How European hepatologists (and clinician scientists) can benefit from the Pro Euro DILI Net Cost?

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Hannover Medical School



Medizinische Hochschule Hannover

Acknowledgements

- Benjamin Maasoumy
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- Markus Cornberg

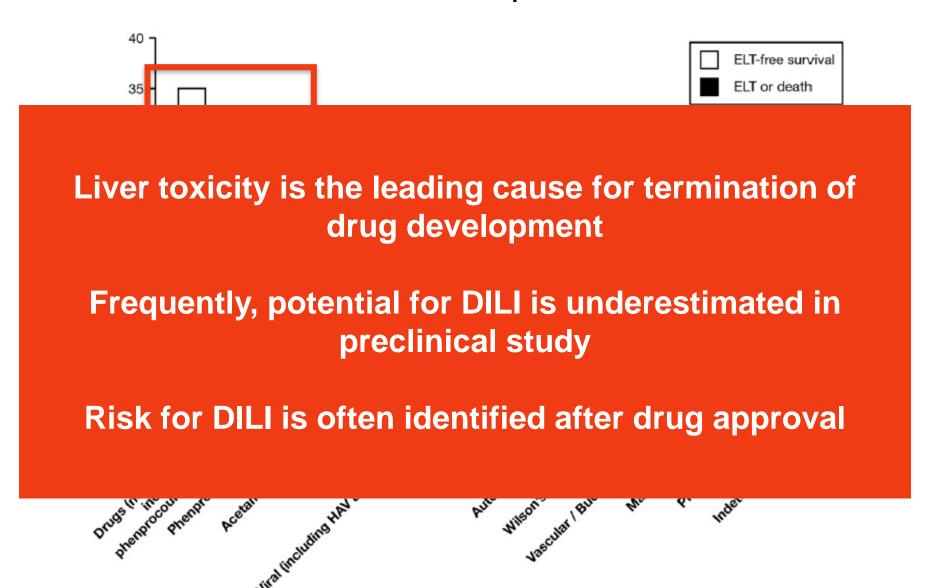


"Drugs, the scapel of internal medicine"

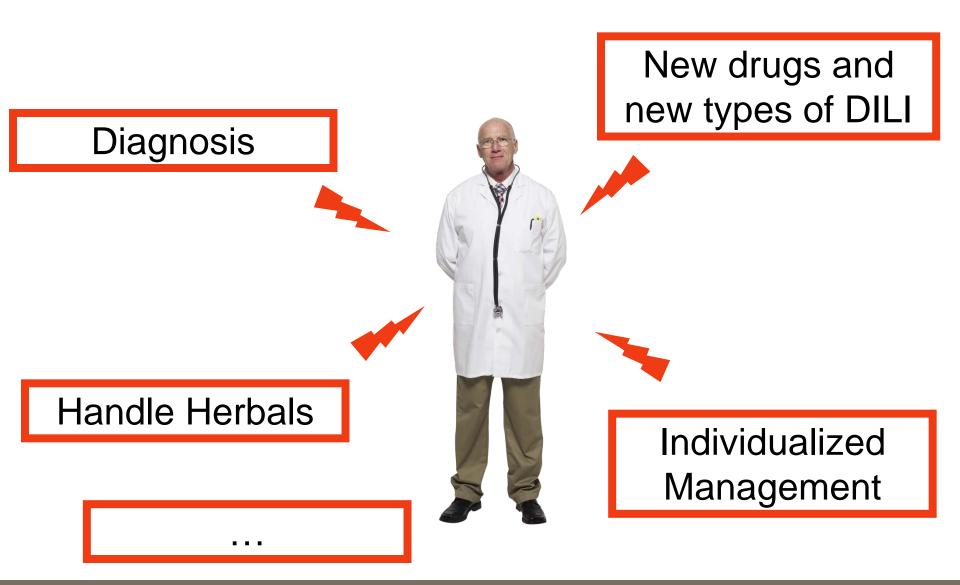
Effective, but dangerous?



DILI: One of the most frequent causes of ALF



DILI: Several challenges ahead for Hepatologists



>1000 drugs have the potential to cause liver injury

y wikipedia.org

Table 1. Distribution of the Main Drugs Suspected in 446 Cases of Drug-Induced Liver Disease Reported to the Registry Between 1984 and 2004 According to the Type of Liver Damage, Severity of Hepatic Injury, and Presence of Eosinophilia

	Total	Type o	f liver injury (N)		Casinanhilia	Liver-related	ALE /liver tv	Dooth
Drug	cases	Honotocollular	Chalactatia	Mixad	Eosinophilia (N)	hospitalization	ALF/liver tx	Death
Amoxici Ebrotidi INH + F					opean			
Ibuprofe Flutami	hepa	tologis	sts (ar	nd c	linicia	n scier	ntists)	
IOOTIIGZI	bene	efit fro	m the	Pro	Euro	DILIN	Vet Co	ost?
Medicinar neros	9	ŏ	1	_	1	၁ (၁၀%)	_	T
Nimesulide	9	7	2	_	2	3 (33%)	2/1	1
Carbamazepine	8	4	1	3	4	3 (38%)	1/0	1
Bentazepam	7	5	_	2	_	3 (43%)	_	_
Tetrabamate	7	6	1	_	_	2 (29%)	_	_
Azathioprine	6	1	4	_	1	1 (17%)	_	_
Erythromycin	6	_	4	2	1	3 (50%)	_	_
Paroxetine	6	3	1	2	_	3 (50%)	_	
Valproic acid	5	4	1	_	1	2 (40%)	_	_
Trovafloxacin	5	4	_	1	2	3 (60%)	_	_
Thiamazole	5	1	4	_	1	3 (60%)	_	_

ALF, acute liver failure; Tx, liver transplantation; INH, isoniazid; RIP, rifampicin; PIZ, pirazinamide.

^aOne case of acute chronic liver damage (cirrhosis), another case of inadvertent rechallenge leading to cirrhosis and liver transplant.

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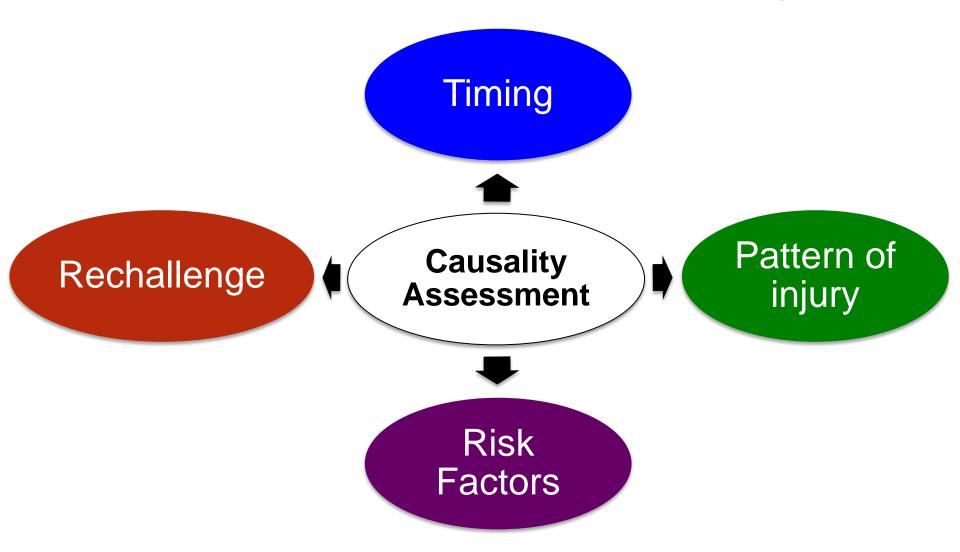
wikipedia.org

