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Pharmacoeconomic evaluation of artesunate-amodiaquine and artesunate- mefloquine artemisinin-based combination therapies.

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Abstract

These two artemisinin-combination therapies (ACTs) have been found to be rarely prescribed due to various reasons relating to both clinical and marketing promotional considerations. This study aims at uniting these factors by evaluating the pharmacoeconomic considerations on the choice of these two drugs. Published data on efficacy/ effectiveness trials were reviewed from where the data for this study were extracted. A pharmacoeconomic analysis was carried out using the various tools of *pharmacoeconomics. It was found out that clinically derivable utilities and health outcomes (Side-effects and, probably, convenience of dosage regimen) did not favour the frequent choice of these drugs. Side effects and, probably, convenience of dosage regimen mainly affected the choice of these drugs.Clinical cure should not be the only health outcome to be guided in therapy. Other unfavourable health outcomes should be considered also. Disability/Distress to the patients should be considered also. However, Artesunate-Amodiaquine (AAQ) has a superior pharmacoeconomic advantage over Artesunate-Mefloquine (AM) in terms of cost and cost utility. Artesunate-Mefloquine (AM) has a higher cost-benefit than AAQ but this is rarely used in health considerations. Side effects of these drugs limit their choice as antimalarials. in effective in treating uncomplicated Plasmodium falciparum malaria*

Key words: *Pharmacoeconomics; health outcomes; disability/distress scale; recrudescence; health utility; sensitivity analysis; effectiveness-efficacy data*

INTRODUCTION

Pharmacoeconomics has become a subject of great interest. Riding the wave of managed care-and the increased cost consciousness of government, employers, insurers, and patients, pharmacists, providers, and pharmaceutical companies use economic models to prove the value of their drugs and therapeutic interventions.[1] This must include the use and cost of laboratory and diagnostic services, physician and ambulatory visits, hospitalizations, and other resources consumed; more importantly, they must now include the costs and benefits to the patients, their families and to the society.The utility of a particular health state is a cardinal measure of the strength of one's preference for a health state. [2,3] The time spent in various health states by an individual, weighted by the utility values assigned by this individual, represents the health-related quality of life for this individual as measured in Quality-adjusted life years (QALYs).

The gains in QALY for an individual or a group of individuals due to a health programme can be used as a measure of that programme's effectiveness. When changes in cost before and after the implementation of the programme, are calculated and matched with the gains (or losses) in QALY due to the programme, the resulting ratio is the cost-utility ratio of that programme. It should be recognized that a number of researchers have been working in the area of measurement of health state utilities and changes in QALY as a measure of effectiveness of health programmes.[2,4,5] The results of Torrance showed varying utility values of 1.00 for health and 0.00 for dead as reference states.[2] The health states with negative values are viewed as worse than death. The Rosser and Watts Matrix (Table 1) also provide another index for utility values.[6] It should be recognized that measures of improvement in health states due to any programme or treatment simply provide data that may be used by pharmacists and other healthcare professionals to improve their decisions. They do not provide definitive answers nor do they make decisions for us. The study, therefore, aims at evaluating the Pharmacoeconomic basis for guiding the choice of the Artemisinin-based combination therapies (ACTs), particularly focusing

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on Artesunate-Amodiaquine (AAQ) with Artesunate - Mefloquine (AM) as antimalarial drugs.

METHODOLOGY

Literature search was carried out on the effectiveness and other health related parameters of these WHO approved ACTs. Thus, it was the efficacy data obtained from randomized clinical trials that were applied in this pharmaco-economic analysis whose aim was to determine the relative PE data of these drugs and use them in their ratings for real life situations.

Artesunate-Amodiaquine (AAQ) and Artesunate - Mefloquine (AM) are two Artemisinin-based combination therapies (ACTs) that have been widely used for the treatment of uncomplicated malaria across the sub-Saharan Africa. The efficacy of these two regimens is well established. [7-12]

Aside from their efficacy, no convincing evidence of artemisinin neurotoxicity has been demonstrated during routine clinical use in humans. [7] The absence of longitudinal studies limits the prospective areas of study.

The major pharmacoeconomic evaluation tools are Cost Minimisation Analysis (CMA); Cost-Effectiveness Analysis (CEA) Cost-Utility Analysis (CUA) and Cost-Benefit Analysis (CBA). [19-24]

Cost Minimization Analysis (CMA)

The average prices of AAQ and AM in retail pharmacies in Nigeria are respectively N800 and N1050. The too ACTs produce a very rapid therapeutic response, [25] no resistance to them has been reported [26-29] and the outcomes are the same--cure to malaria episodes. Hence, only the costs of the drug are considered more so as the other costs are equal for the interventions. Since CMA identifies the intervention with the lowest possible costs bearing in mind that the outcomes are the same, it is glaring that AAQ has a lower cost than AM. Hence, AAQ is the drug of choice under this evaluation tool as only the cost differences are the main determinants of the decision about the choice of therapy.

