Adalimumab in the Treatment of Moderate-Severe Hidradenitis Suppurativa: A Cost-Effectiveness Analysis

Adalimumab no Tratamento da Hidradenite Supurativa Moderada-Grave: Análise de Custo-Efetividade

Sofia Borges[1], Tiago Torres[2], Nuno Menezes[3], Catarina Silva[4,5]

1. PharmD, Lisboa, Portugal
2. Centro Hospitalar e Universitário do Porto, Porto, Portugal
3. Hospital de Vila Nova de Gaia, Vila Nova de Gaia, Portugal
4. Eurotrials-Scientific Consultants, Lisboa, Portugal/CISP, Escola Nacional de Saúde Pública - ENSP, Lisboa, Portugal
5. Centro de Investigação em Saúde Pública (CISP) - Escola Nacional de Saúde Pública, Lisboa, Portugal

Corresponding Author:
Catarina Silva, Catarina.Silva@eurotrials.com
Rua Tierno Galvan, Torre 3, Piso 16, 1070-274 Lisboa, Portugal
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Abstract

Introduction: To assess the cost-effectiveness of adalimumab versus supportive care in the treatment of adults with active moderate to severe hidradenitis suppurativa who have had an inadequate response to or are intolerant of conventional systemic therapy in Portugal.

Methods: A Markov model with five health states (high response, response, partial response, non-response, or death) and 4-week cycles was developed to estimate long-term effectiveness and cost of treating patients with adalimumab versus supportive care. Data from head-to-head clinical trials (PIONEER I and II) were used to estimate transition probabilities and utilities. Resource use was characterized by Portuguese experts' panel. Unitary costs were extracted from national official sources and expressed in 2015 Euros. Incremental cost per quality adjusted life years gained was estimated for a lifetime horizon in the societal perspective, assuming a 3.5% annual discount rate for costs and consequences. Deterministic and probabilistic sensitivity analyses were performed.

Results: From the societal perspective, for a lifetime horizon, the model predicted a cost of €241,957 for adalimumab and €223,903 for supportive care, resulting in 12.32 and 11.55 quality adjusted life years (QALY), respectively. Thus, the incremental cost-effectiveness ratio is estimated to be €23,332/QALY gained (or €35,225/QALY from the Portuguese National Health System perspective). Patients receiving adalimumab incurred more treatment costs (+€39,243), partially offset by less direct medical costs (-€13,130) and indirect costs (-€7,877) than patients receiving supportive care. In deterministic sensitivity analyses, incremental cost-effectiveness ratios ranged between €1,347 (0% discount) and €42,465 (utilities' assumption). The probability of adalimumab's cost-effectiveness was 61.2% for a willingness-to-pay threshold of €30,000 and 78% for €50,000.

Conclusion: Adalimumab is the first and only drug approved by the European Medicines Agency for hidradenitis suppurativa and its cost-effectiveness in Portugal is demonstrated in this economic analysis.

Keywords: Adalimumab; Cost-Benefit Analysis; Hidradenitis Suppurativa/drug therapy; Portugal

Resumo

Introdução: Avaliar o custo-efetividade de adalimumab *versus* cuidados de suporte no tratamento de adultos com hidradenite supurativa moderada a grave com resposta inadequada ou intolerância à terapêutica convencional sistémica em Portugal.

Métodos: Modelo de Markov com cinco estadios (resposta elevada, resposta, resposta parcial, não-resposta ou morte) para estimar a efetividade e o custo de adalimumab *versus* prática clínica, a longo prazo. As probabilidades de transição e as utilidades foram extraídas de ensaios clínicos controlados (PIONEER I e II). O consumo de recursos foi estimado por um painel de peritos portugueses. Os custos unitários foram extraídos de fontes nacionais oficiais e expressos em Euros 2015. O rácio de custo-efetividade incremental por anos de vida ajustados pela qualidade ganhos foi calculado para um horizonte temporal "tempo de vida" considerando uma taxa de atualização de 3,5% para custos e consequências. Foram medidos custos diretos e indiretos. Realizaram-se várias análises de sensibilidade.

Resultados: Na perspetiva da sociedade, o modelo prevê um custo de 241 957€ para adalimumab e 223 903€ para os cuidados de suporte resultando num benefício de 12,32 e 11,55 anos de vida ajustados pela qualidade (QALY), respetivamente. Estima-se assim um rácio de custo-efetividade incremental de 23 332€/QALY (e de 35 225€/QALY na perspetiva do Serviço Nacional de Saúde Português). Os doentes em adalimumab incorrem num maior dispêndio com o custo do tratamento (+39 243€) o qual é parcialmente amortizado por um menor custo nos restantes cuidados médicos (-13 130€) e nos custos indiretos (-7877€), inferiores aos dos doentes em cuidados de suporte. Nas análises de sensibilidade determinísticas, os rácios de custo-efetividade incremental variaram entre 1347€ (taxa de atualização 0%) e 42 466€ (pressuposto relacionado com as utilidades). A probabilidade de adalimumab ser custo-efetivo para um limiar de disposição a pagar de 30 000€ e 50 000€ é de 61,2% e 78%, respetivamente.

Conclusão: Adalimumab é o primeiro e único medicamento aprovado pela Agência Europeia do Medicamento para a hidradenite supurativa tendo-se demonstrado ser uma opção custo-efetiva para Portugal nesta análise económica.

Palavras-chave: Adalimumab; Análise Custo-Benefício; Hidradenite Supurativa/tratamento; Portugal

Introduction

Hidradenitis suppurativa (HS) is a chronic, debilitating, inflammatory, systemic skin disease characterized by recurrent, painful, deep-seated lesions in apocrine gland–bearing areas of the body,[1,2] abscesses and inflammatory nodules often lead to fistulae and sinus tracts with suppuration and hypertrophic scarring.[2] Due to its clinical manifestations and subsequent symptoms, complications and disabilities (impairments, activity limitations, and participation restrictions), HS has a severe adverse impact on patient health-related quality of life (QoL).[3-5] Patients with HS have significantly decreased QoL (which reflects the disability caused by a disease) compared with the general population.[4] Alongside the physical complications (pain, discomfort, swelling, malodorous discharge, limitation of motility), patients are often psychologically distressed, suffering from embarrassment, helplessness, dependency, depression, and frustration, leading to social isolation.[2,3,6] The QoL impairment in HS is greater than in many other debilitating dermatologic conditions, such as psoriasis, acne *vulgaris* and chronic urticaria, even when the disease is mild.[6-8]

Diagnosis of HS is clinically established based on three criteria: typical lesions, typical topography, and chronicity and recurrence.[7] HS is highly underdiagnosed, and is often confounded with other diseases.[2,7] Moreover, there is a paucity of knowledge of this disease among general practitioners, surgeons, and even dermatologists.[2] As such, an established diagnosis takes an average of 8 years (*AbbVie Market Research: Living with HS, data on file*, July 2013).