	Total	Type of liver injury (N)			Liver-related			
Drug	cases	Honotocollular	Chalactatia	Mixad	Eosinophilia (N)	hospitalization	ALF/liver tx	Death
Amox Ebrot INH - Ibupr Fluta Ticlor Diclo Isonia Medi Nime	Rau	ul and	Marib	el's	Span	ish Ex	perier	nce!
Carbamazepine	8	4	1	3	4	3 (38%)	1/0	1
Bentazepam	7	5	_	2	_	3 (43%)	_	_
Tetrabamate	7	6	1	_	_	2 (29%)	_	_
Azathioprine	6	1	4	_	1	1 (17%)	_	_
Erythromycin	6	_	4	2	1	3 (50%)	_	_
Paroxetine	6	3	1	2	_	3 (50%)	_	_
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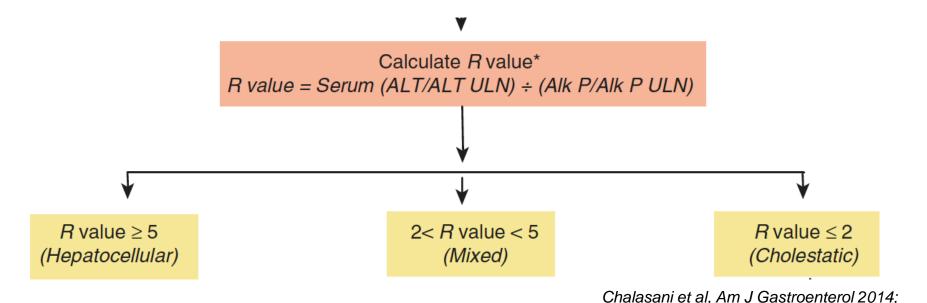
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DILI – How to diagnose? How to identify the responsible drug?



Hepatocellular, Cholestatic, Mixed?





Problem:
One drug may cause different patterns



Timing?



Amoxicillin/Clavulanic acid 1-89 days

Cisplatin 1-5 days

Diclofenac 2-12 weeks

Dihydralazin up till several months

Problems:
lack of data, highly variable
Multiple drugs may have been used

Potential causes of liver toxicity? How to identify?

-LiverTox® (http://livertox.nih.gov/)

-Roussel Uclaf Causality Assessment Method (RUCAM)

Multiple Itams

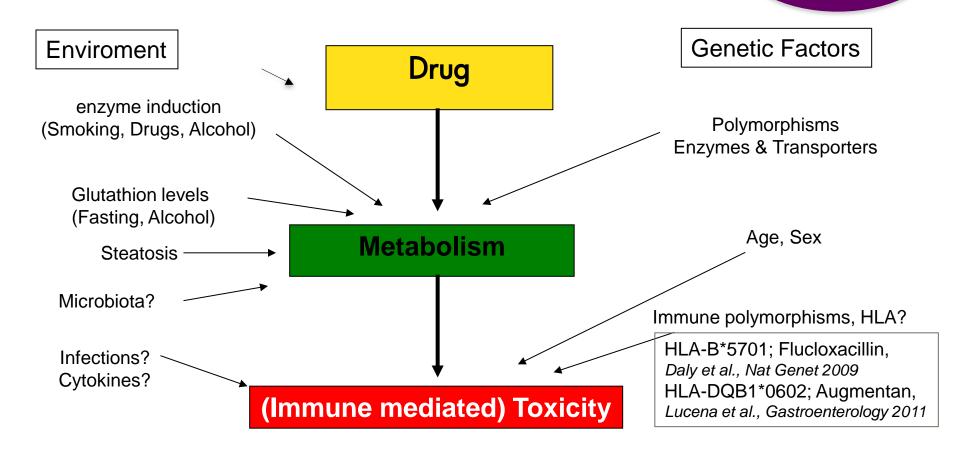
COST should develop a better Causality Assessment Method based on COST database



Kullak-Ublick et al., Gut 2017;66:1154-1164.

Idiosyncratic liver toxicity – Who and When?

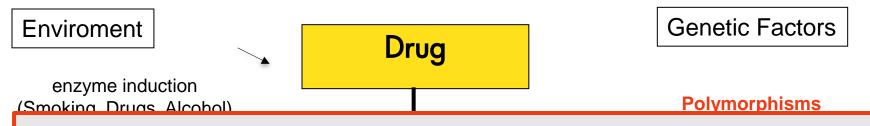




Incomplete understanding of the underlying mechanisms

Idiosyncratic liver toxicity – Who and When?





COST can form a research consortium exploring environmental (e.g. microbiota) or genetic risk factors (polymorphisms) based on human material and data from COST biobanks and databases

1

Incomplete understanding of the underlying mechanisms

DILI: Unmet needs of Hepatologists



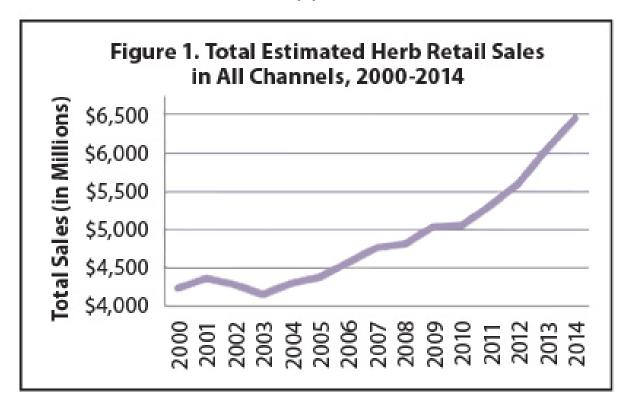


Unmet need: Improve and facilitate diagnosis of DILI!



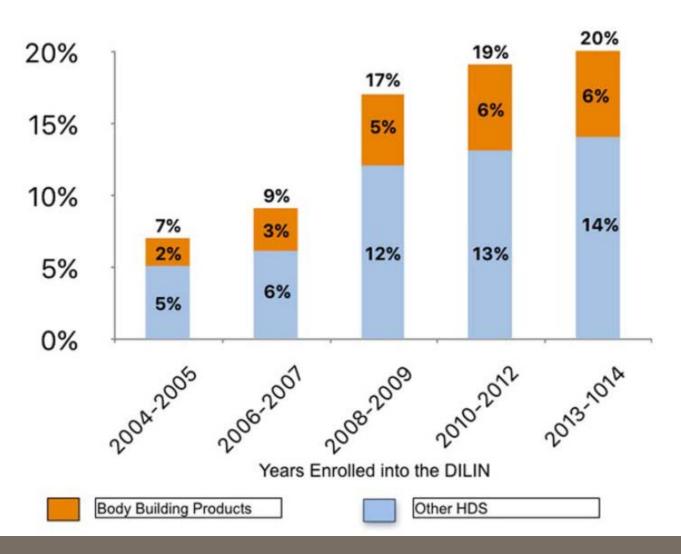
Herbals - an emerging market...

