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ORIGINAL ARTICLE

An economic analysis of using rhBMP-2 for lumbar fusion in Germany, France and UK from a societal perspective

Volker Alt · Amit Chhabra · Jörg Franke · Matthieu Cuche · Reinhard Schnettler · Jean-Charles Le Huec

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Abstract Recombinant human Bone Morphogenetic Protein-2 (rhBMP-2) can replace autogenous bone grafting in single-level lumbar interbody fusion. Its use is associated with a higher initial price for the intervention; 2,970€ in Germany, 2,950€ in France and 2,266€ (£1,790) in UK. The aim of this study was to calculate the financial impact of rhBMP-2 treatment in Germany, UK and France from a societal perspective with a two-year time horizon. Based on clinical findings of a previously published study with a pooled data analysis, a health economic model was developed to estimate potential cost savings derived from reduced surgery time and secondary treatment costs, and faster return-to-work time associated with rhBMP-2 use compared with autogenous bone grafting. Country-specific costs are reported in 2008 Euros. From a societal perspective, overall savings from the use of rhBMP-2 in ALIF surgery compared with autograft are 8,483€, 9,191€ and 8,783€ per case for Germany, France and UK, respectively. In all the three countries savings offset the upfront price for rhBMP-2. The savings are mainly achieved by reduced productivity loss due to faster return-to-work time for patients treated with rhBMP-2. Use of rhBMP-2 in anterior lumbar fusion is a net cost-saving treatment from a societal perspective for Germany, France and UK. Improved clinical outcome for the patient combined with better health-economic outcome for the society support rhBMP-2 as a valuable alternative compared with autograft.

Keywords Bone morphogenetic protein · rhBMP-2 · Health economics · Lumbar fusion · Societal perspective

Introduction

Estimates of prevalence of low back pain in the western world generally range between 20 and 40% of the general population [17, 18, 29] and surgical treatment may be a viable alternative to traditional conservative treatment for chronic low back pain. Among other techniques, anterior lumbar interbody fusion is one possible option in this context [28].

In the 1960s, Marshall Urist discovered the capability of demineralized bone matrix to induce de novo bone formation [26] attributable to Bone morphogenetic proteins, which, are part of the TGF-β superfamily [27]. Bone Morphogenetic Protein-2 was isolated in 1998 and led to recombinant production (recombinant human Bone Morphogenetic Protein-2–rhBMP-2) [30]. Several experimental studies showed rhBMP-2 to have significantly higher fusion rates in anterior lumbar interbody fusions

V. Alt and A. Chhabra contributed equally to this work.

V. Alt (✉) · R. Schnettler
Department of Trauma Surgery,
University Hospital Giessen-Marburg GmbH,
Site Giessen, Rudolf-Buchheim-Str. 7,
35385 Giessen, Germany
e-mail: volker.alt@chiru.med.uni-giessen.de

A. Chhabra · M. Cuche
Medtronic International Trading Sàrl, Tolochenaz, Switzerland

J. Franke
Department of Orthopaedic Surgery,
Otto-von-Guericke University, Magdeburg, Germany

J.-C. Le Huec
Department of Orthopaedics and Traumatology,
Bordeaux University Hospital, Bordeaux, France

(ALIF) in goats [31] and in a non-human primate model in rhesus monkeys [5] compared to autogenous bone grafting.

