Eur J Health Econ (2015) 16:341–345
DOI 10.1007/s10198-014-0653-x

EDITORIAL

Pricing of forthcoming therapies for hepatitis C in Europe: beyond cost-effectiveness?

Katelijne van de Vooren · Alessandro Curto · Livio Garattini

Published online: 19 November 2014

Introduction

The worldwide economic crisis has put enormous pressure on national health care expenditures, not only in developing countries but also in developed ones. Some have adopted various cost-saving measures to keep pharmaceutical expenses sustainable, which are one of the most variable shares of the health care budget, and thus easier to influence. To back hard choices on pricing and reimbursement, decision-makers increasingly require full economic evaluations (FEEs), which are becoming popular in the general attempt to gain efficiency in the allocation of scarce resources [1].

We take as an example the new drugs for hepatitis C, widely debated at present. Although these drugs seem to be a good step forward in the struggle against this illness, they pose a major threat to pharmaceutical expenditure because of their sky-high prices combined with large target groups. After a brief introduction on the epidemiology of hepatitis C and its treatment options, we critically analyze the FEEs published in the EU on the first generation of direct-acting antivirals (DAAs) indicated for hepatitis C, to assess their contribution to rational decision-making according to the key drivers of their results [2]. We focused on this new subclass of drugs to draw lessons for the forthcoming generation of even more effective anti-HCV therapies, offering both greater efficacy and safety.

K. van de Vooren · A. Curto · L. Garattini (✉)
CESAV, Center for Health Economics, IRCCS Institute for Pharmacological Research 'Mario Negri', Via Camozzi 3, 24020 Ranica, Italy
e-mail: livio.garattini@marionegri.it

Epidemiology and treatment

Hepatitis C is caused by exposure to blood infected with the hepatitis C virus (HCV). The pathology ranges in severity from a mild illness lasting a few weeks to a serious, lifelong condition that can lead to liver cirrhosis or cancer. HCV infection is typically marked by slowly progressive hepatic fibrosis, from stage 0 (no fibrosis) to stage 4 (cirrhosis). Around 75–85 % of the newly infected people develop chronic infection and 60–70 % chronic liver disease, 5–20 % of those leading to cirrhosis and 1–5 % dying from cirrhosis/liver cancer (hepatitis C is the cause of 25 % of liver cancers).

The diagnosis is often lacking because most infected people are asymptomatic and common methods of antibody detection cannot distinguish acute from chronic infection. Thus, not surprisingly, prevalence data on hepatitis C are scarce in Europe and vary a lot from one country to another, ranging from >3 % in Italy to >1 % in France [3, 4].

There are several genotypes of the HCV, which may respond differently to treatment. In Europe, genotype 1 is predominant, followed by genotypes 2 and 3 [5]. The efficacy of therapies is measured by the surrogate endpoint "sustained virological response (SVR)", used in all the clinical trials (CTs) for approval [6]. SVR is defined as an undetectable HCV viral load 6 months after completing a successful course of HCV treatment.

The current standard of care for chronic HCV infection is a weekly subcutaneous injection of PEGylated interferon α in combination with twice-daily ribavirin (the so-called "double therapy"). Response varies from 66 to 80 % for patients with genotype 2 or 3 to only about 45 % for those with genotype 1 or 4 [7]. Unfortunately, interferon is often not well tolerated because of side effects (anemia,

neutropenia, thrombocytopenia, thyroid dysfunction, etc.) so many patients do not complete the course [8].

Two new therapeutic agents, boceprevir (BOC) and telaprevir (TEL), were given market authorization in 2011 by the European Medicine Agency. Both belong to the same subclass of DAAs and are indicated (in combination with peginterferon α and ribavirin) for adult patients with chronic hepatitis C genotype 1 who are naive or have failed previous therapy. The efficacy of these new drugs has appeared to be promising, with an average increase almost double in SVR for genotype 1 patients than with standard dual therapy, although responses are typically lower in those with advanced cirrhosis or other markers of poor outcome [7]. The most challenging complication in both "triple therapies" is still anemia, which occurs in 36–50 % of cases [9].

