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Abstract

The aim of this study was to estimate the budget impact of collagenase Clostridium histolyticum (CCH) vs. fasciectomy (FSC) surgery for the treatment of Dupuytren’s disease (DD) in Spain. A cost minimization analysis was adopted (effectiveness was assumed to be equivalent for both techniques). DD related costs were considered. CCH costs (including drug, administration and visits) were obtained from clinical trials and a real-life study. FSC costs (including type of admission, visits, operating room, re-admissions, tests, drugs and rehabilitation costs) were collected through a retrospective, observational, local study. Unit costs were obtained from local database systems (e-SALUD and BOT). Results were presented from the NHS perspective for the next 3 years. We assumed that there were 5100 fasciectomies per year (with a 5% annual increase) and that 20%, 30% and 40% of them will annually utilize CCH. In addition, a 10%, 15% and 20% of untreated diagnosed patients were expected to receive CCH. All the data were validated through an expert panel. A sensitivity analysis was performed with the main variables. The average FSC cost was € 2250 (72% inpatients), € 1703 for outpatients and € 2467 for inpatients. The average CCH cost was € 1220 (1.5 vial/injection and four visits) and could drop to € 898 (1.1 vial/injections and three visits). The accumulated 3 years budget impact analysis (BIA) was 45,971 € (K€ – 2993; 3870). According to this study, the inclusion of the CCH should produce a 3-year cumulative budgetary impact of € 45,971 (K€ – 2993; 3870) for the NHS.

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Keywords: Dupuytren contracture; Cost minimization; Budget impact analysis; Fasciectomy; Collagenase Clostridium histolyticum

Résumé

Le but de cette étude était d’évaluer l’impact budgétaire de la collagénase de Clostridium histolyticum (CCH) vs la chirurgie, en se focalisant uniquement sur la fasciectomie (FSC) pour le traitement de la maladie de Dupuytren (MD) en Espagne. Une analyse de diminution de coûts fut adoptée (l’efficacité fut considérée équivalente pour les deux techniques). Les coûts liés à MD ont été pris en considération. Les coûts, y compris la CCH (médicaments, administration et visites), ont été obtenus à partir d’essais cliniques et d’une étude en vie réelle. Les coûts de la FSC (type d’admission, visites, salle d’opération, réadmissions, tests, médicaments et les coûts de rééducation) ont été recueillis à travers d’une étude locale rétrospective observationnelle. Les coûts unitaires ont été obtenus à partir de bases de données locales (e-SALUD et BOT). Les résultats sont présentés du point de vue du système national de santé (SNS) pour les trois prochaines années. Nous avons considéré 5100 fasciectomies par an (+5 % par an) et que 20, 30 et 40 % d’entre elles seraient substituées par une CCH chaque année. En outre, 10, 15 et 20 % des patients non traités atteints par la MD devraient bénéficier de la CCH. Toutes les données ont été validées par un panel d’experts. Une analyse de sensibilité a été effectuée avec les variables principales. Le coût moyen de la FSC fut de 2250 € (72 % de patients hospitalisés), allant de 1703 € à 2467 € pour les
patients ambulatoires et les hospitalisés respectivement. Le coût moyen de la CCH fut de 1220 € (considérant 1,5 flacon/rayon traité et quatre visites) et peut diminuer jusqu’à 898 € (1,1 flacon/rayon et trois visites). L’impact budgétaire cumulé des trois années est estimé à 45 971 € (−2993, 3870 K€). Selon cette étude, l’inclusion de la CCH produit un impact budgétaire cumulé à trois ans de 45,971 € (−2993, 3870 K€) pour le SNS espagnol.
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Mots clés : Maladie de Dupuytren ; Analyse de réduction des coûts ; Impact budgétaire ; Fasciectomie ; Collagénase de Clostridium histolyticum

1. Introduction

Dupuytren’s disease (DD) is a fibroproliferative condition of the palmar fascia that results in thickening and shortening of the normal fibrous bands in the hand and fingers. Although benign, the disease can cause disabling, progressive digital contractures [1], which can severely limit hand function and have a negative impact on the patient’s health-related quality of life [2,3].

