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From the Editor

This quarter's bulletin is virtually all dedicated to the immune system, a focus of growing relevance in pharmacological mechanisms. The immune system can be involved in different ways: from immunosuppressant drugs for various indications (leflunomide, mycophenolate, anakinra), to drugs used for conditions in which the immune system is the major affected target, such as the antiretroviral agents, to vaccines (anti-HPV, anti-influenza) – medicinal products with an immunological action par excellence.

Further in this issue, a feature on the occurrence of biphosphonate-associated osteonecrosis in a relatively unexpected site – the external auditory canal -, and a brief literature scan including an article on drug-associated gynecomastia.

Current and previous safety alerts issued by Infarmed can be found at:

http://www.infarmed.pt/portal/page/portal/INFARMED/MAIS_ALERTAS/ALERTAS_DE_SEGURANCA

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Human Papilloma Virus Vaccine
Favourable risk-benefit ratio

Quick Read

Concerns have been raised over a possible relationship between anti-HPV vaccine and complex regional pain and postural orthostatic tachycardia syndromes. A recent safety review has concluded that there is no reason for the use of this vaccine to be changed.

Following reports of cases of complex regional pain syndrome (CRPS) and postural orthostatic tachycardia syndrome (POTS), **PRAC** at **EMA** conducted a safety review of human papilloma virus (HPV) vaccines. All the available data were assessed, a group of experts was consulted, and consideration was given to information from patient groups on the impact those conditions can have on patients and their families. No reason was found to make it necessary to change the use of the vaccine, its risk-benefit ratio remaining favourable.

These vaccines are used to prevent cervical cancer of the uterus, as well as other types of cancer and complications caused by HPV. It is estimated that over 80 million women have been vaccinated worldwide and in some European countries the vaccine has already been administered to 90% of the recommended age group.[1]

Telma Rijo, Margarida Guimarães

[1] http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2015/11/news_detail_002436.jsp&mid=WC0b01ac058004d5c1

Biphosphonates
Risk of External Auditory Canal Osteonecrosis

Quick Read

Osteonecrosis, as a biphosphonate-associated adverse reaction, has been reported not only in the mandible but also in the external auditory canal.

During routine pharmacovigilance activities, and based on literature cases[1-5] and the EudraVigilance database, the UK has raised a safety signal concerning the use of bisphosphonates and the occurrence of osteonecrosis in the external auditory meatus.

Initially it was thought that biphosphonate-induced osteonecrosis was limited to the mandible, given its unique structure, function and bone microbiology. However, similarities between the mandible and the external auditory canal may explain why the latter is similarly susceptible. This risk also seems to be related to treatment duration and has been reported in association both with orally and IV administered biphosphonates.[6-8]

Following an in-depth analysis, **EMA** has concluded that external auditory canal osteonecrosis is indeed an **ADR** that can be induced by bisphosphonates. EMA has further recommended that the **MA** Holders of medicines containing bisphosphonates (**alendronic acid, cholecalciferol, clodronic acid, etidronic acid, ibandronic acid, neridronic acid, pamidronic acid, risedronic acid, tiludronic acid, zoledronic acid**) submit changes to the **SmPC** (sections 4.4 and 4.8) and **PIL** (section 4) texts, in order to include external auditory canal osteonecrosis. The Portuguese version of the texts to be implemented can be found at:

http://www.ema.europa.eu/docs/pt_PT/document_library/Other/2015/10/WC500195097.pdf

Although at the beginning it was suspected that external auditory canal osteonecrosis could also be associated with the use of **denosumab** – a drug which acts on bone tissue and calcium metabolism – the data so far available have proved to be insufficient for an unequivocal causal link to be determined. **PRAC** has therefore not recommended any changes to the **SmPC** or **PIL** of this medicinal product.

Leonor Chambel

References:

[1] Polizzotto MN et al. Bisphosphonate-associated osteonecrosis of the auditory canal. Br J Haematol. 2005 Jan; 132(1):114.

