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Original Article

Modelling the cost effectiveness and budget impact of uterine botulinum toxin injections versus conventional treatment in severe dysmenorrhoea: A French perspective

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ABSTRACT

Objective: To assess the cost-effectiveness sand the budgetary impact of the combination of botulinum toxin (BT) + conventional treatment (CT) (hormonal treatments + analgesics) compared with CT alone in patients suffering from severe dysmenorrhoea, using a Markov model.

Methods: A Markov model was developed to estimate, from the perspective of French Health Insurance (HI), the cost effectiveness and the budgetary impact of BT+CT compared with CT alone. The main health states in the model were based on Visual Analogue Scale (VAS) scores and expert opinion. All model parameters were derived from a cohort of patients treated for 12 months at the Centre de Recherche de la Santé et de la Femme (CRSF) for severe dysmenorrhoea in 2021. A Cost-Utility Analysis (CUA) was carried out to assess the quality of life of patients, crucial in this context, in which the direct healthcare costs were considered in and Budget Impact Analysis (BIA). The main decision-making criteria were the Incremental Cost-Utility Ratio (ICUR) for the CUA and the net impact for the BIA. Deterministic and probabilistic univariate sensitivity analyses were performed to assess the robustness of our results.

Results: Over the 1-year time horizon (main analysis), the costs and quality-adjusted life year (QALY) of BT+CT versus CT alone were equal to €1895.65 vs €3055.20 and 2.03 QALYs vs 1.23 QALYs, respectively. Consequently, the ICUR equalled -€1651.5/QALY, which shows that, although the initial costs of BT are higher than those of CT, the reduced follow-up costs associated with the long-term efficacy of BT make it the most effective and economically dominant option at 1, 5 and 10 years. Sensitivity analyses show that 100 % of Monte Carlo iterations are below the willingness-to-pay threshold of €30,000[1]/QALY, making BT+CT an efficient strategy that could be adopted and reimbursed.

Conclusion: In the absence of a reference treatment for the management of severe dysmenorrhoea, BT+CT offering an improvement in quality of life, as well as a reduction in follow-up costs. It is therefore the most cost-effective strategy over 10 years.

1. Introduction

Chronic pain is a major public health problem in terms of frequency, difficulty of management and impact on quality of life. Young women suffer from dysmenorrhoea, with a cost effective treatment rates ranging from 41 % and 91.5 %, but severe dysmenorrhea (Grade 3 classification)

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[1] In the French system there is no defined threshold for cost effectiveness value, for evaluate cost effectiveness of BT we used values close to the threshold defined by NICE: £20000-£30000 per QALY

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occur in 16 % to 20 % [1–6]. Severe dysmenorrhoea often leads to negative cognitive, behavioural, sexual and emotional consequences and can even lead to disabling conditions in young women [7]. This is accompanied by a significant reduction in quality of life and work efficiency, as well as an increase in absenteeism and healthcare needs [6,8]. Management is based on conventional treatment (CT) (analgesics and hormonal treatments), with the aim of reducing pain and promoting amenorrhoea, but these prove ineffective for many patients, who experience severe pain both during and between their periods.

To date, there is no validated treatment for severe dysmenorrhoea for which conventional treatments have failed. A recent meta-analysis highlights interesting clinical results and concludes that the injection of botulinum toxin (BT) into the pelvic floor muscles could be an effective treatment for severe dysmenorrhoea [9].

In addition to these, promising results observed in patients who have failed CT, this innovative treatment (BT+CT) is costly, not reimbursed by French health insurance (HI) and has a potentially significant organisational and financial impact, both for institutions and patients. In this context, the main objective of this study was to evaluate the short- and long-term cost effectiveness of innovative treatment (BT+CT) compared with CT alone, using a Cost-Utility Analysis (CUA) defined by the Incremental Cost-Utility Ratio (ICUR) and the budgetary impact of adopting BT from the French HI's perspective.

