ABSTRACT

Objective. The aim of this study was to assess the value of four drug regimens for newly diagnosed severe LN from a societal perspective.

Methods. A model-based cost-utility analysis was devised to measure lifetime costs and health outcomes. Current treatment options consisting of different combinations of i.v. CYC, AZA and MMF were compared with a baseline regimen of i.v. CYC in both the induction and maintenance phases. Resource use and costs were derived from medical records reviews and databases. Event rates were elicited from randomized controlled trials. Relative treatment effects were obtained from meta-analyses. Health utilities were obtained from a real cohort of patients to estimate the outcome of quality-adjusted life years.

Results. It was found that a treatment regimen that combined i.v. CYC in the induction phase with AZA in the maintenance phase was cost saving compared with the baseline regimen. Treatment with i.v. CYC in the induction phase and MMF in the maintenance phase and treatment with MMF in the induction phase and a reduced dose of the same in the maintenance phase turned out to be a negatively dominated regimen.

Conclusion. In the Thai context, the combination of i.v. CYC for the induction phase followed by AZA for the maintenance phase should be considered as the first-line therapy for newly diagnosed severe LN, as it seems to be the most cost-saving regimen.

Key words: lupus nephritis, mycophenolic acid, cyclophosphamide, azathioprine, immunosuppressive agents, health care rationing, decision support techniques, costs and cost analysis, economic models, Thailand.

INTRODUCTION

SLE is an autoimmune disease with symptoms ranging from minor skin and joint complaints to serious organ issues, such as nephritis and neuropsychiatric problems. Although the disease is found in populations all over the world, its prevalence, clinical spectrum, seriousness and burden differ depending on the location [1]. In developing countries, patients with SLE are far more likely to exhibit LN than patients in more developed countries and this impacts directly on their morbidity and mortality. The existing evidence has shown that 64–69% of SLE patients in South East Asia have LN compared with 28% in Europe [2]. LN, in Thailand, presents a 5-year survival rate of 77%, with infection (51%) and renal failure (29%) as the main causes of death [3].

LN treatment is usually administered in two phases—the first phase aims to halt progression (known as the induction phase) and the second phase aims to avoid recurrence and prevent end-stage renal disease (ESRD), renal and extra-renal lupus activity and death (known as the maintenance phase). Current Thai clinical practice guidelines recommend oral prednisolone (60 mg/day) plus i.v. CYC (0.5–1 g/m²) as appropriate treatment.
during both the induction phase (monthly for 6 months) and the maintenance phase (every 3 months for 2 years) [4]. However, this approach can cause adverse effects in patients, including major and minor infections, amenorrhea and haematological and gastrointestinal events [5, 6].

Evidence from a number of randomized control trials (RCTs) has suggested that there are other drugs that may be more appropriate for treating LN. Oral AZA, for instance, which has limited use in induction therapy due to its relatively high relapse rate, has shown efficacy in treating LN in the maintenance phase and has a better safety profile than i.v. CYC [7]. In addition, there is evidence that MMF, which is increasingly being used as an immunosuppressive agent in autoimmune disease, can be used in both the induction and maintenance phases for LN with equal efficacy and fewer side effects than the standard therapy of i.v. CYC [8].

Effective treatment of LN at an early stage reduces the number of patients who go on to suffer irreversible ESRD and thus reduces the cost of treatment [9]. Given the high cost of renal dialysis (which has a lifetime cost at an onset age of 30 years of about 8 000 000 baht) [10], the prevention of ESRD in severe LN patients is likely to be a cost-saving intervention. Policymakers must decide how best to distribute health resources in a way that guarantees the best outcomes for patients while maintaining financial efficiency. Economic evaluations are an essential tool in the decision-making process of any healthcare system.

To date, no economic evaluation studies have been conducted that examine this issue in the context of developing countries. This study was conducted in response to a request from the Subcommittee for Development of the Health Benefit Package and Service Delivery of the National Health Security Office in the hope that the data will inform recommendations on the best treatment option for patients with LN within the Universal Coverage scheme in Thailand [11]. This study aims to compare, from a societal perspective, the cost and utility of different drug regimens for both the induction and maintenance phases of newly severe LN treatment in patients.