The estimated global prevalence among the general population is 3 to 6%, being more prevalent in Scandinavian and people of Western European descent [4–6]. DD is more common in men than in women, increases in incidence with advancing age [4,5,7]. Quintana Guitian estimated through a case control study conducted in Zaragoza (Spain) that the incidence among people older than 75 is up to 18% [8]. It has also been associated with smoking [5,9], alcoholism [5,9,10], diabetes [5,11], epilepsy [12] and human immunodeficiency virus infection [13].

Historically, the standard of care and most effective treatment for DD has been surgery [2,14]. Current surgical treatments include fasciectomy (FSC) and fasciotomy. FSC is the surgical procedure for partial or complete removal of the cord; it is used to treat the mildest to most severe forms of DC and has been shown to be associated with complications in a considerable number of cases. Convalescence can be prolonged, with long rehabilitation periods or extensive hand therapy sessions, and disease extension or recurrence may occur in many patients [15–18]. Classic fasciotomy involves sectioning the cords with a scalpel. Using needles to puncture the diseased cord is an alternative treatment popularized by French rheumatologists with less morbidity and moderate success in mild cases, but it has a recurrence rate greater than 60% at midterm follow-up in more severe cases [18].

FSC remains the gold standard and most widely used procedure to treat DC [18,19], 88% in France [20], 91% between April 2003 and March 2007 in England, 71% from April 2007 to March 2008 in England [21], 95% in Erlangen (Germany) [22] and 97% in Spain [23].

According to the Ministry of Health, 5100 fasciectomies were performed in 2009 in Spain [24]. Recently, a study has been conducted in Spain in order to estimate costs and the utilization of health care resources associated with FSC for DD performed under usual medical practice. This study concluded that total direct costs oscillate between € 2450 for inpatients and € 1703 for outpatients ($< 0.001), with € 2250 being the average cost for usual medical practice [2]. Other studies across Europe using retrospective medical records and expert opinion found that the average cost per patient treated in England ranged from £ 2736 (day-case FSC) to £ 9210 (day-case revision digital FSC) [21]; in France (where patients were mostly treated by FSC) from € 707 in private hospitals to € 1795 in public hospitals [20]; in Portugal, the average direct cost per patient treated by FSC was € 2323 increasing to € 3441 when indirect costs were taken into consideration [25].

Injectable collagenase Clodiostium histolyticum (CCH), Xiapex®, is the first licensed nonsurgical treatment for adult patients with Dupuytren’s contracture with a palpable cord [26]. The ex-factory prices (VAT included) for Spain, England, France, and Portugal were € 725, € 796.68, € 725, and € 670.65 respectively. The efficacy of CCH in correcting the DC has been demonstrated in clinical trials [2,15,27]. CCH lyses collagen and leads to disruption of the contracted cord [2,28].

Healthcare decisions should be based not only on efficacy and safety data, but also on economic considerations [29]. It is appropriate to perform a budget impact analysis (BIA) that values the introduction of new alternatives in DD [30].

The purpose of this study was to estimate the BIA of CCH vs. FSC (FSC), as it is the most common procedure in Spain [18,19,23] for the treatment of Dupuytren’s contracture (DC) following a cost minimization approach in Spain.

2. Methods

This cost minimization analysis is a tool used to compare the costs of FSC, the traditional surgical treatment [31] with a new pharmacological treatment, the collagenase injection, both performed in Spanish adults with DC. A 3-year BIA was then conducted.

2.1. Effectiveness

Crean et al. presented results of efficacy and safety for DC in European patients through a structured review of published studies. Concerning FSC, the proportion of patients with a 100% correction in contracture angle ranged from 61 to 97%, the mean improvement in contracture angle ranged from 58 to 79% and cases judged excellent/good ranged from 63 to 90% [18].

Collagenase injections reduced the contracture of the metacarpophalangeal (MP) and proximal interphalangeal (PIP) joints to 0 to 5° of full extension in 67% [2,15,27]. In open label trials, the response rate ranged from 88% to 100% [31]. Anesthesia is not mandatory during the injection into the affected cord; the treated joint is manipulated to attempt cord rupture the next day [2].