2. Methods

2.1. Data source

Most of the data for the Markov model were derived from: the cohort of patients treated at the Centre de Recherche de la Santé et de la Femme (CRSF) for severe dysmenorrhoea; the demographic databases of the INED (National Institute of Demographic Studies); the literature; and the opinions of gynaecological experts. The cohort of patients studied was comprised of 220 patients, 120 of whom were on CT and 100 on innovative treatment (BT+CT).

Ethics approval: As regards Ethical approval letter, study was registered by the ethics committee (French /CPP south Mediterranean) under the number: 22.00391.000059 and by ANSM (The National Agency for the Safety of Medicines and Health Products) under the number: MEDAECNAT-2022–10–0055_2020–006,147–25; N° EudraCT 2020–006,147–25.

2.2. Treatments

Two treatments were compared in this study: Conventional treatment (CT) and innovative treatment (BT+CT). Patients referred to the CRSF in France who have failed first-line CT receive either an adapted CT (combined with a cognitive-behavioural approach or an injection of BT (After informed consent).

The adapted CT is composed as follows: level 2 and 3 analgesics (anti-inflammatories; opioids) and/or a specific treatment for neuropathic pain (duloxetine; venlafaxine) and/or hormonal treatments (progestogen and/or oestrogen) combined with cognitive-behavioural management (psychological follow-up + physiotherapy) as part of the conventional treatment, or a dose of 200 IU of BT as part of the innovative treatment.

2.3. Model structure & overview

The cost effectiveness of the innovative BT+CT treatment was evaluated using a Markov-type analytical decision model (Fig. 1) built and analysed with Microsoft Excel 2017 (with Visual Basic programming) [10]. Four health states were defined in the model to represent the evolution of the pathology. The three main health states were determined from the scores of the visual analogue scale (EQ-VAS), (from 0 "worst imaginable health state" to 100 "best imaginable health state") which provides a global assessment of the patients' health state [11]. As suggested by the Markov model, we have added the "death from all causes" health state, which constitutes the absorbing state from which individuals no longer transit.

Based on the advice of gynaecological experts and the work of [12, 13], the health states in the model were defined as follows: For a VAS score <30, pain is considered severe (SP); for a VAS score from [30-70], pain is considered mild to moderate (MMP); and for a VAS score >70, treatment is considered successful (S).

On the other hand, transitions to the death state were based on mortality rates according to sex and age in the general French population (Source INED France) [14].

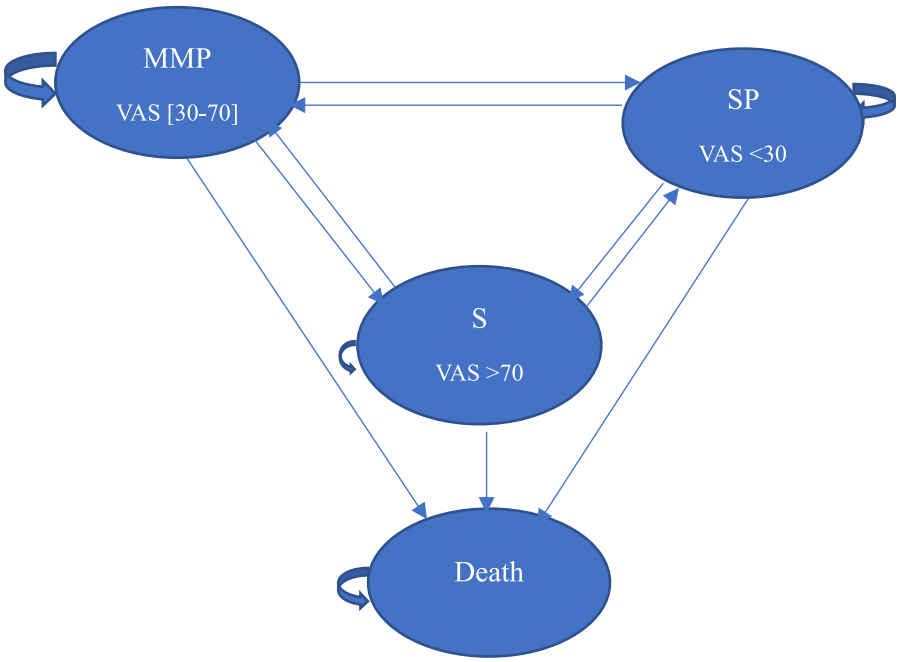

Fig. 1. Markov model.

