effectiveness of CPG. However, this issue remains controversial,[19–23] and there are some differences in the intensity of regulatory actions among regulatory authorities. In Japan, the MHLW did not issue the highest level warning, similar to the FDA black-box warning. Instead, they cautioned against the concurrent use of OPZ and CPG (OPZ+CPG) in April 2010 through changes to the conventional label. Esomeprazole was not approved by the MHLW at the time. This caution was not applied to the co-administration of CPG with lansoprazole or rabeprazole (LPZ/RPZ+CPG) because of the difference in the inhibitory effects on CYP2C19.

Recently, there has been considerable anticipation of the effective use of medical information databases (MIDs) for pharmacovigilance. To this end, many countries have directed large efforts towards establishing nationwide MID systems and the scientific methodologies to exploit them for active drug surveillance. In May 2008, the FDA announced the Sentinel Initiative with a Sentinel System for performing active nationwide surveillance using the electronic health data of a minimum of 100 million people.[24,25] In Japan, the MHLW launched its Sentinel Project in Japan (J-Sentinel) in 2010 for more accurate and comprehensive benefit-risk assessment.[26] An extensive MID covering 10 million individuals by 2015 is to be established under its J-sentinel plan.

To achieve the aims of the J-Sentinel project, we initiated collaborative research with four hub hospitals in Japan with the goal of establishing appropriate epidemiological methodology for pharmacovigilance using MIDs. In our research project, we used the four MIDs to conduct a quantitative assessment of the direct impact of the two regulatory actions on the prescribing of the target drugs in a timely and effective manner.

METHODS

Data source and study organization

We used MIDs of the University of Tokyo Hospital (Tokyo, Japan), Hamamatsu University Hospital (Shizuoka, Japan),[27] Kagawa University Hospital (Kagawa, Japan) and Kyushu University Hospital (Fukuoka, Japan), which covered nearly one million individuals. The average numbers of outpatients and inpatients per day in the four hospitals were more than 7200 and 3100, respectively. In each hospital, the number of target patients per defined period was counted using their local MID, and the summary data without personally identifiable information were submitted to the National Institute of Health Sciences (Tokyo, Japan). The summary data from the four hospitals were combined and used for the current analysis. The study was approved by the ethics committees of the Hamamatsu University Hospital and the National Institute of Health Sciences together with other pharmacoepidemiological studies. For the other three university hospitals, such approval was not necessary according to current ethical regulations in Japan.

Study design for oseltamivir

The outcome and intervention were defined as the proportion of patients prescribed oseltamivir relative to those prescribed neuraminidase inhibitors, and the *Dear Doctor* letter for oseltamivir issued on 20 March 2007, respectively. We used the number of patients taking any neuraminidase inhibitors as the denominator assuming that these patients in our four hospitals were representative of influenza cases in Japan (Figure S1). Period from the beginning of April of one year to the end of March of the following year was defined as a season, and the number of patients in each season was measured during the observation period from the 2002/2003 season to the 2010/2011 season. The seasons of 2007/2008 and later were assigned to the post-intervention period. Patients were classified into two different age groups: 10–19 years as the target group and 20 years or over as the control group. Children aged 0–9 years were not included in the study, because oseltamivir in dry syrup formulation was used preferentially for this age group, regardless of the regulatory action. The neuraminidase inhibitors examined in this study included oseltamivir, zanamivir, peramivir and laninamivir. As peramivir and laninamivir were approved in Japan in January 2010 and September 2010, respectively, the patient number for these two prescriptions was counted over two seasons (2009/2010 to 2010/2011) and one season (2010/2011), respectively. Oseltamivir and zanamivir were approved in December 2000 and December 1999 in Japan, respectively, and were in clinical use before the observation period.

Study design for OPZ+CPG

The outcome and intervention were defined as the proportion of patients prescribed OPZ+CPG relative to those prescribed CPG, and the label revision issued on 27 April 2010, respectively. The number of patients prescribed CPG per month was counted during the study period from the beginning of May 2009 to the end of April 2011. The period from beginning of May 2010 and later was assigned to the post-intervention period. PPIs examined in this study included oral OPZ, lansoprazole and rabeprazole, but PPI-antibiotic combination products for the treatment of *Helicobacter pylori* only were excluded because of the different indications. A prescription including one of the PPIs and CPG within the same day was defined as co-administration. Patients were classified into two different treatment groups: OPZ+CPG as the target group and LPZ/RPZ+CPG as the control group. *New users* were defined as patients who had not received CPG within six months prior to the month in which CPG was prescribed.

Statistical analysis

To estimate the effects of the two regulatory interventions, we conducted segmented regression analysis using interrupted time series data.[28] The effect was assessed using two parameters, level (β_2) and trend (β_3), according to the following linear regression model:

$$Y_t = \beta_0 + \beta_1 \times \text{time}_t + \beta_2 \times \text{intervention}_t + \beta_3 \times \text{time after intervention}_t + e_t$$

where Y_t is the proportion of patients prescribed the target drug in regularly spaced intervals at time t; *time* is a continuous variable indicating time from the start of the observation period; *intervention* is a binary variable for pre ($\text{intervention}_t = 0$)- or post-intervention ($\text{intervention}_t = 1$); *time after intervention* is a continuous variable indicating time from the intervention; β_2 represents the change in the level at the intervention, from the last point before intervention to the first point after intervention, indicating the short-term effect; β_3 represents the trend change in the slope in the post-intervention period compared with that in the preintervention period, indicating the long-term effect.

Ordinary least squares regression analysis assumes that the error terms associated with each observation are independent.[28,29]

As autocorrelation was detected in some linear regression models, the autoregressive error model using the Yule-Walker estimation method for first-order autoregression was applied as appropriate.[30] After adjusting for autocorrelation, the Durbin–Watson statistics for the final model indicated no autocorrelation. Values of $P < 0.05$ (two-sided) were considered statistically significant. All statistical analyses were conducted using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Results of action against oseltamivir use

Mean seasonal numbers of the patients prescribed neuraminidase inhibitors prior to and after the regulatory action in the four hospitals are shown in Table 1. There was no significant difference in the total number of patients prescribed neuraminidase inhibitors between pre- and post-intervention periods (686 vs. 647, $P = 0.858$, Student's *t*-test), although the numbers varied from year to year due to variability in the prevalence of influenza.

The time series plots and results of the segmented regression analysis of mean seasonal proportions of patients prescribed oseltamivir to the total number of patients prescribed any neuraminidase inhibitor between different age groups using data from the four hospitals are shown in Fig. 1 and Table 2, respectively. There were significant reductions in prescription levels after the intervention (β_2): 63·16% for ages 10 to 19 years ($P = 0.0008$) and 16·50% for ages ≥20 years ($P = 0.0354$), respectively. The trends (β_3) for ages 10–19 years and ages ≥20 years were −1·37 ($P = 0.6948$) and 2·47 ($P = 0.2380$), respectively, indicating an insignificant 1·37% decrease per season for the target group, and an insignificant 2·47% increase by per season for the control group compared with the baseline trends.

