Detection and evaluation of a drug safety signal concerning pancreatic cancer: lessons from a joint approach of three European biologics registers

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Abstract

Objectives. A high incidence of pancreatic cancer (PCa) in patients exposed to leflunomide (LEF) was observed in the German biologics register. To evaluate this possible safety signal, a concerted analysis with the national biologics registers in the UK and Sweden was performed.

Methods. Patients with enrolled in the British Society of Rheumatology Biologics Register (BSRBR), the Swedish Rheumatology Register (SRR) or the German Biologics Register (Rheumatoid Arthritis Observation of Biologic Therapy (RABBIT)) were analysed. The patients were exposed to biologic or conventional DMARDs. Outcomes were obtained from physician reports, health authorities and via linkage to national cancer and death registers. Age- and gender-standardized incidence ratios (SIRs) of PCa were calculated based on the expected rates available from the individual national cancer registers.

Results. Data from 5126 (Germany), 16 930 (UK) and 19 351 (Sweden) RA patients were available for the analysis. The highly discrepant prescription rates of LEF in the respective countries resulted in 11 343 (Germany), 30 787 (UK) and 2518 (S) patient-years of exposure to LEF. Compared with the general population, the incidence of PCa in patients ever exposed to LEF corresponded to a SIR of 3.1 (95% CI 1.3, 6.5) in Germany, 1.05 (95% CI 0.5, 2.1) in the UK and 1.8 (95% CI 0.1, 10.2) in Sweden.

Conclusion. The results of the replication analyses do not support the hypothesis of an increased risk of PCa in patients exposed to treatment with LEF. However, they do not completely rule out concerns, and therefore further verification in other data sets is recommended.

Key words: Pharmacovigilance, Leflunomide, Malignancies, Pharmacoepidemiology, German Biologics Register, British Society for Rheumatology Biologics Register, Swedish Rheumatology Register, Collaborative analyses.

Introduction

Biologics registers were established in several European countries at the beginning of this century in order to assess the long-term safety and effectiveness of approved biologic agents in patients with rheumatic diseases (especially). These powerful pharmacoepidemiological tools facilitate efforts to answer the burning questions of drug safety, which arise when new agents are prescribed to a large number of unselected patients in everyday rheumatological care.

To put the adverse events occurring under treatment with newly approved drugs into perspective, biologics registers have established comparator groups either embedded in the register itself or through comparison with external cohorts. Since the comparator groups commonly consist of patients treated with non-biologic DMARDs such as MTX and LEF, these non-biologic...
drugs are observed with the same scrutiny and the same level of monitoring and case ascertainment as the biologic agents. Therefore, new safety signals may be detected not only in the group of patients treated with the new biologic agents, but also in the group of patients treated with non-biologic DMARDs.

In the context of a regular safety update in the German Biologics Register [Rheumatoid Arthritis Observation of Biologic Therapy (RABBIT)], an unexpected high number of cases of pancreatic cancer (PCa) were observed in the biologics-naïve comparator group. All of these patients had been treated with LEF either during the observation in RABBIT (five cases) or before enrolment (two cases) [1]. Restricting the analysis to cases treated with LEF during observation in the register, we found a significantly elevated age- and gender-standardized incidence ratio (SIR) compared with the general population of Germany, whereas no increased risks were observed for patients exposed to biologics or MTX [1].

To evaluate this possible safety signal, we took advantage of the availability of further independent data sources in which RA patients exposed to LEF had been carefully observed as part of the comparator groups and performed a concerted analysis with the British Society for Rheumatology Biologics Register (BSRBR) and the Swedish Rheumatology Register (SRR).

