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ORIGINAL RESEARCH ARTICLE

Results from the First Decade of Research Conducted by the Research on Adverse Drug Events and Reports (RADAR) Project

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Abstract
Introduction In 1998, a multidisciplinary team of investigators initiated the Research on Adverse Drug events And Reports (RADAR) project, a post-marketing surveillance effort that systematically investigates and disseminates information describing serious and previously unrecognized serious adverse drug and device reactions (sADRs).
Objective Herein, we describe the findings, dissemination efforts, and lessons learned from the first decade of the RADAR project.
Methods After identifying serious and unexpected clinical events suitable for further investigation, RADAR collaborators derived case information from physician queries, published and unpublished clinical trials, case reports, US FDA databases and manufacturer sales figures.
Study selection All major RADAR publications from 1998 to the present are included in this analysis.
Data extraction For each RADAR publication, data were abstracted on data source, correlative basic science findings, dissemination and resultant safety information.
Results RADAR investigators reported 43 serious ADRs. Data sources included case reports (17 sADRs), registries (5 sADRs), referral centers (8 sADRs) and clinical trial reports (13 sADRs). Correlative basic science findings were reported for ten sADRs. Thirty-seven sADRS were described as published case reports (5 sADRs) or published case-series (32 sADRs). Related safety information was disseminated as warnings or boxed warnings in the package insert (17 sADRs) and/or 'Dear Healthcare Professional' letters (14 sADRs).

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Conclusion An independent National Institutes of Health-funded post-marketing surveillance programme can supplement existing regulatory and pharmaceutical manufacturer-supported drug safety initiatives.

1 Introduction

Most pharmacovigilance efforts rely on governmental agencies, such as the US Food and Drug Administration (FDA) and the pharmaceutical industry to identify serious adverse drug reactions (sADRs). Adverse Event Reporting System (FAERS), an FDA database, depends on voluntary reporting, making it susceptible to under-reporting, incomplete reporting, over-reporting and absent epidemiological data. Indeed, the definition of sADRs often generates significant over-reporting of events as does the de facto voluntary reporting of these events. Regulations also mandate that manufacturers forward adverse events reports to the FDA. Other potential sources of safety data, such as electronic files maintained by insurers, health maintenance organizations or the Department of Veterans Affairs, are not publicly available. The Institute of Medicine has therefore called for new drug safety approaches [1], but independent investigators are frequently overlooked when these approaches become tangible initiatives.

The Research on Adverse Drug Reactions And Reports (RADAR) project is a clinically based academic post-marketing surveillance programme. RADAR bears no relation to RAD-AR, Risk Assessment of Drugs—Analysis and Response, a programme initiated in 1989 under the aegis of the pharmaceutical industry and academia. RAD-AR developed a worldwide catalogue of databases that was recruited for drug safety research (the so-called RAD-AR Data Resource Handbooks); these have since been digitally modernized and are classified as the BRIDGE-to-DATA initiative (http://www.bridgetodata.org) [2, 3]. During the decade of our RADAR's funding by the National Institutes of Health, RADAR comprised a multidisciplinary team of investigators from various disciplines (basic science, immunology, clinical medicine, epidemiology, statistics, pharmacovigilance, haematology, oncology and clinical pharmacology). The programme systematically investigates and disseminates information describing serious and previously unrecognized adverse drug and device reactions (ADRs), 43 being reported since 1998. The overarching goals of the programme are to identify, evaluate and disseminate reports on sADRs (Tables 1, 2), thus improving patient safety primarily within the domain of cancer care. Herein, we summarize RADAR's findings, lessons learned and future implications.

2 Methods

When an unexpected clinical event (a signal) representing a possible sADR is identified by a RADAR co-investigator, RADAR collaborators postulate clinical hypotheses and derive case series and incidence estimates from physician queries, published and unpublished clinical trials, published case reports, FDA databases and manufacturer sales figures [4, 5]. Collaborators also review the relevant package inserts. Institutional Review Board (IRB) requests are submitted at collaborating institutions when patient health information is required. Relevant FDA reports, usually received within 3 weeks of request, are preliminarily reviewed to specifically generate hypotheses related to the ADR of interest. During weekly meetings, investigators adapt case classification forms to the sADR being investigated. The case classification forms include generic core data elements comprising patient demographics (e.g. age, sex), information source (e.g. clinical trial, physician queries), concomitant medication history, event description (e.g. date of the event, time elapsed between exposure and ADR event, event duration, other relevant history, physical finding, study results), organ-specific history, and treatments (e.g. hospitalization, medications). World Health Organization Uppsala Monitoring Centre (WHO-UMC) criteria [6] are used to score causal associations (certain, probable, possible, unlikely, conditional and unassessable) for each case between the suspect drug and the event. A sample of cases is reviewed by the RADAR team, followed by refinement of hypotheses relative to the pathophysiology of the ADR of interest. Syndrome-specific case report forms are populated with information relevant to the hypotheses and experience from the preliminary case review. Data elements and coding are chosen to accommodate the range of data available in the FDA reports and also to address the underlying hypotheses about the specific type of ADR. Coding of the case classification form is designed to facilitate algorithmic analysis of case findings and case-based causality assessments.

