Assessment of sofosbuvir (Sovaldi®)

Summary of the national assessments of sofosbuvir (Sovaldi®) for the treatment of Hepatitis C

December 18, 2014

Health Care Institute, Diemen, NL
Lead Partner WP5 EUnetHTA JA2 and EUnetHTA secretariat, Copenhagen, DK

Hedi Schelleman, Finn Borlum Kristensen and Wim Goettsch

Special thanks to all representatives of the Member States that provided their national input within very limited timeframe

Outline

- Background
- Introduction
- Description of technical characteristics of technology
- Health problem and current use of technology
- International assessment
    - Questionnaire
    - Clinical Effectiveness and Safety
    - Costs
    - Economic evaluation

Background

- Treatment hepatitis C will change substantially

  $\Rightarrow$ Several drugs will be introduced with high cure rates

- Large group of potential patients

- Budget-impact of treatment like sofosbuvir can exceptionally high because
  - Price of drug is high
  - Eligible population is substantial

Introduction

- SANCO request:
  - Summary of the national and regional assessment results of sofosbuvir
    - ⇒ Support the discussion among the MS about the therapeutic value
    - ⇒ Support the discussion about the price

- EUnetHTA in collaboration with MEDEV:
  - Send out a questionnaire
  - Checked EUnetHTA Planned and Ongoing Projects, **POP Database**
  - Searched for (publically available) assessment reports
    - These national assessments reports are in general based on (or seen as critique or review of) submission files from the manufacturers*

**Kleijnen etal, Relative Effectiveness Assessment of Pharmaceuticals: Similarities and Differences in 29 Jurisdictions. Value in Health 2012: 954-960)*

Description of technical characteristics (1)

- Market authorisation: January 2014

- Registered indication = in combination with *other medicinal products* for the treatment of hepatitis C in adults

- Posology: 400 mg 1 dd (oral)

- Features of the sofosbuvir:
    - Inhibits hepatitis C NS5B RNA polymerase (a new class)
    - First medicine licensed for interferon-free regiments

Description of technical characteristics (2)

Patient population*	Treatment	Duration
genotype 1, 4, 5 or 6 HCV	sofosbuvir + ribavirin + peginterferon alpha or sofosbuvir + ribavirin (*Only for use in patients ineligible or intolerant to peginterferon alpha)*	12 weeks [a,b] 24 weeks
genotype 2 HCV	sofosbuvir + ribavirin	12 weeks [b]
genotype 3 HCV	sofosbuvir + ribavirin + peginterferon alpha or sofosbuvir + ribavirin	12 weeks [b] 24 weeks
awaiting liver transplantation	sofosbuvir + ribavirin	Until liver transplantation

* Includes patients co-infected with human immunodeficiency virus (HIV).

[a] For previously treated patients with HCV genotype 1 infection, no data exists with the combination of Sovaldi, ribavirin and peginterferon alpha (see section 4.4).

[b] Triple therapy: Consideration should be given to potentially extending the duration of therapy beyond 12 weeks and up to 24 weeks; especially for those subgroups who have one or more factors historically associated with lower response rates to interferon-based therapies (e.g. advanced fibrosis/cirrhosis, high baseline viral concentrations, black race, IL28B non CC genotype, prior null response to peginterferon alpha and ribavirin therapy).

Health problem and current use (1)

- This information is obtained from the available national assessment reports

-Hepatitis C = blood born virus

- Easily transmitted by blood-to-blood contact

- Hepatitis C infected:
  - WHO = 2-3% of world's population
    - ⇒ 5-10 million people in Europe
  - In EU reported prevalence varies significantly between 0.4 en 5.5% (~5.5 million people) also even more between countries at a global level, and even in some population groups within the countries .
- Majority have genotype 1 or 3
- Minority genotype 2 (5-10%) or 4-6

Country	Genotype 1	Genotype 3
France	61%	19%
Scotland	49%	46%
Netherlands	~50%	~30%

Health problem and current use (2)

- Hepatitis C: 15-20% clear the infection within 6 months

  ⇒ Progression to chronic hepatitis C (CHC) influenced by genotype IL28B

- Infected often no symptoms => often undiagnosed
  - When symptomatic: usually mild (non-specific) fever; nausea; abdominal pain; flu-like symptoms
  - Long term: liver fibrosis, cirrhosis, liver failure, hepatocellular carcinoma
    - After 3 decades: 15-30% of patients have cirrhosis; once cirrhosis is present, complications occur quickly (e.g. hemodynamic decompensation)
    - Disease can be seriously debilitating
      - 1:3 liver transplantation are linked to CHC

Health problem and current use (3)

- Current treatment of chronic hepatitis C
    - Aim = eradicate virus

- Possible treatment options:
    - Genotype 1: protease inhibitors (telaprevir or boceprevir) + pegylated interferon + ribavirin *(24-48 weeks)*
    - Genotype 2-6: pegylated interferon + ribavirin *(24-48 weeks)*
        - Patients with HIV co-infection might need treatment for 72 weeks

