

Blood glucose related adverse drug reaction of antitumor monoclonal antibodies: a retrospective analysis using Vigibase

Jincheng Yang¹, Bin Zhao², Haiyan Zhou¹, Bei Jia¹, Lianzhen Chen^{1*}

¹Department of Pharmacy, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100021, China, ²Department of Pharmacy, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, 100730, China

On the increasing prevalence of using mAbs (monoclonal antibodies) in cancer therapy and the severe risk of hyperglycemia, we aimed to analyze the main clinical ADRs of mAbs, with a focus on adverse hyperglycemic events associated with currently clinically used mAbs. mAbs as well as target information were selected from Martinadale book and published articles. Drug approving information was collected from each government website, and ADR statistic data were collected from Vigibase[®], comparing with Adverse Event Reporting System of US FDA. Top 10 mAbs were classified within listing in total ADR records, ADRs per year, hyperglycemic ADR records. Vigibase data were updated onto 15 Feb 2019. 20 mAbs were analyzed with 263217 ADR reports, wherein 16751 records on Metabolism and nutrition disorders and 1444 records on Glucose metabolism disorders. The geographic, age, gender distributions and annual ADR report numbers were listed respectively. Of the top 10, Rituximab, Bevacizumab and Nivolumab were on the top 3 in total ADR record and hyperglycemic record. Top 3 record results were similar in Vigibase and FDA database. It is of increasing importance for clinicians to be aware of early detection, patient management, or drug selection strategies when using mAbs, particularly within the high glyceemic risk-reported mAbs, to improve the efficacy and tolerability of mAbs regiment and optimize patient outcomes.

Keywords: mAbs. ADR. Hyperglycemia. Vigibase. Antitumor.

INTRODUCTION

Over the past 10 years, cancer treatment has been significantly changed by targeted therapies, and monoclonal antibodies (mAbs) play an important role here. (Gül *et al.*, 2015). MAbs therapies has been widely used strategies for many common cancers (Weiner, 2015). There are two main tactics for the development of a highly specific cancer treatment: a specific target (antigen) present only on targeted cancer cells and a therapy directed toward that target (Mehta *et al.*, 2015).

Targeting both tumor and its micro-environment, mAbs have been potential cornerstones of new more personalized cancer treatment patterns (Nicodemus 2015). Monoclonal antibody targets include CD20(cluster of differentiation 20), HER-2(human epidermal growth factor receptor-2), EGFR(Epidermal Growth Factor Receptor), IL-6(interleukin-6) receptor, TNF- α (Tumor Necrosis Factor- α), CD30(cluster of differentiation 30), VEGF-A(Vascular endothelial growth factor-A), IgE(Immunoglobulin E), and more, and examples of immune mediated and inflammatory diseases that respond to monoclonal antibodies include rheumatoid arthritis, Crohn's disease, ulcerative colitis, juvenile idiopathic arthritis, psoriasis and psoriatic arthritis, Wegener's granulomatosis, microscopic polyangiitis,

*Correspondence: L. Chen, Dept of Pharmacy, National Cancer Center, Cancer Hospita, Chinese Academy of Medical Sciences, Panjiayuan Nanli 17, Chaoyang Dist. Beijing, PRChina. Phone: +861087788581. E-mail: yjkclz@163.com

ankylosing spondylitis, plaque psoriasis, and asthma (Bonamichi-Santos *et al.*, 2018).

MABs therapy is becoming increasingly important in clinical oncology treatment, even becoming standards of care in several tumor types, within inhibiting signaling pathways in tumor growth and/or inducing immunological responses against tumor cells (Henricks *et al.*, 2015).

For example, inhibiting HER2 and EGFR1 mAbs have established commercial success (Nicodemus, 2015). Rituximab, a monoclonal antibody against CD20, was the first mAb approved by FDA (US Food and Drug Administration) for treatment of B-NHL (B cell non-Hodgkin lymphoma). Gemtuzumab ozogamicin was the first ADC (antibody drug conjugate) approved by the FDA for treatment of acute myeloid leukemia. Brentuximab vedotin is approved for both HL and anaplastic large cell lymphoma. These new therapies are changing the landscape of B-NHL treatment away from the traditional “CHOP (Cyclophosphamide, Hydroxydaunorubicin, Oncovin and Prednisone or Prednisolone)”-based chemotherapies (Mehta A *et al.*, 2015).

Notwithstanding, mAbs also have their own ADRs (adverse drug reactions), such as dyspnea, nausea, headache and abdominal pain (Guan *et al.*, 2015). For example the most common ADRs of VEGF inhibitors are dermatologic effects, including hand foot syndrome, hypertension, fatigue, proteinuria and hematologic abnormalities (Patel *et al.*, 2011). ADRs in hematologic aspect during ofatumumab, brentuximab vedotin, and alemtuzumab treatment included anemia, neutropenia, and thrombocytopenia (Guan *et al.*, 2015).

Hyperglycemia is a common side effect among in-patients, especially cancer patients during chemotherapy (Yang *et al.*, 2016). One clinical research based on a fully human mAbs as monotherapy in metastatic, well-differentiated neuroendocrine cancer patients indicated the incidence of hyperglycemia was 32% (Reidy-Lagunes *et al.*, 2012). Another clinical trial of combination treatment with Temsirolimus and Cixutumumab indicated the incidence of hyperglycemia had risen upto 63% (Busaidy *et al.*, 2015).

