BRIEF REPORT

Patient Perspectives on Switching from Infliximab to Infliximab-dyyb in Patients with Rheumatologic Diseases in the United States

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Objective. The introduction of biosimilars for rheumatologic diseases (RDs) has provided a potentially lower-cost therapy compared with their bio-originator products; however, adoption of biosimilars may be challenged by patient perceptions. The objective of this study was to describe patients’ perspectives of switching from infliximab to infliximab-dyyb.

Methods. This was a survey of adult patients with RDs who qualified for switching from infliximab to infliximab-dyyb therapy between September 1 2017 and January 31 2018. Verbal consent was obtained prior to administration of a telephone survey. Survey questions were focused on the safety, efficacy, and knowledge of biosimilar therapy.

Results. A total of 108 patients were identified with 52 (48%) patients consenting to study participation. Forty (77%) and 12 (23%) patients reported switching and not switching, respectively, to infliximab-dyyb. Regarding disease control, most respondents (80%) were satisfied to very satisfied with the switch to infliximab-dyyb. Major concerns reported for switching included not knowing enough about the medication (38%), potential side effects (35%), and loss of disease activity control (35%).

Conclusion. Overall, patients reported satisfaction with switching from infliximab to infliximab-dyyb, but concerns regarding safety and efficacy were expressed. Patient involvement in the switching decision-making process may allay concerns and enhance biosimilar uptake.

INTRODUCTION

Although the introduction of biologic disease-modifying antirheumatic drugs (biologics) (eg, infliximab, adalimumab, etanercept) has significantly improved clinical outcomes for patients with rheumatologic diseases (RDs), including rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS), biologics have increased medication costs (1,2). The introduction of “biosimilars” provides a potentially lower-cost therapy compared with biologics (3). Biosimilars are considered comparable to their bio-originator reference medication in safety, purity, and potency, and they lack any clinically meaningful differences (4). In the United States, the Food and Drug Administration approved Inflectra (infliximab-dyyb), a biosimilar to Remicade (infliximab), in 2016 (5).

The biosimilar infliximab-dyyb offers patients a potentially lower-cost treatment option compared to its bio-originator, infliximab (6). Unfortunately, it is unclear if infliximab-dyyb will result in medication savings. In 2009, the US Congressional Budget Office predicted a 10-year $5.9 billion decrease in federal spending with the use of biosimilars; however, the actual savings have been estimated to be approximately $241 million (8%) (7). Patient- and prescriber-related factors are believed to contribute to the low uptake. Glintborg and colleagues reported that 7% of Danish patients who were switched from etanercept to its biosimilar SB4 switched back to etanercept for subjective reasons.
**SIGNIFICANCE & INNOVATIONS**

- We conducted a telephone survey of patients with rheumatologic disease to elicit their perspectives on switching from the bio-originator infliximab to the biosimilar infliximab-dyyb.
- Patients were generally satisfied with a switch to infliximab-dyyb.
- Patients, however, expressed concerns with the safety and efficacy of infliximab-dyyb.
- Though limited to a sample of patients from one integrated health care delivery system in the United States, our results support findings from European countries on patients’ perspectives of the switch to infliximab-dyyb.

(8). In addition, approximately 20% of patients eligible for switching refused to switch to the biosimilar (8).

Although switching studies have identified similar safety and efficacy effects between infliximab and infliximab-dyyb (9–11), and though infliximab-dyyb offers an efficacious and potentially less expensive treatment option, only a limited number of non-US studies have evaluated patient perspectives and opinions on the infliximab to infliximab-dyyb switch (12,13). In 2017, Kaiser Permanente Colorado (KPCO), an integrated health care delivery system in the United States, its patients with RA, PsA, and/or AS who qualified to switch from infliximab to infliximab-dyyb. The survey was administered via telephone between January 22 2018 and March 9 2018. Informed consent was obtained verbally prior to telephone survey administration. KPCO provides care to more than 660,000 patients in Colorado at 30 medical offices, with 5 offices having internal infusion centers where patients receive medication infusion services. The KPCO Institutional Review Board reviewed and approved all study activities.

