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ORIGINAL RESEARCH

Preferred S-adenosylmethionine prescription in routine practice for intrahepatic cholestasis management: results of a multinomial logistic regression grid-optimization approach

This article was published in the following Dove Press journal:
Open Access Medical Statistics

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Background: S-adenosylmethionine (AdoMet) is available for the treatment of intrahepatic cholestasis in different doses and in different administration forms. The aim of this study was to develop a categorization model, also called a nomogram, to discern if there was a relationship between prescribers' treatment preferences and patient baseline characteristics for the treatment options, and to assess whether effectiveness was positively correlated with prescriber preference.
Materials and methods: Baseline characteristics of patients in a post-marketing observational study (PMOS) were analyzed by multinomial logistic regression to produce preference probabilities for the prescription of different AdoMet starting regimens: 400 mg injection, 800 mg injection, and 800 mg oral tablets. Grid-optimization based on the preference probabilities was used to subdivide the patients into seven relative treatment preference categories. Subsequently, for each category, the effectiveness of the three treatments was assessed by determining the response rate after 2 weeks of treatment for each treatment group.
Results: Elevated total bilirubin values, high Child–Pugh scores, and symptomatic cholestasis were associated with prescriber preference for the 800 mg injection, whereas low total bilirubin and low Child–Pugh scores were related to prescriber preference for the 400 mg injection. In the absence of cholestatic symptoms, the 800 mg tablet starting regimen was preferred. In the category where the baseline characteristics did not come to a more- or less-preferred treatment, the response rates were highest for the 800 mg tablets group (67%) and lowest in the 400 mg injection group (50%); however, the total sample size in this category was small (N = 22).
Conclusion: Categorization of patients into treatment preference groups based on baseline data might be an interesting approach to assess the validity of the treatment preference versus the respective treatment effectiveness as shown in a PMOS with three AdoMet treatment regimens.
Keywords: S-adenosylmethionine, intrahepatic cholestasis, multinomial logistic regression, propensity scores, grid optimization, prescriber preference

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Introduction

The term "cholestasis", meaning "bile stoppage", was coined in the 1930s to describe cirrhosis resulting from obstruction of the smallest biliary passages.[1] More than 20 years later, the clinical definition of the term "cholestasis" was widened to include any liver disorder characterized by impaired bile flow, irrespective of the site.[1] Subsequently, injuries to both large (extrahepatic cholestasis) and small, microscopic (intrahepatic cholestasis [IHC]) ducts were covered by the term.[1] In parallel, there was a change in

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http://dx.doi.org/10.2147/OAMS.S143058

the clinical diagnosis of jaundice, a hallmark for cholestasis, from a physical observation to an abnormal serum alkaline phosphatase (ALP) test.[1]

IHC is the most common cause of cholestasis and is reported in 35% of patients with chronic liver disease. It represents a clinical subphenotype of many chronic liver diseases, including non-alcoholic fatty liver disease and drug-induced liver injury, and correlates with disease severity in alcoholic liver disease and viral hepatitis.[2,3] Cholestasis is an important clinical finding as it may promote disease progression and, therefore, requires special attention and treatment.[4]

S-adenosylmethionine (AdoMet) has been shown to be effective in the treatment of established cholestasis. [5] The efficacy of AdoMet therapy has been demonstrated in clinical trials in a range of chronic liver conditions;[6–14] the drug has been widely adopted in China, Eastern Europe, Russia, South America, and Southern Asia as a therapy for IHC in pre-cirrhotic and cirrhotic states and for IHC in pregnancy.[5]

Several different therapeutic options are available for starting an AdoMet regimen, including oral, intravenous, and intramuscular preparations. In this context, a prescriber must select the most appropriate treatment regimen based on specific patient characteristics, which may include the patient's total bilirubin level and the severity of their liver disease (as measured by Child–Pugh classification [CPC]). CPC is based on bilirubin levels (<2, 2–3, or >3 mg/dL), presence or absence of hepatic encephalopathy, serum albumin levels (>3.5, <3.5–2.8, or <2.8 g/dL), and prothrombin time (1–<4, 4–6, or >6 seconds) and consists of three grades relating to prognosis (A [best], B [moderate], or C [worst]).[15,16]

Determining the correct treatment regimen from multiple options may be relatively difficult when guidelines are limited or unavailable and hence will be highly subjective. To discover any correlation between the prescriber's choice of an AdoMet treatment regimen and patient characteristics at presentation, a model must be used that takes into account the multinomial nature of the choice, for example, multinomial logistic regression (MLR) producing multiple preference probabilities.

