UNIVERSIDADE
BEIRA INTERIOR

Drug Induced Liver Injury
Perspective of the Adverse Drug Reaction Reports to the Portuguese Pharmacovigilance System from 2010 to 2019

David Ricardo da Conceição Marçal Alves Nunes

Dissertação para obtenção do Grau de Mestre em
Medicina
(mestrado integrado)

Orientador: Prof. Doutor Jorge Luiz dos Santos
Co-orientador: Mestre Cristina Sofia de Jesus Monteiro
Co-orientador: Doutora Michèle Claire Breton

maio de 2021

Agradecimentos

Em primeiro lugar, gostaria de agradecer à minha família, o meu pai, a minha mãe, o meu irmão e os meus avós, por todo o apoio, encorajamento e dedicação, agora e ao longo da minha vida. Em especial, sem descorar ninguém, agradeço ao meu irmão, também aluno de medicina, pela sua enorme paciência para comigo (P.S. vivemos na mesma casa), pelo seu apoio, dedicação, suporte, pelos meus desabafos e pelas suas incontáveis ajudas preciosas, que desde sempre, me permitiram superar os obstáculos profissionais e da vida e assim chegar mais longe do que poderia imaginar. Muito obrigado. Sem a minha família, nada disto teria sido possível. Agradeço muito sinceramente, do fundo do meu coração pelo vosso amor incondicional. Muito obrigado.

Em segundo lugar, gostaria de agradecer aos meus orientadores da minha tese.

Ao meu professor e orientador principal, Dr. Jorge Santos, pelo seu apoio, pelos seus comentários importantes e preciosos, a sua disponibilidade, encorajamento e entusiasmo com a minha tese.

À Dra Cristina Monteiro, por ter sido a ponte entre mim e o INFARMED, mas também pelo seu apoio, a sua disponibilidade, pela sua dedicação e pelos seus comentários e sugestões imprescindíveis e certeiros.

À Dra Michèle Breton, pelo seu apoio, disponibilidade e a sua ajuda inestimável durante a análise estatística.

Muito obrigado por me orientarem durante este meu percurso académico.

A todos vós um muitíssimo obrigado.

Resumo alargado

O sistema de farmacovigilância tem como funções a deteção, o registo e a avaliação de reações adversas ao medicamento (RAM). As RAMs para além dos elevados custos financeiros, sociais e pessoais têm também um elevado impacto na saúde publica, uma vez que têm uma morbilidade e mortalidade significativa. Por estes motivos, os sistemas de farmacovigilância tornaram-se essenciais de forma a detetar os efeitos secundários de medicamentos. Os medicamentos poderão não evidenciar hepatotoxicidade durante o seu desenvolvimento, quer durante as fases pré-clinicas quer clínicas, e apenas evidenciar após a comercialização do medicamento. Certas RAMs, devido à sua baixa frequência, apenas podem ser detetadas na fase 4 de desenvolvimento de medicamentos. Por esta razão é que é vital a notificação espontânea de reações adversas do medicamento ao sistema de farmacovigilância.

A lesão hepática induzida por medicamentos, também conhecida por DILI (Drug Induced Liver Injury) a sua sigla em Inglês, pode ocorrer após o consumo de medicamentos, chás, infusões, outros produtos de ervanárias e de suplementos alimentares. Este tema é de uma importância fundamental não só para os profissionais de saúde, mas também para a indústria farmacêutica. Porque apesar de apresentar uma baixa incidência, exibe uma elevada morbilidade e mortalidade, podendo esta última chegar aos 10%. A lesão hepática por medicamentos, também denominada de hepatite medicamentosa caracteriza-se por ser um diagnóstico de exclusão. Actualmente, não existem testes de diagnóstico objetivos para a DILI. A DILI pode apresentar-se clinicamente de diversas formas, desde um doente assintomático que apenas apresenta elevação de enzimas hepáticas até um doente com insuficiência hepática aguda. Entre estes dois extremos, existem uma vasta gama de sintomas apresentados por DILI. A DILI é capaz de simular diversas outras doenças hepáticas que são necessárias excluir aquando do diagnóstico diferencial. A DILI é a principal razão da não aprovação de novos fármacos durante os ensaios clínicos, da inserção de avisos nos folhetos informativos dos medicamentos e pela retirada do mercado de diversos fármacos. No entanto, apresenta um baixo nível de notificação ao sistema de farmacovigilância.

Este trabalho tem como objectivo a avaliação da situação de DILI em Portugal num período de 10 anos, compreendido entre Janeiro de 2010 e Dezembro de 2019, através da análise de notificações enviadas ao Sistema Nacional de Farmacovigilância, coordenado pela Autoridade Nacional do Medicamento e Produtos de Saúde, I.P.

(INFARMED). Este estudo retrospectivo analisou as notificações enviadas ao Sistema Nacional de Farmacovigilância com pelo menos 1 RAM relacionada com DILI. As notificações são anónimas pelo que seria desnecessário a aprovação deste estudo por uma comissão de ética.

Para que uma RAM ocorra, é necessário que um medicamento cause um efeito prejudicial e não deliberado. Para a RAM ser considerada grave, esta deve causar uma deficiência persistente ou significativa, criar incapacidade, criar um defeito congénito, levar a internamento hospitalar ou ao aumento do tempo de internamento, cria risco de vida ou leva à morte do doente.

As notificações podem ser enviadas ao Sistema Nacional de Farmacovigilância, quer directamente por médicos, enfermeiros, farmacêuticos, doentes ou outros profissionais de saúde, quer indirectamente pelas entidades que detenham a autorização de introdução no mercado (AIM). As notificações foram selecionadas usando Standardised MedDRA Queries (SMQs) relacionadas com DILI, previamente definidas. Foram obtidos inicialmente 2896 notificações que após seleção cuidadosa restaram 2038 que foram analisados mais pormenorizadamente. A análise estatística foi realizada com o programa SPSS 27.0.

Este estudo não demonstrou uma prevalência de qualquer sexo para qualquer grupo de idade. Ambos o sexo e a idade não revelaram ser factores de risco para a DILI.

Das 2038 notificações, a maioria (n=1120, 55.0%) encontravam-se no grupo de idades de 19-64 anos e o grupo de idades 1-3 anos foi o que registou o menor número de notificações (n=21, 1.0%). A RAM mais frequente foi hepatite (n=626, 26.7%). A hepatotoxicidade (n=362, 15.5%) e hepatite (n=333, 14.2%) foram mais frequentes nos grupos de idade 19-64 anos. Colestase foi mais prevalente em adultos, independentemente da idade. A fibrose hepática e a encefalopatia foram mais comuns em idosos. Há a salientar uma baixa ocorrência de RAMs em idade pediátrica.

A causalidade apenas é analisada se as notificações forem consideradas graves. Das iniciais 2038 notificações, 1828 eram graves. No entanto, a maioria foi classificada como “não avaliada”. A indústria farmacêutica apenas faz análise de causalidade se ocorrer morte do doente, risco de vida e anomalia congénita. Visto que, no nosso estudo a maioria das notificações provieram da indústria, tal poderá explicar os nossos resultados. A categoria “definitiva” (n=24, 1.3%) teve uma baixa prevalência.

A maioria das notificações tinha entre 1-4 medicamentos suspeitos (n=1867, 92%) e a maioria destes evoluiu para a cura (n=746; 36.6%). Hepatite (n=610; 25.9%), hepatotoxicidade (n=489; 20.8%) e icterícia (n=260; 11.0%) tiveram uma maior frequência em doentes que tomavam 1-4 medicamentos suspeitos. A fibrose hepática ocorreu mais em doentes que tomavam entre 5-9 medicamentos suspeitos (n=55; 2.3%).

Dos doentes que morreram, ocorreu um predomínio de Mulheres em hepatotoxicidade (n=23; 13.8%) e hepatite (n=21; 12.6%). Os Homens predominaram em colúria (n=8; 4.8%) e esplenomegalia (n=8; 4.8%).

