COST IMPACT OF PROSPECTIVE HLA-B*5701-SCREENING PRIOR TO ABACAVIR/LAMIVUDINE FIXED DOSE COMBINATION USE IN GERMANY

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INTRODUCTION

To date, various host genetic factors are known to affect adverse drug reactions and therapeutic response to drugs [1, 2]. The implementation of genetic screening into clinical practice requires the evidence of improved safety or effectiveness of pharmaceutical care in prospective clinical trials. Due to limited financial resources in health care pharmacogenomic-based strategies also should aim to be cost-effective [3, 4]. Besides improved clinical outcome, avoiding adverse drug effects may lead to cost savings which could offset the costs of genetic screening.

The application of pharmacogenomics in HIV-treatment is relatively recent. Genetic factors associated with drug metabolism, transport of drugs or immunogenetic factors have been described [5-11]. The human leukocyte antigen allele HLA-B*5701 is the first pharmacogenetic marker with proven clinical utility of genetic screening for improving patient safety in HIV-therapeutics. The presence of HLA-B*5701 is strongly associated with an increased risk for an abacavir-related hypersensitivity reaction (HsR) in Caucasian and also in non-Caucasian HIV-positive populations [12]. Abacavir is one of seven approved reverse transcriptase inhibitors used for combination therapy in HIV-positive patients.

The most treatment-limiting effect is an abacavir HSR occurring in 4.9% of patients, mainly during the first six weeks of treatment [13-16]. In a large, double-blinded, prospective two-arm clinical trial the incidence of clinically diagnosed abacavir HSR was reduced significantly when avoiding abacavir in patients tested positive for HLA-B*5701 [14]. Moreover, the risk of immunologically confirmed HSR has been completely eliminated.

Most guidelines for the treatment of HIV-infection have recently included the recommendation for prospective HLA-B*5701-screening prior to the initiation of abacavir [17-20]. Two studies assessed the costs attributed to an abacavir HSR and the potential

Abstract

Objective: Avoiding abacavir in HIV-infected patients tested positive for HLA-B*5701 reduces the risk of abacavir hypersensitivity reaction (ABC-HSR). Our aim was to assess the costs of clinically suspected HSR and to estimate potential cost savings of implementing prospective HLA-B*5701-screening for HIV-infected patients initiating abacavir/lamivudine fixed-dose combination (ABC/3TC FDC) compared to initiating respective treatment without screening.

Methods: Employing a decision tree model the expected HSR-related costs of screening vs. no screening were estimated from the societal and healthcare payer perspective (reference year 2007). A retrospective standardized assessment of all clinically suspected ABC-HSR cases without screening at 5 German HIV-centres was performed to measure resource consumption. In- and outpatient care, discarded ABC/3TC FDC and concomitant medication were considered. Direct resource utilization was valued using German fees (EBM, G-DRGs). Indirect costs were measured with the human capital approach. Estimates for the HLA-B*5701-prevalence, HSR-incidence, and hospitalization rate were based on clinical trials and cohorts and it was assumed that screening reduces the incidence of clinically suspected ABC-HSR from 10% to 0.5%.

Results: Thirty-two ABC-HSR cases were identified from 1998 to 2007. Mean direct and total costs per clinically suspected HSR case were €1,362 and €2,235, respectively. Hospital costs contributed 63.3% to direct costs. Potential cost savings when implementing genetic screening were estimated at €44 and €127 per screened patient, from a healthcare payer or societal perspective.

Conclusion: HLA-B*5701 screening prior to ABC/3TC FDC initiation prevents significant HSR-related costs per screened patient and is likely to lead to overall net savings.

Key words: HLA-B*5701, pharmacogenomics, abacavir
HLa-B*5701-screening is employed prior to the use to measure the resource consumption related to an decision tree model was employed to simulate the expected costs of two alternative therapeutic strategies consisting of using ABC/3TC FDC as part of an antiretroviral treatment regimen either with prior prospective HLA-B*5701-screening or without genetic screening as previous standard of care. The model covered the time span until remission of abacavir-related HSR or up to six weeks of treatment with abacavir. Costs were estimated from the societal (direct + indirect costs) and health care payer (direct costs) perspective. Input parameters were derived from clinical trials or cohorts, specified German registries and reimbursement data of social and private health insurances as described below.