Impaired metabolism, obesity, hyperglycemia and hyperinsulinemia may also play a role in cancer development, progression and prognosis (Yang *et al.*, 2015). Hyperglycemia contributes to the risk for adverse outcomes such as infections and nonmalignancy related mortality. Chemotherapy induced hyperglycemia for hematologic and solid tumors is correlated with

increased toxicity (Yang *et al.*, 2016). In NHL (non-Hodgkin lymphoma) patients, hyperglycemia correlates with non-hematological toxicity, and a similar although less clear pattern is suggested in prostate cancer patients (Brunello *et al.*, 2011). Several epidemiologic studies had clearly illuminated a positive correlation between impaired glucose tolerance or diabetes mellitus and increased long-term cancer risk (Dankner *et al.*, 2007).

Hyperglycemia has been mechanically demonstrated to be a class of effect adverse event in response to anti-IGF1R (insulin-like growth factor) mAbs (Haluska *et al.*, 2014). Elevated glucagon levels and increased hepatic glucagon receptor signaling contribute to hyperglycemia in T2DM (type 2 diabetes mellitus) (Mukund *et al.*, 2013). The proposed mechanism of glucose-level elevation is disruption of the negative feedback loop at the hypothalamic level by anti-IGF1R mAbs, leading to increased hormone secretion growing and following hyperinsulinemia, insulin resistance and terminal hyperglycemia (Gualberto A *et al.*, 2009).

T2DM is preceded by insulin resistance that is compensated for by increased insulin secretion from pancreatic beta cells. Initially, this compensation maintains glycemic control. Generally progressive β -cell dysfunction occurs, resulting in hyperglycemia and ultimately clinical diabetes mellitus (Issafras H *et al.*, 2014).

Although efficacy and safety have been demonstrated prior to approval in clinical trials, pharmacovigilance in drug risk identification and assessment is still necessary for any post-marketing mAbs (Kalaivani M *et al.*, 2015). Here, this study analyzed the main ADRs from mAbs based on the increasing prevalence of mAbs in cancer therapy and the severe risk of hyperglycemia, as well as the Vigibase report, with a focus on the glycemic related ADR in these mAbs that required special care.

MATERIALS AND METHODS

The study was a retrospective analysis of ADR records on Vigibase from Uppsala Monitoring Center, the WHO's (World Health Organization) collaborating center for international drug monitoring. We enter the website on 15 Feb 2019.

The comparing database was from U.S. Food and Drug Administration's (FDA). The Adverse Event Reporting System (AERS) is a computerized information database designed to support FDA's post-marketing safety surveillance program for all approved drug and therapeutic biologic products. The FDA uses AERS to

monitor for new adverse events and medication errors that might occur with these marketed products. FDA data were collected from AERS during January 2004 and September 2018.

Inclusive criteria: monoclonal antibodies were selected from anyone of the publications: 1) the book of Martindale-The Complete Drug Reference (36th edition); 2) the published articles searching from pubmed; 3) the websites of www.google.com, or www.baidu.com.

Exclusive criteria: 1) indication of mAbs was not cancer; 2) mAbs were not approved by any district of US, EU, China, Japan or Australia; 3) those mAbs were withdrawn from market; 4) no records from Vigibase^R.

Numbers in figure 1-4 were from Vigibase; figure 5 and 6 were from FDA database. The countries/regions listed in table I were included in Vigibase.

Table I - Status of mAbs in various countries and their main indications*

mAbs	Years of approval					Target(s)	Main Indication(s)
	AU	JP	EU	CN	US		
Bevacizumab	2005	2007	2009	2015	2004	VEGF	mCRC, Breast Cancer, NSCLC
Brentuximab	2013	N/A	2012	N/A	2011	CD30	HL, sALCL
Catumaxomab	N/A	N/A	2009	N/A	N/A	EpCam, CD3, Fcγ receptors	Malignant ascites
Cetuximab	2007	2008	2009	2013	2004	EGFR	Squamous cell cancer of the head and neck, Colorectal Cancer, mCRC
Dinutuximab	N/A	N/A	2015	N/A	2015	GD2	High-risk Neuroblastoma
Fresolimumab	N/A	N/A	2011	N/A	N/A	TGF-β	Glioblastomas, focal segmental glomerulosclerosis
Gemtuzumab	N/A	2005	2008	N/A	N/A	CD33	Acute myeloid leukemia
Ipilimumab	2011	2015	2011	N/A	2011	CTLA-4	Melanoma
Necitumumab	N/A	N/A	2016	N/A	2015	EGFR	metastatic squamous NSCLC
Nimotuzumab	N/A	N/A	2004	2012	N/A	EGFR	HNC, nasopharyngeal cancer
Nivolumab	2016	2014	2015	N/A	2014	PD-1	Unresectable or metastatic melanoma, NSCLC, advanced clear cell RCC, cHL, SCCHN
Obinutuzumab	2014	N/A	2014	N/A	2013	CD20	CLL
Ofatumumab	2011	2013	2010	N/A	2009	CD20	CLL
Panitumumab	2008	2010	2009	N/A	2006	EGFR	Wild-type RAS mCRC
Pembrolizumab	2015	N/A	2015	N/A	2014	PD-1	Melanoma, NSCLC HNSCC, cHL, Urothelial Carcinoma, MSI-H
Pertuzumab	2013	2013	2013	N/A	2012	HER2	HER2-positive MBC, Neoadjuvant Treatment of HER2-positive Breast Cancer