HS is more frequent in women[2,9-12] and usually appears after puberty, with a peak age at onset of 22.1 years (± 8.2); prepubertal cases are exceptional.[2,13] Its etiology is essentially unknown and is probably multifactorial.[14] Risk factors include female gender, smoking habits, overweight/obesity, infection, familial history/genetics, and immunologic dysregulation (*Global Pipeline Summit, AbbVie internal document, 2012*).

There is no gold standard to measure HS severity; however, Hurley classification and Sartorius Severity classification are 2 commonly used scoring systems.[15,16]

HS affects approximately 1% of the general population,[17-19] though some estimates suggest numbers as high as 4%.[14,16] In Portugal, there is no HS

epidemiologic data available; however, an independent Portuguese experts' panel reviewed internationally published data and confirmed a prevalence of 1% for the Portuguese adult population, estimating that this disease affects > 80,000 Portuguese adults. Moreover, their perception is that approximately 25% - 30% have moderate to severe HS, with only 15% - 20% diagnosed, and only 65% of these patients receiving active treatment. The low treatment rate suggests that most patients are not treated by a dermatologist and/or abandon their physician or treatment.

The economic burden of HS is not well described, and to the best of our knowledge, no data are available for Portugal. Nevertheless, it is expected that medical resource use may be substantial (due to the recurrent nature of the disease, inaccuracy or time lag until diagnosis, and delay in treatment initiation), and that productivity loss may be high (due to absenteeism related to chronicity, clinical manifestations and symptoms, substantial morbidity, recurrence of episodes, invasiveness of treatments, and/or consequences of surgery). A recent study using a US medical claims database indicated that over a 3-year period, costs were $19,863 (about $6,666/year) for HS patients, with hospitalization representing 37.4% of total HS medical costs.[20] Regarding costs associated with HS productivity loss, data are lacking; nevertheless, a Polish study noted work absence in 58.1% of employed and professionally active HS patients (n = 30), 2.9 times/year, with an overall duration of 33.6 days. During a 2-year follow-up, 10% were dismissed from work due to frequent absenteeism and 23% experienced disease-related obstacles to promotion or advancement.[5]

HS represents a real therapeutic challenge. Treatment is not well established; however, it is now accepted that HS is associated with marked systemic inflammation. Therefore, the goal of treatment is to achieve systemic control of inflammation.[21] Choice of therapeutic modality depends on disease stage, clinical presentation, and patient characteristics.[22] Treatments vary from topical and systemic antibiotics, topical antiseptics and intralesional corticosteroids, to systemic retinoids and antiandrogen therapy, oral immunosuppressive agents or immunotherapy. Acute inflammation is often also treated with minor surgeries, such as abscess drainage with irrigation, and in more severe stages, wide surgical excision is frequently considered. Still, recurrence rate is high, even after wide-scale surgery, and post-surgical complications remain frequent, such as wound infections and suture dehiscence.[22-25] Many conventional treatments result in marginal and temporary efficacy and there is a lack of scientific evidence to support their use. Therefore, treatment of moderate to severe HS has been generally considered unsatisfactory.[26] By nature, the disease is multifocal and therefore not suitable for targeted therapy alone. Generally, a therapeutic strategy combining a medical and surgical approach best serves many patients. Initially, control of disease progression and inflammation is sought using medical therapy; once progression has been controlled, surgery is used to remove scar tissue predisposing to flares and continued progression of the disease. Throughout treatment, adjuvant therapy should be offered both to gain better control of the disease and to empower patients.[22]

Adalimumab (ADA), a fully human immunoglobulin G1 (IgG1) monoclonal antibody specific for tumour necrosis factor (TNF)-α, is the first and only drug approved by the European Medicines Agency (EMA) for the treatment of adults and adolescents from 12 years of age with active moderate to severe HS who have had an inadequate response to or are intolerant of conventional systemic HS therapy (*First Medicine Approved for Hidradenitis Suppurativa, press releases. EMA, June 26, 2015 and November 10, 2016*). No other medical treatments for HS have been approved by regulatory agencies, and the few available treatment algorithms are based primarily on expert opinion, case reports, and case series.[27,28] The clinical efficacy of ADA for the treatment of HS patients has been demonstrated in two phase III clinical trials, PIONEER I (M11-810) and PIONEER II (M11-313).[29] Both trials have shown that treatment with ADA, compared with placebo, was associated with better HS clinical response,[29] a composite measure defined by improvement in abscesses, inflammatory nodules, and draining fistulas.[30]

To date, an evidence-based therapeutic approach has not been the standard of care in HS and this is likely due to the lack of evidence-based treatment guidelines.[31] In 2014, treatment guidelines for HS were developed by the European Dermatology Forum (2014). More recently, based upon these guidelines, an evidence-based approach was suggested that includes level of evidence and strength of recommendation to produce a comprehensive and rational approach, which was then presented during the World Congress of Dermatology.[27,32] In this evidence-based approach, ADA is recommended as first-line treatment after failure of antibiotics (clindamycin

and rifampicin during 10 weeks), in patients with moderate to severe HS (Hurley's stage II to III).[32]
Besides safety and efficacy, it is critical that innovative health technologies demonstrate they are cost-effective for the society in which they will be delivered (this is also a requirement to obtain reimbursement in Portugal).[33] Hence, the aim of this economic evaluation was to assess the cost-effectiveness of ADA versus supportive care (SC) in the treatment of adults with active moderate to severe HS who have had an inadequate response to or are intolerant of conventional systemic therapy. This type of analysis incorporates health-related QoL impact based on the clinical effects of ADA and SC, and translates this impact into a generic outcome measure (i.e., cost per quality-adjusted life-year [QALY] gained), a widely used measure of health improvement that enables informed comparisons across different conditions and interventions and is used to guide healthcare resource allocation decisions.[34]

