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ORIGINAL ARTICLE

Safety signal detection and evaluation in clinical development programs: A case study of tofacitinib

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Abstract

Adverse events are anticipated during a clinical development program. Tofacitinib is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA). We describe here the process undertaken by Pfizer to investigate a safety signal for pancreatic cancer with tofacitinib. Potential cases of pancreatic cancer across indications from Pfizer's clinical trials and safety databases were identified and underwent in-depth case review and external expert consultation. The magnitude of the signal was quantified. The feasibility of formal signal evaluation via a hypothesis-testing study was explored. As of July 2016, 14 cases of potential pancreatic cancer were identified: eight cases in clinical development trials (psoriasis n = 6; RA n = 1; psoriatic arthritis n = 1), four cases in a postmarketing study in RA patients in Japan, and two spontaneous reports. Incidence rates (95% confidence intervals) per 100 patient-years ranged from 0 (0, 0.02) to 0.14 in RA, 0.05 (0.01, 0.15) to 0.07 (0.02, 0.16) in psoriasis, and 0.25 (0.01, 1.37) in psoriatic arthritis. The majority of patients had established risk factors for pancreatic cancer. The pharmaceutical industry's rapid and transparent response to safety signals is essential for ensuring patient safety and enabling physicians and patients to adequately assess a drug's risk:benefit. Safety signals emerging through pharmacovigilance may be true or false indicators of a causative association with drug exposure. In this example, it was determined that tofacitinib exposure was unlikely to be related to induction and promotion of pancreatic cancer; however, a relationship with pancreatic cancer promotion could not be excluded.

KEYWORDS

Epidemiology, malignancy, pharmacovigilance, safety, tofacitinib

1 | INTRODUCTION

Adverse events related and not related to a drug's mechanism of action are anticipated during clinical development programs. An excess of adverse events associated with a product's use compared with the expected rate is referred to as a safety signal.[1] Signals can arise at any time during the life-course of a drug, from the preclinical phase through the postmarketing phase. Signals are generated through the intentional, but hypothesis-free, comparison of the number of events observed in a population with the number expected. The determination of whether an excess of an adverse event represents a true causal relationship between the drug and the event is a challenge faced by drug developers and clinical

Abbreviations: ASRs, age standardized incidence rates; EPAR, European Public Assessment Report; IRR, incidence rate ratio; KPNC, Kaiser Permanente Northern California; PDAC, pancreatic ductal adenocarcinoma; SBA, Summary Basis of Approval; SEER, Surveillance, Epidemiology, and End Results database; SIRs, standardized incidence rates; THIN, The Health Improvement Network UK database.

researchers, and is particularly difficult with infrequent adverse events.

Upon identifying a safety signal, the signal must be further refined to ascertain whether an association between the event and the drug exists. Specifically, cases must be reviewed for biologic plausibility and potential confounding factors, and the signal must be quantified and contextualized. Finally, causality between product exposure and safety outcomes may be assessed via formal epidemiological hypothesis-testing studies (signal evaluation).[2] Careful and comprehensive signal refinement and evaluation efforts are of paramount importance, and have substantial implications for patient welfare. Here, we describe a case study concerning the drug tofacitinib to illustrate the complexities and challenges of refining and evaluating a signal for an infrequent adverse event.

1.1 | Tofacitinib: background to the case study

Tofacitinib is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA). A 5 mg twice daily (BID) dose of tofacitinib was first approved for the treatment of RA in the US in November 2012 and is now available in more than 80 countries for the treatment of moderate to severe RA. An 11 mg once daily extended-release formulation of tofacitinib had first approval in the US in 2016 and now is approved in additional countries at a global level.[3] Tofacitinib 5 and 10 mg BID doses are currently in clinical development for other immune-mediated inflammatory conditions such as psoriatic arthritis and ulcerative colitis. Tofacitinib has also been evaluated for psoriasis, Crohn's disease, ankylosing spondylitis, and as an antirejection agent in renal allograft transplant. The total tofacitinib clinical development program is extensive, having included more than 13 000 patients and provided more than 29 000 patient-years (PYs) of exposure (up to November 2015; cut-off date used for the original signal evaluation).[4] In addition, postmarketing experience accrued in patients with RA amounted to more than 45 000 PYs of exposure to tofacitinib (to April 2016; cut-off date used for the original signal evaluation).[4] Postmarketing surveillance studies are ongoing in the US and other countries where tofacitinib is approved for the treatment of RA, including a US Consortium of Rheumatology Researchers of North America (CORRONA) registry postapproval safety study (NCT01402661), a postmarketing safety study of tofacitinib vs tumor necrosis factor (TNF) inhibitors in subjects with RA (A3921133; NCT02092467), and a Japanese postmarketing all-case surveillance study (A3921194; NCT01932372).