In this study, the MLR grid-optimization model was applied to data obtained from a post-marketing observational study (PMOS) conducted in Ukraine, which examined clinical and biochemical treatment outcomes in patients with IHC according to three AdoMet starting regimens. The aim of this study was to develop and implement an MLR grid-optimization model to inform the selection of the AdoMet starting regimen for patients with a diagnosis of IHC, in a situation where multiple treatment options were available. In case of two treatments, the method would be similar to that of using propensity scores for three categorizations: one clearly more preferred than the other and vice versa, and the third situation with both "equally" preferred (for more information about propensity scores, refer e.g., Patorno et al).[17]

Materials and methods

Patients and study design

A total of 401 patients with a clinical diagnosis of IHC were enrolled from 29 Ukrainian centers into the PMOS study, after giving informed consent. The assignment of the patient to an AdoMet-containing therapy fell within current clinical practice. The investigators were physicians (gastroenterologists, general practitioners, infectious disease specialists, and hepatologists) who managed patients with IHC and observed them for up to 2 months.

Inclusion criteria were signs of IHC, serum conjugated bilirubin above the upper limit of normal, and serum levels of liver-associated enzymes (ALP and/or gamma-glutamyl transferase [GGT]) above the upper limit of normal. Patients with extrahepatic cholestasis or IHC in pregnancy and those taking hepatoprotectors or supplementary vitamins and amino acids were excluded from the trial.

This study was a prospective, single-arm, multicenter PMOS, in which AdoMet (Heptral®; Abbott India Ltd, Mumbai, India) was prescribed in accordance with the terms of the local marketing authorization with regards to dose, population, and indication. As this study was observational in nature, follow-up was noninterventional and left to the judgment of the physician within the 2-month period following initiation of AdoMet therapy. The first follow-up visit normally occurred ~2 weeks after the inclusion visit (usually at the end of the second treatment week), and the second follow-up visit occurred ~2 months after the inclusion visit (usually at the end of the second treatment month). At the 2-week time point, all patients were converted to an oral treatment regimen. AdoMet treatment response was defined as either a normalization/50% reduction in total bilirubin/conjugated bilirubin or a normalization/30% reduction in ALP and was assessed at both the 2-week and 2-month time points.

In this study, analysis was limited to the group of patients initially receiving AdoMet by 400 mg injection, 800 mg injection, or 800 mg tablets, which accounted for 80% of the PMOS patient population (N = 321).

This study was conducted in compliance with local laws and regulations relating to ethical conduct of medical research. The PMOS, which provided the data used in this study, was approved by the Central Ethics Committee of the Ministry of Health of Ukraine (EC No. 5.12-460/KE). The

patients were required to provide written informed consent for the investigator to use and/or disclose personal and/or health-related data before entry into the PMOS. Patient confidentiality was maintained throughout the study.

Statistical analysis

In this study, an MLR was first used to gain insight into the AdoMet treatment decision process resulting in three preference probabilities totaling to 1: preference for 400 mg injection, for 800 mg injection, or for 800 mg tablets. Second, the seven categories of relative treatment preferences were defined as follows:

- Categories I–III: clear preference for one treatment regimen (400 mg injection, 800 mg injection, or 800 mg tablets, respectively), defined as a preference probability of at least "a", more than that for the other two treatments.
- Categories IV–VI: little to no preference for one treatment regimen (400 mg injection, 800 mg injection, or 800 mg tablets, respectively) versus the others, defined by a preference probability of at least "b", less than that for the other two treatments, while the probability for the other two treatments is less than "a" different.
- Category VII: indifference between all treatments, defined as the complement of all other categories combined.