Methods

Model structure

A Markov model with 4 response states and a death state (Fig. 1) was developed based on the efficacy measures of the PIONEER clinical trials where: (a) high response is defined as ≥ 75% total abscess and inflammatory nodule (AN) count reduction, with no increase in abscesses or draining fistulas from baseline; (b) response, defined as ≥ 50% but < 75% AN reduction, with no increase in abscesses or draining fistulas from baseline; (c) partial response is defined as ≥ 25% but < 50% AN reduction, with no increase in abscesses or draining fistulas from baseline or ≥ 25% AN reductions, with an increase in abscesses and/or draining fistulas; (d) non-response, defined as < 25% AN reduction. A cycle length of 4 weeks was selected (except for the first 2 cycles of 2 weeks, each), taking into account the dosing schedule of ADA and the efficacy assessment time points in the PIONEER I and II trials (i.e., baseline, week 2, week 4, week 8, and every 4 weeks onwards). To estimate the cost and effectiveness of treatments, a half-cycle correction was applied to all calculations, except for ADA treatment and educational costs for patient's self-administration (which occur only once at the beginning of the cycle of the model as discrete events and not gradually over the model cycle). We assumed that all patients enter the model in the non-response health state and immediately after starting treatment with ADA or SC. At the beginning of each cycle, patients either remained in the same response state or transitioned to a different state based on transition probabilities. Moreover, patients in each response state can transition to death. During the simulation, costs and consequences were accumulated across the selected time horizon. The simulation stops when all patients are in the death state.

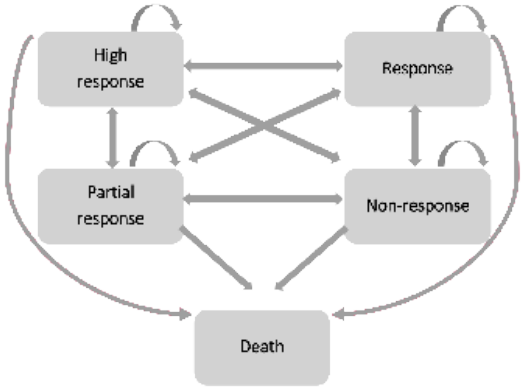


Figure 1 - Markov model structure

Data sources

Clinical trials

The clinical development program of ADA comprised phase III double-blind, placebo-controlled trials - PIONEER I (study M11-810) and PIONEER II (study M11-313)[29] - and a phase III, open-label extension study - OLE PIONEER (study M12-555) - to evaluate long-term safety, tolerability, and efficacy of ADA in patients with moderate to severe HS.[36]
PIONEER I (n = 307) and PIONEER II (n = 326) trials were similarly designed with two double-blind, placebo controlled periods.
In period 1 (induction), patients were randomized in a 1:1 ratio to ADA 40 mg every week (EW) or matching placebo for 12 weeks. All patients who received ADA and completed period 1 at week 12 underwent a second randomization for period 2 (maintenance) to ADA 40 mg weekly, every other week or placebo for 24 weeks; patients who received placebo in period 1 were reassigned in period 2 to ADA 40 mg weekly (in PIONEER I) or to placebo (in PIONEER II) and received that regimen for 24 weeks.
In PIONEER I, patients were required to stop any oral

antibiotics for HS for at least 28 days before baseline. Oral antibiotics during the trial were allowed only as rescue therapy (and patients were considered non-responders). In PIONEER II, patients were allowed to continue treatment with oral antibiotics for HS in stable doses (at the end of period 1, 15.3% of patients randomised to placebo were taking antibiotics). In both trials, patients were required to use a daily antiseptic wash on their lesions.

The primary efficacy endpoint was the proportion of patients achieving hidradenitis suppurativa clinical response (HiSCR) at week 12, defined as ≥ 50% reduction in AN count, with no increase in abscess count and no increase in draining fistula count relative to baseline (corresponding to high response and response states of the Markov model).

Patients who achieved HiSCR at week 12 continued in period 2 until end of study (week 36) or until loss of response (LOR), defined as an AN count greater than the average AN counts at baseline and week 12. Patients who did not achieve HiSCR at week 12 continued in period 2 until week 16 (and up to week 36). At or after week 16, patients who experienced a worsening or no improvement, defined as total abscess and AN count greater than or equal to count at baseline on two consecutive visits, at least 14 days apart, were discontinued from the study.

Patient-reported HS-related QoL outcomes were collected in the two studies: EuroQol-5 Dimensions (EQ-5D) index and visual analogue scale in PIONEER I and Short Form-36 Health Status Survey and Hospital Anxiety and Depression Scale in PIONEER II. The Work Productivity and Activity Impairment (WPAI) questionnaire was applied to evaluate the overall work impairment in both trials.

During period 2, patients who discontinued the study treatment had the opportunity to enter to OLE PIONEER study and receive open-label ADA 40 mg every week for at least 60 weeks. Only limited interim data was available at the time of model development and sample size was small (n = 57). Specifically, less than half of the patients had a follow-up longer than 24 weeks at the time of the interim data cut-off. Currently, this trial is still ongoing and patients have a mean follow up of 168 weeks.

Expert panel

An expert panel was conducted using Delbecq methodology specifically to collect data needed to customize the model to address the requirements for Portugal, as local data were not available from the literature/publically recognized sources. This panel was conducted in June 2015 by an independent contract research organization and included six expert Portuguese dermatologists (with or without surgery specialization) with recognized experience in the treatment of HS, who worked in Portuguese hospitals, treated HS patients in the 3 years prior to the panel, and had ≥ 5 patients with moderate/severe HS over the 12 months prior to the panel. Experts were selected from the 3 most populated regions of Portugal, providing national representation. Experts completed a questionnaire, developed based on international literature; presented individual estimates to the other members of the panel; and discussed until consensus. Consensus was obtained for all considered data: epidemiologic data, patient characteristics, characterization of current supportive treatment for HS, health resource use by health state and by adverse events (AEs), and productivity loss due to HS.

