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1. Replace (Ins) Tool – for replacing text.
   - Stripes a line through text and opens up a text box where replacement text can be entered.
   - **How to use it**
     - Highlight a word or sentence.
     - Click on the Replace (Ins) icon in the Annotations section.
     - Type the replacement text into the blue box that appears.

2. Strikethrough (Del) Tool – for deleting text.
   - Stripes a red line through text that is to be deleted.
   - **How to use it**
     - Highlight a word or sentence.
     - Click on the Strikethrough (Del) icon in the Annotations section.

3. Add note to text Tool – for highlighting a section to be changed to bold or italic.
   - Highlights text in yellow and opens up a text box where comments can be entered.
   - **How to use it**
     - Highlight the relevant section of text.
     - Click on the Add note to text icon in the Annotations section.
     - Type instruction on what should be changed regarding the text into the yellow box that appears.

4. Add sticky note Tool – for making notes at specific points in the text.
   - Marks a point in the proof where a comment needs to be highlighted.
   - **How to use it**
     - Click on the Add sticky note icon in the Annotations section.
     - Click at the point in the proof where the comment should be inserted.
     - Type the comment into the yellow box that appears.
5. **Attach File** Tool – for inserting large amounts of text or replacement figures.

   Inserts an icon linking to the attached file in the appropriate place in the text.

   **How to use it**
   - Click on the Attach File icon in the Annotations section.
   - Click on the proof to where you’d like the attached file to be linked.
   - Select the file to be attached from your computer or network.
   - Select the colour and type of icon that will appear in the proof. Click OK.

6. **Drawing Markups** Tools – for drawing shapes, lines and freeform annotations on proofs and commenting on these marks.

   Allows shapes, lines and freeform annotations to be drawn on proofs and for comment to be made on these marks.

   **How to use it**
   - Click on one of the shapes in the Drawing Markups section.
   - Click on the proof at the relevant point and draw the selected shape with the cursor.
   - To add a comment to the drawn shape, move the cursor over the shape until an arrowhead appears.
   - Double click on the shape and type any text in the red box that appears.
Letter to the Editor

Letter: estimating the cost-neutral price of sofosbuvir-based triple therapy for the treatment of naive patients with genotype 1 HCV infection in Italy

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Sir, The article by Koff exhaustively reviewed the clinical literature on sofosbuvir, but did not address the issue of cost, which is presently the main point of debate on this agent. In many European countries, special attention is currently focused on costs because a decision is being made on whether sofosbuvir can be reimbursed by public health-care systems. Numerous simulation models have therefore been proposed to estimate the cost-effectiveness of sofosbuvir-based triple therapy (SBTT).3–8

The case of naive patients with genotype 1 is the most studied one, and has been evaluated for dual therapy and previr-based triple therapies.7,8

We have previously described a modified version of Shepherd’s simulation model4 to estimate the effectiveness of anti-HCV treatments. In the present analysis, we have firstly applied this model to the effectiveness of SBTT vs. dual therapy. The resulting estimates (22.3 and 20.7 quality adjusted life years (QALYs) per patient, respectively) showed a gain of 1.5 QALYs per patient (Table 1). Then, we have applied this model for predicting costs (Table 1). Our estimations of cost and effectiveness (Table 1) indicate that SBTT can be ‘dominant’ (more effective and less costly) over dual therapy only if sofosbuvir’s cost per patient is reduced to less than € 11 000 (cost-neutral price). The current European price of sofosbuvir is around € 50 000.

Table 1 | SBTT vs. dual therapy in naive patients with genotype 1 HCV infection: cost effectiveness and ICER

<table>
<thead>
<tr>
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<th>Cost per patient (excluding anti-HCV drugs)*</th>
<th>Effectiveness per patient (SVR)*</th>
<th>Effectiveness per patient (QALYs)*</th>
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<tbody>
<tr>
<td>SBTT</td>
<td>€ 22 434†</td>
<td>92%</td>
<td>22.3‡</td>
</tr>
<tr>
<td>Dual therapy</td>
<td>€ 33 533†</td>
<td>45%</td>
<td>20.7‡</td>
</tr>
<tr>
<td>ICER§</td>
<td>ICER = (€ 22 434 + € 50 000 – € 33 522)/1.5 QALY = € 25 433 per QALY gained</td>
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ICER, incremental cost-effectiveness ratio; SBTT, sofosbuvir-based triple therapy.

* This scenario is based on a 30-year horizon, 1.5% annual discount for benefits;9 estimates of SVR were obtained from References 6 and 7.
† Information from a study by Mennini10 (in which the annual costs per patient were reported for exactly the same five health states previously included in our model and with reference to the Italian setting). These cost estimates were the following: chronic hepatitis, € 300; cirrhosis, € 5465; hepatocellular carcinoma, € 200 000 (including monitoring costs); eradicated disease, € 0. These estimates include 3% annual discount (year of costing: 2012).
‡ Calculated according to the following equation that predicts effectiveness according to Bennett’s model as a function of SVR (see Reference 9 for details): QALY_SVRn% = 0.01 × [QALY_SVR100% × n + QALY_SVR0% × (100 – n)] where n represents any value of SVR between 0% and 99% in the present analysis, the value of n was 92% for SBTT and 45% for dual therapy.
§ According to these data (where € 50 000 is the sofosbuvir cost per patient) and a willingness to pay threshold of 40 000 € per QALY gained, SBTT proves to be cost-effective up to a cost of € 71 000 per patient (where € 71 000 = 1.5 QALYs × € 40 000/QALY + € 11 000).

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In the debate on reimbursement of sofosbuvir, one misconception that has frequently been reported is that the drug cost would be completely offset by the savings in health-care costs resulting from incremental clinical benefits. This is not true. Unless the cost per patient of sofosbuvir is reduced to €11,000 per patient, the expenditure on this new drug will not be entirely recouped by reduced direct costs for reduced morbidity. However, while an extra cost therefore remains, this extra cost has a favourable pharmacoeconomic profile at least in this base-case scenario.

ACKNOWLEDGEMENT

Declaration of personal and funding interests: None.

REFERENCES

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