Serious adverse events with tocilizumab: Pharmacovigilance as an aid to prioritize monitoring in COVID-19

Gatti Milo (Orcid ID: 0000-0003-3018-3779)

Raschi Emanuel (Orcid ID: 0000-0003-0487-7996)

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Milo Gatti[1], Michele Fusaroli[1], Paolo Caraceni[1, 2], Elisabetta Poluzzi[1], Fabrizio De Ponti[1], Emanuel Raschi[1]

[1] Department of Medical and Surgical Sciences, Alma Mater Studiorum, University of Bologna, Bologna, Italy

[2] Centre for Applied Biomedical Research (C.R.B.A.), Alma Mater Studiorum, University of Bologna, Bologna, Italy

Corresponding author:

Emanuel Raschi

Pharmacology Unit, Department of Medical and Surgical Sciences, Alma Mater Studiorum, University of Bologna, Bologna, Italy

Via Irnerio 48, 40126, Bologna, Italy

Tel.: +39 051 2091794

Fax: +39 051 2091780

E-mail: emanuel.raschi@unibo.it

ORCID ID: 0000-0003-0487-7996

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What is already known about this subject

- Tocilizumab is a humanized monoclonal antibody acting as an interleukin-6 receptor antagonist approved for the treatment of different rheumatological diseases and of cytokine release syndrome.
- In mid-2019, some regulatory agencies issued safety warnings on serious liver injury with tocilizumab.
- Off-label tocilizumab use is currently under investigation for the management of pneumonia in severe coronavirus disease 2019 (COVID-19), a life-threatening infection often associated with liver injury.

What this study adds

- Our large-scale real-life pharmacovigilance assessment found increased reporting of hepatic, pancreatic and pulmonary reactions.
- The non-negligible proportion of death (18.4%) for life-threatening hepatic reactions, coupled with rapid onset, calls for attention also in severe COVID-19 patients receiving two doses.
- These serious unpredictable reactions occurring in real-world tocilizumab use may support patients' care and monitoring of ongoing clinical trials.

Abstract

Given its approval for the treatment of cytokine release syndrome, tocilizumab is under investigation in severe coronavirus disease-2019. To characterize serious adverse events (AEs) with tocilizumab, we queried the worldwide FDA Adverse Event Reporting System and perform disproportionality analysis, selecting only designated medical events (DMEs) where tocilizumab was reported as suspect, with a focus on hepatic reactions. The reporting odds ratios (RORs) were calculated, deemed significant by a lower limit of the 95% confidence interval (LL95%CI)>1. 2,433 reports of DMEs were recorded with tocilizumab, mainly in rheumatic diseases. Statistically significant RORs emerged for 13 DMEs, with *drug-induced liver injury* (N=91; LL95%CI 3.07), *pancreatitis* (151; 1.41), and *pulmonary fibrosis* (222; 7.21) as unpredictable AEs. 174 cases of liver-related DMEs were retrieved (proportion of death=18.4%), with median onset of 27.5 days. These serious unpredictable reactions occurring in chronic real-world tocilizumab use may support patients' care and monitoring of ongoing clinical trials.

Introduction

A dramatically increased number of patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causing coronavirus disease 2019 (COVID-19), is reported worldwide [1].

COVID-19 may cause severe pneumonia associated with liver damage, leading to acute respiratory distress syndrome (ARDS) and requiring admission to intensive care unit (ICU) [2]. Dysregulated immune system coupled with cytokine storm, mainly leading to high serum levels of pro-inflammatory cytokines (tumor necrosis factor [TNF]- α, interleukin [IL]-1 and IL-6), was found in patients with severe pneumonia due to COVID-19 compared to mild disease [3].

Tocilizumab is a humanized monoclonal antibody approved in 2009 by European Medicines Agency (EMA) and in 2010 by Food and Drug Administration (FDA) for the treatment of adult patients with rheumatoid arthritis. It acts as an IL-6 receptor antagonist, thereby inhibiting IL-6-mediated signalling and reducing expression of proinflammatory cytokines [4]. By virtue of its approval in cytokine release syndrome, tocilizumab may have a promising role in severe COVID-19 infections, and it has been included in China's latest version of diagnosis and treatment guidelines on COVID-19 [5]. Furthermore, recently the Italian Medicines Agency

(AIFA) has formed a dedicated task force to face the COVID-19 outbreak, which approved specific clinical trials on tocilizumab (TOCIVID-19; EudraCT Number: 2020-001110-38, RCT-TCZ-COVID-19; EudraCT Number: 2020-001386-37, and EudraCT Number: 2020-001154-22) [6-7].