There are 31 core investigators on the RADAR team, comprising two haematologist/oncologists, three health services researchers, three internists, one emergency medicine physician, and various medical subspecialties, including two geriatricians, two bone health experts, one infectious disease physician, two neurologists, two dermatologists, one clinical pharmacologist, four radiologists, two statisticians, two attorneys, two nephrologists and two pharmacists. These core investigators are located at academic medical centres in Chicago, IL; Albuquerque, NM; Rochester, MN; New Haven, CT; and Leuven, Belgium. RADAR sometimes recruits other co-investigators with relevant expertise for a specific sADR. RADAR convenes weekly in-person meetings at Northwestern University Feinberg School of Medicine in Chicago and

Table 1 Summary of Research on Adverse Drug events and Reports (RADAR) findings: 1998–2010

sADR count	Drug (year of FDA approval)	Clinical setting	sADR	No. years to initial detection[a]	Findings to clarify pathophysiology	Initial ADR identifier[b]	Introduced to RADAR[c]	Verification	Incidence/RR
1	Ticlopidine (1991)	Intermittent claudication, thrombotic strokes and cardiac stents	TTP	<1 (1991)	Antibodies (lab)	Plasmapheresis technician	RADAR investigator	BSI	Estimated incidence 1 per 1,600–5,000 pts treated
2	Clopidogrel (1997)	Stroke prevention, thrombosis in pts with stents, peripheral vascular disease and cardiac ischaemia	TTP	1 (1998)	Antibodies (lab)	Plasmapheresis technician	RADAR investigator	BSI	1 in 20,000
3 + 4	DES (sirolimus [2003]/ paclitaxel [2004])	PCI	Thrombotic events with off-label use	2 (2006)	ECG and CPK-MB	Cardiologist	Cardiologist	Observational registry	1 in 20
5	G-CSF/GM-CSF (1991)	BC with CTX and G-CSF	AML and MDS	12 (2003)	Unknown	Oncologist	Clinical trial investigator	SEER-Medicare database	1 in 50
Clinical trials									
6 + 7	Epoetin/darbepoetin (1993/2001)	Cancer	VTE	10 (2003)/ 3 (2004)	None	Oncologist	RADAR investigator	Meta-analysis	1 in 20
8 + 9	Epoetin/darbepoetin (1993/2001)	Cancer	Death	10 (2003)/ 3 (2004)	None	Oncologist	RADAR investigator	Meta-analysis	1.18
10 + 11	Epoetin/darbepoetin (1989/2001)	CKD	Death	18 (2007)/ 6 (2007)	None	Nephrologist	RADAR investigator	Meta-analysis	1.23
12 + 13	Bevacizumab (2004)	Advanced non-squamous NSCLC	Acute diverticulitis	3 (2006)	CT scan	Oncologist	Clinical trial investigator	On-going investigation	1 in 10
14	Lenalidomide (2005)	Multiple myeloma	VTE	<1 (2005)	None	Oncologist	Published report	Meta-analysis	1 in 4
15	Gemcitabine (1996)	Hodgkin's with bleomycin	Serious acute lung injury	7 (2003)	None	Oncologist	Published report	Meta-analysis	1 in 5 (22 %)
16	PEG-rHuMGDF (not approved)	Healthy volunteers	Immune		thrombocytopenia	NA	Antibodies	Haematologist	Lawyer
BSI	1 in 33 (healthy volunteers) and 4 of 650 oncology pts								
17	Gemtuzumab (2000)	Leukaemia or AML	SOS	<1 (2000)	Liver biopsy	Oncologist	Clinical trial investigator	BSI	1 in 7 (14 %)
18	Thalidomide (1998)	Multiple myeloma	VTE	1 (1999)	Laboratory studies	Oncologist	Clinical trial investigator	Meta-analysis	1 in 5
Referral centres									
19 + 20	Paclitaxel (2004)/ sirolimus (2003)-eluting cardiac stents	PCI		Hypersensitivity reactions	<1 (2004/2003)	Autopsy	Cardiologist	RADAR investigator	BSI
Very low									
21	Epoetin (1993)	CKD	PRCA	5 (1998)	Antibodies (laboratories)	Haematologist	Published report	BSI	1 in 9,000