The preference probabilities for each treatment regimen, further referred to as preferences, and the values for "a" and "b" were used to assign each patient to a category. Table 1 shows some example categorizations. For each combination of "a" and "b", each patient is assigned to a category I–VII. In order to evaluate the discriminatory power of the categorization by the respective "a" and "b", three univariate logistic regression models were used to model prescription of 400 mg injection versus 800 mg injection, prescription of 400 mg injection versus 800 mg tablets, and prescription of 800 mg injection versus 800 mg tablets. The only independent (class) variable in the logistic models was the variable indicating the categorization I–VII. This resulted for each value of "a" and "b" in three receiver operator characteristic (ROC) curves and associated Gini coefficients (two times the area under the curve minus one), for which a value more than 0.60 indicates that a good discriminatory model is developed.[18] The mean of the three Gini coefficients is used as a summary of the overall discriminatory power. The "a" and "b" values that resulted in the largest mean Gini coefficient were chosen for the final categorization, which is maximized over a grid for "a" and "b", ranging from 5% to 95% in steps of 5%.

Table 1 Example categorization of patients following AdoMet treatment

Preference probability margins	Sample patient 1 preferences 400 mg injection, 50% 800 mg injection, 15% 800 mg tablet, 35%	Sample patient 2 preferences 400 mg injection, 50% 800 mg injection, 45% 800 mg tablet, 15%
a = 20%, b = 10%	Category V	Category VI
a = 20%, b = 20%	Category VII	Category VI
a = 10%, b = 20%	Category I	Category VI

Notes: a = minimal distance between highest preference probability and the two other preference probabilities; b = distance between the lowest preference probability (of three) and the two other preference probabilities.

Treatment response at 2 weeks was subsequently used to evaluate the treatment efficacy for each of the seven categories. The treatment response by category was used to adjust for confounding patient category differences.

In summary, an MLR model was fitted to obtain preference estimates for the three regimens. Values "a" and "b" were chosen from a grid and applied to the preferences to group patients into seven categories, where the categorization was subsequently used in three univariate logistic regression models to compute three Gini coefficients, over which the mean was taken in order to get an overall impression of the discriminatory power of the categorization. The "a" and "b" values leading to the optimal Gini coefficient were selected for final categorization.

Stepwise MLR was performed by SAS statistical software release 9.3 (SAS Institute Inc., Cary, NC, USA) using glogit link with p-in = 0.01 and p-out = 0.02. Low p-values were chosen to ensure that changes in the predictor's value were related to changes in treatment prescription, while preserving a good discriminating model with a Gini coefficient of ≥0.60 for each of the pairwise comparisons.

Results

A total of 401 patients were enrolled in the PMOS study; the majority of the patients were white (98.5%) and included proportionally more males (58.9%) (Table 2). The most common liver diseases underlying the cause of IHC were hepatitis (75.8%), liver cirrhosis (24.9%), and steatosis (19.0%) (Table 2). The study data set that was used to apply the new method to evaluate the decision-making process for assigning effective treatments included 321 patients, which accounted for 80% of the PMOS population; these were the patients initially receiving AdoMet by 400 mg injection, 800 mg injection, or 800 mg tablets. Table 3 lists the indicators that went into the stepwise multinominal logistic regression, and the resulting equations are shown from which the conditional

Table 2 Patient demographics and baseline characteristics

Parameters	All patients (N = 401)
Patient characteristics	
Gender, n (%)	
Male	236 (58.9)
Female	165 (41.1)
Mean age, years (SD)	47.9 (12.4)
Mean weight, kg (SD)	79.3 (15.9)
Race, n (%)	
White	395 (98.5)
Black	0 (0.0)
Asian	2 (0.5)
Others	4 (1.0)
Distribution of patients depending on the cause of IHC[a]	
Liver diseases, n (%)	
Hepatitis	304 (75.8)
Liver cirrhosis	100 (24.9)
Steatosis	76 (19.0)
Cholangitis	31 (7.7)
Other liver diseases	19 (4.7)
Non-liver disease, n (%)	
Congestive heart failure	9 (2.2)
Others	3 (0.7)

Note: [a]One patient could have more than one cause of IHC.
Abbreviations: IHC, intrahepatic cholestasis; SD, standard deviation.

