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Editorial

Dear Reader

At the start of the COVID-19 vaccination campaign, a number of non-serious and very frequent adverse events following immunization (AEFI) were already known from observations in controlled clinical trials.

Today, after billions of vaccinations have been administered worldwide, there are many new findings as regards adverse reactions to COVID-19 vaccines. One signal noted internationally is the onset of pericarditis/myocarditis following vaccination with mRNA vaccines. Three articles in this issue of Swissmedic Vigilance News deal with this topic: One covers reporting rates of myocarditis and/or pericarditis following primary and booster vaccinations with COVID-19 mRNA vaccines in Switzerland, while another looks at the risk of myocarditis following COVID-19 vaccination in children aged 5–11 years. A case report concerns a successful re-exposure with COVID-19 mRNA vaccine at a reduced dose in a patient with a history of clinically suspected pericarditis/myocarditis following the first dose of COVID-19 vaccine.

There are few examples of other signals in the literature, meaning spontaneous individual reports and case reports play a major role in recording and evaluating these previously unknown, rare AEFI in pharmacovigilance databases. Other articles in this issue concern the onset of persistent headaches, thromboembolic events and multiple sclerosis or MS relapses following vaccination with COVID-19 vaccines.

The AEFI recorded by Swissmedic are analysed and evaluated using a range of methods to detect potential signals. An article on signal detection using disproportionality analysis gives insights into this process, while another explains the use of "observed versus expected analyses" in post-marketing surveillance of COVID-19 vaccines.

Once a signal has been confirmed, appropriate risk mitigation measures are introduced. Modification of the information for healthcare professionals and/or patient information is usually necessary. The following pages contain an overview of updates for the COVID-19 vaccines authorised in Switzerland: Comirnaty® (tozinameran), Spikevax® (COVID-19 mRNA vaccine (nucleoside modified)) and COVID-19 Vaccine Janssen (COVID-19 vaccine (Ad26.COV2-S [recombinant]). As yet, there is no corresponding overview for the COVID-19 vaccine Nuvaxovid, which was authorised in April 2022.

Although the focus of pharmacovigilance efforts is currently on the COVID-19 vaccines, signals for other active substances are, of course, also being monitored. The case report "Unexpected cause of aphthous ulcers, diarrhoea and thrombocytopenia in a patient with COVID-19 vaccine breakthrough infection" recalls the issue of different methotrexate dosages.

The article on advanced therapy medicinal products (ATMP), in particular CAR-T cell (chimeric antigen receptor T cell) therapies, demonstrates yet another aspect of vigilance.

We hope you find this issue a stimulating and interesting read.

Eva Eyal

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Drug safety and signals: COVID-19 vaccines

COVID-19 vaccines: tabular overview of changes to warnings and adverse reactions in the Information for healthcare professionals

To date, four vaccines have been authorised in Switzerland for vaccination against the novel coronavirus (SARS-CoV-2): Comirnaty® (first authorised 19.12.2020), Spikevax (12.01.2021), COVID-19 Vaccine Janssen (22.03.2021) and Nuvaxovid (12.04.2022). These vaccines were already being very widely used shortly after launch as part of the global vaccination campaign to combat the COVID-19 pandemic. Thanks to this special starting situation, further knowledge of the safety profiles of these vaccines, such as very rare adverse effects, was obtained rapidly after authorisation. Inflammation of the heart muscle or pericardium in connection with the mRNA vaccines is one example of such adverse effects that were not observed during the authorisation studies. When indications of previously unknown risks are subsequently confirmed, the information for healthcare professionals (and if necessary the vaccine recommendations) are revised accordingly. The following table gives an overview of the changes that have been made to the "Warnings" and "Adverse reactions" sections of the information for healthcare professionals for the first three COVID-19 vaccines authorised.

The following table is available in German/French only.

Comirnaty®

Häufigkeit	Neu eingefügte Nebenwirkung	Rubriken
Nicht bekannt	Parästhesie, Hypoästhesie	Angstbedingte Reaktionen Erkrankungen des Nervensystems
Nicht bekannt	Ausgedehnte Schwellung der geimpften Gliedmasse, Anschwellen des Gesichts	Allgemeine Erkrankungen und Beschwerden am Verabreichungsort
	Bei Teilnehmenden, die in Studie 4 eine Auffrischimpfung (Boosterdosis) erhielten, wurde eine höhere Häufigkeit von Schmerzen in den Extremitäten (1,1 % vs. 0,8 %) beobachtet, verglichen mit Teilnehmenden, die 2 Dosen erhielten.	Skelettmuskulatur-, Bindegewebs- und Knochenerkrankungen
Gelegentlich	Lymphadenopathie: Bei Teilnehmenden, welche eine Auffrischimpfung (dritte Dosis) erhielten, wurde eine höhere Häufigkeit von Lymphadenopathie beobachtet als bei Teilnehmenden, die 2 Dosen erhielten (5,2 % gegenüber 0,4 %).	Erkrankungen des Blutes und des Lymphsystems
	Myokarditis und Perikarditis: Sehr seltene Fälle von Myokarditis und Perikarditis wurden nach der Impfung mit Comirnaty beobachtet. Diese Fälle traten häufiger bei jüngeren Männern und nach der zweiten Dosis des Impfstoffs auf, in der Regel innerhalb von 14 Tagen nach der Impfung. Die verfügbaren Daten deuten darauf hin, dass sich der Verlauf einer Myokarditis und Perikarditis nach einer Impfung nicht von dem einer Myokarditis oder Perikarditis im Allgemeinen unterscheidet.	Warnhinweise und Vorsichtsmassnahmen

	Medizinische Fachkräfte sollten in Bezug auf Anzeichen und Symptome von Myokarditis und Perikarditis wachsam sein. Geimpfte Personen sollten angewiesen werden, sofort einen Arzt oder eine Ärztin aufzusuchen, wenn sie nach der Impfung Symptome entwickeln, die auf Myokarditis oder Perikarditis hinweisen, wie (akute und anhaltende) Brustschmerzen, Kurzatmigkeit oder Herzklopfen. Medizinische Fachkräfte sollten Leitlinien beachten und/oder Spezialisten/Spezialistinnen konsultieren, um diesen Zustand zu diagnostizieren und zu behandeln.	
Nicht bekannt	Myokarditis, Perikarditis	Herzerkrankungen
	Angstbedingte Reaktionen, einschliesslich vasovagaler Reaktionen (Synkope), Hyperventilation oder stressbedingte Reaktionen (z. B. Schwindelgefühl, Palpitationen, Erhöhungen der Herzfrequenz, Blutdruckveränderungen, Gefühl des Kribbelns und Schwitzen) können in Zusammenhang mit der Impfung als psychogene Reaktion auf die Injektion mit einer Nadel auftretendem Impfprozess als solchem auftreten. Stressbedingte Reaktionen sind vorübergehend und klingen von selbst ab. Personen sollten darauf hingewiesen werden, dass sie solche Symptome dem Impfanbieter zur Abklärung mitteilen sollten.	Warnhinweise und Vorsichtsmassnahmen Angstbedingte Reaktionen
Gelegentlich	Appetit vermindert	Stoffwechsel- und Ernährungsstörungen
Gelegentlich	Lethargie	Erkrankungen des Nervensystems
Gelegentlich	Hyperhidrosis, nächtliche Schweissausbrüche	Erkrankungen der Haut und des Unterhautgewebes
Gelegentlich	Überempfindlichkeitsreaktionen (z. B. Ausschlag, Pruritus, Urtikaria, Angioödem).	Erkrankungen des Immunsystems
Nicht bekannt	Anaphylaxie, Überempfindlichkeit. Urtikaria und Angioödem wurden mit der Häufigkeit «selten» gemeldet.	
Sehr häufig	Diarrhoe (15,7 %).	Erkrankungen des Gastrointestinaltrakts
Häufig	Erbrechen	

Spikevax

Häufigkeit	Neu eingefügte Nebenwirkung	Rubriken
Selten	Parästhesie	Erkrankungen des Nervensystems
Nicht bekannt	Erythema multiforme	Erkrankungen der Haut und des Unterhautgewebes
Unbekannt	Myokarditis Perikarditis	Herzerkrankungen

COVID-19 Vaccine Janssen

Häufigkeit	Neu eingefügte Nebenwirkung	Rubriken
	Guillain-Barré-Syndrom und transverse Myelitis : Das Auftreten des Guillain-Barré-Syndroms (GBS) und der transversen Myelitis (TM) wurde sehr selten nach einer Impfung mit COVID-19 Vaccine Janssen berichtet. Medizinisches Fachpersonal soll auf Anzeichen und Symptome von GBS und TM achten, um eine richtige Diagnose sicherzustellen, angemessene unterstützende Massnahmen und die Behandlung einzuleiten und andere Ursachen auszuschliessen.	Warnhinweise und Vorsichtsmassnahmen
Nicht bekannt	Transverse Myelitis	Erkrankungen des Nervensystems
	Vorgeschichte eines bestätigten Thrombose-mit-Thrombozytopenie-Syndroms (TTS) nach einer Impfung mit einem COVID-19-Impfstoff	Kontraindikationen
	Blutgerinnungsstörungen	Warnhinweise und Vorsichtsmassnahmen
	Die Kombination von Thrombosen mit Thrombozytopenie erfordert eine spezifische fachärztliche klinische Behandlung. Medizinisches Fachpersonal sollte die geltenden Leitlinien zu Rate ziehen und/oder Spezialisten (z B. Hämatologen, Gerinnungsspezialisten) zur Diagnose und Behandlung dieser Erkrankung hinzuziehen. Immunthrombozytopenie: Fälle von Immunthrombozytopenie (ITP) mit sehr niedrigen Thrombozytenwerten (<20.000 pro µl) wurden sehr selten nach der Impfung mit COVID-19 Vaccine Janssen berichtet, in der Regel innerhalb der ersten vier Wochen nach der Verabreichung von COVID-19 Vaccine Janssen. Bei Personen mit ITP in der Vorgeschichte sollte vor der Impfung das Risiko der Entwicklung niedriger Blutplättchenwerte berücksichtigt werden, und nach der Impfung wird eine Überwachung der Blutplättchenwerte empfohlen. Kapillarlecksyndrom: In den ersten Tagen nach der Impfung mit COVID-19 Vaccine Janssen wurden sehr seltene Fälle des Kapillarlecksyndroms (Capillary-Leak-Syndrom (CLS)) berichtet. Einige dieser Fälle hatten einen tödlichen Ausgang. Über CLS in der Anamnese wurde berichtet. CLS ist eine seltene Erkrankung, die durch akute Episoden von Ödemen, die hauptsächlich die Gliedmassen betreffen, Hypotonie, Hämokonzentration und Hypoalbuminämie gekennzeichnet ist. Bei Patienten mit einer akuten CLS-Episode nach einer Impfung ist eine sofortige Erkennung und Behandlung erforderlich. In der Regel ist eine intensive unterstützende Therapie notwendig. Personen mit einer bekannten CLS-Vorgeschichte sollen nicht mit diesem Impfstoff geimpft werden.	Thrombosen mit Thrombozytopenie-Syndrom
Selten	Schwindelgefühl	Erkrankungen des Nervensystems
Nicht bekannt	Kapillarlecksyndrom (Capillary-Leak-Syndrom)	Gefässerkrankungen

