Mission Impossible
...real life!

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

February 11, 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
Case: Mission Impossible

In 2009, Mr. L, aged 50 year old, was diagnosed with Hepatitis C. Genotype 1a. Compensated liver cirrhosis.

2010: Pegetron (INF/RBV) 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 collected: Not detectable! = cured???
2011, 2012: HCV PCR repeated: Not detectable!!!

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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 G5 with GFR level of <15 ml/min.

Starts hemodialysis 11/2013
And then....
2014: HCV PCR: detectable! Same genotype!

Source of exposure?
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].”

Case: Mission Impossible

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

HE reversed; liver stabilized \[\rightarrow\] referred to **Transplant clinic**

**Outcome**, Mr. L is put on the transplant list for liver/kidney.
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

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-Rosset
- 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
- Heart transplants
As per the World Journal of Hepatology:

“Carefully treating HCV and achieving SVR 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

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

Roth D; Bruchfeld A; Martin P; Nelson DR; Silva M; Monsour H Jr; Alric L; Wan S; Jackson B; Nguyen B-Y; Wahl J; Barr E; Greaves W

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For training purposes only
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 failure\(^1\-\(^3\)
  - 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 <30 mL/min and poor tolerability of regimens that include ribavirin\(^4\)
- 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)
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 TREATMENT GROUPS

- The study evaluated grazoprevir + elbasvir in HCV-infected patients with CrCl<30 mL/min, including patients on hemodialysis.
- Patients were treated with EBR/GZR for 12 weeks

HCV Genotype:
G1a: 52%
G1b: n=58, 48%
G1 other : 1, < 1%

- 83% were treatment naïve
- 6% were cirrhotic
- 75% (n=95) of patients on dialysis

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ADVERSE EVENT SUMMARY (≥ 10%)

<table>
<thead>
<tr>
<th>AEs, n (%)</th>
<th>EBR/GZR (DTG) (n = 111)</th>
<th>EBR/GZR (DTG) (n = 102)</th>
<th>Placebo (DTG) (n = 113)</th>
<th>Difference in % estimate ITT vs placebo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEs, n (%)</td>
<td>84 (75.7)</td>
<td>61 (59.8)</td>
<td>95 (84.1)</td>
<td>-8.3 (-18.9, 2.2)</td>
</tr>
<tr>
<td>Headache</td>
<td>19 (17.1)</td>
<td>7 (6.9)</td>
<td>19 (16.8)</td>
<td>0.3 (-9.6, 10.4)</td>
</tr>
<tr>
<td>Nausea</td>
<td>17 (15.3)</td>
<td>10 (9.8)</td>
<td>18 (15.9)</td>
<td>-0.6 (-10.3, 9.1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>11 (9.9)</td>
<td>9 (8.8)</td>
<td>17 (15.0)</td>
<td>-5.1 (-14.1, 3.7)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>7 (6.3)</td>
<td>2 (2.0)</td>
<td>12 (10.8)</td>
<td>-4.3 (-12.2, 3.2)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>6 (5.4)</td>
<td>5 (4.9)</td>
<td>18 (15.9)</td>
<td>-10.5 (-19.1, -2.6)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6 (5.4)</td>
<td>5 (4.9)</td>
<td>15 (13.3)</td>
<td>-7.8 (-16.1, -0.2)</td>
</tr>
<tr>
<td>Serious AEs, n (%)</td>
<td>16 (14.4)</td>
<td>13 (12.7)</td>
<td>19 (16.8)</td>
<td>-2.4 (-12.1, 7.3)</td>
</tr>
<tr>
<td>Discontinued due to an AE, n (%)</td>
<td>0 (0)</td>
<td>3 (2.9)</td>
<td>5 (4.4)</td>
<td>-4.4 (-10.0, -1.0)</td>
</tr>
<tr>
<td>Deaths, n (%)</td>
<td>1 (0.9)</td>
<td>0 (0)</td>
<td>3 (2.7)</td>
<td>-1.8 (-6.7, 2.5)</td>
</tr>
</tbody>
</table>

SAE = serious adverse event
1AE reported in ≥10% of patients in either treatment group (AlbA1)
2SAE in the DTG (placebo) was considered drug-related (elevated bilirubin level)
3SAE in the AlbA1 (EBR/GZR) was considered drug-related (interstitial nephritis)
4ITG patient died of cardiac arrest and 3 DTG patients died of aortic aneurysm, pneumonia, and unknown causes

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

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

BACKGROUND AND AIM

- DAA 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).

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.

*Of the 144 HCV CKD patients treated with EBR/GZR in the per protocol analysis, 2 patients did not achieve SVR12. Both patients had 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.
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).


AbbVie Inc. (2017)
MAGELLAN-2: Safety and Efficacy of G/P (Glecaprevir/ Pibrentasvir) in Liver or Renal Transplant Adults with Chronic Hepatitis C Genotype 1–6 Infection

Phase 3 study to evaluate the efficacy and safety of G/P for 12 weeks in adults with chronic HCV GT1–6 infection without cirrhosis who have had liver (n = 80) or renal (n = 20) transplant

Safety, n/%

G/P, 12 weeks N = 100

SAE 8
DAA-related SAEs 2
AE leading to study drug d/c 1
DAA-related AE leading to study drug d/c 0
Death 0
Transplant rejection 1

Patient with mild liver transplant rejection unrelated to DDIs and did not lead to treatment interruption

Grade 3 laboratory abnormalities were rare

GT: 1 (57%), 2 (13%), 3 (24%), 4–6 (6%)
Fibrosis: F0–1 (80%), F2 (6%), F3 (14%)

BL immunosuppressant medication:
tacrolimus (68%), mycophenolic acid (30%), cyclosporine (13%), prednisone (13%), prednisolone (11%), everolimus (8%), azathioprine (6%), and sirolimus (7%)

Nancy Reau1, Paul Y. Kwo2, Susan Rhee3, Robert S. Brown, Jr-4, Kosh Agarwal5,
MAGELLAN-2 Study: glecaprevir/pibrentasvir in liver or kidney transplanted patients

**Design**

- ≥ 18 years, BMI ≥ 18 kg/m²
- HCV genotype 1-6
- Treatment-naïve or treatment-experienced with IFN or PEG-IFN ± RBV or SOF + RBV ± PEG-IFN
- HCV RNA > 1 000 IU/mL
- Liver or kidney transplantation > 3 months with stable immunosuppression regimen
- No cirrhosis
- No HBV or HIV co-infection

- GLE/PIB: 100/40 mg 3 tablets QD
- Patients enrolled in Australia, Canada, Italy, New Zealand, Puerto Rico, Spain, Taiwan, the United Kingdom and the United States

**Objectives**

- Primary endpoint: SVR12 (HCV < 15 IU/mL)
- Non-inferiority to historical 94% SVR12 standard-of-care rate, achieved if > 86% (8% margin)

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**SUMMARY:**

- Glecaprevir/pibrentasvir for 12 weeks achieved a 99% SVR12 rate in patients with liver or kidney transplant and genotype 1-6
- This rate was not inferior to historical standard of care
- Treatment was well-tolerated
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. Hemodialysis does not excret Zepatier

Private insurance request was made in September 2016: Accepted!

Mr. L start Zepatier in October 2016. Completes the 12 weeks treatment with no AEs.

August 2017, post 24 wks HCV PCR: not detectable: SVR!

Overall, Mr. L’s condition stabilizes and now he’s waiting for “the call”.

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
Mission accomplished!

Thank you!