In mid-2019, Therapeutic Goods Administration in Australia and Public Health Agency of Canada issued safety warnings on serious liver injury (8 cases, with median latency of 98 days) [8-9]. Given the potential growing off-label use of tocilizumab associated with COVID-19 outbreak, characterization of life-threatening adverse events (AEs) is necessary.

We queried the US FDA Adverse Event Reporting System (FAERS) database to characterize only AEs of clinical interest, as an aid for ongoing research during this health emergency.

Methods

An observational, retrospective disproportionality analysis was performed to highlight and characterize AEs of clinical interest with higher-than-expected increased reporting. The FAERS database (public dashboard), the US repository of AEs and medication errors comprising more than 18 million reports gathered worldwide, was queried to retrieve tocilizumab reports recorded between the first quarter (Q1) of 2004 and Q4 of 2019.

In order to assign a clinical priority to emerging safety issues, the public list developed by the EMA including 62 different reactions was used to select designated medical events (DMEs), namely rare, serious AEs with a recognized drug-attributable risk, which may constitute a safety issue under certain circumstances (e.g., plausible causality with exclusion of alternative causes) [10]. Furthermore, given the remarkable prevalence of liver injury in COVID-19 (especially in severe cases) [11], hepatic reactions classified as DMEs were characterized: demographic information, fatality rate (i.e., proportion of death reports), time to onset and concomitant drugs known to be hepatotoxic (based on classification proposed by Björnsson et al. [12], including agents in category A and B).

The reporting odds ratio (ROR) with relevant 95% confidence interval (CI) was calculated as a measure of disproportionality, using all other drugs/events recorded in FAERS as a comparator. Specifically, a case-non case approach was applied: cases were defined by DME reports for tocilizumab in which the drug was suspiciously recorded, while non-cases were represented by AE reports recorded for all other drugs in FAERS. The ROR is the odds of

exposure to tocilizumab among the cases divided by the odds of exposure to tocilizumab among the non-cases. If the proportion of the DME of interest is greater in patients exposed to tocilizumab (cases) than in patients exposed to all other drugs reported in FAERS (non-cases), a disproportionality signal emerges. Cases counted as many-fold as the number of DMEs recorded in a given report. Traditional criteria for signal detections were used, i.e., lower limit of the 95% CI of the ROR >1 with at least three cases of interest reported [13].

Finally, DMEs showing statistically significant disproportionality were classified into three broad categories, according to the predictability of the reaction: 1. expected AEs, anticipated from pre-marketing pivotal trials; 2. disease-related AEs, for which underlying rheumatologic disease represents *per se* a risk factor; 3. unpredictable AEs, on the basis of pharmacodynamic properties.

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY.

Results

During the study period, 39,572 reports mentioning tocilizumab as suspect agent were found (78.8% were serious), and DMEs were reported in 2,433 cases (6.1%). Among DME reports, subjects aged > 50 years old were the most represented (26.6% in aged 51-65), with female preponderance (66.9%). Rheumatoid arthritis was the most frequent reason of use (72.5%), while the cytokine release syndrome was recorded in 3.1% of reports (Supplementary Table 1).

Fifty DMEs were reported at least once, being anaphylactic reaction (N= 288), renal failure (N = 249) and pulmonary fibrosis (N = 222) the most common (Supplementary Table 2).

Disproportionality analysis was performed for 44 DMEs (six AEs were reported in less than three cases). Statistically significant ROR was found for 13 DMEs, of which six and four were classified respectively as disease-related and expected AEs (**Table 1**). *Drug-induced liver injury* ([DILI]; N = 91; ROR 3.77; 95% CI 3.07-4.64), *acute pancreatitis* (61; 1.99; 1.55-2.56) and *pancreatitis* (151; 1.65; 1.41-1.94) emerged as unpredictable AEs. Mortality proportion was over 20% for *pulmonary hypertension* (N = 57; ROR 1.39; 95% CI 1.07-1.80) and *renal failure* (249; 1.15; 1.01-1.30).