Sales of herbal supplements in the US



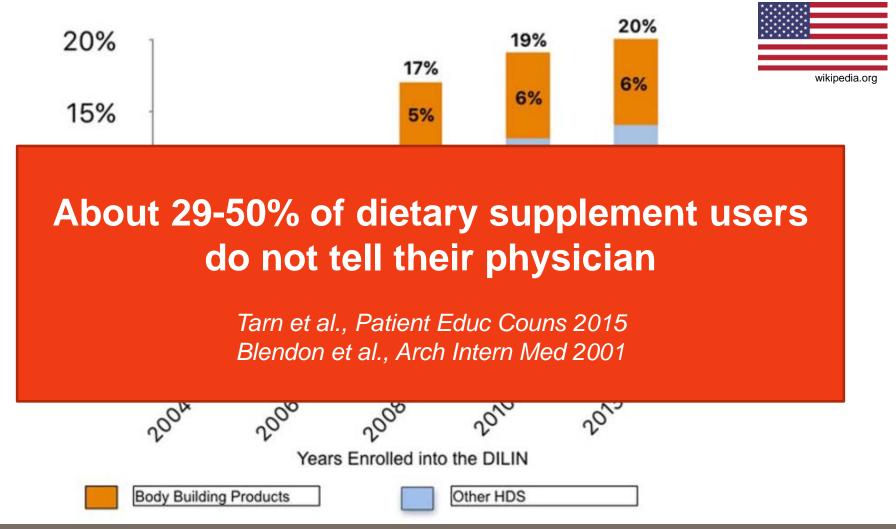
2014: 11th consecutive increase! About 330 Million Dollar in 2014

Increase in liver failure due to anabolic steroids and herbal/dietary supplements





Increase in liver failure due to anabolic steroids and herbal/dietary supplements



"I take only Happy Heart"

"Happy heart is an ayurvedic herbal medicine" "Strengthens the heart, lowers cholesterol level and improves blood circulation"

Ingredients:

- 1.Ashwagandha
- 2.Lahsun
- 3.Arjun
- 4. Sarpagandha
- 5.Brahmi
- 6.Gokhru
- 7.Amla
- 8.Tagar
- 9.Punarnava
- 10.Sankhpushpi
- 11.Mulethi
- 12.Shilajeet
- 13.Mukta Pisti
- 14.Praval Pisti
- 15. Muktasukti Pisti

Any of those causing DILI?

source: http://yugrishi.com

"I take only Happy Heart"

"Happy heart is an ayurvedic herbal medicine" "Strengthens the heart, lowers cholesterol level and improves blood circulation"

63-68% of HDS-induced liver injuries caused by multi-ingredient products

Medina-Caliz et al, Clinical Gastroenterology and Hepatology 2018
Navarro et al, Hepatology 2014

10.Sanknpusnpi

11.Mulethi

12.Shilajeet

13.Mukta Pisti

14.Praval Pisti

15.Muktasukti Pisti

source: http://yugrishi.com



DILI: Unmet needs of Hepatologists





Unmet need:
Improve and facilitate
diagnosis of DILI!

Unmet need: Increase awareness of the potential risks of herbals





How European hepatologists (and clinician scientists) can benefit from the Pro Euro DILI Net Cost?

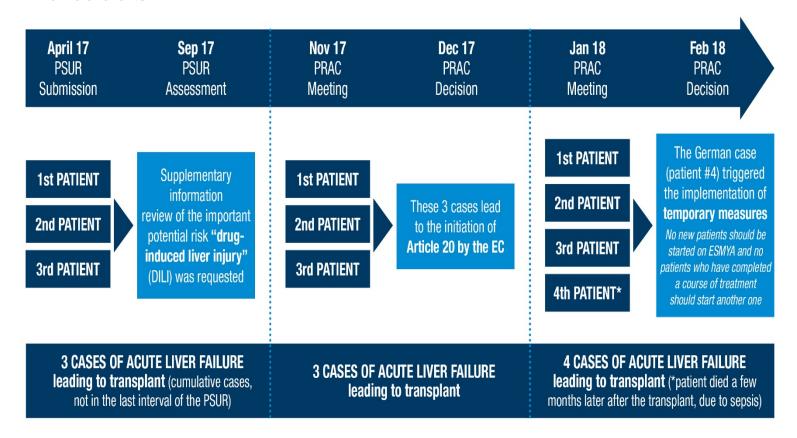
- COST hepatologists need to reach out to other medical specialties:
 - Gastroenterologists
 - Rheumatologists
 - Nephrologists
 - Oncologists
 - Neurologists
 - Gynaecologists



Ulipristalacetate - ESMYA

Sequence of acute liver failure reports leading to liver transplantation

Timeline of events



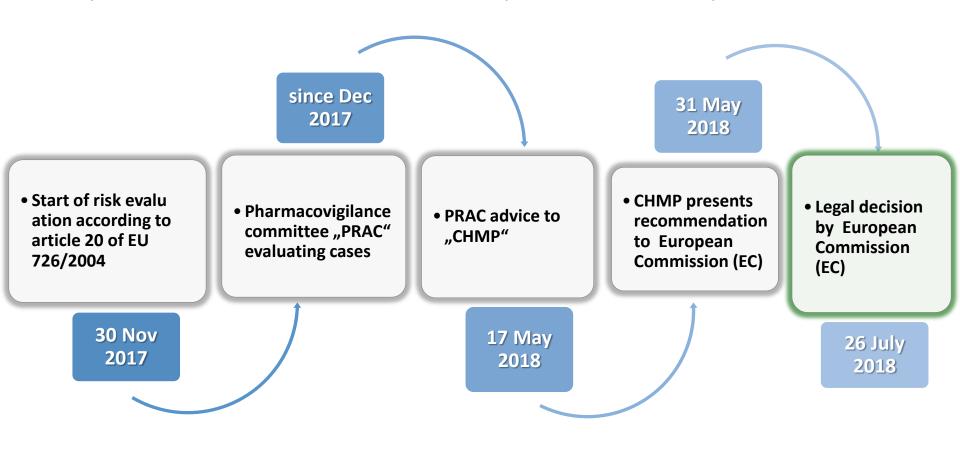


The 1st patient was from Portugal, the 2nd and 3rd patients were from France and the 4th patient was from Germany





Sequence of events for the Ulipritalacetate process?



Emerging class of biologics: High potential for DILI?

Spanish Registry	DILIN Study	Icelandic Study	
Amoxicillin-clavulanate	Amoxicillin-clavulanate	Amoxicillin-clavulanate	
Isoniazid	Isoniazid	Diclofenac	
RIP + INH + PIZ	Nitrofurantoin	Azathioprine	
Flutamide	SMZ/TMP	Infliximab	
Ibuprofen	Minocycline	Nitrofurantoin	

RIP + INH + PIZ: Rifampin, Isoniazid and Pyrazinamide; SMZ/TMPSulfamethoxazole/Trimethoprim.

Table 3. Number of DILI Cases of All Outpatients Treated and All Prescriptions During the 2-Year Study Period, and the Proportion of 1 Case of All Patients Treated With the Specific Drug

	Patients				Per				
Drug	treated, n	Prescriptions, n	Cases, n	Proportion	100,000	95% CI	95% CI	Jaundice	Symptomatic
Amoxicillin/clavulanate	35,252	83,379	15	2350	43	24	70	6/15 (40%)	13/15 (87%)
Diclofenac	54 889	112.801	6	9148	11	4	24	2/6 (33%)	5/6 (83%)
Azathioprine	532	3054	4	133	752	205	1914	0%	4/4 (100%)
Infliximab	593	а	4	148	675	184	1718	1/4 (25%)	2/4 (50%)
ivitroturantoin	5476	12,034	4	1369	73	20	187	2/4 (50%)	4/4 (100%)
Isotretinoin	2169	7978	3	732	138	29	404	0%	1/3 (33%)
Atorvastatin	7385	34,171	2	3693	27	4	98	1/2 (50%)	1/2 (50%)
Doxycycline	32,677	54,232	2	16,339	6	1	22	0%	1/2 (50%)

NOTE. Only drugs associated with at least 2 cases of DILI are shown. The proportion with jaundice and symptomatic DILI are given. CI, confidence interval.

^aMost patients on infliximab received continuous prescriptions.

