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Title: Development of a population-based cost-effectiveness model of chronic graft versus host disease in Spain

Article Type: Original Article - PEHP

Keywords: Cost-effectiveness; chronic graft host disease; extra-corporeal photopheresis

Corresponding Author: Mr Carlos Crespo, MHecon, Mstat, BSC

Corresponding Author's Institution: Oblikue Consulting

First Author: Carlos Crespo, MHecon, Mstat, BSC

Order of Authors: Carlos Crespo, MHecon, Mstat, BSC; José A Perez-Simon; José M Rodríguez; Jordi Sierra; Max Brosa

Abstract: Background: Chronic graft-versus-host disease (cGvHD) is the leading cause of late non-relapse mortality (transplant-related mortality) after hematopoietic stem cell transplant. Given that there are a wide range of treatment options for cGvHD, assessment of the associated costs and efficacy can help clinicians and healthcare providers allocate healthcare resources more efficiently.
Objective: The purpose of this study was to assess the cost-effectiveness of extra-corporeal photopheresis (ECP) vs. rituximab (Rmb) and vs. imatinib (Imt) in patients with cGvHD at five years from the perspective of the Spanish National Health System.
Patients and methods: The model assessed the incremental cost-effectiveness/utility ratio of ECP versus Rmb or Imt for 1,000 hypothetical patients through microsimulation cost-effectiveness techniques. Model probabilities were obtained from the literature. Treatment pathways and adverse events were evaluated taking clinical opinion and published reports into consideration. Local data on costs (2010 Euros) and health care resources utilization were validated by the clinical authors. Probabilistic sensitivity analyses were used to assess the robustness of the model.
Results: The greater efficacy of ECP resulted in a gain of 0.011-0.024 quality-adjusted life years (QALY) in the first year and 0.062-0.094 at year five compared to Rmb or Imt. The results showed that the higher acquisition cost of ECP vs. Imt was compensated for at 9 months by greater efficacy and vs. Rmb was partially compensated for (517€ year 5). After 9 months, ECP was dominant vs. Imt. The incremental cost-effectiveness ratio of ECP vs. Rmb was 29,646€ per LY gained and 24,442 € per QALY gained at year 2.5. Probabilistic sensitivity analysis confirmed the results. The main study limitation was that to assess relative treatment effects, only small studies were available for indirect comparison.
Conclusion: ECP as a third-line therapy for cGvHD is a more cost-effective strategy than Rmb or Imt.

Dear Editor,

We would like to thank you and the reviewers for your comments. We have revised and improved the paper by incorporating the comments as far as possible (see attached file –track changes). The revised manuscript has been read and approved by all authors.

Carlos Crespo
University of Barcelona
Facultat Biología
Av. Diagonal, 645
08028 Barcelona, Spain
Mail: ccrespo@ub.edu

Oblikue Consulting
C/ Josep Irla i Bosh, 5-7, 1ª planta 08034
Barcelona, Spain.
Tel.: +34 932 521 377. Fax: +34 932 051 447.
Mail: carlos.crespo@oblikue.com

***Detailed Response to Reviewers**

Editor's Notes:

1) In the Introduction, please include some context for the fact that this study was conducted in Spain - e.g., prevalence of disease, utilization and expenditure rates of the treatments, reimbursement system, etc.?

Authors' comments: We have now added some comments on the Spanish context of the disease and the Spanish health system. However, as there are only around 200 patients susceptible to cGvHD in Spain annually, data are limited.
Page:3 Line: 4-5
Page:3 Line:12-14
Page:5 Line:10-12

2) In the Introduction, ECP was discussed as a third-line therapy but little background was provided on the other treatments of interests (i.e., Rmb and Imt).

Author's comments: We now include a brief explanation of the use of Rituximab and Imatinib
Page:4 Line:20-30

3) The rationale for CEA in the first paragraph of Patients and Methods seems more appropriate in the Introduction to discuss the rationale for this study.

Authors' comments: This section has now been moved to the Introduction as suggested.
Page:5 Line: 4-7

4) The perspective of the CEA should be presented in the Abstract.

Author's comments: We now state in the Abstract that the study was carried out from the perspective of the Spanish National Health System.
Page:1 Line:14

5) There are numerous grammatical errors/typos throughout the paper that should be carefully addressed during the revision stage perhaps by a native English writer - just three examples: "Incremental cost per Life year (LY) gained and incremental cost per Quality Adjusted Life year (QALY) gained in comparison with the other options" is a fragment and contains improper capitalizations. And "Both future costs and effects where discounted at 3% as indicated by the Spanish guidelines..." should contain "were" and not "where."

Authors' comments: The entire revised manuscript has been reviewed by a native English writer. As there were various errors, the changes are shown in the Track Changes version but are not indicated here by line and page numbers.

Finally, the sentence - "The model follows the patients until death or when the five year time horizon was reached" is missing a clause in the end stating whichever of the two events had occur first.

Authors' comments: This sentence has been changed and corrected.
Page:6 Line:13-14

6) Terming "experts" implies that a level of external validity was employed in the study design process and that the experts have no role in the study other than to evaluate the process/findings. While the authors are experts in their own rights, I believe that if the experts are themselves authors, the manuscript should term them as "authors" and not as "experts" to avoid unintended implications of impartiality.

Authors' comments: We understand the comment. To avoid doubt, we now distinguish between clinical authors and experts, when necessary.
Page:1 Line:18
Page:6 Line:25
Page:7 Line:27-30
Page:8 Line:2, 10-11

7) It is unclear whether the experts evaluating the structured questionnaire were the same as those who were termed "clinical experts." If not, who were these clinical experts, their expertise/credentials, and whether they were authors of the paper. If yes, they should be termed "authors" and not "clinical experts" for the same reasons I have provided above.

Authors' comments: The opinions were those of the clinical authors or clinical experts according to the case, as stated in point 6.
Page:1 Line:18
Page:6 Line:25
Page:7 Line:27-30
Page:8 Line:2, 10-11

8) If possible, the employment of sensitivity analysis should be noted in the Abstract to indicate that consistent findings were produced.

Authors' comments: We now state in the Abstract that sensitivity analysis was used and that it confirmed the results.
Page:1 Line:20-21, 27-28

9) This sentence is confusing to me: "These models simulate what occurs in larger populations in order to reach conclusions applicable to larger groups."

Authors' comments: This sentence has been rewritten.
Page:6 Line: 20-24

10) "Probabilistic Sensitivity Analysis", "The Cost-effectiveness acceptability", and "Lung" are just three examples of inappropriate capitalization throughout the paper. A native English writer is recommended to help revise this paper.

Authors' comments: The entire revised manuscript has been reviewed by a native English writer. As there were various errors, the changes are shown in the Track Changes version but are not indicated here by line and page numbers.

11) In the Discussion section, the first three sentences should be written more scientifically without the colloquial tone ("more and more limited") or unnecessary superlative ("utmost importance").

Authors' comments: These sentences have been rewritten.
Page:12 Line:27-30

Variation in care can cause differences in expenditures but the sentence is not within context.

Authors' comments: We have now provided context using the example of the situation studied.
Page:13 Line:2-4

12) The following sentence is needs to be revised more thoughtfully - "Our conclusions must be considered under certain perspective because ECP regimen and reimbursement system may vary among countries, and this is a fact that makes it necessary to adapt these results for each country." While the scope of inference of any CEA should be carefully considered, the authors should address elements of CEAs that are more influential than others that will allow for greater generalizability for these treatments for cGVHD from Spain to other countries.

Authors' comments: This paragraph has now been rewritten and more information provided.
Page:13 Line:20-23

13) Citation is needed for the following sentence: "A recent Spanish study, for instance, evaluated posaconazole vs. fluconazole cost-effectiveness in preventing invasive fungal infections in allogeneic hematopoietic SCT patients with GVHD."

Authors' comments: This sentence now includes a reference.
Page:14 Line:1

Furthermore, a more balanced discussion is warranted in the paragraph that compares the pros and cons of using Markov models vs. the microsimulation technique used in this study.

Authors' comments: We now include more discussion of the pros and cons of using Markov models and microsimulation techniques.
Page:14 Line:7-18

And a rationale for choosing the microsimulation technique and the details/history of its application should be elaborated more earlier in the Methods section when the method is introduced to get the readers acquainted with the technique early on.

Authors' comments: We now include, in the Patients and Methods section a more detailed description of the microsimulation technique which we have put earlier in the section.
Page:5 Line:17
Page:6 Line:16-30
Page:7 Line:1-11

14) In the Conclusion's first paragraph, the sentence - "...our study results demonstrated that..." - should be specified as "...our microsimulation study results provide evidence that..."

Authors' comments: We have made the proposed change
Page:15 Line:22-25

Furthermore, the second paragraph currently is a standalone, dangling thought but needs to be incorporated into the first paragraph and rewritten as a concluding thought for the paper.

Authors' comments: The paragraph to which you refer has now been included in the Discussion and rewritten.
Page:15 Line:7-13

Reviewer #1:

1. Please include a brief mention of limitations in the abstract.

Authors' comments: This has been done.
Page:1 Line:28-29

2. May be useful to include the distinctive clinical manifestations of cGVHD in conjunction with lines 28-30, page 2.

Authors' comments: We now describe the main clinical manifestations of cGvHD
Page:3 Line:21-25

3. Whilst, page 2.

Authors' comments: This has been corrected
Page:3 Line:30

4. Line 42, page 2: Should this be cGVHD?

Authors' comments: We now refer to cGvHD throughout the manuscript
Page:4 Line:1

5. The background describing chronic graft-vs-host disease (cGVHD) is well written.

6. Line 2, page 5: pooled analysis.

Authors' comments: This has been corrected
Page:7 Line:27

7. Lower case for "cost-effectiveness", line 55, page 7.

Authors' comments: This has now been corrected.
Page:11 Line:5

8. Please be consistent with abbreviations. See "cGvHD" in line 7, page 8.
Authors' comments: We now refer to cGvHD throughout the manuscript

9. Please revise, "talking about the published information," line 18, page 8, to less colloquial language.

Authors' comments: This has been rewritten. The manuscript has been reviewed by a native English writer.
Page:11 Line:18

10. Change, "3th year," line 6, page 9.

Authors' comments: This has been changed and unified.
Page:12 Line:16-18

11. First para in Discussion not necessary. Would be more relevant to provide greater context to the use of microsimulations and how this serves to advance the economic modeling

Authors' comments: The first part of the Discussion has been modified to illustrate the context of the present study. More discussion is included later in the Discussion on the pros and cons of using microsimulation or Markow models.

Page:5 Line:17
Page:6 Line:16-30
Page:7 Line:1-11
Page:15 Line:22-25

12. Please include in the discussion the deficiencies of a microsimulation when compared to a markov model rather than the generic limitations of a cost-effectiveness study on page 10.

Authors' comments: As stated above, we now include more discussion of the pros and cons of the different models.

Page:5 Line:17
Page:6 Line:16-30
Page:7 Line:1-11
Page:15 Line:22-25

Original Article

Development of a population-based cost-effectiveness model of chronic graft versus host disease in Spain

Running title: Cost-effectiveness of chronic graft versus host disease in Spain

Crespo C[1,2], Pérez-Simón J[3], Rodríguez JM[4], Sierra J[5], Brosa M[2]

[1] Statistics Department. University of Barcelona. Barcelona, Spain. Av. Diagonal, 645 08028 Barcelona.

[2] Oblikue Consulting. Barcelona, Spain. C/ Josep Irla i Bosh, 5-7, 1ª planta 08034 Barcelona.

[3] Haematology Service. Instituto de Biomedicina de Sevilla (IBIS) Hospital Universitario Virgen del Rocío/CSIC/ Universidad de Sevilla, Spain. Campus Hospital Universitario Virgen del Rocío Avda. Manuel Siurot, s/n. 41013, Sevilla.

[4] HE&R Department, Director EMEA Therakos (Johnson & Johnson Company). Madrid, Spain. Paseo de las Doce Estrellas, 5, 28042, Madrid.

[5] Haematology Service. Hospital de la Santa Creu i Sant Pau. Barcelona, Spain. C/ Sant Antoni Maria Claret, 167 08025 Barcelona.

Corresponding author:

Carlos Crespo. C/ Josep Irla i Bosh, 5-7, 1ª planta 08034 Barcelona, Spain. Tel.: +34 932 521 377. Fax: +34 932 051 447. Mail: carlos.crespo@oblikue.com

Development of a population-based cost-effectiveness model of chronic graft versus host disease in Spain

Running title: Cost-effectiveness of cChronic graft versus host disease in Spain

Abstract

Background: Chronic graft-versus-host disease (cGVHDcGvHD) is the leading cause of late non-relapse mortality (transplant-related mortality) after hematopoietic stem cell transplant. It deleteriously affects the quality of life in surviving patients who have otherwise have been cured of their underlying disease. Given that there are ae existence of a wide range of treatment options for cGVHDcGvHD, assessment of the associated costs and efficacy associated can help clinicians and healthcare providers to allocate healthcare resources more efficientlyin a more efficient way.

Objective: The purpose of this study was to assess the cost-effectiveness of extra-corporeal photopheresis (ECP) vsvs. rRituximab (Rmb) and vsvs., iImatinib (Imt) in patients with cGVHDcGvHD at five years from the perspective of the Spanish National Health Systemin Spain.

Patients and methods: The model assessed the incremental cost-effectiveness/utility ratio of ECP versus Rmb or Imt for 1,000 hypothetical patients through microsimulation cost-effectiveness techniques. Model probabilities were obtained from the literature. Treatment pathways and adverse events were evaluated taking expertclinical opinion and published reports into consideration expert opinion (as well as publications and studies). Local data on costs (2010 Euros 2010) and health care resources utilization use were also validated by the clinical expertsauthors. Probabilistic sensitivity analyses were used to assess the robustness of the model.

Results: The greater higher efficacy of ECP resulted in a leads to a gain of 0.011–0.024 qQuality-Aadjusted lLife yYears (QALY) in the first year and 0.062-0.094 at year five compared to Rmb or Imt. The rResults showed that the higher acquisition cost of ECP vsvs. Imt was compensated for at 9 months by greater higher efficacy and vsvs. Rmb was partially compensated for (517€ year 5). After 9 months, ECP was dominant vsvs. Imt. The incremental cost-effectiveness ratio of ECP vvs.ersus Rmb was 29,646€ per LY gained and 24,442 € per QALY gained at year 2.5. Probabilistic sensitivity analysis confirmed the results. The main study limitation was that to assess relative treatment effects, only small studies were available for indirect comparison.

Conclusion: ECP as a third-line therapy for cGVHDcGvHD is a more cost-effective strategy than Rmb or Imt.

Key words: Cost-effectiveness, chronic graft, host disease, extra-corporeal photopheresis.

Introduction

In Spain, between 2,000 and 2,500 hematopoietic stem cell transplants are carried out annually, a maximum rate of 54.~~,~~14 per million inhabitants, of which 34% are allogeneic~~)~~[1]. Chronic graft-versus-host disease (~~cGVHD~~cGvHD) is the leading cause of late non-relapse mortality (transplant-related mortality) after hematopoietic stem cell transplant. It deleteriously affects the quality of life in surviving patients who have otherwise ~~have~~ been cured of their underlying disease[~~1,~~ 2,3]. ~~cGVHD~~cGvHD may have ~~can lead to~~ debilitating consequences resulting from profound chronic immune suppression leading to recurrent or life-threatening infections[~~3~~4]. ~~cGVHD~~cGvHD occurs in at least 30% to 50% of recipients of transplants from human leukocyte antigen matched siblings, and in at least 60% to 70% of recipients from unrelated donors[~~4~~5]. A Spanish study found a cumulated incidence of mild, moderate or severe cGvHD of 29%, 42% and 28%, respectively, in patients undergoing allogeneic hematopoietic stem cell transplant using peripheral blood from related donors[6].