A pivotal, prospective, randomized, clinical trial in 279 patients showed non-inferiority in clinical outcomes, e.g. in the Oswestry disability index, and fusion rates in L4-S1 single level ALIF surgery with a tapered cage filled with rhBMP-2 compared to the same cage filled with autogenous bone graft [7]. A pooled data analysis combining the 279 patients from the pivotal trial with another 400 patients from a non-randomized prospective trial revealed a statistically significant better outcome with reference to operative time, blood loss, duration of hospital stay, revision rates, return-to-work time and fusion rates after 24 months by rhBMP-2 filled cages compared to autogenous bone graft filling [8]. Additionally, in other studies of ALIF surgery with cortical bone allografts [9] and postero-lateral fusion [6], rhBMP-2 showed statistically significant higher fusion rates than the control group. Recently, a Health Technology Assessment of BMP [12] found an evidence for the effectiveness of rhBMP-2 in comparison with autograft for patients with single-level degenerative disc disease. According to evidence from seven trials, the use of rhBMP-2 increased radiographic fusion among patients with single-level degenerative disc disease [pooled OR: 3.87 (95% CI 1.74–8.59].

Recombinant human BMP-2 with an absorbable collagen sponge (InductOs® Wyeth, Maidenhead, UK) was introduced for use in spine fusion in Europe in 2005 following approval by the EMEA for its use in single-level, anterior interbody fusion from L4 to S1 as a substitute for autogenous bone grafting in adults. Like many new technologies, rhBMP-2 provides added clinical benefit at an incremental monetary cost. One InductOs® kit is 2,970€ in Germany, 2,950€ in France and £1,790 (2,266€) in UK.

Health economics define clear criteria for the cost effectiveness and the cost benefit of a specific treatment [10, 25]. A new treatment strategy can be analysed and defined as both "better and cheaper" than the standard of care (dominant strategy), "worse and more expensive" (rejected strategy), or "better and more expensive". In the latter case, a more complex decision-making process has to be performed [24].

The aim of this work was to determine the financial impact of using rhBMP-2 in lumbar fusion surgery in Germany, UK and France from a societal perspective by taking into consideration the possible savings from reduction of secondary treatment costs and faster return-to-work to offset the upfront price compared to autogenous bone grafting.

Materials and methods

Clinical data used for the health economic analysis

The clinical data for the economic analysis were obtained from the pooled data analysis of 679 patients published by Burkus et al. [8] in which the effects of rhBMP-2 on an absorbable collagen sponge in single level lumbar fusion (L4–S1) surgery was compared to autogenous bone grafting. In this study, 277 patients were treated with rhBMP-2 and 402 patients with autogenous bone grafting for degenerative disc disease and up to grade 1 spondylolisthesis, filled in a tapered cage (LT-Cage® lumbar tapered fusion device; Medtronic Sofamor Danek, Memphis, USA). 279 (rhBMP-2: 143 patients, autogenous bone graft control group: 136 patients) of the 679 patients were from a prospective randomized controlled trial with an open surgical approach to the lumbar spine [7] and the remaining 400 patients (rhBMP-2: 134; autogenous bone graft control group: 266 patients) from prospective non-randomized clinical trials in which rhBMP-2 was used with the LT-CAGE Tapered Lumbar Fusion Device and implanted laparoscopically. The inclusion and exclusion criteria for the non-randomized trials were identical to those for the patients in the randomized trial with the minor exception of not having a minimum Oswestry low back pain disability score for entry in one of the studies. Regarding the pooled data analysis [8], the population demographic data, there were no statistically significant differences in the female to male ratio, the material status, the education level, workers compensation involvement, tobacco or alcohol use. Those statistically significant differences that were found between the two groups, e.g. in the mean age (BMP-2: 42.9 years, autograft: 40.8 years) or in the preoperative medical condition or medication usage, were adjusted by covariance analysis to ensure comparability between the two groups. The study showed a significant reduction in surgery time of 54 min as well as a reduction in blood loss of 66 ml with rhBMP-2 treatment compared to autogenous bone grafting. Patients in the rhBMP-2 group underwent significantly less revision operations and returned to work significantly earlier than patients in the control group.

The fusion rate at 24 months after rhBMP-2 treatment was 94.4% (201 of 213 patients); significantly higher when compared to 89.4% (252 of 282 patients) ($P = 0.022$) after autogenous bone grafting. The post-operative improvements in Oswestry Disability Index and the Physical Component Score and the Pain Index Scores of the SF-36 Health Survey were statistically superior in the rhBMP-2 treatment group at all follow-up time points after 3, 6, 12 and 24 months after surgery when compared to the autogenous bone grafting group.

