International Journal of Infectious Diseases 123 (2022) 70–75

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Effectiveness of fluoroquinolone antimicrobials in addition to tetracyclines for Japanese spotted fever: A retrospective analysis using a national inpatient database

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ARTICLE INFO

Article history:
Received 30 May 2022
Revised 8 August 2022
Accepted 10 August 2022

Keywords:
Fluoroquinolone
In-hospital mortality
Japanese spotted fever
Tetracycline

ABSTRACT

Objectives: This study aim to evaluate the effectiveness of fluoroquinolone (FQ) antimicrobial therapy in combination with tetracyclines (TCs) in patients with Japanese spotted fever (JSF) using a nationwide inpatient database in Japan.

Methods: We identified hospitalized patients diagnosed with JSF who were enrolled in the Japanese Diagnosis Procedure Combination inpatient database from July 2010 to March 2021. Patients who received FQ plus TC on the day of admission were compared with patients who received TC alone on the day of admission, using inverse probability of treatment weighting. The primary outcome was in-hospital mortality. Secondary outcomes were in-hospital complications, total hospitalization costs, and length of hospital stay.

Results: We identified 1060 eligible patients. Of these, 434 (41%) received FQ plus TC on the day of admission and 626 (59%) received TC alone on the day of admission. Inverse probability of treatment weighting showed no statistically significant differences between the groups in in-hospital mortality, in-hospital complications, total hospitalization costs, and length of hospital stay.

Conclusion: This study did not show any significantly improved effectiveness using FQ antimicrobials in combination with TCs for treating JSF. Clinicians may need to be cautious in administering FQ and TC antimicrobials concomitantly in routine practice.

Introduction

Japanese spotted fever (JSF) is one of the most prevalent tick-borne infectious diseases in Japan (Mahara, 1984). JSF is a rickettsial disease caused by *Rickettsia japonica* and is characterized by clinical symptoms such as fever, headache, arthralgia, skin rash, and eschars. It has been reported not only in Japan but also in South Korea (Chung *et al.*, 2006), China (Li *et al.*, 2018), and Thailand (Gaywee *et al.*, 2007), and the number of reports in Japan has increased in recent years.

Tetracyclines (TCs) are the first-line agents used to treat JSF (Mahara, 1997). However, a combination therapy with fluoroquinolones (FQs) may be recommended in severe cases (Mahara, 1997). Although FQs have been shown to be active against *R. japonica in vitro* (Suto *et al.*, 1989), it has not been scientifically proven whether the addition of FQs to TCs improves the prognosis of patients with JSF. Therefore, this study aimed to evaluate the effectiveness of FQ antimicrobial therapy in addition to TCs in patients with JSF, using a nationwide inpatient database in Japan.

Methods

Data source

This was a retrospective cohort study using the Japanese Diagnosis Procedure Combination (DPC) inpatient database, which contains discharge abstracts and administrative claims data from more

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https://doi.org/10.1016/j.ijid.2022.08.006

than 1200 acute-care hospitals in Japan that voluntarily contribute to the database (Yasunaga, 2019). This database includes the following patient-level data for all hospitalizations: age; sex; diagnoses recoded with International Classification of Diseases, Tenth Revision codes; daily procedures recorded using Japanese medical procedure codes; daily drug administrations; admission status; and discharge abstract. A previous validation study for this database showed high specificity and moderate sensitivity for diagnoses and high specificity and sensitivity for procedures (Yamana *et al.*, 2017).

Study population

Using the Japanese DPC inpatient database from July 2010 to March 2021, we identified adult patients hospitalized for JSF defined by the primary diagnosis with International Classification of Diseases, Tenth Revision code A778a. We did not include patients with suspected diagnoses of JSF. We excluded patients aged <18 years and patients who did not receive intravenous or oral TC on the day of admission.

Treatment

Eligible patients who received intravenous or oral FQs plus intravenous or oral TCs on the day of admission were defined as the FQ plus TC group. Patients who received TC but no FQ on the day of admission were defined as the TC group.