Interventions

Adalimumab

In the model, all patients treated with ADA had a complete 12-week induction period and received 160 mg at week 0, 80 mg at week 2, and 40 mg EW starting at week 4. At the end of the induction period, patients with non-response to ADA discontinued treatment and the remaining patients continued receiving ADA at a dose of 40 mg EW until treatment discontinuation or death. This was consistent with ADA treatment in PIONEER I and II and aligned with EMA recommended posology.

Supportive care

Considering there are no currently approved medical treatments available for HS other than ADA, and that HS treatment guidelines or characterization literature for Portugal are non-existent, SC was defined based upon the expert panel's opinion as a combination of drugs from various therapeutic classes, taking into account the severity (moderate/severe) and the phase of the disease (acute exacerbation/maintenance phase). In moderate HS, experts reported the use of antibiotics (oral, intravenous, topical) and analgesics with or without corticosteroids (intralesional or topical) for the acute phase (for a period of 3 months) and retinoids and hormonal treatments (oral corticosteroids and 5-α inhibitors) for the maintenance phase. In severe HS, experts described the use of antibiotics, analgesics, and antiseptics with or

without corticosteroids (systemic, intralesional, and topical) for acute exacerbations (for a period of 4.5 months) and retinoids and hormonal treatment (oral corticosteroids and 5-α inhibitors; in 90% of patients), immunosuppressive drugs (10%), or biologics (5%) for the maintenance period. In the model, SC is represented by the placebo arms in the PIONEER I and II clinical trials and provided to patients until discontinuation or death.

Surgery was not considered a comparator, given that surgery and ADA are not alternative or exclusive treatment choices. Patients receiving ADA in the clinical trials were allowed surgery for symptom control[29] (use of surgery after initiation of ADA is permitted by the EMA label, with possible dose interruption of ADA). Surgery is often considered only as a last resort, due to the risks it carries and the impact on patient QoL.[22-25]

Target population

The target population consisted of adults with active moderate to severe HS with an inadequate response to or intolerance of conventional systemic HS therapy consistent with the licensed population in the European Union, and also in line with the patient population evaluated in the PIONEER clinical trials. On average, patients were 35 years of age and 65.9% were female; the expert panel validated these characteristics as being applicable to Portuguese patients with HS.

Transition probabilities

Transition probabilities (TPs) during week 0-36 were derived separately for ADA and SC arms based on the observed cross-tabulations of patient's distribution among the 4 health states observed in PIONEER I and II studies.[29] Missing values were imputed using the non-responder imputation method (missing assessments including early roll-overs to the OLE PIONEER were counted as non-responders) to be consistent with the primary efficacy analysis imputation method specified in the clinical trial protocols.

Until week 12, the TPs for ADA treatment were based on all patients randomized to ADA observed during period 1. As the model discontinued ADA patients in non-response at week 12, the TPs of ADA during week 12-36 were based on ADA-treated patients who were week 12 responders. Only ADA-treated patients who received every week dosing regimens during the period 2 were considered to be consistent with the dosing regimen evaluated in the model. The TPs for ADA discontinuers during week 12-36 were generated based on patients who received ADA in period 1 and who then switched to placebo in period 2. The TPs for the SC arm were estimated using all patients who received placebo in both period 1 and period 2 of the clinical trials (i.e. disregarding patients who were switched from SC to ADA).

After week 36, extrapolation was required to estimate long-term transition probabilities. This extrapolation was based on week 12-36 data from the PIONEER I and II studies using generalized logit models (modelled TPs extrapolation). Last Health State Carried Forward (LSCF) extrapolation method, used as sensitivity analysis, assumed that proportions of patients in each health state after week 36 are kept constant for the remaining model period for ADA and SC. Because HS does not increase the risk of death, TPs from each response state to death were calculated based on all-cause mortality tables stratified by gender and age for the Portuguese population.[37]

Discontinuation rate from ADA

During the induction period (week 0–12), the model assumes no discontinuation from ADA. At the end of this period, non-responders are discontinued from ADA and responders continue to the maintenance period. Discontinuation rates during week 12 to 36 are based on constant discontinuation rates derived from the PIONEER I and II studies. For the period extending beyond week 36, patients on ADA are projected to discontinue ADA according to the response-specific discontinuation rates for responders and non-responders observed in the OLE PIONEER study[36] using generalized logistic models.

Utilities

Utilities for each health state were estimated using EQ-5D data from the PIONEER I study collected at weeks 12 and 36 (when patient responses to treatments were evaluated) independently of the treatment received. Utility values for patients with high response, response, partial response, and non-response were 0.782, 0.718, 0.576, and 0.472, respectively. Death was assumed to have a utility value of 0. The model did not separately consider disutilities for AEs because those were captured intrinsically during the clinical trial and because types and rates of AEs for the ADA arm were comparable to those of the SC arm. Moreover, disutilities for surgeries were not considered in the model due to lack of data.

Adverse events rates

The rates of AEs for patients receiving ADA and SC were based on rates of treatment-emergent mild, moderate, and severe AEs observed in the PIONEER I and II studies in the entire induction and maintenance periods. For simplicity, AEs were assumed to occur in the first 4 weeks of both the induction and the maintenance periods.

Time horizon, perspective, and discount rate

A lifetime horizon was chosen because HS is a chronic recurrent condition that adversely affects patient QoL over a long period of time. The base-case analysis was conducted from the societal perspective. An annual discount rate of 3.5% was applied to costs and consequences.

Costs

Direct medical costs included intervention costs (ADA or SC), other healthcare costs by health state, and costs of treatment-related AEs. Indirect costs included only costs due to work absenteeism due to surgery or incapacity to work due to symptoms. Costs are expressed in Euros for 2015.

Interventions

Adalimumab treatment cost was estimated based on dosing schedule and unit cost provided by the hospital price catalogue[38] adjusted to the compliance rate of ADA for the induction period (weeks 0–12, 88.8%) and maintenance period (week 12+: 87.4%). Compliance rates are based on the PIONEER I and II studies, minus 10% for adjustment to a real-world setting (theoretical assumption). Since ADA is self-injected subcutaneously, only patient education cost to self-inject ADA at the beginning of treatment was included, assuming a one-time session with a nurse (expert panel). SC cost was based expert panel recommendations after adjusting for a compliance rate identical to that of ADA.

