H.12 Methotrexate and risk factors for hepatotoxicity

H.12.1 Case Series

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>R. E. Ashton, G. H. Millward-Sadler, and J. E. White. Complications in methotrexate treatment of psoriasis with particular reference to liver fibrosis. J.Invest.Dermatol. 79 (4):229-232, 1982.

Ref ID: ASHTON1982</td>
<td>Observational: Retrospective case series</td>
<td>N: 38</td>
<td>Inclusion criteria: Patients taking MTX for psoriasis

Exclusion criteria: No follow-up biopsy, any signs of fibrosis on pre-treatment biopsy

<table>
<tr><th>Parameter</th><th>All (n=38)</th></tr>
<tr><td>Mean age – years</td><td>53</td></tr>
<tr><td>Gender M/F (%)</td><td>45/55</td></tr>
<tr><td>Cumulative MTX dose (MG), mean (range)</td><td>1928 (800-5500)</td></tr>
<tr><td>Duration of treatment (mean)</td><td>32.7 months</td></tr>
</table>
</td>
<td>Methotrexate:

Oral or intramuscular, up to 30 mg weekly, fortnightly or every 10 days

Mean total cumulative dose: 1928 mg (range: 800-5500 mg)

Histological techniques:

Biopsy by a right lateral technique; staining with H&E, Pearl’s Prussian blue, periodic acid-Schiff, orcein and non-gold-toned</td>
<td>Mean treatment duration: 32.7 weeks (range: 12-102 weeks)</td>
<td>Hepatotoxicity: fatty change (1-4 scale), fibrosis (mild: foci of reticulin proliferation scattered throughout the lobules or occasionally adjacent to portal tracts; moderate: more extensive enlargement of portal tracts seen by reticulin or presence of mature collagen; or severe:</td>
<td>Not mentioned</td>
</tr>
</table>

			<table><tr><td>Oral MTX</td><td>25</td></tr><tr><td>Intramuscular MTX</td><td>7</td></tr><tr><td>Oral then intramuscular route</td><td>6</td></tr><tr><td>Heavy alcohol intake (n)</td><td>8</td></tr></table>	reticulin (trichrome and Van Giesen preparations did not detect all fibrosis) Each biopsy initially assessed blind, further assessment included comparison with previous biopsies **Definitions** Alcohol intake 1. Occasional: <25 g/week 2. Moderate: 25-100 g/week 3. Heavy: >100 g/week **Prognostic factors:** alcohol, cumulative dose **Confounders** In those who developed hepatotoxicity: - duration of treatment mean 28.3 (range 16-38) months;		linking of portal tracts usually with extension of fibrous spurs) or **cirrhosis**	

				- mean MTX dose 1954 mg (range 1060-3375 mg); - average monthly dose 70 (range 41-112.5 mg) - mean age 57.4 (range 30-77) years			

Effect Size

Outcomes

Summary

- **Alcohol consumption is a risk factor for hepatotoxicity**
  - Of 8 heavy drinkers, 4 developed fibrosis or cirrhosis (50%); none of these had evidence of significant fibrosis on initial biopsy
  - Of 30 non-heavy drinkers 5 developed fibrosis or cirrhosis (16.7%)
  - Of the 9 patients who developed hepatotoxicity, 4 showed significant progression of fibrosis; of these 4 only one developed cirrhosis, and this patient had moderate/heavy alcohol intake
  - Of the 9 patients who developed hepatotoxicity, 3 showed classical features of alcoholic hepatitis
  - Of the 9 patients who developed hepatotoxicity 4 were heavy drinkers and 1 was a moderate drinker:

Age (years)	**Alcohol consumption**	**Route**	**Duration of treatment (months)**	**MTX dose (mg)**	
				Total	Mean/month
77	1	Oral	16	1060	66.2
56	3	Oral-IM	26	1300	50.0

66	1	Oral	31	1300	41.9
54	1	Oral	21	1367	65.1
66	2	Oral	36	1950	54.2
54	3	Oral	38	2080	54.7
56	3	Oral	30	2500	83.3
58	1	IM	26	2655	102.1
30	3	Oral	30	3375	112.5

Cumulative dose of MTX

Group	N	Total MTX dose (mg)	Mean dose per month
Total	38	1928	59.0
Fibrosis	9	1955	69.3
No fibrosis	29	1920	56.5

Author's conclusion

- MTX should be used only:
  - If satisfactory control of psoriasis cannot otherwise be achieved
  - In the absence of other hepatotoxic factors or any regular alcohol intake
  - If a pre-treatment biopsy does not show any pre-existing liver disease
  - If follow-up liver biopsies do not contra-indicate further therapy

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>M. J. Boffa, R. J. Chalmers, N. Y. Haboubi, M. Shomaf, and D. M. Mitchell. Sequential liver biopsies during long-term methotrexate treatment for psoriasis: a reappraisal. Br.J.Dermatol. 133 (5):774-778, 1995.

Ref ID: BOFFA199</td>
<td>Observational: Prospective case series</td>
<td>N: 49</td>
<td>Inclusion criteria: Long-term low-dose once weekly oral MTX for severe psoriasis; 2 or more biopsies

Exclusion criteria: Not stated

<table>
<tr><th>Parameter</th><th>Treated (n=49)</th></tr>
<tr><td>Mean age – years</td><td>54.8 (at last biopsy)</td></tr>
<tr><td>Gender M/F (%)</td><td>61/39</td></tr>
<tr><td>Cumulative MTX dose (mg), mean (range)</td><td>At first biopsy: 2743 (315-10,024 mg) plus mean of 2362 mg during FU</td></tr>
<tr><td>Duration of treatment weeks, mean (range)</td><td>275 (26-738)</td></tr>
</table>
</td>
<td>Methotrexate:

Long-term low-dose once weekly oral MTX (mean weekly dose 10.5 mg; range 3.9-19.2 mg)

Histological techniques:

Biopsy by Menghini technique; staining with H&E, periodic acid Schiff, Perl’s stain for iron, orcein, Hep B surface antigen and metallothionein, untoned reticulin and haematoxylin/picrosirius red

Prognostic factors: alcohol, cumulative dose

Confounders</td>
<td>10-years</td>
<td>Hepatotoxicity by histology score

Grading:
1. Normal histology
2. Steatosis alone (not abnormal)
3. Inflammation (±steatosis) without fibrosis
4. Fibrosis (±steatosis ± inflammation)
5. Cirrhosis</td>
<td>None stated</td>
</tr>
</table>

5				Histology score at initial biopsy, cumulative dose and mean weekly MTX dose presented (no multivariate analysis)			

Effect Size

Outcomes

Patient group	**First biopsy**		**Interval (weeks)**	**Last biopsy**						
	Histology score	Alcohol (units/week)		Age (years)	Alcohol (units/ week)	Change in alcohol intake (units/week)	Cumulative MTX dose (mg)	Duration of MTX	Histology score	Change in histology score
Improved (n=12)	3.4	8.2	301	55.0	3.7	-4.5	7082	613	1.9	-1.5
No change (n=28)	2.2	5.6	190	53.5	4.0	-1.6	4265	441	2.2	0
Deteriorated (n=9)	1.6	2.1	233	55.8	1.3	-0.8	5078	535	3.4	+1.8

Summary

- **Alcohol consumption not a risk factor for hepatotoxicity**
  - Histology score at end point greater in those with lowest alcohol consumption

- But, reduction in alcohol intake is associated with improved histology score
- No significant correlation between liver histology group (improved, no change or deteriorated) and cumulative MTX dose (r = -0.013; p = 0.46) or duration of treatment (r = -0.036013; p = 0.40)

Cumulative MTX dose not a risk factor for hepatotoxicity

- Change in histological group and the dose of methotrexate (cumulative at the time of the last biopsy or doses between biopsies) were not statistically significant (Spearman correlation coefficient = 0.11, p=0.23 and r = 0.23, p=0.06 respectively).
- At the last biopsy, cumulative dose and duration of treatment were also not correlated with the liver histology groups (r = -0.013, p=0.46 and r = -0.036, p=0.40 respectively).

Author's conclusion

- Although no correlation between stated alcohol consumption and likelihood of histological deterioration was demonstrated, alcohol restriction should be advised during long-term treatment with MTX because alcohol is a well-known hepatotoxin
- Liver biopsy near the start of treatment may be justified where there is doubt about previous alcohol consumption, to exclude hepatic pathology not apparent on enzyme tests

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>A. Nyfors. Liver biopsies from psoriatics related to methotrexate therapy. 3. Findings in post-methotrexate liver biopsies from 160 psoriatics. Acta Pathologica et Microbiologica Scandinavica - Section A, Pathology 85 (4):511-518, 1977.

Ref ID: NYFORS1977</td>
<td>Observational: Retrospective case series</td>
<td>N: 160 (92 in part A and 68 in part B)</td>
<td>Part A – single liver biopsies
Inclusion criteria: Patients who have had: severe psoriasis unresponsive to previous treatment; MTX therapy; one post-MTX liver biopsy >5 mm; willingness to co-operate

Part B – serial liver biopsies
Inclusion criteria: Patients who have had: severe psoriasis unresponsive to previous treatment; MTX therapy; at least 2 post-MTX liver biopsy >5 mm; willingness to co-operate

Exclusion criteria: none stated

<table>
<tr><th>Parameter</th><th>Part A (n=92)</th><th>Part B (n=68)</th></tr>
<tr><td>Mean age – years</td><td>57</td><td>57</td></tr>
<tr><td>Gender M/F (%)</td><td>50/50</td><td>49/51</td></tr>
<tr><td>Cumulative</td><td>2287 (</td><td>3940</td></tr>
</table>
</td>
<td>Methotrexate:

Part A – Single weekly oral 25-mg dose maximum in 23 patients; 69 had MTX therapy discontinued after clearing of psoriasis

Histological techniques: Biopsy by Menghini technique; staining with H&E and van Gieson; in cases of suspected fibrosis/cirrhosis a reticulin stain was also used

Definitions

Alcohol intake
1. Occasional
2. 1-3 drinks/week
3. 1-3 drinks/day
4. >3 drinks/day</td>
<td>Mean treatment duration: 52 months (range: 2-105 months)

Part B: mean time between biopsies = 19 months</td>
<td>Hepatotoxicity: cirrhosis (diffuse nodular regeneration with fibrosis, with lobular architecture disturbed), fibrosis (portal fibrosis: enlarged portal tracts with preservation of lobular architecture), mixed changes, non-specific reactive hepatitis, fatty change (all but cirrhosis graded as 0, +, ++, or +++)</td>
<td>Research grant from Lederle</td>
</tr>
</table>

			MTX dose (mg), mean (range)	50-5075)	(325-8355) at last biopsy	**Prognostic factors:** alcohol, obesity, cumulative dose **Confounders:** not controlled for but individual patient data presented on age, obesity, alcohol intake, cumulative MTX dose for those with fibrosis/cirrhosis			
			Duration of treatment (mean)	52 months	52 months				
			Previous jaundice	12	11				
			Gallstones	14	8				
			Diabetes	0	5				
			Obese	29	23				

Effect Size

Outcomes

Study	**Alcohol intake**	**Pre-MTX (n)**		**During MTX (n)**	
		Total	**Fibrosis or cirrhosis, n (%)**	**Total**	**Fibrosis or cirrhosis, n (%)**
Part A	Occasional	40	3 (7.5)	44	2 (4.5)
	1-3 a week	14	0 (0.0)	33	1 (3.0)
	1-3 a day	23	2 (8.7)	19	3(15.8)
	>3 a day	15	2 (13.3)	6	1(16.7)