**METHODS**

**Study design and setting.** This was a cross-sectional survey of adult patients at KPCO with RA, PsA, and/or AS who qualified to switch from infliximab to infliximab-dyyb. The survey was administered via telephone between January 22 2018 and March 9 2018. Informed consent was obtained verbally prior to telephone survey administration. KPCO provides care to more than 660,000 patients in Colorado at 30 medical offices, with 5 offices having internal infusion centers where patients receive medication infusion services. The KPCO Institutional Review Board reviewed and approved all study activities.

**Study population.** Patients aged ≥18 years with an indication of RA, PsA, and/or AS who qualified to switch from infliximab to infliximab-dyyb between September 1 2017 and January 31 2018 were eligible for inclusion. To qualify for switching, a rheumatologist either gave approval to switch a patient or gave approval after the patient was assessed for disease stability. Qualified patients were sent a letter with notification of their impending switch. If a patient was contacted by telephone or seen in the medical office by her/his rheumatologist prior to the switching infusion date, she/he was provided an opportunity to discuss the switch.

Patients had to have had at least 6 months of KPCO membership prior to initial attempted survey contact date (index date). Patients without RA, PsA, and/or AS, patients pregnant as of the index date, and patients with a diagnosis of dementia prior to the index date were excluded.

**Study outcomes.** The primary outcome was an assessment of patients’ perspectives related to the switch from infliximab to infliximab-dyyb. Questions for the survey (Appendix 1) were derived from the Waller and colleagues survey of patients with RD in Germany and included assessments of patients’ satisfaction with current therapy and concerns with infliximab-dyyb (13). Questions were adapted to make the questionnaire shorter, minimize open-ended questions, and provide actionable results to rheumatology practitioners. The secondary outcomes were comparisons of patient perceptions between respondents who identified themselves as receiving infliximab vs. infliximab-dyyb at time of consent and consented vs. nonconsented patients’ characteristics.

**Data collection.** Characteristic (eg, date of birth, sex, race, health plan membership), laboratory value, comorbidity, and medication dispensing/infusion information for switch-qualified patients was obtained through queries of KPCO’s administrative and claims electronic databases. Patients were screened electronically for eligibility. Telephone calls were made to eligible patients within 100 days of last infliximab/infliximab-dyyb infusion. A minimum of three attempts on three separate days were made to contact the patient with a voicemail request-ing a callback, with no information regarding the study being left with each attempt. Following contact with a patient, investigators (JC and TO) followed a script to verbally consent patients. If the patient consented, the investigator asked survey questions. If the patient refused consent, no further follow-up was performed. No participant compensation was provided. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Data analysis.** Age was determined as of the index date. Patient characteristic, laboratory measurement, comorbidity, and medication dispensing and infusion information was obtained during the 6 months prior to the index date. Clinical Disease Activity and Routine Assessment of Patient Index Data 3 (RAPID3) measured prior to but most proximal to the index date were assessed as a measure of RD severity. A chronic disease
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| Characteristic                        | Consented (n = 52) | Nonconsented (n = 56) | P value |
|--------------------------------------|--------------------|-----------------------|---------|
| Mean age (SD)                        | 60.0 (13.5)        | 60.3 (12.1)           | 0.559   |
| Female, no. (%)                      | 40 (76.9)          | 35 (62.5)             | 0.104   |
| White race, no. (%)                  | 49 (94.2)          | 42 (75.0)             | 0.006   |
| Hispanic ethnicity, no. (%)          | 4 (7.7)            | 8 (14.3)              | 0.364   |
| Rheumatologic disease type, no. (%)  |                    |                       | 0.515   |
| Ankylosing spondylitis               | 3 (5.8)            | 7 (12.5)              |         |
| Psoriatic arthritis                  | 9 (17.3)           | 5 (8.9)               |         |
| Rheumatoid arthritis                 | 40 (76.9)          | 42 (75.0)             |         |
| Health plan type, no. (%)            |                    |                       | 0.932   |
| Commercial                            | 24 (46.2)          | 23 (41.1)             |         |
| Medicaid                             | 1 (1.9)            | 2 (3.6)               |         |
| Medicare                             | 25 (48.1)          | 29 (51.8)             |         |
| Self-funded                          | 2 (3.9)            | 2 (3.6)               |         |
| Mean family income (no., SD)         | $69,187 (39, $23,606) | $67,172 (42, $29,403) | 0.909   |
| Mean percent of household with some college education (no., SD) | 66.3% (39, 20.8%) | 65.0% (42, 22.1%) | 0.442   |
| Mean RAPID3 score (no., SD)          | 3.3 (4, 2.7)       | 10.4 (6, 5.1)         | 0.014   |
| Mean Clinical Disease Activity Index (no., SD) | 5.2 (19, 4.9) | 5.0 (19, 3.6) | 0.730   |
| Mean C-reactive Protein Value (no., SD) | 45.8 (9, 103.8) | 1.2 (14, 0.8) | 0.156   |
| Mean CDS (SD)                        | 4.1 (3.2)          | 4.9 (3.6)             | 0.728   |
| Mean Charlson Comorbidity Index (SD) | 1.3 (1.3)          | 1.5 (1.2)             | 0.120   |