Table 3 Clinical indicators in the stepwise multinomial logistic regression selection model

Nature of measurement	Clinical indicator	Value used in MLR grid-optimization model
Laboratory test	Total bilirubin, aspartate aminotransferase, platelet count, total cholesterol	Laboratory values
Symptoms	Jaundice, pruritus, dyspepsia, fatigue, appetite, sleep, pain, malaise, weakness, mobility, ability to perform usual activities, irritability, anxiety, difficulties with concentration	Number of these symptoms
Indication	CPC	1 = indicated category 0 = category not indicated –1 = "unknown"
	Steatosis	0 = not present 1 = present
Ultrasound	Intrahepatic bile duct dilation	1 = no 2 = yes
	Increased liver size	1 = no 2 = yes
Resource	Hospital admission in the previous 2 months before the start of treatment	1 = yes 0 = no

Notes: The preference (probability) for the 400 mg versus 800 mg injection (reference) was calculated as follows (clinical indicators are ordered by *p*-value from low to high; dark grey highlight: $P<0.01$; light grey highlight: $P=0.01$–0.05; others: $P>0.05$): Logit(preference probability 400mg injection vs 800mg injection)= −1.89 −1.15*ln (total bilirubin) −1.96* CPC (A) −0.84* CPC (B) +1.97* CPC (C) −1.41* steatosis +1.64* intrahepatic bile duct dilation −1.06* hospital days 'yes' in 2 months before start of treatment −0.46*ln(AST) + 1.57*ln(total cholesterol) + 1.29*ln(platelet count) −0.088 *number of symptoms −0.44* liver size increased. For the 800 mg tablets versus 800 mg injection (reference) the following equation as obtained: Logit(preference probability 800mg tablets vs 800mg injection)= 11.31 −0.39* number of symptoms −0.82*ln(AST) + 2.49* ln (total cholesterol) −1.78* steatosis −1.42* liver size increased −0.67*ln(platelet count) −0.25* CPC (A) −0.20* CPC (B) + 0.56 * CPC (C) −0.29* hospital days 'yes' in 2 months before start of treatment −0.18 *ln(total bilirubin) −0.29 *intrahepatic bile duct dilation.
Abbreviations: AST, aspartate transaminase; CPC, Child–Pugh classification; MLR, multinomial logistic regression.

treatment preference probabilities were derived. From this, the marginal preference probabilities were derived by using the rule that all probabilities must equal 100%.

From the MLR, it can be observed that total bilirubin values and CPC were important for physicians when deciding on the 400 mg injection versus 800 mg injection, but not for 800 mg tablets versus 800 mg injection, where the number of symptoms was more important. Patients with lower total bilirubin values more commonly received the 400 mg injection than those with high values (80% versus 20%, respectively [Figure 1A]); those with high bilirubin values were more likely to receive the 800 mg injection than those with lower bilirubin values (60% versus 10%, respectively). The 800 mg tablets were more often prescribed to patients with a small number of IHC-related symptoms; an increase in symptoms was associated with increased prescriber preference for the 800 mg injection (Figure 1B). Patients with a CPC were more likely to have received the 800 mg injection, with the 400 mg injection preferred in those patients without a CPC (Figure 1C).

The categorization at which the Gini coefficient was maximal (following 5% grid of "a" and "b" values evaluation) was based on a "strong" preference probability margin a = 40% and "little/reduced" preference probability margin b = 10% with a corresponding mean Gini coefficient equal to 0.69, indicating a good level of discrimination in the pairwise models in this data set.