Direct costs included costs of HLA-B*5701-screening, physicians services, concomitant medication for symptomatic treatment of HSR, diagnostic procedures, laboratory parameters, discarded ABC/3TC FDC and costs for inpatient care (according to diagnoses, procedures and length of stay). Indirect costs include costs for productivity loss due to temporary disability to work. ‘MICE’, a module for indirect cost estimation, was used for the calculation of indirect costs for productivity loss. The module has been developed at the University of Ulm, Germany [23].

To determine whether the results of the base case scenario are robust to plausible variations in input parameters we conducted one-way and multi-way (low cost scenario, high cost scenario) sensitivity analyses (see Table 1). On the basis of Australian data, it was assumed that withholding ABC/3TC FDC from HLA-B*5701 positive patients reduces the incidence of clinically suspected abacavir-related HSR from 10% to 0.5% [29].

Estimated private health insurance rates of HIV-infected patients were based on the German-wide situation [30] and on the analysis of more than thousand patients of a large German HIV-specialised private practice.

Average length of inpatient hospital stay and period of disability leave from work were derived from the 5C study. Distribution of age groups and gender among the HIV-positive population in Germany was chosen according to the federal annual health report of the Robert Koch Institute concerning incidence HIV-infections in 2006 [31, 32]. Labour market data (rates of employed, unemployed and retired persons) were extracted from the statistical yearbook of the Federal Statistical Office [33].

Resource Valuation

Direct and indirect costs were calculated using 2007 as reference year. Resource utilization was valued using the Physicians’ fee scale (EBM) of the social health insurance for outpatient treatment [34] and the per-case fees of the G-DRG system for inpatient treatment [35, 36]. For patients with private health insurance, the outpatient fees were based on the doctors’ fee ordnance for private health services [30, 37]. For inpatient patients with private health insurance, an extra charge for single rooms or chief physician attendance was included. Pharmacy prices [38] were used for calculating the costs for antiretroviral and other drugs. Currently, there is no official German price for HLA-B*5701-screening. Instead, laboratories have different options to charge for HLA-B*5701-screening, resulting in a price range instead of a single price. We estimated the
costs associated with HLA-B*5701-screening on the basis of the different calculation schemes retrieved from 3 independent laboratories, taking into account the patient shares with private or statutory health insurance (Table 1). Productivity loss was valued with age- and sex-specific labour costs and related to the length of hospital stay and/or period of disability leave from work (corrected for weekends). Labour costs included average annual gross income and employer's contributions and were related to the annual number of working days [39-41].

Table 1. Data and assumptions used for the base case analysis (using estimated average values) and for sensitivity analyses.

| Probabilities                                      | Base case               | Low cost scenario          | High cost scenario          |
|---------------------------------------------------|-------------------------|----------------------------|-----------------------------|
| Incidence of clinically suspected HSR             | 10.0% EPI-001 + PREDICT-1 [14, 27] | 7.8% PREDICT-1 [14]       | 12% EPI-001 (Eastern Europe ethnicity) [27] |
| Prevalence of HLA-B*5701                          | 7.3% EPI-001 [27]       | 5.6% PREDICT-1 [14]       | 9.5% EPI-001 (Eastern Europe ethnicity) [27] |
| Negative predictive value of genetic HLA-B*5701 test | 99.5% assumption       | 99% assumption            | 100% PREDICT-1 [14]         |
| Hospitalization rate                              | 12.0% unpublished data¹ | 10% unpublished data¹    | 15% unpublished data¹      |
| Private health insurance rates                    | 15% 5C study + single centre evaluation | 10% private health insurance rate in total population in Germany [30] | 20% private health insurance rate in HIV-infected population in Germany [30] |
| Percentage of antiretroviral medication (ABC/3TC FDC) being discarded | 53.7% 5C study | 50% assumption            | 56.2% PREDICT-1 [14]         |
| Costs                                             |                         |                            |                             |
| Costs of HLA-B*5701-screening                      | €86 assumption         | €108 assumption          | €64 assumption               |
| Costs of a monthly pack of ABC/3TC                | €758 Lauertaxe [38]    | NA                        | NA                          |
| Concomitant medication                            | €20 5C study           | *                          | *                           |
| Costs for outpatient care                         | €73 5C study           | *                          | *                           |
| Hospital costs for cases receiving inpatient care | €6,904 5C study        | €4,623 5C study: lump sum for standard inpatient care (DRG-Code S63B) | €8,436 5C study: mean hospital costs in 5-centre study when excluding hospital stays of only one day |
| Extra charge for patients with private health insurance | €1,884 5C study       | NA                        | NA                          |
| Indirect costs                                    | €873 MICE module [23, 31-33] | €0                        | NA                          |

