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From the Director and the Editor

As part of the celebrations of INFARMED's 30th anniversary, to mark the 30th anniversary of the National Pharmacovigilance System and the 1st Pharmacovigilance Day, a commemorative session was organized last December 13th.

The session included an exhibition of posters of research work in the field of pharmacovigilance, selected from several submitted to INFARMED.

In this issue of the Bulletin and in the upcoming ones, a selected set of those posters will be published, so that they can reach a wider audience. We start with a paper analyzing the impact of the COVID-19 pandemic on the profile of adverse reactions (ADRs) reported in general. Next, two regional pharmacovigilance units illustrate the profile of ADRs received in the context of COVID-19 vaccination in the following two sub-groups of immunised populations: women and healthcare professionals. Finally, two other studies look at specific ADRs: facial paralysis and ocular reactions.

INDEX CARD

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The Impact of the COVID-19 Pandemic on Spontaneous Reporting of Adverse Drug Reactions in the Central Region of Portugal

Joana Abrantes[1,2,3], Inês Tavares[1,2,3], Ana Penedones[1,2,3], Daniel Figueiredo[1], Diogo Mendes[3], Carlos Alves[2,3] , Francisco Batel Marques[1,2,3]

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www.aibili.pt (Encore publication)

Introduction

The COVID-19 pandemic has had an impact on several sectors of the society. Whether it has disrupted drug safety monitoring is yet to be determined.

Aim

To investigate whether the COVID-19 pandemic has had an impact on the proportions of spontaneous reports (SRs) of serious and unexpected adverse drug reactions (ADRs).

Methods

SRs received by the Coimbra Pharmacovigilance Unit (UFC) between January 2017 and December 2021 were included, except for those containing COVID-19 vaccines as suspected medicines.

The SRs were categorized into two groups: pre-pandemic (2017-2019); and post-pandemic (2020-2021). The SRs were classified as serious or non-serious, and expected or unexpected, depending on the seriousness and expectedness of the suspected ADRs, according to the WHO criteria and the Summary of Product Characteristics [SmPC] of each suspected medicine, respectively.

To study the impact of the COVID-19 pandemic on the patterns of spontaneous reporting of suspected ADRs, two null hypotheses were proposed to test whether i) the seriousness, and ii) the expectedness were independent of the pandemic (i.e., if the pandemic has had no impact, then the proportions of SRs containing i) serious and ii) unexpected ADRs were expected to be the same in both periods). The qui-square test was used to test the hypotheses; p-values <0.001 were considered statistically significant.

Microsoft Excel® was used for the statistical analyses.

Results

A total of 1,311 and 657 SRs were received in the pre-pandemic and post-pandemic periods, respectively.

Of the 1,311 SRs received in the three pre-pandemic years, 1,012 (77%) were serious and 657 (13%) contained unexpected ADRs; of the 657 SR received during the two post-pandemic years, 434 (66%) were serious and 133 (20%) contained unexpected ADRs.

The changes from pre- to post-pandemic on both proportions of SRs containing serious (an absolute decrease of 11%; p=0.01) or unexpected ADRs (an absolute increase of 7%; p=0.01) were not statistically significant.

Figure 1: Distributions of serious ADRs of suspected ADRs reports between 2017 and 2021 in UFC

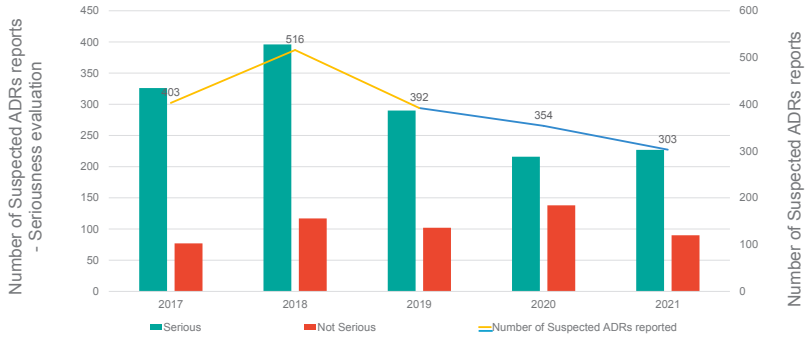
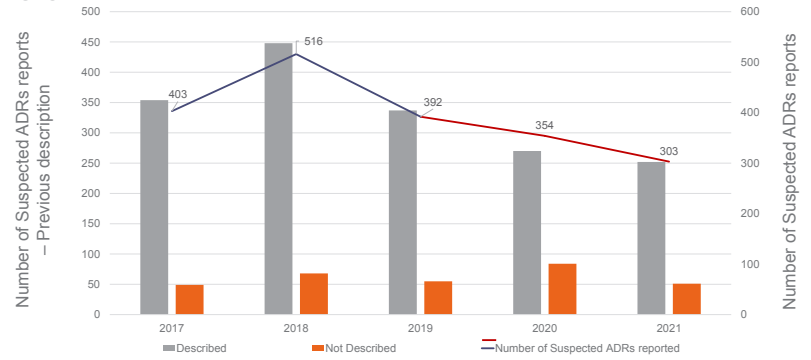


Figure 2: Distributions of unknown ADRs of suspected ADRs reports between 2017 and 2021 in UFC



The proportion of spontaneous reports of serious ADRs has decreased, and the proportion of spontaneous reports containing unknown ADRs has increased from the pre-pandemic to the post-pandemic period.

Conclusions

The COVID-19 pandemic has had not a significant impact on the proportions of SRs of serious or unexpected ADRs in the Central Region of Portugal. Further research should be carried out in other pharmacovigilance databases to understand if the present conclusions are applicable to other geographic regions.

Funding

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Reações adversas notificadas para a Unidade de Farmacovigilância da Beira Interior às vacinas usadas na imunização contra a COVID-19

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Introdução

O COVID-19 é uma doença respiratória aguda causada pelo SARSCov-2, que surgiu pela primeira vez em Wuhan em dezembro de 2019 e se tornou uma emergência de saúde pública, levando ao rápido desenvolvimento de vacinas. No entanto, tal como todos os medicamentos, as vacinas podem apresentar respostas nocivas e não intencionais, que podem ser notificadas ao Sistema Nacional de Farmacovigilância (SNF). O objetivo deste estudo prendeu-se com a caracterização das reações adversas a medicamentos (RAMs) notificadas na região abrangida pela Unidade de Farmacovigilância da Beira Interior (UFBI) entre dezembro de 2020 e dezembro de 2021.