The distribution of patients in each category (I–VII) following the maximal categorization using the MLR grid-optimization model is shown in Figure 2. In the maximized categorization, predicted category I (strong preference for 400 mg injection) matched the actual prescription in the majority of patients (in category I, 100 patients received the 400 mg injection, while only nine received the 800 mg injection). Similar results were obtained in the predicted category II (strong preference for 800 mg injection). It can be observed in Figure 2 that, where the circles intersect, actual prescription

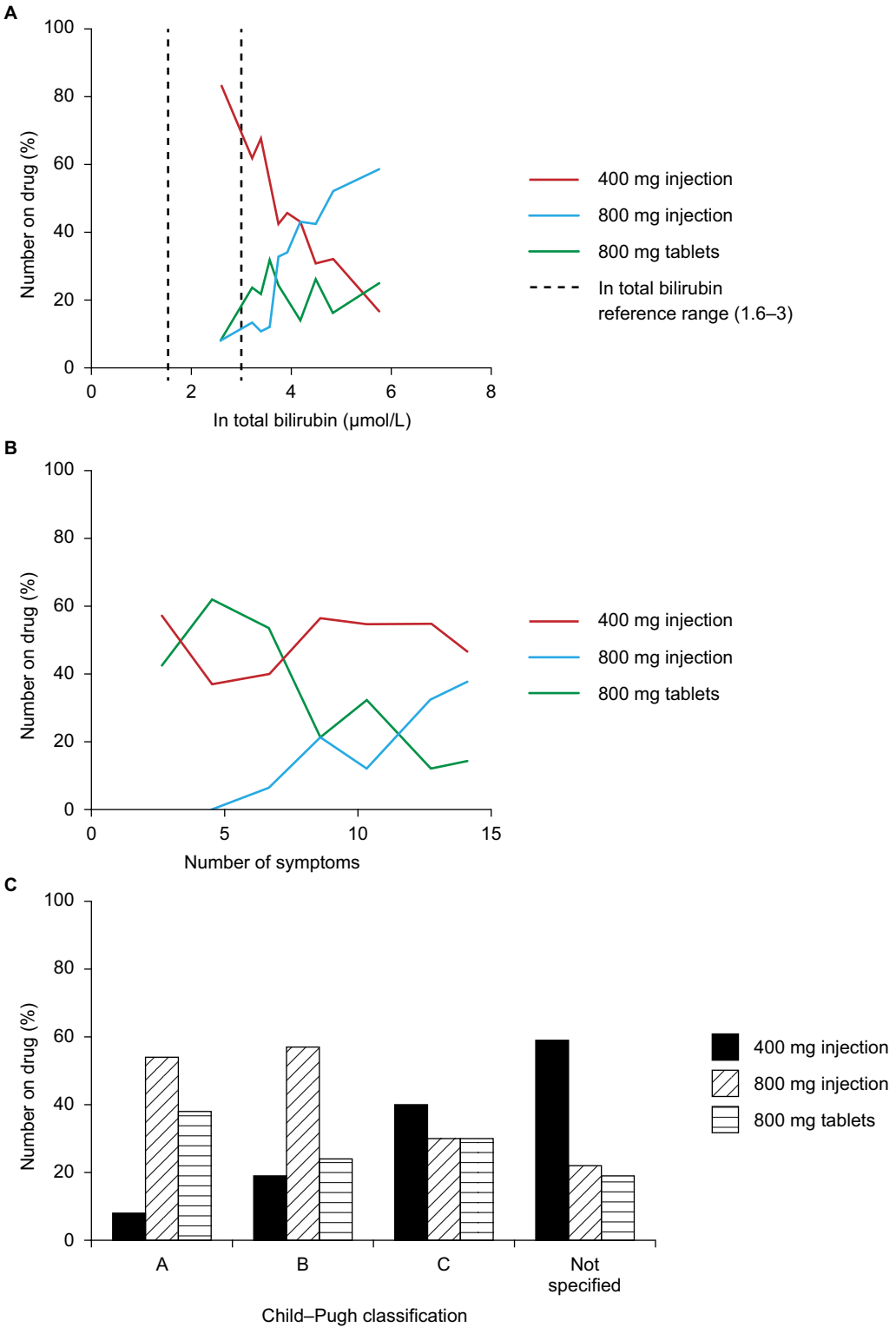

Figure 1 (**A**) AdoMet treatment prescription versus total bilirubin; (**B**) AdoMet treatment prescription versus number of symptoms; and (**C**) AdoMet treatment prescription versus Child–Pugh classification.

of treatments was lowest for those treatments predicted to have reduced preference as expected. For the low number of patients predicted to be in category VII (indifference between all treatments), actual numbers of prescriptions were also low.

The treatment response at the 2-week time point, per predicted category for the different medications, is shown in Table 4. The treatment responses by category were particularly variable at 2 weeks. In categories that had a sample size

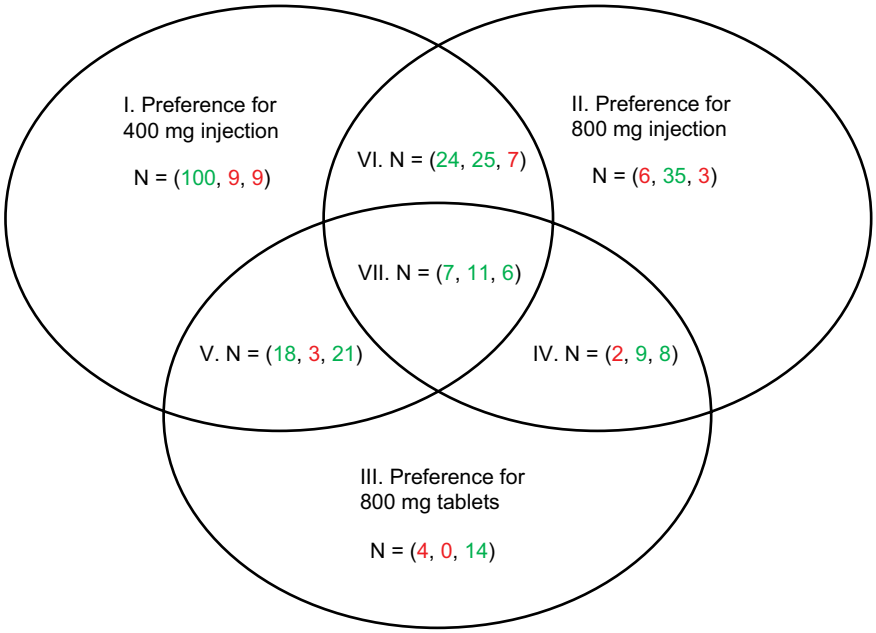

