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Biological therapy-associated adverse reactions in asthma: analysis of reporting to the Portuguese Pharmacovigilance System

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Dedicatória

Pai, Mãe e Ju

é por vocês.

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Resumo + Palavras-chave

Introdução

Medicamentos biológicos foram testados com sucesso na asma, sendo especialmente eficazes nas formas mais graves da doença. Paralelamente, emergiu a questão da segurança, tendo sido reconhecida como um aspecto crucial que necessita ser monitorizado. O objetivo deste estudo foi caracterizar o perfil de segurança dos biológicos utilizados na asma, através de uma análise das notificações espontâneas (NE) de suspeitas de reações adversas a esses medicamentos (RAM) notificadas em Portugal.

Métodos

Análise retrospectiva das NE de suspeitas de RAM atribuídas ao omalizumab e ao mepolizumab, enviadas ao Sistema Nacional de Farmacovigilância (SNF), desde o início da sua comercialização até outubro de 2018. Foram avaliados os dados demográficos dos pacientes, bem como as características e gravidade das reações.

Resultados

No caso do omalizumab, desde fevereiro de 2006 a outubro de 2018, houve uma taxa de notificação média anual de 0.1978 casos/1000 asmáticos graves, com uma tendência de notificação crescente com a progressão dos anos. Nos dois anos em que o mepolizumab foi alvo de notificações, houve uma taxa de notificação média anual de 0.1257 casos/1000 asmáticos graves.

Após exclusão dos duplicados, registaram-se 127 NE, incluindo 391 suspeitas de RAM para o omalizumab, e 10 NE, incluindo 20 suspeitas de RAMs para o mepolizumab.

Nos casos do omalizumab e do mepolizumab, a grande maioria dos pacientes era do sexo feminino (75.6% e 90.0%, respectivamente) e idade compreendida entre 18 e 64 anos (61,4% e 50,0%, respectivamente).

Com o omalizumab, as suspeitas de RAM mais frequentes foram "doenças respiratórias, torácicas e do mediastino", "exames complementares de diagnóstico" e "perturbações gerais e alterações no local de administração", de acordo com o *System Organ Class* (SOC), e "asma", "artralgia" e "ausência de resposta terapêutica", segundo o *Preferred Term* (PT). No caso do mepolizumab, as suspeitas de RAM mais frequentes foram os SOCs "afecções musculosqueléticas e dos tecidos conjuntivos" e "perturbações gerais e alterações no local de administração", e o PT "artralgia".

Em relação à gravidade, 71.7% das notificações do omalizumab foram graves, com um único episódio fatal, dois casos de anafilaxia, 12 casos de neoplasias malignas e dois abortos. Apenas 20.0% das notificações do mepolizumab foram consideradas graves.

Conclusões

Apesar das limitações associadas a este tipo de estudo, as nossas conclusões estão de acordo com outros estudos que demostram um perfil favorável de risco-benefício desta terapêutica recente. O nosso estudo sugere também que é necessário continuar a desenvolver programas educacionais para obter um sistema de notificação mais eficaz.

Palavras-chave

Reações adversas medicamentosas; Asma; Mepolizumab; Anticorpos monoclonais; Omalizumab; Farmacoepidemiologia; Farmavigilância; Segurança; Efeitos Colaterais

Resumo Alargado

Introdução

Medicamentos biológicos foram testados com sucesso na asma, sendo especialmente eficazes nas formas mais graves da doença. Paralelamente, emergiu também a questão da segurança, tendo sido reconhecida como um aspecto crucial que necessita ser monitorizado. Estima-se que a grande maioria das reações adversas medicamentosas (RAM) graves seja apenas detectada na fase pós-comercialização, sendo fundamental a implementação de farmacovigilância contínua dos medicamentos e os sistemas de notificação espontânea são um dos pilares dessa vigilância. O objetivo deste estudo foi caracterizar o perfil de segurança dos biológicos utilizados na asma, através de uma análise das notificações espontâneas (NE) de suspeitas de RAM notificadas em Portugal.

Métodos

Análise retrospectiva das NE de suspeitas de RAM atribuídas ao omalizumab e ao mepolizumab, enviadas ao Sistema Nacional de Farmacovigilância (SNF), desde o início da sua comercialização até outubro de 2018.

Foi avaliada a evolução anual da frequência das NE, bem como foi realizada uma caracterização demográfica dos casos, considerando sexo e faixa etária. Cada notificação foi classificada de acordo com a sua gravidade e, nos casos graves, foi especificado qual o critério de gravidade em questão. As suspeitas de RAM foram avaliadas e categorizadas de acordo com o *Preferred Term* (PT) e *System Organ Class* (SOC) do dicionário MedDRA (*Medical Dictionary for Regulatory Activities*). Também foi verificado se as suspeitas de RAM do estudo estavam ou não descritas no Resumo das Características do Medicamento (RCM) do respectivo fármaco. Por último, foi realizada uma análise mais aprofundada dos casos graves com termos da terminologia MedDRA pertencentes à lista de *Important Medical Event* (IME).

Resultados

No caso do omalizumab, desde fevereiro de 2006 a outubro de 2018, houve uma taxa de notificação média anual de 0.1978 casos/1000 asmáticos graves, com uma tendência de notificação crescente à medida que os anos progrediram e com quase metade de todos os casos (48.5%) a serem registrados em 2017 e 2018. Nos dois anos em que o mepolizumab foi alvo de notificações, registou-se uma taxa de notificação média anual de 0.1257 casos/1000 asmáticos graves.

Após exclusão dos duplicados, houve um total de 127 NE, incluindo 391 suspeitas de RAM para o omalizumab, e 10 NE, incluindo 20 suspeitas de RAMs para o mepolizumab.

Quanto à caracterização demográfica, nos casos do omalizumab e do mepolizumab, a grande maioria dos pacientes era do sexo feminino (75.6% e 90.0%, respectivamente) e de idade compreendida entre 18 e 64 anos (61.4% e 50.0%, respectivamente).

Com o omalizumab, as suspeitas de RAM mais frequentes foram "doenças respiratórias, torácicas e do mediastino", "exames complementares de diagnóstico" e "perturbações gerais e alterações no local de administração", de acordo com o SOC, e "asma", "artralgia" e "ausência de resposta terapêutica", segundo o PT. Houve 8 casos de reacções no local da injecção. No caso do mepolizumab, as suspeitas de RAM mais frequentes foram os SOCs "Afecções musculosqueléticas e dos tecidos conjuntivos" e "perturbações gerais e alterações no local de administração", e o PT "artralgia".

Após analisar quanto à presença das suspeitas de RAM nos RCMs, 53.4% não estavam descritas com o omalizumab e 41.2% não estavam descritas com o mepolizumab.

Em relação à gravidade, 71.7% das notificações do omalizumab foram graves, com um único episódio fatal (um acidente de viação), dois casos de anafilaxia, 12 casos de neoplasias malignas (com 6 casos de tumores malignos da mama) e dois abortos. Apenas 20.0% das notificações do mepolizumab foram consideradas graves.

Conclusões

Apesar das limitações associadas a este tipo de estudo, as nossas conclusões estão de acordo com outros estudos que demostram um perfil favorável de risco-benefício desta terapêutica recente. O nosso estudo sugere também que é necessário continuar a desenvolver programas educacionais para obter um sistema de notificação mais eficaz, informando as pessoas acerca da importância de terem um papel ativo na monitorização da segurança dos fármacos através da notificação de suspeitas de RAM às autoridades, e fazendo uma descrição o mais completa possível dos casos.

Abstract + Keywords

Background

Biological drugs have been successfully tested in asthma, being especially effective in the most severe forms of the disease. In parallel, safety issues have also emerged and have been recognized as a crucial aspect that needs to be monitored. The purpose of this study was to characterise the safety profile of biologicals used in asthma, by carrying out an analysis of Portuguese spontaneous reports (SR) of suspected adverse reactions to these drugs (ADR).

Methods

Retrospective analysis of SR of suspected ADR attributed to omalizumab and mepolizumab, sent to the National Pharmacovigilance System (SNF), since market launch until October 2018. We evaluated patients´ demographic data, as well as characteristics and seriousness of reactions.

Results

For omalizumab, from February 2006 to October 2018, there was an average annual reporting rate of 0.1978 reported cases per thousand severe asthmatics, with an increasing trend as years progressed. In the two years that mepolizumab has been subject to reports there was an average annual reporting rate of 0.1257 reported cases per thousand severe asthmatics.

After all duplicate reports were removed, there was a total of 127 SR including 391 suspected ADR for omalizumab, and 10 SRs including 20 suspected ADRs for mepolizumab.

For both omalizumab and mepolizumab the vast majority of patients were female (75.6% and 90.0%, respectively), and between 18 and 64 years old (61.4% and 50.0%, respectively).

With omalizumab, the most frequent suspected ADRs were “respiratory, thoracic and mediastinal disorders”, “investigations” and “general disorders and administration site conditions”, according to System Organ Class (SOC), and “asthma”, “arthralgia” and “drug ineffective”, according to Preferred Term (PT). With mepolizumab, the most frequent suspected ADR were the “musculoskeletal and connective tissue disorders” and “general disorders and administration site conditions” SOCs, and the “arthralgia” PT.