Medical costs by health state (excluding interventions)

The model considered the cost of the following medical resources that are used to treat HS patients in primary and secondary healthcare settings: hospitalization related to HS surgery, outpatient follow-up visits related to HS surgery, outpatient visits for wound-care related to HS surgery, hospitalization unrelated to surgery, non-surgical follow-up outpatient visits, outpatient visits for wound care unrelated to HS surgery, and emergency department visits (without hospitalization). The model assumed that resource use was only dependent upon health state, and independent of treatments received. Resource use by health states was estimated based on inputs from the expert panel as previously described. The information was collected for patients with moderate and severe HS, separately, and was weighted based on the proportion of patients in each disease severity category, as observed in the PIONEER I and II studies. Health resource use is described in Table 1 and costs are described in Table 2.

Adverse events

The cost to treat/manage a mild or a moderate/severe AE was calculated based on the resource use provided by the expert panel (Table 2). These costs were then multiplied by incidence rates and applied in the simulation as a one-time cost in the first 4 weeks of both the induction and maintenance periods.

Productivity loss

Indirect costs were estimated based on the Human Capital approach considering earnings per patient and overall work impairment experienced by HS patients in working age. It was assumed that, for 2015, a lost working day corresponded to a loss of €94.33 for the Portuguese society. We used data on monthly net wages in the private sector reported by the National Statistics Institute,[39] grossed up by the employee's and employers' Social Security contributions and individual income taxes to estimate 2015 monthly labour costs for employers. We then multiplied them by 14 salaries so as to include the Portuguese standard vacation and Christmas extra monthly pay and divided by 230 working annual days (excluding weekends and official holidays).

Indirect costs were considered only in 80% of HS patients who were active workers (expert panel). On average, these patients missed 7 working days following surgery in moderate HS and 14 working days in severe HS (expert panel) for both genders. Indirect costs were considered until the patient reached retirement age (66 years in Portugal). Overall work impairment by health state was estimated based on the Work Productivity and Activity Impairment questionnaire applied in the PIONEER I and II studies. Mean overall work impairment (%) estimates by health state were: 15.13% in high response, 21.45% in response, 33.02% in partial response and 36.96% in non-response state.

Table 1 - Yearly health resource consumption in moderate and severe hidradenitis suppurativa by response state

	Moderate HS								Severe HS							
	High response		Response		Partial response		Non-response		High response		Response		Partial response		Non-response	
HS health resources	%	Units/ year	%	Units/ year	%	Units/ year	%	Units/ year	%	Units/ year	%	Units/ year	%	Units/ year	%	Units/ year
Surgery-related resources																
Inpatient HS surgery*	0%	-	0%	-	10%	1	20%	1	0%	-	0%	-	15%	1	30%	1
Outpatient HS surgery	5%	1	10%	1	20%	3	30%	4	5%	1	10%	1	35%	2	40%	2
General/plastic surgery visit	1%	2	2%	2	10%	2	20%	2	1%	2	2%	2	10%	2	40%	2
Dermatology visit	5%	2	10%	2	40%	4	50%	4	5%	2	10%	2	40%	4	30%	4
Home nursing for lesions/ wounds treatment	0%	-	0%	-	10%	2 weeks†	20%	3 weeks†	0%	-	0%	-	10%	2 weeks†	20%	3 weeks†
Outpatient treatment of lesions/ wounds	4%	2 weeks†	8%	2 weeks†	20%	3 weeks†	30%	3 weeks†	4%	2 weeks†	8%	2 weeks†	30%	3 weeks†	40%	3 weeks
Ambulatory drugs for treatment of lesions/ wounds	5%	1 week	10%	1 week	15%	2 weeks	30%	3 weeks	5%	1 week	10%	1 week	50%	2 weeks	70%	3 weeks
Ambulatory drugs for post-surgery pain	5%	1 week	10%	1 week	30%	2 weeks	50%	3 weeks	5%	1 week	10%	1 week	50%	2 weeks	70%	3 weeks
Not surgery-related resources																
Emergency visit	5%	1	20%	1	30%	3	50%	3	10%	1	20%	1	30%	3	50%	3
Hospitalization (e.g., cellulitis)	1%	1	3%	1	8%	1	12%	1	1%	1	5%	1	10%	1	20%	1
Dermatology visit	20%	2	40%	2	60%	3	75%	4	20%	2	30%	2	60%	3	70%	4
Home nursing for lesions/ wounds treatment	0%	-	0%	-	0%	-	5%	3weeks†	0%	-	0%	-	0%	-	5%	3weeks†
Outpatient treatment of lesions/wounds	0%	-	5%	2weeks†	10%	2weeks†	20%	3 weeks†	0%	-	5%	2weeks†	10%	3 weeks†	20%	3 weeks†
Ambulatory drugs for treatment of lesions/ wounds	0%	-	0%	-	30%	2 weeks	50%	3 weeks	0%	-	0%	-	5%	2 weeks	15%	3 weeks
Ambulatory drugs for HS--related pain	1%	2 weeks	10%	2 weeks	30%	3 weeks	50%	4 weeks	1%	2 weeks	10%	2 weeks	30%	3 weeks	50%	4 weeks

HS = hidradenitis suppurativa; *Surgery, complications, follow-up surgery, or re-surgery; †Three times weekly.