The duration of the cycle was set at 6 months, which was consistent with CT guidelines [15] and the average duration of efficacy of BT observed in the majority of clinical studies is 6 months [16–20]. The total time horizon (TH) of this study is 10 years, with analysis points at 1 year (main analysis), 5 years and 10 years. The model is based on 1000 hypothetical patients who begin cycle 0 in the MMP state, then in cycle 1 remain in the same state (MMP) or change health state (SP, S, Death) according to transition probabilities.

Finally, we undertook a budgetary impact analysis (BIA), which is a financial approach designed to estimate the economic consequences of the introduction of BT in the management of severe dysmenorrhoea. It results from the difference in expenditure between the different treatment scenarios (with and without BT), over a TH of five consecutive years according to the perspective of the French HI. In practice, we estimated the size of the population in each scenario on the basis of data on the prevalence of dysmenorrhoea in France and determined the change in the number of patients per year using the incidence rate for the condition, which was equal to 3 %. Finally, expenditure in each scenario was equal to the number of patients per year, multiplied by the average cost of each treatment and the net impact was equal to the difference in expenditure per year between the two scenarios.

2.4. Model parameters

All of the model parameters are summarised in Table 1 and were derived from data from the CRSF patient cohort. The estimation methods are described in the following chapters.

2.4.1. Probability of transition

According to the evolution of the VAS score between the different time points M_0 (initiation of treatment), M_6 (follow-up visit) and M_{12} (review visit), we determined the different health states of the patients according to the classification of VAS scores established on the advice of gynaecological experts. At M_6 and M_{12}, for each health state, we counted the number of patients and then calculated the probability of transition. The probability of transition is the probability of observing the event in exposed individuals: it is therefore equal to the number of events observed during the period/number of individuals monitored during the same period [21].

The transitions included in the model reflect the natural clinical course of our cohort. We considered that there was a change in health status when the VAS score at M_6 and M_{12} was different from that at M_0. Otherwise, the patient had not experienced a change in health status. Although no transitions to death were observed in our cohort, the probabilities of transitions to death were derived from the age- and sex-specific mortality rates of the general French population [14].

As the total follow-up time of the cohort was 12 months, we made the assumption that the transition probabilities beyond the second cycle, i.e. after 12 months, would be the same as those for the second cycle [14]. We therefore applied the same probability of transition between the states of health in the second cycle to the rest of the cycles in the 5 to 10 year TH.

Finally, all our transition probabilities were derived from the CRSF patient cohort, as no economic study comparing the two treatments BT+CT vs CT in the management of dysmenorrhoea was available in the literature.

Table 1
Model parameters.

	(BT+CT)	CT	Sources
Probability of transition			
MMP →SP	0.17	0.75	Cohort CRSF
MMP → S	0.63	0.10	Cohort CRSF
SP → MMP	0.20	0.73	Cohort CRSF
SP → S	0.60	0.07	Cohort CRSF
S → SP	0.11	0.30	Cohort CRSF
S → MMP	0.68	0.50	Cohort CRSF
DEATH	0.000169986		INED
QALY			
MMP	0.79	0.74	Cohort CRSF
DS	0.38	0.29	Cohort CRSF
S	0.92	0.90	Cohort CRSF
COST			
MMP	937.09	1143.77	Cohort CRSF
DS	427.00	1378.04	Cohort CRSF
S	731.87	182.66	Cohort CRSF

2.4.2. Resource use and costs

This study includes both direct medical and direct non-medical costs. Direct medical costs we considered include medical consultations, paramedical procedures (physiotherapy, cognitive therapy), paraclinical procedures (imaging, biological tests), pharmacy (drugs and medical devices), and outpatient hospitalisation for the administration of BT, transport (car, bus) to go to the CRSF.