Anti-TNF alpha may cause AIH

- Induction of AIH following TNF alpha antagonists:
 - Harada K et al. Clin Rheumatol 2008 AIH Exacerbation following Etanercept in patients with rheumatoid arthritis
 - Ozorio G et al. Med J Aust 2007 AlH following infliximab therapy of ankylosing spondylitis.
 - Cravo M. BioDrugs 2010 AlH induced by Infliximab in a patient with Crohn's disease, no relapse after switch to adalimumab

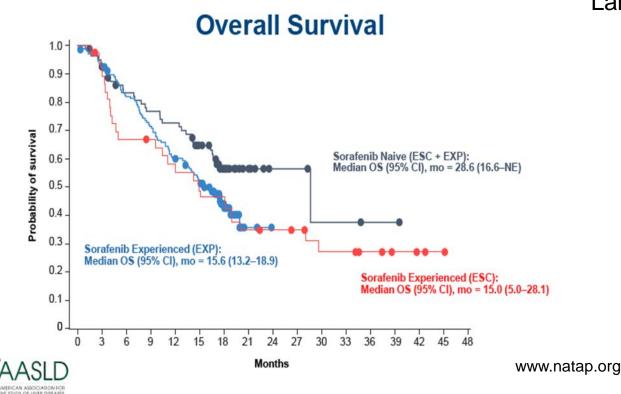
Check-Point Inhibitors: The holy grail of oncology?

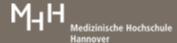


Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial

Anthony B El-Khoueiry, *Bruno Sangro, *Thomas Yau, Todd S Crocenzi, Masatoshi Kudo, Chiun Hsu, Tae-You Kim, Su-Pin Choo, Jörg Trojan, Theodore H Welling 3rd, Tim Meyer, Yoon-Koo Kang, Winnie Yeo, Akhil Chopra, Jeffrey Anderson, Christine dela Cruz, Lixin Lang, Jaclyn Neely, Hao Tang, Homa B Dastani, Ignacio Melero

Lancet 2017





Check-Point Inhibitors: New kind of DILI?

Letters to the Editor





Managing immune checkpoint-inhibitor-induced severe autoimmune-like hepatitis by liver-directed topical steroids

2017

Research Article



JOURNAL OF HEPATOLOGY

Characterization of liver injury induced by cancer immunotherapy using immune checkpoint inhibitors

Eleonora De Martin¹, Jean-Marie Michot², Barbara Papouin³, Stéphane Champiat², Christine Mateus⁴, Olivier Lambotte⁵, Bruno Roche¹, Teresa Maria Antonini¹, Audrey Coilly¹, Salim Laghouati⁶, Caroline Robert⁴, Aurélien Marabelle², Catherine Guettier³, Didier Samuel^{1,*}

2018

N = 536 patients who received immonotherapy

N= 16 Immune-mediated hepatitis

N= 7 Required immunosuppresive treatment

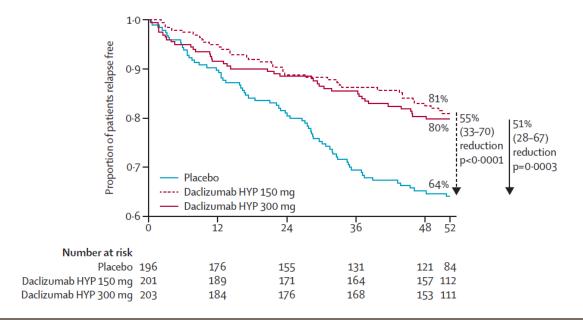
New BILI Example: Daclizumab (Zinbryta®; Biogen)

Mode of action:

- humanised monoclonal antibody
- blocking the α subunit (CD25) of the interleukin-2 receptor

Indication (approved 2016):

Relapsing Multiple sclerosis



New BILI Example: Daclizumab (Zinbryta®; Biogen)

	Placebo (n=204)	Daclizumab HYP 150 mg (n=208)	Daclizumab HYP 300 mg (n=209)
Summary of adverse events			
Incidence of ALT or AST abnormalities			
1–3×ULN	64 (31%)	54 (26%)	62 (30%)
3–5×ULN	6 (3%)	7 (3%)	6 (3%)
>5×ULN	1 (<1%)	9 (4%)	8 (4%)

Overview

EMA concludes review of Zinbryta and confirms further restrictions to reduce risk of liver damage

Zinbryta to be used in restricted patient group, with strict liver monitoring

On 9 November 2017, the European Medicines Agency (EMA) concluded its review of the multiple sclerosis medicine Zinbryta (daclizumab) and confirmed further restrictions to reduce the risk of serious liver damage.

The review found that unpredictable and potentially fatal immune-mediated liver injury can occur during treatment with Zinbryta and for up to 6 months after stopping treatment. In <u>clinical trials</u>, 1.7% of patients receiving Zinbryta had a serious liver reaction.

DILI: Unmet needs of Hepatologists





Unmet need: Improve and facilitate diagnosis of DILI!

Unmet need: Increase awareness of the potential risks of herbals



Unmet need:
Timely investigation and information of the DILI potential of biologicals/immunotherapy





How European hepatologists (and clinician scientists) can benefit from the Pro Euro DILI Net Cost?

- Hepatologists, basic and clinician scientists can use the COST network to develop and validate novel diagnostic tools for DILI:
 - Genetic markers (GWAS)
 - In vitro tests

Biomakers

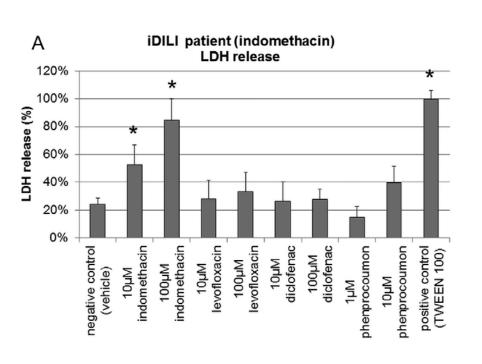


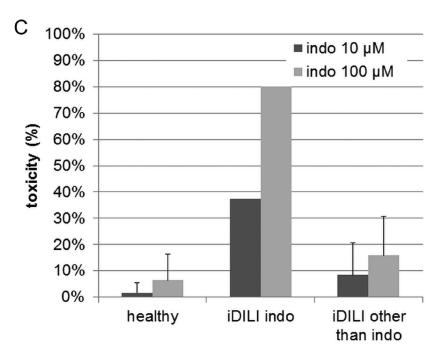
Potential of Genetics to estimate risk for DILI

Drug studied	Cohort (ethnicity)	Association described	SNP (gene) ¹⁰⁹	OR
Ximelagatran ¹¹⁰ thrombin inhibitor	74 cases, 130 T controls (European)	HLA-DRB1*07	HLA-DRB1	4.4
Flucloxacillin ¹¹¹ β-lactam antibiotic	51 cases, 282 P controls (European)	HLA-B*5701	rs2395029 <i>HCP5</i>	45.0
•		ST6GAL1	rs10937275 <i>ST6GAL1</i>	4.1
		OR5H2	rs1497546 <i>OR5H8P—OR5K4</i>	6.6
		ALG10B	rs6582630 <i>ALG10B—CPNE8</i>	2.8
		MCTP2	rs4984390 <i>MCTP2</i>	3.3
		C9orf82 (CAAP1)	rs10812428 <i>FAM71BP1—CAAP1</i>	2.9
Lumiracoxib ¹¹² Cyclo-oxygenase-2 inhibitor	41 cases, 176 T controls; Replic: 24 cases (Europeant)	HLA-DRB1	rs3129900 <i>C6orf10</i>	7.5
Lapatinib ¹¹³ kinase inhibitor	37 cases, 1071 T controls, (Europeant)	HLA-DRB1*0701 Perfect linkage disequilibrium with DQA1*0201	NR	NR
Lapatinib ¹¹⁴ kinase inhibitor	34 cases, 810 T controls, (Europeant)	HLA-DRB1 *0701	NR	NR
Amoxicillin-clavulanate ¹¹⁵ antibiotic	201 cases, 532 P controls (European)	HLA-DQB1 *0602	rs9274407 HLA-DQB1	3.1
		HLA-A*0201	rs2523822 <i>TRNAI25</i>	2.3
Multiple (Diclofenac ¹¹⁶ non-steroidal anti-inflammatory drug)	783 cases (30 diclofenac) 3001 P controls (European)	PPARG‡	rs17036170 <i>PPARG</i>	11.3
Multiple (Flupirtine ¹¹⁷ non-opioid analgesic)	614 cases (6 flupirtine) 10 588 P controls (<i>European</i>)	HLA-DRB1*16:01-DQB1*05:02	HLA-DRB1	18.7