(Continuing)

Table I - Status of mAbs in various countries and their main indications*

mAbs	Years of approval					Target(s)	Main Indication(s)
	AU	JP	EU	CN	US		
Ramucirumab	2015	2015	2015	N/A	2014	VEGFR2	Advanced gastric or Gastro-esophageal junction adenocarcinoma, mNSCLC, mCRC
Rituximab	1998	2008	2009	2012	1997	CD20	NHL, CLL RA, GPA and MPA
Trastuzumab	2000	2008	2000	2015	1998	HER2	HER2-positive early breast cancer, HER2-positive locally advanced breast cancer, HER2-overexpressing MBC, HER2 positive advanced adenocarcinoma of the stomach or gastroesophageal junction

*Data were collected from respective government websites, indications were summarized from package inserts of different countries..

AU: Australia; JP: Japan; EU: Europe; CN: China; US: United States of America.

mCRC: metastatic colorectal cancer; ALL: acute lymphoblastic leukemia; HL: Hodgkin lymphoma; mNSCLC: metastatic non-small-cell lung carcinoma; HNC: Head and neck carcinoma; CLL: Chronic lymphocytic leukaemia; NHL: non-Hodgkin lymphoma; CTLA-4: cytotoxic T-lymphocyte-associated protein 4; EpCam: Epithelial cell adhesion molecule; GD2: ganglioside GD2 (disialoganglioside); HER-2: human epidermal growth factor receptor-2; PD-1: Programmed cell death protein 1.

All data accessed on 5 Aug 2016. <http://www.tga.gov.au/>; <http://www.pmda.go.jp/>; <http://www.ema.europa.eu/ema/>; <http://www.sda.gov.cn/WS01/CL0001/>; <http://www.fda.gov/>.

Descriptive analysis and Figures was performed using Microsoft Office Excel 2013 worksheet (Microsoft Corporation, Seattle, WA, USA), and interpretation and analysis of obtained data were done using summary statistics. The count data were described statistically using the number of cases (n) and percentage (%). Analyses for FDA data were performed using SAS, Version 9.4 (SAS Institute Inc, North Carolina, USA). Descriptive analyses were reported as sums of records.

This article does not contain any studies with human or animal subjects performed by any of the authors.

RESULTS

Vigibase, a reliable drug database, was utilized as a dictionary for the batch conversion and compilation of drug names Data from Vigibase were taken. Adverse events in the database are coded according to the terminology preferred by the Medical Dictionary for

Regulatory Activities (MedDRA). 20 mAbs were analyzed, with 263217 ADR reports, where 16751 records of *Metabolism and nutrition disorders* and 1444 records of *Glucose metabolism disorders (including Hyperglycaemia and Diabetes mellitus)*. The main information of the 20 mAbs in various countries are summarized in Table I. Total distribution of Geographic, age and gender characteristics of total ADR records were depicted in Figure 1. Geographically, the records from America weighted near one half (48.5%) in total, and the following was Europe (32.7%). In age groups, 45~64-year group weighted most (28.9%); maybe this group was most suitable group for chemotherapy with mAbs. Female group weighted a little more than male group (47.6% vs 41.4%). The annual number of ADR report increased greatly since 2009 in Figure 2; since the collection ended in early 2019, the number of 2019 is undoubtedly expected more than 70000 reports. (See Table I and Figures 1-2).

