First line treatment for metastatic renal cell carcinoma in Colombia: a cost-effectiveness analysis§

Tratamiento de primera línea para el carcinoma de células renales metastásico en Colombia: un análisis de costo-efectividad

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Abstract

Objective: To perform a local study based on an economic evaluation of first-line treatment of metastatic renal cell carcinoma in Colombia, since 2006-2007.
Methods: We developed a Markov model using 6-week cycles to evaluate the cost-effectiveness of 4 interventions (IFN, sunitinib, bevacizumab + IFN, sorafenib) used as standard first-line treatment for mRCC in Colombia. The model used the third-party payer perspective and a 10-year time-line with all patients continuing with active treatment until progression, when it became acceptable to proceed to a second-line treatment or best supportive care (BSC).
Results: Incremental analysis indicated a difference of US$21.796 in the average total cost of treatment when sunitinib was compared to IFN. Opposite, comparing sorafenib and bevacizumab + IFN to sunitinib demonstrated that the average total cost was less for sunitinib by US$25.857 and US$110.947 respectively. The ratios of incremental cost-effectiveness by life years gained (LYG) demonstrated sunitinib's cost saving compared to sorafenib and the combination of bevacizumab + IFN, and an average by LYG of US$50.564,25 compared to IFN. Uncertainy is principally about sample size analized for Colombian population data.
Conclusions: Sunitinib was the most cost-effective option as first-line treatment for mRCC patients in Colombia (2006-2007), compared with the other available options. Current pharmacoeconomic data is important to improve knowledge and define the best sequence model to treat this disease in our country.

Key words: Renal cell carcinoma, cost effectiveness analysis, Colombia, metastatic, targeted therapy.

Resumen

Objetivo: Realizar un estudio local para tener una base que permita evaluar económicamente el tratamiento de primera línea para el carcinoma de células renales metastásico en Colombia considerando el periodo entre 2006 y 2007.
Métodos: Se desarrolló un modelo con ciclos de 6 semanas para evaluar la costo-efectividad de diversas intervenciones (IFN, sunitinib, bevacizumab + IFN, sorafenib) utilizadas como agentes de primera línea para el tratamiento del carcinoma de células renales metastásico. El modelo utilizó la perspectiva del tercer pagador y una proyección de 10 años considerando que todos los pacientes continuaron con el tratamiento activo hasta la progresión como momento en el cual se consideró aceptable proceder a una segunda línea o al mejor tratamiento de soporte.
Resultados: El análisis incremental indicó una diferencia de US$21.796 para el costo medio total del tratamiento cuando se comparó sunitinib contra interferon. Cuando se comparó sorafenib y bevacizumab + IFN con el sunitinib se demostró que el costo promedio total del sunitinib fue menor por US$25.857 y US$110.947 respecto de las otras dos intervenciones, respectivamente. Las razones de costo efectividad incremental por año de vida ganado (AVG) demostraron un ahorro con el sunitinib en comparación con el sorafenib y con la combinación de bevacizumab + IFN, obteniendo en promedio un AVG de

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US$50.564,25 contra el IFN. La incertidumbre se dio principalmente por el tamaño de la muestra analizada que se extrapoló a la población colombiana.
Conclusiones: El sunitinib fue la opción más costo efectiva como tratamiento de primera línea para los pacientes con carcinoma de células renales metastásico en Colombia (2006-2007), en comparación con las otras opciones disponibles. La evaluación fármaco económica es importante para el conocimiento que permita definir el mejor modelo de secuencia para el tratamiento de esta enfermedad en nuestro país.

Palabras clave: Carcinoma de células renales, análisis de costo-efectividad, Colombia, metástasis, terapia dirigida.

Introduction

Renal cell carcinoma (RCC) represents 90% of the tumours originating in the kidneys and 3% of the malign disease in adults[1]. Despite it being a rare entity, its incidence has increased 126% since 1950[2,3]. This disease occurs more frequently in males between the 5th and 7th decade of life, a third part of the cases are diagnosed with metastases, and 50% with early lesions die as a result of progression of the disease[4]. Currently, the mean overall survival (OS) without treatment varies between 6 and 12 months, and the survival at 2 years is around 10%[5].

