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ORIGINAL ARTICLE

Valuing Treatment With Infliximab for Ankylosing Spondylitis Using a Willingness-to-Pay Approach

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Objective. **To investigate willingness to pay (WTP) for treatment with infliximab by patients with ankylosing spondylitis (AS) and explore factors associated with WTP.**

Methods. **Data from 85 patients participating in the European AS Infliximab Cohort (EASIC) open-label extension of the AS Study for the Evaluation of Recombinant Infliximab Therapy (ASSERT) were used. WTP was included at baseline in EASIC and comprised a hypothetical scenario exploring whether the patient would be willing to pay for beneficial effects of infliximab and, if so, what amount they would be willing to pay per administration. Factors associated with WTP were explored using zero-inflated negative binomial (ZINB) regressions.**

Results. **Of the 85 patients, 63 (74.1%) were willing to pay, and among these, the mean amount they were willing to pay per administration was €275 (median €100 [interquartile range €50–200]). Multivariable ZINB analysis showed that Assessment of SpondyloArthritis international Society criteria for 20% improvement (ASAS20) response was associated with a 7-fold lower likelihood to pay 0 euros (odds ratio [OR] 0.14 [95% confidence interval (95% CI) 0.03–0.71]) and a 3-fold increase in the amount willing to pay (exp(β) = 3.32 [95% CI 1.44–7.69]). In addition, the country of residence was associated with a lower likelihood to pay 0 euros (OR 0.07 [95% CI 0.02–0.36]), while increased age was associated with the amount willing to pay (exp(β) = 1.05 [95% CI 1.01–1.09]).**

Conclusion. **In a hypothetical scenario, three-quarters of patients with AS receiving long-term infliximab stated that they were willing to pay an out-of-pocket contribution for this treatment. Treatment response contributed to the willingness as well as to the amount patients were willing to pay.**

INTRODUCTION

Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease characterized by onset at relatively young age and potentially important long-term disability that can result in considerable costs (1). Treatment with anti–tumor necrosis factor (TNF) agents provides substantial and longstanding improvement in pain and function in AS (2–4) and can reduce the burden of illness for patients and society (5). However, these agents are costly, and their impact on health care budgets is considerable (6,7). It is therefore essential to develop a comprehensive view on the value of biologic treatments. Improvements in health in AS have traditionally been assessed using the Assessment of

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Significance & Innovations

- In this contingent valuation study, the majority of patients with ankylosing spondylitis (AS) were willing to pay a hypothetical out-of-pocket contribution for infliximab treatment.
- Treatment response contributed significantly to both the willingness to pay and the amount the patient was willing to pay.
- The willingness-to-pay method provides an alternative view of treatment benefits and could be valuable alongside common approaches for investigating treatment in AS.

SpondyloArthritis international Society (ASAS) core outcome domains, which evaluate the impact of interventions on those aspects of health that are typically affected in AS, comprising pain, stiffness, fatigue, physical functioning, mobility, inflammation, and structural damage (8). Such an approach is limited in helping to understand the value for the overall improvement in health state and limits comparisons in health gain across diseases. Therefore, preference-based methods have been developed to explore the nonmonetary value for (changes in) overall health state in the setting of choice and are grounded in the utility and decision-making theory. Alternatively, contingent valuation methods (CVMs) explore the monetary valuation of improvements in health state, and are grounded in welfare economic theory. Within the CVMs, a willingness-to-pay (WTP) approach asks patients (usually in hypothetical scenarios) how much they would pay for a certain improvement in health (9–11). Both preference-based valuation and contingent valuation allow comparison of improvements in health state across diseases, and results can be used in economic evaluations.

WTP has been used in a wide range of diseases to estimate improvement in overall health from the patient's perspective (11,12). WTP studies in rheumatology have been performed in rheumatoid arthritis (RA), psoriatic arthritis, and gout (13–16). There is only 1 WTP study on patients with AS. It revealed, in a randomized controlled trial, that patients were willing to contribute out of pocket for improvements in health experienced following a spa treatment, and that the amount of personal contribution was influenced by the level of expected improvement, but also by the treatment environment (rehabilitation clinic versus spa resort) (17). In the current study, patients receiving treatment with infliximab were asked to imagine a situation in which they should pay an out-of-pocket contribution to be able to continue treatment. The aim was to investigate the monetary value patients attach to improvements in health by infliximab, and to explore factors associated with both willingness to pay and the amount they were willing to pay. We hypothesized that almost all patients would be willing to pay, and that willingness and the amount they were willing to pay would be influenced by the level of treatment response.