Cost Benefit Analysis

Under this tool, it is the benefit that arises as a result of applying the intervention that is considered relative to the cost and this parameter is measured in monetary values. [30] The studies by Bukirwa et al, [8] Mattenson et al [10] and van der Broek [31] showed AL as the 'gold standard' being the most effective of all the ACTs followed by AM. Hence, AM is more efficacious than AAQ in the treatment of malaria episodes. Hence the net cost of using AAQ is higher than the net cost of using AM (alternatively, the net benefit of using AAQ is less than that of AM). The pharmaco-economic decision rule to choose the drug with the higher net benefit (of the two) favours AM. Hence, in terms of CBA, AM will be drug of choice.

Cost-Effectiveness, Analysis

Outcomes to be compared are efficacy, side effects, productivity cost and all patient and family costs etc. Although AM has been widely studied in Asia, data are limited in malaria-endemic areas in Africa. [32-34] Stoher et al [35] has shown the excellent efficacy and tolerability of AL and AM in Northern Laos while that of Hutagalung et al [36] and Sagara et al [37] showed that AM was well tolerated and is as effective as AL for the treatment of *Plasmodium falciparum* malaria. The two drugs remained highly effective and resulted in equivalent therapeutic responses and prevented more new infections. Hence, AM is more effective and well tolerated than AAQ. Therefore, in effectiveness ratio, AM has a higher cost-effectiveness than AAQ. This was confirmed by the studies by Mattenson et al, [10] and Bukirwa et al, [8] that compared AL to AAQ (an effectiveness study in Tanzania and an efficacy trial in Burundi). AL resulted in fewer failures and fewer parasitological failures. Thus AL provided greater protection against re-infection compared with AAQ. AL was superior to AAQ in preventing new infections. [8] Therefore, since AM and AL were found to be highly efficacious and equivalent in there therapeutic responses and AL was found to be superior to AAQ, hence AM is superior to AAQ.

It should be noted that CEA is not useful to decision makers in deciding among programmes with different or multiple health effects involving morbidity and mortality. It does not provide an overall measure of healthcare programmes.

Cost-Utility Analysis (CUA)

Here the consequences are expressed in utilities such as the quality-adjusted life years (QALY) as opposed to natural units in CEA - recrudescence, re-infection and treatment-related adverse events are variables that affect the QALY measurements. Ndiaye et al, (2009) showed that these adverse events are milder in AAQ (insomnia, somnolence and gastro-intestinal system disorders) when compared with AM (neuropsychiatric reactions cardiac conduction disorders, circulatory disorders etc). (www.lariam.com). Other reported effects of Mefloquine included bad dreams, ringing in the ears, emotional instability, numbness, rashes and itching. Recrudescence was higher in AAQ than AM. [38]

Table 1 shows the DDS for these drugs using the Rosser and Watts Disability/Distress Scale. From this Table, AAQ has 0.973 and 0.956 value for AM. The cost per QALY gained is calculated as: (Cost B – Cost A)/(QALY of B – QALY of A).

Table 1: Showing the Rosser and Watts Disability/Distress Scale for these drugs

Drug	Disability	Distress
AAQ	Slight social disability	0.978
AM	Severe social disability	0.956

Table 2: Showing the cost per QALY for the Drugs

Drug	AAQ	AM
AAQ	-	-14705.88
AM	-14705.88	-

Table 2 showed that substituting either of these drugs for the other cost - #14705.88 per QALY. Hence, neither is cost effective over the other in treating *P. falciparum* malaria. The cost /QALY surpassed the cut-off threshold for cost-effectiveness by this value. Hence, it is not cost effective to use these drugs where an alternative ACT is available.

Sensitivity Analysis

Increasing the DDS for AM to 0.995 made the drugs to become alternative cost-effective replacement therapy for each other (Table 3).

Table 3: Showing the Sensitivity Analysis

Drug	AAQ	AM
AAQ	-	-11363.64
AM	-11363.64	-

It cost N11, 363.64 above the cut-off threshold for cost-effectiveness per QALY gained for either therapy 9 Table 3). Hence, it is not cost-effective using AM in place of AAQ. Reducing the price of AM by 20% (N840) while maintaining the DDS of 0.973, increased the cost per QALY gained by # 2392.94 above the cut-off threshold this discounting reduced the cost/QALY gained but none is cost-effective over the other. Again, the drugs are equally cost-effective over each other.

Conclusion:

Apart from being of a lower cost, AAQ has superior advantage over AM in terms of CUA. AM has higher CBA, and CEA than AAQ while they are equally cost-effective over each other. Side effects of these drugs (particularly AM) limit their choice as anti-malarial.

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