	Thrombose mit Thrombozytopenie nach Verabreichung von COVID-19 Vaccine Janssen hat einen klinischen Verlauf, der der autoimmun Heparin-induzierten Thrombozytopenie (HIT) ähnelt. Personen, bei denen bereits eine CVST mit Thrombozytopenie oder Heparin-induzierte Thrombozytopenie (HIT) aufgetreten ist, sollten COVID-19 Vaccine Janssen nur erhalten, wenn der erwartete Nutzen die potenziellen Risiken überwiegt. Guillain-Barré-Syndrom: Das Auftreten des Guillain-Barré-Syndroms (GBS) wurde sehr selten nach einer Impfung mit COVID-19 Vaccine Janssen berichtet. Medizinisches Fachpersonal soll auf Anzeichen und Symptome von GBS achten, um eine richtige Diagnose sicherzustellen, angemessene unterstützende Massnahmen und die Behandlung einzuleiten und andere Ursachen auszuschliessen.	Warnhinweise und Vorsichtsmassnahmen
Sehr selten	Lymphadenopathie	Erkrankungen des Blutes und des Lymphsystems
Sehr selten	Parästhesie, Hypoästhesie, Guillain-Barré Syndrom	Erkrankungen des Nervensystems
Sehr selten	Thrombosen in Kombination mit Thrombozytopenie (Schwere und sehr seltene Fälle von Thrombosen in Kombination mit Thrombozytopenie sind nach Markteinführung berichtet worden. Diese schlossen venöse Thrombosen wie zerebrale Sinusvenenthrombosen, Splanchnikus-Venenthrombosen sowie arterielle Thrombosen ein).	Gefässerkrankungen
Sehr selten	Tinnitus	Erkrankungen des Ohrs und des Labyrinths
Sehr selten	Diarrhoe, Erbrechen	Erkrankungen des Gastrointestinaltrakts
	Vorgeschichte eines Kapillarlecksyndroms (Capillary-Leak-Syndroms (CLS)	Kontraindikationen

Reporting rates of myocarditis and/or pericarditis following basis and booster vaccinations with COVID-19 mRNA vaccines in Switzerland

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Here, we present an interim assessment of local reporting rates of myocarditis and/or pericarditis cases received by Swissmedic following booster immunisation (3rd dose) with mRNA vaccines. Although the COVID-19 immunisation programme is still ongoing, the number of vaccinations administered has visibly stabilised over recent weeks at national level, and hence the present estimates will most likely not change considerably towards the end of the vaccination campaign.

By 12 March 2022, Swissmedic had received 34 reports of myocarditis or pericarditis in relation to a booster vaccination against COVID-19. According to vaccination figures provided by the FOPH/BAG (1), approx. 3.61 million boosters have been administered in Switzerland so far, which results in an overall reporting rate of 9.4 cases of myocarditis/pericarditis per million booster doses of mRNA vaccines. Of these 34 cases, 18 were reported in association with Spikevax® (with 2.13 million booster doses administered) and 16 for Comirnaty® (1.48 million booster doses). These figures result in reporting rates of 8.4 cases of myocarditis/pericarditis per million booster doses of Spikevax and 10.8 cases per million booster doses of Comirnaty.

By 8 March 2022, 377 cases of myocarditis and/or pericarditis with a suspected link to mRNA vaccinations had been reported in Switzerland (3). Of these, 338 cases occurred in relation to approx. 12 million basis vaccine doses (1st/2nd dose), resulting in an overall reporting rate of 28.2 cases per million basis doses. Hence, the currently assessed reporting rate of myocarditis/pericarditis following booster vaccination (approx. 9.4 cases per million) is 3 times lower than the overall reporting rate following basis vaccination doses (28.2 cases per million).

With regard to the main mRNA vaccines currently in use in Switzerland, the following data trends are currently apparent.

For Spikevax, 266 myocarditis/pericarditis cases had been recorded by 8 March 2022 following 7.65 million basis vaccine doses (1st/2nd dose) administered, resulting in a reporting rate of 34.8 cases per million basis doses of Spikevax. This was > 4 times higher compared to the currently observed reporting rate of 8.4 cases for Spikevax booster (see above).

Of all cases recorded by 8 March 2022, 71 were reported in relation to Comirnaty, out of 4.31 million basis doses (1st/2nd dose), resulting in a reporting rate of approx.16.5 cases per million basis doses. The reporting rate of myocarditis/pericarditis for Comirnaty booster was 10.8 reports per million doses (see above) and thus lower compared to basis doses.

Table 1. Estimated reporting rates following mRNA COVID-19 vaccination, by vaccination dose and gender

Vaccine dose	Reporting rate estimates myocarditis/pericarditis per 1,000,000 doses	
	Female	*Male*
Cormirnaty 1st/2nd	9.8	21.4
Comirnaty booster	9.5	12.2
Spikevax 1st/2nd	14.7	53.9
Spikevax booster	3.7	13.1

The gender distribution (Table 1) shows higher reporting rates in males, particularly for basis vaccine doses (1st/2nd), which is consistent with data from previous pharmacoepidemiological studies (e.g. Ref. 2). The Spikevax booster shows lower reporting rates of myocarditis/pericarditis in both males and females.

The current reporting rates of myocarditis/pericarditis per million doses following booster vaccination are rather similar for Spikevax (8.4 cases) and Comirnaty (10.8 cases). However, the decline in reporting rates following booster vaccinations as compared with basis doses (1st/2nd dose) is more prominent (> 4 times) for Spikevax. There are several possible causes for this observation.

Firstly, the booster dose of Spikevax contains only half of the amount of the basis vaccine dose, i.e. 50 µg mRNA, which may possibly result in reduced incidence rates of various adverse reactions, including myocarditis/pericarditis.

In addition, national and international safety data have shown that inflammation of the heart muscle and heart sac in persons under 30 years of age was observed more frequently with Spikevax than with Comirnaty (3).The Swiss Federal Commission for Vaccination (FCV/EKIF) has subsequently reviewed the national vaccination recommendation for mRNA vaccines against COVID-19 (4), and only Comirnaty is currently recommended for use in persons below 30 years of age. Indeed, although reporting figures in particular age groups are still rather low for conclusive assessments, only a very small number of myocarditis/pericarditis cases was recorded in persons under 30 years following Spikevax booster.

Furthermore, general reporting awareness as regards myocarditis/pericarditis may have decreased in Switzerland during the booster vaccination campaign.

Although comparisons of spontaneous reporting rates for different vaccine doses at different time points during the vaccination campaign should be made with caution, there is currently no evidence that myocarditis/pericarditis is more frequent after booster vaccinations. Our data suggest that they could possibly occur less often than after the first two vaccination doses.

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Successful re-exposure to COVID-19 mRNA vaccination at a reduced dosage in a patient with clinically suspected pericarditis/myocarditis after a first dose of COVID-19 vaccine

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Introduction

Following the authorisation of the COVID-19 mRNA vaccines, cases of pericarditis/myocarditis have been described as very rare adverse drug reactions (ADR). These have occurred particularly in young males and more frequently after the second dose of vaccine. Since data on the course after re-exposure to a second dose of a COVID-19 mRNA vaccine following an episode of pericarditis/myocarditis in connection with COVID-19 mRNA vaccination are almost non-existent, specific recommendations for action in this situation are lacking. We report here on the re-exposure to a COVID-19 mRNA vaccine (tozinameran, Comirnaty®) at a reduced dosage (10 µg) in a male patient with a history of clinically suspected pericarditis/myocarditis connected with the first dose (elasomeran, Spikevax®).

Case narrative

A man who was 24-years-old at the time of the suspected ADR was actively immunised in the spring of 2021 against SARS-CoV-2-induced COVID-19 for the first time with elasomeran (Spikevax®, COVID-19 mRNA vaccine from Moderna). The patient had a history of asthma, hay fever and allergies to various foods and latex. For these conditions the patient took medication as required with formoterol / budesonide and cetirizine. After the vaccination (with a latency period of approx. 5 hours), he experienced swelling at the injection site. On the following day, the patient suffered fever, for which he took paracetamol, and shortly thereafter presented himself at an emergency department with palpitations and a resting pulse of 140/minute, although he was discharged home on the same day after an ECG showed normal findings. On the second day after the vaccination, he experienced aggravated symptoms of dyspnoea and chest pains related to exertion, position and respiration, which prompted his readmission to hospital. Laboratory tests showed elevated inflammatory parameters (CRP maximum: 63 mg/L), a dynamic troponin profile (peak: 28 ng/L) and normal D-dimer levels (259 µg/L, reference value: < 500 µg/L). The electrocardiogram recorded a sinus rhythm with a normal heart rate without re-/depolarisation abnormalities and with lateral PQ-segment depressions (V5/V6). With typical symptoms and minimally elevated cardiac enzymes over time, the patient was assumed to be suffering from pericarditis/myocarditis in connection with COVID-19 mRNA vaccination, while a viral origin was considered in the differential diagnosis (although there had been no symptoms of a viral infection before the vaccination). Treatment was started with colchicine and ibuprofen. This produced a positive outcome within a few days, and the patient could be discharged home in an improved general condition. However, the patient's subsequent recovery was slow, and he was unable to work at all for approx. 8 weeks. In June 2021, a blood sample tested negative for anti-nucleocapsid IgG, which suggested that the patient had not experienced a COVID infection as a trigger overlapping with the vaccination.

At the patient's request, and following a comprehensive discussion of the risk of a further episode of pericarditis/myocarditis associated with re-exposure to a second dose of a COVID-19 mRNA vaccine, he was given a reduced dose (10 µg instead of 30 µg) of the COVID-19 mRNA vaccine tozinameran (Comirnaty®) at the start of 2022. This dose was well tolerated by the patient, who merely reported pain at the injection site and tiredness, and otherwise experienced no further side effects and no fever. One month after the 10 µg dose of tozinameran, since the patient showed a very high SARS-CoV-2-IgG anti-spike protein titre (> 400 AU/ml resp. > 1040 BAU/ml), no further administration of a reduced dosage is currently planned.

In the spring of 2022, the patient suffered a COVID-19 infection with a moderate but self-limiting course without hospitalisation (three days of fever above 39°C, feeling very ill with headaches, coughing, sore throat, tiredness and exhaustion).