Methods

Lifetime costs and outcomes were simulated for a hypothetical cohort of newly diagnosed active severe LN patients at an average age of 40 years receiving different immunosuppressive therapy drug regimens. All future costs and outcomes were discounted at a rate of 3% per annum, as recommended by Thailand’s health technology assessment guidelines [12]. Primary outcomes of interest were lifetime costs, quality-adjusted life-years (QALYs) and the incremental cost-effectiveness ratio (ICER) in Thai baht per QALY gained.

Intervention and comparators

The current Thai guidelines for the management of severe LN recommend a treatment of oral prednisolone plus i.v. CYC monthly (in the induction phase), followed by i.v. CYC treatment administered every 3 months (in the maintenance phase); this treatment was thus set as the baseline comparator. A number of immunosuppressive agents, such as AZA and MMF, which have been widely available and commonly used in the treatment of autoimmune diseases, were assessed to see whether they can be used as effective alternative interventions for LN patients.

Although treatment dosage can vary from patient to patient, for our analysis we examined RCTs that included the most common dosages. The dosages of the drug regimens included in this economic evaluation were as follows:

Regimen 1: i.v. CYC at an average dose of 1000 mg/m² monthly for 6 months during the induction phase followed by i.v. CYC every 3 months to complete 3 years during the maintenance phase (i.v. CYC → i.v. CYC as the baseline comparator).

Regimen 2: i.v. CYC at an average dose of 1000 mg/m² monthly for 6 months during the induction phase followed by AZA at an average dose of 50 mg/day to complete 3 years during the maintenance phase (i.v. CYC → AZA).

Regimen 3: i.v. CYC at an average dose of 1000 mg/m² monthly for 6 months in the induction phase followed by MMF at an average dose of 1000 mg/day to complete 3 years in the maintenance phase (i.v. CYC → MMF).

Regimen 4: MMF at an average dose of 2000 mg/day for 6 months in the induction phase followed by a reduced dose of MMF of 1000 mg/day for 6 months and then AZA at an average dose of 50 mg/day to complete 3 years in the maintenance phase (MMF → low-dose MMF).

Model structure

A Markov simulation model was constructed with Microsoft Excel 2007 (Microsoft Corp., Redmond, WA, USA) to calculate the lifetime costs and health outcomes of the patient sample. The time horizon used in this study was the patient’s lifetime. The cycle lengths were set at 6 months in the first year and 12 months in the following year—reflecting the induction and maintenance phases. Three mutually exclusive alternative regimen treatment options (i.v. CYC → AZA, i.v. CYC → MMF and MMF → low-dose MMF) were compared with the baseline comparator (i.v. CYC → i.v. CYC).

Five represented health states (active disease, complete and partial remission, ESRD and death) were defined to reflect the main outcome measurement typically reported by RCTs in the area of LN treatment (Fig. 1). For the active disease, complete and partial remission were divided into three substrates (induction phase of treatment, maintenance phase of treatment and after 3 years of treatment) to reflect the fact that cost components and transition probabilities among various health states vary depending on treatment time. Treatment complications were included within health states as, typically, they
were resolved in <1 year. The arrows in the figure represent the possible transitions from one state to another at the end of each cycle length. Parameters that were employed in the model include transitional probability, relative treatment effect, resources use and cost and utility.

Transitional probabilities and relative treatment effects

An extensive literature review was conducted and several relevant studies were identified that compared alternative treatment strategies for LN. The PubMed database was searched using the following keywords: (lupus nephritis [MeSH]) AND (cyclophosphamide [MeSH] OR azathioprine [MeSH] OR mycophenolic acid [MeSH]). Only articles published between January 2000 and July 2012 that were written in English, Spanish or Thai were considered, and only studies pertaining to humans were included in the sample. Study types that were considered included controlled clinical trials, RCTs, clinical trials and comparative studies. We identified 10 studies that met the inclusion criteria; that is, they gave details of the dosage of the drugs under consideration and examined the treatment outcomes for any of our five defined health states.