The diagnosis and staging working group of the National Institutes of Health Consensus Development Project on ~~cGVHD~~cGvHD proposed standard criteria for the diagnosis, organ scoring and global assessment of ~~cGVHD~~cGvHD severity[~~1~~2, ~~7~~5]. Th~~us, th~~e diagnosis of ~~cGVHD~~cGvHD requires the presence of at least one clinical diagnostic ~~clinical~~ sign of ~~cGVHD~~cGvHD or ~~the presence of a~~at least one distinctive clinical manifestation confirmed by biopsy or other relevant tests. cGVHD may be restricted to a single organ system, but ~~usually~~ several organs are usually involved. ~~-~~Clinical features range from edema, erythematous rash, mucositis, diarrhea, and elevated transaminases, to more fibrotic and chronic manifestations such as sclerotic, lichen-planus skin changes, fasciitis, sicca syndrome, joint contractures, esophageal strictures, and bronchiolitis obliterans[7]. T~~Furthermore, t~~he proposed global assessment of severity (mild, moderate, or severe) is derived by combining organ and site-specific scores[~~1~~2, ~~5~~7].

Prednisone, together with a calcineurin inhibitor ~~(CI),~~ is considered the standard regimen for the primary treatment of ~~cGVHD~~cGvHD[~~6~~8]. ~~Whilst~~ While half of the patients respond to first-line treatment, the prognosis of steroid~~-~~-refractory ~~cGVHD~~cGvHD remains poor[~~7~~9]. There is no standard approach to treat

refractory ~~GVHD~~cGvHD, although there is a long list of immunosuppressive drugs and other agents for salvage therapy. I~~Thus, different i~~mmunosuppressive treatments that inhibit T cell activation, proliferation or survival include~~are available such as~~ mycophenolate mofetil, daclizumab, sirolimus (rapamycin), extra-corporeal photopheresis (ECP) and pentostatin (deoxycoformycin) [8,10]. In addition, new strategies such as etanercept, rituximab (Rmb) and ~~or~~ imatinib (Imt) have also been evaluated[6,8, 10,8]. However, responses to immunosuppressive drugs are often partial, and patients continue to experience disease symptoms ~~of the disease~~ that can significantly impair the quality of life.

ECP is a therapeutic approach based on the biological effect of liquid 8-methoxypsoralen (8-MOP) and ultraviolet light A on mononuclear cells collected by apheresis, and reinfused into the patient[8,10]. This therapy allows ~~patient~~ treatment using a closed system specifically designed to treat these cells. Therakos photopheresis instruments are the only integrated system available for photopheresis with an independently--validated operating standard and CE Mark granted. The liquid 8-MOP eliminates the side effects of oral 8-MOP (such as the gastrointestinal side effects of psoralen and blood concentration variability in its pharmacokinetics), and the need for premedication with this drug and further monitoring of blood levels[9,11]. ECP, originally developed for the treatment of skin manifestations of cutaneous T-cell lymphoma[12,9~~,~~] has proven effective across a variety of indications, especially ~~most widely~~ acute and chronic graft-versus-host disease~~GvHD~~, in both adult and pediatric patients~~,~~ resistant to standard protocols[13,1].

Although T lymphocytes are the therapeutic target of options for the treatment of cGvHD, there is growing evidence of the importance of B lymphocytes in the development of the disease. These findings have led to evaluation of the role of rituximab, a chimeric (mouse/human) monoclonal antibody against the protein CD20, in the treatment of cGvHD[8].

Imatinib is a potent inhibitor of the tyrosine kinases ABL, platelet-derived growth factor receptor alph~~f~~a and beta, c-KIT, ARG, and LCK. It has proven clinical efficacy in the treatment of the following malignant neoplasms, which are characterized by constitutive activation of these tyrosine kinases: chronic myeloid leukemia, Philadelphia chromosome--positive acute lymphocytic leukemia, dermatofibrosarcoma protuberans, myeloproliferative disorders due to chromosomal rearrangements in the PDGF-R locus, and gastrointestinal stromal tumors with mutations in c-KIT[8].

Given that there is ~~e existence of~~ a wide range of treatment options for ~~cGVHD~~cGvHD, assessment of the associated costs and efficacy ~~associated~~ can help clinicians and healthcare providers ~~to~~ allocate healthcare resources more efficiently~~in a more efficient way~~. Cost-effectiveness analysis (CEA) is a tool decision-makers can use to assess and potentially improve the performance of ~~their~~ health systems[124, 135]. It indicates which interventions provide the best ~~highest "~~value for money~~"~~ and enables ~~helps them choose the~~the ~~–~~interventions which maximize health for the available resources to be chosen. T~~herefore, t~~he purpose of this study was to develop a cost-effectiveness population-based simulation analysis of ~~cGVHD~~cGvHD in Spain that may ~~can~~ be used to quantify the future health and economic benefits of ECP versus Rmb or Imt in addition to the usual care of ~~cGVHD~~cGvHD after prior treatment failure. Spain is a country with 47 million inhabitants with access to universal public health care free at the point of delivery.

Patients and methods

We used a ~~The~~ microsimulation model to ~~-~~assess~~ed~~ the incremental cost-effectiveness ratio (ICER) and the incremental cost-utility ratio (ICUR) of ECP versus Rmb or Imt for 1,000 hypothetical patients (~~f~~Figure 1). ~~Cost-effectiveness analysis (CEA) is a tool decision-makers can use to assess and potentially improve the performance of their health systems[12, 13]. It indicates which interventions provide the highest "value for money" and helps them choose the interventions which maximize health for the available resources.~~ Mean cumulative costs and cumulative scores of effectiveness at the end of the 5-year cycle were ~~then~~ obtained to facilitate ICER and ICUR in terms of incremental cost per improvement gained measured as the i~~. I~~ncremental cost per l~~L~~ife year (LY) gained and incremental cost per q~~Q~~uality a~~A~~djusted l~~L~~ife year (QALY) gained in comparison with the other options.

The ICER of ECP versus the alternatives was ~~,~~ compared using ~~by means of~~ the ~~following~~ formula:

$$\frac{Costs_{ECP} - Costs_{Alternative}}{Effectiveness_{ECP} - Effectiveness_{Alternative}}$$

We ~~have also~~ calculated the ~~incremental cost utility ratio (I~~ICUR~~)~~ by using effectiveness units expressed in QALYs (cost–utility analysis). This is widely recognized as a useful approach for measuring and comparing the efficiency of different health interventions. QALYs are overall measures of health outcome that weight the life expectancy of a patient with an estimate of their health-related quality ~~-~~of~~-~~ life score (on a scale of 0 to 1, where 0 is equivalent to death, and 1 is equivalent to full health).

The study was designed from the perspective of the Spanish National Health System ~~(NHS)~~ and health-care decision-makers, including only direct health-care costs. F~~B~~oth ~~f~~uture costs and effects w~~h~~ere discounted at 3% as indicated by ~~the~~ Spanish ~~guidelines~~[13] ~~-~~guidelines[15] and all costs were ~~we infl~~inflated ~~all costs~~ to 2010 Euros~~€~~ using the consumer price index for all goods and services[16~~4~~]. The cycle length of the model was three~~3~~ months, as most of the data sources, for the sake of efficacy, are calculated using ~~on~~ this frequency. The model followeds ~~the~~ patients until death or the ~~when the~~ five year time horizon ~~was reached~~, whichever occurred first.

Microsimulation

Microsimulation is a discrete simulation technique that facilitates modeling of the behavior of single individuals in a complex system, i.e. multiple organ dysfunction syndrome[17-19]. Microsimulation models are mathematical computer-based models that operate from the level of the individual upwards. They simulate the behaviour of the population, taking into account the heterogeneous composition of the target population without focusing on a representative or average individual. This implies that the population is stratified across health states and attributes (e.g. age, disease severity, risk exposure) identified as relevant to the problem analysed. A hypothetical stable sample of patients with clinical characteristics based on published reports and adjusted by clinical opinion is used to generate representative patients randomly[19].

In our cost-effectiveness microsimulation analysis, up to 1,000 hypothetical patients were randomly generated, one by one, taking into account the probability that every organ in the body was affected and the degree of severity (Table 1). Patients were entered in the model one at a time with the same or

different characteristics. Each organ involvement was scored from 0 to 3 (from none to severe organ involvement) and cGvHD was classified as (i) mild cGvHD: one or two organs involved (except lungs) with no clinically-significant impairment, i.e. maximum score 1 in all affected organs; (ii) moderate cGvHD: three or more organs involved without functional impairment (maximum score 1) or at least one organ with clinically significant involvement but no major disability (maximum score 2) or lung involvement with score 1; and (iii) severe cGvHD: major disability in any organ (score of 3) or lung score 2[2]. The efficacy of each treatment and organ evaluated and survival for each disease state was applied (Table 2). Transition probabilities were dependent on the individual characteristics (organ, degree of severity per organ and previous NIH global score). Patient characteristics were considered independently (eg. selection of the affected organ and degree of severity), as this potential relationship is not available in the literature. Patients generated in the same way were evaluated for each alternative treatment.

Parameters of the model

Model probabilities concerning the efficacy of ECP, Rmb and Imt and the degree of severity per organ affected were obtained from published reports ~~literature~~ and internet searches of relevant medical databases (e.g. PUBMED, CINAHL, DARE, NHS EED, HTA) as well as a targeted search of relevant b~~B~~one m~~M~~arrow t~~T~~ransplantation related journals [6,~~1~~20~~5~~-48~~52~~]. (Table 1 and 2). Key words searched for included extracorporeal photopheresis, ECP, ~~treatment cGVHD~~cGvHD treatment, ~~cGVHD~~cGvHD, r~~R~~ituximab and i~~I~~matinib. The systematic review was limited to evaluations involving adults published in ~~and whose publication language was~~ Spanish or English. Studies of ~~about~~ treatment efficacy per affected organ for any time horizon were included (clinical trial, observational studies, cohort studies, cases studies). The summary measure from a meta-analysis was used to derive the probability of treatment success in our cost-effectiveness analysis. To ~~In order to~~ detect which organs would be globally affected in our hypothetical patients, we searched for information on the ~~looked for the~~ organs affected in the studies reviewed and made a pooled analysis. ~~information, which were published in the reviewed studies, and we did a pooled analysis with them.~~ Based on the clinical ~~expert~~ opinion and experience of ~~of~~ two authors (JP and JS)~~clinical authors~~, the probabilities of continuing with ~~the~~ treatment were dependent on the health status reached in each cycle (complete response 100%, partial response 65%, stable disease 33% and progression 0%). ~~Expert~~ Clinical opinion was compiled using a structured questionnaire in two

interviews, the first ~~. The first one had an~~ exploratory and the second for ~~objective and the second had a goal based on~~ validation and consensus. Clinical authors~~Expert~~ were selected according to clinical experience and national and international research achievements~~selection was carried out according to their practice experience and their national and international achievements in research~~. ~~Experts were included in the manuscript authorship.~~ Table 3 shows the utilities associated with ~~to~~ different disease states, the disutility associated with ~~to~~ neutropenia and survival rates. Neutropenia is an adverse event associated with drug treatments included in our study [~~49~~53, 54~~0~~].

T~~On the other hand, t~~reatment pathways and adverse events were derived from the clinical ~~expert~~ opinion of two authors (JP and JS). ~~clinical authors.~~ Local data on healthcare resource use and costs were used and validated by the same authors~~clinical authors, experts in that~~ [~~51~~]~~field~~[55,56~~2~~] Table 4 shows the cost derived from ~~by~~ the pre-administration of treatments, pharmacological costs based on the type of response, the cost associated with ~~to~~ different disease states and adverse events. To determine the cost of the whole ECP treatment, the following ~~se~~ factors were taken into account: ~~the~~ Therakos' European list price for the ECP Kit (990€), ~~as well as~~ the need for ~~of~~ 20 minutes of light assembly, 5 ml of m~~M~~ethoxsalen (Uvadex[1]), 10,000 IU~~I~~ of enoxaparin, 0.5 L of physiological saline, a hematology consultation visit and 2 hours of nursing time. The initial guideline for ECP sessions, recommended by study ~~our~~ clinicians ~~participating in the study,~~ was 3 sessions per week during the first 2 weeks and a single session every 15 days until patient ~~the evaluation of the~~ evaluation at ~~patient after~~ 3 months.

In contrast to other treatments, including various monoclonal antibodies, independent reports including Wolff et al.[8], Flowers et al.[37], Jagasia et al.[38] and Miller et al.[29] have shown that ECP does not result in ~~lead to~~ an increased risk of infection. ~~This has been shown in several independent publications such as Wolff et al.[68]. Flowers et al.[337], Jagasia et al.[384] or Miller et al.[295]. T~~The incidence of complications or reported side-effects is ~~approximately~~ < 0.003% after more than 500,000 ECP treatments worldwide since 1987 in patients with cutaneous T-cell lymphoma and graft-versus-host disease ~~GVHD patients~~ [2~~17~~]. All studies essentially reported ~~essentially~~ only mild side-effects, including ~~of the treatment. These were~~ nausea, high temperature and headache, without any associated cost. Our study made a conservative

[1] Uvadex is a registered trade name of Johnson And Johnson Medical Limited, New Brunswick, US.

assumption which ~~In our study we have~~ excluded the cost of infection, even though ~~cost although~~ a major disadvantage of Rmb and Imt is the strong immunosuppressive effect, which may lead to life-threatening fungal infections, bacterial sepsis and viral reactivations[79]. ~~This was a conservative assumption in our study.~~ Another factor ~~assumption~~ that was not taken into consideration was the steroid sparing effect reported after ECP treatment: ~~, for example~~ Couriel ~~D~~ et al. reported a 22% cumulative discontinuation of steroids ~~at one year after ECP initiation~~ and a 10% discontinuation rate of all immunosuppressive therapy at one year after ECP initiation~~at one year after ECP initiation~~ [57~~3~~].

~~Microsimulation~~

~~Microsimulation is a discrete simulation technique that facilitates modeling of which allows us to model the behavior of single individuals in a complex system, i.e. multiple organ dysfunction syndromemultiorganic failure[5174-5619]. Microsimulation models are mathematical computer based models that operate from the level of the individual upwards. They simulate the behaviour of the population, taking into account the heterogeneous composition of the target population without focusing on a representative or average individual.These models simulate what occurs in larger populations in order to reach conclusions applicable to larger groups. This implies that the population is stratified across health states and attributes (e.g. age, disease severity, risk exposure) identified as being relevant to the problem analysedfor the decision problem. A Starting with a hypothetical stable sample of patients with clinical characteristics based on published reportsthe literature and adjusted by clinicalexpert opinion is used to generate representative patients' randomly[5619].~~

~~In our cost-effectiveness microsimulation analysis, up to 1,000 hypothetical patients were randomly generated, one by one, taking into account the probability that every organ in the body was affected and the degree of its severity (Table 1). Patients wereare entered in the model one at a time with the same or different characteristics. Each organ involvement was scored from 0 to 3 (from none to severe organ involvement) and so that cGVHDcGvHD was classified asinto (i) mild cGVHDcGvHD: one or two organs involved (except lungs) with no clinically significant impairment, i.e. maximum score 1 in all~~

~~affected organs; (ii) moderate cGVHDcGvHD: three or more organs involved without functional impairment (maximum score 1) or at least one organ with clinically significant involvement but no major disability (maximum score 2) or lung involvement with score 1; and (iii) severe cGVHDcGvHD: indicates major disability in any organ (score of 3) or lung score 2[12]. TFurthermore, the efficacy of each treatment and organ evaluated and survival for each disease state was applied (Table 2). Transition probabilities were dependent on the individual's characteristics (organ, degree of severity per organ and previous NIH global score previous). Patients characteristics were considered independently (eg. selection of the affected organ and degree of severity degree), as because this potential relationship is not available in the literature. Patients generated in the same way were evaluated for each alternative treatment.~~

Probabilistic ~~Sensitivity~~ sensitivity ~~Analysis~~ analysis

To evaluate the influence of uncertainty due to patient~~s~~ characteristics, parameter values and modeling assumptions on the results of the model ~~results~~, and to confirm the robustness of the outcomes obtained, a probabilistic sensitivity analysis was performed by simulating 1,000 times (each parameter being randomly selected from the distribution) and with 1,000 trials per analysis [5~~7~~8]. For the sensitivity analysis, fixed probability distributions were selected for each variable (log-normal distribution for ~~to~~ costs, resources used and utilities, a normal distribution for ~~was used to~~ patient's weight and height and a D~~d~~irichlet distribution for ~~to the~~ probabilities) and the parameters of each distribution were estimated according to the primary data collected[5~~9~~8].

