

**LOW DOSE METHOTREXATE THERAPY
FOR PATIENTS WITH STEROID
DEPENDENT ASTHMA**

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Summary:

Severe asthma that is intractable to therapy may require long term or high dose steroid. Since steroid therapy is associated with a lot of side effects. Many therapeutic modalities had been studied; Methotrexate represents new therapeutic modality for treatment of patients with bronchial asthma. There are conflicting report regarding the role of methotrexate in management of pts with steroid dependent asthma.

The aim of this study was to investigate the steroid sparing activity and adverse effects of low dose weekly methotrexate (7.5mg /week) in pts with steroid dependent bronchial asthma

14patients were studied, 10 were female and 4 were male, their age range from 25-70years with mean age of 50.7 years (See Table1), whom had sever asthma, they were on high doses of steroid range from 15-45mg\day (average does of 28.8mg), and they are unable to discontinue steroid despite full bronchodilators therapy, or those whom were developing side effect of steroid were included in the study. Those pts were given 7.5mg\week methotrexate orally; they follow by repeated exam and investigations every 2 weeks for 1st 3month then monthly for 2 years.

This study show marked reduction in no. of admission to hospital, 73.5% reduction in the dose of steroid, and improvement of peak expiratory flow rates from average of 121.3 before treatment to 221.8 (p value less than 0.01). No serious side effect reported with this study in contrast with other studies using higher doses, only 2 pts developed gastroenteritis in one of them was severe and the treatment was stopped.

We conclude that methotrexate is an effective alternative and steroid sparing agent for pts with steroid dependent asthma, that low dose 7.5mg\week is more effective and associated with less side effect than higher doses.

Introduction:

Severe asthma that is intractable to therapy may require long term steroid, or the long term steroid by the patients for the relief they found with this type of treatment. However steroid therapy is associated with a lot of side effects. The inflammatory process underlying bronchial asthma is well established and attracted clinical interest in non-steroid anti-inflammatory form of treatment(2,3).

Although unproven it has been suggested that effective treatment of allergic inflammation may prevent long term complication of asthma and arrest deterioration in pulmonary function.

Methotrexate represent new therapeutic modality in-patients with bronchial Asthma. It has been used as immunosuppressing agent. And has a potent anti-inflammatory action. Its mechanism of action through competitive inhibition of dihydrofolate reductase reducing enzyme converting folic acid into tetrahydro-folate during the-S-phase of cell cycle. There are conflicting reports regarding the role of methotrexate in management of steroid dependent asthma, which were first reported at 1986.

The aim of this study was to investigate the steroid sparing activity and adverse effects of low dose weekly methotrexate (7.5mg) in severe steroid dependent bronchial asthma. The consent of the scientific committee of the medical department regarding the safety and ethical aspect of the study was taken.

Patients and method.

14 patients were studied, 10 were female and 4 were male age range from 25-70 years mean age 50.7 years (See Table 1), with severe asthma on high doses of steroid range from 15-45mg/day (average dose of 28.8mg), and they are unable to discontinue steroid despite with bronchodilators, (beta-agonist like salbutamol, and theophylline) nebulizer and systemic, and developing side effect of steroid, were included in the study. Three patients were excluded from the study, two of them because of non-compliance, and one of them because of severe gastroenteritis after methotrexate therapy. Full history regarding duration of asthma, types of treatment, doses of steroid, frequency of admission to hospital (emergency room and ward) before and after treatment with

methotrexate, physical examination was performed regarding severity and side effect of steroids, and to exclude liver diseases, investigations including peak expiratory flow rate (PEFR) complete blood picture (CBP), chest X Ray (CXR) liver function test (LFT) with 7.5mg/week of methotrexate orally, and repeated assessment and investigations done each two weeks orally, and repeated assessment and investigations done each two weeks for three months, then monthly to see the response and the effect of methotrexate on the liver and bone marrow.

