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1 **Methylprednisolone-related liver injury: a descriptive study using the French**
2 **pharmacovigilance database**

3 **Short title:** methylprednisolone liver toxicity

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26 **Key words:** liver injury; methylprednisolone; pharmacovigilance; safety

27

28 **Key points:**

29 Intravenous methylprednisolone causality should be considered in case of acute liver injury

30 Liver injury was mainly hepatocellular

31 Data for oral methylprednisolone is insufficient to draw any conclusion

32 Systematic liver monitoring for high-dose intravenous methylprednisolone may be of value

33

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35

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37 This manuscript has not been previously published except in the form of an abstract that

38 appeared in Drug Safety 2018; 41 (11): 1167 (Abstract 119).

39 **Abstract:**

40 **Purpose:** Hepatotoxicity associated with methylprednisolone (MP) is rarely reported in the
41 literature. The aim of the present study was to review the characteristics of acute liver injury
42 associated with intravenous (IV) or oral MP registered in the French pharmacovigilance
43 database (FPD).

44 **Methods:** All cases with MP coded as suspected, concomitant, or interacting drug associated
45 with liver injury as the adverse effect reported up to May 2016 were extracted from the FPD.
46 Cases were identified using the “Drug related hepatic disorders” Standard Medical Query.

47 **Results:** A total of 97 cases of liver injury associated with MP were analysed; 58.8% were
48 women and the median age was 46 years (range: 1-91). MP was used for an autoimmune
49 disease in 47.6% of cases including 26 cases of multiple sclerosis, and was IV in 79.4% of
50 cases. Nearly three-quarters of patients (73,2%) had a hepatocellular type of injury, the
51 severity of which was mainly mild (45%) or moderate (31%). Most patients (92%)
52 spontaneously and fully recovered within a mean 38.4 days. A rechallenge using the IV route
53 was performed in 13 patients and for 10 (76.9%) this was positive (the initial type of injury
54 was hepatocellular for all these cases). Regarding IV route of administration (n=77), MP was
55 coded as the only suspected drug in 22% of cases.

56 **Discussion:** The results suggest that IV MP causality should be considered in case of acute
57 liver injury while data for oral MP is insufficient; systematic liver monitoring for high-dose
58 IV MP may be recommended.

59

60

61 **Introduction**

62 Glucocorticoids are compounds that have long been used for a variety of diseases, both as
63 chronic therapy and in acute cases. Methylprednisolone (MP) pulses are recommended for
64 critical events that require urgent treatment for an exacerbation of a known disease or when
65 vital organs are compromised ⁽¹⁾.

66 Although generally well tolerated, several side effects are attributed to MP, many of which
67 are dose and duration dependent ⁽²⁾. Before June 2018, the summary of product characteristics
68 for MP mentioned transient increase in serum liver enzyme levels and hepatomegaly, but not
69 clinically relevant hepatotoxicity ⁽³⁾. However, over the past 20 years, many case reports of
70 hepatotoxicity induced by MP and a few case series have been published ⁽³⁻²⁶⁾; all concerned
71 the use of high-dose intravenous (IV) MP, mainly in patients with multiple sclerosis or
72 Basedow disease. MP-induced seems rare, but the reintroduction of this drug in the majority
73 of reported cases illustrates the under-recognition of this effect.

74 In 2016, a case of high-dose MP-induced acute hepatitis in a 27-year-old with multiple
75 sclerosis notified to the pharmacovigilance centre of Lyon (France) ⁽⁸⁾ led us to retrospectively
76 analyse all cases of liver damage associated with the use of IV or oral MP registered in the
77 French pharmacovigilance database (FPVD); a particular focus was made on the route of MP
78 administration.

79 **Methods**

80 This study was performed in the FPVD, in which spontaneously reported cases have been
81 registered since 1985 by 31 French pharmacovigilance centres. The present dataset analysis
82 was approved by 31 regional pharmacovigilance centres and the French medicines agency
83 (*Agence nationale de sécurité du médicament et des produits de santé*, ANSM), which
84 manages the database and helped us with data extraction.