Overall, 2,010 liver events were found, with DMEs accounting for 174 cases (8.7%). Six out of seven DMEs concerning hepatic reactions were reported in at least one case (no cases of hepatic infarction were recorded), being DILI (N = 91) and *hepatic failure* (N = 49) were the most frequently reported. Disproportionality analysis was performed for five DMEs (hepatic necrosis was reported in only two cases). Statistically significant ROR was only found for DILI (ROR 3.77; 95% CI 3.07-4.64). Median onset of all liver-related DMEs was 27.5 days (interquartile range [IQR] 5-104 days; data available for 44 out of 174 events), ranging from 15 days (IQR 7.5-55.5) for DILI to 94 days (IQR 47.5-133.5) for hepatitis fulminant. Concomitant hepatotoxic drugs were retrieved in 44.3% of cases, ranging from 0.0% for hepatic necrosis to 60.0% for hepatitis fulminant, being omeprazole (N = 21), methotrexate (N = 18), and celecoxib (N = 14) the most reported (**Table 2**). Overall proportion of deaths was 18.4%, ranging from 0.0% for hepatitis autoimmune to 60.0% for hepatitis fulminant.

Discussion

To the best of our knowledge, this is the first large-scale study describing the reporting of serious AEs with tocilizumab. Our analysis shows increased reporting of hepatic, pancreatic and pulmonary reactions, and extends our knowledge on DILI reporting in the real world.

These findings apply to chronic consolidated tocilizumab uses (middle-aged women suffering from rheumatological diseases). However, considering the expected long-lasting pharmacodynamic effect, there are clear implications also for emerging short-term uses, including management of cytokine release syndrome, refractory toxicities with immune checkpoint inhibitors and severe COVID-19 pneumonia. Considering these rapidly evolving, mostly off-label applications of tocilizumab, awareness of potentially severe and life-threatening AEs is essential.

Of note, our analysis retrieved different reports (3.1% of overall DMEs, and specifically 4.1% of hepatic failure cases) in which tocilizumab was used for the management of the cytokine release syndrome, a clinical picture similar to cytokine storm found in severe COVID-19 infections.

Although most of DMEs showing statistically disproportionality were classified as expected (namely anaphylactic reaction/shock, intestinal perforation, and pancytopenia [14]) or disease-related (namely renal failure, pulmonary hypertension and fibrosis, sensory organ disorders

[15-17]), unpredictable AEs were also retrieved, namely DILI and acute pancreatitis, though expected from post-marketing experience.

In clinical trials, DILI with tocilizumab was mainly identified as mere elevations in serum liver enzyme levels, but also cases of acute hepatic failure were reported [18]. Notably, liver injury has been reported to occur up to 80% of severe COVID-19 patients [2, 11, 19], mainly in the phenotype of increased serum transaminases and slight elevation in bilirubin levels, likely caused by direct virus-induced cytopathic damage to bile duct cells coupled with inflammatory cytokine storm [19].

In our analysis, DILI associated with tocilizumab administration occurred after a median of 15 days, a time frame closely overlapping with clinical course of severe COVID-19 infections. Consequently, in this setting, occurrence of DILI should be carefully monitored, especially considering the administration schedule of tocilizumab in COVID-19 (second infusion after 12 h if respiratory function has not recovered, at physician' discretion). Of note, the five ongoing randomized controlled trials (three Italian and two Chinese in clinicaltrials.gov as of March 31, 2020) used baseline serum transaminases levels five times above the upper limit of the normality as exclusion criterion. Considering the aforementioned prevalence of liver injury in severe COVID-19, this threshold may partially compromise recruitment of patients that could benefit from tocilizumab treatment. An approach based on less stringent exclusion criteria (i.e. transaminases levels up to 7-10 times above the normality) could represent on option, taking into account, however, that higher baseline transaminases or an increase during hospitalization could predispose to the onset of severe liver injury [20-22].