Materiais e métodos

Este trabalho consiste num estudo observacional retrospetivo das notificações, em que o medicamento suspeito eram as vacinas contra a COVID-19, recebidas no SNF pela UFBI, considerando a Denominação Comum Internacional (DCI) de cada vacina e período de estudo (dezembro 2020-dezembro 2021). As notificações foram analisadas quanto ao género e faixa etária dos pacientes envolvidos, tipo de notificador, gravidade e RAMs de acordo com a terminologia *System Organ Class* (SOC) do dicionário médico para atividades regulamentares.

Resultados e discussão

Durante este período, foram administradas 2 vacinas de mRNA com nucleósido modificado e 2 vacinas com um vetor viral não replicativo. Este estudo englobou 2134 notificações correspondentes a 5685 RAMs. Os nossos resultados evidenciaram que as vacinas mais notificadas durante este período de estudo foram as vacinas mRNA (figura 1), estando a maioria das notificações associadas ao género feminino (figura 2) e à faixa etária dos 25 aos 49 anos (tabela 1). Os três grupos SOC mais frequentemente notificados foram “Perturbações gerais e alterações no local de administração”, “Doenças do Sistema Nervoso”, e “Afeções musculosqueléticas e dos tecidos conjuntivos”(tabela 2), sendo que a maioria das RAMs foram consideradas “Não graves”. Em geral, as RAMs foram resolvidas em poucas horas ou dias sem sequelas, o que confirma um perfil de segurança favorável das vacinas.

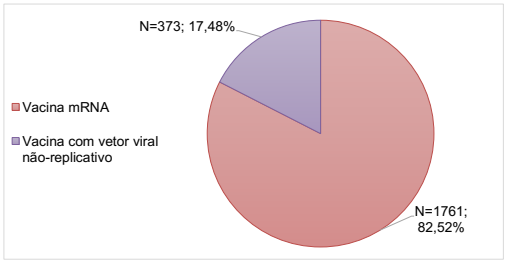

Figura 1- Caraterização das notificações de acordo com o tipo de vacina associada à RAM.

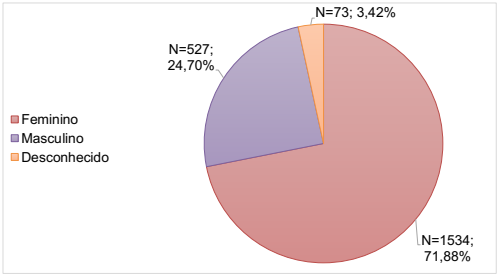

Figura 2 - Caraterização das notificações de acordo com o género.

Tabela 1 - Distribuição das notificações tendo por grupo etário.

Grupo etário	Frequência	Percentagem (%)
[5-11]	0	0,0
[12-17]	7	0,33
[18-24]	108	5,06
[25-49]	1230	57,64
[50-64]	574	26,90
[65-79]	97	4,55
≥80	66	3,09
Desconhecido	52	2,44
Total	2134	100,00

Tabela 2 - Caraterização das RAMs por sistemas e órgãos afetados

Grupo SOC	Frequência	Percentagem (%)
Perturbações gerais e alterações no local de administração	2454	43,17
Doenças do Sistema Nervoso	1048	18,43
Afeções musculosqueléticas e dos tecidos conjuntivos	1015	17,85
...	...	...
Total	5685	100,00%

Conclusão

Este estudo confirmou o perfil de segurança destas vacinas e demonstrou a importância da Farmacovigilância na deteção e prevenção de RAMs..

Agradecimentos

Os dados presentes neste trabalho pertencem ao Sistema Nacional de Farmacovigilância. Os autores gostariam de agradecer à Autoridade Nacional do Medicamento e Produtos de Saúde, I.P (INFARMED) por terem permitido a utilização dos dados.

Identification of Unknown Adverse Drug Reactions for COVID-19 Vaccines in Spontaneous Reports Received by the Pharmacovigilance Unit of Coimbra

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www.aibili.pt

Introduction

The pandemic caused by SARS-CoV-2 infection, responsible for the COVID-19 disease, motivated the accelerated clinical development of the vaccines currently available, due to the urgency in mass vaccination of the population. Consequently, the safety profile of these vaccines is incompletely established. There was a notable contribution on behalf of healthcare professionals and consumers in reporting suspected adverse reactions to the COVID-19 vaccines. Subsequently, it is necessary to identify and evaluate the reported unknown ADRs, as well as to disaggregate the information, providing a substantial contribution to the knowledge of the vaccines' safety profile, and its subsequent inclusion in the evaluation of benefit-risk ratio.

Aim

The primary objective of this study is to identify unknown ADRs for COVID-19 vaccines among SRs received by the UFC. The secondary objective of the study is to characterize unknown ADRs according to demographic variables (sex, age and reporter origin), seriousness and causality, as well as comparing unknown ADRs among the administered vaccines.

Methods

The identification of COVID-19 vaccines currently used in Portugal was performed using the Infomed database. The information was further complemented with the data available on the European Medicines Agency (EMA) website. The identification and characterization of ADRs was performed through the analysis of SRs received by UFC in a 1-year period (from December 30th 2020, to December 31st 2021).

Results

Four COVID-19 vaccines were identified as administered to the Portuguese population during the year of 2021: COVID-19 mRNA Vaccine (nucleoside modified) (tozinameran and elasomeran), COVID-19 Vaccine (ChAdOx1-S [recombinant]), and COVID-19 vaccine (Ad26.COV2-S [recombinant]). The Pharmacovigilance Unit of Coimbra received 2322 spontaneous reports containing at least one adverse reaction associated with at least one COVID-19 vaccine: 1469 SRs (4382 ADRs) associated with COVID-19 mRNA Vaccine (nucleoside modified) (tozinameran), 476 SRs (1544 ADRs) associated with COVID-19 Vaccine (ChAdOx1-S [recombinant]), 195 SRs (545 ADRs) associated with COVID-19 mRNA Vaccine (nucleoside modified) (elasomeran), 180 SRs (437 ADRs) associated with COVID-19 vaccine (Ad26.COV2-S [recombinant]) and 5 SRs (7 ADRs) for non-identifiable vaccines.

