Risk of hepatitis B reactivation and cytomegalovirus related infections with Mogamulizumab: A retrospective study of international pharmacovigilance database

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Abstract

Background: Mogamulizumab (Moga) is a C−C chemokine receptor-4 antibody approved in the United States for relapsed/refractory mycosis fungoides and Sézary syndrome. Few cases reported an increased risk of hepatitis B reactivation and cytomegalovirus (CMV) related infection post-Moga. However, literature is limited to mainly case reports and series, while no study has used the Food and Drug Administration adverse events reporting system (FARES) database to investigate the relationship.

Methods: Using United States Food and Drug Administration adverse events reporting system database, we collected all cases of hepatitis B reactivation and CMV related infection between January 1, 2011, and December 31, 2019, for Moga and other drugs. The reporting odds ratio (ROR) was calculated, which was considered significant when the lower limit of 95% confidence interval (CI) > 1.

Findings: Three hundred and thirty-eight total adverse cases were reported for Moga during the study period, with 261 cases reported indication for use, including cutaneous T cell lymphoma (47.04%), and adult T cell leukemia/lymphoma (30.18%). Eight cases were reported for hepatitis B reactivation with Moga use, compared to 2290 cases with other medications. The ROR is 143.67 (p < 0.001, 95% CI, 71.17–290.04). CMV related infection was noted in 17 cases using Moga, while 12,849 cases with others. The ROR is 55.89 (p < 0.001, 95% CI, 34.31–91.06). In the Moga group, five deaths occurred in hepatitis B reactivation patients and nine deaths with CMV cases.

Interpretation: A signal has been identified between Moga exposure and hepatitis B reactivation as well as CMV related infection. A consideration in future studies should be placed on determining the relationship and investigating the need for pre-treatment screening, close monitoring, and utilization of prophylaxis in this population-based on pre-treatment risks.

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1. Introduction

Adult T cell leukemia/lymphoma (ATL), a rare and aggressive malignancy, can be classified into four clinical subtypes: acute, lymphoma, chronic, and smoldering types based on presenting features [1]. First-line treatment encompasses high-intensity chemotherapy combination with good response. However, for relapsed/refractory cases, the treatment options are limited [2]. Advanced stage cutaneous T cell lymphomas (CTCL) also pose significant treatment challenge to physicians [3]. Novel targeted medications have been studied actively in the past 20 years, with some of them showing a significant survival benefit in these conditions [4,5]. Mogamulizumab (Moga), a defucosylated humanized monoclonal antibody against C−C chemokine receptor 4 (CCR4) [6], has been approved for the treatment of CCR4-positive relapsed/refractory ATL in Japan in 2012 [7]. And, further approved for CCR4-positive relapsed/refractory CTCL in 2014 [7]. In the United States, the Food and Drug Administration (FDA) approved Moga for the treatment of relapsed/refractory mycosis fungoides and Sézary syndrome in 2018 [8]. The phase I and phase II clinical trials illustrated the efficacy of Moga in treating both ATL and CTCL with tolerable toxicities [6,9–11]. In one phase II clinical trial in ATL patients, overall response rate (ORR) was observed to be 50%, whereas progression free survival (PFS) and overall survival...
Research in context

Evidence before this study

Before the study, we reviewed literature via PubMed, Scopus, and Google search for Moga and infectious events, including hepatitis B reactivation and CMV related infections. Only a few case reports and case series discussed the possible risk. We used FAERS to conduct disproportionality analysis for possible signal, and the last access date is July 29, 2020. As a voluntary reporting database, FAERS allows for signal data mining, but with the limitations as mentioned above.

Added value of this study

Our study is the first study using a large scale database to investigate the relationship between Moga and hepatitis B reactivation and cytomegalovirus related infection. Through disproportionality analysis, a signal was determined between the use of Moga and the above infections.

Implications of all the available evidence

Our study result warrants further studies to determine the risk and discuss the need for pre-treatment screening, monitoring and even prophylaxis in particular high-risk population.

2. Methods

The FAERS database is a voluntary drug and product reporting system that contains data submitted by health care professionals, manufacturers, and consumers [15,16]. AE was coded according to the Medical Dictionary for Regulatory Activities (MedDRA) [17]. This spontaneous reporting system, containing both reports from the United States (US) and other countries, has received more than 17 million reports since 1968. FAERS, functioning as one of the FDA’s post-marketing surveillance tools receives AE, and medical error signal, and the last access date is July 29, 2020. As a voluntary reporting database, FAERS allows for signal data mining, but with the limitations as mentioned above.