Results:

Eleven patients completed the study, 8 pts were female, and 3 pts were male. (See Table 1) In all pts there was marked reduction in the number of admissions to the hospital (emergency room and ward) and 6 (54.5%) pts did not need further admission during period of the study. (See Tab II) The dose of steroid was significantly reduced during treatment with methotrexate, 6(54.5%) pts stopped taking steroids completely and 5(45.4%) pts tolerate reduction of the dose of steroids from mean of 38.75mg/day to 8.75mg/day, that's to say there were (78.5%) reduction in the dose of steroids. (See table III)

Table IV illustrate improvement in PEER after therapy, mean value was 121.8 before treatment, this was improved to 221.8 l/min after treatment. (P value less than 0.01).

Table V illustrates the side effects due to methotrexate therapy; 2(16.6) pts developed gastroenteritis, in one of them, it was severe so that the treatment stopped and the patient was excluded from the study. No serious side effects like liver damage or bone marrow suppression was occurred, but one patient develop increase level of liver enzyme, that was asymptomatic and was responded to with withdrawal of treatment. One patient develops hepatitis that was proved to be due to hepatitis B virus infection. This needed temporarily withdrawal of treatment.

Once the treatment was stopped for two weeks, many patients relapsed, so the duration of treatment is unknown and further studies needed to clarify this point.

Discussion:

This study show marked reduction in the dose of the steroid by using low dose methotrexate therapy in pt with steroid dependent asthma, this consistent with other studies that used higher doses (15-40mg/week). (7,8,9,10) This study also report less frequent side effect than other studies

with no evidence of bone marrow suppression or liver damage reported in this study (7,8,9,10), but this in contrast with the finding of Trigg who show no significant reduction in the dose of steroid after 70mg\week of methotrexate (11)

This may suggest that lower dose is more effective than higher dose methotrexate, this fact need further study to confirm and to explain the mechanism.

This study show marked reduction in the no. of admission to hospital, which is consistent with other studies (7,8,9,10)

Serious side effect, like bone marrow suppression, and hepatitis were not observed in our study, this consistent with other study (7,8,9,19)

We observed lower no. of side effect than other studies, this may be explained by the lowest dose of methotrexate used in this study .In fact we didn't come across any study that used this low dose at till the time of the study.

Conclusion:

We think that methotrexate is an effective alternative treatment for pts with steroid dependent asthma, and that low dose (7.5mg\week) is both effective and associated with fewer side effects, and may be even more effective than higher doses.

References:

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Table I show the pts characteristic, the dose of steroid the pts were on

Case no.	age	sex	Dose of steroid	Long acting steroid
1	60	M	35	+
2	62	M	20	+
3	45	F	30	+
4	45	F	40	-
5	48	F	45	+
6	47	F	30	+
7	35	F	15	-
8	48	F	30	+
9	52	F	15	+
10	56	M	45	+
<u>11</u>	49	F	30	+
12	40	F	30	+
<u>13</u>	37	M	20	+
<u>14</u>	42	F	15	-

Table II shows the duration of admission to emergency room or medical ward before and after treatment

CASE NO	Days of admission before treatment \month	Days of admission after treatment\month
1	8	-
2	20	-
3	20	1
4	20	-
5	12	10
6	18	2
7	12	-
8	28	1
9	12	-
10	12	-
12	11	1

Table III shows the steroid dose before and after treatment

Case No.	Dose of steroid before treatment	Dose of steroid after 6M of treatment
1	35	5
2	20	0
3	30	0
4	40	0
5	45	5
6	30	0
7	15	0
8	30	0
9	15	5
10	45	15
12	30	10
average	30.45	6.25

Table IV shows the PEFR before and after treatment

Case No.	PEFR before Rx	PEFR after Rx
1	110	180
2	150	250
3	110	200
4	150	250
5	100	140
6	120	190
7	150	250
8	110	300
9	120	240
10	120	180
12	100	160
Average	100	160

* P value less than 0.01
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