Regarding seriousness, 71.7% of the reports for omalizumab were serious, with a single fatal episode, 2 cases of anaphylaxis, 12 cases of malignant neoplasms and 2 abortions. Only 20.0% of the reports for mepolizumab were considered serious.

Conclusions

Despite limitations to this kind of study, our conclusions are in line with other studies, which show the favourable benefit-risk profile of this recent therapeutic approach. Our study also

suggests that it is necessary to continue to develop educational programmes in order to get a better reporting system.

Keywords

Adverse drug reaction; Asthma; Mepolizumab; Monoclonal antibodies; Omalizumab; Pharmacoepidemiology; Pharmacovigilance; Safety; Side-effects

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List of Acronyms

ADR(s)	Adverse drug reaction(s)
AE(s)	Adverse event(s)
CSU	Chronic Spontaneous Urticaria
ILC2	Group 2 innate lymphoid
IgE	Immunoglobulin E
IME	Important Medical Event
IL	Interleukin
MedDRA	Medical Dictionary for Regulatory Activities
mABs	Monoclonal antibodies
INFARMED	National Authority for Medicines and Health Products
INE	National Institute of Statistics
SNF	National Pharmacovigilance System
OR	Odds ratio
PT	Preferred Term
SR(s)	Spontaneous report(s)
SmPC	Summary of Product Characteristics
SOC	System Organ Class
TH2	T helper 2
TSLP	Thymic stromal lymphopoietin
WHO	World Health Organization

1. Introduction

Asthma is a common chronic disease that is estimated to affect 339 million people worldwide, with future increases expected in terms of prevalence.[1] It is defined by chronic airway inflammation, reversible airflow obstruction and enhanced bronchial reactivity, and its clinical manifestations can range from mild to severe. The subgroup of severe asthmatic patients represents a particular problem as they are at a higher risk of asthma-related hospitalization and mortality, have significantly reduced quality of life and account for a disproportionately high burden on asthma-associated healthcare costs.[1] There is, therefore, an urgent need for improved treatment options that will provide asthma control in these patients.

At the same time, it is recognized that allergic diseases are heterogeneous in terms of clinical phenotypes, but also at cellular level. In fact, there has been a dramatic change in our understanding of the immunopathology of allergic diseases in the past decades, with important steps having been taken towards unveiling the complexity of the different mechanisms underlying disease pathogenesis.

An important molecular mechanism of asthma is type 2 inflammation, which occurs in many but not all patients. Airway type 2 immune responses are mainly mediated by eosinophils, mast cells, basophils, T helper 2 (TH2) cells, group 2 innate lymphoid (ILC2) cells and immunoglobulin E (IgE)-producing B cells.[2] According to Fahy, it is generally accepted that upstream events in the airway epithelium, involving master regulators such as thymic stromal lymphopoietin (TSLP), interleukin (IL)-25 or IL-33, result in increased production of type 2 cytokines, including IL-4, IL-5, IL-9, IL-13, IL-25, and IL-31. These drive a cascade of downstream events, such as, IgE-triggered hypersensitivity to aeroallergens, activation of airway epithelial cells, chemoattraction of effector cells (mast cells, eosinophils and basophils), and increased airway remodelling.[2]

This improved understanding of the molecular networks underlying airway disease, has led to its definition by distinct functional or pathobiological mechanisms, in other words, the detection of endotypes. Examples include Th2-high asthma, involving allergic, IgE-mediated asthma, and eosinophilic asthma, involving IL-5 in its pathogenesis. The advantage of this classification is that each endotype can be targeted by treatments that are specific for the underlying molecular mechanism.[2]

In this context, biological drugs (namely monoclonal antibodies (mABs)) specifically constructed to antagonise relevant mediators and cytokines (e.g. IgE, IL-5) have been clinically tested. According to available results, many of these approaches are clinically effective especially in the most severe forms of asthma.[3, 4] In parallel, the safety issue has also emerged and has been acknowledged as a crucial aspect that needs to be monitored.

Biologicals differ from other drugs not only in terms of size, but also in how they are produced, how they behave and mode of action in the body, their stability and their potential to evoke an immune response.[5] Additionally, in pre-market clinical studies, it is difficult to detect most of the adverse drug reactions (ADRs), especially those which are rare or have long latency. It has been estimated that the great majority of serious ADR are only detected in the post-market phase.[6] For these reasons, it is fundamental to implement continuous pharmacovigilance after the drug has been approved for commercialization. Spontaneous reporting is one of the pillars of this surveillance.[7]

Nevertheless, to the best of our knowledge, with regard to biologicals used in asthma, there are no studies exploring all suspected ADR obtained from spontaneous reporting to a national pharmacovigilance authority.

Thus, we aim to characterise the safety profile of mAbs used in the treatment of asthma, through the analysis of Portuguese spontaneous reports (SRs) of suspected ADRs related to those drugs.

2. Materials & Methods

2.1. Study design

Retrospective, observational study, based upon data from the period between February 2006 and October 2018. It focused on SRs of suspected ADRs involving biologicals that have been approved and are prescribed for the treatment of severe asthma in Portugal.

2.2. Procedures

2.2.1. Identification of biologicals prescribed in asthma

This study included all biologicals that have been approved for marketing in Portugal up to 31 October 2018, and which have asthma as a therapeutic indication. Four biologicals meeting these criteria were identified: omalizumab, mepolizumab, reslizumab and benralizumab.

2.2.2. Reported iatrogeny with biologicals indicated for asthma

ADR data were obtained from SRs of suspected ADR sent to the National Pharmacovigilance System (SNF) by health professionals, by drug market authorisation holders and by consumers. The SNF is coordinated by the National Authority for Medicines and Health Products (INFARMED).

The study included SRs of suspected ADRs received by the SNF, involving biologicals, since market launch in Portugal until 31 October 2018. All SRs were included in the study, independently of the therapeutic indications for which the drugs had been prescribed. Initially, 134 SRs were detected for omalizumab, and 12 SRs for mepolizumab. After removal of duplicates, there were 127 SRs for omalizumab and 10 SRs for mepolizumab (Figures 1 and 2), which were regarded as the total number of reports for all purposes of our analysis, except for the "Annual ADR evolution", where the original number of reports was considered, in order to include all reports.

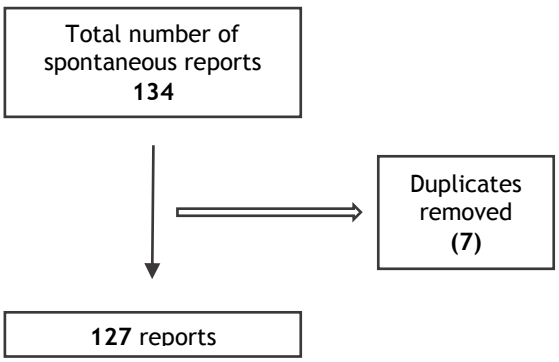

Figure 1 - Flowchart of case selection of omalizumab

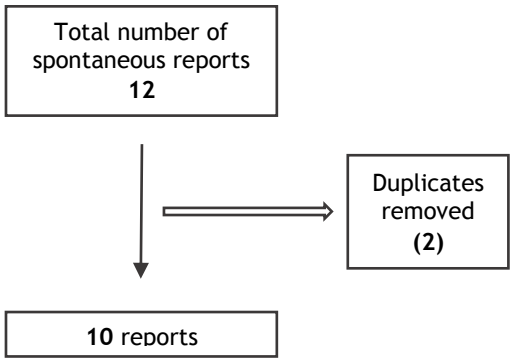

Figure 2 - Flowchart of case selection of mepolizumab

No reporting of ADRs was detected for reslizumab and only one SR was assigned to benralizumab, since these biologicals have been more recently introduced into the market. Thus, these drugs were not further analysed in this study.

An analysis of the SRs was carried out, with reference to the annual evolution of their frequency adjusted to the estimated population of severe asthmatics in Portugal. This was calculated as follows: prevalence of severe asthma in Portugal (7.4% of the asthmatic population),[8] global prevalence of asthma in Portugal (6.8% of general population),[9] and estimates of Portugal´s general population were obtained for each year via the National Institute of Statistics (INE) website.[10] A demographic characterisation, considering gender and age group, was also performed. Each SR was classified according to its seriousness and, in serious cases, the seriousness criterion in question was specified. It is noteworthy saying that each case was given one or more seriousness criteria. According to the World Health Organization (WHO), a serious ADR corresponds to any untoward medical occurrence that, at any dose, results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, is a congenital anomaly/birth defect, or may be considered clinically important and requiring an intervention to prevent one of the abovementioned consequences.[11]

Each SR corresponds to a single individual. But each individual case may correspond to more than one ADR and more than one suspect drug.