In practice, costs were valued as follows: direct medical costs - outpatient hospitalisation for the administration of BT 200UI was valued on the basis of the HLG[2] tariff: (300.76 euros) or the cost of procedures (medical or paraclinical or paramedical) or drugs was equal to the tariff reimbursed for (the procedure or drug) by the French HI; and direct non-medical costs - were valued on the basis of the tariffs reimbursed for transport by the French HI. These various reimbursed tariffs were taken from the Ameli.fr website. The costs used in the model were calculated on the basis of the consumption of care by CRSF patients in each of the health states. Thus, the cost of a health state is equal to the average cost of care consumed by patients in that state at M6 and M12. For each cycle of the model, the expected costs of the treatment groups were calculated by multiplying the number of surviving patients in each health state by the average cost associated with the health state under consideration and then summing the costs obtained in the different health states. Depending on the TH (1, 5 and 10 years), the total cost of treatment was calculated by adding together the discounted costs of the different cycles. Finally, the average cost is equal to the total cost divided by 1000. Adverse events and their potential cost implications have not been explicitly considered in the model, but they are taken into account in the QALYS estimate. Moreover, they were relatively minor, transient and unlikely to be associated with significant implications for overall costs [22].

2.4.3. Effectiveness and QALYs

In practice, quality-adjusted life-years (QALY) data, measured using the EQ-5D-5l scale, were analysed in detail at M6 and M12 in order to estimate the mean QALYs corresponding to each of the health states in the model, as well as their evolution over time. At each cycle of the model, the expected QALYs of the treatment groups were calculated by multiplying the number of patients surviving in each health state by the QALYs associated with the health state under consideration, then summing the QALYs obtained in the various health states. As the total duration of follow-up was 12 months, the assumption was made that the average QALYs per health state beyond the second cycle, i.e. 12 months, would be the same as those for the second cycle [14].

2.5. Sensitivity analyses

The statistical uncertainty surrounding the estimation of the model parameters and the ICUR was taken into account respectively from univariate deterministic and probabilistic sensitivity analyses (PSA) based on Monte Carlo simulations with 1000 replications for each treatment group [10,14,23,24].

The PSA was initiated to take into account the uncertainty associated with sampling fluctuations. The corrected beta distribution was used to

[2] Homogeneous living group (HLG) tariff defined by French HI

adjust the uncertainty around the TPs because our Markov model had more than two states of health. The beta distribution was also defined for health-related utility data and the gamma distribution for cost parameters [14].

In addition, a Cost-Effectiveness acceptability curve was plotted to determine the probability of cost effectiveness of the innovative treatment (BT+CT) compared with CT alone as a function of the cost effectiveness threshold selected by the decision-maker.

Finally, the uncertainty surrounding the ICUR was assessed using two separate deterministic sensitivity analyses. The first sensitivity analysis consisted of an increase in HLG tariffs of 10, 20 and 30 %, while the second examined the effect of a variation in the discount rate of 0 %, 2.5 % and 6 % as well as the impact of the TH. The duration of the analysis was thus extended to 5 and 10 years, assuming that the effects and the costs would remain the same [10].

3. Results

3.1. Cost-utility

The innovative strategy (BT+CT) was associated with a reduction in pain and a reduction in the consumption of care compared with CT over the THs of 1 year (main analysis), 5 years and 10 years. The results of the CUA, summarised in Table 2, show that the estimated ICUR for the innovative strategy (BT+CT) versus CT alone was equal to -€1651.5/QALY gained at 1 year (main analysis); then -€1486.63/QALY gained and -€1314.46/QALY gained at 5 and 10 years respectively.

Analyses at 1, 5 and 10 years show that the ICUR for the innovative strategy (BT +CT) are below the cost effectiveness threshold of €30,000/QALY. Thus, the reduction in healthcare expenditure and the improvement in quality-of-life show that the monetary value of the health gain is greater than the additional cost incurred by outpatient hospitalisation for the injection of BT.

