Immunotherapies and COVID-19 mortality: a multidisciplinary open data analysis based on FDA's Adverse Event Reporting System

During the COVID-19 pandemic, the risks and potential benefits of immunotherapies for the treatment of autoimmune disorders are still not well defined, and many cohort studies neither took the epidemiological dynamics of COVID-19 nor the potential capacities of the local healthcare systems in their outcome analysis into account. Due to a pronounced heterogeneity in the outcome reports of different participating countries, the large 'COVID-19 Global Rheumatology Alliance registry' addressed this issue using a 'cluster design' and shed light on factors associated with a more severe COVID-19 course in their study population.[1] We here present data of the US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS),[2] a postmarketing, self-reporting, open-access pharmacovigilance platform that contains international data of COVID-19 cases. Sources of FAERS are voluntary reports from healthcare professionals and consumers. We combine this data set with local measurements of the course of the pandemic (from Oxford University's 'Our World in Data'[3]) and the potential resiliency of the respective healthcare systems (from 'World Bank'; see online supplemental table 1 for full source information). Only patients with the diagnosis of an autoimmune disorder and a single immunotherapy (required group size: n≥100) at the time point of COVID-19 were analysed by multivariable regression analysis (online supplemental figure 1), limiting the generalisability of our data, for example, concerning combination therapy scenarios (online supplemental figure 1).

The mean age of patients in our cohort (n=2103) was 51.3 years (range 3–92 years; SD 14.9), female sex was more prevalent (1372/2103, 65.2%) and the majority of cases was reported in the USA/Canada (1285/2103, 61.1%). Inflammatory joint disease (846/2103, 40.2%), multiple sclerosis (474/2103, 22.5%) and inflammatory skin disease (435/2103, 20.7%) were the most prevalent diagnoses. Anti-tumour necrosis factor α (TNFα) therapies were the most frequently used medications for the underlying autoimmune disease (714/2103, 34%), followed by anti-CD20 therapies (388/2103, 18.4%). Additional cohort characteristics are shown in online supplemental table 2 and the monthly distribution of cases and cases by country in online supplemental figure 2.