[2] Froelich K et al. Bisphosphonate-induced osteonecrosis of the external ear canal: a retrospective study. Eur Arch Otorhinolaryngol. 2011 Aug;268(8):1219-25

[3] Bast F, Fuss H, Schrom T. Bilateral bisphosphonate-associated osteonecrosis of the external ear canal: a rare case. HNO. 2012 Dec;60(12):1127-9

[4] Salzman R et al. Osteonecrosis of the external auditory canal associated with oral bisphosphonate therapy: case report and literature review. Otol Neurotol. 2013 Feb; 34(2):209-13.

[5] Wickham N, et al. Bisphosphonate-associated osteonecrosis of the external auditory canal. J Laryngol Otol. 2013 Jul; 127 Suppl 2:S51-3

[6] Amiraraghi N, et al. Osteonecrosis of the temporal bone secondary to bisphosphonates: a potentially life-threatening complication. Otolaryngology–Head and Neck Surgery 151: P220

[7] Kharazmi M, et al. Bisphosphonate-associated osteonecrosis of the auditory canal. Br J Oral Maxillofac Surg. 2013 Dec;51(8):e285-7

[8] Thorsteinsson AL, et al. External auditory canal and middle ear cholesteatoma and osteonecrosis in bisphosphonate-treated osteoporosis patients: a Danish national register-based cohort study and literature review. Osteoporos Int. 2014 Jul;25(7):1937-44

Leflunomide
Risk of Pulmonary Hypertension

Quick Read
Pulmonary hypertension is a possible adverse reaction from exposure to leflunomide.

During routine pharmacovigilance activities, **EMA** detected a safety signal of pulmonary hypertension associated with leflunomide, a disease modifying antirheumatic agent. This was based on eight case reports from the Eudravigilance (EV) database, including three also found in the literature.[1-3] A cumulative review and in-depth analysis of pulmonary hypertension cases and related terms was conducted, which included data from clinical and non-clinical studies, spontaneous **ADR** reports, ongoing registries and scientific literature. Additionally, the **MA** Holder of the centralized innovative medicinal product (Arava®) was asked to present a discussion on a possible underlying pathophysiological mechanism.

Following the assessment of the available evidence, **PRAC** could not rule out a causal relationship between the use of leflunomide and pulmonary hypertension. It recommended that the **MA** Holders submit a request for an **SmPC** and **PIL** alteration to include a warning in section 4.4 and the adverse reaction pulmonary hypertension in section 4.8.. Sections 2 and 4 of the **PIL** will correspondingly be updated as well. The Portuguese versions of the texts to be implemented are available on the **EMA** website at: New product information wording: extracts from PRAC recommendations on signals adopted at the 7-10 September 2015 PRAC.

Magda Pedro

References:

[1] Alvarez PA et al. Leflunomide-induced pulmonary hypertension in a young woman with rheumatoid arthritis: a case report. Cardiovasc Toxicol. 2012 Jun;12(2):180-3 (EV case 4)

[2] Votavova R et al. Therapy of pulmonary arterial hypertension. Lekarske listy, Extra 2012:10 Toxicology 2012;12:180-183 (EV case 3)

[3] Martinez-Taboada VM et al. Pulmonary hypertension in a patient with rheumatoid arthritis treated with leflunomide. Rheumatology (Oxford). 2004 Nov;43(11):1451-3

Mycophenolate
Pregnancy: new safety recommendations

Quick Read
Given the risk of spontaneous abortion and congenital malformations, measures to prevent exposure to mycophenolate during pregnancy should be taken, from 10 days before therapy is started, throughout treatment and up to several weeks after its end.

Mycophenolate is an immunosuppressant used in transplanted patients to prevent acute kidney, heart or liver transplant rejection. In Portugal, several products containing mycophenolate (mycophenolate mofetil or its pro-drug mycophenolic acid) are marketed.

