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Novel Adverse Events of Bevacizumab in the US FDA Adverse Event Reporting System Database

A Disproportionality Analysis

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Abstract

Background: Bevacizumab is the first in its class, vascular endothelial growth factor (VEGF) inhibitor that was initially approved by the US FDA in 2004 for the treatment of metastatic colon cancer and other solid tumors. Pre-approval clinical trials, particularly for oncology drugs, are limited in their ability to detect certain adverse effects and, therefore, the FDA and pharmaceutical sponsors collect and monitor reports of adverse events (AEs) following approval.

Objective: The purpose of this study was to screen the FDA's Adverse Event Reporting System (AERS) database for novel AEs that may be attributed to bevacizumab.

Methods: The FDA AERS database was used to identify all AE reports for bevacizumab from February 2004 to September 2009. Disproportionality analysis was conducted for bevacizumab against all other drugs in the background by setting statistical significance at proportional reporting ratio (PRR) ≥2, observed case count ≥3 and chi-square ≥4. Subsequent clinical evaluation was performed to determine the clinical relevance of the findings and to group related events.

Results: A total of 523 Preferred Terms (PTs) were disproportionally reported; following clinical review 63 (12%) were found to be both unlabelled and of clinical importance. These PTs were grouped into 15 clinical disorder groups. Among the clinical disorders, electrolyte abnormalities had the greatest number of reports (n = 426) followed by cardiovascular events (n = 421), gastrointestinal events (n = 345), nervous system disorders (n = 106) and pneumonitis (n = 96). On sensitivity analysis, a number of clinically important

unlabelled disorders, such as necrotizing fasciitis, vessel wall disorders, arrhythmia and conduction disorder and autoimmune thrombocytopenia still met the statistical significance criteria.

Conclusions: During the study period, out of 12 010 AE reports mentioning bevacizumab, it was listed as the suspect drug in 94.2% of the reports. Our disproportionality analysis identified many events that are already recognized as AEs of bevacizumab, but it also identified a number of clinically important unlabelled terms, which if confirmed in future studies would have potential implications for use of bevacizumab in clinical practice.

Background

Bevacizumab is a humanized monoclonal antibody targeting vascular endothelial growth factor (VEGF). VEGF is essential for the induction, maintenance and growth of vascular endothelial cells (angiogenesis) and therefore plays an essential role in normal tissue and cancer growth. The first drug in this class on the US market, bevacizumab (Avastin®, Genentech/Roche, South San Francisco, CA, USA) was initially approved by the US FDA in February 2004 for use in metastatic colorectal cancer in combination with other chemotherapeutic agents. It was also approved as a targeted therapy for a number of cancers alone or in combination with other chemotherapeutic drugs.

Bevacizumab has extended survival for certain cancer patients; however, it is associated with a number of serious adverse events (AEs). While some of the AEs were identified during the premarketing and preapproval clinical trials, there are significant and well documented limitations in the ability of premarketing studies to elucidate the full spectrum of potential harms. Small numbers of patients exposed to the study drug, a narrowly defined indication, restrictive eligibility criteria and the limited length of exposure in premarketing clinical trials limit the ability to detect rare adverse reactions. Therefore, it is expected that new AEs will be identified when the drug is used by a larger group of patients. Indeed, after approval there have been published reports of bevacizumab-associated AEs in the medical literature, including myocardial infarction, stroke, pulmonary hypertension and polyserositis.[1] These newly identified AEs were added to the product labelling (product package insert) in a postmarketing revision.[1]

There are now 7 years of postmarketing experience with bevacizumab. Since first approved it has seen widespread usage in a variety of cancers, as well as off-label usage in age-related macular degeneration.[2,3] Based on the results of an FDA pilot programme to evaluate postmarketing safety, which found previously unrecognized AEs for the five molecular drugs studied (duloxetine, ranolazine, apomorphine, aripiprazole and rasagiline), there may be AEs related to bevacizumab that are yet to be identified.[4] One method used in the discovery of novel and potentially drug-related AEs is data mining. Data mining is a term used to describe a variety of analytic techniques used to find anomalies or statistical deviations from what is 'expected' within large databases. In this study, we conducted a data mining analysis of the FDA database of AE reports (Adverse Event Reporting System [AERS]) for the drug bevacizumab. Here we present the results of this analysis, which identified a number of clinically relevant AEs that are statistically associated with bevacizumab AE reports.