* Due to only minimal impact on cost outcomes, no sensitivity analyses performed; NA = not available
¹ GSK studies, data on file

RESULTS

5C STUDY

Thirty-two cases of clinically suspected abacavir HSR have been identified between January 1998 and May 2007, among them 29 Caucasians, two Asians and one African patient. Median age was 39.7 years (range 25-71 years). Mean time on drug until the first reported symptoms was 10.8 days. After the occurrence of the first symptoms it took 9.7 days (mean) until abacavir was discontinued. Twenty patients suffered from symptoms of grades 1-2, and 12 patients suffered
from symptoms of grades 3-4 [42], respectively. Twenty-two patients received outpatient care (18/22 with grade 1-2 symptoms); ten cases were admitted to hospital (8/10 with grade 3-4 symptoms). Mean length of hospital stay was 20.8 days (range 1 – 58 days), mean number of days off due to sick leave (medical certificate) was 6.4 (excluding hospitalizations). On average, 53.7% of a monthly pack of ABC/3TC FDC was discarded due to premature discontinuation.

**BASE CASE ANALYSIS**

At a price of €757.90 for a monthly pack of ABC/3TC FDC [38] the cost of discarding 53.7% of a monthly pack on average was €407 per case. Mean costs for other concomitant medication were estimated at €20. Mean costs for outpatient care amounted to €73 per case. Costs for inpatient care were a major cost driver in the 5C study and ranged from €775 for single day hospitalizations to €16,865 for a 58-day hospital stay. Mean hospital costs for cases receiving inpatient care were estimated at €6,904 (median: €5,800). For patients with private health insurance, an extra charge of €1,884 for a single room or chief physician attendance was added.

With a 12% hospitalization rate and an estimated 15% private health insurance rate in HIV-infected patients in Germany, the mean hospital costs per clinically suspected HSR case were calculated at €862. Costs for in- and outpatient care, discarded ABC/3TC FDC and concomitant medication added up to mean direct costs per clinically suspected HSR case of €1,362.

Direct costs summed up to an average of €873 per case. Mean total costs per clinically suspected HSR were €2,235.

Assuming costs of HLA-B*5701-screening of €86 and that withholding ABC/3TC FDC from HLA-B*5701 positive patients reduces the incidence of clinically suspected abacavir-related HSR from 10% to 0.5%, potential cost-savings when implementing genetic screening were estimated at €44 (direct costs) and €127 (total costs) per screened patient.

**SENSITIVITY ANALYSES**

Taking the societal perspective, the most influential model parameter was the prevalence of HLA-B*5701 (€78 to €165) (Fig. 2). Total costs were moderately sensitive to variations in costs of HLA-B*5701-screening (€105 to €149), in costs for inpatient care (€101 to €145) and to variations in the hospitalization

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**Fig. 1.** Decision tree comparing two alternative strategies: Prospective HLA-B*5701-screening prior to using abacavir/lamivudine FDC as part of an antiretroviral treatment regimen versus initiation of abacavir/lamivudine FDC without genetic screening.

**Fig. 2.** One-way sensitivity analyses considering total costs (Tornado diagram). The vertical line depicts the base-case analysis with an expected value of €127. The input parameters for the low and high cost scenarios are shown in Table 1. Abbreviations: NPV = negative predictive value; ABC/3TC FDC = abacavir/lamivudine fixed dose combination.
rate (€113 to €148). The results remained qualitatively robust (i.e. still rendering net savings) with respect to extreme value assumptions of the negative predictive value of genetic testing, the percentage of discarded antiretroviral medication, or the rate of private health insurance. When simultaneously employing extreme values of all parameters (low and high cost scenarios), total cost savings ranged from €16 (low cost scenario) to €254 (high cost scenario). By taking the healthcare payers’ perspective and thus considering direct costs only, results of the sensitivity analysis remained similar with respect to the sensitivity of the model parameters (Figure not shown). Results ranged from additional costs of €43 (low cost scenario) to cost savings of €152 (high cost scenario).