Health economic model

An economic model was developed to evaluate cost differences between spine-fusion surgery with rhBMP-2 and fusion with bone autograft for Germany, France and UK. The costs associated with both arms were estimated for 2 years after surgery using costs applicable in 2008. UK costs in £ have been converted into € using an exchange rate of 0.79 £/€ (18 April 2008).

This analysis is primarily based on the evidence that rhBMP-2

- reduces operating time,
- decreases rate of revision surgery and
- reduces return-to-work time.

The comparison was done from a societal perspective and, therefore, includes both direct (costs for index procedures, revision surgeries) and indirect costs (return-to-work time with productivity loss).

The results for each country are presented as net average cost per patient or case over 2 years after spinal fusion surgery.

Model inputs

Initial treatment costs

The country-specific costs of single-level spinal fusion procedure were assigned to the patients in the autograft group. The local cost of rhBMP-2 [2,970€ in Germany; 2,950€ in France; 2,266€ (£1,790)] in UK was added to determine the initial treatment cost per patient in the rhBMP-2 group.

Financial savings with the use of rhBMP-2

Financial savings from reduction in operating time

Compared to autograft-treated patients, patients treated with rhBMP-2 during fusion surgery had 54 min shorter operation time. Operating room costs were estimated to be 403€ [16], 1,202€ [15] and 1,221€ [20] per hour for Germany, France, and UK, respectively (Table 1).

Table 1 Savings by rhBMP-2 by shorter operating time

	Reduced operating time by rhBMP-2	OR costs per hour (€/h)	Savings by rhBMP-2 (€)
Germany	0.9 h	403	363
France	0.9 h	1,202	1,082
UK	0.9 h	1,221	1,099

Financial savings from reduction of secondary surgery costs with the use of rhBMP-2

The pooled data analysis from Burkus et al. [8] showed that patients in the rhBMP-2 arm had fewer re-operations, revision, removals, and supplementary fixations after the index procedure compared to the patients in autograft group (Table 2). In the study, revisions were defined as procedures that adjusted or in any way modified the original device configuration. Interventions that removed one or more components of the original device configuration without replacement with the same type of device were classified as removals. Procedures in which an additional spinal device or uninstrumented posterior or posterolateral fusion were performed, and considered as a supplemental fixation. Re-operations were defined as procedures that, at the original fusion level, did not remove, modify or add any components. For each type of secondary intervention, the respective costs were determined by 2008 tariffs for Germany (G-DRG 2008), France (Classification Commune des Actes Médicaux CCAM) and UK (National Tariff 2008/2009 coding) (Table 3).

Financial savings from reduction of productivity loss

The use of rhBMP-2 resulted in faster return-to-work when compared to use of autograft over 2 years after spinal fusion surgery [8]. Taking into account the pre- and post-surgery work status of patients, the average number of productive (working) days gained using rhBMP-2 was calculated based on the raw data of the study of Burkus et al. [8] (Table 4). The gain in working days would reduce productivity loss for the society.

For patients who did not return to work, a loss of 730 days productivity (2 × 365 days) was assumed. For patients returning to work, the time to resumption of work was taken as the period of productivity loss.

