Letter to the Editor

Producing evidence in support of disinvestment: The experience of the Tuscany region in Italy

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To the Editor:

In this journal, Macchi and Pavan [1] have described how, in Italy, a research hospital can be managed at the times of a global economic crisis and have pointed out that, as a matter of fact, sustainability has become the main concern for hospital managers and physicians. This implies to promote a more critical evaluation of health-care interventions leading in some cases to negative approval decisions. While other countries have debated the question of ‘saying No’ for nearly 20 years particularly in the field of pharmaceutics and medical devices [2], Italy has had some delay not only in recognizing that these interventions of governance are needed, but also in effectively implementing the interventions themselves.

Experiences of disinvestment are thought to play a role in this context, but–as pointed out by Howard and Gross [3] in the JAMA Internal Medicine–these experiences continue to be a few because a series of hurdles continue to limit their implementation [3]. Among these, several practical problems have been pointed out (e.g., disinvestment is more complex in the presence of patients already under treatment), but also the lack of priority assigned by NHS to these activity plays a role. Anyhow, generating the evidence in support of disinvestment is recognized to be the first step in this overall process. For this reason, we would like to briefly describe an experience in this field conducted in the Tuscany region of Italy.

Owing to constraints in the regional pharmaceutical budget, in January 2014 the regional institution responsible for in-hospital drug acquisition (ESTAV) started a project aimed at identifying a series of pharmacological treatments that were suitable for disinvestment (i.e., suitable to be replaced by an equi-effective and less costly alternative). The project was also supported by a national scientific society of hospital pharmacists (SIFACT) that participates in the Choosing Wisely project. In particular, ESTAV fostered the hospital pharmacists of the Region (as well as clinicians) to submit proposals of disinvestment. At the same time, a group of experts (AM, ST, VF, DM) was formed that was assigned the duty of evaluating the base of evidence for each individual proposal. In the analysis of the evidence, one criterion adopted by our group was to write a full scientific report focused on comparative effectiveness for each therapeutic issue.

As regards the data of pharmacological treatment costs, drug prices were those set at national level and reported in the official databases. These data could not include some confidential discounts granted to the NHS (e.g., for anti-HCV treatments[5]) because this piece of information is not publicly available.

Table 1 summarizes the main 10 analyses of disinvestment that were completed within this project (from January 2014 to September 2015). As expected, the submissions we received followed no specific order and covered very different areas of in-hospital pharmacological treatment. In all of these reports, comparative effectiveness was studied by undertaking a non-inferiority analysis (N = 8) or an equivalence analysis (N = 2).

The rationale whereby B-drugs were promoted in replacement of A was essentially related to the lower cost of treatment for B calculated on the basis of “full” national prices. Another tool for in-hospital drug acquisition managed by ESTAV is represented by competitive tenders that find their best application when equivalence is demonstrated; however, no tenders have yet been run on these agents (with the exception of that involving anti-HCV drugs that has however been unsuccessful [5]). As pointed out by Howard and Gross [3], public institutions can have a crucial role in conducting non-inferiority or equivalence research focused on less costly treatments because industry has generally little interest in doing these studies or these analyses.

In the framework of these 10 therapeutic issues, even without undertaking any tenders, considerable savings can be expected from replacing the more costly treatment with the less costly one (at least 15% savings across the 10 analyses). While the evidence-based analyses have already been completed, the process of running the administrative procedures for drug acquisition is still underway; likewise, the interventions for sharing these projects with the hospital clinicians are still in progress. Of course, among these disinvestment proposals, some appeared to be quite easy to be implemented (e.g., in the case of anti-HCV treatments), but others were clearly more problematic (e.g., replacing interferon with azathioprine in multiple sclerosis patients).

In conclusion, this series of 10 proposals are of interest because they represent a real-world scenario within the NHS of a European country. Furthermore, it is noteworthy that, in our NHS, building an evidence of equivalence or non-inferiority was recognized to be a pre-requisite for any subsequent initiative of pharmaceutical governance.

Conflict of interest

Each of the four authors declares no conflict of interest.