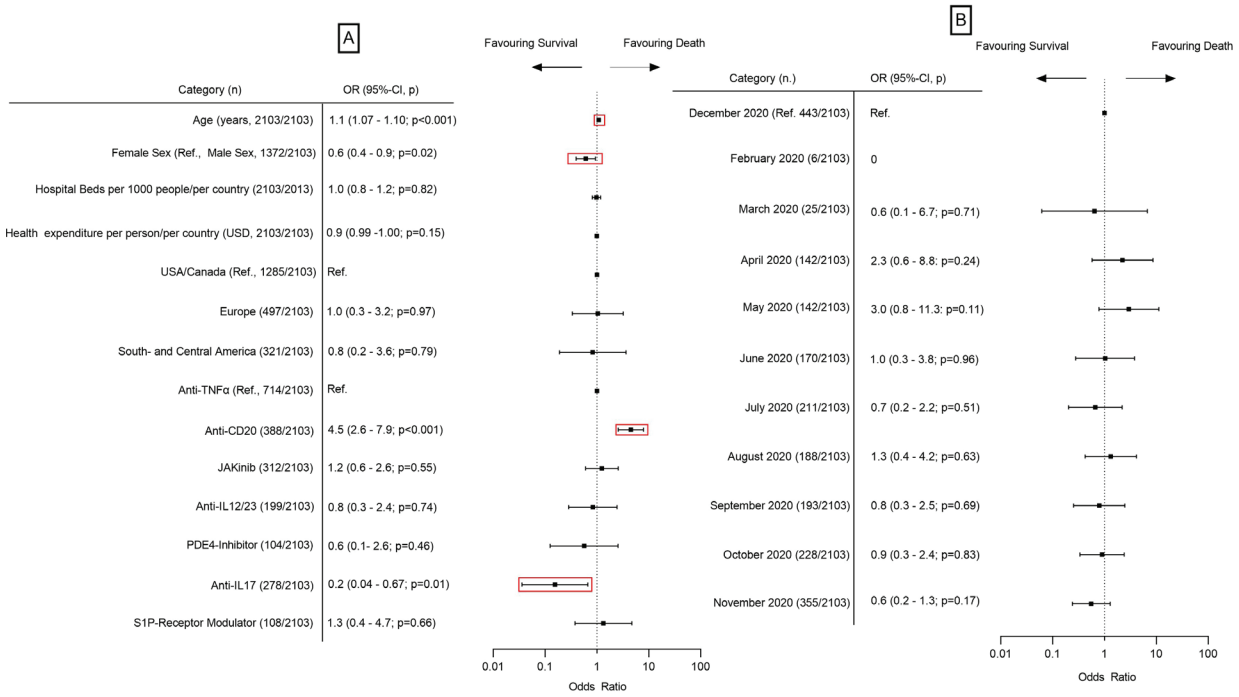

Figure 1 MLR showing the OR for 'death': 95% CIs and p values of the independent variables on a 10-log scale. (A) ORs for age, sex, hospital beds per 1000 persons/per country, health expenditure per person/per country (in US$), region and immunotherapy. (B) ORs for each month of 'initial FDA received date'. To control for the potential 'expectation bias' of FAERS, we included the variable 'ratio of total reports to FAERS to the number of reported deaths to FAERS for each drug in 2018–2020 excluding COVID-19 cases' (2.8; 0.1 to 84.2; p=0.56; not displayed). As reference groups (Region, Immunotherapy, Month), we chose the one with the highest number. Nagelkerke's R^2 is 0.24. For February 2020, no deaths have been reported to FAERS; therefore, the OR for February is 0. MLR was conducted with SPSS V.25 (IBM, USA, 2017). For more information regarding multivariable analysis adjusted for "month of event" instead of "initial FDA received date" see online supplemental figure 3 and for univariable analysis online supplemental figure 4. Not displayed: 'case fatality rate per month of initial FDA received date/country' (OR 0.5; 0.0 to 2479.3; p=0.86), 'new cases per population per month and country' (OR 51.5; 0.00 to 3.124E+37; p=0.93) and 'new deaths per population per month and country' (OR 0; p=0.54). CD-20, Cluster of Differentiation-20; FAERS, US Food and Drug Administration (FDA) Adverse Event Reporting System; IL-12/23, interleukin 12/23; IL-17, interleukin 17; JAKinib, Janus kinase inhibitor; MLR, multivariable logistic regression; PDE4-Inhibitor, phosphodiesterase-4 inhibitor; S1P-Receptor Modulator, sphingosine-1 phosphate receptor modulator; TNFα, tumour necrosis factor α.

In all, 26.3% of the reported patients were hospitalised (553/2103), and the overall reported mortality rate in our cohort was 5.1% (107/2103; for other outcomes, see online supplemental table 3). In the multivariable logistic regression analysis, age (OR per year 1.1; 95% CI 1.07 to 1.1; p<0.001) and female sex (OR 0.6; 95% CI 0.4 to 0.9; p=0.02) were significant predictors of mortality. Regarding immunotherapies, patients under anti-CD20 therapies had an increased mortality (OR 4.5; 95% CI 2.6 to 7.9; p<0.001), whereas those under anti-IL17 therapies had a reduced mortality (OR 0.2; 95% CI 0.04 to 0.67; p=0.01) compared with anti-TNFα therapies (reference group; figure 1).

In summary, using international open data sets and adjusting for local infectious diseases dynamics and the potential resilience of the national healthcare systems, our study demonstrates that anti-CD20 therapies are associated with a higher COVID-19 mortality risk in people with autoimmune disorders. This finding is in line with other cohort studies.[1 4] Regarding the potential protective capacities of anti-IL17 treatments, further studies are needed. This study also identified age and male sex as relevant predictors of COVID-19-associated mortality, which should therefore be taken into account in individual risk–benefit assessments. Our study has several limitations, for example, the fact that FAERS reports basic information on patients. We could not analyse disease-specific characteristics, comorbidities and risk factors, which have previously shown to influence mortality risks, thus representing a limitation of our analysis. Furthermore, adjustment for individual disease groups was not possible due to multicollinearity to immunotherapies. Biological therapies and recently approved oral immunotherapies are over-represented compared with classical immunotherapies, pointing towards a selection bias of FAERS. Furthermore, we cannot report the method of SARS-CoV-2 detection, as this information is not included in the FAERS data set.

Finally, we consider the use of combined open-access, pharmacoepidemiological data and a multidisciplinary approach, despite its limitations, as a valuable tool to address the various issues posed by the SARS-CoV-2 pandemic. Our findings might represent a complement to already published data and call for intensified investigations within larger cohort and translational studies.

