COVID-19 vaccines and Autoimmune hemolytic anemia

Introduction

To date, five COVID-19 vaccines have been authorized for active immunization against SARS-CoV-2 in The Netherlands: BioNTech/Pfizer (Comirnaty®) [1], Moderna (Spikevax®) [2], AstraZeneca (Vaxzevria®) [3], Janssen (Jcovden®) [4], and Novavax (Nuvaxovid®) [5]. BioNTech/Pfizer and Moderna are both mRNA vaccines, AstraZeneca and Janssen are both vector-based vaccines, and Novavax is a protein subunit vaccine containing a saponin based matrix-M immune-stimulating adjuvant [1-5]. All five COVID-19 vaccines encode the SARS-CoV-2 spike glycoprotein and induce a cellular and humoral immune response, including SARS-CoV-2 neutralising antibodies.

Autoimmune hemolytic anemia (AIHA) is rare autoimmune disorder with an estimated incidence of 1-3 cases per 100,000 persons per year [6]. In AIHA IgG, IgM and/or IgA autoantibodies are formed and bind to the host's red blood cell surface antigens and initiate red blood cell destruction via the complement system and the reticuloendothelial system [6]. The degree of hemolysis depends on certain characteristics of the autoantibody and the target antigen.[6] Patients with AIHA may have the following symptoms due to anemia or hemolysis: tachycardia, pale skin or jaundice, shortness of breath, weakness, chest pain or hemoglobinuria [7-9].

AIHA cases can be divided based on etiology in primary, or idiopathic, AIHA and secondary AIHA. Underlying causes of secondary AIHA include lymphoproliferative diseases, autoimmune disorders, infections, immunodeficiency disorders, medication and tumors [6,7]. Lymphoproliferative diseases account for approximately half of secondary AIHA cases [6].

AIHA can be classified according to the temperature reactivity of the red blood cell autoantibody in warm AIHA, cold AIHA, paroxysmal cold hemoglobinura, and mixed-type(AIHA. Warm autoantibodies react most strongly near 37°C and have a decreased affinity at lower temperatures [6,11]. Cold autoantibodies bind to red blood cells most strongly near 0-4°C and typically show little affinity at physiological temperatures [6]. Warm AIHA is the most common type of AIHA (~70-80% of the cases) and is typically caused by IgG autoantibodies [10,11]. In cold AIHA, hemolysis is mostly caused by IgM autoantibodies [10].

Diagnosis of AIHA is based on the presence of hemolysis in combination with a positive direct anti-globulin test (DAT), also known as a direct Coombs test [10]. The treatment for AIHA varies and is based on the classification and severity of AIHA and can include corticosteroids, rituximab and splenectomy [6,10].

Reports

Until March 10th 2023, the Netherlands Pharmacovigilance Centre Lareb received a total of 10 cases of autoimmune hemolytic anemia associated with COVID-19 vaccines. Of these cases, four were reported to Lareb by the spontaneous report system and six were reported via our multicenter retrospective cohort study in which individual cases are retrieved from electronic health care reports (EHR) of two Dutch hospitals, using a clinical data collector tool with text mining possibilities, to supplement the current spontaneous report system and optimize pharmacovigilance [12].
Of these 10 reports, 9 were reported by a health care professional (six reports via EHR) and one was reported by a consumer. Seven reports contained the COVID-19 Moderna vaccine, of which one was the Moderna omicron BA1 variant, one report was on the Pfizer/BioNTech vaccine, one on the AstraZeneca vaccine and one on a non-specified COVID-19 vaccine. Seven reports were of females and three were of males. Age ranged from 28-89 years, with an average age of 58 years old. Six of the ten reports were recurrences of already existing AIHA. The latency times ranged from 3-36 days (one latency time was unknown) with an average of 15 days and a median of 14 days. When differentiating between recurrent AIHA and new-onset AIHA the median latency was 6 days and 20 days respectively. At the time of reporting, one patient was not recovered, three patients were recovering, four patients were recovered, one patient passed away and the outcome of one patient was unknown.

Table 1 provides a detailed overview of the ten AIHA cases reported for COVID-19 vaccines.

Table 1. AIHA cases reported after COVID-19 vaccines.

