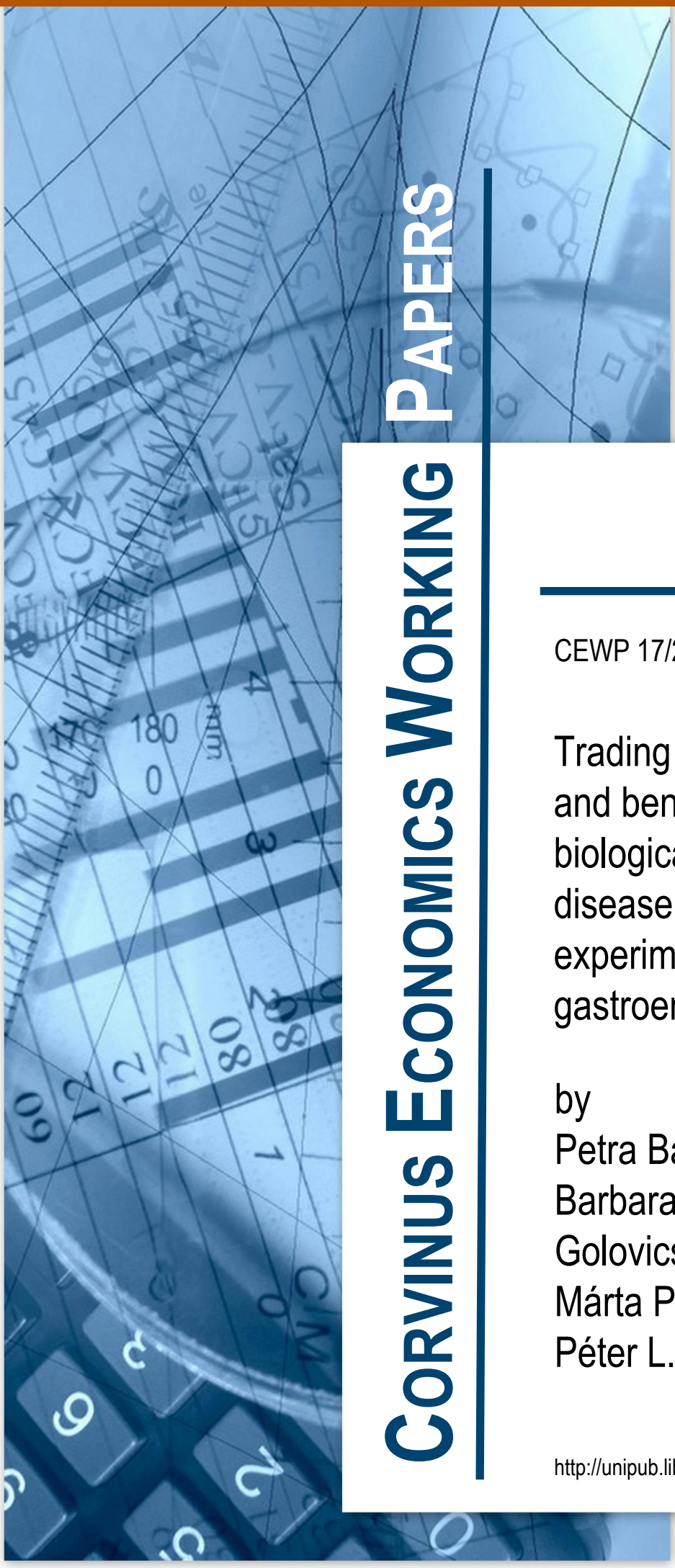

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by
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Trading between perceived risks and benefits related to biosimilar biological treatment in Crohn's disease; discrete choice experiment among gastroenterologists

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Abstract

Objective: The objective of the study is to explore preferences of gastroenterologists for biosimilar drugs in Crohn's Disease and reveal trade-offs between the perceived risks and benefits related to biosimilar drugs.

Method: Discrete choice experiment was carried out involving 51 Hungarian gastroenterologists in May, 2014. The following attributes were used to describe hypothetical choice sets: 1) type of the treatment (biosimilar/originator) 2) severity of disease 3) availability of continuous medicine supply 4) frequency of the efficacy check-ups. Multinomial logit model was used to differentiate between three attitude types: 1) always opting for the originator 2) willing to consider biosimilar for biological-naïve patients only 3) willing to consider biosimilar treatment for both types of patients. Conditional logit model was used to estimate the probabilities of choosing a given profile.