Part B	Occasional	27	3 (11.1)	28	4 (14.3)
	1-3 a week	20	5 (25.0)	26	7 (26.9)
	1-3 a day	18	5 (27.8)	11	3 (27.3)
	>3 a day	3	1 (33.3)	3	0 (0.0)

Part A

- **Alcohol** intake significantly decreased in the group as a whole during MTX therapy ($p<0.01$), but was unchanged in the 7 patients who had cirrhosis or fibrosis
- When comparing the 13 patients with normal histology and the 7 with fibrosis or cirrhosis:
  - No significant difference between **total MTX dose** ($p<0.45$)
  - Those with hepatic damage were significantly older ($p<0.002$) and had consumed more **alcohol** during therapy ($p<0.016$)
  - No significant difference in the number of patients with **obesity**

Patients with cirrhosis or fibrosis

Age	**Obesity**	**Ethanol intake***		**Cumulative MTX dose (mg)**	**Diagnosis**
		Pre-MTX	**During MTX**		
75	0	3	3	1895	Fibrosis, moderate
79	0	1	1	305	Fibrosis, mild
63	+	3	3	1642	Fibrosis, mild
85	0	4	4	1612	Cirrhosis
59	0	1	1	2718	Fibrosis, mild
84	+	1	3	1015	Fibrosis, mild

54	0	4	2	2640	Fibrosis, mild
Mean: 71.3				Mean: 1689.6	

*1: occasionally; 2: 1-3 drinks a week; 3: 1-3 drinks a day; 4 >3 drinks a day

Part B

- **Alcohol** intake significantly decreased in the group as a whole during MTX therapy (p<0.01)
- When comparing the 9 patients with normal histology and 14 with cirrhosis:
  - No statistically significant difference between MTX **cumulative dose**: 3000 mg vs 3061mg (p=0.245)
  - Patients with cirrhosis had significantly higher **alcohol** intake during MTX therapy (p=0.041)
  - A significantly higher number of patients with cirrhosis were also **obese** (p=0.033) and were older (p=0.058)
- No significant correlation between histological subgroups with respect to sex of intake of hepatotoxic medicine

Patients with cirrhosis

Age	**Ethanol intake***		**Cumulative MTX dose (mg)**	
	Pre-MTX	**During MTX**	**First biopsy**	**Latest biopsy**
56	3	3	2994	4469
71	1	1	2378	2378
67	3	1	2510	2610
66	2	2	3260	3850
72	2	2	2500	2500
58	2	2	2345	2595

59	3	3	2205	2580
58	2	2	3408	3423
70	1	2	1755	1790
64	1	1	2748	5798
65	2	1	328	4065
60	4	2	325	325
61	3	2	3633	4045
66	3	3	2415	2430
Mean: 63.8			Mean: 2343.1	Mean: 3061.3

*1: occasionally; 2: 1-3 drinks a week; 3: 1-3 drinks a day; 4 >3 drinks a day

Summary

- **Alcohol consumption is a risk factor for hepatotoxicity**
  - A – Those who developed fibrosis or cirrhosis consumed statistically more alcohol during therapy than those with normal histology
  - B – Those who developed cirrhosis consumed statistically more alcohol during therapy than those with normal histology (p=0.041)

Author's conclusion

- The liver damage seen suggests a multifactorial aetiology produced by: MTX, alcohol, age, obesity and potentially hepatotoxic medicine

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>M. Newman, R. Auerbach, H. Feiner, R. S. Holzman, J. Shupack, P. Migdal, M. Culubret, P. Camuto, and H. Tobias. The role of liver biopsies in psoriatic patients receiving long-term methotrexate treatment. Improvement in liver abnormalities after cessation of treatment. Arch.Derm</td>
<td>Observational: Case series and within-group comparison

New York University Hospital and office records; all those undergoing biopsy 1968-1986</td>
<td>N: 168</td>
<td>Inclusion criteria: Patients who have diagnosed psoriasis unresponsive to previous treatment; liver biopsy before and/or during therapy with MTX

Exclusion criteria: none stated

<table>
<tr><th>Parameter</th><th>All (n=168)</th></tr>
<tr><td>Mean age (at biopsy) – years</td><td>47.7</td></tr>
<tr><td>Gender M/F (%)</td><td>52/48</td></tr>
<tr><td>Pre-MTX biopsy (%)</td><td>49%</td></tr>
<tr><td>Median monthly MTX dose before biopsy (range)</td><td>67.3 (7.5-205.6) mg</td></tr>
<tr><td>Duration of treatment (median)</td><td>48 months</td></tr>
</table>
</td>
<td>Methotrexate:

Most received oral administration in either a single weekly or a divided weekly dose

MTX treatment stopped when biopsy specimen was grade IIIB or greater

Histological techniques:

Biopsy by Menghini technique; fixed and embedded in paraffin; staining with H&E, reticulin and trichrome stains

Diagnosis made by blinded assessor

Definitions</td>
<td>Median treatment duration: 48 months (range: 1-218 months)</td>
<td>Hepatotoxicity: grading by Roenigk classification</td>
<td>Honors Research Program of New York State University School of Medicine; partial funding from Lederle Laboratories</td>
</tr>
</table>

atol. 125 (9):1218-1224, 1989. Ref ID: NEWMAN1989			IBD or gallbladder disease: 0 History of high alcohol intake: 14 (8 of whom received MTX) Diabetes: 16 Obese: 67 (40%)	**Obesity:** 40% increase above ideal body weight **High alcohol intake:** >200g pure alcohol (>14 drinks) per week **Moderate alcohol intake:** 1-7 fluid oz pure alcohol (2-14 drinks) **Prognostic factors:** alcohol, obesity, diabetes, cumulative dose **Confounders:** States univariate and bivariate analyses performed but combined factors for bivariate not specified in methods - Oral therapy less likely to result in abnormal biopsy independent of cumulative dose			
Effect Size							

Outcomes

Summary

Cumulative dose analysis: calculated the actuarial probability of a normal (grade I or II) biopsy as a function of cumulative MTX dose

The probability of a normal liver biopsy result dropped to below 50% when the cumulative dose of methotrexate was 3115 mg (for those who had a pre and post methotrexate biopsy).

Cumulative dose (mg)	Probability ±SE	N still at risk
Patients with paired biopsies before and after MTX (N=31)		
1000	0.88 ± 0.06	21
2000	0.65 ± 0.10	15
3000	0.51 ± 0.11	8
4000	0.25 ± 0.10	4
5000	0.13 ± 0.13	1
Patients without biopsies before MTX (N=137)		
1000	0.93 ± 0.03	62
2000	0.77 ± 0.05	41
3000	0.68 ± 0.06	33
4000	0.63 ± 0.07	25

5000	0.54 ± 0.07	18
6000	0.48 ± 0.08	15
7000	0.32 ± 0.09	6
8000	0.24 ± 0.09	3

Risk factor analysis performed on all patients (not all of whom had post-MTX data)

Alcohol

- No significant association between high or moderate alcohol consumption before MTX treatment (patients instructed to cease intake during therapy) and biopsy grade. Therefore, despite evidence that alcohol intake correlates with biopsy grade, a history of pre-treatment alcohol consumption may not.

Obesity

- Obesity increased the risk of hepatotoxicity
  - Significant association between biopsy grade and obesity in the MTX-treated group (but not in untreated; p=0.003)

Diabetes

- No association between diabetes and hepatotoxicity

Liver function tests

- Liver function tests were not predictive of liver histology findings

<table>
<tr><th>Reference</th><th>Study type and quality</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>R. Themido, M. Loureiro, M. Pecegueiro, Brandáo M, and M. C. Campos. Methotrexate hepatotoxicity in psoriatic patients submitted to long-term therapy. Acta Derm.Venereol. 72 (5):361-364, 1992.

Ref ID: THEMIDO1992</td>
<td>Case series

Department of Dermatology at Hospital de Santa Maria, Lisbon: review of mediccal records 1965-1990</td>
<td>N: 84 (51 with post-treatment biopsies)

Data on alcohol consumption only available for 29</td>
<td>Inclusion criteria: Psoriasis patients treated with MTX (or aminopterin)

Exclusion criteria: none stated

<table>
<tr><th>Parameter</th><th>All (n=84)</th></tr>
<tr><td>Mean age – years</td><td>49.5</td></tr>
<tr><td>Gender M/F (%)</td><td>75/25</td></tr>
<tr><td>Cumulative MTX dose (mg), mean (range)</td><td>200-10.650 mg</td></tr>
<tr><td>Use of potentially hepatotoxic drugs</td><td>49 (58.3%)</td></tr>
<tr><td>Hepatitis</td><td>4</td></tr>
<tr><td>Alcohol intake
High (>80 g/day)
Moderate (39-</td><td>
15/48
23/48</td></tr>
</table>
</td>
<td>Methotrexate:

Unclear dosing/administration schedule

Histological techniques:

Biopsy by Menghini technique with Jamshidi needle; staining with H&E, reticulin and trichrome stains

All biopsy specimens reviewed by the same pathologist and categorised according to Roenigk grading

Definitions

Alcohol intake

High (>80 g/day)

Moderate (40-60 g/day)

Mild (≤40g/day)</td>
<td>Median treatment duration: unclear</td>
<td>Hepatotoxicity: grading by Roenigk classification</td>
<td>None stated</td>
</tr>
</table>

			60 g/day) Mild (≤40g/day) 10/48 Diabetes 8 Psoriatic arithritis 30 Pustular psoriasis 8 Erythrodermic psoriasis 11	**Prognostic factors:** alcohol, diabetes, pre-existing liver disease, hepatitis, MTX dose **Risk factors** - Alcohol - Diabetes - Hepatitis - MTX dose			

Effect Size

Outcomes

N	Heaptotoxic or liver disease	Alcohol	Liver biopsy Pre-MTX	MTX dose (mg) at follow-up biopsy	Follow-up liver biopsy
1	Hepatitis	High	I	200	I
2		NA	II	1640	II
3	NSAID	Moderate	III	2910	III
4	Etetinate	High	III	10650	III
5		Mild	II	440	III
6		Moderate	II	4435	II
7		Moderate	I	2500	I
8		Moderate	III	3750	II
9	NSAID + diabetes	NA	II	1700	IV
10		NA	III	370	II
11	NSAID + hepatitis	NA	I	1380	III
12	NSAID + etretinate	NA	I	2435	III
13	NSAID + etretinate + azathioprine	NA	I	3900	III

14		NA	I	1060	II	
15	NSAID	Mild	I	2250	III	
16	NSAID	NA	I	690	I	
17	NSAID + corticosteroid	NA	III	3165	III	
18	Corticosteroid + hydantoin	High	I	1000	I	
19		Mild	I	3690	III	
20		Moderate	I	2500	III	
21	Etretinate		II	1400	III	
22	NSAID	Moderate	II	1700	IV	
23	NSAID	Mild	III	4700	III	
24	Corticosteroid	Moderate	II	3800	II	
25	NSAID + Diabetes	Moderate	III	4270	III	
26		High	II	1600	IV	
27	Etretinate + arsenic	Moderate	II	4000	II	
28		Mild	II	4280	III	
29		Moderate	II	7000	II	
30		Moderate	III	3500	III	
31	Hepatitis	Moderate	NA	3600	III	
32	Etretinaate	NA	NA	960	I	
33		High	NA	2400	I	
34	NSAID + corticosteroid	Moderate	NA	3000	IV	
35	NSAID + corticosteroid + diabetes	NA	NA	3145	III	
36	NSAID	NA	NA	4170	II	
37	NSAID + diabetes	High	NA	3000	IV	
38	NSAID	High	NA	6570	III	
39	NSAID + etretinate	NA	NA	1700	I	
40	Etretinate	NA	NA	4335	I	
41	NSAID	NA	NA	1500	II	
42	NSAID	NA	NA	1420	II	
43		Moderate	NA	3500	II	
44	NSAID	Moderate	NA	9360	III	