Patients with chronic autoimmune and inflammatory diseases are at increased risk of developing certain types of malignancies,[5] and immunomodulatory therapies for these conditions have also been associated with a further increased risk.[6] Tofacitinib has a novel mechanism of action and, therefore, safety events of special interest that might relate to its effects on the immune system (eg, malignancies and serious infections) have been closely monitored throughout its clinical development.[7,8]

1.2 | Pancreatic cancer

Pancreatic cancer is the 12th most common type of malignancy and the 7th most common cause of cancer-related deaths worldwide, with incidence varying somewhat by region.[9] For instance, the age standardized incidence rates (ASRs; per 100 PYs) for men and women, respectively, are 0.006 and 0.004 in East Asia, 0.009 and 0.005 in Central/Eastern Europe, and 0.009 and 0.006 in North America.[9] Risk factors for pancreatic cancer include age, history of chronic pancreatitis, smoking, diabetes mellitus, family history of pancreatic cancer, and metabolic syndrome. Less strongly associated factors include obesity, heavy alcohol intake, non-O blood group, and *Helicobacter pylori* infection.[10,11]

In this case study, we describe the process undertaken by Pfizer to investigate (ie, identify, refine and evaluate) a signal for pancreatic cancer with tofacitinib therapy, as well as the conclusions and actions from the investigation. By describing this investigation, it is hoped that healthcare professionals can acquire further insight into this aspect of the drug development process and to the importance of timely, complete reports of adverse events.

2 | MATERIALS AND METHODS

2.1 | Signal identification

The signal for pancreatic cancer with tofacitinib was initially identified in 2014 through routine safety monitoring of the tofacitinib psoriasis clinical development program. After internal review of the cases, the signal was closed because no cases were observed outside of the psoriasis development program, and all patients had one or more risk factors for developing pancreatic cancer. The signal was then reopened in 2015 after an additional case was identified in the tofacitinib psoriasis clinical development program.

2.2 | Signal refinement

2.2.1 | Development of case series

After reopening the signal, during the period from October to November 2015, Pfizer's clinical trials and global safety databases were searched across indications using the standard Medical Dictionary for Regulatory Activities (MedDRA) search criteria for malignant tumors to identify reports containing the following MedDRA (Version 18.1) preferred terms (PTs): adenocarcinoma pancreas, ductal adenocarcinoma of the pancreas, acinar cell carcinoma of pancreas, intraductal papillary mucinous carcinoma of pancreas, mucinous cystadenocarcinoma of pancreas, pancreatic carcinoma, pancreatic carcinoma metastatic, pancreatic carcinoma recurrent, pancreatic carcinoma stage 0, pancreatic carcinoma stage I, pancreatic carcinoma stage II, pancreatic carcinoma stage III, pancreatic carcinoma stage IV, pancreatoblastoma, serous cystadenocarcinoma of pancreas, and solid pseudopapillary tumor of the pancreas. By November 17, 2015, these databases comprised >55 000 PYs of tofacitinib exposure for clinical trials, postmarketing

studies, and surveillance across all indications. Data collection and analyses for many of these sources were still ongoing at the time of the cut-off and had not been locked (ie, some values may change for final, locked clinical study databases).

