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ORIGINAL ARTICLE

Subacute thyroiditis and COVID-19 vaccines: a case/non-case study

Montserrat García[1] · Itziar Albizua-Madariaga[2] · Unax Lertxundi[3] · Carmelo Aguirre[1,4]

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Abstract

Purpose Some case reports have suggested a possible association between COVID-19 vaccines and subacute thyroiditis (SAT), however, to our knowledge, no study has analyzed this possible relationship. This study aimed to analyze whether a disproportionate number of cases of SAT were reported in the EudraVigilance database for four COVID-19 vaccines (BNT162b2, mRNA-1273 ChAdOx1-S or Ad26.COV2.S).

Methods A case/non-case study was conducted to assess the association between SAT and COVID-19 vaccines, calculating the reporting odds ratios (RORs) up to December 2, 2021. Cases were selected using the preferred term 'subacute thyroiditis'. First, cases involving COVID-19 vaccines were compared with those involving all other drugs. Secondly, the RORs for COVID-19 vaccines compared with other viral vaccines (overall and influenza vaccines only) were obtained.

Results Until December 2, 2021, of 1,221,582 spontaneous cases of adverse reactions with the four vaccines, we found 162 SAT cases: BNT162b2 ($n = 103$), mRNA-1273 ($n = 27$), ChAdOx1-S ($n = 31$) and Ad26.COV2.S ($n = 1$). SAT cases were found to be reported more frequently in association with BNT162b2, mRNA-1273, and ChAdOx1-S vaccines than with other drugs. Moreover, we found a signal of disproportionate reporting for SAT with BNT162b2 and mRNA-1273 vaccines comparing with other viral vaccines (BNT162b2 ROR 3.58, 95% CI 1.92–6.66; mRNA-1273 ROR 3.44, 95% CI 1.71–6.94). However, this association was absent when these COVID-19 vaccines were compared with influenza vaccines.

Conclusions In EudraVigilance, SAT is relatively more frequently reported in association with mRNA COVID-19 vaccines than with other viral vaccines. Well designed observational studies are needed to confirm these results.

Keywords Subacute thyroiditis · COVID-19 vaccines · Pharmacovigilance · Disproportionality · EudraVigilance

Introduction

Subacute thyroiditis (SAT), also known as De Quervain's thyroiditis or granulomatous thyroiditis, is a self-limiting inflammatory disease of the thyroid gland associated with pain in the thyroid area and symptoms of hyperthyroidism. The disease should not be overlooked, since the associated thyrotoxicosis can aggravate the course of concomitant disorders (e.g., respiratory distress, diabetes mellitus), leading to multiple organ failure in extreme cases [1, 2]. Moreover, long-term sequelae, such as permanent hypothyroidism, have also been reported.

In the US, between 1970 and 1997, the incidence of SAT was around 12.1 cases per 100,000/year, with a higher incidence amongst women than men (19.1 and 4.1 per 100,000/year, respectively) [3]. SAT is presumed to be caused by a viral infection or a post-viral inflammatory process. Most patients have a history of upper respiratory tract infection prior to the onset of thyroiditis (usually 2–8 weeks before). Many viruses, such as Coxsackievirus, mumps, measles, influenza, and adenovirus have been described as being causative agents of SAT [4]. Cases of SAT have also been reported following COVID-19 [5]. SAT has also been associated with administration of the influenza vaccine [6].

✉ Montserrat García
farmacovigilancia@osakidetza.eus

1 Osakidetza Basque Health Service, Galdakao-Usansolo Hospital, Basque Country Pharmacovigilance Unit, Biocruces Bizkaia Health Research Institute, Barrio Labeaga 46 A, Galdakao 48960, Spain

2 Osakidetza Basque Health Service, Galdakao-Usansolo Hospital, Basque Country Pharmacovigilance Unit, Galdakao, Bizkaia, Spain

3 Bioaraba Health Research Institute, Osakidetza Basque Health Service, Araba Mental Health Network, Araba Psychiatric Hospital, Pharmacy Service, Gasteiz, Alava, Spain

4 Department of Pharmacology, Faculty of Medicine and Nursing, University of the Basque Country, Leioa, Spain

A number of vaccines have been developed in response to the coronavirus disease 2019 (SARS-CoV-2) pandemic. These vaccines have been produced with unprecedented speed using a variety of technologies. In order to allow for rapid evaluation of safety signals, active vaccine safety surveillance systems are essential. EudraVigilance, the centralized European database of suspected adverse reactions to medicinal products (including vaccines), is regularly used to identify possible safety signals. Unsurprisingly, with the roll-out of COVID-19 vaccination campaigns, new adverse events have emerged as vaccination rates increase.

