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ORIGINAL ARTICLE

KJG

아시아 의사들의 바이오시밀러 단일 클론 항체에 대한 지식과 관점: 유럽 의사들과 비교

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Knowledge and Viewpoints on Biosimilar Monoclonal Antibodies among Asian Physicians: Comparison with European Physicians

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Background/Aims: Current knowledge and viewpoints regarding biosimilars among physicians in Asia are unknown, even though these were investigated by European Crohn's and Colitis Organization (ECCO) members in 2013 and 2015. Thus, this study conducted a multinational survey to assess the awareness of biosimilar monoclonal antibodies among Asian physicians.
Methods: A 17-question multiple-choice anonymous web survey was conducted with the logistic support of the Asian Organization of Crohn's and Colitis (AOCC). Randomly selected AOCC members were invited by e-mail to participate between February 24, 2017 and March 26, 2017.
Results: In total, 151 physicians from eight Asian countries responded to the survey. Most of the participants were gastroenterologists (96.6%), and 77.5% had cared for inflammatory bowel diseases (IBD) patients for more than 5 years. The majority of the respondents (66.2%) were aware that a biosimilar is similar but not equivalent to the originator. The majority of respondents (77.5%) considered cost saving to be the main advantage of biosimilars, but a high percentage of respondents (38.4%) were concerned about a different immunogenicity from that of the originator (92.4% and 27.1% respectively in ECCO 2015). Only 19.2% considered that the originator and biosimilars were interchangeable, and only 6.0% felt very confident in the use of biosimilars (44.4% and 28.8% respectively in ECCO 2015).
Conclusions: Asian gastroenterologists in 2017 are generally well informed about biosimilars. On the other hand, compared to the ECCO members surveyed in 2015, Asian gastroenterologists had more concerns and less confidence about the use of biosimilars in clinical practice. Thus, IBD-specific data on the comparison of the efficacy, safety, and immunogenicity in Asian patients are needed. **(Korean J Gastroenterol 2019;74:333-340)**

Key Words: Biosimilar pharmaceuticals; Infliximab; Asia

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INTRODUCTION

The introduction of biological therapies has led to marked changes in the management of debilitating immune-mediated inflammatory bowel diseases (IBD), including ulcerative colitis (UC) and Crohn's disease (CD).[1,2] On the other hand, the long-term use of these agents may be costly, placing a significant burden on the National Healthcare System. The development of the first biosimilar to infliximab, CT-P13 (Remsima®; Celltrion Inc., Incheon, Korea, and Inflectra®; Hospiral, Lake Forest, IL, USA) was conceived to decrease the medical care costs and increase the patient treatment options. Recently, infliximab biosimilar monoclonal antibodies (mAb) have been approved for IBD. The current knowledge and viewpoints regarding biosimilars among European physicians were investigated by European Crohn's and Colitis Organization (ECCO) members in 2013. The survey showed that a minority of IBD specialists were aware and confident about the benefits and issues of biosimilars.[3] In 2015, an ECCO survey was conducted to examine the evolution of IBD specialists' views after 2 years. The opinion of IBD experts on the use of biosimilar monoclonal antibodies has changed dramatically toward a more favorable and confident position.[4] These might be because of the increased knowledge from postgraduate education and published evidence from clinical practice.

Although the incidence of IBD in Asia has increased rapidly in recent years[5-8] and the first infliximab biosimilar, CT-P13 (Remsima®; Celltrion Inc.), was produced by a Korean biopharmaceutical company and licensed for the Korean market in 2012, the current knowledge and viewpoints regarding biosimilars among physicians in Asia is unknown. Therefore, this study conducted a multinational survey to assess the awareness of biosimilar mAb among physicians in Asian countries.