Methods

Data Source

This study utilized the AERS database of AE reports. Since the 1960s, the FDA has maintained a passive surveillance system to detect problems with drugs and other regulated products. Reports

of AEs that the reporter thought related to the use of a pharmaceutical product are reviewed, coded, and accumulated into an electronic database. This passive surveillance programme functions as an early-warning system for the detection of serious AEs not identified during premarketing testing.

Our study was based on all reports for bevacizumab received by the FDA from February 2004, when bevacizumab was first approved in the US, through September 2009 and released in the publically-available version of AERS. This version of AERS is stripped of potentially identifying information, including medical notes or narratives. Original and follow-up reports of the same event were counted as single case.

Study Variables

Information contained within an AERS report includes the name of one or more suspect drugs (those suspected by the reporter of causing, or being causally related to, an AE), concomitant drugs, patient characteristics (age and sex) and the outcome. Reporters can check any number of patient outcomes from a list that includes death, hospitalization, life-threatening, disability, congenital anomaly and other serious outcomes. An unlimited number of AEs can be reported in a single report. Each event is coded using the standardized terminology of the Medical Dictionary for Regulatory Activities (MedDRA®).[5] Similar to the International Classification of Diseases (ICD) coding scheme, MedDRA® is a multilevel, hierarchical coding scheme that was developed specifically for AEs. The highest level is the system organ class (SOC), which usually identifies the physiological or anatomical system affected (e.g. cardiovascular system), but also includes a number of categories (i.e. investigations, general and administration site disorders, injuries and poisonings, social circumstance, and surgical and medical procedures) not associated with a single organ system. The lowest evaluable level is the preferred term (PT).

Each of the more than 19 000 PTs identifies a single medical concept. While having a large number of PTs reduces the amount of interpretation needed to code reports upon entry, it does result in a highly granular dictionary. For example, blood pressure abnormal, increased or decreased are three separate unique PTs. Data mining analysis was initially conducted at the level of the PT to generate a list of statistically significant PTs. All significant PTs were then grouped into clinically relevant categories (described below in the Clinical Review section) for further analysis and interpretation.

Statistical Analysis

The frequency of each PT, as reported for bevacizumab, was compared with an expected or background frequency for that PT by calculating a Proportional Reporting Ratio (PRR). PRRs are calculated using the same formula as relative risk, but are a comparison of reporting rates and not incidence or prevalence. The expected or background reporting rate was calculated as the frequency of that same PT among all AERS reports received during the study period. The PRRs and associated Chi-square test statistics were calculated using QScan® software (DrugLogic®, Inc., Reston, VA, USA).

The threshold for statistical significance was predefined as a PRR of ≥2.0 with a Chi-squared test statistic of ≥4.0 and at least three reports (n ≥3) of that PT with bevacizumab listed as the suspect or a concomitant drug. Any PT that met all three of these criteria was considered disproportionally reported for bevacizumab at a higher rate than expected.[6] Some PTs might be reported at high rates with bevacizumab when they are actually associated with the underlying disease and not the drug. To check for this potential source of bias, a sensitivity analysis was conducted by recalculating the data mining statistics against the background of reports that listed one or more chemotherapy drugs commonly used to treat metastatic colorectal cancer.