Outcomes and covariates

The primary outcome was in-hospital mortality. The secondary outcomes were in-hospital complications, total hospitalization costs (with 1 US dollar equivalent to 115 Japanese yen), and length of hospital stay. In-hospital complications included intensive/high-dependency care unit admission, mechanical ventilation, catecholamine therapy, renal replacement therapy, transfusion, and in-hospital death between the second day of hospital admission to discharge.

The covariates included age, sex, smoking history, body mass index at admission, physical function at admission measured by the Barthel Index (BI) (Mahoney and Barthel, 1965), Japan coma scale at admission (Shigematsu *et al.*, 2013), Charlson comorbidity index score (Quan *et al.*, 2011), fiscal year, admission on a weekend (Saturday or Sunday), ambulance use, organ support therapies on the day of admission (including the in-hospital complications listed previously), and teaching hospital status. Body mass index was categorized by the following ranges: <18.5, 18.5-24.9, 25.0-29.9, and ≥30.0 kg/m^2. Physical function at admission was categorized as total/severe dependence (BI: 0-60), slight/moderate dependence (BI: 61-99), and independent (BI = 100). The Japan coma scale is well correlated with the Glasgow Coma Scale and was categorized as alert consciousness, confusion, somnolence, and coma (Shigematsu *et al.*, 2013). The Charlson comorbidity index was scored using the diagnosis for each patient and categorized as 0, 1, 2, or ≥3 (Quan *et al.*, 2011).

Statistical analysis

Our primary approach was to compare outcomes between two groups through an inverse probability of treatment weighting (IPTW) (Griswold *et al.*, 2010; Rosenbaum and Rubin, 1985). A multivariable logistic regression model using the previously mentioned covariates was used to compute the propensity scores for patients who received FQ plus TC on the day of admission. We used stabilized average treatment effect weight, which allowed us to maintain the total sample size of the original data and provide a more accurate interval estimate of the variance of the main effect and controls for type I error compared with the nonstabilized IPTW (Cole and Hernán, 2008). To assess the performance of the IPTW, all covariates were compared using standardized differences, with absolute standardized differences ≤10% considered to denote negligible imbalances between the two groups (Austin, 2009). The odds ratios and their 95% confidence intervals (CIs) for binary outcomes and risk differences and their 95% CIs for continuous outcomes were calculated with weighted generalized linear models, with cluster-robust standard errors and treating individual hospitals as clusters.

Sensitivity analysis

To assess the robustness of IPTW by a different statistical model, we performed a traditional multivariable regression analysis through a generalized linear model, using the outcomes as the dependent variable and FQ administration on the day of admission and all the covariates as the independent variables. All analyses were performed using Stata/MP 17.0 software (StataCorp LLC, College Station, TX, USA). Continuous variables are presented as a median and interquartile range (IQR), and categorical variables are presented as numbers and percentages. All reported *P*-values were two-sided, and $P < 0.05$ was considered statistically significant.

Subgroup analysis

For subgroup analysis, only severe cases were selected for the analysis of primary and secondary outcomes. Severe cases were defined as patients who received one or more of the following organ supportive therapies: admission to the intensive care unit or high care unit, supplemental oxygen, mechanical ventilation, catecholamine use, renal replacement therapy, or transfusion.

Data sharing statement

The datasets analyzed in the current study are not publicly available because of contracts with the hospitals providing data to the database.

Results

We identified 1386 patients hospitalized for JSF from 238 hospitals during the study period. After excluding 26 patients aged <18 years and 300 patients who did not receive TC on the day of admission, we included 1060 patients. Of these, 434 (41%) patients who received FQs plus TC on the day of admission were allocated to the FQ plus TC group and remaining 626 (59%) patients were allocated to the TC group. The overall duration of TC in all 1060 cases was a median of 8 days (IQR 6-11 days) and the duration of quinolone was a median of 6 days (IQR 4-9 days).