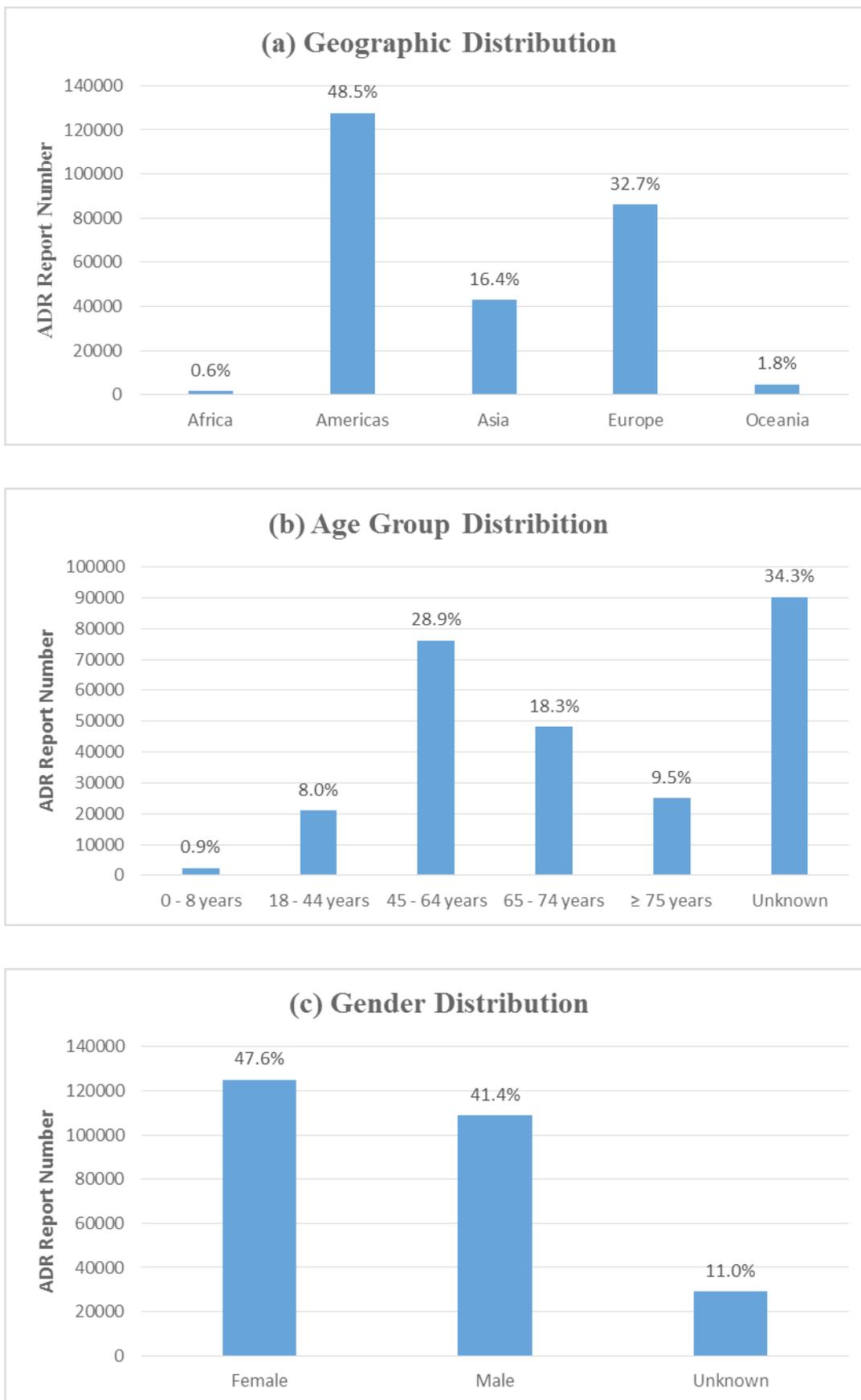


Figure 1 - Distributions of total records of 20 mAbs in geographic, age and gender.

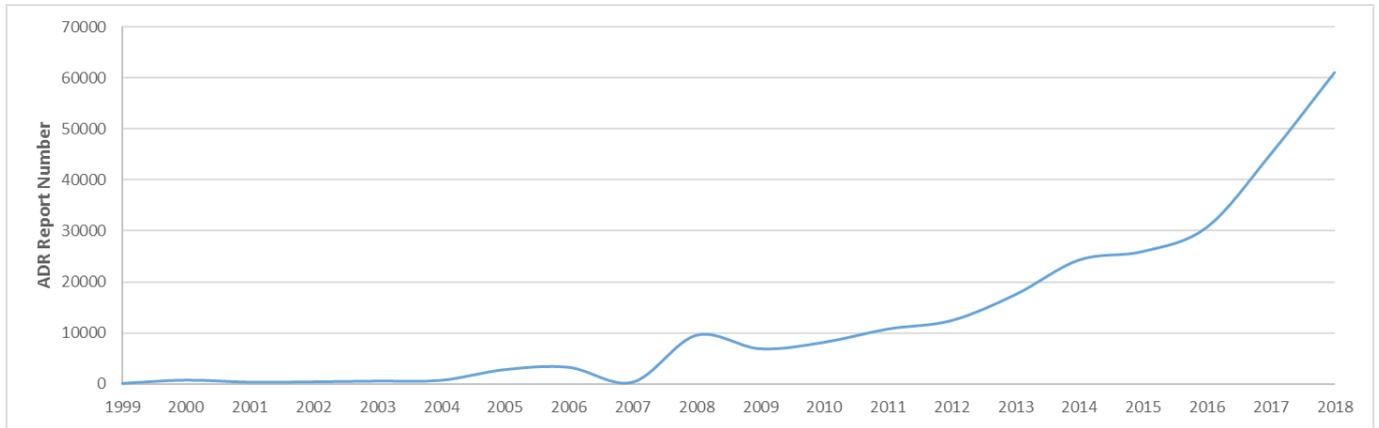


Figure 2 - Total annual number of ADR report.

As the record number of the 20 mAbs fluctuated seriously (from 66368 to 1 records) and the numbers of the last 10 mAbs were relatively tiny, we listed the top 10 mAbs in Figure 3a. As the “old” drugs always were

reported with more ADR report than that of “new” drugs, we also list the top mAbs per year in Figure 3b. [ADR per year = total record / (2018 - first approved year + 1)].