85 For each reported ADR, information on patient (e.g. age, gender), description of the ADR
86 (e.g. date of occurrence, progression) and drug exposure (e.g. dates of introduction and
87 withdrawal, dose) are recorded in the FPVD, along with a summary of the clinical report. The
88 regional pharmacovigilance centre analyses each ADR (coded according to the Medical
89 Dictionary for Regulatory Activities, MedDRA – version 21 ⁽²⁸⁾) and evaluates the
90 relationship between drugs and ADR. For each report, causality is assessed according to the
91 French national pharmacovigilance system's standard procedure ⁽²⁹⁾. If a drug is considered
92 probably responsible for the ADR, it is defined as “suspect”; if not, it is defined as
93 “concomitant”. If an ADR is considered probably caused by drug-drug interaction, drugs are
94 coded as “interacting” drugs. An ADR is categorized as “serious” when it leads to
95 hospitalization or prolongation of hospitalization, permanent disability/incapacity, is life-
96 threatening, or leads to the death of the patient. Concerning outcome, a favourable outcome of
97 ADR is defined as full or on-going recovery at the time of notification

98 *Selection of cases*

99 All cases with MP coded as suspected, concomitant, or interacting drug associated with liver
100 injury as ADR reported since 1985 up to 22 May 2016 were extracted from the FPVD. Cases
101 were identified using the broad-ranging “Drug related hepatic disorders” standardized

102 MedDRA Query (SMQ); this was chosen so as not to omit cases of liver injury coded under
103 another MedDRA term.

104 Selected cases were then checked individually by a pharmacologist, irrespective of the level
105 of MP causality and filtered by applying the following exclusion criteria: MP associated with
106 any cytotoxic agent in cancer protocols, cases other than liver injury, cases with a possible
107 other cause, chronology of events incompatible with MP causality (MP intake occurring after
108 liver injury), cases insufficiently documented.

109 *Liver injury criteria*

110 Diagnosis criteria described by Aithal *et al.*, considering transaminase above 5N as clinically
111 significant, were used ⁽³⁰⁾. We also used their classification of liver injuries into 4 grades of
112 severity (Table 1) and only retained grade ≥ 1 cases. When laboratory normal values of liver
113 enzymes were not documented, the following were used: alanine aminotransferase (ALT) [10-
114 50 UI/l], alkaline phosphatase (ALP) [0-120 UI/l], total bilirubin [5-17 $\mu\text{mol/l}$].

115 The type of liver injury was defined according the ratio $R = \text{ALT}/\text{ALP}$: $R \geq 5$ for hepatocellular
116 pattern, $R \leq 2$ for cholestasis pattern, $2 < R < 5$ for mixed liver injury ⁽³¹⁾. When R could not
117 be calculated, information was drawn from MedDRA codes or the narrative.

118

119 **Results**

120 The first search using the “drug induced liver disorders” SMQ found 414 cases; among these
121 97 were included in the final analysis (Figure 1).

122 *Demographic data*

123 Among the 97 patients, 58.8% were female (sex ratio H/F: 0.7) and the mean age was 45.7
124 years (SD=18.3); patients were most frequently aged 40-49 and 50-59 years. The most
125 frequent route of MP administration was IV (79.4%) followed by the oral route (17.5%); the
126 intramuscular route concerned 3 cases (3.1%). The most frequent MP indication was multiple
127 sclerosis (26.8%), followed by other auto-immune diseases (20.6%, including thyroiditis,
128 polyarthritis, alopecia areata, Crohn’s disease...; Table 2).

129 *Characteristics of liver injuries*

130 The most frequent type of liver injury was hepatocellular (73.2%), and most cases were of
131 grade 1 (45.4%) or 2 (30.9%) irrespective of injury type; higher grades (≥ 3) were found in 6
132 cases (Table 3) :

133 - fulminant hepatitis (prothrombin rate 27 %) which recovered spontaneously but slowly after
134 stopping suspected drugs (amoxicillin/clavulanic acid and IV MP)

135 - cholestasis and decreased prothrombin rate in a patient treated by oral MP for 3 months.

136 Liver recovered after stopping all the drugs recently introduced excepted MP.

137 - severe liver cytolysis (prothrombin rate 32%, factor V 37%, transaminases x30 N) after the
138 third course of MP for alopecia aerata

139 - severe liver deficiency with encephalopathy and hypovolemic shock, leading to death,
140 occurring 3 weeks after one dose of cyclophosphamide and a course of IV MP for multiple
141 sclerosis

142 - severe liver deficiency thirteen days after the patient received piperacillin/tazobactam,
143 tobramycin, ciprofloxacin and IV MP.

144 - hepatocellular failure 2 months after the 4th course of IV MP for alopecia aerata. The
145 evolution was not known.