Results: Men, senior consultants, working in IBD center and treating more patients are more likely to willing to consider biosimilar for biological-naïve patients only. Treatment type (originator/biosimilar) was the most important determinant of choice for patients already treated with biologicals, and the availability of continuous medicine supply in the case biological-naïve patients. The probabilities of choosing the biosimilar with all the benefits offered over the originator under current reimbursement conditions are 89% vs 11% for new patients, and 44% vs 56% for patients already treated with biological.

Conclusions: Gastroenterologists were willing to trade between perceived risks and benefits of biosimilars. The continuous medical supply would be one of the major benefits of biosimilars. However, benefits offered in the scenarios do not compensate

for the change from the originator to the biosimilar treatment of patients already treated with biologicals.

JEL: D12, I12, I18

Keywords: risk perception, biologicals, biosimilars, Crohn's Disease, Discrete Choice Experiment, Preferences

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Introduction

The biosimilar infliximab drugs (brand names Remsima™ and Inflectra™) is the first biosimilar monoclonal antibody medicines in chronic inflammatory conditions approved by the European Medicine Agency in 2013 [1,2]. These drugs were registered under the same conditions as the originator infliximab[2] for the treatment of six adult conditions and in two pediatric indications. Nevertheless, randomized clinical trials (RCT) have been carried out only in two adult rheumatic disorders: a non-inferiority study in rheumatoid arthiritis (RA) and another in anklyosing spondylitis (AS) [1,2]. These studies did not find significant differences either in efficacy or in safety between the originator and the biosimilar substance [3,4][3]. In the other four conditions (Ulcerative Colitis - UC, Crohn's Disease - CD, Psoriatic Arthritis - PsA, and Psoriasis) no RCTs were carried out with the biosimilar agent.[4] Due to the lack of evidence from RCTs, physicians are cautious, and have several concerns about using biosimilars in these indications. Since clinical guidelines often do not contain recommendations regarding the use of biosimilar products [5], the use of biosimilars strongly depend own individual risk perception of clinicians.

[2] According to the definition of EMA, 'A biosimilar medicine is a medicine which is similar to a biological medicine that has already been authorized (the 'biological reference medicine'). The active substance of a biosimilar medicine is similar to that of the biological reference medicine. Biosimilar and biological reference medicines are used in general at the same dose to treat the same disease.'

[3] Also, two meta-analysis indirectly compared the infliximab-biosimilar to other biological agents indicated in RA and AS, and found no differences between biological treatments [1,2]

[4] Evidence is though accumulating from observational studies and a cross-over study is underway in inflammatory bowel disease (IBD) [6].

On the other hand, biosimilar drugs are substantially (20% to 70%) cheaper than the originator [7]. The availability of cheaper treatment options means that from the same budget more patients could be treated. For example a previous budget impact study in RA showed that in three years, that the number of patients on biological therapy could be increased by 7-10% in the Central and Eastern European region, if cost-savings were spent on reimbursement of additional biological treatment [8]. At present, access to biologicals is rather unequal, up to 96-fold difference were found in access to biological treatments even across the EU member states of the CEE countries [7]. Biosimilars have the potential to improve this situation, by providing access to a larger number of patients, and/or allow to start the biological treatment in less severe health states, which would contribute to substantial health gains [8].

Thus, health care actors (physicians as well as payers) face trade-off between perceived risks and potential benefits when making decisions about the use of biosimilar medicines. So far, little is known about preferences of health care actors. Although the penetration of biosimilars to clinical practice and consequently potential benefits related to their use might strongly depend on these preferences. Previous studies examined clinicians' attitudes to biosimilars did not consider these trade-offs, and did not connect the risks with potential benefits [9,10].