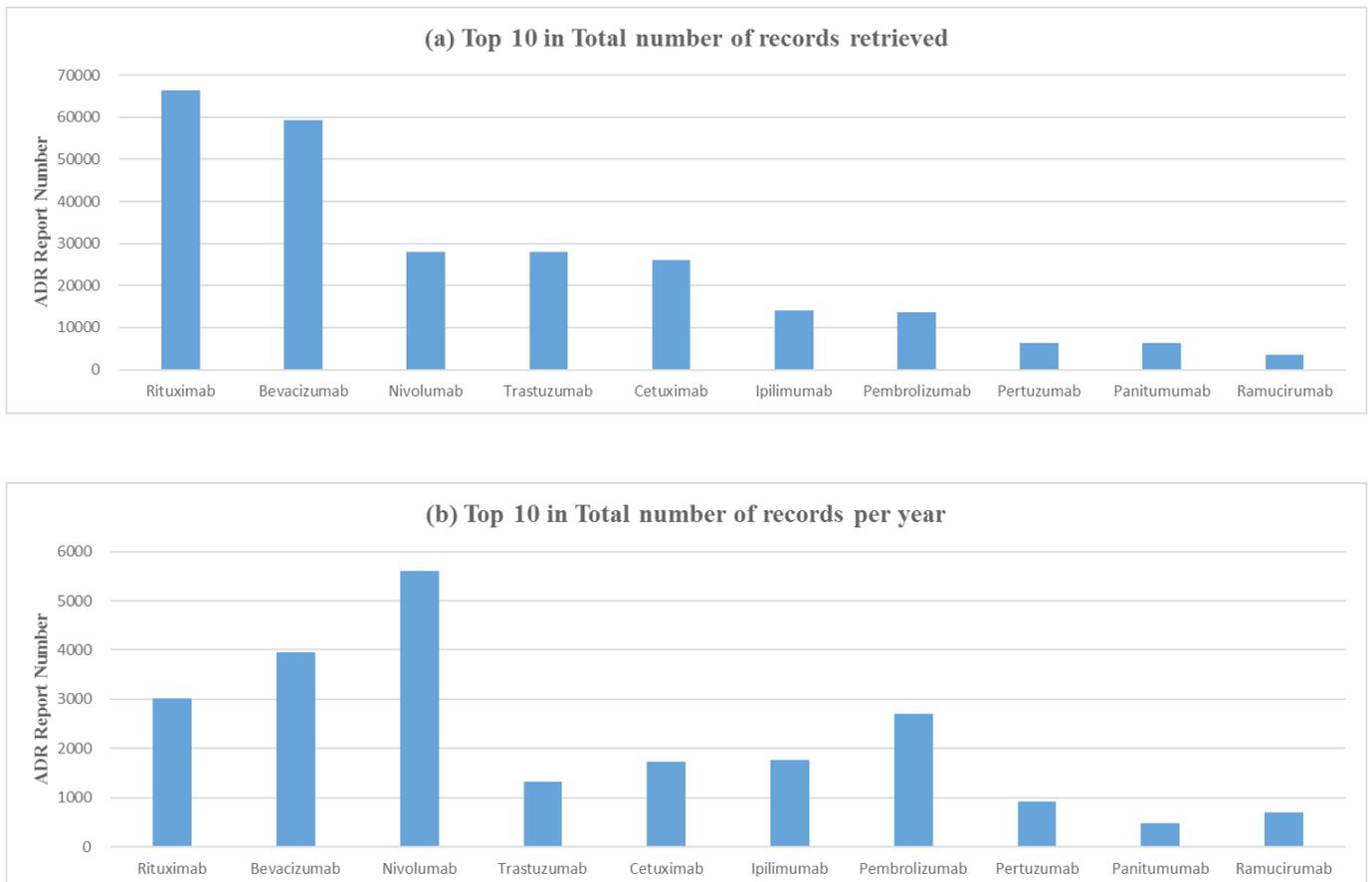


Figure 3 - Top 10 mAbs in total ADR record and ADR per year.

Related to comparing “old” and “new” drugs, the distributions in Figure 4a and 4b were verisimilar. Also, the mAbs were ordered by blood glucose related condition record; numerically its sequence was the same to the record of High blood glucose record in Figure 4. With high Diabetes mellitus record in Figure 4, all the mAbs’ hyperglycemic ratios were higher than Diabetes mellitus (DM). On the other hand, diabetes was the following serious condition from hyperglycaemia, Rituximab and Nivolumab have more severe impact on blood glucose. Of the diabetes mellitus records, there

were 136 records of Nivolumab and 161 records of Rituximab in Diabetes mellitus, besides which others’ records were less than 100. (See Figure 4).

The results from Vigibase also compared with data from US FDA. The total ADR records and hyperglycemic ADR records were demonstrated respectively in Figure 5 and Figure 6. In total records, 2 mAbs were the same to that in Vigibase: bevacizumab, rituximab. In hyperglycemic records, top 3 were the same in two databases: Bevacizumab, Rituximab and Nivolumab. (See Figure 5-6).