The baseline transitional probabilities of patients who received the treatment regimen of i.v. CYC → i.v. CYC (baseline comparator) were retrieved from three eligible studies. The probability of transitioning from partial to complete remission was obtained from Melo et al. [13]. The rest of the transitional probabilities were obtained from Ong et al. [14] and Illei et al. [15], for induction and maintenance data, respectively. Age-specific data on the probability of dying for the Thai general population was taken from the Thai Working Group on Burden of Disease and Injuries report [16] to account for deaths that were not caused by LN disease. Lastly, a hazard function from Teerawattananon et al. [10] was included to calculate the renal death risk of ESRD in Thai patients. This study assumed that patients in the cohort would not suffer from ESRD during the first 6 months of treatment.

Relative treatment effects of intervention regimens in the induction phase were retrieved using the same approach. The PubMed database was searched using the same keywords mentioned above but examined only systematic reviews and meta-analyses. The study by Lee et al. [17] was selected to estimate the relative treatment effect in the induction phase, since this study provided the most comprehensive set of treatment effect parameters, including complete and partial remission, ESRD and death.

Due to the absence of any meta-analyses that compare all maintenance treatment comparators simultaneously in head-to-head RCTs, it was necessary to create an indirect evidence synthesis to establish the efficacy of the treatments. Six RCTs that investigated the therapeutic strategies of interest were identified [18-23]. An observational study by Mok et al. [24] was also included to complement the data from the RCT by Yee et al. [21]. A fixed effects multitreatment meta-analysis of unobserved heterogeneity among treatment strategies was performed using WinBUGS 1.4.3. (Medical Research Council, Cambridge, UK and Imperial College London, UK). This approach allowed us to combine direct with indirect comparisons; the concurrent analyses of the relative effects of several treatment strategies were performed with 50 000 iterations.

Rates of major infection occurring as a severe complication in patients receiving different regimens were retrieved from five RCTs that explicitly reported patients suffering from major infections [18, 19, 22-24]. To account for heterogeneity in the included studies, a random effects pooled mean meta-analysis was performed using WinBUGS 1.4.3 with 50 000 iterations.

Resource use and costs

Resource use and costs were measured in terms of direct medical and non-medical costs. Direct medical costs
consisted of drug costs and health care services costs for treatment of LN and its complications. Drug costs were calculated on the basis of the median procurement price for the drug from all public hospitals across the country, as collected by the Ministry of Public Health [25]. Health care resource use was estimated using data from a medical records review on LN treatment at four tertiary care hospitals in Thailand (laboratory tests and drug administrative costs). The resources used were multiplied by the unit costs from the standard costing list for health technology assessment to estimate the total direct medical costs of the treatment [26]. The health care cost of treating major infections (the main complications that require hospitalization) was obtained from the Thai hospitals database [27]. The cost of treating Thai patients with ESRD was retrieved from Teerawattananon et al. [10].

In addition, direct non-medical costs (costs of transportation, meals, accommodations, facilities and informal care) and the costs of productivity loss due to sick leave were estimated from the standard costing list for health technology assessment [26]. As this study was a comparison of treatment strategies, cost items that were approximately identical in all of the assessed regimens were excluded, such as the cost of prednisolone among treatment options. All costs were adjusted using the consumer price indexes published by the Ministry of Commerce in Thailand for the price year 2012 [28].

Utility weights

Using the EQ5D instrument, utility weights in which values ranged from 0 (death) to 1 (full health) for calculating QALY were obtained from 216 observations of patients (18 patients for 12 visits each, on average) in four tertiary care hospitals in Thailand. The subjects’ written consent was obtained according to the Declaration of Helsinki and the study was approved by the Committee on Human Rights related to Research involving Human Subjects from Chulalongkorn Hospital, Nopparat Rajathanee Hospital, Tammasart Hospital and Srinakarin Hospital. The mean age of patients was 40 years. The LN patients’ quality of life, classified by the disease health stage of interest—namely complete remission, partial remission, active LN in developed countries was conducted in 2007 [30]. The results suggested that MMF was the best choice for first-line therapy, since it led to better quality of life and cost less than i.v. CYC. However, it was conducted with a short-term time horizon for the induction phase and did not consider critical outcomes such as renal failure and comparing the estimated life-years with those of a study in Thailand [3] and another conducted in multiple countries [29].