Adverse events reported as potential malignancies in tofacitinib clinical trials are submitted at the time of diagnosis for third party pathologist review and to an external independent Malignancy Adjudication Committee comprised of US board-certified practicing medical oncologists. These reviewers are independent of the investigative sites and sponsor, and are blinded to sponsor, study, and treatment. Cases identified during the postmarketing period (including the Japanese postmarketing all-case surveillance study) are not adjudicated.

For further investigation of the signal, a comprehensive review of cases identified was undertaken (ie, a case series was developed) to also take into consideration the epidemiology and biology of pancreatic cancer, clinical presentation, distribution of cases across indications, and risk factors. In addition, data from the nonclinical development tofacitinib program on the mechanism of action of tofacitinib and findings related to the pancreas were also reviewed. This further investigation included consultation with an independent panel of experts. Five medical oncologists (three with expertise in pancreatic cancer) reviewed detailed case profiles, including results from the malignancy adjudication process, where available. The cases were classified according to whether they were most likely to be pancreatic ductal adenocarcinoma (PDAC), other types of pancreatic cancer, or nonpancreatic cancer, and the potential role of tofacitinib in the etiology, progression, and mechanistic relationship with tofacitinib was assessed.

2.2.2 | Signal contextualization

Having characterized the case series, their occurrence was quantified and considered in the context of the overall exposed population and other populations, ie, contextualized. Five experts in epidemiology/pharmacoepidemiology reviewed high-level details of the cases, the estimated incidence rates (IRs)/standardized incidence rates (SIRs), and the epidemiology analysis plan for investigation of the signal.

Given the differences in patient populations (different indications studied) and methods of ascertainment in clinical trials and postmarketing surveillance, IRs of pancreatic cancer per 100 PYs were calculated by indication. To contextualize observed IRs of pancreatic cancer, a search was conducted for pancreatic cancer rates among psoriasis patients, RA patients, and in the general population from the published literature, publically available FDA Summary Basis of Approval (SBA), and/or European Public Assessment Report (EPAR) documents, as well as data available in the CORRONA registry.

Observed vs expected analyses were conducted, using different data cut points and methods, as available in the course of the signal refinement process. Initial analyses comprised SIRs, comparing the ratio of observed cases in psoriasis patients vs expected cases in four reference populations: the general population in the Japan National Cancer Program (http://www.ncc.go.jp/en/); the US general population in the Surveillance, Epidemiology, and End Results (SEER) database (http://seer.cancer.gov/); moderate to severe patients in the Kaiser Permanente Northern California (KPNC) database; and patients with psoriasis of various levels of severity in The Health Improvement Network (THIN) UK database. All SIRs were adjusted for age and gender, and those using the THIN database as a reference population were also adjusted for smoking and diabetes. These analyses, using data accrued through June 2015, were included in communications to regulatory agencies in December 2015.

Additional analyses were then conducted using an updated data cut (December 2015) from the tofacitinib clinical development program, and adjusted for additional/refined potential confounding variables in the KPNC (smoking, diabetes, and age as a time-dependent variable) and THIN populations (age as a time-dependent variable). In addition to SIRs, incidence rate ratios (IRRs) were calculated via Poisson regression. It was not possible to adjust for other pancreatic cancer risk factors such as chronic pancreatitis, alcohol use, *Helicobacter pylori* infection, obesity, etc., due to the inability to measure these factors either in the study and/or reference populations.

Definitions of pancreatic cancer differed across comparator data sources. Pancreatic cancers in the SEER and Japanese registries and the KPNC comparison cohort were defined as any invasive or in situ pathology type within specific sites of the pancreas (ICD-10 code C25); KPNC cases were adjudicated. Within THIN, the definition included only invasive neoplasms within similar sites, as well as ectopic pancreatic tissue; these cases were not adjudicated.

SIRs were not calculated for the tofacitinib RA program as there were no cases in the Phase 1, 2, or 3 studies, or long-term extension studies, and the remaining cases occurred in an ongoing trial, a Japanese postmarketing study, and from spontaneous reports where overall demographic data were not available.

2.3 | Signal evaluation

Pfizer commissioned a feasibility assessment for the evaluation of the signal in the postmarketing clinical practice setting.