Innovative tools to improve DILI diagnosis

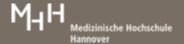
Monocyte-derived hepatocyte-like cells from DILI patients





Superior to RUCAM Useful if multiple drugs are suspected?

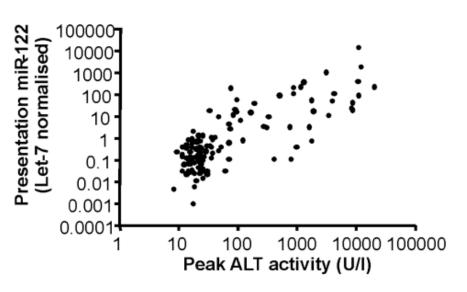
"Limited number of patients (n=31)"

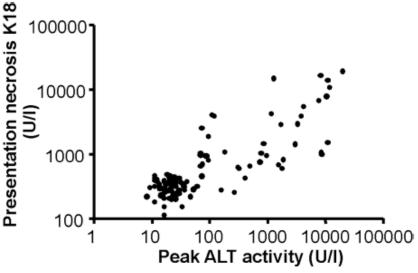




New biomarkers in DILI management

n = 129 patients with acetaminophen-induced acute liver injury Different baseline biomarkers to predict severity of liver injury





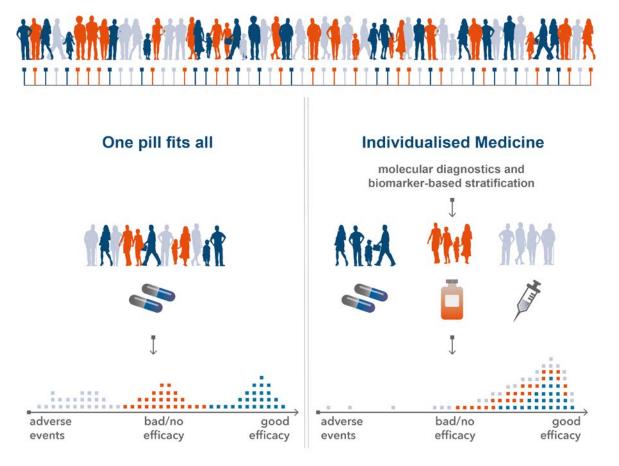


Technical innovations allow individualised medicine

					2000s to
1950s	1960s	1970s	1980s	1990s	Present
Watson and Crick discover the structure of the DNA double-helix	Researchers crack the genetic code	- First DNA sequencing technology developed - Researchers discover first enzyme linked to individual variation in response to dosing	Polymerase chain reaction (PCR) first developed, allowing for fast amplification of DNA sequences	- Human genome project launched - FDA approves first personalized medicine with a companion diagnostic, for the treatment of HER2 positive breast cancer	- Human Genome Project completed - First targeted therapies for lung cancer, leukemia, melanoma, cystic fibrosis, HIV, and many other diseases - 42% of the industry's pipeline has the potential to be personalized medicines

PhRMA, Value of Personalized Medicine, 2015

The promise of individualised medicine



Due to technical innovations one can spot interindividual differences and predict individual's course of disease or success of treatment.

DILI: Unmet needs of Hepatologists





Unmet need: Improve and facilitate diagnosis of DILI!

Unmet need: Increase awareness of the potential risks of herbals



Unmet need: Timely investigation and information of the DILI potential of biologicals/immunotherapy



Develop individualized approaches for DILI risk assessment





DILI: Opportunities and challenges for science



Plenty of new biotechnologies

New digital technologies Allowing "Big Data" Machine Learning Limited resources and capacities of research groups

Lack of data harmonization

Small data sets

Data Protection Laws

How to be successful in Hepatology 2019? Possibilities but also challenges!

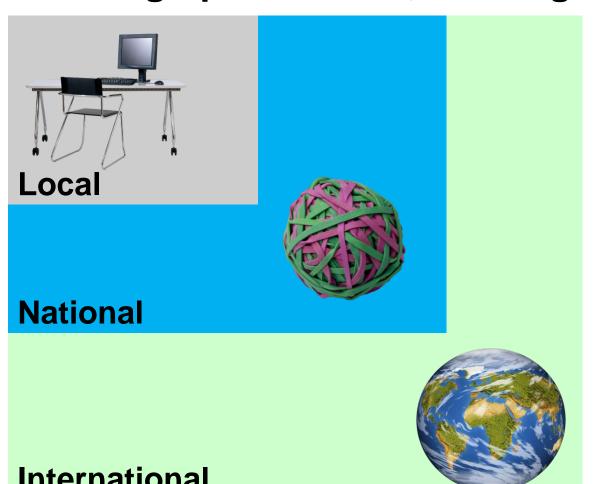
- New techniques = increased complexity in clinical and translational science
- Increasing number of new drugs = increased need for fast access to information of reliable sources
- New media = new challenges to achieve awareness



The team is the star!

www.wikipedia.de

A Must in Future Hepatology: Local, National and International Networking Building up sustained, working networks!



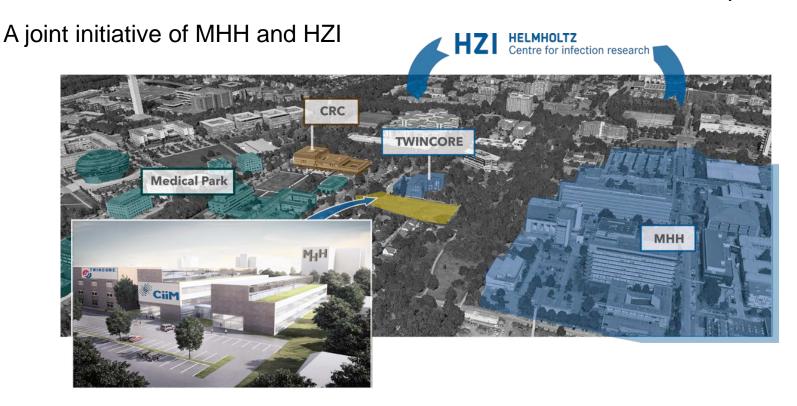


Industry



International

Example from Hannover: Centre for Individualised Infection Medicine (CiiM)