Table 2- Input costs of the model by perspective

	Society	NHS	Description
Unitary costs			
Inpatient/outpatient HS surgery*	€2,088.00	€2,088.00	51
Hospitalization not- HS surgery related (e.g. cellulitis)	€1,418.79	€1,418.79	49
Emergency visit	€170.94	€161.08	50
General/plastic surgery visit	€78.98	€75.27	50
Dermatology visit	€73.93	€70.22	50
Home nursing for lesions/wounds treatment: moderate/severe HS	€126.81/128.91	€119.41/121.51	49,50
Outpatient treatment of lesions/wounds: moderate/severe HS	€148.80/189.70	€145.09/185.99	49,50
Ambulatory drugs for treatment of lesions/ wounds, week	-	-	Not relevant
Ambulatory drugs for post-surgery pain, week	€11.85	€4.39	48, 52
Ambulatory drugs for HS-related pain, week	€8.46	€3.13	
Cost by health state			
High response	€204.43	€200.58	Resources for moderate and severe HS are described in Table 1 and unitary costs are described above; overall cost by health state was calculated assuming a ratio of 87.6%/12.4% for moderate/severe HS (expert panel)
Response	€487.22	€476.78	
Partial response	€2,525.31	€2,480.93	
Non-response	€4,709.54	€4,623.72	
Cost of interventions			
Adalimumab	€449.39	€449.39	Price for one pre-filled pen (40 mg/0.8 mL); ex--factory price
Supportive care	€43.68/cycle €568.05/year	€28.94/cycle €376.17/year	Most common drugs for each drug class were identified by the expert panel; hospital drug prices: ex-factory prices (estimated based on RRP minus VAT minus commercialization tax); ambulatory drugs: RRP prices without VAT
Cost of nurse educational session	€18.47	€16	One nurse visit
Cost of adverse events			
Mild	€165.51	€155.78	50% of patients require one consultation (not dermatology) and one emergency admission; 50% require antibiotics and the remaining are treated with analgesics
Moderate/severe	€1,787.38	€1,780.40	Average cost for moderate/severe infection (€1,290), upper respiratory tract infection (€4,107), pharyngitis (€1,601), diarrhoea (€1,537), and headache (€402)

HS = hidradenitis suppurativa; RRP = recommended retail price; VAT = value-added tax; *Surgery, complications, follow-up surgery or re-surgery. Notes: Society unitary costs included user charges and patient's drug out-of-pocket expenses; prices taken from reference [50] were updated to 2015 prices using Consumer Price Index.

Model outputs

It is expected that a new HS therapeutic drug will result in better patient QoL (or that patients will spend more time in health states with better health-related QoL). No gains are expected in overall survival because mortality risk is not increased with HS. Therefore, QALY was chosen as the effectiveness parameter.

The model estimated total costs and QALYs associated with each treatment arm. Total costs were estimated as the sum of drug costs, education costs for ADA administration, costs for treatment-related AEs, and resource use costs. QALYs for each arm were estimated as the time spent in each health state, weighted by the utility for each state.

The incremental cost-effectiveness ratio (ICER) was calculated as:

$$ICER = \frac{Cost_{Adalimumab} - Cost_{Supportive\ care}}{QALY_{Adalimumab} - QALY_{Supportive\ care}}$$

Sensitivity analyses

Deterministic univariate sensitivity analyses tested parameters related to model settings and model inputs, namely perspective, annual discount rate, clinical trial source, missing value imputation methods, extrapolation methods for estimating TPs beyond the trial period, compliance rate, medical costs (excluding interventions), utilities of health states, and ADA discontinuation rate.

A probabilistic sensitivity analysis simultaneously varied multiple parameters, based on their distributions, and re-estimated model outputs. Monte Carlo simulation of 5,000 random draws was applied in order to make random draws for parameter inputs. Dirichlet distributions were considered for TPs. Gamma distributions were used for direct medical costs and AE costs. Beta distributions were used for utilities and discontinuation rates.[40] A scatterplot of cost and QALY values on the cost-effectiveness plane was generated to display the simulation results of this probabilistic sensitivity analysis comparing ADA to SC. A cost-effectiveness acceptability curve was generated to illustrate the probability that ADA is cost-effective compared with SC at varying levels of willingness-to-pay (WTP) thresholds.

Results

Base-case analysis

Over a lifetime horizon, the model predicts a total cost of €241,957 for ADA and €223,903 for SC, leading to a cost difference of €18,054. Treatment with ADA and SC results in a total of 12.32 and 11.55 QALYs, respectively, corresponding to a gain of 0.77 additional QALYs with ADA (+7% than SC) (Note: model estimated a total of 26.5 discounted life years in both arms). Thus, the ICER is estimated to be €23,332 per QALY gained from a societal perspective (Table 3).

Patients receiving ADA had a higher intervention cost, which was partially offset by less medical costs and less indirect costs. Indirect cost was the major

Table 3 - Incremental analysis for base-case analysis

	Adalimumab	Supportive care	Incremental analysis
Total cost	**€241,957**	**€223,903**	**€18,054**
Intervention costs	€42,465	€3,222	€39,243
Education costs for ADA administration	€18	€0	€18
Medical costs (excluding interventions)	€79,461	€92,591	€-13,130
AE costs	€1,031	€1,232	€-200
Indirect costs	€118,981	€126,858	€-7,877
Total QALYs	**12.32**	**11.55**	**0.77**
ICER (€/QALY)	**€23,332**		

ADA = adalimumab; AE = adverse event; ICER = incremental cost-effectiveness ratio; LY = life-year; QALY = quality-adjusted life-year.

cost driver in both arms (49% and 57% in ADA and SC, respectively), followed by direct medical costs (33% and 41% in ADA and SC, respectively). Education costs for ADA administration and AE costs had a marginal impact in the incremental analysis.

Sensitivity analyses

Deterministic univariate sensitive analyses are described in Table 4. The ICER ranged between €1,347/QALY and €45,559/QALY and was more sensitive to the perspective, discount rate, clinical trial source, TPs for the ADA arm after week 36 and non-responder utility; ICER was less sensitive to the extrapolation method used in TP estimation after week 36, missing value imputation method used in TP estimation and medical costs.

In the cost-effectiveness plane of ADA versus SC (Fig. 2) obtained from the probabilistic sensitivity analysis, 4% of results were dominant cases and 57.2% had an ICER ‹€30,000, which led to 61.2% cases in which ADA was considered cost-effective relative to SC under a willingness-to-pay threshold of €30,000 (ADA was dominated in 0.6% cases). The probability of ADA being cost-effective at a threshold of €50,000 was 78% (Fig. 3).

Discussion

To the best of our knowledge, this is the first economic evaluation of HS treatment performed in Portugal. Due to the clear unmet need in the treatment of this burdensome disease, this study intended to demonstrate that the acquisition of ADA by Portuguese National Health System (NHS) hospitals is cost-effective independently of adopted perspective, as ADA has an added value for patients, third-party payers and society. In this study, we demonstrated that ICERs obtained in base-case and sensitivity analyses do not exceed the usual limits considered in other countries (Portugal does not have an official threshold for ICERs). Moreover, for a lifetime horizon, the model predicted that patients with active moderate to severe HS treated with ADA would experience marked improvement in terms of QALYs and disease severity relative to those treated with SC.