SUBJECTS AND METHODS

1. Study design and data collection

This study adopted the questions used to survey ECCO members in 2013, 2015 or both. In 2013, a 15-question multiple-choice anonymous web survey was conducted in Europe, with questions covering the most relevant aspects of biosimilars.[3] In 2015, a 14-question multiple-choice anonymous web survey was conducted in Europe again. Most of the questions used in 2013 were retained, but other questions were added or adapted on some new issues relevant to biosimilars in IBD.[4]

In this study, a 17-question multiple-choice anonymous web survey was performed with the logistic support of the Asian Organization of Crohn's and Colitis (AOCC) (Supplementary Table 1). Randomly selected AOCC members were invited by

Table 1. Baseline Characteristics of the Participants

Characteristic	Patients (n=151)
Country	
Korea	53 (35.1)
Japan	47 (31.1)
China	34 (22.5)
Others[a]	17 (11.3)
Sex	
Males	112 (74.2)
Females	39 (25.8)
Practice	
Academic teaching hospital	142 (94)
Private clinic	5 (3.3)
Others	4 (2.6)
Specialty	
Gastroenterologist specializing in IBD	102 (67.5)
General gastroenterologist	44 (29.1)
Surgeon	3 (2.0)
Pediatrician	0 (0.0)
Others	2 (1.3)
Time caring for patients with IBD (years)	
<5	34 (22.5)
5-10	38 (25.2)
>10	79 (52.3)
Number of registered IBD patients	
<100	18 (11.9)
100-500	68 (45.0)
>500	63 (41.7)
NA	2 (1.3)
Number of registered UC patients	
<10	41 (27.2)
10-30	66 (43.7)
>30	41 (27.2)
NA	3 (2.0)
Number of registered CD patients	
<10	46 (30.5)
10-30	56 (37.1)
>30	46 (30.5)
NA	3 (2.0)

Values are presented as n (%).
IBD, inflammatory bowel disease; NA, not available; UC, ulcerative colitis; CD, Crohn's disease.
[a]Other countries included Hong Kong (n=7), Malaysia (n=4), Taiwan (n=3), Singapore (n=2), India (n=1).

e-mail to participate between February 24, 2017, and March 26, 2017 and their responses were provided to the coauthors for analysis.

2. Statistics analysis

Referring to the published results of 2013 and 2015 ECCO surveys,[3,4] a simple comparison between European and Asian participant responses was performed with no statistical analysis. Within Asian countries, a chi-square test was performed to compare the results between countries. p-values ≤0.05 were considered significant. All calculations were performed using SPSS ver. 24.0 software (SPSS Inc., Chicago, IL, USA).

RESULTS

1. Participant characteristics

Initially, 320 AOCC members were selected randomly and invited to this study. The response rate was 47%. Overall, 151 physicians from eight Asian countries (Korea, Japan, China, Hong Kong, Malaysia, Taiwan, Singapore, and India) responded to the survey (Table 1). Most participants were gastroenterologists (96.6%), including IBD specialists (67.5%). Of these, 94% worked in academic teaching hospitals, and 77.5% had cared for IBD patients for more than 5 years. Similar to the ECCO members response in 2015, the majority (49.6%) had access to biosimilars and had already prescribed them, whereas 26.4% had access to biosimilars but had not yet prescribed them, and 19% of respondents had no access to biosimilars (ECCO members in 2015: 60%, 22%, and 18%, respectively). Within Asian countries, a higher proportion of physicians in Korea (41.5%) had prescribed biosimilars for more than 2 years compared to other countries (Japan 4.3%, China 20.6%, and others 0%, p<0.001) (Supplementary Table 2).

2. General aspects and advantages of biosimilars

In the definition of mAb, the majority of respondents (66.2%) were aware that a biosimilar is a similar product, but not equal to the originator; 27.8% responded that it is a copy of a biological agent, identical to the originator (like a generic), and a further 8% confused a biosimilar with a different anti-tumor necrosis factor (TNF) agent, like adalimumab to infliximab, which was similar to the ECCO members response in 2013 (70%, 19%, and 8%, respectively). Interestingly, among Asian countries, a higher proportion of physicians in Korea (47.2%) defined a mAb as a copy of a biological agent that was identical to the originator compared to participants from other Asian countries (Japan 4.3%, China 20.6%, and others 0%, p<0.001) (Supplementary Table 2).