45	NSAID + etretinate + corticosteroid	NA	NA	7000	I
46	Etretinate	Moderate	NA	3000	I
47		Moderate	NA	4800	III
48	NSAID	NA	NA	7460	III
49	NSAID + etretinate	NA	NA	5400	I
50	NSAID	NA	NA	7340	III
51		NA	NA	1500	I

Summary

Methotrexate is valuable in the treatment of psoriasis but the risk/benefit must be considered on an individual basis, especially taking account of alcohol consumption

Reference	**Study type**	**Number of patients**	**Patient characteristics**	**Intervention**	**Length of follow-up**	**Outcome measures**	**Source of funding**
B. Collin, A. Vani, M. Ogboli, and C. Moss. Methotrexate treatment in 13 children with severe plaque psoriasis. Clin.Exp.D	**Observational:** Retrospective case series Birmingham Children's hospital; 1997-2007	N: 13	**Inclusion criteria:** Severe plaque psoriasis, recalcitrant to topical therapy, treated with MTX **Exclusion criteria:** none stated **Parameter** / **All (n=13)**	**Methotrexate**: Initial: 2.5-10 mg oral once weekly, increased to 7.5-20 mg according to response **Histological techniques:** Biopsy technique not	Mean treatment duration: 71 weeks	Treatment response Hepatotoxicity: disturbed liver function tests (aspartate transaminase, alanine transaminase)	None declared

<table>
<tr>
<td>ermatol. 34 (3):295-298, 2009.

Ref ID: COLLIN2009</td>
<td></td>
<td></td>
<td>
<table>
<tr><td>Mean age (years)

- presentation

- MTX initiation</td><td>
8.1

12.1</td></tr>
<tr><td>Gender M/F (%)</td><td>31/69</td></tr>
<tr><td>Family history of psoriasis (n)</td><td>11</td></tr>
<tr><td>Cumulative MTX dose (mg), mean (range)</td><td>993.1 (45.0-3637.5)</td></tr>
<tr><td>Duration of treatment (mean)</td><td>71 weeks</td></tr>
</table>

Full blood count, urea, electrolytes and creatinine and liver function tests were all normal at baseline
</td>
<td>stated; staining not defined

Prognostic factors: obesity

Confounders:

Treatment duration and cumulative dose presented for each patient</td>
<td></td>
<td></td>
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<td colspan="7">
Effect Size

Outcomes

Obesity may increase the risk of hepatotoxicity in children

3/13 cases were obese and 2 of these 3 had disturbed liver function tests (but no fibrosis on histology in one biopsied) vs 0 of the 10 non-obese children
Those with disturbed liver function tests had low cumulative doses of MTX (45 and 432.5 mg) compared with the mean (993.1 mg)

Author’s conclusion

MTX treatment is efficacious in severe childhood psoriasis and can be safe when closely monitored; obesity may be a relative contra-indication as associated NAFLD is likely to increase hepatotoxicity

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</table>

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<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>P. Rosenberg, H. Urwitz, A. Johanneson, A. M. Ros, J. Lindholm, N. Kinnman, and R. Hultcrantz. Psoriasis patients with diabetes type 2 are at high risk of developing liver fibrosis during methotrexate treatment. J.Hepatol. 46 (6):1111-1118, 2007.

Ref ID: ROSENBE</td>
<td>Observational: Retrospective case series

Karolinska Hospital or out-patient clinic (Stockholm); 1975-2003</td>
<td>N: 71</td>
<td>Inclusion criteria: At least one liver biopsy for monitoring during MTX treatment for psoriasis

Exclusion criteria: none stated

<table>
<tr><th>Parameter</th><th>No risk factors (n=45)</th><th>Risk factors (n=26)</th></tr>
<tr><td>Median age (years)
First biopsy
Start of treatment</td><td>
48
47</td><td>
52
49</td></tr>
<tr><td>Gender M/F (%)</td><td>68.9/31.1</td><td>57.7/42.3</td></tr>
<tr><td></td><td colspan="2">All (n=71)</td></tr>
<tr><td>Cumulative MTX dose, range</td><td colspan="2">0-17.2 g</td></tr>
<tr><td>Maximum</td><td colspan="2"></td></tr>
</table>
</td>
<td>Methotrexate:

Dosage schedule not stated

Histological techniques:

Biopsy technique not stated; staining not defined

Assessed by blinded evaluators

Prognostic factors: alcohol, diabetes, hepatitis B/C

Confounders: no apparent controlling in analyses (but survival analysis performed – fibrosis vs cumulative dose)</td>
<td>N/A</td>
<td>Hepatotoxicity: biopsy – inflammation, fibrosis, steatosis and ballooning according to Kleiner and Brunt; disturbed liver function tests (aspartate transaminase, alanine transaminase, gamma-glutamyl transferase)

Fibrosis staged as 0:none; 1:perisinusoidal or periportal; 2:perisinusoidal and periportal; 3: bridging fibrosis; 4: cirrhosis</td>
<td>Swedish Research Council, The Bengt Ihre Foundation and Karolinska Institutet</td>
</tr>
</table>

RG2007			weekly dose: ≤12.5 mg 15-20 mg >20mg 46 30 2	**Definitions:** **Alcohol overconsumption:** >30g daily **Diabetes mellitus**: fasting blood glucose >6.0 mmol/l or blood glucose >11 mmol 2 h after intake of 75 g glucose			

Effect Size

Outcomes

Summary

Data presented in Kaplan-Meier curves

Risk factor	**% developing fibrosis**		**p-value**	**% developing severe fibrosis**		**p-value**
	With risk factor	**Without risk factor**		**With risk factor**	**Without risk factor**	
Alcohol	100% (9/9)	66% (41/62)	-	22% (2/9)	18% (11/62)	0.599
Overweight	93% (14/15)			33% (5/15)		0.0132
Diabetes	100% (7/7)	52% (37/64)		57% (4/7)	14% (9/64)	0.003
Viral hepatitis	100% (3/3)			33% (1/3)		

Any of the above	96%	58%				

- Alcohol, overweight, diabetes and hepatitis increased the risk of fibrosis
- Risk for severe fibrosis dependent on the presence of at least one of the risk factors (p=0.002)
- Serum ALT, AST and γGT before treatment did not significantly predict hepatotoxicity

Author's conclusion

- There is a correlation between the presence of a risk factor for steato-hepatitis, particularly diabetes, and development of severe liver fibrosis in MTX-treated psoriasis patients, even when lower cumulative doses of MTX are given
- It is important to thoroughly assess risk factors for liver disease before and during MTX therapy

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>Anonymous. Psoriasis-liver-methotrexate interactions. Arch.Dermatol. 108 (1):36-42, 1973.

Ref ID: ANON1973</td>
<td>Observational:
Case series and within-group comparison

Multicentre</td>
<td>N: 550

(212 pre-MTX, 38 pre- and post-MTX, 356 post-MTX)</td>
<td>Inclusion criteria: Psoriatic patients with liver biopsies prior to or after MTX therapy

Exclusion criteria: none stated

<table>
<tr><th>Parameter</th><th>All (n=550)</th></tr>
<tr><td>Mean age (years)</td><td>46.9±15.4</td></tr>
<tr><td>Gender M/F (%)</td><td>57/43</td></tr>
<tr><td>Mean duration of psoriasis (years)</td><td>16.8±12.2</td></tr>
<tr><td>Mean cumulative dose MTX (g)</td><td>1.84</td></tr>
<tr><td>Diabetes (n)</td><td>33</td></tr>
<tr><td>Obesity (n)</td><td>108</td></tr>
<tr><td>Previous systemic therapy

Corticosteroids

Anti-metabolites</td><td>127</td></tr>
</table>
</td>
<td>Methotrexate:

4 main dosage schedules:
1. Daily oral administration of low doses interspersed with rest periods
2. Weekly oral administration of a single dose
3. Weekly intra-oral or intramuscular administration of a single dose
4. Weekly oral administration of divided dosage; 3-4 dosages over a 36-h periods weekly

Histological techniques:

Biopsy technique not stated; staining with H&E, trichrome or Van Gieson stains – graded by blinded pathologists</td>
<td>Mean treatment duration: 2.8±2.0 years</td>
<td>Hepatotoxicity: biopsy – fatty changes, nuclear variability, periportal inflammation, focal necrosis and fibrosis (all graded 1-4; not present-severe), cirrhosis (present,1, or absent, 2)

Disturbed liver function tests (BSP retention, SGOT, SGPT, alkaline phosphatase)</td>
<td>None stated</td>
</tr>
</table>

			<table><tr><td></td><td>111</td></tr><tr><td colspan="2">Alcohol intake</td></tr><tr><td>Non-drinkers</td><td>197</td></tr><tr><td>1-3 drinks/week</td><td>190</td></tr><tr><td>1-3 drinks/day</td><td>79</td></tr><tr><td>4+ drinks/day</td><td>68</td></tr></table>	Assessed by blinded evaluators **Prognostic factors:** alcohol, diabetes, obesity, cumulative dose **Confounders:** states matching for cumulative MTX dose and drug schedule in analysis of alcohol intake as a risk factor			

Effect Size

Outcomes

Summary

- In 338 post-MTX patients, increasing alcohol intake significantly correlated with presence of periportal inflammation, fibrosis and cirrhosis (even after correction for confounders)
- Obesity significantly correlated with presence of fatty metamorphosis
- Diabetes significantly correlated with presence of fatty metamorphosis and fibrosis

Morphologic variable	**Post MTX (mean histologic grade)**		
	No diabetes (n=360)	**With diabetes (n=24)**	**p-value (less than)**

Fatty metamorphosis	1.99	2.62	0.001
Nuclear variability	2.31	2.58	0.088
Periportal inflammation	1.70	2.00	0.086
Necrosis	1.92	2.00	0.550
Fibrosis	1.55	1.96	0.029
Cirrhosis	1.96	1.96	0.888

- In 38 patients with pre- and post-MTX biopsies, there were significant increases in fatty change and fibrosis
- Increasing BSP retention significantly associated with abnormal morphologic findings in both pre- and post-MTX patients ($p < 0.001$), but ~50% of patients with fibrosis or cirrhosis did not have elevated BSP
- Increasing total cumulative dose of MTX correlates with periportal inflammation ($p<0.001$), fibrosis ($p<0.001$) and cirrhosis ($p<0.002$)
- Daily oral dose schedule significantly increases nuclear variability, necrosis and fibrosis (independent of cumulative dose)
- No correlation of sex, extent of psoriasis or history of systemic corticosteroids on body surface with liver changes

Authors' conclusion

- Factors found to be significantly associated with histologic liver damage include increased alcohol intake, daily oral MTX doing, obesity and diabetes

Reference	Study type	Number of patients	Patient characteristics	Intervention	Length of follow-up	Outcome measures	Source of funding
M. A. Berends, J.	**Observational:**	N: 125	**Inclusion criteria:** Psoriatic patients receiving a weekly dosage	**Methotrexate**:	Median	Hepatotoxicit	None

<table>
<tr>
<td>Snoek, E. M. de Jong, P. C. van de Kerkhof, M. G. van Oijen, J. H. Van Krieken, and J. P. Drenth. Liver injury in long-term methotrexate treatment in psoriasis is relatively infrequent. Aliment.Pharmacol.Ther. 24 (5):805-811, 2006.