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Competing interests AGFH (Department of Banking & Finance, Michael Smurfit Graduate Business School, University College Dublin, Dublin, Republic of Ireland and Platform for Sustainable Finance, Department for Financial Stability and Capital Markets (DG FISMA), European Commission, European Union (EU)) and YL (Department of Banking & Finance, Michael Smurfit Graduate Business School, University College Dublin, Dublin, Republic of Ireland) acknowledge funding from the European Union's Horizon 2020 research and innovation program for research on Fintech (Grant No. H2020-ICT-825215) and Science Foundation Ireland (Award 19/FIP/AI/7539). The views expressed in this paper are not necessarily shared by other members of the Platform for Sustainable Finance or DG FISMA. AC (Department of Neurology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland) has served on advisory boards for, and received funding for travel or speaker honoraria from, Actelion-Janssen, Almirall, Bayer, Biogen, Celgene, Sanofi-Genzyme, Merck, Novartis, Roche and Teva, all for hospital research funds, and received research support from Biogen, Genzyme and UCB. AC is associate editor of the European Journal of Neurology and serves on the editorial board for Clinical and Translational Neuroscience and as topic editor for the *Journal of International Medical Research*; all not related to that work. AS received speaker honoraria and/or travel compensation for activities with Almirall Hermal GmbH, Biogen, Merck, Novartis, Roche, and Sanofi Genzyme and research support by the Swiss MS Society; all not related to this work. RH received speaker/advisor honorary from Merck, Novartis, Roche, Biogen, Alexion, Sanofi, Bristol-Myers Squibb and Almirall. He received research support within the last 5 years from Roche, Merck, Sanofi, Biogen and Bristol-Myers Squibb. He also received research grants from the Swiss MS Society; all not related to that work.

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Online-Only Supplements

Table of Content

Supplemental Table 1: Data sources

	Unit	Source
Age	years	FAERS
Sex		FAERS
Mortality		FAERS, based on "Outcomes"
Diagnosis		FAERS, based on «Reason for use»
Region		FAERS, based on "Country"
Medication		FAERS, based on "Product Active Ingredient"
Ratio of total reports to FAERS to the number of reported deaths to FAERS for each drug in 2018-2020 excluding COVID-19 cases		FAERS (Computed)
Hospital beds per 1000 persons per country		The World Bank
Health expenditure per Capita (USD) per country	USD	The World Bank
Case fatality rate per month and country		Our World in Data (Computed)
New cases per population, month and country		Our World in Data (Computed)
New deaths per population/ month and country		Our World in Data (Computed)

Variables and data sources. The following search terms were used in FAERS[1]: “COVID-19”, “Coronavirus-Infection”, “Exposure to SARS-CoV2”, “SARS-CoV2-Test”, “Exposure/ occupational exposure to SARS-CoV2”. Healthcare system variables (derived from “Our World In Data”[2] and World Bank[3,4]) were matched with the FAERS data set on case level by country code and FDA or event reported month. For categorical variables with more than two groups, we choose the category with the highest number of cases as reference being “anti-TNFα” (medication), USA/Canada (region) and December (month “initial FDA received date” or “event”). Sex is coded by FAERS as male, female or not specified. Only male and female cases were included in analyses. Region based on the FAERS country code, diagnoses on FAERS “Reason for use”. Outcome was generated from the FAERS variable “Outcomes” with the following categories: non-serious, hospitalized, life threatening, congenital anomaly (not present in our cohort), disabled, other outcomes, died. Following the FAERS information[5], all categories except “died” were grouped as “survived” (0) and the category “died” was labelled as “died” (1). The case fatality rate per month and country, the new cases and –deaths per population, month and country were computed based on “World in Data”. The ratio of total reports to FAERS to the number of reported deaths to FEARS for each drug in 2018-2020 (without the COVID-cases) was computed based on the FAERS public dashboard. Abbreviations: FAERS; FDA Adverse Event Reporting System; USD: U.S. Dollar; COVID-19: Coronavirus Disease 2019

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1 U.S. Food and Drug Administration (FAERS) - FDA Adverse Event Reporting System. 2021.https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard (accessed 22 Feb 2021).

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3 Worldbank. Hospital beds (per 1,000 people). 2021.https://data.worldbank.org/indicator/SH.MED.BEDS.ZS (accessed 13 Mar 2021).

4 Worldbank. Current health expenditure per capita (current US$). https://data.worldbank.org/indicator/SH.XPD.CHEX.PC.CD (accessed 13 Mar 2021).