The National Cancer Institute of the USA (US NCI) predicts 51,190 new cases of RCC for the year 2007, of which 12,890 will die of the disease within the year[6]. As well, it is estimated that the losses attributable to RCC for the year 2004 were 192.800 years of life, which translates as a mean of 15.7 years of life lost per individual[7]. There is no information, as yet, on the epidemiologic profile of RCC in Colombia, but the behaviour of the disease in other Latin America countries differs from the data previously reported[8,9]. The incidence is greater in Uruguay and in Brazil where the frequency is reported as 10.6 cases per 100,000/inhabitants/year. The presentation of the disease appears to be similar among males and females and, in some populations the survival at 5 years exceeds 16%[10].

Chemotherapy and radiotherapy have demonstrated marginal efficacy on metastatic renal cell carcinoma (mRCC) and immunotherapy modestly improves long-term survival in selected patients[11]. The absence of effective interventions and the increasing knowledge of tumour molecular biology have stimulated the search for new alternative therapies centred on the genomic evolution of the disease. It is well documented that 80% of clear cell tumours have inactivated von Hippel-Lindau gene resulting from deletion, mutation or methylation and, consequently, inhibitors of multiple tyrosine-kinase inhibitors that delay angiogenesis, tumour increase and metastases have been included in standard clinical practice[12].

There have been 3 new drugs introduced for the treatment of mRCC within the National Health Service in Colombia *[Sistema General de Seguridad Social en Salud (SGSSS)]* since 2006. These are: Sunitinib (Sutent®; Pfizer) an inhibitor of multiple kinases that block the VEGFR/PDGFR (Vascular Endothelial Growth Factor/Platelet Derived Growth Factor Receptors); Sorafenib (Nexavar®; Bayer/Onyx) another selective inhibitor that blocks the Raf pathway and the PDGFR; Bevacizumab (Avastin®; Roche Pharmaceuticals) a monoclonal agent that binds to the circulating VEGF[13]. However, the availability of these products on the market implies a radical modification of the health costs for chronic disease cover, at the local and national level[14].

According to the estimations of the International Agency for Research in Cancer (IARC) during the year 2002 there were 70.750 new cases of cancer in Colombia, 38.648 females and 32.102 males. The numbers of resultant deaths registered for the year were 28.629 (13.987 and 14.642 in males and females, respectively)[15]. In 1960, malignant tumours represented the 6th highest place at 3.7% of the total deaths. By the year 2000, this had risen to 3rd place following cardiovascular disease and violent death, and represented 14.7% of all deaths[16,17]. While developed countries include estimations of chronic diseases in the load on their health systems, in Colombia unfortunately, the system of monitoring only provides a rough approximation of medical interventions in cancer; in the year 2002, the estimate was US$3.890 millions *(unpublished data)*[15].

A study that used data from the National Inpatient Sample (NIS) of the Health Care Cost Utilization Project (HCUP) of the USA calculated that, for the year 2002, the costs attributable to intra-hospital treatment for mRCC was US$418 millions[18]. Extrapolating these results to the reality of Colombia, it is possible to deduce

that, for the same period, mRCC represented approximately 4% of the resources destined for the management of cancer; a value that is very high especially if we consider that the renal tumours are not within the top 10 causes of cancer in our country[16].

Recently, an economic evaluation was conducted in Colombia comparing sunitinib versus interferon-alfa (IFN; Intron®) as first-line treatment for mRCC[18]. The study established a cost of < US$7.105 in the sunitinib treatment arm and an effectiveness of > 0.23 years of life free of disease progression (or progression-free life years; PfLY), an increase of 0.05 years of life gained (LYG) and an increase of 0.07 years of quality-adjusted life gained (or quality adjusted life years; QALY).

The present study had as its objective an evaluation of the cost-effectiveness (CE) of the first-line treatments used for the management of mRCC in Colombia.