Suspected ADRs were studied and displayed according to the Preferred Term (PT) and System Organ Class (SOC) coding of the Medical Dictionary for Regulatory Activities (MedDRA). It was also checked whether or not suspected ADRs of the cases were described in the Summary of Product Characteristics (SmPC) of the respective drug. Finally, a more in-depth analysis of the MedDRA terms belonging to the Important Medical Event (IME) terms list[12] was carried out.

3. Results

3.1. Reported iatrogeny with biologicals indicated for asthma

3.1.1. Annual ADR evolution

In the period from February 2006, the date of the first SR sent to SNF, to 31 October 2018, a total of 134 SRs related to omalizumab were received by the SNF.

Table 1 shows the distribution over the years of the frequency of reports of suspected ADRs to omalizumab and presents these values adjusted to estimates of the prevalence of severe asthma in Portugal, for each year.

Table 1 - Annual distribution of SRs of omalizumab.

Year	Number of SRs	Number of SRs/1000 severe asthmatics
2006	1	0.0189
2007	1	0.0188
2008	2	0.0376
2009	2	0.0376
2010	4	0.0752
2011	9	0.1697
2012	11	0.2084
2013	9	0.1715
2014	10	0.1915
2015	12	0.2306
2016	8	0.1542
2017	22	0.4248
2018	43	0.8325

Figure 3 shows the graph of the temporal evolution of SRs adjusted to the estimates of the prevalence of severe asthma in the resident population in Portugal in each year.

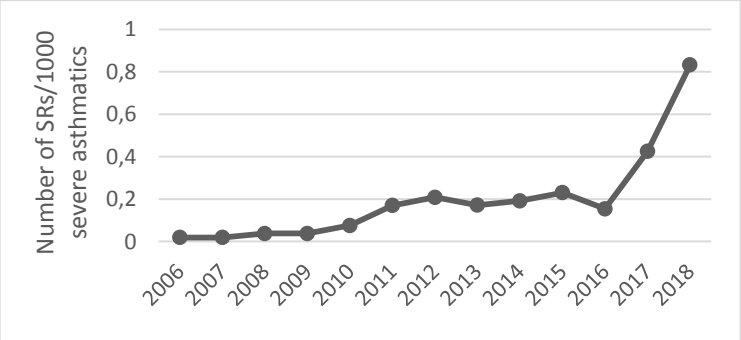

Figure 3 - Temporal evolution of SRs of suspected ADRs to omalizumab adjusted to the estimated total of patients with severe asthma in Portugal.

Overall, the reporting trend was increasing between 2006 and 2018, with a large increase in the number of notifications in 2017 and 2018, with 65 SRs in those two years, almost half

(48.5%) of the total number of SRs registered since the beginning of marketing of omalizumab.

For mepolizumab, since the date of the first SR sent to SNF, November of 2017, up to 31 October 2018, there were 12 SRs. In 2017, one SR was sent (0.019 SR/1000 severe asthmatics) and the remaining 11 SRs were reported in 2018 (0.2323 SR/1000 severe asthmatics).

3.1.2. Demographic aspects

The patients´ demographic profile, gender and age, is shown in Tables 2 and 3, respectively.

Table 2 - Distribution of the gender of patients involved in SRs of suspected ADRs to biologicals.

	Gender					
	Feminine		Masculine		Not specified	
	n	%	n	%	n	%
Omalizumab	96	75.6	29	22.8	2	1.6
Mepolizumab	9	90.0	1	9.0	0	0.0

In terms of gender, the vast majority of patients were female with both omalizumab and mepolizumab (Table 2). In only two patients (1.6%) of omalizumab SRs was information about their gender missing.

Table 3 - Distribution of the age group of the patients involved in SRs of suspected ADRs to biologicals.

	Age group													
	2 to 11 years		12 to 17 years		18 to 44 years		45 to 64 years		65 to 74 years		≥75 years		Unknown	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Omalizumab	1	0.8	5	3.9	39	30.7	39	30.7	8	6.3	1	0.8	34	26.8
Mepolizumab	0	0.0	0	0.0	2	20.0	3	30.0	1	10.0	1	10.0	3	30.0

Regarding omalizumab, age was reported in 93 cases, which corresponds to 73.2% of the total. The two most frequent age groups were those between 18 and 44 years of age (30,7%) and between 44 and 64 years of age (30.7%).
In the case of mepolizumab, 3 (30.0%) SRs did not present the information of the age group. Still, half (n = 5; 50.0%) of SRs involved patients who were between 18 and 64 years old.

3.1.3. Clinical characterisation of suspected ADRs

Table 4 shows the frequency distribution of the suspected ADRs reported with omalizumab, categorised according to the SOC and PT terms (with frequency greater than or equal to 1%). This table also includes information about whether the ADR is described in the SmPC of the drug.

Table 4 – Suspected ADRs reported with omalizumab, according to SOC and PT (frequency ≥1%) and state of description in the SmPC (d - described; nd - not described).

SOC PT	Number of events (%)	Presence of ADR (PT) in SmPC
Respiratory, thoracic and mediastinal disorders	**98 (25.1%)**	
Asthma	73 (18.7%)	d
Dyspnoea	6 (1.5%)	d
Bronchospasm	4 (1.0%)	d
Investigations	**73 (18.7%)**	
Blood pressure increased	6 (1.5%)	nd
Weight increased	6 (1.5%)	d
Forced expiratory volume decreased	5 (1.3%)	d
Heart rate increased	5 (1.3%)	d
Blood pressure decreased	4 (1.0%)	d
Blood pressure systolic increased	4 (1.0%)	nd
Heart rate decreased	4 (1.0%)	nd
Weight decreased	4 (1.0%)	d
General disorders and administration site conditions	**45 (11.5%)**	
Drug ineffective	7 (1.8%)	nd
Fatigue	4 (1.0%)	d
Oedema peripheral	4 (1.0%)	d
Skin and subcutaneous tissue disorders	**33 (8.4%)**	
Pruritus	4 (1.0%)	d
Urticaria	4 (1.0%)	d
Musculoskeletal and connective tissue disorders	**22 (5.6%)**	
Arthralgia	8 (2.0%)	d
Myalgia	5 (1.3%)	d
Infections and infestations	**18 (4.6%)**	
Respiratory tract infection	5 (1.3%)	d
Influenza	4 (1.0%)	nd
Nervous system disorders	**15 (3.8%)**	
Headache	5 (1.3%)	d
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**15 (3.8%)**	
Breast cancer	4 (1.0%)	nd
Gastrointestinal disorders	**13 (3.3%)**	
Injury, poisoning and procedural complications	**10 (2.7%)**	
Maternal exposure during pregnancy	5 (1.3%)	nd
Cardiac disorders	**8 (2.0%)**	
Immune system disorders	**6 (1.5%)**	
Pregnancy, puerperium and perinatal conditions	**6 (1.5%)**	
Reproductive system and breast disorders	**5 (1.3%)**	
Vascular disorders	**5 (1.3%)**	
Metabolism and nutrition disorders	**5 (1.3%)**	
Eye disorders	**4 (1.0%)**	
Surgical and medical procedures	**3 (0.8%)**	
Hepatobiliary disorders	**3 (0.8%)**	
Ear and labyrinth disorders	**1 (0.3%)**	
Psychiatric disorders	**1 (0.3%)**	
Endocrine disorders	**1 (0.3%)**	
Blood and lymphatic system disorders	**1 (0.3%)**	

Of the 27 SOCs of the MedDRA dictionary, only "renal and urinary disorders", "congenital, familial and genetic disorders", "social circumstances" and "product issues" SOCs were not associated with any ADR.

Suspected cases of ADRs included in "respiratory, thoracic and mediastinal disorders" were the most frequently reported (n = 98; 25.1%) and together with "investigations" and "general disorders and administration site conditions" totaled more than half (n = 216; 55.2%) of all suspected ADRs reported. The "asthma" reaction was the most frequent ADR (n = 73; 18.7%), followed by "arthralgia" reaction (n = 8, 2.0%) and "drug ineffective" reaction (n = 7; 1.8%). There were 8 different reactions (2.0%), according to PT terms, that could be grouped in a wider group of injection-site reactions. The majority of suspected ADRs (n = 211; 54.0%) were reported less frequently than 1%. A list of all suspected ADRs reported with omalizumab is given in Table 8 (Appendix).

Of the 7 cases of "drug innefective", 6 had a known condition for which omalizumab had been prescribed (3 cases with Chronic Spontaneous Urticaria (CSU), 2 cases with Atopic Eczema; 1 case of Asthma). Only two reports (the two Atopic Eczema cases) had a baseline IgE value (20000 IU/mL and 42 IU/mL). The administered dose of omalizumab was only known in two cases of CSU, with 300 mg/month and 150 mg/month, respectively.

The total number of suspected ADRs reported with omalizumab was 391, according to the PT term, comprising 191 different types of suspected ADRs. Of these, 102 (53.4%) are not described in the SmPC of omalizumab.

Table 5 shows the frequency distribution of the suspected ADRs reported to mepolizumab, categorised according to SOC and PT terms. This table also includes information about whether the ADR is described in the SmPC of the drug.