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Supplemental Table 2: Cohort Characteristics

		Overall n = 2103 No. (%)	Dead n = 107 No. (%)	Survived n = 1996 No. (%)
Age in years (mean (SD))		51.3 (SD 14.9)	62.7 (SD 14.2)	50.6 (SD 14.7)
Sex	Male	731 (34.8)	51 (47.7)	680 (34.1)
	Female	1372 (65.2)	56 (52.3)	1316 (65.9)
Region	USA/Canada	1285 (61.1)	51 (47.7)	1234 (61.8)
	Europe	497 (23.6)	42 (39.3)	455 (22.8)
	South- and Central America	321(15.3)	14 (13.1)	307 (15.4)
	Inflammatory joint disease	846 (40.2)	39 (36.5)	807 (40.4)
	Vasculitis	12 (0.6)	3 (2.8)	9 (0.5)
	Connective tissue disease	4 (0.2)	1 (0.9)	3 (0.2)
	Sarcoidosis	1 (0.04)	0 (0)	1 (0.1)
Immunotherapy Indication	Inflammatory bowel disease	168 (8.0)	5 (4.7)	163 (8.2)
	Inflammatory eye disease	5 (0.2)	0 (0)	5 (0.3)
	Inflammatory skin disease	435 (20.7)	12 (11.2)	423 (21.2)
	Spondyloarthropathy	135 (6.4)	5 (4.7)	130 (6.5)
	Neuroimmunological disease without MS	6 (0.3)	2 (1.9)	4 (0.2)
	Multiple Sclerosis	474 (22.5)	38 (35.5)	436 (21.8)
	Immunotherapy - NOS	4 (0.2)	0 (0)	4 (0.2)
	Multiple autoimmune diseases	13 (0.6)	2 (1.9)	11 (0.6)
	Anti-TNFα	714 (34.0)	34 (31.8)	680 (34.1)
	Adalimumab	336 (47.1)	20 (58.8)	316 (46.5)
	Etanercept	145 (20.3)	3 (8.8)	142 (20.9)
	Certolizumab	76 (10.6)	3 (8.8)	73 (10.7)
	Golimumab	97 (13.6)	3 (8.8)	94 (13.8)
	Infliximab	60 (8.4)	5 (14.7)	55 (8.1)
	Anti-CD20	388 (18.4)	43 (40.2)	345 (17.3)
	Rituximab	58 (15.0)	16 (37.2)	42 (12.2)
Immunotherapy	Ocrelizumab	320 (82.5)	27 (62.8)	293 (84.9)
	Ofatumumab	10 (2.6)	0 (0)	10 (2.9)
	JAKinib	312 (14.8)	14 (13.1)	298 (14.9)
	Tofacitinib	248 (79.5)	10 (71.4)	238 (79.9)
	Upadacitinib	58 (18.6)	4 (28.6)	54 (18.1)
	Baricitinib	6 (1.9)	0 (0)	6 (2.0)
	Anti-IL12/23	199 (9.5)	9 (8.4)	190 (9.5)
	Ustekinumab	152 (76.4)	7 (77.8)	145 (76.3)
	Risankizumab	32 (16.1)	2 (22.2)	30 (15.8)