3 | RESULTS

3.1 | Signal identification

The initial signal identification is described in the methods section.

3.2 | Signal refinement

3.2.1 | Case series summary

As of July 2016, 14 cases of potential pancreatic cancer had been identified: eight cases in clinical development trials (psoriasis n = 6; RA n = 1; psoriatic arthritis n = 1), four cases in a postmarketing study in RA patients in Japan, and two spontaneous reports (Table 1). Eleven cases (8 from clinical trials and 3 of the cases from the Japanese postmarketing study) underwent review by an independent panel of experts, and all 14 cases underwent internal review

(Figure 1). The additional three cases were reported to Pfizer after the independent panel of experts performed their review.

The panel of medical oncologists recommended excluding 2 of the first 10 reported cases from PDAC classification. Specifically, the carcinoma of the ampulla of Vater in a psoriasis patient was excluded on the basis of differences in biology from PDAC.[12,13] The case reported in the psoriatic arthritis program was excluded as PDAC classification by the oncologists due to absence of abnormalities on a computed tomography scan of the pancreas. However, the case in the psoriatic arthritis program was subsequently adjudicated by the Malignancy Adjudication Committee as being pancreatic cancer. This individual was exposed to adalimumab for 1 year in the index study and was also exposed to tofacitinib for 84 days prior to diagnosis. Among the eight cases for which there was agreement among the panel of oncologists that the cancer was consistent with PDAC, one or more established risk factors for pancreatic cancer were identified in 6 of the cases, and the remaining 2 cases were reported in patients aged >70 years.

The panel also considered the cases in terms of a temporal relationship between tofacitinib and PDAC diagnosis. Research suggests that the span of time from tumorigenesis induction to tumor appearance may be an average of 12 years, with metastasis occurring on average of 5 years later.[14] The tofacitinib-exposure time until clinical presentation (sponsor's assessment of onset of symptoms compatible with pancreatic cancer) was <1 year for 4 out of the 8 cases (range 56-339 days), and in 1 case, clinical presentation very likely predated treatment with tofacitinib. Among the 3 other cases, the longest tofacitinib-exposure time until clinical presentation was 946 days. Thus, induction was deemed implausible for all cases.

The panel then considered the cases with respect to promoting tumor progression. Any potential effect on tumor promotion was thought to be very unlikely for the four cases with clinical presentation beginning <6 months after the start of tofacitinib treatment. Such cases were removed from the sensitivity analyses for the contextualization of events in the psoriasis program as described below. Although thought by the experts to be unlikely, a role in promotion could not be excluded in the remaining four cases (three of which occurred in the psoriasis program) in which tofacitinib-exposure time until clinical presentation ranged from 339 to 946 days.

3.2.2 | Contextualization of the signal

Patient exposure by indication and the IRs of pancreatic cancer per 100 PYs are shown in Table 2. For comparison, there were no pancreatic cancer cases among malignancies reported in EPARs/SBAs for apremilast [15,16] and secukinumab,[17,18] and one case of pancreatic cancer was reported in the etanercept EPAR.[19] However, patient follow-up was considerably shorter in those clinical development programs than in the tofacitinib program. In the tofacitinib program, 68% of participants were followed up for >1 year, compared with 35% to 48% with etanercept, secukinumab, and apremilast; furthermore, 45% of tofacitinib patients were followed up for >2 years, compared with 13% and 3% for adalimumab and apremilast,