Table 1 shows the baseline characteristics before and after IPTW. In the original cohort, patients in the FQ plus TC group tended to have severe dependent physical function at admission, clear consciousness at admission, higher Charlson comorbidity index score and were admitted between 2013 and 2018, were less frequently admitted using an ambulance, and less frequently admitted to teaching hospitals than patients in the TC group. The distributions of propensity scores before and after IPTW are shown in Supplemental Figures 1 and 2. After IPTW, the patients' characteristics were well balanced between the two groups, except Japan coma scale coma at admission (Table 1 and Figure 1)

Table 2 shows the outcomes before and after IPTW. After IPTW, there were no statistically significant differences in in-hospital mortality between patients in the FQ plus TC group and those in the TC group (2.0% vs 1.0%; odds ratio 1.94; 95% CI 0.69-5.43). There were no statistically significant differences between

Table 1
Patient characteristics before and after IPTW.

Baseline characteristics	Before IPTW			After IPTW		
	FQ + TC (n=434)	TC (n=626)	SD	FQ + TC (n=435)	TC (n=625)	SD
Age, years, median (IQR)	71 (64-78)	71 (64-79)	-1	69.22	69.63	-3
Male, n (%)	207 (48)	297 (47)	1	47%	48%	0
Smoking history, n (%)						
Nonsmoker	300 (69)	432 (69)	0	69%	69%	-1
Current/past smoker	97 (22)	138 (22)	1	22%	22%	0
Unknown	37 (9)	56 (9)	-2	9%	9%	2
BMI at admission, kg/m^2, n (%)						
<18.5	40 (9)	55 (9)	2	8%	8%	-2
18.5-24.9	268 (62)	369 (59)	6	60%	60%	-2
25.0-29.9	75 (17)	121 (19)	-5	20%	19%	4
≥30.0	12 (3)	14 (2)	3	3%	3%	2
Missing data	39 (9)	67 (11)	-6	9%	10%	-2
Physical function at admission, n (%)						
Total/severe dependence (BI 0-60)	144 (33)	149 (24)	21	26%	26%	-1
Slight/moderate dependence (BI 61-99)	53 (12)	113 (18)	-16	17%	16%	2
Independent (BI = 100)	217 (50)	303 (48)	3	49%	50%	-1
Missing	20 (5)	61 (10)	-20	8%	8%	-1
Japan Coma Scale at admission, n (%)						
Clear	380 (88)	527 (84)	10	87%	86%	5
Confusion	44 (10)	83 (13)	-10	10%	11%	-4
Somnolence	10 (2)	11 (2)	4	2%	2%	1
Coma	0 (0)	5 (1)	-13	0%	1%	-13
Charlson comorbidity index, n (%)						
0	302 (70)	449 (72)	-5	71%	71%	-1
1	84 (19)	125 (20)	-2	20%	20%	0
2	39 (9)	29 (5)	17	7%	6%	4
≥3	9 (2)	23 (4)	-10	3%	3%	-2
Fiscal year, n (%)						
2010-2012	59 (14)	87 (14)	-1	14%	14%	-1
2013-2014	78 (18)	67 (11)	21	13%	13%	0
2015-2016	108 (25)	104 (17)	21	20%	20%	0
2017-2018	126 (29)	130 (21)	19	24%	24%	1
2019-2020	63 (15)	238 (38)	-55	29%	29%	1
Ambulance use, n (%)	68 (16)	131 (21)	-14	18%	19%	-2
Admission at weekend, n (%)	112 (26)	137 (22)	9	22%	23%	-1
Organ supportive therapies, n (%)						
ICU/HCU admission	53 (12)	72 (12)	2	11%	12%	-1
Supplemental oxygen	68 (16)	91 (15)	3	14%	15%	-2
Mechanical ventilation	5 (1)	6 (1)	2	1%	1%	-1
Catecholamin	22 (5)	27 (4)	4	5%	5%	0
Renal replacement therapy	3 (1)	4 (1)	1	1%	1%	0
Transfusion	4 (1)	4 (1)	3	1%	1%	0
Teaching hospital	365 (84)	550 (88)	-11	87%	86%	1

BI, Barthel Index; BMI, body mass index; FQ, fluoroquinolone; HCU, high care unit.
ICU, intensive care unit; IPTW, inverse probability of treatment weighting; SD, standardized difference; TC, tetracycline.