Furthermore, it is noteworthy that in our analysis, several reports of acute hepatic failure, hepatitis fulminant and hepatic necrosis were found, including cases in which tocilizumab was used for the management of the cytokine release syndrome, although disproportionality was not significant. Notably, the rapid onset (27.5 days in median) of life-threatening hepatic reactions reported with tocilizumab may potentially aggravate liver injury caused by severe COVID-19 infection, thus calling for strict monitoring of acute and post-acute COVID-19 patients receiving two doses of agent. Particularly, assessment of host-dependent risk factors (i.e. age, sex, comorbidities, pre-existing chronic liver disease, concomitant hepatotoxic drugs) coupled with intensive liver test monitoring (i.e. serum transaminases, total bilirubin level, alkaline phosphatase) in the first 7-10 days after tocilizumab administration and, where appropriate, liver imaging should be implemented, in line with the first documented case of

DILI with tocilizumab in a patient with COVID-19-induced cytokine storm, who developed acute liver injury one day after drug administration with normalization of transaminases in 10 days [23]. Additionally, long-lasting monitoring of liver function should be performed up to eight weeks after tocilizumab administration, with timing and frequency based on case-by-case assessment. Clinicians should refer to EASL guidelines for management, where both general and specific approaches are provided [24].

The higher reporting of pancreatitis confirmed a previous review of FAERS database [25]. Our analysis found a mortality proportion greater than 10%, and, notably, pancreatitis occurred in almost 5% of cases using tocilizumab for management of cytokine release syndrome. These findings further strengthen the importance of awareness in treating severe COVID-19 forms.

We observed a disproportionality signal for pulmonary fibrosis with tocilizumab. Since this is a well-known complication associated with rheumatological diseases, including rheumatoid arthritis, we cannot rule out indication bias as an explanation of our findings, but it is noteworthy that cases of interstitial pneumonitis and alveolar damage leading to severe hypoxemic events were previously reported with tocilizumab [26]. Consequently, in patients with severe COVID-19, pulmonary AEs under tocilizumab administration should be considered in differential diagnosis if aggravation of respiratory failure occurs.

We acknowledge the limitations of our study, mainly related to the inherent nature of FAERS data, which do not allow to establish a causal relationship between drug exposure and occurrence of AEs, also due to missing clinical details. Given the lack of a denominator and the under-reporting phenomenon, the ROR and its magnitude cannot quantify the real risk in clinical practice. Furthermore, criteria used for classifying an adverse event as DILI (i.e., thresholds of transaminases for DILI definition) are not indicated in pharmacovigilance databases. Moreover, reporting biases cannot be ruled out with certainty, although notoriety bias has negligible impact on our findings, given that only 16.7% of DILI reports were recorded following issued safety warnings. Our approach prioritized life-threatening AEs with high suspicion to be drug-induced, and analyzed the largest publicly accessible pharmacovigilance database, thus supporting a high generalizability of findings.

In conclusion, worldwide COVID-19 outbreak will be likely associated with a growing use of off-label tocilizumab for the management of severe cases. This could be reflected in increasing occurrence of life-threatening unpredictable AEs. The higher-than-expected reporting of serious hepatic, pancreatic and pulmonary reactions, mainly for chronic rheumatic diseases,

should be considered in patients' care and monitoring of ongoing clinical trials, including current studies in severe COVID-19 patients, where long-lasting vigilance is justified.

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Author contribution

MG and ER contributed to the conception and design of the study. MG and MF contributed to the acquisition and analysis of data. MG, EP, FDP and ER contributed to the interpretation of data. MG drafted the manuscript. PC, EP, FDP and ER critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work ensuring integrity and accuracy.

Conflict of interest statement

The authors have none to declare.

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Data availability

Data supporting the findings of this study were derived from the following resource available in the public domain: https://www.fda.gov/drugs/questions-andanswers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard.

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Table 1 – Designated medical events (DMEs) reported with tocilizumab showing statistically significant disproportionality.