PATIENTS AND METHODS

Patients. Data from the European AS Infliximab Cohort (EASIC), a 2-year open-label investigator-initiated extension of the AS Study for the Evaluation of Recombinant Infliximab Therapy (ASSERT), was used for the current study (18). In brief, patients originally included in ASSERT had a diagnosis of AS according to the modified New York Criteria for AS (19), a Bath AS Disease Activity Index (BASDAI) score ≥4 (range 0–10), and spinal pain of ≥4 on a visual analog scale (range 0–10 cm) (4). EASIC baseline visits occurred between December 2005 and November 2006. In the period between the end of ASSERT and the start of EASIC, all patients were treated by their rheumatologist according to the local standard of care. In summary, 89 patients received continuous infliximab (on average, every 6–8 weeks at a dosage of 4–6 mg/kg body weight). Of the 14 patients who had discontinued infliximab after ASSERT, 9 patients experienced a relapse and were reintroduced to infliximab at the start of EASIC (18). The study protocols of ASSERT and EASIC were reviewed and approved by the respective institutional or independent ethics committee of each country. All patients provided written informed consent.

Assessments. Several demographics (age, sex, and country of residence) and clinical outcomes were collected in ASSERT and EASIC. Disease activity was assessed using the the BASDAI (20) and laboratory tests, including the C-reactive protein (CRP) level and the erythrocyte sedimentation rate. Physical function was assessed using the Bath AS Functional Activity Index (BASFI) (21). Patient global well-being was assessed using the patient global (the question regarding well-being during the last week from the Bath AS Global score) (22). The Bath AS Metrology Index (BASMI) was used to measure spinal mobility (23). Available data from the ASSERT baseline assessment allowed for the calculation of absolute change in BASDAI, CRP level, BASFI, BASMI, and patient global between the start of ASSERT and the start of EASIC, as well as the Assessment of SpondyloArthritis international Society criteria for 20% improvement (ASAS20) and 40% improvement (ASAS40) response and ASAS partial remission at the start of EASIC (24,25).

WTP. A WTP self-report questionnaire was included at baseline in EASIC. Patients were asked whether they would be willing to pay a personal contribution to sustain the beneficial effect of treatment with infliximab, in the hypothetical situation that the drug treatment would not be (completely) reimbursed by the payer (health insurer/national health service) under the current conditions. If they were willing to pay, patients were asked an open-ended question regarding what amount (in euros) they would be willing to pay out of pocket per administration of infliximab. The full scenario presented to the patient is shown in Supplementary Appendix A (available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23299/abstract). Those not willing to pay were asked to indicate whether they felt the

treatment was not worth a personal contribution, whether their financial situation did not allow a personal contribution, or whether there was another reason for being unwilling to pay. To assess spending power, patients were asked how much they spend yearly on luxury (vacations) or common (shoes) products. Finally, patients were asked whether they knew the price of 1 administration of infliximab in euros, and, if yes, to state the true price. In addition, the true country-specific market price for 1 administration per patient was calculated, assuming a dosage of 5 mg/kg, while adjusting the price of infliximab to the year of data collection of the WTP using the country-specific consumer price index. To better understand the possible influence of country of residence, the payment flows in different health care systems in 2005–2006 in the countries participating in EASIC were checked and are described in Supplementary Appendix B (available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23299/abstract).

Statistical analysis. Differences in characteristics between patients willing to pay and patients not willing to pay were explored with independent *t*-tests, the Mann-Whitney test, or chi-square test, depending on the level of measurement and distribution. Fisher's exact test (with Freeman-Halton extension, if appropriate) was preferred over the chi-square test for small samples (expected count <5). To detect possible selection bias due to nonresponse to the question about WTP, a subgroup analysis was performed comparing outcomes for patients who did not complete the WTP question with those who did.