TABLE 1 Summary of case series

Gender/age (years)	Exposure time to clinical presentation (days)	Relevant risk factors	Tofacitinib dose[a]
Psoriasis program			
Male/66[g]	107	Ex-smoker Diabetes High BMI Family history of malignancy	10 mg BID
Male/68[h]	136[b]	Ex-smoker Chronic pancreatitis Family history of pancreatic cancer and other malignancies	10 mg BID
Female/52[c,h]	339	Smoker Chronic pancreatitis High BMI	10 mg BID
Male/65[c,h]	946	Ex-smoker Diabetes Family history of pancreatic cancer	10 mg BID
Male/53[c,h]	921	Smoker	10 mg BID
Male/54[d,h]	Unknown	Diabetes Overweight	5 mg BID
Psoriatic arthritis			
Male/54[e,i]	84	Smoker Overweight	5 mg BID
Rheumatoid arthritis			
Female/66[j]	395	Ex-smoker Overweight	5 mg BID
Female/75[k]	132[b]	None reported	5 mg BID
Female/73[k,l]	56[b]	None reported	5 mg BID
Female/72[f,k,l]	5 months	Smoker	5 mg BID
Female/80[f,k]	578	None reported	5 mg QD
Female/85[f,l]	~3-4 months[b]	Ex-smoker Obesity	5 mg BID
Female/78[f,l]	~5-6 months[b]	None reported	5 mg BID

BID twice daily, *BMI* body mass index, *QD* once daily.
[a]Dose at time of event.
[b]Time to diagnosis; time to clinical presentation unknown.
[c]Case included as part of sensitivity analyses in the contextualization of events in the psoriasis program.
[d]Ampulla of Vater carcinoma.
[e]Case excluded from PDAC classification by expert panel review due to absence of abnormalities on CT scan of pancreas; note that the patient had been exposed to adalimumab in the index study and was exposed to tofacitinib for 84 days prior to diagnosis.
[f]Case not reviewed by expert panel.
[g]A3921111, NCT01186744
[h]A3921061, NCT01163253
[i]A3921092, NCT01976364
[j]A3921133, NCT02092467
[k]A3921194, NCT01932372
[l]Spontaneously reported postmarketing case.

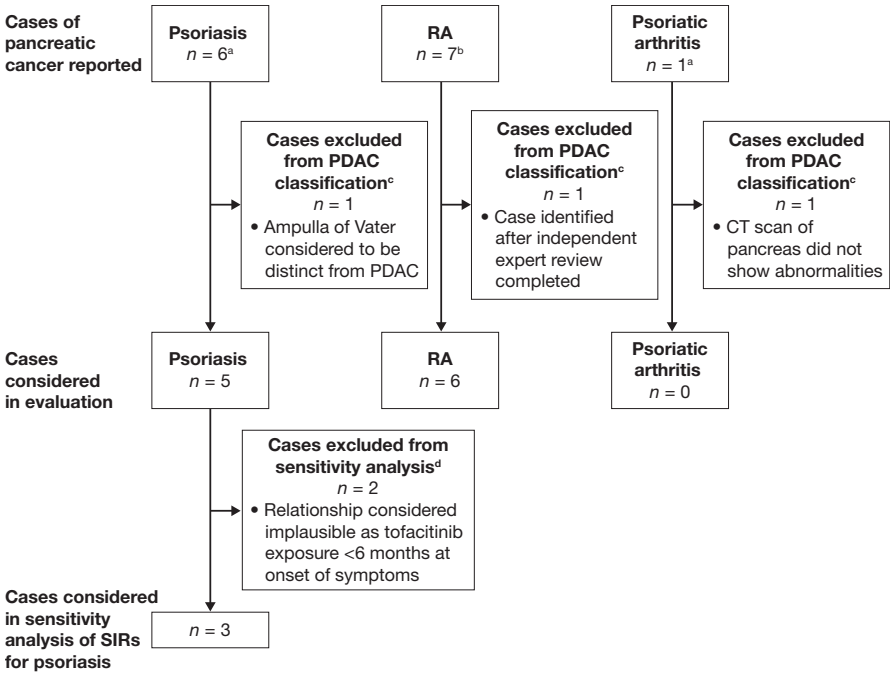

FIGURE 1 Disposition of the 14 cases identified for analysis. (A) All cases identified in the clinical trial program. (B) One case identified in the clinical trial program; 4 cases identified in a postmarketing study in Japan and; 2 cases identified in spontaneous postmarketing reports. (C) Cases excluded from PDAC classification by an independent panel of experts following detailed case review. (D) Cases excluded based on input from independent experts. *PDAC* pancreatic ductal adenocarcinoma, *RA* rheumatoid arthritis, *SIR* standardized incidence ratio