Figure 2 Distribution of patients (N) across categories (I–VII) following the calculated allocation model based on statistical significance and grid-optimization.
Notes: The number of actual prescriptions is provided for each of the categories I–VII as N = (n_1, n_2, n_3), where n_1 = number of patients to whom the 400 mg injection was prescribed, n_2 = number of patients to whom the 800 mg injection was prescribed, and n_3 = number of patients to whom the 800 mg tablets were prescribed. Numbers in green represent actual prescriptions that match the model prediction; those in red are non-matching actual prescriptions.

Table 4 Treatment response per AdoMet medication for the predicted categories produced by the MLR grid-optimization model

Predicted category	Actual prescription					
	400 mg injection		800 mg injection		800 mg tablets	
	Treatment response, % (95% CI)	N	Treatment response, % (95% CI)	N	Treatment response, % (95% CI)	N
I (clear preference for 400 mg injection)	72 (62–81)	86	86 (42–98)	7	67 (27–92)	6
II (clear preference for 800 mg injection)	50 (17–83)	6	47 (31–64)	34	50 (6–94)	2
III (clear preference for 800 mg tablets)	100	4	0	0	63 (28–87)	8
IV (reduced preference for 400 mg injection)	0	2	38 (13–72)	8	67 (27–92)	6
V (reduced preference for 800 mg injection)	93 (63–99)	14	100	3	71 (46–87)	17
VI (reduced preference for 800 mg tablets)	62 (40–80)	21	73 (51–87)	22	50 (17–83)	6
VII (indifference between treatments)	50 (17–83)	6	60 (30–84)	10	67 (27–92)	6