As the amount of money patients would be willing to pay was nonparametrically distributed, with an excess of zeros (i.e., for patients not willing to pay), a zero-inflated negative binomial (ZINB) regression was used to investigate factors associated with WTP. This technique can be used for modeling overdispersed count variables (such as euros). Specifically, ZINB models counts of zero ("zeros") assuming these originate from different processes (i.e., patients declaring unwillingness to pay out of protest [certain/structural zeros] or patients declaring unwillingness to pay because they consider the treatment not worthy of payment [likely/sampling zeros]). ZINB regression was preferred over both ordinary negative binomial regression and zero-inflated Poisson regression based on model fit reflected by the Akaike and Bayesian information criteria (AIC and BIC, respectively). The results of ZINB analysis therefore consist of 2 components: the zero-inflated model (logistic), reflecting the variables that identify whether patients would never be willing to pay (i.e., predicting a "certain zero"); and the expected count model (negative binomial model), reflecting the factors that contribute to the amount patients are willing to pay (including both zeros and non-zeros).

In view of small sample size and to ensure sufficient power to detect significance of possible covariates, a limited number of variables could be explored within the multivariable models. Therefore, the possible explanatory or confounding variables were first categorized into 4 groups that were considered to have a distinct but meaningful influence on WTP. The groups were as follows: demographics (sex, age, and disease duration), clinical characteristics reflecting improvement and/or achieved health state (such as ASAS20 response or current BASDAI), country of residence (residing in The Netherlands versus not residing in The Netherlands, as exploratory analyses showed a large difference in WTP across this variable), and spending power (each variable separately or the sum). Within each group (clinical characteristics/country of residence/spending power), the variables associated with outcome, defined as a P value less than 0.20 in univariable analysis after adjustment for sex and age, were identified. Next, these variables were further explored in consecutive order in a multivariable model, based on a manual forward-selection method. Variables were retained when they significantly contributed to the model ($P < 0.05$). Several models were built with different combinations of variables, while at the same time we aimed to ensure representation of the variables of each of the 4 groups and avoid the inclusion of variables with collinearity. All statistical analyses were performed with SPSS, version 22.0, and Stata, version 12.

RESULTS

Of the 216 European patients included in ASSERT, 103 (48%) continued in EASIC. For the current study, 2 cases were excluded because of data inconsistency. Of the remaining 101 patients, 85 (84.1%) completed the WTP question and were included in the analysis. Comparing these patients (n = 85) to those who did not provide data on WTP (not participating in EASIC or not completing the WTP question [n = 129]), patients included in the current analysis more frequently fulfilled the ASAS20 response criteria at the end of ASSERT (88.2% versus 58.4%; $P < 0.01$).

In the current sample, 67/85 patients (78.8%) were male and the mean ± SD age was 43.4 ± 10.3 years. The majority of the patients (85.9%) resided in Germany, The Netherlands, or Belgium. Sixty-two patients (72.9%) fulfilled the ASAS20 response criteria (deemed ASAS responders) at entry in EASIC after treatment with infliximab (Table 1).

Sixty-three of 85 patients (74.1%) were willing to pay a personal contribution for treatment with infliximab. The amount they were willing to pay per administration ranged from €10 to €2,500 per patient, with a mean of €275 and a median of €100 (interquartile range €50–200). On average, this amount was 11.3% of the actual price. Of the 22 patients who were not willing to pay, 14 (63.6%) indicated this was due to their financial situation and 6 (27.3%) gave other reasons, e.g., "the health insurance company should pay" and treatment with infliximab would "reduce other current and future health expenditures." None of the patients indicated that the treatment effects were not worth a personal contribution.

Fifty-eight patients (69.0%) indicated knowing the true price of treatment with infliximab, which they estimated at mean ± SD €2,187 ± €1,043 per administration. Forty-three of these patients were willing to pay, and the amount they were willing to pay for 1 administration was on average 16.9% of what they estimated to be the true price, and 9.9% of the actual true price in this group of patients.