Table 5 - Suspected ADRs reported with mepolizumab, according to SOC and PT, and state of description in the SmPC (d - described; nd - not described).

SOC PT	Number of events(%)	Presence of ADR in SmPC
Musculoskeletal and connective tissue disorders	**5 (25.0%)**	
Arthralgia	4 (20.0%)	nd
Myalgia	1 (5.0%)	d
General disorders and administration site conditions	**3 (15.0%)**	
Cough	1 (5.0%)	d
Fatigue	1 (5.0%)	nd
Pyrexia	1 (5.0%)	d
Infections and infestations	**2 (10.0%)**	
Pharyngitis	1 (5.0%)	d
Respiratory tract infection	1 (5.0%)	d
Gastrointestinal disorders	**2 (10.0%)**	
Abdominal pain lower	1 (5.0%)	nd
Abdominal pain upper	1 (5.0%)	d
Social circumstances	**1 (5.0%)**	
Impaired quality of life	1 (5.0%)	nd
Investigations	**1 (5.0%)**	
Weight increased	1 (5.0%)	nd
Skin and subcutaneous tissue disorders	**1 (5.0%)**	
Pruritus	1 (5.0%)	d
Respiratory, thoracic and mediastinal disorders	**1 (5.0%)**	
Wheezing	1 (5.0%)	d
Eye disorders	**1 (5.0%)**	

Optic ischaemic neuropathy	1 (5.0%)	nd
Nervous system disorders	**1 (5.0%)**	
Headache	1 (5.0%)	d
Psychiatric disorders	**1 (5.0%)**	
Middle insomnia	1 (5.0%)	nd
Immune system disorders	**1 (5.0%)**	
Hypersensitivity	1 (5.0%)	d

Of the 27 SOCs of the MedDRA dictionary, only 12 were associated with ADRs.

Half (n = 10; 50.0%) of the suspected ADRs reported with mepolizumab are included in three SOCs: "musculoskeletal and connective tissue disorders", "general disorders and administration site conditions" and "infections and infestations". The “arthralgia” reaction was the most frequent suspected ADR.

The total number of suspected ADRs reported with mepolizumab was 20, according to the PT term, including 17 different types of suspected ADRs. After analysing them, 7 of the 17 suspected ADRs, (41.2%) are not described in the SmPC of mepolizumab.

3.1.4. Seriousness

The distribution in terms of the seriousness of SRs of each biological is shown in Table 6.

Table 6 - Frequency distribution of serious cases per biological drug.

	Seriousness			
	Serious		Not serious	
	n	%	n	%
Omalizumab	91	71.7	36	28.3
Mepolizumab	2	20.0	8	80.0

Of the suspected ADRs reported with omalizumab, 71.7% were serious, whereas for mepolizumab only 20.0% of the reports were considered serious, with the majority being not serious (n = 8, 80.0%).

Figure 4 shows the distribution of each seriousness criterion in relation to the total number of seriousness criteria present in the serious cases of omalizumab.

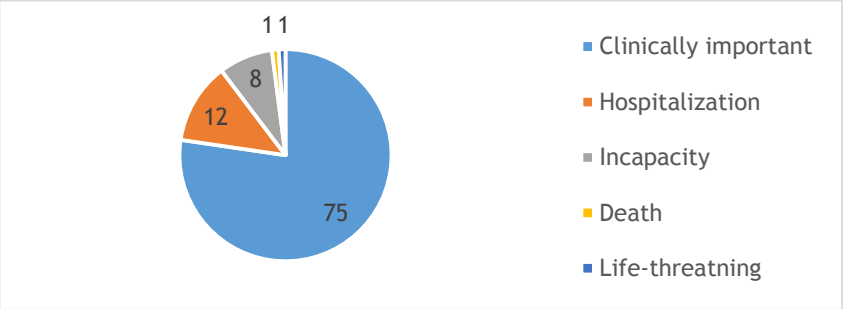

Figure 4 - Distribution of seriousness criteria in serious SRs of omalizumab.

Of the 91 serious cases that occurred with omalizumab, 97 criteria of severity were recorded, and 75 (77.3%) corresponded to the "clinically important" criterion. There was a fatal case, a road traffic accident, and one life-threatening case, with patient experiencing loss of consciousness, 3 to 5 minutes after drug administration, lasting approximately 20 minutes. A more detailed description of these cases is shown in table 9 (Appendix).
With mepolizumab, there were 3 seriousness criteria reported in the two serious cases, the "clinically important" criterion in both cases, and "hospitalization".

Of the 91 serious cases associated with omalizumab, 35 included MedDRA terms belonging to the IME list. There was a total of 46 suspected ADRs that belong to this list and which are presented in table 7.

Table 7 – Suspected ADRs belonging to the IME list.

GROUP	ADRs (number)
IMMUNE SYSTEM DISORDERS	Angioedema (3) Anaphylactic shock (1) Anaphylactic reaction (1) Autoimmune disorder (1)
MALIGNANT NEOPLASMS	Breast malignant tumours (6) Gastric cancer (1) Metastases to liver (1) Leukemia (1) Lymphoma (1) Malignant melanoma (1) Neoplasm malignant (1)
INFECTIONS	Respiratory tract infection (5) Tuberculosis (2) Urinary tract infection bacterial (1) Abscess neck (1) Subcutaneous abscess (1) Pneumonia (1)
CARDIOVASCULAR DISORDERS	Pericardial effusion (2) Deep vein thrombosis (2) Myocardial ischaemia (1) Stress cardiomyopathy (1) Bradycardia (1)
RESPIRATORY DISORDERS	Bronchial obstruction (1) Asthmatic crisis (1) Pulmonary embolism (1)
GASTROINTESTINAL AND HEPATOBILIARY DISORDERS	Pancreatitis acute (1) Gallbladder enlargement (1)

METABOLISM DISORDERS	Diabetes mellitus (1)
NERVOUS SYSTEM DISORDERS	Loss of consciousness (1)
SURGICAL AND MEDICAL PROCEDURES	Thyroidectomy (1)
PREGNANCY DATA	Abortion (2)

For mepolizumab, both serious cases that were reported had MedDRA terms belonging to the IME list. One of the cases was “optic ischaemic neuropathy” and the other was “respiratory tract infection”.

Two tables, Table 10 and 11, are presented in the appendix, with a brief summary of the cases that presented MedDRA terms belonging to the IME list of omalizumab and mepolizumab, respectively.

4. Discussion

4.1. Annual ADR evolution

Reports of suspected ADRs submitted to the SNF database were used to conduct a retrospective pharmacovigilance analysis aimed at evaluating the safety profile of omalizumab and mepolizumab use in Portugal.

A total of 134 SRs were collected for omalizumab from 2006 to October 2018 (average of 0.1978 reported cases per thousand severe asthmatics per year). In general, there was a trend toward increased reporting as the years progressed, and 48.5% of the cases were reported during the last 2 years of the study period. The SNF received a total of 12 SRs of mepolizumab, 1 in 2017 and 11 and 2018 (average of 0.1257 reported cases per thousand severe asthmatics per year).

This increasing reporting rate can be possibly explained by the raising use of these drugs, as mAbs represent a current trend in the pharmaceutical industry. With their increasing clinical use, the total number of ADR reports is expected to increase, as is shown by a study from Korea where there was a 295-fold increase from 11 reports in 2005 to 3241 reports on mAbs in 2014.[13]

It is worth mentioning that SRs sent in November and December 2018 were not considered in our study and those reports could further emphasize this general tendency of increased reporting particularly in more recent years. Even more important is the fact that the number of reports shown does not necessarily reflect the actual frequency for an ADR to occur, as the SNF does not receive reports for every adverse event that occurs with these drugs.[14] Besides that, no exact information on the number of patients exposed to omalizumab and mepolizumab was known to the authors; thus, the estimates of Portuguese severe asthmatics were used to calculate the reporting rate but, as not every severe asthmatic is on mAb therapy, the incidence rate of an event cannot be correctly determined this way. Consequently, based on available data, we can just speculate about the true reporting rate.

4.2. Demographic aspects

In terms of demographic characteristics, with both omalizumab and mepolizumab, the vast majority of patients were female (75.6% and 90.0%, respectively), and between 18 and 64 years old (61.4% and 50.0%, respectively).

Gender discrepancy in omalizumab ADRs was also shown in a long-term post-marketing study in Japan, with an ADR incidence in women and men of 9.82% and 4.90%, respectively.[15] Zopf et al had previously shown that the female gender has a significant influence on the risk of having ADRs (odds ratio (OR) 1.596). This higher incidence was observed in all age classes, except for children and younger adults. Potential reasons for this different risk profile are

female differences in physical aspects (body-water space, muscle mass, organ blood flow, organ function), physiological characteristics (menopause, pregnancy and menstruation) and in pharmacodynamics and pharmacokinetics (bioavailability, distribution, metabolism and excretion).[16] Furthermore, asthma is characterised by gender disparity in prevalence. It shows a male predominance before puberty and a female predominance in adulthood.[17] Since in our study the majority of patients were adults, this could explain the increased prevalence of ADRs in women.