- Pegylated interferon + ribavirin:
    - ⇒ >80% had serious side effects
    - ⇒ <50% did not complete treatment course
    - Not an option for patients awaiting liver transplantation

Questionnaire on national assessments (1)

Results of the questionnaire:

- 28 out of 30 jurisdictions* responded
  - 11 jurisdictions **no** assessment started
    - No application received (n=5)
    - No assessment needed =>
      - drug falls into the category of communicable diseases (n=2)
      - hospital drug (n=1)
    - Unknown (n=3)
  - 9 countries assessment **ongoing**
    - Two jurisdictions provided interim results
      - Full report: England (and Wales)
      - No full report: Spain, Slovenia**

** EU plus Norway, Switzerland and Turkey. For UK there were separate responses from England (and Wales) and from Scotland. For Romania and Estonia no contact address was available*

*** In Slovenia the assessment was done by National Viral Hepatitis Expert group*

Questionnaire on national assessments (2)

Results of the questionnaire:

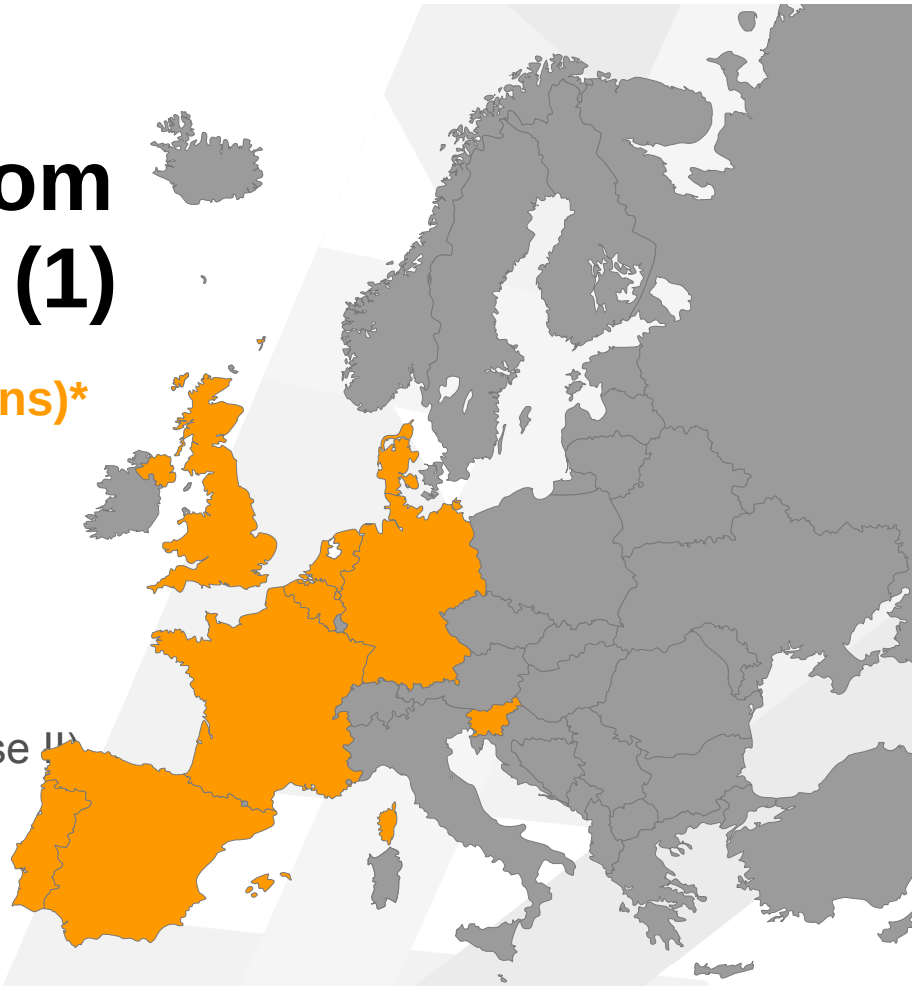
- 8 jurisdictions assessment **complete**
  - Full report: Denmark; France; Germany (IQWiG and G-BA*); Netherlands; Scotland

  - No full report: Belgium; Portugal; Switzerland**

**IQWIG und the G-BA do not make two different separate assessments: IQWiG is commissioned by the G-BA to assess the manufacturer dossier's studies for the G-BA. The G-BA makes the final assessment for Germany after a hearing procedure consisting of written statements and an oral hearing with clinical experts, scientific medical societies and other stakeholders.*

***confidential*

Summary of results from national assessments (1)



Data available: **full reports (6 jurisdictions)*** **and statements (4 jurisdictions**

Sofosbuvir effectiveness data:

- 8 RCTs (**4 phase III** and 4 phase II)
- 5 non-randomised studies (**2 phase III**, 3 phase II)
    - > 1500 patients