Table 1. Baseline (EASIC) comparison of patients willing to pay and patients not willing to pay*

Variable	Total group (n = 85)	Willing to pay (n = 63)	Not willing (n = 22)	*P*†
Age, years	43.4 ± 10.3	42.9 ± 9.5	44.7 ± 12.3	0.48
Male, no. (%)	67 (78.8)	49 (77.8)	18 (81.8)	0.77
Country of residence, no. (%)‡				< 0.01
Germany	31 (36.5)	27 (42.9)	4 (18.2)	
The Netherlands	21 (24.7)	9 (14.3)	12 (54.5)	
Belgium	21 (24.7)	18 (28.6)	3 (13.6)	
UK	9 (10.6)	7 (11.1)	2 (9.1)	
Finland	2 (2.4)	2 (3.2)	0 (0.0)	
France	1 (1.2)	0 (0.0)	1 (4.5)	
Disease duration, years	13.5 ± 8.3	14.3 ± 8.3	11.4 ± 7.8	0.16
Dose of infliximab, mg	405 ± 63	403 ± 68	412 ± 45	0.55
Market price of IFX treatment, €	2,659 ± 876	2,718 ± 925	2,491 ± 709	0.24
BASDAI (0–10)	3.2 ± 2.0	2.9 ± 1.9	4.2 ± 2.0	0.01
CRP, mg/liter§	7.8 ± 11.1	7.3 ± 10.0	9.3 ± 14.0	0.71
BASFI (0–10)	3.5 ± 2.2	3.2 ± 2.1	4.5 ± 2.3	0.02
BASMI (0–10)	2.2 ± 1.6	2.0 ± 1.5	2.8 ± 1.9	0.06
Patient global (0–10)	3.5 ± 2.4	3.1 ± 2.2	4.7 ± 2.5	< 0.01
Change in BASDAI¶	−3.3 ± 2.1	−3.5 ± 2.1	−2.5 ± 2.1	0.05
Change in CRP, mg/liter#	−20.0 ± 24.7	−22.0 ± 23.5	−14.2 ± 27.6	0.05
Change in BASFI¶	−2.5 ± 2.0	−2.6 ± 2.0	−2.2 ± 2.2	0.39
Change in BASMI¶	−1.9 ± 1.5	−1.8 ± 1.5	−2.2 ± 1.6	0.40
ASAS20 response, no. (%)¶	62 (72.9)	50 (79.4)	12 (54.5)	0.02
ASAS40 response, no. (%)¶	36 (44.4)	31 (51.7)	5 (23.8)	0.02
ASAS partial remission, no. (%)¶	17 (30.9)	15 (37.5)	2 (13.3)	0.08
Willingness to pay, € (median, IQR)				
Amount willing to pay for 1 IFX administration	199 (50, 0–150)**	275 (100, 50–200)		
% true price willing to pay		11.3		
Reason not willing to pay, no. (%)				
Not worthwhile			0 (0.0)	
Personal financial situation			14 (70.0)	
Other			6 (30.0)	
Spending power				
On vacations, €/person/year (n = 65)	1,060 ± 1,161	1,157 ± 1,229	528 ± 398	0.06
On shoes, €/person/year (n = 71)	163 ± 130	176 ± 127	113 ± 131	0.03
Stated to know costs IFX, no. (%)	58 (69.0)	45 (72.6)	13 (59.1)	0.24
Self-estimated cost per administration (in those stated knowing), €	2,187 ± 1,043	2,168 ± 1,028	2,255 ± 1,135	0.79

* Values are the mean ± SD unless otherwise indicated. EASIC = European Ankylosing Spondylitis Infliximab Cohort; IFX = infliximab; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; CRP = C-reactive protein; BASFI = Bath Ankylosing Spondylitis Functional Index; BASMI = Bath Ankylosing Spondylitis Metrology Index; ASAS20 = Assessment of SpondyloArthritis international Society criteria for 20% improvement; ASAS40 = ASAS criteria for 40% improvement; IQR = interquartile range.
† Two-tailed statistics for patients willing to pay versus patients not willing to pay. For continuous data, independent *t*-tests were used for normally distributed variables and Mann-Whitney tests for non-normally distributed variables. For categorical data, chi-square tests were used. Fisher's exact test (with Freeman-Halton extension, if appropriate) was used for small samples (expected count <5).
‡ The percentages shown reflect the proportion of patients from the country in the total, willing, or not willing to pay group.
§ CRP level considered 1.0 mg/liter if below limit of detection (<1.0 mg/liter).
¶ Change in outcome between start of ASSERT (Ankylosing Spondylitis Study for the Evaluation of Recombinant Infliximab Therapy) to start of EASIC.
# Change in outcome between start of ASSERT to start of EASIC. CRP level considered 1.0 mg/liter if below limit of detection (<1.0 mg/liter).
** Including patients that were not willing to pay (amount willing to pay equal to zero).