Abbreviation: CDS, Chronic Disease Score; RAPID3, Routine Assessment of Patient Index Data 3;

Table 2. Baseline patient characteristics of consented patients by self-reported switching and not switching status (n = 52)

| Characteristic                        | Switched (n = 40) | Not Switched (n = 12) | P value |
|--------------------------------------|-------------------|-----------------------|---------|
| Mean age (SD)                        | 60.3 (12.5)       | 60.4 (17.2)           | 0.956   |
| Female, no. (%)                      | 31 (77.5)         | 9 (75.0)              | 0.856   |
| White race, no. (%)                  | 38 (95.0)         | 11 (91.7)             | 0.664   |
| Hispanic ethnicity, no. (%)          | 3 (7.5)           | 1 (8.3)               | 0.924   |
| Health plan type, no. (%)            |                   |                       | 0.885   |
| Rheumatologic disease type, no. (%)  |                   |                       | 0.379   |
| Ankylosing spondylitis               | 3 (7.5)           | 0 (0.0)               |         |
| Psoriatic arthritis                  | 8 (20.0)          | 1 (8.3)               |         |
| Rheumatoid arthritis                 | 29 (72.5)         | 11 (91.7)             |         |
| Commercial                            | 19 (47.5)         | 5 (41.7)              |         |
| Medicaid                             | 1 (2.5)           | 0 (0.0)               |         |
| Medicare                             | 18 (45.0)         | 7 (58.3)              |         |
| Self-funded                          | 2 (5.0)           | 0 (0.0)               |         |
| Mean family income (no., SD)         | $68,675 (28, $24,022) | $70,490 (11, $23,596) | 0.652   |
| Mean percent of household with some college education (no., SD) | 67.2% (28, 20.6%) | 64.1% (28, 21.9%) | 0.340   |
| Mean RAPID3 score (no., SD)          | 3.3 (4, 2.7)      | ...                   | n/a     |
| Mean Clinical Disease Activity Index (no., SD) | 4.9 (11, 4.2) | 5.6 (8, 5.9) | 0.905   |
| Mean C-reactive Protein Value (no., SD) | 16.1 (6, 33.0) | 105.1 (3, 180.0) | 0.654   |
| Mean CDS (SD)                        | 3.6 (3.1)         | 5.6 (3.4)             | 0.116   |
| Mean Charlson Comorbidity Index (SD) | 1.1 (0.9)         | 2.3 (3.4)             | 0.058   |

Abbreviation: CDS, Chronic Disease Score; n/a, not applicable; RAPID3, Routine Assessment of Patient Index Data 3.
Patients received an individual probability (converted to a percentage) of having begun college (ie, had some college education). Characteristics and outcomes are reported using means with SDs for interval-level data and percentages for nominal- and ordinal-level data. Characteristics and outcomes were compared between groups with chi-square tests of association/Fisher’s exact tests and two-sample t-tests for nominal- and ordinal-level and interval-level data, respectively. The α was set at 0.05. Analyses were performed with SAS v.9.4 (SAS Institute).

RESULTS

A total of 108 patients qualified to switching and were contacted by an investigator, with 52 (48.0%) consenting to the telephone survey. Overall, qualified patients primarily were older, female, white, diagnosed with RA, were enrolled in a Medicare health plan, and had a moderate burden of disease (Table 1). Consented patients were more likely to be white and, among those with an available measurement value, had a lower mean RAPID3 score (both P < 0.05).