Subacute thyroiditis is not mentioned in the Summary of Product Characteristics of COVID-19 vaccine brands. However, several cases of SAT have recently been reported following exposure to mRNA-based COVID-19 vaccines [7, 8], adenovirus-vectored vaccines [9], and inactivated virus vaccines [10]. In order to validate this possible safety signal, this study uses the European pharmacovigilance database (EudraVigilance) to analyze the potential disproportionality in reported cases of SAT associated with four COVID-19 vaccines,—namely BNT162b2 (Pfizer-BioNTech), mRNA-1273 (Moderna), ChAdOx1-S (Oxford/AstraZeneca), and Ad26.COV2.S (Johnson & Johnson's Janssen)—and to describe the characteristics of these cases.

Material and methods

We selected spontaneous reports of subacute thyroiditis recorded in EudraVigilance up to December 2, 2021, in which the involvement of BNT162b2, mRNA-1273, ChAdOx1-S, or Ad26.COV2.S vaccines was suspected.

For each individual case safety report, we retrieved demographic and clinical characteristics of the case and the country reporting it. We also retrieved information on adverse reaction (seriousness, start date of reaction and outcome). In addition, we evaluated the temporal and biological plausibility, taking into account the demographic and clinical characteristics of the case and the time to onset or TTO (time from the drug administration start date to the reaction start date, in days). Cases considered not to be sufficiently informative after careful evaluation were excluded.

A case/non-case analysis was performed to evaluate the association between exposure to COVID-19 vaccines and subacute thyroiditis. Cases were identified using the following preferred term (from the Medical Dictionary for Regulatory Activities, MedDRA, version 23.0): "subacute thyroiditis". The non-cases used as controls included all other adverse drug reaction reports recorded in EudraVigilance for the same period. Exposure was defined as being exposure to the administration of the vaccines of interest (BNT162b2, mRNA-1273, ChAdOx1-S, or Ad26.COV2.S) among cases and non-cases.

The case/non-case analysis calculated reporting odds ratios (RORs) and their 95% confidence Intervals (CIs) as a measure of disproportionality between a drug and a particular adverse drug reaction. The ROR was calculated using a two-by-two table, ROR = ad/cb (where a = exposed cases; b = exposed noncases; c = nonexposed cases; and d = nonexposed noncases). As per European Medicines Agency recommendations, a signal of disproportionate reporting is identified when the following conditions are met: the lower bound of the 95% CI of the ROR is >1, the number of individual cases is ⩾3. Litigation cases are excluded, and subgrouping is used by geographical region of reporting (North America, Europe, Japan, rest of Asia, rest of the world) [11]. Thus, in EudraVigilance a drug-event combination is a signal of disproportionate reporting if the lower bound of the 95% CI of the ROR is above 1 in one region and the number of individual cases is ⩾3 in the same region.

We performed analyses comparing BNT162b2, mRNA-1273, ChAdOx1-S, and Ad26.COV2.S vaccines with all other drugs listed in the entire EudraVigilance database. Subsequently, we also obtained the ROR of these COVID-19 vaccines compared with other viral vaccines (overall and restricted to influenza vaccines). For this purpose, viral vaccines were defined as being any drug from the J07B group (excluding COVID-19 vaccines) and influenza vaccines as being any drug from the J07BB group in the Anatomical Therapeutic Chemical classification system. Data management and statistical analysis were performed using software package SPSS Statistics version 27 (IBM, Armonk, New York).

Results

Descriptive data

During the study period, an estimated 627,500,000 doses of COVID-19 vaccines from BNT162b2, mRNA-1273, ChAdOx1-S, and Ad26.COV2.S were administered in the European Union/European Economic Area [12], and 1,221,582 spontaneous cases of adverse reactions were registered in EudraVigilance for these vaccines. Of these, 174 were subacute thyroiditis: 110 with BNT162b2, 30 with mRNA-1273, 32 with ChAdOx1-S and 2 with Ad26.COV2.S.