With regard to the issues or advantages of biosimilar mAb, 19.9% of respondents estimated that biosimilars had differ-

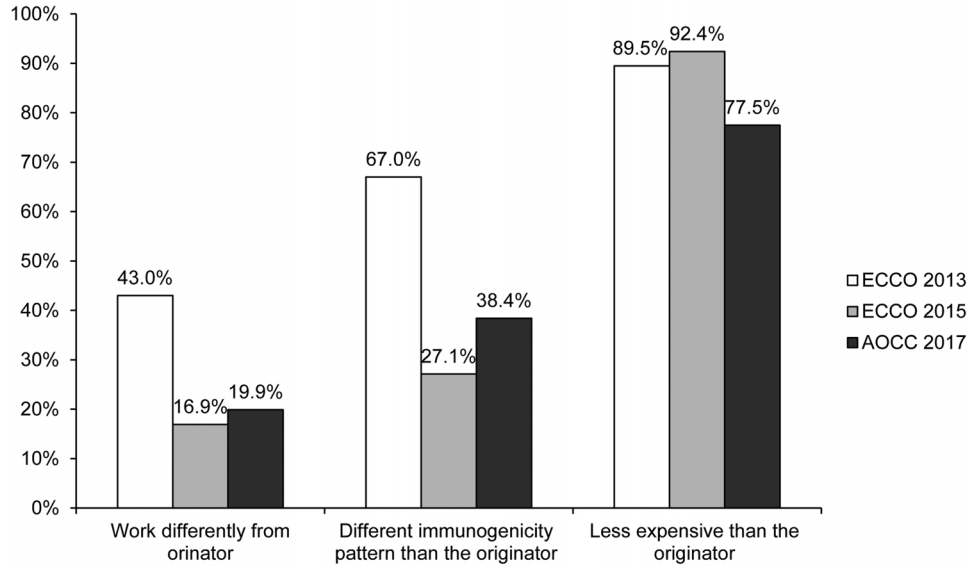

Fig. 1. Issues or advantages of monoclonal antibodies biosimilars. ECCO, European Crohn's and Colitis Organization; AOCC, Asian Organization of Crohn's and Colitis.

ent activities than the originator, and 38.4% of respondents estimated that these would present a different immunogenicity pattern than the originator, proportions which were similar to the ECCO members' opinions in 2015 (16.9% and 27.1% respectively), but lower than those of the ECCO members in 2013 (43% and 67% respectively) (Fig. 1). On the other hand, a smaller percentage of respondents (77.5%) considered cost saving to be the main advantage of biosimilars compared to 92.4% of ECCO members in 2015 and 89.5% in 2013 (Fig. 1). Within Asian countries, a higher proportion of physicians in Korea (47.2%) believed that biosimilars would have only a marginal impact on the healthcare costs (Japan 27.7%, China 5.9%, and others 11.8%, p=0.002) (Supplementary Table 2).

Compared to other biosimilars available (erythropoietin, growth factors, etc.), 41.7% of respondents thought that mAb were more complex agents than other biosimilars, and thus had a higher risk of not being sufficiently similar. Approximately 45% of respondents believed that biosimilars required well-designed clinical trials evaluating each indication for which the originator was approved, which was lower than the ECCO 2013 respondents (62% and 65% respectively), but higher than those of the ECCO 2015 (32% and 27% respectively). Similar to the ECCO 2015 (54%) results, 53.6% of respondents believed that biosimilars required more accurate post-marketing pharmacovigilance.

3. Interchangeability and automatic substitution

Of the physicians who participated in the survey, 51.7% agreed that biosimilars should carry distinct International Nonproprietary Names (INN), which was lower than the results from the ECCO 2013 (67%), but higher than the ECCO 2015 (35%) survey (Fig. 2). Within Asian countries, a higher proportion of physicians in China (73.5%) thought that biosimilars should carry distinct INN (Korea 54.7%, Japan 29.8%, and others 58.5%, p=0.006) (Supplementary Table 2).