**DISCUSSION**

Treatment guidelines have implemented HLA-B*5701-screening prior to using abacavir as part of antiretroviral treatment regimens [17-20]. These recommendations are based on clinical studies and cohorts showing a marked reduction in clinically suspected HSRs when avoiding abacavir in patients screened positive for HLA-B*5701 [14]. Our study addresses the economic issues related to the implementation of HLA-B*5701-screening in Germany. Using a decision tree model we compared direct and indirect HSR-related costs of either HLA-B*5701-screening prior to ABC/3TC FDC initiation or previous standard of care treatment without prospective genetic screening. The evaluation of direct costs was based on a small retrospective cohort of 32 HIV-patients with clinically suspected abacavir-related HSR. Since one inclusion criterion was that HSR did not occur later than May 2007, the genetic information on HLA-B*5701 carriage – thus representing unbiased clinical diagnoses of abacavir-related HSRs.

Cost evaluation of clinically suspected HSR cases was limited by the relatively small sample size of only 32 cases. Resource utilization for outpatient care may vary in different settings and depends on symptoms. However, due to its relatively low contribution to total costs, variations do not have any strong influence on estimated potential cost savings. The costs for discarded antiretroviral medication when prematurely discontinuing ABC/3TC FDC were a major cost driver. Like in PREDICT-1 [14] more than 50% of medication prescribed for one month was discarded in the 5C study. We did not include the costs for replacing ABC/3TC by another drug combination.

Our model covered the time span until remission of abacavir-related HSR or up to six weeks of treatment with abacavir. The goal of this analysis was to compare short-term outcomes of the two ABC/3TC-based strategies and to show the cost savings potential of genetic screening prior to using ABC/3TC. The goal was not to model long-term outcomes including different treatment regimens and treatment changes due to side effects or virological failure. This has been done by Schackman and colleagues who published a computer-based state transition model of HIV-disease in the United States to project long-term outcomes of first-line ABC/3TC- or tenofovir/emtricitabine (TDF/FTC)-containing regimens and respective expenses [22]. In this model, prospective genetic screening for all patients prior to initiating HAART and treatment initiation with an ABC/3TC-based regimen as long as the costs for ABC/3TC were lower than those for TDF/FTC (at least 2 US $) and provided that ABC/3TC-based therapy had equivalent efficacy to TDF/FTC therapy (<1% difference for 48-week virological responses rate defined as <400 copies/ml).

In contrast to Schackman’s work, the goal of our analysis was different, as is the conclusion: We modelled a situation in which the physician has already decided, for whatever reasons, to treat a patient with ABC/3TC. Identifying patients at risk of ABC-HSR using prospective genetic screening and withholding ABC/3TC treatment from those patients turned out to have cost-saving potential compared to treatment initiation without genetic screening.

The prevalence of HLA-B*5701 varies in different ethnic groups of a population. In our model, the base case assumption for the situation in Germany was based on a German epidemiological study (EPI-001) in HIV-patients [27]. For sensitivity analysis we simulated the European and Australian populations of the PREDICT-1 study with a lower HLA-B*5701-prevalence than in the German survey (5.6% versus 7.1%) [14]; the corresponding cost savings decreased from €127 to €78.

Since in PREDICT-1 approximately 0.5% of patients negative for HLA-B*5701 had a clinically suspected HSR, we accounted for this proportion in the base case analysis. Negative predictive values of genetic screening between 99% and 100% were used in the sensitivity analysis resulting in cost savings between €117 and €137.

HLA-B*5701 screening prior to ABC/3TC FDC initiation prevents significant HSR-related costs per screened patient and is likely to lead to overall net savings. Irrespective of economic considerations, there is a clear medical benefit of prospective HLA-B*5701-screening will be an important milestone for using genetic testing to improve drug safety and bringing individualized medicine to clinical practice.

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