The difference in the average productivity loss was then related to country-specific daily costs for productivity loss (Table 5). Country specific daily costs for productivity loss were estimated using national average gross wages per

Table 2 Difference in rates for secondary intervention between rhBMP-2 and autograft treatment

	Autograft (in %)	rhBMP-2 (in %)	Difference (in %)
Revisions	1.99	0.36	1.63
Removals	1.74	1.44	0.30
Supplemental fixation	6.97	6.14	0.83
Reoperations	7.96	2.89	5.07

Data from Burkus et al. [8]

Table 3 Savings by rhBMP-2 by reduced needed for secondary surgery

Type of secondary intervention	Difference between autograft and rhBMP-2 (in %)	Type of procedure	Cost per procedure (in €)	Savings by rhBMP-2 (in €)	Sum of savings by rhBMP-2 (in €)
Germany					
Revision	1.63	I 53 Z	4,173	68	337
Removal	0.3	I 23 A	2,113	6	
Supplemental fixation	0.83	I 09 D	6,206	52	
Reoperations	5.07	I 53 Z	4,173	212	
France					
Revision	1.63	GHM 08C26Z	9,654	157	756
Removal	0.3	GHM 08C26Z	9,654	29	
Supplemental fixation	0.83	GHM 08C26Z	9,654	80	
Reoperations	5.07	GHM 08C26Z	9,654	489	
UK					
Revision	1.63	HRG code R09	5,315	87	416
Removal	0.3	HRG code R09	5,315	16	
Supplemental fixation	0.83	HRG code R09	5,315	44	
Reoperations	5.07	HRG code R09	5,315	269	

Table 4 Difference in return-to-work time for all patients between rhBMP-2 and autograft treatment for a 2 years perspective

	Total number of patients	Number of patients returning to work within 2 years	Productivity loss in days of patients returning to work within 2 years	Patients not returning to work within 2 years	Productivity loss in days of patients not returning to work within 2 years	Sum of productivity loss in days within 2 years	Average productivity loss in days per patient within 2 years
Control	402	246	28,590	156	113,880	142,470	354
rhBMP-2	277	188	21,268	89	64,970	86,238	311

Table 5 Savings by rhBMP-2 by faster return-to-work time

	Faster return-to-work-time by rhBMP-2	Costs for productivity loss per day (in €)	Savings by rhBMP-2 by avoided sickness payment/ productivity loss (in €)
Germany	43 days	181	7,783
France	43 days	171	7,353
UK	43 days	164	7,052

hour including employer-paid benefits of 181€, 171€ and 164€ for Germany, France and UK, respectively [20]. The estimated wage assumed an 8-h working day. Figures for Germany were averaged between wages for Western and Eastern parts of Germany.

Results

Results for Germany

A reduced operating time of 0.9 h lead to a cost saving of 363€ per case (Table 1). Savings as a result of reduced need for secondary surgery attributable to rhBMP-2 use accounted for 337€ per case (Table 3). With an average prevented lost productivity of 43 days and an average daily wage of 181€, a recovered productivity loss of 7,783€ (Table 5) was estimated. The overall saving for Germany was 8,483€ per case with the use of rhBMP-2 compared to autograft treatment (Table 6).

Results for France

For France, decreased surgical time achieves cost savings of approximately 1,082€ (Table 1). 756€ are estimated to be saved by a lower re-operation rate with rhBMP-2 treatment (Table 3). As for Germany, the highest savings are achieved by recouping productivity loss in the amount of 7,353€ (Table 5). Overall, there are savings of 9,191€ per case (Table 6).

Table 6 Sum of savings by rhBMP-2

	Savings by shorter operating time (in €)	Savings by reduced needed for secondary surgery (in €)	Productivity loss (in €)	Sum of savings by rhBMP-2 (in €)
Germany	363	337	7,783	8,483
France	1,082	756	7,353	9,191
UK	1,099	416	7,052	8,567

Results for UK

Savings in operating room time as a result of the absence of bone grafting procedures due to the use of rhBMP-2 were estimated to be 1,099€ per case (Table 1). The difference in rate of secondary surgery accounted for 416€ per case. rhBMP-2 use led to a saving of 7,052€ gained from prevented productivity loss. There were overall savings of 8,567€ for rhBMP-2 treatment.

In all the three countries, savings offset the upfront price of rhBMP-2, making rhBMP-2 a dominant strategy in ALIF surgery from a societal perspective. rhBMP-2 therapy led to better clinical outcome for the patient and net cost savings for the society.