Although there is an increased risk for ADRs with age and polypharmacy,[16] in our study, the age group with more suspected ADRs was 18-64 years. Adachi et al, in a Japanese long-term post-marketing study, also demonstrated a lower incidence of ADRs in patients ≥65 years (6.57%) compared with patients aged <65 years (9.25%).[15] A study of asthma epidemiology in Portugal found a higher prevalence of asthma in older adult population (8.0%) compared to the age groups 0-17 years (7.2%) and 18-65 years (6.3%). However, after adjusting for conditions with similar symptoms in order to exclude possible confounding, the prevalence of asthma dropped significantly in elderly people without heart disease, to 4.9% (whereas it dropped to 5.8% in the 18-65 years group).[9] Thus, although the period of childhood and adolescence is the most prevalent one for asthma after controlling confounding factors, the fact that, according to INE[10], the 18-64 years age group contains the majority of Portuguese population may explain why most suspected ADRs are reported in adults.

4.3. Clinical characterisation of suspected ADRs

After all duplicate reports were removed, we identified a total of 127 SRs including 391 suspected ADRs for omalizumab, and 10 SRs including 20 suspected ADRs for mepolizumab.

With omalizumab, the most frequently involved SOC groups were “respiratory, thoracic and mediastinal disorders”, “investigations” and “general disorders and administration site conditions”. In a real-world clinical practice setting study of a large Japanese adult population with severe asthma, the most frequently reported adverse events (AEs) by SOC were “respiratory, thoracic and mediastinal disorders”, “infections and infestations” and “general disorders and administration site conditions”.[15] On the other hand, when specifically analysing AEs regarded as being drug-related, in other words, the ADRs, the distribution changed, with “general disorders and administration site conditions”, “skin and subcutaneous tissue disorders” and “nervous system disorders” being the most frequent.[15]

According to the PT term, the suspected ADRs most frequently reported in our study were “asthma”, “arthralgia” and “drug ineffective”. In the same Japanese study mentioned earlier, asthma was also the most frequent reaction, and other common AEs were

nasopharyngitis, pneumonia, and bronchitis; however, the most common ADRs were malaise, urticaria, dizziness, pyrexia, and rash.[15] In an analysis of four randomized controlled trials, omalizumab was well tolerated, and common AEs included: lower respiratory tract infection, nasopharyngitis, headache, injection site pain, injection site reaction and arthralgia.[18]
In our research, we identified 8 injection-site reactions, totaling 2% of all suspected ADRs. Previously, a Cochrane systematic review had demonstrated that omalizumab had a good safety profile, but more injection site reactions were observed (from 5.6% with placebo to 9.1% with omalizumab).[3]

Our analysis revealed "asthma" reaction as the most frequent suspected ADR. We could speculate whether before starting omalizumab the asthma control in these patients was even worse or if the treatment with omalizumab was ineffective and should be discontinued. In favour of the former, a Cochrane systematic review evidenced a significant advantage favouring subcutaneous omalizumab with regard to experiencing an asthma exacerbation (OR 0.55), compared with the control group receiving background inhaled corticosteroid steroid therapy.[3] Furthermore, a French study has shown that more than double the number of under-dosed patients discontinued omalizumab therapy due to unsatisfactory therapeutic effect, compared with correctly dosed patients (36.4% versus 15.0%).[19] Therefore, it is essential that the correct dose of omalizumab is calculated and administered for each individual patient before assuming the drug is innefective, but also keeping in mind that despite being highly effective in reducing the risk of exacerbations it does not eliminate it.

In our study, the "drug ineffective" reaction was reported seven times (3 cases with CSU, 2 with Atopic Eczema, 1 with Asthma and 1 with unknown condition). Only two reports had a baseline IgE value. In addition, only two cases had a known administered dose (300 milligrams (mg)/month and 150 mg/month), both being related to CSU. According to its SmPC, omalizumab has two approved therapeutic indications, allergic asthma and CSU.[20] For asthma, dosing is determined on an individual basis from body weight and serum baseline IgE level.[20] For CSU, the administration of 300 mg every four weeks is recommended.[20] Knowing this, one of the cases of "drug ineffective" could be explained by under-dosing. It should be noted that 5 of the 7 cases did not have any information on the dose administered. Moreover, in the asthma case neither baseline IgE value nor body weight were described, which impairs any conclusion as to whether these cases were caused by inappropriate dose or in fact due to ineffectiveness of the drug.

With mepolizumab, the most frequently involved SOC groups correspond to "musculoskeletal and connective tissue disorders" and "general disorders and administration site conditions".
According to PT term, "arthralgia" reaction was the most frequently suspected ADR, and all other suspected ADRs were reported only once. In a long-term safety assessment study, with

a group of 347 patients enrolled for an average of 3.5 years, arthralgia was a reaction that occurred in 17% of patients of that study; however, the most frequent AEs were respiratory tract infection, headache, asthma worsening and bronchitis.[21] Safety data from pivotal studies that investigated the clinical efficacy of mepolizumab indicated it was well tolerated, with the most frequently reported AEs being headache, nasopharyngitis, worsening of asthma, and local injection reactions.[22] Finally, a Cochrane systematic review of the effects of mepolizumab versus control group on conventional therapy for asthma, concluded there were no excess serious AEs with mepolizumab, and there was indeed a reduction in favour of it, which could be due to a beneficial effect on asthma-related serious adverse events.[4]

A significant finding of our study is the great proportion of suspected ADRs that are not described in the drug SmPC. This absence of description was found with omalizumab and mepolizumab in 53.4% and 41.2% of the reactions reported, respectively.

4.4. Seriousness

With omalizumab, 71.7% of the reports involved serious suspected ADRs, whereas for mepolizumab only 20.0% of the reports were considered serious. This difference in the frequency of serious cases is worth of note as it suggests there may be a different safety profile in terms of seriousness between the two drugs. However, both mepolizumab and omalizumab are associated with a decrease in the occurrence of serious AEs when compared with placebo,[3, 4] and, in addition, a comparison study between both drugs in severe asthmatics found comparable safety profiles, although it had limitations given the indirect nature of the comparison and heterogeneity between included trials.[23]

In our study, there were 2 episodes of anaphylaxis reported with omalizumab. In previous studies, the frequency of anaphylaxis in omalizumab-treated patients has varied, with anaphylaxis rates of 0.09%[24], 0.17%[15] and 0.20%[25]. Nonetheless, it is comparable to the estimated frequency of anaphylaxis in the general population, as Lieberman et al[26] estimated it to be between 50 and 2000 episodes per 100,000 persons, or a lifetime prevalence of 0.05% to 2.0%.

Due to mAbs interference with the immune system, one of the major concerns from the very beginning was the risk of inducing or unmasking malignancies. Our study revealed 12 cases of malignancies, with 6 cases of malignant breast tumours and other 6 cases being reported only once. In 2003, an analysis of pooled clinical trial data detected malignancies in 0.5% of omalizumab-treated patients compared with 0.2% of control subjects.[27] Since then, new studies were performed that did not corroborate the findings above. A pooled analysis of clinical trials, using a much larger data set than the earlier, and the EXCELS study (Study of

Xolair® to Evaluate Effectiveness and Long-Term Safety in Patients With Moderate to Severe Asthma) did not identify any association between omalizumab therapy and risk of malignancy.[28, 29] However, the latter study had limitations in the study design that precluded definitively ruling out a malignancy risk.[30]

Regarding the risk of infections with omalizumab, we found 11 cases of infections including terms that belong to the IME list. There is a concern of a potential increased susceptibility to parasitic infections among patients receiving omalizumab, since IgE is known to be actively involved in the immune response against parasites.[31] In a study addressing this subject, it is suggested that individuals at high-risk for geohelminth parasite infections may be at greater risk for infection during omalizumab treatment; however, no differences were observed in terms of infection severity or response to antihelmintic drugs. Thus, in spite of this possible increased risk, the authors believed this was likely to be of no clinical significance.[32] Regarding infections in general, no significant differences in the incidence of infection were found between study groups in pivotal randomised controlled trials performed in pre-market period, with most events being upper or lower respiratory tract infections.[31]

Concerning cardiovascular safety, in our investigation, there were 7 cases of cardiovascular disorders including terms that belong to the IME list: pericardial effusion and deep vein thrombosis, twice each; and myocardial ischaemia, stress cardiomyopathy and bradycardia, reported just once. In the literature, a long-term safety study, the EXCELS study, showed that patients receiving omalizumab had a higher incidence at 5 years of cardiovascular events. However, this study had several limitations, and further evidence is needed.[33] Such events were not described in previous analyses of clinical data, and systematic reviews have not observed increased cardiovascular risk among patients taking omalizumab in studies shorter than one year.[18, 34]

Our research showed two cases of abortions associated with omalizumab. In the EXPECT study (The Xolair® Pregnancy Registry study), data concerning the use of omalizumab in humans during pregnancy revealed the absence of an increased prevalence of major birth anomalies or patterns of major birth anomalies beyond that seen in the general asthma population, although authors recognized the small sample size as a limitation.[35]

Mepolizumab was associated with a case of infection that belongs to the IME list, particularly a respiratory tract infection. The clinical development programme for mepolizumab in severe eosinophilic asthma has not demonstrated significant differences in the incidence of infection between mepolizumab-treated and control groups. Only two mepolizumab-treated patients recruited in two separate trials developed herpes zoster during the respective study periods.[31] More recently, in a study assessing long-term safety, twenty-four (7%) patients experienced

an on-treatment opportunistic infection, of whom 8 (2%) patients experienced herpes zoster infection.[21] The critical role displayed by IL- 5 in eosinophil survival and functionality can represent an at least theoretical concern about the eventual risk of parasitic infections among patients receiving mepolizumab, since eosinophils are involved in the natural defense against parasites. Despite this, no cases of parasitic infection have been reported to date in patients receiving IL-5-targeted agents.[31]

According to our best knowledge, the current pharmacovigilance analysis of mAbs used in asthma is the first complete analysis of the spontaneous reporting of a national pharmacovigilance authority. Because of this, comparison with other studies is harder to make but the conclusions of the present study are generally in concordance with available information from other studies of different design format.