Clinical Review

The disproportionately reported PTs identified by data mining analyses were then evaluated

Table I. Clinically novel preferred terms categorized by clinical disorder

Clinical disorder	PTs[a]	PRR	N for bevacizumab[b]	Per 1000 cases of bevacizumab in AERS	N for all drugs in AERS	Per 1000 cases of all drugs in AERS
Bowel obstruction	**Duodenal obstruction**	20.88	5	0.42	31	0.02
	Small intestinal obstruction	15.95	143	12.07	1085	0.8
	Obstruction gastric	14.31	16	1.33	133	0.1
	Gastrointestinal obstruction	8.7	9	0.75	109	0.008
	Intestinal obstruction	7.7	156	12.98	2287	1.69
	Intussusception	8.6	6	0.5	80	0.06
	Colonic obstruction	15.2	15	1.25	123	0.09
	Large intestinal obstruction	13.1	5	0.42	41	0.03
Hepatic disorders	Hyperbilirubinaemia	3.25	30	2.5	1003	0.74
	Hepatic atrophy	3.05	3	0.25	106	0.08
	Hepatic cirrhosis	2.18	32	2.66	1593	1.18
	Hepatic ischaemia	8.9	3	0.25	35	0.03
	Portal hypertension	6.61	22	1.83	374	0.28
Cardiomyopathic disorders	Stress cardiomyopathy	3.34	4	0.33	95	0.07
	Cardiomyopathy	2.46	49	4.08	2161	1.6
	Diastolic dysfunction	2.05	8	0.66	432	0.32
	Left ventricular dysfunction	8.16	26	2.16	330	0.24
	Ventricular dysfunction	2.69	25	2.08	1055	0.78
	Ejection fraction decreased	3.2	55	4.58	1883	1.39
	Brain natriuretic peptide increased	3.05	10	0.83	363	0.27
Arrythmia and conduction disorders	Nodal arrhythmia	3.25	6	0.5	202	0.15
	Tachyarrhythmia	2.4	9	0.75	403	0.3
	Arrhythmia supraventricular	7.67	17	1.42	258	0.19
	Sinus tachycardia	2.11	44	3.66	2255	1.67
	Supraventricular tachycardia	3.15	41	3.5	1473	1.09
	Electrocardiogram QRS complex abnormal	6.04	3	0.25	57	0.04
Vessel wall disorders	Aortic disorder	4.11	5	0.42	133	0.1
	Aneurysm ruptured	7.31	7	0.58	106	0.08
	Aortic aneurysm rupture	6.07	7	0.58	119	0.09
	Aortic dissection	8.25	18	1.5	254	0.19
Sudden cardiac death	Cardiac death	3.13	4	0.33	131	0.1
	Sudden cardiac death	2.68	13	1.08	533	0.39
	Sudden death	3.63	81	6.75	2468	1.83
	Pulse absent	2	20	1.67	1076	0.8

Continued next page

Table I. Contd

Clinical disorder	PTs[a]	PRR	N for bevacizumab[b]	Per 1000 cases of bevacizumab in AERS	N for all drugs in AERS	Per 1000 cases of all drugs in AERS
Capillary leak syndrome	**Capillary leak syndrome**	6.23	11	0.92	212	0.16
Necrotizing fasciitis	**Necrotizing fasciitis**	8.61	22	1.83	292	0.22
Urinary disorders	**Glomerulonephritis**	28.99	7	0.58	279	0.21
	Bladder perforation	2.77	9	0.75	42	0.03
Electrolyte abnormalities	Hypophosphataemia	3.55	16	1.33	487	0.36
	Hypomagnesaemia	5.57	48	4.08	967	0.72
	Hypokalaemia	2.89	131	10.91	4894	3.62
	Hypocalcaemia	2.07	29	2.41	1490	1.10
	Hypernatraemia	2.33	11	0.92	499	0.37
	Electrolyte imbalance	2.34	24	2.00	1120	0.83
	Blood sodium increased	2.35	10	0.83	471	0.35
	Blood sodium decreased	3.99	107	8.91	2960	2.19
	Blood potassium decreased	3.24	102	8.58	3504	2.59
	Blood phosphorus decreased	3.80	12	1.00	340	0.25
	Blood magnesium increased	2.77	4	0.33	163	0.12
	Blood magnesium decreased	2.50	15	1.25	647	0.48
	Blood calcium decreased	3.80	47	3.91	1347	1.00
Autoimmune thrombocytopenia	**Thrombotic thrombocytopenic purpura**	4.24	27	2.25	670	0.50
	Haemolytic uraemic syndrome	4.23	18	1.50	471	0.35
	Autoimmune thrombocytopenia	3.17	5	0.42	172	0.13
Thrombocyte count abnormality	**Platelet count increased**	2.70	35	2.91	1508	1.12
Neurological disorders	**Neurodegenerative disorder**	7.86	3	0.25	46	0.03
	Intracranial hypotension	10.98	19	1.58	196	0.14
	Encephalopathy	2.35	59	4.91	2702	2.00
	Cholinergic syndrome	5.05	3	0.25	66	0.05
	Peripheral motor neuropathy	5.40	8	0.66	157	0.12
	Peripheral sensory neuropathy	4.09	17	1.42	455	0.34
Adrenal disorder	**Adrenal disorder**	4.28	5	0.42	138	0.10
Pneumonitis	Interstitial lung disease	2.21	96	7.99	4355	3.22