Comparison between patients willing to pay and patients not willing to pay. No significant differences regarding age, sex, or disease duration, nor in the time elapsed since the start of ASSERT, were found between those willing to pay and those not willing to pay. Patients willing to pay had significantly better current BASDAI, BASFI, and patient global scores, and specifically reported less fatigue, spinal pain, and joint pain (Table 1). The average changes in BASDAI, BASFI, and BASMI scores since the start of treatment with infliximab were not significantly different between those willing to pay and those not willing to pay. However, patients who were willing to pay perceived significantly more change in patient global well-being and more frequently fulfilled ASAS20 and ASAS40 response criteria (Table 1). Finally, patients who were willing to pay indicated that they spent more money annually on common (shoes) and luxury (vacations) products. However, patients willing to pay did not differ from those not willing to pay in their stated knowledge of the price of infliximab (Table 1).

Table 2. Multivariable ASAS20 zero-inflated negative binomial regression model exploring determinants of willingness to pay for infliximab treatment in ankylosing spondylitis*

	β	Exp(β) or OR (95% CI)†	*P*
Amount willing to pay, exp(β)‡			
Sex (male)	0.57	1.76 (0.79–3.94)	0.17
Age	0.05	1.05 (1.01–1.09)	< 0.01
ASAS20 response	1.20	3.32 (1.44–7.69)	< 0.01
Unwillingness to pay, OR§			
Sex (male)	0.90	2.45 (0.37–16.12)	0.35
Age	0.06	1.06 (0.97–1.16)	0.17
ASAS20 response	−1.93	0.14 (0.03–0.71)	0.02
Country of residence (The Netherlands)¶	2.61	13.6 (2.76–66.59)	< 0.01

* ASAS20 = Assessment of SpondyloArthritis international Society criteria for 20% improvement; OR = odds ratio; 95% CI = 95% confidence interval.
† Exp(β) = factor change in expected count for unit increase in independent variable. OR = factor change in odds for unit increase in independent variable.
‡ Negative binomial model, predicting expected count.
§ Logistic model, predicting unwillingness to pay (the amount willing to pay being a "certain zero").
¶ The Netherlands versus other (Belgium, Germany, Finland, France, or UK).

Multivariable exploration of WTP and amount willing to pay. The associations between each of the explanatory variables and the willingness to pay, as well as the amount they were willing to pay, after adjustment for age and sex, are shown in Supplementary Table 1 and Supplementary Table 2 (available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23299/abstract). Several multivariable models were explored using the variable groups (demographics, clinical characteristics, country of residence, and spending power). Of all variables explored, only ASAS20/ASAS40 response and country of residence (The Netherlands) were consistently associated with willingness and/or amount willing to pay. Although univariable analyses showed an association between spending power and willingness to pay, adding spending power in the multivariable analysis provided diverging results and unstable models. This was mainly due to a large amount of missing data on spending power: 71 patients (83.5%) reported their spending on at least 1 of the products. Missing values on spending power were especially prevalent among the 22 patients not willing to pay (n = 14/22 [64%] and n = 10/22 [45%] of the spending power on common and luxury goods, respectively, missing). For this reason, we had to exclude spending power from the multivariable models.

Table 3. Multivariable ASAS40 zero-inflated negative binomial regression model exploring determinants of willingness to pay for infliximab treatment in ankylosing spondylitis*

	β	Exp(β) or OR (95% CI)†	*P*
Amount willing to pay‡			
Sex (male)	0.62	1.87 (0.73–4.79)	0.20
Age	0.06	1.06 (1.02–1.10)	< 0.01
BASDAI	−0.19	0.82 (0.66–1.04)	0.10
Unwillingness to pay§			
Sex (male)	1.22	3.41 (0.25–47.18)	0.36
Age	0.03	1.03 (0.96–1.11)	0.40
ASAS40 response	−2.41	0.09 (0.01–0.54)	< 0.01
Country of residence (The Netherlands)¶	3.40	29.88 (4.17–214.11)	< 0.01

* ASAS40 = Assessment of SpondyloArthritis international Society criteria for 40% improvement; OR = odds ratio; 95% CI = 95% confidence interval; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index.
† Exp(β) = factor change in expected count for unit increase in independent variable. OR = factor change in odds for unit increase in independent variable.
‡ Negative binomial model, predicting expected count.
§ Logistic model, predicting unwillingness to pay (the amount willing to pay being a "certain zero").
¶ The Netherlands versus other (Belgium, Germany, Finland, France, or UK).