Following an assessment of the Periodic Safety Update Reports of medicinal products containing mycophenolate, **PRAC** at **EMA** has concluded that there is evidence for a risk of congenital anomalies and spontaneous abortion when a pregnant woman is exposed to the drug. It therefore recommends that mycophenolate should not be used during pregnancy, unless there are no appropriate therapeutic alternatives.

Although the information documents already contain warnings and precautions regarding pregnancy, they will be reinforced and updated to include new contraindications and recommendations:

- Mycophenolate has a confirmed teratogenic effect; it is associated with an increased rate of **spontaneous abortion and congenital malformations**, when compared to other immunosuppressants.
- It should not be used in pregnancy, unless there is no alternative.
- Pregnancy should be ruled out by means of **pregnancy tests: 8 to 10 days before starting mycophenolate and immediately after the beginning** of therapy.
- Mycophenolate should not be used in women of child-bearing age, unless effective contraception is being used simultaneously with **two contraceptive methods before, during and up to 6 weeks after the end** of treatment.
- Sexually active men (including the vasectomized) should use a condom for sexual intercourse for as **long as** they are taking mycophenolate and until as late as **90 days after** its discontinuation. It is recommended that their **partners use an additional contraceptive method** throughout the same period of time.
- Patients should be advised **not to donate sperm during** therapy and until **90 days after** its end.
- Patients should be advised **not to donate blood during and up to 6 weeks** after the end of treatment.

In November 2015 a communication to healthcare professionals was disseminated and educational materials will be handed out regarding teratogenic risk and including recommendations on contraception and the need for pregnancy testing.

Sílvia Duarte

Dimethyl Fumarate (Tecfidera®)
Update on PML

Quick Read

New recommendations have come out to minimize and mitigate the risk of progressive multifocal leucoencephalopathy (PML) associated with treatment with Tecfidera.

EMA has issued new recommendations to minimize the risk of occurrence of progressive multifocal leucoencephalopathy (PML) in patients with multiple sclerosis who are being treated with Tecfidera® (dimethyl fumarate).

PML is a rare cerebral infection caused by the John Cunningham (JC) virus. This virus is very common in the population at large and is usually harmless. However, in patients with a compromised immune system, it can lead to the appearance of PML with symptoms that can be similar to those of a flare of multiple sclerosis; they may result in severe disability or death.

Following a report of a first case of PML, **EMA** initiated a safety review which included the cases of PML with other medicinal products containing dimethyl fumarate and used in the treatment of psoriasis. To prevent the risk of PML, healthcare professionals should adopt the following recommendations which will be transposed to the **SmPC** and **PIL**:

- **Before starting** Tecfidera, a **full blood cell count**, including lymphocyte count, as well as an MRI (preferably less than 3 months before) should be obtained as reference.
- **During** treatment, **blood cell counts** should be obtained **every 3 months**. If the lymphocyte count drops below $0.5x10^9$/L for 6 months, the risk/benefit ratio of continuing treatment should be assessed, taking into account the available therapeutic alternatives, clinical factors, lab results and imaging findings.
- During treatment, the need for additional **MRI** exams should take into consideration the **national guidelines**.[1] Magnetic resonance imaging can be part of reinforced surveillance for patients at increased risk of PML.
- **In case PML is clinically suspected**, a magnetic resonance imaging exam should be obtained for diagnosis, treatment should be immediately suspended, and additional assessment considered.
- PML can only occur in the presence of JC virus infection. If **anti-JC antibody testing** is undertaken, it should be borne in mind that the influence of lymphopoenia on the accuracy of those tests has not been previously studied in patients on Tecfidera. A negative result (in the presence of a normal lymphocyte count) does not exclude the possibility of subsequent JC virus infection.
- There are no efficacy and safety data on patients who discontinue other therapies to start Tecfidera. The role of previous immunosuppressant therapy in the development of PML in patients treated with Tecfidera is unknown. **Whenever previous therapy is changed to Tecfidera**, the half-life and mechanism of action of the former should be taken into account, in order to avoid an additive immunological effect and to reduce the risk of disease reactivation.