Table 1 continued

sADR count	Drug (year of FDA approval)	Clinical setting	sADR	No. years to initial detection[a]	Findings to clarify pathophysiology	Initial ADR identifier[b]	Introduced to RADAR[c]	Verification	Incidence/RR
22 + 23	Sildenafil/tadalafil (1998/2003)	ED	Optic neuropathy	2 (2000)/2 (2005)	None (clinical)	Ophthalmologist	Published report	On-going investigation	Causality still under investigation
24	Zoledronate (2001)	Multiple myeloma	Osteonecrosis of the jaw	2 (2003)	Jaw biopsy	Dentist	RADAR investigator	Meta-analysis	1 in 10 of 11.6 in 10,000
25	Amiodarone (1985)	Cardiologic arrhythmia	Optic neuropathy	2 (1987)	None (clinical)	Cardiologist	Published report	On-going investigation	Causality still under investigation
26	Voriconazole (2002)	Stem cell transplants	Zygomycosis	2 (2004)	Culture and skin biopsy	Leukaemia centre	Published report	Case-control studies	Causality still under investigation
Case reports									
27	Rituxan (1997)	Purine analogue therapy and haematopoietic transplant in lymphoma pts	PML/death	NA	Biopsy	Oncologist	RADAR investigator	BSI	Rare
28	G-CSF (1991)	Health stem cell donors	Splenic rupture	5 (1996)	None	Haematologist	Hospital pathologist	On-going investigation	Rare
29	AIs (anastrozole) (1995)	BC pts >50 years old	Hip and pelvic fractures	13 (2008)	NA	Literature review	Literature review	On-going investigation	Not available
30	Enoxaparin (1993)	Cardiac catheterization or PCI	Severe haemorrhagic or vascular	complications	13 (2006)	None (clinical)	Cardiologist	RADAR investigator	Toxicity recognized in other settings
1 in 20									
31	Nevirapine (1996)	Healthcare workers	SJS	2 (1998)	Liver biopsy	Occupational health	Clinical inquiry	BSI	3 in 26 (12 %)
32	Nevirapine (1996)	Healthcare workers	Fulminant and acute	hepatotoxicity	2 (1998)	Liver biopsy	Occupational health	RADAR investigator	BSI
From 1 in 10 to 6.2 in 10									
33	Bicalutamide (1995)	Prostate cancer	Interstitial pneumonitis	3 (1998)	None	Oncologist	Published report	MedWatch	1 in 10,000
34	Flutamide (1989)	Prostate cancer	Interstitial pneumonitis	10 (1999)	None	Oncologist	Published report	MedWatch	1 in 2,500
35	Piperacillin (1981)	Suspected infection	Neutropenia	26 (2007)	Antibodies	Literature review	Medical resident	Systematic overview of phase III trials	Not available
36	Sorafenib (2005)	Renal cell carcinoma	AK/SCC	1 (2006)	Skin biopsy	Dematologist	RADAR investigator	On-going investigation	Not available
37	PEG-rHuMGDF (not approved)	Healthy volunteers			Lymphoproliferative disorder	NA	Antibodies (1 of 3 pts)	Oncologist	Attorney
On-going	investigation	Causality still under investigation							

Table 1 continued

sADR count	Drug (year of FDA approval)	Clinical setting	sADR	No. years to initial detection[a]	Findings to clarify pathophysiology	Initial ADR identifier[b]	Introduced to RADAR[c]	Verification	Incidence/RR
38	Erlotinib (2004)	Non-small cell cancers	Severe rash	2 (2006)	Biopsy	Oncologist	RADAR investigator	Common	Not available
39	GBCM (1988)	CKD pts	NSF	18 (2006)	Biopsy	Nephrologist	RADAR investigator	Epidemiology studies	2–5 % among CKD
40	Paclitaxel (1998)	Cancer pts	Hypersensitivity reactions/ anaphylaxis/ death	10 (2008)	Temporal relationship	Oncologist	Clinical query	Not available	
Rare									
41	Natalizumab (2004)	MS	PML	1 (2005)	Biopsy	Clinical trialist	RADAR investigator	BSI	0.10 %
42	Efalizumab (2003)	Psoriasis	PML	5 (2008)	Biopsy	Dermatologist	RADAR investigator	Not available	Not available
43	Ceftriaxone (2010)	Hospitalized adult pts treated for various infections	Drug embolization causing end organ toxicity	<1 (2010)	Capture of drug emboli, though this has not been reported	FDA identification	RADAR investigator	MedWatch	Very rare, if ever

ADR adverse drug reaction, *AI* aromatase inhibitors, *AK* actinic keratoses, *AML* acute myeloid leukaemia, *BC* breast cancer, *BSI* basic science information, *CKD* chronic kidney disease, *CT* computed tomography, *CTX* chemotherapy, *DES* drug-eluting stent, *ECG* electrocardiogram, *ED* erectile dysfunction, *FDA* US Food and Drug Administration, *GBCM* gadolinium-based contrast material, *G-CSF/GM-CSF* granulocyte colony-stimulating factor/granulocyte macrophage colony-stimulating factor, *MDS* myelodysplastic syndrome, *MS* multiple sclerosis, *NA* not applicable, *NSCLC* non-small cell lung cancer, *NSF* nephrogenic systemic sclerosis, *PCI* percutaneous coronary intervention, *PEG-rHUMGDF* pegylated recombinant human megakaryocyte growth and development factor, *PML* progressive multifocal leukoencephalopathy, *PRCA* pure red cell aplasia, *pts* patients, *RR* relative risk, *sADR* severe adverse drug and device reactions, *SCC* squamous cell carcinoma, *SEER* Surveillance Epidemiology and End Results, *SJS* Stephens Johnson syndrome, *SOS* sinusoidal obstructive syndrome, *TTP* thrombotic thrombocytopenic purpura, *VTE* venous thromboembolism

[a] Time to initial detection means the time from drug launch until a RADAR-affiliated physician/technician detected the event of interest in a patient

[b] Initial ADR identifier is the first person to identify the ADR and also the person to report the event to RADAR under time to detection

[c] Introduced to RADAR means the vehicle (person) through which the sADR is made known to the RADAR team

utilizes teleconferencing to communicate with off-site collaborators. After a detailed review of sample cases, the RADAR team collaborates to refine the hypothesis relative to the pathophysiology of the candidate ADR. Senior members of the RADAR team (JMM, DW, SB, DWR, BJE, MC) review the indicator event and oversee a review of the published literature and relevant package inserts; if there is agreement that further investigation of the ADR is warranted, additional case reports queries are submitted (DWR) to the FDA, a broader review of the literature is conducted, and IRB approvals are requested.