Based on p~~P~~robabilistic s~~S~~ensitivity a~~A~~nalysis, the incremental cost and incremental effect of ECP ~~vs~~*vs*~~.~~ comparators was represented visually using the incremental cost-effectiveness plane[5~~6~~09]. The horizontal axis divides the plane according to incremental cost (positive above, negative below) and the vertical axis divides the plane according to incremental effect (positive to the right, negative to the left). This divides the incremental cost-effectiveness plane into four quadrants through the origin. We included the unofficial, but broadly accepted, Spanish threshold line (30,000€/QALYs) in the plane, in order to decide whether ~~if~~ ECP offered ~~"~~good~~"~~ value for money[6~~1~~0]. This threshold represents the maximum amount ~~that~~

the decision- maker is willing to pay for health effects (maximum acceptable ceiling ratio). The intervention is deemed cost-effective if the ICER falls below this threshold and deemed not cost-effective otherwise.

An acceptability curve was then constructed from the incremental cost and QALYs between different strategies for the 1,000 simulations. The Costcost-effectiveness acceptability curve showed the probability that ECP was cost-effective against compared to comparators over a range of values for the maximum acceptable ceiling ratio.

Results

The main organs affected in for patients with cGvHD were the skin (88%), mucosamucous membranel (43%), lLiver (37%), lungs (22%) and gGastro-intestinal tract (14%). Severity was mainly mild In all cases the most observed severity was mild severity (range 60.7% - 93.5%) in all cases except in the lung where severity was moderate in 60% of casesseverity was the most observed (60%).

With respect to the Talking about the published information we obtained on the for the three comparedtreatments comparedtreatments, , the number of patients included in studies reporting data on ECP data was higher than in those the ones related to Rmb or Imt. Data related to complete response and improvement rates (complete or partial response) were higher with ECP for all the affected organs except for skin, where improvement was similar to Rmb. The On the other hand, the progression rate was higher with Imt for the skin and mucosamucous membranel, higher with with Rmb for the liver the progression rate was higher for liver and higher with ECP for the lungs and gastrointestinal tract. the progression rate was higher for Lung lung and GI. However, the number of patients studied with Lung lung and gastrointestinal involvement was lower for GI for Rmb and Imt than for were smaller in comparison with ECP studies.

The higher purchasing cost of ECP ~~vs~~*vs*~~.~~. Imt was compensated for at 9 months due to its greater ~~months for its higher~~ efficacy. Our results show the ~~In our results, the~~ global treatment cost of ECP was~~is~~ € 518-4,000 higher than Rmb. The difference in disease improvement (% of complete or partial response) shows that ECP produced~~s~~ an improvement ~~gain~~ of 6.2% after the first year ~~v~~*vs.* ~~ersus~~ Rmb and 6.7% *vs.*~~compared to~~ Imt (Table 5). The results show that the greater ~~higher~~ efficacy of ECP lead~~s~~ to a gain of 0.011 ~~Quality~~ ~~quality~~ ~~Adjusted~~ ~~adjusted~~ ~~Life~~ ~~life~~ ~~Year~~ ~~year~~ ~~(~~QALY~~)~~ ~~v~~*vs.* ~~ersus~~ Rmb and 0.024 QALY v~~s~~ersus~~.~~ Imt at one ~~first~~ year and a gain of 0.062 QALY ~~v~~*vs.*~~ersus~~ Rmb and 0.094 QALY ~~v~~*vs.*~~ersus~~ Imt at year five (Table 5). After 9 months, ECP was dominant (cheaper and more effective) ~~v~~*vs.*~~ersus~~ Imt for all ~~regarding all the~~ parameters: the cost per improvement gained, the cost per ~~life year (~~LY~~)~~ gained and the cost per QALY gained (Table 5). After ~~On the other hand, after~~ 2.5 years ECP was cost-effective ~~vs~~*vs*~~.~~. Rmb with an ICER below € 30,000 (29,646€ per LY gained and 24,442 € per QALY gained).

The results of the probabilistic analysis (1,000,000 different simulated patients) showed that, taking into account the uncertainty in the variables of the model, starting ~~the~~ treatment of cGvHD with ECP remained~~s~~ dominant and more cost-effective versus the other alternatives (30.7% dominant ~~vs~~*vs*~~.~~. Rmb and 83.0% dominant ~~vs~~*vs*~~.~~. Imt at year 3~~3~~th ~~year~~ and 32.1% dominant ~~vs~~*vs*~~.~~. Rmb and 78.2% dominant ~~vs~~*vs*~~.~~. Imt at year 5~~5~~th ~~year~~) (Figures 2 and 3). Assuming a willingness-to-pay threshold of €30.000 per QALY gained, there was a 56.5% chance at year 3 and a ~~3th year and~~ 70.1% chance at year 5~~5~~th ~~year~~ that ECP was a cost-effective intervention ~~vs~~*vs*~~.~~. Rmb and Imt. ~~On the other hand,~~ Imt was the leastss cost-effective treatment ~~vs others~~. This indicates that, even when the ~~being a~~ decision- maker's willingness to pay for the increment in quality-adjusted life months is almost 30,000 €, the treatment of choice should still be ECP.

Discussion

Economic evaluations are acquiring greater importance due to limitations on ~~because~~ economic resources, the expense of many new treatments and the need to allocate health spending as effectively as possible and to inform decision making ~~are getting more and more limited~~. ~~Some new treatments are expensive and economic evaluations are of utmost importance to allocate the best healthcare resources and help~~

~~healthcare providers to decision making.~~ Furthermore, variations in clinical practice can cause substantial differences in expenditures. For example, the number of sessions of ECP is not standardized yet in all countries. Likewise the escalation of therapy is not yet clear, which is important given that this is a salvage therapy. Traditionally, healthcare companies were required to provide evidence to demonstrate ~~their~~ product~~'s~~ safety, efficacy and quality for the purpose~~s~~ of registration and reimbursement [1,2,4, 13,5]. Increasingly, a value for money demonstration, ~~has been added~~ which requires companies to make ~~develop~~ economic evaluation~~s studies~~ to support the reimbursement process, has been added, increasing the importance of ~~. Therefore, h~~Health e~~E~~conomic~~s~~ e~~E~~valuations ~~have become very relevant nowadays~~. New national and international guidelines are being published and updated continuously, representing an i ~~what means an i~~ncrease in ~~of~~ healthcare sources to aid decision making ~~in the processes decision~~ and in the number of countries with value for money demonstration~~s~~[15,3, 61].

There are no reported ~~For the time being there is not any published~~ economic evaluations including ECP, Rmb or Imt as third-line treatment of ~~in the treatment of cGVHD~~cGvHD. However, a recent consensus conference on clinical practice in cGvHD involving German-speaking countries ~~Therefore, the present study is the first economic evaluation analysis comparing these 3 therapies of reference as third line treatment in cGVHDcGvHD. Although we studied ECP in third line treatment, a recent German speaking Countries consensus conference on clinical practice in cGvHD chronic GVHD~~ included ECP as a second-line treatment due to its safety profile and well documented activity [6,8]. Evaluation of our conclusions should consider not only that the Spanish health system is universal and public, but also that the elements that most influenced the results of the CEA were the number of sessions of ECP, the dosing guidelines of rituximab and imatinib and the cost of day hospital. ~~Our conclusions must be considered with some perspective, because the under certain perspective because ECP regimen and reimbursement system may vary between among countries, making it necessary to adapt our results to each countryand this is a fact that makes it necessary to adapt these results for each country.~~

There are some ~~Some~~ economic evaluations of ~~related to cGVHD~~GvHD ~~treatment already exist~~. A recent Spanish study~~, for instance,~~ evaluated the cost-effectiveness of posaconazole ~~vs~~*vs*~~.~~. fluconazole ~~cost-effectiveness~~ in preventing invasive fungal infections in allogeneic hematopoietic stem cell

transplantation ~~SCT~~ patients with graft-versus-host disease ~~GVHD~~[62]~~.~~, using a ~~However, in contrast to our study, they performed a~~ Markov model. Our study used ~~In the present study we developed a~~ microsimulation ~~technique~~ because it allowed~~s~~ us to start from the clinical behaviour of the patient~~clinical patient level behavior~~ and can ~~it is possible~~ incorporate different responses at different organ levels. Therefore, the model differs from ~~is is what makes these models different from~~ aggregate models (Markov models), in which the explanatory variables represent group ~~properties~~[54] properties[17-~~56~~19]. Although Markov models are widely used in economic evaluation, as they facilitate the representation of recurrent events, they assume that patients who reach a health status are homogenous. ~~—~~This is usually overcome by creating more health states in order to ensure that this is so. In our specific case, the proliferation of health states, and of possible responses (complete response, partial response, stable disease and progression) for each organ (skin, liver, lungs,..) does not solve the problem because, in order to evaluate the result of treatment, a combined score which indicates disease severity (mild, moderate, severe) must be calculated. This require around 1024 (4^5) different health states grouped according to severity, meaning that the use of a Markov model would be unviable. In contrast, microsimulation, which evaluates the individual dynamically, is capable of following the complete natural history of that individual. However, on drawback of microsimulation is that it requires the generation of a large number of individuals in order to adjust to the pre-established parameters and minimize the error of the simulation. This requires many hours, or even days, of computing time.

Our study ~~The present cost-effectiveness study~~ has some ~~everal~~ limitations. Firstly, we used a theoretical mathematical model which ~~has~~ made different assumptions and ~~has~~ used data from different sources. However, economic evaluation models are tools that help decision making, and make it easier to ~~the~~ represent~~ation of~~ real world complexity in a simplified and understandable way. Thus, models help to simulate alternative scenarios if there is no evidence available to estimate some probabilities or ~~medical literature~~ there is a lack of published studies investigating long term outcomes of patients receiving these treatments or costs. In fact, microsimulation models have ~~present~~ some major advantages over cohort-based models, increasing the reliability of the results and being largely compatible with the existing state of the art, evidence-based literature. Secondly, the protocols of treatment and the time horizon of studies were ~~quite~~ variable, ranging from a cycle of treatment every 1 and 4 weeks and a time horizon of 3 and 6

months, but in most cases the treatment is tailored to the ~~patient~~ clinical response. Thirdly, ~~in o~~our analysis ~~we~~ excluded ~~the incorporation of~~ the reduction in ~~of~~ immunosuppressive ~~ant~~ therapies attributable to~~by~~ ECP, even though some ~~. Although some~~ studies have provided evidence of such as ~~suggested a~~reduction ~~n immunosuppressant therap~~due to the fact that ~~ies reduction related to~~ ECP treatment is associated with ~~to~~ lower morbidity and mortality[63~~1~~, 64~~2~~].

C~~On the other hand, Overall, c~~ost-effectiveness evaluations of healthcare interventions depend on strong clinical evidence in order to establish benefits and risks. ~~Data validity is crucial for the overall validity of the model predictions.~~ Estimates derived from large-scale, multicenter, randomized clinical trials are widely considered as the 'gold standard' for assessing efficacy, ~~but these data are not available in our case.~~ Therefore, our results should be taken with caution, as they depend on data from small studies or case studies, which are inherently more uncertain and have a lower level of evidence. However, no other data is available.

Conclusion

The efficacy and safety profile of ECP has been widely proven. ~~has widely demonstrated its good efficacy and safety profile. Thus, a~~Although only 5–10% of circulating mononuclear cells are~~is~~ treated during one ECP procedure, the treatment has long-lasting immunomodulatory effects[65~~3~~]. The main advantage of ECP treatment is the lower frequency of treatment-related side effects ~~related to treatment~~, and the only disadvantages are the practical efforts required (availability of trained staff ~~availability~~) and higher acquisition ~~treatment~~ costs to implement the ~~ed~~ therapy in a specific center[63~~5~~]. However, our microsimulation study results ~~results~~ provide evidence ~~demonstrated~~ that ECP is cheaper and more effective than ~~compared to~~ imatinib ~~Imt~~ and more cost-effective than ~~compared to~~ rituximab~~Rmb~~, when using currently accepted Spanish willingness to pay thresholds ~~in Spain~~.

~~Overall, cost-effectiveness evaluations of healthcare interventions depend on strong clinical evidence in order to establish benefits and risks. Data validity is crucial for the overall validity of the model predictions. Estimates derived from large-scale, multicenter, randomized clinical trials are widely considered as the 'gold standard' for assessing efficacy, but these data are not available in our case.~~

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Conflict of interest

Dr. JP and Dr. JS received consulting fees from Therakos and Dr. JS has public research grants RD06/0020/0101 from Cancer Cooperative Research Thematic Network [Red Temática de Investigación Cooperativa en Cáncer (RTICC)]. CC and MB works for ~~ed in~~ an independent consulting ~~ant~~ company that received ~~and they got~~ funds from Therakos (Johnson & Johnson Company). JR is an employee of Johnson & Johnson~~'s employee~~.

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JR developed the idea for the study, supervised the whole study, and was involved in its design. Dr. JP and Dr. JS provided background information based on their experience as principal investigators in ~~on~~ this field. CC and MB were involved in the study design, carried out the research, the data analysis and drafted the report. All the investigators contributed to the final version of the report. This s~~S~~tudy was sponsored by Therakos (a Johnson & Johnson, Company).

References

1. The Spanish National Transplant Organization (ONT) tumor registry.[Report 2010: hematopoietic stem cell transplant]. ONT 2010 [Cited on: June 14, 2011]. Available at http://www.ont.es/infesp/Memorias/Memoria_tph_2010p1.pdf

~~1.~~2. Filipovich AH, Weisdorf D, Pavletic S, Socie G, Wingard JR, Lee SJ et al.~~÷~~ National Institutes of Health consensus development project on criteria for clinical trials in chronic graft versus host disease: I. Diagnosis and Staging Working Group report. Biol Blood Marrow Transplant 2005; 11: 945-956.

~~2.~~3. Pidala J, Anasetti C, Jim H. ~~÷~~Quality of life after allogeneic hematopoietic cell transplantation. Blood 2009; 114(1): 7-19.

~~3.~~4. Pasquini MC.~~÷~~ Impact of graft-versus-host disease on survival. Best Pract Res Clin Haematol 2008; 21(2): 193-204.

5. Barton-Burke M, Dwinell DM, Kafkas L, Lavalley C, Sands H, Proctor C et al.~~÷~~ Graft-versus-host disease: a complex long-term side effect of hematopoietic stem cell transplant. Oncology (Williston Park) 2008 Oct; 22(11 Suppl Nurse Ed): 31-45.