Em conclusão, apesar de DILI ser de ocorrência rara, esta pode ter um desfecho fatal. A hepatite foi a RAM mais frequentemente reportada e a maioria dos doentes teve uma recuperação completa. Este estudo poe em evidencia a necessidade de maiores esforços na avaliação da causalidade, uma vez que a maioria não foi analisada. Mais estudos são necessários nesta área em Portugal.

Palavras-chave

Lesão hepática induzida por medicamentos;Farmacovigilância;Reacções adversas a medicamentos;número de medicamentos suspeitos;Código químico terapêutico anatómico.

Abstract

The pharmacovigilance system has as its functions the detection, registry and assessment of adverse drug reactions (ADRs). Adverse drug reactions have a high morbimortality and certain ADRs are only apparent during phase IV of drug development. For that reason, it is vital that ADRs are notified to the Pharmacovigilance systems.

Drug induced liver injury (DILI), can be caused by drugs, herbal products and food supplements. The spectrum of clinical presentations of DILI is wide, from asymptomatic patients with only elevation of liver enzymes to acute liver failure. Unfortunately, there are not known biomarkers. Rendering DILI as a diagnosis of exclusion. DILI is the main reason of new drugs non approval, black boxes warnings and withdrawn from the market. This topic is important not only to health professional but also to the pharmaceutical industry.

This retrospective study analysed the reports sent to the Portuguese Pharmacovigilance system in a 10-year period from January 2010 to December 2019. A total of 2038 reports with at least 1 liver related RAM were analysed. There was not a prevalence of either sex in any age group. Most reports (n=1120, 55.0%) belonged to patients in age group 19-64 years old. Age group 1-3 years had the lowest number of reports (n=21, 1.0%). Hepatitis (n=626, 26.7%) was the most common RAM in our study. Hepatotoxicity (n=362, 15.5%) and hepatitis (n=333, 14.2%) were more frequent in age group 19-64 years old. Cholestasis was more prevalent in adults independently of age. Hepatic fibrosis and encephalopathy were more common in the elderly.

The causality assessment was not performed in 1303 cases (71.3%) and category “definitive” (n=24, 1.3%) had a low prevalence. Most patients consumed between 1-4 suspected drugs (n=1867, 92%). Most patients in our study evolved to “cure” (n=796; 39%). Hepatitis (n=610; 25.9%), hepatotoxicity (n=489; 20.8%) and jaundice (n=260; 11.0%) were more common in patients who took 1-4 suspected drugs. Hepatic fibrosis (n=55; 2.3%) was more frequent in who consumed 5-9 suspected drugs. Hepatotoxicity (n=23; 13.8%) and hepatitis (n=610; 25.9%) had a female predominancy while choluria (n=8; 4.8%) and splenomegaly (n=8; 4.8%) were of male predominance.

In conclusion, although DILI is a rare occurrence, it can be serious and even fatal. Our study highlights the need for more efforts to assess causality. More studies concerning DILI are needed in Portugal.

Keywords

Drug induced liver injury, pharmacovigilance, adverse drug reactions, number of suspected drugs, anatomical therapeutic chemical code.

Index

List of tables

List of acronyms

AIDS	Acquired Immunodeficiency Syndrome
AIH	Autoimmune Hepatitis
AIM	Autorização de Introdução no Mercado
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	The Anatomical Therapeutic Chemical Classification
CIOMS	Council for International Organizations of Medical Sciences
CMG	Cytomegalovirus
DILI	Drug Induced Liver Injury
EASL	European Association for the Study of the Liver
EBV	Epstein-Barr Virus
FC	Fibrosis Cirrhosis
FH	Fulminant Hepatitis
GGT	Gamma-Glutamyl Transferase
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HEV	Hepatitis E Virus
HIV	Human Immunodeficiency Virus
HLA	Human Leucocyte Antigens
HM	Hepatomegaly
IH	Indication for Hospitalization
INFARMED	National Authority of Medicines and Health Products, I.P.
n	Number of Cases
ND	Not Described
NI	Not Informed
NR	Not Relevant
PPS	Portuguese Pharmacovigilance System
RAM	Reação Adversa a Medicamento
RUCAM	Roussel Uclaf Causality Assessment Method
SmPC	Summary of Product Characteristics
SMQs	Standardised MedDRA Queries
SPSS	Statistical Package for the Social Sciences
USA	United States of America
WHO	World Health Organization

Chapter 1

Introduction

Drug induced Liver Injury (DILI) has a low incidence in the clinical environment (1,2,3). However, since it is frequently associated with high morbimortality levels, it is an extremely relevant subject for doctors, other health professionals and also the pharmaceutical industry (7).

DILI can be caused by pharmaceutical drugs, herbal medicines and food supplements (4,5). Its incidence is hard to estimate, nevertheless, some studies point to between 14-19 cases per 100,000 population (1,2,3). There are several difficulties in estimating DILI's incidence, since it is a diagnosis of exclusion, there are no objective diagnostic tests and, usually, adverse drug reactions (ADR) are under-reported to Pharmacovigilance systems (1,2,3,5).

DILI can mimic any kind of liver disease (3,5). The range of symptoms and signs of DILI is quite broad, ranging from asymptomatic elevation of liver enzymes, to acute liver failure. (2) Furthermore, DILI is responsible for 3%-5% of cases of jaundice that need hospital care and for more than 50% of cases of acute liver failure (1,2,3,6). DILI leads to a mortality rate of around 10% (6).

Additionally, during drug development, DILI is the main reason for new medicines non-approval in clinical trials, black boxes warnings and recall from the market place (2,3,6,7,8).

DILI can be classified as direct, namely intrinsic injury, or as idiosyncratic injury (1,5).

Direct injury is dose dependent (1,9,10), predictable (9,10), presents a short latency time (1), and its effects can be induced in animal models (1). The most paradigmatic example of this type of injury is Acetaminophen intoxication by overdose (4,5).

Idiosyncratic injury, instead, is not dose dependent (1,9,10,11), and thus it is unpredictable (9,10,11), presents variable latency time periods, from a few days to some years (1), and their effects cannot be reproduced in animal models (1).

The aforementioned differential features of DILI types explain why most DILIs are idiosyncratic (5,9).

The number drugs that cause hepatotoxicity has increased worldwide (4), as well as the number of publications related with the issue indexed in PubMed (20). During drug development, a drug may not show evidence of hepatotoxicity, due to several reasons such as limited predictive value assays, lack of a validated biomarker, etc, and when the drug is already on the market (phase IV), a DILI ensues (20). As such, spontaneous reporting of adverse reactions is essential in order

to detect safety issues related to drugs that escaped previous assessment, especially the idiosyncratic type due to its unpredictability (20).

The pharmacolovigilance systems have an important role in detecting, registering and evaluating ADRs (12,13,15). Adverse drug reactions have high costs economically as well as social and individual (13,16). They require the patient to stop taking the suspected medication and increase the use of health services (13).

Adverse drug reactions have a significant morbimortality, and thus a considerable impact in public health (14). They are responsible for 5% of hospital admissions (15) and cause 197,000 deaths/year in the European Union. (15).

As such, pharmacovigilance has become central in terms of detecting side effects of both new and common use drugs (12).

Although effectiveness and safety of drugs are essential, ADRs are frequently detected only in Phase IV (12).

The objective of this work was to assess DILI in Portugal in a 10-year period, from 2010 to 2019, by analysing the reports of DILI sent to the Portuguese National Pharmacovigilance System (PPS), which is coordinated by INFARMED – National Authority of Medicines and Health Products, I.P.

Chapter 2

Materials and methods

Section 2.1 Study design and ethics

This retrospective study analysed the reports sent to PPS with at least one liver related ADR, between January 1st 2010 to December 31st 2019. Reports were anonymous and thus Ethical committee approval was deemed unnecessary.

Section 2.2 Liver adverse drug reactions

ADRs related to the liver can range from asymptomatic laboratory abnormalities to patients presenting with clinical signs of almost any liver disease, either acute or chronic (1,2,3,5,8). Laboratory alterations of liver ADRs include increased serum levels of bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase

(GGT), alkaline phosphatase (ALP) and prothrombin time (3,4). Liver ADRs include hepatitis, hepatic necrosis, hepatic steatosis, cholestasis, autoimmune hepatitis, among others (3,4).