Results of action against OPZ+CPG

The average monthly numbers of patients prescribed the study drugs prior to and after the regulatory action in the four hospitals are summarized in Table 3. After the regulatory action, the mean number of individuals prescribed PPIs, CPG and co-administration increased significantly and to the same extent, 9·7% (8 070 vs. 8 856, $P = 0.0017$; Mann–Whitney *U*-test), 13·2% (903 vs. 1 022, $P = 0.0020$) and 13·2% (342 vs. 387, $P = 0.0029$), respectively.

The time series plots for mean proportions of the numbers of OPZ+CPG and LPZ/RPZ+CPG prescribed to patients prescribed CPG per month in the four hospitals are shown in Fig. 2, and the results of the segmented regression analysis are summarized in Table 4. The number of individuals prescribed OPZ+CPG did not

Table 1. Mean seasonal numbers of patients prescribed neuraminidase inhibitors prior to and after the regulatory action (20 March 2007) in four hospitals, by age group

Drug group	Age group / Period	Total (≥ 10)		10–19		≥20	
		Pre[a]	Post[b]	Pre[a]	Post[b]	Pre[a]	Post[b]
Total		686(201)	647(411)	109(50)	145(161)	576(189)	502(252)
Oseltamivir		641(185)	470(312)	106(49)	40(54)	535(175)	430(259)
Zanamivir		44(23)	159(120)	3(4)	100(111)	41(24)	59(35)
Peramivir[c]		–	4(4)	–	0·5(0·7)	–	4(4)
Laninamivir[d]		–	65	–	20	–	45

[a]From 2002/2003 to 2006/2007 season (5 seasons).
[b]From 2007/2008 to 2010/2011 season (4 seasons).
[c]Counted for 2009/2010 and 2010/2011 seasons (2 seasons) after approval of peramivir in January 2010.
[d]Counted for 2010/2011 season after approval of laninamivir in September 2010. Data in parentheses indicate SD.

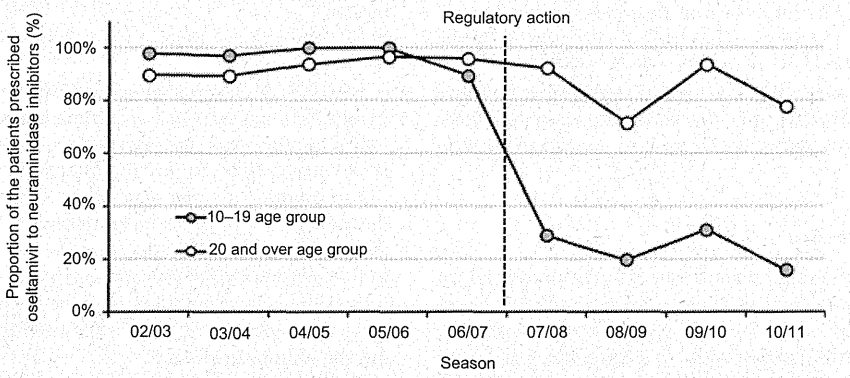

Fig. 1. Time series plots of seasonal change in the proportion of patients prescribed oseltamivir to neuraminidase inhibitors, by age group.

Table 2. Interrupted time series regression analysis of seasonal change in the proportion of the patients prescribed oseltamivir to neuraminidase inhibitors, by age group[a]

Group	Parameter	Coefficient	Standard error	*P*-value
10–19	Level change after action β_2	−63·16	8·69	0·0008
	Trend change after action β_3	−1·37	3·28	0·6948
≥20	Level change after action β_2	−16·50	5·28	0·0354
	Trend change after action β_3	2·47	1·78	0·2380

[a]Each model is adjusted for first-order autocorrelation as appropriate.

change significantly in level (P = 0·9250) or trend (P = 0·8040). In contrast, a slight but significant change in trend (a 0·60% increase per month compared with the preintervention trend, P = 0·0017) was observed in the LPZ/RPZ+CPG group.

For higher sensitivity in the detection of the intervention effect, we conducted a subanalysis of new users of CPG. Figure 3 shows the time series plots of mean proportions for OPZ+CPG and LPZ/RPZ+CPG among new CPG users. OPZ+CPG prescriptions did not show any change in level (P = 0·2814) or trend (P = 0·9945) in the new-user study. Prescriptions for LPZ/RPZ+CPG did not show any significant decline in level (4·99%, P = 0·1183), but there was an evident increase in trend (2·06% per month, P = 0·0001).

DISCUSSION

The interrupted time series is the strongest, quasi-experimental design for the evaluation of the longitudinal effects of an intervention that occurs at a particular time-point.[28,31–33] In addition, this design is recommended as a method with strong internal validity in a FDA-sponsored Mini-Sentinel project, the aim of which is to facilitate the Sentinel Initiative and to identify appropriate designs for evaluating FDA regulatory actions.[34] The interrupted time series design also allows analysis of aggregate data without identifiable personal information, which is suitable for a multicenter study. The analysis has the advantage of presenting the results in a graphical and intuitive way. Therefore, we adopted the interrupted time series analysis to evaluate the impact of regulatory actions in this study.

The regulatory action on oseltamivir had immediate effects, not only for the 10–19 years target age group, but also for the ≥20 years age group in our study. However, a steep decline was more prominent in the target group (63·16%) than in the control

Table 3. Mean monthly numbers of patients prescribed proton pump inhibitors, clopidogrel, or both prior to and after the regulatory action (27 April 2010) in four hospitals

		CPG total		PPIs total		OPZ subgroup		LPZ/RPZ subgroup	
Group	Period	Pre[a]	Post[b]	Pre[a]	Post[b]	Pre[a]	Post[b]	Pre[a]	Post[b]
PPIs				8 070(487)	8 856(454)	1 701(81)	1 708(54)	6 369(418)	7 147(432)
				Co-administration of PPI with CPG					
CPG		903(78)	1 022(52)	342(31)	387(36)	62(6)	51(7)	281(31)	335(38)

PPIs, proton pump inhibitors; OPZ, omeprazole; LPZ/RPZ, lansoprazole or rabeprazole; CPG, clopidogrel.
[a]From May 2009 to April 2010 (12 months).
[b]From May 2010 to April 2011 (12 months). Data in parentheses indicate SD.