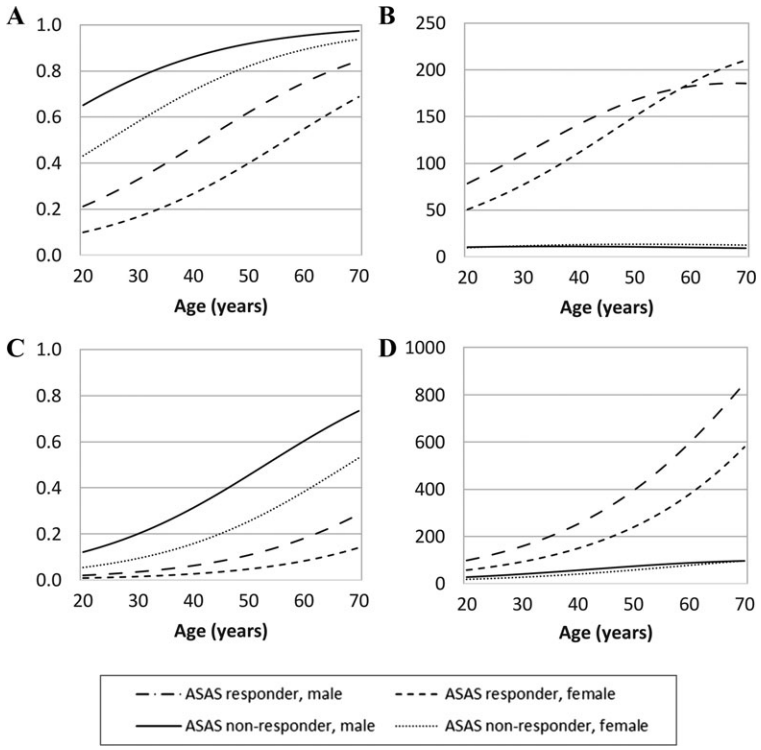

Figure 1. Predicted probabilities of being a certain zero (i.e., unwilling to pay) as well as the predicted amount patients are willing to pay for 1 administration of infliximab. **A,** Predicted probability not willing to pay for patients residing in The Netherlands; **B,** predicted amount willing to pay for patients residing in The Netherlands; **C,** predicted probability not willing to pay for patients residing in other participating countries; **D,** predicted amount willing to pay for patients residing in other participating countries. ASAS = Assessment of SpondyloArthritis international Society. Note that the amount patients are willing to pay (**B** and **D**) is predicted using the ASAS20 response zero-inflated negative binomial regression model shown in Table 2, taking into account the predicted probability that a patient is certainly not willing to pay (being a "certain" zero). For example, for a male patient of 45 years not residing in The Netherlands and who is an ASAS responder, the model predicts a probability of willingness to pay for infliximab of 0.92. If he is willing to pay, the predicted amount that he is willing to pay for 1 administration is €343. Therefore, taking into account the probability of 0.08 (1.00 − 0.92 = 0.08) that he was not willing to pay anything, this patient would be willing to pay 0.92 × €343 + 0.08 × €0 = €316. If the same male patient was an ASAS nonresponder, our model predicts a lower probability of willingness to pay for infliximab (0.62), with a predicted amount willing to pay of €103, if he is willing to pay. Again, taking into account the probability of not willing to pay (1.00 − 0.62 = 0.38), the average willing-to-pay amount is €64 (0.62 × €103 + 0.38 × €0). Because ASAS responder status is associated with both parts of the model (willingness to pay as well as willing-to-pay amount), ASAS response in this patient leads to an almost 5-fold increase in the willing-to-pay amount.