Twelve cases were excluded due to duplication, insufficient information or co-occurrence of SAT and autoimmune thyroiditis, leaving 162 cases: 103 with BNT162b2, 27 with mRNA-1273, 31 with ChAdOx1-S, and 1 with Ad26.COV2.S. Taking into account the number of COVID-19 vaccine doses administered and the number of SAT cases reported in the study period, the SAT reporting rate was 0.3 cases per 1 million doses administered.

The general characteristics of the cases are summarized in Table 1. Of the 162 patients, 120 (74.1%) were female.

Table 1 General characteristics of cases of subacute thyroiditis associated with COVID-19 vaccines in EudraVigilance

	BNT162b2 ($n = 103$)	mRNA-1273 ($n = 27$)	ChAdOx1-S ($n = 31$)	Ad26.COV2.S ($n = 1$)	All cases ($n = 162$)
Sex (n, %)					
Female	72 (69.9)	21 (77.8)	26 (83.9)	1 (100)	120 (74.1)
Male	31 (30.1)	6 (22.2)	5 (16.1)		42 (25.9)
Median age (years) (range)	47 (27–86)	42 (18–65)	50,5 (34–73)	29	48 (18–86)
Dose (*n*, %)					
1st	37 (35.9)	7 (25.9)	14 (45.2)	1 (100)	59 (36.4)
2nd	37 (35.9)	15 (55.6)	3 (9.6)	0	55 (34)
3rd	1 (1.0)	0	0	0	1 (0.6)
Unknown	28 (27.2)	5 (18.5)	14 (45.2)	0	47 (29)
Median TTO (days) (range)	12 (1–87)	7 (1–42)	10 (1–72)	7	10,5 (1–87)
Serious (*n*, %)	70 (68)	16 (59.3)	18 (58)	1 (100)	105 (64.8)
Outcome (*n*, %)					
Recovered	17 (16.5)	6 (22.2)	7 (22.5)	0	30 (18.5)
Recovering	25 (24.3)	10 (37.1)	8 (25.8)	0	43 (26.6)
Not recovered	50 (48.5)	5 (18.5)	14 (45.2)	1 (100)	70 (43.3)
Recovered with sequelae	1 (1)	0	0	0	1 (0.6)
Unknown	10 (9.7)	6 (22.2)	2 (6.5)	0	18 (11.1)
Region (*n*, %)					
Europe	84 (81.6)	21 (72.8)	31 (100)	1 (100)	137 (84.6)
United States of America	15 (14.6)	4 (14.8)	0	0	19 (11.7)
Japan	4 (3.9)	2 (7.4)	0	0	6 (3.7)

TTO time to onset

Two patients had a history of autoimmune thyroiditis. The median age was 48 years (18–86) and the median TTO until the appearance of SAT was 10.5 days (range 1–87 days). In 59 (36.4%) cases, the SAT occurred after the first dose, in 55 (34%) after the second dose, and in one after the third dose; for the other 47 cases (29%), no information was provided. The median TTO was 10 days following the first dose, as compared to a median TTO of 18.5 days after the second dose. At the time of the report, 70 (43.3%) of the patients had not recovered. In 56 cases (34.6%) the SAT occurred in spring, 41 (25.3%) in summer, 29 (17.9%) in winter, 3 (1.9%) in autumn. In 33 (20.4%) cases, the season was unknown.

One hundred five cases (64.8%) were classified as being severe according to EU criteria, with most of these being classified as medically important conditions ($n = 72$, 68.6%). Other criteria included causing hospitalization ($n = 28$, 26.7%) and being disabling ($n = 5$, 4.8%). Of the 28 cases requiring hospitalization, detailed information indicating the cause of hospitalization was only available for nine. In general, these relate to the persistence of symptoms and signs during the hyperthyroid phase: tachycardia, palpitations, persistent hyperthermia with inflammatory syndrome of undetermined origin, exacerbation of SAT with corticosteroid de-escalation, weight loss (7 kg in 1 month) and very high inflammatory markers. One patient received concomitant eculizumab and two patients received tamoxifen. At time of diagnosis, one patient had influenza-like symptoms, and another had an upper respiratory tract infection. In 21 patients, Covid-19 PCR testing proved negative and for 141 cases, no information was provided.