Discussion

At the start of the major vaccination campaigns (starting in Switzerland in January 2021, beginning with the defined risk groups as per the national vaccination strategy (1)), pericarditis/myocarditis was not a known adverse drug reaction (ADR) to COVID-19 mRNA vaccines. Cases of pericarditis/myocarditis occurring shortly after COVID-19 mRNA vaccinations were subsequently observed (2–4). After an evaluation of the data available at the time, in August 2021 Swissmedic reported a possible connection between mRNA COVID-19 vaccination and the onset of pericarditis/myocarditis (5). Most of the cases occurred within 14 days of the vaccination, more frequently after the second dose and in young men (5). The Swiss Information for healthcare professionals for Spikevax® (Moderna) and Comirnaty® (Pfizer) was revised accordingly. Chest pain, shortness of breath and palpitations were also listed as symptoms potentially indicative of pericarditis or myocarditis in the "Warnings and precautions" section (6).

The case report described here concerns a male patient with clinically possible pericarditis/myocarditis (7) but not with a probable or confirmed myocarditis diagnosis according to the CDC criteria, which are listed in Table 1 (8).

Table 1. Classification of the probability of myocarditis diagnosis according to CDC criteria (8)

Myocarditis diagnosis **probable**	Myocarditis diagnosis **confirmed**
1. Symptoms • Chest pain/pressure/discomfort • Dyspnea/shortness of breath • Palpitations	1. Symptoms • Chest pain/pressure/discomfort • Dyspnea/shortness of breath • Palpitations
2. Abnormal testing • Elevated troponin • Electrocardiogram (ECG or EKG) findings • Decreased function on echo or MRI • MRI findings consistent with myocarditis	2. Abnormal testing • Biopsy • Elevated Troponin AND MRI findings consistent with myocarditis
3. No other identified cause	3. No other identified cause

The precise mechanism explaining how pericarditis/myocarditis might occur after COVID-19 mRNA vaccination is not known (9). Various hypotheses, including a hyperimmune/inflammatory response, autoimmunity and delayed hypersensitivity, are currently under discussion (9).

Experts recommend that, until further safety data are available, those who develop pericarditis/myocarditis after mRNA COVID-19 vaccination should not receive any further

dose of a COVID-19 vaccine (10). If, after a risk assessment, the decision is made to administer a further dose of a COVID-19 vaccine, the pericarditis/myocarditis episode must at least have completely regressed beforehand (10). For men aged 18 and over who opt for a further dose of COVID-19 vaccine, some experts recommend the use of the COVID-19 vaccine from Janssen instead of the COVID-19 mRNA vaccines, although the increased risk of "thrombosis with thrombocytopenia syndrome" should be taken into account (10). It has also been recommended that those who have experienced a confirmed episode of pericarditis/myocarditis should receive, after being informed of the corresponding risks, a second dose of the COVID-19 mRNA vaccine from Pfizer (Comirnaty®), since the rate of reported cases of pericarditis/myocarditis is slightly lower for this vaccine than for the COVID-19 mRNA vaccine from Moderna (Spikevax®) (11).

Little information is available in the literature on re-exposure to a COVID-19 mRNA vaccine after an episode of pericarditis/myocarditis following an earlier COVID-19 vaccination. There are reports of individual patients who reacted with a further episode of pericarditis/myocarditis following a second vaccination (12) but also of two patients who received a second dose of vaccine after experiencing myocarditis without the reappearance of symptoms (13). An analysis from Canada (article not yet peer-reviewed/published, Public Health Ontario) showed evidence suggesting that the risk of pericarditis/myocarditis is reduced with a longer interval between the vaccine doses (14).

Conclusion

Reports of ADR during the post-marketing phase are extremely important for drug safety. Well-documented courses following re-exposure would be a great help in clinical decision-making in respect of the repeat administration of a vaccine or medicine to a patient after a previous adverse reaction. Unfortunately, such data are not recorded systematically. Additional data, ideally collected systematically, are urgently needed in order to better evaluate the safety of re-exposure to a COVID-19 mRNA vaccine after an episode of pericarditis/myocarditis. The interval between the preceding vaccine dose or adverse reaction and the re-exposure, the selected vaccine and its dosage for re-exposure are of particular interest. A comparison of cases with positive and negative rechallenges after re-exposure to a COVID-19 mRNA vaccine would facilitate the risk assessment for a re-exposure in an individual patient.

Until further safety data are available, an individual risk assessment should be carried out for patients who have developed pericarditis/myocarditis following COVID-19 vaccination before a further dose of a COVID-19 vaccine is administered. However, this is possible only to a limited extent because of the lack of data. For example, if the decision is taken to give a further vaccine dose to someone with a high personal risk of experiencing severe COVID-19, the considerations described above should be taken into account. Although clear dose dependence is not apparent for many adverse reactions, in the case described here a reduced dosage (10 µg) was administered after a prolonged interval (8 instead of 6 months) and was tolerated by the patient without the recurrence of symptoms. Whether a reduced vaccine dose for subsequent injections is beneficial generally in these situations cannot be determined on the basis of this single case report. If a reduced vaccine dose is administered, the immune response should subsequently be monitored by measuring the antibody titres.

Reporting adverse reactions

For reporting adverse drug reactions (ADR), Swissmedic recommends the use of its own reporting portal developed specifically for this purpose (Electronic Vigilance System, ElViS). All the necessary information about this system can be found at www.swissmedic.ch

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COVID-19 vaccination for children aged 5–11 years; low risk of serious vaccination reactions such as myocarditis or seizures

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On 29 October 2021 the *Food and Drug Administration (FDA)* extended the emergency authorisation for the Pfizer-BioNTech COVID-19 (BNT162b2) mRNA vaccine for children aged 5–11 years.

Between 3 November and 19 December 2021, approximately 8.7 million doses of the COVID-19 vaccine from Pfizer-BioNTech were administered to children aged 5–11 years in the USA. During that period, no other vaccines were authorised for this age group.

In the same period, the US database system VAERS (Vaccine Adverse Event Reporting System), which is operated by the *Food and Drug Administration (FDA)* and the *Centers for Disease Control and Prevention (CDC)*, received 4,249 reports of adverse events following vaccinations in this age group, which were analysed by CDC staff (1). In total, 4,149 (97.6%) of the VAERS reports related to non-serious events and 100 (2.4%) to serious events. The most commonly reported disorders and diagnostic findings among the 100 reports of serious adverse events were fever (29; 29.0%), vomiting (21; 21.0%) and elevated troponin levels (15; 15.0%).

The latter is indicative of myocarditis which, following COVID-19 vaccination, has appeared most frequently in male vaccine recipients aged 12–29 years (2). Of the 11 confirmed cases of myocarditis in the 5–11 years age group, seven children had recovered by the time of reporting while four were in the recovery phase.

Of the ten high-severity reports concerning seizures, two children had a febrile seizure, one child had a history of seizures, two children were believed to be developing a possible convulsive disorder and five suffered a first-time onset of seizures.

VAERS received two reports of fatalities during the evaluation period. These concerned two female children aged 5 and 6 years, both of whom had a complicated medical history and had already been in a critical condition prior to vaccination. According to the authors, the data available did not point to any causal link between death and vaccination.

These results confirm the good tolerability of the Pfizer-BioNTech COVID-19 (BNT162b2) mRNA vaccine in children aged 5–11 years, as already evident in the study reviewed for the authorisation and in an earlier evaluation of the US VAERS database (3, 4).

In Switzerland, Comirnaty® has been temporarily authorised for the vaccination of children aged 5–11 years since 10 December 2021. To date, Swissmedic has received 12 reports of adverse events from approximately 83,000 administered doses of Comirnaty® in this age group (as at 24 March 2022). Eight reports were non-serious while four were serious. In the latter cases, the following vaccination reactions were reported: abdominal pain, diarrhoea, vomiting, fever, loss of consciousness, febrile seizure, fatigue and headache.

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Reports of new daily persistent headache in a temporal context after receiving mRNA vaccines

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Headache is listed in the Information for healthcare professionals as a "common" side effect of the two pandemic vaccines Comirnaty® and Spikevax® (occurring in 1/10 to 1/100 vaccinated individuals). The Pharmacovigilance Unit of the Safety of Medicines division has received reports connected with Comirnaty and Spikevax from patients who experienced persistent headaches, sometimes occurring daily, after receiving COVID-19 vaccination with an mRNA vaccine. In some cases these had still not subsided after several weeks and, on the whole, responded poorly to analgesic medication. Neurological investigations did not usually reveal any finding that could have been explained as the cause.

In some cases these persistent headaches occurred in patients who had almost never previously suffered from headaches in their life.

As at 9 November 2021, 16 cases of persistent headache with symptoms lasting for at least four weeks and for which no clear cause could be found by neurological investigation had been identified. The patients were vaccinated with Spikevax in 13 cases and Comirnaty in three cases. Five cases occurred after the first dose of the vaccine and 11 cases after the second. The headaches affected 11 women aged between 26 and 63 and five men aged between 17 and 54. The average age in all 16 cases was 41.5 years. Most of the cases (n=13) were reported directly by the affected patients, while three cases were reported by healthcare professionals. In all 16 patients the headaches were still present at the time of the report. To investigate the symptoms, MRI scans of the head were carried out in ten patients, and a lumbar puncture was additionally performed in four cases, but none of these showed any indicative findings.

Painkillers administered were Novalgin (metamizole), Dafalgan (paracetamol), Tramal (tramadol), ibuprofen and Voltaren (diclofenac), but in most cases these only produced slight pain relief. In two cases the persistent headaches were treated with morphine preparations.

As representative examples, two patient case reports are described below.

First case report

Middle-aged woman, second dose of Spikevax:

"On the day after the vaccination I experienced severe, dull, crushing headaches across my forehead and down the side. These remained constant and no painkillers worked. A visit to the doctor after two weeks did not find anything. My condition then deteriorated: flashes in my head – I felt as if I were electrified and was unable to sleep for several nights. A few days later I underwent investigations in the Neurology department of a cantonal hospital. Nothing was found. I was prescribed a cocktail of painkillers over two days. The headaches have not disappeared, and I occasionally also have a burning headache across my scalp, but that is not constant. The dull, crushing pain has persisted for four weeks now. The headache is different from ones that I've had in the past, and it's always there. I've never had any problems to date with migraine or similar conditions. My doctor is unable to explain the headaches. My quality of life is seriously impaired and I had not had any health problems before."

Second case report

Younger woman, second dose of Comirnaty:

"Onset three hours after the second injection: nosebleed, headaches, dizziness. The

headaches persisted from then on (six weeks) and became more intense from week to week (most recently a 9 on the pain scale). As a result, I was unable to work at all. Normal analgesics (combination of Irfen [ibuprofen], Dafalgan and Novalgin) provided no, or only minimal, pain relief. Pain relief could only be achieved with tramadol in addition to the painkillers mentioned above. Increasing sensitivity to light and noise. Head MRI and lumbar puncture were normal."