Two final and robust multivariable models were selected: an ASAS20 and an ASAS40 model, shown in Table 2 and Table 3, respectively. In the ASAS20 model, ASAS responders had 7 times lower likelihood to pay zero compared to ASAS nonresponders (odds ratio [OR] 0.14 [95% confidence interval (95% CI) 0.03–0.71]; $P < 0.01$). Likewise, patients not residing in The Netherlands had 14 times lower likelihood to pay zero compared to those residing in The Netherlands (OR 0.07 [95% CI 0.02–0.36]; $P < 0.01$). In addition, if prepared to pay, the expected amount that patients would be willing to pay for 1 administration of infliximab was on average 3 times higher in ASAS responders compared to nonresponders ($\exp(\beta) = 3.32$ [95% CI 1.44–7.6]; $P < 0.01$), and the amount willing to pay increased with increasing age ($\exp(\beta) = 1.05$ [95% CI 1.01–1.09]; $P < 0.01$) (Table 2). The ASAS40 model showed similar results, with the exception that ASAS40 was associated with willingness to pay, but not with the amount willing to pay. In this model, none of the selected parameters were significantly associated with the amount willing to pay. As it was felt that a measure of (current or change in) disease should be included, alternative disease characteristics were explored, and BASDAI score, albeit not statistically significant, was selected in this part of the model based on effect size and model fit reflected by AIC/BIC.

Predicting patients' absolute WTP. Using the coefficients of the ASAS20 model described, WTP was predicted for several specific patient scenarios (Figure 1). It revealed that a hypothetical male patient of 45 years who is not residing in The Netherlands and who is likely willing to pay for infliximab (unlikely to have a count of zero), would contribute a predicted €343 per administration if he was an ASAS20 responder and €103 if he was an ASAS20 nonresponder. The 3.3-fold difference (€343/€103) in the amount he was willing to pay corresponds to the $\exp(\beta)$ for ASAS20 response in the final model (Table 2). On the contrary, if this person was not necessarily willing to pay

(could have a count of zero), the amount he was willing to pay was found to be €316 (ASAS20 responder) and €64 (ASAS20 nonresponder) per administration.

DISCUSSION

This study showed that 74% of patients with AS receiving long-term infliximab treatment were willing to pay to continue treatment in a hypothetical situation that infliximab would not be further reimbursed and patients should pay a personal contribution for experienced benefits. Those who were not willing to pay indicated this was due to financial considerations and not due to the fact that the treatment was not worth an out-of-pocket payment. As such, this indicates the high value patients attribute to the health gains they experienced. The average price patients were willing to pay for 1 administration of infliximab was roughly 17% of the self-estimated price and 11% of the (country-specific) actual market price. ASAS20/ASAS40 response and not residing in The Netherlands were associated with willingness to pay, while ASAS20 response and increasing age were associated with a higher amount they were willing to pay. As the ASAS40 response criteria are more stringent than the ASAS20 response criteria, they are apparently less sensitive to capture the amount that patients are willing to pay (even if they are willing to pay).

When interpreting the results in light of the literature on WTP for medical interventions, the strong association that we found between treatment response and willingness to pay as well as the amount patients are willing to pay was in line with our hypothesis. Other studies also found WTP (either willingness or amount willing to pay) to be higher when more improvement in health was expected or experienced (14,15,26–28). It should be noted, though, that most WTP studies use a hypothetical improvement in health (ex ante, nonuser perspective), whereas in the current study the improvement was truly experienced by the patients (ex post, user perspective). Although the ex ante perspective is useful from an economic point of view to understand the preparedness of potential users (or the general population) to pay for new treatments, such as biological agents, this was not our objective. We were interested in the monetary value that patients attribute to the benefits and harms of treatment. In addition, the investigated treatment (infliximab) had already been approved and was reimbursed in Europe when EASIC started. We therefore adopted an ex post perspective. It is difficult to state how the expected WTP would change if we had chosen another perspective, as studies investigating multiple perspectives are limited and report conflicting results (11,12).

Conflicting results with respect to WTP and age have also been reported (15,16,29–31). More specifically, lower age has been associated with WTP in studies investigating a hypothetical cure for RA and for gout (15,31). On the other hand, higher age has been associated with WTP in a study investigating total knee replacement (30). Our analysis was able to distinguish between the willingness to pay itself and the amount patients are willing to pay. Age was not associated with the willingness to pay itself, indicating that the value for treatment was independent of age. On the other hand, the amount patients were willing to pay was higher in older patients, possibly because of higher lifetime earnings in older patients or less fear of long-term side effects.