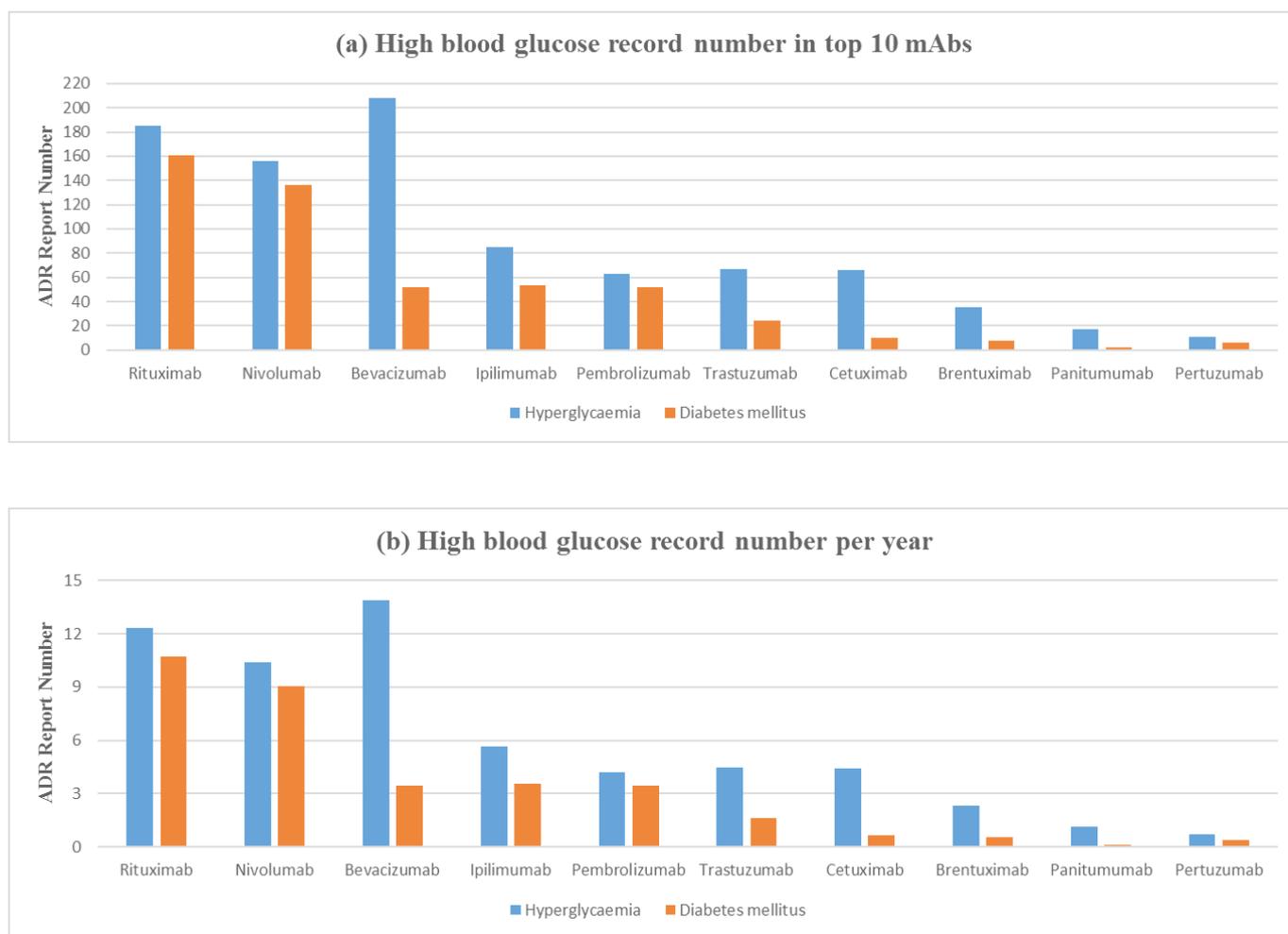


Figure 4 - Top 10 mAbs in High blood glucose ADR record from Vigibase.

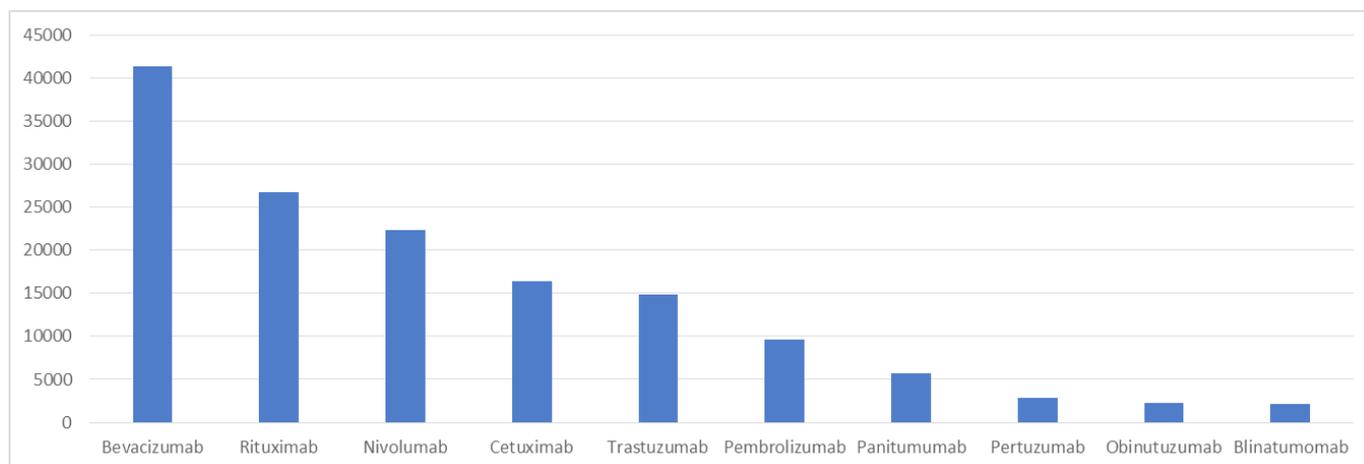


Figure 5 - Top 10 mAbs in total ADR record from FDA database.