Conclusion

Isolated reports received via the spontaneous reporting system indicate that the known and common side effect of "headache" can persist for a prolonged period in individual cases, requiring further diagnostic investigation and treatment.

A new meta-analysis of headache after vaccination against COVID-19 shows that headache represents the third most common adverse event, occurring in 22% and 29%, respectively, of vaccinated individuals after the first and second doses, although it also occurred in 10% to 12% of those receiving placebo (1). However, no evidence of cases of persistent headaches can be found, either in this meta-analysis or in the rest of the literature currently available to us.

New-onset persistent headache has a considerable negative impact on the quality of life of the sufferers. Whether a causal connection with the administered vaccinations exists, and how such a connection can be explained in pathophysiological terms, cannot be conclusively determined at this time. The described observations from the spontaneous reports have not been confirmed to date by published investigations. The new onset of headaches that persist for prolonged periods will continue to be monitored closely in connection with the monitoring of the safety profile of COVID-19 vaccines.

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mRNA COVID-19 vaccines and thromboembolic events

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Introduction

Since the start of COVID-19 vaccination, several cases of pulmonary embolism, myocardial infarction, or cerebrovascular events occuring with a reasonable chronological link to vaccination have been published. A slightly elevated risk of thromboembolic events has been confirmed for adenovirus vector-based vaccines (1–4), but a causal link with mRNA vaccines has yet to be established.

Methods

We analysed cases of thromboembolic events reported in 2021 to the Geneva Regional Pharmacovigilance Centre (RPVC) and reviewed the scientific literature on the subject.

Results

In 2021, the Geneva RPVC received 300 reports of adverse drug reactions associated with COVID-19 vaccines, 22 of which involved thromboembolic events. The majority of cases concerned women (n=14, 64%) with an average age of 76. The men were younger, with an average age of 48. The commonest thromboembolic events were pulmonary embolism (8 cases) and deep vein thrombosis (5 cases). Onset occurred after an average of 13 days (ranging from 1 to 44 days), while the majority of events (n=17, 77%) occurred within three weeks following vaccination. In 19 of the 22 cases of thromboembolic events following administration of an mRNA vaccine, at least one risk factor was present. By way of comparison, the total number of reports submitted in Switzerland for the same terms and same period was 392.

Table 1. Patient characteristics for 22 individual case safety reports processed by RPVC Geneva in 2021:

		Number (RPVC Geneva)	Number in Switzerland (as extracted from VigiLyze)
Age (years)	≥ 80	6	
	70-79	6	
	60-69	1	
	50-59	5	
	40-49	2	
	0-39	2	
Sex	Female	14	
	Male	8	
Adverse event preferred term (PT)*	Pulmonary embolism	8	178
	Deep vein thrombosis	5	95
	Haemorrhagic stroke	1	3

	Ischaemic stroke	1	47
	Cerebral thrombosis	2	5
	Cerebrovascular accident	1	27
	Thrombophlebitis	1	8
	Intestinal ischaemia	1	1
	Myocardial infarction acute	1	23
	Acute coronary syndrome	1	4
	Urticarial vasculitis	1	1
Delay between vaccination and AE occurrence (days)	1-21 days	17	
	22-44 days	5	
Suspected COVID-19 vaccine	Comirnaty®	9	
	Spikevax®	12	
	Unknown	1	
Dose	After first dose	10	
	After second dose	12	
Outcome	Fatal	2	
	Resolving	2	
	Resolved with sequelae	1	
	Resolved	14	
	Unknown	3	
Risk factors **	At least 3	1	
	At least 2	3	
	At least 1	9	
	Not known risk factors	6	
	Unknown	3	

* Patients may present more than one AE

** Reported risk factors for venous thromboembolism included: previous history of pulmonary embolism, peripheral vein thrombosis, malignancy, carotid artery stenosis, ischaemic cardiomyopathy, fracture (hip or leg), prolonged immobilisation (more than 3 days) and obesity (5).

Some medicines regulatory agencies, including ANSM (the French national medicines safety agency), Swissmedic, or Singapore's HSA, are currently monitoring thromboembolic events, particularly cases of cerebral venous sinus thrombosis associated with the Comirnaty and Spikevax vaccines and systemic ANCA-associated vasculitis associated with the Spikevax vaccine (6). Two cases of cerebral venous sinus thrombosis were reported to the Geneva RPVC in 2021:

Case no. 1: A 52-year-old woman with a history of disc herniation with sciatica which had been treated with dexamethasone for 12 days. Eighteen days after receiving her first dose of the Comirnaty® vaccine, she attended the emergency department after an episode of nausea, vomiting, confusion, and right-sided neck pain. She was given a brain

scan, the results of which were described as normal, and returned home. Three days later, she presented with sensory ataxia of her right arm, apraxia, and optic ataxia. She had two generalised tonic-clonic seizures in the emergency department. A cerebral angiogram identified cerebral venous sinus thrombosis of the right superior sagittal sinus, extending to the right internal jugular vein with parenchymal haematoma in the left parietal area, haemorrhagic transformation of the lower left parietal area and signs of venous stasis. While she was in the hospital, hormonal, inflammatory, infectious, and neoplastic causes were ruled out. Thrombophilia screening was negative, but the family history included pulmonary embolism with a fatal outcome in the patient's father. The patient was put on curative anticoagulation for a minimum of three months. Her symptoms improved gradually while she was in hospital.

Case no 2: A 50-year-old man with a history of left fronto-parietal grade III anaplastic astrocytoma for which he had received radiotherapy and chemotherapy and with a history of treated secondary epilepsy. The day after receiving his second dose of Spikevax®, he presented with slight paresis of the lower right face, slight aphasia, and moderate dysarthria. A cerebral MRI scan revealed subacute venous thrombosis of the left transverse and sigmoid sinuses extending to the root of the left internal jugular vein. The patient's history included very frequent and painful headaches for two weeks and an increase in the number of epileptic seizures. No personal or family history of venous thromboembolic disease was reported. The patient was put on long-term curative anticoagulation in response to his suspected paraneoplastic coagulant state. His clinical progress was positive, with neurological normalisation and a distinct decrease in headaches.

Discussion

Several case reports of thromboembolic events have been published since mRNA COVID-19 vaccines were first launched (7–11), but none has established a causal link with the vaccines. Several case-control studies have been conducted to assess this potential association. Thus, adverse events such as cerebral venous sinus thrombosis, myocardial infarction, Bell's palsy, Guillain Barré syndrome, myocarditis and pericarditis, pulmonary embolisms, cerebrovascular accident (CVA), and thrombotic thrombocytopenia syndrome were investigated in a recent US study of 6.2 million individuals (average age 49, 54% women) who had received an mRNA COVID-19 vaccine. The incidence of these events in the period up to the 21st day following vaccination (regarded as the risk period) was not significantly higher than the incidence in the period from 22 to 44 days after vaccination (control period) (12).

A national-scale study in France of people aged 75 and over who had received the BNT162b2 mRNA vaccine evaluated the relative risk of presenting myocardial infarction, haemorrhagic or ischaemic CVA, and pulmonary embolism. No evidence was found of an increased risk of these adverse events in the 14 days following the first or second dose of the vaccine (13). In January 2022, the same group of French pharmaco-epidemiology experts (EPI-PHARE) published a second study, which set out to evaluate the short-term risk of acute myocardial infarction, haemorrhagic or ischaemic CVA, and pulmonary embolism after administration of the BNT162b2, mRNA-1273, Ad26.COV2.S and ChAdOx1 nCoV-19 vaccines in subjects aged between 18 and 74. This study investigated a population of more than 46 million subjects, from which every individual who had experienced a severe cardiovascular event needing hospital admission was included. The incidence of the different events did not differ significantly between the three weeks

following the first, second or third dose of mRNA vaccine (BNT162b2 and mRNA-1273) and the reference periods (4).

Finally, an Israeli study of nearly 900,000 subjects who had received the BNT162b2 mRNA vaccine and a control group with the same number of subjects did not find any increased risk of cerebrovascular events in the 42 days following vaccination (21 days after the first dose of vaccine plus 21 days after the second) (14). However, BNT162b2 was strongly associated with a risk of myocarditis, lymphadenopathy, appendicitis, and herpes zoster infection. This same article also presented the data of a 173,106-person cohort (average age 34, 54% women) who had been infected with SARS-CoV-2. Notably, SARS-CoV-2 infection increased the risk of presenting myocarditis and pericarditis, renal failure or arrhythmia, as well as thromboembolic events such as pulmonary embolism, deep vein thrombosis, myocardial infarction and intracranial haemorrhage.

Conclusion

The case-control studies published to date show no evidence of an increased short-term risk of thromboembolic events following administration of mRNA COVID-19 vaccines. The risk of thromboembolic events is greater and potentially longer-lasting following SARS-CoV-2 infection. Thus, despite spontaneous reports of post-vaccination thromboembolic events, the benefits of using mRNA vaccines largely outweigh the risks.

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Multiple sclerosis and COVID-19 vaccines

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Introduction

Multiple sclerosis (MS) is a chronic, progressive neurological disease in which, on the one hand, an autoimmune response leads to demyelination and, on the other, genetically related dysmyelination can occur in the central nervous system (CNS). A distinction is made in diagnosis between three main forms: relapsing-remitting MS, primary progressive MS and secondary progressive MS. The first symptoms of MS usually appear between the ages of 15 and 45, with an average range at diagnosis of 28–31 years, and MS affects women more often than men. Other risk factors for the development of MS include a genetic predisposition (primarily changes in the HLA-DRB1 locus), other autoimmune diseases, viral infections, smoking, being overweight in childhood, the microbiome and geographic factors (1). Cases of CNS demyelination after the administration of various vaccinations, for example against influenza, human papillomavirus (HPV), hepatitis A and B, measles and rubella, are also documented in the literature, although there is still no clear evidence showing a causal link between the onset of MS and these vaccinations (2). Since a wide variety of vaccines has been associated with MS in the past in the literature, the question also arises in the context of the COVID-19 pandemic as to whether the newly authorised COVID-19 vaccines can also cause multiple sclerosis. Since vaccination as a trigger for a relapse in someone with pre-existing MS has also been discussed in the past, the question also arises for patients who have already been diagnosed with MS as to whether the SARS-CoV-2 vaccines may lead to a deterioration in the disease, and whether COVID-19 vaccination is beneficial, safe and effective.