Amongst consented patients, 40 (76.9%) and 12 (23.1%) patients self-reported as having infliximab-dyyb and infliximab, respectively, as current therapy (Table 2). Patients who reported switching were similar to patients who did not report switching; however, those who reported not switching had numerically a higher mean CDS and Charlson Comorbidity Index.

Table 3. Survey responses overall and by self-reported switching and not switching status

| Item                                                                 | Overall (n = 52) | Switched (n = 40) | Not Switched (n = 12) | P value |
|----------------------------------------------------------------------|-----------------|-------------------|-----------------------|---------|
| Biologic Characteristics                                           |                 |                   |                       |         |
| Mean years receiving infliximab prior to request to switch to infliximab-dyyb (SD) | 9.3 (5.8)       | 9.2 (6.0)         | 9.4 (5.4)             | 0.630   |
| Satisfaction with current treatment in controlling condition/symptoms (satisfied/very satisfied, no., %) | 44 (84.6)       | 32 (80.0)         | 12 (100)              | 0.092   |
| Knowledge of infliximab-dyyb prior to request to switch to infliximab-dyyb (yes, no., %) | 17 (32.7)       | 12 (30.0)         | 5 (41.7)              | 0.496   |
| Biosimilar Concerns                                                 |                 |                   |                       |         |
| Did not know enough about infliximab-dyyb safety and efficacy prior to switching (yes, no., %) | 20 (38.5)       | 15 (37.5)         | 5 (41.7)              | 0.750   |
| Infliximab-dyyb may be too expensive (yes, no., %)                   | 7 (13.5)        | 3 (7.5)           | 4 (33.3)              | 0.022   |
| Infliximab-dyyb has potential side effects (yes, no., %)             | 20 (38.5)       | 14 (35.0)         | 6 (50.0)              | 0.349   |
| Concerned that would lose control over disease with infliximab-dyyb switching (yes, no., %) | 20 (38.5)       | 14 (35.0)         | 6 (50.0)              | 0.349   |
| Not confident that there is enough information to switch to infliximab-dyyb (yes, no., %) | n/a             | n/a               | 7 (58.3)              | n/a     |

Abbreviation: n/a, not applicable.

Overall, patients had received biologic therapy for a mean of 9.3 years and were largely satisfied with their current therapy for disease control (Table 3). In general, approximately one-third of patients reported prior knowledge of infliximab-dyyb. Specifically, 35.8% of patients did not know enough about infliximab-dyyb’s safety and efficacy and had concerns regarding the potential for infliximab-dyyb to have side effects and allow loss of disease control after switching. Of the patients who reported not switching, 58.3% stated that a reason for them not to switch was the lack of information available. Relatively few patients (13.5%) overall were concerned that infliximab-dyyb may be too expensive. Perceptions were similar between patients who self-reported as having infliximab-dyyb vs. infliximab as current therapy; however, patients who switched to infliximab-dyyb were less likely to report that infliximab-dyyb may be too expensive (7.5% vs. 33.3%, P = 0.022).

DISCUSSION

This survey of adult patients with RA, PsA, and/or AS who qualified to switch from infliximab to its biosimilar infliximab-dyyb identified that, in general, patients were satisfied with their current therapy, whether it was infliximab or infliximab-dyyb, but had concerns with switching. Although relatively few patients reported concern with infliximab-dyyb being expensive, many patients expressed concern with their knowledge of the safety and efficacy elements of infliximab-dyyb. Our findings are important because
they provide contemporary data and the first evidence of US patients’ perceptions of the infliximab to infliximab-dyyb switch.