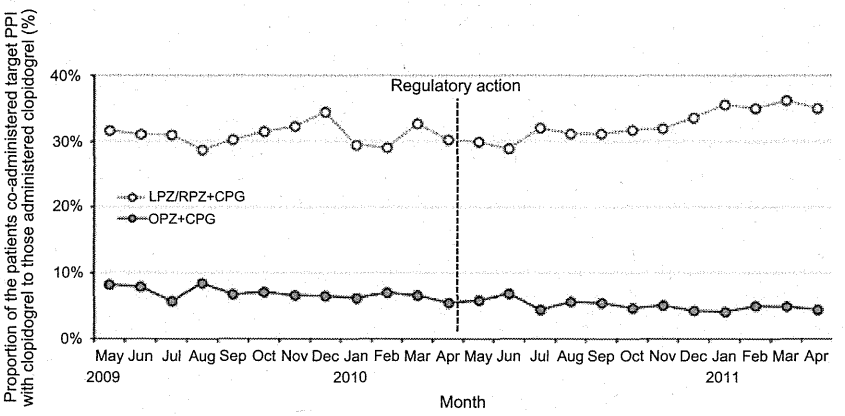

Fig. 2. Time series plots of monthly change in the proportion of patients co-administered proton pump inhibitors with clopidogrel to those administered clopidogrel, by treatment group.

Table 4. Interrupted time series regression analysis of monthly change in the proportion of patients co-administered proton pump inhibitors with clopidogrel, by treatment group[a]

Group	Parameter	Coefficient	Standard error	*P*-value
OPZ+CPG				
Total				
	Level change after action β_2	−0·06	0·58	0·9250
	Trend change after action β_3	0·02	0·08	0·8040
New-user subgroup[b]				
	Level change after action β_2	−1·90	1·71	0·2814
	Trend change after action β_3	0·001	0·25	0·9945
LPZ/RPZ+CPG				
Total				
	Level change after action β_2	−2·33	1·14	0·0550
	Trend change after action β_3	0·60	0·16	0·0017
New-user subgroup[b]				
	Level change after action β_2	−4·99	3·06	0·1183
	Trend change after action β_3	2·06	0·44	0·0001

OPZ+CPG, co-administration of omeprazole with clopidogrel; LPZ/RPZ+CPG, co-administration of lansoprazole or rabeprazole with clopidogrel.
[a]Each model is adjusted for first-order autocorrelation as appropriate.
[b]Patients who had not received clopidogrel within six months prior to the month in which clopidogrel was prescribed.

group (16·50%). The change in the control group was assumed to be due to external influences such as media publicity. The lower proportion of oseltamivir users after the intervention in the target group remained until the end of the follow-up period, suggesting a prolonged inhibitory effect for the regulatory action. Although a small but significant number of teenage patients were still prescribed oseltamivir after the action, this was considered reasonable because the restriction was not applied to patients at high risk of influenza[10] Therefore, the current results indicate that the regulatory action against oseltamivir use was effective both in the short-term and long-term.

To evaluate the generalizability of the current result to a larger population, our data were compared with those of two other Japanese studies, the MIHARI project conducted by the Pharmaceuticals and Medical Devices Agency, and Urushihara's report.[35,36] A comparison of the three data sets showed that our data were graphically consistent with both the MIHARI and Urushihara's results (Figure S2). In addition, a comparison of data from each hospital in this study revealed that the influence of the two regulatory actions was essentially identical among the four hospitals (data not shown). All our hospitals are equipped with a drug information (DI) room, the installation of which is encouraged by the MHLW to disseminate drug safety information. We estimated based on the MHLW documents[37] that approximately 65% of all hospitals in Japan already had a DI room in 2010, and therefore, our study hospitals were not considered to be special cases in terms of their response capability to regulatory actions. These findings indicate our four-hospital database is representative of the general population in Japan and is appropriate for use in a preliminary survey for pharmacovigilance purposes.

Regarding regulatory action against the use of OPZ+CPG, the target group showed no significant changes in prescription status after the regulatory action, but the control LPZ/RPZ+CPG group had a slight increase in trend. A comparison of the two groups indicates that this regulatory action might have a relatively small inhibitory effect in the target group.

To further examine the impact of this regulatory action, the data were stratified by selecting new users (i.e. patients without a medical history of CPG in the preceding six months) because continuous users of CPG were likely to continue receiving the same medication regardless of the regulatory action unless they experienced some problem. The results of the new-user study showed a significant increase in LPZ/RPZ+CPG prescriptions, which was consistent with the results from the complete data set. The difference between the two PPI groups, that is, no long-term change in OPZ+CPG prescriptions and gradual increase of LPZ/RPZ+CPG prescriptions, may reflect the response to the label change, suggesting that the intention of the regulatory action (label addition in drug-interaction section) is not communicated

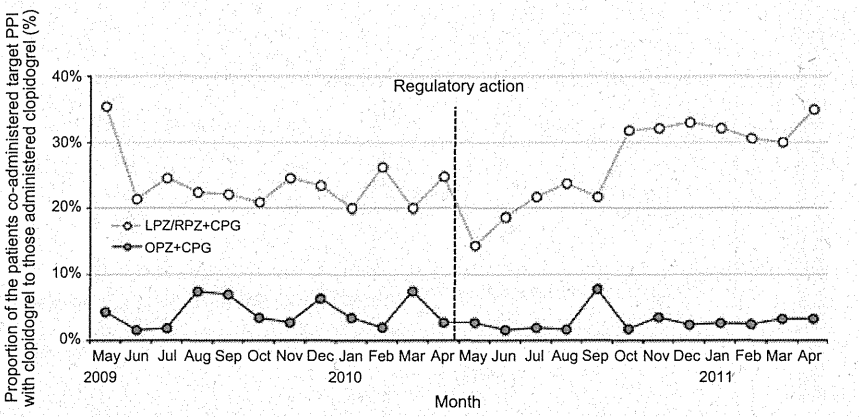

Fig. 3. Time series plots of monthly change in the proportion of patients co-administered proton pump inhibitors with clopidogrel to those administered clopidogrel only in the clopidogrel new-user population, by treatment group.

immediately, but leading to slower translation to the clinical setting. In addition, stratification by new users would be useful for eliminating bias due to the possible hangover effects in continuous users.

Drug regulatory authorities implement different levels of safety measures depending on the type of adverse reactions involved. In this study, we analysed the impact of two different levels of regulatory action, the *Dear Doctor* letter advisory for oseltamivir and a label change for OPZ+CPG. It was difficult to judge, based on our results, whether the *Dear Doctor* letter was more effective than the conventional label change. Moreover, the difference in time units of the two regulatory actions should be taken into account, especially when comparing their short-term effects. Additional evidence from future studies will be required to more accurately assess the impact of these regulatory actions. In particular, a comparative analysis of the impact of different levels of regulatory action for the same or related drugs would be beneficial.