- The outcomes most mentioned in the reports:
    - **SVR12: Sustained virological response 12 weeks after the end of treatment**
    - QoL: Health-related quality of life
    - Mortality
    - **Safety**

**from one jurisdiction (Germany) there are two full reports (IQWIG and G-BA) available.*

Effectiveness / safety: discussion

Effectiveness of sofosbuvir (based on the comments in the assessment reports*)

+ Several subgroups => high SVR12 response rates

+ Generally well tolerated

+ Inclusion criteria were broader than for previous trials in hepatitis C

+ More patients can be treated than with other available regiments (e.g. no peginterferon needed)

+ Reduced treatment duration en simple regiment

+/- Effectiveness seems to differ by genotype group and other factors (e.g. cirrhosis or no cirrhosis)

+/- Like most agents, no long-term data available

- (Very) limited data for some subgroups

=> No data for treatment-experienced patients with genotype 1

- In clinical practise sofosbuvir may be used in other combinations

- Great uncertainty around the true magnitude of benefit

=> STUDY DESIGN; NUMBER OF PATIENTS INCLUDED; INDIRECT COMPARISONS

** In the discussion we included all comments that were made by at least 2 of the 6 countries .*

Effectiveness / safety: conclusions

Conclusion of some of the assessment reports of the individual jurisdictions:

- Germany IQWiG = no added benefit proven; only indication of benefit for HCV genotype 2 treatment naïve patients
- Germany G-BA = no proof (e.g., genotype 1, treatment experienced), hint of minor additional benefit (e.g., genotype 1, treatment naïve), indication of considerable benefit (HCV genotype 2 treatment naïve patients)*
- Netherlands = added value
- Portugal = added value
- Scotland = added value; restricted in genotype 2 (ineligible for / unable to tolerate peginterferon alpha) en genotype 3 (only 24 week treatment in those ineligible for / unable to tolerate peginterferon alpha)
- Spain = added value

**G-BA resolution is time-limited until 15 July 2016 because of lack of long-term data for sofosbuvir on SVR and other endpoints.*

Summary of results from national assessments: Cost of the technology

- List prices of sofosbuvir in 6 countries:
    - ranges: ~€13.525 and €19.000 for 28 pills
        = ~€40.575 and €57.000 for 12-week course

- Budget impact (based on list prices?):

Country	Incidence	Added cost in upcoming years:
Denmark	~500	Not reported
Scotland	~1000	6 to 20 million
Netherlands	~1000-2000	44 to 79 million

Summary of results from national assessments: cost effectiveness (1)

Results questionnaire:

- 12 countries stated they have/are evaluating the cost effectiveness (CE) of sofosbuvir
    - Most countries do not have the results yet.
        - CE results are available from: France, Netherlands, Scotland, UK.
            - ⇒ Difficulty = there are many subgroup/scenario-analyses
              number of subgroups varies between 15 and 50
            - ⇒ In the next slide is an example show of the CE results

Cost effectiveness: conclusions

- In most national assessment reports, in which cost-effectiveness was taken into account, treatment scenarios were judged to be cost-effective.
    - However, C-E thresholds may differ between countries or may not be defined explicitly, so it is difficult assess these judgments

Overall conclusion

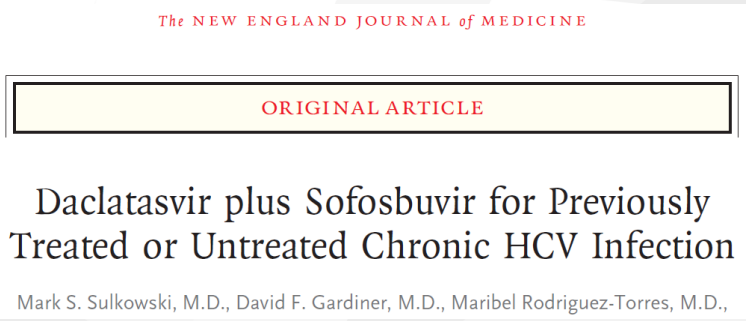
This is based on the summary of the national available assessment reports (10 jurisdictions):

- Most available national assessments => added therapeutic benefit for all/most subgroups

- Overall conclusion: the main problem seems to be the high budget impact due to the high price of sofosbuvir and substantial eligible population for treatment with this pharmaceutical

  - Questionnaire: 8 countries started price negotiations

- Future perspective: in clinical practise combined with other (expensive?) hepatitis C drugs (e.g., daclatasivir)


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Daclatasvir plus Sofosbuvir for Previously Treated or Untreated Chronic HCV Infection

Mark S. Sulkowski, M.D., David F. Gardiner, M.D., Maribel Rodriguez-Torres, M.D.,

Thank you

Any questions?

This presentation arises from the EUnetHTA Joint Action 2 which has received funding from the European Union, in the framework of the Health Programme