Despite the lack of national information on HS, we used the best available International and European data, as well as data from Portuguese hospital databases (Diagnosis Related Groups - DRGs), to triangulate data obtained. Moreover, this issue was partially overcome by convening a Portuguese experts' panel, which confirmed epidemiologic data, the characterization of current Portuguese clinical practice, and healthcare resource use.

This cost-effectiveness analysis (CEA) was managed following mainly national guidelines[35] (except discount rate) as well as Health Technology Assessment (HTA) agency requirements, such as National Institute of Health and Care Excellence (NICE) and pan-Canadian Oncology Drug Review (pCODR).[41] Moreover, the model was designed following Good Modelling Practices released by the International Society for Pharmacoeconomics and Outcomes Research Task Force.

The main strength of the model is that the core analysis comparing ADA to SC is based on direct evidence from the randomized PIONEER I and II studies, which evaluated ADA and SC among adults with active moderate to severe HS who have had inadequate response to or are intolerant of conventional systemic HS therapy. Evidence from direct head-to-head comparison in randomized controlled clinical trials is considered the "gold standard" because it eliminates the impact of unobserved confounders.[42] In addition, the model used all available data to inform relevant inputs (data from both phase III clinical trials were pooled for analyses where feasible). Alternative trial sources, such as only using one trial for either the maintenance period or both the induction and maintenance periods, were explored in sensitivity analyses.

Furthermore, EQ-5D results were collected in the PIONEER I study; these data were directly used to inform the utility values for each health state. EQ-5D is an appropriate QoL measurement instrument in patients with skin conditions[43,44] and is highly recommended by NICE,[45,46] with no need for alternative or indirect measures of determining QoL outside the trial setting. Extensive sensitivity analyses were also conducted to test the robustness of the model. Overall, the model results were robust to all studied inputs and the great majority of ICERs were below €35,000.

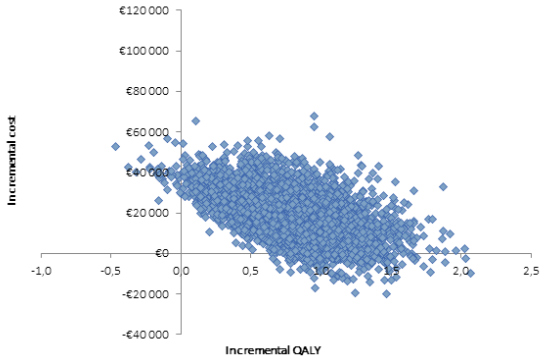
Limitations of the model include the following:

(a) There is a lack of long-term efficacy data for ADA and SC requiring extrapolation beyond the trial period. Modelled TPs extrapolation was the preferred approach and was applied in the base-case analysis. Sensitivity analyses were also conducted using mean TPs extrapolation where the TPs were estimated based on the mean TPs matrices from weeks 12 to 36. The extrapolation may be improved when long-term results from the OLE PIONEER study become

Table 4 - Deterministic univariate sensitivity analysis

Parameters	Base-case setting	Sensitivity analysis setting	ICER
Perspective	Society	NHS*	€35,225
Annual discount rate	3.5%	0%	€1,347
		5%	€33,084
		5% and NHS perspective	€45,559
Clinical trial source	Induction: PIONEER I and II for ADA and SC Maintenance: PIONEER I and II for ADA and PIONEER II for SC	Induction: PIONEER I and II for ADA and SC Maintenance: PIONEER II for ADA and SC arms	€34,892
		Induction: PIONEER II for ADA and SC Maintenance: PIONEER II for ADA and SC	€40,498
Transition probabilities extrapolation after week 36	Modelled TP extrapolation	Mean TP extrapolation	€20,929
Transition probabilities for the ADA arm after week 36	PIONEER I and II	PIONEER OLE	€35,556
Missing value imputation for transition probabilities	Non-responder imputation	Last observation carried forward	€18,923
Compliance in induction/maintenance period	88.8%/87.4%	98.8%/97.4% (PIONEER I and II)	€29,481
Medical costs (excluding interventions)			
Surgery-related medical costs	According to Table 2	-25%/+25%	€26,693/€19,972
Surgery not related medical costs	According to Table 2	-25%/+25%	€24,214/€22,450
Overall		-25%/+25%	€25,754/€19,090
Source of unitary costs	BDEA[50] and Portaria nº 20[49]	Portaria nº 20[49]	€27,172
Utilities			
High response	0.782	95% CI limit: lower/upper	€24,271/€22,463
Response	0.718	95% CI limit: lower/upper	€25,774/€21,313
Partial response	0.576	95% CI limit: lower/upper	€26,355/€20,931
Non-response	0.472	95% CI limit: lower/upper	€17,432/€35,271
ADA discontinuation rate per cycle	PIONEER I and II	Discontinuation rates for week 12–36 using PIONEER OLE	€24,844€
		-25% for non-responders after week 36	€31,915
		+25% for non-responders after week 36	€17,713

ADA = adalimumab; CI = confidence interval; NHS = National Health System; OLE = open-label extension; SC = supportive care; TP = transition probabilities.
* Considering only the drug cost part reimbursed by the NHS and excluding user charges and indirect costs.



QALY = quality-adjusted life-year.

Figure 2 - Monte Carlo simulations

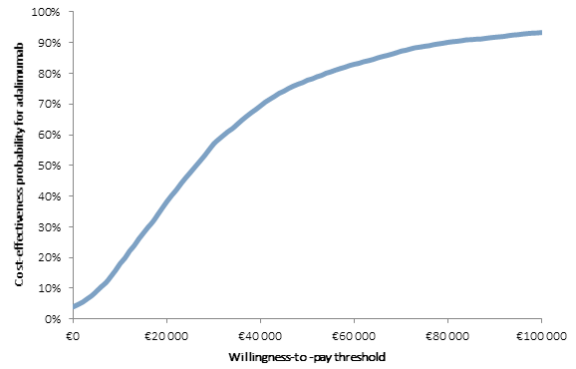


Figure 3 - Cost-effectiveness acceptability curve for adalimumab versus supportive care

available in the future (data were not available at the time of this cost-effectiveness study).