Results

The cost-utility of alternative treatment regimens was assessed by calculating the ICERS. Three treatment regimens were compared with the one used as the baseline comparator (i.v. CYC → i.v. CYC). It was found that, for patients at the average age of 40 years, the regimen of i.v. CYC → AZA was a better option, as it both saves cost (13,300 baht) and offers more benefits in terms of QALYs gained (0.27). However, in comparison with the baseline regimen, the regimen of i.v. CYC → MMF and MMF → low-dose MMF were found to provide more benefits, albeit at a higher cost (ICER = 618 000 and 350 000 baht/QALY, respectively). Three regimens (i.v. CYC → i.v. CYC, i.v. CYC → MMF and MMF → low-dose MMF) are dominated by i.v. CYC → AZA (Table 1). These results suggest that the regimen of i.v. CYC → AZA was likely to be the most effective regimen of all the alternatives. The regimen of MMF → low-dose MMF and i.v. CYC → MMF could be considered as inferior alternatives, as they provided similar benefits but at a higher cost. A cost-effectiveness plane was used to illustrate the findings in Fig. 2.

After conducting a PSA with 1000 iterations, the maximum expected net monetary benefit was estimated for each ceiling ratio value in which society would be willing to pay for a QALY gained. It was found that at the current cost-effectiveness ceiling threshold in the Thai context of 120 000 baht/QALY gained [11], the regimen of i.v. CYC → AZA constituted the highest probability of a cost-effective regimen at this threshold and also across a wide range of willingness to pay (WTPs), ranging from 50 000 to 1 000 000 baht/QALY gained (supplementary Figs S1 and S2, available at Rheumatology Online). In addition, one-way sensitivity analysis indicated that the parameters of drug efficacy, especially the relative risks of complete remission, partial remission and renal failure, were the most influential parameters on the level of ICER uncertainty (supplementary Figs. S3–S5, available at Rheumatology Online).

Discussion

This study compares the cost-utility of alternative treatment regimens for LN. The analysis indicates that, in the context of developing countries, the regimen of i.v. CYC → AZA was likely to be the cost-saving regimen compared with baseline regimen (i.v. CYC → i.v. CYC). To compare this finding with other previous study results, another analysis that evaluated the cost-effectiveness of MMF and i.v. CYC in the context of induction therapy for active LN in developed countries was conducted in 2007 [30]. The results suggested that MMF was the best choice for first-line therapy, since it led to better quality of life and cost less than i.v. CYC. However, it was conducted with a short-term time horizon for the induction phase and did not consider critical outcomes such as renal failure and
Therefore our study identified the regimen i.v. CYC lower than that for the regimen of i.v. CYC!

Moreover, while the rate of major infection for the MMF first-line therapy (78 000 baht in the first year of treatment).

The hospital costs for administering this regimen in day-case procedures and the patient costs for transportation, the costs of i.v. CYC treatment were not particularly high. In contrast, in the context of Thailand, our study found that the regimen of i.v. CYC → AZA was found to be the most appropriate treatment option, other alternative MMF regimens that offered a better safety profile for gastrointestinal events and amonorrhoea may be considered as appropriate. Second, this model estimate was based on fixed dose regimens regardless of the outcomes of treatment and complications that may lead physicians to reduce the dose of drugs, which would then potentially reduce the treatment benefits accordingly. Third, due to policy-related time constraints and the rarity of the condition, the sample size for estimating some utility parameters was not big enough to obtain high statistical power to represent the Thai patient population. Fourth, the generalizability of results is restricted to similar patient populations from contexts with similar characteristics to Thailand. Issues such as the structure of healthcare delivery and ethnicity may play an important role in limiting the use of these results in other settings and therefore careful judgment should be used for their extrapolation.

A number of parameter limitations were identified and this suggests that our findings require further research. The sensitivity analysis indicated a wide range of parameter uncertainty, especially in the parameter of efficacy leading to complete or partial remission and renal failure in all alternative drug regimens compared with the baseline regimen. An analysis that takes into account a selection of head-to-head RCTs that examine both the induction and maintenance phases and concurrently compares all possible treatment regimens will be required to derive precise efficacy parameters. Moreover, this study did not include treatment data on rituximab and new immunomodulatory agents since their role has yet to be fully explored [31]. Therefore economic evaluation studies should be conducted in this area when data become available.