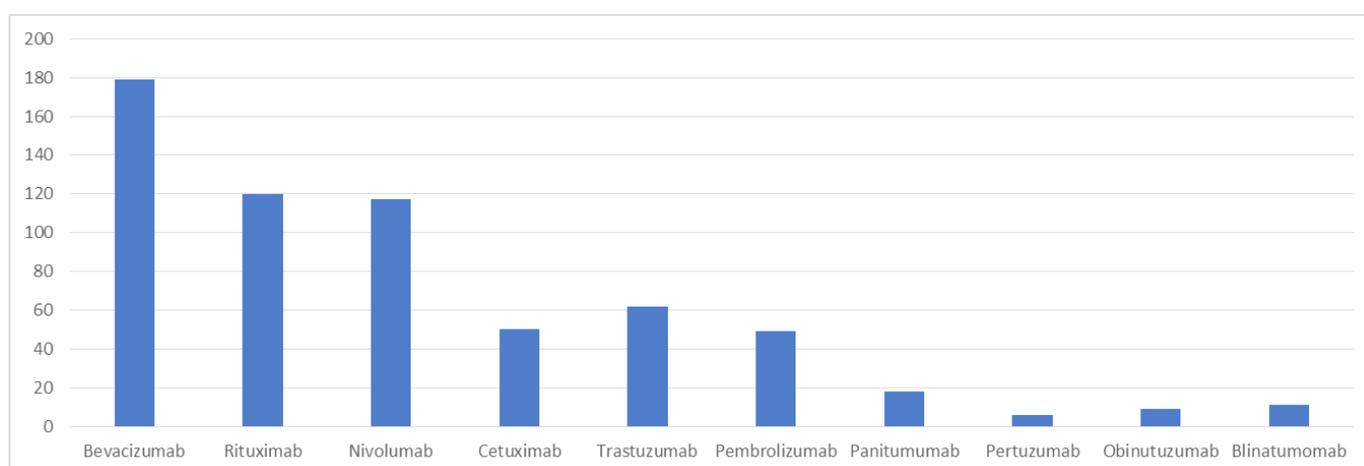


Figure 6 - Top 10 mAbs in Hyperglycemic ADR record from FDA database.

DISCUSSION

This study was undertaken to examine the different ADR distributions of mAbs. To analyze the results, we measured the top 10 mAbs in total ADR records as well as the ADR records per year. For hyperglycemic ADR, we also listed the top 10 mAbs in glucose metabolism and the hyperglycemic ratio hereby. Despite the limitations of spontaneous reporting, we obtained significant results in the context of the reported literature. Although the data from Vigibase did not provide different exposure period length in different trials, our results firstly suggested an association between anticancer mAbs and hyperglycemic adverse events, and the reporting ratio was increased with administration of mAbs, in that the column distributions were similar in ADR per year (Figure 3b) and Hyperglycaemia (Figure 4). This

study provides information useful to improve anticancer treatment using mAbs.

Distributions

In Table I, most of the included mAbs were approved by US and EU, and the approval years were very near in the two districts, whose reported ADR numbers were No.1 and 2 in Figure 1a. The possible reason is that the pharmacy administration and post-marketing pharmacovigilance system were mature and similar in two developed areas. The number of mAbs was less and approved years were later in Australia and Japan than that in US and EU. However, China has the least approved mAbs (5 in total in Aug 2016). All other approval years were much later in China. China's post-market pharmacovigilance adopts spontaneous

reporting system, and its network was not so mature in less developing districts. Hereby, wish China's health care reform can improve this situation.

The ADR of mAbs was measured by ADR reports in Figure 2, however there were more other impact factors, such as market shares, publicities etc. For one kind of mAb, deeper analysis should include these factors in future.

Both ADR record in total and ADR per year, Rituximab, Bevacizumab and Nivolumab were on top 3 in Figure 3a, which indicated the frequent and extensive usage of the three mAbs, including China. Adjusted by year of approval of 20 mAbs, ranking of Nivolumab, Pembrolizumab and Pertuzumab were listed forward. This indicated these 4-mAb ADR will increase years later, and should be paid excessive attention in pharmacovigilance.

In *Metabolism and nutrition disorders*, Rituximab, Nivolumab and Bevacizumab were also on top 3 in Figure 4 as in Figure 3a. Catumaxomab, Dinutuximab, Fresolimumab, Nimotuzumab had little hyperglycaemic ADR record(s) within the whole *Glucose metabolism disorders*, so to calculate and analyze their hyperglycaemic ratio was meaningless. Both Hyperglycaemia and Diabetes mellitus records of Rituximab were high in Figure 4. Ratio of Hyperglycaemia and Diabetes mellitus were relatively equal in Rituximab, Nivolumab, Ipilimumab and Pembrolizumab, which demonstrated these mAbs influenced severely on glucose metabolism. While the ratio of Hyperglycaemia was higher than Diabetes Mellitus in Bevacizumab, Trastuzumab, Cetuximab and Brentuximab, which indicated the well-controlled blood glucose might result less DM.

Suggestions

Hyperglycemia may result in thirst or increased urination and may require a dose increase or initiation of insulin and/or oral hyperglycemic agent (pATEL, P, Srinivas S., 2011). Patients with baseline disorders such as diabetes could also be managed well. Patients with metabolic toxicities had higher response rates and more tumor shrinkage without compromise in survival (Busaidy *et al.*, 2015). Closer monitoring is urgently needed.

CONCLUSION

As the Vigibase reported numbers, mAb therapies can induce hyperglycemic symptoms during treatment.