Figure 1: SRs received by the UFC according to previous knowledge (where applicable) and seriousness

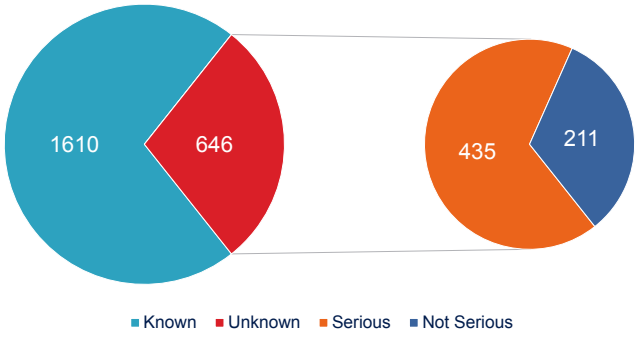
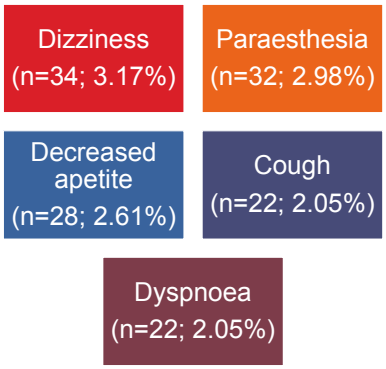


Figure 2: Top Five most frequently reported unknown ADRs



Of the identified SRs, 646 (30.75%) were Unknown. These SRs contained 1074 unknown ADRs, with the Top 5 pertaining to System Organ Classification (SOC) Nervous System Disorders, Metabolism and Nutrition Disorders and Respiratory, thoracic and mediastinal disorders. These ADRs are currently described in the SmPC of COVID-19 vaccines.

Conclusions

Spontaneous reporting allowed for the inclusion of many previously unknown ADRs in the Summary of Product Characteristics (SmPC) of all COVID-19 vaccines. This knowledge allows for the implementation advertences and precautions that contribute towards the well-being of the vaccinated population. The COVID-19 pandemic has allowed for the promotion of pharmacovigilance activities, in particular, spontaneous reporting. These efforts should be continuously maintained in order to combat the limitations of spontaneous reporting.

Funding

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A Farmacovigilância das vacinas contra a COVID-19
Experiência de uma Unidade Regional

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Introdução

Em dezembro de 2019 surgiu uma nova estirpe de Coronavírus, na China, responsável pelo síndrome respiratório agudo grave coronavírus 2 (SARS-CoV-2), a qual originou a doença por coronavírus 2019 (COVID-19) que evoluiu para uma pandemia. De forma a reduzir a suscetibilidade da população, a 27 de dezembro de 2020 iniciou-se a vacinação contra a COVID-19 em Portugal. O rápido processo de desenvolvimento destas vacinas gerou grande preocupação mundial sobre o seu perfil de segurança.

Objetivo

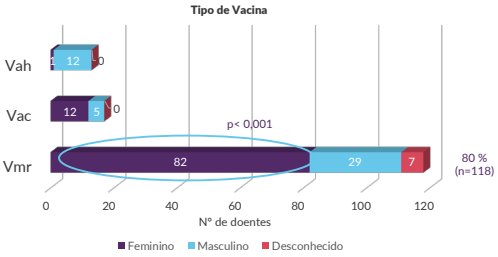
Caraterizar as reações adversas a medicamentos (RAM) notificadas à nossa Unidade Regional (UR) em 2021 e que se associaram à administração das vacinas com indicação para a imunização contra a COVID-19 *Vacina de mRNA contra a COVID-19 (com nucleósido modificado)* -Vmr, *Vacina de vetor viral não-replicativo contra a COVID-19 (adenovírus de chimpanzé)* - Vac e *Vacina de vetor viral não-replicativo contra a COVID-19 (adenovírus humano* -Vah). Adicionalmente investigámos a existência de fatores de risco associados às diferentes RAM.

Métodos

Estudo retrospetivo com consulta e análise crítica das RAM relacionadas com as vacinas utilizadas contra a COVID-19 e que foram notificadas à nossa UR no ano de 2021. Analisaram-se as variáveis: dados do doente (idade, género, co-morbilidades e medicação concomitante), identificação da vacina suspeita e dados das RAM notificadas (sintomas, gravidade, evolução clínica, tipo do notificador e resultado da imputação de causalidade nas RAM graves). A análise estatística foi realizada no software SPSS ®.

Resultados

N = 148 RAM, 64% (n=95) em mulheres
Idade média 42 anos (± 14)

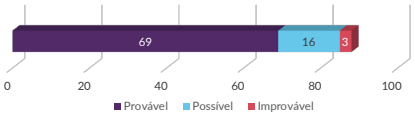


Vah: Vacina de vetor viral não-replicativo contra a COVID-19 (adenovírus humano)
Vac: Vacina de vetor viral não-replicativo contra a COVID-19 (adenovírus de chimpanzé)
Vmr: Vacina de mRNA contra a COVID-19 (com nucleósido modificado)

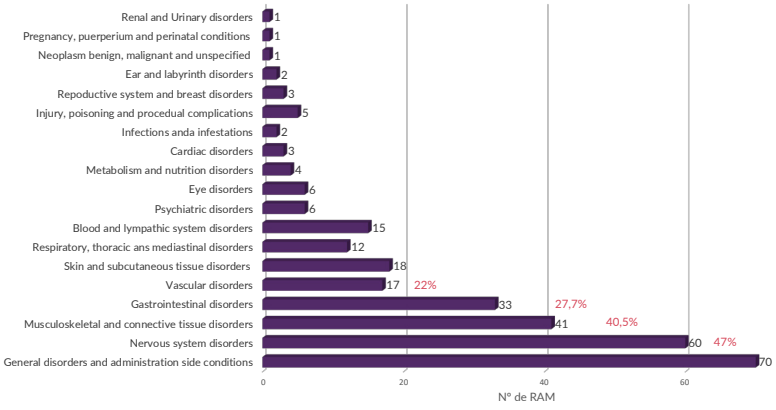
Na região Autónoma dos Açores, durante o ano de 2021, foram vacinados 202.529 utentes, dos quais 50,04% (101345) eram do sexo masculino e 49,96% (101184) do feminino.

Observaram-se 60% (n=88) de RAM graves.

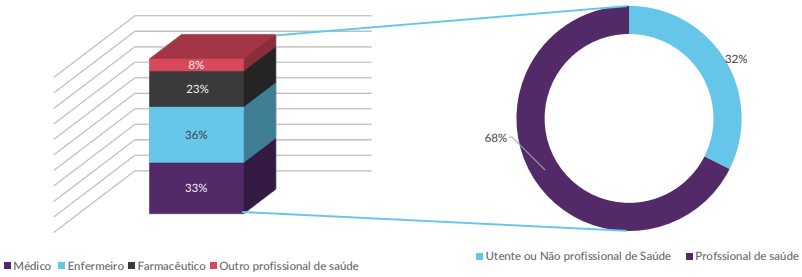
A imputação de causalidade foi considerada como provável em 78% (n=69) dos casos



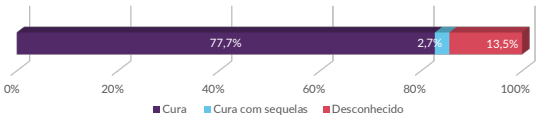
Das RAM notificadas, 57% (n=84) afetaram mais do que um grupo System Organ Class-SOC (MedDRA)



