Market Access of ATMPs: Overview and Expected Challenges

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BACKGROUND
- Advanced Therapy Medicinal Products (ATMPs) constitute a class of innovative and regenerative therapies, including stem cells, gene therapy, and cell therapy medicinal products.
- This class encompasses Gene Therapy Medicinal Products (GTMPs), somatic Cell Therapy Medicinal Products (sCTMPs), Tissue Engineered Products (TEPs), and combined products (tissue or cell associated with a device). [1]
- As of October 2015, only 5 ATMPs have been granted a Marketing Authorisation (MA) in the European Union (EU): [2]
  - Chondrocel (MACI), Glybera®, Provenge®, and Haloclair®

OBJECTIVES
- The aim of this study was to review ATMPs’ assessments by EU HTA bodies in the big 5 EU countries: France, Germany, Italy, Spain, and the United Kingdom (UK).

METHODS
- The EU’s 5 HTA bodies websites were searched for their decisions on ATMPs:
  - France: French National Authority for Health (Agence nationale de santé : HAS) [3]
  - UK: National Institute for Health and Care Excellence (NICE) [4], Scottish Medicines Consortium (SMC) [5]
  - Italy: Italian Medicines Agency (Agenzia Italiana del Farmaco: AIFA), and regions [6]
  - Spain: Ministry of Health (Ministerio de Sanidad, Servicios Sociales e Igualdad: MSISs), and regions [7]
  - Germany: Institute for Quality and Efficiency in Healthcare (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen : IQWIG), Federal Joint Committee (Gemeinsame Bundesaussschuß : G-BA) [8]
- Grey literature was also searched for further details.

RESULTS

Chondrocel®
- First ATMP approved in the EU in 2009 for the repair of single symptomatic cartilage defects of the femoral condyle of the knee. [9]
- Chondrocel® is reimbursed in Spain, not recommended in France, and under evaluation in the UK (Figure 1)
- It was rejected in France as the efficacy/adverse effects ratio had not been clearly established. [10]
- Chondrocel® obtained New Diagnostic and Treatment Methods status (NDB) in Germany. These methods are considered invaluable in principle in outpatient cases, but can be reimbursed prior to G-Ba investigation in inpatient cases, as hospitals can agree on treatment remuneration with local health insurance. [11]
- In March 2013, Chondrocel® was approved for reimbursement in Spain.
- In August 2015, after the consultations and scoping workshop, NICE published the block scoping report for Chondrocel® and MACI® with the following remit: “To appraise the clinical and cost-effectiveness of autologous chondrocyte implantation within the applicable licenced indications for repairing symptomatic articular cartilage defects of the knee.” [12] This report helps ministers to decide whether or not these technologies should be formally referred to NICE for appraisal.

Glybera®
- Approved in 2012 in the EU after 3 negative decisions of CHMP for lipoprotein lipase regeneration therapy (efficacy/lipid profile). [13]
- Glybera® is yet to be reimbursed in any of the big 5 EU countries:
  - G-BA assessed Glybera®, but could not conclude on its benefits due to limited data submitted by manufacturer. [9]
  - In June 2015, HAS announced that Glybera does not have a significant budget impact therefore it will not have to go through medico-economic assessment. [14]

MACI®
- Since 1998, before the ATMPs’ regulation, MACI® was available in several European countries: Germany, Italy, Spain, UK.
- In 2013, it was approved in the EU for the repair of symptomatic, full-thickness cartilage defects of the knee. Its MA was suspended in December 2014 due to the closure of EU manufacturing site. [2]
- MACI® is under evaluation in the UK and Germany:
  - G-BA extended the suspension of the review and decisions on quality assurance of MACI® until 31 December 2019 waiting for additional data on long term safety. [9]
  - MACI® will be assessed by NICE with Chondrocel® as mentioned in the block scoping report for autologous chondrocytes implantation. [4]

Provenge®
- Approved in 2013 for asymptomatic or minimally symptomatic metastatic (non-visceral) castrate resistant prostate cancer in male adults in whom chemotherapy is not yet clinically indicated. Its MA was withdrawn in May 2015 in EU due to the bankruptcy of the manufacturer Dendreon. [2]
- It is not reimbursed in any of the big 5 EU countries:
  - It is not recommended in the UK. NICE concluded that Provenge® did not demonstrate either additional benefit or cost-effectiveness compared to best supportive care. [4]
  - IQWIG/G-BA concluded “non-quantifiable” added benefit. [9]

Haloclair®
- Approved in February 2015 [7] in the EU for moderate to severe limbal stem cell deficiency, it has not yet been assessed.

DISCUSSION
- Our results show the difficulties preventing these therapies from reaching the market; Chondrocel® the first ATMP, approved six years ago, is until now, only reimbursed in some countries.
- In addition, these therapies expected to be very expensive, are put under scrutiny from payers and HTA bodies which usually postpone their final decisions due to limited data.
- Proving the added value of ATMPs and their efficacy is the most important challenge facing the manufacturers, as it has to be taken into consideration during the early stages of development.

Table 1. HTA review and reimbursement status of approved ATMPs

<table>
<thead>
<tr>
<th>ATMP</th>
<th>Active ingredient</th>
<th>Type</th>
<th>HTA review</th>
<th>Reimbursement status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chondrocel®</td>
<td>Autologous</td>
<td>TEP</td>
<td>HAS: not recommended</td>
<td>Reimbursed in Spain</td>
</tr>
<tr>
<td>Glybera®</td>
<td>Lipoatec®</td>
<td>GTMP</td>
<td>G-BA: postponed</td>
<td>No national reimbursement</td>
</tr>
<tr>
<td>MACI®</td>
<td>Autologous</td>
<td>TEP</td>
<td>NICE: under evaluation</td>
<td>No national Reimbursement</td>
</tr>
<tr>
<td>Provenge®</td>
<td>Sipuleucel-T</td>
<td>xCTMP</td>
<td>NICE: not recommended</td>
<td>No national Reimbursement</td>
</tr>
<tr>
<td>Haloclair®</td>
<td>Autologous</td>
<td>TEP</td>
<td>Not yet assessed</td>
<td>Not yet assessed</td>
</tr>
</tbody>
</table>

CONCLUSIONS
- Market access of ATMPs is challenging as evidence available at market launch might not be sufficient to address HTA agencies’ expectations.
- However, adaptive pathways for licensing and coverage of drugs might be a relevant approach for these medicines to reduce uncertainty through real-world data collection post-launch.

References
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