Investigators identify additional data sources, such as individual cases or a series of patients with the suspected ADR. Data sources include abstracts or peer-reviewed manuscripts describing published clinical trials and queries of physicians at medical centres treating large numbers of patients with the relevant drug or those receiving treatment for the suspected ADR. Additionally, representatives of clinical research and drug safety at the relevant pharmaceutical firms and safety officials at the FDA and other federal organizations are asked to provide case reports. Investigators abstract the information from individual cases and enter it into a relational database. RADAR has created a system to systematically report ADRs to national databases. The involved databases include the FAERs, the FDA-Centers for Disease Control (CDC)'s FDA Adverse Event Reporting System, which is a national passive voluntary reporting system that accepts reports from the public on adverse events associated with vaccines licensed in the USA, and the National Registry of Drug-Induced Ocular Side Effects, a clearinghouse and reporting entity for drug information on ocular toxicology and suspected adverse drug reactions. Recently, in the area of nephrogenic systemic sclerosis (NSF) secondary to gadolinium-based contrast material (GBCM), RADAR mined a public legal dataset not normally accessed by the medical community.

Hierarchical ordering for case inclusion has been developed: published case report, unpublished case report, and the FAERS or Manufacturer and User Facility Device Experience (MAUDE) system. In order to determine whether an adverse event is drug specific or represents a class effect, hypotheses-based pathophysiological causes are pursued and identified by clinical pharmacologists. Subsequently, specialists in diverse disciplines collaborate based on their expertise and familiarity with the ADRs under study.

3 Results

3.1 Primary Data Sources

The source of data by which the association was first identified included patient registries (specifically cancer registries), clinical trial reports, case reports and medical registries (Table 1). Medical or patient registries are collections of secondary data related to patients with a specific diagnosis, condition or procedure that play an important role in post-marketing surveillance of pharmaceuticals. Registry data were the primary data source for five sADRs. These sADRs were reported between 1 and 12 years after FDA approval of the drug (median 2 years). Sixteen acute myeloid leukaemia (AML) cases were identified in a population-based registry of cancer cases (the Surveillance Epidemiology and End Results [SEER] Registry) developed by RADAR. This information was merged with Medicare records to generate an incidence estimate of 1.8 % of AML/myelodysplastic syndrome (MDS) among chemotherapy-treated breast cancer patients following granulocyte colony stimulating factor/granulocyte macrophage colony stimulating factor (G-CSF/GM-CSF) administration, versus 1 % among chemotherapy-treated breast cancer patients not receiving chemotherapy or G-CSF/GM-CSF (hazard rate of 2.14 [95 % CI 1.12–4.08]) [7]. A second investigation launched by RADAR examined thrombotic thrombocytopenic purpura (TTP) following clopidogrel or ticlopidine initiation [8, 9], and relied on logs maintained by directors of plasmapheresis centres. Review of the FAERS/MedWatch reports data by RADAR investigators also determined that the purported adverse event of calcium-ceftriaxone drug embolization in adults did not likely exist and likely does not cause end organ damage [10]. While we utilized the Common Terminology Criteria for Adverse Events (CTCAE version 3) categories, a standardized classification of side effects used in assessing drugs for cancer therapy, we did not actually assess drug causality, but rather the likelihood that specific clinical events (e.g. renal failure) were related to the adverse event (e.g. embolism) of interest. This method of analysis is not validated and does not follow usual pharmacovigilance practices. While this study did not predate package insert changes by the FDA, our results reinforced the revised FDA recommendations that patients >28 days old may receive ceftriaxone and calcium sequentially and provided a transparent and reproducible methodology for such evaluations. Clinical trial reports were the primary data sources for 13 sADRs reported within a time period ranging from shortly after FDA approval to as late as 18 years post-approval (median: 3 years). These reports included phase II trials (sinusoidal obstructive syndrome [SOS] following gemtuzumab) and phase III trials (mortality and venous thromboembolism [VTE] with epoetin or darbepoetin use in cancer patients and VTE with thalidomide and lenalidomide) [11, 19].