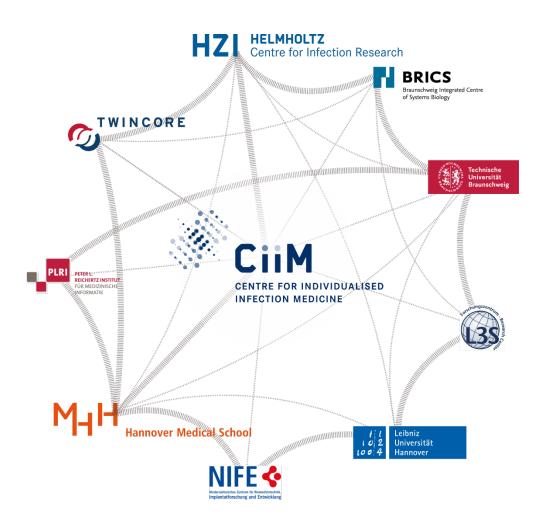


- will bundle interdisciplinary and complementary expertise plus state-of-the-art infrastructures in a newly designed building
- committed to develop individualised approaches for the prevention, diagnosis and treatment of infections with the aim of optimised patient care

Example from Hannover: Centre for Individualised Infection Medicine (CiiM)

CiiM embedding will

- bring the research closer to clinical routine and the clinics closer to innovative technological and research developments
- will support innovative and high-quality solutions in individualised infection medicine



Potential of National and International Networks

Increase awareness

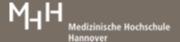
- Influence political decisions
- Approach different types of stakeholders
- Increase knowledge among patients

Optimize current diagnosis and treatment

- Increase knowledge among physicians
- Support collaborations
- Implement clinical guidelines

Improve research activities

- Facilitate collaborations between different researchers
- Allow multicenter investigator initiated trials
- Combine resources

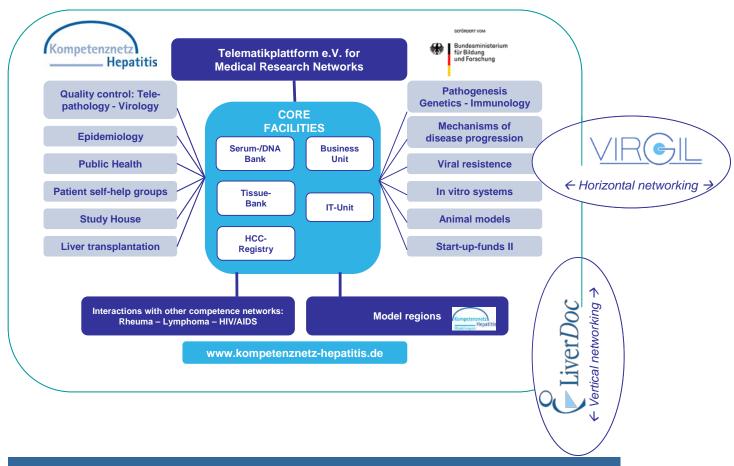


How can networks help hepatologists? Leasons learned in viral hepatitis



Deutschel Leberstiftung

Structure of "Kompetenznetz Hepatitis" 2002-2010



Networking of the project fields within Hep-Net and integration into other (inter-)national networks

German Liver Foundation (est. 2006) for sustainability of Hep-Net >2010



Deutsche Leberstiftung (German Liver Foundation)

Germanl
Liver Foundation Research networking / Promotion of research The liver and liver disease awareness Information and advice Associated doctors, clinics, researchers, pharmacists and self-help groups The Hepatitis Competence Network Central biobanks

Improving patient care

HepNet Study-House

Vertical Networking

Horizontal Networking (26 Universities, Research)









Universities



Municipal Hospitals



Private Practitioners



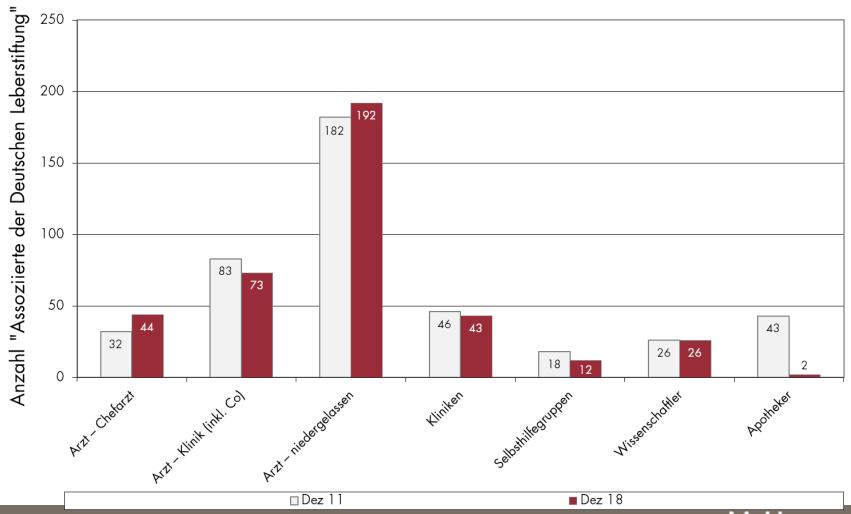
Patients (Advocacy Groups)



Public (i.e. pupils)

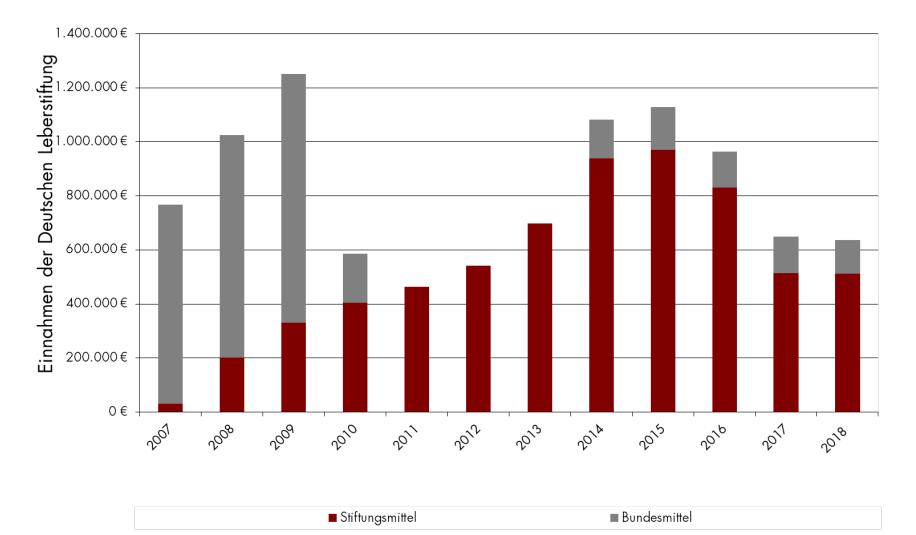
Network of Associates

Involve universities, district hospitals, physicians, patients, scientists, pharmacists, industry...