The regimens of the two triple therapies differ (Fig. 1). Before starting BOC, the patients need to take the double therapy for 4 weeks, after which they add BOC three times a day for up to 44 weeks. TEL should be taken twice a day for 12 weeks, additionally to interferon α and ribavirin. Then, the double therapy will continue for a long period (up to 48 weeks). The total length of the two therapies depends on several factors, such as patients' previous treatment and results of blood tests during treatment.

In January 2014, EMA approved sofosbuvir, a very promising antiviral which belongs to a new subclass of DAAs [10], and many more products are due to be approved in the short run. For instance, simeprevir or daclatasvir combined with sofosbuvir will be used as an interferon-free treatment. Very recently the CHMP adopted a positive opinion following an accelerated review procedure on a fixed combination of sofosbuvir and ledipasvir in a once-daily single pill. Another triple therapy, interferon-free and fixed-dose, is under accelerated investigation by EMA at present [11].

All these forthcoming therapies should be very effective (with SVR rates over 90 %) and have fewer side effects than the present ones.

Literature review

We did a literature search on the PubMed international database to select FEEs on hepatitis C including the new drugs BOC or TEL, conducted in the EU countries and published in English from January 2011 until March 2014. The search terms used were "boceprevir or telaprevir" and "cost". We screened the selected articles to assess the main methodological features of the FEEs, using a common checklist based on the one adopted to abstract studies in the EURONHEED database [12].

We retrieved 52 articles: 41 were discarded because they did not include a FEE on BOC/TEL, and were: (a) partial EEs (1); (b) FEEs on other drugs/subgroups or on clinical procedures (5); (c) studies on clinical issues (30); (d) reviews, comments or methodological articles (5). Since five FEEs did not concern the EU setting, we eventually selected six articles [13–18] (Table 1).

The analyses, all conducted from a third-party payer's perspective, concerned only four jurisdictions (Italy, Portugal, Spain, and the UK) since we found two separate articles for both Italy and the UK (one on naive and one on pre-treated patients, written by the same authors). The studies included a CUA and half of them a CEA, too. The studies compared triple therapy with BOC/TEL to standard dual therapy, except in one case where the 'do nothing' alternative was arguably adopted, assuming that

Fig. 1 Labeled regimens of BOC and TEL [4, 5]

BOC*

Week	**4**	**28**	**36**	**48**
Cirrhotic patients and null responders	PR	PR+BOC		
Naive patients and prior treatment relapsers	PR	PR+BOC		PR
Naive patients with undetectable HCV-DNA at weeks 8 and 24	PR	PR+BOC		-

*All patients: stopping rule depends on assessment of HCV-RNA in week 12 and/or 24.

TEL **

Week	**12**	**24**	**48**
Cirrhotic patients and previously partial or null responders	PR+TEL	PR	
Naive patients and prior treatment relapsers	PR+TEL	PR	
Naive patients and prior treatment relapsers with undetectable HCV-DNA at weeks 4 and 12	PR+TEL	PR	-

