ission Impossible
…real life!

Case study:
The challenges faced while waiting for a double transplant and a HCV treatment

September 22, 2018

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Disclosure

I have an affiliation with the following pharmaceutical companies: AbbVie, BMS, Gilead, Merck
I have acted as an advisor and participated in clinical trial studies

Learning objectives

- ✓ Following this session, participants will be able to understand and acknowledge the challenges faced by patients waiting for a transplant

- ✓ Following this session, participants will be more aware of a population of patients previously denied with available Hepatitis C Virus (HCV) treatments

Did you know?

How many people are infected with Viral hepatitis, worldwide?

Around the world **400 million** people are infected with hepatitis B and C, **more than 10 times the number of people living with HIV.**

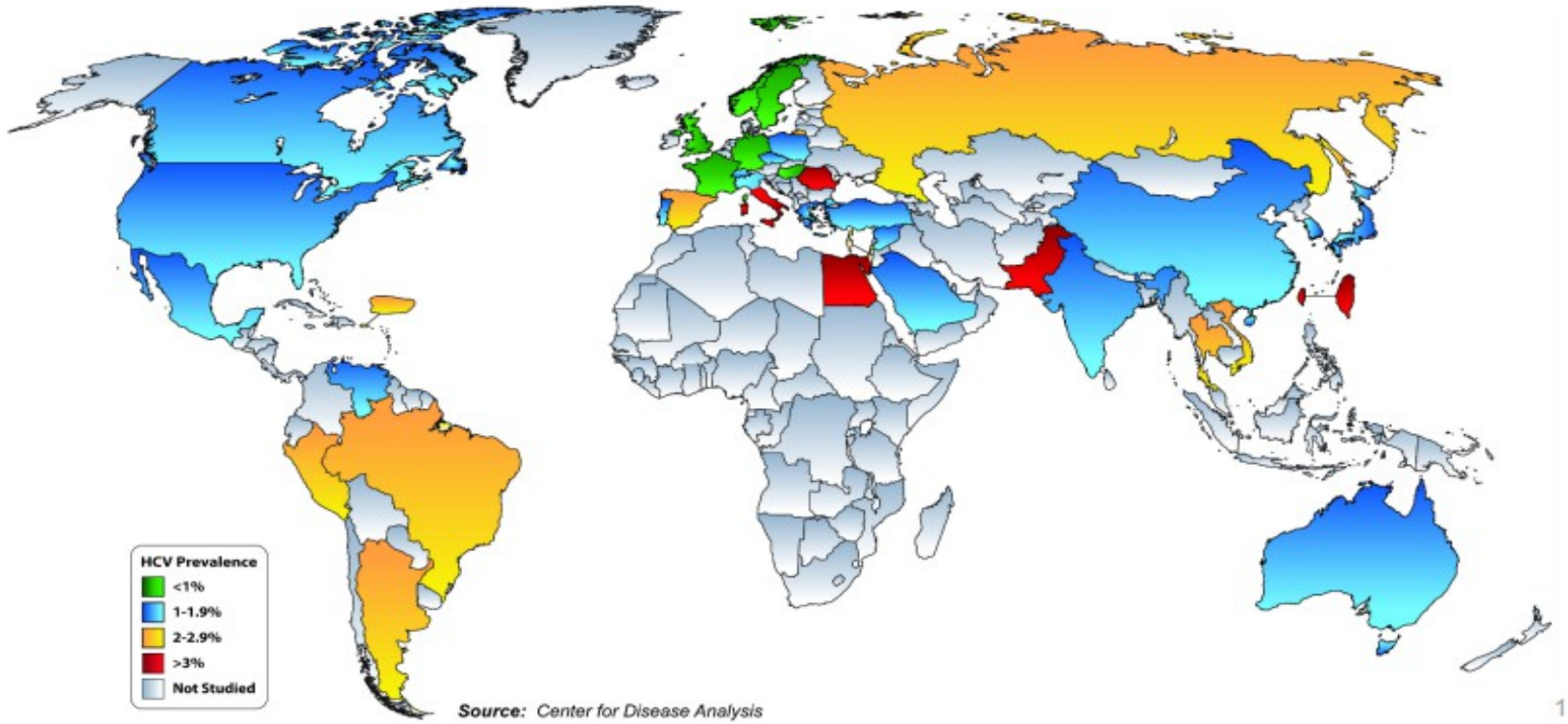
An estimated **130-150 million people have chronic hepatitis C infection**.

WHO. October 2017

Did you know?

Global Prevalence of Hepatitis C

More than **150 million people** worldwide are infected with the hepatitis C virus (HCV), and HCV-related complications cause up to **500,000 deaths** each year.