Methods

Study design

We developed a Markov model to evaluate CE of sunitinib, IFN, sorafenib and the combination of bevacizumab + IFN as first-line treatments of patients with mRCC in Colombia. The effectiveness outcomes were measured as PfLY and LY. The perspective used was that of the 3rd party payer i.e. the State Social Security *[Sistema General de Seguridad Social en Salud (SGSSS)]*. The base case assessment was with a time horizon of 10 years.

Effectiveness

A structured search of the best available evidence for each of the comparators was performed according to the criteria proposed by Lefebvre et al.[19]. Subsequently, two independent pairs of investigators selected the published clinical studies most representative of each scenario. All studies were randomised and controlled with IFN[1,20-24] except one for sorafenib, that was randomized to placebo[34] (annex 1).

Effectiveness modelling

Kaplan-Meier curves were used as reference for overall survival (OS) and progression-free survival (PFS) of IFN obtained from the study of Motzer et al.[1,20]. To estimate long-term survival (10 years), we used the Weibull distribution function[25]. Evaluation of the new drugs in the model was by using estimations of hazard ratios (HR) for the OS and PFS derived from data reported in published clinical studies[1,20-24] (annex 2).

Population

The subjects considered in the model have the characteristics of those included in the clinical studies described mRCC confirmed histologically, with lesions measurable by images, and functional status evaluable on the Eastern Cooperative Oncology Group (ECOG) scale. Information of Colombia was available for 24 patients treated in Manizales, Pereira, Medellín and Bogotá.

Structure of the model

The model was developed using Microsoft Excel® to simulate disease progression up to 10 years in the base case and, as well, to determine the outcomes in terms of PfLY and LYG over time. The Markov model used cycles of 6 weeks to adjust to the duration of treatment recommended for sunitinib (4 weeks of treatment and 2 weeks of rest). The rest period of the comparators were expressed in cycles of equal duration. Figure 1 summarizes the stages considered in the Markov model for mRCC. The assumption was that all the patients commenced with active treatment, without clinical nor image evidence of progression. This implies that the patients continued with active treatment until progression, at which time it was accepted that a second-line treatment or palliative support would be implemented. All the patients who progressed after a second-line received support treatment and were considered that death could occur at any of the transition points. Death related with the cancer and to other causes were tracked separately assuming that the proportion of deaths due to the tumour were constant over time. The probabilities of transition varied with time and were determined by the survival curves already described.

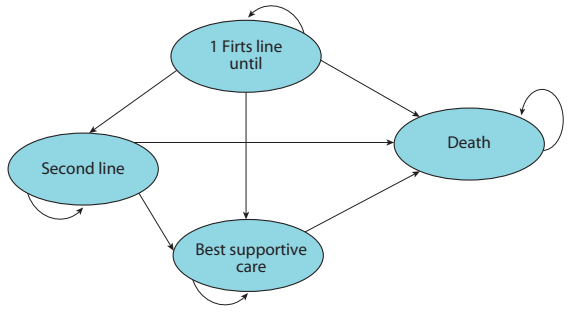

Figure 1. Markov model used in the study.

The analysis also considered reduction and adjustment of doses and interruptions of the cycles due to toxicity, or from other causes, as well as the treatment of the severe adverse events (classified as grade 3 or 4 on the *Common Toxicity Criteria* of the *National Cancer Institute* of the USA) related to the medication under study. The significant use of resources incurred for the adverse event management and the frequencies were derived from the reported clinical studies. The details of the adverse events included in the model are presented in annex 3.

The efficacy of the second-line treatment was not taken into account in the model and only an estimation of the mean costs for each treatment arm was considered. Internal consistency of the analyses was verified and the validity of the calculations was assured by assessing the changes due to introduction of extreme values of the variables. External consistency was assessed by comparing the projections of survival with the observations of the study published by Motzer et al.[20].

