Increased incidence of pancreatic carcinoma in rheumatoid arthritis patients receiving leflunomide

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Conclusion

Our data suggest that therapy with leflunomide might increase the risk for a pancreatic carcinoma. This safety signal has not been reported before. We cannot rule out that the finding is incidental or that it is caused by an undetected background mechanism which has influenced both the treatment decision and the cancer risk. It therefore needs verification with data from other large, prospective drug safety studies.

Background

The German biologics register RABBIT is an ongoing prospective cohort study that was started in May 2001. It investigates the long-term safety of all biologic agents licensed for the treatment of rheumatoid arthritis (RA). To put the results into perspective, a control cohort with patients treated with conventional DMARDs is observed concurrently. This allows to analyse safety signals not only in patients under treatment with biologics, but also in those treated with conventional DMARDs only.

Patients

RA patients are eligible for the cohort at start of one of the approved biologic agents or at start of a new DMARD therapy after at least one DMARD failure. Regular checks for safety signals are performed in both arms of the cohort. Once enrolled each patient is observed for at least five years. Treatment, clinical status and adverse events are assessed half-yearly at fixed time points of follow-up. If patients are lost to follow-up, their vital status and causes of death are ascertained through queries to the health authorities

Methods

We calculated age and gender standardized incidence rates (SIR) of pancreatic carcinoma (pCa) based on expected rates available from the German cancer registries in the general population (figure 1). We took the time under observation and the patient case mix into account. To identify possible associations with exposure, we performed a nested case control study.

Results

Data from 5,126 patients with a mean follow-up of 3.1 (±1.6) years were analysed. Drop out rates were below 5% per year.

In total, we observed seven incident pCa during follow-up in RABBIT. Five of these patients were exposed to leflunomide (LEF) 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 cohort. We took only exposure during the observation in RABBIT into account and therefore considered these patients as unexposed to LEF. In total, 1,970 patients contributing 5,446 patient-years of follow-up were exposed to LEF during observation in the cohort.

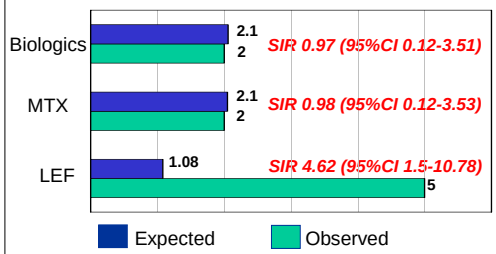

Figure 1. Expected and observed frequency of pancreatic carcinoma under different treatments.

No.	Initial cancer diagnosis	Date of cancer diagnosis	Age at cancer diagnosis	Sex	Outcome	Treatment history	Duration (yrs) of RA at treatment start with LEF
1	Pancreatic cancer with liver metastases	02/2004	58	♀	Died 11/2004	Leflunomide 04/2003 – 07/2004	12
2	Pancreatic cancer with liver metastases and infiltration of the splenic artery and the truncus coeliacus	05/2007	68	♂	Died 06/2007	Leflunomide 07/05 – 06/07 and Hydroxychloroquine 07/06 – 06/07	9
3	Pancreatic cancer with lymph node and peritoneal metastases	05/2006	58	♀	Died 10/2007	Leflunomide 08/2004-10/2007	14
4	Pancreatic cancer	01/2006	72	♂	Died 04/2006	Methotrexate 04/05 – 04/06 and Leflunomide 06/05 – 04/06	1
5	Pancreatic cancer	05/2003	73	♂	Died 06/2003	Methotrexate 03/01 – 06/03 and Leflunomide 07/02 – 06/03	3
6	Pancreatic cancer with lymph node and peritoneal metastases	07/2007	65	♀	Died 02/2008	Adalimumab 09/06 – 07/07 Leflunomide prior to enrolment (09/06)	RA since 2004
7	Pancreatic cancer with lymph node metastases	04/2007	68	♀	alive (May 2009)	Etanercept 05/02 – 02/07 Methotrexate 08/05 – 02/07 Leflunomide prior to enrolment (05/02)	RA since 1990

Table 1. Diagnoses at the time of detection of the cancer and characteristics of the seven patients who developed pancreatic cancer.

Nested case-control study

Risk factors for pCa include smoking and chronic alcohol abuse. For the nested case-control study we matched each pCa case with 10 cancer-free controls for age, sex, year of study entry and the above mentioned risk factors. Twenty one of the 70 controls (30%) were exposed to LEF after study entry. This portion was significantly lower than in the group of cases with pCa (5 out of 7 = 71%, p=0.029).

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Cohort studies vs. spontaneous reporting systems

Carefully conducted long-term observational studies capturing all kinds of treatment are of specific value to detect safety signals that would otherwise be overlooked. Since survival time after the diagnosis of pCa is short, the treating rheumatologist may not be aware that the patient died of this disease.

OF NOTE

In our study, four out of the seven patients were drop-outs from the rheumatologic treatment and the diagnosis was obtained only by queries to the treating general practitioner, by hospital discharge letters and by death certificates. Spontaneous reporting systems will inevitably miss those cases.

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