For ADRs to occur, two conditions needed to be meet: 1) the drug has to cause a noxious effect; 2) the effect was not deliberated (17). For an ADR to be classified as Serious, its outcome has to be one of the following: 1) significant incapacitating disability, including birth defects; 2) hospitalization, or 3) increased hospitalization time, 4) life-threatening illness, or 5) death (17).

Section 2.3 Source and information contained in reports

Each report had information corresponding to a single patient, although each notification could have one or more adverse drug reactions (ADRs) and include one or more suspected medicines. These reports were sent to PPS either directly, by doctors, nurses, pharmacists, patients or others health professionals, or indirectly by the marketing drug authorization holders (AIM).

Age and sex were the only demography variables available for analysis. Liver ADRs were analysed in order to characterize the type, frequency, severity and outcome of each DILI, including hospitalization and death.

Evolution of the patient was evaluated in reports with the following terms: cure, cure with sequels, in recovery, no recovery, death and unknown.

The Anatomical Therapeutic Chemical (ATC) classification system allows comparisons between drug utilization studies to be made. This classification system has been recommended by WHO since 1981. It has become the gold standard to be used in fields of drug utilization, monitoring and research (18). As such, we assessed the number of suspected drugs and from which ATC group they belonged for each report.

The frequency of the following terms was also assessed: off label use, overdose and medical error.

Regulator authority assessment concerning causality of reports was also evaluated. The authority classified the reports using the terms of the WHO-Uppsala Monitoring Centre for causality assessment. Terms used were as follows: certain, probable / likely, possible, unlikely, conditional / unclassified, unassessable / unclassifiable (19).

Section 2.4 Report selection

A search was performed on the PPS database, using Standardised MedDRA Queries (SMQs) related to DILI, previously selected by the authors (annex: 1). This search was conducted in a 10-year time frame, from Jan 1st 2010 to Dec 31st 2019. Initially, 2896 reports were obtained, of which 83 were considered invalid, 773 were duplicates and 2 were clinical trials, all these were

withdrawn. After this first selection, remained 2038 reports, which were further analysed. Data were stored in Excel files.

Section 2.5 Statistical analysis

The statistical analysis was performed using SPSS 27.0 (IBM, Portsmouth, UK). Descriptive statistical methods were used to count the data and the results were expressed as either percentage or constituent ratios. Pearson's chi-square test was used to assess association between the following variables age groups, sex, causality, death rates and the number of suspected drugs. Kruskal-Wallis test, was used to assess for age group variables, adverse drug reactions, evolution of each case and number of suspected drugs. The studied variables were reported to the PPS. P-values <.05 were considered significant for both tests.

Chapter 3

Results

Table 1 presents the demographic distribution of liver ADRs.

Table 1 – Distribution of the reports of hepatic adverse drug reactions, according to age groups and sex

Age group	Sex				X^2	*P*
	Female n=968 n (%)	Male n=980 n (%)	NI[2] n=90 n (%)	Total n=2038 n (%)		
1-3 years	8 (0.4)	12 (0.6)	1 (0.0)	21 (1.0)	0.75	0.383
4-12 years	25 (1.2)	24 (1.2)	2 (0.1)	51 (2.5)	0.02	0.850
13-18 years	18 (0.9)	13 (0.6)	5 (0.2)	36 (1.8)	0.83	0.347
19-64 years	563 (27.6)	542 (26.6)	15 (0.7)	1120 (55.0)	0.37	0.203
>64 years	202 (9.9)	203 (10.0)	11 (0.5)	416 (20.4)	0.01	0.933
NI[1]	152 (7.4)	186 (9.7)	56 (2.7)	394 (19.3)		

Abbreviations**:** NI – Not Informed. 1;2- Data not included in the statistical analysis. White spaces mean no data. Pearson's chi-squared test and Kruskal-Wallis test were used.

Table 1 shows reports from male (n=980, 48.1%) and female (n=968, 47.5%) patients. In n=90 (4.4%) reports patient's sex was uninformed. Regarding age distribution, the youngest individual was 1 year old and the oldest was aged 96 years at the occurrence of ADR. The age group 19-64 years included most ADRs, comprising n=1120 (55%) cases, involving males (n=542, 26.6%) and females (n=563, 27.6%). The age group 1-3 years presented with the least number of reports, in total (n=21, 1.0%), in males (n=12, 0.6%) and in females (n=8, 0.4%).

Table 2 presents the distribution of liver ADRs according to age groups.

Table 2 – More frequently notified hepatic adverse drug reactions, according to age groups.

Adverse reaction	Age group n(%)								
	1-3 years (n=21)	4-12 years (n=51)	13-18 years (n=36)	19-64 years (n=1120)	>64 years (n=416)	NI [1] (n=394)	Total (n=2038)	X^2	*P*
Hepatitis	8 (0.3)	16 (0.7)	14 (0.6)	333 (14.2)	164 (7.0)	91 (3.9)	626 (26.7)	13.98	0.007
Hepatotoxicity	5 (0.2)	10 (0.4)	5 (0.2)	362 (15.5)	114 (4.9)	104 (4.4)	600 (25.6)	11.60	0.020
Jaundice	6 (0.3)	7 (0.3)	4 (0.2)	142 (6.1)	67 (2.9)	37 (1.6)	263 (11.2)	7.13	0.129
Cholestasis	3 (0.1)	6 (0.3)	8 (0.3)	101 (4.3)	80 (3.4)	32 (1.4)	230 (9.8)	34.07	<0.001
Rash	1 (0.0)	4 (0.2)	2 (0.1)	62 (2.6)	21 (0.9)	13 (0.6)	103 (4.4)	0.72	0.947
Hepatic fibrosis				97 (4.1)	1 (0.0)	1 (0.0)	99 (4.2)	45.69	<0.001
Ascites			2 (0.1)	45 (1.9)	24 (1.0)	26 (1.1)	97 (4.1)	5.74	0.218
Pruritus		6 (0.3)	2 (0.1)	60 (2.6)	21 (0.9)	8 (0.3)	97 (4.1)	5.33	0.254
Autoimmune hepatitis		2 (0.1)		43 (1.8)	11 (0.5)	8 (0.3)	64 (2.7)	3.42	0.489
Choluria	1 (0.0)	2 (0.1)	2 (0.1)	26 (1.1)	15 (0.6)	2 (0.1)	48 (2.1)	3.47	0.481
Encephalopathy		1 (0.0)	2 (0.1)	2 (0.1)	12 (0.5)	30 (1.3)	47 (2.0)	29.54	<0.001
Cirrhosis				28 (1.2)	5 (0.2)	8 (0.3)	41 (1.8)	4.96	0.290
Acholic stool		1 (0.0)		13 (0.6)	13 (0.6)		27 (1.1)	8.25	0.082
Laboratory tests									
Aminotransferase	2 (0.1)	18 (0.9)	8 (0.3)	264 (13.0)	101 (5.0)	101 (5.0)	494 (24.2)	6.18	0.186
Bilirubin	5 (0.2)	5 (0.2)	2 (0.1)	153 (7.5)	73 (3.6)	55 (2.7)	293 (14.4)	8.46	0.076
ALT	4 (0.2)	4 (0.2)	5 (0.2)	130 (6.4)	70 (3.4)	31 (1.5)	244 (12.0)	9.23	0.055
AST	5 (0.2)	4 (0.2)	3 (0.1)	112 (5.5)	71 (3.5)	26 (1.3)	221 (10.8)	18.57	<0.001
GGT	4 (0.2)	3 (0.1)	1 (0.0)	117 (5.7)	67 (3.3)	35 (1.7)	227 (11.1)	15.08	0.004
Alkaline phosphatase	2 (0.2)	3 (0.1)		65 (3.2)	50 (2.5)	16 (0.8)	136 (6.7)	20.53	<0.001
Lactate dehydrogenase	1 (0.0)			49 (2.4)	21 (1.0)	6 (0.3)	77 (3.8)	4.48	0.344
Prothrombin time				34 (1.7)	6 (0.3)	1 (0.3)	41(2.0)	6.12	0.189
Drug administration									
Off label use	2 (0.2)	3 (0.1)	4 (0.2)	49 (2.4)	2 (0.2)	18 (0.9)	78 (3.8)	22.03	<0.001
Drug exposure Pregnancy				13 (0.6)		10 (0.4)	23 (1.1)	6.13	0.189
Overdose		1 (0.0)	1 (0.0)	12 (0.6)		2 (0.2)	16 (0.8)	6.71	0.151
Medical error				4 (0.2)	2 (0.2)	2 (0.2)	8 (0.4)	0.55	0.968

Abbreviations: ALT- alanine aminotransferase; AST- aspartate aminotransferase; GGT- Gamma-glutamyl transferase; NI - Not Informed. 1- Data not included in the statistical analysis. White spaces mean no data. Pearson's chi-squared test was used.