Patients and methods

Characteristics of the individual study populations

The RABBIT is an ongoing prospective cohort study that started in May 2001. RABBIT investigates the long-term safety of all biologic agents licensed for the treatment of RA. The register has an internal comparison cohort of patients treated with non-biologic DMARDs. Patients are eligible for enrolment at the start of one of the approved biologic agents or at the start of a new DMARD therapy after at least one DMARD failure. Each patient is observed for at least 5 years. Treatment, clinical status and adverse events are assessed half-yearly at fixed time points of follow-up (the first assessment is 3 months after enrolment). If patients are lost to follow-up, their vital status and causes of death are ascertained through queries to the health authorities. Regular checks for safety signals are performed in both cohorts (biologics and DMARD patients; for further details see [2]).

The BSRBR was established in October 2001 [3]. For this register, patients with RA newly starting a treatment with one of the approved biologic agents were eligible to be enrolled, with a goal recruitment of ~4000 patients starting each of the three available anti-TNF agents (etanercept, adalimumab and infliximab). This target was reached in 2005 for etanercept, 2007 for infliximab and 2008 for adalimumab. Recruitment was supported by the UK National Institute for Health and Clinical Excellence, which included registration in the BSRBR in its guidelines for use of anti-TNF in RA. In addition, the study aimed to recruit a cohort of ~4000 patients with active RA receiving non-biologic DMARD therapy. Recruitment to this cohort was completed in early 2009 and is being followed in an identical manner to the biologic patients. As in the German biologics register RABBIT, the study protocol stipulates each patient be observed for at least 5 years. Assessments of clinical status, treatment and serious adverse events are taken every 6 months for 3 years and then annually. For the first 3 years, patient-derived data are also collected. For malignancy and death, patients are followed up for their entire lifetime via linkage with the relevant national registers.

The SRR was used for the analysis of Swedish data. The SRR is maintained by the Swedish Society for Rheumatology and consists of two components: the Swedish biologics register Anti-Rheumatic Therapies in Sweden (ARTIS) and the Swedish Early RA register. ARTIS was initiated in 1999 when the first biologics became available. Patients are enrolled into ARTIS with the start of a treatment with biologics and followed up biannually. Patients with incident RA have been eligible for enrolment into the Swedish Early RA register since 1995. In both parts of the SRR, information on age, gender, onset of the disease, treatment, disease activity and function are collected. Through linkages, information on drug dispensing (from the Prescribed Drug Register 2005, including LEF and other DMARDs), cancer (from the Swedish Cancer Register 1958) and vital status (through the Population Register) can be identified for all members of the overlapping Swedish RA populations [4]. Ethical approval was obtained for the BSRBR from the Multicentre Research Ethics Committee for the Northwest of England, for ARTIS from the Ethics Review Board of the Karolinska Institute and for RABBIT from the Ethics Committee of the Charité Medical School.

Patients

In the following analyses, patients with RA who were treated by German, British or Swedish rheumatologists were included. Enrolment in RABBIT was between May 2001 and December 2008, in the BSRBR register between October 2001 and December 2008, and in the SRR between 1995 and December 2007.

Occurrence of PCa

Cases were RA patients who developed PCa during the observational period of the corresponding register. Detailed information about the patient’s age, sex, treatment history, their date of PCa diagnosis and outcome is shown in the supplementary table (available as supplementary data at Rheumatology Online). Completeness of ascertainment was achieved in the Swedish and British registries by linkage with the national cancer registries. In Germany, PCa diagnoses were based on regular physician reports within RABBIT and on results of dropout enquiries. Although the dropout rate within RABBIT was only ~6% per year, these requests identified
four additional PCa cases not known to the treating rheumatologist.

**Exposure**

The analyses presented in this article are based on an ever exposed approach. Patients are considered as ever exposed to drug X after having received the first known dose of X. Exposure time for patients who were exposed to drug X before inclusion in the register starts at baseline, for those exposed for the first time after enrolment it begins at this point in time. The exposure time ends at the date of the PCa diagnosis, death, end of follow-up, or the corresponding observational period or at the emigration date, whichever comes first.