**All patients: stopping rule depends on assessment of HCV-RNA in week 4 and/or 12.

PR: peginterferon α+ ribavirin, BOC: boceprevir, TEL: telaprevir

Table 1 Main characteristics of studies

Ref.	Type of FEE (country)	Type of patients	Alternatives	Sources of resource consumption	Most influential variables in SA	Main conclusion	Sponsorship
[13]	CUA (United Kingdom)	Pre-treated CT cohort (F0–F4)	TEL + PR vs. PR TEL + PR vs. BOC + PR	Clinical trials National surveys Assumptions Expert panel	Drug price, discount rate, utility, SVR	Triple therapy with TEL is always cost-effective compared to dual therapy and is cost saving compared to BOC	Yes[a]
[14]	CEA and CUA (Italy)	Pre-treated theoretical cohort (F2)	BOC + PR vs. do nothing TEL + PR vs. do nothing TEL + PR vs. BOC + PR	Clinical trials Market surveys Assumptions Expert panel	Discount rate, disease progression, SVR, drug prices	Triple therapy is cost-effective, particularly with TEL	Yes[b]
[15]	CEA and CUA (United Kingdom)	Naıve CT cohort (F0–F4)	TEL + PR vs. PR TEL + PR vs. BOC + PR	Clinical trials National surveys Assumptions Expert panel	Discount rate, utility, drug prices, SVR	Triple therapy with TEL is cost-effective compared to dual therapy and dominates BOC	Yes[a]
[16]	CUA (Spain)	Naıve CT cohort (F0–F4)	BOC + PR vs. PR TEL + PR vs. PR	Clinical trials Regional registries Assumptions Expert panel	Age, mortality rate, SVR, disease progression, drug prices	Triple therapies with BOC and TEL are cost-effective	No
[17]	CEA and CUA (Italy)	Naıve theoretical cohort (F2)	BOC + PR vs. PR TEL + PR vs. PR	Clinical trials Market surveys Assumption Expert panel	SVR, disease progression, drugs prices	Triple therapies with BOC and TEL are cost-effective	Yes[b]
[18]	CUA (Portugal)	Pre-treated and naıve CT cohort (F0–F4)	BOC + PR vs. PR	Clinical trials Assumption Expert panel	Age, SVR, utility, drug prices, discount rate, disease progression	Triple therapy with BOC is cost-effective in pre-treated and naive patients	Yes[a]

BOC boceprevir, *CEA* cost-effectiveness analysis, *CUA* cost-utility analysis, *F0* no fibrosis, *F1* portal fibrosis without septa, *F2* portal fibrosis with few septa, *F3* numerous septa without cirrhosis, *F4* cirrhosis, *PR* peginterferon + ribavirin, *SA* sensitivity analysis, *SVR* sustained viral response, *TEL* telaprevir

[a] Co-authored by at least one employee of the sponsoring manufacturer

[b] Funded by a consultancy company

experienced patients are never re-treated in clinical practice. Half of the studies included a direct comparison between the two triple therapies as well, although head-to-head CTs are lacking. All studies but one were (directly or indirectly) sponsored by the pharmaceutical industry and three were co-authored by one employee at least.

From a methodological point of view, all studies were based on modeling with a long-term horizon, using virtual cohorts based on CT patients (in two studies even a purely hypothetical cohort), which hardly reflect the real epidemiology of the settings analyzed. Although efficacy was mainly derived from CTs used for registration, all but one used treatment algorithms different from the labels. The probability of disease progression varied a lot from one study to another. Four relied on foreign scores and expert panels to estimate utility. In all studies we found very weak sources like assumptions and expert panels to estimate resource consumption; one Italian study even used the US prices of BOC and TEL as unit costs. Costs of side effects were lacking in two studies.

All studies concluded in favor of triple therapies. Sensitivity analyses highlighted drug prices, discount rate, efficacy, and utility as the most influential variables on baseline results.

Policy implications

Although BOC and TEL have been shown to be more effective than standard therapy, the actual usefulness of the FEEs evaluated, mainly populated by weak sources and based on long-term modeling designed for subgroups of patients and arguable therapeutic regimens, remains uncertain from the health authorities' viewpoint, as underlined by NICE in its separate assessments of BOC and TEL [19, 20].

Assuming that the forthcoming drugs are even more effective and much safer (needing shorter regimens not necessarily with interferon), we wonder whether future FEEs on these therapies focused on specific subgroups of patients really add any value for decision-making, particularly in a value-based pricing perspective. Despite the sky-high prices of all these incumbent drugs, we are sure that companies would manage to select the most suitable inputs to feed long-term models and pick subgroups with different regimens to show an acceptable incremental cost-effectiveness ratio for each of them. However, when treating larger target groups, as seems the most likely scenario in hepatitis C, we believe the real "crux" of the matter will be the difficulty in sustaining the budget impact of these combination therapies, even in developed countries with different prevalences of hepatitis C. For instance, although the financial burden should be much lower in France than in Italy (according to the hepatitis C prevalence), the French government has announced a plan to selectively tax pharmaceutical companies should their total revenue on hepatitis C drugs exceed a fixed yearly amount [21], while in Italy AIFA (the Italian agency for drugs) has just signed a confidential deal with the sofosbuvir marketer after months of hard negotiations, without issuing any information on the agreed price so far.

