COST-UTILITY ANALYSIS OF LEFLUNOMIDE IN THE TREATMENT OF RHEUMATOID ARTHRITIS (RA) IN POLAND

ISPOR 12th Annual European Congress
Health Care Decision Making in Europe: From Patients to Populations
24-27 October 2009, Le Palais des Congrès de Paris, Paris, France

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*A study conducted by **HTA Consulting** **www.hta.pl***

Introduction

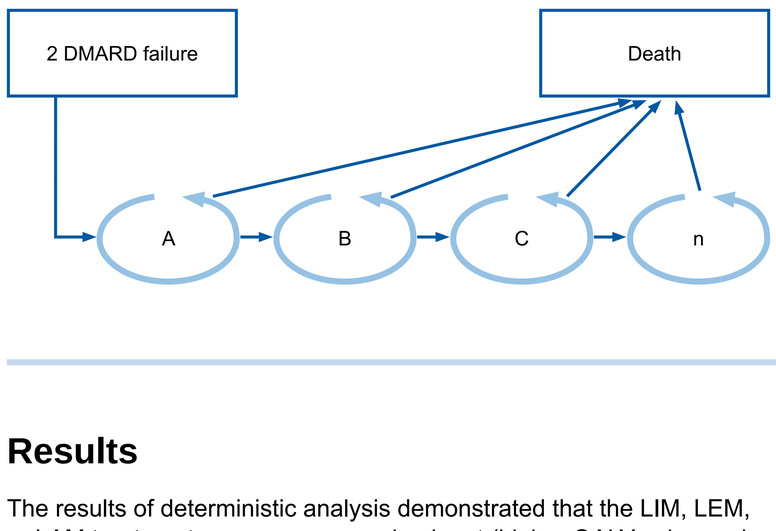
Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disorder that may affect many tissues and organs, but principally attacks the joints producing inflammatory synovitis that often progresses to destruction of the articular cartilage and ankylosis of the involved joints. Rheumatoid arthritis can also produce diffuse inflammation in the lungs, pericardium, pleura, and sclera, and also nodular lesions, most common in the subcutaneous tissue. Although the cause of rheumatoid arthritis is unknown, autoimmunity plays a pivotal role in its chronicity and progression.

About 1% of the world's population is afflicted by rheumatoid arthritis, women three times more often than men. Onset is most frequent between the ages of 40 and 50, but people of any age can be affected. It can be a disabling and painful condition, which can lead to substantial loss of functioning and mobility. It is diagnosed chiefly based on symptoms and signs, but also using blood tests (especially detection of the rheumatoid factor) and imaging investigations. Diagnosis and long-term management are typically performed by a rheumatologist.

Objective

To evaluate the cost-effectiveness of leflunomide used before tumor necrosis factor (TNF) inhibitors compared with leflunomide after TNF inhibitors in the sequence treatment of rheumatoid arthritis (RA) following the failure of 2 disease-modifying antirheumatic drugs (DMARDs) in Polish setting. In the analysis the following sequences with leflunomide used before TNF inhibitors were considered: LIM (leflunomide, infliximab, methotrexate), LAM (leflunomide, adalimumab, methotrexate), and LEM (leflunomide, etanercept, methotrexate). Those sequences were compared to parallel sequences with leflunomide used after TNF inhibitors: ILM (infliximab, leflunomide, methotrexate), ALM (adalimumab, leflunomide, methotrexate), and ELM (etanercept, leflunomide, methotrexate).

Model design



Methods

A cost-utility approach was adopted, evaluating total direct costs incurred by the National Health Fund (NHF) and quality-adjusted life years (QALY). A micro-simulation Markov model was used to estimate utilities and costs. Simulation was performed in 6-month cycles and terminated at the time of the patient's death. Transition probabilities between health states were calculated based on a systematic review of RCTs and supplemented with published literature if necessary. Health state utilities were obtained from published literature. Probabilistic sensitivity analysis was performed. Two scenarios were analyzed. In the first one response rates (ACR 20, ACR, 50, ACR 70) were adjusted between all drugs. In the second one response rates were taken from clinical trials without adjusting.