Ref ID: BERENDS 2006</td>
<td>Retrospective chart review (1976-2005)

Department of dermatology, Nijmegen Medical Centre, The Netherlands</td>
<td></td>
<td>of MTX who underwent at least one liver biopsy

Exclusion criteria: none stated

<table>
<tr><th>Parameter</th><th>All (n=125)</th></tr>
<tr><td>Mean age (years)</td><td>45.0</td></tr>
<tr><td>Gender M/F (%)</td><td>54/46</td></tr>
<tr><td>Cumulative dose MTX (mg), median (range)</td><td>2113 (180-20,235)</td></tr>
<tr><td>Diabetes (n)</td><td>9</td></tr>
<tr><td>Overweight</td><td>39</td></tr>
<tr><td colspan="2">Alcohol intake</td></tr>
<tr><td>Non-drinkers</td><td>64 (51.2%)</td></tr>
<tr><td>Any intake</td><td>61 (49%)</td></tr>
<tr><td>Excessive intake (>14 units/week)</td><td>11 (8%)</td></tr>
</table>
</td>
<td>Dosage schedule not stated

Histological techniques:

Biopsy by right intercostals approach, fixed with paraffin; staining with H&E, and von Gieson stains

Monitoring: complete blood cell count and liver chemistry every 4-8 weeks; follow-up liver biopsy after every 1.5 g MTX

Prognostic factors: alcohol, diabetes, obesity, cumulative dose

Confounders: cumulative MTX dosage did not affect the association</td>
<td>treatment duration: 228 weeks (range: 16-1763)</td>
<td>y: biopsy – graded according to Roenigk classification

Disturbed liver function tests (alanine transaminase, aspartate transaminase, alkaline phosphatase, γ-GT, total bilrubin)</td>
<td></td>
</tr>
<tr><td colspan="8"></td></tr>
</table>

Effect Size

Outcomes

Summary

Characteristics of patients with no histologic abnormalities during treatment:

Risk factor	**Patients without histologic injury (n=88)**
Alcohol	37
Alcohol >14 U/week	5
Diabetes	8

Association between liver function tests and higher Roenigk score:

- More patients with Roenigk ≥2 had g-GT above normal (OR: 1.80; 95%CI: 1.30-2.49)
- ASAT and ALAT concentrations did not correlate with Roenigk scores
- Patients with Roenigk ≥2 had significantly higher AP and ASAT compared with those with Roenigk = 1, but values were well within the normal range.

Association between risk factors and progression to higher Roenigk score:

- Obesity and/or diabetes led to progression to higher Roenigk score (>1) at earlier cumulative MTX dose, while alcohol did not
- Histologic progression to a Roenigk grade 2 or higher most likely when the methotrexate cumulative dose was between 1500mg-6000mg, with limited progression rate below 1500mg
- Progression to higher Roenigk score levelled out above 6000mg, and higher exposure was not associated with any further increase in liver damage.

Distribution of Roenigk score per risk factor

- In comparison to those without risk factors, those with overweight and/or diabetes had higher Roenigk scores, and there was a modest adverse effect of alcohol use on histological scores. The effect of these risk factors was most apparent when considering fibrosis and cirrhosis (grades 3a, 3b and 4):

Patients	**Roenigk n, (%)**						
	1	**2**	**3a**	**3b**	**4**	**Grades 2-4**	**p-value (Roenigk = 1 vs Roenigk >1)**
No risk factors (n=34)	29 (85%)	5 (15%)	0	0	0	15%	0.19
Overweight (n=38)	24 (63%)	10 (26%)	2 (5%)	1 (3%)	1 (3%)	37%	0.01
Alcohol use (n=62)	49 (79%)	8 (13%)	4 (6%)	0	1 (2%)	21%	0.67
Diabetes (n=9)	6 (67%)	1 (11%)	0	1 (11%)	1 (11%)	33%	0.42

Authors' conclusion

- At any given cumulative MTX dosage, patients with obesity and/or diabetes had a significantly worse liver histology compared with those without

risk factors

- Histological monitoring of MTX toxicity could be tailored to obese patients with or without diabetes
- Normal liver enzyme tests do not exclude progression of liver injury, although γ-GT levels may be an exception
- Liver histology deterioration is mostly seen at cumulative MTX doses of 1500-6000 mg.

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention/Prognostic factors</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>Lindsay K, et al. Liver fibrosis in patients with psoriasis and psoriatic arthritis on long-term, high cumulative dose methotrexate therapy. Rheumatology (Oxford).48(5):569-72, 2009

Ref ID: LINDSAY 2009</td>
<td>Observational:
Prospective case series

Leeds General Infirmary and Harrogate District Hospital (Oct 2002-May 2004)
•</td>
<td>N=54 (47 PsA – 32 of whom also had skin involvement)</td>
<td>Inclusion criteria:
Patients with PsA and psoriasis alone on long-term MTX therapy with full assessment of risk factors

Exclusion criteria:
None stated

<table>
<tr><th>Parameter</th><th>Mean ±SD</th><th>Range</th></tr>
<tr><td>Age, years</td><td>54.4±11</td><td>30–78</td></tr>
<tr><td>Disease duration, years</td><td>27.3±15</td><td>3–68</td></tr>
<tr><td>Skin disease duration, years</td><td>25.8±16</td><td>0–68</td></tr>
<tr><td>Arthritis duration, years</td><td>18.6±13</td><td>0–38</td></tr>
<tr><td>MTX duration,</td><td>6.59±4.22</td><td>1.33–30</td></tr>
</table>
</td>
<td>Methotrexate:
Schedule not stated, but 14 on subcutaneous MTX

Techniques:
• Liver biopsy under ultrasound guidance.
• Liver biopsy was performed if >1 g of MTX had been taken cumulatively in keeping with dermatology guidelines
• Two days prior to liver biopsy, patients were assessed clinically for signs of cutaneous and joint psoriasis, liver disease, obesity (BMI >30), diabetes for chronic renal impairment.

Prognostic factors:
Alcohol, diabetes (type I/II), obesity (BMI >30), cumulative dose</td>
<td>Not stated</td>
<td>Hepatic fibrosis detected by liver biopsy (grade 3 according to Roenigk classification)</td>
<td>None stated</td>
</tr>
</table>

			years			**Confounders:** not controlled for **Definitions:** Current or previous excess alcohol consumption was arbitrarily defined as greater than the recommended weekly amounts in the UK (14U of alcohol for women and 21U for men)			
			Weekly dose, mg	15.5±6.17	0–25				
			Cumulative dose, mg	4396±3140	1020–19657				
			Swollen joint count	2.51±3.69	0–12				
			Tender joint count	4.75±6.69	0–24				
			Leeds enthesial tender count	3.55±6.12	0–25				
			Diabetes	4					
			Obese	15					
			Previous excess alcohol intake	9					

Demographic data and methotrexate cumulative dose for patients having liver biopsy

Psoriatic disease characteristics

Ps or PsA	**Ps alone**	**PsA alone**	**Both PsA and Ps**	**PsA**

54	7	15	32	47

Effect Size

- Study showed a prevalence of mild and clinically insignificant fibrosis of 20% and no clinical liver disease or cirrhosis
- Post-liver abdominal pain within 2 hours was present in all to varying degree. This continued up to 24 hours in 21 patients

Significance of risk factors for hepatic fibrosis in long-term MTX treatment for psoriatic disease

	Median (Range)		Mann–Whitney U-test
Parameter	No fibrosis (n=43)	Fibrosis (n=11)	P
Age, years	53 (30–78)	59 (47–78)	NS
Units of alcohol/week	5 (0–40)	0 (0–42)	0.02
BMI	29 (19.3–40)	32.3 (26–46.6)	NS
Disease duration, years	28 (4–68)	24 (3–53)	NS
MTX dose, mg	15 (0.0–25.0)	15 (0.0–25.0)	NS
Duration on MTX, years	6.58 (1.3–30.0)	5.5 (2.0–10.3)	NS
Cumulative dose of MTX, mg	3839 (1020–19657)	3541 (1000–5908)	NS
Diabetic	3	3	NS
Renal impairment	3	1	NS
Number of risk factors[a]	0 (0–3)	1 (0–2)	0.01

[a]The number of risk factors for hepatotoxicity or liver fibrosis was calculated for each patient, with history of excessive alcohol consumption in the past or

current consumption over the recommended weekly amount counting as one risk factor; diabetes, renal impairment or obesity counting as others.

Authors' conclusion

- The sample size in this study is too small to demonstrate an effect of each individual risk factor. However, mild liver fibrosis appears to be more likely the greater the total number of pre-disposing factors for hepatotoxicity.
- None of the individual risk factors predicted the presence of early fibrosis (but the total number of risk factors was linked to the likelihood of fibrosis)
- No link was established between weekly dose, duration of treatment and cumulative dose of MTX

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>Malatjalian DA, et al. Methotrexate hepatotoxicity in psoriatics: report of 104 patients from Nova Scotia, with analysis of risks from obesity, diabetes and alcohol consumption during long term follow-up. Can J Gastroenterol.10(6):369-75. 1996

Ref ID: MALATJALIAN1996</td>
<td>Observational: Retrospective case series

Victoria General Hospital, Canada

1979-1990
•</td>
<td>104</td>
<td>Inclusion criteria: patients with psoriasis who had a pre-MTX liver biopsy and who had regular annual follow-up biopsies while on MTX

Exclusion criteria: Patients with psoriasis receiving MTX <1 year; patients for whom baseline or regular annual follow-up biopsies were not available for histological evaluation

<table>
<tr><th>Parameter</th><th>Mean ±SD</th></tr>
<tr><td>Age, years</td><td>42.8</td></tr>
<tr><td>Gender M/F (%)</td><td>57/43</td></tr>
<tr><td>Mean follow-up (years)</td><td>3.8</td></tr>
</table>
</td>
<td>Methotrexate:
MTX was given in 5–25 mg weekly doses, either as a single dose or as one-third of the dose every 12 h once per week
The estimated annual dose was 1–1.5 g
MTX was discontinued in patients with histological grades IIIB or IV

Histological techniques
Annual liver biopsies serially cut to 5 µm; had a minimum of three hematoxylin and eosin stained sections, one Masson’s trichrome stained section for connective tissue and one section stained for iron using Perls’ reaction; where appropriate, periodic acid Schiff ± pretreatment with diastase, Shikata orcein stain for hepatitis B virus surface antigen and van Gieson stain for connective tissue were done</td>
<td>Mean: 3.81 (range 1–11)</td>
<td>Histological grade of liver biopsies (according to the Roenigk classification)</td>
<td>Not stated</td>
</tr>
</table>

				Histological slides were reviewed unblinded by an author **Histological variables assessed** • Degree of steatosis • Amount and cellular distribution of stainable iron • Presence of centrilobular sinusoidal fibrosis • Amount of portal inflammation • Extent of portal fibrosis • Presence of periportal inflammation • Presence of periportal fibrosis • Presence of bridging fibrosis • Degree of hepatocellular nuclear availability • Presence and extent of hepatocellular degeneration • Presence and extent of hepatocellular necrosis • Presence and extent of lobular inflammation • Presence of cirrhosis **Definitions:**			

				Alcohol use (≤3 drinks/week) **Obesity: unclear definition** (28/35 obese had BMI ≥20% above normal) **Prognostic factors:** Obesity, diabetes, alcohol consumption, pre-existing disease **Confounders**: see results section			