One patient experienced the SAT around three weeks after the first dose with the ChAdOx1-S vaccine and the symptoms reappeared two weeks after the second dose (positive rechallenge).

Disproportionality analysis

In EudraVigilance, BNT162b2, mRNA-1273, and ChAdOx1-S vaccines met the criteria for generating a signal of disproportionate reporting, suggesting that the number of cases is disproportionate—i.e., that this adverse event (subacute thyroiditis) is reported relatively more frequently in association with these COVID-19 vaccines than with other medicinal products. The association was strongest for BNT162b2, $n = 103$; ROR (95% CI) = 5.30 (4.23–6.65). There was also a signal of disproportionate reporting for SAT with BNT162b2 and mRNA-1273 vaccines as compared to other viral vaccines [BNT162b2 ROR 3.58, 95% CI (1.92–6.66) and mRNA-1273 ROR 3.44, 95% CI (1.71–6.94)], while no such signal was detected for the ChAdOx1-S vaccine [ROR 1.56, 95% (CI 0.79–3.11)]. Moreover, no such association was found when

Table 2 RORs for COVID-19 vaccines and subacute thyroiditis in EudraVigilance

Exposure	Cases, *n*	Noncases, *n*	ROR (95% CI)
a) Compared to all other drugs			
All drugs	380	9,199,026	Reference
BNT162b2	103	602,891	5.30 (4.23–6.65)
mRNA-1273	27	164,320	4.21 (2.84–6.22)
ChAdOx1-S	31	415,022	1.88 (1.30–2.71)
b) Compared to other viral vaccines			
Other viral vaccines	11	230,293	Reference
BNT162b2	103	602,891	3.58 (1.92–6.66)
mRNA-1273	27	164,320	3.44 (1.71–6.94)
ChAdOx1-S	31	415,022	1.56 (0.79–3.11)
c) Compared to influenza vaccines			
Influenza vaccines	5	52,842	Reference
BNT162b2	103	602,891	1.81 (0.74–4.43)
mRNA-1273	27	164,320	1.74 (0.67–4.51)
ChAdOx1-S	31	415,022	0.79 (0.31–2.03)

CI confidence interval, *RORs* reporting odds ratios

these COVID-19 vaccines were compared with influenza vaccines (Table 2).

Discussion

The disproportionality analyses in this case/non-case study based on the EudraVigilance database finds, for the first time, a signal of disproportionate reporting between BNT162b2, mRNA-1273, ChAdOx1-S vaccines, and SAT in an analysis of the full database. Notably, for the BNT162b2 and mRNA-1273 vaccines, this signal was confirmed when compared with other viral vaccines. Conversely, when compared with influenza vaccines, these COVID-19 vaccines did not display a signal for SAT.

A recent systematic review has described 51 published cases of SAT secondary to COVID-19 vaccines [13]. Almost three-quarters of the cases (74.5%) described were amongst women, and the median age was 39.5 years. Moreover, most patients in this review ($n = 33$) were vaccinated with an mRNA vaccine. The predominance of female patients is unsurprising, given that SAT has a higher incidence amongst this population [3]. In our study 120 (74.1%) of the 162 cases were in women and the median age was 48 years. In line with the results of the systematic review, our study shows that reporting of SAT with BNT162b2 and mRNA-1273 vaccines was disproportionately more frequent than with other viral vaccines.

The median time to onset was 10 days after the first dose and 18.5 days after two doses. These findings do not support the existence of a dose/response relationship between these COVID-19 vaccines and SAT. Despite information about the season was missing for around one-fifth of the reports, SAT cases did not follow any apparent seasonal trend and were distributed throughout all seasons of the year (except autumn); they therefore do not appear to be related to the peak incidence of respiratory tract infection. Moreover, although SAT was initially thought to have a seasonal incidence (higher in summer), in other case series, no significant difference was found in SAT occurrence by season [14].