Note: 95% CIs were calculated as per binomial distribution.
Abbreviations: CI, confidence interval; MLR, multinomial logistic regression.

large enough to compare treatments (n > 10), the treatment response could be used to determine the most appropriate course. Categories V and VI were the only categories with sufficient subpopulation numbers to compare the selection of treatments in terms of response (unfortunately, no category had more than 10 patients in each treatment group). In category V, the 400 mg injection had a larger treatment response than the 800 mg tablet regimen (93% versus 71%, respectively). In category VI, the 800 mg injection had a larger treatment response than the 400 mg injection (73% versus 62%, respectively).

The results of pairwise comparisons of treatment response at 2 weeks in the categories showing no clear preference for treatment (IV, V, and VI) are provided in Table 5. The results of these comparisons indicate that in the class corresponding to treatment indifference between 800 mg injection and 800 mg tablets (categories IV and VII), the 800 mg tablet starting regimen gave a larger treatment response than the 800 mg injection group (67% versus 50%, respectively). In the case of indifference between the 400 mg injection and 800 mg tablets (categories V and VII), the 400 mg injection had a larger treatment response (80% versus 70%, respectively).

Table 5 Pairwise comparisons of response to AdoMet treatment

Category	400 mg injection, % (95% CI)	N	800 mg injection, % (95% CI)	N	800 mg tablets, % (95% CI)	N
IV and VII (indifference between 800 mg injection and 800 mg tablets)	–	–	50 (28–72)	18	67 (38–87)	12
V and VII (indifference between 400 mg injection and 800 mg tablets)	80 (57–92)	20	–	–	70 (48–85)	23
VI and VII (indifference between 400 mg injection and 800 mg injection)	59 (40–76)	27	69 (51–82)	32	–	–

Note: "–" indicates not applicable.
Abbreviation: CI, confidence interval.

Finally, the 800 mg injection had a larger treatment response than the 400 mg injection (69% versus 59%, respectively) in the category where prescribers showed indifference to these treatments (categories VI and VII). These results confirm the findings demonstrated in Table 4.

Of particular interest would be category VII because the patients in this group have comparable preference probabilities, meaning that their baseline characteristics did not clearly prioritize one treatment over the other. It would allow for a fairer treatment comparison because of the absence of selection bias; however, in this data set, the patient numbers were too small to allow for any meaningful treatment comparisons.

Discussion

The criteria from the European Association for the Study of the Liver indicate that IHC diagnosis should be made by the examination of serum GGT and ALP levels and that severity can be assessed by serum conjugated and total bilirubin levels.[2] The guidelines in Ukraine state that a higher starting total daily dose may be prescribed for patients with more severe disease. The MLR grid-optimization model categorization, when applied to the Ukrainian PMOS study, indicated that patients with low total bilirubin and no CPC score were most often prescribed the 400 mg injection. Normal-to-low bilirubin levels (0.3–1.9 mg/dL) are suggestive of less severe impediment to bile transport, that is, less severe cholestasis.[19] This suggests that, within the PMOS study, patients with less severe disease were appropriately receiving the lower dose regimen. Those patients with markedly reduced bile transport, indicated by high total bilirubin and CPC, had large numbers of symptoms and were, appropriately, more likely to receive the higher 800 mg AdoMet dose.

The subsequent categorization of patients into prescription preference classes matched actual prescriptions in the Ukrainian PMOS study in the majority of cases. There were, however, larger sample numbers with reduced preference for the higher dose preparations (V and VI), indicating a possible bias in the sample population for patients with less severe disease, that is, the majority of patients were classified in the 400 mg injection group, which was correlated with indicators of less severe disease.