Costs

Sources of information on the health services used in Colombia, and their costs

The costs included in the model were those attributable to routine follow-up of the patients, the acquisition of the medications, the costs of the treatment of significant adverse events, the costs of disease progression, and the costs of palliative support in Colombia. Given that the model reflects the perspective of the 3rd payer (the Health Service), this does not include the costs to the patients or to Society resulting from the loss of productivity or of premature death. Information on the frequency of use and units of costs of the health services consumed for the care of the patients with mRCC in our environment were derived from a series of 24 cases treated in Manizales, Pereira, Medellín and Bogotá.

Five investigators reviewed the clinical histories and registered the number and the characteristics of the health-care provision (outpatient clinic, hospitalizations, laboratory tests, images, surgery, therapies and other procedures) during the clinical evolution of the metastatic disease, the active treatments employed for the control of metastases (first- and second-line), the therapies used for palliative care and for the management of adverse events. The information was complemented with data from a structured questionnaire soliciting information from 14 clinical oncologists in 10 cities in the country, corresponding to 10% of the specialists registered (table 1).

The data on costs of the services consumed were solicited from an external consultant (Delta-A-salud) and corresponded to the mean value charged to the HMO calculated from 33 sources of information representative of the country's market. The costs of the medications were derived from prices on sale to the public via the Colombian Anti-cancer League *[Liga Colombiana de Lucha Contra el Cáncer (LCLC)]*. The costs and outcomes presented after the 1st year in the model were discounted at an annual rate of 3%.

Finally, uncertainty in the parameters of effectiveness, frequencies and costs of services in the different phases were evaluated in a probabilistic sensitivity analysis using a second degree Monte Carlo simulation

Table 1. Variables included in the model

Variable		Sunitinib		Sorafenib	INF-α		Bev. + IFN-α
Patients receiving second-line treatment[1]	BSC	52%		52%	52%		52%
	Second-line treatment	48%		48%	48%		48%
Second-line treatment[1]	IFN-α or IL[2]	3.80%		5.60%	1.30%		6.30%
	Sunitinib	0.00%		71.10%	62.90%		75.00%
	Sorafenib	72.50%		0.00%	12.30%		18.70%
	Bev+IFN-α	23.70%		23.30%	23.50%		0.00%
Drug cost in US$ 2007[2]	Cost	Sunitinib (tablets)	Sunitinib (tablets)	Sorafenib (tablets)	IFN-α (Pen 30MU)		Bevacizumab (vials)
		25 mg	50 mg	200 mg	$732		100 mg
		$1.886	$3.932	$3.204			$651
		12.5 mg					400 mg not available
		$943					
							+ IFN
	Dose	37.5 mg	50 mg	400 mg	3-6-9 MU (progressive)	9 MU	10 mg/kg
	Cycle cost (6 weeks)	$2.829	$3.932	$9.611	$3.662	$4.394	$16.108

BSC: best supportive care
Pen: multidose pen 30 million IU
[1] Questionnaire administered to 14 clinical oncologists in 10 cities in Colombia.
[2] Prices to the Colombian Anti-cancer League [Liga Colombiana de Lucha contra el Cáncer (LCLC)].

(5.000 interactions). Subsequently, the distributions of probability were described in which the parameters were adjusted: for the probability of change or adjustment of dose using a beta distribution; for the hazard risk using a log normal distribution; for the frequency of use of resources and their costs using a gamma distribution; and for the parameters without information of variability using a standard deviation of the mean of 10%. Additionally, univariate deterministic analysis of sensitivity was performed applying changes of ±20% based on the variation in the market price of the medications which constitute a very important item in the cost structure. From this last factor, we identified the variables that most affected the outcomes. All the costs are presented in US$ (where US$1 = COL$2.250).