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3. Result

There were in total 13,574,208 reports between January 1, 2011, and December 31, 2019. Among them, 338 (0.00249%) individual cases were related to Moga. Indication for use was reported in only 261 cases, with 159 (47.04%) for CTCL and 102 (30.18%) for ATL. Country of AE origin was reported in 334 cases (98.82%), where 133 (39.35%) were from Asia, 150 (44.37%) from the United States, and 51 (15.09%) from Europe. In the Moga exposure group, five deaths occurred in patients with hepatitis B reactivation, and nine deaths in CMV related infection cases. (Table 2)

Eight cases were reported for hepatitis B reactivation with Moga use, compared to 2290 cases by using other medications (Table 3). The ROR is 143.67 (p<0.001, 95% CI, 71.17–290.04). Two (25%) males and two (25%) females were reported with hepatitis B reactivation, while the gender of rest four (50%) cases was not reported. Only in one case out of eight with hepatitis B reactivation, Moga was suspected without concomitant drug use. Other drugs used concomitantly including cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP), pirarubicin, and carboplatin were also suspected for causing AE. Hepatitis B reactivation was the only reported AE in all eight cases without concomitant AE.

CMV related infections were noted in 17 cases using Moga. CMV infection presented as CMV viremia or infection in seven (41.18%) cases, and CMV end-organ disease, including CMV pneumonia in seven (41.18%) cases, CMV enteritis or enterocolitis in two (11.76%) cases, and CMV end-organ disease, including CMV pneumonia in 11.76% cases, and CMV chorioretinitis in one (5.88%) case, compared with 12,849 cases of CMV related infection using other medications (Tables 4 and 5). The ROR is 55.89 (p<0.001, 95% CI, 34.31–91.06).

Table 1 Reporting odds ratio of drug of interest.

| Drug of interest | Other medications | sum |
|------------------|-------------------|-----|
| AE of interest   | A                 | B   | A + B |
| Other AE        | C                 | D   | C + D |
|                  | A + C             | B + D | A + B + C + D |

AE: Adverse Events

\[
ROR = \frac{A}{BC} = \frac{A}{A+C} \cdot \frac{B}{C+D} \\
95\% CI = e^{\ln(ROR) \pm 1.96\sqrt{\frac{1}{A} + \frac{1}{B} + \frac{1}{C} + \frac{1}{D}}}
\]
Six (35.29%) were males, and two (11.76%) were females, whereas, in nine (52.94%) cases, gender was not specified. In five (29.41%) cases, Moga was the only drug reported to be related to CMV related infection. In comparison, 12 (70.59%) cases have concomitant drug use, including lenalidomide, sulfamethoxazole-trimethoprim, prednisolone, sobuzoxane, etoposide, CHOP, carboplatin, cytarabine, and methotrexate. In patients with only Moga use, one (20.00%) of five died; comparing to eight (66.67%) out of 12 patients died in group receiving Moga and concomitant drugs, though no significant statistical difference of death was noticed between the two groups (\( p=0.079 \)).

Seven (41.18%) cases had only CMV related infection, while four (23.53%) and six (35.29%) cases reportedly had 1 and 2 or more concomitant other reactions, respectively. The most common concomitant AE are skin rash or erythema in five patients (29.41%), neutropenia in four (23.53%), anemia in two (11.76%), thrombocytopenia in two (11.76%), hypoalbuminemia in two (11.76%), interstitial lung disease in two (11.76%). Heart failure, lymphopenia, infusion-related reaction, transaminitis, cystitis, sepsis, herpes zoster infection, fungal infection, systemic candida, mycotic endophthalmitis, disseminated intravascular coagulation (DIC), hypertriglyceridemia, hypothyroidism, hyperglycemia and weight gain each has been reported once (5.88%) (Table 6).