The savings from productivity gain or productivity loss avoided accounted for 91.7, 80.0 and 82.3% of the overall savings to the society in Germany, France, and UK, respectively.

Discussion

To the best of our knowledge, this is the first study to report the health economics of rhBMP-2 use in spine surgery for three large European countries. The study showed that rhBMP-2 in ALIF for the treatment of chronic low back pain achieves savings from a societal perspective that completely offset its upfront price for Germany, France and UK. Based on this study, the use of rhBMP-2 in ALIF surgery can be considered a dominant strategy in Germany, France and UK from a societal perspective as it combines net cost savings with a better clinical outcome for the patient compared with iliac crest autograft. This health economic work is based on clinical data of a pooled data analysis with 679 prospectively followed patients from Burkus et al. [8] with all limitations of pooled data analyses as not all patients have been part of randomized trials. However, this study is the largest published trial on the use of rhBMP-2 in spine surgery and, therefore, its use as underlying clinical data reference for the current health economic work is justified.

The results of this study are inline with results from another preliminary study in the German literature on the use of rhBMP-2 in ALIF surgery [3]. The study by Alt et al. [3] also showed that indirect cost had the highest impact on the cost savings associated with the use of rhBMP-2 in Germany. In a related study, rhBMP-2 was also shown to be a cost-saving strategy for the German health care system in Gustilo-Anderson grade III open tibia fractures [2]. The latter two studies were conducted from a health care payers' perspective in which average sick leave payments, paid to the patient by the public health care insurance companies, were used in the calculations in place of average wages used in the current societal perspective.

Two additional studies present preliminary data on the cost savings by the use of rhBMP-2 in ALIF for the US health care system [1, 19]. Both studies conclude that savings gained from using rhBMP-2 are likely to offset the upfront price when compared to autogenous bone grafting from a payer's perspective. This health economic conclusion is based on a clinical trial with 45 patients.

In general, the treatment of chronic low back pain has an important financial impact on health care systems [4]. For the UK, more than 2 billion € was paid out for the treatment of low back pain in 1998 [20]. An annual treatment cost of 20.700€ per patient suffering from chronic low back pain has been calculated for Sweden for 2002 [11].

Indirect costs resulting from productivity loss have been identified to have the highest impact on overall treatment costs when compared to direct medical costs for back pain; contributing 85–93% to the overall costs [11, 14, 22, 28]. Therefore, from theory point of view, the societal perspective is the relevant perspective for a health economic assessment of spinal fusion [13, 14, 23]. Consequently, this study was limited to costs modelled from a societal perspective including productivity loss. National health care system perspective or hospital perspective with the respective assumptions would have been other potential perspectives for this health economic work.

In societal focussed health economic works productivity loss is the critical component. The study by Burkus et al. [8] only provided the median difference in the return-to-work time of 54 days between rhBMP-2 (116 days) and the control group (170 days). A re-calculation was performed with the raw data from the study to obtain the mean difference in return to work after surgery to calculate the loss of productivity for the society for the current health economic assessment. For all patients in the Burkus (2003) study, regardless of their working status, there was a difference of 43 days in mean work days (productivity) loss,

favouring rhBMP-2 use [8]. If only patients that had worked just prior to surgery were included in the analysis, the difference was reduced to 20 days, which still supports the use of rhBMP-2 (rhBMP-2: 115 days, control group: 135 days). However, the last perspective does not cover the view that a higher percentage of patients treated by rhBMP-2 compared to the control group returned to work whether they had been able to work prior to surgery (75 vs. 65%) or not (35 vs. 31%) [8].