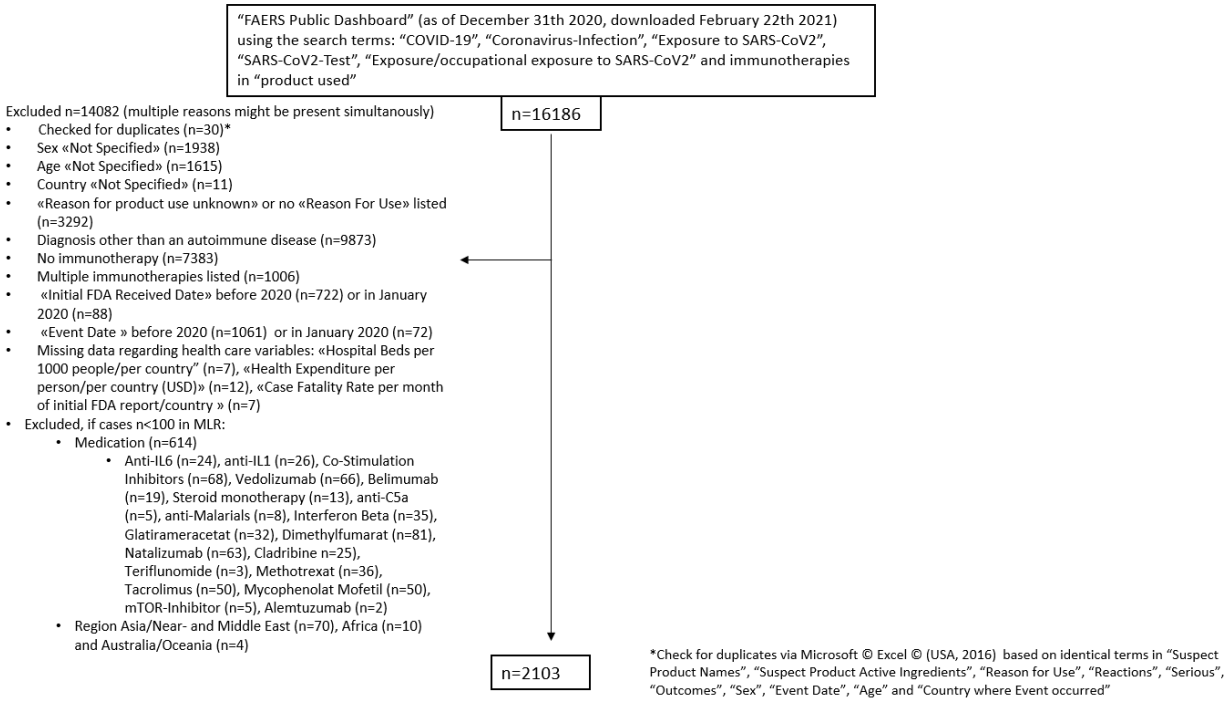
		Overall n = 2103 No. (%)	Dead n = 107 No. (%)	Survived n = 1996 No. (%)
	Guselkumab	15 (7.5)	0 (0)	15 (7.9)
	PDE4-Inhibitor	104 (4.9)	2 (1.9)	102 (5.1)
	Apremilast	104 (100)	2 (100)	102 (100)
	Anti-IL17	278 (13.2)	2 (1.9)	276 (13.8)
	Secukinumab	233 (83.8)	2 (100)	231 (83.7)
	Ixekizumab	43 (15.5)	0 (0)	43 (15.6)
	Brodalumab	2 (0.7)	0 (0)	2 (0.7)
	S1P-Receptor Modulator	108 (5.1)	3 (2.8)	105 (5.3)
	Fingolimod	92 (4.4)	2 (66.7)	90 (85.7)
	Siponimod	15 (0.7)	1 (33.3)	14 (13.3)
	Ozanimod	1 (0.1)	0 (0)	1 (1.0)

Absolute numbers of reported deaths and survived cases are displayed. The percentages here relate to the dead or survived population. Percentage of the drugs listed below the medication groups (e.g. Adalimumab) in respect to their proportion within their medication group (e.g. anti-TNFα). Abbreviations: CD-20: Cluster of Differentiation-20, IL-12/23: Interleukin 12/23, IL-17: Interleukin 17, JAKinib: Janus Kinase inhibitor, MS: Multiple Sclerosis, n: sample size, nos: not otherwise specified, PDE4-Inhibitor: Phosphodiesterase-4 inhibitor, S1P-Receptor Modulator: Sphingosine-1 phosphate modulator, TNFα: Tumor necrosis factor α, USA: United States of America