Source: *Center for Disease Analysis*

Did you know?

How long does the Hepatitis C virus survive outside the body?

The Hepatitis C virus can survive outside the body at room temperature, on environmental surfaces, for up to **3 weeks.** Oct. 2016

https://www.cdc.gov/hepatitis/hbv/bfaq.htm

Can Lysol kill hepatitis C?

Hepatitis C is not an easy bug to **kill**. Store-bought products (such as **Lysol**®, Clorox® Clean-up® Cleaner with Bleach, or Mr. Clean®) are not effective. Bleach is questionable with regard to **killing HCV**. The proper dilution and the state of the **HCV will** vary the efficacy. Dec. 11 2011

https://blog.pkids.org/category/public-restrooms

ContinFACTue…

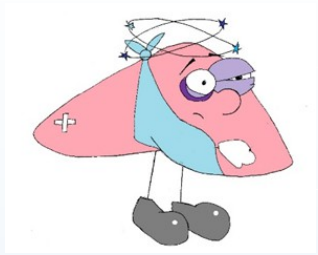
FACT:

HCV is a slow-moving progressive disease. One can be infected with HCV for **10 to 40 years** and not even know about it!

In other words, the HCV multiplies at a low rate and is able to

avoid the immune system. This method allows the virus to persist

with its mission to attack the liver.



Case: Mission Impossible

In 2009, Mr. L, aged 50 years old, was diagnosed with Hepatitis C. **Genotype 1a** with Compensated liver cirrhosis.
Medical Hx: Diabetes type 2. Hypertension. Past MI (2006). Ex-IVDU.
2010: Pegetron (Interferon/Ribavirin) was started. Treatment length: 48 weeks.
But..
The treatment was stopped at 12 weeks because of serious adverse events. (The patient was hospitalized with pneumonia and heart failure)

8 weeks later, Mr. L returns for a follow-up.
HCV PCR (HCV viral load) collected: Not detectable! = cured???

What is Hepatitis C Genotype?

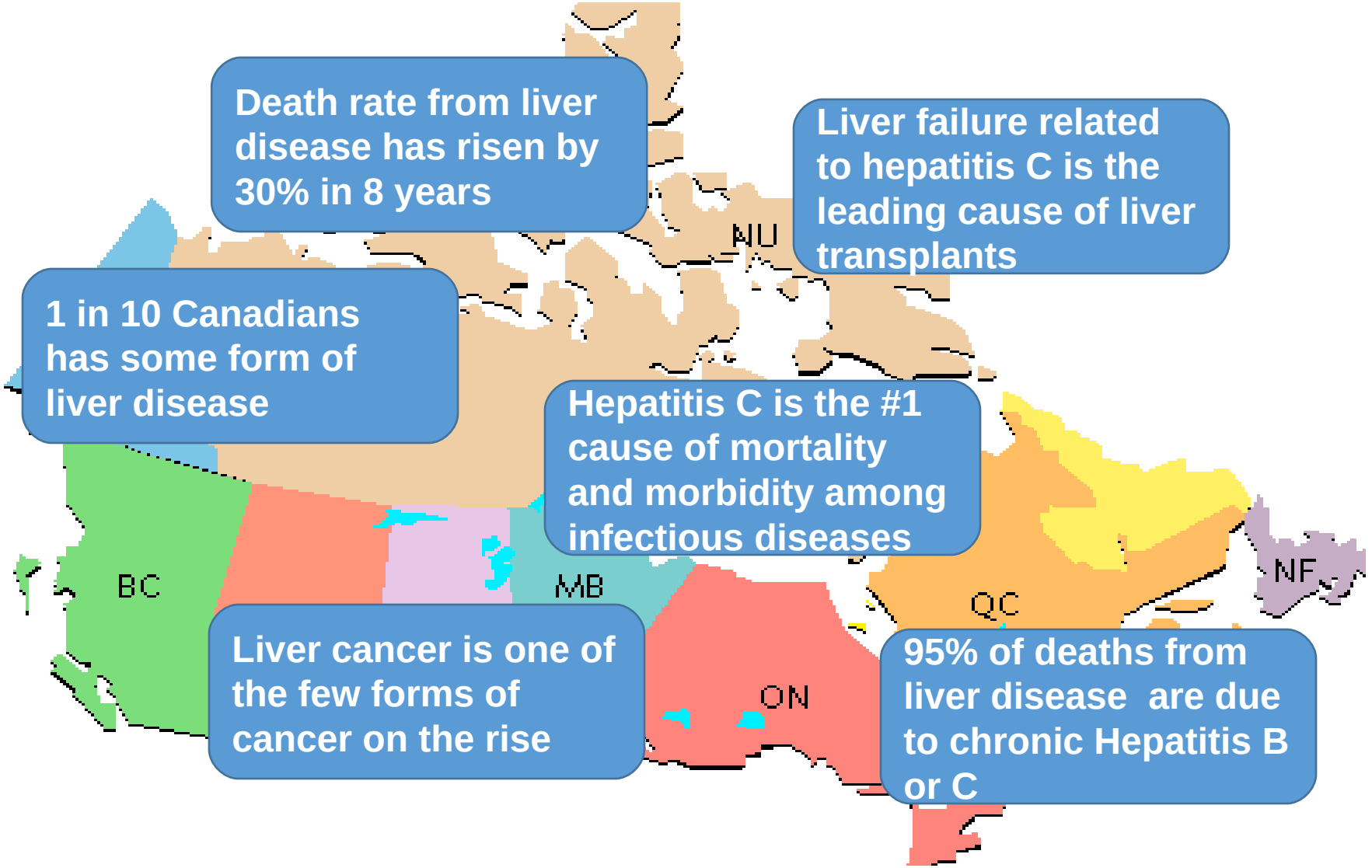
- The hepatitis C virus is not just one type of virus. There are at least 6 different HCV types. They are known as **genotypes.**