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Table 1

Information on the 10 analyses conducted within the present evidence-based project. Reference [4] shows the bibliographic details of the 10 scientific reports that presented the analyses of comparative effectiveness.

<table>
<thead>
<tr>
<th>Therapeutic indication</th>
<th>Intervention to be disinvested (A)</th>
<th>Intervention to be promoted (B)</th>
<th>Analysis of evidence</th>
<th>Cost difference per patient(^b) (EUR)</th>
<th>Percent cost reduction using B</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. First line treatment of previously untreated patients with genotype-1 HCV infection</td>
<td>Sofosbuvir + ledipasvir (12 weeks)</td>
<td>Ritonavir-boosted dual therapy (12 weeks)</td>
<td>B is non-inferior to A</td>
<td>12,206 (81,521 – 69,315)</td>
<td>15%</td>
</tr>
<tr>
<td>2. First line treatment of previously untreated patients with multiple sclerosis</td>
<td>Beta-interferon</td>
<td>Azathioprine</td>
<td>B is non-inferior to A</td>
<td>15,000 (15,300 – 300)</td>
<td>98%</td>
</tr>
<tr>
<td>3. Prevention of venous thromboembolism in major orthopedic surgery</td>
<td>Enoxaparin</td>
<td>Dalteparin</td>
<td>B is non-inferior to A</td>
<td>74.1 (107 – 32.91)</td>
<td>69%</td>
</tr>
<tr>
<td>4. Targeted treatments for pulmonary arterial hypertension</td>
<td>Various agents of recent approval</td>
<td>Sildenafil</td>
<td>B is non-inferior to A</td>
<td>39,718 (49,896 for Adempas/riociguat – 10,178)</td>
<td>80%</td>
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<tr>
<td>5. Thromboprophylaxis in orthopedic surgery</td>
<td>Rivaroxaban</td>
<td>Apixaban</td>
<td>B is non-inferior to A</td>
<td>72.29 (109.13 – 36.84)</td>
<td>60%</td>
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<tr>
<td>6. Treatment of moderate-to-severe psoriasis by subcutaneous route</td>
<td>Ustekinumab 45 mg</td>
<td>Adalimumab</td>
<td>B is non-inferior to A</td>
<td>3864 (17,058 – 13,194)</td>
<td>23%</td>
</tr>
<tr>
<td>7. Anti-reabsorptive treatment in women with osteoporosis</td>
<td>Risedronate or ibandronate or denosumab</td>
<td>Alendronate</td>
<td>B is non-inferior to A</td>
<td>367.3 (658.5 – 291.2)</td>
<td>44%</td>
</tr>
<tr>
<td>8. Intravenous proton pump inhibitors for stress ulcer prophylaxis in critically ill patients</td>
<td>Omeprazole</td>
<td>Pantoprazole</td>
<td>Equivalence of A and B(^c)</td>
<td>3.66 (per vial) (8.58 – 4.92)</td>
<td>43%</td>
</tr>
<tr>
<td>9. Stroke prevention in atrial fibrillation</td>
<td>Novel oral anticoaguants</td>
<td>Devices for closure of appendage (Watchman)</td>
<td>B is non-inferior to A</td>
<td>1632(^c) (6631 – 5000)</td>
<td>25%</td>
</tr>
<tr>
<td>10. Biological drugs for inducing remission in patients with Crohn’s disease</td>
<td>Certolizumab</td>
<td>Adalimumab</td>
<td>Equivalence of A and B(^c)</td>
<td>637 (3682 – 3045)</td>
<td>17%</td>
</tr>
</tbody>
</table>

\(^a\) In these cases, the official national price of the two alternatives included in the comparison does not differ from one another to a meaningful extent; demonstrating equivalence is the pre-requisite for conducting a competitive tender to cover the in-hospital consumption.

\(^b\) With cost of A – cost of B in parenthesis; in case of chronic treatments, both values are meant to represent the annual cost.

\(^c\) Costs were intended to cover a follow-up of 5 years [6]; cost of patients’ monitoring were assumed to be the same across the two treatments and therefore were not included.

References


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