### Table 2
Characteristics of Patients with Hepatitis B Reactivation and CMV Related Infections Post Moga.

| Areas       | Total (proportion%) | Hepatitis B reactivation | CMV related infections |
|-------------|---------------------|--------------------------|------------------------|
| Asia        | 133 (39.35%)        | 6 (75.00%)               | 17 (100%)              |
| US          | 150 (44.38%)        | 0 (0%)                   | 0 (0%)                 |
| Europe      | 51 (15.09%)         | 1 (12.50%)               | 0 (0%)                 |
| Unspecified | 4 (1.18%)           | 1 (12.50%)               | 0 (0%)                 |
| Indication  |                     |                          |                        |
| ATL         | 102 (30.18%)        | 7 (87.50%)               | 14 (82.35%)            |
| CTCL        | 159 (47.04%)        | 1 (12.50%)               | 3 (17.65%)             |
| Unknown/other| 77 (22.78%)        | 0 (0%)                   | 0 (0%)                 |
| Gender      |                     |                          |                        |
| Male        | 61 (18.05%)         | 2 (25.00%)               | 6 (35.29%)             |
| Female      | 63 (18.64%)         | 2 (25.00%)               | 2 (11.76%)             |
| Unknown     | 214 (63.31%)        | 4 (50.00%)               | 9 (52.94%)             |
| Median age (years) (interquartile range) |                     |                          |                        |
| Concomitant medications | |                          |                        |
| No          | 206 (60.95%)        | 1 (12.50%)               | 5 (29.41%)             |
| Yes         | 132 (39.05%)        | 7 (87.50%)               | 12 (70.59%)            |
| Other reactions | |                          |                        |
| No          | 8 (100%)            | 8 (100%)                 | 7 (41.18%)             |
| 1 other reaction | 0 (0%)            | 0 (0%)                   | 4 (23.53%)             |
| 2 or more reactions | 0 (0%)            | 0 (0%)                   | 6 (35.29%)             |
| Outcome     |                     |                          |                        |
| Died        | 78 (23.08%)         | 5 (62.50%)               | 9 (52.94%)             |
| Hospitalized| 95 (28.11%)         | 1 (12.50%)               | 5 (29.41%)             |
| Others      | 165 (48.82%)        | 2 (25.00%)               | 3 (17.65%)             |
| Reporter    |                     |                          |                        |
| Health care professional | 295 (87.28%) | 8 (100%)                 | 17 (100%)              |
| Consumer    | 41 (12.13%)         | 0 (0%)                   | 0 (0%)                 |
| Unspecified | 2 (0.59%)           | 0 (0%)                   | 0 (0%)                 |

Moga=Mogamulizumab; CMV=Cytomegalovirus.

### Table 3
Hepatitis B Reactivation in Moga and Other Medications, 2011–2019.

|                        | Moga | All other medications | Sum       | ROR (95%CI)       | \( P \) value |
|------------------------|-------|-----------------------|-----------|-------------------|--------------|
| Hepatitis B reactivation| 8     | 2290                  | 2298      | 143.67 (71.17–290.04) | 0.000        |
| All other events       | 330   | 13,571,580            | 13,571,910|                   |             |
| Sum                    | 338   | 13,573,870            | 13,574,208|                   |             |

Moga=Mogamulizumab, ROR=Reporting Odds Ratio; CI=Confidence Interval.

### Table 4
CMV Related Infection Post Moga.

| Type of CMV infection | Number of patients | death |
|-----------------------|--------------------|-------|
| CMV viremia or infection | 7                  | 3     |
| CMV end organ disease   | 10                 | 6     |
| CMV pneumonia           | 7                  | 6     |
| CMV enteritis or enterocolitis | 2              | 0     |
| CMV chorioretinitis     | 1                  | 0     |

CMV=Cytomegalovirus.

### Table 5
CMV Related infection in Moga and other medications, 2011–2019.

|                        | Moga | All other medications | Sum       | ROR (95%CI)       | \( P \) value |
|------------------------|-------|-----------------------|-----------|-------------------|--------------|
| CMV related infection   | 17    | 12,849                | 12,868    | 55.89 (34.31–91.06) | 0.000        |
| All other events       | 321   | 13,561,021            | 13,561,342|                   |             |
| Sum                    | 338   | 13,573,870            | 13,574,208|                   |             |

Moga=Mogamulizumab, ROR=Reporting Odds Ratio; CI=Confidence Interval.
4. Discussion

ated myelopathy, have completed [23]. Doi et al. evaluated Moga in ATL and CTCL, some clinical trials evaluating the effectiveness of tumors, and 12% ORR was observed in six tumor subtypes with the combination with nivolumab in treating advanced or metastatic solid major types in CTCL are mycosis fungoides (MF), S. Wang et al. / EClinicalMedicine 28 (2020) 100601

Moga=Mogamulizumab.