Case reports provided primary data sources for 17 sADRs; time to sADR reporting ranged from immediately after FDA approval (ticlopidine) to 26 years (median:

Table 2 Impact of Research on Adverse Drug events and Reports (RADAR) pharmacovigilance on drug package insert and US FDA warning/letters

sADR count	Drug (year of FDA approval)	sADR	Year RADAR action initiated	Alerts	Additional outcomes by regulating agencies and others
1	Ticlopidine (1991)	TTP	1998	DHP letter (1998); boxed warning (1999)	NA
2	Clopidogrel (1997)	TTP	1999	Warning (2006)	NA
3 + 4	DES (sirolimus (2003)/paclitaxel (2004))	Thrombotic events with off-label use	2006	Company alert (2004)	NA
5	G-CSF/GM-CSF (1991)	AML and MDS	2005	NA	NA
6 + 7	Epoetin/darbepoetin (1993/2001)	VTE	2007	DHP letter (2005); boxed warning (2006), DHP letter (2007), FDA alert (2006/7)	ODAC meetings (2004, 2007, 2008)
8 + 9	Epoetin/darbepoetin (1993/2001)	Death	2007	DHP letter (2005); warning (2005), warning (2007), DHP letter (2007)	ODAC meetings (2004, 2007, 2008)
10 + 11	Epoetin/darbepoetin (1989/2001)	Death	2007	DHP letter (2005); boxed warning (2006), DHP letter (2007), FDA alert (2006/7)	Meeting of the Cardiovascular and Renal Drugs Advisory Committee and the Drug Safety and Risk management Committee (2007)
12 + 13	Bevacizumab (2004)	Acute diverticulitis	2007	DHP letter (2007)	NA
14	Lenalidomide (2005)	VTE	2005	Black-box warning (2006)	NA
15	Gemcitabine (1996)	Serious acute lung injury	2006	Warning (2003)	NA
16	PEG-rHuMGDF (not approved)	Immune thrombocytopenia	2005	NA	NA
17	Gemtuzumab (2000)	SOS	2000	Boxed warning (2001)	Postmarketing registry mandated by the FDA
18	Thalidomide (1998)	VTE	2005	Black-box warning (2006)	Citizen's petition filed by AG of Connecticut, FDA upheld four of six requests
19 + 20	Paclitaxel (2004)/ sirolimus (2003)-eluting cardiac stents	Hypersensitivity reactions	2003	Company alert (2004)	NA
21	Epoetin (1993)	PRCA	2003	Boxed warning (2002), DHP letter (2005)	Canadian, European and Australian health officials mandate Epres delivery intravenously, PRCA website now maintained and updated by sponsor, ODAC meeting (2004)
22 + 23	Sildenafil/tadalafil (1998/2003)	Optic neuropathy	2008	Precaution (2005), FDA alert (2005)	NA
24	Zoledronate (2001)	Osteonecrosis of the jaw	2007	DHP letter (2004), precaution (2005), Dear Dentist (2005)	Canadian, Australian and US officials mandate prescriber notification and release of safety literature, ODAC meeting (2005)

Table 2 continued

sADR count	Drug (year of FDA approval)	sADR	Year RADAR action initiated	Alerts	Additional outcomes by regulating agencies and others
25	Amiodarone (1985)	Optic neuropathy	2008	DHP letter (1997), warning (1998)	NA
26	Voriconazole (2002)	Zygomycosis	2006	NA	NA
27	Rituxan (1997)	PML/death	2008	Boxed warning (2007), warning (2006)	NA
28	G-CSF (1991)	Splenic rupture	2006	Warning (2007)	NA
29	AIs (anastrozole) (1995)	Hip and pelvic fractures	2009	NA	NA
30	Enoxaparin (1993)	Severe haemorrhagic or vascular complications among cardiac pts undergoing angioplasties	2006	NA	NA
31	Nevirapine (1996)	SJS	2001	Boxed warning (1998), boxed warning, warning (1999)	Discontinued as recommended post-exposure prophylaxis by the CDC and end use in occupational health programmes
32	Nevirapine (1996)	Hepatotoxicity—among non-HIV infected pts who receive nevirapine-containing post-exposure prophylaxis	2001	Boxed warning, warning (1998), boxed warning (2000), DHP letter (2000), DHP letter (2004)	NA
33	Bicalutamide (1995)	Pneumonitis	2001	NA	NA
34	Flutamide (1989)	Pneumonitis	2001	NA	NA
35	Piperacillin (1981)	Neutropenia	NA	Precaution (2005)	NA
36	Sorafenib (2005)	AK/SCC	2006	NA	Drug withdrawn from development because of high rates of neutralizing antibodies
37	PEG-rHuMGDF (not approved)	Lymphoproliferative disorder	2005	NA	NA
38	Erlotinib (2004)	Severe rash	2008	NA	NA
39	GBCM (1988)	NSF	2008	NA	NA
40	Paclitaxel (1998)	Anaphylaxis	2008	Boxed warning (1998)	NA
41	Natalizumab (2004)	PML	2008	Black-box warning (2006)	Drug temporarily withdrawn by manufacturer (2005–6)
42	Efalizumab (2003)	PML	2008	Black-box warning (2008), voluntarily withdrawn (2009)	Drug voluntarily withdrawn by manufacturer (2009)
43	Ceftriaxone (2010)	Drug embolization causing end organ toxicity	2009	NA	Investigation supported the low likelihood for ADR with ceftriaxone