Telma Rijo, Ana Sofia Martins

[1] Multiple sclerosis modifying therapy in children and adults, Portuguese General Health Directorate Guideline no. 05/2012 updated on 31-07-2015 (in Portuguese): http://www.dgs.pt/directrizes-da-dgs/normas-e-circulares-normativas/norma-n-0052012-de-04122012-png.aspx

Anacinra (Kineret®)
Risk of Thrombocytopoenia

Quick Read
Thrombocytopoenia is a possible adverse effect of anakinra.

Kineret® is an immunosuppressant agent that acts by blocking the biological activity of interleukin-1 through competitive inhibition of its receptors. A plausible mechanism for thrombocytopoenia can be related to inhibition of platelet production induced by interleukin-1β.

Considering the available evidence from the Eudravigilance database, literature data,[1-4] data presented by the MA Holder, as well as the above plausible mechanism, **EMA** has concluded that thrombocytopoenia is a possible undesirable effect of anakinra, and has recommended that the **MA** Holder of Kineret® submit changes to the **SmPC** (section 4.8) and **PIL** (section 4) texts in order to include that risk. The Portuguese versions can be found here:

Recomendações do PRAC decorrentes de avaliação de sinais de segurança.

Márcia Silva

References:

[1] *Giampietro C et al. Anti-Interleukin-1 Agents in Adult Onset Still's Disease. Int J Inflam. 2012;2012:317820. doi: 10.1155/2012/317820. Epub 2012 Apr 29.*

[2] *Quartuccio L et al. Interleukin 1 receptor antagonist therapy-induced thrombocytopenia in adult onset Still's disease. J Rheumatol. 2007 Apr; 34(4):892-3 (case narrative 1)*

[3] *den Broeder AA et al. Observational study on efficacy, safety, and drug survival of anakinra in rheumatoid arthritis patients in clinical practice. Ann Rheum Dis. 2006 Jun;65(6):760-2.*

[4] *Chang Z et al. Anakinra use during pregnancy in patients with cryopyrinassociated periodic syndromes (CAPS). Arthritis Rheumatol. 2014 Nov; 66(11):3227-32.*

Antiretroviral medicines
Recommendations updated

Quick Read

The SmPCs/PILs of antiretroviral drugs are going to be updated to reflect the most recent evidence on the risk of lipoatrophy/dystrophy and of lactic acidosis.

Recommendations following a PRAC (EMA) assessment have been adopted on the risk of lipodystrophy (changes in the quantity and distribution of fat in the body) and lactic acidosis associated with medicines for treating HIV infection. The SmPCs and PILs are to be updated.

In the early 2000s a lipodystrophy warning was inserted in the SmPCs/PILs to reflect clinical data from patients taking the drug combinations then available. Meanwhile, more recent assessments have come to suggest that only some of those medicinal products cause body fat changes (**zidovudine, stavudine** and, probably also **didanosine**) which actually involve the loss of subcutaneous fat (**lipoatrophy**). It was concluded that **there is no clear evidence that antiretrovirals cause lipodystrophy**. Hence the corresponding general warning has been crossed out from the SmPCs/PILs of medicinal products for HIV infection, whereas the specific warning concerning the loss of subcutaneous fat will remain only for zidovudine, stavudine and didanosine (**Table 1**).