3.2. Sensitivity analyses

The results of the various scenarios are presented in Table 3. The results show that the ICUR is not sensitive to a lengthening of the TH; to a variation in the discount rate of 0 %, 6 %; and to an increase in the HLG tariff of 10 % to 30 %. None of these analyses increased the ICUR compared with the main analysis (-€1651.5/QALY gained); on the contrary, the absolute value of the ICUR tended to decrease over time, also showing the robustness of our primary results. No scenario exceeded the willingness-to-pay (WTP) threshold of €30,000/QALY and innovative treatment remained the dominant strategy.

Finally, the probabilistic sensitivity analysis carried out on the 1, 5 and 10-year THs made it possible to plot the various cost-effectiveness acceptability curves for the innovative strategy (Fig. 2). These represent the probabilities that the innovative treatment will be efficient at various WTP. After analysing the cost-effectiveness acceptability curves, 40 % of replications were judged to be efficient at a WTP threshold of €0/QALY gained and 100 % at WTP threshold of €5000/QALY gained, whatever the TH of the analysis.

Table 2
Cost-utility analyses for time horizon of 1, 5 and 10 years.

Treatment	Mean costs, (€)	Mean (QALYs)	ICUR (€/ QALY gained)
1 year (Base case)			
CT	3055.20	1.23	
BT+CT	1895.65	2.03	
Incremental: (BT+CT) vs CT	−1159.55	0.80	−1651.50
5 years			
CT	10,978.86	4.45	
BT+CT	7068.04	7.76	
Incremental: (BT+CT) vs CT	−3910.82	3.31	−1486.63
10 years			
CT	18,698.29	7.59	
BT+CT	12,132.52	13.53	
Incremental:(BT+CT) vs CT	−6565.78	5.94	−1314.46

Table 3
Sensitivity analyses scenari.

Scenario	Key Assumption	ICUR	STATUS
Time horizon	Time horizon increased to:		
	5 years	−1486.63€	Dominant
Dominant	10 years	−1314.46€	Dominant
Discount rate	Discount rate decreased and increased to:		
	Costs and effects discounted at 0 %	−1651.50€	Dominant
	Costs and effects discounted at 2.5 %	−1246.38€	Dominant
	Costs and effects discounted at 6 %	−1249.57€	Dominant
HLG	HLG tariff increased to:		
	10 %	−1117.1€	Dominant
	20 %	−871.2€	Dominant
	30 %	−684.7€	Dominant

3.3. Budget impact analysis

Table 4 summarises the estimated characteristics of the target population and the expenditure associated with the introduction of BT in the management of severe dysmenorrhoea over 5 years in the perspective of the French (HI).

The target population, made up of patients who had failed conventional treatments, was estimated at 450,702 patients based on INSEE data for 2021 and varied annually as a result of incident cases. With an annual incidence rate of severe dysmenorrhoea estimated to be 3 %, the population varied from 450,702 in the first year to 516,539 in the fifth year and expenditure per scenario (with and without BT) was equal to (€320,052,518 vs. €221,961,420) in the first year and (€366,804,745 vs. €254,384,856) in the fifth year. The net impact varied from €98,091,098 to €112,419,889, i.e. a difference of €14,328,791 over the 5 years for the administration of a 200 U dose of BT (Fig. 3).

4. Discussion

In general, dysmenorrhoeic pain is accompanied by severe psychosocial repercussions and an increase in healthcare consumption [25]. Furthermore, healthcare practice indicates that a high number of patients who have failed CT, continue with several changes of therapeutic drug classes, despite the lack of sustained improvement. In view of the numerous treatment failures observed in the management of severe dysmenorrhoea, many centres administer BT to patients who have failed CT for its muscle-relaxing effects. In view of the clinical effectiveness showed in various studies [16,17], it was required to assess the effectiveness of BT to guide institutional decision-making regarding its inclusion on the list of reimbursed products.

Without being a chronic pathology, dysmenorrhoea is defined as cyclical pain [5,6]. Therefore, any appropriate assessment of treatment must reflect a long-term perspective [10]. To date, no published study has evaluated the clinical efficacy and effectiveness of BT+CT compared with CT alone in the long-term. Our preliminary study (under review) evaluated the ICUR of BT over a 1-year TH based on data from the pilot study, but this TH is limited because it does not take into account the administration of a new dose of BT and other cost as well as quality-of-life factors associated with longer-term treatment failures. This new study has therefore been extended to a 5- and 10-year TH to assess the impact of these factors on the efficacy of BT+CT in the medium and long term.