DME	No. cases	No. deaths	Proportion of death	ROR (95% CI)	Most frequently reported indication	Predictability
Anaphylactic reaction	288	8	2.8 %	4.43 (3.94-4.98)	75.7% RA 16.3% NA 3.1% JIA 2.1% Still's disease 1.7% TA 1.1% Castleman's disease	Expected
Anaphylactic shock	94	5	5.3%	2.71 (2.21-3.32)	77.6% RA 10.6% NA 6.4% Castleman's disease 3.2% JIA 1.1% Still's disease 1.1% Behcet's syndrome	Expected
Blindness	76	2	2.6%	1.40 (1.12-1.75)	42.1% RA 28.9% TA 11.8% JIA 7.9% Still's disease 5.3% NA	Disease-related
Deafness neurosensory	75	0	0.0%	17.36 (13.78-21.86)	97.3% RA 2.7% NA	Disease-related
Drug-induced liver injury	91	1	1.1%	3.77 (3.07-4.64)	71.4% RA 13.2% NA 11.0% JIA 2.1% Still's disease 2.1% Castleman's disease 1.1% LES 1.1% TA	Unpredictable
Intestinal perforation	152	18	11.8%	9.83 (8.37-11.54)	74.3% RA 17.1% NA 3.9% TA 2.0% Still's disease 2.0% JIA 0.7% Castleman's disease	Expected
Pancreatitis	151	17	11.3%	1.65 (1.41-1.94)	75.5% RA 14.6% NA 4.6% Cytokine release syndrome 3.3% TA 1.3% JIA 0.7% Polymyalgia rheumatic	Unpredictable

Table 1 – (continued)

Pancreatitis acute	61	4	6.6%	1.99 (1.55-2.56)	77.1% RA 13.2% NA 3.3% TA 1.6% Castleman's disease 1.6% JIA 1.6% Still's disease 1.6% Polymyalgia rheumatic	Unpredictable
Pancytopenia	176	32	18.2%	2.11 (1.82-2.45)	64.2% RA 20.5% NA 4.0% Cytokine release syndrome 4.0% Still's disease 2.8% JIA 1.7% TA 1.7% Castleman's disease 1.1% Polymyalgia rheumatic	Expected
Pulmonary fibrosis	222	28	12.6%	8.23 (7.21-9.40)	95.5% RA 3.3% NA 0.4% JIA 0.4% TA 0.4% Polymyalgia rheumatic	Disease-related
Pulmonary hypertension	57	19	33.3%	1.39 (1.07-1.80)	70.2% RA 15.7% Still's disease 10.5% NA 1.8% TA 1.8% Polymyalgia rheumatic	Disease-related
Renal failure	249	54	21.7%	1.15 (1.01-1.30)	87.6% RA 5.6% NA 3.2% JIA 1.2% TA 0.8% Amyloidosis 0.8% Cytokine release syndrome 0.4% Still's disease 0.4% Castleman's disease	Disease-related
Sudden hearing loss	26	0	0.0%	10.17 (6.90-15.00)	65.5% RA 26.9% NA 3.8% JIA 3.8% Systemic scleroderma	Disease-related

DME: designated medical event; ROR: reporting odds ratio; CI: confidence interval; RA: rheumatoid arthritis; NA: not available; JIA: juvenile idiopathic arthritis; LES: lupus erythematous systemic; TA: temporal arteritis

Table 2 – Features of designated medical events (DMEs) concerning liver damage.