(b) There is a lack of real-world data relating to resource use by health states among HS patients. Frequencies of resource use were obtained from the expert panel, who accounted for specialists actively treating HS patients in Portugal. However, these results could benefit from future validation through comparison with real-world resource use incurred by HS patients through registries and/or observational long-term studies.

(c) Treatment received by patients randomised to placebo arm in PIONEER I and II does not completely overlaps supportive care as described by the Portuguese expert panel. This impacts on the external validity of transposing the effectiveness of placebo arm to the comparator (SC). Nevertheless, we consider that the direct comparison between ADA and placebo available in PIONEER I and II constitutes the best existent evidence to perform this study.

(d) No disutilities of AEs were considered in this economic evaluation. However, this should have a minimal impact on the results because AEs rates were similar between patients who received ADA and patients who received placebo in the phase III clinical trials. In addition, the utility of each health state used in the model was estimated based on all patients with the indicated health state from the clinical trial, which could have already included patients who were experiencing AEs.[47] In an indirect way, these disutilities were captured intrinsically by the QoL instruments administered during the clinical trials.

(e) Similarly, the model did not consider disutilities for surgeries due to lack of data. In addition, real-world surgery rates could be lower for patients who received ADA than for patients who received SC, given the demonstrated effectiveness of ADA for reducing signs and symptoms of HS. In this case, the exclusion of disutilities for surgery would be expected to provide a conservative estimate of the benefits of ADA in this model.

(f) The model used the compliance rate of ADA observed in the phase III clinical trials reduced by 10% (87.4%) because in the real-world, patient compliance is likely to be lower than that observed in clinical trials. This reduction is theoretical and may raise concerns about its implications on ADA treatment effect. Notwithstanding, this assumption may be interpreted and justifiable since a lower price for ADA is expected through hospital tenders (i.e. reducing the compliance on 10% is equivalent to reducing ADA price by the same amount). A sensitivity analysis was conducted, assuming a compliance rate according with PIONEER I and II study and the ICER maintained below €30,000/QALY.

(g) Utilities (patient preferences for a particular health state) were not measured in Portugal and the external validity of the utilities measured in the PIONEER I study may be questioned. Nevertheless, sensitivity analyses using 95% confidence interval limits showed no marked impact on ICERs.

Performing the cost-effectiveness analysis considering the NHS's perspective in the base-case analysis would have been incomplete, as HS appears in young active patients. This causes a tremendous burden on work productivity not only related to lost days of work (absenteeism) due to treatments, surgeries, and sick leaves, but also related to a lack of productivity at work (presenteeism) due to HS signs

and symptoms and their impact on health-related QoL. It is expected that absenteeism and presenteeism have a considerable impact on the economic burden of HS. Therefore, the societal perspective is preferred in the base-case analysis.

Unfortunately, presenteeism, family/caregiver support costs, and medical out-of-pocket costs during treatment, consultations, hospitalizations, and sick leaves due to surgery were not considered. Inclusion of these costs would have been favourable to ADA; a conservative approach was taken due to the lack of concise data. Non-medical costs paid for by patients were also excluded (e.g. homecare support, caregiver support, alternative medicine, homeopathy, bandages, wound dressings, and transportation).

Selecting the comparator is not always straightforward in economic evaluations, namely, when no drugs are approved for the disease and gold-standard guidelines are non-existent or outdated, and when there are no market research studies and no registries. Such was the case for HS. As such, we have selected the comparator based solely on expert opinion. The expert panel described treatment options, based on their clinical practice experience, which were aligned with the European Dermatology Congress guidelines.[27] Differences reflect a more conservative approach by Portuguese clinicians. Surgery was not considered as a comparator, given that surgery and ADA are not alternative or exclusive treatment choices. Patients receiving ADA in the clinical trials were allowed surgery for symptom control. Use of surgery after the initiation of ADA is permitted by the EMA label, with a possible dose interruption. Surgery is often considered only as a last resort, due to the risks it carries and the large impact on patient QoL.[23,24]

In the base-case analysis, a 3.5% discount rate was used rather than 5% as recommended by the Portuguese National Guidelines.[35] These same guidelines indicate that the choice of rate is subjective; there is no empirical way to calculate it. The choice of a lower rate for the base-case analysis is justifiable based on methodologic, economic, and natural dimensions of HS. The effects of a higher discount rate (5%) are considerably more pronounced on the results of a CEA in which interventions have clinical benefits that extend over a longer time horizon. This is the case in HS, a chronic persistent disease in which diagnosis occurs at a young age. Updating this discount rate in the National Guidelines is being discussed to more closely align it with the current economic environment. A lifetime horizon was chosen, as HS is a chronic disease and the benefits of ADA are expected to be maintained over the long-term.

Of note is the fact that the considered price for ADA in the base-case analysis is conservative because it represents the maximum authorized price.[48] In a real-world setting, a lower price is expected for ADA; therefore, real-world ICERs should be lower than those estimated in this economic analysis. Although the cost of treating AEs was considered, this component was irrelevant due to the low incidence rate.

Conclusion

In view of these results, ADA is considered to be a cost-effective option in the treatment of active moderate to severe HS in adult patients with an inadequate response to conventional systemic HS therapy from a societal and Portuguese NHS perspective. It would be of interest to confirm these results with real-world data after introducing ADA into current clinical practice. Effectiveness, health-resource use, productivity loss, and costs could be measured under real-world conditions to substantiate the findings of this study. The limitations of currently available treatment options indicate the significant unmet need in the treatment of HS. ADA is a valuable addition to the therapeutic armamentarium for the treatment of patients with this burdensome disease.

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The independent expert panel was crucial because it allowed for a better characterization of the population with HS in Portugal (epidemiologic characterization); it allowed accurate data to be obtained on clinical and treatment practice of the disease, as well as collection of health resource utilization data due to HS and to its complications.

Responsabilidades Éticas

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.

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Conflicts of interest: The authors have conflicts of interest to declare.

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Author's contributions

Tiago Torres and Nuno Menezes were involved in the independent expert panel, in the improvement and validation of the clinical text, in the review and approval of this manuscript, according to their areas of expertise. Catarina Silva and Sofia Borges customized the model to the Portuguese clinical setting, interpreted and analysed economic data, and developed, reviewed, and approved the publication. Catarina Silva provided medical writing and editing services in the development of this manuscript.

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