We found that the results extracted from the clinical trials and the review showed similar efficacy for both techniques. In addition, “success” measurement had a different rationale for FSC and CCH. We found no significant differences for both treatments and thus assumed equal efficacy. As a common efficacy denominator would have been necessary for conducting a cost-effectiveness study, we decided to conduct a cost minimization analysis.

2.2. Costs

FSC data was obtained through a retrospective, observational, local study that included 123 patients treated by selective FSC in three public hospitals. Costs of the surgery (100% selective FSC technique), hospital admissions (inpatients and outpatients), outpatient follow-up visits, emergency visits, readmissions, tests, drugs and rehabilitation sessions were included.

CCH costs included drug acquisition, administration of injection in an outpatient setting and outpatient follow-up visits. Unitary costs are shown in Table 1. Consumption of CCH per joint and per patient were assumed to be similar to those observed in the main clinical trials [2,15,27] with referral to a real-life study conducted in the USA [32] with more than a year of experience, and an expert panel with extensive clinical experience in the treatment of DC in Spain. An average of 1.5 was injected per treated joint.

Unit costs were obtained from local database e-SALUD for procedures, visits, and tests [33] and BOT for drug ex-factory price [34]. A 7.5% discount to the CCH drug price was applied due to the mandatory rebate imposed by the Spanish Ministry of Health since May 2010 [35]. Results were presented as € 2011 from the NHS perspective per year.

2.3. Budgetary impact analysis

To conduct a 3-year BIA, we assumed 5100 fasciectomy were performed per year [24] with a 5% annual increase. The market share estimations versus FSC were 20%, 30% and 40% of CCH utilization annually. As it is, not all the patients with DC are appropriate candidates for surgery because of contraindications to anesthesia or due to possible intraoperative complications [15,36]. So an additional 10%, 20% and 30% of untreated (or untreatable) but DC diagnosed patients were expected to receive CCH as well. All data was validated through an expert panel.

2.4. Sensitivity analysis

In order to include all the possible scenarios, a sensitivity analysis was performed with the main variables.

The typical FSC case presented an average cost of € 2250 per patient corresponding to 72% of inpatients (mean stay of 1.5 days), out of which 88% conducted at least one test (mean 4.9 tests), 100% had follow-up outpatient visits (mean 4.9 visits), 27% underwent rehabilitation (mean 6.6 sessions) and one joint was treated per procedure. Costs varied with hospital admissions from € 1703 if 0% inpatients to € 2467 if 100% inpatients and according to the number of joints treated per surgery as shown in Table 2.

DC usually affects both hands and more than one joint per subject. Amillo Garayo et al. reported 70% of bilateral DD and 2.1 affected joints per patient [37] in Spain. It is not uncommon to treat more than one joint per surgery (when the same hand is involved), so another scenario was to treat an average of 1.5 joints per FSC.

The typical CCH case included the 92.5% of the hospital drug acquisition cost [35], an average of 1.5 injections per joint rate (as described in the clinical trials [2,15] and the XIapeX® summary of product characteristics [26]), two office visits (injection and manipulation), two outpatient follow-up visits and no rehabilitation sessions or extensive hand therapy. The additional scenarios were based on a real world setting experience carried out in the USA where information about 501 patients treated with collagenase was reported [32]. The study concluded that the injection per joint rate was 1.08 (28% lower than what was observed in CORD-I [15] and CORD-II®; P < 0.05) and the average number of outpatient visits (including injection, manipulation and follow-up) was 2.9 to achieve clinical rates similar to clinical trials [32].