The most frequent ADR was hepatitis (n=626, 26.7%) and the least was acholic stools (n=27, 1.1%). Acute ADRs, such as hepatotoxicity (n=362, 15.5%) and hepatitis (n=333, 14.2%) were more prevalent in age group 19-64 years. Cases of cholestasis were more prevalent in adults, irrespective of age group, 19-64 (n=101, 4.3%) and ≥64 years (n=80, 3.4%). Hepatic fibrosis (n=97, 4.1%) had the highest prevalence in patients aged 19-64 years and encephalopathy (n=12, 0.5%) had the highest prevalence in patients over 64 years old.

The three most frequently altered laboratory tests were: aminotransferases (n=494, 24.2%), bilirubin (n=293, 14.4%) and ALT (n=244, 12%). Prothrombin time (n=41, 2%) was the least frequently altered. Aminotransferases increases were more pronounced in adults, age group 19-64 (n=264, 13.0%) and ≥64 years (n=101, 5.0%). Laboratory markers of cholestasis, such as GGT, had higher frequencies in age group 19-64 (n=117, 5.7%) and ≥64 years (n=67, 3.3%), and alkaline phosphatase was also more prevalent in age group 19-64 (n=65, 3.2%) and ≥64 years (n=50, 2.5%). In age groups corresponding to children and adolescents, there was a low frequency of laboratory results mentioned in the reports.

A high prevalence of drugs used as off label was observed in the age group 19-64 years (n=49, 2.4%). Regarding the total of 78 cases of off label use, in which there had been an ADR, 6.4% occurred in paediatric population and had no indication for their use, 8.9% had been used in accordance with indication, but with higher doses than approved on the SmPC (Summary of product characteristics). The remaining 84.7% occurred in adults and resulted from the use of drugs in conditions without indication on the SmPC.

Supplementary table shows that the highest prevalence of Off label used medication was for onychomycoses (n=5, 6.41%), followed by Abdominal wall haematoma (n=4, 5.13%). Others with equally high prevalence (n=3, 3.85%) were: thalamic pain; chronic hepatitis C; thyrotoxicosis and bradycardia and finally chronic hepatitis C and HIV co-infection.

Table 3 displays the distribution of liver ADRs causality in relation to the number of suspected drugs.

Table 3 – Causality rates in cases of severe hepatic adverse drug reactions in relation to the number of suspected drugs

Causality	n (%)	Average number of suspected drugs	Standard Deviation
Unassigned	1303 (71.3)	2.45	2.451
Likely	273 (14.9)	1.31	0.764
Possible	202 (11.0)	1.56	0.948
Definitive	24 (1.3)	1.08	0.282
Unlikely	11 (0.6)	1.54	0.687
Conditional	7 (0.4)	1.00	0.000
Not Related	5 (0.3)	1.20	0.447
Not Classifiable	3 (0.2)	1.00	0.000

Average number and Standard deviation were used.

Table 3 displays the report's causality assessment. Of the initial 2038 reports only 1828 were serious to merit an assessment. The highest number of reports had the "unassigned" category attributed (n=1303, 71.3%) and the category "definitive" (n=24, 1.3%) had a low prevalence. Other categories had values ranging from (n=273, 14.9%) for "likely" to (n=3, 0.2%) for "not classifiable".

Table 4 presents the liver ADRs distribution in relation with the number of suspected drugs.

Table 4- Frequency of different hepatic adverse drug reactions reported according to the number of suspected drugs

Number of suspected drugs Adverse reactions n (%)	1 – 4	5 - 9	≤ 10	Total	X^2	*P*
Hepatitis	610 (25.9)	12 (0.5)	4 (0.2)	626 (26.6)	68.48	<0.001
Hepatotoxicity	489 (20.8)	74 (3.1)	37 (1.6)	600 (25.5)	41.59	<0.001
Jaundice	260 (11.0)	3 (0.1)	0 (0.0)	263 (11.2)	31.87	<0.001
Cholestasis	204 (8.7)	22 (0.9)	4 (0.2)	230 (9.8)	1.94	0.378
Rash	97 (4.1)	6 (0.3)	0 (0.0)	103 (4.4)	4.70	0.095
Hepatic fibrosis	21 (0.9)	55 (2.3)	23 (1.0)	99 (4.2)	454.55	<0.001
Pruritus	93 (4.0)	0 (0.0)	4 (0.2)	97 (4.1)	9.55	0.008
Ascites	85 (3.6)	12 (0.5)	0 (0.0)	97 (4.1)	4.97	0.083
Encephalopathy	75 (3.2)	10 (0.4)	0 (0.0)	85 (3.6)	3.87	0.143
Autoimmune hepatitis	64 (2.7)	0 (0.0)	0 (0.0)	64 (2.7)	8.67	0.001
Choluria	48 (2.0)	0 (0.0)	0 (0.0)	48 (2.0)	6.45	0.039
Cirrhosis	33 (1.4)	6 (0.3)	2 (0.1)	41 (1.7)	2.53	0.281
Total	2079 (88.4)	200 (8.5)	74 (3.1)	2353 (100.0)		

Pearson chi-square test was used.

Table 4 shows that acute cases of hepatopathy, such as hepatitis, hepatotoxicity and jaundice, were observed in patients who consumed 1-4 drugs suspected of causing ADRs. On the other hand, hepatic fibrosis was more common in patients taking between 5-9 suspected drugs. Pruritus, autoimmune hepatitis and choluria were more common in those patients who consumed 1-4 suspected drugs.

Table 5 shows the distribution of clinical outcomes in relation to the number of drugs suspected to have caused liver ADRs.

Table 5 - Clinical evolution of patients associated with the hepatic adverse reaction, according to the number of suspected drugs.

Number of suspected drugs	1 – 4 (n=1867)	5-9 (n=131)	≥10 (n=40)	X^2	*P*
Age (mean±SD)	52 ± 20	38 ± 16	35 ± 18		
Case evolution n (%)					
Cure	746 (36.6)	36 (1.8)	14 (0.7)	8.28	0.001
In recovery	285 (14.0)	10 (0.5)	0 (0.0)	12.66	0.001
Cure with sequels	25 (1.2)	0 (0.0)	0 (0.0)	2.31	0.313
No recovery	102 (5.0)	2 (0.1)	1 (0.0)	4.46	0.107
Death	115 (5.6)	11 (0.5)	0 (0.0)	3.74	0.153
Unknown[1]	594 (29.1)	72 (3.5)	25 (1.2)		

1- Data not included in the statistical analysis.

Most reports included between 1-4 suspected drugs (n=1867, 92%). Concerning patients' clinical evolution, most patients had a favourable outcome, as "cured" (n=796, 39%) and "in recovery" (n=295, 15%). Death was reported in n=126 (6.2%) patients, "no recovery" in n=105 (5.2%),

whereas n=25 (1.2%) were “cured with sequels”. The highest number of patients that were in categories “cured” (n=746, 36.6%) and “in recovery” (n=285, 14.0%), had taken between 1-4 medications.

Table 6 depicts the distribution of liver ADRs in relation to the number of suspected drugs concerning the patients who died.

Table 6- Sex distribution related to the hepatic adverse reactions in the patients who died.