This study aimed to reveal Hungarian gastroenterologists' preferences for originator vs. biosimilar treatment in Crohn's Disease (CD) using discrete choice experiment (DCE), where respondents are faced with hypothetical scenarios of treatment options. The objective of this study is to explore the willingness of clinicians to use biosimilar drugs for biological agent naïve and already treated patients with CD in exchange for certain

benefits in loosening the conditions of the reimbursement guideline, namely 1) starting the treatment already in less severe health state than allowed by the current reimbursement guideline, 2) ensuring the continuous medicine supply or 3) changing the frequency of the efficacy check-up interventions required by the reimbursement guideline.

Methods

The study was carried out in Hungary, one of the Central and Eastern European countries where the biosimilar medicines have been first marketed for IBD. In Hungary, since May 2014, "newly initiated biological therapy with infliximab must be undertaken with a biosimilar antibody. A mandatory switch is not recommended; however, relapsers should only be treated with a biosimilar (or adalimumab) if more than a year has passed since the termination of the previous biological therapy". [7]

Data were collected among gastroenterologists, who participated on the 56th Meeting of the Hungarian Gastroenterology Society in May, 2014. Altogether 200 questionnaires were distributed. The participation was voluntary. The questionnaire included a detailed explanation of the research. Informed consent was signed. Ethical approval was obtained (Semmelweis University Regional and Instituitional Committee of Science and Research Ethics, Nr.: 103/2014).

Discrete choice experiment (DCE) is a widely used stated preference method to evaluate preferences (see more in: [11, 12]. In DCE respondents are faced with a hypothetical scenarios and choice sets of goods and services characterized by certain attributes. The

profiles differ from each other in the levels of their attributes. The respondents are asked to choose the profile that they prefer the most. In this way we are able to elicit the preferences for health care services, to examine the effect of the changes of attribute levels on the respondents' choice. In a clinical setting DCE is often used to reveal patients' and clinicians' preferences for treatment options [11]. DCE has been used in a study by Johnson and colleagues to evaluate trade-offs between treatment efficacy and potential adverse events in CD [13,14], and by Lichtenstein and colleagues to reveal patients' preferences for treatment characteristics in CD [15].

For the purposes of our study, 4 attributes (all with two levels) were selected based on the current reimbursement guideline and discussions with clinicians to describe the hypothetical scenarios:

1) the type of treatment: originator/biosimilar
2) the disease severity level required for the initiation of biological treatment: Can be applied for patients with (Crohn's Disease Activity Index[5] (CDAI)>300)/ Can be applied for patients with (CDAI>220))
3) the availability of continuous medicine supply: Due to the shortage of medicine excess of the budget, the treatment can be delayed by 3-4 weeks/ The medicine supply is continuous.
4) Frequency of efficacy check-ups required by the reimbursement guideline: Once a year/ Once in two years

[5] The Crohn's disease activity index (CDAI) is a numerical calculation derived from the sum of products from a list of 8 items, and multiplied by weighting factors for each item to define the severity of "disease activity" in patients with CD [16].

According to the clinicians involved in the interviews, starting the biological treatment in a less severe health state would be a potential benefit of using biosimilar treatments. At the moment, CD patient with CDAI<300 are not entitled for reimbursed biological treatment. Budget constrains were also mentioned by the clinicians as a potential problem for the medicine supply, which can lead to delays in the treatment of patients. The frequency of efficacy check-ups was also considered as a potentially important attribute. According to the current reimbursement guideline the treatment cannot be continued without an efficacy check with endoscope or MR in every 12 month. The endoscope examination besides being invasive might be painful and uncomfortable for patients, who would rather avoid this type of procedure; however the access to MR as an alternative technique might be limited or delayed due to the waiting lists.

Seven choice sets were presented to the respondents. In all the choice sets, the base scenario described the current situation under the conditions of the current reimbursement guideline with originator treatment (i.e. can be applied if the CDAI>300, treatment might be delayed by 3-4 weeks due to the lack of supply, efficacy check-up once a year). The alternative scenarios described biosimilar treatments with varying benefits offered (i.e. relaxed the reimbursement conditions step-by-step). Clinicians were asked to choose the preferred treatment option for 1) biological agent naïve patients (hereinafter “new patients”) and 2) patients currently treated with originator biological drug (hereinafter “treated patients”). Table 1 presents an example for the choice set. The questionnaire was piloted with 5 clinicians.