The results of the study at 5 and 10 years confirm that the combination of BT and CT is a cost effective treatment strategy after the failure

Fig. 2. Cost effectiveness acceptability curve.

Table 4
Budget impact analysis.

Target population and incremental potential of BT					
Population effective (women 20- 54 years of age)					14,639,893[3]
Prevalence of dysmenorrhoea in France (women 20- 54 years), % (no.)					47 %[4] (6960,649)
Diagnosed and Treated					80 %* (5568,519.2)
Moderate dysmenorrhoea					74.1 % (5157,840.9)
Severe dysmenorrhoea					25.9 %* (1802,808.1)
In whom CT failed					25 %* (450,702.025)
Target patient population 450,702.025: curent scenario					
Patient treatment rates by therapy in %		CT 98 %			BT + CT 2 %
		Budget impact			
Annual incidence of Severe dysmenorrhoea			3 %*		
	1 year	2 years	3 years	4 years	5years
Evolution of Patients with S dysmenorrhoea/year	450,702	464,223	478,149	492,493	507,267
Total Patients who receive CT alone (Scenario without BT)					
CT alone	441,687	454,938	468,587	491,464	506,208
Total Patients who receive BT+ CT (Scenario with BT + CT)					
(BT+ CT)	450,702	464,223	478,149	492,493	507,267
Budget impact of CT alone treatment, € (Scenario without BT) (a)					
	221,961,420 €	228,620,294€	235,479,427€	246,975,604€	254,384,856€
Budget impact of BT+ CT treatment, € (Scenario with BT + CT) (b)					
	320,052,518€	329,654,107€	339,543,735€	356,121,132€	366,804,745€
Net impact, €	98,091,098€	101,033,813€	104,064,308€	109,145,528€	112,419,889€

[3] INSEE insee.fr/fr/statistiques/2,381,474
[4*] IZidore estelle Dysménorrhées primaires et absentéisme scolaire [13].

of first-line CT. In fact, although the initial costs of BT are higher than those of CT, in the medium and long-term, we observed that these initial costs are offset by a reduction in the costs of follow-up and consumption of care by patients having undertaken BT due to the reduction in pain and to the improvement in quality of life, unlike patients on CT, who require repeated treatments. In addition, the reduced long-term follow-up costs in the BT arm resulted from the reduction in the consumption of conventional care (analgesics, hormonal treatments and neuropathic pain medication) as well as daily allowances linked to time off work. To date, no study has confirmed or refuted the reduction in expenditure associated with the use of BT observed in our study. On the other hand, (Dawood, 1988) [26] work in the United States reports an annual loss of 600 million working hours, or approximately 2 billion dollars ($), due to chronic pelvic pain, which confirms the economic losses due to work stoppages and over-consumption of care that we observed in the CT alone group. In the absence of a marketing authorisation, a standard protocol on dose, side-effects and time to reinjection of BT validated by the FHA, several deterministic sensitivity analyses were carried out on these key parameters. These additional analyses supported the robustness of our results. However, a randomised clinical trial on a representative sample of dysmenorrhoeic patients will be required to confirm or refute the cost effectiveness of BT and to estimate the annual losses in health expenditure associated with the use of CT in France. This will be the subject of future work in the CRSF.

Since 2018, several French centres have offered compassionate uterine BT injections outside the marketing authorization (MA) to patients with severe pain for whom all other treatments have failed, but there are no published studies in the French context to determine the financial consequences of adopting BT, in the management of severe dysmenorrhoea from the French (HI) perspective as well as the