Finally, due to the scope of the study focusing only on newly diagnostic LN patients, the recommendation on treatment for complicated cases of relapse or resistant death, which occur later in treatment. To our knowledge, our analysis was the first study that considered all possible regimens for both the induction and maintenance phases of LN treatment in a developing country. Moreover, this study took into account the main critical consequences (ESRD and death) influencing cost and outcome in the long run.

The findings from the 2007 developed country study indicated that MMF induction therapy was likely to give patients with LN a better quality of life at a lower cost than i.v. CYC. This is predominantly due to the fact that MMF requires no day-case procedures to be administered, unlike i.v. CYC. Moreover, MMF treatment also resulted in significantly decreased incidences of adverse events, particularly major infection, compared with i.v. CYC [30]. In contrast, in the context of Thailand, our study found that the costs of i.v. CYC treatment were not particularly high. The hospital costs for administering this regimen in day-case procedures and the patient costs for transportation, informal care and productivity loss due to sick leave accounted for 6000 baht/year. This does not represent a high burden when compared with the cost of MMF as first-line therapy (78 000 baht in the first year of treatment). Moreover, while the rate of major infection for the MMF regimen was considerably lower than for the regimen of i.v. CYC → i.v. CYC, it was not found to be significantly lower than that for the regimen of i.v. CYC → AZA. Therefore our study identified the regimen i.v. CYC → AZA as the best treatment option due to the relatively low drug costs and long-term benefits that were comparable to those of MMF regimens.

The findings in our study should be interpreted with caution, given the following limitations of the study. First, only the most severe adverse effect (major infection) was taken into account, while other adverse effects, such as haematological and gastrointestinal events, alopecia and amonorrhoea, were not considered. Therefore, although the regimen of i.v. CYC → AZA was found to be the most appropriate treatment option, other alternative MMF regimens that offered a better safety profile for gastrointestinal events and amonorrhoea may be considered as appropriate. Second, this model estimate was based on fixed dose regimens regardless of the outcomes of treatment and complications that may lead physicians to reduce the dose of drugs, which would then potentially reduce the treatment benefits accordingly. Third, due to policy-related time constraints and the rarity of the condition, the sample size for estimating some utility parameters was not big enough to obtain high statistical power to represent the Thai patient population. Fourth, the generalizability of results is restricted to similar patient populations from contexts with similar characteristics to Thailand. Issues such as the structure of healthcare delivery and ethnicity may play an important role in limiting the use of these results in other settings and therefore careful judgment should be used for their extrapolation.

A number of parameter limitations were identified and this suggests that our findings require further research. The sensitivity analysis indicated a wide range of parameter uncertainty, especially in the parameter of efficacy leading to complete or partial remission and renal failure in all alternative drug regimens compared with the baseline regimen. An analysis that takes into account a selection of head-to-head RCTs that examine both the induction and maintenance phases and concurrently compares all possible treatment regimens will be required to derive precise efficacy parameters. Moreover, this study did not include treatment data on rituximab and new immunomodulatory agents since their role has yet to be fully explored [31]. Therefore economic evaluation studies should be conducted in this area when data become available.

Finally, due to the scope of the study focusing only on newly diagnostic LN patients, the recommendation on treatment for complicated cases of relapse or resistant
proliferative LN should be the subject of further study. An economic evaluation alongside a clinical trial has been registered since 2009 at ClinicalTrials.gov (NCT01015456) and the results are to be published in 2014.

In conclusion, this study highlighted that, at the current price, the regimen of i.v. CYC for the induction phase followed by AZA for the maintenance phase (i.v. CYC → AZA) should be recommended as the first-line therapy for newly diagnosed severe LN patients, as it seems to be the most cost-saving regimen. These recommendations have been endorsed by the Subcommittee for the Development of the Health Benefit Package and Service Delivery in Thailand.

**Rheumatology key messages**

- Intravenous CYC followed by AZA appears to be a cost-effective treatment in newly diagnosed LN treatment.
- MMF offers limited value to newly diagnosed severe LN patients in Thailand.

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**Supplementary data**

Supplementary data are available at *Rheumatology* Online.

**References**