In comparison, a total of 69,096 AE reported by rituximab and 9662 AE cases by alemtuzumab from 2011 to 2019. For rituximab, 568 cases reported hepatitis B reactivation, with ROR 64.70 (p<0.05, 95% CI, 58.83–71.15). While 1088 patients developed CMV infection. The ROR is 18.33 (p<0.05, 95% CI, 17.22–19.51). In cases of alemtuzumab, seven reports about hepatitis B reactivation, with ROR of 4.29 (p<0.05, 95%CI, 2.04–9.02); and 578 cases had CMV related infection with a ROR of 70.17 (p<0.05, 95%CI, 64.40–76.47). (Table 7)

4. Discussion

ATL, caused by human T-cell lymphotropic virus type 1 (HTLV-1), is an aggressive peripheral T cell lymphoma with poor prognosis [1]. Moga aims at CCR-4 chemokine receptor, which is expressed on most ATL cells [21]. By binding to CCR-4, Moga enhances antibody-dependent cellular cytotoxicity (ADCC) effect and depletes targeted cells [21]. Moga was later proved to be effective in treating CTCL, which is a heterogeneous group of extranodal non-Hodgkin’s lymphomas. The major types in CTCL are mycosis fungoides (MF), Sézary syndrome (SS), and primary cutaneous peripheral T cell lymphomas not otherwise specified (PCTCL - NOS). Besides advancement in the treatment of ATL and CTCL, some clinical trials evaluating the effectiveness of Moga for other diseases, including solid tumors and HTLV-1 associated myelopathy, have completed [23]. Doi et al. evaluated Moga in combination with nivolumab in treating advanced or metastatic solid tumors, and 12% ORR was observed in six tumor subtypes with the highest one seen in hepatocellular carcinoma cohort (27%; 95% CI, 8–55) [24]. In a phase 1–2a clinical trial in HTLV-1 associated myelopathy, Moga has shown to decrease the HTLV-1 infected cells and level of inflammatory markers [25].

Since Moga approval, accumulating evidence indicates increased infection risk, including hepatitis B reactivation, CMV, bacteremia, herpes zoster, and mycobacterium infection [6,11-14,20,26,27]. To our knowledge, no previous study using an extensive population-based database has investigated the relationship between these two infections and Moga use. Our study result identified the signal between Moga use and a possible increased risk of developing hepatitis B reactivation and CMV related infection.

In order to investigate the relationship between Moga exposure and the above AEs, we applied disproportionality analysis using ROR. In the process of signal detection, disproportionately high AE rates in a drug of interest comparing to background frequency may indicate a signal [18,19]. ROR is one of the methods for disproportionality analysis. In our study, it means the odds of reporting hepatitis B reactivation and CMV related infection with Moga use is 143.67 times and 55.89 times of reporting the AE with other medications use, respectively. This disproportionately high frequencies also referred to as “unexpectedness”, representing possibly important signal between Moga use and the increased infectious risks [18].

Hepatitis B reactivation risk has known to increase in patients receiving rituximab, a CD20 antibody, for B cell lymphoma [34]. In the setting of immunosuppressive conditions, hepatitis B reactivation may attribute to complications from acute hepatitis to fatal fulminant hepatitis [35]. However, antiviral treatment after hepatitis onset may not be sufficient to control the infection [35]. There are some reports of hepatitis B reactivation in ATL patients with Moga use, including pre-treatment HbsAg negative patients [12,13,26,27]. Similarly, CMV related infection and end-organ failure contribute to increased morbidity and mortality in patients receiving hematopoietic stem cell transplant (HSCT) [30]. CMV infection has also been reported in patients undergoing chemotherapy for lymphoma [32], and is a well-known infectious complication related to alemtuzumab and rituximab use [33,34]. Recent studies, including clinical trials, have also shown more CMV related infection in patients receiving Moga, especially in combination with chemotherapy [11,13]. Our study compared reported hepatitis B reactivation and CMV related infection in patients using rituximab and alemtuzumab to Moga during the same period. Surprisingly, ROR with Moga is higher in both infections than rituximab and alemtuzumab. Admittedly, being in the market for longer time, clinical practitioners are more familiar with infectious AE of rituximab and alemtuzumab’s. This knowledge results in less voluntary reporting and can lower the contribution of reported infectious AE to all AE. Increased ROR is a signal that Moga use may increase both infection risk.