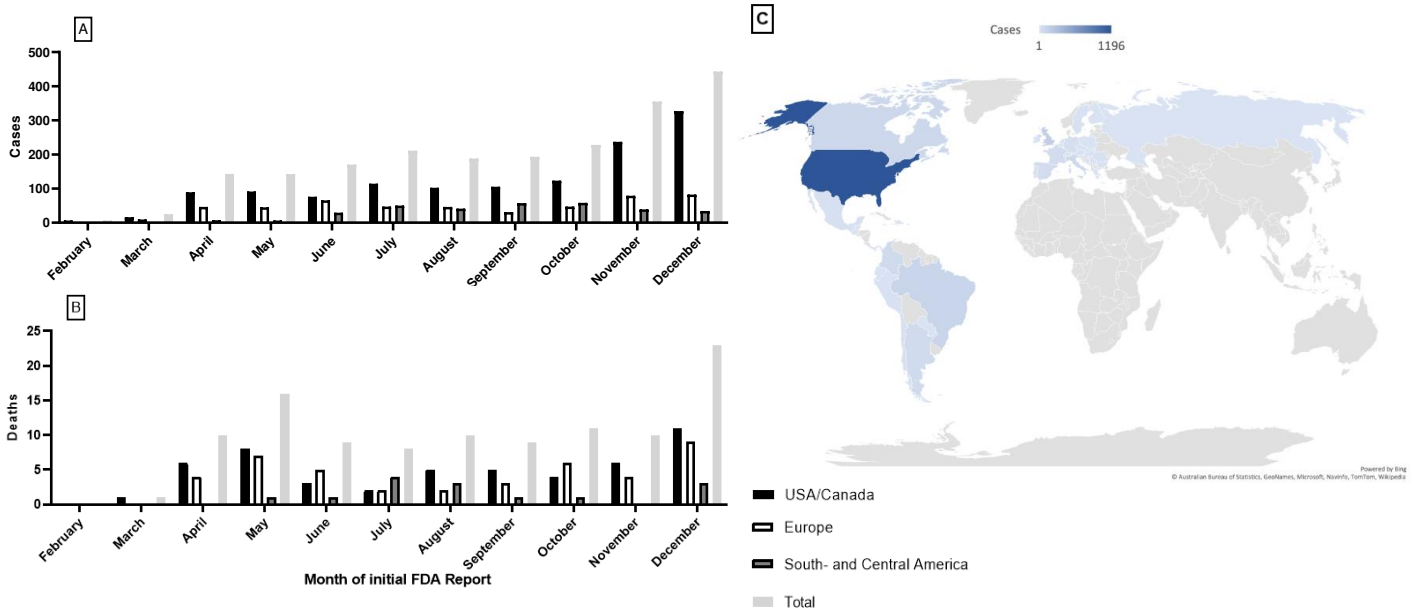
Supplemental Table 3: Numerically reported outcomes.

		n	%
Outcomes	Non Serious	569	27.1
	Hospitalized	553	26.3
	Life Threatening	36	1.7
	Died	107	5.1
	Other Outcomes	834	39.7
	Disabled	4	0.2
Died	Survived	1996	94.9
	Died	107	5.1

Supplemental Figure 1: Exclusion/Inclusion Criteria



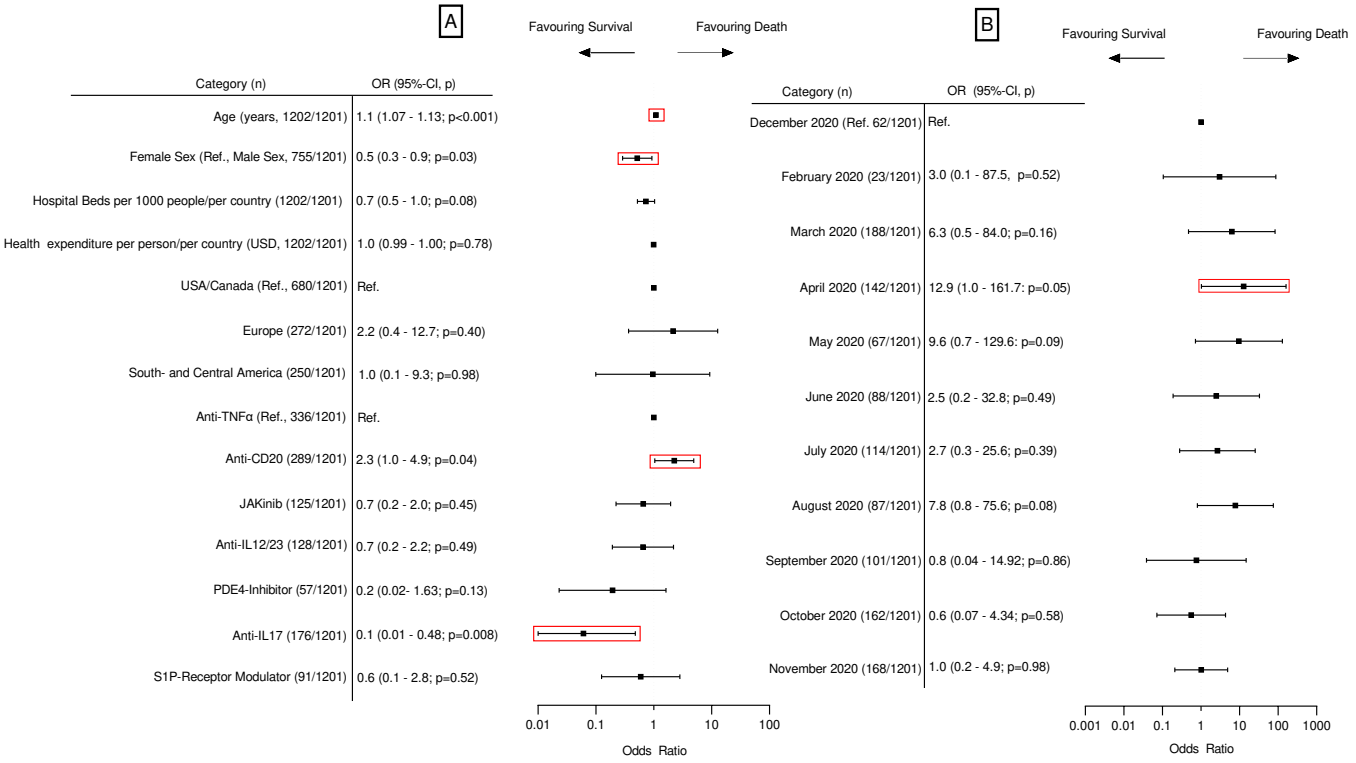
Cohort constitution and exclusion criteria. 16186 cases were initially identified using the search terms in FAERS (up to 5 possible) listed above. Cases with missing values, implausible cases (e.g. coronavirus cases before 2020), duplicates, and cases without immunotherapies or "Reason for Use" that does not constitute an autoimmune disorder were excluded. Medications and regions with <100 cases in final MLR were excluded. The final cohort size is 2103 with regards to the independent variable "month of initial FDA received date". Abbreviations: C5a: Complement Factor 5A, COVID-19: Coronavirus Disease 2019, FDA: U.S. Food and Drug Administration, FAERS: FDA Adverse Event Reporting System, IL-6/IL-1 Interleukin 6 or 1, SARS-CoV2: Severe Acute Respiratory Syndrome Coronavirus Type