INSERT TABLE 1 HERE

The questionnaire contained additional items regarding social-demographic and professional features of the gastroenterologists (age, gender, doctoral degree, position, membership in scientific committees) and their practices (whether it is settled in the capital, in the center of the county, or other town/or village; type of the practice: out-patient or inpatient clinic; whether it is an IBD center – where patients can be treated with biologicals, the number of CD patients treated by the physician, the number of CD patients treated with biological). A multiple choice question regarding clinicians' attitude to biosimilar treatments was also included in the questionnaire with the following options: a) have no concerns about the use of biosimilar medicines in CD, and these can be applied under the same conditions as the originator b) have some concerns using biosimilars and c) biosimilar medicines should not be applied in CD at all. Those, who indicated concerns, were asked whether these concerns are related to a) efficacy, b) safety, c) both or d) other reason.

Two types of analysis were carried out to explore the preferences of physicians. First, multinomial logit model was used to differentiate between three attitude groups formulated based on the choices of clinicians: 1) those who always opt for the originator treatment for both new and treated patients (hereinafter: the "No biosimilar" group) , 2) those who are not willing to change the ongoing originator biological treatment for biosimilar therapy but consider the biosimilar option for new patients groups (i.e. opted for the biosimilar option for new patients at least in one choice set), hereinafter: the "Biosimilar for new patients only" group; 3) those who are willing to consider the biosimilar option for both new and treated patients in exchange for the benefits offered in the DCE, hereinafter the "Biosimilar" group. The following covariates were used in the regressions analysis to predict group memberships: clinicians' age, gender, position

(chief physician or not), having a scientific membership, having a PhD degree, the settlement of the practice (Budapest or not), whether the practice is an IBD center in Hungary, the number of CD patients treated. The effects of the covariates on the predicted probabilities of belonging to the three groups were calculated.

Second, conditional logit model was used to analyze the DCE. The effect of changing attribute levels were calculated on the probabilities of choosing a given profile, while other attributes remain constant. Odds ratios (ratio of the probability of choosing a given profile over the probability of choosing the base option) are presented. Separate analysis was carried out for new patients and patients already treated. We carried out the analysis for the total sample (including traders and non-traders), and also for traders only.

Results

Fifty-one gastroenterologists filled in the survey. The average age of the respondents was 47.6 years (range: 26-74). About 65% of the respondents were female, 41% of them had senior consultant position, 55% had a PhD degree and 41% had scientific committee membership. Altogether, 65% of them are working in an IBD center. About 22 respondents had a practice in Budapest. Regarding the type of the practice, 5 clinicians worked in an out-patient care, 21 in inpatient care and 24 in both out-patient and inpatient care, while one clinician did not answer this question. Clinicians were treating on average 24.7 CD patients on average (range: 0-100) and the rate of patients receiving biological treatment was 24%.

Ten clinicians (19.6%) indicated that he/she has absolutely no concerns using biosimilars in CD, as the EMA registered them under the same conditions as the originators. Thirty-three (64.7%) clinicians indicated some concerns about using biosimilars in CD (two had concerns about efficacy, 7 had concerns about safety and 21 had concerns both with efficacy and safety). Six (11.8%) clinicians said they do not support the use of biosimilars in CD at all due to the lack of evidence from randomized controlled trials in this indication. Two respondents did not answer this question.

Based on their choices, clinicians were categorized in three attitude groups: four clinicians (7.8%) belonged to the "No biosimilar" group, 19 (37.3%) to the "Biosimilar to new patients only" group and 27 (52.9%) to the "Biosimilar" group. One clinician chose biosimilar treatment in at least one choice set for already treated patients, but never chose the biosimilar option in the case of new patients. Being a unique case, this observation was excluded from this analysis.