6. Pérez-Simón JA, Encinas C, Silva F, Arcos MJ, Díez-Campelo M, Sánchez-Guijo FM et al. Prognostic factors of chronic graft-versus-host disease following allogeneic peripheral blood stem cell transplantation: the N~~n~~ational I~~i~~nstitutes of H~~h~~ealth scale plus the type of onset can predict survival rates and the duration of immunosuppressive therapy. Biol Blood Marrow Transplant 2008; 14(10): 1163-71.

~~4.~~

~~5.~~7. Filipovich AH. ~~÷~~Diagnosis and manifestations of chronic graft-versus-host disease. Best Pract Res Clin Haematol 2008 Jun; 21(2): 251-7.

~~6.~~8. Wolff D, Schleuning M, von Harsdorf S, Bacher U, Gerbitz A, Stadler M et al.~~÷~~ Consensus conference on clinical practice in chronic GVHD: Second~~-~~—Line Treatment of C~~c~~hronic Graft-versus-Host Disease. Biol Blood Marrow Transplant 2011; 17(1): 1-17.

~~7.~~9. Bolaños-Meade J, Vogelsang GB.~~÷~~ Novel strategies for steroid-refractory acute graft-versus-host disease. Curr Opin Hematol 2005 Jan; 12(1): 40-4.

~~8.~~10. Pérez-Simón JA, Sánchez-Abarca I, Díez-Campelo M, Caballero D, San Miguel J.~~÷~~ Chronic graft-versus-host disease: Pathogenesis and clinical management. Drugs 2006; 66(8): 1041-57.

9.11. Knobler RM, Trautinger F, Graninger W, Macheiner W, Gruenwald C, Neumann R, et al.÷ Parenteral administration of 8-methoxypsoralen in photopheresis. J Am Acad Dermatol 1993;28:580-4.

10.12.Edelson R, Berger C, Gasparro F, Jegasothy B, Heald P, Wintroub B et al.÷ Treatment of cutaneous T-cell lymphoma by extracorporeal photochemotherapy. Preliminary results. N Engl J Med. 1987 Feb 5;316(6):297-303.

11.13.Baird K, Wayne AS.÷ Extracorporeal photo-apheresis for the treatment of steroid-resistant graft versus host disease. Transfus Apher Sci 2009 Dec; 41(3): 209-16.

12.14.National Institute for Health and Clinical Excellence (NICE). Developing NICE clinical guidelines: The guidelines manual 2009. [Cited on: September 20, 2010]. Available at http://www.nice.org.uk/aboutnice/howwework/developingniceclinicalguidelines/clinicalguidelinedevelopmentmethods/GuidelinesManual2009.jsp

13.15.López-Bastida J, Oliva J, Antoñanzas F, García-Altés A, Gisbert R, Mar J, Puig-Junoy J.÷. Spanish recommendations on economic evaluation of health technologies. Eur J Health Econ. 2010 Oct;11(5):513-20.

16. INE (National Statistics Institute). Consumer Price Index. 2010 [Cited on: March 20, 2011]. Available at http://www.ine.es

17. Weinstein MC. Recent developments in decision-analytic modelling for economic evaluation. Pharmacoeconomics 2006; 24(11): 1043-53.

18. Burton P et al. Modeling in the economic evaluation of healthcare, selecting the appropriate approach. J Health Serv Res Policy. 2004; 9: 110-118.

19. Furiak NM, Ascher-Svanum H, Klein RW, Smolen LJ, Lawson AH, Montgomery W, Conley RR. Cost-effectiveness of olanzapine long-acting injection in the treatment of patients with schizophrenia in the United States: a micro-simulation economic decision model. Curr Med Res Opin. 2011 Apr;27(4):713-30.

14.

15. Pérez-Simón JA, Encinas C, Silva F, Arcos MJ, Díez-Campelo M, Sánchez-Guijo FM et al.: Prognostic factors of chronic graft-versus-host disease following allogeneic peripheral blood stem cell transplantation: the national institutes health scale plus the type of onset can predict

~~survival rates and the duration of immunosuppressive therapy. Biol Blood Marrow Transplant 2008; 14(10): 1163-71.~~

~~16.~~20. Lee SJ, Flowers ME~~.~~. Recognizing and managing chronic graft-versus-host disease. Hematology Am Soc Hematol Educ Program 2008: 134-41.

~~17.~~21. Scarisbrick JJ, Taylor P, Holtick U, Makar Y, Douglas K, Berlin G et al.~~÷~~ U.K. consensus statement on the use of extracorporeal photopheresis for treatment of cutaneous T-cell lymphoma and chronic graft-versus-host disease. Br J Dermatol 2008; 158(4): 659-78.

~~18.~~22. Bolwell B, Fishleder A, Lichtin A, Koo A, Camisa C, Green R et al.~~÷~~ Photopheresis in the treatment of chronic graftversus-host disease (~~cGVHD~~cGvHD). Blood 1990;76:529a.

~~19.~~23. Bloom EJ. Telang GH, Jegosothy BV.~~÷~~ Extracorporeal photochemotherapy in the treatment of chronic graft-versus-host disease after allogenic bone marrow transplantation. American Society of Clinical Oncology Annual Meeting, 1991:19–21.

~~20.~~24. Owsianowski M, Gollnick H, Siegert W, Schwerdtfeger R, Orfanos CE.~~÷~~ Succesful treatment of chronic graft-versus-host disease with extracorporeal photopheresis. Bone Marrow Transplant 1994;14:845–8.

~~21.~~25. Sniecinski I, Smith B, Parker PM, Dagis A~~÷~~. Extracorporeal photochemotherapy for treatment of drug resistant chronic graft-versus-host disease. J Clin Aphresis 1995;10:51.

~~22.~~26. Balda BR, Kostantinow A, Starz H, Gnekow A, Heidemann P.~~÷~~ Extracorporeal photochemotherapy as an effective treatment modality in chronic graft-versus-host disease. J Eur Acad Dermatol Venereol 1996;7:155–62.

~~23.~~27. Crovetti G, Carabelli A, Bertani E.~~÷~~ Case report: chronic graftversus-host disease (~~cGVHD~~cGvHD) treated with extracorporeal photochemotherapy (ECP). Florence, Italy: Sixth World Apheresis Association Meeting, 1996:137a.

~~24.~~28. Abhvankar S, Godder K, Chiang KY, Chrjstiansen N, Brown J, De Rienzo S et al.~~÷~~ Extracorporeal photopheresis (ECP) with UVADEX for the treatment of chronic graft-versus-host disease (~~cGVHD~~cGvHD). J Exp Hematol 1998;26:8.

~~25.~~29. Miller JL, Goodman SA, Stricklin GP, Lloyd EK.~~÷~~ Extracorporeal photochemotherapy in the treatment of graft-versus-host disease. Abstract Book IBMTR/ABMTR Meeting Keystone Resort Colorado, 1998:7a.

26.30. Sniecinski I, Parker P, Dagis A, Smith B.÷ Extracorporeal photopheresis (EP) is effective treatment for chronic refractory graft versus host disease. J AmSoc Hematol 1998;92:454.

27.31. Zic JA, Miller JL, Stricklin GP, King LE Jr.÷ The North American experience with photopheresis. Ther Apher 1999;3:50–62.

28.32. Biagi E, Perseghin P, Buscemi F, Dassi M, Rovelli A, Balduzzi A.÷ Effectiveness of extracorporeal photochemotherapy in treating refractory chronic graft-versus-host disease. Haematologica 2000;85:329–30.

29.33. Alcindor T, Gorgun G, Miller KB, Roberts TF, Sprague K, Schenkein DP, Foss FM.÷ Immunomodulatory effects of extracorporeal photochemotherapy in patients with extensive chronic graft-versus-host disease. Blood. 2001;98(5):1622-5.

30.34. Gorgun G, Miller KB, Foss FM.÷ Immunologic mechanisms of extracorporeal photochemotherapy in chronic graft-versus-host disease. Blood. 2002 Aug 1;100(3):941-7.

31.35. Perseghin P, Dassi M, Balduzzi A, Rovelli A, Bonanomi S, Uderzo C.÷ Mononuclear cell collection in patients undergoing extra-corporeal photo-chemotherapy for acute and chronic graft-vs.*vs.*-host-disease (GvHD): comparison between COBE Spectra version 4.7 and 6.0 (AutoPBSC). J Clin Apher. 2002;17(2):65-71.

32.36. Biagi E, Di Biaso I, Leoni V, Gaipa G, Rossi V, Bugarin C et al.÷ Extracorporeal photochemotherapy is accompanied by increasing levels of circulating CD4+CD25+GITR+Foxp3+CD62L+ functional regulatory T-cells in patients with graft-versus-host disease. Transplantation. 2007;84(1):31-9.

33.37. Flowers ME, Apperley JF, van Besien K, Elmaagacli A, Grigg A, Reddy V et al.÷ A multicenter prospective phase 2 randomized study of extracorporeal photopheresis for treatment of chronic graft-versus-host disease. Blood. 2008;112(7):2667-74.

34.38. Jagasia MH, Savani BN, Stricklin G, Engelhardt B, Kassim A, Dixon S et al.÷ Classic and overlap chronic graft-versus-host disease (eGVHDcGvHD) is associated with superior outcome after extracorporeal photopheresis (ECP). Biol Blood Marrow Transplant. 2009;15(10):1288-95.

35.39. Pérez-Carmona L, Harto-Castaño A, Díez-Recio E, Jaén-Olasolo P.÷ [Extracorporeal photopheresis in dermatology]. Actas Dermosifiliogr. 2009;100(6):459-71.

36.40. Ratanatharathorn V, Ayash L, Reynolds C, et al. Treatment of chronic graft versus host disease with anti-CD20 chimeric monoclonal antibody. Biol Blood Marrow Transplant 2003;9:505-11

37.41. Canninga-van Dijk MR, van der Straaten HM, Fijnheer R, Sanders CJ, van den Tweel JG, Verdonck LF. Anti-CD20 monoclonal antibody-treatment in 6 patients with therapy-refractory chronic graft versus host disease. Blood 2004;104:2603-6.

38.42. Okamoto M, Okano A, Akamatsu S, et al. Rituximab is effective for steroid-refractory sclerodermatous chronic graft versus host disease. Leukemia 2006;20:172-3.

39.43. Cutler C, Miklos D, Kim HT, et al. Rituximab for steroid-refractory chronic graft-versus-host disease. Blood. 2006;108:756-762.

40.44. Zaja F, Bacigalupo A, Patriarca F, et al. Treatment of refractory chronic GVHD with rituximab: a GITMO study. Bone Marrow Transplant 2007;40:273-7.

41.45. von Bonin M, Oelschlagel U, Radke J, et al. Treatment of chronic steroid-refractory graft-versus-host disease with low-dose rituximab. Transplantation 2008;86:875-9.

42.46. Mohty M, Marchetti N, El-Cheikh J, Faucher C, Furst S, Blaise D. Rituximab as salvage therapy for refractory chronic GVHD. Bone Marrow Transplant 2008;41:909-11.

43.47. Teshima T, Nagafuji K, Henzan H, Miyamura K, Takase K, Hidaka M et al. Rituximab for the treatment of corticosteroid-refractory chronic graft-versus-host disease. Int J Hematol. 2009;90(2):253-60.

44.48. Peterson JD, Chan LS. Effectiveness and side effects of anti-CD20 therapy for autoantibody-mediated blistering skin diseases: A comprehensive survey of 71 consecutive patients from the Initial use to 2007. Ther Clin Risk Manag. 2009;5(1):1-7.

45.49. Magro L, Catteau B, Coiteux V, Bruno B, Jouet JP, Yakoub-Agha I. Efficacy of imatinib mesylate in the treatment of refractory sclerodermatous chronic GVHD. Bone Marrow Transplant. 2008;42(11):757-60.

46.50. Stadler M, Ahlborn R, Kamal H, Diedrich H, Buchholz S, Eder M et al. Limited efficacy of imatinib in severe pulmonary chronic graft-versus-host disease. Blood 2009; 114(17): 3718-9.

47.51. Magro L, Mohty M, Catteau B, Coiteux V, Chevallier P, Terriou L et al. ; Imatinib mesylate as salvage therapy for refractory sclerotic chronic graft-versus-host disease. Blood. 2009;114(3):719-22.

48.52. Olivieri A, Locatelli F, Zecca M, Sanna A, Cimminiello M, Raimondi R et al. ; Imatinib for refractory chronic graft-versus-host disease with fibrotic features. Blood 2009; 114(3): 709-18.

49.53. Heim D, Ebnöther M, Meyer-Monard S, Tsakiris D, Linn M, Tichelli A, Gratwohl A. G-CSF for imatinib-induced neutropenia. Leukemia. 2003 Apr;17(4):805-7.

50.54. Grant C, Wilson WH, Dunleavy K. Neutropenia associated with rituximab therapy. Curr Opin Hematol. 2010; 18(1):49-54.

51.55. e-Salud. Spanish cost database. Oblikue Consulting 2010. Available at http:\\www.oblikue.com.

52.56. General Spanish Council of Pharmacists. 2010. Available at http:\\www.portalfarma.com.

53.57. Couriel DR, Hosing C, Saliba R, Shpall EJ, Anderlini P, Rhodes B et al. ; Extracorporeal photochemotherapy for the treatment of steroid-resistant chronic GVHD. Blood. 2006 Apr 15;107(8):3074-80.

54. Weinstein MC.; Recent developments in decision-analytic modelling for economic evaluation. Pharmacoeconomics 2006; 24(11): 1043-53.

55. Burton P et al.; Modeling in the economic evaluation of healthcare, selecting the appropriate approach. J Health Serv Res Policy. 2004; 9: 110-118.

56. Furiak NM, Ascher-Svanum H, Klein RW, Smolen LJ, Lawson AH, Montgomery W, Conley RR.; Cost-effectiveness of olanzapine long-acting injection in the treatment of patients with schizophrenia in the United States: a micro-simulation economic decision model. Curr Med Res Opin. 2011 Apr;27(4):713-30.

57.58. Claxton K, Schupher M, McCabe C, Briggs A, Akehurst R, Buxton M, et al. ; Probabilistic sensitivity analysis for NICE technology assessment: not an optional extra. Health Econ 2005; 14: 339-47.

58.59. Briggs AH. ; Handling uncertainty in cost-effectiveness models. Pharmacoeconomics 2000; 17 (5): 479-500.

59.60. Fenwick E, Marshall DA, Levy AR, Nichol G.÷. Using and interpreting cost-effectiveness acceptability curves: an example using data from a trial of management strategies for atrial fibrillation. BMC Health Serv Res. 2006;6:52.

60.61. Rodríguez JM, Pérez F, Crespo C, González P, Antón E, Brosa M.÷. The use of cost per life year gained as a measurement of cost-effectiveness in Spain: a systematic review of recent publications. Eur J Health Econ. 2011 Jun 10. [Epub ahead of print] DOI 10.1007/s10198-011-0326-y

62. de la Cámara R, Jarque I, Sanz MA, Grau S, Casado MA, Sabater FJ, Carreras E. Economic evaluation of posaconazole vs fluconazole in the prevention of invasive fungal infections in patients with GVHD following haematopoietic SCT. Bone Marrow Transplant. 2010 May;45(5):925-32.

61.63. Dall'Amico R, Livi U, Milano A, Montini G, Andreetta B, Murer L,et al.÷ Extracorporeal photochemotherapy as adjuvant treatment of heart transplant recipients with recurrent rejection. Transplantation 1995;60:45-9.ç

62.64. Dall'Amico R and Messina C.÷. Extracorporeal photochemotherapy for the treatment of graft-versus-host disease. Ther Apher 2002; 6(4): 296-304.

