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COST-EFFECTIVENESS ANALYSIS OF PARENTERAL METHOTREXATE FOR THE TREATMENT OF CROHN'S DISEASE IN THE CZECH REPUBLIC

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BACKGROUND

Parenteral methotrexate (MTX) is a cornerstone treatment in Crohn's disease (CD). Despite its worldwide use, there is a limited high-quality evidence on efficacy and no evidence of its cost--effectiveness in CD.

OBJECTIVE

Clinical evidence suggests that parenteral methotrexate (MTX) provides benefit for induction and maintenance of remission and complete discontinuation of high-dose oral corticosteroid treatment (hdCS; >20mg/day) in patients with CD.[1,2] Our aim was to assess cost-effectiveness of MTX in the treatment of mild-to-moderate CD in comparison to standard of care (SOC), i.e. hdCS with its gradual withdrawal (taper) in the Czech Republic.[3]

METHODS

- We developed a three-year Markov model with one-week cycle length in TreeAge. The model comprises four health states – initial state of mild-to-moderate CD (16-week treatment with MTX or hdCS), steroid-free remission, lack/loss of response and death (**Figure 1**).
- Model settings are shown in **Table 1**.
- Probability of initial response to treatment was based on results of the clinical trial and it was evaluated after 16 weeks (**Table 2**).[1]
- Long-term maintenance of remission is derived from trial's follow-up and extrapolated using survival analysis.[2] Kaplan-Meier curves of both interventions are parallel based on proportional hazard test (p=0.34), Nelson-Aalen cumulative hazard function, smoothed hazard estimate, log survival curve and predicted vs. observed survival (**Figure 2**). Therefore, survival analysis was estimated on SOC curve, while hazard ratio (HR) of 0.48 (95% CI: 0.25-0.95) was applied to estimate MTX.
- Lognormal curve provided best fit by Akaike and Bayesian information criteria (AIC, BIC), second-best fit using log-likelihood. Mainly, lognormal curve had the most plausible extrapolation while it is in the middle of all curves; it is therefore not over- or under-estimating remission over time. It was thus chosen in the base-case (**Figure 2**).
- Utilities were derived from the published mapping algorithm (**Table 3**).[4]
- Costs were based on list prices, reimbursement tariffs and approved previous pharmacoeconomic analyses as of October, 2018 (**Table 4**).[5,6]
- Probability sensitivity analysis (PSA; 10,000 iterations) was run using an implicit willingness-to-pay threshold (WTP) of €47,000/QALY (**Table 5**). One-way sensitivity analysis (OWSA) was performed.

Table 1. Markov model settings

Analysis type and model	Cost-utility analysis, Markov model
Software	TreeAge Pro 2018
Perspective	Healthcare payers' (health insurance funds)
Time horizon	3 years
Cycle length	1 week (7 days)
Discount rate	3% for costs and outcomes
Assessed intervention	Parenteral methotrexate (MTX) in combination with high dose prednisone taper
Comparator	High dose prednisone taper (SOC)
Population	Patients with mild to moderate Crohn's disease (CDAI 150-250) not responding to high dose corticosteroids
Efficacy data	Clinical trials Feagan[1] and Feagan[2]
Outcomes	Quality-adjusted life-years (QALY)
Half-cycle correction	Yes (costs and outcomes)
Sensitivity analysis	One-way (OWSA), probabilistic (PSA)
Mortality	General population mortality adjusted for increased risk for patients with CD (10,14)*

*Odds ratio (OR) relative to remission for mild-moderate CD (1.266).