TABLE 2 Patient exposure and incidence rates by tofacitinib indication (confirmed cases)

Tofacitinib indication	Data cut	Events (n)	No. of patients/PYs of exposure	IRs per 100 PYs (95% CI)
RA	Pooled data for Phase 1, 2, and 3, and LTE	0	6194/19 406	0 (0-0.02)
	Pooled data for Phase 1, 2, and 3, and LTE (Sept 30, 2015)	1	7857/21 391	0.0047 (≤0.01-0.03)
	Japan PMS (Nov 05, 2015)	3	2823/2200[a]	0.14[a]
	PMS (Nov 05, 2015)	0	~34 911 PYs	—
	Total RA	4	>55 000 PYs	—[b]
Psoriasis	Pooled data for Phase 2 and 3, and LTE (Jun 30, 2015)	5	3627/7282	0.07 (0.02-0.16)
	Pooled data for Phase 2 and 3, and LTE censoring for 2 cases occurring after <6 months of exposure (Jun 30, 2015)[c]	3	2969/5663	0.05 (0.01-0.15)
Psoriatic arthritis	Pooled data for Phase 3 and LTE (Nov 02, 2015)	1[d]	783/406	0.25 (0.01-1.37)

CI, confidence interval; IR, incidence rate; LTE, long-term extension study; PMS, postmarketing surveillance; PYs, patient-years; RA, rheumatoid arthritis.
[a]Numbers are estimates based on drug shipping volumes and may not be accurate.
[b]Total exposure accrued in clinical trials, postmarketing studies, and experience. IR not determined due to heterogeneity of data sources.
[c]Excluding the first 6 months, based on expert input that cases occurring within 6 or 12 months of exposure should be excluded from IR estimates; the sponsor took a conservative approach and selected 6 months.
[d]The patient was exposed to adalimumab in the index study and was exposed to tofacitinib for 84 days prior to diagnosis.

respectively. In a long-term safety analysis of ustekinumab, in which average patient follow-up was longer, Papp et al. [20] reported two cases of pancreatic cancer occurring in up to 5 years of follow-up (8998 PYs), corresponding to an IR of 0.02 per 100 PYs. Rates of pancreatic cancer were also obtained from published [21] and internally commissioned observational studies among psoriasis patients; estimates were consistent with those above (IR 0.015-0.02 per 100 PYs; Pfizer, data on file). Among RA populations, rates ranged from 0.01 to 0.04 per 100 PYs across US (Pfizer, data on file) and EU [22] disease registries, respectively.

Standardized incidence ratios and IRRs were produced for the PDAC cases within the psoriasis program using THIN and KPNC (all psoriasis and moderate to severe psoriasis) comparison cohorts as reference populations using a December 2015 data cut, as shown in Table 3. These analyses adjust for time-varying age, gender, diabetes, and smoking status. The SIRs based on an earlier data cut (described in Table 2), and which adjusted for more limited covariates and also used Japan and US SEER general population reference populations (not shown), were consistent with results of the updated analyses. Age- and gender-adjusted SIRs based on the 5 cases of pancreatic cancer, regardless of plausibility, reported in the psoriasis program were five to ~ninefold higher than expected. A sensitivity analysis was conducted censoring the exposure within the first 6 months of tofacitinib (including 2 possible pancreatic cancer cases, as their relationship to tofacitinib was considered by independent experts to be implausible). Age- and gender-adjusted SIRs

TABLE 3 Standardized incidence ratio and incidence rate ratio (95% CI) estimates based on pancreatic cancer cases observed in the tofacitinib psoriasis program compared with reference populations

	THIN Psoriasis patients[a]	KPNC Moderate to severe psoriasis patients[b]	KPNC All psoriasis patients[b]
SIRs			
5 cases	8.44 (2.74, 19.69)	9.11 (2.96, 21.26)	4.92 (1.60, 11.47)
3 cases[c]	5.18 (1.07, 15.15)	5.62 (1.16, 16.43)	3.01 (0.62, 8.80)
IRRs[d]			
5 cases	8.53 (2.63, 21.47)	5.96 (1.32, 24.80)	4.91 (1.45, 13.03)
3 cases[c]	5.21 (1.03, 16.30)	3.82 (0.56, 19.51)	2.97 (0.56, 9.80)