63.65. Maeda A.÷. Extracorporeal photochemotherapy. J Dermatol Sci. 2009 Jun;54(3):150-6.

Development of a population-based cost-effectiveness model of chronic graft versus host disease in Spain

Running title: Cost-effectiveness of chronic graft versus host disease in Spain

Abstract

Background: Chronic graft-versus-host disease (cGvHD) is the leading cause of late non-relapse mortality (transplant-related mortality) after hematopoietic stem cell transplant. Given that there are a wide range of treatment options for cGvHD, assessment of the associated costs and efficacy can help clinicians and healthcare providers allocate healthcare resources more efficiently.

Objective: The purpose of this study was to assess the cost-effectiveness of extra-corporeal photopheresis (ECP) *vs.* rituximab (Rmb) and *vs.* imatinib (Imt) in patients with cGvHD at five years from the perspective of the Spanish National Health System.

Patients and methods: The model assessed the incremental cost-effectiveness/utility ratio of ECP versus Rmb or Imt for 1,000 hypothetical patients through microsimulation cost-effectiveness techniques. Model probabilities were obtained from the literature. Treatment pathways and adverse events were evaluated taking clinical opinion and published reports into consideration. Local data on costs (2010 Euros) and health care resources utilization were validated by the clinical authors. Probabilistic sensitivity analyses were used to assess the robustness of the model.

Results: The greater efficacy of ECP resulted in a gain of 0.011–0.024 quality-adjusted life years (QALY) in the first year and 0.062-0.094 at year five compared to Rmb or Imt. The results showed that the higher acquisition cost of ECP *vs.* Imt was compensated for at 9 months by greater efficacy and *vs.* Rmb was partially compensated for (517€ year 5). After 9 months, ECP was dominant *vs.* Imt. The incremental cost-effectiveness ratio of ECP *vs.* Rmb was 29,646€ per LY gained and 24,442 € per QALY gained at year 2.5. Probabilistic sensitivity analysis confirmed the results. The main study limitation was that to assess relative treatment effects, only small studies were available for indirect comparison.

Conclusion: ECP as a third-line therapy for cGvHD is a more cost-effective strategy than Rmb or Imt.

Key words: Cost-effectiveness, chronic graft, host disease, extra-corporeal photopheresis.

Introduction

In Spain, between 2,000 and 2,500 hematopoietic stem cell transplants are carried out annually, a maximum rate of 54.14 per million inhabitants, of which 34% are allogeneic[1]. Chronic graft-versus-host disease (cGvHD) is the leading cause of late non-relapse mortality (transplant-related mortality) after hematopoietic stem cell transplant. It deleteriously affects the quality of life in surviving patients who have otherwise been cured of their underlying disease [2, 3]. cGvHD may have debilitating consequences resulting from profound chronic immune suppression leading to recurrent or life-threatening infections[4]. cGvHD occurs in at least 30% to 50% of recipients of transplants from human leukocyte antigen matched siblings, and in at least 60% to 70% of recipients from unrelated donors[5]. A Spanish study found a cumulated incidence of mild, moderate or severe cGvHD of 29%, 42% and 28%, respectively, in patients undergoing allogeneic hematopoietic stem cell transplant using peripheral blood from related donors[6].

The diagnosis and staging working group of the National Institutes of Health Consensus Development Project on cGvHD proposed standard criteria for the diagnosis, organ scoring and global assessment of cGvHD severity[2, 7]. The diagnosis of cGvHD requires the presence of at least one clinical diagnostic sign of cGvHD or at least one distinctive clinical manifestation confirmed by biopsy or other relevant tests. cGVHD may be restricted to a single organ system, but several organs are usually involved. Clinical features range from edema, erythematous rash, mucositis, diarrhea, and elevated transaminases, to more fibrotic and chronic manifestations such as sclerotic, lichen-planus skin changes, fasciitis, sicca syndrome, joint contractures, esophageal strictures, and bronchiolitis obliterans[7]. The proposed global assessment of severity (mild, moderate, or severe) is derived by combining organ and site-specific scores[2, 7].

Prednisone, together with a calcineurin inhibitor, is considered the standard regimen for the primary treatment of cGvHD[8]. While half of the patients respond to first-line treatment, the prognosis of steroid-refractory cGvHD remains poor[9]. There is no standard approach to treat refractory cGvHD, although there is a long list of immunosuppressive drugs and other agents for salvage therapy. Immunosuppressive treatments that inhibit T cell activation, proliferation or survival include mycophenolate mofetil, daclizumab, sirolimus (rapamycin), extra-corporeal photopheresis (ECP) and pentostatin (deoxycoformycin) [10]. In addition, new strategies such as etanercept, rituximab (Rmb) and imatinib (Imt)

have also been evaluated[8, 10]. However, responses to immunosuppressive drugs are often partial, and patients continue to experience disease symptoms that can significantly impair the quality of life.

ECP is a therapeutic approach based on the biological effect of liquid 8-methoxypsoralen (8-MOP) and ultraviolet light A on mononuclear cells collected by apheresis, and reinfused into the patient[10]. This therapy allows treatment using a closed system specifically designed to treat these cells. Therakos photopheresis instruments are the only integrated system available for photopheresis with an independently-validated operating standard and CE Mark granted. The liquid 8-MOP eliminates the side effects of oral 8-MOP (such as the gastrointestinal side effects of psoralen and blood concentration variability in its pharmacokinetics), and the need for premedication with this drug and further monitoring of blood levels[11]. ECP, originally developed for the treatment of skin manifestations of cutaneous T-cell lymphoma[12], has proven effective across a variety of indications, especially acute and chronic graft-versus-host disease in both adult and pediatric patients resistant to standard protocols[13].

Although T lymphocytes are the therapeutic target of options for the treatment of cGvHD, there is growing evidence of the importance of B lymphocytes in the development of the disease. These findings have led to evaluation of the role of rituximab, a chimeric (mouse/human) monoclonal antibody against the protein CD20, in the treatment of cGvHD[8].

Imatinib is a potent inhibitor of the tyrosine kinases ABL, platelet-derived growth factor receptor alpha and beta, c-KIT, ARG, and LCK. It has proven clinical efficacy in the treatment of the following malignant neoplasms, which are characterized by constitutive activation of these tyrosine kinases: chronic myeloid leukemia, Philadelphia chromosome-positive acute lymphocytic leukemia, dermatofibrosarcoma protuberans, myeloproliferative disorders due to chromosomal rearrangements in the PDGF-R locus, and gastrointestinal stromal tumors with mutations in c-KIT[8].

Given that there is a wide range of treatment options for cGvHD, assessment of the associated costs and efficacy can help clinicians and healthcare providers allocate healthcare resources more efficiently. Cost-effectiveness analysis (CEA) is a tool decision-makers can use to assess and potentially improve the performance of health systems[14, 15]. It indicates which interventions provide the best value for money and

enables the interventions which maximize health for the available resources to be chosen. The purpose of this study was to develop a cost-effectiveness population-based simulation analysis of cGvHD in Spain that may be used to quantify the future health and economic benefits of ECP versus Rmb or Imt in addition to the usual care of cGvHD after prior treatment failure. Spain is a country with 47 million inhabitants with access to universal public health care free at the point of delivery.

Patients and methods

We used a microsimulation model to assess the incremental cost-effectiveness ratio (ICER) and the incremental cost-utility ratio (ICUR) of ECP versus Rmb or Imt for 1,000 hypothetical patients (Figure 1). Mean cumulative costs and cumulative scores of effectiveness at the end of the 5-year cycle were obtained to facilitate ICER and ICUR in terms of incremental cost per improvement gained measured as the incremental cost per life year (LY) gained and incremental cost per quality adjusted life year (QALY) gained in comparison with the other options.

The ICER of ECP versus the alternatives was compared using the formula:

$$\frac{Costs_{ECP} - Costs_{Alternative}}{Effectiveness_{ECP} - Effectiveness_{Alternative}}$$

We calculated the ICUR by using effectiveness units expressed in QALYs (cost–utility analysis). This is widely recognized as a useful approach for measuring and comparing the efficiency of different health interventions. QALYs are overall measures of health outcome that weight the life expectancy of a patient with an estimate of their health-related quality of life score (on a scale of 0 to 1, where 0 is equivalent to death, and 1 is equivalent to full health).

The study was designed from the perspective of the Spanish National Health System and health-care decision-makers, including only direct health-care costs. Future costs and effects were discounted at 3% as indicated by Spanish guidelines[15] and all costs were inflated to 2010 Euros using the consumer price index for all goods and services[16]. The cycle length of the model was three months, as most of the data sources, for the sake of efficacy, are calculated using this frequency. The model followed patients until death or the five year time horizon, whichever occurred first.

Microsimulation

Microsimulation is a discrete simulation technique that facilitates modeling of the behavior of single individuals in a complex system, i.e. multiple organ dysfunction syndrome[17-19]. Microsimulation models are mathematical computer-based models that operate from the level of the individual upwards. They simulate the behaviour of the population, taking into account the heterogeneous composition of the target population without focusing on a representative or average individual. This implies that the population is stratified across health states and attributes (e.g. age, disease severity, risk exposure) identified as relevant to the problem analysed. A hypothetical stable sample of patients with clinical characteristics based on published reports and adjusted by clinical opinion is used to generate representative patients randomly[19].

In our cost-effectiveness microsimulation analysis, up to 1,000 hypothetical patients were randomly generated, one by one, taking into account the probability that every organ in the body was affected and the degree of severity (Table 1). Patients were entered in the model one at a time with the same or different characteristics. Each organ involvement was scored from 0 to 3 (from none to severe organ involvement) and cGvHD was classified as (i) mild cGvHD: one or two organs involved (except lungs) with no clinically-significant impairment, i.e. maximum score 1 in all affected organs; (ii) moderate cGvHD: three or more organs involved without functional impairment (maximum score 1) or at least one organ with clinically significant involvement but no major disability (maximum score 2) or lung involvement with score 1; and (iii) severe cGvHD: major disability in any organ (score of 3) or lung score 2[2]. The efficacy of each treatment and organ evaluated and survival for each disease state was applied (Table 2). Transition probabilities were dependent on the individual characteristics (organ, degree of severity per organ and previous NIH global score). Patient characteristics were considered independently (eg. selection of the affected organ and degree of severity), as this potential relationship is not available in the literature. Patients generated in the same way were evaluated for each alternative treatment.

Parameters of the model

Model probabilities concerning the efficacy of ECP, Rmb and Imt and the degree of severity per organ affected were obtained from published reports and internet searches of relevant medical databases (e.g. PUBMED, CINAHL, DARE, NHS EED, HTA) as well as a targeted search of relevant bone marrow transplantation-related journals [6, 20-52]. (Table 1 and 2). Key words searched for included extracorporeal photopheresis, ECP, cGvHD treatment, cGvHD, rituximab and imatinib. The systematic review was limited to evaluations involving adults published in Spanish or English. Studies of treatment efficacy per affected organ for any time horizon were included (clinical trial, observational studies, cohort studies, cases studies). The summary measure from a meta-analysis was used to derive the probability of treatment success in our cost-effectiveness analysis. To detect which organs would be globally affected in our hypothetical patients, we searched for information on the organs affected in the studies reviewed and made a pooled analysis. Based on the clinical opinion and experience of two authors (JP and JS), the probabilities of continuing with treatment were dependent on the health status reached in each cycle (complete response 100%, partial response 65%, stable disease 33% and progression 0%). Clinical opinion was compiled using a structured questionnaire in two interviews, the first exploratory and the second for validation and consensus. Clinical authors were selected according to clinical experience and national and international research achievements. Table 3 shows the utilities associated with different disease states, the disutility associated with neutropenia and survival rates. Neutropenia is an adverse event associated with drug treatments included in our study [53, 54].

Treatment pathways and adverse events were derived from the clinical opinion of two authors (JP and JS). Local data on healthcare resource use and costs were used and validated by the same authors[55,56] Table 4 shows the cost derived from the pre-administration of treatments, pharmacological costs based on the type of response, the cost associated with different disease states and adverse events. To determine the cost of the whole ECP treatment, the following factors were taken into account: Therakos' European list price for the ECP Kit (990€), the need for 20 minutes of light assembly, 5 ml of methoxsalen (Uvadex[1]), 10,000 IU of enoxaparin, 0.5 L of physiological saline, a hematology consultation visit and 2 hours of nursing time. The initial guideline for ECP sessions, recommended by study clinicians, was 3 sessions per week during the first 2 weeks and a single session every 15 days until patient evaluation at 3 months.

[1] Uvadex is a registered trade name of Johnson And Johnson Medical Limited, New Brunswick, US.

In contrast to other treatments, including various monoclonal antibodies, independent reports including Wolff et al.[8], Flowers et al.[37], Jagasia et al.[38] and Miller et al.[29] have shown that ECP does not result in an increased risk of infection. The incidence of complications or reported side-effects is < 0.003% after more than 500,000 ECP treatments worldwide since 1987 in patients with cutaneous T-cell lymphoma and graft-versus-host disease[21]. All studies essentially reported only mild side-effects, including nausea, high temperature and headache, without any associated cost. Our study made a conservative assumption which excluded the cost of infection, even though a major disadvantage of Rmb and Imt is the strong immunosuppressive effect, which may lead to life-threatening fungal infections, bacterial sepsis and viral reactivations[9]. Another factor that was not taken into consideration was the steroid sparing effect reported after ECP treatment: Couriel et al. reported a 22% cumulative discontinuation of steroids and a 10% discontinuation rate of all immunosuppressive therapy at one year after ECP initiation[57].

Probabilistic sensitivity analysis

To evaluate the influence of uncertainty due to patient characteristics, parameter values and modeling assumptions on the results of the model, and to confirm the robustness of the outcomes obtained, a probabilistic sensitivity analysis was performed by simulating 1,000 times (each parameter being randomly selected from the distribution) and with 1,000 trials per analysis [58]. For the sensitivity analysis, fixed probability distributions were selected for each variable (log-normal distribution for costs, resources used and utilities, a normal distribution for patient's weight and height and a Dirichlet distribution for probabilities) and the parameters of each distribution were estimated according to the primary data collected[59].

Based on probabilistic sensitivity analysis, the incremental cost and incremental effect of ECP *vs.* comparators was represented visually using the incremental cost-effectiveness plane[60]. The horizontal axis divides the plane according to incremental cost (positive above, negative below) and the vertical axis divides the plane according to incremental effect (positive to the right, negative to the left). This divides the incremental cost-effectiveness plane into four quadrants through the origin. We included the unofficial, but broadly accepted, Spanish threshold line (30,000€/QALYs) in the plane, in order to decide whether ECP offered good value for money[61]. This threshold represents the maximum amount the

decision maker is willing to pay for health effects (maximum acceptable ceiling ratio). The intervention is deemed cost-effective if the ICER falls below this threshold and not cost-effective otherwise.

An acceptability curve was then constructed from the incremental cost and QALYs between different strategies for the 1,000 simulations. The cost-effectiveness acceptability curve showed the probability that ECP was cost-effective against comparators over a range of values for the maximum acceptable ceiling ratio.

Results

The main organs affected in patients with cGvHD were the skin (88%), mucous membrane (43%), liver (37%), lungs (22%) and gastrointestinal tract (14%). Severity was mainly mild (range 60.7% - 93.5%) in all cases except in the lung where severity was moderate in 60% of cases.