Effect Size

Patients with risk factors: obesity, diabetes and alcohol consumption*

Risk factor	Females	Males	Total
Obesity	7	7	14
Diabetes	2	0	2
Alcohol consumption	4	16	20
Obesity + diabetes	5	0	5
Obesity + alcohol consumption	7	7	14
Diabetes + alcohol consumption	1	0	1
Diabetes + obesity + alcohol consumption	1	1	2

*No greater than three drinks per week (a drink constitutes 30 ml of hard liquor, 118 ml of wine or 355 ml of beer); patients advised against drinking

alcohol prior to MTX administration

Effect of initial (pre-MTX) biopsy grade on final biopsy grade

- 62.5% of patients with pre-MTX grade IIIA liver biopsies (5/8) progressed to bridging fibrosis or cirrhosis (compared with 3/16 (18.8%) from grade II and 16/80 (20.0%) from grade I)

Initial grade	**Final grade**				
	I	**II**	**IIIA**	**IIIB**	**IV**
I	37	10	17	14	2
II	3	2	8	3	0
IIIA	0	1	2	4	1

- Increased biopsy grade progression was associated with obesity; but not with alcohol and diabetes
- Progression to final grades IIIB and IV was associated with diabetes but not with obesity or alcohol use

Effect of diabetes, obesity and alcohol on disease progression and final grade of liver biopsies

Risk factor	Odds ratio	95%CI	P
Progression of liver pathology to higher grade			
Diabetes	2.07	0.35–12.35	0.42
Obesity	8.85	3.14–25.00	0.001
Alcohol	0.96	0.38–2.46	0.93
Progression of liver pathology to grades IIIB and IV			

Diabetes	5.68	1.34–24.39	0.02
Obesity	2.23	0.82–6.06	0.12
Alcohol	2.23	0.81–6.10	0.12

Confounders:

- Age and years of follow-up were initially used as covariates and found to be nonsignificant. They were therefore omitted from model producing final estimates
- None of the biopsies showed evidence of alcoholic hepatitis, chronic viral hepatitis or increased accumulation of sustainable iron
- There were no statistically significant differences in the initial biopsy grade by sex (p=0.67), or alcohol use status (p=0.82) but the obese (p=0.006) and the diabetes group (p=0.004) had a higher percentage of grades II and IIIA biopsies, and the initial biopsy grade was positively correlated with age (p=0.003)

Of note: there was unpredictable rapid histological deterioration in 3 patients associated with obesity, pre-exisiting mild hepatic fibrosis and re-exposure to MTX after MTX was discontinued because of high-grade fibrosis

Authors' conclusion

- Significant risk of severe hepatotoxicity is related to diabetes (p = 0.02) but not to obesity (p = 0.12) or occasional alcohol consumption (p = 0.12)
- There may be an increased risk for severe hepatotoxicity on MTX when a patient has pre-existing liver pathology

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>Tobias H and Auerbach R. Hepatotoxicity of long-term methotrexate therapy for psoriasis. Arch Intern Med. 132(3):391-6. 1973

Ref ID: Tobias 1973</td>
<td>Observational:
Case series

New York University Medical Centre

•</td>
<td>88 (69 treated with MTX)</td>
<td>Inclusion criteria:

Patients with severe psoriasis involving ≥80% of the body.

Exclusion criteria:

None stated
<table>
<tr><th>Parameter</th><th>All (n=88)</th></tr>
<tr><td>Average duration of psoriasis (years)</td><td>14.7</td></tr>
<tr><td>Average age (years)</td><td>48.3</td></tr>
<tr><td>Gender % (M/F)</td><td>48/40</td></tr>
</table>
No large difference between MTX-treated and untreated patients with regard to age and severity or duration of psoriasis</td>
<td>Methotrexate:
• Various dosing schedules (no further details)

Histological techniques
Menghini liver biopsy technique
Sections studied by hematoxylin-eosin and trichrome connective tissue strains

Biopsy findings were reviewed by two observers without knowledge of patient identity, history or treatment

Prognostic factors: diabetes, alcohol, obesity, cumulative dose

Alcohol use: categorised as 0, 28–85, or >88 g/week</td>
<td>Duration of treatment: 0.1-10 years</td>
<td>Hepatotoxicity

Biopsy findings: fibrosis, fatty change, portal inflammation, nuclear variability and focal necrosis (all graded 1-4; none to marked) and cirrhosis (present or absent)

Disturbed liver function tests (BSP, SGOT, SGPT, alkaline phosphatase, bilirubin)</td>
<td>Not stated</td>
</tr>
</table>

				Confounders: Total dose, duration of treatment, method of administration, alcohol intake and diabetes presented in individual patient data			

Effect Size

MTX-treated

Alcohol intake	**Hepatotoxicity**			
	Cirrhosis	**Marked-to-moderate fibrosis**	**Slight fibrosis**	**No fibrosis**
0 gm/week	2 (4.9%)	6 (14.6%)	6 (14.6%)	27 (65.9%)
28–85 gm/week	1 (20%)	4 (25.0%)	2 (12.5%)	9 (56.3%)
>85 gm/week	2 (16.7%)	3 (25.0%)	1 (8.3%)	6 (50.0%)

No MTX

Alcohol intake	**Hepatotoxicity**			
	Cirrhosis	**Marked-to-moderate fibrosis**	**Slight fibrosis**	**No fibrosis**
0 gm/week	0	3	4	7
28–85 gm/week	0	1	0	1
>85 gm/week	0	0	1	2

- Note that cirrhosis was only seen in patients who had received >2 g MTX

- **Fatty change –** increased alcohol consumption and diabetes were associated with increased fat
- **Portal inflammation –** associated with MTX dose

- **Nuclear variability –** associated with high MTX dose
- **Focal necrosis –** not associated with MTX dose or alcohol intake (appears to occur independent of therapy)
- Physical findings (e.g., hepatomegaly), and liver function tests were not dependable indicators of liver abnormalities

Cumulative dose

Biopsy grade	N	Mean cumulative dose (mg)
Cirrhosis	5	4140
Marked fibrosis	3	2933
Moderate fibrosis	10	2760
Slight fibrosis	9	2864
No fibrosis	42	1479

Authors' conclusion

- Fatty change and fibrosis occurred to a greater extent in MTX-untreated non-alcohol consuming psoriatic patients than in the normal population.
- Cirrhosis is related to MTX dose and alcohol intake may have an additive or synergistic effect
- Alcohol intake and diabetes are associated with fatty change; however, fatty infiltration alone is not considered to be a contra-indication for MTX therapy in the absence of considerable fibrosis and portal inflammation or cirrhosis
- Liver enzyme elevations may be transient and do not reflect changes in histopathology

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>A. Nyfors and H. Poulsen. Liver biopsies from psoriatics related to methotrexate therapy. 2. Findings before and after methotexate therapy in 88 patients. A blind study. Acta Pathol.Microbiol.Scand.[A]. 84 (3):262-270, 1976.

Ref ID: NYFORS1976</td>
<td>Case series
•</td>
<td>N: 88</td>
<td>Inclusion criteria:
Patients who have had: typical and severe psoriasis unresponsive to previous treatment; at least 2 liver biopsies, including an initial one; willingness to co-operate; no evidence of cirrhosis or fibrosis in pre-MTX biopsy; MTX given in a single, weekly, oral dose of 25 mg maximum

Exclusion criteria:

None stated

Note that patients were warned to avoid alcohol and not to take acetylsalicyclic acid-containing analgesics, barbiturates, thiazides, sulphonamides and other possible hepatotoxic medications
<table>
<tr><th>Parameter</th><th>All (n=88)</th></tr>
<tr><td>Mean duration of MTX therapy</td><td>26 (2-72) months</td></tr>
</table>
</td>
<td>Methotrexate:

Therapy usually started within 2 days of pre-MTX biopsy with initial oral dose of 25 mg

Single, weekly, oral dose of 25 mg maximum

Histological techniques
Menghini liver biopsy technique

Staining not mentioned

Histological evaluation was performed blindly to treatment period (Pre- or post-) and biopsies from other skin diseases were intermingled

Prognostic factors: alcohol, pre-existing liver disease, cumulative dose

Confounders:</td>
<td>Average duration of treatment 26 months</td>
<td>Hepatotoxicity

Biopsy findings: Hepatotoxicity: cirrhosis (diffuse nodular regeneration with fibrosis, with lobular architecture disturbed), fibrosis (portal fibrosis: enlarged portal tracts with preservation of lobular architecture), mixed changes, non-specific reactive hepatitis, fatty change</td>
<td>Not stated</td>
</tr>
</table>

			Mean cumulative MTX dose at time of last biopsy (mg): 1733 (175-4590) Mean age (years): 50 (range: 21-78) Gender % (M/F): 47.7/52.3 Potentially hepatotoxic medicine history (n): 25 Jaundice history (n): 13 Gall stones history (n): 9 Diabetes mellitus (n): 2 Obese (n): 28	Multivariate analysis including: chief histological diagnoses of pre-MTX liver biopsy, MTX cumulative dose, admitted alcohol intake during MTX therapy, age and obesity (but not clear if these confounders were controlled for when assessing the impact of individual risk factors)		(all but cirrhosis graded as 0, +, ++, or +++) Liver function tests (SGOT, alkaline phosphatase, bilirubin, gamma-globulin, creatinine)	
Effect Size **Pre-existing liver disease**							

Laboratory tests	Number of abnormal tests		
	2 days before first biopsy	**During MTX therapy (number of patients)**	**2 days before latest biopsy**
Serum aspartate aminotransferase	2	60	4
Serum bilirubin	0	2	1
Alkaline phosphatase	0	9	4
Serum gamma globulin	32	73	48

Biopsy diagnosis (pre-MTX)	Post-MTX diagnosis				
	Cirrhosis/fibrosis	Mixed changes*	Non-specific reactive hepatitis	Fatty change	Normal
Cirrhosis/fibrosis	0	0	0	0	0
Mixed changes[a]	3	0	0	0	0
Non-specific reactive hepatitis	1	1	2	2	0*
Fatty change	4	3	0	23	2*
Normal	3	0	6	12	26

[a]Mixed changes = on-specific reactive hepatitis and fatty change

*$p<0.05$

- **No significant difference between development of increased histological changes from normal or abnormal pre-MTX biopsies;** although, cirrhosis and fibrosis developed more frequently in patients with abnormal (8/41) than with normal (3/47) pre-MTX biopsies (p = 0.062)

Alcohol intake

Alcohol intake	Pre-MTX (n)		During MTX (n)	
	Total	**With fibrosis/cirrhosis, n (%)**	**Total**	**With fibrosis/cirrhosis, n (%)**
Occasional	46	4 (8.7)	56	6 (10.7)
1-3 a week	12	2 (16.7)	23	3 (13.0)
1-3 a day	22	2 (9.1)	6	1 (16.7)
>3 a day	8	3 (37.5)	3	1 (33.3)

- The 11 patients who developed fibrosis or cirrhosis did not have significantly higher alcohol intake during therapy (p>0.05) or significantly higher cumulative dose MTX (p = 0.19) than the 28 whose liver pathology remained normal
- The three subjects who had cirrhosis diagnosed within the first 3 years of MTX therapy had relatively low cumulative MTX doses but later admitted to an intake of >4 alcoholic drinks a day; therefore, alcohol consumption may contribute to the development of cirrhosis