- **Genotype is defined as the genetic information within the virus**. Represent the accumulated mutations that have occurred over the long-term evolution of the virus
- Genotype 1-2-3 are commonly found in North America,

  (Genotype 1: 74% ; Gen. 2&3 : 22% and Gen. 4,5,6: 4%) genotype 4

  in Egypt and sub-Saharan Africa area and genotype 6 is mostly found in Asia
- By identifying the genotype, this determines what kind of treatment a person will be put on.

Liver Disease in Canada -Facts



Canadian Liver Foundation 2013 Fact Sheet
Liver Disease in Canada, Canadian Liver Foundation March 2013

Case: Mission Impossible

By 2013, Mr. L was starting to have kidney issues due to poorly controlled diabetes. Was diagnosed with CKD (Chronic Kidney Diseases) stage 5 with GFR level of <15 ml/min.

- Started hemodialysis 11/2013

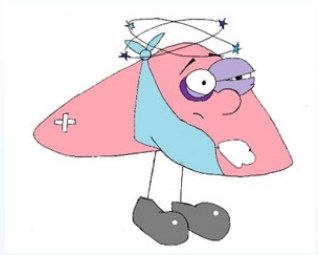
And then….

From the World Journal of Hepatology

"In HD (Hemodialysis) facilities, the most common lapses of healthcare quality are contamination of dialysis systems, inadequate disinfection and cleaning of environmental surfaces, improper contact of health care staff with equipment and patients, and mishandling of parenteral medications[23,24]."

"The readings look good, but just in case, when was the last time the system was checked for bugs?"

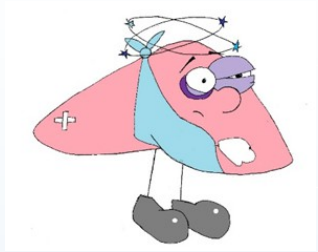
WJH|www.wjgnet.com April 28, 2015|Volume 7|Issue 6|**p.886**



Case: Mission Impossible

2015: Mr. L is admitted at the hospital with hepatic encephalopathy (HE) with decompensate liver cirrhosis.

HE reversed; liver stabilized
referred to **Transplant clinic**

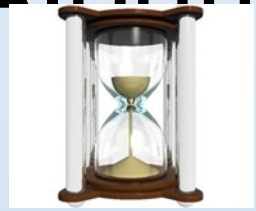


Case: Mission Impossible

Until 2015, Mr. L was not eligible to receive any current HCV treatment because of the use of Ribavirin. **Ribavirin contraindicated in CKD**

Goal??? Preserve liver and kidney function…but for how long?

Lab results: Albumin: 28; Platelets: 36; Hgb: 105



Time is running out…

CORR (Canadian Organ Replacement Register)
Annual Statistics 2017

2,570 solid organs were transplanted in Canada in 2015:

- Kidneys: 1,513
- Livers: 533
- Lungs: 278
- Hearts: 170
- Pancreases: 76

https://www.cihi.ca/en/**corr**-annual-**statistics**-2007-to-2016

Transplant Quebec

Statistics Organ donation in numbers

As of December 31st 2016:

- 170 Donors
- 480 Recipients
- 841 Patients on the Waiting List: Heart: 65
  Lungs: 77
  Liver: 104
  Kidney: 565

Statistique officielle 2016; Transplant Quebec

In Quebec, 10 hospitals manage a variety of organ transplant programs :