146

147 *Outcomes*

148 Favourable outcome (n=82) was observed for 92% of cases with known outcome (n=89).

149 Deaths were reported in 3 cases, 2 of which had multiple potent causes and could not be
150 reliably attributed to MP. The first one was a patient with metastatic prostate cancer,
151 hospitalised for bilateral bronchopneumopathy, presenting with hepatocellular liver injury 3
152 days after administration of IV MP (120 mg/d), leading to death 5 days later; other drugs,
153 including leuprorelin, paracetamol, morphine, ofloxacin, ceftriaxone, and midazolam, could
154 be suspected. The second case was a patient with progressive glioma who presented with
155 hepatitis 21 days after initiation of oral MP (100 mg/day); other drugs could also have been
156 responsible for liver injury, including temozolomide, esomeprazole, and levetiracetam. The
157 third case was woman presenting with acute hepatocellular liver injury, occurring 3 weeks
158 after one dose of cyclophosphamide and a course of IV MP for multiple sclerosis; this rapidly
159 progressed to severe liver deficiency with encephalopathy and hypovolemic shock, leading to
160 death. According to the time to onset after cyclophosphamide introduction only MP was
161 retained as the suspect drug. In addition, 4 patients did not recover at the time of last follow-
162 up (one month), which was too short to draw any conclusion.

163

164 *Intravenous MP*

165 Among the 77 (79.4%) cases in which MP was used intravenously it was the only suspected
166 drug in 17 cases (22%), making causality more probable. Liver injuries occurred a median 9.5

167 days (range: 1-267 days) after starting MP treatment. Moreover, 46.8% of liver injuries
168 (n=36) were observed >24 hours after the end of MP course. The median number of MP
169 courses before the first liver event was 1 (range: 0-35), the median cumulative dose (since the
170 first dose of MP) was 2 g (range: 0.06-42.7), and 23 patients developed liver toxicity after
171 the first exposure of IV MP. When available, the daily dose at the moment of liver injury was
172 <100 mg for 16 patient, included between 100 mg and 1 g for 18 patients, <1 g for 23 patients
173 and > 2g for 1 patient (median daily dose 500 mg (range 10-3000 mg)).

174 The distribution of liver injury types was similar to that observed in the total population
175 analysis: 79.2% hepatocellular and 11.7 % of both cholestasis and hepatocellular. Most cases
176 were of grade 1 (45.5%, n=35) or 2 (28.6%, n=22) irrespective of injury type; higher grades
177 (≥ 3) were found in 5 cases (Table 3).

178 Clinical signs were observed in 18 cases (23.3%) and were mainly asthenia (27.8%) and
179 digestive disorders (38.9%). Among the 38 cases with data available the duration of liver
180 injury was a median of 38 days (range: 4-140 days); two of these patients died, but only one
181 death could be related to MP (see above).

182 Liver biopsy was performed in 13 patients (16.9%). It was not contributory in 2 cases and
183 found mainly fibrosis (n=1), necrosis (n=1), lymphocytic infiltrate (n=2), undefined infiltrate
184 (n=2), inflammatory disorders (n=1). In 2 cases, histology was compatible with autoimmune
185 hepatitis despite a negative auto-immune blood tests, but also with a toxic event for one of
186 them owing to centrolobular damage and eosinophils. Non drug-related causes were
187 investigated in 51 cases (66.2%), without success: viral serology was measured in 43 cases
188 (all were negative), abdominal ultrasound was performed in 36 cases (all without
189 abnormalities), and auto-immune blood tests in 17 cases (all negative).

190 Data regarding MP rechallenge were available for 19 patients (24.7%); MP was not re-
191 introduced for 6 patients, and was re-introduced for 13 patients. Among the latter, 10 had a

192 new episode of liver injury (76.9%). One recurrence was reported for 5 patients, and ≥ 2
193 recurrences for the remaining 5 patients (4 in one patient); there were a total 18 recurrences in
194 10 patients. All recurrences were hepatocellular liver injury (which was the initial injury for
195 all patients concerned) and the grade was the same in all but one patient who had severe liver
196 deficiency (prothrombin rate 36%) after the second MP course. Autoimmune blood tests were
197 positive, and histology was compatible with autoimmune hepatitis. Liver recovered without
198 specific treatment in all patients in whom a recurrence was reported (n=10). In one case of
199 recurrence, a lower single dose of MP was re-introduced, and for a second case MP was re-
200 introduced orally.

201

202 *Oral MP*

203 Among the 17 (17.5%) cases in which MP was used orally, 52.9% (n=9) of liver injuries were
204 hepatocellular and 29.4% (n=5) were mixed. Most cases were of grade 1 (n=7, 41.2%) or 2
205 (n=8, 47%). Only one case could be classified as severe, with a decreased prothrombin rate
206 (value unknown) (Table 3). Clinical signs were mentioned in 7 cases (31.2%) and were
207 digestive disorders in 57.1% (n=4).