- population: patients diagnosed with rheumatoid arthritis, after the failure of two prior DMARDs;
- time horizon: the patient's lifetime;
- perspective: the analysis was conducted from the Polish public payer's perspective;
- cycle length: 6 months;
- discount rate: 5% for costs and effects;
- costs of drugs: the National Health Fund and the reimbursement list;
- costs of therapeutic procedures: the National Health Fund in Poland;
- HAQ progression: annual HAQ progression was taken into account;
- assessment of disease stage: Health Assessment Questionnaire (HAQ) and HAQ Disability Index;
- treatment length: the maximum treatment duration assumed was 5 years;
- assessment of treatment response: ACR20, ACR50 and ACR70, time to treatment failure;
- QALY: in each cycle QALY was calculated based on the HAQ value;
- mortality: mortality probability was calculated based on the standard mortality rates in Poland and HAQ values;
- rebound effect: after treatment failure the HAQ value returns to the previous value (before treatment response);
- costs included: cost of drugs, drug administration, therapy monitoring, medical costs related to the disease and incurred during the patient's lifetime depending on the HAQ value;
- the analysis was conducted according to the Agency for Health Technology Assessment in Poland (AHTAPol) guidelines.

Table 1. Cumulative probability of response to the treatment - results from the studies included into the systematic review

Treatment	Response to treatment			No response
	ACR 20	ACR 50	ACR 70	
Leflunomide	23%	20%	10%	47%
Etanercept	23%	26%	19%	32%
Infliximab	28%	18%	15%	39%
Adalimumab	21%	17%	17%	45%
Metotreksat	18%	6%	3%	73%

Table 2. Adjusted cumulative probability of response to the treatment

Treatment	Response to treatment			No response
	ACR 20-ACR50	ACR 50-ACR70	ACR 70-	
Leflunomide	24%	17%	13%	46%
Etanercept	25%	14%	37%	24%
Infliximab	28%	20%	10%	42%
Adalimumab	19%	16%	16%	49%
Metotreksat	18%	6%	3%	73%

Table 3. Drug dosage

Treatment	Dosage
Leflunomide	20 mg once daily
Etanercept	25 mg, twice a week
Infliximab	3 mg/kg i.v., at the beginning of the therapy, after 2 and 6 weeks, then every 8 weeks
Adalimumab	40 mg, every two weeks

Table 4. Population characteristics

Parameter	Value	Data source
Age (years)	54.28	Systematic review
Body weight (kg)	70.00	Chen
Sex (Male)	0.20	Chen 2006
Initial HAQ value	1.03	Systematic review

Results

The results of deterministic analysis demonstrated that the LIM, LEM, or LAM treatment sequences were dominant (higher QALY value and lower total costs) when compared to their parallel treatment sequences ILM, ELM, or ALM.

The results of probabilistic sensitivity analysis did not change the conclusions from the basic analysis. Additional sensitivity analysis had no influence on the results or conclusions.

Table 5. Deterministic analysis results- sequences comparison (adjusted response rates)

Sequence	Cost	QALY	ICER (QALY)
LIM	138,319	4.4347	Dominant
ILM	146,106	4.4330	
LEM	223,591	4.5985	Dominant
ELM	242,461	4.5946	
LAM	175,710	4.4057	Dominant
ALM	187,087	4.3896	

Table 6. Deterministic analysis results- sequences comparison (response rates from clinical studies)

Sequence	Cost	QALY	ICER (QALY)
LIM	140,738	4.4558	Dominant
ILM	148,508	4.4440	
LEM	210,304	4.5357	Dominant
ELM	227,598	4.5357	
LAM	181,987	4.4266	Dominant
ALM	194,111	4.4120	

Figure 1. Scenario 1 - QALY (LEM vs ELM)

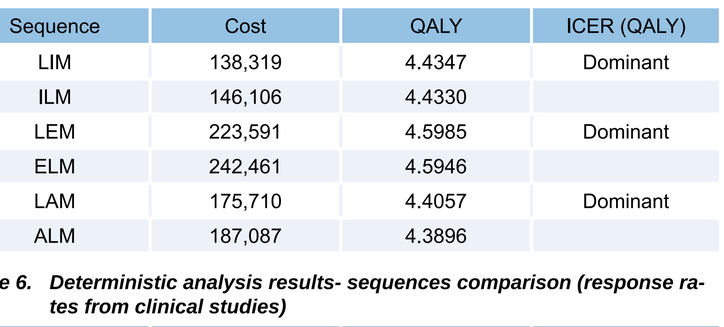


Figure 2. Scenario 1 - QALY (LAM vs ALM)