The mechanism for observed increased risk with Moga use is not well established. Host cells with CCR-4 receptors, like Th2 cells, some CD4+ memory cells, and Tregs [21,22], are all targeted by Moga. With the combined effect of lymphopenia, cellular and innate immune cells depletion, and the immunosuppressive nature of T-cell

Table 6
Other adverse events in patients with CMV related infections post Moga.

| Adverse Events                  | Number of patient(s) |
|---------------------------------|----------------------|
| Skin rash or erythema           | 5                    |
| Neutropenia                     | 4                    |
| Anemia                          | 2                    |
| Thrombocytopenia                | 2                    |
| Hypoalbuminemia                 | 2                    |
| Intestinal lung disease         | 2                    |
| Heart failure                   | 1                    |
| Lymphopenia                     | 1                    |
| Infusion related reaction       | 1                    |
| Transaminitis                   | 1                    |
| Cystitis                        | 1                    |
| Sepsis                          | 1                    |
| Herpes zoster infection         | 1                    |
| Fungal infection                | 1                    |
| Systemic candidia               | 1                    |
| Myotic endopathilmitis          | 1                    |
| DIC                             | 1                    |
| Hypertriglyceridaemia           | 1                    |
| Hyperthyroidism                 | 1                    |
| Hyperglycemia                   | 1                    |
| Weight gain                     | 1                    |

Table 7
Comparison of Hepatitis B Reactivation and CMV Infection in Moga, Rituximab and Alemtuzumab, 2011 – 2019.

|                      | Moga   | Rituximab | Alemtuzumab |
|----------------------|--------|-----------|-------------|
| Hepatitis B Reactivation | Number of events | ROR (95%CI) | Number of events | ROR (95%CI) | Number of events | ROR (95%CI) |
|                      | 8      | 143.67 (71.17–290.042) | 568 | 64.70 (58.83–71.15) | 7 | 4.29 (2.04–9.02) |
| CMV related infection | Number of events | ROR (95%CI) | Number of events | ROR (95%CI) | Number of events | ROR (95%CI) |
|                      | 17     | 55.89 (34.31–91.06) | 1088 | 18.33 (17.22–19.51) | 578 | 70.17 (64.40–76.47) |
| Total reports        | 318    | 69,096 | 9662 |

Moga=Mogamulizumab; ROR=Reporting Odds Ratio; CI=Confidence Interval.
malignancy itself, infectious AE, including hepatitis B reactivation and CMV related infection, are expected. Also, immunologic exacerbation to infection may play a role in end-organ failure under the hypothesis of Treg cell impairment [29].

Our study showed that 10 (58.82%) out of 17 patients with CMV related infection developed CMV end-organ diseases. Nine CMV related infection patients died, of whom six deaths (66.67%) occurred in patients with CMV end-organ disease. This ratio is higher than other reports: Tay et al. studied CMV infection and end-organ disease in Asian patients with lymphoma receiving chemotherapy, and 12 (25.00%) of 48 patients with CMV infection developed CMV end-organ disease [31]. The higher number of deaths in CMV end-organ disease in our study could be related to the under-reporting of CMV viremia patients in FAERS.

Furthermore, 10 (58.82%) of them have other AE reported in addition to CMV related infection. This is different from reports for hepatitis B reactivation, where all eight patients have no other AE documented. Seven (87.50%) of the eight patients with hepatitis B reactivation have concomitant chemotherapy use, some including steroids. Further studies are warranted to assess the impact of Moga alone and with chemotherapy on the increased risk of hepatitis B reactivation and CMV infection.

Many studies have evaluated the efficiency of preventive measures on patients with positive HBSAg [35,36]. For previously resolved hepatitis B (HBSAg negative), high-risk patients, including anti-HBc positive subjects to be treated with rituximab or those undergoing stem cell transplantation, antiviral prophylaxis is recommended [37]. Pre-emptive therapy by monitoring hepatitis B deoxyribonucleic acid (DNA) has been recommended for moderate-risk patients in some guidelines [37]. In one study, a monthly hepatitis B DNA monitoring has shown to be useful in early detection of hepatitis B reactivation of previously resolved hepatitis B infection in patients receiving rituximab and steroid containing chemotherapy [38]. Pre-emptive screening of CMV for patients using alemtuzumab has been described in some guidelines [28]. Our result demonstrated a potential higher risk of infection with Moga use, and pre-emptive screening and risk analysis should be considered in clinical practice.

Our study has some limitations. First, we used FAERS, a voluntary reporting system database without strict research protocol, randomization, and control, for signal mining. The relationship between a specific drug and AE of interest is hard to be determined based only on the database, and causation relationship not necessarily exist even if significant disproportionality analysis result. Also, there is a possibility of duplicate reports when the consumer, and the sponsor submits the same case, and the data may change due to the correction for duplication. Though this change may not be significant in the long term, and FAERS provided quarterly extract files for all previous data. Besides, missing and incomplete information, including dosage, pre-treatment infection condition, patient baseline characteristics, and follow up data, may create bias when analyzing these data. For instance, pre-treatment hepatitis B serostatus is not available from the FAERS, which can lead to selection bias when discussing the risk of hepatitis B reactivation post-Moga exposure.