Centre hospitalier de l'Université de Montréal (CHUM) - Hôpital Notre-Dame

- Lung transplants
- Heart-lung transplants
- Kidney transplants **(including living organ donation)**
- Pancreas transplants

Centre hospitalier de l'Université de Montréal (CHUM) - Hôpital St-Luc

- Liver transplants **(including living organ donation)**

McGill University Health Centre (MUHC) – Royal Victoria Hospital

- **Heart transplants**
- **Heart-lung transplants**
- **Liver transplants**
- **Pancreas transplants**
- **Kidney transplants (including living organ donation)**

McGill University Health Centre (MUHC) – Montreal Children's Hospital

- Heart transplants
- Kidney transplants **(including living organ donation)**

Hôpital Maisonneuve-Rosemont

- Kidney transplants **(including living organ donation)**

Centre hospitalier universitaire CHU Sainte-Justine (pediatrics)

- Heart transplants
- Liver transplants **(including living organ donation)**
- Kidney transplants **(including living organ donation)**

Montreal Heart Institute

- Heart transplants

Centre hospitalier universitaire de Sherbrooke (CHUS) - Hôpital Fleurimont

- Kidney transplants **(including living organ donation)**

Centre hospitalier universitaire de Québec (CHUQ) - Hôtel-Dieu de Québec

- Kidney transplants **(including living organ donation)**

Institut universitaire de cardiologie et de pneumologie de Québec

As per the World Journal of Hepatology:

“Carefully treating HCV and achieving SVR (Sustained Viral Response) prior to KT (Kidney Transplant) should be primary goals to reduce the likelihood of HCV-related complications in the liver and other organs/ systems[74].

Another reason it is important to attain SVR before KT relates to the concern that anti-viral therapy administered post-transplantation is associated with high risk of graft rejection[75]”.

Digdem Ozer Etik, Serkan Ocal, Ahmet Sedat Boyacioglu

WJH|www.wjgnet.com. April 28, 2015|Volume 7|Issue 6|p.890

C-SURFER: GRAZOPREVIR PLUS ELBASVIR IN TREATMENT-NAIVE AND TREATMENT-EXPERIENCED PATIENTS WITH HEPATITIS C VIRUS GENOTYPE 1 INFECTION AND CIRRHOSIS