Limitations

There are some limitations to this study. First, when using interrupted time series analysis to investigate the use of medications, it is generally recommended that 12 data points be used before and after the intervention.[28] However, in the current analysis of oseltamivir, fewer data points were available because data were collected only once annually to incorporate the influenza epidemic season. In addition, the impact of other sources, for example, media publicity and other regulatory notices, could not be distinguished from the effect of the regulatory action because of the annual intervals. Thus, this design may be better suited for the analysis of regulatory actions whose outcomes can be measured over shorter time intervals, for example monthly or weekly. Second, we examined a limited data set from only four hospitals. Although this analysis suggests generalizability of the method, a further large-scale study will be required to provide a more accurate and reliable assessment of the methodology for evaluating the impact of regulatory action.

WHAT IS NEW AND CONCLUSION

We have used analysis of interrupted time series with segmented regression of data from hospital MIDs to investigate the safe use of drugs and demonstrated the effectiveness of regulatory actions on the use of oseltamivir and OPZ+CPG. The results of the current study indicate that MID research can contribute to assessing and improving pharmacovigilance activities.

CONFLICT OF INTEREST

No conflict of interests have been declared.

SOURCE OF FUNDING

This study was supported by the Program for the Promotion of Studies in Health Science of the Ministry of Health, Labour and Welfare (Tokyo, Japan). The research was conducted independently of the funding organization.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1 Seasonal changes in average number of patients prescribed any neuraminidase inhibitors in our four hospitals and infected with Flu per sentinel in Japan.

Figure S2 Time series plots of seasonal change in the proportion of patients prescribed oseltamivir to neuraminidase inhibitors, by age groups compared to other Japanese reported studies.

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BRIEF REPORT

A detection algorithm for drug-induced liver injury in medical information databases using the Japanese diagnostic scale and its comparison with the Council for International Organizations of Medical Sciences/the Roussel Uclaf Causality Assessment Method scale

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ABSTRACT

Purpose Drug-induced liver injury (DILI) is one of the primary targets for pharmacovigilance using medical information databases (MIDs). Because of diagnostic complexity, a standardized method for identifying DILI using MIDs has not yet been established. We applied the Digestive Disease Week Japan 2004 (DDW-J) scale, a Japanese clinical diagnostic criteria for DILI, to a DILI detection algorithm, and compared it with the Council for International Organizations of Medical Sciences/the Roussel Uclaf Causality Assessment Method (CIOMS/RUCAM) scale to confirm its consistency. Characteristics of DILI cases identified by the DDW-J algorithm were examined in two Japanese MIDs.

Methods Using an MID from the Hamamatsu University Hospital, we constructed a DILI detection algorithm on the basis of the DDW-J scale. We then compared the findings between the DDW-J and CIOMS/RUCAM scales. We examined the characteristics of DILI after antibiotic treatment in the Hamamatsu population and a second population that included data from 124 hospitals, which was derived from an MID from the Medical Data Vision Co., Ltd. We performed a multivariate logistic regression analysis to assess the possible DILI risk factors.

Results The concordance rate was 79.4% between DILI patients identified by the DDW-J and CIOMS/RUCAM; the Spearman rank correlation coefficient was 0.952 ($P < 0.0001$). Men showed a significantly higher risk for DILI after antibiotic treatments in both MID populations.

Conclusions The DDW-J and CIOMS/RUCAM algorithms were equivalent for identifying the DILI cases, confirming the utility of our DILI detection method using MIDs. This study provides evidence supporting the use of MID analyses to improve pharmacovigilance.

KEY WORDS—drug-induced liver injury; medical information database; pharmacovigilance; DDW-J; antibiotics; pharmacoepidemiology

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INTRODUCTION

Drug-induced liver injury (DILI) is a clinically problematic issue and a major cause of acute liver failure.[1–3] In general, DILI diagnosis is complex and nonstandardized because of the difficulty in detection and lack of reliable markers.[4,5] Therefore, clinical scales were developed to facilitate DILI diagnosis. The Council for International Organizations of Medical Sciences/the Roussel Uclaf Causality Assessment Method (CIOMS/RUCAM) scale was proposed[6] and has been generally used as a standardized diagnostic tool. In Japan, the Digestive Disease Week Japan 2004 (DDW-J) scale, which is highly sensitive (92.1%) and specific (88.1%), was developed by modifying the CIOMS/RUCAM scale.[7,8] In particular, the factor of co-medication was excluded, and the factors of drug lymphocyte stimulation test and eosinophilia were included according to Japan's clinical environment.

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Challenges using medical information databases (MIDs) for identifying DILI have been addressed worldwide,[9,10] but a standardized method for such analyses has not yet been established. Because a diagnosis scale based on numerical or quantitative information was considered suitable for MID-based research, we constructed a detection algorithm for DILI on the basis of the DDW-J scale.

METHODS

Data source and ethics

This study was performed using two data sources: one was a high-speed retrieval system at the Hamamatsu University Hospital (Shizuoka, Japan),[11] and the other was a commercial MID developed by the Medical Data Vision Co., Ltd. (MDV, Tokyo, Japan) that contained data from 124 large and mainly tertiary hospitals in Japan. The mean follow-up period within this MID was 243 days. MIDs from Hamamatsu and MDV included health records from approximately 200 000 and 4 400 000 patients, respectively. The two MIDs had similar age structures. We used only anonymized data in our analysis. This study was approved by the ethics committees of both the Hamamatsu University School of Medicine and the National Institute of Health Sciences.

Study population

Clarithromycin (CM), azithromycin (AM), levofloxacin (LX), and moxifloxacin (MX) for internal use were examined in this study because of their similar clinical indications and their wide use in Japan. The subject inclusion criteria were as follows: (i) received at least one prescription for one of the study drugs between 1 April 2007 and 31 March 2012 in the Hamamatsu MID and between 1 April 2008 and 31 August 2011 in the MDV MID; (ii) no other study drug prescription between 90 days prior to the index date (the first day of the study drug administration) and the last administration in the first prescription term (>180-day interval between the study drug administrations); (iii) 18 years old or older at the index date; (iv) received alanine aminotransferase, and alkaline phosphatase tests in the preceding period (within 90 days prior to the index date) and the follow-up period (within 180 days after the last administration); (v) no occurrence of liver injury (alanine aminotransferase > 2 × the upper limit of normal value or alkaline phosphatase > upper limit of normal value) in the preceding period; (vi) no medical history in the preceding period of HIV (B20-24) or cancer (C00-97) as determined by the International Statistical Classification of Diseases and Related Health Problems, 10th revision.