Adverse reaction	**Total n (%)**	**Female n (%)**	**Male n (%)**	**NI[1] n (%)**	**X^2**	***P***
Hepatotoxicity	46 (27.5)	23 (13.8)	21 (12.6)	2 (1.2)	7.51	0.006
Hepatitis	37 (22.2)	21 (12.6)	15 (9)	1 (0.6)	10.64	0.001
Encephalopathy	25 (15)	8 (4.8)	17 (10.2)	0 (0)	.14	0.702
Jaundice	17 (10.2)	4 (2.4)	13 (7.8)	0 (0)	1.16	0.280
Ascites	14 (8.4)	2 (1.2)	12 (7.2)	0 (0)	2.97	0.084
Choluria	8 (4.8)	0 (0)	8 (4.8)	0 (0)	4.60	0.031
Splenomegaly	8 (4.8)	0 (0)	8 (4.8)	0 (0)	4.60	0.031
Cholestasis	4 (2.4)	0 (0)	4 (2.4)	0 (0)	2.24	0.134
Cirrhosis	4 (2.4)	0 (0)	4 (2.4)	0 (0)	2.24	0.134
Hepatomegaly	4 (2.4)	0 (0)	4 (2.4)	0 (0)	2.24	0.134
Number adverse reactions	167 (100.0)	58 (24.7)	106 (63.5)	3 (1.8)		
Number of cases	126	51 (40.5)	70 (55.6)	5 (4.)		
Age (mean±SD)	57±20	57±20	57±21	56±00		

Abbreviations: NI – Not Informed. 1- Data not included in the statistical analysis.

As seen on table 6, among patients who died (n=126), most were male (n=70, 55.6%). Concerning the number of ADRs of patients who died (n=167, 100%) in total, the majority occurred in males (n=106, 63.5%). The most frequent liver ADRs of the patients who died were hepatotoxicity (n=46, 27.5%), followed by hepatitis (n=37, 22.2%) and encephalopathy (n=25, 15%). Regarding the sex distribution, both hepatotoxicity (n=23, 13.8%; *P*=0.006) and hepatitis (n=21, 12.6%; *P*=0.001) were more prevalent in females, whereas male predominance occurred in both choluria (n=8, 4.8%; *P*=0.031) and splenomegaly (n=8, 4.8%; *P*=0.031).

Table 7 shows the distribution and characteristics of cases with positive viral markers.

Table 7 – Cases with positive viral markers included in the sample of patients with reported adverse drug reactions.

Viral marker-positive	n	IH	Reactivation Relapse	Coinfection	FH	Cholestasis	Ascites	HM	FC	Other systems
CMG	6	ND	ND	1*		1		5		1
EBV	2	ND	ND				1	1		1
HBV	5	1	4		3	1		1		
HCV	10	1	5	1**			1		3	
HEV	1	ND	ND							
Herpes simplex	1	ND	ND							
Herpes zoster	3	ND	1		1		2			1
HIV	3	3	NR						1	
Total	**31**	**4**	**10**	**2**			**4**	7	**4**	**3**

Abbreviations- ND - not described; NR - not relevant; CMG – Cytomegalovirus; EBV - Epstein-Barr virus; HBV – Hepatitis B virus; HCV - Hepatitis C virus; HEV - Hepatitis E virus; HIV – human deficiency virus; n – number of cases; IH - indication for hospitalization; FH - fulminant hepatitis; HM – hepatomegaly; FC – Fibrosis Cirrhosis. HIV cases were included due to the use of antiretroviral drugs which present potential hepatotoxicity. Indication of hospitalization: report of hospitalization due to the viral infection. Reactivation relapse: report of clinical or laboratory reactivation of viral infection, including the native liver or transplanted liver. Coinfection: reported in 2 cases: *- Cytomegalovirus plus Epstein-Barr; **- HIV plus hepatitis C (patient with cirrhosis). Fulminant hepatitis: report of associated coagulation disorder or encephalopathy. Cholestasis: report of jaundice plus pruritus, choluria or acholic stools. Other systems: report of pleural or pericardial effusion, or pleuritis.

Table 7 depicts a low frequency of viral positivity (n=31, 1.5%) in our study. The viruses were by decreasing order of frequency: hepatitis C virus (n=10, 0.49%), cytomegalovirus (n=6, 0.29%), hepatitis B virus (n=5, 0.25%), both herpes zoster virus (n=3, 0.15%) and HIV (n=3, 0.15%) had the same frequency, Epstein-Barr virus (n=2, 0.1%) and finally both hepatitis E virus (n=1, 0.05%) and herpes simplex (n=1, 0.05%) with the same frequency.

Table 8 presents the distribution of the reported cases of ADRs according to the Anatomical Therapeutic Chemical Code classification (ATCC).

Table 8 - Distribution of reported cases of adverse drug reactions according to the Anatomical Therapeutic Chemical Code (ATCC)

A Alimentary tract and metabolism n=91 (2.76%)	**n (%)**
A01 Stomatological preparations	4 (0.12)
A02 Antacids, medicines to treat peptic ulcer and flatulence	16 (0.49)
A03 Drugs for functional gastrointestinal disorders	1 (0.03)
A05 Biliary and hepatic therapy	4 (0.12)
A06 Laxatives	1 (0.03)
A07 Antidiarrheal, intestinal anti-inflammatory and anti-infectious agents	13 (0.39)
A08 Anti-obesity preparations, excluding diet products	1 (0.03)
A10 Medicines used in diabetes	46 (1.40)
A11 Vitamins	3 (0.09)
A16 Other products for digestive tract and metabolism	2 (0.06)
B Blood and blood forming organs n=52 (1.58%)	
B01 Antithrombotic drugs	41 (1.25)
B02 Anti-haemorrhagic	5 (0.15)
B03 Antianemic drugs	3 (0.09)

Table 8 – Continued	
B05 Blood substitutes and perfusion solutions	1 (0.03
B06 Other haematological products	2 (0.06)
C Cardiovascular system n=198 (6.01%)	
C01 Cardiac therapy	31 (0.94)
C02 Antihypertensives	31 (0.94)
C03 Diuretics	24 (0.73)
C04 Peripheral vasodilators	3 (0.09)
C05 Vasoprotectors	2 (0.06)
C07 Beta blockers	8 (0.24)
C08 Calcium channel blockers	12 (0.36)
C09 Agents that act on the renin-angiotensin system	26 (0.79)
C10 Hypolipidemic	61 (1.85)
D Dermatologicals n=25 (0.76%)	
D01 Antifungals for dermatological use	12 (0.36)
D05 Antipsoriatics	1 (0.03)
D06 Antibiotics and chemotherapy for dermatological use	7 (0.21)
D07 Corticosteroids, dermatological preparations	2 (0.06)
D10 Anti-acne preparations	1 (0.03)
D11 Other dermatological preparations	2 (0.06)
G Genito urinary system and sex hormones n=50 (1.52%)	
G01 Gynaecological anti-infectives and antiseptics	3 (0.09)
G03 Sex hormones and modulators of the genital system	36 (1.09)
G04 Urological medications	11 (0.33)
H Systemic hormonal preparations, excluding sex hormones and insulins n=70 (2.13%)	
H01 Pituitary, hypothalamic and analogous hormones	1 (0.03)
H02 Corticosteroids for systemic use	61 (1.85)
H03 Thyroid therapy	8 (0.24)
J Antiinfective for systemic use n=1192 (36.20%)	
J01 Antibacterials for systemic use	282 (8.56)
J02 Antimycotic for systemic use	41 (1.25)
J04 Antimycobacterials	131 (3.98)
J05 Antivirals for systemic use	713 (21.65)
J06 Immunosorbents and immunoglobulins	5 (0.15)
J07 Vaccines	20 (0.61)
L Antineoplastic and immunomodulating agents n=892 (27.09%)	
L01 Antineoplastic agents	430 (13.06)
L02 Endocrine therapy	37 (1.12)
L03 Immunostimulants	81 (2.46)
L04 Immunosuppressive agents	344 (10.45)
M Musculo-skeletal system n=86 (2.61%)	
M01 Anti-inflammatory and antirheumatic	50 (1.52)
M02 Topical products for joint and muscle pain	3 (0.09)
M03 Muscle relaxants	10 (0.30)
M04 Anti-gout preparations	14 (0.43)
M05 Medicines for treating bone diseases	9 (0.27)
N Nervous system n=567 (17.22%)	
N01 Anaesthetics	4 (0.12)
N02 Pain relievers	101 (3.07)
N03 Antiepileptics	77 (2.34)
N04 Antiparkinsonians	19 (0.58)
N05 Psycholeptics	186 (5.65)
N06 Psychoanalytic	110 (3.34)
N07 Other nervous system medications	70 (2.13)
P Antiparasitic products, insecticides and repellents n=11 (0.33%)	
P01 Anti-protozoa	6 (0.18)
P02 Anthelmintics	5 (0.15)
R Respiratory system n=42 (1.28%)	
R02 Prepared for pharyngeal use	12 (0.36)
R03 Antiasthmatics	17 (0.52)
R05 Prepared against coughs and colds	2 (0.06)
R06 Antihistamines for systemic use	11 (0.33)
V Various n=17 (0.52%)	
V3 Other therapeutic products	10 (0.30)
V8 Contrast media	4 (0.12)
V9 Diagnostic radiopharmaceuticals	3 (0.09)

