46)

Our study has several limitations. Most importantly we could not include a control group or validate the use of the reference equation with a local population of paediatric subjects of similar age. As MTX is the therapeutic standard in severe cases of JIA, there was no group with a similar disease severity without MTX treatment. Our study was retrospective in design and we felt that assessing longitudinal development of pulmonary function in this cohort would allow detection of significant changes.

Furthermore, the interpretation of the last values in our data – especially for DLCO – is limited, as the number of patients performing PFTs decreased during long-term treatment. We could not always measure all values for each lung function test, as measurement methods of DLCO are more difficult to perform and demand a great deal of cooperation of the children. This is why more values were missing for DLCO than for spirometric values.

Due to too many missing values we could not use repeated measurement analysis for our study so we employed *t*-tests instead. We used Bonferroni correction to adjust significance to a meaningful level in the large number of tests performed. Because of the retrospective character of this study we could not analyse confounding factors such as smoking exposure, since this was not usually noted in our charts. Also, our subgroups of patients with different JIA subtypes were small, since this was a single centre study.

It has now become clear that the use of the old cross-sectionally obtained reference data may lead to misinterpretation of current data. Especially young school aged and prepubertal German children tend to be underdiagnosed when Zapletal equations are not used. As Z-scores do not exist for DLCO, we used the percentual reference values in order to provide for comparability. We may therefore have underestimated a deterioration of pulmonary function with long-term MTX treatment.

It is reassuring that diffusion capacity as a sensitive parameter for detecting interstitial pulmonary changes remained above the lower limit of 70% in all subjects who completed the test, except for one adolescent girl who had started smoking in the year prior to the final PFT.

Our study found no evidence for clinically relevant MTX-induced pulmonary damage. The small changes found could not be clearly discriminated from a possible pulmonary involvement of JIA. This supports the relative safety of MTX as basic treatment for severe cases of JIA. Overall however, we feel that more data on the long-term course of pulmonary function in patients with JIA treated with MTX are needed and will continue annual pulmonary function testing in patients at our centre.

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