CI, confidence interval; IRR, incidence rate ratio; KPNC, Kaiser Permanente Northern California database; SIR, standardized incidence ratio; *THIN* the Health Improvement Network UK database.
[a]Age-, time-, gender-, smoking-, and diabetes-adjusted.
[b]Age- gender-, smoking-, and diabetes-adjusted.
[c]6-month exposure censored. As a sensitivity analysis, SIRs were calculated for only three patients in the psoriasis program based on the feedback from the expert consultants that pancreatic cancer in patients with <6 months of exposure is highly unlikely to be related to tofacitinib. As the reference group is defined based on disease status, as opposed to the start of a particular exposure, and therefore there is no equivalent time frame to remove, the exposure time in the reference groups remained the same.
[d]Takes into account variability of external comparator population.

based on these three cases ranged from 3.01 to 5.62. The IRRs were consistent with SIRs, with the exception of analyses conducted within the moderate to severe psoriasis subcohort in KPNC, likely due to few cases and many zero cells in this smaller comparison population.

3.2.3 | Interpretation of results

The overall conclusion of the independent medical oncologists' and epidemiologists' review of the data was that, despite the elevated SIR within the psoriasis development program, they considered it unlikely that tofacitinib had a role in the etiology of pancreatic cancer based on the evidence associating both pancreatic cancer with immunosuppression and small molecule drugs as promoters of tumor growth/progression, and also the known latency of PDAC in relation to tofacitinib-exposure times. Given the above, the majority of experts deemed the signal most likely due to chance or selection bias.

3.3 | Signal evaluation

Given that tofacitinib is currently approved for RA, and the majority of its use is in the US, the study population required to evaluate the signal in the postmarketing clinical practice setting would comprise RA patients in the US. There were an estimated 18 000 current users of tofacitinib in the US (as of September, 2015). To rule out a relative risk of 3 with 80% power for a one-sided test at alpha of 0.05, 21 000 PYs of tofacitinib exposure would be required, achievable with 5250 tofacitinib users, followed up for an average of 4 years, and four times the number of PYs in the comparator population. For such a study to be feasible, several large automated data resources with linkage to the US national death index (eg, Truven, Optum, etc.) would need to be combined. It was deemed that a study designed to rule out a relative risk in the order of 2 would not be feasible with observational data available in the US in the next few years, given estimates of tofacitinib use and the required follow-up time (54 000 PYs).

4 | DISCUSSION

As part of the ongoing clinical development of tofacitinib, we identified a signal of pancreatic cancer. The initial preponderance of cases was limited to the psoriasis trial population compared with other indications; however, it should be noted that this finding had no bearing on the decision to discontinue the clinical development program in patients with psoriasis. Among the four cases identified among RA patients, three cases were reported in the Japanese RA postmarketing surveillance study. It is important to recognize that the latter observations are also spontaneous reports from the tofacitinib arm of an observational study.

The body of evidence presented can also be considered using the Bradford Hill framework of causality, which consists of criteria for strength, consistency, specificity, temporality, dose-response, plausibility, coherence, experimental evidence, and analogy.[23] The only causal consideration within the Bradford Hill framework that was clearly met was 'strength of association', demonstrated in elevated incidence rates and SIRs/IRRs. The lack of a signal in other indications in the tofacitinib clinical program (ie, lack of 'consistency') mitigates the strength of association and makes it less likely that the signal is a true positive. Further, in terms of temporality, pancreatic cancer has a long latency period (21 years on average from the initiating event to patient death),[24] rendering induction of pancreatic cancer by tofacitinib implausible, though a role in cancer promotion cannot be excluded.