Characteristics

On the basis of the general considerations for usage and dosage in each label, a long treatment was considered ≥8 days with CM, LX, and MX and ≥4 days with AM; a high dose was considered an average daily dose of >400 mg/day for CM and MX, >500 mg/day for AM and LX, and >2000 mg/day for AM in dry syrup form for single administration.

Algorithm for identifying drug-induced liver injury

We applied the original DDW-J scoring to the DILI detection algorithm consistently.[12] In addition, the algorithm based on the CIOMS/RUCAM scale was used as a reference.[6] Details regarding these two scales are summarized in Table S1. According to the definition of each scale, DILI was defined as a total score ≥5 in the DDW-J and ≥6 in the CIOMS/RUCAM algorithm.

Statistical analysis

To calculate the odds ratios (ORs) for DILI onset and those between DILI and non-DILI groups, we performed a multivariate logistic regression analysis adjusting for age (≥55 years), gender, in/outpatient status, diabetes mellitus, treatment duration, and high dose. Values of $P < 0.05$ (two-sided) were considered statistically significant. All statistical analyses were conducted using SAS software, version 9.3 (SAS Institute Inc., NC, USA).

RESULTS

Assessment of drug-induced liver injury detection algorithm

Using the DDW-J algorithm in the Hamamatsu population, we detected 182 DILI patients. To assess the utility of the DDW-J algorithm, we compared the results with those obtained with the CIOMS/RUCAM algorithm. Because the CIOMS/RUCAM scale excludes the delayed onset cases (>15 days for hepatocellular type or >30 days for cholestatic or mixed type after stopping the drug) from scoring except when dealing with slowly metabolized chemicals, the comparison was performed in the nondelayed onset population (Figure 1). The concordance rate for DILI patients between the two algorithms was 79.4%; the Spearman rank correlation coefficient was 0.952 ($P < 0.0001$). Although the CIOMS/RUCAM scale does not explicitly define slowly metabolized chemicals, AM has a longer half-life than other drugs.

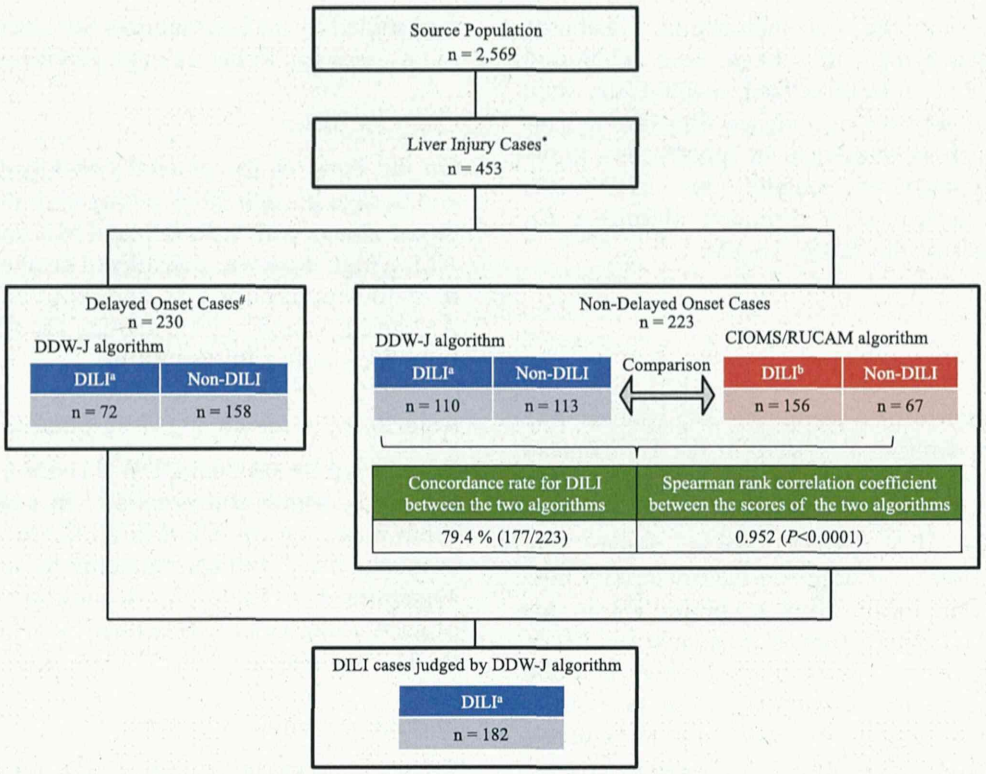

Figure 1. Identification of drug-induced liver injury (DILI) cases in the Hamamatsu population. *Patients with alanine aminotransferase > 2 × the upper limit of normal value (ULN) or alkaline phosphatase >ULN from the index date to 180 days after the last administration. #Patients in which the liver injury occurred after 15 days for the hepatocellular type, or more than 30 days for the cholestatic or mixed type, following the last administration. [a]Defined as a total score ≥5 in the Digestive Disease Week Japan 2004 (DDW-J) algorithm. [b]Defined as a total score ≥6 in the Council for International Organizations of Medical Sciences/the Roussel Uclaf Causality Assessment Method (CIOMS/RUCAM) algorithm

We therefore performed sensitivity analysis that incorporated the delayed onset cases prescribed AM into the comparison. This analysis showed consistent findings with a concordance rate of 78.4%.

Presence of possible alternative causes in DILI cases was compared with liver injury cases judged as non-DILI by the DDW-J algorithm in the Hamamatsu population (Table S2). The results showed that patients with alternative causes, such as viral hepatitis, were effectively excluded by this algorithm.

Characteristics of drug-induced liver injury patients

The study population sizes in MIDs from Hamamatsu and MDV were 2569 and 3856, respectively. To examine the characteristic of DILI patients, the ORs for DILI identified by the DDW-J algorithm were calculated (Table 1, with details in Table S3). The ORs of DILI onset in men were 1.44 (95% confidence interval, 1.05–1.98) in the Hamamatsu MID and 1.32 (95% confidence interval, 1.01–1.72) in the MDV MID. Because there were considerable differences in the average treatment duration, we performed an additional sub-analysis on treatment duration stratified by the study drugs. In the MDV MID, CM and LV subpopulations showed a significant association between a long treatment duration and DILI.