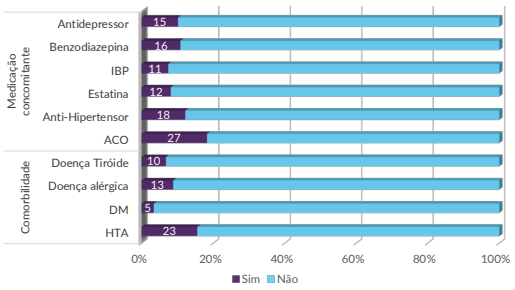
Os notificadores foram profissionais de saúde em 68% (n=100) dos casos



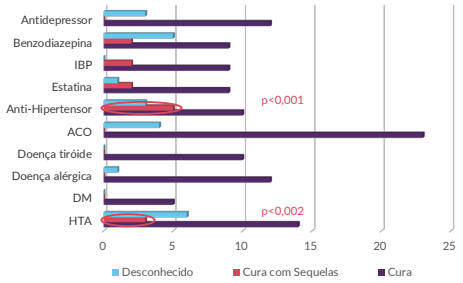
A maioria das RAM (77,7%, n=115) evoluíram para cura



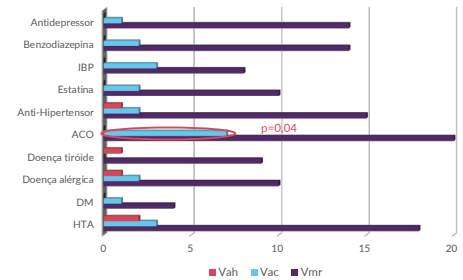
Co-morbilidades e medicação concomitante



A presença de HTA/medicação anti-hipertensora associou-se a evolução para cura com sequelas



A toma concomitante de ACO evidenciou associação a RAM à Vac



A toma concomitante de ACO associou-se à ocorrência de Musculoeskeletal and connective tissue disorders p=0,002 (n=14)

Conclusão

A maioria das RAM notificadas ocorreram em adultos e mulheres, tendo sido a vacina mais implicada a Vmr. Os grupos SOC mais frequentemente afetados estão de acordo com o descrito na literatura sobre as reações adversas às vacinas contra a COVID-19. Na amostra estudada, a presença de HTA/medicação anti-hipertensora parece ser um fator de risco para evolução desfavorável das RAM e a toma concomitante de ACO associou-se a reação à Vac e envolvimento do grupo SOC MCTD. Tendo em conta os resultados encontrados, seria pertinente estudar a contribuição destas associações numa amostra maior, com o intuito de avaliar a eventual necessidade de implementação de medidas de minimização de risco. Apesar das suas limitações, as notificações espontâneas continuam a constituir uma das principais metodologias na recolha de informação sobre segurança pós –AIM, sendo essencial para a Farmacovigilância.

Women's health and COVID-19 vaccination

Assessment of adverse reactions communicated to the Portuguese National Pharmacovigilance System

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INTRODUCTION

Women's health encompasses the physical, social, emotional and material dimension. The Portuguese National Pharmacovigilance System has received reports of several suspected adverse reactions closely linked to female health after inoculation of COVID-19 vaccines, such as breast changes and changes in the cycle or duration of the menstrual period, which directly impacts women's health and her quality of life[1].

Safety updates were recently published by the European Medicines Agency regarding Tozinameran and Elasomeran, where is recommended that heavy menstrual bleeding should be added to the vaccine's product information as a side effect of unknown frequency. However, healthcare professionals and patients are encouraged to continue to report cases of menstrual disorders following COVID-19 vaccination[2].

AIM

We aim to identify and describe the number of Individual Case Safety Reports (ICSR) that include adverse reactions related to women's health.

METHODS

We conducted a retrospective search on Portal RAM, between December 27, 2020 and September 30, 2022, using the MedDRA primary System Organ Class (SOC) Reproductive System and Breast Disorders. Selected reports included females aged 18 years and above where at least one of the medicinal products identified as suspect/interaction was one of the COVID-19 vaccines.

RESULTS

We found for the studied period 362 ICSR, with an average age of 39.9 ± 11.7 years, containing 455 adverse reactions belonging to the primary SOC Reproductive System and Breast Disorders. Overall, the most reported MedDRA preferred terms (PTs) were Menstrual Disorder (MD) (75|16.5%), Heavy Menstrual Bleeding (HMB) (56|12.3%) and Breast Pain (33|7.3%).

The age group from 31 to 40 was the one with the highest number of adverse reactions reported (ARR) (125|34.5%), followed by the age group of 41 to 50 years (113|31.2%). The PTs most reported for these age groups were MD (35|22.9%) and HMB (24|16.1%), respectively.

58.4% — 266 ARR (58.4%) were classified as "Non-Serious"

29.7% — 135 ARR (29.7%) were classified as "Clinically Relevant"

11.2% — 51 ARR (11.2%) were classified as "Incapacity"

0.7% — 3 ARR (0.7%) were classified as "Hospitalisation"

303 — Tozinameran vaccine had the highest absolute number of adverse reactions reported - 303 (66.6%). The majority occurred after inoculation of the second dose.

2.6 — Elasomeran vaccine had the highest incidence of adverse reactions reported (2.6 ARR/100.000 administered doses).

1 — Elasomeran vaccine had the highest incidence of serious adverse reactions reported (1 serious ARR/100.000 administered doses).

Menstrual Disorder and Heavy Menstrual Bleeding were the most frequent reactions for Tonizameran and Elasomeran (48|15.8% vs 21|21.9% and 39|12.9% vs 12|12.5%, respectively).

CONCLUSION

The impact of medicines on women's health is a topic of great importance with increasing prominence, however, the approach to it becomes complex and difficult, since subjective component prevails. Some of the reported PTs identified by our study are not possible to quantify and/or specify, which does not allow us to say with certainty whether the change presented in the ICSR is confirmed or not. The assessment becomes even more difficult since many of the terms may have other confounding factors and might not be associated with the inoculation of COVID-19 vaccines.

It is therefore important to design and develop strategies in order to gather pertinent and relevant information that allows a robust assessment and as accurate as possible, in order to be able to timely minimize the potential risk inherent of medicines, thus ensuring women's health.

Literature

Acknowledgements

INFARMED – National Authority of Medicines and Health Products- I.P., Directorate for Risk Management for Medicines, Lisboa, Portugal and Unidade de Farmacologia Clínica, do Centro Hospitalar e Universitário de Coimbra; Faculdade de Medicina da Universidade de Coimbra, Laboratory of Clinical Pharmacology and Therapeutics, Coimbra, Portugal

Adverse Reactions Associated with COVID-19 Vaccination Among Healthcare Professionals: A Cohort Event Monitoring Study in a Portuguese Hospital

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Introduction

The Portuguese government put into practice a vaccination plan soon after the approval of the first COVID-19 vaccine, prioritizing healthcare professionals (HCPs) and other population groups at risk.