According to the results multinomial logit model[6] characteristics such as 1) being male, 2) being a senior consultant, 3) having practice in Budapest, 4) working in IBD center significantly increases the probability of belonging to the "Biosimilar to new patients only" group by 32, 58, 43 and 48 percentage points respectively. The probability of belonging to this group decreases with age (marginal effect 3 percentage points), but increases with the number of CD patients (marginal effect of 2 percentage points). Not being a senior consultant and working in a practice outside Budapest increases the probability of belonging to the "Biosimilar" group by 58 and 52 percentage points,

[6] Model characteristics: Number of observations: 49; Wald Chi^2=54.95 ($p<0.001$); Pseudo R^2= 0.4905. Detailed results are presented in Supplementary Table 2.

respectively. Being older, as well as treating fewer patients significantly increases the probability of belonging to this group (marginal effects are 3 and 2 percentage points). Being female increases the probability of belonging to the "No biosimilar" group (marginal effect of 56 percentage points). Detailed results of the

Comparing the regression results with the answers to the multiple choice question regarding concerns about the use of biosimilars, we find that in the "Biosimilar group" 26% of clinicians indicated no concerns regarding the use of biosimilars, compared to 16% in the "Biosimilar to new patients only" and 0% in the "No biosimilar" group.

The estimated coefficients of the conditional logit model are presented in Table 2. According to the results, for new patients, the continuity of the medicine supply was the most important treatment attribute, followed by the severity of the disease and the frequency of efficacy check-ups. The type of the treatment (biosimilar or originator) was found not to be a significant determinant of choice. For patients already treated with biologicals, the type of the treatment was the most important factor, followed by the continuity of the medicine supply. Severity had positive but insignificant, and the frequency of check-ups had negative but insignificant coefficients.

INSERT TABLE 2 HERE

Predicted probabilities of choosing biosimilar medicine over the originator treatment under the current reimbursement conditions (i.e. can be applied when the CDAI>300, treatment might be delayed by 3-4 weeks due to the lack of supply, efficacy check-up once a year) were calculated (see Table 2). For new patients the estimated probability of choosing the originator treatment over the biosimilar, when all the attributes describe

the current reimbursement situation, is 60%. For patients already treated with biologicals this probability is higher, 74%. The probabilities of choosing the biosimilar with all the benefits offered over the originator in the current situation are 89% vs 11% for new patients and 44% vs 56% for patients already treated with biologics.

Discussion

In this experiment we identified important determinants of different attitudes towards biosimilars.

We found that opinion leaders of the profession (i.e. men, senior consultants who are treating more CD patients and working in IBD centers) have strong concerns of changing the originator treatment to biosimilar, but willing to consider starting the treatment of new patients with biosimilar.

We also explored what benefits could potentially compensate for the perceived risk of using biosimilars. Our results suggest that clinicians are more willing to apply biosimilar treatment for new patients than to change to biosimilar. For patients already treated with biologicals, the type of treatment (originator/biosimilar) was the most important determinant of treatment choice and the benefits offered in the choice sets could not compensate for the change from the originator to biosimilar treatment. On the other hand, physicians had less concerns choosing biosimilar treatment option for new (biological-naïve) patients in exchange for the benefits offered in the choice sets.

We found that for gastroenterologist, the continuity of the medical supply is one of the major benefits of using biosimilar treatment. This finding is especially important in low income countries such as Hungary, where continuous medicine supply might not be

available due to the providers' budget constraints. Apparently there is a heterogeneity regarding the preferences for the frequency of efficacy check-ups. The negative but insignificant coefficient for patients already treated with biological suggests that some clinicians have concerns about the less frequent efficacy check-ups when changing the originator to biosimilar. However for new patients, less frequent efficacy check-ups are significantly preferred.

In the literature, preferences of clinicians have been relatively widely studied for small molecular generic drugs (e.g. [17,18]), nevertheless limited number of studies examined attitude towars biosimilars, although it seems to be a more complex and debated issue. So far only one previous study has presented results on the attitude of gastroenterologists regarding biosimilar medicines from a web-based survey with 307 IBD specialists [9]. According to their results, less than 10% of clinicians would replace the originator with a biosimilar for a patient already under treatment, while 25% would consider interchangeability only for new prescriptions. Another, Canadian survey with 81 rheumatologists explored physicians' attitudes towards biosimilars and found that about one-third of the clinicians were unlikely or very unlikely to offer a biosimilar treatment to a biologic naïve patient as initial therapy, even though evidence from RCTs are available in this indication [10]. These studies presented only descriptive results and did not analyze determinants of attitude types, and benefits which might compensate for the risks of using biosimilar treatments.