DISCUSSION

We demonstrated that the DDW-J algorithm was highly compatible with the CIOMS/RUCAM algorithm in the Hamamatsu MID (Figure 1). This indicates the DDW-J algorithm has adequate generalizability in assessing DILI. Using the DDW-J algorithm, we examined the characteristics of DILI cases by assessing the potential risk factors. Furthermore, we used the same study protocol to investigate a second population that included patients from multiple hospitals (MDV MID) to improve the robustness of our results. As a result, men showed a significantly higher risk for DILI in both populations. This finding is inconsistent with those of previous reports, although the role of gender in DILI remains controversial.[4] Alcohol consumption is one of the criteria in both the DDW-J and CIOMS/RUCAM scales, but this information was not available in the

DOI: 10.1002/pds

Table 1. Comparison of odds ratios (ORs) for onset of drug-induced liver injury (DILI) in two medical information databases (MIDs)

	Hamamatsu University Hospital MID				MDV MID			
Characteristics	*n*	OR*	95% CI	*P*-value	*n*	OR*	95% CI	*P*-value
Total	2569				3856			
Age ≥55 years		1.49	1.02–2.17	0.0371		0.85	0.63–1.16	0.3052
Male		1.44	1.05–1.98	0.0237		1.32	1.01–1.72	0.0409
Inpatient		1.38	1.01–1.90	0.0452		1.30	0.99–1.72	0.0624
Diabetes mellitus		0.81	0.47–1.38	0.4316		0.90	0.60–1.36	0.6225
Long treatment[a]		1.14	0.83–1.57	0.4225		1.46	1.10–1.94	0.0082
High dose[b]		1.83	0.81–4.16	0.1473		1.34	0.73–2.48	0.3436
Clarithromycin sub-group	524				845			
Days ≥8		1.19	0.56–2.52	0.6531		3.18	1.59–6.37	0.0011
Days ≥28		2.08	0.91–4.80	0.0846		2.97	1.43–6.15	0.0034
Levofloxacin sub-group	1551				2441			
Days ≥8		1.15	0.75–1.76	0.5273		1.57	1.10–2.23	0.0122

CI, confidence interval; DILI, defined as Digestive Disease Week Japan 2004 score ≥5.
[a]Patients whose treatment duration was ≥8 days in clarithromycin, levofloxacin, and moxifloxacin and ≥4 days in azithromycin.
[b]Patients whose average dose was beyond the usual approved dose.
*Adjusted for age (≥55 years), gender, in/outpatient status, diabetes mellitus, treatment duration, and high dose.

current study. Because the national survey in Japan indicated that alcohol consumption was remarkably higher in men than in women (35.1% vs. 7.7%),[13] the gender difference in alcohol consumption might have led to a higher risk in men.

Regarding treatment duration, a longer treatment with CM and LX, which included an adequate population size in this study, was significantly associated with DILI in the MDV population. In the Hamamatsu population, the long treatment groups, especially the ≥28-day CM group, showed a tendency toward a higher risk for DILI, although the associations were not significant. These results might indicate that DILI should be carefully monitored during the long-term treatments with antibiotics. Although further confirmation in a larger-scale study is necessary, our algorithm, which is based on a clinical diagnostic scale, could be a useful method to identify DILI and access its risk-related information through MID research.

The current study has some limitations. The DDW-J and CIOMS/RUCAM scoring systems were designed for prospective diagnoses of individual cases, and their utilities in retrospective studies, including the quality of DILI cases identified by our algorithms, were not validated. Furthermore, we could not retrieve additional information from the MIDs used in this study, such as drinking habits and pregnancy, which constitutes parts of the scoring systems. This might lead to underestimation of DILI risk. In addition, articles on the DDW-J were predominantly published in Japanese-language journals, which makes it difficult for non-Japanese researchers to assess and utilize the DDW-J scale. Although regional DILI scoring would still be required for diagnostic purpose when considering the Japanese medical environment, the adoption of a uniform diagnostic approach will be preferable in future.

In conclusion, we have proposed a useful method that uses MIDs for identifying DILI. Our study supports the utility of MID research in pharmacovigilance.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

KEY POINTS
- A standardized detection method for DILI using MIDs has not yet been established because of the complexity of diagnosis.
- We applied a Japanese DILI diagnostic scale, DDW-J, to a DILI detection algorithm that is applicable for assessment of potential risk factors.
- The DDW-J algorithm was compatible with the international CIOMS/RUCAM scale, which indicates the utility of the algorithm.
- This study supports the utility of MID-based research for improving pharmacovigilance.

ETHICS STATEMENT

This study was approved, including procedures for informed consent, by the ethics committees of both the Hamamatsu University School of Medicine and the National Institute of Health Sciences.

ACKNOWLEDGEMENTS

We thank Ms. Kaori Ota and Mr. Masaki Nakamura (MDV) for their technical support. This study was supported by the Program for the Promotion of Studies in Health Science from the Ministry of Health, Labour and Welfare of Japan (H23-iyaku-shitei-025). The authors' research was conducted independently of the funding organization.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web site.

Ⅲ.研究成果の刊行物・別刷

【学会発表】

1. M. Kimura:

Medical Institutions Implementing SS-MIX: What can be done?,

10th Annual Meeting DIA Japan 2013,

Tokyo, Japan, November 7, 2013.

Medical institutions implementing SS-MIX standardized storage; What is this, and what can be done

Michio Kimura, MD, PhD, FACMI
Hamamatsu University, School of Medicine
HL7 Japan Chair

Japan's Cabinet's New IT Project "Pharmacovigilance by HIS data"

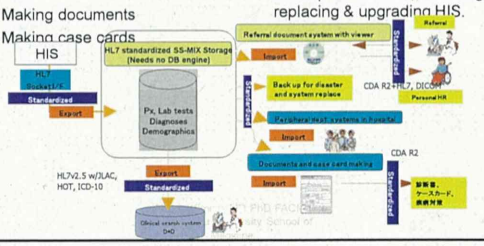
- PMDA(FDA of Japan) already launched 5 year project in 2009
- Because of court order of slow disqualification of hepatitis C virus contaminated drug case, and drug rag problem
- "Not only pre market clinical trials, post market surveillance, spontaneous report, also HIS data should be utilized"
  - HL7 standardized SS-MIX infrastructure makes reporting easier

CPOE(Computerized Physician's Order Entry) in Japan

- 90%+ in large hospitals (400+ beds)
- Top 2 vendors became able to export patient demographics, prescriptions, lab results, diagnoses, in HL7 v2.5 messages
  - Ministry of Health standard designation ...March 2010
    - HL7 v2.5, HL7 CDA R2, DICOM and IHE PDI, Codes (ICD10, drug code, lab exam code)

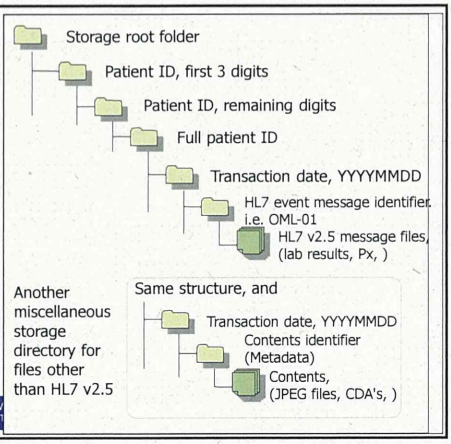
Ministry of Health Project: SS-MIX: HL7 standardized clinical information storage Wide variety of applications

- We have patient demographics, prescriptions & injections, lab results, diagnosis classifications in HL7 v2.5
  - PHR
  - Making documents
  - Making case cards
  - Clinical database
  - Interoperability with peripheral systems
  - Backup for disaster, including replacing & upgrading HIS.