208 Liver injuries occurred a median 13 days (range: 2-3360) after starting MP treatment, or 2 to
209 15 days from MP discontinuation in 6 cases. The median cumulative dose before liver injury
210 was 0.864 g (range: 0.004-3). When available, the daily dose at the moment of liver injury
211 was <10mg for 1 patient, included between 20 and 50 mg for 5 patients and > 50mg for 2
212 patients (median daily dose 40 mg (range 4-240 mg) . Among the 16 for whom MP was
213 continued and who had outcome data, 6 (37.5%) recovered without sequelae. No positive re-
214 introduction of MP was reported.

215 In the majority of cases (94.1%), MP was associated to at least one other drug classified as
216 chronologically suspect: 8 cases with antibiotics (47.1%), 3 cases with temozolomide

217 (17.6%). Viral serology, abdominal ultrasound, autoimmune blood tests were negative
218 (47.1%).

219 MP was the only suspected drug and the only potent cause of liver injury in one case: a 26-
220 year-old woman receiving MP (daily dose not available) for Gougerot-Sjogren disease and
221 who presented with hepatocellular liver injury 3 days after treatment initiation. One month
222 previously, she had corticosteroids (unknown drug name) which were discontinued after 6
223 days owing to abnormal serum liver enzymes (without any further detail). Histology at the
224 time of this event was found to be compatible with toxic hepatitis. The patient later had a
225 similar event without any drug exposure. Prednisolone was re-introduced later and was well
226 tolerated.

227

228 **Discussion**

229 The present study found that liver injury associated with MP was more frequently reported
230 with MP administered intravenously. A majority were female and this is probably due to the
231 indication of MP (multiple sclerosis in over a quarter of cases). For nearly three-quarters of
232 patients liver injury was hepatocellular, the severity of which was mainly evaluated as mild or
233 moderate. Most patients spontaneously and fully recovered, and, among the 3 deaths reported,
234 only one could be reliably related to MP. Mortality herein was thus 1%, which is concordant
235 with a previously published observational study ⁽³³⁾. The responsibility of IV MP was
236 supported by 10 cases of positive re-introduction or the absence of other suspected drugs in
237 nearly a quarter of cases. With regards to MP delivered via the oral route, it is difficult to
238 draw any conclusion as many other suspect drugs were associated with MP and there was no
239 case of re-introduction. It is of note that the summary of product characteristics have been
240 recently updated to consider this adverse reaction ⁽³⁾.

241 The results are consistent with the 38 published cases of MP-related liver injuries ^{(4-7,10-}
242 ^{23,25,26,32,34-36)} (Table 4). These were reported between 2000 and 2018, and the main
243 indications were auto-immune (multiple sclerosis, n=25, 64.1%; Basedow ophthalmopathy,
244 n=10, 28.2%), patients were aged from 11 to 71 years, and the majority were female (n=31,
245 79.5%). This can be explained by the high incidence of MS and thyroid disorders among
246 women ⁽³⁷⁾. Most received high-dose IV MP pulse therapy; only in two cases MP was
247 administered orally. Clinical presentation varied from isolated increase in transaminases to
248 fulminant hepatitis, with fatal outcome in 4 cases ^(22,32). The time to liver injury onset varied
249 greatly, occurring during MP treatment up to a few days to several months after the end of
250 pulse therapy. There were 13 cases of re-introduction (all IV), 12 of which were positive,
251 strengthening the causal link, in particular for IV MP. These positive rechallenges occurred
252 between a few weeks ^(7,16) and several years (1 to 4 years) ^(4,5,10,11,18,25,34) after the last liver

253 injury event. As found herein, MP dosage regimens varied, making it difficult to evaluate the
254 correlation between the treatment duration or the cumulative dose and the risk for liver injury.
255 However, published data does suggest a dose effect, and in particular for IV MP. For instance,
256 in a prospective observational study that included 29 patients with Graves' ophthalmopathy
257 with either dysthyroid optic neuropathy (treated with high-dose IV MP) or moderately severe
258 disease (low-dose IV MP) and followed for 24 weeks, AST and ALT were increased in 38%
259 of the high-dose group, and 14% of the low-dose group (relative risk: 1.8, 95% CI [1.2; 2.6])
260 ⁽³⁸⁾. A similar finding was found in a study conducted in the World Health Organization
261 database; liver injuries occurred in 3.6% of those receiving high-doses IV MP ($\geq 2\text{g}$) *versus*
262 0.9% of those receiving low-doses ($\leq 1\text{g}$) ⁽³⁹⁾.