ADR adverse drug reaction, *AG* Attorney general, *AI* aromatase inhibitors, *AK* actinic keratosis, *AML* acute myeloid leukaemia, *CDC* Centers for Disease Control, *DES* drug-eluting stent, *DHP* Dear Healthcare Professional, *FDA* US Food and Drug Administration, *GBCM* gadolinium-based contrast agent, *G-CSF/GM-CSF* granulocyte colony-stimulating factor/granulocyte macrophage colony-stimulating factor, *MDS* myelodysplastic syndrome, *NA* not applicable, *NSF* nephrogenic systemic fibrosis, *ODAC* Oncologic Drug Advisory Committee, *PEG-rHUMGDF* pegylated recombinant human megakaryocyte growth and development factor, *PML* progressive multifocal leukoencephalopathy, *pts* patients, *sADR* serious adverse drug reaction, *SCC* squamous cell carcinoma, *SJS* Stephens Johnson Syndrome, *SOS* sinusoidal obstructive syndrome, *TTP* thrombotic thrombocytopenic purpura, *VTE* venous thromboembolism

7.5 years). For most of these sADRS, initial safety reports were submitted to peer-reviewed journals, but not to the FDA or drug manufacturers. Clinicians at referral centres provided information for eight sADRs. Reporting of these sADRs ranged from immediately after FDA approval to 5 years post (median: 2 years). In several instances, clinicians reported the original case information directly to RADAR, but not to the FDA or the manufacturers. In turn, RADAR de-identified the case reports and submitted the clinical information to the FDA and the respective manufacturers.

3.2 Data Quality

The quality of safety data in registries is often poor and constrained by funding limitations. A RADAR study that focused on adverse drug events (ADE) reporting to IRBs at 49 National Cancer Institute (NCI)-designated cancer centres, confirmed that the validity of information regarding drug toxicity in humans is dependent on the quality of the methods and instruments used to assess ADEs [12]. Compared with global introspection, the use of a validated tool to describe and assess event type, severity, and causality augurs well for more timely and accurate identification of safety signals in the domain of cancer therapy. RADAR therefore developed checklists that included information on history, physical examination, laboratory tests, basic science, treatment, clinical outcomes, prophylaxis and causality assessments to evaluate database quality [5]. RADAR safety-focused databases, such as the SERF-TTP (Surveillance, Epidemiology, Risk Factors—Thrombotic Thrombocytopenia Purpura) and the Tysabri Outreach Unified Commitment to Health, include this information [13].

For clopidogrel- and ticlopidine-associated TTP, case reports included ADAMTS13-metalloprotease activity levels, facilitating evaluations of pathophysiological mechanisms [13, 14]. Our review identified 45 % completeness rates for history and physical examination information, 46 % for laboratory studies and 3 % for basic science studies versus completion rates of 90 %, 54 % and 34 %, respectively, in RADAR databases [5]; poor completeness emanates from the voluntary nature of adverse event reporting [15, 16]. FDA reports do not include information on specific product types (for sADRs involving pharmaceutical classes) pathology, treatment or outcome. AERS was utilized to evaluate pure red cell aplasia (PRCA) following epoetin administration in chronic kidney disease (CKD) patients ($n = 170$ cases) and NSF post-magnetic resonance angiography with gadolinium ($n = 351$ cases) [17, 18]; relevant individual case reports for these two sADRs were incomplete, often lacking information about which epoetin or gadolinium product had been administered.

A meta-analysis of 51 phase III trials for cancer patients identified a statistically significant 1.10-fold increased risk of mortality and a 1.57-fold increased VTE risk with erythropoietin-stimulating agents (ESAs) [19]. A meta-analysis of individual patient data identified a statistically significant 1.17-fold increased mortality risk. In several reports, incidence estimates were based on numbers of cases identified by RADAR (numerator data) and estimates of numbers of unique users based on marketing data (denominator data) [8, 20]; recently, a case-control study provided information on odds for developing clopidogrel-associated TTP [21].

3.3 Dissemination

Four sADRs were published by RADAR investigators as case histories. These reports described G-CSF-associated acute leukaemia occurring among three donors of peripheral stem cells, lymphoproliferative diseases among two volunteers who received megakaryocyte growth and development factor, fulminant hepatitis among two healthcare workers after receiving 2 weeks of nevirapine for post-HIV exposure from needle sticks, and a pancreas/kidney transplant patient developing a thrombotic microangiopathy after receiving several days of clopidogrel [14, 22, 23]. Thirty-two sADRs were summarized as case series or summary reviews [5, 8, 9, 15, 16, 20, 21, 24–33]. For 17 sADR case series, comparisons of quality of adverse event data illustrated that case information in FDA databases were markedly less complete than similar case reports in RADAR databases [5].

Recognizing that sADR incidence rates are context specific, data tables report rates as a function of concomitant drugs and extent of disease (e.g. thalidomide-associated VTE and gemtuzumab-associated SOS) [4, 34]; for epoetin-associated PRCA, a graph displayed exposure-adjusted incidence rates over time for different formulations and among different countries [15, 35]

sADR information was disseminated widely. For 22 sADRs, findings were presented at meetings initiated by RADAR to pharmaceutical suppliers at their corporate headquarters; conversely, additional cases were sometimes described by the manufacturer to the RADAR team.