As rhBMP-2 treatment results in a higher percentage of patients returning to work, that were out of work before surgery, the perspective of including all patients in the lost productivity calculation, regardless of work status, seems more appropriate. However, even when the average return-to-work difference of 20 days was included in the analysis, the savings were 3,620€, 3,420€ and 3,280€ for Germany, France and UK, respectively, which also offset the upfront price of rhBMP-2. The main difference between the two analyses is the percentage of patients that were out of work before surgery and did not return to work within the 2-year period following surgery. It should be stated that although the return to work status has been an outcome evaluated in the pooled data analysis of Burkus et al. [8] there remain some limitations to this point, e.g. not all patients may have comparable nature of the work performed. However, the best available data on this topic have been used in the current study to estimate potential productivity loss.

From a health economic perspective, the use of gross wages may be considered a reliable approach for the calculation of productivity loss [10]. The work of Schröder et al. [21] was used as a reference for the average wage in Germany, France and UK which presents gross average wages including gross earnings plus employer paid benefits for each country.

A striking difference between the OR costs between the three different countries was found. There are only very limited published data on OR costs for Europe, e.g. for UK [20]. The data for France were taken from national statistics [15] and for Germany from single hospital data [16]. There might be a different underlying definition for the OR costs which might help to explain the differences. However, as OR costs contribute to only 5–12% of the overall savings a difference in the OR costs per hour between the different countries has only limited impact on the overall results.

A recent Health Technology Assessment (HTA) on BMP [12] also assessed the pooled data studied by Burkus et al. [8]. The HTA states that since the proportion of patients working preoperatively in the BMP group was considerably higher than that in the control group (48 vs. 37%), the proportions of patients working after surgery should be adjusted accordingly. In comparison, our study contains a detailed analysis of the raw data on the average return-to-work time of patients of the study of Burkus et al. [8]. It is shown that, for all patients working before surgery, there is a difference in the return-to-work time of 20 days in favour of BMP-2 (average return-to-work time: autograft: 135 days, BMP-2: 115 days). When preoperative working status is disregarded, the difference increases to 43 days in favour of BMP-2 (average return-to-work time: autograft: 354 days, BMP-2: 311 days). This confounds the HTA re-calculation of the return-to-work time that suggested patients in the BMP group actually tended to return to work later than those in the control group.

Further savings could be achieved by reduced expenses for physical therapy, pain relief medication, outpatient treatment, etc. as the overall clinical result in the BMP-2 group was better compared to the autograft control group. These aspects had not been integrated in the underlying clinical study from Burkus et al. [8] and could therefore not be assessed for this health economic analysis. These costs will most likely have only a limited impact on the overall financial results and will, therefore, not change considerably the conclusion of the study.

Additional potential savings for the hospitals might be achieved from shorter length of hospital stay (2.2 vs. 3.1 days) associated with rhBMP-2 use [8]. However, the difference in length of stay was not included in the cost analysis as the shorter average hospital stay reflects a US-specific situation. In general, the current European health care systems require a minimum length of stay for each patient.

From this study we observe that the increased upfront price of a new treatment strategy should not be immediately cast in a negative light but rather assessed by sound health economic evaluations for a more detailed analysis of their potential value for money.

Conclusion

This study shows that rhBMP-2 use in ALIF surgery achieves significant savings for the society compared with autograft. These savings offset the upfront price of rhBMP-2 when compared to autogenous bone grafting in ALIF for the treatment of chronic low back pain in Germany, France and UK. With the statistically significant better outcome from a large clinical pooled data analysis compared to autograft, rhBMP-2 can be considered from a health economic perspective as dominant strategy in ALIF surgery as it combines net cost savings with a better clinical outcome for the patient.

The largest contribution to the cost savings associated with the use of rhBMP-2 in ALIF surgery is achieved by reducing employee productivity loss by enabling a quicker return to work. Additional cost savings for health care

insurances may result from shorter operative time and reduced need for secondary surgery.

Conflict of interest statement Volker Alt, Jörg Franke and Jean-Charles LeHuec are working as external independent consultant for Medtronic Sàrl, Tolochenaz, Switzerland.

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