| Table 2 |
| Costs per alternative by assumptions. |

<table>
<thead>
<tr>
<th>Assumptions</th>
<th>Fasciectomy</th>
<th>CCH</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 injection</td>
<td>4 office visits for injection</td>
<td>€ 951</td>
</tr>
<tr>
<td>per joint rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.5 injection</td>
<td>3 office visits for injection</td>
<td>€ 1166</td>
</tr>
<tr>
<td>per joint rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.1 injection</td>
<td>3 office visits for injection</td>
<td>€ 898</td>
</tr>
<tr>
<td>per joint rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0% inpatients</td>
<td>1 joint per patient treated</td>
<td>€ 1703</td>
</tr>
<tr>
<td>100% inpatients</td>
<td>1 joint per patient treated</td>
<td>€ 2467</td>
</tr>
<tr>
<td>0% inpatients</td>
<td>2.1 joint per patient treated</td>
<td>€ 1135</td>
</tr>
<tr>
<td>72% inpatients</td>
<td>2.1 joint per patient treated</td>
<td>€ 1500</td>
</tr>
<tr>
<td>100% inpatients</td>
<td>2.1 joint per patient treated</td>
<td>€ 1645</td>
</tr>
</tbody>
</table>

CCH: collagenase Clostridium histolyticum.
3. Results

The average cost of FSC was € 2250 (72% inpatients), with € 1703 for outpatients and € 2467 for inpatients. The main cost (> 80%) was related to the surgery and the hospital admission. The average CCH cost was € 1220 (1.5 vial per injection and four visits). Cost distributions are represented in Fig. 1. In the typical CCH case, treatment costs € 1030 less than FSC.

Considering that 5100 FSC were performed in Spain annually, the current cost of DD (before CCH was approved) amounted to € 11,475 per year.

For the next 3 years, with a market share of 20, 30 and 40% versus FSC and a 5% annual increase of patients, the budgetary impact should be € 1104 for 2012; € 1734 for 2013 and € 2417 for 2014. In total the cumulative impact for the following 3 years should be € 5255.

When we consider an additional 10, 20 and 30% of untreated (or untreatable) but DC diagnosed patients and a 5% annual increase, the total budgetary impact should increase to € 45,971 at national level. Results for the typical case are presented in Table 3.

The 3-year total budgetary impact was positive for savings for a joint treated by surgery and all cases were inpatients, with a 72% of inpatients except for the base case (1.5 injection/joint and four office visits). When for FSC all were outpatients, for all the cases the 3-year total BI remained with expenses (€ 1092; 5731).

![Fig. 1. Costs distribution per alternative. Fasciectomy hospital admission included inpatient/outpatient, readmission, emergency, drugs and test during hospital stay.](image)

All the possible combinations of the sensitivity analysis are presented in Table 4.

4. Discussion

This study is the first attempt to compare the costs of FSC, the most common procedure in Spain [18,19,23] and collagenase injection, and to estimate the budget impact of CCH vs. FSC for the treatment of Dupuytren’s contracture in Spain using a cost minimization approach. The analysis is very complete, as it has been done for multiple scenarios in order to cover all the possible procedures performed in all the hospitals across Spain.

Table 3
Results of the base case budgetary impact.

<table>
<thead>
<tr>
<th></th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasciectomy</td>
<td>9,639,000</td>
<td>8,835,750</td>
<td>7,917,750</td>
<td>26,392,500</td>
</tr>
<tr>
<td>CCH</td>
<td>2,484,198</td>
<td>3,819,591</td>
<td>5,217,181</td>
<td>11,520,971</td>
</tr>
<tr>
<td>Budgetary impact</td>
<td>12,123,198</td>
<td>12,655,341</td>
<td>13,134,931</td>
<td>37,913,471</td>
</tr>
<tr>
<td>Without CCH</td>
<td>12,048,750</td>
<td>12,622,500</td>
<td>13,196,250</td>
<td>37,867,500</td>
</tr>
<tr>
<td>Without CCH (only substitution)</td>
<td>−1,103,625</td>
<td>−1,734,268</td>
<td>−2,417,465</td>
<td>−5,255,359</td>
</tr>
<tr>
<td>Without CCH (only substitution + untreated patients)</td>
<td>74,448</td>
<td>32,841</td>
<td>−61,319</td>
<td>45,971</td>
</tr>
</tbody>
</table>

Market share (%)