a PTs in bold were statistically significant on sensitivity analysis. Sensitivity analysis was conducted by specifying the background to chemotherapy drugs used to treat colorectal cancer only.

b One case report for bevacizumab can have more than one reaction mentioned, e.g. the bowel obstruction clinical disorder group has a total 355 reactions (PTs) mentioned in 345 case reports.

AERS = Adverse Event Reporting System; **PRR** = proportional reporting ratio; **PTs** = Preferred Terms

by two clinicians to exclude events previously associated with bevacizumab.[1] PTs representing diseases and medical disorders that are known to be clinically attributed to the underlying cancer were identified and excluded. Previously identified AEs of bevacizumab that were noted in the 'warning and precaution', 'adverse reaction' and 'postmarketing' sections of the product label[1] (July 2009) were also excluded. For example, gastrointestinal fistulae (n = 81; PRR = 112.7), hypertensive crisis (n = 22; PRR = 17.8) and proteinuria (n = 158; PRR = 11.1). This resulted in 103 remaining PTs. We further excluded 37 PTs (35.6%) describing ocular disorders. Based on the mode of administration (intraocular injection), these were most likely related to the off-label use of bevacizumab in the treatment of age-related macular degeneration.[3,7]

The remaining PTs were accumulated into 15 clinical disorders. Each clinical disorder consisted of one or more PTs which describe a similar medical condition or event. For example, all reports that mentioned any of seven related cardiovascular PTs ('stress cardiomyopathy', 'cardiomyopathy', 'left ventricular dysfunction', 'ventricular dysfunction', 'diastolic dysfunction', 'ejection fraction decreased' and 'brain natriuretic peptide increased') were combined together into the clinical disorder cardiomyopathic disorders (table I). This step eliminated the double-counting that would otherwise occur when several closely related PTs are reported in a single AE report. Descriptive statistics were calculated using QScan® software and Excel® (Microsoft Corporation, Redmond, WA, USA).[8]

Results

The total number of AE reports in AERS that mentioned the drug bevacizumab and were received by the FDA from February 2004 through September 2009 was 12 010 (table II). Bevacizumab was reported as the suspect drug in 11 312 (94.2%) cases. Reports were evenly distributed by sex, with 5526 (46.0%) females and 5397 (44.9%) males. The remainder (n = 1087, 9.1%) did not have sex specified. The highest numbers of reports were in the age group 51–75 years (n = 3984) and the lowest number in children <16 years of age (n = 21). Age was listed as unknown or missing in 51.1% of reports (table II).