Case reports

In January 2022, the Zurich Regional Pharmacovigilance Centre (RPVC) received three case reports of multiple sclerosis occurring shortly after vaccination with Spikevax (elasomeran) or Comirnaty® (tozinameran):

Case 1: A 33-year-old male patient was vaccinated against COVID-19 with two doses of Spikevax. Two weeks after the first dose, he experienced the onset of episodes of progressive hypoaesthesia with fluctuating, stabbing pains. These symptoms increased after the second dose. About one month after the second vaccine dose, an MRI scan showed spinal cord lesions at the level of thoracic vertebrae 10/11. After further investigations, a relapsing form of multiple sclerosis was diagnosed for the first time. Further details on the outcome of this case were not yet available at the time of the report.

Case 2: A 26-year-old female patient experienced episodes of tingling paraesthesia for the first time four days after the first dose of the COVID-19 vaccine Comirnaty® (tozinameran). The patient also suffered fine motor deficits in her left hand. Four months after vaccination, an MRI scan detected several demyelination foci, and relapsing multiple sclerosis was subsequently diagnosed. A three-day treatment with high-dose steroids and immunomodulatory therapy was started with Tecfidera® (dimethyl fumarate). The subsequent course of this case is not yet known.

Case 3: A 45-year-old female patient received two doses of the COVID-19 vaccine Spikevax (elasomeran) and, two days after the second dose, first noticed a warm sensation in her left leg, followed by tingling on the side of her thigh and pain. Two weeks later, the symptoms had regressed completely. After a few more weeks, the patient

experienced two further episodes of weakness, dysaesthesia and tingling in her legs and arms. This patient also had a documented history of several episodes of paraesthesia and tingling (for the first time in 2018), and these had always subsequently regressed. Three months after the vaccination, an MRI showed several demyelinating lesions at the level of the cervical spine. Relapsing-remitting multiple sclerosis was diagnosed. The patient was treated with Solu-Medrol® (methylprednisolone), which produced an improvement in her symptoms.

Discussion

COVID-19 vaccines as triggers of MS or MS relapses

The onset of MS or an MS relapse has not been mentioned to date as an adverse drug reaction to COVID-19 vaccines in their respective Swiss product information texts (3).

The international spontaneous reporting system includes reports of the onset of multiple sclerosis after COVID-19 vaccination. However, when interpreting cases from spontaneous reporting systems, it must always be borne in mind that an assertion about an actual causal connection cannot usually be made since, for example, risk factors or non-drug-related causes often remain unknown. After the administration of over 15 million vaccine doses in Switzerland (4), the WHO pharmacovigilance database currently contains just 13 suspected reports of "multiple sclerosis acute and progressive (High-Level Term, HLT)" for "elasomeran" and seven suspected reports for "tozinameran" in Switzerland. No cases of MS after the administration of the COVID-19 Vaccine Janssen in Switzerland are currently listed in the WHO database. According to the VigiBase disproportionality analysis, the Reporting Odds Ratio (ROR) for all three vaccines, both for "multiple sclerosis (PT)" and "multiple sclerosis relapse (PT)", is still under 0.3 (lower limit of the 95% confidence interval likewise ≤ 0.3), which means that fewer MS cases than expected have been reported after COVID-19 vaccinations (as at 5 April 2022) (5).

Several more case reports of new-onset MS and MS relapses after COVID-19 vaccinations are also documented in the literature. For example, a review by Ismail and Salama identified 12 cases of CNS demyelination with a clinical presentation of MS after COVID-19 vaccinations up to 30 September 2021 (over a period of 10 months). Six of these patients with previously diagnosed MS suffered an MS relapse after vaccination; only a clinically isolated syndrome had previously been identified in one male patient newly diagnosed with MS, while another male patient had previously experienced neurological episodes (without a diagnosis of MS). Four patients suffered their first MS episode after the COVID-19 vaccination. Women were affected in 11 of the 12 documented cases. The median age of the affected patients was 33.5 years (24–48 years), and the median period between the COVID-19 vaccination and the onset of the clinical symptoms was six days (1–21 days). Half of the patients developed the MS symptoms after the first dose of the COVID-19 vaccine. Nine patients received an mRNA vaccine, and two patients were immunised with a vector vaccine (6).

In both the case reports of the Zurich RPVC and those of the review by Ismail and Salama, more women than men were affected by an MS event after COVID-19 vaccination. According to the literature, approximately two-thirds of MS disorders affect women. This may be due to a stronger immune response to foreign and self-antigens in women than in men (7). One article in the literature also reports that those with a history of a suspected or diagnosed autoimmune disease are at higher risk of devel-

oping a new (additional) autoimmune disorder than those without a previous immune-mediated disease (8). None of the cases reported to the Zurich RPVC or included in the review by Ismail et al. had a documented history of an autoimmune disease.

A precise mechanism to explain how a COVID-19 vaccination could lead to an autoimmune disorder such as MS is not currently known (6). Moreover, since autoimmune diseases are presumably caused by multiple factors, it is unlikely that COVID-19 vaccination would be the single trigger for the development of MS (9).

A causal connection between the COVID-19 vaccines and the onset of MS is currently doubtful. It should also be borne in mind that very large numbers of people have been immunised against COVID-19 and that cases of newly-diagnosed MS or MS relapses will have therefore inevitably occurred shortly after vaccination without necessarily implying a causal link (6). A meta-analysis conducted in 2011 showed that the causal evidence for the onset of MS after various vaccines was insufficient (10). Moreover, an analysis of data from the Vaccine Adverse Event Reporting System (VAERS) managed by the CDC (Centers for Disease Control and Prevention) and the FDA (Food and Drug Administration), showed that COVID-19 vaccinations were also not associated with an increased risk of neuroautoimmune adverse events: Compared to other vaccines routinely administered in adulthood, the COVID-19 vaccines have the lowest ROR for neuroautoimmune adverse effects, at 0.246 (median ROR for the other vaccines: 0.292; $p<0.0001$) (11). According to the Swiss Multiple Sclerosis Society, despite the millions of vaccine doses administered, including to MS sufferers, no evidence has been found of an increased risk of an MS relapse after COVID-19 vaccination. However, the authors do mention that flu-like symptoms, such as a raised temperature after vaccination, can temporarily exacerbate previous MS symptoms, and they suggest that the raised temperature reduces the nerve conductivity of previously damaged nerve pathways, but without triggering an inflammation in the central nervous system (as occurs in a relapse) (12). In a study from Israel, such exacerbations resembling MS relapses were observed in 2% of MS patients after the first dose and in 4.8% after the second dose. The rates of actual MS relapses observed after the COVID-19 vaccinations during the study (2.1% after the first dose and 1.6% after the second dose) corresponded to the rates of MS relapses in patients who had not received a vaccination in the years before the pandemic (ranging from 2.3–2.9%). Therefore, this study also failed to show a link between COVID-19 vaccination and increased MS disease activity (13). No clear evidence can be found in the literature at this time to indicate a causal connection between COVID-19 vaccination and the onset of MS or the triggering of an MS relapse. In view of the increased risk of contracting an infectious disease during an immunomodulatory or immunosuppressive MS treatment and the possibility of suffering from a serious illness with complications, the benefit of COVID-19 vaccination appears to outweigh the risks according to the current data situation.

COVID-19 vaccination recommendations for MS patients

The immunomodulatory treatment of MS patients can pose a challenge for an effective immunisation against COVID-19. However, no officially approved guidelines currently exist for this situation. In their review, Cabreira et al. stress that the COVID-19 vaccination schedule should be precisely coordinated depending on the treatment in each case in order to achieve the best possible effect. The review also includes a number of

vaccination recommendations. If the immunotherapy has not yet started, administration of the COVID-19 vaccination is recommended immediately if possible (ideally at least two weeks before the start of treatment) (14, 15). The authors also mention that, during treatment with interferon-ß, glatiramer acetate or natalizumab, a COVID-19 vaccination can be administered at any time, since the relevant studies have not shown a reduced response to the vaccination. If the patient is taking dimethyl fumarate, fingolimod or teriflunomide, a vaccine can also basically be administered at any point in the treatment although, given the risk of lymphopenia and therefore an increased risk of infection during the treatment, vaccination is recommended as soon as possible. To ensure that the effect of the COVID-19 vaccination is as strong as possible, a pre-vaccination lymphocyte count is also recommended. However, it has been observed that the COVID-19 vaccination in MS patients with lymphopenia resulted in a weakened, though still protective, immune response. Since other drugs, including the anti-CD20 antibodies (e.g. ocrelizumab), can lead to a reduced immune response to the vaccination, it is recommended that, in addition to the lymphocyte count, the COVID-19 vaccination should ideally be administered towards the end of a cycle with these medicines. This means, for ocrelizumab for example, that vaccination should be started, at the earliest, 12 weeks after the last dose of a cycle but should be completed, at the latest, four to six weeks before the next cycle. In order to ensure an adequate immune response to the COVID-19 vaccination, the antibody status should be determined in all severely immunosuppressed patients following the vaccination and, if the levels are low, a further vaccination should be considered (14). The Swiss MS Society recommends an antibody test four weeks after administration of the second COVID-19 vaccine dose. If an adequate antibody reaction is still not detected after a third vaccination, a fourth vaccination is not recommended (12).

Conclusion

A few cases of new-onset multiple sclerosis and MS relapses in connection with COVID-19 vaccination have been documented in the literature to date. However, it should be borne in mind that very large numbers of people have been vaccinated during the pandemic and that new MS cases or MS relapses will have therefore inevitably occurred shortly after vaccination. No evidence of a causal link has been found to date. According to the current data situation, the COVID-19 vaccines can continue to be considered as safe both for those with and without a history of MS and therefore constitute an important measure in reducing the risk of COVID-19 infection in MS patients as well.

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Signal detection by disproportionality analysis in the monitoring of COVID-19 vaccine safety in Switzerland

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Since COVID-19 vaccines have been approved and used in large scale vaccination campaigns, Swissmedic has been conducting intensive surveillance activity on their safety. Initial knowledge of the vaccines' safety from pivotal randomised clinical trials was limited and concerned mostly common local and systemic adverse events related to vaccine immunogenicity occurring a short time after vaccination (1, 2). Pharmacovigilance activities with the collection and analysis of spontaneous reports from healthcare professionals and patients are therefore of paramount importance in identifying potential unknown risks (3). Indeed, by 8 March 2022, Swissmedic and the regional pharmacovigilance centres had evaluated more than 10,000 spontaneous reports of suspected adverse events following immunisation (AEFI) associated with COVID-19 vaccines, which occurred among 6,105,171 vaccinated people who received at least one dose. Notably, spontaneous reports handled by Swissmedic are shared with VigiBase®, the global database of the World Health Organization (WHO) Programme for International Drug Monitoring. In this way, the Swiss reports are also available for the international identification of potential signals. Furthermore, the WHO database offers the possibility of signal detection activities by means of disproportionality analysis.