**Analysis**

First, we calculated age and gender standardized incidence ratios (SIRs) of PCa based on the expected rates available from the individual national cancer registries [5–7]. Five-year age bands were used with the corresponding incidence rates to calculate the expected numbers of cases based on the age and gender distribution of the patients and their follow-up time. Follow-up time of patients with an observational period >1 year was allocated to each relevant age band over the course of individual follow-up.

**Power considerations**

The power considerations are based on the German data, with an expected rate of approximately one case of PCa per 5000 patient-years in RA patients with a mean age of 55 years. A 2.5-fold increase (SIR = 2.5) in the risk of PCa for patients treated with LEF could be detected with a power of ~80%, if 30 000 patient-years were available for the analysis. With a slightly higher mean age in the BSRBR, a similar proportion of males compared with the German data, the 30 787 patient-years of exposure to LEF available in the BSRBR were sufficient to detect a SIR of 2.5 or larger in this evaluation study.

**Results**

**Patients and exposure**

Data from a total of 5126 RA patients in the RABBIT, 16 930 RA patients in the BSRBR and 19 351 RA patients in the SRR were available for the analysis. The patient-years under observation as well as some characteristics of the patient populations are shown in Table 1.

**Signal detection with data from RABBIT**

In RABBIT, a total of seven PCa patients were observed during follow-up in the register. Five of these patients had received LEF after enrolment either as monotherapy (n = 2) or in combination with MTX (n = 2) or HCQ (n = 1). One patient was exposed to adalimumab and one to etanercept. Both of these patients had received LEF before entering the database.

Compared with the general population in Germany, the seven PCa patients correspond to a significantly elevated age and gender SIR of 3.1 in patients ever exposed to LEF (Table 2). No increased SIRs were found for patients never exposed to LEF.

**Signal evaluation by comparing the PCa incidence in the British and Swedish registers with national population data**

In the UK data, a total of 15 cases of PCa were reported to the BSRBR. Two of these patients had received LEF at the time of the cancer diagnosis and a further six patients had received LEF. In the six patients who had stopped LEF before the PCa diagnosis, the mean time between termination of LEF and diagnosis was 4.5 years and the mean time on LEF before stopping was 7.2 months. The two patients who developed PCa under treatment had been on LEF for ~55 and 61 months, respectively. In SRR, 17 of the 19 351 patients developed PCa during the observation period. Only one of those patients was registered as having a treatment with LEF preceding the PCa diagnosis (2 years, in 2003; supplementary data available at *Rheumatology* Online).

**Comparison of PCa incidence with national population data**

Table 3 shows age and gender SIRs of PCa based on the expected rates according to the general population rates in Britain and Sweden. Although the crude incidence rates of PCa in the BSRBR and SRR were higher in patients ever exposed to LEF than in patients never exposed to this treatment, the SIRs did not show any increase over the population rates (Table 3, last two columns).