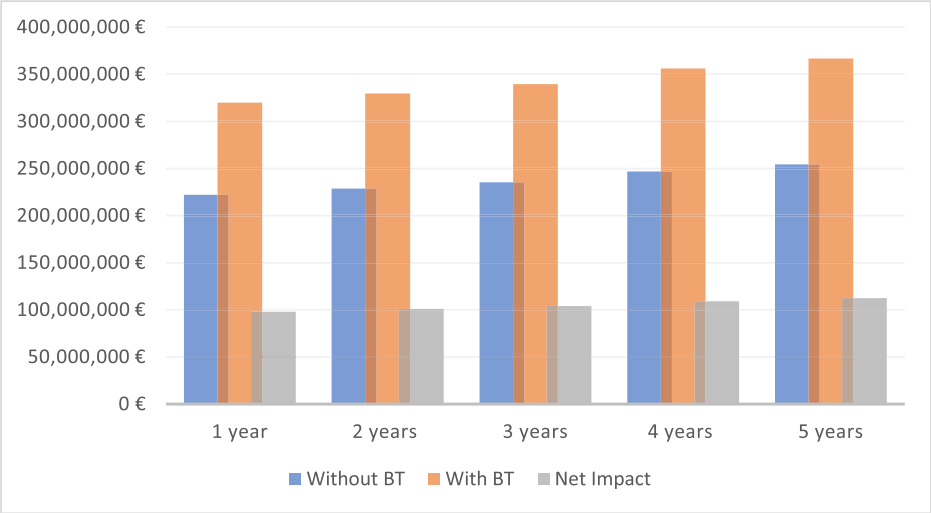

Fig. 3. Potential budget impact of introducing BT to Severe dysmenorrhoea during five years.

consequences in terms of quality of life. This study therefore fills the data gap and provides information on the healthcare expenditure associated with the introduction of BT in this context. Our results indicate an annual increase in healthcare expenditure of around 30 % when all patients receive BT. These results need to be confirmed by more recent data on the target population to better guide the decision-making.

One of the main limitations of our study is the lack of clinical data comparing BT+CT and CT in terms of efficacy, resources consumed complication rates and effects on long-term quality of life. As a result, we had to make several assumptions, including the extrapolation of probability of transition, costs and health state utility scores observed during the 1- to 10-year follow-up period, keeping them constant. This may not be an accurate representation of the real benefit of treatment, as there may also be uncertainties associated with extrapolating model parameters beyond the follow-up period [10]. Further clinical studies comparing BT+CT and CT in terms of efficacy, resources consumed and their effect on long-term quality of life need to be conducted to better assess the cost-effectiveness ratio. This will be the subject of future research planned at the CRSF.

In addition, the parameters of the model are mainly derived from the cohort of patients followed at the CRSF; consequently, the generalisation of the results of the model to all centres could be limited due to the variability of practices. Finally, the scope of the costs is limited to the direct use of healthcare resources and does account for indirect costs such as per diem, related to absences from work (due to the unavailability of data), which could probably impact the cost effectiveness results and the budgetary impact of BT, in favour of BT.

However, the robustness of our results is showed by deterministic and probabilistic sensitivity analyses. Consequently, our results may be used to guide decision-making to include BT in the list of products reimbursed by the French (HI), as its use is consequently increasing in patients suffering from severe dysmenorrhoea, despite the absence of a marketing authorisation and indication for this condition [27]. Finally, the benefits of TB have clearly been showed for other conditions in urology (overactive bladder) [10].

5. Conclusion

The innovative treatment constituted by BT+CT has been shown to be associated with cost savings and an increase in QALYs compared with CT alone (that is the innovative treatment is an efficient option: the most effective and economically dominant). Thus, the adoption of BT+CT in the management of severe dysmenorrhoea could make it possible to significantly improve patients' quality of life, to reduce time off work and healthcare consumption and thus benefit the healthcare system.

Availability of data and materials

Not Applicable

Ethics approval

As regards Ethical approval letter, study was registered by the ethics committee (French /CPP south Mediterranean) under the number: 22.00391.000059 and by ANSM (The National Agency for the Safety of Medicines and Health Products) under the number: MEDAECNAT-2022–10–0055_2020–006,147–25; N° EudraCT 2020–006,147–25.

Informed consent statement

not Consent to participate

Consent for publication

Not Applicable

Data availability

Not Applicable

Author contributions

Same. All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Declaration of competing interest

Not Applicable

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Not Applicable

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