Table II. Characteristics of adverse event reports that mentioned bevacizumab, FDA Adverse Event Reporting System 2004–9

Characteristics	Reports [N (%)]
Total reports	12 010 (100.0)
Bevacizumab as suspect drug	11 312 (94.2)
Patient sex	
Male	5397 (44.9)
Female	5526 (46.0)
Unknown/missing	1087 (9.1)
Patient age group [y]	
<16	21 (0.2)
16–30	87 (0.7)
31–50	1032 (8.6)
51–75	3984 (33.2)
>75	750 (6.2)
Unknown/missing	6136 (51.1)
Patient outcome	
Serious[a,b]	8202 (68.3)
Non-serious	3503 (29.2)
Report type	
Direct	1480 (12.3)
Expedited	8739 (72.8)
Periodic	1791 (14.9)
Commonly reported drugs with bevacizumab	
Oxaliplatin	3256 (27.1)
Fluorouracil	3086 (25.7)
Leucovorin calcium	2160 (17.9)
Capecitabine	1692 (14.1)
Irinotecan hydrochloride	1385 (11.5)

a Data not reported for some cases.

b Serious: death, hospitalization (initial or prolonged), life-threatening condition, required intervention to prevent permanent damage, congenital anomaly, or other serious outcomes.

As expected due to industry reporting requirements, the majority of reports (n = 8202) noted one or more serious outcomes. Hospitalization was the most frequently reported outcome (n = 6496), followed by death (n = 1980), life-threatening event (n = 932), disability (n = 353), required intervention to prevent permanent impairment/damage (n = 297) and congenital anomaly (n = 1). Oxaliplatin was the most commonly reported drug with bevacizumab (27%) [table II].

Data Mining and Clinical Review

Using data mining algorithms to identify PTs that were reported in combination with the drug bevacizumab more often than expected, a total of 523 PTs (17.7% of a total 2760 PTs contained in bevacizumab reports) were identified. Based upon our clinical review and application of the study exclusions, 63 PTs (12% of the disproportionately reported PTs) were determined to be novel and clinically relevant. Bevacizumab was reported as a suspect drug in 94% of these reports. The remaining analysis was limited to AE reports that contained one or more of these 63 PTs.

The value of the PRR indicates how many times more often bevacizumab is reported with that PT than would be expected by random chance. The PRR for these 63 PTs ranged from 2.0 (the lower cut-off point defining statistical significance) for the PT 'pulse absent' to 20.88 for the PT 'duodenal obstruction'. An additional four PTs related to bowel obstruction had PRR greater than 10: 'small intestinal obstruction' (PRR = 15.95), 'obstruction gastric' (PRR = 14.31), 'colonic obstruction' (PRR = 15.2) and 'large intestinal obstruction' (PRR = 13.1).

Because there is no limit to the number of PTs that can be coded on a single case report, and with the high level of specificity in the MedDRA® coding scheme, AE reports sometimes contain multiple PTs that describe the same clinical disorder. For example, both a general and a more specific term were noted together on one AE report (e.g. 'aneurysm ruptured' and 'aortic aneurysm rupture') and similarly when both a clinical disorder and the diagnostic laboratory findings were recorded (e.g. 'cardiomyopathy' and 'brain natriuretic peptide increased'). Therefore, AE cases were grouped into 15 clinical disorders by combining those PTs that described the same or similar, but pathologically related, clinical conditions.

The largest grouping of PTs was cardiovascular disorders; 22 PTs (33.3% of disproportionately reported PTs) were grouped into five clinical disorders: cardiomyopathic disorders, arrhythmia and conduction disorders, vessel wall disorders, sudden cardiac death and capillary leak syndrome. Among the clinical disorders, electrolyte abnormalities had the greatest number of reports (n = 426) followed by cardiovascular events (n = 421), gastrointestinal events (n = 345), nervous system disorders (n = 106), pneumonitis (n = 96), hepatic disorder (n = 82), autoimmune disorders (n = 83), thrombocyte count disorders (n = 34), necrotizing fasciitis (n = 22) and urinary disorders (n = 16) [table III].