Figure 1. Markov model structure

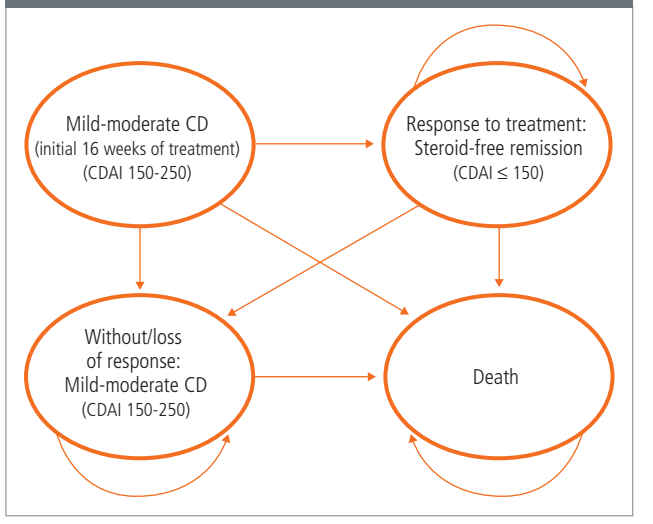


Table 4. Costs

	Costs (€/week)
Drugs	
MTX 25mg (initial 16 weeks)	€ 27.6
MTX 15mg (follow-up)	€ 16.6
Health states	
Remission	€ 3.0
Mild-moderate CD	€ 11.1

Table 5. Settings of PSA

Parameter	Distribution
Age	Uniform
Costs	Gamma
Response to treatment, hazard ratio of remission survival, utilities	Beta
Initial survival curve, relative risk of death	Normal

Table 2. Probability of response to treatment[†]

Therapy	Probability of achieving SFR[†]
MTX	39%*
SOC	10%*

*Statistically significantly different with p=0.003.
[†]SFR = steroid-free remission.

Table 3. Utility values

Health state	Average CDAI*	Utility (EQ-5D) (SE)[†]
Mild-moderate CD	184.0	0.6960 (0.01372)
Remission	89.3	0.8097 (0.01088)

*These values were taken from Feagan trial and average CDAI (Crohn's disease activity index) in given health states.
[†]Estimated using Baxton mapping algorithm: EQ-5D = 0,9168 (SE: 0.0082) – 0,0012 (SE: 0,0003)×CDAI.

RESULTS

- Over a three-year time horizon, MTX yields additional 0.07 QALYs (1.93 vs. 1.86) at the additional total cost of €789 (€2,278 vs. €1,489) compared with SOC (hdCS) (**Table 6**).
- **Incremental cost-effectiveness ratio (ICER) is equal to €11,952/QALY** (**Table 6**).
- PSA showed that probability of MTX to be cost-effective was 99.84% at the WTP (**Figure 3** & **Figure 4**).
- OWSA confirmed the robustness of the base-case result with all one-way changes and scenarios deeply below WTP (**Figure 5**).

Table 6. Base-case results of cost-effectiveness analysis

	MTX	SOC	Increment
Total costs (€)	€2,278	€1,489	€789
Of those: initial MTX costs	€450	€0	€450
Costs of MTX in remission state	€559	€0	€559
Total costs of MTX (initial + remission)	€1,008	€0	€1,008
Healthcare costs in initial 16 weeks	€181	€181	€0
Healthcare costs in remission state	€102	€19	€83
Healthcare costs in mild-moderate CD	€987	€1,289	–€302
Total QALYs	1.93	1.86	0.07
Of those: initial 16 weeks	0.22	0.22	0.00
Remission state	0.53	0.10	0.43
Mild-moderate CD state	1.19	1.55	–0.36
ICER (€/QALY)	€11,952/QALY		

Figure 2. Survival analysis (after initial response evaluation)[2]