Aim

To characterize the case reports of adverse drug reactions (ADRs) associated with the administration of COVID-19 mRNA Vaccine (nucleoside modified) (tozinameran) to HCPs in a Portuguese oncology hospital (IPO Coimbra).

Methods

This study was a nine-month prospective, observational study following a cohort event monitoring approach focused on signalling ADRs associated with the administration of COVID-19 mRNA Vaccine (nucleoside modified) (tozinameran) to HCP in IPO Coimbra. The case reports of ADRs were sent to the Pharmacovigilance Unit of Coimbra (UFC) between 14/01/2021 and 13/10/2021. The population of HCP was characterized according to gender and age distribution. The seriousness of ADRs was assessed for each individual case in accordance with WHO criteria. ADRs were coded with MedDRA® version 24.0 (System Organ Classification [SOC] and Preferred Term [PT]). ADRs were classified as "expected" or "unexpected" according to their description in the Summary of Product Characteristics (SmPC) of COVID-19 mRNA Vaccine (nucleoside modified) (tozinameran).

Results

A total of 816 HCPs were inoculated with at least one dose of the vaccine. The case reports of ADRs concerned 469 (57.5%) HCPs: 386 (82.3%) females; 642 (78.7%) aged 30-59 years old. Of the 469 case reports, 24 (5%) were assessed as serious, 44 (9.4%) as unexpected, and 11 (2.3%) as both serious and unexpected. The 469 case reports contained a total of 1,955 ADRs. The 11 case reports classified as both serious and unexpected contained a total of 17 ADRs, including hyperhidrosis and paraesthesia.

Figure 1: Overview of Serious, Unexpected and Serious + Unexpected case reports

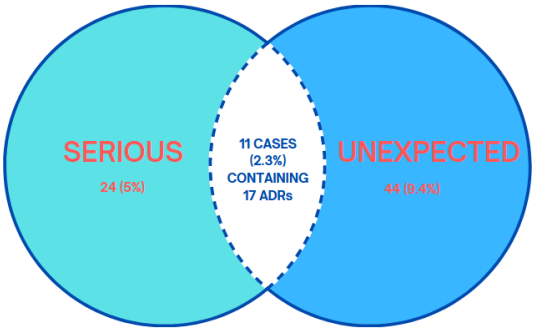
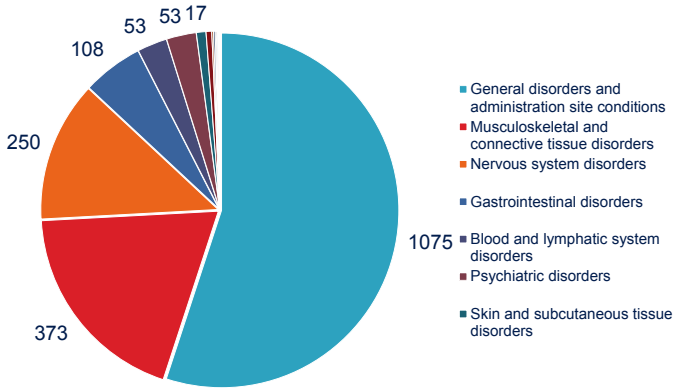


Figure 2: Distribution of individual ADRs per System Organ Classification (SOC)



"General disorders and administration site condition" (n=1,075; 54,9%), such as vaccination site pain, chills and vaccination site swelling; "Musculoskeletal and connective tissue disorders" (n=373; 19.1%), including myalgia and arthralgia; and "Nervous system disorders" (n=250; 12.8%), including headache, were the most frequently reported ADRs, which is in line with the SmPC of the vaccine.

Conclusions

The results of this study bring value to the characterization of the safety profile of Comirnaty® since the use of a cohort of individuals allows to estimate frequencies of ADRs in the real-world. Further, serious, and unexpected ADRs were identified. Importantly, this type of safety data was further included in the SmPC of the vaccine. In conclusion, the results are in favor of the positive benefit-risk ratio of COVID-19 mRNA Vaccine (nucleoside modified) (tozinameran) and reinforce the importance of post-marketing pharmacovigilance to increase knowledge on drug safety.

Funding

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Bell's Palsy after COVID-19 vaccination

Assessment of Individual Case Safety Reports communicated to the Portuguese National Pharmacovigilance System

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INTRODUCTION

Peripheral Facial Palsy results from facial nerve dysfunction, being the primary form its most common etiology, with about 75% of cases. The most typical example is idiopathic palsy, also known as Bell's Palsy (BP). BP manifests itself in both sexes, being more incident between 30 and 50 years, with a second peak between 60 and 70 years [1,2,3,4].

The Portuguese National Pharmacovigilance System (SNF) has received reports of BP cases after inoculation with COVID-19 vaccine. Since the diagnosis of this entity is essentially clinical, it is necessary that the reports have enough information to reflect this verdict, in order to understand the degree of diagnostic certainty which is essential for instance to the management of safety signal process.

AIM

We aim to explore the degree of diagnostic certainty of the reports associated with Bell's Palsy, in addition to making its description and assessing its causal relationship.

METHODS

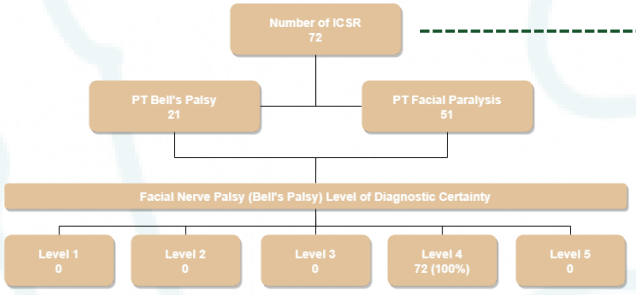
We conducted a retrospective search on the Portal RAM between December 27, 2020 and September 30, 2022, using the MedDRA preferred terms (PT) Bell's Palsy and Facial Paralysis. Selected reports included patients aged 18 years and over where at least one of the medicinal products identified as suspect/interaction was one of the COVID-19 vaccines.

The causality assessment was performed by both the Global Introspection Method - using as an expression of the evaluation the terminology of the classification of the World Health Organization - as by Liverpool algorithm [5]. For the evaluation of diagnostic certainty, the Brighton Collaboration algorithm specific to BP was used [3].

RESULTS

We found for the studied period 72 Individual Case Safety Reports (ICSR), with an average age of 52.6 ± 18.5 years. The majority of ICSR refers to women (48|66.7%), being the age group of 41 to 50 years the one that registered the largest number of cases (14 | 19.4%). Regarding the seriousness assessment, the greater part of the cases was classified as "Clinically Important" (50 | 70%).