Roth D, Brucefield A; Martin P, Nelson DR, Sniva M; Monsour H Jr, Amit C

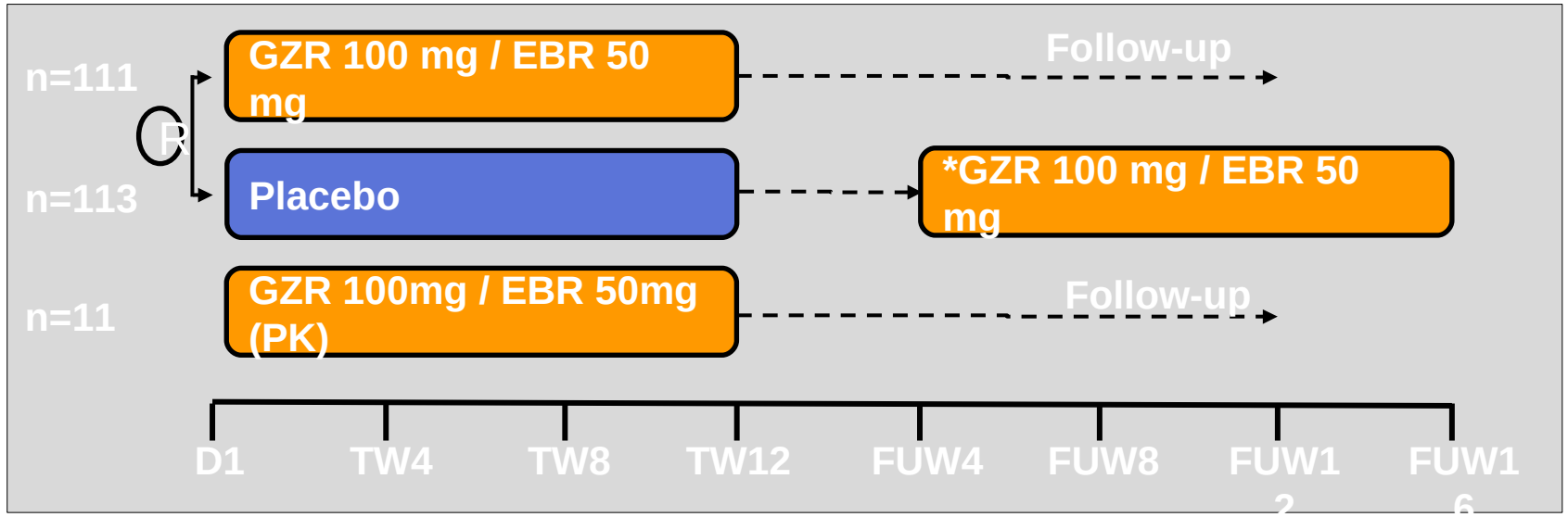
MERCK

C-SURFER

Background and Aim

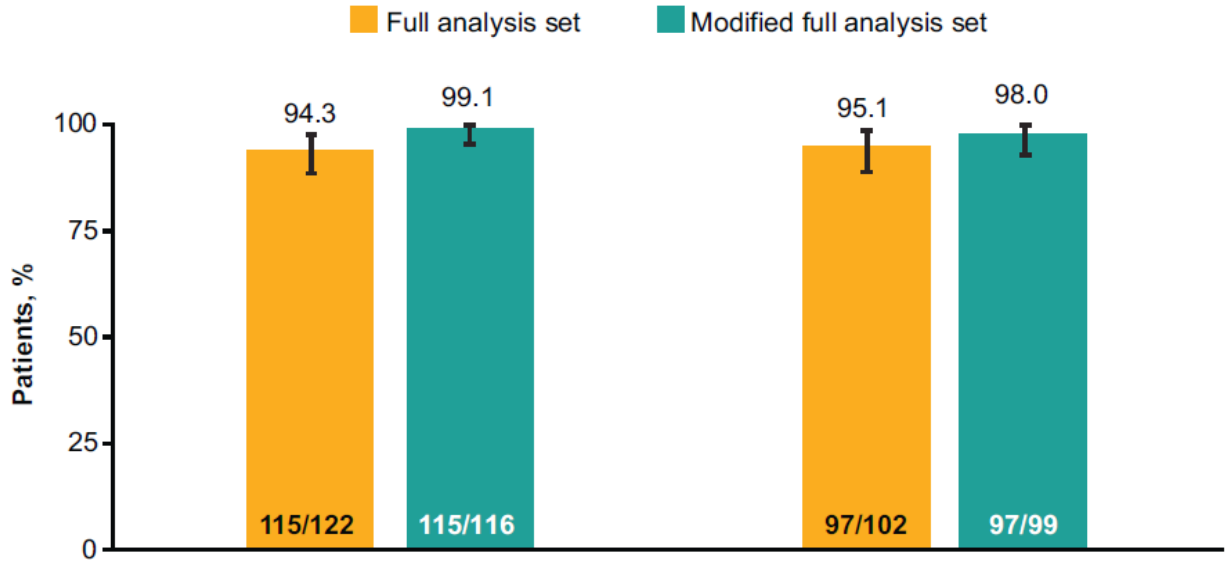
- HCV infection in patients with advanced chronic kidney disease is associated with an increased risk of death, accelerated loss of remaining kidney function and kidney transplant failure1-3
  - Patients with HCV and stage 4/5 CKD have limited HCV treatment options due to lack of safety/efficacy data for DAAs in patients with CrCl <30mL/min and poor tolerability of regimens that include ribavirin4
- This study evaluated grazoprevir + elbasvir in HCV-infected patients with CrCl <30 mL/min, including patients on hemodialysis

STUDY DESIGN



- Randomized, parallel-group, multi-site, placebo-controlled trial
- Stratification by diabetes (yes/no) and hemodialysis status (HD/non-HD)
- 224 patients randomized to immediate treatment with GZR/EBR or deferred treatment where patients received placebo for 12 weeks then open-label GZR/EBR starting at FUW4

Once daily GZR/EBR for 12 weeks was highly effective for treatment of HCV GT1 infection among patients with CKD stage 4/5: C-SURFER IMMEDIATE AND DEFERRED



	Immediate treatment		Deferred treatment	
Relapse	1†	1	2§	2
D/c unrelated to study medication	6‡	0	3‖	0

D/c = discontinued; MFAS = primary efficacy analysis; Tx = treatment.
FAS was a secondary analysis
†Noncirrhotic, interferon-intolerant patient with HCV GT1b infection relapsed at FUW12.
‡Lost to follow-up (n = 2); n = 1 each for death, noncompliance, withdrawal by subject, and withdrawal by physician (owing to violent behavior).
§Two patients in the DTG, both with G1a infection, relapsed at FUW4 and FUW12.
‖Withdrawal by subject, n = 1; AE, n = 1; death, n = 1.