Review of the 8 confirmed cases revealed established risk factors for pancreatic cancer for the majority of the patients, and for all of the cases from the psoriasis program. Risk factors for pancreatic cancer, such as smoking and diabetes, were prevalent among patients in the psoriasis clinical development program as expected for this patient population.[25] Nonetheless, the observed number of cases was higher than expected even after adjustment for these risk factors. While this imbalance might be accounted for by additional unidentified risk factors, extraordinary conditions would need to be met for this to be the case. For instance, chronic pancreatitis is the strongest risk factor for pancreatic cancer.[11] In order for chronic pancreatitis to explain the magnitude of effect detected, the tofacitinib trial population would need to have a 100-fold greater risk of chronic pancreatitis than the reference population and the relative risk between chronic pancreatitis and pancreatic cancer would need

to be in the order of 42, lending credibility to chance or selection bias as alternative explanations.

With regard to selection bias, analogies may be drawn with illnesses such as pancreatitis and recent-onset diabetes, which have been noted to occur in the year or two prior to pancreatic cancer diagnosis.[26] A Swedish study [27] found a particularly high incidence of pancreatic cancer in the year following an index hospitalization for psoriasis, suggesting that a psoriatic flare may also be a marker of undiagnosed pancreatic cancer. Thus, selection bias could occur if patients enrolling in tofacitinib clinical trials were more likely to be those recently experiencing health problems, such as pancreatitis and diabetes, or were experiencing psoriatic flare, due to extant pancreatic neoplasms.

In summary, based on the lack of a signal in RA and other indications, the latency of pancreatic cancer, and lack of a plausible biologic mechanism, an independent external panel of experts deemed it unlikely that there is a causal association between tofacitinib use and pancreatic cancer. Pfizer agreed with this conclusion. However, in December 2015, Pfizer reported the signal to several regulatory agencies, including the FDA, PMDA, and EMA, as well as to country ethics committees and investigators, if required by regulatory agencies. There had been no accumulation of evidence since this regulatory communication, which if observed, would indicate a causal association between tofacitinib and pancreatic cancer, and the company determined the signal investigation closed. Nonetheless, Pfizer took the decision to include reference to pancreatic cancer in the tofacitinib product label and will continue pharmacovigilance through systematic monitoring of the clinical database and postmarketing surveillance via routine adverse event reporting systems and prospective studies in disease registries. Indeed, it is possible that the publication of this article may lead to an increase in spontaneously reported events, resulting from reporting/notoriety bias, thereby complicating continuous signal evaluation efforts. Clinicians must remain vigilant regarding this potential drug–event association, while taking care in their reports to provide as much contextual information as possible to facilitate signal investigation. If the pancreatic cancer signal investigation is reopened, Pfizer will reconsider evaluating the signal via a formal hypothesis-testing study, provided that there is sufficient tofacitinib exposure, or a determination that the study that can rule out a relative risk of 3 with 80% power meets signal evaluation needs.

In conclusion, the pharmaceutical industry's commitment to rapid and open response to safety signals is essential for ensuring patient safety and enabling physicians and patients to consider the risk:benefit of a drug for their individual circumstances. Safety signals emerging through pharmacovigilance may be true or false indicators of a causative association with drug exposure. The tofacitinib example reported here illustrates the challenges of evaluating malignancy signals and emphasizes the need for comprehensive and complete case reporting by physicians. Based on currently available evidence, we believe that tofacitinib exposure is unlikely to be related to the induction or promotion of pancreatic cancer; however, a relationship to promotion cannot be excluded. Pfizer will continue to monitor pancreatic cancer incidence both via routine pharmacovigilance as well as long-term prospective active surveillance efforts.

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AUTHOR CONTRIBUTIONS

All authors provided substantial contribution to the collection, evaluation, and interpretation of data described in this article. All authors provided intellectual input into every stage of the manuscript's development and approved the final manuscript.

DISCLOSURE

All authors are employees and shareholders of Pfizer Inc. Pfizer Inc was responsible for all aspects of the data collection, analysis, and interpretation and the reporting of safety findings and recommendations to regulatory authorities. The opinions expressed in this article reflect those of the authors, not necessarily Pfizer Inc.

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