Relapse and Long-Acting Injectable Risperidone: A 1-Year Mirror Image Study with a National Claims Database in Taiwan

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ABSTRACT

Objectives: The development of long-acting, injectable atypical antipsychotics has provided a new paradigm for schizophrenia treatment. The study was designed to assess whether a risperidone long-acting injection (RLAI) is associated with reduced relapses and service utilization in the real world.

Methods: The Psychiatric Inpatients Medical Claims dataset was used for the analysis. It is a longitudinal dataset that includes the National Health Insurance claims of service uses by a cohort of mentally ill patients. The inclusion criteria for this analysis were patients who: 1) had available information for at least 12 months after the first dose of RLAI; 2) had a primary diagnosis of schizophrenia; and 3) were regularly treated with RLAI for at least 1 year. Patients who accumulatively received at least 75-mg RLAI per 3-month period were considered to be undergoing regular treatment. Wilcoxon signed rank tests were performed to compare differences in numbers of acute admissions, hospital days, emergency room visits, and relapses between the pre- and post-RLAI periods in this 1-year mirror-image study.

Results: In total, 108 patients were eligible for analysis. Significant reductions in the total annual numbers of acute hospital admissions by 55% (80 vs. 36, $P = 0.0003$), hospital days by 48% (4106 vs. 2126, $P = 0.0021$), and relapses by 54% (115 vs. 53, $P = 0.0005$) were observed. A reduction of emergency room visits was also observed, but did not reach statistical significance (55 vs. 25, $P = 0.1255$).

Conclusions: This 1-year mirror-image analysis with claims-based data demonstrated that RLAI treatment was associated with reductions in relapses and hospital service utilization.

Keywords: National Health Insurance, relapse, risperidone long-acting injection, schizophrenia, Taiwan.

Introduction

Schizophrenia is a debilitating illness resulting in significant costs for as much as 3% of total health–care expenditure [1], primarily a reflection of the frequent need for inpatient or other intensive emergent services required to manage acute relapses which are often related to poor compliance [2]. Indeed, relapses lead to acute admissions, deterioration of health status, functioning [3,4] adverse neurological sequela [5], and disease chronicity [2].

Achieving good compliance to antipsychotic medications for patients with schizophrenia remains the most challenging issue for relapse prevention. For example, patients receiving antipsychotics took an average of only 58% of the recommended amount of the medications [6], although it is slightly less an issue for newer than for older antipsychotic agents found in recent studies [7]. It is striking to find that, in the recent landmark Clinical Antipsychotic Trials of Intervention Effectiveness study, 74% of trial participants discontinued the study medication before the planned 18 months [8]. Discontinuation and poor compliance to antipsychotic medications potentially lead to a disease relapse and an increase of hospital utilization. For example, in the classic studies of maintenance antipsychotic medication from a Veterans Administration study of schizophrenia, the relapse rate for inpatients randomly assigned to receive placebo was 15% per month, as compared to 1.5% per month of relapse rate for inpatients assigned to receive continuous medication [9,10]. Interestingly, the relapse rate for outpatients assigned to receive continuous medication was slightly higher (3–5% per month) [9,10] than that for inpatients (1.5% per month), implying that an increased unreliability in medication taking (noncompliance) from inpatient to outpatient settings can make difference in disease relapse [11].

Because relapses in patients with schizophrenia are associated with poor outcome and prognosis, the improvement of medication compliance becomes a major issue when dealing with relapse prevention [12]. Long-acting injection of antipsychotics is a valuable strategy to improve medication compliance, and hence, could potentially improve treatment outcomes [12]. Recent clinical trials and mirror-image studies support that the oral route of administration results in a higher risk of relapse than depot injections. For example, a systematic review with randomized-controlled clinical trials on comparing oral and depot forms of conventional antipsychotic medications revealed that the 1-year relapse rate was 42% for oral administration compared with 27% for the depot route [11]. Mirror-image studies, in which each patient acts as his/her own control, of long-acting injection of conventional antipsychotics have shown significant decreases of numbers and days of hospitalization. For example, in Denham and Adamson's study, enrolling 103 patients with chronic schizophrenia who were currently receiving either fluphenazine enanthate or decanoate, the number of hospitalizations was reduced by 73% and the number of days of hospitalization by 82% after patients' switching from oral to depot administrations [13].