C-SURFER

Adverse event summary (≥ 10%)

	EBR/GZR (ITG) (n = 111)	EBR/GZR (DTG) (n = 102)	Placebo (DTG) (n = 113)	Difference in % estimate ITG vs placebo (95% CI)
AEs,† n (%)	84 (75.7)	61 (59.8)	95 (84.1)	–8.3 (–18.9, 2.2)
Headache	19 (17.1)	7 (6.9)	19 (16.8)	0.3 (-9.6, 10.4)
Nausea	17 (15.3)	10 (9.8)	18 (15.9)	–0.6 (–10.3, 9.1)
Fatigue	11 (9.9)	9 (8.8)	17 (15.0)	–5.1 (–14.1, 3.7)
Insomnia	7 (6.3)	2 (2.0)	12 (10.6)	–4.3 (–12.2, 3.2)
Dizziness	6 (5.4)	5 (4.9)	18 (15.9)	–10.5 (–19.1, –2.6)
Diarrhea	6 (5.4)	5 (4.9)	15 (13.3)	–7.8 (–16.1, –0.2)
Serious AEs, n (%)	16‡ (14.4)	13§ (12.7)	19 (16.8)	–2.4 (–12.1, 7.3)
Discontinued due to an AE, n (%)	0 (0)	3 (2.9)	5 (4.4)	–4.4 (–10.0, –1.0)
Deaths,‖ n (%)	1 (0.9)	0 (0)	3 (2.7)	–1.8 (–6.7, 2.5)

SAE = serious adverse event.
†Reported in ≥10% of patients in either treatment group (ASaT).
‡1 SAE in the DTG (placebo) was considered drug-related (elevated lipase level).
§1 SAE in the DTG (EBR/GZR) was considered drug-related (interstitial nephritis).
‖1 ITG patient died of cardiac arrest and 3 DTG patients died of aortic aneurysm, pneumonia, and unknown cause.

C·SURFER

Conclusions

- Once daily GZR/EBR for 12 weeks was highly effective for treatment of HCV GT1 infection among patients with CKD stage 4/5
- Efficacy is consistent across different subpopulations:
  - GT1a and 1b
  - Diabetes
  - Hemodialysis
- Failure to achieve SVR12 is rare
  - 3 patients relapsed
- Once daily GZR/EBR for 12 weeks was generally well-tolerated in this study population of patients with advanced kidney disease

Elbasvir/Grazoprevir effectiveness in patients with Chronic Hepatitis C and Chronic Kidney Disease: Real-world experience from the TRIO Network

Z. YOUNOSSI1, B. BACON2, M. CURRY3, D. DIETERICH4, S.L. FLAMM5, K.KOWDLEY6, S.MILLIGAN7, C. NWANKWO8, N. TSAI9, AND N. AFDHAL3

1Center for Liver Diseases, Department of Medicine, Inova Fairfax Hospital, Falls Church, VA USA, 2Saint Louis University School of Medicine, St. Louis, MO USA, 3Beth Israel Deaconess Medical Center, Boston, MA USA, 4Icahn School of Medicine at Mount Sinai, New York, NY USA, 5Northwestern University Feinberg School of Medicine, Chicago IL USA, 6Liver Care Network, Swedish Medical Center, Seattle, WA USA, 7Trio Health Analytics, La Jolla, CA USA, 8Merck & Co., Inc., Kenilworth, NJ USA and 9Queens Medical Center, University of Hawaii, Honolulu, HI USA

BACKGROUND AND AIM

- **DAA** (Direct-Acting Antivirals) therapy with elbasvir/grazoprevir (EBR/GZR) is recommended for genotype (GT) 1 and 4 HCV patients including those with renal impairment.
- The purpose of this study is to understand the real-world effectiveness and use of EBR/GZR in treatment of patients with chronic HCV and chronic kidney disease (CKD).

Younossi et al. RWE of EBR/GZR HCV from TRIO Network-EASL 2017 Amsterdam, The Netherlands. Apr. 19-23, 2017.SAT-297

***Definition: **DAA** directly attacks the hep C virus in different ways and stops it from making copies of itself. DAAs treatments are shorter with higher cure rates, and fewer side effects.

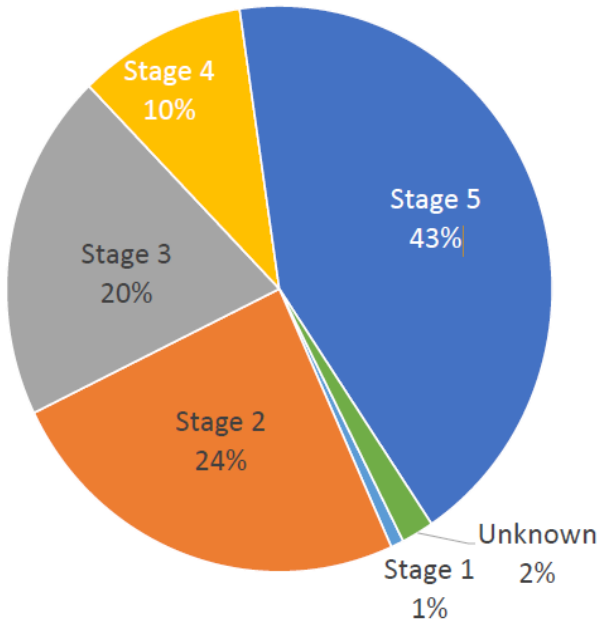
Elbasvir/Grazoprevir effectiveness in patients with Chronic Hepatitis C and Chronic Kidney Disease: Real-world experience from the TRIO Network