Brief reports were disseminated for 24 sADRs; seven were published in high-impact general medical journals and 18 in specialty journals. Half of RADAR publications appeared as peer-reviewed articles within 2 years after pharmaceutical manufacturers described these sADRs in 'Dear Healthcare Professional' letters or package-insert revisions. Incident to these peer-reviewed articles were summary reports from RADAR that were placed on websites maintained by Consumer's Union, the Veterans Administration MedSafe Project (a patient safety centre of

inquiry) and Northwestern University's MedRADAR site. These summary reports provided very timely access to the information that subsequently appeared in peer-reviewed reports.

Pharmaceutical manufacturers described 23 RADAR-identified sADRs (a part of the 43 ADRs mentioned in this report) in 'Dear Healthcare Professional' letters (nine sADRs) or revisions to the FDA-approved package inserts (14 sADRs). For thalidomide-associated VTE, Connecticut Attorney General Richard Blumenthal filed a 31-page Citizen Petition in 2005, triggered by a RADAR poster. In the USA, a Citizen Petition allows any person to request the FDA Commissioner to "issue, amend, revoke a regulation or order or take or refrain from taking any other form of administration action" subject to the Commissioner's statutory authority. In the thalidomide case, the Attorney General raised concerns about ADRs in off-label settings (a RADAR haematologist had reported a 25 % VTE rate when thalidomide was given with doxorubicin or dexamethasone, specifically noting that thalidomide, which was then approved to treat a rare illness, was being used off-label in more than 90 % of cases) [36]. The Attorney General subsequently requested six safety-related actions for manufacturer consideration. This was the fourth Citizen Petition filed with the FDA by a State Attorney General and the second to be filed with the FDA by Blumenthal. One year later, the FDA approved four of the six recommendations in the petition, including a request to include the related safety information in the 'boxed' warning section of the package insert.

4 Discussion

4.1 Lessons Learned

After a decade of pharmacovigilance studies, we can offer ten major lessons learned.

First, though observant clinicians play critical roles in identifying the first instances of several sADRs, they are frequently reluctant to forward summary information to the FDA or to pharmaceutical manufacturers. Indeed, it is estimated that only 1–10 % of ADRs are reported to the FDA [37]. For several sADRs, clinicians submitted case histories to medical journals for publication consideration, but did not forward the same reports to the FDA or the manufacturer. In interviews with these providers, stated barriers to report submission included concerns about follow-on requests for updated information and clarification of the original case information; fear that reporting might jeopardize collaborative relationships with the pharmaceutical manufacturers; uncertainty related to association between the clinical event and the particular drug [38]; time limitations; and litigation fears. The MedWatch form states that "The public reporting burden for this collection of information has been estimated to average 30 min per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information." It is also well settled that many physicians are concerned about litigation by their patients or third parties. In a 1992 survey of physicians regarding adverse event reporting, more than 37 % of those responding to the survey agreed with the statement that reporting increases the risk of litigation involvement; 18 % listed fear of involvement in the administrative or legal process as a significant factor for not reporting serious ADRs [39, 40]. Similar concerns, reported by the National Registry of Drug-Induced Ocular Side Effects, dissipated once investigators obtained a certificate of confidentiality from the Oregon State Attorney General [41].

Second, obtaining adverse event reports from MedWatch requires patience. Requests are processed under the Freedom of Information Act and can take years. Furthermore, many pieces of useful clinical information are still not included; in the past, age and sex were redacted, but are now retained. Allowing appropriately vetted investigators timely access to MedWatch information could improve its usefulness. RADAR investigations proceed at an accelerated pace due to both facility in accessing the FAERS and collaboration with expert navigators of the AERS database [42].

Third, quality 'trumps' quantity. While large numbers are needed for rare events, for most of the individual sADRs, RADAR case series include description of fewer than 100 cases. Conversely, pharmacovigilance initiatives by the FDA and pharmaceutical manufacturers focus on mining large data sets—many of which have compromised quality. Pharmaceutical manufacturers are beginning to adopt computer-based disproportionality analysis in an effort to expedite signal detection, but greater effort is needed. Future pharmacovigilance pilot efforts should focus on obtaining comprehensive adverse event reporting from a small number of sentinel sites, such as referral centres.

Fourth, product liability attorneys are untapped information sources, some of which might be credible. Twenty-three law firms developed a large and comprehensive database of cases of gadolinium-associated NSF. The database includes information on specific gadolinium brands—an important element not included in FDA reports. In a novel initiative, RADAR received approval to review these individual medical records and to submit these findings for peer review [43, 44].

Fifth, safety notification dissemination is uncoordinated and often conflicting. For example, advisories from

medical organizations, the FDA, the European Medicines Agency (EMA) and pharmaceutical manufacturers include different estimates of the underlying cause, incidence and recommendations for prevention and treatment of bisphosphonate-associated osteonecrosis of the jaw [32]. RADAR researchers previously noted that manufacturer-sponsored epidemiological studies reported the first estimates of the incidence of osteonecrosis of the jaw, ranging from 0.1 % to 1.8 %. By contrast, independent epidemiological efforts from clinicians and the International Myeloma Foundation reported incidence estimates between 5 % and 10 % [32]; this lack of coordination slowed dissemination efforts relative to this serious ADR. Similarly, EMA classifies GBCM into low- and high-risk compounds, while the FDA considers all GBCMs to pose a similar risk for NSF. While inconsistencies in the nature and amount of information provided and in methods of dissemination exist, Risk Evaluation and Mitigation Strategy (REMS) mandated by the FDA and EMA have resulted in more consistent standards and have potentially improved drug safety.