With respect to the published information obtained on the three treatments compared, the number of patients included in studies reporting data on ECP was higher than in those related to Rmb or Imt. Data related to complete response and improvement rates (complete or partial response) were higher with ECP for all affected organs except for skin, where improvement was similar to Rmb. The progression rate was higher with Imt for the skin and mucous membrane, higher with Rmb for the liver and higher with ECP for the lungs and gastrointestinal tract. However, the number of patients studied with lung and gastrointestinal involvement was lower for Rmb and Imt than for ECP.

The higher purchasing cost of ECP *vs.* Imt was compensated for at 9 months due to its greater efficacy. Our results show the global treatment cost of ECP was € 518-4,000 higher than Rmb. The difference in disease improvement (% of complete or partial response) shows that ECP produced an improvement of 6.2% after the first year *vs.* Rmb and 6.7% *vs.* Imt (Table 5). The results show that the greater efficacy of ECP lead to a gain of 0.011 QALY *vs.* Rmb and 0.024 QALY vs. Imt at one year and a gain of 0.062 QALY *vs.* Rmb and 0.094 QALY *vs.* Imt at year five (Table 5). After 9 months, ECP was dominant (cheaper and more effective) *vs.* Imt for all parameters: the cost per improvement gained, the cost per LY gained and the cost per QALY gained (Table 5). After 2.5 years ECP was cost-effective *vs.* Rmb with an ICER below € 30,000 (29,646€ per LY gained and 24,442 € per QALY gained).

The results of the probabilistic analysis (1,000,000 different simulated patients) showed that, taking into account the uncertainty in the variables of the model, starting treatment of cGvHD with ECP remained dominant and more cost-effective versus the other alternatives (30.7% dominant *vs.* Rmb and 83.0% dominant *vs.* Imt at year 3 and 32.1% dominant *vs.* Rmb and 78.2% dominant *vs.* Imt at year 5) (Figures 2 and 3). Assuming a willingness-to-pay threshold of €30.000 per QALY gained, there was a 56.5% chance at year 3 and a 70.1% chance at year 5 that ECP was a cost-effective intervention *vs.* Rmb and Imt. Imt was the least cost-effective treatment. This indicates that, even when the decision maker's willingness to pay for the increment in quality-adjusted life months is almost 30,000 €, the treatment of choice should still be ECP.

Discussion

Economic evaluations are acquiring greater importance due to limitations on economic resources, the expense of many new treatments and the need to allocate health spending as effectively as possible and to inform decision making. Furthermore, variations in clinical practice can cause substantial differences in expenditures. For example, the number of sessions of ECP is not standardized yet in all countries. Likewise the escalation of therapy is not yet clear, which is important given that this is a salvage therapy. Traditionally, healthcare companies were required to provide evidence to demonstrate product safety, efficacy and quality for the purpose of registration and reimbursement [14, 15]. Increasingly, a value for money demonstration, which requires companies to make economic evaluations to support the reimbursement process, has been added, increasing the importance of health economic evaluations. New national and international guidelines are being published and updated continuously, representing an increase in healthcare sources to aid decision making and in the number of countries with value for money demonstrations[15, 61].

There are no reported economic evaluations including ECP, Rmb or Imt as third-line treatment of cGvHD. However, a recent consensus conference on clinical practice in cGvHD involving German-speaking countries included ECP as a second-line treatment due to its safety profile and well documented activity [8]. Evaluation of our conclusions should consider not only that the Spanish health system is

universal and public, but also that the elements that most influenced the results of the CEA were the number of sessions of ECP, the dosing guidelines of rituximab and imatinib and the cost of day hospital.

There are some economic evaluations of GvHD. A recent Spanish study evaluated the cost-effectiveness of posaconazole *vs.* fluconazole in preventing invasive fungal infections in allogeneic hematopoietic stem cell transplantation patients with graft-versus-host disease[62], using a Markov model. Our study used microsimulation because it allowed us to start from the clinical behaviour of the patient and can incorporate different responses at different organ levels. Therefore, the model differs from aggregate models (Markov models), in which the explanatory variables represent group properties[17-19]. Although Markov models are widely used in economic evaluation, as they facilitate the representation of recurrent events, they assume that patients who reach a health status are homogenous. This is usually overcome by creating more health states in order to ensure that this is so. In our specific case, the proliferation of health states, and of possible responses (complete response, partial response, stable disease and progression) for each organ (skin, liver, lungs,..) does not solve the problem because, in order to evaluate the result of treatment, a combined score which indicates disease severity (mild, moderate, severe) must be calculated. This require around 1024 (4^5) different health states grouped according to severity, meaning that the use of a Markov model would be unviable. In contrast, microsimulation, which evaluates the individual dynamically, is capable of following the complete natural history of that individual. However, on drawback of microsimulation is that it requires the generation of a large number of individuals in order to adjust to the pre-established parameters and minimize the error of the simulation. This requires many hours, or even days, of computing time.

Our study has some limitations. Firstly, we used a theoretical mathematical model which made different assumptions and used data from different sources. However, economic evaluation models are tools that help decision making, and make it easier to represent real world complexity in a simplified and understandable way. Thus, models help to simulate alternative scenarios if there is no evidence available to estimate some probabilities or there is a lack of published studies investigating long term outcomes of patients receiving these treatments or costs. In fact, microsimulation models have some major advantages over cohort-based models, increasing the reliability of the results and being largely compatible with the existing state of the art, evidence-based literature. Secondly, the protocols of treatment and the time

horizon of studies were variable, ranging from a cycle of treatment every 1 and 4 weeks and a time horizon of 3 and 6 months, but in most cases the treatment is tailored to the clinical response. Thirdly, our analysis excluded the reduction in immunosuppressive therapies attributable to ECP, even though some studies have provided evidence of such as reduction due to the fact that ECP treatment is associated with lower morbidity and mortality[63, 64].

Cost-effectiveness evaluations of healthcare interventions depend on strong clinical evidence in order to establish benefits and risks. Estimates derived from large-scale, multicenter, randomized clinical trials are widely considered as the 'gold standard' for assessing efficacy, Therefore, our results should be taken with caution, as they depend on data from small studies or case studies, which are inherently more uncertain and have a lower level of evidence. However, no other data is available.

Conclusion

The efficacy and safety profile of ECP has been widely proven. Although only 5-10% of circulating mononuclear cells are treated during one ECP procedure, the treatment has long-lasting immunomodulatory effects[65]. The main advantage of ECP treatment is the lower frequency of treatment-related side effects, and the only disadvantages are the practical efforts required (availability of trained staff) and higher acquisition costs to implement the therapy in a specific center[65]. However, our microsimulation study results provide evidence that ECP is cheaper and more effective than imatinib and more cost-effective than rituximab, when using currently-accepted Spanish willingness-to-pay thresholds.

Declaration of funding

This study was funded by Therakos (Johnson & Johnson Company), manufacturer of ECP devices.

Conflict of interest

Dr. JP and Dr. JS received consulting fees from Therakos and Dr. JS has public research grants RD06/0020/0101 from Cancer Cooperative Research Thematic Network [Red Temática de Investigación Cooperativa en Cáncer (RTICC)]. CC and MB work for an independent consulting company that received funds from Therakos (Johnson & Johnson Company). JR is an employee of Johnson & Johnson.

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JR developed the idea for the study, supervised the whole study, and was involved in its design. Dr. JP and Dr. JS provided background information based on their experience as principal investigators in this field. CC and MB weres involved in the study design, carried out the research, the data analysis and drafted the report. All the investigators contributed to the final version of the report. This study was sponsored by Therakos (a Johnson & Johnson, Company).

References

1. The Spanish National Transplant Organization (ONT) tumor registry.[Report 2010: hematopoietic stem cell transplant]. ONT 2010 [Cited on: June 14, 2011]. Available at http://www.ont.es/infesp/Memorias/Memoria_tph_2010p1.pdf
2. Filipovich AH, Weisdorf D, Pavletic S, Socie G, Wingard JR, Lee SJ et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft versus host disease: I. Diagnosis and Staging Working Group report. Biol Blood Marrow Transplant 2005; 11: 945-956.
3. Pidala J, Anasetti C, Jim H. Quality of life after allogeneic hematopoietic cell transplantation. Blood 2009; 114(1): 7-19.
4. Pasquini MC. Impact of graft-versus-host disease on survival. Best Pract Res Clin Haematol 2008; 21(2): 193-204.
5. Barton-Burke M, Dwinell DM, Kafkas L, Lavalley C, Sands H, Proctor C et al. Graft-versus-host disease: a complex long-term side effect of hematopoietic stem cell transplant. Oncology (Williston Park) 2008 Oct; 22(11 Suppl Nurse Ed): 31-45.
6. Pérez-Simón JA, Encinas C, Silva F, Arcos MJ, Díez-Campelo M, Sánchez-Guijo FM et al. Prognostic factors of chronic graft-versus-host disease following allogeneic peripheral blood stem cell transplantation: the National Institutes of Health scale plus the type of onset can predict survival rates and the duration of immunosuppressive therapy. Biol Blood Marrow Transplant 2008; 14(10): 1163-71.
7. Filipovich AH. Diagnosis and manifestations of chronic graft-versus-host disease. Best Pract Res Clin Haematol 2008 Jun; 21(2): 251-7.
8. Wolff D, Schleuning M, von Harsdorf S, Bacher U, Gerbitz A, Stadler M et al. Consensus conference on clinical practice in chronic GVHD: Second-Line Treatment of Chronic Graft-versus-Host Disease. Biol Blood Marrow Transplant 2011; 17(1): 1-17.
9. Bolaños-Meade J, Vogelsang GB. Novel strategies for steroid-refractory acute graft-versus-host disease. Curr Opin Hematol 2005 Jan; 12(1): 40-4.
10. Pérez-Simón JA, Sánchez-Abarca I, Díez-Campelo M, Caballero D, San Miguel J. Chronic graft-versus-host disease: Pathogenesis and clinical management. Drugs 2006; 66(8): 1041-57.

11. Knobler RM, Trautinger F, Graninger W, Macheiner W, Gruenwald C, Neumann R, et al. Parenteral administration of 8-methoxypsoralen in photopheresis. J Am Acad Dermatol 1993;28:580-4.
12. Edelson R, Berger C, Gasparro F, Jegasothy B, Heald P, Wintroub B et al. Treatment of cutaneous T-cell lymphoma by extracorporeal photochemotherapy. Preliminary results. N Engl J Med. 1987 Feb 5;316(6):297-303.
13. Baird K, Wayne AS. Extracorporeal photo-apheresis for the treatment of steroid-resistant graft versus host disease. Transfus Apher Sci 2009 Dec; 41(3): 209-16.
14. National Institute for Health and Clinical Excellence (NICE). Developing NICE clinical guidelines: The guidelines manual 2009. [Cited on: September 20, 2010]. Available at http://www.nice.org.uk/aboutnice/howwework/developingniceclinicalguidelines/clinicalguidelinedevelopmentmethods/GuidelinesManual2009.jsp
15. López-Bastida J, Oliva J, Antoñanzas F, García-Altés A, Gisbert R, Mar J, Puig-Junoy J. Spanish recommendations on economic evaluation of health technologies. Eur J Health Econ. 2010 Oct;11(5):513-20.
16. INE (National Statistics Institute). Consumer Price Index. 2010 [Cited on: March 20, 2011]. Available at http://www.ine.es
17. Weinstein MC. Recent developments in decision-analytic modelling for economic evaluation. Pharmacoeconomics 2006; 24(11): 1043-53.
18. Burton P et al. Modeling in the economic evaluation of healthcare, selecting the appropriate approach. J Health Serv Res Policy. 2004; 9: 110-118.
19. Furiak NM, Ascher-Svanum H, Klein RW, Smolen LJ, Lawson AH, Montgomery W, Conley RR. Cost-effectiveness of olanzapine long-acting injection in the treatment of patients with schizophrenia in the United States: a micro-simulation economic decision model. Curr Med Res Opin. 2011 Apr;27(4):713-30.
20. Lee SJ, Flowers ME. Recognizing and managing chronic graft-versus-host disease. Hematology Am Soc Hematol Educ Program 2008: 134-41.
21. Scarisbrick JJ, Taylor P, Holtick U, Makar Y, Douglas K, Berlin G et al. U.K. consensus statement on the use of extracorporeal photopheresis for treatment of cutaneous T-cell lymphoma and chronic graft-versus-host disease. Br J Dermatol 2008; 158(4): 659-78.

22. Bolwell B, Fishleder A, Lichtin A, Koo A, Camisa C, Green R et al. Photopheresis in the treatment of chronic graftversus-host disease (cGvHD). Blood 1990;76:529a.
23. Bloom EJ. Telang GH, Jegosothy BV. Extracorporeal photochemotherapy in the treatment of chronic graft-versus-host disease after allogenic bone marrow transplantation. American Society of Clinical Oncology Annual Meeting, 1991:19–21.
24. Owsianowski M, Gollnick H, Siegert W, Schwerdtfeger R, Orfanos CE. Succesful treatment of chronic graft-versus-host disease with extracorporeal photopheresis. Bone Marrow Transplant 1994;14:845–8.
25. Sniecinski I, Smith B, Parker PM, Dagis A. Extracorporeal photochemotherapy for treatment of drug resistant chronic graft-versus-host disease. J Clin Aphresis 1995;10:51.
26. Balda BR, Kostantinow A, Starz H, Gnekow A, Heidemann P. Extracorporeal photochemotherapy as an effective treatment modality in chronic graft-versus-host disease. J Eur Acad Dermatol Venereol 1996;7:155–62.
27. Crovetti G, Carabelli A, Bertani E. Case report: chronic graftversus-host disease (cGvHD) treated with extracorporeal photochemotherapy (ECP). Florence, Italy: Sixth World Apheresis Association Meeting, 1996:137a.
28. Abhvankar S, Godder K, Chiang KY, Chrjstiansen N, Brown J, De Rienzo S et al. Extracorporeal photopheresis (ECP) with UVADEX for the treatment of chronic graft-versus-host disease (cGvHD). J Exp Hematol 1998;26:8.
29. Miller JL, Goodman SA, Stricklin GP, Lloyd EK. Extracorporeal photochemotherapy in the treatment of graft-versus-host disease. Abstract Book IBMTR/ABMTR Meeting Keystone Resort Colorado, 1998:7a.
30. Sniecinski I, Parker P, Dagis A, Smith B. Extracorporeal photopheresis (EP) is effective treatment for chronic refractory graft versus host disease. J AmSoc Hematol 1998;92:454.
31. Zic JA, Miller JL, Stricklin GP, King LE Jr. The North American experience with photopheresis. Ther Apher 1999;3:50–62.
32. Biagi E, Perseghin P, Buscemi F, Dassi M, Rovelli A, Balduzzi A. Effectiveness of extracorporeal photochemotherapy in treating refractory chronic graft-versus-host disease. Haematologica 2000;85:329–30.