DME	No. cases	Mean age (years)	Gender	Proportion of death	Median onset (days)[a]	Most frequently reported indication	Concomitant hepatotoxic drugs (proportion of cases and specific agents)[b]			
							Category A	Category B	Category C	Category D
Acute hepatic failure	16	44±18	4 M 10 F 2 NA	31.3%	38 (20.75-67.25)	43.8% SLE 25.0% RA 12.5% JIA 12.5% NA 6.2% Castleman's disease	1 **Methotrexate** 1 **Cotrimoxazole** 1 **Sulfasalazine**	2 Omeprazole 1 Sertraline 1 Fluconazole 1 Ceftriaxone 1 Venlafaxine	2 Pantoprazole 1 Metronidazole 1 Vancomycin	1 Metoprolol 1 Hydroxychloroquine 1 Spironolactone 1 Cyclosporine
Autoimmune hepatitis	11	47.1±28.5	3 M 7 F 1 NA	0.0%	24 (19.5-131.5)	54.5% RA 27.3% NA 9.1% Still's disease 9.1% JIA	1 **Simvastatin** 1 **Azathioprine** 1 **Isoniazid** 1 **Diclofenac**	2 Omeprazole 1 Enalapril 1 Amitriptyline 1 Metformin	1 Fluoxetine 1 Losartan 1 Lansoprazole 1 Glimepiride 1 Famotidine 1 Etodolac	2 Cyclosporine 1 Atenolol
Drug-induced liver injury	91	47.5±17.7	14 M 73 F 4 NA	1.1%	15 (7.5-55.5)	71.4% RA 13.2% NA 11.0% JIA 2.1% Still's disease 2.1% Castleman's disease 1.1% SLE 1.1% TA	13 **Methotrexate** 3 **Diclofenac** 2 **Allopurinol** 2 **Atorvastatin** 1 **Sulfasalazine** 1 **Simvastatin** 1 **Desogestrel**	11 Omeprazole 10 Celecoxib 9 Leflunomide 6 Etanercept 3 Azithromycin 2 Amitriptyline 2 Clopidogrel 2 Ciprofloxacin 2 Metformin 1 Fluconazole 1 Sertraline 1 Cyclophosphamide 1 Levofloxacin 1 Naproxen 1 Fenofibrate	12 Pantoprazole 3 Topiramate 2 Meloxicam 2 Fluoxetine 2 Ramipril 1 Ketoprofen 1 Bupropion 1 Lansoprazole 1 Montelukast 1 Verapamil 1 Metronidazole 1 Amlodipine 1 Acebutolol 1 Adalimumab	7 Hydroxychloroquine 3 Clonazepam 1 Febuxostat 1 Alprazolam 1 Cyclosporine 1 Valacyclovir 1 Acyclovir 1 Metoprolol 1 Nortriptilyine 1 Atenolol 1 Repaglinide 1 Mycofenolate 1 Spironolactone

Table 2 – (continued)

Hepatic failure	49	50.3±22	11 M 36 F 2 NA	44.9%	50 (3-210.5)	73.5% RA 10.2% NA 6.1% Still's disease 6.1% JIA 4.1% Cytokine release syndrome	4 Methotrexate 3 Ibuprofen 2 Diclofenac 1 Infliximab 1 Atorvastatin	5 Omeprazole 3 Acetaminophen 2 Celecoxib 2 Cyclophosphamide 1 Etanercept 1 Leflunomide 1 Amitriptyline 1 Metformin 1 Enalapril	7 Pantoprazole 2 Amlodipine 1 Lansoprazole 1 Ketoprofen 1 Indomethacin 1 Adalimumab 1 Amphotericin 1 Warfarin 1 Gabapentin 1 Famotidine	2 Tamsulosin 1 Rabeprazole 1 Cyclosporine 1 Tacrolimus 1 Carvedilol 1 Oxcarbazepine
Hepatic necrosis	2	41	1 F 1 NA	50.0%	NA	50% SLE 50% Cytokine release syndrome	-	-	-	-
Hepatitis fulminant	5	48.8±16.7	2 M 3 F	60.0%	94 (47.5-133.5)	60% RA 20% JIA 20% Vasculitis	1 Cotrimoxazole	2 Celecoxib 1 Omeprazole	1 Pantoprazole	-

M: male; F: female; NA: not available; RA: rheumatoid arthritis; TA: temporal arteritis; JIA: juvenile idiopathic arthritis; SLE: systemic lupus erythematous

[a] available data in 19 cases for hepatic failure, 15 for drug-induced liver injury, 4 for acute hepatic failure, 3 for autoimmune hepatitis, and 3 for hepatitis fulminant

[b] cases of concomitant agents in category A+B [12] were: 6 (37.5%) for acute hepatic failure, 4 (36.4%) for autoimmune hepatitis, 49 (53.8%) for drug-induced liver injury, 15 (30.6%) for hepatic failure, 0 (0.0%) for hepatic necrosis, and 3 (60.0%) for hepatitis fulminan