Abbreviations: n – number of cases.

Table 8 shows that there were 3293 (100%) suspected drugs. The most frequent ATC groups were, by descending order: J05 Antivirals for systemic use (n=713, 21.65%), L01 Antineoplastic agents (n=430, 13.06%), L04 Immunosuppressive agents (n=344, 10.45%), J01 Antibacterials for systemic use (n=282, 8.56%) and N05 Psycholeptics (n=186, 5.65%).

Chapter 4

Discussion

This study investigated the picture of DILI under the perspective of the ADRs informed to the Portuguese PPS in the last decade.

Table 1 does not demonstrate a prevalence of either sex in any age group for DILI. This finding agrees with the EASL Clinical Practice Guidelines (4) in that "sex does not appear to be a general risk factor for DILI". Other studies (23,24) also did not find a relation between sex and increased incidence of DILI.

Age, on the other hand, is generally accepted as a risk factor for DILI (6). For instance, in causality assessment methods used for DILI, namely the RUCAM, or the CIOMS scale, age constitutes a risk factor, as people over 55 years of age are attributed 1 extra point (3,11,21). In this study (table 1), age was not a risk factor for DILI, which is in line with data from large DILI registries in Spain and the USA (22,32). Since there is increased evidence suggesting that elderly are more susceptible to certain drugs (22,23), it is inferable that age may function as a contributing factor.

Acute cases of liver ADRs, such as hepatotoxicity and hepatitis were found to be more frequent in adults with less than 65 years old (table 2). Considering the clinical descriptions used in the evaluated reports, the term hepatotoxicity seemed to refer to acute hepatitis. Hepatitis can be caused by virus (23,24,30,32), autoimmune diseases (24,32), drugs (24) and some genetic metabolic diseases (36). In this study, there was a low prevalence of hepatotropic virus (Table 7), which may indicate a low frequency of viral hepatitis in the evaluated sample. In this study, neither autoimmune or genetic metabolic diseases were evaluated.

Cholestasis and its laboratory markers, GGT and ALP, were more prevalent in patients above 18 years of age (table 2). This finding is in agreement with other studies, in which it was also observed that cholestatic pattern of injury had a higher occurrence in older patients (23,24,30,32,38). Certain drugs have a higher tendency to cause a cholestatic pattern of liver

injury than others (23,27). For instance, drugs that are excreted via bile are more likely to induce cholestatic liver injury in susceptible patients (38). Drugs known to be associated to cholestatic liver damage include several agents with different properties, such as antibiotics, anti-inflammatory drugs, psychotropics drugs, anticonvulsants, statins, immunosuppressants and hypoglycaemic drugs (24,27). Cholestatic liver injury can be due to mixed hepatocellular cholestatic damage or to an alteration of bile flow in bile canaliculi, resulting in pure canalicular cholestasis and even in obstructive cholangiopathy (25,26,38). Canalicular cholestasis can result from use of anabolic steroids and oestrogens (38). Other causes of cholestasis such such as biliary mechanical obstruction, primary biliary cholangitis, primary sclerosing cholangitis, viral hepatitis, alcoholic and non-alcoholic liver disease, gestational cholestasis, genetic-metabolic disorders, associated with different age groups should be excluded (37, 38). There was a low prevalence of viral hepatitis (table 7), meaning a low likelihood for this type of aetiology. Genetic variations of liver transport proteins between patients could also explain why some individuals are more susceptible than others to cholestatic injury (38). Cholestatic idiosyncratic DILI reactions are unpredictable and result from immune-mediated biliary disruption (1,8). Drug-protein adducts are formed and are presented as a new type of antigen, which leads to the immune reaction (8). Patients that harbour alleles HLA-DBR1*15 and HLA-DQB1*06 seem to have a higher propensity to develop cholestatic DILI (30), and certain human leucocyte antigens (HLA) play a significant role in this type of injury (43).

Hepatic fibrosis was highest in age group 19-64 years (table 2). Hepatic fibrosis occurs when there is an alteration in the process of the wound healing response to chronic liver damage that favours the increased deposition of extracellular matrix proteins, including fibrillary collagens (28). Alcohol, hepatotropic virus and non-alcoholic steatohepatitis are among the most common causes of hepatic fibrosis (28). Table 7 shows a low frequency of viral markers, as such these viruses had a low impact in our study. However, it is possible that the hepatic fibrosis described in some patients of this study resulted from non-diagnosed primary chronic liver diseases.

In our study, encephalopathy had the highest frequency in patients over the age of 64 years (Table 2). Encephalopathy can be caused by several factor, such as metabolic alterations, brain atrophy, brain oedema and liver failure (29). Given that the reports under analysis were selected using keywords related to liver disease, it is likely that encephalopathy was caused by hepatic failure (29), but the influence of additional causes was not ascertained. Fulminant liver failure leads to death or the need of liver transplantation (23). It occurs more frequently in females that harbour a hepatocellular patter of injury (23,30). Most cases of fulminant liver failure are due hepatotoxicity caused by acetaminophen, whereas the second leading cause is idiosyncratic DILI (23). Acute liver failure due to acetaminophen has risen over the years and most cases are due to unintentional overdoses (23), although, suicide attempt must be excluded (23). We did not ascertain if DILI cases were idiosyncratic or intrinsic because the reports neither mentioned the terms nor had enzyme values to calculate the R-value. We did not find any mention of possible suicide attempts on the reports analysed. Drugs which have more than 50% of their metabolism

executed by the liver have a higher likelihood of fulminant liver failure (30). There is also a significant relationship between high oral drug doses and the higher likelihood of liver failure (30). In this study, neither the site of drug metabolization nor the route of administration of the medications described in the ADRs were evaluated.

Concerning the age groups of children and adolescents (table 2), there was a low frequency of liver ADRs and a low frequency of laboratory results mentioned in the reports. DILI is a rare occurrence in the paediatric population (41) and children do not seem to be more at risk of DILI than the rest of the population (23). Certain drugs, especially drugs that act on the central nervous system, such as antiepileptics and psychotropics, and antimicrobials, are more frequently associated to cases of DILI in children (23,30,41). Children are also more affected by drugs that cause a hepatocellular pattern of injury (23,41). However, as mentioned before, we did not assess whether DILI was idiosyncratic or intrinsic. Nonetheless, most cases of DILI in children are scored as either mild or moderate (41). Another possibility for the findings observed on table 2 was under recognition, and thus underreporting of DILI in those age groups. However, the effects of childhood particularities regarding drug pharmacokinetics (41) could not be excluded in the present study.

Table 2 shows that drugs used as “off label” had a high prevalence among adult patients younger than 65 years old. “Off label” use of drugs occurs commonly (44). “Off label” prescription results from the use of different drugs of the same class and with similar effects, therapeutic attempts when additional therapies have failed, or in populations for which a specific drug use is not yet approved (44). In the present study, the justification of the “off label” use of medications was not analysed.