Results

Applying the Markov model, the mean accumulated cost per patient was within the range of US$46.440 and US$179.184 for IFN and the bevacizumab + IFN combination, respectively. It is important to note that bevacizumab have not been explored alone for the treatment of mRCC, and with other combination instead IFN. Table 1 summarises the mean values of the costs and effectiveness of the treatment of the patients with mRCC in Colombia. Similarly, examining the distribution of the costs for each phase, between 83% and 94% is the accumulated proportion attributable to the costs of the medications used in first- and second-line treatments for mRCC (figure 2). These costs are followed in frequency by the costs related to the integrated palliative support (4% to 12%) and, then, by the remaining phases which represent < 5% of the total accumulated cost for each one of the sequences of intervention.

The base case analysis demonstrated a difference of US$21.797 in the mean total cost of the treatment of 1 patient in the time-horizon of 10 years with sunitinib vs. IFN, while in the comparison of sorafenib and the bevacizumab + IFN combination the mean total cost was less for sunitinib; US$25.857 and US$110.948, respectively (table 2).

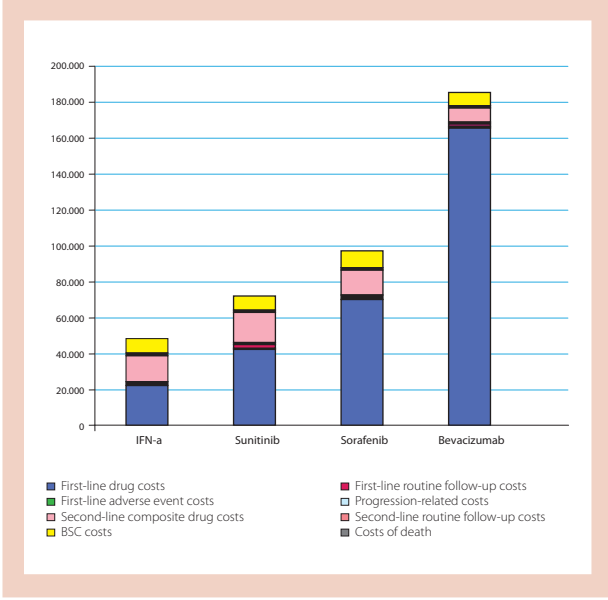

Figure 2. Cost break-down by phase (US$ at 2009 prices).

In terms of effectiveness, sunitinib showed the best parameters in PfLY and LYG at 10 years, while sorafenib and IFN were less favourable (table 2). The analysis of incremental cost effectiveness reason (ICER) showed that the IFN alone was cheaper but less effective; translating into a mean cost per LYG of US$50.564 using sunitinib; while sunitinib was more effective and less costly (cost-saving) compared to sorafenib and the bevacizumab + IFN combination (table 2).

In the probabilistic sensitivity analysis, the ability to pay US$50.000 was observed as sunitinib being cost-effective 60% of the times compared to IFN, while that for sorafenib and the bevacizumab + IFN combination the probability of being cost-effective was equal to zero. Figure 3 illustrates the probability of cost effectiveness at various willingness-to-pay thesholds for mRCC treatment.

Table 2. Mean values for the cost and effectiveness of treating patients suffering from mRCC in Colombia and sunitinib's cost-effectiveness compared to IFN, sorafenib and the bev + IFN combination in mRCC patients in Colombia (US$2009)

First-line treatment	Cost per patient	Effectiveness per patient		First-line treatment				
Medication	Total costs USD$ (SD)	Progression-free life-years	Life-years	Medication	Incremental Cost	Incremental efectiveness		Incremental cost per life-years gained
Sunitinib	68.236 (5.141)	1.35 (0.16)	2.90 (0.29)	Sunitinib vs. Others	Δ Cost	Δ PfLY	Δ LYG	ICER ($/LYG)
IFN	46.439 (6.514)	0.72 (0.05)	2.47 (0.17)	IFN	$21.796	0.62	0.43	50,564
Sorafenib	94.093 (13.288)	0.83 (0.16)	2.74 (0.26)	Sorafenib	$-25.857	0.52	0.16	Dominated
Bevacizumab + IFN	179.184 (16.902)	1.15 (0.12)	2.67 (0.27)	Bevacizumab + IFN	$-110.947	0.19	0.23	Dominated