In our study similar share of clinicians (77%) indicated concerns regarding the use of biosimilars in CD in the multiple-choice question. However, a relatively higher share of clinicians was willing to consider treatments with biosimilar in the DCE task when

certain benefits (with regards to the reimbursement conditions) were offered in the choice sets to compensate for the risk of using of biosimilar drugs. Thus, we learned from this experiment that clinicians are more willing to use biosimilar medicines if they and their patients are the beneficiaries of the cost-savings (i.e. are allowed to use the savings to ensure continuous medicine supply, treat more patients, or patients in less severe conditions). However in real practice, this might not be the case, which results in higher resistance towards biosimilars.

When interpreting the results, we have to be aware, that in Hungary it is now mandatory to treat all new and relapsing patients with a biosimilar infliximab product (or adalimumab), otherwise the treatment is not reimbursed. Thus, the current practice might have an influence on preferences as well. It should be noted also that the relatively small sample size might limit the robustness of the statistical analysis. Furthermore, we have to account for the potential of sample selection bias, as those who agreed to participate in the survey might have different preferences compared to those who refused to participate.

In conclusion we have identified important determinants of different attitudes towards biosimilars with availability of continuous medical supply and less prescription restrictions as the major possible benefits of using biosimilar treatment. In contrast, gastroenterology specialists have strong concerns of changing the originator treatment to biosimilar, but they are willing to consider starting the treatment of new patients with biosimilar. We believe that our study contributes to the literature with new and important evidence on the preferences of clinicians of using biosimilar medicine, as

these preferences may directly or indirectly influence treatment practices and choice of medication, and consequently the budget impact of biosimilars.

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Table 1 Example for a choice set

Type of the treatment	**Originator**	**Biosimilar**
Indication	Can be applied for patients with (CDAI>300)	Can be applied for patients with (CDAI>300)
Supply of medicine	Due to the shortage of medicine excess of the budget, the treatment can be delayed by 3-4 week	The medicine supply is continuous.
Frequency of efficacy check-up	Once a year	Once a year
For new patients: For treated patients:	A) I start therapy with the originator B) I start the therapy with the biosimilar treatment, if I find the situation appropriate. A) I continue to use the originator agent B) I change the therapy with originator to biosimilar treatment, if I find the situation appropriate.	

Table 2 Results of the conditional logit model and predicted probabilities of choosing biosimilar medicine over the originator treatment under the current financial conditions

	Type: Biosimilar	Benefit: less severe condition	Benefit: secure supply	Benefit: Efficacy check-up less frequent	Number of observations	Wald Chi^2	Pseudo R^2
Regression results							
New Patients Coefficient (Std.err)	-0,40 (0,31)	0,86*** (0,24)	1,15*** (0,24)	0,53** (0.22)	708	27.23 (p<0.001)	0.20
Treated Patients Coefficient (Std.err)	-1,04*** (0,31)	0,09 (0,12)	0,74*** (0,18)	-0,02 (0,15)	706	21.99 (p<0.001)	0.07

Estimated probabilities								
Scenarios	**Type: Biosimilar**	**Benefit: less severe condition**	**Benefit: secure supply**	**Benefit: Efficacy check-up less frequent**	**New Patients**		**Treated Patients**	
					Pr[a]	OR = Pr(alt) / Pr(base)	Pr[a]	OR = Pr(alt) / Pr(base)
Base scenario	NO	NO	NO	NO				
Biosimilar scenario 1	YES	NO	NO	NO	40%	0.67	26%	0.35
Biosimilar scenario 2	YES	YES	NO	NO	61%	1.58	28%	0.39
Biosimilar scenario 3	YES	NO	YES	NO	68%	2.11	43%	0.74
Biosimilar scenario 4	YES	NO	NO	YES	53%	1.14	26%	0.35
Biosimilar scenario 5	YES	YES	YES	NO	83%	4.97	45%	0.82
Biosimilar scenario 6	YES	YES	NO	YES	78%	3.59	42%	0.73
Biosimilar scenario 7	YES	NO	YES	YES	73%	2.69	28%	0.38
Biosimilar scenario 8	YES	YES	YES	YES	89%	8.48	44%	0.80