Antiretroviral medicines	SmPC/PIL changes
Aptivus, Atripla, Combivir, Crixivan, Edurant, Emtriva, Epivir, Eviplera, Evotaz*, Intelence, Invirase, Kaletra, Kivexa, Lamivudine ViiV*, Norvir, Prezista, Reyataz, Rezolsta*, Stocrin, Stribild, Sustiva*, Telzir, Triumeq*, Trizivir, Truvada, Viramune, Viread, Zerit, Ziagen	Warning on lipodystrophy eliminated
Combivir, Trizivir, Zerit	Warning on fat loss (lipoatrophy)

Table 1. Changes to SmPCs/PILs of antiretroviral medicines (lipoatrophy/dystrophy)

* The centrally authorized medicines Evotaz, Lamivudine ViiV, Rezolsta, Sustiva and Triumeq are not marketed in Portugal.

Similarly, a warning regarding **lactic acidosis** had been inserted in the SmPCs/PILs of the drug class of nucleoside and nucleotide analogues. However, a recent analysis of available studies, cases reported and literature published demonstrates that the risk of lactic acidosis varies substantially within medicines of the same class. As such, and in accordance with current evidence, the class warning on lactic acidosis has been crossed out from the SmPCs/PILs of nucleoside/nucleotide analogues, except in the case of zidovudine, stavudine and didanosine (Table 2).

Antiretroviral medicines	SmPC/PIL changes
Atripla, Emtriva, Epivir, Eviplera, Kivexa, Lamivudine ViiV, Stribild, Triumeq, Truvada, Viread, Ziagen	Warning on lactic acidosis eliminated
Combivir, Trizivir, Zerit	Warning on lactic acidosis maintained

Table 2. Changes to SmPCs/PILs of antiretroviral medicines (lactic acidosis)

Telma Rijo, Margarida Guimarães

Influenza A (H_1N_1) virus vaccine: no adverse effect in mortality of offspring of women vaccinated during pregnancy

Ludvigsson JF et al. BMJ 2015;351:h5585

This prospective study of a Swedish population cohort followed between October 2009 and November 2010 tried to find out whether there had been an impact in terms of offspring mortality of women who received the AS03-adjuvated monovalent vaccine against influenza A (H_1N_1) virus during pregnancy. A few methodological limitations notwithstanding, results support the conclusion that vaccination during pregnancy is not associated with adverse fetal effects, such as still-birth and early or late neonatal death.

Gynecomastia associated with exposure to drugs

Nuttall FQ et al. Eur J Clin Pharmacol (2015) 71:569–578

Gynecomastia is not rare in adult men. Its prevalence increases with age, supposedly in relation to a rising estradiol/testosterone ratio. If one excludes this physiological decline in the relative levels of testosterone, as well as pathological conditions of a metabolic/hormonal, genetic or neoplastic nature, gynecomastia can also appear as a side effect of medicines. The authors of this study undertook a systematic literature review encompassing articles from over one hundred publications. The result was the following list of medicines that are potentially associated with the occurrence of gynecomastia:

Amlodipine
Atorvastatine
Benserazide
Captopril
Ciclosporin
Cimetidine
Citotoxic agents,combination
Cladribine
Dasatinib
Diazepam
Didanosine
Diethylpropion
Digoxin
Diltiazem
Domperidone
D-penicillamine
Efavirenz
Etretinate
Fenofibrate
Finasteride
Fluoresone
Fluoxetine
Gabapentin
HAART
Imatinib
Indinavir
Isoniazide
Ketoconazole
Marinol
Methotrexate
Metronidazole
Nettle
Nifedipine
Omeprazole
Paroxetine
Phenytoin
Pregabalin
Ranitidine
Rosuvastatine
Saquinavir
Spironolactone
Stavudine
Sulindac
Sulpiride
Sunitinib
Tandospirone
Thalidomide
Theophylline
Venlafaxine
Verapamil
Vincristine

Educational Materials published on the Infarmed website
(September to November 2015)