Second, even though more AE reports have been noticed than previous studies [9–14], the total number of reported hepatitis B reactivation and CMV related infections in this study is still low, given the limited period and nature of spontaneous reporting database.

Using FAERS, we identified a positive signal between Moga exposure and hepatitis B reactivation as well as CMV related infection. A consideration in future studies should be placed on confirming the relationship and investigating need for pre-treatment screening, close monitoring, and utilization of prophylaxis in this population-based on pre-treatment risks.

Declaration of Competing Interest

Dr. Abhishek Kumar declared the following interest: Stocks in Abbvie Inc, Acadia Pharmaceuticals, ADMA Biologics, Agneus Inc, Aikido Pharma Inc, Albireo Pharma Inc, Amgen Inc, Aveo Pharma, Astrazeneca PLC, Bristol Meyer Squibb, Biopath Holdings, BeyondSpring Inc, Blueprint Medicine, Cara Therapeutics, Chembio Diagnostics, contrast Corp, Cardiff Oncology, CRISPR Therapeutics, CVS Health Corporation, Precision Biosciences, Editas Medicine Inc, Five Prime Therapeutics, Globus Medical Inc, IDEXX Laboratories, Immune- nomedics Inc, IOVance Biosciences, Johnson & Johnson, Eli Lilly and Co, Novavax Inc, Northwest Biotherapeutics, Pfizer, Poseida Therapeutics, PTC Therapeutics, Spectrum Therapeutics, Surgicalin Holdings, Viking therapeutics, and, Vertex Pharmaceuticals. The other authors declared no conflicts of interest.

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Data sharing statement: All data can be freely accessed by FAERS website. By “search by product” and “search by reaction term”, and case listing, data can be exported for analysis.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2020.100601.

Reference

[1] Shimoyama M. Diagnostic criteria and classification of clinical subtypes of adult T-cell leukaemia-lymphoma. A report from the Lymphoma Study Group (1984–87). Br J Haematol 1991;79:428–37.
[2] Pui CH, Robison LL, Look AT. Acute lymphoblastic leukaemia. Lancet 2008;371:1030–43. doi: 10.1016/S0140-6736(08)60457-2.
[3] Jacobsen ED and Wennstock DM. 2018. Challenges and implications of genomics for T-cell lymphomas. Hematology 2014, the American Society of Hematology Education Program Book, 2018(1), pp. 63–68.
[4] El Haji H, Tsukasaki K, Cheminant M, Bazarbachi A, Watanabe T, Hermine O. Novel treatments of adult T cell leukemia lymphoma. Front Microbiol 2020;11.
[5] Bazarbachi A, Suarez F, Fields P, Hermine O. How I treat adult T-cell leukemia/lymphoma. Blood 2011;118(7):1736–45.
[6] Yamamoto K, Utsunomiya A, Tobinai K, Tsukasaki K, Uike N, Uozumi K, Yamaguchi K, Yamada Y, Hanada S, Tamura K, Nakamura S. Phase I study of KW-0761, a defucosylated humanized anti-CC4 antibody, in relapsed patients with adult T-cell leukemia-lymphoma and peripheral T-cell lymphoma. J Clin Oncol 2010;28(9):1591–8.
[7] Yu X, Marshall MJ, Cragg MS, Crispin M. Improving antibody-based cancer therapeutics through glycan engineering. BioDrugs 2017;31(3):151–66.
[8] Press announcements-FDA approves treatment for two rare types of non-Hodgkin lymphom (Last access date: June 29, 2020) https://www.fda.gov/news-events/press-announcements/fda-approves-treatment-two-rare-types-non-hodgkin-lymphoma.
[9] Ishida T, Joh T, Uike N, Yamamoto K, Utsunomiya A, Yoshida S, Saburi Y, Miyamoto T, Takemoto S, Suzushima H, Tsukasaki K. Defucosylated anti-CCR4 monoclonal antibody (KW-0761) for relapsed adult T-cell leukemia-lymphoma: a multicenter phase II study. J Clin Oncol 2012;30(8):837–42.
[10] Ogura M, Ishida T, Hatake K, Taniwaki M, Ando K, Tobinai K, Fujimoto K, Yama moto K, Miyamoto T, Uike N, Tamimoto M. Multicenter phase II study of mogamulizumab (KW-0761), a defucosylated anti-cc-chemokine receptor 4 antibody, in patients with relapsed peripheral T-cell lymphoma and cutaneous T-cell lymphoma. J Clin Oncol 2014;32(11):1157–63.
[11] Ishida T, Po T, Takemoto S, Suzushima H, Uozumi K, Yamamoto K, Uike N, Saburi Y, Nosaka K, Utsunomiya A, Tobinai K. Dose-intensified chemotherapy alone or in combination with mogamulizumab in newly diagnosed aggressive adult T-cell leukemia-lymphoma: a randomized phase II study. Br J Haematol 2015;169(5):572–82.
[12] Kiku H, Kusumoto S, Tanaka Y, Totani H, Ishida T, Okada M, Murakami S, Mizokami M, Ueda R, Iida S. Fatal reactivation of hepatitis B virus infection in a patient with adult T-cell leukemia-lymphoma receiving the anti-CC chemokine receptor 4 antibody mogamulizumab. Hepatology Res 2015;45(13):1363–7.
[13] Ishitsuiki K, Yurimoto S, Kawamura K, Tsuji Y, Iwabuchi M, Takahashi T, Tobinai K. Safety and efficacy of mogamulizumab in patients with adult T-cell leukemia–lymphoma in Japan: interim results of post-marketing all-case surveillance. Int J Hematol 2017;106(4):522–32.