In relation to causality assessment (table 3), only reports classified as serious are required to be assessed for causality, and of the 2038 initial reports, only 1828 (89.7%) were serious. Moreover, the pharmaceutical industry must only make a causality assessment if death occurs, if there is a risk of life or of congenital anomaly. As most of the reports analysed in this study came from the pharmaceutical industry, it may explain why most analysed reports did not have causality attributed and belonged to the category “unassigned”.

Acute cases, including hepatitis, hepatotoxicity, jaundice and choluria were more frequent in patients that used between 1-4 suspected drugs (table 4). This may be related to the fact that these patients might had taken drugs that caused intrinsic DILI. As this type of injury has a short latency time (8).

Hepatic fibrosis was more common in patients taking more than 4 suspected drugs (table 4). Certain drugs can cause cholestasis (23,27), and cholestasis can evolve into hepatic fibrosis (28). Which could explain our study results.

Pruritus was more common in patients that had taken less than 5 suspected drugs (table 4). There are several causes of pruritus, such as, hepatic cholestasis, renal failure, dermatological causes, drugs, iron deficiency anaemia, thyrotoxicosis, oncologic diseases, among others (34,35). In the present study, the cause of pruritus, if associated to cholestasis or not, could not be ascertained.

Autoimmune hepatitis (AIH) was described in 64 (2.7%) patients in table 4. AIH is a cause of chronic liver disease with different triggers including prescription drugs, viral infections, associated systemic autoimmune disorders and liver transplant (31). Given the low prevalence of viral markers positivity, or of liver transplants, in this study, other factors should explain the occurrence of AIH observed. In this study, we could not identify if AIH was the primary disease or was caused by the suspected drugs under report. Contrary to hepatic fibrosis, autoimmune hepatitis was more common in people that had taken less than 5 suspected drugs, suggesting that if AIH was triggered by drugs it may have not been triggered by drug interactions.

In relation to the number of suspected drugs used and the cases evolution (table 5), few reports included more than 5 suspected drugs in use. Most patients presenting DILI received between 1-4 suspected drugs. In categories “cure” and “in recovery”, most patients had taken less than 5 suspected drugs. The higher number of drugs can result in drug interaction leading to DILI aggravation and lower frequencies of cure or recovery (30,33,42).

Table 6 showed that in patients who died, there were more females than males with hepatis and hepatotoxicity. Choluria and splenomegaly, features of cholestasis and portal hypertension had more males representation than females. This finding agrees with other studies showing that females have a higher tendency for hepatocellular damage, while cholestatic disorders occur more often in males than females (23,30).

In this study, we used the ATC classification system (table 8) to ascribe the drugs related to liver ADRs. We obtained ATC codes in every 1st level, with the notable exception of sensory organs. The 5 most frequent drugs belonged to the following groups by descending order: antivirals for systemic use (most were used in HIV/AIDS patients), antineoplastic agents, immunosuppressive agents, antibacterials for systemic use and psycholeptics, both included in the group of drugs that cause idiosyncratic DILI (23). In the EASL Clinical Practice Guidelines (4), it is referred that the following drugs are associated with idiosyncratic DILI: antimicrobials, central nervous system, cardiovascular, immunomodulatory, antineoplastic, rheumatologic. If we consider that antivirals for systemic use are in the same category as antimicrobials, our study results are in agreement with the EASL Clinical Practice Guidelines (4). However, we had few cases of cardiovascular drugs related to DILI. This might either be explained by a difference in population genetics or local variations of prescription patterns (4,30).

Regarding our study’s limitations, most of them are attributable to the low quality of information and lack of essential clinical-laboratory data obtained from the ordinary reports of

ADRs to the PPS. Reports were not filled completely, sometimes relevant patient information was missing, such as age and sex. Laboratory tests were only mentioned in reports as either altered, increased or decreased. As such, it was impossible to ascertain the degree of change from normality. For the same reason, it was also not possible to qualify the type of DILI as either hepatocellular, cholestatic or mixed. Another limitation was the high number of serious reports that had not been assessed for causality. Possible influences in this study results are other drugs, not suspected of causing ADRs, over-the-counter medication, alcohol consumption, herbal products and food supplements. These variables were not mentioned in the reports and their possible impact on our study results should be taken into account.

Conclusions

In conclusion, DILI is a rare occurrence, although it can be serious and sometimes even fatal. In our study, Hepatitis was the most common liver ADR. Fatal cases were reported from 2010 to 2019 to the PPS, however, most patients presented full recovery. This study has put in evidence that further efforts are needed in causality assessment by the pharmaceutical industry as most cases deemed serious did not receive causality assessment. Pharmacovigilance systems are extremely important in order to assess the existence, frequency and seriousness of putative ADRs that are only known when a drug is administered to a large population. This is a matter of public health and safety, which the present results highlight. Further studies of DILI in Portugal are needed, however.

Bibliography

1. Hoofnagle JH, Björnsson ES. Drug-Induced Liver Injury — Types and Phenotypes. The New England Journal of Medicine. 2019 July 18; 381:264-273.

2. Katarey D, Verma S. Drug-induced liver injury. Clinical Medicine. 2016; 16(6):104-109.

3. Drug-induced liver injury (DILI): Current status and future directions for drug development and the post-market setting. A consensus by a CIOMS Working Group. Geneva: Council for International Organizations of Medical Sciences (CIOMS); 2020.

4. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Drug-induced liver injury. Journal of Hepatology. 2019; 70:1222-1261.

5. Chalasani NP, Fontana RJ, et al. ACG Clinical Guideline: The Diagnosis and Management of Idiosyncratic Drug-Induced Liver Injury. The American Journal of Gastroenterology. 2014; Practice Guidelines.

6. Singh D, Cho WC, Upadhyay G. Drug-Induced Liver Toxicity and Prevention by Herbal Antioxidants: An Overview. Frontiers in Physiology. 2016; 6:363.

7. Tolosa L, Donato MT, et al. Long-term and mechanistic evaluation of drug-induced liver injury in Upcyte human hepatocytes. Archives of Toxicology. 2019; 93:519-532.

8. Kullak-Ublick GA, Aithal GP, et al. Drug-induced liver injury: recent advances in diagnosis and risk assessment. Gut. 2017; 66:1154-1164.
9. Kuna L, Smolic M, et al. Models of Drug Induced Liver Injury (DILI) – Current Issues and Future Perspectives. Current Drug Metabolism. 2018; 19:830-838.
10. Schenker S, Martin RR, Hoyumpa AM. Antecedent liver disease and drug toxicity. Journal of Hepatology. 1999; 31:1098-1105.
11. Teschke R. Idiosyncratic DILI: Analysis of 46,266 Cases Assessed for Causality by RUCAM and Published From 2014 to Early 2019. Frontiers in Pharmacology. 2019; 10:730.
12. The Importance of Pharmacovigilance Safety Monitoring of Medicinal products. United Kingdom. Publications of the World Health Organization; 2002.
13. Inácio P, Cavaco A, Airaksinen M. The value of patient reporting to the pharmacovigilance system: a systematic review. British Journal of Clinical Pharmacology. 2017; 83:227-246.
14. Batel-Marques F, Macedo T, et al. Pharmacovigilance in Portugal: Activity of the Central Pharmacovigilance Unit. Acta Medica Portuguesa. 2015; 28 (2):222-232.
15. Santoro A, Arlett P, et al. Promoting and Protecting Public Health: How the European Union Pharmacovigilance System Works. Drug Saf. 2017; 40:855–869.
16. Coleman JJ, Pontefract SK. Adverse drug reactions. Clinical Medicine. 2016; 16 (5):481-485.
17. Guideline on good pharmacovigilance practices (GVP) Module VI – Management and reporting of adverse reactions to medicinal products (Rev 1). EMA/873138/2011 Rev 1. European Medicines Agency and Heads of Medicines Agencies; 2014.
18. WHO Collaborating Centre for Drug Statistics Methodology, Norwegian Institute of Public Health. International Language for drug utilisation research ATC/DDD. Available from: https://www.whocc.no/. last accessed 16th December 2020.
19. The Uppsala Monitoring Centre. The use of the WHO-UMC system for standardised case causality assessment. WHO Publication; 2013.
20. Raschi E, Ponti F. Drug- and herb-induced liver injury: Progress, current challenges and emerging signals of post-marketing risk. World Journal of Hepatology. 2015; 7 (13):1761-1771.
21. Teschke R, Eickhoff A, et al. Drug and herb induced liver injury: Council for International Organizations of Medical Sciences scale for causality assessment. World Journal of Hepatology. 2014; 6 (1):17-32.
22. Stine J, Sateesh P, Lewis J. Drug-Induced Liver Injury in the Elderly. Current Gastroenterology Reports. 2013; 15:299.
23. Bell L, Chalasani N. Epidemiology of Idiosyncratic Drug-Induced Liver Injury. Semin Liver Dis. 2009; 29 (4): 337-347.
24. Andrade R, Martin-Vivaldi R, et al. Drug-Induced Liver Injury: An Analysis of 461 Incidences Submitted to the Spanish Registry Over a 10-Year Period. Gastroenterology. 2005; 129: 512-521.
25. Yang K, Köck K, Sedykh A, Tropsha A, Brouwer K. An updated review on drug-induced cholestasis: Mechanisms and investigation of physicochemical properties and pharmacokinetic parameters. Journal of Pharmaceutical Sciences. 2013; 102(9):3037-3057.
26. Erlinger S. Drug-induced cholestasis. Journal of Hepatology. 1997; 26(1):1-4.