Among the Covid-19 vaccines reported as suspect Tozinameran had the highest absolute number of cases (47 | 65.3%). The majority occurred after inoculation of the first dose. Chimpanzee adenovirus vector had the highest incidence (0.6/100.000 doses administered).



On the assessment of the level of diagnostic certainty and despite the fact of containing PT Facial Paralysis (51 | 70.8%) or PT Bell´s Palsy (21 | 29.2%), level 4 has been assigned to all ICSR after using the Brighton Collaboration algorithm.

Causality Assessment		Global Introspection			
		Definite	Probable	Possible	Unlikely
Liverpool algorithm	Definite	-	-	1 (1.4%)	-
	Probable	1 (1.4%)	9 (12.5%)	5 (6.9%)	-
	Possible	-	4 (5.5%)	47 (65.3%)	2 (2.8%)
	Unlikely	-	-	-	3 (4.2%)

A predominance of cases (47 | 65.3%) had an assessment of "Possible", both through the usage of the Global Introspection Method, as well as the Liverpool algorithm.

CONCLUSION

Although efforts are still needed to minimize underreporting of adverse reactions in Portugal, it is of increasing importance to have a bigger focus on the quality of information present in ICSR. Scarce or incomplete information impacts both on the causality assessment and on the degree of diagnostic certainty as the results of our study illustrates, where 100% of ICSR were included in level 4, meaning that we did not have enough information to satisfy any level of certainty.

It is important to develop strategies so that SNF receive reports with the needed information for a robust assessment aiming an effective monitoring of drug safety.

Literature

Acknowledgements

INFARMED – National Authority of Medicines and Health Products- I.P., Directorate for Risk Management for Medicines, Lisboa, Portugal and Unidade de Farmacologia Clínica, do Centro Hospitalar e Universitário de Coimbra; Faculdade de Medicina da Universidade de Coimbra, Laboratory of Clinical Pharmacology and Therapeutics, Coimbra, Portugal

Reações Adversas Oculares a Vacinas Contra a COVID-19 - Casos Recebidos no Ano 2021

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Introdução
A **COVID-19** assinalada pela **OMS** como **pandemia em 11 de março de 2020** despoletou o rápido desenvolvimento de **vacinas** cuja utilização ainda se iniciou no final do mesmo ano. Na prática clínica a opinião é consensual, a vacinação e a subsequente administração do reforço, são um fator epidemiológico vital para mitigar os efeitos devastadores da pandemia de COVID-19. No entanto, é essencial que profissionais de saúde e investigadores avaliem as suspeitas de reações adversas decorrentes da vacinação.
A Farmacovigilância assume um papel preponderante na utilização segura das vacinas contra a COVID-19 (VacCOVID) face às autorizações condicionais concedidas. Ao Sistema Nacional de Farmacovigilância (SNF) foram comunicadas **reações adversas oculares (RAMOC)** às VacCOVID, consideradas relevantes na rotina diária dos utentes. Assim, é fundamental investigar a suspeita de relação entre vacinação contra COVID-19 e a ocorrência de complicações oculares.

Objetivo
Caracterizar os casos RAMOC às VacCOVID recebidos em 2021 no SNF.

Métodos
Os casos foram selecionados no **Portal RAM**, base de dados do SNF, através da Terminologia Médica Internacional **MedDRA** (*Medical Dictionary for Regulatory Activities*) pela Classe de Órgão e Sistema (SOC) designada por *Eye disorders* e através da Classificação Internacional **ATC** (*Anatomical Therapeutic Chemical),* por pesquisa dos casos com os códigos: *Other Vaccines*, *Other viral vaccines* ou *Covid-19 vaccines,* atribuídos ao longo dos meses às VacCOVID. As variáveis estudadas foram: **via da notificação** - **direta** para a **Autoridade** pelos profissionais de saúde e utentes ou **indireta** através da comunicação aos **TAIM**, tipo de notificador, sexo e idade do doente, tipo de vacina, critério de gravidade da RAMOC, **as mais notificadas** e se descritas no RCM e FI das VacCOVID.

Resultados
Estudo observacional e retrospetivo. Foram identificados **520 casos** com RAMOC a VacCOVID comunicados ao SNF de 01/01/2021 a 31/12/2021. O mês de julho apresenta o maior n.º de casos recebidos (92), acima do dobro da média dos restantes meses (40) e novembro, o menor n.º (7) de casos (Fig.1). Por via direta foram recebidos 53% dos casos com RAMOC e por via indireta através da EMA, enviados pelos TAIM, os restantes 47% (Fig.2).

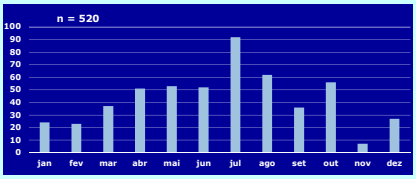

Figura 1. Evolução mensal no SNF -casos RAMOC em 2021

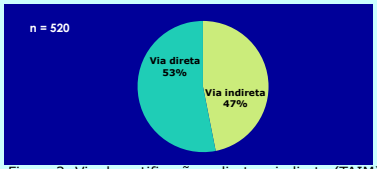

Figura 2. Via da notificação – direta e indireta (TAIM)

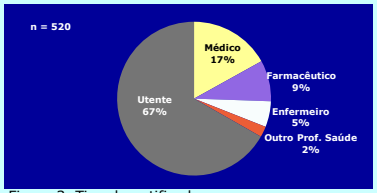

Figura 3. Tipo de notificador

Figura 4. Profissional de Saúde por via direta e indireta

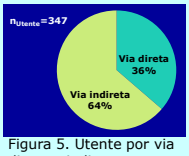

Figura 5. Utente por via direta e indireta

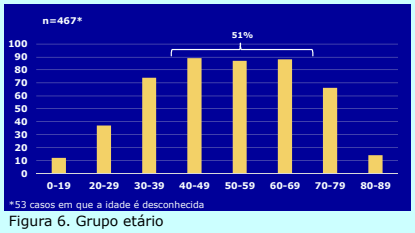

Figura 6. Grupo etário

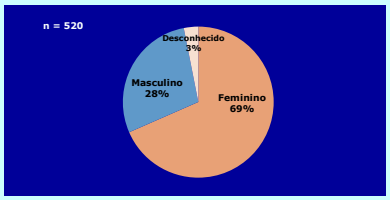

Figura 7. Sexo do doente

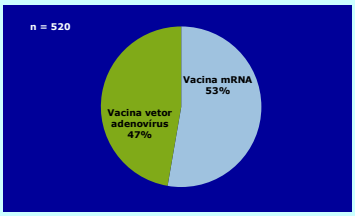

Figura 8. Casos de RAMOC - Tipo de VacCOVID

No universo dos notificadores 17% dos casos são de médicos, 9% de farmacêuticos, 5% de enfermeiros, 2% de outros prof. de saúde e destacam-se **67% de casos enviados por utentes** (Fig. 3), dos quais 64% comunicados por via indireta (Fig. 5). Nos prof. de saúde, foram 87% que notificaram os casos por via direta (Fig.4).
Nos grupos etários destacam-se 51% dos casos nos grupos dos 40 aos 69 anos. (Fig. 6). Na variável sexo do doente, identificam-se 69% dos casos no sexo feminino, (Fig. 7).
Relativamente às vacinas administradas, 53% dos casos de RAMOC são a vacinas mRNA e os restantes 47%, a vacinas de vetor adenovírus (Fig. 8).