### Table 1. Characteristics of the patient populations in the register cohorts

<table>
<thead>
<tr>
<th></th>
<th>Sweden (SRR)</th>
<th>UK (BSRBR)</th>
<th>Germany (RABBIT)</th>
</tr>
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<tbody>
<tr>
<td>n</td>
<td>19 351</td>
<td>16 930</td>
<td>5126</td>
</tr>
<tr>
<td>Patient-years</td>
<td>77 860</td>
<td>68 790</td>
<td>15 825</td>
</tr>
<tr>
<td>Follow-up time, mean (s.d.), years</td>
<td>4.0 (3.1)</td>
<td>4.1 (1.8)</td>
<td>3.1 (1.6)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>13 971 (72.2)</td>
<td>12 974 (76.6)</td>
<td>4010 (78.2)</td>
</tr>
<tr>
<td>Age at baseline, mean (s.d.), years</td>
<td>58.2 (14.3)</td>
<td>57.0 (12.4)</td>
<td>54.6 (12.1)</td>
</tr>
<tr>
<td>Ever exposed to LEF</td>
<td>n (%)</td>
<td>Patient-years</td>
<td>n (%)</td>
</tr>
<tr>
<td>n (%)</td>
<td>1056 (5.5)</td>
<td>7111 (42)</td>
<td>3797 (74.1)</td>
</tr>
<tr>
<td>Patient-years</td>
<td>2523</td>
<td>30 787</td>
<td>11 343</td>
</tr>
<tr>
<td>Ever exposed to MTX</td>
<td>n (%)</td>
<td>Patient-years</td>
<td>n (%)</td>
</tr>
<tr>
<td>n (%)</td>
<td>15 635 (80.8)</td>
<td>16 243 (95.9)</td>
<td>5021 (98.0)</td>
</tr>
<tr>
<td>Patient-years</td>
<td>57 305</td>
<td>65 614</td>
<td>15 499</td>
</tr>
<tr>
<td>Ever exposed to biologics</td>
<td>n (%)</td>
<td>Patient-years</td>
<td>n (%)</td>
</tr>
<tr>
<td>n (%)</td>
<td>8652 (44.7)</td>
<td>13 206 (78.0)</td>
<td>3808 (74.3)</td>
</tr>
<tr>
<td>Patient-years</td>
<td>34 923</td>
<td>56 669</td>
<td>11 187</td>
</tr>
<tr>
<td>Past or current smoker, n (%)</td>
<td>–</td>
<td>10 280 (60.7)</td>
<td>1442 (40.3)</td>
</tr>
</tbody>
</table>
The total number of cases with PCa observed in all three registers was 16. The corresponding total number of expected cases was 10.36, leading to a pooled SIR of 1.54 (95% CI 0.88, 2.50).

Discussion

This is an example of a safety signal generation and evaluation enabled by the existence of, and coordination across, different biologics registers. After the observation of an unexpectedly high number of cases of PCa in one register, a concerted analysis was planned and performed between the registers.

Data from the German RABBIT suggested a >3-fold increased risk of PCa in RA patients exposed to LEF compared with the general population. This significant increase could not be confirmed in the subsequently performed analyses in the UK and Sweden.

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The strength of these register data lies in the verification and nearly complete ascertainment of exposures and events. In the German register, this is done by thorough monitoring and tracking of patients who experienced serious adverse events or dropped out of observation. In the case of the British and Swedish registers, where linkages to cancer registers are possible, all patients are flagged and can be followed up for their entire lifetime in case of the development of a malignant neoplasm. Registers are of specific value to detect safety signals that might otherwise be overlooked. In this case, spontaneous reporting systems would inevitably have missed most of the PCa cases because survival time after the diagnosis of PCa is short and the treating rheumatologist (prescribing a certain therapy) was not always aware that the patient had died of this disease. In the German RABBIT, four out of the seven patients were dropouts from the rheumatological treatment and the diagnosis was obtained only by queries to the treating general practitioner, by hospital discharge letters and by death certificates.

Even though this analysis was planned in collaboration, we discovered that the health care structures, prescription patterns and characteristics of the individual registers limit the options for joint analyses. Reflective of the varying position of LEF in the therapeutic arsenal against RA in different countries, large differences in the exposure rates to LEF were found; 5.5% in the SRR, 42% in the BSRBR and 74% in RABBIT. This raises the question to what extent patients receiving LEF in Sweden, Germany and the UK are comparable. For example, in Germany, LEF is the usual second treatment option for patients with RA after the failure of MTX. This prescription rate is higher than that in countries like Sweden or the UK [8]. In the UK, SSZ is the second most commonly prescribed

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Crude rates, observed and expected numbers of PCas and the corresponding SIRs with 95% CI of RA patients enrolled in RABBIT</th>
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<tbody>
<tr>
<td></td>
<td>Observed numbers of PCa</td>
</tr>
<tr>
<td>All patients</td>
<td>7</td>
</tr>
<tr>
<td>Ever exposed to LEF</td>
<td>7</td>
</tr>
<tr>
<td>Never exposed to LEF</td>
<td>0</td>
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</tbody>
</table>

*SIR of ‘0’ does not imply a reduced incidence (see corresponding 95% CI).