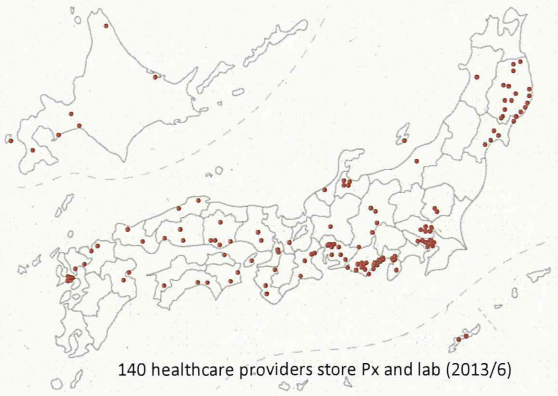
SS-MIX Storage

- Patient ID
  - birth date
    - contents
- Filesystem directory service only
- No DB engine needed
  - but, quick retrieval



HL7 exportable HIS, and SS-MIX standardized storage counts(2013/6)

- Hospitals with HL7 message exportable HIS
  - Fujitsu (FX, GX) 461
  - NEC (ADv4+, HR) 172
  - SBS 22
  - Software Service Inc. 342
  - others 65 (total 1,059)
- SS-MIX standardized storage, counts by installer
  - Fujitsu 50
  - NEC 19
  - SBS 84
  - Software Service Inc. 36
  - others 27 (total 216)



140 healthcare providers store Px and lab (2013/6)

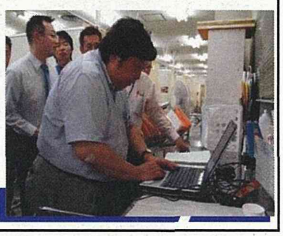
How many people covered by SS-MIX storage?

- 140: storing prescription and lab results
- Average hospital (250 beds) stores 2 years of data, first year 20,000 plus second year increase 7,000
- 27,000*140=3,780,000
- Possible duplication deducted: 3,000,000.

Ministry projects on SS-MIX storage

- MoH and PMDA's MIHARI and MID-NET (Japan Sentinel) for drug safety
- MoH's regional healthcare information sharing (Noto, Urasoe, Miyako, 100+)
- METI(Economics, Trade, Industry)'s "My Hospital, Everywhere" project (Noto)
- MoE's 42 national university hospital EMR backup for disaster.

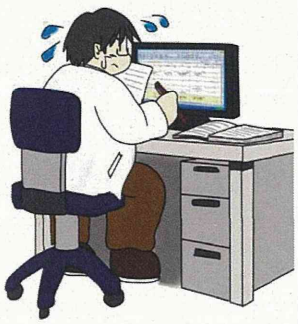
20 SS-MIX storage in PC can provide Px, lab, Dx without power, network



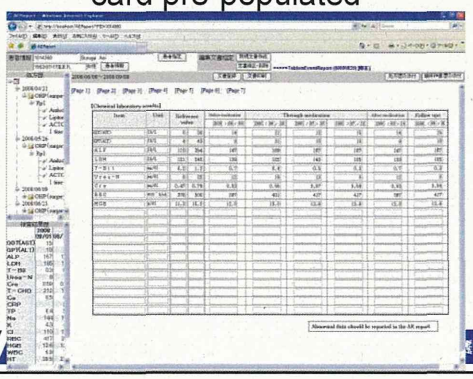
At Hamamatsu Univ. Hosp.

Case cards

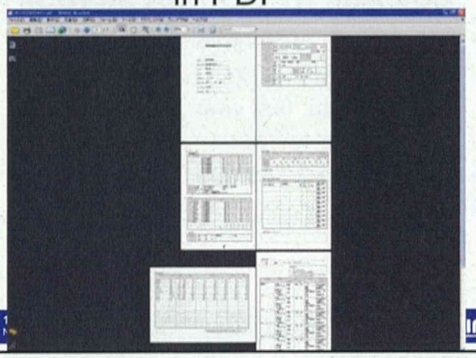
- Made by hand
- But, most of the data are in CPOE
  - Prescription history of the drug
  - Concurrent drugs
  - Lab results

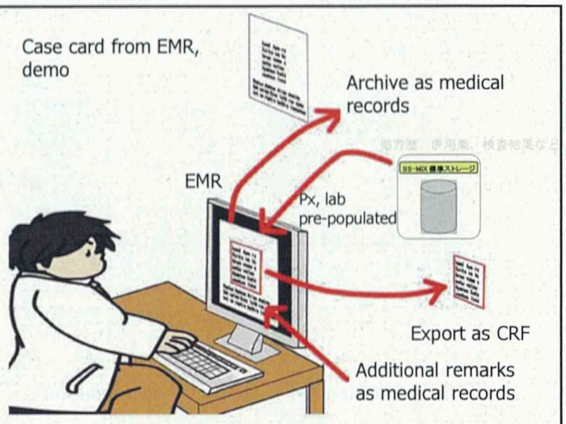


Prescription history of the case card pre-populated



Adverse event reports are ready in PDF

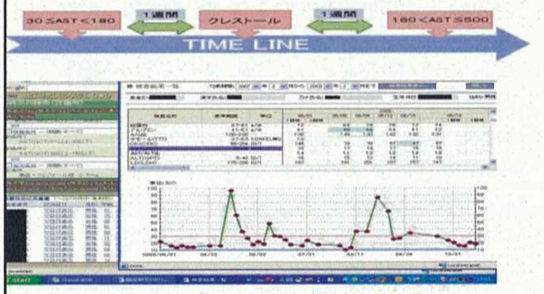




Clinical Information Retrieval System: D*D

10 years, 73,709,298 records of prescription, lab results, diagnosis classification s at Hamamatsu Univ. Hosp. Searchable in time sequence in a few minutes

Search example



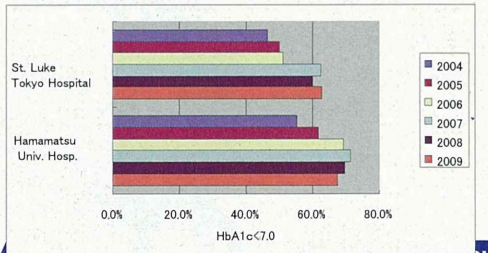
Listing up of patients, with AST:30-180 one week before the first prescription of "Crestor" (Rosuvastatin, anti-hyperlipidemia), then AST elevated to 180-500 within one week

Other examples at Hamamatsu Univ. Hosp.