Nos 520 casos foram identificadas 673 RAMOC, não graves (NG) ou graves, que podem estar associadas a mais de 1 critério de gravidade, no total 701 com a seguinte distribuição, não graves (45%) e com critério de gravidade: 33% clinicamente importantes, 16% incapacidade, 5% hospitalização e 1% risco de vida (Fig. 9).
As 10 RAMOC mais notificadas representam 59% do total, destacando-se a visão turva com 18%, seguida da insuficiência visual (8%) e dor ocular (7%). As RAMOC seguintes são: vermelhidão ocular, cegueira, edema ocular, irritação ocular, edema palpebral, hemorragia ocular e fotofobia (Fig. 10).

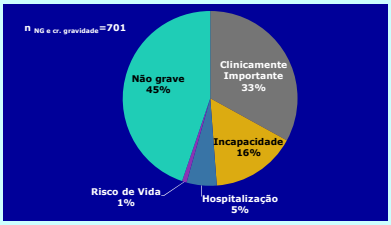

Figura 9. RAMOC Não graves e Critério de gravidade

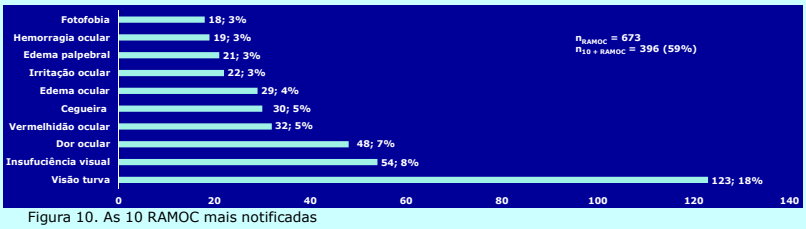

Figura 10. As 10 RAMOC mais notificadas

Das 673 RAMOC identificadas, 138 (21%) motivaram hospitalização ou incapacidade, das quais as 10 mais frequentes foram: visão turva, insuficiência visual, cegueira, dor ocular, fotofobia, oclusão da veia da retina, nistagmo, edema ocular, hemorragia ocular e astenopia (Fig. 11).
Das RAMOC mais notificadas as que mais contribuíram para a hospitalização ou incapacidade foram: visão turva, insuficiência visual, cegueira, dor ocular, fotofobia, edema ocular e hemorragia ocular.
Nos RCM e FI das VacCOVID **não se encontram descritas RAMOC.**

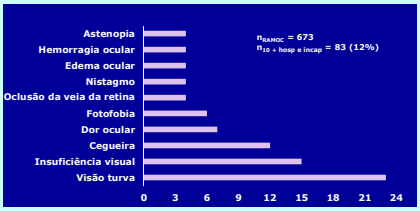

Figura 11. As 10 mais RAMOC –Hosp. ou Incapacidade

Conclusões

A comunicação direta das RAMOC ao SNF foi a forma preferencial dos profissionais de saúde, mas os utentes optaram mais pela via indireta através dos TAIM. O maior n.º de casos recebidos em julho de 2021 poderá estar relacionado com o aumento do n.º de vacinados para a obtenção do certificado para viajar.
De salientar que a maioria das RAMOC às VacCOVID foram comunicadas por utentes a comprovar o impacto que tiveram na sua rotina diária. Cerca de metade (49%) foram consideradas clinicamente importantes ou motivaram incapacidade.
O sexo feminino destaca-se por estar provavelmente, mais atento à sua saúde. Os grupos etários dos 40 aos 69 anos apresentam mais de metade dos casos (51%) eventualmente, por terem maior n.º de indivíduos vacinados.
Não se verificaram diferenças relevantes entre a ocorrência de RAMOC a vacinas mRNA ou a vacinas de vetor adenovírus.
Nas RAMOC mais notificadas encontram-se as que mais motivaram hospitalização ou incapacidade. As RAMOC não se encontram descritas nos RCM e FI das VacCOVID o que poderá contribuir para a menor notificação dos profissionais de saúde face aos utentes.
É relevante para o conhecimento do perfil de segurança das VacCOVID, desenvolver esforços para melhorar a qualidade da informação que é enviada para a análise dos casos. Justifica-se a continuação de uma monitorização estreita das RAMOC a VacCOVID a fim de evidenciar relações de causalidade mais robustas que possam nortear e implementar as medidas de minimização do risco adequadas para a salvaguarda da saúde pública.

Siglas: FI –Folheto Informativo; **RAMOC** -Reação Adversa Ocular; **RCM** -Resumo das Características do Medicamento; **SOC -***System Organ Class;* **VacCOVID** –Vacina contra a COVID-19.

Bibliografia
1. Sen M, Honavar SG. After the Storm: Ophthalmic Manifestations of COVID-19 Vaccines. Indian J Ophthalmol 2021;69:3398-420.
2. Haseeb, A.A.; Solyman, O.; Abushanab, M.M.; Abo Obaia, A.S.; Elhusseiny, A.M. Ocular Complications Following Vaccination for COVID-19: A One-Year Retrospective. Vaccines 2022, 10, 342. https://doi.org/10.3390/vaccines10020342

Possible mechanisms of action of ocular adverse reactions to COVID-19 vaccines

The poster on the previous page characterizes the cases of ocular adverse reactions (OcADRs) to vaccines, received in 2021 by the National Pharmacovigilance System. Mechanisms of action for OcADRs with COVID-19 vaccines (COVIDvacs) are proposed in the scientific literature.

Cases of suspected OcADRs reported occurred both after mRNA and adenovirus vectored vaccines. Ocular ADRs to COVIDvacs are common, **most being mild and transient.**

The eyelid, ocular surface and cornea are all eye structures that can be easily observed, thus making ADR detection fairly straightforward. ADRs occurring in the eyelid are transient, limited and characterized by unilateral erythematous oedema and bilateral purpuric rash. They may occur within hours of vaccination or up to a week afterwards. Proposed mechanisms include complement-induced reactions and molecular mimicry with autoimmune response.