Close monitoring, and early intervention for glucose levels, collaboration among endocrine specialists, oncologists and pharmacists, as well as rapid individualized treatment of metabolic toxicities allowed for fewer dosage interruptions and reductions due to the most common adverse events are recommended in all of the patients with mAbs therapy. We suggest that individuals with baseline metabolic disorders need not be excluded from studies of these agents, and that patients who develop metabolic toxicities should be given appropriate supportive care rather than having study drug discontinued. Clinically, this paper provided a view on mAbs attention as well as mAbs analysis, and indicated a new direction on basic research such as hyperglycemic mechanism from mAbs.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

ACKNOWLEDGMENTS

The work was supported by National Natural Science Foundation of China (No. 81603218).

Authors' contributions

Jincheng Yang performed statistical analysis data from Vigibase and wrote the manuscript. Bin Zhao performed statistical analysis database from US FDA. Haiyan Zhou collected and checked main mAbs information. Bei Jia collected database from Vigibase. Lianzhen Chen planned the study and revised the manuscript.

REFERENCE

Bonamichi-Santos R, Castells M. Diagnoses and Management of Drug Hypersensitivity and Anaphylaxis in Cancer and Chronic Inflammatory Diseases: Reactions to Taxanes and Monoclonal Antibodies. *Clin Rev Allergy Immunol*. 2018;54(3):375-385.

Brunello A, Kapoor R, Extermann M. Hyperglycemia during chemotherapy for hematologic and solid tumors is correlated with increased toxicity. *Am J Clin Oncol*. 2011;34(3):292-296.

Busaidy NL, LoRusso P, Lawhorn K, Hess KR, Habra MA, Fu S, et al. The prevalence and impact of hyperglycemia and hyperlipidemia in patients with advanced cancer receiving combination treatment with the mammalian target of rapamycin inhibitor temsirolimus and insulin growth factor-

- receptor antibody cixutumumab. *Oncologist*. 2015;20(7):737-741.
- Dankner R, Chetrit A, Segal P. Glucose tolerance status and 20 year cancer incidence. *Isr Med Assoc J*. 2007;9(8):592-596.
- Gualberto A, Pollak M. Emerging role of insulin-like growth factor receptor inhibitors in oncology: early clinical trial results and future directions. *Oncogene*. 2009;28(34):3009-3021.
- Guan M, Zhou YP, Sun JL, Chen SC. Adverse events of monoclonal antibodies used for cancer therapy. *Biomed Res Int*. 2015;2015:428169.
- Gül N, van Egmond M. Antibody-dependent phagocytosis of tumor cells by macrophages: a potent effector mechanism of monoclonal antibody therapy of cancer. *Cancer Res*. 2015;75(23):5008-5013.
- Haluska P, Menefee M, Plimack ER, Rosenberg J, Northfelt D, LaVallee T, et al. Phase I dose-escalation study of MEDI-573, a bispecific, antiligand monoclonal antibody against IGF1 and IGFII, in patients with advanced solid tumors. *Clin Cancer Res*. 2014;20(18):4747-4757.
- Henricks LM, Schellens JH, Huitema AD, Beijnen JH. The use of combinations of monoclonal antibodies in clinical oncology. *Cancer Treat Rev*. 2015;41(10):859-867.
- Issafras H, Bedinger DH, Corbin JA, Goldfine ID, Bhaskar V, White ML, et al. Selective allosteric antibodies to the insulin receptor for the treatment of hyperglycemic and hypoglycemic disorders. *J Diabetes Sci Technol*. 2014;8(4):865-873.
- Kalaivani M, Singh A, Kalaiselvan V. Therapeutic monoclonal antibodies and the need for targeted pharmacovigilance in India. *MAbs*. 2015;7(1):276-280.
- Mehta A, Forero-Torres A. Development and integration of antibody-drug conjugate in non-hodgkin lymphoma. *Curr Oncol Rep*. 2015;17(9):41.
- Mukund S, Shang Y, Clarke HJ, Madjidi A, Corn JE, Kates L, et al. Inhibitory mechanism of an allosteric antibody targeting the glucagon receptor. *J Biol Chem*. 2013;288(50):36168-36178.
- Nicodemus CF. Antibody-based immunotherapy of solid cancers: progress and possibilities. *Immunotherapy*. 2015;7(8):923-939.
- Patel P, Srinivas S. Toxicities of targeted agents in advanced renal cell carcinoma. *Curr Clin Pharmacol*. 2011;6(3):181-188.
- Pubmed: <https://www.ncbi.nlm.nih.gov/pubmed/>
- Reidy-Lagunes DL, Vakiani E, Segal MF, Hollywood EM, Tang LH, Solit DB, et al. A phase 2 study of the insulin-like growth factor-1 receptor inhibitor MK-0646 in patients with metastatic, well-differentiated neuroendocrine tumors. *Cancer*. 2012;118(19):4795-4800.
- Vigibase data. [cited 2019 Feb 15]. Available from: <http://www.who-umc.org/>.
- Weiner GJ. Building better monoclonal antibody-based therapeutics. *Nat Rev Cancer*. 2015;15(6):361-370.
- Yang J, Jia B, Qiao Y, Chen W, Qi X. Variations of blood glucose in cancer patients during chemotherapy. *Niger J ClinPract*. 2016;19(6):704-708.
- Yang JC, Dai YY, Wang LM, Xie YB, Zhou HY, Li GH. Glycemic variation in tumor patients with total parenteral nutrition. *Chin Med J (Engl)*. 2015;128(15):2034-2039.

Received for publication on 26th July 2018
Accepted for publication on 07th May 2019