Of 462 patients that initiated EBR/GZR-based therapy between January 28, 2016 (FDA approval) and October 2016, 440 with known CKD status were included in the analyses.

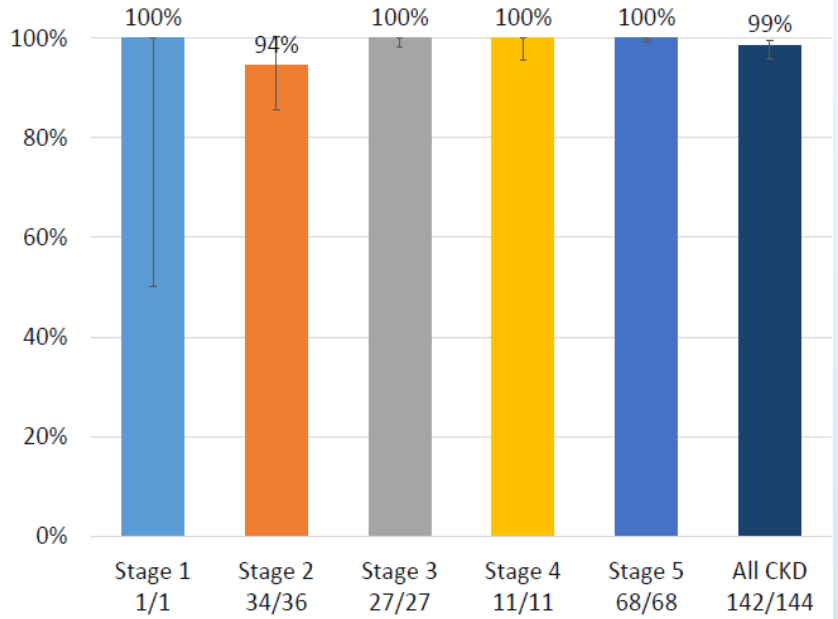
The primary SVR analysis was the Per Protocol (PP) analysis defined as all patients that completed their intended therapy and who received SVR testing at 12 weeks (SVR12).

93% of G1 patients and 92% of G4 patients were treated with EBR/GZR for 12 weeks

Distribution of All EBR/GZR-treated Patients by CKD Stage (n=261)



*SVR12 (PP) in EBR/GZR-treated Patients with an SVR12 Test Result by CKD Stage (n=144)**

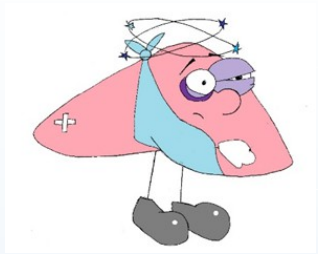


ents treated with EBR/GZR in the per protocol analysis, 2 patients did not achieve CKD Stage 2, cirrhosis, and received 12 week EBR/GZR. The first patient was treated for GT1b HCV and had previously failed PEG+RBV. The second patient was treated for GT4 HCV and had previously failed LDV/SOF.

Younossi et al. RWE of EBR/GZR HCV from TRIO Network-EASL 2017 Amsterdam, The Netherlands. Apr. 19-23, 2017.SAT-297

SUMMARY

- The EBR/GZR utilization described in this study reflects the initial uptake observed immediately after the drug approval.
- In HCV patients with CKD (Stages 1 to 5), EBR/GZR was observed to be highly effective with an overall SVR12 (PP) of 99% (142/144) and an SVR12 (PP) of 100% (79/79) in patients with severe to end stage CKD (Stage 4 to 5).



Case: Mission Impossible

In 2016, Health Canada approves Zepatier (Elbasvir 50 mg/ Grazoprevir 100mg) from Merck: 1 capsule/day x 12 weeks

- At that time, it was the only HCV treatment available for those with CKD and end stage kidney failure.