No	ID, sex, age, primary source, medical history	Drug	Reported ADRs	Latency AIHA	Treatment	Outcome	Diagnostics
1	NL-LRB-00526107, female, 40-50 years, Physician, Unknown	COVID-19 vaccine Moderna	Autoimmune hemolytic anemia Thrombocytopenia Leucopenia Fatigue Palpitations	5 days	Prednisone	Not recovered	Blood test (no results reported)
2	NL-LRB-00869909, female, 60-70 years EHR case via pharmacist AML, allogenic stem cell transplantation	COVID-19 vaccine Moderna	Autoimmune hemolytic anemia	36 days	Rituximab, IVIG, epoetin beta	Recovering	Blood test: Hb 4.8, reticulocyte count 209, increased LD and bilirubin DAT: IgG positive
3	NL-LRB-00870154, female, 50-60 years EHR case via pharmacist Hypo-thyreoidism	COVID-19 vaccine Pfizer	Autoimmune hemolytic anemia Pulmonary embolism	2 weeks	Prednisolon, erythrocyte transfusions	Recovered	Blood test: Hb 3,1, increased bilirubin, LD and reticulocyte count and decreased haptoglobin DAT: IgG/IgA positive CT scan, Thorax X ray, Immunopheno-typing, ANA showed no underlying causes
4	NL-LRB-00870182, male, 60-70 Years EHR case via pharmacist Atrial fibrillation, decompensation cardiac	COVID-19 vaccine AstraZeneca	Autoimmune haemolytic anaemia Thrombocytopenia Cardiac arrest Splenic bleeding Cerebral infarction Acute tubular necrosis	4 weeks	Prednisone, transfusion of packed cells, rituximab	Recovered	Blood test: Hb 5.2 with increased bilirubin, reticulocytes, LDH and decreased haptoglobin and thrombocyte count DAT: IgG positive CT scans, thorax X ray, ECG, ANA showed no underlying causes
5	NL-LRB-00841959, male, 50-60 years, Physician, AIHA	COVID-19 vaccine Moderna omicron BA1	Autoimmune hemolytic anemia Clinical flare reaction Multiorgan failure	3 days	Steroids, rituximab, splenectomy bortezomib, plasmapher esis	Fatal	Blood test: Hb 2.9, thrombopenia, Coombs test: warm and cold anitbodies,
6	NL-LRB-00550537, female, 70 years and older, Physician, CLL, AIHA	COVID-19 vaccine Moderna	Autoimmune hemolytic anemia Aggravation of existing disorder	4 days	-	Recovering	Blood test (no results reported)
7	NL-LRB-00528368, female, 20-30 years, Consumer or other non-health care professional AIHA	COVID-19 vaccine Moderna	Chills Headache Nausea Generalized joint pain Malaise Fatigue Hyperpyrexia Renal failure acute Autoimmune haemolytic anaemia	unknow n	Paracetamol rituximab, dialysis	Unknown	Blood test (no results reported), CT scan: no abnormalities seen
8	NL-LRB-00869904, male, 60-70 Years EHR case via pharmacist AIHA, B-CLL	COVID-19 vaccine Moderna	Autoimmune haemolytic anaemia	3 weeks	Prednisone	Recovering	Blood test: Hb of 7.1, reticulocyte count of 267, increased LD and bilirubin, unmeasurable low

							haptoglobin. DAT: IgG positive Immuno-phenotyping: minimal disease activity of CLL.
9	NL-LRB-00870194, female, 30-40 Years EHR case via pharmacist AIHA, thrombopenia	COVID-19 vaccine Moderna	Autoimmune hemolytic anemia	3 weeks	Prednisolon	Recovered	Blood test: Hb of 4.9 and reticulocyte count of 115, haptoglobin is unmeasurable low. DAT: IgG and IgM positive
10	NL-LRB-00870205, female, 70 years and older EHR case via pharmacist AIHA, splenectomy	COVID-19 vaccine not specified	Autoimmune hemolytic anemia Influenza like symptoms	6 days	Prednisolon dose increase	Recovered	-

*EHR= electronic health records

Other sources of information

SmPC

Autoimmune hemolytic anemia is not included in the SmPC of any of the COVID-19 vaccines as an adverse drug reaction. Also, new-onset or relapse autoimmune disease is not included in any of the SmPC. [1-5]

Considering other vaccines, hemolytic anemia is included in the SmPC of the pneumococcal vaccine Pneumovax 23.[13]

Other databases

In the WHO global database of individual case safety reports, Vigibase, a total of 410 autoimmune hemolytic anemia cases associated with COVID-19 vaccines were reported as of March 1st 2023. This association was not disproportional, with an IC_{025} of -0,2 and a ROR_{025} of 0,8 (number of cases in background 34.560.379).

Literature

A literature search on PubMed on the association of autoimmune hemolytic anemia with vaccination in general provided several case reports. Cases of AIHA have been reported in association with oral poliomyelitis, DTP, influenza and pneumococcal vaccines [14-19]. Also one case report of Evans syndrome after influenza vaccine is reported [20]. Evans syndrome is an uncommon condition defined by the combination of immune thrombocytopenia purpura and AIHA [20].