Bevacizumab was listed as a suspect drug (primary or secondary) in the majority of reports within each clinical disorder, ranging from 88.0%

Table III. Characteristics of reports according to clinical disorder

Clinical disorder	No. of reports	Bevacizumab as suspect (%)	Sex (%)		Age group [y] (%)			Outcome
			Males	Females	<30	31–75	>75	[patient died] (%)
Bowel obstruction	345	94.5	53.0	43.8	0.6	52.5	2.3	20.0
Hepatic disorder	82	92.7	40.2	56.0	1.2	51.2	1.2	19.5
Cardiomyopathic disorders	149	94.6	34.2	60.4	0.0	55.7	4.7	12.8
Arrhythmia and conduction disorders	109	96.3	50.5	42.2	0.0	48.6	10.1	17.4
Vessel wall disorders	35	97.1	62.9	34.3	0.0	54.3	8.6	37.1
Sudden cardiac death	117	97.0	62.0	35.0	3.2	48.4	9.0	95.0
Capillary leak syndrome	11	100.0	45.5	54.5	0.0	36.4	0.9	45.5
Necrotizing fasciitis	22	100.0	59.1	22.7	0.0	45.5	0.0	13.6
Urinary disorders	16	100.0	56.3	12.5	0.0	31.3	0.0	25.0
Electrolyte abnormality	426	93.2	46.0	49.8	0.0	57.3	10.6	18.1
Autoimmune thrombocytopenia	83	90.4	40.9	46.9	1.2	51.8	2.4	13.3
Thrombocyte count disorder	34	100.0	61.8	38.2	0.0	76.5	5.9	20.5
Neurological disorder	106	94.3	48.1	46.2	0.0	46.2	0.0	22.6
Pneumonitis	96	97.9	58.3	37.5	0.0	39.6	3.1	26.0

for peripheral neuropathy reports to 100% of reports in the following categories: capillary leak syndrome, necrotizing fasciitis and urinary disorders (table III). Death rates varied considerably across categories, with the lowest and highest percentage of death reports among autoimmune thrombocytopenia clinical disorder (13.3%) and sudden cardiac arrest clinical disorder (95.0%), respectively. There was also variation in the distribution of males and females. Cardiomyopathic disorders had proportionally more reports involving female patients (60.4%), while male patients were more frequently included in reports of vessel wall disorders (62.9%) and sudden cardiac arrest (62.0%).

A number of cardiovascular AEs were disproportionately reported for which bevacizumab was the suspect drug in the majority of case reports (>95%). All parts and cell types of the cardiovascular system, including myocardium, pericardium, cardiac conductive system and large vessels were involved. There were a total of 293 case reports of myocardial dysfunction, aortic vessel wall disorders and arrhythmic disorders in our study (table III).

On conducting sensitivity analysis by limiting the background to chemotherapy agents used for colorectal cancer, 54% of the PTs (34) from the full analysis continued to meet the statistical significance criteria for disproportional reporting. While this would seem to be a major loss of information, at least one or more PTs from each of the identified clinical disorders, except for the clinical disorder pneumonitis, remained statistically significant (table I).

Discussion

Data mining is used by regulatory agencies and increasingly in the pharmaceutical industry to screen large databases and nominate drug-AE pairs for further clinical review. Using data mining techniques to identify previously unknown AEs of marketed medications, we identified a number of novel AEs that were disproportionately reported and potentially associated with the use of bevacizumab. In addition to identifying novel AEs, our analysis generated statistical alerts for a number of previously established AEs of bevacizumab, including gastrointestinal fistulae, hypertensive crisis and proteinuria (as mentioned in the Clinical Review section). In the majority of AE reports that listed bevacizumab, it was identified as a suspect drug by the reporter.