[14] Ishii Y, Itabashi M, Numata A, Yamamoto W, Motohashi K, Hagihara M, Matsu moto K, Fujisawa S. Cytomegalovirus pneumonia after anti-CC-chemokine recep tor 4 monoclonal antibody (mogamulizumab) therapy in an angioimmunoblastic T-cell lymphoma patient. Internal Med 2016;55(5):673–5.

[15] United States Food and Drug Administration. FDA Adverse Reporting System Public Dashboard (Last access date: july 29, 2020). https://tsf.fda.gov/sense/app/d106eb5b-49be-4cd2-82e4-0135608dcd13/sheet/33a0f68e-845c-48e2-bc81-8141c6a8772/state/analysis.

[16] Kessler DA, Natanblut S, Kennedy D, Lazar E, Rheinstein P, Anello C, Barash D, Bernstein I, Bolger R, Cook K, Coug MP. Introducing MEDWatch: a new approach to reporting medication and device adverse effects and product problems. JAMA 1993;269(21):2765–8.

[17] Medical Dictionary for Regulatory Activities. (last accessed on Jul 27, 2020) https://www.meddra.org/entry/403481.

[18] Bate A, Evans SJ. Quantitative signal detection using spontaneous ADR reporting. Pharmacoeconomics Drug Saf 2009;18(6):427–36.

[19] Van Puijenbroek EP, Van Grootheest K, Diemont WL, Leufkens HG, Egberts AC. Determinants of signal selection in a spontaneous reporting system for adverse drug reactions. Br J Clin Pharmacol 2001;52(5):579–86.

[20] van der Wekken L, Herbrink J, Snijders D, Hamelink E, van den Hoogen A, Dissemi nated Mycobacterium chelonae infection in a patient with T-cell lymphoma. Hematol Oncol Stem Cell Ther 2017;10(2):89–92.

[21] Ishida T, Utsunomiya A, Iida S, Inagaki H, Takatsuki Y, Kusumoto S, Takeuchi G, Shimizu S, Ito M, Komatsu H, Wakita A. Cytomegalovirus infection in patients with adult T-cell leukemia–lymphoma: its close association with skin involvement and unfavorable outcome. Clin Cancer Res 2003;9(10):3625–34.

[22] Imai T, Nagira M, Takagaki S, Kakizaki M, Nishimura M, Wang J, Gray PW, Matsushima K, Yoshie O. Selective recruitment of CC chemokine receptor 4-bearing Th2 cells toward antigen-presenting cells by the CC chemokines thymus and activation-regulated chemokine and macrophage-derived chemokine. Int Immunol 1999;11(1):81–8.

[23] ClinicalTrials.gov (last accessed on May 16, 2020) https://clinicaltrials.gov/ct2/results?cond=mogamulizumab&term=&entry=&state=&ccty=8&site=8&cty=8&lst=8

[24] Doi T, Muro K, Ishii H, Kato T, Tsuchina T, Takeyama M, Ozumi S, Gemmoto K, Suna H, Enokitani K, Kawakami T. A Phase I Study of the Anti-CC Chemokine Receptor 4 Antibody, Mogamulizumab, in Combination with Nivolumab in Patients with Advanced or Metastatic Solid Tumors. Clin Cancer Res 2019;25(22):6614–22.