A literature search on PubMed resulted in 14 case reports and one systematic review of cases of autoimmune hemolytic anemia after COVID-19 vaccination. Twelve of the fourteen published case reports were included in the systematic review. In this review, Jafarzedeh et al. [21] describe 11 patients with new-onset AIHA and 7 patients with recurrent AIHA after COVID-19 vaccination. The median age of the 11 patients with new-onset AIHA was 67 years. In 7 of 11 cases the onset of symptoms occurred after the first vaccine dose with a median of 7 days. In 3 of 11 cases the onset of symptoms occurred after the second dose with a median of 14 days. In 1 case the symptoms occurred 17 days after a booster vaccination. In 10 of 11 cases patients were vaccinated with a mRNA vaccine. A recurrent AIHA was described in 7 patients with a median age of 73 years. In 4 of 7 cases the symptoms occurred after the first dose with a median time of 7 days and in 2 of 7 cases they occurred after the second dose with a median time of 3 days. In 1 case the symptoms occurred on day 2 after a booster vaccination. All patients were vaccinated with a mRNA vaccine.

The two additional case reports describe a 71-year-old male who developed warm AIHA after the second dose of a mRNA vaccine with an unknown latency time and a 52-year-old female who developed cold AIHA 7 days after a booster vaccination [22, 23].

There are also case reports published on the association of AIHA and COVID-19 infection. Jacobs et al. [24] performed a systematic review including all literature on this association. This review included 50 patients who developed cold AIHA, warm AIHA, mixed type AIHA or Evans syndrome after a COVID-19 infection. The median time from COVID-19 infection to onset of symptoms of AIHA was 7

days. Of 42 cases that described the outcome of AIHA, 19% (8/42) were deceased. In 7 of these deceased patients there were multiple other underlying medical comorbidities, including hemolytic risk factors.

Mechanism
The precise mechanism of AIHA and how infection or vaccination can induce AIHA is not fully understood yet. The most described and accepted hypothesis involves molecular mimicry between the epitopes on the SARS-Cov-2 spike protein and ankyrin-1. Ankyrin-1 is an integral protein in the membrane of erythrocytes that is important for red blood cell differentiation and function. Angileri et al. found that ankyrin-1 shares an epitope with 100% similarity as the viral spike protein. The hypothesis is that this cross-reactivity may also contribute to the development and exacerbation of AIHA after COVID-19 vaccination [24,25].

Discussion and conclusion

From January 6th 2021 to March 10th 2023 the Netherlands Pharmacovigilance Centre Lareb received ten reports of the rare autoimmune disorder AIHA after COVID-19 vaccination. Most cases were reported by health care professionals and were well documented. Six cases describe a recurrent AIHA with a median latency time to onset of symptoms of 6 days and four cases describe a new-onset AIHA with a median latency time of 20 days. In literature, 20 cases of AIHA after COVID-19 vaccination are described of which 13 patients developed new-onset AIHA and 7 patients developed a recurrence of their previously diagnosed AIHA. Latency time in these cases ranged from 2 to 7 days for recurrent AIHA and from 7 to 17 days for new-onset AIHA, which is comparable to cases reported to the Netherlands Pharmacovigilance Centre Lareb. The range of latency times for new-onset and recurrent AIHA was deemed plausible by consulted haematologists.

Other possible causes for AIHA were examined and excluded in many of our cases. In one case the patient had had a COVID-19 infection 4 months prior to developing symptoms of AIHA. In one case ANA was tested positive as part of auto-immune serology screening but without presence of any disease-specific auto-antibodies and was therefore considered irrelevant in the absence of any auto-immune disorder manifestations. In some cases of recurrent AIHA, a lymphoproliferative disorder was previously diagnosed as the cause of AIHA. But even in most of these cases, COVID-19 vaccination was considered the trigger (direct cause) of the flare up of AIHA or decompensation of previously compensated AIHA by consulted haematologists. Besides triggering of auto-immunity by COVID-19 vaccination, another possible mechanism was suggested for cases that developed decompensation of previously compensated AIHA after COVID-19 vaccination. In these cases AIHA was already active but the bone marrow was able to compensate for the rate of red blood cell destruction by increased production of new red blood cells. Inflammation is known to have an inhibitory effect on this compensatory mechanism of the bone marrow and is therefore a more plausible mechanism than auto-immunity flare up in these cases.

In conclusion, a causal relationship between AIHA and COVID-19 vaccination seems plausible and should therefore be further investigated.