In contingent valuation studies, spending power is recognized to confound or influence WTP. While theoretically this relationship seems sound, results regarding independent associations between income and WTP are not equivocal (16,17,27,29–31). Although our univariable analyses suggest an influence of spending power on WTP, due to missing values (in an overall small sample), spending power could not be explored fully in multivariable analyses. Household income, corrected for the number of people in the household, is a more common indicator of spending power. However, it had been shown that nonresponse on income questions is considerable and concentrated mostly in the tails of the income distribution (32). Unfortunately, replacing income with personal or household expenditure could not avoid nonresponse in the current study.

While the overall proportion of patients in our study not willing to pay (26%) is similar compared to other studies investigating WTP for treatment for musculoskeletal or rheumatic diseases (15,28,30,31), we found a large influence of willingness to pay depending on the country of residence. Apparently, different policies on health care financing influenced WTP. Willingness to pay tended to be lower in those countries in which a direct copayment is less common (The Netherlands, the UK, and France). Dutch patients, paying relatively high premiums but not being accustomed to out-of-pocket expenditures including copayments, seemed especially reluctant to pay extra costs (33). Of note, at the time of the WTP questionnaire, the Dutch health care system had introduced a major transition to a compulsory (rather than private) premium-based insurance system (34). The public discussion on compulsory premiums might have further influenced attitudes toward copayments. Even when emphasizing the hypothetical context of the scenario that aimed to understand the value of treatment with anti-TNF, this level of abstraction is apparently difficult. For Dutch patients, "treatment of AS" is felt to be a public right associated with paying the premium, rather than an additional commercial good (protest zeros). Interestingly, the multivariable models showed that those "playing the game" (i.e., those willing to pay) would contribute a similar amount of money. As such, this issue also illustrates the value of zero-inflated models, which allow for the identification of the "excess zeros" and at the same time allow for insight into factors contributing to the willingness to pay and the amount that patients are willing to pay.

There are some limitations in this study that need to be addressed. Possibly, selection bias occurred, as not all patients from ASSERT participated in EASIC and not all patients within EASIC responded to the WTP questionnaire. As patients from ASSERT not included in EASIC were less frequently ASAS20 responders, treatment responders were probably overrepresented. This possibly resulted in overestimation of the proportion of patients willing to pay and of the absolute mean amount they were willing to pay. The results mostly apply to long-term users, as those without treatment response might be expected to discontinue treatment and not be interested in continuing in EASIC. The relatively small sample size (85 patients) limited the number of explanatory factors in the multivariable models, thereby

reducing the statistical power to detect true effects, or possibly overestimating the effect size. The use of open-ended questions, as in this study, has been associated with response effect bias (i.e., patients giving strategic, socially desirable, or protest answers) and with nonresponse bias (11). The participants in this study had experienced benefits and/or harms from treatment (ex post). Although this could be a strength with regard to the evaluation of treatment effects, it could also increase the risk of response bias. This likely occurred in our study, as not all patients "played the game" (as mentioned above). However, alternative elicitation methods, such as bidding games or payment cards, are also associated with forms of bias (11,35).

Despite the limitations of the WTP method (10,11,35), this technique has strong theoretical grounds and is a valuable approach to assess treatment benefits using a different but additional perspective. Also, it should be acknowledged that common approaches to assess outcome have advantages and disadvantages, but are so generally accepted that these disadvantages are almost no longer noticed. The relevance of the current study is that it sheds additional light on the value of biologic agents for the treatment of AS.

In summary, 74% of patients with AS who received long-term treatment with infliximab were willing to pay a (hypothetical) out-of-pocket contribution for treatment with infliximab. Treatment response contributed to the willingness to pay as well as to the amount that patients were willing to pay. The WTP method seems to be a valuable addition to the common approaches used for investigating treatment benefits in AS.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Webers had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Braun, Boonen.
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ROLE OF THE STUDY SPONSOR

Janssen Biologics and Merck had no role in the study design or in the collection, analysis, or interpretation of the data, the writing of the manuscript, or the decision to submit the manuscript for publication. Publication of this article was not contingent upon approval by Janssen Biologics or Merck.

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