The novel MLR grid-optimization model proposed in this study resulted in good discriminatory power in the assignment of AdoMet starting regimen to patients with IHC, as classified by key clinical indicators, in the context of multiple treatment regimen availability. This represents a substantial improvement on the standard MLR model, which results in vague probabilities. The post-MLR grid-optimized selection of AdoMet treatment allowed a more effective evaluation of treatment response per stratum. A similar approach using propensity scoring to differentiate between the three treatments was used to study the safety and effectiveness of multiple treatments for rheumatoid arthritis.[20]

The model proposed in this study was, in six out of seven classes, able to classify patients into appropriate treatment groups with good discriminatory power (signified by high Gini and pairwise comparison coefficients) despite the small sample size. Low numbers in the subgroup populations were somewhat mitigated by the use of ROC analysis, as the ROC curves produced were insensitive to variability of this nature, due to their basis on the ratio of true and false positives, and lack of dependence on class distribution.[21]

The outcomes of this analysis of the Ukrainian PMOS study should be interpreted in the context of its relatively small sample size, which limited the power of the effectiveness evaluations, due to the use of treatment response, which is a binary variable. There are, however, limitations to the interpretation of this study in the wider clinical context. There may be undisclosed baseline differences between patient groups, which predispose them to bias and/or correlation with other clinical indicators, meaning that the actual prescription may have depended on associated characteristics other than those included in the current model. In extending this model to wider clinical practice, the spectrum of treatment regimen choice may also be

larger than that evaluated in this paper. In the Ukrainian PMOS trial, AdoMet treatment appeared to be consciously prescribed based on the clinical status of the patient, which resulted in very small numbers of patients for whom there was treatment preference indifference. Whether prescription preference in other countries would be equivalent depends partly not only on the prescriber's expertise and on country-specific clinical guidance but also on the clinical indications for AdoMet preparations in those countries.

Conclusion

Categorization of patients into treatment preference groups based on baseline data in an observational study might be an interesting approach, in order to assess the validity of the treatment preference versus the respective treatment effectiveness in case of more than two treatments. In a PMOS with three AdoMet treatment regimens, this approach did not consistently associate the treatments that were more preferred with better effectiveness, but the sample size was too small to conclude that better treatment guidance would be warranted. Further research in this group of patients within a larger, more diverse population would be required before a change in practice could be considered. However, the novel model proposed in this study provides valuable discussion points to initiate this process.

Acknowledgments

The authors would like to thank several people involved in the post-marketing observational study used as the basis for the MLR analysis, without whom research would have been impossible: Prof Natalia Kharchenko, Department of Gastroenterology, Dietology and Endoscopy; PL Shupik, National Medical Academy of Post-Graduate Education, Ukraine; as well as Irina Magdik, Volodymyr Moshchych, Nadiia Sotnychenko, Oleksandr Kuzmenko, and Ruslan Nafieiev from Abbott Laboratories, Ukraine. Also, the authors would like to thank the following colleagues for their support and assistance: Elke Kahler from Abbott Laboratories GmBH, Germany, and Heike Dreher from Abbott Healthcare Products B.V., The Netherlands. Josh Lilly of Alpharmaxim Healthcare Communications provided medical writing support, which was funded by Abbott Healthcare Products B.V., The Netherlands. Abbott Products Operations AG sponsored the design, research, analysis, data collection, and interpretation of the study, and the writing, reviewing of the publication. The current affiliation of Mario JNM Ouwens is AstraZeneca R&D, Mölndal, Sweden.

Author contributions

All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

At the time of writing, Mario JNM Ouwens was an employee of Abbott Healthcare Products B.V., The Netherlands. Suntje Sander-Struckmeier is an employee of Abbott Laboratories GmbH, Germany, and Stefan GAJ Driessen is an employee of Abbott Established Pharmaceuticals Division, The Netherlands. The authors report no other conflicts of interest in this work.

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