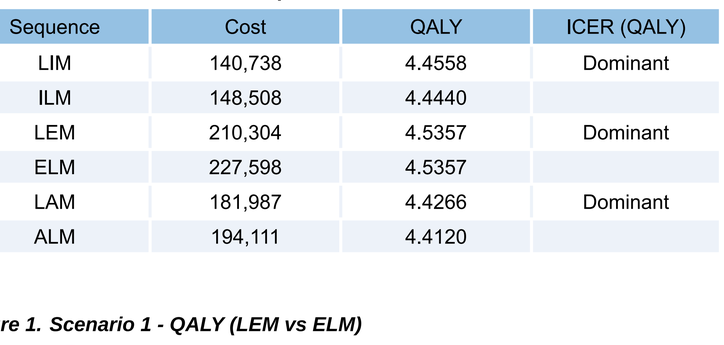


Figure 3. Scenario 1 - QALY (LIM vs ILM)

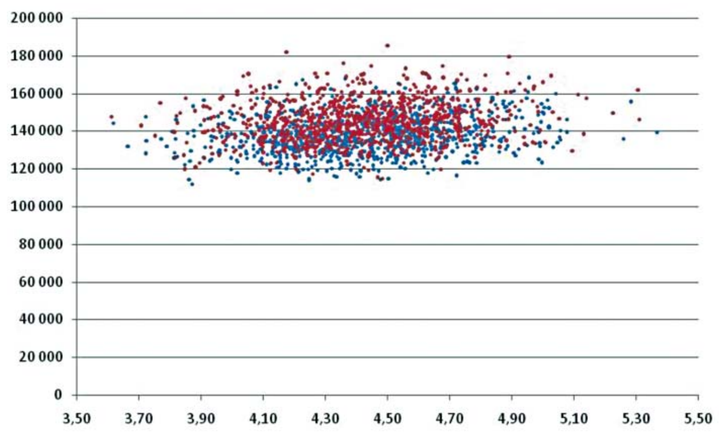


Figure 4. Scenario 2 - QALY (LEM vs ELM)

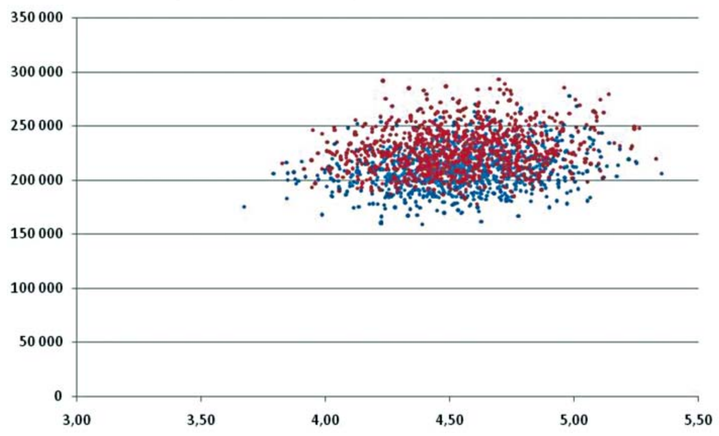


Figure 5. Scenario 2 - QALY (LAM vs ALM)