The development of second-generation antipsychotics (SGA) has provided a new treatment paradigm because of their superior tolerability and efficacy [14–16], and in some cases, cost-effectiveness [17,18]. In addition, a recent study by Dolder et al. also showed that medication compliance was better with SGA

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than first-generation antipsychotics (FGA) in schizophrenia patients [7]. Specifically, outpatients receiving haloperidol or perphenazine (FGA) were without medication for approximately 7 days per month, although patients receiving risperidone, olanzapine, or quetiapine (SGA) were without medication for approximately 4 days per month. Risperidone long-acting injection (RLAI) is the first licensed long-acting injectable SGA and was recently reported to be cost effective in reducing the total admission numbers and inpatient days in a mirror-image analysis from a community-based inpatient setting [19]. A study from Chang et al. based on national claim-based database reported preliminary results on changes in hospital service utilization among a sample of patients in Taiwan who regularly used RLAI for 6 months but changes in relapses were not reported [20]. In this study, we tested the hypothesis that RLAI can reduce 1-year relapses and hospital service utilization in a mirror-image analysis with the National Health Insurance (NHI) claims database from Taiwan.

Method

Data Sources

The data for this study were obtained from the Psychiatric Inpatients Medical Claims Data (PIMC) compiled from claims data of the NHI program and released by the National Health Research Institutes, Taiwan. The NHI claims database contains nationwide population-based data. It provides comprehensive information on health-care resource utilization by more than 21 million enrollees, representing about 97% of the Taiwanese population. The PIMC contains longitudinal data from January 1, 1996 to December 31, 2006 of a cohort of 91,104 mentally ill patients who were admitted to hospitals by psychiatry departments with ICD-9-codes 230–319 or A-codes A210–A219 during 1996–2001.

Study Subjects

From June 1, 2004, the NHI program began to include the RLAI in its formulary. To the end of 2006, 1449 patients had been prescribed RLAI. The index date was defined as the date of the outpatient/emergency visit, or the discharge date of the hospitalization, when RLAI was prescribed for the first time. The inclusion criteria for study subjects in this study were patients who: 1) could be observed for at least 1 year before the index date (pre-RLAI periods); 2) had a primary diagnosis of schizophrenia (ICD-9-CM code 295) at the index visit/hospitalization; and 3) were regularly treated with RLAI for at least 1 year (post-RLAI periods). Patients who received at least 75-mg RLAI every 3 months were considered to be undergoing regular treatment (see Fig. S1 at Relapse and Long-Acting Injectable Risperidone: A 1-Year Mirror Image Study with a National Claims Database in Taiwan at *Value in Health*, Supporting Information at: http://www.ispor.org/Publications/value/ViHsupplementary/ViH12s3_Tang2.asp. for the selection process for study subjects).

The final sample available for analysis was 108 patients. Because the average hospital stay for single acute psychiatric hospitalization was 33 days in Taiwan in 2007, a secondary analysis excluding patients who had long hospital stays (90 days per acute ward admission) in either period was conducted to minimize the possible impact of extreme cases of prolonged hospitalization. The sample available for this secondary analysis was 91 patients.

Outcome Measurement

Health-care utilization in 12 months before the initial RLAI use (the pre-RLAI period) and in 12 months after the initial RLAI use (the post-RLAI period) was compared. Specific health-care utilization measures were numbers of acute admissions, hospital days, emergency room (ER) visits, and relapses. The number of relapses was defined as the sum of number of admissions and ER visits. Nevertheless, admissions and emergency visits occurred within 2 days were considered as the same episode of care and were defined as one relapse.

Statistical Analyses

Wilcoxon signed rank tests were performed to compare differences in the numbers of acute admissions, hospital days, ER visits, and relapses between the pre- and post-RLAI periods in this 1-year mirror-image study. All analyses were performed using the SAS/STAT system for Windows, version 9.01 (SAS Institute, Cary, NC, USA).

Results

There were 108 subjects eligible for analysis, and their characteristics are reported in Table S1 (see Table S1 at Relapse and Long-Acting Injectable Risperidone: A 1-Year Mirror Image Study with a National Claims Database in Taiwan, *Value in Health*, Supporting Information at: http://www.ispor.org/Publications/value/ViHsupplementary/ViH12s3_Tang2.asp). The mean age was 42.01 ± 10.44 (range, 20.67–67.44) years. The mean dose of RLAI in the post-RLAI period was 175.44 ± 54.47 mg per 3-month period. None of them had received more than one dosage of typical long-acting injectable antipsychotics in the pre-RLAI period. More than three quarters of the subjects (78.70%) were on monotherapy before their switching to RLAI, among them, about two-thirds (68.23%) were on SGAs and one-third (31.77%) were on FGAs. Among those who were on SGAs, about 30% were using oral risperidone. About 13.89% of subject received both SGAs and FGAs medication at the same time.