[25] Sato T, Coler-Reilly AL, Yagishita N, Araya N, Inoue E, Furuta R, Watanabe T, Uchimaru K, Matsuzaka M, Matsumoto N, Hasegawa Y. Mogamulizumab (Anti-CCR4) in HTLV-1–associated myelopathy. New Engl J Med 2018;378(6):529–38.

[26] Totani H, Kusumoto S, Ishida T, Masuda A, Yoshida T, Ito A, et al. Reactivation of hepatitis B virus (HBV) infection in adult T-cell leukemia-lymphoma patients with resolved HBV infection following systemic chemotherapy. Int J Hematol 2015;101:398e404.

[27] Nakano N, Kusumoto S, Tanaka Y, Ishida T, Takeuchi T, Takatsuki Y, et al. Reacti vation of hepatitis B virus in a patient with adult T-cell leukemia-lymphoma receiving the anti-CC chemokine receptor 4 antibody mogamulizumab. Hepatol 2014;44:354e6.

[28] Sandnberg E, Einiell H, Hebart H, et al. Antiviral prophylaxis in patients with haematological malignancies and solid tumours: guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society for Hematology and Oncology (DGHO). Ann Oncol 2006;17:1051–9.

[29] Reinwald M, Silva JT, Mueller NJ, Fortuin J, Carzton C, de Fijter JW, Fernandez-Ruiz M, Grossi P, Aguado JM. ESCMID study group for infections in compromised hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an infectious diseases perspective (Intracellular signaling pathways: tyrosine kinase and mTOR inhibitors). Clin Microbiol Infect 2018;24:533–70.

[30] Borck M, Nichols W, Papanicolaou G, Rubin R, Wingard JR, Zaia J. Cytomegalovirus in hematopoietic stem cell transplant recipients: current status, known challenges, and future strategies. Biol Blood Marrow Transpl 2003;9(9):543–58.

[31] Tay MJ, Lim ST, Tao M, Quek RH, Tay K, Tan TT. Cytomegalovirus infection and end-organ disease in Asian patients with lymphoma receiving chemotherapy. Leuk Lymphoma 2014;55(1):182–7.

[32] Torres HA, Kontoyiannis DP, Aguilera EA, Younes A, Luna MA, Tarrand JJ, Nogueras GM, Raad II, Chemaly RF. Cytomegalovirus infection in patients with lymphoma: an important cause of morbidity and mortality. Clin Lymphoma Myeloma 2006;6(5):393–8.

[33] Lundin J, Hagberg H, Repp R, Cavallin-Stahl E, Fredén S, Juliusson G, Rosenblad E, Tjernlund G, Wiklund T. A Phase 2 study of alemtuzumab (anti-CD52 monoclonal antibody) in patients with advanced mycosis fungoides/Sézary syndrome. Blood 2003;101(11):4267–72.

[34] Aksoy S, Harputluoglu H, Kilickap S, Dede DS, Dizdar O, Altundag K, Barista I. Rituximab-related viral infections in lymphoma patients. Leuk Lymphoma 2007;48(7):1307–12.

[35] Oketani M, Ido A, Uto H, Tsubouchi H. Prevention of hepatitis B virus reactivation in patients receiving immunosuppressive therapy or chemotherapy. Hepatol Res 2012;42(7):627–36.

[36] Loomba R, Rowley A, Wesley R, Liang TJ, Hoofnagle JH, Pucino F, Csako G. Systematic review: the effect of preventive lamivudine on hepatitis B reactivation during chemotherapy. Ann Intern Med 2008;148(7):519–28.

[37] EASL clinical practice guidelines. Management of chronic hepatitis B virus infection in patients receiving immunosuppressive therapy or chemotherapy. Hepatol Res 2012;42(7):627–36.

[38] Huang J, Chang CS. Chemotherapy induced hepatitis B reactivation in lymphoma patients with resolved HBV infection. Int J Hematol 2012;95(3):355–7.

[39] de Drijver AM, van der Valk M, de Jager P, van der Poll T, Kerkvliet I, de Vries I, van Rijen P, de Wit S, de Graeff PA, de Vries ES, den Nier AJ, den Boer WA, Kerkvliet IM. Hepatitis B virus reactivation in patients receiving chemotherapy or immunosuppressive therapy for hematological malignancies. Am J Hematol 2012;87(11):1051–5.

[40] Hsu C, Tsou HH, Lin SJ, Wang MC, Yao M, Hwang WL, Kao WY, Chiu CF, Lin SF, Lin J. Chemotherapy induced hepatitis B virus reactivation in patients with resolved HBV infection: a prospective study. Hepatology 2014;59(6):2092–100.