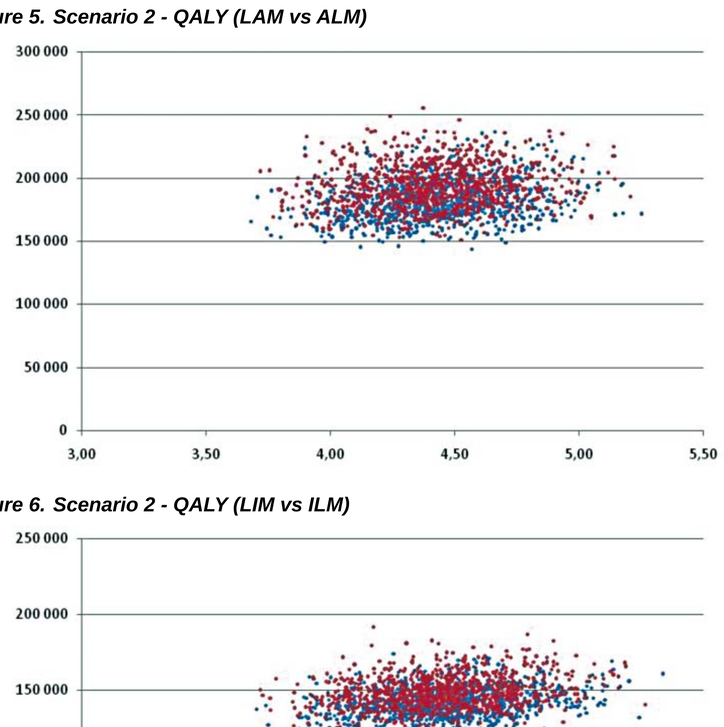
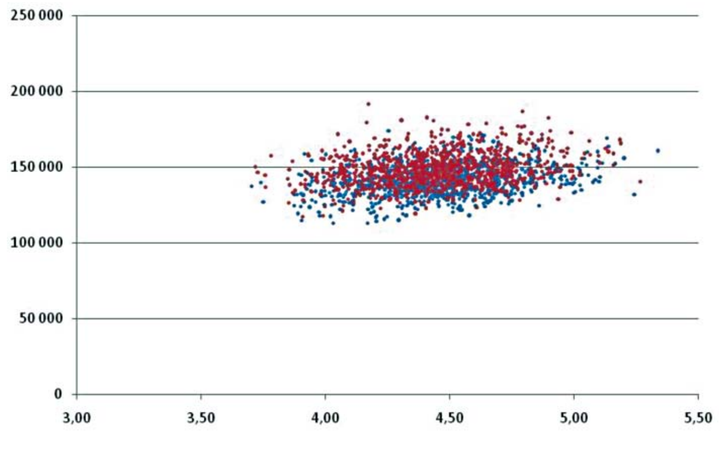


Figure 6. Scenario 2 - QALY (LIM vs ILM)



Conclusions

According to the model findings, leflunomide should be used before TNF inhibitors. LEM, LAM, or LIM sequences in rheumatoid arthritis patients who have failed DMARDs therapy are less costly and more effective than parallel sequences with leflunomide administrated after TNF inhibitors (ILM, ELM, or ALM).

Summary

Objectives: To evaluate the cost-effectiveness of leflunomide used before tumor necrosis factor (TNF) inhibitors compared with leflunomide after TNF inhibitors in the sequence treatment of rheumatoid arthritis (RA) following the failure of 2 disease-modifying antirheumatic drugs (DMARDs) in Polish setting.

Methods: A cost-utility approach was adopted, evaluating total direct costs incurred by the National Health Fund (NHF) and quality-adjusted life years (QALY). A micro-simulation Markov model was used to estimate utilities and costs. Simulation was performed in 6-month cycles and terminated at the time of the patient's death. Transition probabilities between health states were calculated based on a systematic review of RCTs and supplemented with published literature if necessary. Health state utilities were obtained from published literature. Probabilistic sensitivity analysis was performed.

The starting time-point of the model was the failure of two previous DMARDs. Six treatment options were compared. It was assumed that upon treatment failure patients would follow an identical lifetime treatment strategy consisting of: LIM – leflunomide, infliximab, methotrexate, LEM - leflunomide, etanercept, methotrexate, LAM - leflunomide, adalimumab, methotrexate, ILM – infliximab, leflunomide, methotrexate, ELM – etanercept, leflunomide, methotrexate, or ALM – adalimumab, leflunomide, methotrexate.

Results: The sequences with leflunomide at the beginning (LIM, LAM, or LEM) were dominant over the regimens with leflunomide used after TNF inhibitors (ILM, ELM, or ALM). Detailed results: LIM vs ILM (cost difference – 7,788 PLN, QALY difference – 0.002); LEM vs ELM (cost difference – 18,871 PLN, QALY difference – 0.004); LAM vs ALM (cost difference – 11,377 PLN, QALY difference – 0.016).

Conclusion: According to the model findings, leflunomide should be used before TNF inhibitors. LEM, LAM, or LIM sequences in RA patients who have failed DMARDs therapy are less costly and more effective than sequences with leflunomide administrated after TNF inhibitors (ILM, ELM, or ALM).

References

1. Chen YF, Jobanputra P, Barton P, A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness., Health Technol Assess. 2006 Nov;10(42):iii-iv, xi-xiii, 1-229.
2. www.nfz.gov.pl,
3. Rys P. Kucia K, Pankiewicz P. Porównanie efektywności klinicznej leflunomidu z wybranymi opcjami terapeutycznymi w leczeniu reumatoidalnego zapalenia stawów. HTA Consulting 2007