The data mining algorithms, when applied to spontaneous reports of AEs, can identify events that are disproportionally reported for a particular drug. However, they cannot establish a causal relationship between the drug and an AE. During the clinical review, prior knowledge and potential mechanisms are integrated to determine if data mining identified a clinical signal that may need to be further investigated. Despite the limitations of data mining in spontaneous reports, we found clinical case reports and animal studies[9-12] in the literature regarding a number of AEs that data mining had identified (interstitial lung disease [ILD], necrotizing fasciitis, hepatic toxicity, and autoimmune thrombocytopenia), suggesting some rationale for further investigation of a possible causal link with bevacizumab.

VEGF plays a role in the maintenance of vascular integrity and normal function in non-cancerous tissues. VEGF also promotes cancer-associated angiogenesis, which is an important and essential step in progression and survival of cancer cells.[13-15] There is some evidence in the literature about single nucleotide polymorphisms in the *VEGF* gene which might be responsible for the variable efficacy and safety profile of bevacizumab in different patients.[16] Inhibition of VEGF receptors in normal cells during the course of chemotherapy may cause or contribute to the development of many of the AEs that were identified in our analysis, particularly those affecting the cardiovascular, gastrointestinal, blood and immune systems.

The premarketing clinical trials, as well as other studies, showed that VEGF inhibition is associated with more detrimental effects on left ventricular function compared with other chemotherapeutic agents.[1,17] On the other hand, VEGF delayed onset of failure in pressure overload hypertrophied heart.[18] Production and release of nitric oxide (NO) in the endothelium and coronary circulation in heart failure is decreased by VEGF inhibition.[19,20] Conversely, some fa-

vourable effects of VEGF are mediated by its ability to stimulate endothelial NO release and production.[21-25] Therefore, it is possible that VEGF inhibition may cause abnormal NO production, endothelial dysfunction and/or microvascular rarefactions in cardiovascular tissues. These deleterious effects on the cardiac vasculature may cause ischaemia, which subsequently can lead to cardiac rhythm abnormalities through lowering the threshold for the generation of arrhythmia, and contractile dysfunction.[26,27]

AEs related to large vessel involvement, such as aortic dissection and aneurysms, were detected in our analysis. These relatively rare and life-threatening AEs have not been reported in bevacizumab premarketing clinical trials. However, currently, several active clinical trials of bevacizumab specifically exclude patients with a history of aortic aneurysm and/or dissection.[28,29] Lee et al.[30] suggested that VEGF may play an important role in the development of angiopathy, through upregulation of endothelial nitric oxide synthase (eNOS) gene expression in aortic endothelial cells by a protein kinase C-dependent pathway. VEGF inhibitor-induced hypertension may also indirectly predispose the impaired endothelial layers of vessel wall to dissection by an increased shear force within the vessel wall.[31] This is thought to be a result of the capillary rarefaction and alteration in endothelial function throughout the systemic vascular network.[31,32]

A number of gastrointestinal AEs were also found in our analysis, including a number of hepatic disorders. Recently, cases of VEGF inhibitor-induced hepatic toxicity have appeared in the medical literature.[9] VEGF has been shown to play an essential role in the hepatocyte regeneration.[33,34] Following hepatic injury, VEGF production is increased and its receptors are upregulated in the liver; thus, inhibition of VEGF may potentially make the liver more vulnerable to the hepatotoxic effects of other chemotherapeutic agents by reducing its regenerative capacity. VEGF inhibitors may directly cause hepatotoxicity or indirectly induce ischaemic hepatic injury through microcirculation rarefaction or hepatic vessel thrombosis formation.[29,30,35] In the gastrointestinal system analysis, gastrointestinal obstruction also emerged as a potential adverse effect among bevacizumab-exposed cases. Despite the fact that many patients, especially those with advance colorectal cancer, might develop gastrointestinal obstruction either due to the physical expansion of the tumour, usage of opioids or post-surgical complications, bevacizumab was reported as the suspect drug in 94.5% of our cases. Six of the eight bowel obstruction PTs were statistically significant on sensitivity analysis, which was designed to reduce the potential events related to colorectal cancer.