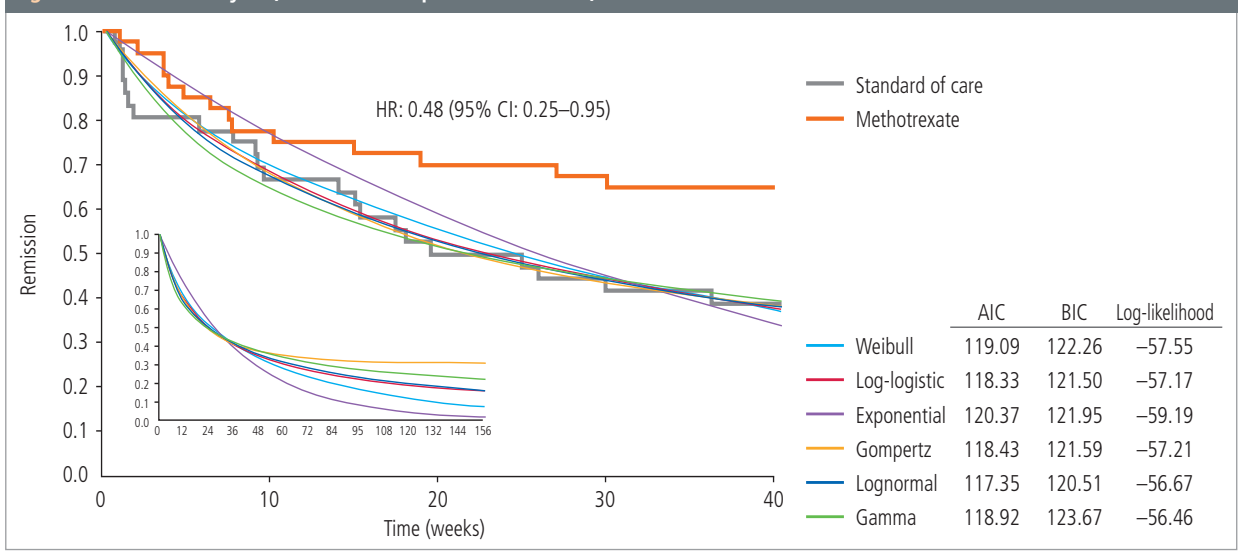


Figure 3 Incremental cost-effectiveness scatter plot

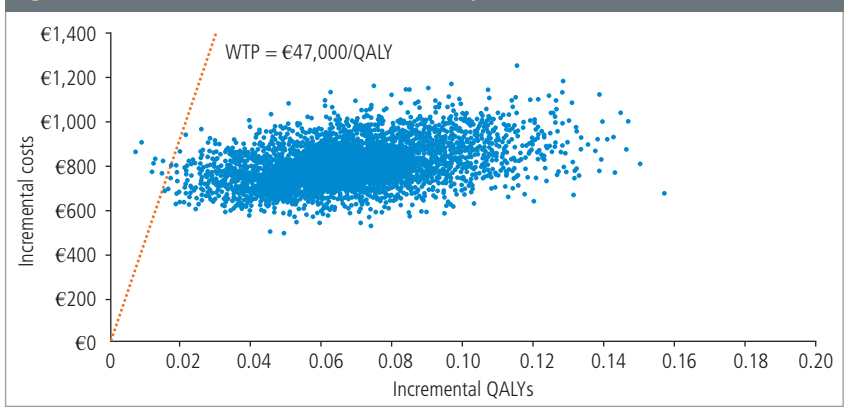


Figure 4 Cost-effectiveness acceptability curve

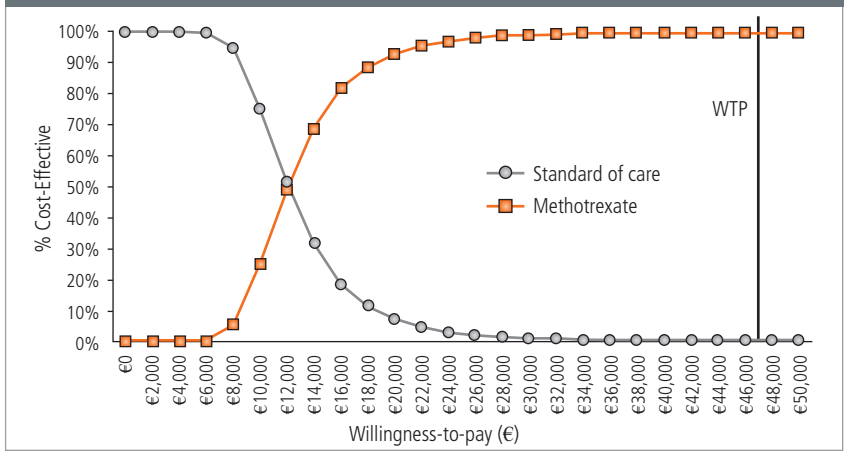
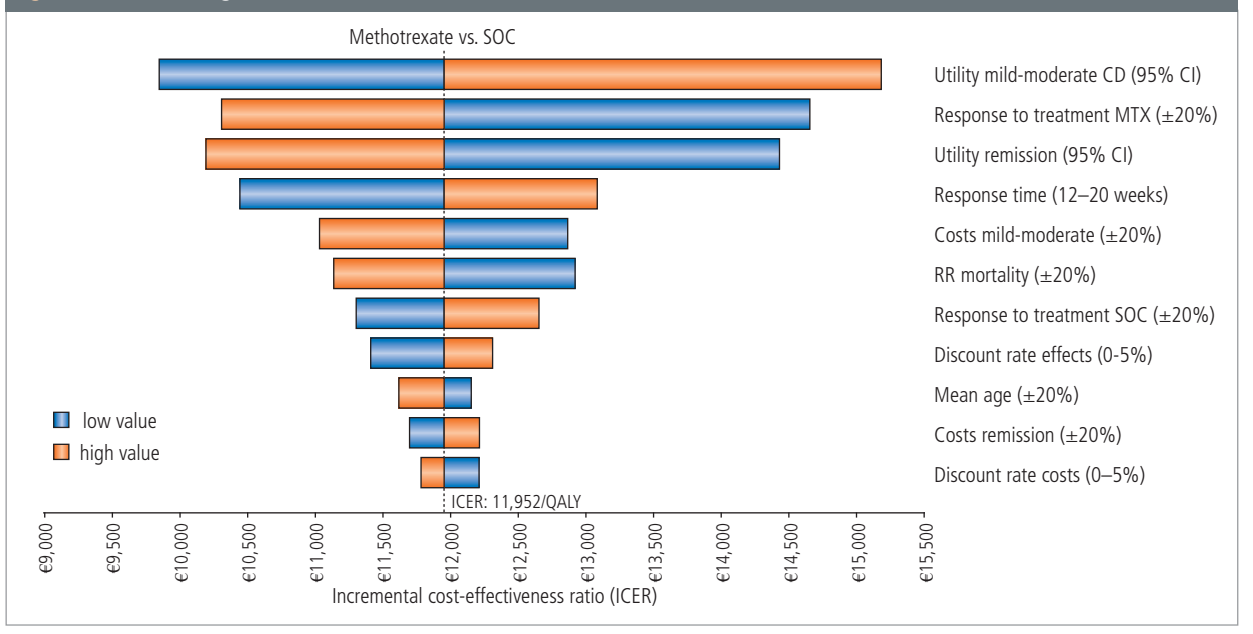


Figure 5. Tornado diagram (ICER (€/QALY))



CONCLUSIONS

- **Parenteral MTX is a cost-effective therapy for patients with mild-to-moderate CD receiving hdCS. Therefore, it was swiftly and positively assessed by State Institute for Drug Control (SUKL, local HTA agency).**
- **Due to the limited high-quality clinical data, MTX efficacy/effectiveness should be subject of further research. Especially in combination with new therapies (biologics or others) which is standard in other diagnoses (rheumatoid arthritis etc.).**
- **To our knowledge, this is the first published cost-effectiveness analysis of parenteral MTX for this indication.**

REFERENCES

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