Supplemental Figure 2: Case numbers and deaths reported to FAERS.

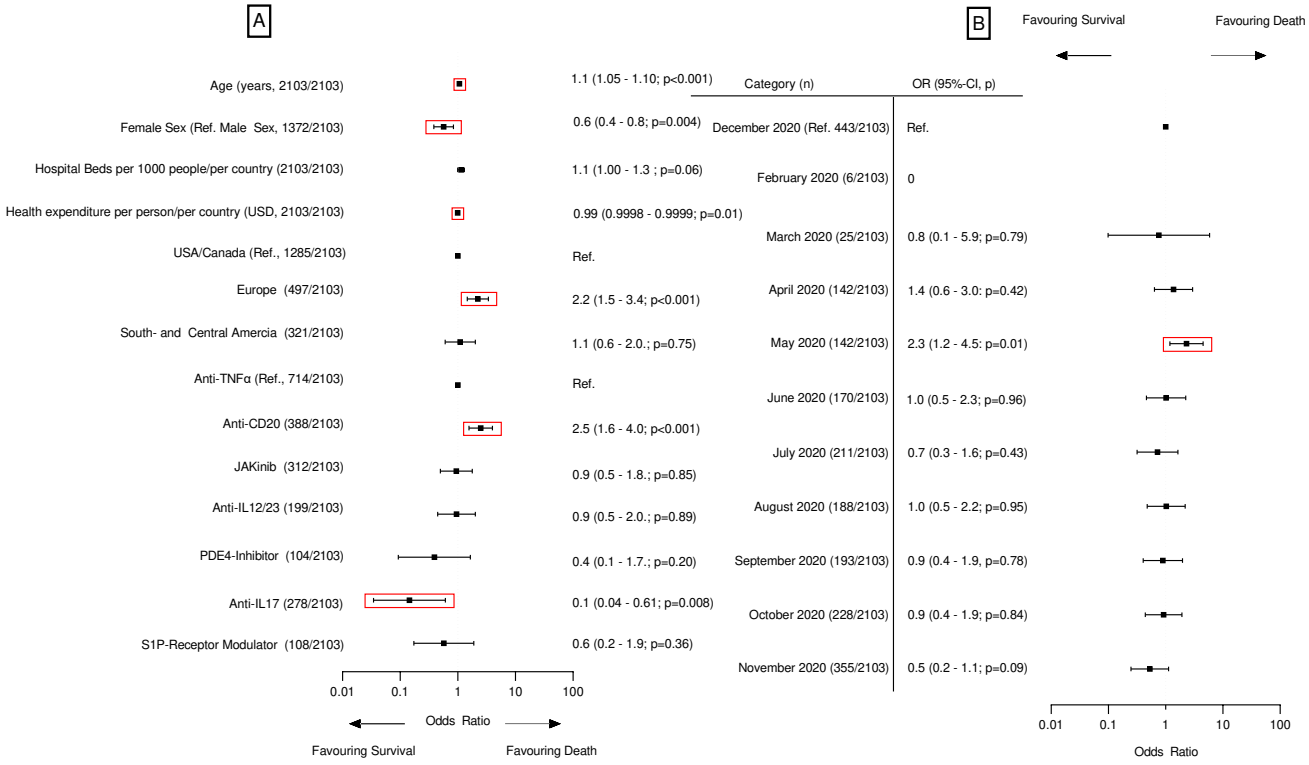
Supplemental Figure 2: A: Distribution of cases and B: deaths reported to FAERS for each month of initial FDA received date (February 2020 – December 2020) for each region (USA/Canada, Europe, South- and Central America) and in total. C) Geographical distribution of reported cases (Feb 2020 – Dec 2020). Depth of blue represents higher number. Created with Microsoft© Powerpoint©, Bing©, Australian Bureau of Statistics©, GeoNames©, Navinfo©, TomTom© andWikipedia. Abbreviations: FDA: U.S. Food and Drug Administration