Medicinal product	Click on the links (in Portuguese)
Abacavir (includes Kivexa, Trizivir, Ziagen and Triumeq)	***Information for prescribing physicians*** Informação de segurança: reações de hipersensibilidade graves associadas à utilização de Abacavir – 3.ª versão aprovada em agosto de 2015
Incresync (pioglitazone + alogliptin)	***Information for physicians*** Incresync (Alogliptina/Pioglitazona) – Guia para o prescritor: seleção apropriada do doente e gestão de risco do doente – 1.ª versão aprovada em abril de 2015 For family physicians, internal medicine physicians, endocrinologists and cardiologists.
Keytruda (pembrolizumab)	***IInformation for healthcare professionals*** Brochura para os profissionais de saúde - perguntas e respostas – 1ª versão aprovada em agosto de 2015 For oncologists and dermatologists, as well as nurses working in oncology departments, pharmacists in hospitals with an oncology service, and other healthcare professionals involved in the treatment of patients with Keytruda. ***Information for patients*** Brochura com informação de segurança para o doente – 1.ª versão aprovada em agosto de 2015 Cartão de alerta para o doente – 1.ª versão aprovada em agosto de 2015
Relmus (thiocolchicoside)	***Information for physicians*** Guia de prescrição para o médico sobre o medicamento Relmus (tiocolquicosido) – 1.ª versão aprovada em agosto de 2015 For general practitioners, family physicians, orthopaedic surgeons, rheumatologists, gynaecologists, rehabilitation medicine physicians, internists, and occupational physicians. ***Information for patients*** Cartão do Doente sobre o medicamento Relmus (tiocolquicosido) – 1.ª versão aprovada em agosto de 2015

Educational Materials published on the Infarmed website
(September to November 2015)

Medicinal product	Click on the links (in Portuguese)
RoActemra (tocilizumab)	***Information for patients*** Brochura para o doente com artrite idiopática juvenil poliarticular – 1.ª versão aprovada em agosto de 2015 Brochura para o doente com artrite idiopática juvenil sistémica – 1.ª versão aprovada em agosto de 2015
Sevelâmero Teva (sevelamer)	***Information for physicians*** Informação de Segurança importante para o médico - 1ª versão aprovada em outubro de 2015 For nephrologists. ***Information for patients*** Informação importante para os doentes – 1.ª versão aprovada em outubro de 2015

Compiled by Magda Pedro

Communications to Healthcare Professionals (September to November 2015)

Medicinal product	Click on topic for details (in Portuguese)
CellCept (mycophnolate mofetil)	Serious risk of teratogenicity new important recommendations for women and men concerning pregnancy prevention.
Chirocaine 7,5 mg/ml (levobupivacaine)	PIL error corrected – this medicine should not be used for epidural anaesthesia in cesarian section surgery.
Intrauterine contraceptive devices containing copper (NovaT380) and levonorgestrel (Mirena, Jaydess)	Update on the risk of uterine perforation.
InductOs (dibotermin alfa)	Limited availability of InductOs 1.5 mg/ml powder, solvent and matrix for implant.
Thalidomide Celgene (thalidomide)	The initial dosage of thalidomide when associated with melphalan should be reduced in patients over 75 years of age.
Xalkori (crizotinib)	Inclusion of a new warning concerning cardiac failure.
Zelboraf (vemurafenib)	Potentiation of radiotoxicity.

Compiled by Sílvia Duarte

Online reporting of adverse drug reactions by health professionals and patients

Portal RAM for ADR reporting.
Online forms for both
health professionals and patients.

How can I report an adverse reaction?

- **ADR Portal (Portal RAM):**
http://extranet.infarmed.pt/page.seram.frontoffice.seramhomepage
- **Report Card online printout link:**
http://www.infarmed.pt/portal/page/portal/INFARMED/MEDICAMENTOS_USO_HUMANO/FARMACOVIGILANCIA/NOTIFICACAO_DE_RAM
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What do they stand for?

ADR Adverse Drug Reaction

EMA (European Medicines Agency)

MA Marketing Authorisation

PIL Patient Information Leaflet

PRAC Pharmacovigilance Risk Assessment Committee

SmPC Summary of the Product's Characteristics

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