The concerns we identified—not knowing enough about biosimilars’ safety and efficacy and potential side effects—similarly were identified by van Overbeeke and colleagues in their survey of patients with RA in Belgium (17). Unlike our study, their study did not include patients who had converted to a biosimilar, and the study was not focused on infliximab-dyyb. Waller and colleagues reported on German patients with RD who completed an in-office questionnaire regarding biosimilar and bio-originator perceptions (13). They identified that the majority of patients were satisfied with their current therapy; however, patient concerns regarding biosimilars included not enough knowledge about the therapy, potential side effects, and potential long-term problems (eg, loss of disease activity control) (13). Aladul and colleagues reported that patients with RA or AS in their United Kingdom survey who were receiving a biosimilar were optimistic about biosimilars’ safety, efficacy, and switching, whereas patients who were receiving the originator biologic were reluctant to switch to a biosimilar (12). Peyrin-Biroulet and colleagues reported from their survey of European patients with inflammatory bowel disease who were receiving the bio-originator that most patients were not familiar with biosimilars and, of those who were, doubts and concerns about the safety and efficacy of biosimilars were raised (18). In addition, the authors found that patients requested to be notified about and involved in decision making regarding biosimilars (18). These findings suggest that although patients are amenable to biosimilar therapy, patient education regarding biosimilars and involvement of patients in the switch decision-making process may be necessary to allay their concerns.

We identified that numerically higher proportions of patients who self-reported that they had not switched expressed concern with infliximab-dyyb than patients who reported switching to infliximab-dyyb. In patients who reported not switching, a majority expressed concern that not enough information exists to switch, that there would be a loss of disease activity control after switching, and that infliximab-dyyb has potential side effects. No more than 38% of patients who reported undergoing switching to infliximab-dyyb expressed concern for these items, and patients, overall, were satisfied with the switch. Our results are similar to the Waller and colleagues study that reported that patients who had continued with the bio-originator had more concerns with safety and efficacy issues, whereas the majority of patients who switched from a bio-originator to a biosimilar were indifferent to the switch (13).

Our survey identified notable findings, but there are several study limitations to consider. Given our small sample size and the fact that the survey was conducted in only one health care delivery system, generalizability of the findings may be limited. Additionally, nonrespondents may have answered questions differently from those who chose to respond. But as our findings were similar to those reported by other studies, we believe that the generalizability is sufficient for other health care sys-

tems to value our findings. As this was a survey, biases (eg, recall, nonresponse, social desirability) may have been present. We attempted to avoid bias by designing the questions using information from the literature, using short, nonleading questions, keeping the time between qualification for switching and surveying relatively brief, using simple response options, and personalizing the questions (eg, patients who reported infliximab as current therapy were asked questions specific to not switching). Unfortunately, this required our questions primarily to have yes/no responses and did not allow in-depth exploration of patient’s concerns. In addition, we reached out by telephone to all eligible patients and thus did not limit the patient sample selection. Furthermore, there was no patient participation in the questionnaire adaptation; however, rheumatology practitioners provided input on the appropriateness of the questions.

In conclusion, patients with RD who switched to infliximab-dyyb generally had high satisfaction with the switch and concerns with infliximab-dyyb were limited, whereas more patients who did not switch had concerns. Uptake of biosimilars will be challenging when patients and their care providers have concerns over biosimilar safety and/or quality. Patient involvement in the switching decision-making process may allay concerns and enhance their uptake.

REFERENCES

1. Becciolini A, Raimondo MG, Crotti C, Agape E, Biggioggero M, Favalli EG. A review of the literature analyzing benefits and concerns of infliximab biosimilar CT-P13 for the treatment of rheumatologic diseases: focus on interchangeability. Drug Des Devel Ther 2017;11:1969–78.
2. Lapadula G, Ferraccioli GF. Biosimilars in rheumatology: pharmacological and pharmacoeconomic issues. Clin Exp Rheumatol 2012;30 Suppl 73:S102–6.
3. Goel N, Chance K. Biosimilars in rheumatology: understanding the rigor of their development. Rheumatology (Oxford) 2017;56:187–97.
4. U.S. Food and Drug Administration. Prescribing biosimilar and interchangeable products. 2017. URL: https://www.fda.gov/Drugs/Approved/ApprovedApplications/TherapeuticBiologicApplications/Biosimilars/ucm580430.htm.
5. The Medical Letter. Inflectra – an infliximab biosimilar. Med Lett Drugs Ther 2017;59:23–5.
6. Kay J, Schoels MM, Dörner T, Emery P, Kvien TK, Smolen JS, et al. Consensus-based recommendations for the use of biosimilars to treat rheumatological diseases. Ann Rheum Dis 2018;77:165–74.
7. Burrell A. Can real-world evidence improve market access for biosimilars in the U.S.? [column]. 2018. URL: https://www.biosimlardevelopment.com/doc/can-real-world-evidence-improve-market-access-for-biosimilars-in-the-u-s-0001.
8. Glintborg B, Loft AG, Omerovic E, Hendricks O, Linauskas A, Espesen J, et al. To switch or not to switch: results of a nationwide guideline of mandatory switching from originator to biosimilar etanercept. One-year treatment outcomes in 2061 patients with inflammatory arthritis from the DANBIO registry. Ann Rheum Dis 2019;78:192–200.
9. Abdalla A, Byrne N, Conway R, Walsh T, Mannion G, Hanly M, et al. Long-term safety and efficacy of biosimilar infliximab among patients with inflammatory arthritis switched from reference product. Open Access Rheumatol 2017;9:29–35.