	Chief histologic diagnosis		**Time between biopsies (years)**	**Age (years)**	**Ethanol intake**		**MTX total dose (mg)**	**SGOT at last biopsy**
	Pre-MTX	Post-MTX			Before MTX	During MTX		
1	Moderate fatty change	Cirrhosis	1.5	44	d	b	925	Elevated
2	Mild mixed changes	Cirrhosis	2.2	56	d	b	1395	Normal
3	Normal	Cirrhosis	2.3	71	b	c	1405	Elevated
4	Moderate fatty change	Cirrhosis	3.3	57	a	a	3010	Normal

5	Mild fatty change	Cirrhosis	4.8	68	c	b	2253	Elevated
6	Mild mixed changes	Possible cirrhosis	2.0	50	d	d	525	Normal
7	Mild non-specific reactive hepatitis	Fibrosis	3.5	46	a	a	3588	Normal
8	Normal	Fibrosis	3.7	71	a	a	845	Normal
9	Mild fatty change	Fibrosis	3.8	62	a	a	2819	Normal
10	Moderate mixed changes	Fibrosis	4.0	53	c	a	2165	Normal
11	Normal	Fibrosis	4.5	52	b	a	4590	Normal

Ethanol intake – a: occasionally; b: 1-3 drinks a week; c: 1-3 drinks a day; d: more than 3 drinks a day

Cumulative methotrexate dose is not a risk factor for hepatotoxicity

- No significant correlation between the cumulative methotrexate dose and the number of pathological post methotrexate liver biopsies.
- No significant difference in mean cumulative does between the 11 who developed fibrosis or cirrhosis and those whose liver histology remained normal ($p = 0.19$)

Combination risk factors

- Highly statistically significantly more frequent development of cirrhosis or fibrosis in patients with combinations of the following: pathological pre-MTX liver histology, high total MTX dose, daily alcoholic intake during MTX therapy, advanced age and obesity ($p<0.001$)

Authors' conclusion

- There was a statistically significant increase in the number of pathological findings in liver biopsies during MTX therapy
- Individually, none of the following risk factors (cumulative MTX dose, duration of MTX therapy, admitted alcohol intake during MTX therapy or

obesity) were significantly correlated with increasing liver changes

- There was a highly statistically significant association between the number of patients with fibrosis or cirrhosis and the following factors grouped together: pathological pre-MTX liver histology, high MTX dose, regular daily alcohol intake during MTYX therapy, advanced age and obesity
- Tendency for cirrhosis and fibrosis to develop more frequently in patient swith pathological pre-MTX biopsies (p = 0.062)

Reference	Study type	Number of patients	Patient characteristics	Intervention	Length of follow-up	Outcome measures	Source of funding
G. T. O'Connor, E. M. Olmstead, K. Zug, R. D. Baughman, J. R. Beck, J. L. Dunn, P. Seal, and J. F. Lewandowski. Detection of hepatotoxicity associated with methotrexate therapy for psoriasis. Arch.Dermatol. 125 (9):1209-1217, 1989. Ref ID: OCONNOR 1989	**Observational:** Retrospective case series Dartmouth-Hitchcock Medical Centre, USA	N: 78	**Inclusion criteria:** Psoriasis patients who had undergone biopsy associated with MTX therapy **Exclusion criteria:** Not stated No baseline data presented	**Methotrexate**: Dosing schedules not stated **Histological techniques:** Biopsy by Menghini technique; staining with H&E, and Masson trichrome **Prognostic factors:** alcohol, obesity **Confounders** Logistic regression analysis controlling for confounders performed to compare liver function tests with biopsy results Age, gender, obesity, alcohol use, cholecystitis also assessed	N/A	Hepatotoxicity by biopsy: graded by the Roenigk classification by blinded assessor Liver function tests: total bilirubin, aminotransferase, alkaline phosphatase	None stated

Effect Size

Outcomes

Summary

Data from those not known to have abnormal pre-treatment liver biopsy specimen

Variable	**Liver biopsy specimen results after treatment by grade, % (95% CI)**		
	I	**II**	**III-IV**
BMI	30.5 (45.8-51.8)	34.1 (29.7-38.6)	28.3 (25.7-30.9)
Alcohol consumption (% >1 drink/day)	17.6 (8.4-30.9)	16.7 (2.1-48.4)	11.1 (1.4-34.7)

- Alcohol consumption and obesity showed no significant association with abnormal findings from liver biopsy post-MTX
- Patient age and history of cholecystitis significantly positively associated with biopsy grade III or IV
- Abnormal liver function tests and biopsy specimen grade III or IV significantly correlated

Test	**Association of abnormal LFT and biopsy specimen grade III or IV**					
	Crude analysis			**Adjusted analysis (age and history of cholecystitis)**		
	OR	**X^2**	**p-value**	**OR**	**X^2**	**p-value**
AST	4.7	7.98	0.005	14.7	12.83	<0.001
ALP	3.5	5.99	0.014	2.1	1.58	0.209

TB	2.2	0.69	0.406	5.1	2.38	0.123
AST or ALP	6.4	10.50	0.001	5.5	6.78	0.009
AST, ALP or total bilrubin	8.4	12.27	<0.001	14.7	8.00	0.005

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>H. H. Roenigk, Jr., W. F. Bergfeld, R. St Jacques, F. J. Owens, and W. A. Hawk. Hepatotoxicity of methotrexate in the treatment of psoriasis. Arch.Dermatol. 103 (3):250-261, 1971.

Ref ID: ROENIGK 1971</td>
<td>Observational: Retrospective case series</td>
<td>N: 50 (37 treated)</td>
<td>Inclusion criteria: psoriasis patients with at least one liver biopsy

Exclusion criteria: Not stated

<table>
<tr><th>Parameter</th><th>All (n=50)</th></tr>
<tr><td>Mean age – years</td><td>Pre-MTX group: 40

Post-MTX group: 45</td></tr>
<tr><td>Gender M/F (%)</td><td>56.8/43.2</td></tr>
<tr><td>Cumulative MTX dose (mg), mean (range)</td><td>Range: 25-10,000 mg</td></tr>
</table>
</td>
<td>Methotrexate:

Dosing usually 25 mg/week orally

Histological techniques:

Biopsy with Menghini technique; staining with H&E, Masson’s trichrome

Specimens reviewed by blinded assessor

Definitions

Alcohol intake

0 No intake

1+ One drink/week (beer or hard liquor)

2+ One drink per day (beer or hard liquor)</td>
<td>N/A</td>
<td>Hepatotoxicity by biopsy: fatty infiltration, hepatocellular damage, anisonucleosis, periportal inflammatory infiltrate, nuclear glyconeogenesis, fibrosis or cirrhosis

Grading: 1 (normal); 2 (mild fatty infiltration); 3 (moderate-to-severe fatty infiltration, anisonnucleosis, nuclear changes, glycogenosis); 4 (periportal inflammation, early fibrosis); 5 (cirrhosis)</td>
<td>None stated</td>
</tr>
</table>

				3+ More than one drink/day (beer or hard liquor; but <1/5 of liquor) 4+ One or more pints of hard liquor/day **Prognostic factors:** alcohol, obesity, diabetes, cumulative dose **Confounders** Alcohol, MTX dose, MTX duration, obesity, diabetes (no multivariate analysis or adjustment but data presented for individual patients) pre-MTX data not available for all		Liver function tests: bilirubin, alkaline phosphatase, SGOT, SGPT, LDH, total proteins	

Effect Size

Outcomes

Incidence of abnormal liver results:

- 7/13 (53.8%) pre-MTX patients

- 29/37 (78.4%) post-MTX patients

Post-MTX group – risk factors:

- AGE: Those with abnormal liver biopsy results were significantly (mean 15 years) older than those with normal results (this difference was only 5 years in the pre-MTX group)
- DIABETES AND OBESITY: of 6 diabetics 5 had liver damage (mild-to-severe fatty change, plus early fibrosis in two), but all of these 5 were also obese and had relatively high cumulative MTX dose (2500-5000 mg); compared with the one diabetic who didn't develop liver damage, who was not obese and not a heaver drinker and had received only 50 mg MTX

Obesity	**Liver biopsy classification (%)**				
	1	**2**	**3**	**4**	**5**
No	26.3	36.8	21.1	0.0	15.8
Yes	11.1	22.2	38.9	16.7	11.1

Obesity level	**Liver biopsy classification (n)**				
	1	**2**	**3**	**4**	**5**
0	5	7	4	0	3
1	2	2	3	3	1
2	0	1	3	0	1
3	0	1	1	0	0

Diabetes	**Liver biopsy classification (%)**

	1	2	3	4	5
No	19.4	35.5	25.8	6.5	12.9
Yes	16.7	0.0	50.0	16.7	16.7

Diabetes level	Liver biopsy classification (n)				
	1	2	3	4	5
0	6	11	8	2	4
+	1	0	1	1	1
1+	0	0	2	0	0

ALCOHOL: poor correlation between the severity of abnormality on liver biopsy and level of alcohol consumption

Alcohol intake	Liver biopsy classification (n)				
	1	2	3	4	5
0	5	3	2	2	2
1+	2	3	6	0	2
2+	1	5	1	1	1
3+	0	1	0	0	0
4+	0	1	2	0	1

Alcohol intake	Liver biopsy classification (%)

	1	2	3	4	5
0,1+ (minimal-to-non drinkers)	25.9	22.2	29.6	7.4	14.8
2+-4+ (moderate-to-heavy drinkers)	7.1	50.0	21.4	7.1	14.3

- 21% of moderate-to-heavy drinkers developed cirrhosis vs 9% of minimal-to-non-drinkers (plus 9% with early fibrosis)
- Correlation between level of alcohol consumption and liver biopsy results:

Category	**Liver biopsy**	
	Abnormal	**Normal**
Minimal to non drinkers	17 (73.9%)	6 (26.1%)
Moderate to heavy drinkers	13 (92.9%)	1 (7.1%)

- Poor correlation between liver function tests and liver biopsy grade
- No close correlation between total MTX dose and severity of liver damage
- 6 post-MTX patients developed cirrhosis:

Case	**Risk factors**					
	Excessive alcohol	**Obesity**	**Diabetes**	**Age (years)**	**MTX cumulative dose (mg)**	**Other**
1	Yes	No	No	50	5000	
5	No	No	No	34	875	
24	Yes	No	No	16	600	Heroin and other addictive drug use; infectious hepatitis

27	Yes	Yes	Yes	56	5000	
31	No	Yes		50	260	
34	Yes	Yes	Yes	47	2520	

Cumulative methotrexate dose is not a risk factor for hepatotoxicity

- No close correlation between the cumulative methotrexate dose and the severity of liver damage.
- Mean cumulative dose at time of biopsies showing fibrosis or cirrhosis (n= 8): 2056 mg vs 2037 mg at time of biopsies graded as no fibrosis (n=33)

Author's conclusion

- Increased alcohol consumption may not necessarily be an additive risk in possible hepatotoxicity from MTX
- The obese, diabetic patient with psoriasis who receives MTX seems to acquire severe hepatic damage

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>U. Wollina, K. Stander, and U. Barta. Toxicity of methotrexate treatment in psoriasis and psoriatic arthritis--short- and long-term toxicity in 104 patients. Clin.Rheumatol. 20 (6):406-410, 2001.

Ref ID: WOLLINA 2001</td>
<td>Observational: Retrospective case series

Data from patient files (department of dermatology and allergology) in a single hospital in Germany</td>
<td>N: 104</td>
<td>Inclusion criteria: patients (from Oct 1968 to Oct 1998) with psoriasis or psoriatic arthritis and had MTX treatment.