Spontaneous reporting of suspected ADRs has been of special value in alerting health professionals to possible iatrogenic disorders.[14] However, the analysis of such reports may have several limitations, which require consideration prior to drawing conclusions about such findings. First, only a very small proportion of the reactions that occur are reported. Rawlins[14] has estimated that reported ADRs rarely exceed 10 to 15% of the real total. Under-reporting reduces sensitivity because it underestimates the frequency and thus the impact of the problem and makes the system more vulnerable to selective reporting which may introduce a serious bias.[7] Second, the presence of confounding factors, for example, underlying medical disorders and concomitant medications, besides the fact that a significant proportion of reports may omit critical information,[14] makes confirmation whether a drug product actually caused a specific event a rather difficult task in several cases.
Nevertheless, it routinely monitors the safety of all drugs in the market from their inception, being the best method to generate signals on new or rare ADRs.[7]

5. Conclusions

In conclusion, in our study, an increasing trend of ADRs reporting was found. With both omalizumab and mepolizumab the majority of reports were in females and in adults. Most reports were serious, for omalizumab, and not serious, for mepolizumab. Even though there are some limitations to this kind of study, it confirms the favourable benefit-risk profile of this recent therapeutic approach, despite a significant proportion of suspected ADRs in our study not being described in the SmPc of the respective drugs. Finally, our study suggests that it is necessary to continue to develop educational programmes in order to get a better reporting system, informing people about the importance of them having an active role in drugs´ safety monitoring by reporting suspected ADR to authorities, and giving the fullest possible description of cases.

Future studies comparing the Portuguese reality with other nations´ spontaneous reporting databases will be of value. We suggest health authorities to regularly develop awareness activities targeting health professionals and public in general, in order to reduce under-reporting and towards better reporting, so that new studies even closer to reality can be performed.

In addition, new mAbs, other than omalizumab and mepolizumab, have recently been approved for use in asthma and are making their first steps in post-market period, so “real-life” studies of their effectiveness and safety will also be important in the future.

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7. Appendices

Appendix 1 - Listing of all suspected ADRs reported to omalizumab

Table 8 - Complete listing of suspected ADRs to omalizumab.

SOC PT	Number of events (%)	Presence of ADR in SmPC
Respiratory, thoracic and mediastinal disorders	**98 (25,1%)**	
Asthma	73 (18,7%)	d
Dyspnoea	6 (1,5%)	d
Bronchospasm	4 (1,0%)	d
Cough	2 (0,5%)	d
Wheezing	2 (0,5%)	d
Asthmatic crisis	1 (0,3%)	d
Bronchial obstruction	1 (0,3%)	d
Dysphonia	1 (0,3%)	nd
Dyspnoea exertional	1 (0,3%)	nd
Lung disorder	1 (0,3%)	d
Nasal disorder	1 (0,3%)	nd
Paranasal cyst	1 (0,3%)	nd
Pulmonary embolism	1 (0,3%)	nd
Respiratory disorder	1 (0,3%)	d
Rhinitis allergic	1 (0,3%)	nd
Throat irritation	1 (0,3%)	d
Investigations	**73 (18,7%)**	
Blood pressure increased	6 (1,5%)	nd
Weight increased	6 (1,5%)	d
Forced expiratory volume decreased	5 (1,3%)	d
Heart rate increased	5 (1,3%)	d
Blood pressure decreased	4 (1,0%)	d
Blood pressure systolic increased	4 (1,0%)	nd
Heart rate decreased	4 (1,0%)	nd
Weight decreased	4 (1,0%)	d
Blood immunoglobulin E increased	2 (0,5%)	nd
Blood pressure diastolic increased	2 (0,5%)	nd
Blood pressure systolic decreased	2 (0,5%)	d
Blood triglycerides increased	2 (0,5%)	nd
Forced vital capacity decreased	2 (0,5%)	d
Peak expiratory flow rate decreased	2 (0,5%)	d
Transaminases increased	2 (0,5%)	nd
Blood cholesterol abnormal	1 (0,3%)	nd
Blood cholesterol increased	1 (0,3%)	nd
Blood glucose increased	1 (0,3%)	nd
Blood immunoglobulin E decreased	1 (0,3%)	d
Blood pressure abnormal	1 (0,3%)	nd
Blood pressure diastolic decreased	1 (0,3%)	d
Blood triglycerides abnormal	1 (0,3%)	nd
Blood uric acid increased	1 (0,3%)	nd
Body height increased	1 (0,3%)	nd
Ejection fraction decreased	1 (0,3%)	nd
Eosinophil count increased	1 (0,3%)	d
Forced expiratory flow decreased	1 (0,3%)	d
Forced expiratory volume increased	1 (0,3%)	d
Heart rate irregular	1 (0,3%)	nd
High density lipoprotein decreased	1 (0,3%)	nd
Human anti-human antibody test	1 (0,3%)	nd
Oxygen saturation decreased	1 (0,3%)	d
Peak expiratory flow rate increased	1 (0,3%)	d

Plateletcrit decreased	1 (0,3%)	nd
Troponin increased	1 (0,3%)	nd
Weight abnormal	1 (0,3%)	d
General disorders and administration site conditions	**45 (11,5%)**	
Drug ineffective	7 (1,8%)	nd
Fatigue	4 (1,0%)	d
Oedema peripheral	4 (1,0%)	d
Pain	3 (0,8%)	d
Asthenia	2 (0,5%)	d
Chest pain	2 (0,5%)	d
Face oedema	2 (0,5%)	d
Feeling hot	2 (0,5%)	nd
Malaise	2 (0,5%)	nd
Pyrexia	2 (0,5%)	d
Chest discomfort	1 (0,3%)	d
Condition aggravated	1 (0,3%)	nd
Influenza like illness	1 (0,3%)	d
Injection site erythema	1 (0,3%)	d
Injection site hypoaesthesia	1 (0,3%)	nd
Injection site nodule	1 (0,3%)	d
Injection site oedema	1 (0,3%)	d
Injection site pain	1 (0,3%)	d
Injection site papule	1 (0,3%)	d
Injection site reaction	1 (0,3%)	d
Injection site warmth	1 (0,3%)	d
Peripheral swelling	1 (0,3%)	d
Swelling	1 (0,3%)	d
Therapeutic response decreased	1 (0,3%)	nd
Therapy non-responder	1 (0,3%)	nd
Skin and subcutaneous tissue disorders	**33 (8,4%)**	
Pruritus	4 (1,0%)	d
Urticaria	4 (1,0%)	d
Angioedema	3 (0,8%)	d
Dermatitis atopic	3 (0,8%)	nd
Erythema	3 (0,8%)	d
Pruritus generalised	2 (0,5%)	d
Alopecia	1 (0,3%)	d
Alopecia areata	1 (0,3%)	nd
Blister	1 (0,3%)	d
Chronic spontaneous urticaria	1 (0,3%)	d
Eczema	1 (0,3%)	nd
Hyperhidrosis	1 (0,3%)	nd
Macule	1 (0,3%)	d
Papule	1 (0,3%)	d
Rash	1 (0,3%)	d
Rash erythematous	1 (0,3%)	d
Rash maculo-papular	1 (0,3%)	d
Rash papular	1 (0,3%)	d
Skin lesion	1 (0,3%)	d
Skin reaction	1 (0,3%)	d
Musculoskeletal and connective tissue disorders	**22 (5,6%)**	
Arthralgia	8 (2,0%)	d
Myalgia	5 (1,3%)	d
Fibromyalgia	2 (0,5%)	nd
Back pain	1 (0,3%)	nd
Intervertebral disc protrusion	1 (0,3%)	nd
Joint effusion	1 (0,3%)	d
Limb deformity	1 (0,3%)	nd
Muscle fatigue	1 (0,3%)	nd
Musculoskeletal pain	1 (0,3%)	d
Osteoporosis	1 (0,3%)	nd
Infections and infestations	**18 (4,6%)**	
Respiratory tract infection	5 (1,3%)	d

