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 glycemic 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). MAb 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,
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 (Nicolodemus, 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 up to 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\textsuperscript{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*

<table>
<thead>
<tr>
<th>mAbs</th>
<th>Years of approval</th>
<th>Target(s)</th>
<th>Main Indication(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AU</td>
<td>JP</td>
<td>EU</td>
</tr>
<tr>
<td>Brentuximab</td>
<td>2013</td>
<td>N/A</td>
<td>2012</td>
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<tr>
<td>Catumaxomab</td>
<td>N/A</td>
<td>N/A</td>
<td>2009</td>
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<tr>
<td>Cetuximab</td>
<td>2007</td>
<td>2008</td>
<td>2009</td>
</tr>
<tr>
<td>Dinutuximab</td>
<td>N/A</td>
<td>N/A</td>
<td>2015</td>
</tr>
<tr>
<td>Fresolimumab</td>
<td>N/A</td>
<td>N/A</td>
<td>2011</td>
</tr>
<tr>
<td>Gemtuzumab</td>
<td>N/A</td>
<td>2005</td>
<td>2008</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>2011</td>
<td>2015</td>
<td>2011</td>
</tr>
<tr>
<td>Necitumumab</td>
<td>N/A</td>
<td>N/A</td>
<td>2016</td>
</tr>
<tr>
<td>Nimotuzumab</td>
<td>N/A</td>
<td>N/A</td>
<td>2004</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>2016</td>
<td>2014</td>
<td>2015</td>
</tr>
<tr>
<td>Obinutuzumab</td>
<td>2014</td>
<td>N/A</td>
<td>2014</td>
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<tr>
<td>Ofatumumab</td>
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<td>2013</td>
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<td>Panitumumab</td>
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<td>2009</td>
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<td>Pembrolizumab</td>
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<tr>
<td>Pertuzumab</td>
<td>2013</td>
<td>2013</td>
<td>2013</td>
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</tbody>
</table>

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

<table>
<thead>
<tr>
<th>mAbs</th>
<th>Years of approval</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AU</td>
<td>JP</td>
<td>EU</td>
</tr>
<tr>
<td>Ramucirumab</td>
<td>2015</td>
<td>2015</td>
<td>2015</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>2000</td>
<td>2008</td>
<td>2000</td>
</tr>
<tr>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>

*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.


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.
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)].
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 hyperglyceamic 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 hyperglycaemic records, top 3 were the same in two databases: Bevacizumab, Rituximab and Nivolumab. (See Figure 5-6).

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

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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.

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