<table>
<thead>
<tr>
<th></th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCH (costs)</td>
<td>1220</td>
<td>20</td>
<td>30</td>
<td>40</td>
</tr>
<tr>
<td>Fasciectomy (costs)</td>
<td>2250</td>
<td>80</td>
<td>70</td>
<td>60</td>
</tr>
<tr>
<td>Untreated patients with DD (#)</td>
<td>9660</td>
<td>10</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td>Surgery/year (#)</td>
<td>5100</td>
<td>5</td>
<td>10</td>
<td>15</td>
</tr>
</tbody>
</table>

All the costs were given in € 2011. Substitution: related to the market share taken from fasciectomies; substitution + untreated patients: refers to the market share taken from fasciectomies + market share relative to the untreated patients. CCH: collagenase Clostridium histolyticum; DD: Dupuytren’s disease.

Table 4
Sensitivity analysis results of the budgetary impact.

<table>
<thead>
<tr>
<th></th>
<th>1.5 IPJR</th>
<th>1.1 IPJR</th>
<th>1.5 IPJR</th>
<th>1.1 IPJR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4 OV</td>
<td>4 OV</td>
<td>3 OV</td>
<td>3 OV</td>
</tr>
<tr>
<td>Fasciectomy Assumptions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>72% inpatient, 1 joint/surgery</td>
<td>46</td>
<td>−2488</td>
<td>−0458</td>
<td>−2993</td>
</tr>
<tr>
<td>72% inpatient, 1.5 joint/surgery</td>
<td>3870</td>
<td>1336</td>
<td>3366</td>
<td>832</td>
</tr>
<tr>
<td>0% inpatient, 1 joint/surgery</td>
<td>4603</td>
<td>1680</td>
<td>4021</td>
<td>1098</td>
</tr>
<tr>
<td>0% inpatient, 1.5 joint/surgery</td>
<td>5731</td>
<td>3196</td>
<td>5226</td>
<td>2692</td>
</tr>
<tr>
<td>100% inpatient, 1 joint/surgery</td>
<td>−1061</td>
<td>−3595</td>
<td>−1565</td>
<td>−4099</td>
</tr>
<tr>
<td>100% inpatient, 1.5 joint/surgery</td>
<td>3133</td>
<td>599</td>
<td>2628</td>
<td>95</td>
</tr>
</tbody>
</table>

All the costs were given as × € 1000; IPJR: injection per joint rate; OV: office visit; CCH: collagenase Clostridium histolyticum.
There are other surgical procedures to treat DC, such as fasciotomy as well as needle fasciotomy (NF). Fasciotomy had a similar outcome to FSC, with a mean improvement in contraction ranging from 46 to 88%, but a higher average recurrence rate of 62% in a mean time of about 4 years [18]. NF is performed under local anaesthetic as a day-case or an outpatient’s procedure. This is obviously less costly than FSC. The 2005 French tariff for NF performed during an outpatient visit for one side is € 37 and € 65 for both sides [20]. Fasciotomy costs in England amounted to 630,986 £, but represented only a 1.5% of the total surgical procedure costs [21]. So, if similar efficacy was assumed and costs of FSC, NF, and CCH were compared in a Spanish context, the least expensive treatment would be NF, followed by CCH and then FSC. Nevertheless, this study focuses on the comparison between FSC and CCH only since FSC remains the gold standard and the most widely-used procedure for DC treatment [18,19,31]; in fact, FSC constituted 97% of all Spanish surgeries [23].

Surgical FSC costs were obtained from a local retrospective, observational, study conducted on 123 patients treated by FSC in three tertiary hospitals in Madrid using routine medical practice for DC5. The typical case was chosen according to the results of the study; that was 72% inpatients for FSC surgery. Not all hospitals across the country followed the same protocols for surgical admission, so we decided to modify the percentage of inpatients, as it is the most important cost after the surgery itself. The sensitivity analysis included both outpatients 0% and 100% inpatients.

For CCH utilization, actually there was no local information about healthcare utilization, so we decided to follow the Xiapex® summary of product characteristics [26] for the typical case with 1.5 injection per joint and four office visits and ranged it according to real life data even if those data were not local ones [32]. The trend in the countries where CCH is already in use in real life, as Spain, is similar, probably due to the anesthesia used at manipulation, the use of patient-related outcome evaluation, and the progression of the learning curve [32]. In some patients, full release of the two cords (Y type) was obtained with only one injection between both joints, the injection per joint rate was thus lower than 1, and costs could be further reduced.