In general, we hope national authorities will play a double role in this field. Before deciding on pricing and reimbursement of the forthcoming drugs, the main decision should be what subgroups to treat, trying to separate patients who can wait until the arrival of better treatments after early detection from those who should start treatment as early as possible to prevent severe complications in the future.

To treat as many patients as possible, national authorities could offer industry a sort of "block contract", a budget estimated from the health care costs potentially avoided thanks to these new therapies. Setting an "average price per volume" (i.e., the ratio between the total budget and the number of patients to treat as a target) should reflect the trade-off between increasing pharmaceutical costs and future inpatient savings for health care services. Like what happened at the end of the last century in a different epidemiological context with the DAAs for HIV/AIDS [22], these new combination therapies, which come from the same drug pipeline, could prevent many future hospital admissions by eradicating the HCVs. The main clinical challenge in such an exercise would be to set the "volume" of treatable patients, taking into account that hepatitis C can be a silent pathology for years, but that liver damage cannot be repaired. This volume could be stratified according to disease severity, hence the urgency for these therapies.

From the supply side, because many companies have stepped into this area, so many drugs should soon be available, broad negotiation could lead industry to accept the "sustainable" prices for the combination therapies, set as above. Alternatively, failing to achieve a "gentleman's agreement" with the different companies offering combination/single marketed therapies, national authorities could opt for tendering as a valuable alternative. A sufficient number of regional tenders, like what might happen in Italy, would prevent the threat of generating dominant positions and thus the risk of market failure induced by centralized public procurement [23]. A major hurdle could be to assume all these combination therapies of equivalent efficacy. However, real clinical differences could be addressed by adding a 'quality score' in tender clauses for specific groups of patients, with the aim of maximizing cost-effectiveness rather than simply minimizing cost. It is also worth noting that these new hepatitis C drugs are not

manufactured through complicated processes, an argument often put forward by industry (e.g., for human antibodies) to justify high prices. Their prices can be affected more by trade agreements when the company that discovered and then developed the drug is not the one that markets it, so the marketer has to pay high royalties to the manufacturer.

To conclude, we think new technical solutions are now needed for pricing therapies that are as innovative as they are expensive, to make their total cost sustainable in a period of unprecedented financial crisis for health care services. Here, starting from the promising combination therapies against hepatitis C which are to be launched in the near future, we put forward a very general proposal open to debate, based on real financial budgeting rather than economic evaluation.