In Table S2, the Wilcoxon signed tests showed that number of acute admissions, number of hospital days, and number of relapses were significantly lower in the 1-year pre-RLAI period than those in the 1-year post-RLAI period. In the secondary analysis, the case number was slightly decreased (n = 91), but differences in acute admissions, hospital days, and relapses remained significant (see Table S2 at Relapse and Long-Acting Injectable Risperidone: A 1-Year Mirror Image Study with a National Claims Database in Taiwan, *Value in Health*, Supporting Information at http://www.ispor.org/Publications/value/ViHsupplementary/ViH12s3_Tang2.asp). A reduced number of emergency room visits was observed in both the primary and the secondary analyses, but did not reach statistical significance.

Table S3 showed that, compared to the 1-year pre-RLAI period, the total annual number of acute admissions was reduced by 55% (80 vs. 36), total hospital days were reduced by 48% (4106 vs. 2127), and numbers of relapses were reduced by 54% (114 vs. 53) in the 1-year post-RLAI period (see Table S3 at Relapse and Long-Acting Injectable Risperidone: A 1-Year Mirror Image Study with a National Claims Database in Taiwan, *Value in Health*, Supporting Information at: http://www.ispor.org/Publications/value/ViHsupplementary/ViH12s3_Tang2.asp). A reduced number of ER visits was also observed (55 vs. 25), but did not reach statistical significance. The secondary analysis showed similar reducing patterns in the health-care resource use before and after the initial use of RLAI.

Discussion

In this 1-year mirror-image study using a national claims-based database in Taiwan, we found that RLAI was associated with reductions in relapses and hospital service utilization, measured

by days of hospital stays, and numbers of acute admissions and ER visits, in patients with schizophrenia. This implies that there might be a correlation between a positive treatment outcomes and improved medication compliance by changing from oral to injectable antipsychotics. Our findings, using a national claims-based database, are consistent with previous mirror-image studies comparing oral and depot forms of fluphenazine [13,21,22] or risperidone [19] using data from hospital settings.

In mirror-image studies, a period before an index event, in our case the starting date of RLAI treatment, can be compared with a period of equal length after that event. The strength of this method is that each patient serves as his/her own control. Nevertheless, the advantage of long-acting injectable agents can be overestimated due to: 1) the selection bias (e.g., the long-acting injection was begun when previous treatments failed, and the including criteria might be too restricted and rule out many patients; 2) the changes in service delivery may be associated with administration of the RLAI rather than RLAI itself (e.g., enhanced follow-up after the implementation of a new treatment); 3) the natural disease course of tending stabilization; and 4) the exclusion of patients with partial compliance in traditional mirror-image studies conducted in clinical settings (e.g., patients who lost some of their psychiatric follow-up were not included in certain study appointments). With the claims-based database, we can mildly minimize the latter bias by obtaining most of the data meeting the minimal requirement in the database. In this study, we used an including criteria of "receiving at least 75 mg RLAI every three-month period," which is a relatively flexible criterion because the usual dose of RLAI is 25 to 50 mg every 2 weeks according to the US Prescribing Information. The dosage of risperidone in treating schizophrenia has been found to be lower in Taiwan than that in the United States [23]. Therefore, criteria with this low dose of RLAI might not be irrelevant in clinical practice in Taiwan.

There were some other limitations in our study. First, the PIMC database only includes patients admitted for psychiatric inpatient care between January 1, 1996 and December 31, 2001, which would result in the exclusion of schizophrenic patients with only outpatient service use during that time period. Second, the lack of control group is associated with some other drawbacks. Oral medications in the pre-RLAI period being not controlled; hence, the better outcomes in the post-RLAI period could have been due to medication effects rather than effects of the drug form. In addition, the medication prescription patterns may differ by hospital level, physician personal preference, and shifting policy. Third, although acute hospitalizations and ER visits as outcome measurement of relapse for schizophrenia have good face validity [24], the real number of relapses might have been underestimated. Furthermore, the meaning and entity of "acute hospitalizations" might translate poorly among different health-care contexts [24]. Finally, it is not available for the specific information on side effects, clinical status, patient types, or the real drug compliance because of the entity of the study design with national claims database. Because of these methodological limitations, the reductions in the numbers of relapses and hospital service utilization could not be attributed to RLAI on its own. For the future study, a prospective clinical trial in clinical settings or a case-controlled design using the claim data are warranted for generalizability and to provide more information across nations on the comparison of the effect of RLAI use on relapse for the patients with schizophrenia.

Conclusion

In conclusion, this 1-year mirror-image analysis showed that RLAI treatment is associated with reductions in the numbers of relapses and hospital service utilization in Taiwan, and further investigations are warranted for long-term outcomes, including costs.

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Part of the results of this study were presented at the ISPOR 3rd Asia-Pacific Conference held September 7–9, 2008 at the Grand Hilton, Seoul, South Korea, as a poster presentation entitled "Changes of Hospital Service Use in Schizophrenia Patients Treated With Long-Acting Injectable Risperidone: A One-Year Mirror Image Study Using A Population-Based Database In Taiwan."

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