Influenza	4 (1,0%)	nd
Tuberculosis	2 (0,5%)	nd
Abscess neck	1 (0,3%)	nd
Conjunctivitis	1 (0,3%)	nd
Herpes zoster	1 (0,3%)	nd
Pneumonia	1 (0,3%)	nd
Subcutaneous abscess	1 (0,3%)	nd
Upper respiratory tract infection	1 (0,3%)	d
Urinary tract infection bacterial	1 (0,3%)	nd
Nervous system disorders	**15 (3,8%)**	
Headache	5 (1,3%)	d
Dizziness	2 (0,5%)	d
Movement disorder	2 (0,5%)	nd
Loss of consciousness	1 (0,3%)	d
Muscle contractions involuntary	1 (0,3%)	nd
Paraesthesia	1 (0,3%)	d
Presyncope	1 (0,3%)	nd
Somnolence	1 (0,3%)	d
Syncope	1 (0,3%)	d
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**15 (3,8%)**	
Breast cancer	4 (1,0%)	nd
Breast neoplasm	3 (0,8%)	nd
Breast cancer in situ	1 (0,3%)	nd
Gastric cancer	1 (0,3%)	nd
Invasive breast carcinoma	1 (0,3%)	nd
Leukaemia	1 (0,3%)	nd
Lymphoma	1 (0,3%)	nd
Malignant melanoma	1 (0,3%)	nd
Metastases to liver	1 (0,3%)	nd
Neoplasm malignant	1 (0,3%)	nd
Gastrointestinal disorders	**13 (3,3%)**	
Abdominal pain	2 (0,5%)	d
Nausea	2 (0,5%)	d
Vomiting	2 (0,5%)	nd
Abdominal distension	1 (0,3%)	nd
Abdominal pain upper	1 (0,3%)	d
Gastrooesophageal reflux disease	1 (0,3%)	nd
Intra-abdominal fluid collection	1 (0,3%)	nd
Pancreatitis acute	1 (0,3%)	nd
Stomatitis	1 (0,3%)	nd
Tongue oedema	1 (0,3%)	d
Injury, poisoning and procedural complications	**10 (2,7%)**	
Maternal exposure during pregnancy	5 (1,3%)	nd
Inappropriate schedule of drug administration	2 (0,5%)	nd
Product use in unapproved indication	1 (0,3%)	nd
Product use issue	1 (0,3%)	nd
Road traffic accident	1 (0,3%)	nd
Cardiac disorders	**8 (2,0%)**	
Pericardial effusion	2 (0,5%)	nd
Bradycardia	1 (0,3%)	nd
Cardiac disorder	1 (0,3%)	d
Cardiac ventricular disorder	1 (0,3%)	nd
Myocardial ischaemia	1 (0,3%)	d
Stress cardiomyopathy	1 (0,3%)	nd
Systolic dysfunction	1 (0,3%)	nd
Immune system disorders	**6 (1,5%)**	
Oral allergy syndrome	2 (0,5%)	nd
Anaphylactic shock	1 (0,3%)	d
Anaphylactic reaction	1 (0,3%)	d
Autoimmune disorder	1 (0,3%)	nd
Hypersensitivity	1 (0,3%)	d
Pregnancy, puerperium and perinatal conditions	**6 (1,5%)**	
Normal newborn	3 (0,8%)	nd

Abortion	1 (0,3%)	nd
Abortion spontaneous	1 (0,3%)	nd
Prolonged rupture of membranes	1 (0,3%)	nd
Reproductive system and breast disorders	**5 (1,3%)**	
Breast mass	2 (0,5%)	nd
Ovarian cyst	1 (0,3%)	nd
Pelvic fluid collection	1 (0,3%)	nd
Pelvic pain	1 (0,3%)	nd
Vascular disorders	**5 (1,3%)**	
Deep vein thrombosis	2 (0,5%)	nd
Hypotension	2 (0,5%)	d
Hot flush	1 (0,3%)	d
Metabolism and nutrition disorders	**5 (1,3%)**	
Hypercholesterolaemia	2 (0,5%)	nd
Diabetes mellitus	1 (0,3%)	nd
Tetany	1 (0,3%)	nd
Weight fluctuation	1 (0,3%)	d
Eye disorders	**4 (1,0%)**	
Eye oedema	1 (0,3%)	d
Eyelid oedema	1 (0,3%)	d
Parophthalmia	1 (0,3%)	nd
Periorbital oedema	1 (0,3%)	d
Surgical and medical procedures	**3 (0,8%)**	
Off label use	2 (0,5%)	nd
Thyroidectomy	1 (0,3%)	nd
Hepatobiliary disorders	**3 (0,8%)**	
Gallbladder enlargement	1 (0,3%)	nd
Hepatic steatosis	1 (0,3%)	nd
Hepatomegaly	1 (0,3%)	nd
Ear and labyrinth disorders	**1 (0,3%)**	
Tinnitus	1 (0,3%)	nd
Psychiatric disorders	**1 (0,3%)**	
Decreased activity	1 (0,3%)	nd
Endocrine disorders	**1 (0,3%)**	
Goitre	1 (0,3%)	nd
Blood and lymphatic system disorders	**1 (0,3%)**	
Lymphadenopathy	1 (0,3%)	d

Appendix 2 – Description of two serious cases associated with omalizumab

Table 9 - Narrative of two serious cases associated with omalizumab

Death (1)	An adult male patient of about 65 years old started taking omalizumab for the treatment of severe asthma. Two months later, the patient was admitted to the hospital emergency room for an unknown condition and was discharged on the same day. After being discharged the patient had a car accident and died. The physician considered that death was not related to the treatment with omalizumab. The patient's medical history included some comorbidities which were not reported and concomitant medications included several active substances which were not specified.
Life-threatning (1)	A 61-year-old male patient with severe asthma had profuse sweating and hypotension immediately after first injection of omalizumab. In his second dose, two weeks later, the patient has new reaction, this time with loss of consciousness, with recovery in minutes without the need for urgent care. Adverse reaction developed 3 to 5 minutes after drug administration. Loss of consciousness lasted approximately for 20 minutes. Treatment with omalizumab was interrupted. The seriousness criteria was updated to life-threatening.

Appendix 3 - Brief summary of the cases that presented MedDRA terms belonging to the IME list

Table 10 - Brief summary of the cases that presented MedDRA terms belonging to the IME list of omalizumab.

GROUP	ADRs (number)
IMMUNE SYSTEM DISORDERS	**Anaphylactic shock** (1) and **Anaphylactic reaction** (1) - Case of female patient with 20 years that experienced an anaphylactic shock after Xolair administration. Due to this event, she went to the emergency room and recovered completely from the symptoms. Causality of the event was assessed as suspected with Xolair. Months later, and immediately after (10 minutes) a new administration of the drug, she developed urticarial reaction and accentuated respiratory difficulties with important associated desaturation to 80 percent. It was necessary to administrate therapy with hydrocortisone, clemastine and adrenaline. Due to transitory improvement, with repetition of the episode in about 45 minutes, therapy was repeated and it was necessary to administer oxygen under the high flow system and transfering to the intensive care unit. The situation would normalize after 20 hours hospitalized. Therapy with omalizumab was discontinued. **Angioedema** (3) - Two cases of female patients (31-years-old and unknown age) receiving omalizumab for the treatment of chronic spontaneous urticaria. They experienced angioedema. Physician considered it to be due to lack of efficacy of the drug and so he increased the dose of Xolair. At the time of the report, there wasn´t yet any evolution of the case. The other case refers to a 35-year-old male patient, receiving omalizumab for the treatment of chronic spontaneous urticaria. Historical conditions also included angioedema. Six months after initiating treatment, there was a reappearance of angioedema and a CSU relapse which motivated going several times to the emergency room and which did not subside to the quadruple dose of antihistaminics and oral corticoid cycles, due to which a new 6 months cycle of omalizumab was proposed. The reporter did not consider suspicion of lack of efficacy of the product, but to be a case of refractory urticaria, which justified prolonging the treatment. **Autoimmune disorder** (1) - A 37-year-old female patient with severe asthma experienced a reaction in the arm, on an unknown date after one administration. On an unknown date, the patient had autoimmune disease and suspicion of fibromyalgia and lombalgia. Treatment with Xolair was discontinued.
MALIGNANT NEOPLASMS	**Breast malignant tumours** (6) - A 53 year old female patient receiving treatment with omalizumab for severe asthma. More than three years after starting the suspect drug the patient experienced breast cancer. A 55 year old female patient, after nearly six years of therapy with omalizumab for severe asthma, the patient was diagnosed with stage 1 ductal breast cancer of right