PfLY = progression-free life years
LYG = life years gained

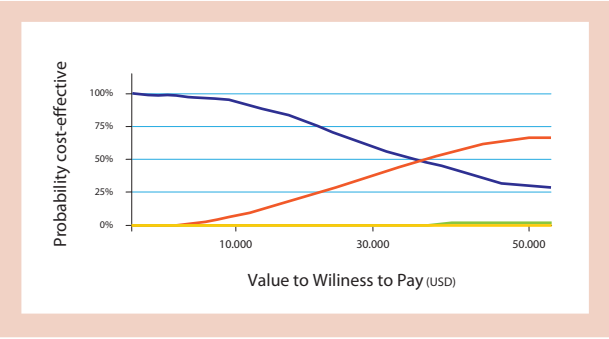

Figure 3. Cost-effectiveness acceptability curve for different treatments (US$ at 2009 prices).

Based on the univariate analysis of sensitivity, the variable having the most influence on the outcomes of CE i.e. hazard risk for OS and DFS was identified as the cost of the first-line and the second-line medications.

Discussion

Despite the not-inconsiderable scientific progress in oncology research over the past decade, it would be incorrect to adopt new alternatives without considering all their consequences, including the economic impact and resource consumption. Hence, it is necessary to develop pharmaco-economic studies that provide support when taking clinical and administrative decisions with respect to efficient management of the resources, especially when taking into account clinical practice in Colombia.

Recently, Remak et al presented the final results of the complete economic analysis of 3 interventions (IFN, IL-2 and sunitinib) used most frequently in the treatment of mRCC in the USA[24], The study included variables similar to those described in the evaluation of sunitinib vs. IFN as first-line treatment of mRCC initially developed by our group for Colombia[26]. The principal findings in the US clinical scenario were: sunitinib was associated with a gain in LYG of 0.41 and 0.35 over IFN and IL-2, respectively. Similarly, the gain estimated with sunitinib over that of IFN was 0.11 LYG and 0.14 QALY, results concordant with the data described in Colombia[26]. In our country, sunitinib was more effective and less costly in a temporal horizon of 1 year. This information justifies the use of sunitinib as first-line treatment of mRCC[27].

However, both studies have a common methodological criticism i.e. the projection of the OS benefit from the original report[1,28], to the outcome in a subsequent analysis relating to another population study[29,30]. Demonstrating the effectiveness of the medications used in the management of mRCC presents certain limitations including the need to use secondary outcomes such as DFS and the rate of overall response. The original difficulty of obtaining definitive data OS in phase III clinical trials in cancer, principally via comparison of treatment arm crossover, is translated into the intention-to-treat underestimation of the real outcome of the medication which is more effective than the statistically-diluted estimation[31,32].

For the case of sunitinib, the effect is greater when the analysis of data of the population involves no crossover between the treatment arms; HR for OS of 0.64 (95%CI: 0.48-0.87). Applying these data in the model, the ICER was US$27.877; a level that is below the threshold accepted worldwide for this type of pathology (US$50.000-100.000) and very close to the threshold suggest by the WHO for developed countries; equivalent to 3 points PIB per capita for whatever pathology in Colombia (US$22.000)[33].

The results for sorafenib within the first-line treatment of mRCC in Colombia need to be interpreted with caution, taking into account that, at the time of implementing the present study, there were no clinical trials comparing the multi-targeted inhibitor of IFN-alfa. Hence, in our model, we opted to use information from a study in which sorafenib versus placebo was compared; this magnifies the effect and the CE of the medication[34]. Moreover, population between different clinical trials are comparable in terms of line of administration of the drugs, stage at treatment (all were stage IV), clinical performance status, MSKCC score, age, gender distribution, etc. Population is comparable to Colombian population analized in our study because those people were candidate to active treatment in first-line, and have similar characteristics of those shown in the large clinical trials, based on the trials that use interferon as comparator. We discuss first line treatment option, only. At the moment we planned the model, there is no authorization for using everolimus or pazopanib in our country.