263 Some authors have proposed a systematic monitoring of liver enzymes during and after the
264 administration of MP bolus ^(7,38), because of the delayed discovering of the liver injury. In our
265 study, liver injuries were discovered after discontinuation of MP in 46.8% of patients
266 receiving MP intravenously and in 35.3% patients receiving MP orally. In the setting of long
267 treatment protocols, such as for thyroid-induced orbitopathy for which weekly MP infusions
268 (500 mg) are given for 6 weeks, followed by another 6 weeks at 250 mg ⁽⁴⁰⁾, early
269 identification during treatment of increased liver function test values may allow prompt
270 withdrawal of MP. Conversely, the treatment protocol for multiple sclerosis is 1g daily for 3
271 days, and changes in liver function tests were generally discovered when patients had
272 symptoms, late after MP administration. For both situations, therefore, performing liver
273 function test routinely during MT administration could be beneficial, as the timely recognition
274 of this complication and early drug withdrawal may prevent progression of necrosis hepatic
275 injury. In general, monitoring of liver enzymes can be provided during and after treatment.
276 This would make it possible to better document these cases of liver damage and the
277 responsibility of MP. Considering the appreciable number of positive rechallenge, prescribers

278 should be informed about the possible and delayed toxic effect of MP to avoid re-introduction
279 as very severe liver failure is possible although not frequent. In any case, liver function test
280 should be performed systematically in case of symptoms.

281 The mechanism of methylprednisolone-induced liver injury is unclear due to the small
282 number of reported cases. Use of steroids may cause three forms of hepatic injury: steatosis/
283 steatohepatitis, hepatitis B virus reactivation and DILI (drug-induced liver injury) (41).
284 However, the cases in our study or those found in the literature do not support viral
285 reactivation or steatosis. The cause of this apparent hepatotoxicity it may represent severe
286 autoimmune hepatitis triggered by the sudden profound immunosuppression and subsequent
287 immune reconstitution (26).

288 **Conclusion** 289

290 In conclusion, the results suggest that IV MP causality should be considered in case of acute
291 liver injury while data for oral MP is insufficient. It would be interesting to further investigate
292 the value of systematic liver monitoring for high-dose IV MP.

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297

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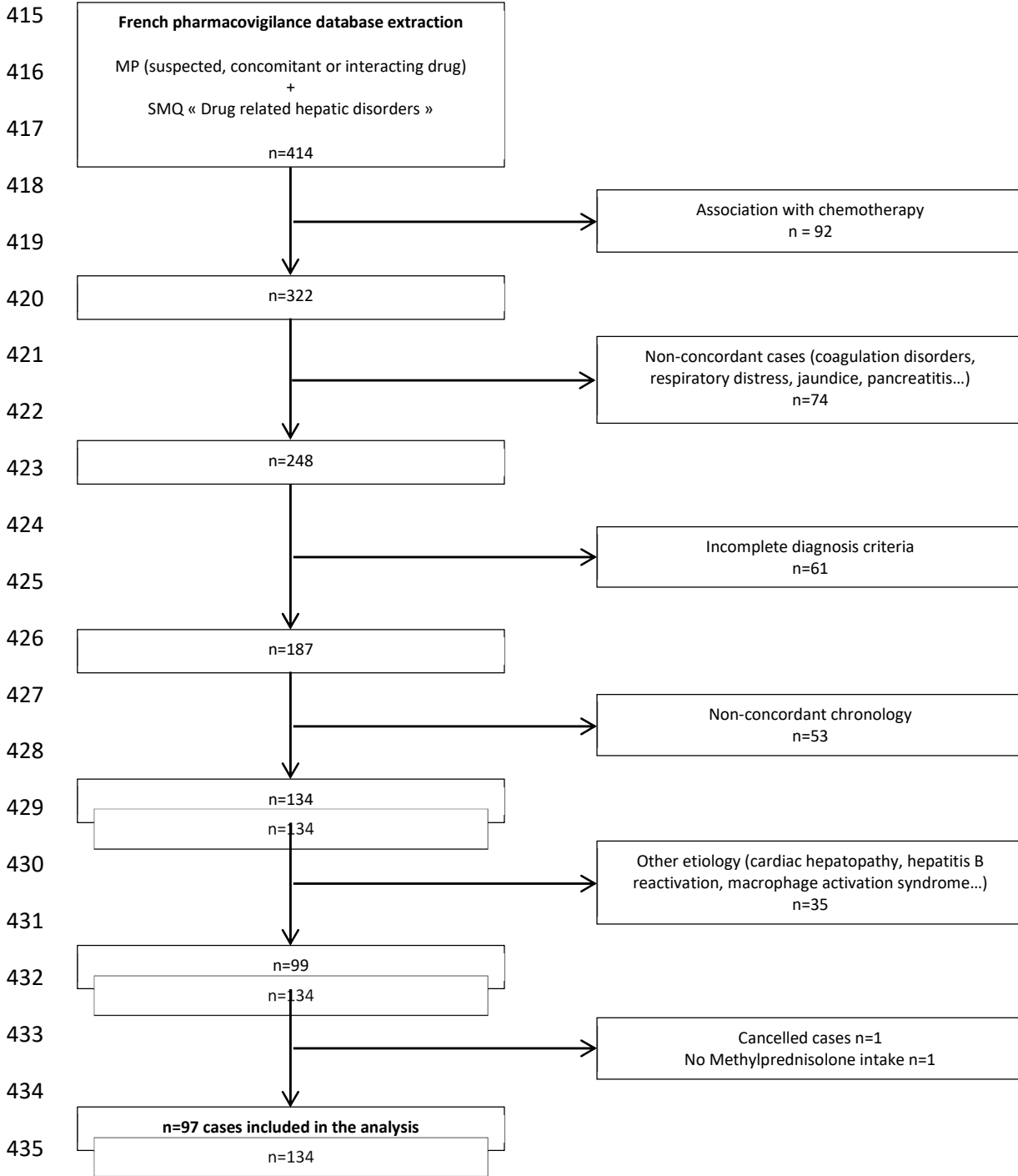
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437 **Figure 1:** Flow chart