References
1. European Medicines Agency. SmPC Comirnaty 2022 [Available from: https://www.ema.europa.eu/en/documents/product-information/comirnaty-epar-product-information_en.pdf
2. European Medicines Agency. SmPC Spikevax 2022 [Available from: https://www.ema.europa.eu/en/documents/product-information/spikevax-previously-covid-19-vaccine-Spikevax-epar-productinformation_en.pdf
3. European Medicines Agency. SmPC Vaxzevria 2022 [Available from: https://www.ema.europa.eu/en/documents/product-information/vaxzevria-previously-covid-19-vaccine-Vaxzevria-epar-productinformation_en.pdf
4. European Medicines Agency. SmPC Jcovden 2022 [Available from:

https://www.ema.europa.eu/en/documents/product-information/jcovden-previously-covid-19-vaccine-Jcovden-epar-productinformation_en.pdf
5.European Medicines Agency. SmPC Nuvaxovid 2022 [Available from: https://www.ema.europa.eu/en/documents/product-information/nuvaxovid-epar-product-information_en.pdf
6. Gehrs BC, Friedberg RC. Autoimmune Hemolytic Anemia. Am J Hematol. 2002;69(4):258-271.
7. WebMD. Autoimmune Hemolytic Anemia. Last update: 25-02-2022. [Available from https://www.webmd.com/a-to-z-guides/autoimmune-hemolytic-anemia]
8. Norfolk and Norwich University Hospitals. Autoimmune haemolytic anaemia. Last update: unknown. [Available from: https://www.nnuh.nhs.uk/departments/haematology-department/non-malignant-haematology/autoimmune-haemolytic-anaemia/]
9. Hill QA. Autoimmune hemolytic anemia. Hematology. 2015;20(9):553-554.
10. Hill A, Hill QA. Autoimmune hemolytic anemia. Hematology Am Soc Hematol Educ Program. 2018;2018(1):382-389.
11. Kalfa TA. Warm antibody autoimmune hemolytic anemia. Hematology Am Soc Hematol Educ Program. 2016;2016(1):690-697.
12. Kant A, Zwaveling J, Kalkhoran HA, van Hunsel F. Oral Presentation: Search for Additional Cases in Electronic Health Records (EHRs) to Strengthen Potential Signals from Spontaneous Reporting. 21st ISoP Annual Meeting ''A New Era of Pharmacovigilance: Challenges and Opportunities'' 20–23 September 2022 Verona, Italy. 2022;2022(45).
13. College ter Beoordeling van Geneesmiddelen. SmPC Pneumovax 23 [Available from: https://www.geneesmiddeleninformatiebank.nl/smpc/h25853_smpc.pdf]
14. Seltsam A, Shukry-Schulz S, Salama A. Vaccination-associated immune hemolytic anemia in two children. Transfusion. 2000;40(8):907-9.
15. Downes KA, Domen RE, McCarron KF et al. Acute autoimmune hemolytic anemia following DTP vaccination: report of a fatal case and review of the literature. Clin Pediatr (Phila). 2001;40(6):355-8.
16. Johnson ST, McFarland JG, Kelly KJ et al. Transfusion support with RBCs from an Mk homozygote in a case of autoimmune hemolytic anemia following diphtheria-pertussis-tetanus vaccination. Transfusion. 2002;42(5):567-71.
17. Montagnani S, Tuccori M, Lombardo G et al. Autoimmune hemolytic anemia following MF59-adjuvanted influenza vaccine administration: a report of two cases. Ann Pharmacother. 2011;45(1):e8.
18. Gani I, Hinnant G, Kapoor R et al. Autoimmune Hemolytic Anemia in a Renal Transplant Patient Following Seasonal Influenza Vaccination. Case Rep Hematol. 2019;2019:3537418.
19. Bowen L, LePage N, Lewandowska M et al. Anti-Pr antibody induced cold autoimmune hemolytic anemia following pneumococcal vaccination. Clin Case Rep. 2019;7(9):1763-65.
20. Shlamovitz GZ, Johar S. A case of Evans' syndrome following influenza vaccine. J Emerg Med. 2013;44(2):e149-51.
21. Jafarzadeh A, Jafarzadeh S, Pardehshenas M et al. Development and exacerbation of autoimmune hemolytic anemia following COVID-19 vaccination: A systematic review. Int J Lab Hematol. 2023 Apr;45(2):145-155.
22. Sogabe N, Kuno M, Nakagama Y et al. Warm autoimmune hemolytic anemia and IgM-monoclonal gammopathy following BNT162b2 COVID-19 vaccine in a patient with splenic marginal zone lymphoma. Rinsho Ketsueki. 2022;63(10):1379-1385.
23. Suzuki Y, Shiba T. Chronic cold agglutinin disease after a third COVID-19 mRNA vaccination. Int J Hematol. 2023; 117(4): 618–621.
24. Jacobs JW, Booth GS. COVID-19 and Immune-Mediated RBC Destruction. Am J Clin Pathol. 2022 Jun 7;157(6):844-851.
25. Angileri F, Légaré S, Gammazza AM et al. Is molecular mimicry the culprit in the autoimmune haemolytic anaemia affecting patients with COVID-19? Br J Haematol. 2020 Jul; 190(2): e92–e93.

This signal has been raised on June 21, 2023. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbg-meb.nl