Signal detection in spontaneous reports associated with COVID-19 vaccines first relies on a case-by-case analysis by clinically qualified assessors who take into account detailed information provided by reporters. This includes the timing and course of the AEFI, as well as background information such as the number of vaccines administered. However, with the number of reports increasing, the clinical review could benefit from the use of statistical methods for signal detection (4). In light of this, the Institute of Pharmacological Sciences of Southern Switzerland, in close collaboration with Swissmedic, set up a signal detection activity by disproportionality analysis in VigiBase® using spontaneous reports originating from Switzerland and concerning AEFI associated with the Moderna (Spikevax®) and Pfizer/BioNTech (Comirnaty®) COVID-19 vaccines. To this end, disproportionality analyses have been routinely performed at national level and by vaccine type. These included the measurement of the reporting odds ratios (ROR) for COVID-19 vaccine/AEFI combinations meeting predefined statistical signal detection criteria. These criteria were a minimum of five reports concerning a COVID-19 vaccine/AEFI combination and an ROR lower limit of a 95% confidence interval greater than one to reduce the likelihood of false positives. In the ROR calculation, the numerator is the number of reports concerning a specific AEFI reported in association with a suspected COVID-19 vaccine divided by the number of reports of adverse events other than the one of interest with the same COVID-19 vaccine. The denominator is the number of reports of the AEFI of interest among all other drugs presented in the database divided by the number of reports of adverse events other than the one of interest among all other drugs. Excluding AEFI

either already labelled in the Swiss information for healthcare professionals for the Moderna (Spikevax®) and Pfizer/BioNTech (Comirnaty®) vaccines, or already debated internationally, a panel of pharmacovigilance and clinical pharmacology experts from both our Institute and Swissmedic are examining and discussing findings on novel and unexpected COVID-19 vaccine/AEFI combinations in order to promptly detect COVID-19 vaccine-related safety concerns that could warrant further investigation. One possible next step to evaluate such a potential safety signal could be an observed vs. expected analysis of a specific reaction which additionally takes into account the natural background incidence of a reaction. Since the start of signal detection activity in August 2021, an early signal of disproportionate reporting in VigiBase® for paraesthesia with the Moderna (Spikevax®) vaccine was detected in Switzerland. This occurred a few months before the same signal was assessed and validated by the European Medicines Agency, which ultimately added paraesthesia to the European summary of product characteristics for the Moderna (Spikevax®) vaccine (5).

Disproportionality analysis has some limitations. First, the absolute number of reports and the level of disproportionality are not indicative of the frequency of the adverse event in the population. Second, the reporting rate, defined as the number of reports divided by the number of vaccines administered, cannot be interpreted as an incidence rate. Third, spontaneous reports suffer from reporting biases including underreporting and notoriety bias. Nevertheless, by properly weighing findings from disproportionality analysis against its limitations, continued research on newly identified safety signals can provide valuable information to support public health, guide regulatory decisions and design specific follow-up confirmatory studies.

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Observed versus expected analyses in the post-marketing surveillance of COVID-19 vaccinations

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In the post-marketing surveillance of vaccines, *observed versus expected analyses* (OE analyses) have established themselves as an important tool in quantitative pharmacovigilance and have also been used internationally for COVID-19 vaccines (1). The primary role of OE analyses is to check the evidence for possible side effects arising from spontaneous reports. New illnesses or symptoms may also occur purely by chance shortly after a vaccination. An OE analysis can delve deeper into this situation to establish whether the number of reports of a particular symptom or illness after a vaccination is higher than would be expected if no vaccination had been administered.

Two variables are considered in the OE analysis: firstly, the number of cases actually reported ($N_{observed}$) and, secondly, the expected number of chance cases ($N_{expected}$) over a specified time period. If a particular adverse event after a vaccination is identified as a possible signal, the risk interval is first determined, e.g. 21 days after the vaccination. The calculation of expected cases ($N_{expected}$) in this time period includes the background incidence rate of adverse events and what is termed the *person-time at risk*, i.e. the persons exposed to the vaccination during this period.

Example of a calculation:

The background incidence rate for a particular reaction is e.g. **15.5 cases per 100,000** person years. If 1,000,000 people are vaccinated in 21 days, this gives a *person-time at risk* of: 1,000,000 × 21 *[person-days]* or 1,000,000 × 21/365 × 1/100,000 [100,000 *person-years*] = **0.57 [100,000 *person-years*].** The expected number of cases ($N_{expected}$) in this example corresponds to: background incidence rate × *person-time at risk* = **0.57 × 15.5 = 8.8**. The background incidence rate is often taken from publications and should correspond to a non-vaccinated population with demographic characteristics that are similar to those of the exposed group.

Since a spontaneous reporting system is assumed to involve *under-reporting* (= not all occurring cases are reported), this factor can be included in the calculation. Assuming, for example, that only 50% of cases are reported, the number of observed cases can be doubled in order to create a more realistic picture. Thus, if two cases of a reaction after vaccination are observed within 21 days, and taking into account an *under-reporting* rate of 50% , this gives an O/E ratio of **4/8.8 = 0.45**. The final output of an analysis is a ratio. If this is <1, as in our example, then fewer cases were observed than expected. A value greater than 1 corresponds to an increase and may be indicative of a signal.

The OE analysis is based on a series of assumptions: the number of vaccine doses administered is known, realistic estimate of the *under-reporting* rate, background incidence rate is roughly similar in the vaccinated population and the non-vaccinated comparative population, and the selected risk interval in days corresponds to the period in which the reaction can actually occur (i.e. is not too short or too long) (1).

OE analyses are useful for promptly checking the evidence from spontaneous reports, particularly if quick conclusions about the safety of a vaccine are needed, or if the event of interest occurs shortly after the administered vaccination, e.g. within three weeks.

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Methotrexate

Case report: Unexpected cause of aphthous ulcers, diarrhoea and thrombocytopenia in a patient with COVID-19 vaccine breakthrough infection

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Case narrative

A 71-year old female patient was hospitalised with COVID-19 pneumonia resulting from a breakthrough infection two months after receiving a booster shot of Spikevax®, Moderna Switzerland GmbH. She had a history of ductal breast carcinoma with lymphatic and bone metastases for which she had been receiving treatment with fulvestrant (Faslodex®) and palbociclib (Ibrance®) for more than 18 months. She also had a history of peripheral arterial occlusive disease and hypothyroidism. In addition to the oncologicals, the following medication was recorded on admission: acetylsalicylic acid (Aspirin Cardio®), amlodipine (Amlodipin Pfizer®), candesartan (Candesartan Sandoz®), rosuvastatin (Rosuvastatin Mepha®), lorazepam (Temesta®), allopurinol (Zyloric®), levothyroxine (Eltroxin®), nimesulide (Nisulid®) and oxycodone/naloxone (Targin®).

In addition to a general deterioration in condition, fever, painful limbs and lateral pain in the right knee, the patient reported that she had been experiencing loss of appetite and pronounced pain in her mouth with aphthous ulcers and angular cheilitis for two to three weeks and diarrhoea (occasionally bloody) and stomach pain for three to four days. Antibiotic treatment with i.v. ceftriaxone was initiated for probable cellulitis of the right lower leg and additional bacterial superinfected COVID-19 pneumonia. In addition, thromboprophylaxis with dalteparin was started.

Tests on admission revealed elevated creatinine of 146 µmol/l (calculated GFR after CKD-EPI 31 ml/min/1.73 m^2). The non-steroidal anti-inflammatory (NSAID) nimesulide was discontinued. The following day's tests showed a drop in platelet count from 94 to 44 G/l; the following day, this value fell to 27 G/l. Blood cultures showed *Streptococcus pyogenes* bacteremia focused on the cellulitis of the right lower leg. The patient's general condition deteriorated and she was septic, despite the commencement of antibiotic treatment. In the differential diagnosis, heparin-induced thrombocytopenia, haemolytic uraemic syndrome, thrombotic thrombocytopenic purpura, idiopathic immune thrombocytopenic purpura and folic acid and vitamin B12 deficiency were excluded as the cause of the fall in platelet count. In view of the diagnostic assessment, splenomegaly seemed unlikely from an aetiological standpoint, and calculating the DIC score revealed no evidence of current severe disseminated intravascular coagulation.

Given the ultimately unclear symptom complex (COVID-19 breakthrough infection despite having had a booster two months pre-

viously, fall in platelet count, leukopenia, intra-oral aphthous ulcers and diarrhoea), the patient's history was reviewed again in detail and the oncology centre responsible for her treatment was consulted. Two days after she was admitted to hospital, this line of active enquiry revealed that the patient possibly had rheumatoid arthritis for which she had been receiving low-dose methotrexate treatment (10 mg/week s.c.) for about three months.

Since the patient was suspected to be experiencing methotrexate intoxication resulting from an acute deterioration in kidney function and interaction with the NSAID, she was given 10 mg i.v. calcium folinate four times a day for one week as well as a platelet concentrate for her platelet count, which had by then fallen to 17 G/l. The patient's kidney function deteriorated further while she was in hospital. An ultrasound scan ruled out a postrenal cause. A urine test indicated that the renal impairment was most likely due to mixed prerenal and renal factors. Severe tubular proteinuria and crystals in the patient's urine sediment were compatible with kidney injury associated with methotrexate intoxication. In the differential diagnosis, additional tubular necrosis with initially longer sepsis-associated hypertension seemed plausible.

While the patient was in hospital, her oxygen saturation levels fell as a result of the COVID-19 pneumonia and she was therefore given temporary oxygen therapy and a course of dexamethasone (Fortecortin®) lasting seven days. Haemodynamically relevant pulmonary embolism was excluded. The patient's platelet count subsequently normalised and her kidney function improved significantly. Methotrexate was discontinued. The cause of the sudden and dramatic drop in platelet count was subsequently identified as a combination of methotrexate accumulation associated with the acute deterioration in kidney function, sepsis with *Streptococcus pyogenes* bacteremia and COVID-19 pneumonia. After four weeks, the patient was discharged for rehabilitation in a good general condition.

Discussion

The risk of accidental overdosage with low-dose methotrexate has been known for many years. In Switzerland, Swissmedic and Patient Safety Switzerland repeatedly addressed the issue in specialist publications intended for medical professionals in November 2012 and December 2015 (1, 2, 3). Nevertheless, cases continued to occur, so in January 2016 a package of measures that included a boxed warning on the packaging and in the Information for healthcare professionals and Patient information as well as a patient card was adopted in Switzerland. Furthermore, the authorisation holders issued a DHPC in June 2016 with the aim of avoiding accidental methotrexate overdose in Switzerland.

Longer-term measures were also adopted, including a restriction on pack sizes/dosage strengths or specialities authorised separately by indication. Thus, in July 2016, Methotrexat-Mepha rheuma/derm was approved as the first preparation in Switzerland to carry a name that restricted use to rheumatology and dermatology.