Note: * p<0.1, ** p<0.05, *** p<0.001. OR= odds ratio. [a] Pr=Probability: estimated probability of choosing the profile when the alternative biosimilar scenario is the base scenario (i.e. originator with no benefits)

Supplementary Table 1 Descriptive statistics of the sample

Variable	N (%)	Mean (St. Dev.)	Range [Min-Max]
Clinicians' characteristics			
Age	51-(100%)	47.6 (11.4)	[26-74]
Years of practice	48 (94.1%)	19.0 (11.3)	[0-45]
Gender=Female	33 (64.7%)	-	-
Head=Yes	21 (41.2%)	-	-
Scientific committee member=Yes	21 (41.2%)	-	-
PhD=Yes	28 (54.9%)	-	-
Practice			
Settlement of practice		-	-
Budapest	21 (41.2%)		
County capital	23 (45.1%)		
Other town/city	4 (7.8%)		
Multiple	3 (5.9%)		
Type of the Practice		-	-
Out-patient care	5 (9.8%)		
Inpatient	21 (41.2%)		
Both	24 (47.1%)		
Missing	1(2.0%)		
Practice: Mainly hepatology	5 (9.8%)	-	-
Practice: Mainly gastroenterology	33 (64.7%)	-	-
Practice: Mainly IBD	19 (37.3%)	-	-
IBD centrum=Yes	33 (64.7%)	-	-
Number of CD patient	50 (98.0%)	24.7 (26.8)	[0-100]
Number of CD patients treated with biologicals	50 (98.0%)	5.9 (10.1)	[0-46]
Risk perception regarding the use of biosimilars		-	-
No concerns	10 (19.6%)		
Concerns regarding the safety or efficacy	33 (64.7%)		
Should not be applied	6 (11.8%)		
Missing	2 (3.9%)		

Supplementary Table 2 Results of the multinomial logit model - Marginal effects and predicted probabilities of belonging to three groups

	"No biosimilar"	"Biosimilar to new patients only"	"Biosimilar"	"No biosimilar"	"Biosimilar to new patients only"	"Biosimilar"
Predicted probability of belonging to the group	-	-	-	0,03	0,32	0,65
	Group characteristics			**Regression: Marginal effects**		
Clinician						
Female = yes	3 (75%)	6 (32%)	9 (33%)	0,56** (0,24)	-0,32* (0,18)	-0,24 (0,27)
Age (years)	45.5 (11.6)	45.8 (8.1)	48.6 (11.4)	-0,001 (0,004)	-0,03** (0,01)	0,03** (0,01)
Senior consultant = yes	2 (50%)	9 (47%)	9 (33%)	0,0001 (0,04)	0,58** (0,25)	-0,58** (0,24)
Scientific Committee = yes	2 (50%)	7 (37%)	12 (44%)	0,18 (0,13)	-0,36 (0,28)	0,18 (0,30)
PhD = yes	2 (50%)	11 (58%)	14 (52%)	-0,01 (0,04)	-0,29 (0,36)	0,30 (0,35)
Practice						
Budapest = yes	2 (50%)	10 (53%)	9 (33%)	0,09 (0,07)	0,43* (0,26)	-0,52** (0,24)
Ibd centrum = yes	1 (25%)	17 (90%)	15 (56%)	-0,18 (0,17)	0,48*** (0,15)	-0,29 (0,21)
Number of CD patients	35.5 (43.9)	39.9 (31.7)	13.5 (12.8)	0,001 (0,001)	0,02*** (0,01)	-0,02*** (0,01)
				Model characteristics		
Number of obs	4	19	27	49[+]		
Wald chi2(8)	-	-	-	54.95		
Prob > chi2	-	-	-	<0.001		
Pseudo R2	-	-	-	0.4905		

Note: * p<0.1, ** p<0.05, *** p<0.001; One observation was excluded as not belonging to any of the three groups, and for one clinician the number of CD patients were missing. "No biosimilar" group refers to those who always opt for the originator treatment for both new and treated patients. "Biosimilar for new patients only" group refers to those who are not willing to change the ongoing originator biological treatment for biosimilar therapy but consider the biosimilar option for new patients groups. "Biosimilar" group refers to those who are willing to consider the biosimilar option for both new and treated patients in exchange for the benefits offered in the DCE.