Exclusion criteria: Not stated

<table>
<tr><th>Parameter</th><th>Total (N=104)</th></tr>
<tr><td>Mean age – years</td><td>27.7 years (SD 15.1)</td></tr>
<tr><td>Gender, male (%)</td><td>60 (58)</td></tr>
<tr><td>Psoriatic arthritis, N (%)</td><td>81 (77.9)</td></tr>
<tr><td>Extensive and /or recalcitrant psoriasis vulgaris, N (%)</td><td>15 (14.4)</td></tr>
<tr><td>Pustular psoriasis, N (%)</td><td>6 (5.8)</td></tr>
<tr><td>erythrodermic form, N (%)</td><td>2 (1.9)</td></tr>
</table>
</td>
<td>Methotrexate:

MTX was given once a week in an individualised dosage (7.5 to 40 mg iv or po) followed by 15 mg folate po the next day

2 groups:
- ≤2000 mg (N=23)
- >2000 mg (N=81)

This cut-off dose was chosen because from literature hepatic ADRs seem to be more common above 1500-2500 mg MTX.

Prognostic factors: cumulative dose

Confounders: not controlled for</td>
<td>N/A</td>
<td>Serum enzymes increase: ASAT, ALAT, γ-GT

Short-term toxicity: any side-effect within 90 days of starting MTX therapy

Long-term toxicity; any side-effect after this time.

Severity of ADRs were classified according to the CTC (common toxicity criteria): ranges from 0 (absent) to 4 (very severe, with the need for additional interventions)</td>
<td>Not stated</td>
</tr>
</table>

Effect Size

Outcomes

- within 90 days of initiating MTX Tx, 4 patients stopped Tx because of grade 2 side-effects or Tx failure.

Outcome measure	MTX ≤2000 mg (N=23)	MTX >2000 mg (N=81)	Difference, p-value
Serum enzyme increase: Total ASAT ALAT γ-GT	7 (35%) 6 (30%) 6 (30%) 1 (5%)	42 (52%) 40 (49%) 42 (52%) 9 (11%)	0.216 - - -
Serum enzyme increase >2.5 x ULN: Total ASAT ALAT γ-GT	6 (30%) 5 (22%) 5 (22%) 1 (5%)	19 (23%) 17 (21%) 19 (23%) 5 (6%)	
Serum enzyme increase >5 x ULN: Total	1 (5%)	5 (6%)	0.888
Liver changes Total Steatosis hepatis (by sonography) Liver cirrhosis (by biopsy)	3 (15%) 3 (15%) 0 (0%)	27 (33%) 26 (32%) 1 (1.2%)	0.102 - -

Note: biopsy only performed in 12 patients with sonographically confirmed steatosis hepatis (not even all those with this diagnosis)

Author's conclusion

- Liver changes and serum enzyme level increases were not significantly more frequent in the higher cumulative dose group

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention/Prognostic factors</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>R. J. van Dooren-Greebe, A. L. Kuijpers, J. Mulder, T. de Boo, and P. C. van de Kerkhof. Methotrexate revisited: effects of long-term treatment in psoriasis. Br.J.Dermatol. 130 (2):204-210, 1994.

Ref ID: VAN DOOREN-GREEBE 1994</td>
<td>Observational: Retrospective case series

Patient records from a single hospital in The Netherlands (Aug 1970 to July 1992)</td>
<td>N=113

(N=25 still taking MTX at end of the study)

Tx discontinued in 71 cases and 17 patients were lost to follow-up. N=2 patients died during MTX therapy (carcinoma and MI)</td>
<td>Inclusion criteria:

Patients with psoriasis treated with MTX. The indication for MTX therapy was severe psoriasis unresponsive to local therapy, photo(chemo)therapy or oral retinoids.

Exclusion criteria: Contraindications to therapy; people with cytopenia, abnormal liver function tests, infectious diseases, receiving concomitant medication which might interact with MTX, pregnant women or those wishing to become pregnant (and male partners of those wishing to become pregnant)

<table>
<tr><th>Parameter</th><th>Mean</th><th>Range</th></tr>
<tr><td>Age, years</td><td>45.5</td><td>17–81</td></tr>
<tr><td>Gender, male N</td><td>66</td><td>-</td></tr>
<tr><td>Recalcitrant psoriasis vulgaris, N</td><td>95 (84%)</td><td>-</td></tr>
</table>
</td>
<td>Methotrexate:

Mean cumulative dose: 4803 mg (range 90 mg to 16580 mg).

Weekly dosage did not exceed 15 mg in any patient.

Oral MTX: Tx started 3 x 5 mg/week or 3 x 2.5 mg/week (from 1986 onwards), and thereafter gradual dose adjustments were made until a satisfactory minimum maintenance level was reached. Maximum dosage was 15 mg/week.

Techniques:
• From 1983 onwards policy to perform liver biopsies before Tx or during the first 3 months of Tx, and after every 1.5 g of MTX.

In N=108 of the patients,</td>
<td>Mean duration of therapy: 8 years, 11 months (range 8 weeks to 20 years)</td>
<td>liver biopsy features, liver function tests, adverse events</td>
<td>None stated</td>
</tr>
</table>

			erythrodermic psoriasis, N: 1 (9%) - generalised pustular psoriasis, N: 2 (2%) - annular pustular psoriasis, N: 1 (1%) - Concomitant Tx (N) Topical CS: 105 - Short contact dithranol (home Tx): 15 - coal tar products: 10 -	concomitant Tx was intermittently given in limited amounts **Histological techniques:** Biopsy method unclear Biopsy graded according to Roenigk classification **Prognostic factors:** cumulative dose **Confounders**: not controlled for			

Effect Size

Outcome measure	**N (%)**
Abnormal liver function tests	37 (33)
Liver biopsy classification	
0 (not evaluable)	2 (4)
I (normal histology / minimal disturbances)	35 (62)
II (moderate to severe fatty infiltration)	9 (17)
	6 (11)
	1 (2)

IIIA (mild portal fibrosis) IIIB (moderate to severe portal fibrosis) IV (cirrhosis) Total	2 (4) 55 (100)

- Analysis showed that there was no clear relation between liver biopsy classification and cumulative dose of MTX or duration of therapy (data shown on a graph)

Cumulative dose (mg)	**Biopsy grade**				
	I N=30	**II N=9**	**IIIA N=6**	**IIIB N=1**	**IV N=2**
0-2000	7 (23.3%)	1 (11.1%)	0	0	1 (50%)
2001-4000	5 (16.7%)	4 (44.4%)	3 (50%)	1 (100%)	0
4001-6000	7 (23.3%)	2 (22.2%)	2 (33.3%)	0	0
6001-8000	5 (16.7%)	1 (11.1%)	1 (16.7%)	0	0
8001-10000	6 (20.0%)	1 (11.1%)	0	0	0
10,001-12,000	0	0	0	0	1 (50%)

However, in the high dose group (>1.5g): 32/40 (80%) had grades I-II and 8/40 (20%) had grades IIIA-IV while in the low dose group (≤1.5g): 7/8 (87.5%) had grades I-II and 1/8 (12.5%) had grades IIIA-IV

Authors' conclusion

- Low dose MTX (≤ 15 mg/week) is a relatively safe therapy for severe psoriasis, if patients are carefully selected beforehand and regular monitoring of side-effects and drug interactions are performed during therapy
- A liver biopsy during the first 3 months of Tx, and subsequently after each 1.5 mg of MTX, should be part of the Tx protocol, until equally reliable non-invasive screening methods for liver damage are developed.

Reference	Study type	Number of patients	Patient characteristics	Intervention/Prognostic factors	Length of follow-up	Outcome measures	Source of funding
S. Khan, D. Subedi, and M. M. Chowdhury. Use of amino terminal type III procollagen peptide (P3NP) assay in methotrexate therapy for psoriasis. Postgrad.Med.J. 82 (967):353-354, 2006. Ref ID; KHAN 2006	**Observational:** Retrospective case series Patient records from a single hospital in Cardiff, Wales (1999 to 2003)	N=65	**Inclusion criteria:** Patients with moderate to severe psoriasis treated with MTX. **Exclusion criteria:** Not stated **Baseline details:** not given	**Methotrexate**: Mean cumulative dose: 2000 mg (SD 1838 mg). **Histological techniques:** Biopsy by Tru-Cut needle; graded according to Roenigk classification **Prognostic factors:** cumulative dose **Confounders:** not controlled for	Mean duration of therapy: total of 278.9 years with a follow-up period of 1-14 years and mean duration of 4.3 (SD 3.9) years.	Liver biopsy histology, P3NP assays, liver function tests	Stated as: none.

Effect Size

- Patients with high mean P3NP levels (>4.2 µg/l) had received significantly higher cumulative dose (>1.5 g) MTX (p=0.002)

- The cumulative dose of MTX had significant correlation with the maximum P3NP levels (p=0.03)
- Long duration (>3 years) of MTX treatment, irrespective of the cumulative dose, was consistent with high (>4.2 ug/l) mean and maximum P3NP values but did not reach significance (p=0.217, p=0.112 respectively).
- 28% of P3NP estimations >4.2 ug/l correlated at some stage with an abnormal liver biopsy
- The median P3NP of those with abnormal liver histology was higher than other patients (>5.8 ug/l)
- Those with fibrosis or cirrhosis (n=4) had received a higher cumulative dose of MTX (median = 4260 mg; mean = 4247.5 mg) than those without fibrosis or cirrhosis (median = 3585 mg; mean = 3811.3 mg).

H.12.2 Cohort Studies – treated and untreated groups or different population groups

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>J. Almeyda, D. Barnardo, H. Baker, G. M. Levene, and J. W. Landells. Structural and functional abnormalities of the liver in psoriasis before and during methotrexate therapy. Br.J.Dermatol. 87 (6):623-631, 1972.

Ref ID: ALMEYDA 1972</td>
<td>Observational: Retrospective cohort</td>
<td>N: 67 (42 treated)</td>
<td>Inclusion criteria: Not stated

Exclusion criteria: Not stated

<table>
<tr><th>Parameter</th><th>Treated (n=42)</th><th>Untreated (n=25)</th></tr>
<tr><td>Mean age – years</td><td>55</td><td>48</td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td>Cumulative MTX dose (mg), mean (range)</td><td>N/A</td><td>N/A</td></tr>
<tr><td>Duration of psoriasis (years), mean (range)</td><td>17 (8-47)</td><td>18 (1-35)</td></tr>
</table>
</td>
<td>Methotrexate:

3 dosing schedules
- 2.5 mg orally 4 or 5 days a week (or daily on alternate weeks) n=11
- 12.5-25 mg orally once a week (n=18)
- 20-40 mg intramuscular or intravenous at weekly or greater intervals

Histological techniques:

Biopsy by Menghini or Vim Silverman needles; staining with H&E, iron, reticulin and van Giesen stains

Definitions</td>
<td>N/A</td>
<td>Hepatotoxicity by biopsy: fibrosis or cirrhosis

Liver function tests: bilirubin, aminotransferase, alkaline phosphatase

Fibrosis grading: 0: none; 1: sparse intralobular; 2: just bridging portal tracts; 3: bridging portal tracts</td>
<td>One author in receipt of a MRC grant</td>
</tr>
</table>

			Parameter / **All (n=67)** Gender M/F (%) / 58/42 Severe disease - Widespread discoid / 61.9% - Erythrodermic / 21.4% - Generalised pustular / 16.7% History of liver disease - Jaundice (due to hepatitis) / 1/67 - Cholelithiasis / 3/67	Alcohol intake Light or nil: Moderate: Heavy: regular average daily intake >3.5 litres beer or equivalent **Prognostic factors:** alcohol, cumulative dose **Confounders** Those who developed fibrosis or cirrhosis had significantly greater mean cumulative dose of MTX than those with normal biopsies (p=0.05); no SS differences in duration of treatment between those with and without abnormal biopsies; the 3 patients with cirrhosis received MTX for a mean of 52 months vs 33		

				months for those with normal biopsies; the 3 patients with cirrhosis had all received MTX by the daily oral regime, but fibrosis was found with approximately equal frequency in all 3 regimes Note: most patients had previously been exposed to tar, dithranol or corticosteroids			

Effect Size

Outcomes

Summary

- **Alcohol consumption may be a risk factor for cirrhosis**
  - 3/3 (100%) with cirrhosis had heavy alcohol intake
  - 0/12 (0%) with fibrosis had heavy alcohol intake
  - 2/10 (20%) with minor liver abnormalities had heavy alcohol intake
  - 2/17 (12%) with normal histology had heavy alcohol intake

- Of 25 untreated patients none had cirrhosis but 4 had fibrosis (16%) – this is compared with 31.6% fibrosis and 7.9% cirrhosis in the treated group
- Of the 4 untreated patients who developed fibrosis 1 (25%) had heavy alcohol intake

- Liver function test results did not correlate with histologically determined liver abnormalities

Cumulative methotrexate dose is a risk factor for fibrosis and cirrhosis

The mean cumulative dose of methotrexate was significantly higher in those with fibrosis and cirrhosis compared with those with normal liver biopsy, p=0.05.