In our study, an alternative possible etiology or exposure to other drugs was suspected in five cases. At the time that SAT was diagnosed, one patient had an influenza-like illness, and another was suffering from an upper respiratory tract infection. In addition, two patients were concomitantly receiving tamoxifen. Although the effect of tamoxifen on thyroid function has been the subject of debate, one study observed that tamoxifen treatment was accompanied by increases in thyroxine-binding globulin concentration levels, and secondarily in T4 concentration levels, without changes in thyroid-stimulating hormone levels [15]. Finally, another patient was concomitantly receiving eculizumab (a complement inhibitor), a drug that may increase the risk of infections, favoring the appearance of SAT.

At the same time, SAT cases have also been associated with COVID-19, with most such cases occurring in women aged under 50. The clinical features are similar to those cases resulting from other etiologies, and include neck pain, increase in inflammatory markers, and thyrotoxicosis [5, 16]. The expression of the SARS-CoV-2 receptor (angiotensin-converting enzyme 2) mRNA in follicular thyroid cells suggests that the thyroid might be a target organ of SARS-CoV-2 infection [17]. In our study, infection by the SARS-CoV-2 virus could not be ruled out, given the small number of cases for which data were available. At the same time, a systematic review of the published literature has called into question the possible relationship between COVID-19 and SAT, given that the relevant data published are low in terms of both quantity and quality and are only available as case reports and case series [18].

During the study period, the reporting rate for SAT associated with COVID-19 vaccines was very low. Nonetheless, this figure is likely to have been underestimated, given that SAT may go unnoticed by doctors due to the non-specific clinical symptoms with which it can begin and a lack of awareness of the possible association.

Several possible mechanisms by which COVID-19 vaccines might be associated with thyroid dysfunction have been advanced. First, vaccine adjuvants are used as immunogenicity-enhancing agents and are essential for directing the adaptive immune response. However, they can also trigger unwanted autoimmune reactions such as ASIA (autoimmune/inflammatory syndrome induced by adjuvants) [19]. Another possibility is that of cross-reactivity between viral spicule proteins produced by the vaccine and

certain antigens expressed on the surface of the thyroid follicular cell [20]. At the same time, severe COVID-19 has been associated with an uncontrolled systemic immune and inflammatory response, the so-called "cytokine storm," which resembles (at least in part) the immune activation occurring in immune-mediated thyroid diseases. Specifically, hyperactivation of the Th1 and Th17 response in peripheral lymphocytes has been described in patients with autoimmune and drug-associated thyroiditis and increased IL-6 in destructive thyroiditis [21]. Subacute thyroiditis might be a hyperinflammatory response in the context of the cytokine storm, which could result from an excessive innate immune response against COVID-19 vaccines in genetically predisposed patients.

As in any pharmacovigilance study based on spontaneous reporting, the limitations of this study include underreporting, overreporting and reporting bias. This makes it difficult to quantify the true incidence of this event. In addition, the presence of multiple confounding factors (comorbidity), and the absence of critical data hinders a proper causality assessment for some of the cases [22]. This disproportionality analysis is therefore helpful for identifying signals of disproportionate reporting, but may not be as useful for comparing risks, given that the ROR does not quantify the risk. Despite these limitations, however, one of the strengths of our study is its extent, given the large number of individual case safety reports (9,199,406 spontaneous cases in total), which enables rare adverse events to be detected. Moreover, these statistically significant signals offer hypotheses that could be studied in future research.

On the other hand, it is worth noting that a recent systematic review found only 51 cases of SAT while our study reports three times as many. This is very probably due to the fact that not all reported cases are actually published in scientific journals.

In conclusion, the findings of our pharmacovigilance study show that SAT was disproportionately more frequently reported with BNT162b2, mRNA-1273, and ChAdOx1-S vaccines than other medicinal products over the entire database. Moreover, this signal of disproportionate reporting persists when the BNT162b2 and mRNA-1273 vaccines are compared with other viral vaccines. Still, it should be noted that the benefit of COVID-19 vaccines outweighs the potential risk associated with SAT. Moreover, future observational analytical studies will be needed to confirm these results.

Author contributions M.G., U.L.: study concepts and data acquisition; M.G., I.A., U.L., C.A.: data analysis and interpretation; The manuscript was written by M.G. and reviewed by all the authors.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

Consent for publication All the authors involved in this study give their consent for this article to be published in Endocrine—International Journal of Basic and Clinical Endocrinology.

Ethical approval This study was approved by the institutional review board of Galdakao-Usansolo Hospital.

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