33. Alcindor T, Gorgun G, Miller KB, Roberts TF, Sprague K, Schenkein DP, Foss FM. Immunomodulatory effects of extracorporeal photochemotherapy in patients with extensive chronic graft-versus-host disease. Blood. 2001;98(5):1622-5.
34. Gorgun G, Miller KB, Foss FM. Immunologic mechanisms of extracorporeal photochemotherapy in chronic graft-versus-host disease. Blood. 2002 Aug 1;100(3):941-7.
35. Perseghin P, Dassi M, Balduzzi A, Rovelli A, Bonanomi S, Uderzo C. Mononuclear cell collection in patients undergoing extra-corporeal photo-chemotherapy for acute and chronic graft-*vs.*-host-disease (GvHD): comparison between COBE Spectra version 4.7 and 6.0 (AutoPBSC). J Clin Apher. 2002;17(2):65-71.
36. Biagi E, Di Biaso I, Leoni V, Gaipa G, Rossi V, Bugarin C et al. Extracorporeal photochemotherapy is accompanied by increasing levels of circulating CD4+CD25+GITR+Foxp3+CD62L+ functional regulatory T-cells in patients with graft-versus-host disease. Transplantation. 2007;84(1):31-9.
37. Flowers ME, Apperley JF, van Besien K, Elmaagacli A, Grigg A, Reddy V et al. A multicenter prospective phase 2 randomized study of extracorporeal photopheresis for treatment of chronic graft-versus-host disease. Blood. 2008;112(7):2667-74.
38. Jagasia MH, Savani BN, Stricklin G, Engelhardt B, Kassim A, Dixon S et al. Classic and overlap chronic graft-versus-host disease (cGvHD) is associated with superior outcome after extracorporeal photopheresis (ECP). Biol Blood Marrow Transplant. 2009;15(10):1288-95.
39. Pérez-Carmona L, Harto-Castaño A, Díez-Recio E, Jaén-Olasolo P. [Extracorporeal photopheresis in dermatology]. Actas Dermosifiliogr. 2009;100(6):459-71.
40. Ratanatharathorn V, Ayash L, Reynolds C, et al. Treatment of chronic graft versus host disease with anti-CD20 chimeric monoclonal antibody. Biol Blood Marrow Transplant 2003;9:505-11
41. Canninga-van Dijk MR, van der Straaten HM, Fijnheer R, Sanders CJ, van den Tweel JG, Verdonck LF. Anti-CD20 monoclonal antibody-treatment in 6 patients with therapy-refractory chronic graft versus host disease. Blood 2004;104:2603-6.
42. Okamoto M, Okano A, Akamatsu S, et al. Rituximab is effective for steroid-refractory sclerodermatous chronic graft versus host disease. Leukemia 2006;20:172-3.
43. Cutler C, Miklos D, Kim HT, et al. Rituximab for steroid-refractory chronic graft-versus-host disease. Blood. 2006;108:756-762.

44. Zaja F, Bacigalupo A, Patriarca F, et al. Treatment of refractory chronic GVHD with rituximab: a GITMO study. Bone Marrow Transplant 2007;40:273-7.
45. von Bonin M, Oelschlagel U, Radke J, et al. Treatment of chronic steroid-refractory graft-versus-host disease with low-dose rituximab. Transplantation 2008;86:875-9.
46. Mohty M, Marchetti N, El-Cheikh J, Faucher C, Furst S, Blaise D. Rituximab as salvage therapy for refractory chronic GVHD. Bone Marrow Transplant 2008;41:909-11.
47. Teshima T, Nagafuji K, Henzan H, Miyamura K, Takase K, Hidaka M et al. Rituximab for the treatment of corticosteroid-refractory chronic graft-versus-host disease. Int J Hematol. 2009;90(2):253-60.
48. Peterson JD, Chan LS. Effectiveness and side effects of anti-CD20 therapy for autoantibody-mediated blistering skin diseases: A comprehensive survey of 71 consecutive patients from the Initial use to 2007. Ther Clin Risk Manag. 2009;5(1):1-7.
49. Magro L, Catteau B, Coiteux V, Bruno B, Jouet JP, Yakoub-Agha I. Efficacy of imatinib mesylate in the treatment of refractory sclerodermatous chronic GVHD. Bone Marrow Transplant. 2008;42(11):757-60.
50. Stadler M, Ahlborn R, Kamal H, Diedrich H, Buchholz S, Eder M et al. Limited efficacy of imatinib in severe pulmonary chronic graft-versus-host disease. Blood 2009; 114(17): 3718-9.
51. Magro L, Mohty M, Catteau B, Coiteux V, Chevallier P, Terriou L et al. Imatinib mesylate as salvage therapy for refractory sclerotic chronic graft-versus-host disease. Blood. 2009;114(3):719-22.
52. Olivieri A, Locatelli F, Zecca M, Sanna A, Cimminiello M, Raimondi R et al. Imatinib for refractory chronic graft-versus-host disease with fibrotic features. Blood 2009; 114(3): 709-18.
53. Heim D, Ebnöther M, Meyer-Monard S, Tsakiris D, Linn M, Tichelli A, Gratwohl A. G-CSF for imatinib-induced neutropenia. Leukemia. 2003 Apr;17(4):805-7.
54. Grant C, Wilson WH, Dunleavy K. Neutropenia associated with rituximab therapy. Curr Opin Hematol. 2010; 18(1):49-54.
55. e-Salud. Spanish cost database. Oblikue Consulting 2010. Available at http:\\www.oblikue.com.
56. General Spanish Council of Pharmacists. 2010. Available at http:\\www.portalfarma.com.

57. Couriel DR, Hosing C, Saliba R, Shpall EJ, Anderlini P, Rhodes B et al. Extracorporeal photochemotherapy for the treatment of steroid-resistant chronic GVHD. Blood. 2006 Apr 15;107(8):3074-80.
58. Claxton K, Schupher M, McCabe C, Briggs A, Akehurst R, Buxton M, et al. Probabilistic sensitivity analysis for NICE technology assessment: not an optional extra. Health Econ 2005; 14: 339-47.
59. Briggs AH. Handling uncertainty in cost-effectiveness models. Pharmacoeconomics 2000; 17 (5): 479-500.
60. Fenwick E, Marshall DA, Levy AR, Nichol G. Using and interpreting cost-effectiveness acceptability curves: an example using data from a trial of management strategies for atrial fibrillation. BMC Health Serv Res. 2006;6:52.
61. Rodríguez JM, Pérez F, Crespo C, González P, Antón E, Brosa M. The use of cost per life year gained as a measurement of cost-effectiveness in Spain: a systematic review of recent publications. Eur J Health Econ. 2011 Jun 10. [Epub ahead of print] DOI 10.1007/s10198-011-0326-y
62. de la Cámara R, Jarque I, Sanz MA, Grau S, Casado MA, Sabater FJ, Carreras E. Economic evaluation of posaconazole vs fluconazole in the prevention of invasive fungal infections in patients with GVHD following haematopoietic SCT. Bone Marrow Transplant. 2010 May;45(5):925-32.
63. Dall'Amico R, Livi U, Milano A, Montini G, Andreetta B, Murer L,et al. Extracorporeal photochemotherapy as adjuvant treatment of heart transplant recipients with recurrent rejection. Transplantation 1995;60:45-9.
64. Dall'Amico R and Messina C. Extracorporeal photochemotherapy for the treatment of graft-versus-host disease. Ther Apher 2002; 6(4): 296-304.
65. Maeda A. Extracorporeal photochemotherapy. J Dermatol Sci. 2009 Jun;54(3):150-6.

Figure

Fig. 1 Model structure

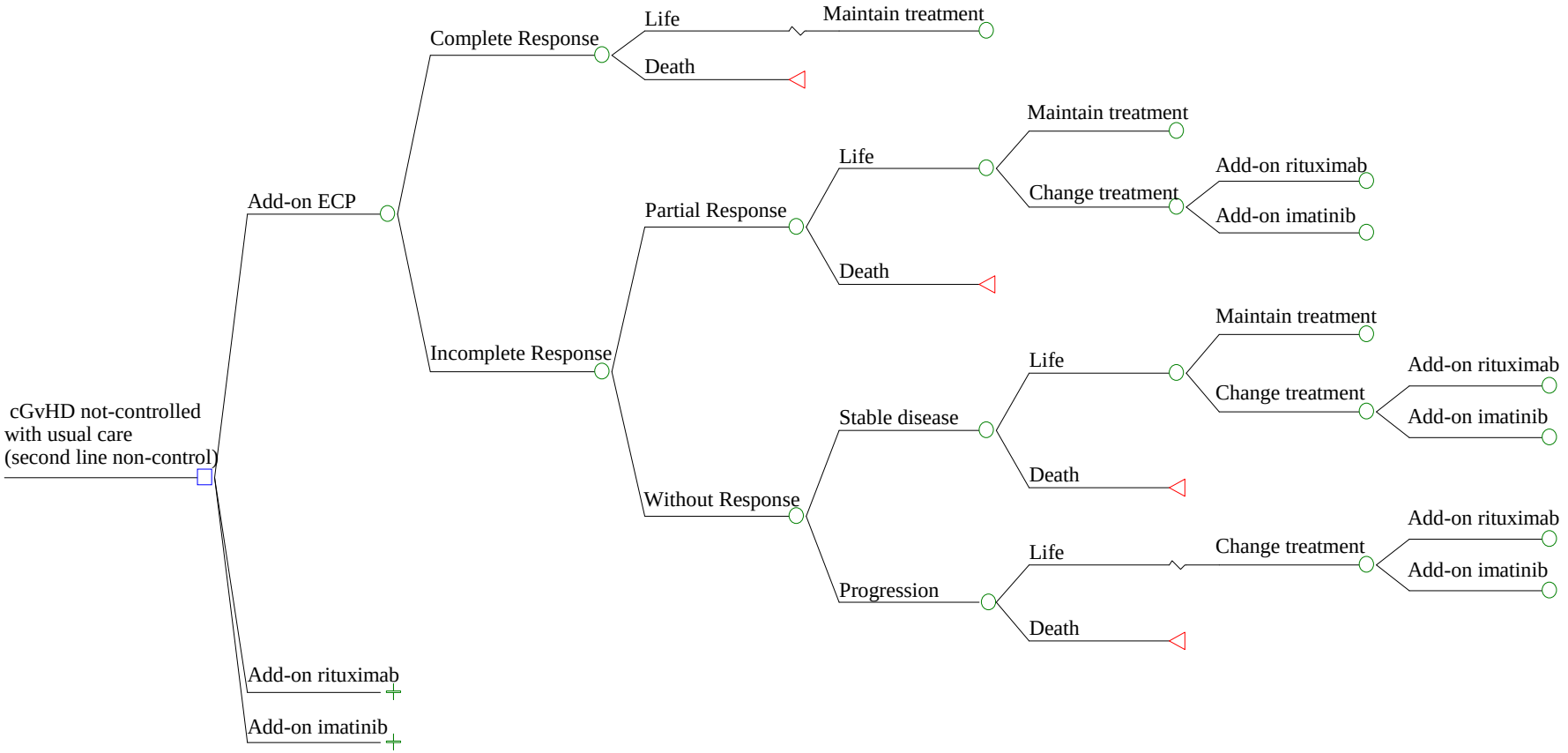
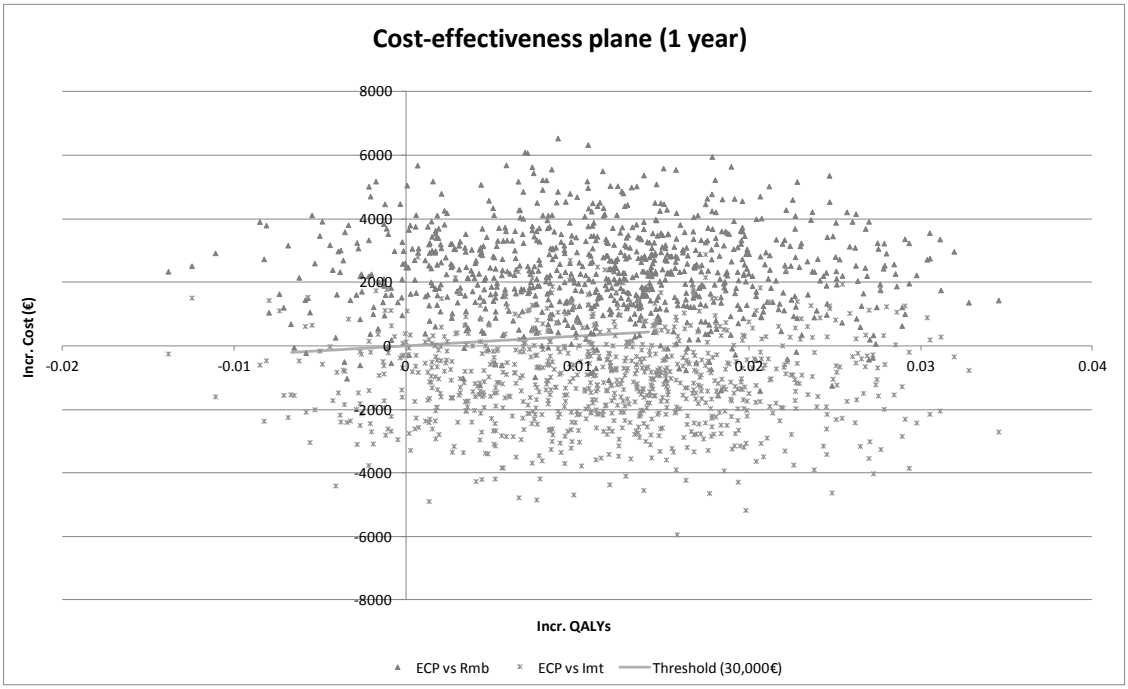
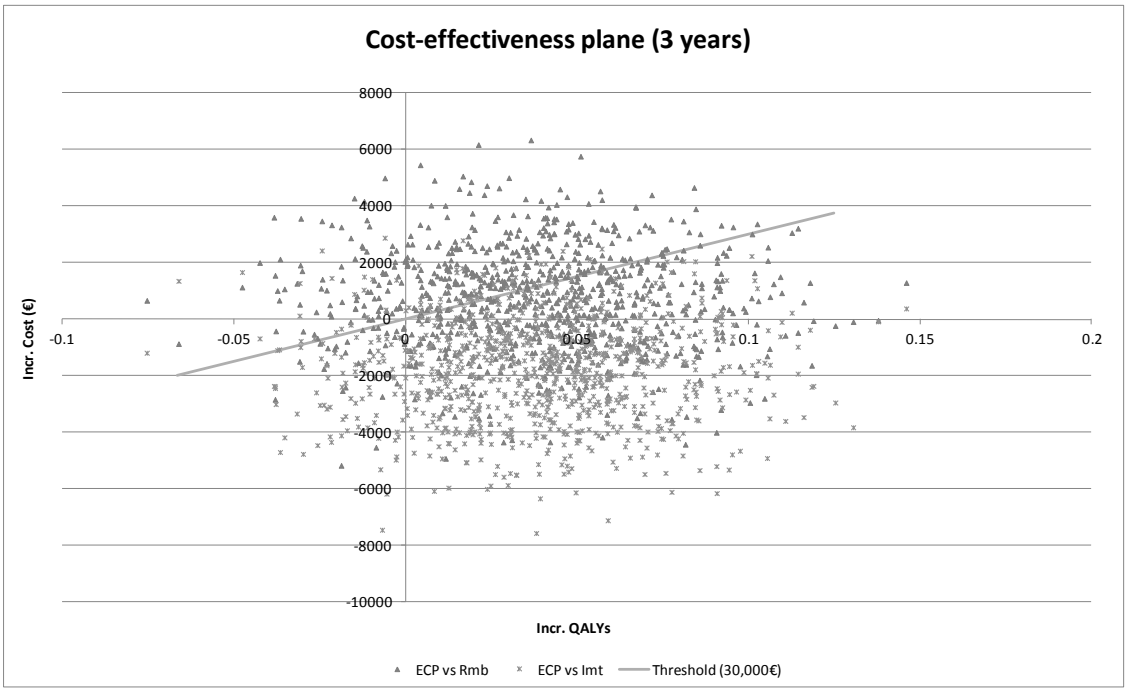


Fig. 2 Incremental cost-effectiveness plane (1, 3 and 5 years)