	breast. A female patient of unknown age and receiving omalizumab for unknown indication, was diagnosed with breast cancer, invasive carcinoma and "*in situ*" ductal carcinoma of the right breast, more than three years after starting treatment. She had a history of immunosuppression therapy (long term corticotherapy for asthma) and family history of malignancy (paternal aunt with breast cancer diagnosed at 65 years of age). A 52-year-old female patient that, five years later from starting the treatment for chronic spontaneous urticaria, developed left breast carcinoma with hepatic metastasis. A 41-year-old female patient, whose family history included breast cancer affecting paternal great-aunt (at 40 years old) and third degree cousin (at 55 years old), pancreatic cancer from paternal grandmother (at 70 years old), and a maternal grandmother that passed away from cancer at the age of 80. Received omalizumab for severe asthma and was diagnosed invasive breast carcinoma. **Gastric cancer** (1) - Female patient of unknown age, which medical history included adenocarcinoma, received omalizumab for severe asthma. After 7 months of therapy, the patient was diagnosed with gastric cancer in stomach fundus. **Metastases to liver** (1) - A 52-year-old female patient that, five years later from starting the treatment for chronic spontaneous urticaria, developed left breast carcinoma with hepatic metastasis. **Leukemia** (1) and **Lymphoma** (1) - An adult male patient, receiving omalizumab for severe asthma, experienced leukemia and cutaneous lymphoma on an unspecified date. **Malignant melanoma** (1) - An elderly female patient that less than two years after starting treatment with omalizumab, for severe asthma, developed melanoma. **Neoplasm malignant** (1) - A 42-year-old female patient, with a medical history of multinodular bilateral goiter, received omalizumab due to severe asthma. After being submitted to left hemithyoidectomy, the subsequent anatomic-pathologic analysis showed papillary microcarcinoma.
INFECTIONS	**Respiractory tract infection** (5) **Urinary tract infection bacterial** (1) **Abscess neck** (1) **Subcutaneous abscess** (1) **Pneumonia** (1) **Tuberculosis** (2) - A case described as "*positive IGRA (without active tuberculosis)*". A case of pleural tuberculosis.
CARDIOVASCULAR DISORDERS	**Myocardial ischaemia** (1) - A 52 year old female patient, taking omalizumab for unknown indication, had myocardial ischaemia. Therapy with omalizumab was discontinued, but later, as the physician confirmed that the patient was alright, restarted treatment. The cardiology service associated the cardiac event to salbutamol overdose. **Pericardial effusion** (2) - A 53-year-old female patient with medical history of chronic spontaneous urticaria, smoking and also exertional dyspnoea. Months

	after starting treatment with omalizumab, the patient had worsening of dyspnea on effort and worsening of systolic function and small volume circumferential pericardial effusion. Another case of a patient, of unknown age, taking omalizumab for chronic spontaneous urticaria that developed pericardial effusion. **Stress cardiomyopathy** (1) - A 75-year-old female patient with chronic spontaneous urticaria, whose medical history includes dyslipidaemia, hypothyroidism, diabetes mellitus and hypertension. Thirty minutes after the 11th administration of omalizumab, a pre-chordial pain began, of oppressive type and with a duration of more than 20 minutes. Analytically, there was elevation of troponins. Electrocardiogram showed left anterior hemiblock again. The echocardiogram evidenced meso-apical hypokinesia of all segments of the left ventricle and apical ablation, hyperkinesis of the basal segments, with a severe reduction of ejection fraction (30 percent left ventricular ejection fraction). Coronary angiography confirmed the existence of extensive meso-apical dyskinesia, without recoverable changes in the coronary arteries, being compatible with Takotsubo Syndrome (stress cardiomyopathy). The patient was hospitalized in cardiology intensive care treatment unit. Eight days later, normalization of troponin values was observed, with total recovery of global systolic function and improvement of cardiac contractility. The therapy with omalizumab was discontinued on an unknown date. **Deep vein thrombosis** (2) - Two cases, one of a 44-year-old female patient and another referring to a 65-year-old male patient, developed deep vein thrombosis. **Bradycardia** (1) - A case of a 33-year-old female patient, taking omalizumab for asthma, with an episode of bradycardia after administration of the drug. After 15 days she made an electrocardiogram which showed normal pulse.
RESPIRATORY DISORDERS	**Bronchial obstruction** (1) - A case of 23-year-old female patient taking omalizumab for severe asthma with a resulting clinical improvement with asthma control test questionnaire, although maintaining moderate to severe bronchial obstruction on the lung function tests. **Asthmatic crisis** (1) - An asthmatic 55-year-old female patient was hospitalized in intensive care unit with an episode of an asthma crisis. Had necessity of orotracheal intubation and invasive ventilation for 3 days, but the patient eventually recovered. The patient confessed that as she felt very well and had economic difficulties that she did not use her inhalers. Later, the patient was restarted with omalizumab without problems. **Pulmonary embolism** (1) - A male patient of unknown age, whose medical history included diabetes mellitus and high cholesterol, started taking omalizumab for severe asthma. After 6 months of therapy the patient had the first symptom, and a pulmonary cyntigraphy detected pulmonary thromboembolism (in both lungs). Omalizumab was temporarily interrupted and the outcome of the event was reported as condition improving.
GASTROINTESTINAL	**Pancreatitis acute** (1) - A 67-year-old male patient, that started taking

AND HEPATOBILIARY DISORDERS	omalizumab a year ago, was hospitalized with an episode of an acute pancreatitis that lasted for 7 days. Once the physician did not believe the omalizumab to be the causing factor, he did not suspend the treatment. The patient was taking montelukast concomitantly, and this drug was classified as co-suspect in this case. **Gallbladder enlargement** (1) - A female patient that, in the diagnostic workup of a breast cancer, completed an abdominal ultrasound which revealed a liver of increased dimensions, with a diffuse increase in echogenicity, in relation with steatotic infiltration, and distended gallbladder without other appreciable changes.
METABOLISM DISORDERS	**Diabetes mellitus** (1) - A 57-year-old male patient, whose medical history included allergic asthma and overweight, was diagnosed with diabetes, 6 months after starting treatment with omalizumab. The physician did not think there was a direct relationship between omalizumab and diabetes, but with a recent weight increase.
NERVOUS SYSTEM DISORDERS	**Loss of consciousness** (1) – Case of a male patient with severe allergic asthma. He had profuse sweating and hypotension immediately after injection that occurred at unkown date. On 16 December 2009, the patient was treated with the second dose and has new reaction, this time with loss of consciousness, with recovery in minutes without the need for urgent care. Adverse reaction developed 3 to 5 minutes after drug administration and lasted approximately for 20 minutes. After the episode, patient was already seated and collaborative. Patient had also some episodes of lipothymia and was kept under observation for 4 hours. His cardiac rate did not fall beyond 70 beats/minute and blood pressure did not fall beyond 95-65 mmHg.
SURGICAL AND MEDICAL PROCEDURES	**Thyroidectomy** (1) - A 42-year-old female patient, with a medical history of multinodular bilateral goiter, received omalizumab due to severe asthma. After being submitted to left hemithyoidectomy, the subsequent anatomic-pathologic analysis showed papillary microcarcinoma.
PREGNANCY DATA	**Abortion** (2) - A case of a 40-year-old pregnant female patient whose fetus died at 7 weeks of gestation according to echo studies. There was a beginning of spontaneous abortion by 8 weeks and after, due to incomplete expulsion, there was induced expulsion. Earlier the treatment with omalizumab was interrupted on the 6th week of pregnancy. A pregnant female patient of 35 years old, with a previous medical history including one abortion and three gestations with 3 children, one that passed away as a baby. Patient decided to continue with the treatment with omalizumab, even though she was informed by the doctor of the lack of knowledge on the absolute safety of the medicine. One month later, it was documented by echography that the fetus stopped growing from pregnancy week 6-7 onwards, and by week 10 she started spontaneous abortion, which was ongoing. NOTE: A noteworthy fact of this study is the existence of 5 reported cases of maternal exposure during pregnancy, the two aforesaid cases of abortion and three cases with a birth of a normal newborn. On one of these cases, the

	omalizumab´s dose was halved after the discovery of pregnancy and there wasn´t any record of complications during pregnancy and the delivery was without intercurrence. In another case, it was reported that mother stopped treatment when it was discovered she was pregnant (of about 2 to 3 weeks). The patient had a pregnancy without events or adverse reactions. On delivery, a caesarian section was performed, firstly because there was a rupture of membranes lasting more than 24 hours, and also because patient had previously underwe**nt** a cesarean section and there was a context of severe asthma. The baby was healthy. In the last case, it was decided to suspend the therapy. The patient delivered a normal male neonate. It was reported that no contraceptive methods were used prior to pregnancy.

Appendix 4 - Brief summary of the cases that presented MedDRA terms belonging to the IME list of mepolizumab

Table 11 - Brief summary of the cases that presented MedDRA terms belonging to the IME list of mepolizumab.

Optic Ischaemic Neuropathy (1) - A 57-year-old female patient who received mepolizumab for asthma. Concurrent medical conditions included dyslipidemia and patient had family history including maternal death due to acute myocardial infarction. The outcome of the ischemic optic neuropathy was recovering.
Respiratory tract infection (1) - After the last administration of mepolizumab (it was unknown the time between the administration and the onset of the respiratory tract infection), a 36-year-old male patient experienced a respiratory tract infection, that led to his hospitalization.