Endothelial dysfunction-induced thrombosis and thrombocytopenia are known AEs of bevacizumab in premarketing trials.[36] However, autoimmune thrombocytopenia has not been reported in association with bevacizumab in the medical literature. A hypothesis proposed by Meyer et al.[10] suggested that the combination of heparin (used to flush the access ports for infusion of chemotherapeutic agents) with bevacizumab and VEGF can form an immune complex and induce platelet aggregation and thrombosis. The authors proposed that this immune complex activates the FcγRIIa receptor through a mechanism similar to that of heparin-induced thrombocytopenia.

An increased incidence of infections was reported in the early premarketing trials.[9] Necrotizing fasciitis, which is a rare and life-threatening disease, was reported for 22 bevacizumab-exposed cases. This is in congruence with a clinical case report recently published in the medical literature.[11] Given the seriousness of this AE, further investigation of this finding may be warranted.

The PT ILD was statistically significant against the background of all FDA drugs, but on sensitivity analysis this PT was no longer statistically significant. Chemotherapy-induced ILD is known to occur with FOLFOX (oxaliplatin, 5-fluorouracil [5-FU], leucovorin) and FOLFIRI (folinic acid, fluouracil [5-FU], irinotecan) regimens for metastatic colorectal cancer. Usui et al.[12] reported four cases of ILD among colorectal cancer patients who were treated with bevacizumab and with FOLFOX/FOLFIRI. Among the 96 cases of ILD reported to the FDA for which bevacizumab was mentioned, the following drugs

were reported concomitantly: fluorouracil (61%), oxalaplatin (52%), leucovorin (43%) and irinotecan (22%).

The indications for bevacizumab have expanded to more cancers since its initial market approval for the treatment of advanced colon cancer in 2004. The FDA recommended the removal of the breast cancer indication based on its review of clinical trials data in December 2010; however this decision did not impact its use for other cancer indications (colon, kidney, brain and lung cancers). We identified a number of potentially serious AEs, a number of which may be related to its mechanism of action. Importantly, if confirmed they are indeed causally related to bevacizumab, some of these events may be predictable, and possibly preventable, through informed patient selection and increased monitoring of high-risk patients. Given the cardiotoxic potential of bevacizumab, we recommend that preventive measures such as cardiac investigations be considered in patients with preexisting medical conditions prior to bevacizumab therapy, as well as ongoing monitoring during extended therapy.

Our study has several limitations, chiefly, that data mining of spontaneous reports only identifies AEs that are disproportionally reported and, as such, do not prove a causal relationship. Our analysis suffers from biases inherent in spontaneous AEs, such as underreporting of AEs in general, overreporting of particular events, and wide variations in data quality. Despite these limitations, the AERS database has been found useful in making safety-related changes for drugs, undertaking active surveillance studies and for enabling risk minimization strategies by the FDA.[37] The FDA acknowledges that data mining results do not establish causal relationship between drug and event and should be complemented by other safety signal detection tools. Signal detection results should be put into perspective by information from estimates from other well conducted pharmacoepidemiological studies and information of exposure from drug utilization databases.[38] All findings reported here were reviewed for both clinical significance and novelty, which may eliminate some events that may be disproportionately reported due to random error or their known association with other chemotherapies or with cancer. Conversely, we may have been unable to detect some AEs that may be caused by bevacizumab because they are common among patients with cancers typically treated with bevacizumab, or they may not be recognized by the treating physician as potentially related to therapy. Despite such limitations, we identified a number of clinically important AEs that should be interpreted within the context of other safety data for bevacizumab.

Conclusions

Postmarketing studies help in identifying potential safety issues. Our postmarketing analysis identified a number of clinically relevant AEs disproportionally reported for bevacizumab for which further investigation may be warranted. If confirmed, the findings from this study would have potential implications for the use of bevacizumab and patient management in clinical practice. Healthcare providers should be vigilant about the possibility of encountering serious AEs identified in this analysis and should report them to the regulatory authorities.

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