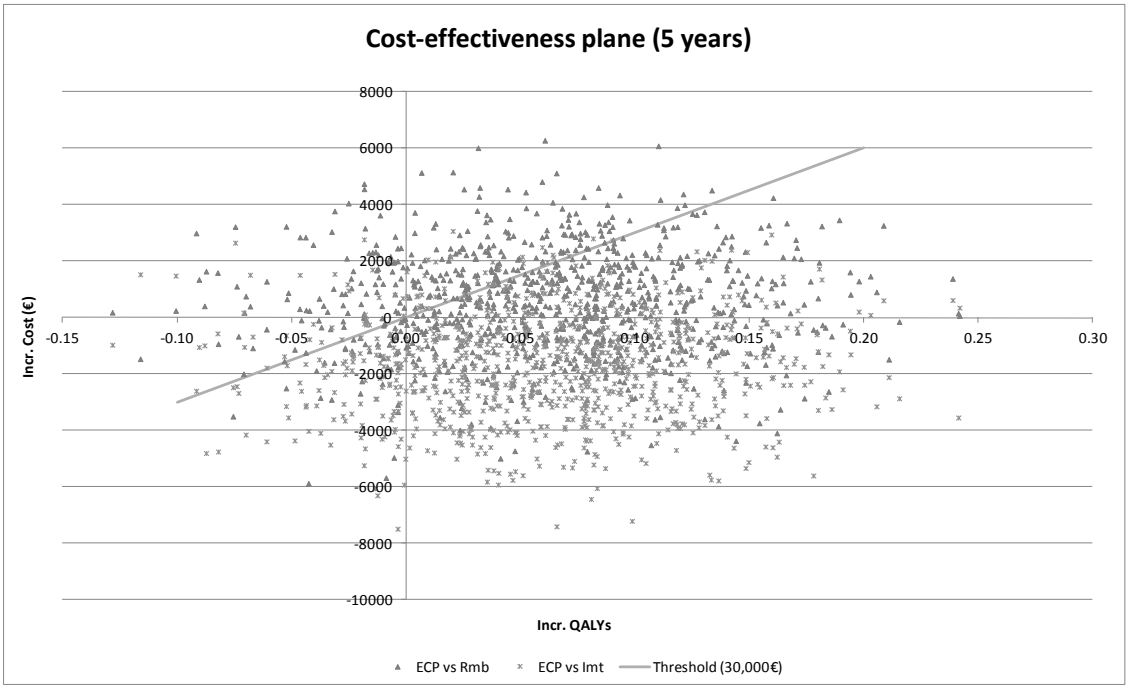
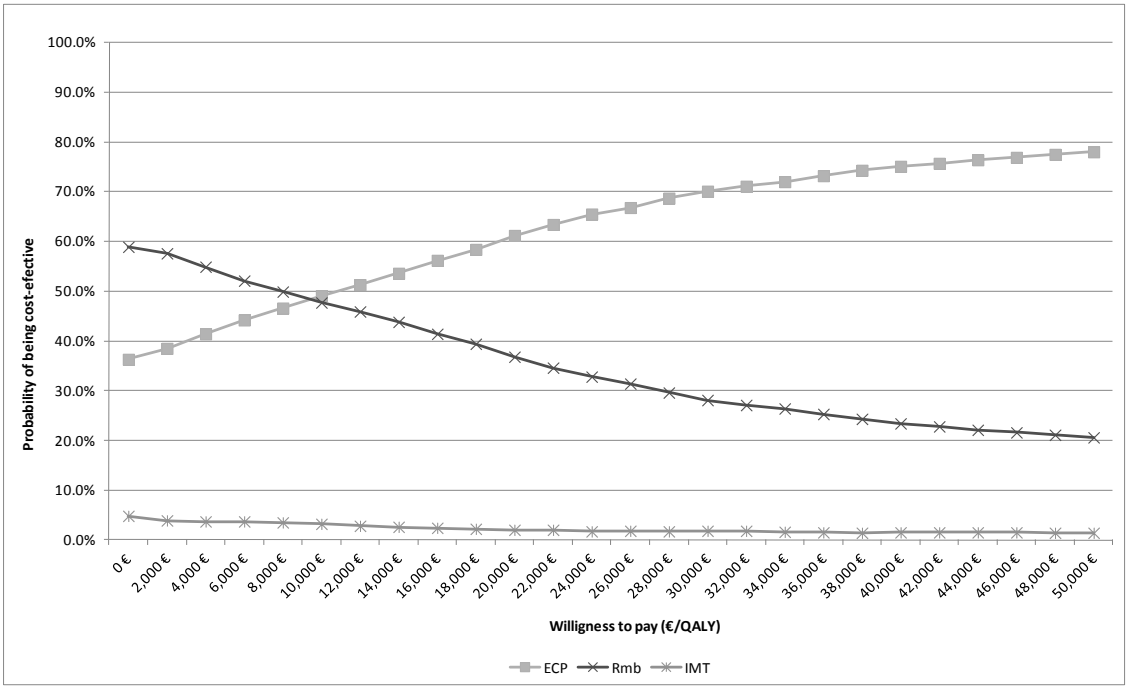

Cost-effectiveness plane (5 years)
8000
6000
4000
2000
0
-2000
-4000
-6000
-8000
-10000
-0.15
-0.10
-0.05
0.00
0.05
0.10
0.15
0.20
0.25
0.30
Incr. Cost (€)
Incr. QALYs
ECP vs Rmb
ECP vs Imt
Threshold (30,000€)

Fig. 3 Acceptability curve (5 years)



ECP: Extra-corporeal photophoresis. Rmb: Rituximab. Imt: Imatinib. QALY: Quality adjusted life year.

Table 1. Organ involvement

	Proportion of organ affected	Severity per organ	
Skin	88% (95%CI[a]: 86-90)	Mild	73.1% (95%CI: 61-85)
		Moderate	17.3% (95%CI: 7-28)
		Severe	9.6% (95%CI: 2-18)
Mucous membrane	43% (95%CI [a]: 40-48)	Mild	93.5% (95%CI: 87-100)
		Moderate	6.5% (95%CI: 0-13)
		Severe	0.0% (-)
Lung	22% (95%CI [a]: 17-26)	Mild	33.3% (95%CI: 9-57)
		Moderate	60.0% (95%CI: 35-85)
		Severe	6.7% (95%CI: 0-19)
Liver	38% (95%CI [a]: 34-42)	Mild	70.2% (95%CI: 57.83)
		Moderate	14.9% (95%CI: 5-25)
		Severe	14.9% (95%CI: 5-25)
GI	14% (95%CI [a]: 10-19)	Mild	60.7% (95%CI: 43-79)
		Moderate	32.1% (95%CI: 15-49)
		Severe	7.1% (95%CI:0-17)

a.95%CI: 95% Confidence Interval. GI: Gastrointestinal tract.

Sources: Pérez-Simón et al., 2008; Lee and Flowers, 2008; Scarisbrick et al., 2008; Bolwell et al. 1990; Bloom et al. 1991; Owsianowski et al. 1994; Sniecinski et al. 1995; Balda et al. 1996; Crovetti et al. 1996; Abhvankar et al. 1998; Miller et al. 1998; Sniecinski et al. 1998; Zic et al.1999; Biagi et al. 2000; Alcindor et al. 2001; Gorgun et al. 2002; Perseghin et al. 2002; Biagi et al. 2007; Flowers et al. 2008; Jagasia et al. 2009; Pérez-Carmona et al. 2009; Ratanatharathorn et al. 2003; Canninga-van et al. 2004; Okamoto et al. 2006; Cutler et al. 2006; Zaja F, 2007; von Bonin et al. 2008; Mohty et al. 2008; Teshima et al. 2009; Peterson et al. 2009; Magro et al. 2008; Stadler et al. 2009; Magro et al. 2009; Olivieri et al. 2009.

Table 2. Efficacy (Mean and 95% Confidence Interval) of ECP, Rtm and Imt. Literature review results. Model probabilities per cycle (3 months)

	Skin	Muc. memb	Lung	Liver	GI
ECP	(n: 723)	(n: 256)	(n: 128)	(n: 261)	(n: 70)
Complete Response	42% (38-45)	47% (41-53)	25% (17-33)	42% (36-48)	23% (13-33)
Partial Response	27% (23-30)	9% (5-12)	14% (8-20)	16% (12-21)	9% (2-15)
Stable disease	9% (7-11)	1% (0-2)	1% (0-2)	0% (-)	0% (-)
Progression	23% (20-26)	43% (37-49)	60% (52-69)	42% (36-48)	69% (58-79)
Rmb	(n: 167)	(n: 44)	(n: 10)	(n: 30)	(n: 0)*
Complete Response	41% (33-48)	18% (7-30)	0% (-)	3% (0-10)	0% (-)
Partial Response	35% (28-43)	30% (16-43)	30% (2-58)	27% (11-42)	0% (-)
Stable disease	4% (1-7)	9% (1-18)	20% (0-45)	10% (0-21)	0% (-)
Progression	20% (14-26)	43% (29-58)	50% (19-81)	60% (42-78)	0% (-)
Imt	(n: 58)	(n: 20)	(n: 31)	(n: 1)	(n: 10)
Complete Response	17% (8-27)	5% (0-15)	13% (1-25)	0% (-)	20% (0-45)
Partial Response	43% (30-56)	25% (6-44)	39% (22-56)	0% (-)	40% (10-70)
Stable disease	7% (0-13)	0% (-)	10% (0-20)	0% (-)	30% (2-58)
Progression	33% (21-45)	70% (50-90)	39% (22-56)	100% (-)	10% (0-29)

*100% stable disease assumed in the model. ECP: Extra-corporeal photopheresis. Rmb: Rituximab. Imt: Imatinib. Muc.memb: Mucous membrane. GI: Gastrointestinal tract.

Sources: ECP: Scarisbrick et al., 2008; Bolwell et al. 1990; Bloom et al. 1991; Owsianowski et al. 1994; Sniecinski et al. 1995; Balda et al. 1996; Crovetti et al. 1996; Abhvankar et al. 1998; Miller et al. 1998; Sniecinski et al. 1998;

Zic et al.1999; Biagi et al. 2000; Alcindor et al. 2001; Gorgun et al. 2002; Perseghin et al. 2002; Biagi et al. 2007; Flowers et al. 2008; Jagasia et al. 2009; Pérez-Carmona et al. 2009. Rmb: Ratanatharathorn et al. 2003; Canninga-van et al. 2004; Okamoto et al. 2006; Cutler et al. 2006; Zaja F, 2007; von Bonin et al. 2008; Mohty et al. 2008; Teshima et al. 2009; Peterson et al. 2009. Imb: Magro et al. 2008; Stadler et al. 2009; Magro et al. 2009; Olivieri et al. 2009.

Table 3. Model utilities, disutility and survival.

	Value	Source
Utilities		
Complete response	0.836	Lee et al., 1998
Partial response	0.786	Pidala et al., 2009
Stable disease	0.736	Pidala et al., 2009
Progression	0.696	Pidala et al., 2009
Disutility		
Neutropenia	0.09	Nafees et al., 2008
Neutropenia (days per episode)	6	Expert Opinion
Survival		
Low risk	92%	Pérez-Simón, 2009
Medium risk	71%	Pérez-Simón, 2009
High risk	9%	Pérez-Simón, 2009

Table 4. Pre-administration costs, pharmacological and administration costs, cost per disease state and cost of adverse events.

	ECP	Rituximab	Imatinib
Pre-administration costs	140.03	140.03	140.03
Pharmacological and administration costs			
Cost per session	1,125.50*	1,996.43	58.83
Standard care (3 months)	1,177.38		
First 3 months	12,380.49	7,985.73	5,294.50
Complete response			
From 4 months to 6 months	3,376.50	-	5,294.50
From 7 months to 9 months	3,376.50	-	-
From 10 months to end of treatment	-	-	-
Partial response			
From 4 months to 6 months	4,502.00	7,985.73	5,294.50
From 7 months to 9 months	3,376.50	-	5,294.50
From 10 months to end of treatment	3,376.50	-	5,294.50
Stable disease			
From 4 months to 6 months	6,752.99	7,985.73	5,294.50
From 7 months to 9 months	4,502.00	7,985.73	5,294.50
From 10 months to end of treatment	3,376.50	-	5,294.50
Cost per disease state			
Complete response (cost per visit)	59.87	119.74	59.87
First 3 months	299.35	598.70	299.35
From 4 months to 6 months	119.74	239.48	119.74
From 7 months to 9 months	59.87	119.74	59.87
From 10 months to end of treatment	59.87	119.74	59.87
Partial response (cost per visit)	1,735.92		
First 3 months	10,415.52		
From 4 months to 6 months	5,207.76		
From 7 months to 9 months	3,471.84		
From 10 months to end of treatment	1,735.92		
Stable disease (cost per visit)	2,674.96		
First 3 months	16,049.73		
From 4 months to 6 months	8,024.87		

From 7 months to 9 months	5,349.91		
From 10 months to end of treatment	2,674.96		
Progression	5,290.04		
First 3 months	42,320.32		
From 4 months to 6 months	21,160.16		
From 7 months to 9 months	21,160.16		
From 10 months to end of treatment	21,160.16		
Adverse events (AEs)			
Neutropenia			
Cost	689,18		
Frequency (%)	0	20	16
Hypogammaglobulinemia			
Cost	475,66		
Frequency (%)	0	20	0
AEs related to infusion			
Cost	8,58		
Frequency (%)	0	27	0
Catheter-related			
Cost	15,18		
Frequency (%)	10	0	0
Total cost AEs (annual)	1.52	235.32	108.09

Sources: eSalud, 2010; General Spanish Council of Pharmacists, 2010; expert opinion; Includes ECP kit, light assembly, Uvadex™ (methoxsalen), enoxaparin, physiological saline, hematology visits and nursing hours. Source: Johnson & Johnson internal data and panel of experts. All costs are expressed in 2010 euros. ECP: Extra-corporeal photophoresis.

Table 5. Cost per improvement gained, cost per life year gained and cost per quality-adjusted life year gained at 1, 3 and 5 years (ECP versus alternatives)

	COST Cumulative (€)	COST Difference	Imp[a]	Imp[a] gained	Cost per imp[a]	LY[b]	LY [b] gained	ICER [c]	QALY [d]	QALY [d] gained	ICUR [e]
1 year											
ECP	66,880.80 €		76.2%			0.933			0.740		
Rmb	64,554.14 €	2,326.66 €	69.9%	6.2%	37,412.75 €	0.928	0.005	501,868.32 €	0.728	0.011	202,646.35€
Imt	67,966.49 €	- 1,085.68 €	69.4%	6.7%	Dominant	0.919	0.014	Dominant	0.715	0.024	Dominant
3 years											
ECP	78,140.95 €		83.0%			2.581			2.111		
Rmb	77,465.83 €	675.12 €	81.0%	2.0%	34,031.64 €	2.547	0.034	20,053.89 €	2.073	0.038	17,745.12 €
Imt	80,012.36 €	- 1,871.41 €	80.8%	2.2%	Dominant	2.523	0.058	Dominant	2.049	0.062	Dominant
5 years											
ECP	85,700.66 €		79.2%			4.044			3.335		
Rmb	85,182.83 €	517.83 €	77.5%	1.7%	31,260.52 €	3.981	0.063	8,178.73 €	3.273	0.062	8,330.16 €
Imt	87,438.76 €	-1,738.10 €	77.0%	2.1%	Dominant	3.947	0.097	Dominant	3.240	0.094	Dominant

a. Imp: Improvement (% of complete or partial response). b. LY: Life year. c. ICER: Incremental cost-effectiveness ratio. d. QALY: Quality adjusted life year.

e. ICUR: Incremental cost-utility ratio. ECP: Extra-corporeal photophoresis. Rmb: Rituximab. Imt: Imatinib.