Table 2
Outcomes before and after IPTW.

	Before IPTW		After IPTW		Odds ratio or risk difference (95% CI)	*P*- value
	FQ + TC (n=434)	TC (n=626)	FQ + TC (n=435)	TC (n=625)		
In-hospital mortality, n (%)	9 (2.1)	6 (1.0)	9 (2.0)	6 (1.0)	1.94 (0.69, 5.43)	0.206
In-hospital complications, n (%)	37 (8.5)	38 (6.1)	37 (8.4)	39 (6.3)	1.36 (0.85, 2.18)	0.195
Total hospitalization cost, USD	3260 (2489-5084)	3345 (2574-5044)	3254 (2470-5013)	3342 (2577-5047)	300 (-643, 1242)	0.533
Length of hospital stay, days	10 (8-14)	10 (8-14)	10 (7-14)	10 (8-14)	1.4 (-0.3, 3.0)	0.104

FQ, fluoroquinolone; IPTW, inverse probability of treatment weighting; TC, tetracycline; USD, United States dollars.

the groups in in-hospital complications (8.4% vs 6.3%; odds ratio 1.36; 95% CI 0.85-2.18), total hospitalization costs, and length of hospital stay. The results of the sensitivity analysis using traditional multivariate regression showed similar results to those in the main analysis (Table 3). As a subgroup analysis, 223 patients were classified as severe cases (87 in the FQ plus TC group, 136 in the TC group). There were no statistically significant differences in in-hospital mortality, in-hospital complications, total hospitalization costs, or length of hospital stay among the severe cases (Table 4).

Discussion

Our study did not demonstrate a statistically significant additional effectiveness of quinolone antimicrobials in addition to TCs for the treatment of JSF. In Japan, diagnoses with specific infec-