References

1. WHO. Health, health systems and economic crisis in Europe: impact and policy implications. http://www.euro.who.int/en/media-centre/events/events/2013/04/oslo-conference-on-health-systems-and-the-economic-crisis/documentation/working-documents/health,-health-systems-and-economic-crisis-in-europe-impact-and-policy-implications. Accessed 29 Oct 2014
2. Anderson, R.: Systematic reviews of economic evaluations: utility or futility? Health Econ. **19**, 350–364 (2010)
3. European Centre for Disease Prevention and Control: Surveillance and prevention of hepatitis B and C in Europe. ECDC, Stockholm (2010)
4. Cornberg, M., Razavi, H.A., Alberti, A., et al.: A systematic review of hepatitis C virus epidemiology in Europe, Canada and Israel. Hepatitis C virus genotyping in chronic hepatitis C patients. Liver Int. **31**(Suppl 2), 30–60 (2011)
5. Qattan I, Emery V. Hepatitis C virus genotyping in chronic hepatitis C patients. Eur. Sci. J. Nov. 8(27) (2012)
6. Gluud, C., Koretz, R., Gurusamy, K.: Hepatitis C: a new direction, but an old story? Lancet **383**, 2122–2123 (2014)
7. Feeney, E.R., Chung, R.T.: Antiviral treatment of hepatitis C. BMJ **349**, g3308 (2014)
8. WHO. Hepatitis C, Factsheet No 164. http://www.who.int/mediacentre/factsheets/fs164/en/ (2014). Accessed 29 Oct 2014
9. Liang, T.J., Ghany, M.G.: Current and future therapies for hepatitis C virus infection. N. Engl. J. Med. **368**, 1907–1917 (2013)
10. EMA. Sovaldi: EPAR—product information. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002798/human_med_001723.jsp&mid=WC0b01ac058001d124. Accessed 29 Oct 2014
11. AbbVie press release. European medicines agency validates marketing authorization applications for AbbVie's investigational, all-oral, interferon-free therapy for the treatment of genotype 1 chronic hepatitis C http://abbvie.mediaroom.com/2014-06-17-European-Medicines-Agency-Validates-Marketing-Authorization-Applications-for-AbbVies-Investigational-All-Oral-Interferon-Free-Therapy-for-the-Treatment-of-Genotype-1-Chronic-Hepatitis-C Accessed 29 Oct 2014
12. De Pouvourville, G., Ulmann, P., Nixon, et al.: The diffusion of health economics knowledge in Europe. The EURONHEED (European network of health economic evaluation databases) project. Pharmacoeconomics **23**, 113–120 (2005)
13. Cure, S., Bianic, F., Gavart, S., et al.: Cost-effectiveness of telaprevir in combination with PEGylated interferon alpha and ribavirin in treatment-experienced chronic hepatitis c genotype 1 patients. J. Med. Econ. **17**(1), 77–87 (2014)
14. Cammà, C., Petta, S., Cabibbo, G., et al.: Cost-effectiveness of boceprevir or telaprevir for previously treated patients with genotype 1 chronic hepatitis C. J. Hepatol. **59**(4), 658–666 (2013)
15. Cure, S., Bianic, F., Gavart, S., et al.: Cost-effectiveness of telaprevir in combination with PEGylated interferon alpha and ribavirin in previously untreated chronic hepatitis c genotype 1 patients. J. Med. Econ. **17**(1), 65–76 (2014)
16. Blázquez-Pérez, A., San Miguel, R., Mar, J.: Cost effectiveness analysis of triple therapy with protease inhibitors in treatment-naïve hepatitis c patients. Pharmacoeconomics **31**(10), 919–931 (2013)
17. Cammà, C., Petta, S., Enea, M., et al.: Cost-effectiveness of boceprevir or telaprevir for untreated patients with genotype 1 chronic hepatitis c. Hepatology **56**(3), 850–860 (2012)
18. Elbasha, E.H., Chhatwal, J., Ferrante, S.A., et al.: Cost-effectiveness analysis of boceprevir for the treatment of chronic hepatitis c virus genotype 1 infection in Portugal. Appl. Health Econ. Health Policy **11**(1), 65–78 (2013)
19. NICE technology appraisals [TA253]. Boceprevir for the treatment of genotype 1 chronic hepatitis C. https://www.nice.org.uk/guidance/ta253 (2012). Accessed 29 Oct 2014
20. NICE technology appraisals [TA252]. Telaprevir for the treatment of genotype 1 chronic hepatitis C. http://www.nice.org.uk/guidance/ta252 (2012). Accessed 29 Oct 2014
21. Reuters. France uses tax to put pressure on hepatitis C drug prices. http://www.reuters.com/article/2014/09/30/us-france-deficit-gilead-idUSKCN0HP15N20140930 (2014). Accessed 29 Oct 2014
22. Garattini, L., Tediosi, F., Di Cintio, E., et al.: Gruppo di studio ARCA (AIDS resources and costs analysis). Resource utilization and hospital cost of HIV/AIDS care in Italy in the era of highly active antiretroviral therapy. AIDS Care **13**, 733–741 (2001)
23. Garattini, L., Van de Vooren, K., Freemantle, N.: Tendering and value-based pricing: lessons from Italy on human papilloma virus vaccines. J. R. Soc. Med. **107**, 4–5 (2014)