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Crude rates, observed and expected numbers of PCas and the corresponding SIRs with 95% CI of all patients in the cohort and those ever or never exposed to LEF</th>
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<tbody>
<tr>
<td></td>
<td>Observed numbers of PCa</td>
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<td>Ever exposed to LEF</td>
<td>7</td>
</tr>
<tr>
<td>Never exposed to LEF</td>
<td>0</td>
</tr>
</tbody>
</table>

|          | Observed numbers of PCa | Crude rate per 100 000 patient-years | Expected number of cases | SIR (observed/expected) | 95% CI |
| All patients | 7 | 44.2 | 3.09 | 2.26 | 0.91, 4.67 |
| Ever exposed to LEF | 7 | 61.7 | 2.26 | 3.10 | 1.25, 6.45 |
| Never exposed to LEF | 0 | 0 | 0.85 | 0° | 0, 4.32 |

Pooled SIR
The total number of cases with PCa observed in all three registers was 16. The corresponding total number of expected cases was 10.36, leading to a pooled SIR of 1.54 (95% CI 0.88, 2.50).
DMARD. In Sweden, starting LEF (following failure of MTX) is less common than adding SSZ to MTX, or switching to a biologic.

The increased incidence of PCAs observed in the German register could be the result of a protopathic bias. This means that the high disease activity that led to the change of DMARD treatment might have been a paraneoplastic phenomenon of an already existing PCA. However, patients with high disease activity might also have been started on biologics, but in contrast to LEF, there was no increased risk under these treatments. One possible explanation is that, before starting a biologic treatment, patients might have been screened more carefully for the presence of malignancies than before starting a conventional DMARD. Therefore, patients in whom a neoplasm was detected would not have been switched to biologics, and therefore would not have been recruited to the biologics arm of the register.

Another aspect is the different age and gender distributions in the registers that might, especially in the case of malignancies, play an important role. We tried to overcome this limitation with the calculation of standardized incidence rates (for age and gender) based on the respective general population rates. Further explanations for differences between the registers could be national differences in lifestyles leading to generally different expected rates of PCa. However, European data [6] show that the incidences are quite comparable, with slightly higher rates for Germany.

This example shows that safety signals like this one may only be captured in carefully conducted long-term observational studies covering all kinds of treatments. However, since there is a certain probability that such signals may emerge by chance, the evaluation necessitates collaborative analyses with independent data sets. The data from the two other registers used to validate the German results did not support the hypothesis of an elevated PCA risk in patients treated with LEF. However, since there was a small, non-significant risk elevation also in the Swedish and British data, we suggest that researchers who have access to large databases with ascertainment of drug exposure as well as outcome verify these results.

Rheumatology key messages

- The hypothesis of an increased PCA risk in LEF-treated patients was not confirmed.
- Collaborative analyses with independent data sets are needed to evaluate safety signals of rare events.
- Comparison of separate analyses in different data sets seems more appropriate than pooling of data.

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A.S. (RABBIT)—study design, verification, data analysis and interpretation, writing of the article.

J.L. (RABBIT)—study design, statistics, data analysis and interpretation, writing of the article.

A.Z. (RABBIT)—study design, data analysis and interpretation, writing of the article.

J.A. (SRR)—study design, data analysis and interpretation, writing of the article.

K.W. (BSRBR)—data analysis and interpretation, writing of the article.

K.H. (BSRBR)—study design, data analysis and interpretation, writing of the article.

D.S. (BSRBR)—study design, interpretation of analysis, writing of the manuscript

R.D. (BSRBR)—data analysis and interpretation, writing of the article.

A.S. (RABBIT)—data analysis and interpretation, writing of the article.

E.A. (SRR)—data analysis and interpretation, writing of the article.

J.S. (SRR)—data analysis and interpretation, writing of the article.

M.N. (SRR)—data analysis and interpretation, writing of the article.
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Supplementary data
Supplementary data are available at Rheumatology Online.

References