10. Yoo DH, Prodanovic N, Jaworski J, Miranda P, Ramitere E, Lanzon A, et al. Efficacy and safety of CT-P13 (biosimilar infliximab) in patients with rheumatoid arthritis: comparison between switching from reference infliximab to CT-P13 and continuing CT-P13 in the PLANETRA extension study. Ann Rheum Dis 2017;76:355–63.

11. Park W, Yoo DH, Miranda P, Brzosko M, Wiland P, Gutierrez-Ureña S, et al. Efficacy and safety of switching from reference infliximab to CT-P13 compared with maintenance of CT-P13 in ankylosing spondylitis: 102-week data from the PLANETAS extension study. Ann Rheum Dis 2017;76:346–54.

12. Aladul MI, Fitzpatrick RW, Chapman SR. Patients' understanding and attitudes towards infliximab and etanercept biosimilars: result of a UK web-based survey. BioDrugs 2017;31:439–46.

13. Walker J, Sullivan E, Piercy J, Black CM, Kachroo S. Assessing physician and patient acceptance of infliximab biosimilars in rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis across Germany. Patient Prefer Adherence 2017;11:519–30.

14. Kaiser Permanente Colorado. Care and coverage together help Colorado thrive. 2018. URL: https://thrive.kaiserpermanente.org/care-near-colorado.

15. Clark DO, Von Korff M, Saunders K, Baluch WM, Simon GE. A chronic disease score with empirically derived weights. Med Care 1996;33:783–95.

16. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care 2005;43:1130–9.

17. Van Overbeeke E, De Beleyr B, De Hoon J, Westhovens R, Huys I. Perception of originator biologics and biosimilars: a survey among Belgian rheumatoid arthritis patients and rheumatologists. BioDrugs 2017;31:447–50.

18. Peyrin-Biroulet L, Lönnfors S, Robin X, Danese S, Avedano L. Patient perspectives on biosimilars: a survey by the European Federation of Crohn’s and Ulcerative Colitis Associations. J Crohns Colitis 2017;11:128–33.

APPENDIX

Patient Survey Questions

Are you currently on Inflectra or Remicade?

How many years had you been on Remicade?

Had you heard about Inflectra previously (yes/no)?

Which option best describes your satisfaction with how well your current treatment is controlling your condition/symptoms (very dissatisfied, dissatisfied, neither satisfied or dissatisfied, satisfied, very satisfied)?

IF ON INFLIXIMAB-DYYB:

When you were changed to Inflectra, did you have any of the following concerns:

1. You felt that you didn’t know enough about Inflectra in terms of safety and efficacy (yes/no)

2. Inflectra may be too expensive (yes/no)

3. There are potential side effects (yes/no)

4. You were concerned that you would lose control over your disease by switching to Inflectra® (yes/no)

5. You didn’t feel confident that there is enough information for you to switch (yes/no)

IF ON REMICADE (INFLIXIMAB):

(1) You felt that you didn’t know enough about Inflectra in terms of safety and efficacy (yes/no)

(2) Inflectra may be too expensive (yes/no)

(3) There are potential side effects (yes/no)

(4) You were concerned that you would lose control over your disease by switching to Inflectra (yes/no)

(5) You didn’t feel confident that there is enough information for you to switch (yes/no)