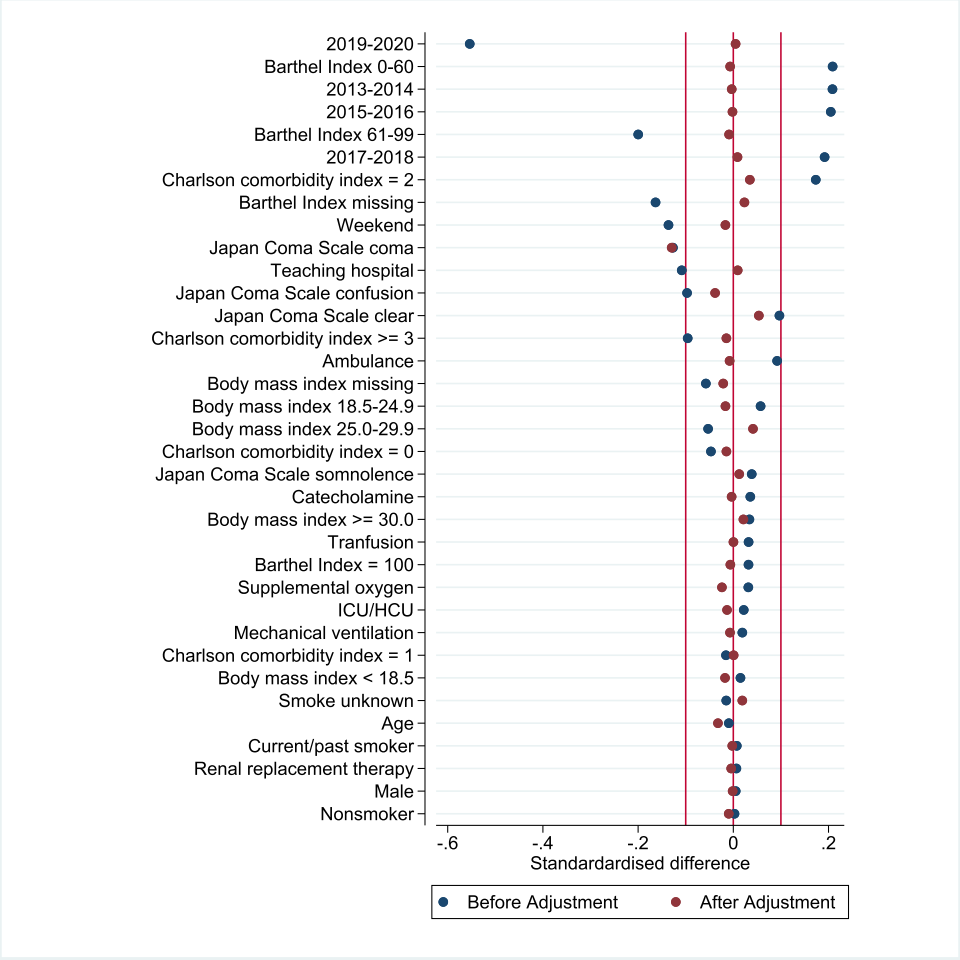

Figure 1. Balance of the covariates before and after IPTW.
ICU, intensive care unit; IPTW, inverse probability of treatment weighting; HCU, high care unit.

Table 3
Outcomes of the sensitivity analysis using traditional multivariable regression.

	FQ + TC (n=434)	TC (n=626)	Odds ratio or risk difference (95% CI)	*P*-value
In-hospital mortality, n (%)	9 (2.1)	6 (1.0)	3.86 (0.52, 28.9)	0.188
In-hospital complications, n (%)	37 (8.5)	38 (6.1)	1.41 (0.75, 2.67)	0.285
Total hospitalization cost, USD	3260 (2489-5084)	3345 (2574-5044)	251 (-571, 1073)	0.549
Length of hospital stay, days	10 (8-14)	10 (8-14)	1.2 (-0.4, 2.7)	0.142

FQ, fluoroquinolone; TC, tetracycline; USD, United States dollars.

Table 4
Results of subgroup analyses among severe cases.

	After IPTW FQ + TC (n=87)	TC alone (n=136)	Odds ratio or risk difference (95% CI)	*P*-value
In-hospital mortality, n (%)	7 (8.3)	4 (3.3)	2.68 (0.78, 9.14)	0.116
In-hospital complications, n (%)	20 (23.2)	31 (22.7)	1.02 (0.54, 1.96)	0.943
Total hospitalization cost, USD	6067 (3958-10245)	6488 (3944-11832)	-832(-3882, 2217)	0.593
Length of hospital stay, days	12 (10-19)	14 (10-20)	0.1 (-4.3, 4.4)	0.979

FQ, fluoroquinolone; IPTW, inverse probability of treatment weighting; TC, tetracycline; USD, United States dollars.

tious diseases must be reported to the government through a public health center; physicians are required to report a diagnosis of JSF within 7 days. Notification is based on one of the following two conditions: (i) detection of *R. japonica* genes in whole blood or tissue and (ii) detection of immunoglobin M antibodies or a positive antibody result or significant increase in antibody titer by paired sera. Generally, these tests are performed in specialized laboratories in each prefecture, and it takes several days to several weeks to obtain test results. For this reason, most cases in Japan are started on antimicrobial therapy before a confirmed diagnosis is made. In recent years, the number of JSF cases reported in Japan has been increasing, with 2781 cases reported in the 11 years from

January 2010 to December 2020 (National Institute of Infectious Diseases, 2020). Our study enrolled 1060 JSF cases, which corresponds to about one-third of the cases notified in the same period.