- In 2007, patients recorded HbA1c=6.6-8.0, and re-examined within 3 weeks
  - -5.8: 55 cases, 5.9-6.5: 289 cases, 6.6-8.0: 657 cases, 8.1+: 192 cases
- Gemzar (Gemcitavin for cancer) first prescription: 181 cases in 2007
  - Then, diagnosed as interstitial pneumonia (ICD-10 J84.x) : 7 cases
- Stroke onset, and recurrence within 3 years?
  - "Stroke" is a disease used for the reason to examine CT or MRI, which includes full of noises.

Hospital performance indicators

- HbA1c control of diabetes patients by the year

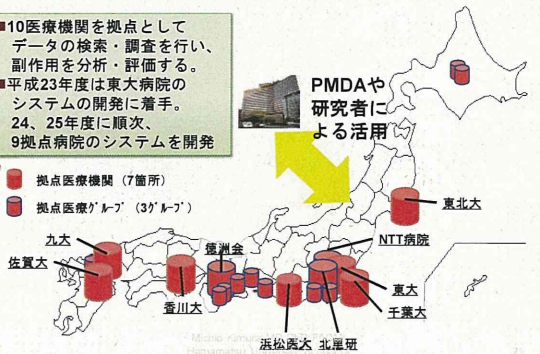


A New HIS Network Project by MHLW/PMDA (MID-NET project)

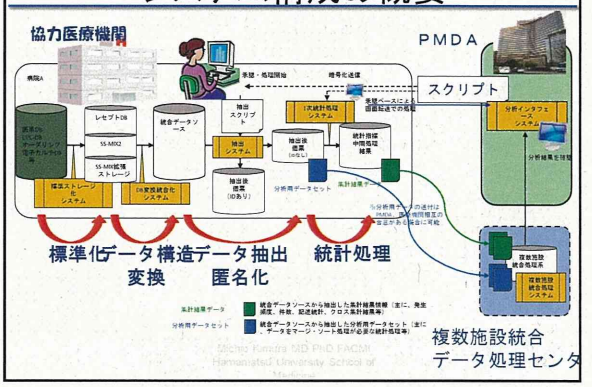
- Drug safety assessment and validation from 10,000,000 patients (hopefully)
- Budget 110M yen($1.1M) for 2011
  - 3 year total 260M yen
  - Planned to install the clinical search system D*D, which was based on MIHARI in Shizuoka to 10 core hospitals including Hamamatsu University hospital
  - 2012 Tokyo Univ., 2013 6, 2014 3
  - Trial use starts April 2014
- "CPOE based" means AE can be detected real time without delay.

本事業の拠点医療機関

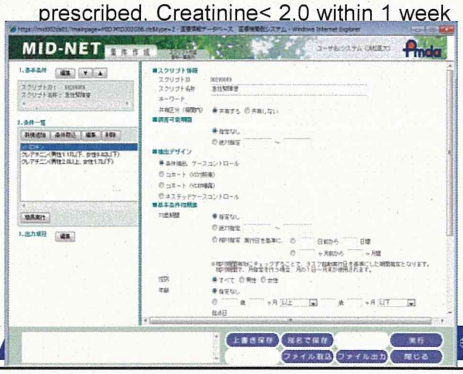
■10医療機関を拠点として
データの検索・調査を行い、
副作用を分析・評価する。
■平成23年度は東大病院の
システムの開発に着手。
24、25年度に順次、
9拠点病院のシステムを開発



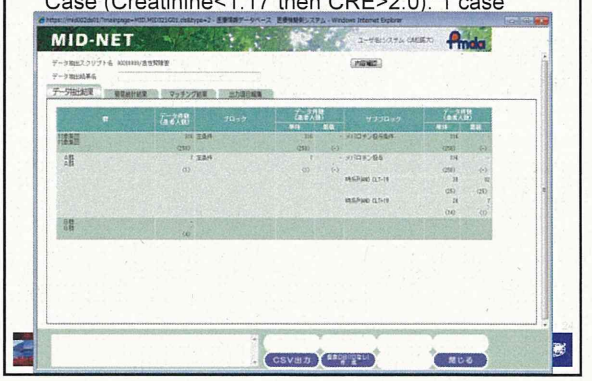
システム構成の概要



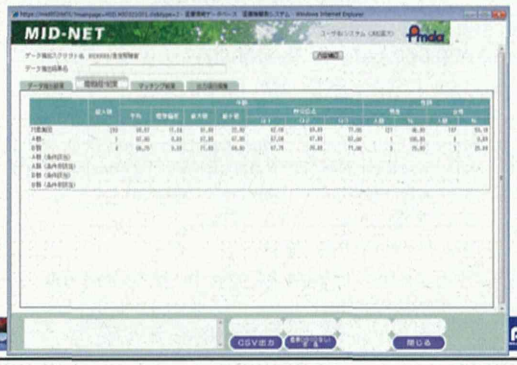
Setting script: Creatinine< 1.17,
then Pravastatine (Mevalotine^{R})(any titer)
prescribed, Creatinine< 2.0 within 1 week



Control (Pravastatin prescribed): 253 cases
Case (Creatinine<1.17 then CRE>2.0): 1 case



Demographics of Case and Control (mean, SD, min, max, age, sex,,)



21 CFR Part11 (21 Code of Federal Regulations)

- Can SS-MIX w/ EMR in Japan conform?
- Most hospital's EMR conforms
  - MOH guideline for secure HIS
  - EMR printouts are submitted to lawsuits as evidences
- With some more, EMR in Japan can conform easily
  - log and certificate for testing, updating.

"Pharmacovigilance by HIS data" pros & cons

- "Early detection of side effects" will be welcomed by citizens
- We have cases out of "population", which we could not get by spontaneous reports
- Japan's high percentage of CPOE makes advantage
- Easy importable information is Px history, lab results. Disease classifications are doubtful. (They are in HL7 format in 117 hospitals)
- But sign and symptom descriptions are difficult.

Thank you for your attention and helping hands

TOKYO 1964

TOKYO 2020

2. 木村通男：
大規模医療データベースのバリデーション
（日本医療情報学会、日本薬剤疫学会、
日本臨床薬理学会、日本臨床試験研究会の
共同ワークショップ），
第 33 回医療情報学連合大会，
医療情報学，第 33 回医療情報学連合大会
論文集 33-Suppl, 12-13, 2013.