Despite all efforts, methotrexate still tops the list of medications that cause serious or even fatal adverse drug reactions (4, 5). We are using this case report to highlight the persistently topical nature of the risk of methotrexate intoxication.

According to the WHO's VigiBase database (accessed via VigiLyze), 959 reports of adverse drug reactions to methotrexate were registered in Switzerland between 2016 and 2021 (see table 1). Of these, 46 involved cases with a fatal outcome. 184 cases – or

around 20% of reports – were reported using the Preferred Terms "Accidental exposure to product, Accidental overdose, Overdose, Product administration error, Product prescribing error or Incorrect dose administered" (6). According to these data, one in five adverse drug reactions to methotrexate were connected with the wrong dosage or incorrect administration. In 2018, there was a clear decline in the number of ADR to methotrexate compared to the two previous years, and this decline has persisted since then. We see the cumulative effect of the measures that have been discussed and implemented since the beginning of 2016 as the cause for this development. The fall in 2021 could also stem from reporting bias, since pharmacovigilance reporting during that year focused on COVID-19 vaccines both in Switzerland and internationally.

Table 1: Data from the WHO pharmacovigilance database concerning methotrexate in Switzerland 2016-2021

	2016	2017	2018	2019	2020	2021
Number of ADR cases for MTX in VigiLyze in Switzerland per year	233	258	118	158	105	87
Of which fatal cases	12	11	4	7	3	9
Of which reported under PT Accidental exposure to product	66	35	9	5	1	0
Of which reported under PT Accidental overdose	6	1	2	6	1	1
Of which reported under PT Overdose	9	3	1	1	1	0
Of which reported under PT Product administration / prescribing error	12	5	0	9	0	0
Of which reported under PT Incorrect dose administered	4	1	0	1	2	2

The commonest causes of incorrect dose administration for methotrexate are (7, 8):

- Interfaces: Communication problems and misunderstandings result in incorrect dispensing and use – for example when treatment changes from once-weekly s.c or i.m injection to tablets or, as in this case, when information gets lost when the patient is admitted to hospital.
- Incorrect prescription owing to lack of specialist knowledge; failure to adapt dose to reduced [renal function] or acute or chronic renal impairment; failure to take account of drug interactions (as in the present case – concomitant administration of NSAIDs can result in renal impairment and thus encourage methotrexate accumulation).
- Dispensing: Unclear written instructions, for example the use of abbreviations, where "M" could stand for Monday or midday.
- Use: Patient fails to take the medication correctly because the timing of doses has changed; confusion with prophylactic folic acid.

Accidental methotrexate overdosage is primarily observed in cases where patients have to take or apply the medication daily rather than weekly (8, 9). However, overdosage can also occur with once-weekly dosage, for example as a result of drug interactions or acute deterioration in renal function, as in the present case.

Unintentional intoxication is often attributable to interface issues where information is lost owing to communication problems or misunderstandings between inpatient and outpatient care teams. In our case, a crucial piece of information was not communicated when the patient was admitted to hospital, resulting in a transitory deterioration in her condition and in time being lost until calcium folinate was administered.

There could be various reasons for the decline in reported ADR to methotrexate observed in Switzerland since 2018. The awareness among healthcare professionals has been heightened by the measures that have been introduced and, in addition, technological systems such as computerised prescribing systems or pharmacy software issue warnings when the medicine is prescribed and dispensed.

During 2021/2022, the Patient Safety Foundation is running an investigation into the use of low-dose methotrexate and precautionary measures to prevent accidental overdosage (10). The results of this investigation are keenly anticipated.

Conclusion

This case report spotlights the importance of pharmacovigilance as a way of identifying long-known ADR. Owing to its different indications, dosages and use regimens, its narrow therapeutic index, the need to adjust dosages and its contraindication in patients with renal or hepatic impairment, methotrexate is a high-risk substance in terms of serious adverse drug reactions.

Through the stakeholders' efforts, the measures implemented to date have reduced the number of such incidents. According to VigiLyze, a higher than average number of ADR to methotrexate were registered in Switzerland in 2016 and 2017. The number of reported cases has been stagnating since 2018, and in 2021 it declined further.

All involved healthcare professionals should work with the affected patients to avoid adverse events in connection with low-dose methotrexate. Regular reviews of methotrexate dosage, renal function and issuing repeated instructions to patients are essential in doing so, as are careful documentation and communication at interfaces.

Reporting adverse reactions

For reporting adverse drug reactions (ADR), Swissmedic recommends the use of its own reporting portal developed specifically for this purpose (Electronic Vigilance System, ElViS). All the necessary details can be found at www.swissmedic.ch.

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Advanced Therapy Medicinal Products

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Advanced Therapy Medicinal Products (ATMP) are a new class of biopharmaceutical agents that can be used for the targeted treatment of patients. Produced mainly from genes, tissues or cells, ATMP have opened up new possibilities for treating cancers, as well as rare genetic, neurodegenerative and infectious diseases.

These products are evolving extremely rapidly because we now have a better understanding of the pathogenic and molecular mechanisms of diseases, and tools have been developed for transferring specific genes and transporters and enabling precise targeting. A substantial number of ATMP for numerous indications, containing various active substances and with differing administration routes, are currently being developed worldwide. The most active regions are North America and Europe, and Switzerland is among the leading countries in this field.

From the legislative standpoint, ATMP are considered to be equivalent to medicines and are therefore subject to the Swiss Therapeutic Products Act. However, the evaluation criteria and the type and volume of the analytical, preclinical and clinical data required to demonstrate quality, safety and efficacy are specific and differ, to a certain extent, from those in traditional pharmaceutical practice due to the biological and functional properties of ATMP and their particular risks. On the other hand, the need for patients to have fast access to medicinal products for treating hitherto incurable illnesses necessitates a rapid, but adequate, assessment of the benefit-risk profile for these products.

In January 2022, a new Advanced Therapy Medicinal Products division (the former Transplant Unit) was formed at Swissmedic with the aim of responding to these specific requirements. The ATMP division is tasked with the regulatory and scientific oversight of all ATMP in the strict sense of the term (products for gene therapy, somatic cell therapy and tissue engineering), but also of other products for which genetic information is introduced into the somatic cells, including oligonucleotides, mRNA or antisense RNA (asRNA). The remit of this division also includes interventions related to autologous grafts and other products such as bacteriophages, the transfer of microbiota, procedures for inactivating pathogens in the blood, and non-standardised medicines.

The new ATMP division is responsible for all activities connected with these types of medicines or procedures, including inspections, marketing authorisations (MA), clinical trial authorisations and biovigilance.

The existing – relatively low – level of commercialisation of ATMP is due to the complexity of these technologies and the associated manufacturing and research processes. Currently, 21 advanced therapy medicinal products have received a marketing authorisation (MA) in Switzerland (including three out of four authorised COVID vaccines), which is comparable with the authorisations granted in other countries. On the other hand, between 15 and 20 applications for the authorisation of clinical trials are submitted each year.

Some of the applications for MA and for the authorisation of clinical trials relate to CAR-T (chimeric antigen receptor T-cell) products. These are immunotherapies that employ genetically modified T lymphocytes with the aim of equipping them with specific receptors and causing them to attack certain types

of malignant cancers of the blood or lymphatic system. These treatments need to take numerous factors into account, from the collection of the cells, via the production, transport, storage and administration to the patient, through to the short- and long-term follow-up of the patient. Each of these stages can affect both safety and efficacy, because the very principle of this therapy, which is based on "living" medicines, induces potentially severe side effects.

CAR-T products are currently used to treat cancers such as DLBCL (diffuse large B-cell lymphoma), primary mediastinal large B-cell lymphoma, B-cell acute lymphoblastic leukaemia (B-ALL), mantle cell lymphoma, etc., and experience has shown that they can successfully prolong the lives of numerous patients. However, these products occasionally cause serious adverse events which, if not recognised and treated promptly, can even lead to the death of the patient. Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), tumour lysis and cytopenias are common side effects and pose challenges in the treatment of patients. This specific toxicity profile means that the risks need to be managed by trained personnel in a specialist hospital setting. The treatments based on CAR-T cells therefore require close monitoring in hospital, with daily checks for at least ten to twelve days. Strict procedures must be put in place to monitor each indication in order to improve the management of risks and knowledge of these risks. Treatment with tocilizumab and steroids may be needed in an emergency and should be available.

Below are a few examples of adverse events that occurred in Switzerland with products manufactured from CAR-T cells and which werde observed for marketed products or during clinical trials. These examples were obtained from biovigilance reports for ATMP received in 2021. Only the most significant cases requiring a prolonged hospital stay are mentioned. Over this time period, no deaths were reported in connection with these treatments.

Examples from marketed CAR-T products:

An evaluation of 19 treated patients revealed four who had experienced a serious (CRS) and/or neurotoxic (ICANS) adverse effect during the six-month period covered by the report in 2021:

1) Grade 2 cytokine release syndrome (CRS) with a neurotoxicity syndrome associated with CAR-T cell therapy (ICANS) and pulmonary oedema (resolved);
2) Neurotoxicity syndrome associated with CAR-T cell therapy (toxic and metabolic encephalopathy);
3) Neurotoxicity syndrome associated with CAR-T cell therapy (ICANS), toxic and metabolic encephalopathy;
4) Grade 3 neurotoxicity syndrome associated with CAR-T cell therapy (ICANS 3 – resolved).

Examples from CAR-T products used in clinical trials:

1) G4 hemiparesis in connection with an ICANS (immune effector cell-associated neurotoxicity syndrome)
2) G3 convulsive seizures in connection with an ICANS (immune effector cell-associated neurotoxicity syndrome)
3) Macrophage activation syndrome (MAS)
4) Elevated LDH, coagulopathy, CRS, haemophagocytic lymphohistocytosis (HLH), elevated ferritin
5) Life-threatening grade 3 CRS with hepatotoxicity and DIC between one and eight days after treatment. On day 9, the patient also suffered potentially fatal symptomatic sinus bradycardia.

Since the products are obtained by leukapheresis and manufactured specifically for a patient, the established specifications are not always respected. In these cases, the need to take decisions based on the benefit-risk profile and to deviate from the strict established procedures was a significant factor.

Adverse events that were not connected with the treatment generally involved disease progression or early relapses (even in the presence of CAR-T cells that were still detectable). Some patients also reported that their underlying condition had progressed when the production of the CAR-T cells was still incomplete or in the first few months after the treatment (often due to an early relapse). On the other hand, it has been reported that some of the patients who are cancer-free for more than six months to a year after the treatment can then remain relapse-free for up to several years .

As shown by the above examples, CAR-T products all cause similar adverse effects. It should be noted that the serious adverse effects related to treatment with CAR-T products do not stop any cancer treatment from being successful. Some patients who had to be hospitalised for long periods because of serious adverse events remained nevertheless relapse-free for up to five years or more. The accumulation of knowledge and improved risk management are making these treatments increasingly promising.