The model for economic evaluation used in our study indirectly compared the 4 therapeutic options available under the Colombian National Health Service (SGSSS). This constitutes a methodological restriction since there is a lack of experimental studies comparing head-to-head effectiveness. This is controlled by

selecting the best evidence published for each of the medications employed in first-line treatment of mRCC[35]. Another restriction of the analysis is the use of data derived from studies with short follow-up. This forces the projection of a wider temporal horizon, and which is susceptible to imprecision.

The structure of costs encountered in our study differ from that reported by investigators in developed countries where palliative care constitutes 40%-50% of the total cost of management of the advanced disease (followed by overall cost of the medications). This effect could be explained by the characteristics of the costs of palliative support in Colombia, which is neither normalised nor regulated[36]. Data amount obtained for Colombian population (24 patients) is the largest available cohort of treatment in our country, for the moment when the analysis was done, that met the criteria for being analized (administration of an active first-line treatment, principally). The most limiting situation was availability of complete medical records.

In the USA, Spain and Sweden there have been studies comparing therapies available for mRCC[37-39]. The results are, in all cases, consistent with those reported in the present study. Procopio et al performed a cost analysis that evaluated the differences between the costs of the adverse effects attributable to sunitinib and the bevacizumab + IFN-alfa combination as first-line treatment for mRCC. They observed that the cost for the management of grade 3 and 4 events were €891 and €402, respectively[40]. Similar results were observed in the UK, Germany and France[41]. The present study, as well, encountered a difference in favour of the bevacizumab + IFN-alfa combination with respect to the cost generated by the adverse effects. However, this represents < 2% of the total cost in each of the lines of treatment. Hence, performing an economic evaluation including all the relevant costs, sunitinib becomes less costly and more effective compared to the bevacizumab + IFN combination. Results were maintained in spite of variations in the most important parameters, as shown in the tornado graph (figure 4).

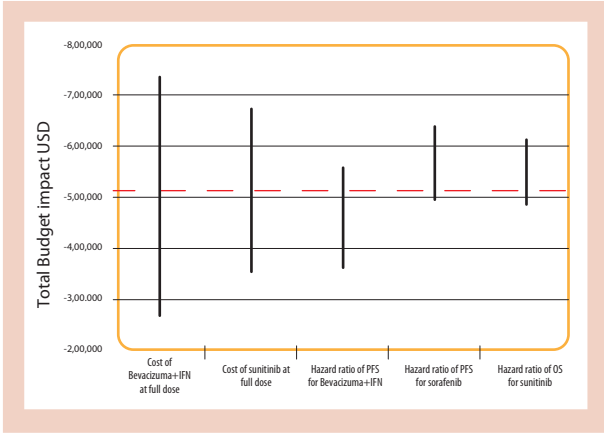

Figure 4. Analysis of the sensitivity of budget impact regarding adopting SU as therapy of choice for mRCC in the Colombian SGSSS (95%CI or 75%-125% range; Tornado graph USD) USD 2008.

When proposing a therapy-of-choice for the first-line treatment of mRCC, the marginal efficacy of IFN implies that the sunitinib profile is more efficacious and cost-effective compared to the sorafenib and the bevacizumab + INF combination.

'Key points for decision makers'

1. Between 2006 and 2007 there are four interventions approved for the treatment of metastatic renal cell carcinoma in Colombia: IFN, sunitinib, bevacizumab + IFN and sorafenib.
2. In Colombia during 2006 and 2007, sunitinib was more effective and less costly in a temporal horizon of 1 year. This information justifies the use of sunitinib as first-line treatment of mRCC.
3. This study shows that sunitinib saves LYG of US$50.564,25 compared to IFN in Colombia.
4. This data has to be taken with caution due to the major changes occurred in Colombia health system and in mRCC first and second line treatment scenario since its conception (2006) and execution.