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439 **Table 1.** Criteria of liver injury severity according to Aithal *et al.* ⁽³⁰⁾

Grade	Severity	Criteria
1	Mild	ALAT $\geq 5N$ or ALP $\geq 2N$ and TB $< 2N$
2	Moderate	ALAT $\geq 3N$ or ALP $\geq 2N$ and TB $\geq 2N$ or symptomatic hepatitis
3	Severe	ALAT $\geq 3N$ or ALP $\geq 2N$ and TB $\geq 2N$ + one of following criteria: INR ≥ 1.5 ; Ascites and/or encephalopathy; Other organ failure due to liver injury
4	Life threatening or transplantation	

440 ALT: alanine aminotransferase; ALP: alkaline phosphatase; TB: total bilirubin

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442 **Table 2.** Characteristics of the study population

	Total population n = 97
Mean age, years (SD)	45.7 (18.3)
Age-group, years, n (%)	
<10	5 (5.2)
10-20	4 (4.1)
20-30	12 (12.4)
30-40	14 (14.4)
40-50	21 (21.7)
50-60	26 (26.8)
60-70	8 (8.3)
70-80	4 (4.1)
> 80	3 (3.1)
Sex, female, n (%)	57 (58.8)
Methylprednisolone indication, n (%)	26 (26.8)
Multiple sclerosis	20 (20.6)
Auto-immune disease	18 (18.6)
Not specified	9 (9.3)
Infection	7 (7.2)
Brain tumour	6 (6.2)
Pain	4 (4.1)
Other	3 (3.1)
Neurological disorder	2 (2.1)
Haematological malignancy	2 (2.1)
Bone marrow transplant	
Route of administration, n (%)	
Intravenous	77 (79.4)
Oral	17 (17.5)
Intramuscular	3 (3.1)
443 MP: methylprednisolone	

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452 **Table 3.** Characteristics of liver injuries

	Intravenous MP	Oral MP	Total population n = 97
Type of liver injury, n (%)			
Hepatocellular	61 (79.2)	9 (52.9)	71 (73.2)
Cholestatic	6 (7.8)	2 (29.4.8)	15 (15.5)
Mixed	9 (11.7)	5 (6.5)	9 (9.3)
Not specified	1 (1.3)	1 (5.9)	2 (2.1)
Severity grade, n (%)			
1	35 (45.5)	7 (41.2)	44 (45.4)
2	22 (28.6)	8 (47)	30 (30.9)
3	4 (5.2)	1 (5.9)	5 (5.2)
4	1 (1.3)	0	1 (1)
Unknown	15 (19.5)	1 (5.9)	17 (17.5)

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464 **Table 4.** Published cases of methylprednisolone-induced liver injury