27. Morales M, Vélez L, Muñoz M. Hepatotoxicity: A Drug-Induced Cholestatic Pattern. Rev Col Gastroenterol. 2016; 31(1):34-45.
28. Bataller R, Brenner D. Liver fibrosis. The Journal of Clinical Investigation. 2005; 115(2):209-218.
29. Ferenci P. Hepatic Encephalopathy. Gastroenterology Report. 2017; 5(2):138-147.
30. Chalasani N, Björnsson E. Risk Factors for Idiosyncratic Drug-Induced Liver Injury. Gastroenterology. 2010; 138(7):2246-2259.
31. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Autoimmune hepatitis. Journal of Hepatology. 2015; 63:971-1004.
32. Chen M, Lucena M, et al. Drug-induced liver injury: Interactions between drug properties and host factors. Journal of Hepatology. 2015; 63:503-514.
33. Ylä-Rautio H, Siissalo S, Leikola S. Drug-related problems and pharmacy interventions in non-prescription medication, with a focus on high-risk over-the-counter medications. International Journal of Clinical Pharmacy. 2020; 42:786-795.
34. Tivoli Y, Rubenstein R. Pruritus An Updated Look at an Old Problem. The Journal of Clinical and Aesthetic Dermatology. 2009; 2(7):30-36.
35. Huang A, Kwatra S, et al. Pruritus Associated with Commonly Prescribed Medications in a Tertiary Care Center. Medicines. 2019; 6, 84.
36. Arroyo M, Crawford J. Hepatitic inherited metabolic disorders. Seminars in Diagnostic Pathology. 2006; 23(3-4):182-189
37. Irwin M. Arias, Harvey J. Alter, James L. Boyer, David E. Cohen, David A. Shafritz, Snorri S. Thorgeirsson and Allan W. Wolkoff. The Liver Biology and Pathology. 6th edition. Oxford: John Wiley and Sons; 2020.
38. Padda M, Boyer J, et al. Drug Induced Cholestasis. Hepatology. 2011; 53(4):1377-1387
39. Teschke R, Eickhoff A. Herbal hepatotoxicity in traditional and modern medicine: actual key issues and new encouraging steps. Frontiers in Pharmacology. 2015; 6:72.
40. Douros A, Bolbrinker J. Herb-Induced Liver Injury in the Berlin Case-Control Surveillance Study. International Journal of molecular Sciences. 2016; 17:114.
41. Molleston J, Chalasani N, et al. Characteristics of Idiosyncratic Drug-induced Liver Injury in Children: Results From the DILIN Prospective Study. J Pediatr Gastroenterol Nutr. 2011; 53(2):182-189.
42. Masnoon N, Caughey G, et al. What is polypharmacy? A systematic review of definitions. BMC Geriatrics. 2017; 17:230.
43. David S, Hamilton J. Drug-induced Liver Injury. US Gastroenterol Hepatol Rev. 2010; 6:73-80.
44. Carneiro A, Costa J. Off-label prescription: Practice and problems. Portuguese Journal of Cardiology. 2013; 32(9):681-686.

Annexe

Annex 1: SMQs used for searching reports on the PPS.

Esteato-hepatite, Esteatose hepática não alcoólica, Hepatite, Hepatite aguda, Hepatite alérgica, Hepatite auto-imune, Hepatite colestática, Hepatite crónica, Hepatite crónica activa, Hepatite crónica persistente, Hepatite fulminante, Hepatite imunomediada, Hepatite tóxica, Inflamação do tracto portal, Ascite, Atrofia amarela aguda do fígado, Atrofia hepática, Cirrose biliar, Cirrose hepática, Colangite biliar primária, Coma hepático, Degeneração hepatocerebral adquirida, Doença do fígado, Doença do fígado gordo não alcoólico, Doença hepatobiliária, Encefalopatia hepática, Encefalopatia hepática mínima, Esteato-hepatite, Esteatose hepática não alcoólica, Fibrose biliar, Fibrose e esteatose hepática, Fibrose hepática, Fibrose portal, Fígado danificado, Hepatite fulminante, Hepatotoxicidade, Hipertensão portal não cirrótica, Infiltração hepática eosinofílica, Insuficiência hepática, Insuficiência hepática aguda, Insuficiência hepática crónica, Insuficiência hepática subaguda, Insuficiência hepatorrenal, Lesão colestática do fígado, Lesão hepática, Lesão hepática induzida por fármacos, Lesão hepática mista, Necrose hepática, Síndrome de Reye, Síndrome hepatopulmonar, Síndrome hepatorrenal, Surto agudo de insuficiência hepática crónica, Transplante hepático, Cancro hepatobiliar, Colangiocarcinoma hepatocelular misto, Colangiossarcoma, Alteração da excreção de bilirrubina, Colemia, Colestase, Doença hepática associada a nutrição parenteral, Hepatite colestática, Hiperbilirrubinemia, Icterícia, Icterícia colestática, Icterícia hepatocelular, Icterícia ocular, Índice ictérico aumentado, Lesão colestática do fígado, Lesão hepática induzida por fármacos, Lesão hepática mista, Prurido colestático, Deficiência de secreção da bílis, Pele amarela, Ácidos da bílis total aumentados, Alanina aminotransferase anormal, Alanina aminotransferase aumentada, Amónia aumentada, Ascite, Aspartato aminotransferase anormal, Aspartato aminotransferase aumentada, Aspartato aminotransferase mitocondrial aumentada, Bilirrubina conjugada anormal, Bilirrubina conjugada aumentada, Bilirrubina directa no sangue aumentada, Bilirrubina na urina aumentada, Bilirrubina no sangue anormal, Bilirrubinemia aumentada, Biopsia hepática anormal, Débito da bílis anómalo, Débito da bílis diminuído, Ecografia hepática anormal, Enzima hepática anormal, Enzima hepática aumentada, Fígado palpável, Função hepática anormal, Gama glutamiltransferase anómala, Gamaglutamiltransferase aumentada, Hepatoesplenomegalia, Hepatomegalia, Hiperamonemia, Hiperbilirrubinemia, Hipercolia, Hipertransaminassemia, Hipertrofia hepática, Imagiologia de ressonância magnética do fígado anormal, Presença de bilirrubina na urina, Prova da função hepática anormal, Prova da função hepática aumentada, Razão AST/ALT anormal, Scan hepático anormal, Scan hepatobiliar anormal, Transaminases anormais, Transaminases aumentadas, 5'-nucleotidase aumentada, Deficiência de secreção da bílis, Fosfatase alcalina no

sangue anormal, Fosfatase alcalina no sangue aumentada, Urobilinogénio urinário aumentado e Urobilinogénio urinário diminuído.