Supplemental Figure 3: Multivariable regression analysis for the event month.



Multivariable-adjusted OR for "death" using the reported "month of event" instead of the month of the initial FDA report: 95% - CIs and p-values of the independent variables on a 10-log scale. A: ORs for age, sex, hospital beds per 1000 persons/per country, health expenditure per person/per country (in USD), region and medication. B: ORs of the reported "month of event". The following controls are not displayed: case fatality rate per month of event/country" (3.4; 0.0 - 250982244.8, p=0.89), the "ratio of total reports to FAERS to the number of reported deaths to FAERS for each drug in 2018-2020 excluding COVID-19 cases" (0.93; 0.02 – 49.02: p=0.97), "new cases per population per month and country" (1.4746E70; 1401551.6- 1.5514E134, p=0.03) and "new deaths per population per month and country" (0; p=0.155). Nagelkerkes R^2 is 0.268. For February 2020, no deaths have been reported to FAERS, therefore the OR for February is 0. Abbreviations: CD-20: Cluster of Differentiation 20, CI: confidence interval, FDA: U.S. Food and Drug Administration, IL-12/23: Interleukin 12/23, IL-17: Interleukin 17, JAKinib: Janus kinase inhibitor, MLR: multivariable logistical regression, OR: Odds Ratio, n: sample size, Ref./ref.: Reference; p: p-value, PDE4-Inhibitor: Phosphodiesterase-4 inhibitor, S1P-Receptor Modulator: Sphingosine-1 phosphate modulator, TNFα: Tumor necrosis factor α, USA: United States of Americas

Supplemental Figure 4: Univariable regression analysis



Univariate OR for "death" for the month of the Report to FDA: 95% - CIs and p-values of each independent variable on a 10-log scale. A: ORs for age, sex, hospital beds per 1000 persons/per country, health expenditure per person/per country (in USD), region and medication B: ORs for each individual "month of the initial FDA report". The following controls are not displayed: case fatality rate per month of event/country" (1833.1; 26.0 - 129348.8, p=0.001), the "ratio of total reports to FAERS to the number of reported deaths to FAERS for each drug in 2018-2020 excluding COVID-19 cases" (1.8, 0.2 – 13.0; p=0.56), "new cases per population per month and country" (6.4815E20; 8.158E-35 - 0.000052, p=0.01) and "new deaths per population per month and country" (1.0054E-165; 0.0E0; p=0.73). Abbreviations: CD-20: Cluster of Differentiation 20, CI: confidence interval, FDA: U.S. Food and Drug Administration, IL-12/23: Interleukin 12/23, IL-17: Interleukin 17, JAKinib: Janus kinase inhibitor, OR: Odds Ratio, n: sample size, Ref./ref.: Reference; p: p-value, PDE4-Inhibitor: Phosphodiesterase-4 inhibitor, S1P-Receptor Modulator: Sphingosine-1 phosphate modulator, TNFα: Tumor necrosis factor α, USA: United States of America