Pharmacoeconomic aspects of Ketosteril® treatment in stage 3-4 CKD patients

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Summary

The authors analyzed the pharmacoeconomic impact of an early versus late Ketosteril treatment start in stage 3 (early) and stage 4 (late) of chronic kidney disease (CKD). CKD patient outcome data of two Hungarian studies and recent multicenter resource utilization questionnaire survey were used for cost-effectiveness modelling. Utility values of different CKD stages were taken from international publications. Deterministic modelling of the cost and utility at individual patient levels showed dominance of the „active arm" (early Ketosteril start). Distribution of the results in the scatter plot diagram confirmed the deterministic results in the probabilistic analysis (less costs, better efficacy) as well.

Introduction

There are numerous publications on various effects of Ketosteril® (a ketoacid-aminoacid oral preparate of Fresenius-Kabi) both in predialysis and dialysis patients. No data exist however to the knowledge of the authors regarding its pharmacoeconomic impact on the treatment of predialysis patients. Our aim was to compare the cost-effectiveness of Ketodiet (low/very low protein diet plus Ketosteril) started „early", in stage 3 (GFR 60-30 ml/min) of chronic kidney disease (CKD) versus starting it „late" in stage 4 (GFR 30-15 ml/min) of CKD.

Materials and methods

A cost-effectiveness model had been developed to compare the relative costs and health-benefits of the two alternatives. (i.e. early and late Keto-therapy). Patient data of the Hungarian Ketosteril Study (1) and data of a recent publication (2) had been used for cost-effectiveness analysis of the two treatment strategies (n=171). On the basis of the Se-Creatinin data we determined the average progression rate on different levels, extrapolating measured values to GFR levels. Multicenter (n=9) data of 80 recent Hungarian CKD patients were used for financial resource utilization calculations, considering only direct medical costs (Table 1.).

Table 1. The cost inputs of the model*

Cost categories	Value	SD
Direct medical cost with Ketosteril	3 155,11 €	866,91 €
Direct medical cost without Ketosteril	963,27 €	794,46 €
Dialysis cost	17 691,65 €	2 520,94 €

**Hungarian results were transformed to € on exchange rate: 270 HUF/€*

Utility values of different states were taken from international publications (3) (Table 2.).

Table 2. The utility inputs of the model[3]

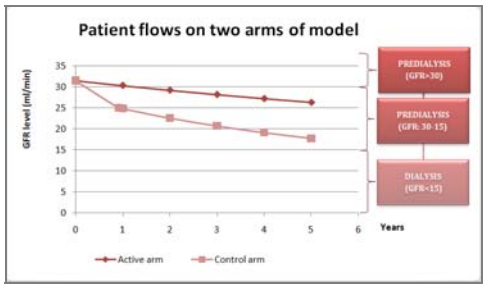
States	Utility value
GFR > 30	0,87
GFR 30-15	0,85
GFR < 15	0,5662

Modelling techniques

The model can manage the input data in different levels:

- **Analysis with patient types**: We fitted a curve to each arm of data taken from Hungarian Ketosteril studies (1,2). Data were aggregated by type, depending on the starting level of Ketosteril® therapy. To determine the equation for the GFR progression we fitted a mixed (fixed and random effect) regression.
- **Analysis with patient level data**: This model manages the input data on an individual level. Individual curves were fitted to all individual patient input data. Cost and utility were calculated on individual level for all patients during the modelling. Results of each arm were generated from average values of individual costs and utilities.
- **Simulation modelling**: During simulation modelling 1000 hypothetical patient curves were generated using Bayesian approach. It was our aim by this mean to assure the validity of our preliminary hypothesis regarding the expected time to dialysis. Patient characteristics had been allocated to profiles (according to gender, age and starting GFR level). For purposes of probabilistic modelling hypothetical curves dependent on a defined iteration number were chosen randomly. In the base case 100 iterations were modelled for 132 patient profiles each

Figure 1. Schematic structure of the model



Cost-effectiveness results (Table 3.)