Information on the Swissmedic website

In focus

COVID-19 Pandemic

Information on the new coronavirus (SARS-CoV-2)

Side effects of COVID-19 vaccines in Switzerland

06.05.2022
Reports of suspected adverse reactions to COVID-19 vaccines
15,228 reports of suspected adverse vaccination reactions evaluated

08.04.2022
Reports of suspected adverse reactions to COVID-19 vaccines
14,624 reports of suspected adverse vaccination reactions evaluated

11.03.2022
Reports of suspected adverse reactions to COVID-19 vaccines
13,388 reports of suspected adverse vaccination reactions evaluated

11.02.2022
Reports of suspected adverse reactions to COVID-19 vaccines
12,334 reports of suspected adverse vaccination reactions evaluated

14.01.2022
Reports of suspected adverse reactions to COVID-19 vaccines
11,467 reports of suspected adverse vaccination reactions evaluated

17.12.2021
Reports of suspected adverse reactions to COVID-19 vaccines
10,842 reports of suspected adverse vaccination reactions evaluated

Healthcare Professional Communication

Some of the links are available in German/French only

19.04.2022
DHPC – Anagrelid-haltige Arzneimittel
Erhöhtes Thromboserisiko einschliesslich Hirninfarkt nach abruptem Absetzen der Behandlung

17.03.2022
DHPC – Ocaliva® (Obeticholsäure)
Einschränkung der Indikation aufgrund des Risikos von schweren Leberschäden

28.02.2022
DHPC – Dexdor® (Dexmedetomidin)
Belege für erhöhtes Mortalitätsrisiko bei Intensivpatienten ≤ 65 Jahren, wenn Dexmedetomidin zur tiefen Sedierung angewendet wird

15.02.2022
DHPC – Alecensa® (Alectinib)
Warnhinweise und Vorsichtsmassnahmen sowie spezifische Anleitung zur Dosisänderung im Falle einer hämolytischen Anämie

21.01.2022
DHPC – Diazepam-Mepha rectal, Mikroklisma
Wichtige sicherheitsrelevante Mitteilung

03.12.2021
DHPC – Mitem 20 mg, Pulver zur Herstellung einer Injektions- bzw. Infusionslösung oder zur Herstellung einer Lösung zur intravesikalen Anwendung
Wichtige Mitteilung – für Spitalapotheker und Anwender in Urologie und Onkologie

Announcements

Some of the links are available in German/French only

18.05.2022
Spikevax COVID-19 vaccine for children up to 5 years: application for indication extension submitted
Swissmedic is reviewing application from Moderna Switzerland GmbH

13.05.2022
Moderna COVID-19 vaccine authorised in Switzerland for children aged 6 to 11 years
Swissmedic approves application for indication extension of Spikevax® for children 6 years and older

12.05.2022
Regulatory training for French-speaking authorities in May 2022
Swissmedic training courses

04.05.2022
Update – Warning about supposedly herbal products
Swissmedic is issuing an urgent warning regarding slimming products and other supposedly natural products

04.05.2022
Technical requirements for the submission of clinical trial applications for medicinal products
The technical requirements have been summarised and clearly presented.

01.05.2022
Out-of-Stock – COVID-19 – Authorisations for the temporary import and distribution of human medicines – Update
Licences in accordance with art. 22 para. 3 of the COVID 19 Ordinance 3

01.05.2022
Questions and answers on the packaging and labelling requirements for medicinal products intended to prevent or combat COVID-19
new version

01.05.2022
Changes to guidance document Authorisation procedures for COVID-19 medicinal products during a pandemic HMV4
Clarifications on the prioritisation and fast-tracking of pandemic medicinal products and on the patient information requirements

20.04.2022
Important information – Comirnaty, concentrate for the manufacture of a dispersion for injection for children 5 to < 12 years of age
New shelf life at ultra-low temperature

20.04.2022
Important information – Comirnaty, concentrate for the manufacture of a dispersion for injection for individuals 12 years of age and older
New shelf life at ultra-low temperature

13.04.2022
Swissmedic grants temporary authorisation for the Nuvaxovid COVID-19 vaccine from Novavax
Protein-based vaccine from manufacturer Novavax authorised in Switzerland

12.04.2022
Twelve rather than nine-month shelf life for Pfizer/BioNTech vaccine «Comirnaty»
The Agency for Therapeutic Products has reviewed the application and approved the extension

05.04.2022
Public Consultation on Guidelines of the International Council for Harmonisation (ICH Guidelines)
Swissmedic procedure for public consultation on ICH Guidelines

01.04.2022
Update to Guidance document "Information on PSUR / PBRER submission"
This guidance document enters into force on 1 April 2022 with a transitional period of 30 days.

01.04.2022
Aid for Ukraine: export of medicinal products to the conflict area – update
Swissmedic recommends cooperation with established aid organisations

01.04.2022
Reporting quality defects
The form for notifying a quality defect is now also available online.

28.03.2022
Empfehlung bezüglich COVID-19 für die autologe Blutstammzellspende
Beschluss Vorschriften SBSC – Blutstammzellspende

23.03.2022
Swissmedic information event «Regulatory & Beyond»
Save the date: 20 September 2022

23.03.2022
Changes to the guidance document Formal requirements HMV4 and the form Import of a medicinal product according to Art. 14 (2) TPA (parallel import) HMV4
ZL_00_020e_WL / ZL106_00_002e_FO

16.03.2022
HPC – Pharmasin 200 ad us. vet., Injektionslösung
Neue Absetzfristen bei Rindern und Schweinen reactions evaluated

08.03.2022
War in Ukraine: export of medicinal products to the conflict area
Private individuals should support Ukraine via aid organisations

03.03.2022
Update of the information sheet - Unique identification number (CHRN – Swiss Single Registration Number)
Additional information on the unique identification number (CHRN – Swiss Single Registration Number)

01.03.2022
Miracle Mineral Supplement (MMS), COVID-19 lozenges and other "wonder drugs": Swissmedic issues another warning against contact with the caustic substance chlorine dioxide
Sodium chlorite products in the form of lozenges pose a considerable risk to health

01.03.2022
Changes to template for Information for healthcare professionals VMP / Changes to template for Package leaflet VMP
The revised templates are valid as of 1 March 2022

25.02.2022
Authorisations of human medicinal products with a new active substance and additional indications 2021
Overview of new authorisations 2021

21.02.2022
Illegal imports 2021: Swissmedic seizes significantly more packages than in 2020
Buying prescription-only medicinal products online from unknown sources is risky

16.02.2022
Authorised complementary and herbal medicinal products
This report provides, among other things, an overview of the number of authorisations of complementary and herbal medicines with indication and complementary medicines without indication in 2021.

15.02.2022
Validity of GMP certificates during the COVID-19 pandemic
Further detail

14.02.2022
Authorisation application submitted for the COVID-19 vaccine from Novavax
Another COVID-19 vaccine under review

10.02.2022
Current status of authorisations for combating COVID-19
Astra Zeneca submits application for authorisation of antibody combination to prevent COVID-19

02.02.2022
HPC – Vetmulin Premix 10% ad us. vet., Arzneimittelvormischung
Anpassung der Rubriken «Anwendungsgebiete» und «Dosierung und Art der Anwendung»

01.02.2022
Use of titanium dioxide in medicinal products
The pharmaceutical excipient titanium dioxide remains permissible in Switzerland until further notice

28.01.2022
New versions of the application forms for establishment licences apply from 28 January 2022

28.01.2022
Early revision of ordinance on veterinary medicinal products legislation
The implementing ordinances revised under the revision of the ordinance on veterinary medicinal products legislation came into force on 28 January 2022.

20.01.2022
Training as a specialist in pharmaceutical medicine at Swissmedic
Swissmedic certified as a category A training institution

19.01.2022
Important information – Spikevax, dispersion for injection
Extension of the shelf-life from 7 to 9 months for storage

18.01.2022
Pfizer submits authorisation application for Paxlovid for treatment of COVID-19
New oral medicinal product Paxlovid (active substances nirmatrelvir/ritonavir) for the treatment of COVID-19 in rolling review process

14.01.2022
Swissmedic grants temporary authorisation to Xevudy® for COVID-19 patients
Corona medication Xevudy from GlaxoSmithKline (containing the active substance sotrovimab) granted temporary authorisation in Switzerland

13.01.2022
Swissmedic grants temporary authorisation to Regkirona® for COVID-19 patients
Corona medication Regkirona from iQone Healthcare Switzerland (containing the active substance regdanvimab) granted temporary authorisation in Switzerland

07.01.2022
Questions on delimitation
Information on unauthorised products such as teas or capsules containing senna

05.01.2022
New list of the (Direct) Healthcare Professional Communications (DHPC/HPC)
published by Swissmedic from 01.01.2018 onwards

03.01.2022
Report regarding suspected illegal trading in medicinal products
The form for submitting a report is now only available online.

01.01.2022
Changes to the guidance document Project Orbis HMV4
Change in procedure for Project Orbis: Swissmedic information requests now to be sent exclusively to the applicant in Switzerland

01.01.2022
Changes to the guidance document Temporary authorisation of human medicinal products HMV4
Simplification of the procedure for “ex officio" temporary authorisation

01.01.2022
Happy Birthday Swissmedic

30.12.2021
Update of the information sheet on the obligations of economic operators
Swissmedic has updated the information on the indications of the Swiss authorised representative and the importer on the product and its accompanying documents

27.12.2021
Swissmedic approves "Ronapreve®" for COVID-19 patients
Coronavirus medication Ronapreve from Roche (with the active substances casirivimab and imdevimab) approved in Switzerland

27.12.2021
Swissmedic approves booster dose with the COVID-19 vaccine from Janssen-Cilag AG
Persons aged 18 years and older can now receive a booster dose after a first vaccination.

22.12.2021
HPC – Bravecto spot-on ad us. vet., Lösung zum Auftragen auf die Haut bei Hunden und Katzen
Vorsichtsmassnahmen für die Anwendung

20.12.2021
HPC – Enzaprost ad us. vet., Injektionslösung
Neue Wartezeit für essbare Gewebe beim Rind

20.12.2021
Clinical trials on medicinal products
Paperless submission as of 01 January 2022

17.12.2021
ICH and IPRP meetings – Swissmedic has ICH Assembly Vice-Chair once more
Swissmedic supports the ICH's ongoing development into a global initiative

16.12.2021
Easier access to the Electronic Vigilance Reporting Portal (ElViS) for pharmacists via hp-id
Healthcare professionals can now use their Healthcare Professional Identity (hp-id) to access ElViS

The complete list is available at the following web address www.swissmedic.ch/updates-en