Reports have described cases of responses to quinolone administered to treat JSF (Iwasaki *et al.*, 2001; Nakata *et al.*, 2012; Seki *et al.*, 2006). However, in a retrospective study of 31 JSF cases, in which FQs were not used at all, there were no fatality cases (Sando *et al.*, 2018), and FQs were not necessarily used in severe cases. In the largest retrospective report to date of 239 cases of JSF, 98.3% of patients were treated with quinolone in addition to a TC (Sakabe *et al.*, 2022). Thus, the decision to add a quinolone in the treatment of JSF is likely to depend not only on the severity of the disease but also on practices at the treating facility. However, these case reports do not scientifically prove the advantage of FQs over TCs in JSF. In fact, to date, there are no studies showing the additive effects of FQs on JSF. At this time, there are no treatment guidelines for JSF in Japan, and our study results underscore the need for standard treatment guidelines for JSF.

In general, FQs are not recommended for treating spotted fever group rickettsioses. Although FQs had been considered as possible alternatives to TCs, they were less effective than standard agents in treating patients with Mediterranean spotted fever (Botelho-Nevers *et al.*, 2011). The authors of the report hypothesized that the association between FQ treatment and poor outcomes in patients with Mediterranean spotted fever might be caused by toxin liberation. In addition, certain rickettsiae (e.g., *Orientia tsutsugamushi*) contain genes that encode known quinolone resistance factors (Jang *et al.*, 2013). Thus, the benefits of using quinolone antimicrobials in rickettsiosis are largely unproven, and our study is consistent with these results.

FQs are generally safe and well tolerated. However, rare but severe adverse events have been reported, leading to restrictions on their use. FQs are known to be a risk for *Clostrioides difficile* infection due to their broad spectrum (Guh *et al.*, 2017). They are also known to be associated with an increased risk of arrhythmia, aortic aneurysm and dissection (Gorelik *et al.*, 2019; Lee *et al.*, 2015), tendon rupture, retinal detachment (Etminan *et al.*, 2012), and dysglycemia (Chou *et al.*, 2013). Inappropriate use of FQs can also lead to an increase in quinolone-resistant bacteria (Peña *et al.*, 1995). Administration of FQs for JSF should be determined after considering the benefits and disadvantages.

This study had some limitations. First, we used a multicenter, real-world database in Japan and there was no national protocol or guidelines for the treatment of JSF. Therefore, administration of FQ for patients with JSF was not random and was based on the decision of the attending physician, which may have led to confounding by indication. We attempted to control for measured confounders in the IPTW; however, there still may have been unmeasured confounders. Second, although we included cases registered as JSF in the DPC database in this study, we cannot guarantee that diagnoses were made using ideal methods. A previous validation study in the DPC database showed the moderate sensitivity (78.9%) and high specificity (93.2%) to the diagnosis (Yamana *et al.*, 2017). Therefore, the low sensitivity in this study may not mean that all JSF cases were picked up. However, the high specificity suggests that cases registered as JSF in the DPC are likely to be true JSF. As testing for JSF is available through regional health laboratories in each Japanese prefecture, it is generally assumed that disease registration in the DPC database is based on these test results. Third, we only analyzed the additive effect of FQs in treatment of JSF with TCs. It should be noted that this is not a comparison of the efficacy between TCs and FQs and does not indicate that FQs are ineffective against JSF.

Conclusion

We were unable to confirm additional effectiveness of FQ antimicrobials in patients with JSF who had already received TCs. Clinicians may need to use caution when using FQ and TC antimicrobials concomitantly in routine practice.

Declaration of Competing Interest

The authors have no competing interests to declare.

Funding

This work was supported by grants from the Ministry of Health, Labour and Welfare of Japan (21AA2007 and 22AA2003) and the Ministry of Education, Culture, Sports, Science and Technology of Japan (20H03907).

Ethical approval

The study was approved by the institutional review board of The University of Tokyo (approval number, 3501-3; December 25, 2017). No information allowing the identification of individual patients, hospitals, or physicians was obtained, and the requirement for written informed consent was waived because of the anonymous nature of the data.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.08.006.

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