Patient-type data : (Table 3., left 2 columns) - The data showed, that an earlier Ketosteril® start (GFR 30 to 40 ml/min/1.73 m^2) is less costly on a 30 year time horizon, than starting the medication at the recent indication level of 25 ml/min/1.73m^2 . Health benefit could not be attributed however in this setting to the early treatment start (the group comparison has been probably biased through distortive effects of the averaging approach).

Patient-level data : (Table 3., right 2 columns) Cost and utility calculations at individual patient levels showed clear dominance of the „active arm" (early Ketosteril start). This means, that not only costs of this approach are lower, but there is also a higher health benefit for these patients. In this model the dominance could be strengthened further by an earlier Keto-therapy. We assumed that this –individual - type of modelling is more reliable since it largely eliminates distortion bias inherent to the patient-type comparison method.

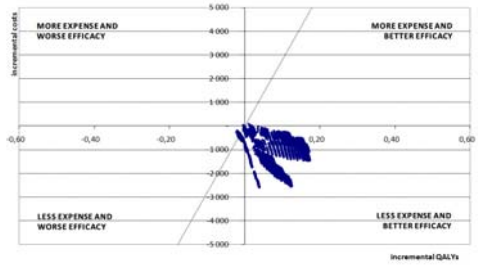
Table 3. Results of the deterministic modelling

	Analysis with patient type data		Analysis with individual patient data	
starting GFR	30 ml/min	40 ml/min	30 ml/min	40 ml/min
COSTS				
active arm	14 432,59 €	14 432,59 €	19 805,70 €	15 784,61 €
control arm	39 448,60 €	33 810,59 €	24 893,97 €	22 985,27 €
incremental	-25 016,01 €	-19 378,00 €	-5 088,27 €	-7 200,66 €
QALYs				
active arm	3,89	3,89	5,08	5,14
control arm	4,07	4,22	4,34	4,43
incremental	-0,18	-0,34	0,75	0,71
ICER	**138 978 €**	**56 994 €**	**-6 784 €**	**-10 142 €**
	Cost-effective	**Cost-effective**	**Dominant**	**Dominant**

Results of the probabilistic analysis

The simulation included 13200 iterations on both arms (6 age-groups x 2 gender x 11 starting GFR values x 100 iterations). The distribution of ICER values on the active arm in the probabilistic analysis showed that the majority of cases (10 942 cases, 82,89%) can be found in the dominant field.

Figure 2. Scatter plot diagram of the probabilistic analysis



X-axis of the scatter plot figure represents the utility difference and the Y-axis shows the cost difference (in 1000 EUR steps). According to the distribution of the results the early Ketosteril® therapy appears to be clearly dominant (less costs, better efficacy)

Figure 3. Histogram of the probabilistic results

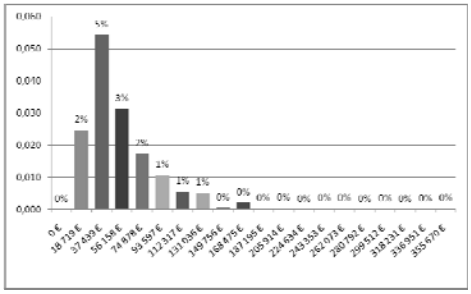


Fig.3. The histogram illustrates the distribution of the 17%, not dominant cases by clusters.

Conclusions

Based on the data of our modelling, initiation of the Ketodiet in CKD stage 3 proved to be more advantageous both in terms of healthcare costs and effectiveness than starting the treatment in later stages (CKD 4) of the disease.

Definitions of analytical terms:

ICER *– Incremental Cost Effectiveness Ratio (ICER) represents the analized strategies relation in cost-effectiveness context. The difference in cost (incremental cost) is compared to their difference in outcomes (incremental effect) by dividing the former by the latter. The ratio is interpretable with a threshold, corresponds appr. 3 x GDP per capita according the WHO.*

QALY *- A quality adjusted life year (QALY) is a universal health outcome measure applicable to all individuals and all diseases, thereby enabling comparisons across diseases and across programmes. A QALY combines, in a single measure, gains or losses in both quantify of life (mortality) and quality of life (morbidity).*

References

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