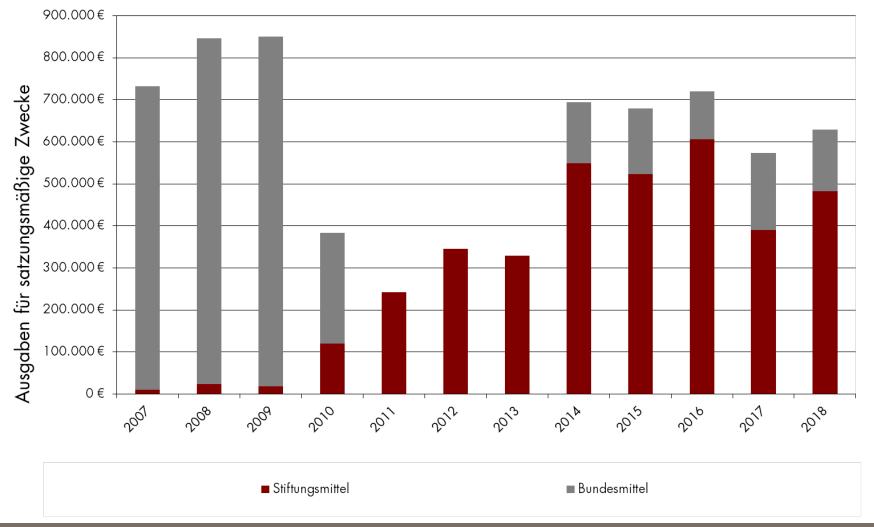
Deutsche Leberstiftung

Revenue



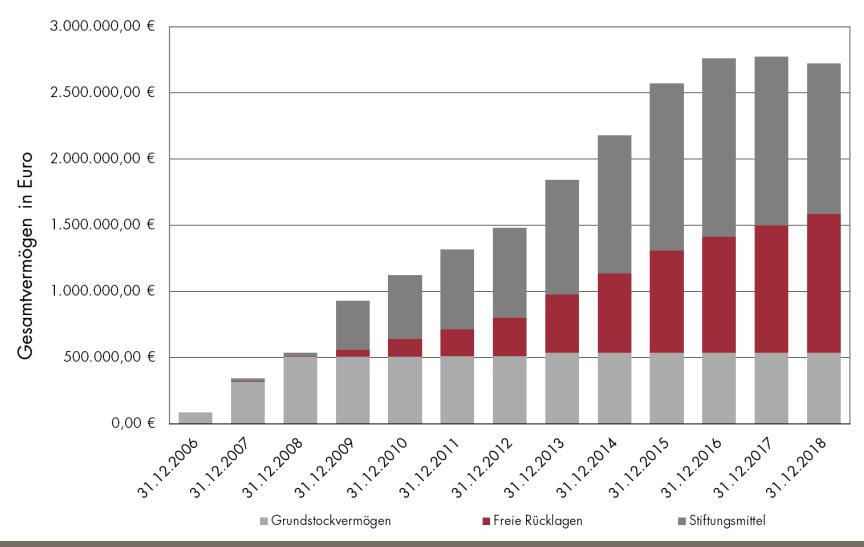
Deutsche Leberstiftung

Statutory expenditure



Deutsche Leberstiftung

Capital account



Successful tools to increase public awareness

- Press releases, articles
- Events: National German Liver Day
- Campaigns: e.g. with 1300 LINDA Pharmacies
- "The Liver Book"
- Image Film "German Liver Foundation"
- Liver Seminar Series: for Doctors and Patients

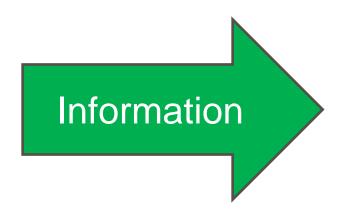


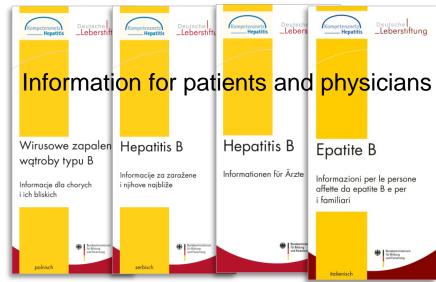






Transfer of Knowledge



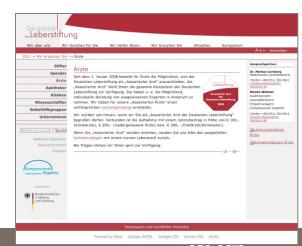




Telefone hotline



Homepage



Transfer of Knowledge

Liver-Seminars for Associated Members

Support of events dealing with the Liver

Offer: Presentations, Press Releases, Speakers, Lecturers



Annual HepNet Symposium

- 18 Sponsors / Exhibitors / Sponsors
- 250 Delegates

HepNet Journal

Support of Research Networking

- Stipends to promote research networking between basic science and clinical research
- Exchange of young scientists





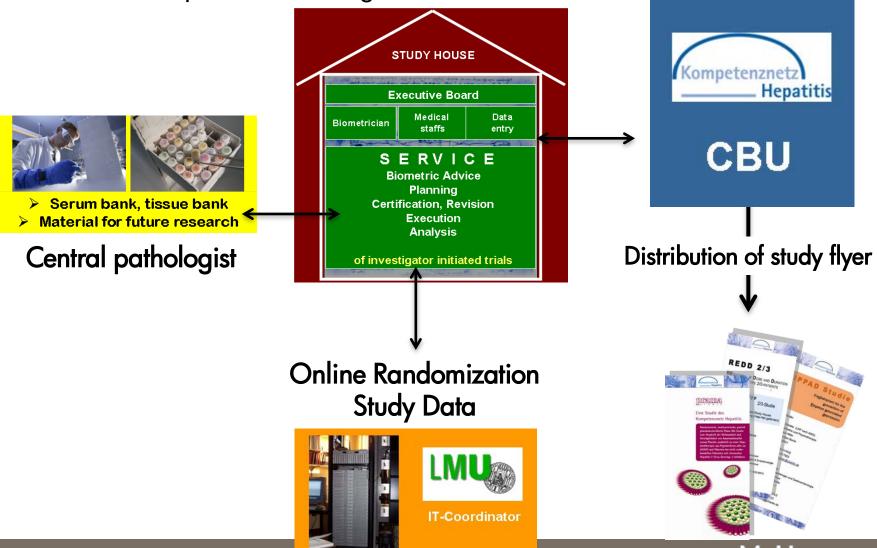
ein Projekt der Deutschen Leberstiftung



HepNet Study-House

HEP-NET Study House

... in order to perform investigator initiated trials



Aedizinische Hochschule

History of the HepNet Study-House



2002





HepNet Study-House

funding:

BMBF: Kompetenznetz Hepatitis; Total funding :ca. 2,5

Mio. €/ year (in total: 12,5 Mio. €)

HepNet Study-House funding from 2002-2010

2006

~ 1 Mio €

Founding of the "Deutsche Leberstiftung" and continuation of the Study-House as a project of the liver foundation

funding:

- german liver foundation
- Industry through support of IITs

HepNet Study-House as a central unit of the TTU-Hepatitis

2014 HepNet Study-House as a central unit of the TTU-Hepatitis With the German Liver Foundation as an external DZIF member

2019

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HepNet Study-House Achievments



ein Projekt der Deutschen Leberstiftung



HepNet Study-House

Rare indications

Acute Hepatitis C
Acute HCV studies I-IV

HCV-genotype 1 prolonged treatment

Optimized Therapy

Hepatitis B/C Coinfection

HCV-genotype 1
AMANTADIN (PRAMA)

Hepatitis delta (B/D)
HIDIT I+II studies
HDIN registry

HCV-genotype 2/3 Reduction, prolongation REDD2/3; OPTEX

Chronic Hepatitis E SofE study

CIPPAD Studie
+ Antidepressive Therapie

Acute Hepatitis C

1x NEJM, 1x Hepatology, 2x Lancet Infectious Diseases

The New York Times

Treatment of Early-Stage Hepatitis C Advances



The New England Journal of Medicine

Notice: Because of its potential clinical implications, this article is being published early (on October 1, 2001). It will appear in the November 15 issue of the *Journal*.