Chen et al. set up a specific survey utility to run up a cost-utility model in the USA that indicated that open partial FSC is not cost-effective, whereas NF is cost-effective if the success rate is high, collagenase injection is cost-effective when priced under $ 945 for a threshold pricing of $ 50,000/QALY [31]. Currently, there is no local specific scale evaluating quality of life for the Spanish population for this disease, thus we were not able to compare with these results.

Our study showed results very similar to those observed in the Portuguese cost minimization analysis, where CCH direct costs were € 1569 and € 2323 for FSC. They concluded that the adoption of CCH as an alternative intervention to FSC may result in savings as much as € 491,243 per year [25]. Those “savings” mainly corresponded to the non-hospitalization of the patients treated with the collagenase, so they may also apply to NF patients.

A 3-year cumulative BIA of € 45,971 at the national level may be attained by the Spanish NHS. In addition, the trend of the BIA was to reduce costs over the years; it even showed some saving from the 3rd year (€ 61,319) that may balance the expenses of the first two years. This is due to untreated patients who were affected but may not have had joint affection severe enough to warrant surgery. More than 85% of patients treated by FSC presented at least one contracture classified as stage I on the Tubiana scale [38]. During surgery more than a joint of the same hand could be treated, 43% of the patients that underwent FSC in France had two fingers or more [20]. In this study, the possibility to have more than one joint treated has been also taken into account in the sensitivity analysis. Not all patients diagnosed with CD are actually treated; it has been estimated that surgery was performed in around only 35% of those subjects. Surgeons usually preferred patients with only one contracture or ‘simpler disease’ for CCH utilization. Thus, patients with one affected joint that would have been left untreated were actually treated with the collagenase. Those were included in the BIA.

As we previously mentioned, “success” was not measured with the same rationale for FSC and CCH, and this could be perceived as a limitation; nevertheless, clinicians assumed both techniques as equivalent in terms of efficacy. In addition, a Portuguese study adopted a cost-minimization approach after considering similar effectiveness for both treatments [25].

Another limitation of the study was that this analysis only considered direct costs, and around 36% of DD patients were active members of the population7. After FSC, as other surgeries, recuperation is long and requires substantial postoperative hand therapy, restricting patients’ return to work or resuming daily activities. In contrast, hand therapy is not required after treatment with injectable CCH [2]. Those costs will probably be added to the costs of surgical treatment versus collagenase.

It is important to add that FSC may causes complications in 20% of cases, mostly mild and prolong the recovery period 2 to 3 weeks [39]. According to the review carried out by Crean et al. on the efficacy and safety of FSC and fasciotomy in Europe for patients with Dupuytren’s contracture, recurrence is estimated as an average of 39% in FSC and 62% in fasciotomy after 4 years [18]. This study did not take into account the use of resources due to postoperative complications or recurrence, other than emergency visits and re-admissions, which would increase overall costs significantly.

Surgery for DC is often successful; nevertheless a surgical approach is not always the best option for all patients. CCH is a minimally invasive, effective and well tolerated alternative for DD patients that provides the benefit of allowing physicians and patients to obtain similar results in terms of effectiveness, with the advantage of no physiotherapy needed, and, in general, a prompt recuperation [27]. CCH had even been shown to be equally effective in both patients treated for the first time and patients with recurring DC [40].

5. Conclusion

The study suggests that compared to FSC, CCH is cost saving (€ 2250 vs. € 1220). The adoption of CCH as an
alternative to FSC, and considering that more diagnosed patients will actually be treated, the 3-year cumulative budgetary impact may result in a €45,971 (K€−2.993, 3.870) positive balance for the NHS.

Disclosure of interest

This study was sponsored by Pfizer Spain. Marina de Salas-Cansado is employee of Pfizer Spain. The rest of the authors declare that they have no conflicts of interest concerning this article.

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Références

[34] Catálogo del Consejo General de Colegiós Farmaceúticos de España 2011.