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Reference	Age/ sex	Indication	Route	Cumulative dose/ treatment duration	Time after treatment initiation (days)	ALT (xN)	PAL (xN)	R value	Recovery time (weeks)	Histology	Rechallenge	Outcome
Weissel et al. 2000 ⁽³²⁾	71/F	Basedow ophthalmopathy	IV	3g/3 days	28	NA	NA	NA	NA	Post-mortem: hepatic parenchymal necrosis	NA	Death
Marino et al. 2004 ⁽³²⁾	56/NA	Basedow ophthalmopathy	IV	15g/NA	During treatment	49.8	4.2	12.0	NA	Hepatic necrosis	NA	Death
Marino et al. 2004 ⁽³²⁾	63/NA	Basedow ophthalmopathy	IV	9.3g/NA	During treatment	3.6	0.8	4.3	NA	NA	NA	Death
Marino et al. 2004 ⁽³²⁾	47/NA	Basedow ophthalmopathy	IV	8.3g/NA	29	NA	NA	NA	NA	NA	NA	Death after liver transplantation
Marino et al. 2004 ⁽³²⁾	45/NA	Basedow ophthalmopathy	IV	9.3g/NA	During treatment	39.4	1.5	26.6	22	Hepatic necrosis	NA	Recovery
Marino et al. 2004 ⁽³²⁾	30/NA	Basedow ophthalmopathy	IV	7.2g/NA	45	18.6	2.0	9.4	18	Lymphocyte and eosinophil infiltration	NA	Recovery
Marino et al. 2004 ⁽³²⁾	55/NA	Basedow ophthalmopathy	IV	10.7g/NA	29	20.9	2.0	10.2	9	NA	NA	Recovery
Marino et al. 2004 ⁽³²⁾	54/NA	Basedow ophthalmopathy	IV	4g/NA	During treatment	36.3	1.5	23.8	20	Lymphocyte and plasma cell infiltration	NA	Recovery
Salvi et al. 2004 ⁽¹⁹⁾	43/F	Hashimoto thyroiditis	IV	7.5 mg/kg/NA	77	23.0	NA	NA	30	Lobular hepatitis with central lobular necrosis, lymphomonocytic and plasmacellular infiltrates, acidophil bodies, and Kupffer cell hyperplasia	NA	Recovery
Marino et al. 2005 ⁽³⁵⁾	43/F	Basedow ophthalmopathy	IV	4.7g/NA	42	28.4	NA	NA	9	Lymphocyte and plasma cell infiltration, involving mainly one interlobular bile duct. Focal centrilobular necrosis	NA	Recovery
Hofstee et al. 2005 ⁽³⁴⁾	46/F	Multiple sclerosis	IV	3g/3 days	42	21.9	1.2	18.8	18	NA	Positive	Recovery
Das et al. 2006 ⁽⁶⁾	48/F	Multiple sclerosis	IV	NA/NA	42	32.0	1.7	19.2	NA	Lymphocyte and eosinophil infiltration,	NA	Recovery

										rare plasma cells in zone 3		
Topal et al. 2006 (21)	47/F	Central nervous system vasculitis	O	0.224g/7 days	7	50.0	1.2	43.5	7	NA	NA	Recovery
Reub et al. 2007 (17)	42/F	Multiple sclerosis	IV	NA/NA	21	21.6			NA	Active hepatitis with portal lymphocyte infiltration and fibrosis	NA	Ongoing
Rivero et al. 2008 ((18)	57/F	Multiple sclerosis	IV	3g/3 days	5	53.7	1.0	56.0	13	Acute hepatitis with necrosis and ceroid-pigmented hyperplastic macrophages	Positive	Recovery
Takahashi et al. 2008 (20)	47/F	Multiple sclerosis	IV	1g/6 days	28	21.3	3.1	6.8	12	Bridging perivenular necrosis with infiltration of inflammatory cells including eosinophils	Negative	Recovery (prednisolone 10g/d)
Maàouri et al. 2009 (15)	37/F	Multiple sclerosis	IV	3g/6 days	21	NA	NA	NA	NA	Portal lymphocyte infiltration, hepatitis, fibrosis	NA	Recovery
Loraschi et al. 2010 (14)	33/H	Multifocal demyelinating disease	IV	2.5g/NA	35	20.8	NA	NA	3	Focal necrosis of ascinus area 2 and 3, monocyte and macrophage infiltration, Kupffer cell hyperplasia, acidophilic inclusions, focal microvesicular steatosis	NA	Recovery
Loraschi et al. 2010 (14)	27/F	Retrolbulbar neuritis	IV	4.5g/NA	6	2.4	NA	NA	1	NA	NA	Recovery
Furutama et al. 2011 (10)	11/F	Multiple sclerosis	IV	3g/3 days	40	8.6	NA	NA	2	NA	Positive	Recovery
Gutkowski et al. 2011 (12)	24/F	Multiple sclerosis	IV	0.5g/6 days	90	22.6	1.4	16.5	6	NA	NA	Recovery
Carrier et al. 2013 (4)	30/F	Multiple sclerosis	IV	1g/NA	14	56.5	1.2	45.8	9	Necrotic lesions, lymphocyte infiltration, plasma cells and rare eosinophils, intrahepatic cholestasis	Positive	Recovery
D'Agnolo et al.	48/F	Multiple sclerosis	IV	3g/3 days	19	60.6	NA	NA	NA	NA	Positive	Recovery