TREATMENT OF ACUTE HEPATITIS C WITH INTERFERON ALFA-2b

ELMAR JAECKEL, M.D., MARKUS CORNBERG, M.D., HEINER WEDEMEYER, M.D., TERESA SANTANTONIO, M.D.,
JULIKA MAYER, M.D., MYRGA ZANKEL, D.V.M., GIUSEPPE PASTORE, M.D., MANFRED DIETRICH, M.D.,
CHRISTIAN TRAUTWEIN, M.D., AND MICHAEL P. MANNS, M.D., FOR THE GERMAN ACUTE HEPATITIS C THERAPY GROUP



Prompt Use of Antiviral Drug Lessens the Toll of Hepatitis C



Eine schnelle Behandlung kann Hepatitis-C-Infektionen heilen. Doch die Diagnose kommt meist zu spät



HepNet acute HCV studies 2001-2019:

ein Projekt der Deutschen Leberstiftung



HepNet Study-House

starting in April 2019 acute HCV-V

Multicenter trial for the treatment of acute Hepatitis C for 8 weeks with Sofosbuvir/Velpatasvir fix dose combination_The HepNet acute HCV-V study

Akute HCV IV - Lancet Infectious Diseases 2017

Ledipasvir plus sofosbuvir fixed-dose combination for 6 weeks in patients with acute hepatitis C virus genotype 1 monoinfection (HepNet Acute HCV IV): an open-label, single-arm, phase 2 study.

Akute Hepatitis C III - Lancet Infectious Diseases 2013

Delayed versus immediate treatment for patients with acute hepatitis C: a randomised controlled non-inferiority trial.

Peginterferon plus adefovir versus either drug alone for hepatitis delta.

Akute Hepatitis C II - Hepatology. 2006

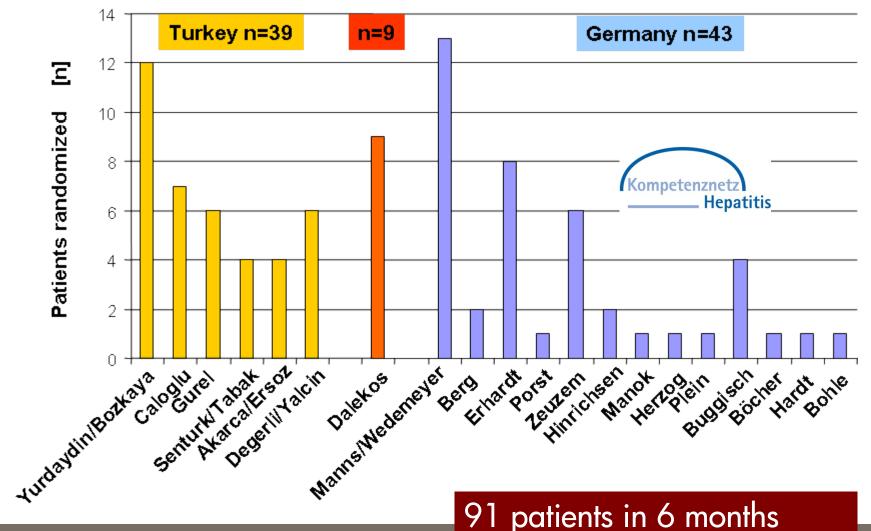
Early monotherapy with pegylated interferon alpha-2b for acute hepatitis C infection: the HEP-NET acute-HCV-II study

Akute Hepatitis I - N Engl J Med. 2001

Treatment of acute hepatitis C with interferon alfa-2b.

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The Hep-Net/International Delta Hepatitis Intervention Trial (HIDIT-1)





HepNet Hepatitis D trials 2004-2019:

HIDIT-II – Lancet Infectious Diseases 2019

Peginterferon alfa-2a plus tenofovir disoproxil fumarate for hepatitis D (HIDIT-II): a randomised, placebo controlled, phase 2 trial.

HIDIT I longterm Follow up- Hepatology 2014 Late HDV RNA relapse after peginterferon alpha-based therapy of chronic hepatitis delta.

HIDIT-I - N Engl J Med. 2011

Peginterferon plus adefovir versus either drug alone for hepatitis delta.





German Hepatitis C-Registry (DHC-R)

The DHC-R (German Hepatitis C-Registry) is a national realworld registry including approximately 15,500 patients documented by >250 centers

90 congress contributions (25 orals, 65 poster)

- e.g. The Liver Meeting[®], AASLD
- International Liver Congress™, EASL
- Viszeralmedizin, DGVS
- International Symposium on Hepatitis Care in Substance Users (INSHU)
- Conference on Retroviruses and Opportunistic Infections (CROI)



17 publications (peer-reviewed)

AP&T Alimentary Pharmacology and Therapeutics

Aliment Pharmacol Ther 2017; 45: 688-700

Real-world use, effectiveness and safety of anti-viral treatment in chronic hepatitis C genotype 3 infection

M. Cornberg* D, J. Petersen[†], A. Schober[‡], S. Mauss[§], K. H. W. Böker[¶], R. Link**, R. Günther^{††}, Y. Serfert^{‡‡}, H. Pfeiffer-Vornkahl^{§§}, M. P. Manns*, C. Sarrazin[¶], D. Hüppe***, T. Berg^{†††} & C. Niederau^{‡‡‡}

Received: 12 May 2018 | Revised: 4 July 2018 | Accepted: 15 July 2018 | DOI: 10.1111/liv.13932

BRIEF DEFINITIVE REPORT



Clinical significance of detectable and quantifiable HCV RNA at the end of treatment with ledipasvir/sofosbuvir in GT1 patients

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Benjamin Maasoumy<sup>1</sup> | Peter Buggisch<sup>2</sup> | Stefan Mauss<sup>3</sup> | Klaus H. W. Boeker<sup>4</sup> | Tobias Müller<sup>5</sup> | Rainer Günther<sup>6</sup> | Tim Zimmermann<sup>7</sup> | Michael P. Manns<sup>1</sup> | Christoph Sarrazin<sup>8,9</sup> | Dietrich Hüppe<sup>10</sup> | Heiner Wedemeyer<sup>1,11,12</sup> | Johannes Vermehren<sup>8</sup>
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DZIF



HDIN "The Hepatitis Delta International network" www.hepatitis-delta.org

> 2000 patients included from ~ 20 center worldwide

Hepatitis D (Delta) – Rare but Severe

3. Double check the patient's data

eCRF: Marvin



Häufigkeit und Risikofaktoren medikamentöstoxischer Leberschäden: eine umfragebasierte Studie in Apotheken

Prevalence and risk factors of drug induced liver disease: a survey based study in pharmacies

Autoren

C. Jüngst¹, S. Gräber², D. Klahn³, H. Wedemeyer⁴, F. Lammert¹

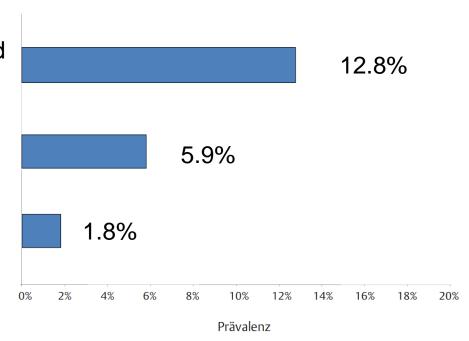
Z Gastroenterol 2016; 54: 131–138

Self-reported questionaires (n=1098) in 30 pharmacies Prevalence of drug-associated elevations of liver encymes

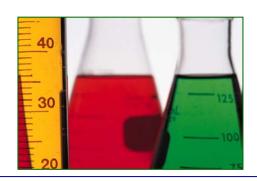
Prevalence of drug-associated increase of liver encymes

Discontinueation of the suspected drug

Hospitalization due to suspected DILI



How can/will the Pro Euro DILI Net Cost help hepatologists and clinical scientists?



Collect data and biomaterials from DILI patients

Harmonize definitions and data sets

Facilitate exchange of expertise at different levels

Develop new diagnostic tools

Staff dedicated to investigator initiated trials



Provide easy and open access to DILI information

Knowledge transfer by conferences/schools

Promote international and national guidelines

Regular presence at conferences



i.e. HILI, BILI

Improve reporting on a GP level

THANK YOU FOR YOUR ATTENTION