In the anterior segment of the eye, **corneal graft** rejection is the most common ADR to COVIDvacs and presents with decreased vision, erythema, photophobia with or without pain, graft oedema, Descemet's folds and anterior chamber changes. Although more frequent after the second dose, it has occurred in several cases about 5 days after the first dose of vaccine. The mechanisms suggested are COVIDvac-induced increased immune response and cross-reactivity of T cells (specific for virus antigen) with human leukocyte antigen (HLA) from corneal allograft endothelial cells, increased vascular permeability after vaccination, and the presence of mRNA in the aqueous humour after a previous COVID-19 infection. The COVID-19 vaccine moreover, induces a strong CD4+ Th1 cell antibody response, which also mediates corneal graft rejection.

The **uvea** and **retina** are the structures of the posterior segment of the eye most involved in ocular ADRs. Reported cases of Vogt-Koyanagi-Harada (VKH) syndrome are characterized by acute onset of painless bilateral vision loss, granulomatous inflammation of the anterior chamber and exudative retinal detachment. VKH Syndrome is a multisystem autoimmune disease mediated by T-cells against melanocytes, with ocular, neurological, audio-vestibular and dermatological symptoms. It may result from a T- and B-cell-induced hypersensitivity reaction, an inflammatory reaction to a vaccine adjuvant, or sensitization to melanocyte antigens by viral antigens. Although lacking viral antigen or adjuvants, mRNA vaccines induce humoral immunity and an immune response of cytotoxic T cells and T helper (CD4+) cells, which can potentially trigger an inflammatory response.

Cases of uveitis have occurred within hours of the first dose and up to 20 days after the second dose of an mRNA vaccine. Vaccine-induced uveitis occurs most frequently when **two or more vaccines are administered simultaneously**. Vaccine-induced uveitis is a common ADR, anterior segment uveitis of the eye being mild and transient, and posterior segment uveitis and panuveitis more severe. In addition to molecular mimicry between the peptide fragments of the vaccine and the uveal peptides themselves, delayed hypersensitivity and immunocomplex deposition have also been suggested as triggers of inflammation. Mechanisms involving stimulation of cytokine production, modification of surface antigens and induction of new antigens with molecular mimicry to host tissue antigens, activation of polyclonal B cells and reaction to vaccine adjuvants are are all suggested as well.

Most **neuro-ophthalmic ADRs** to COVIDvacs are transient, moderate and resolve spontaneously. In acute optic nerve-related vision loss, there is sudden darkening of the field of vision and visual distortion that could be explained by acute arterial vasospasm.

OcADRs to COVIDvacs are not described in the SmPCs. The causality of all reported OcADRs is uncertain and can only be robustly confirmed or ruled out with further data and large scale studies. It is important for healthcare professionals in general and ophthalmologists in particular to be aware of the possibility of ocular ADRs following administration of vaccines. Reporting these suspected ADRs is essential to improve the knowledge base in this field.

Fátima Pereira de Bragança

SELECTED REFERENCES

- *Abousy M, Bohm K, Prescott C, Bonsack JM, Rowhani Farid A, Eghrari AO. Bilateral EK rejection after COVID 19 vaccine. Eye Contact Lens 2021;47:625 8.*
- *Crnej A, Khoueir Z, Cherfan G, Saad A. Acute corneal endothelial graft rejection following COVID 19 vaccination. J Fr Ophtalmol 2021;44:e445 7.*
- *ElSheikh RH, Haseeb A, Eleiwa TK, Elhusseiny AM. Acute uveitis following COVID 19 vaccination. Ocul Immunol Inflamm 2021:1 3.*
- *Goyal M, Murthy SI, Annum S. Bilateral multifocal choroiditis following COVID 19 vaccination. Ocul Immunol Inflamm 2021;29:753 7.*
- *Goyal M, Murthy SI, Srinivas Y. Unilateral retinal vein occlusion in a young, healthy male following Sputnik V vaccination. Indian J Ophthalmol 2021;69:3793-4.*
- *Koong LR, Chee WK, Toh ZH, Ng XL, Agrawal R, Ho SL. Vogt Koyanagi Harada disease associated with COVID 19 mRNA vaccine. Ocul Immunol Inflamm 2021:1 4.*
- *Sen M, Honavar SG. After the Storm: Ophthalmic Manifestations of COVID 19 Vaccines. Indian J Ophthalmol 2021;69:3398-420.*

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Compiled by Patrícia Catalão

What do they mean?

ADR	Adverse Drug Reaction
EMA	European Medicines Agency
MA	Marketing Authorization
PL	Patient Information Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee (EMA)
SmPC	Summary of Product Characteristics

Communications to Healthcare Professionals published on the Infomed product information webpage

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INN Medicinal product	Target	Materials Online publication date
Crizotinib *Xalkori*	**Physicians:** heads of hospital departments with the following specialities: oncology, paediatrics, haematology, ophthalmology **Pharmacists:** heads of hospital pharmacy services	Visual changes, including risk of severe vision loss, and need for monitoring of paediatric patients 08-11-2022
Chloromadinone / nomegestrol *Belara, Chariva, Clarissa, Libeli, Lutenyl, Zoely*	**Physicians:** endocrinology, gynaecology, general/ family medicibe, Portuguese Society of Endocrinology, Diabetes and Metabolism, Portuguese Society of Gynaecology, Portuguese Society of Obstetrics and Maternal-Fetal Medicine, Portuguese Society of Contraception, Portuguese Society of Reproductive Medicine, and Portuguese Association of General/Family Medicine	Meningioma risk minimization measures 09-11-2022
Ibrutinib *Imbruvica*	**Physicians:** hospital haematologists, oncologists and cardiologists **Pharmacists:** heads of hospital pharmacy services	New risk minimization measures, including recommendations for dose change due to increased risk of serious cardiac events 03-11-2022
Vandetanib *Caprelsa*	**Physicians:** nuclear medicine specialists and oncological endocrinologists (thyroid) **Pharmacists:** pharmaceutical services in hospitals treating patients with unresectable medullary thyoid cancer	Indication restriction 20-12-2022
Terlipressin *Glypressine, Terlipressina Altan, Terlipressina EVER Pharma*	**Physicians:** hepatologists, gastroenterogists, internists, nephrologists, anaesthetists, intensive care and liver transplant centre specialists **Pharmacists:** at hospital pharmacies in hospitals procuring terlipressin-containing medicinal products	Severe or fatal respiratory failure and sepsis/septic shock in patients with type 1 hepato-renal syndrome (HRS) 02-12-2022

Compiled by Patrícia Catalão