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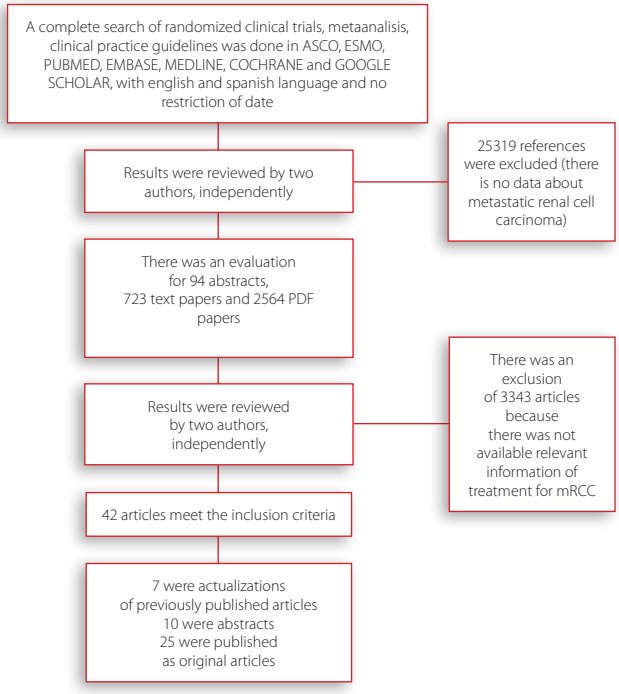
Annex 1. Search flowchart for clinical trials and other articles included in the fulltext

Supplemetary material



Annex 2. Estimated PFS and OS hazard ratios (HR) for the new generation medications compared to IFN

Hazard ratios of the different comparators (vs. IFN)				
Drug	**HR**	**lower 95%CI**	**upper 95%CI**	**Source**
Progression-free survival (PFS)				
Sunitinib	0.539	0.451	0.643	Negrier et al. 2008[33]
Sorafenib	0.877	0.786	1.631	Szczylik et al. 2007[22]
Bevacizumab+ IFN	0.63	0.59	0.8	Escudier et al. 2007[23]
Overall Survival (OS)				
Sunitinib	0.821	0.673	1.001	Motzer et al. 2009[20]
Sorafenib	0.88	0.74	1.04	Bukowski et al. 2007[42]
Bevacizumab+ IFN	0.91	0.76	1.1	Escudier et al. 2009[23]

Annex 3. Record of the toxicities associated with the first-line intervention in mRCC

Medication	**IFN**	**Sunitinib**	**Sorafenib**	**Bevacizumab + IFN**
Source	**Trial 1034[a]**	**Trial 1034[a]**	**Szczylik[b]**	**Escudier[c]**
Cycles administered; N	1947	3793	1928	1755
Sample size; N	360	375	451	234
Events observed; N	141	515	217	112
Fatigue/asthenia	65	81	23	12
Stomatitis	1	5	23	n/a
Hypertension	4	64	14	19
Thrombocytopenia	4	47	n/a	n/a
Neutropenia	10	87	23	16.38
Abnormal ejection fraction	7	14	n/a	n/a
Nausea/vomiting	11	54	18	29
Diarrhoea	3	51	27.06	5
Anaemia	27	45	12	n/a
Hand-foot syndrome*	7	58	49.61	n/a
Infection	1	2	n/a	n/a
Proteinuria	n/a	n/a	n/a	15.21
Rash	1	7	27.06	n/a
Haemorrhage	0	0	n/a	7.722
Venous thromboembolism	n/a	n/a	n/a	4.212
Gastrointestinal perforation	n/a	n/a	n/a	3.51

* Palmar-plantar erythrodysesthesia syndrome
[a] Pfizer: A6181034-A3 - A Phase III, randomised study of SU011248 versus interferon as first-line systemic therapy for patients with metastatic renal cell carcinoma. Data on file, December 2008.
[b] Szczylik C, Demkow T, Staehler M, Rolland F, Negrier S, Hutson T, et al. Randomized phase II trial of first-line treatment with sorafenib versus interferon in patients with advanced renal cell carcinoma: Final results. J Clin Oncol. 2007;25(18S):5025.
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