Case: Mission Impossible
Update:

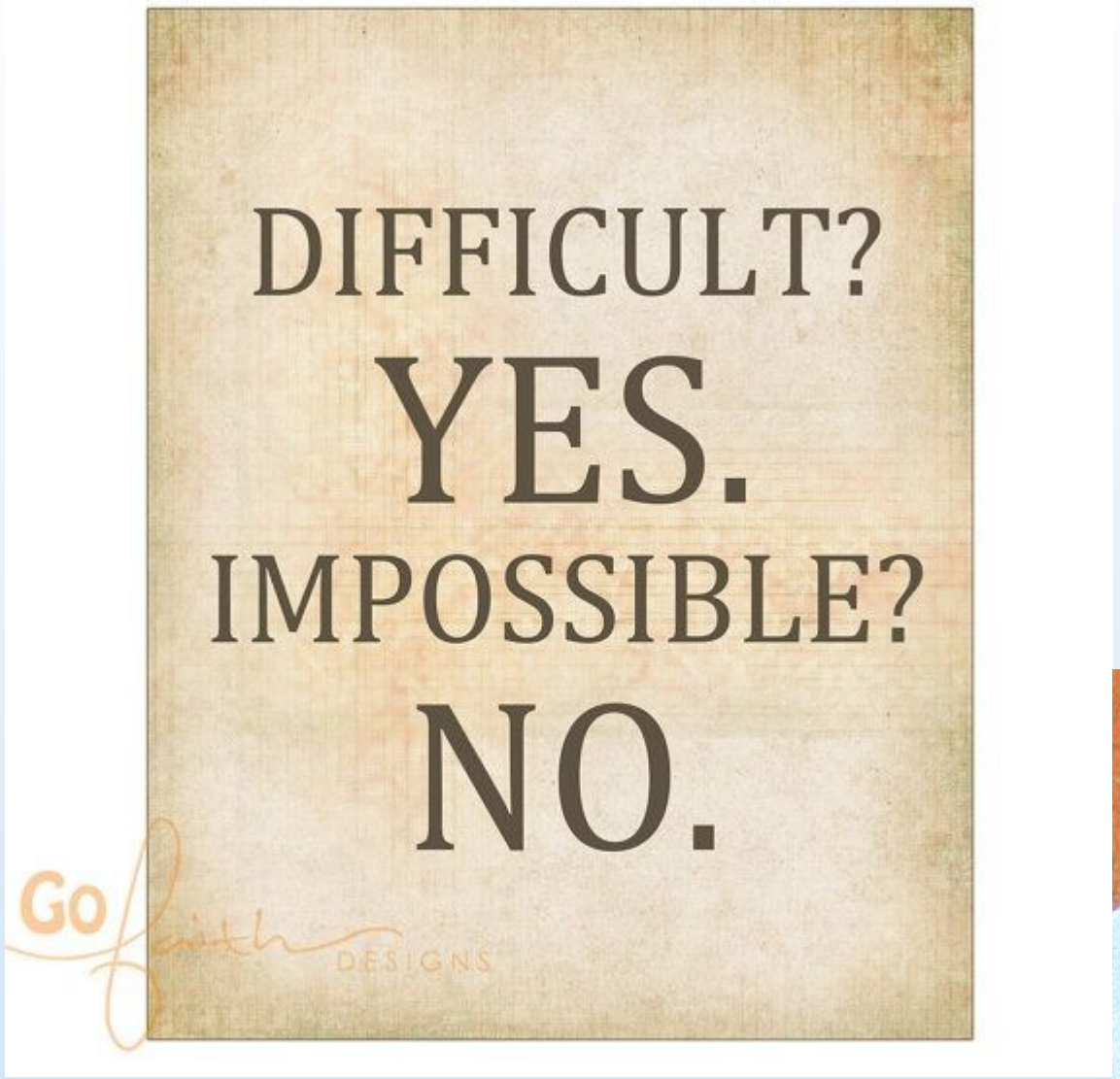
Since August 2017, Mr. L has been called twice but had to be put back on the list! Both times, the potential organs were not a good fit.

Mr. L is still waiting….willing to receive a HCV (+) infected kidney!

“Open-label, single-group, pilot trial at the University of Pennsylvania (Transplanting Hepatitis C Kidneys into Negative Kidney Recipients [THINKER]; ClinicalTrials.gov number,NCT02743897) to determine the safety and efficacy of transplantation of kidneys from HCV genotype 1–viremic donors into HCV-negative patients, followed by elbasvir–grazoprevir (Zepatier) treatment.”

CONCLUSION:
“This pilot trial showed that transplantation of HCV genotype 1–infected kidneys into HCV negative recipients, followed by the use of direct acting antiviral agents, can provide potentially excellent allograft function with a cure of HCV infection.”

n engl j med 376;24 nejm.org June 15, 2017


DIFFICULT?
YES.
IMPOSSIBLE?
NO.
Go
DESIGNS


IMPOSSIBLE
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impossible.

Mission accomplished!

Thank you!