Histology	**Mean cumulative dose ±SE (g)**
Normal	0.96±0.24
Non-specific changes	1.06±0.21
Fibrosis	1.54±0.34
Cirrhosis	2.73±1.19

The patient with the highest cumulative dose of 5.35g had a normal biopsy, although most of those with a normal biopsy had received less than 1.0g.

Author's conclusion

- Alcohol may be an important additive factor in the production of liver damage

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>L. T. Reese, J. W. Grisham, R. D. Aach, and A. Z. Eisen. Effects of methotrexate on the liver in psoriasis. J.Invest.Dermatol. 62 (6):597-602, 1974.

Ref ID: REESE1974</td>
<td>Observational: Prospective cohort

Washington University Medical Centre</td>
<td>N: 70 (35 treated)</td>
<td>Inclusion criteria: psoriasis considered severe enough to require MTX

Exclusion criteria: Not stated

<table>
<tr><th>Parameter</th><th>Treated (n=35)</th><th>Untreated (n=35)</th></tr>
<tr><td>Mean age – years</td><td>43.4</td><td>42.9</td></tr>
</table>
</td>
<td>Methotrexate:

Post-biopsy dosing: single intermittent (IM or oral) but moderately high doses (25-50 mg); some cases used the divided dose, intermittent oral schedule over a 36-h period.

Histological techniques:

Biopsy with Menghini 1-sec technique; staining with H&E, Masson’s trichrome

Definitions

Alcohol intake
1. No to minimal intake (1-2 ox hard liquor or equivalent)</td>
<td>Studied at periods of 6-12 months</td>
<td>Hepatotoxicity by biopsy: non-diagnostic changes, fibrosis or cirrhosis

Grading: 0-4 scale including the following parameters: hyperploid nuclei, fat, inflammation, fibrosis (similar to Scheuer), necrosis degeneration

Liver function tests: bilirubin, alkaline phosphatase, SGOT, SGPT, BSP</td>
<td>US Public Health Service Research Grants AM 05611 and RR 00036</td>
</tr>
</table>

				2. Moderate-to-excessive intake (regular daily intake or sporadic heavy use) Alcohol abstinence encouraged following biopsy **Prognostic factors:** alcohol, cumulative dose **Confounders** Multivariate analysis: alcohol, MTX dose, MTX duration			

Effect Size

Outcomes

Summary

- **No clear association between alcohol consumption and hepatotoxicity in treated patients**

	No to low alcohol intake (n=16)	Moderate-to-high alcohol intake (n=19)
BSP abnormal	5/13 (38.6%)	6/14 (42.9%)
Normal biopsy	6 (37.5%)	1 (5.3%)
Non-diagnostic changes (excl. mild fibrosis)	5 (31.2%)	11 (57.9%)
Mild fibrosis	3 (18.8%)	6 (31.6%)
Fibrosis	1 (6.3%)	1 (5.3%)
Cirrhosis	1 (6.3%) Comorbid diabetes	0

- **Potential association between alcohol consumption and hepatotoxicity in untreated patients**

	No to low alcohol intake (n=17)	Moderate-to-high alcohol intake (n=18)
BSP abnormal	7/16 (43.8%)	8/16 (50.0%)
Normal biopsy	5 (29.5%)	1 (5.6%)
Non-diagnostic changes (excl. mild fibrosis)	11 (64.7%)	9 (50%)
Mild fibrosis	1 (5.9%)	7 (38.9%)
Fibrosis	0	1 (5.6%)
Cirrhosis	0	0

- BSP level showed a modest association with histological changes in those in whom it was performed

- Multivariate analysis:
  - No significant effect of MTX (treated vs untreated); p=0.4
  - Statistically significant effect of alcohol intake on biopsy histology ($p < 0.001$), mostly due to fat score and to a lesser extent the fibrosis score
  - But, moderate-to-excess alcohol plus MTX showed no greater tendency to fat or fibrosis than other groupings
  - Continuous therapy (any dose or duration) may result in more hyperploid nuclei and fibrosis ($p = 0.02$); c.f. intermittent regimen shows no evidence of significant hepatic damage.

Cumulative dose effect (in subset of 21 patients with repeat biopsies)

- No progression of fibrosis was found in those with follow up biopsies (average dose of methotrexate between biopsies was 823mg).

Author's conclusion

- MTX can cause cirrhosis in the absence of alcohol ingestion
- The adverse effect of alcohol on the liver may be synergistic with the potential hepatotoxic action of MTX, but more data are needed

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>H. Amital, Y. Arnson, G. Chodick, and V. Shalev. Hepatotoxicity rates do not differ in patients with rheumatoid arthritis and psoriasis treated with methotrexate. Rheumatology 48 (9):1107-1110, 2009.

Ref ID: AMITAL 2009</td>
<td>Observational: Retrospective cohort

Database of patients in Israel</td>
<td>N: 809 (n=690 psoriasis, n=119 RA)</td>
<td>Inclusion criteria: Cases of psoriasis and RA diagnosed between Jan 1998 and July 2007. Patients diagnosed with Psoriasis, RA or PsA.

Exclusion criteria: Not stated

<table>
<tr><th>Parameter</th><th>Psoriasis (n=690)</th><th>RA (n=119)</th></tr>
<tr><td>Mean age – years</td><td>52.6</td><td>59.9</td></tr>
<tr><td>Gender, male (%)</td><td>333 (48.3)</td><td>41 (34.5)</td></tr>
<tr><td>Cumulative MTX dose (mg), median (range)</td><td>1000</td><td>3625</td></tr>
<tr><td>Weekly dose (mg) median</td><td>19.0</td><td>20.0</td></tr>
</table>
</td>
<td>Methotrexate:

Median dose:

• Psoriasis group: 1000 mg cumulative dose (dispensed at average amount of 182 mg)

• RA group: 3625 mg cumulative dose (dispensed at average amount of 195 mg per prescription)

Prognostic factors: cumulative dose

Definitions

Elevated liver enzymes: anything above ULN</td>
<td>Mean follow-up: 883 days (psoriasis group) and 843 days (RA group).</td>
<td>Liver function tests: GGT, ALKP, AST and albumin</td>
<td>Not stated</td>
</tr>
</table>

				Confounders: controlled for age, gender, cumulative dose as a time-dependent variable			

Effect Size

Outcomes

- RA patients did not differ from patients with either psoriasis or PsA in the rates of elevated liver function tests (or for each test separately).
- Analysis of risk showed that an elevation in liver enzymes was found to be related to the cumulative dose of MTX
  - Combined results for GGT/ALKP/AST: HR 1.07, 95%CI 1.01 – 1.12, p=0.01
  - AST: HR 1.07, 95% CI 1.02 – 1.12, p<0.001
- However there was no relationship for the following liver enzymes:
  - ALKP: HR 1.01, 95% CI 0.95 – 1.08, p=0.69
  - GGT: HR 0.86, 95% CI 0.70 – 1.04, p<0.12
  - Albumin: HR 0.97, 95% CI 0.70 – 1.34, p=0.85

H.12.3 Case-Control Study

Reference	Study type	Number of patients	Patient characteristics	Intervention	Length of follow-up	Outcome measures	Source of funding
H. Zachariae, E. Grunnet, and H. Sogaard. Liver biopsy in methotrexate-treated psoriatics-a re-evalution. Acta Derm.Venereol. 55 (4):291-296, 1975. Ref ID: ZACHARIAE1975	**Observational:** Case-control	N: 139	**Cases** **Inclusion criteria:** severe psoriasis **Exclusion criteria:** Not stated No baseline data presented **Controls** 18 patients with Parkinson's considered for L-DOPA treatment; 42 biopsies from 6-58 hours after sudden death due to cardiac failure or traffic accidents	**Methotrexate**: Initially IM weekly 10-50 mg (occasionally shorter or longer intervals) Post-1971: divided-dose intermittent oral dose schedule over 36-h period **Histological techniques:** Biopsy by Menghini technique; staining with H&E and van Gieson **Prognostic factors:** alcohol **Definitions**	Unclear	Hepatotoxicity: Steatosis, nuclear variability, periportal inflammation, focal necrosis, fibrosis, cirrhosis Liver function tests: alkaline phosphatase, SGPT, BSP **Grading of 1-4 for each of**: Fatty infiltration, periportal inflammation, nuclear variability, focal necrosis, cholestasis and fibrosis (1: not present; 2: slight; 3: moderate; 4:severe); plus presence or absence of	None stated

				High alcohol intake: >4 drinks per day **Confounders**: not controlled for		cirrhosis	

Effect Size

Outcomes

Summary

- **In pre-MTX biopsies, fibrosis was significantly increased in patients with the highest alcohol intake (p<0.05); following MTX this difference disappeared:**
- **No significant association between alcohol consumption and hepatotoxicity in MTX-treated patients**
  - 6/76 (7.9%) with low alcohol consumption developed cirrhosis; 0/20 with moderate or high alcohol consumption developed cirrhosis
  - No significant difference in average biopsy grading between high and low alcohol consumers for fibrosis

Drinks per day prior to MTX	**N**	**Average grading**					**Cirrhosis**
		Steatosis	**Nuclear variability**	**Periportal inflammation**	**Focal necrosis**	**Fibrosis**	
<1	76	2.00±0.10	1.97±0.09	1.37±0.07	1.57±0.06	1.28±0.06	6
1-3	10	1.90±0.28	1.70±0.30	1.20±0.13	1.10±0.10	1.00±0.00	0
≥4	10	2.70±0.26	2.40±0.34	1.60±0.22	1.70±0.21	1.20±0.13	0

- Non-significant trend towards increased fibrosis and cirrhosis in treated vs untreated patients (only fatty infiltration found to be significantly increased; $p<0.05$)
- Significantly more liver abnormalities in people with psoriasis than in controls (with Parkinson's disease or death due to sudden cardiac failure or traffic accidents; $p<0.05$)
- Cirrhosis can occur with no or very small abnormalities in laboratory liver function tests

Author's conclusion

- A history of alcohol consumption correlated significantly with liver fibrosis in *pre*-MTX biopsies but not in *post*-MTX biopsies, where other factors seems to influence the data (e.g., dosing schedule)