2013 (5)

Alva et al. 2013 (36)	38/F	Interstitial pneumonitis	O	0.96g/30 days	During treatment	52.4	1.1	46.9	25	Cholestatic hepatitis with early fibrosis	NA	Recovery
Melamud et al. 2014 (16)	52/F	Basedow ophthalmopathy	IV	0.5g/week during 4 weeks then 0.25g/week	30	9.3	0.7	14.0	30	NA	Positive	Recovery
Grilli et al. 2015 (11)	35/F	Multiple sclerosis/ optic neuritis	IV	5g/5 days	30	40.0	1.0	42.1	4	Partial cirrhosis, portal lymphocyte infiltration, plasma cells, eosinophils, neutrophils. Necrosis	Positive	Recovery
Ferraro et al. 2015 (23)	50/F	Multiple sclerosis	IV	1g/5 days	4	7	NA	NA	3	NA	NA	Recovery
Ferraro et al. 2015 (23)	30/F	Multiple sclerosis	IV	1g/5 days	3	12	NA	NA	2	NA	NA	Recovery
Ferraro et al. 2015 (23)	38/F	Multiple sclerosis	IV	1g/5 days	60	5	NA	NA	4	Inflammatory infiltrates, focal piecemeal necrosis, periportal fibrosis and numerous ceroid-laden macrophages	NA	Recovery
Ferraro et al. 2015 (23)	24/F	Multiple sclerosis	IV	1g/5 days	120	13	NA	NA	8	Inflammatory infiltrates, focal piecemeal necrosis, periportal fibrosis and numerous ceroid-laden macrophages	Positive	Recovery
Davidov et al. 2016 (7)	23/F	Multiple sclerosis	IV	3g/3 days	21	40.2	1.2	32.6	14	Decrease in hepatocyte number in central area, chronic inflammation, portal lymphocyte infiltration, eosinophils and plasma cells, acidophil bodies	Positive	Recovery
Cruz et al. 2017 (13)	28/F	Multiple sclerosis	IV	1g/3 days then 0.5g/3 days	30	NA	NA	NA	4	lymphocyte oedematous background and fibrotic changes related to mild chronic hepatitis	NA	Recovery

Cruz et al. 2017 (13)	37/H	Multiple sclerosis	IV	5g/5 days	42	18	18	1	8	No inflammation	NA	Recovery
Cruz et al. 2017 (13)	35/F	Multiple sclerosis	IV	5g/5 days	3	42	42	NA	NA	NA	NA	Recovery
Adamec et al. 2018 (25)	37/F	Multiple sclerosis	IV	6g/6 days	30	63	NA	NA	NA	Centrilobular with some and eosinophilic infiltration compatible with toxic liver necrosis	Positive	Recovery
Adamec et al. 2018 (25)	46/F	Multiple sclerosis	IV	3g/3 days	30	11	NA	NA	NA	Mild diffuse hepatic steatosis	Positive	Recovery
Adamec et al. 2018 (25)	44/F	Multiple sclerosis	IV	3g/3 days	120	37	NA	NA	NA	Portoportal and portocentral necrosis with some lymphocytic infiltration compatible with toxic liver necrosis	NA	Recovery
Breseau et al. 2018 (26)	35/F	Multiple sclerosis	IV	5g/5 days	60	43	1	43	6	Confluent necrosis, more severe near the terminal hepatic venule, portal tracts inflammation without damage of the bile ducts	NA	Recovery

468 NA: not available, F: female, M: male, IV: intravenous, O: oral; g: grams, ALT: alanine aminotransferase, PAL, phosphatase alkaline, R: rati