Sixth, sharing safety findings with drug manufacturers facilitates information exchange. RADAR routinely shares findings from its investigations with pharmaceutical companies. In-person meetings with pharmaceutical company epidemiologists to facilitate development of collaborative prospective safety studies have also been convened, but no proposals have been funded to date.

Seventh, manufacturers, regulatory authorities, insurers and clinicians tend to react to safety reports. These responses include 'boxed' warnings, public health advisories and/or review of findings at advisory meetings or by guideline committees. RADAR provided Attorney General Blumenthal with thalidomide-associated thromboembolism material in response to concerns about anaemic dissemination to providers and the public. For erythropoietin and darbepoetin, responses included recommendations by the manufacturer not to administer these agents to cancer patients receiving chemotherapy with curative intent. Ultimately, use of these agents throughout the oncology community decreased by 80 %, primarily due to safety concerns. For rituximab, the FDA denied a request to extend the licensed indication to first-line treatment of rheumatoid arthritis because of safety concerns resulting from identification of several cases of progressive multifocal leukoencephalopathy (PML) among individuals receiving this drug.

Eighth, safety is a 'life-long' concern. Several sADRs were identified 1–2 decades after commonly used drugs received regulatory approval; these include epoetin-associated PRCA, VTE; ticlopidine-associated TTP, and rituximab-associated PML [15, 33, 45].

Ninth, class-related toxicities should be anticipated. Awareness of sADRs associated with ticlopidine, thalidomide and nilutamide facilitated identification of similar toxicities with clopidogrel, lenalidomide and flutamide/bicalutamide, respectively. Anticipation of these toxicities was helpful in early identification of these sADRs.

Finally, reporting safety assessments can be controversial. RADAR presentations describing increased mortality among cancer patients who received erythropoietin or darbepoetin and PML following rituximab treatment were viewed as particularly dissentious, as the results were not embraced by clinicians or readily accepted by manufacturers. Additional investigations conducted by the relevant pharmaceutical manufacturers eventually supported RADAR's findings with resultant changes in product labelling [33, 46, 47]; this controversy underscores the importance of partnering proactively with relevant stakeholders (e.g. pharmaceutical companies) in the pursuit of ADRs. Furthermore, it highlighted the importance of communicating with providers and manufacturers that the goal of surveillance is not always to remove an efficacious drug product from the market, but often to support its continued use within the constraints of specific indications, dosage, co-use with other drug products, and use by well informed (through product insert and direct-to-consumer advertisements) providers and patients.

4.2 Looking Forward

In May 2008, the FDA launched the Sentinel Initiative. A proactive national electronic system involving electronic health records, administrative and insurance claims databases, and registries, Sentinel, like RADAR, is designed to augment already existing safety surveillance systems.

In addition to Sentinel and in concert with its expanded powers under Title IX of the FDA Amendments Act (FDAAA) of 2007, 49 the FDA approved the class-wide REMS programme for ESAs [49, 50]; this REMS requires physicians and hospitals using ESAs for cancer-related anaemia to register and undergo training relative to their risks and benefits. The FDAAA provides a new statutory framework and authority for the FDA to require REMS for drugs and biologics either prior to approval relative to a risk-benefit analysis or post-approval based on new safety information [48].

Limitations to RADAR's approach must still be acknowledged. Dissemination of ADR data by pharmaceutical suppliers and the FDA continues to be evaluated based on reviews of package inserts and 'Dear Healthcare Professional' letters, these being the only relevant sources of safety information from a regulatory perspective. While several of the major proposed changes alluded to in our previous manuscript in 2005 have come to fruition, large databases often are not mined in contradistinction to RADAR-related investigations. RADAR is also limited in

that it does not address non-serious ADRs, seeking instead to focus on serious and/or life-threatening adverse events; consequently, RADAR's range is arguably limited. Over a period of 7 years, RADAR investigated 16 serious ADRs utilizing 25 investigators in parallel with the FDA, which reviewed more than 900,000 reports and contributed to at least 1,500 safety-related labelling changes with the support of a large team of investigators and a multi-million dollar budget [51].

In conclusion, the RADAR programme has adapted an approach to adverse event assessment originally proposed in the context of systematic reviews [52]. Data sources include clinical trials, referral centres and databases and registries—sources with varied data quality. Incidence estimation is challenging, with registries and observational databases providing information for sADRs with low incidences. A range of data synthesis and dissemination efforts has been utilized, involving non-profit organizations, medical journals, regulatory agencies, the private sector and the medical community. New partnerships have been established with organizations such as the Consumer's Union [53], trade journals and the Veterans Affairs MedSafe programme [54]. We have demonstrated that our method complements traditional surveillance efforts conducted by the FDA and pharmaceutical manufacturers and provides support for including independent programmes in public-private safety collaborations.

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