Most respondents (86.7%) disagreed with the automatic substitution of the originator with a biosimilar by a pharmacist, which was generally in line with the findings among ECCO members (85% in 2013 and 89.8% in 2015) (Fig. 2). In a detailed questionnaire regarding which specific cases should be applied to automatic substitution, most respondents (44.3%) said automatic substitution should not be applied in all kinds of cases. Within Asian countries, a higher proportion of physicians in Korea (62.3%) disagreed with automatic substitution in any case (Japan 38.3%, China 11.8, and others 12.6%, p<0.001) (Supplementary Table 2).

When participants were asked, in the case of an IBD patient in prolonged remission under an originator mAb, whether the scheduled therapy should be continued with a biosimilar, 36.4% disagreed citing a lack of disease-specific evidence of interchangeability (72.2% in ECCO 2013 and 39.9% in ECCO 2015); 49.7% agreed but stated that they would provide detailed information to their patient regarding the limited data

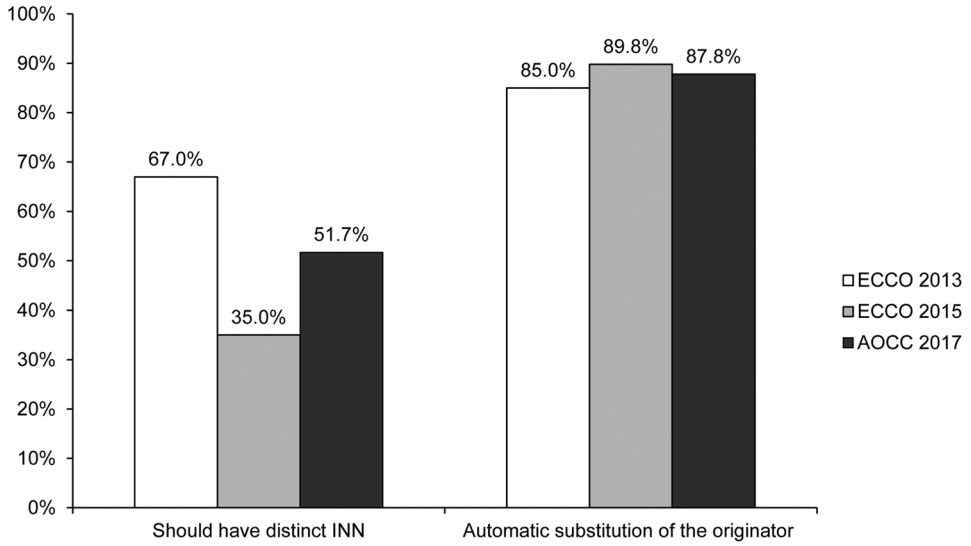

Fig. 2. Interchangeability and automatic substitution. ECCO, European Crohn's and Colitis Organization; AOCC, Asian Organization of Crohn's and Colitis; INN, International Nonproprietary Names.

on the safety of the biosimilar (22% in ECCO 2013 and 27.4% in ECCO 2015), and only 19.2% said the two molecules were interchangeable (6% in ECCO 2013 and 44.4% in ECCO 2015).

4. Extrapolation across indications

In the theoretical case of a randomized controlled trial for rheumatology patients showing no differences between a biosimilar and its originator, 39.1% believed the biosimilar should be approved for all indications of the originator (24.2% in ECCO 2013 and 50.8% in ECCO 2015). In the case of IBD, in which a theoretical randomized controlled trial showed no differences between a biosimilar and the originator in CD, 52.3% would use it only in CD (53% in ECCO 2013 and 25% in ECCO 2015); 21.2% would also use the biosimilar in UC (16% in ECCO 2013 and 31% in ECCO 2015), and 23.8% would still wait for more evidence for both CD and UC (30% in ECCO 2013 and 8.6% in ECCO 2015) (Fig. 3).

For the actions required of medical societies, 45.7% thought that medical societies should promote information on

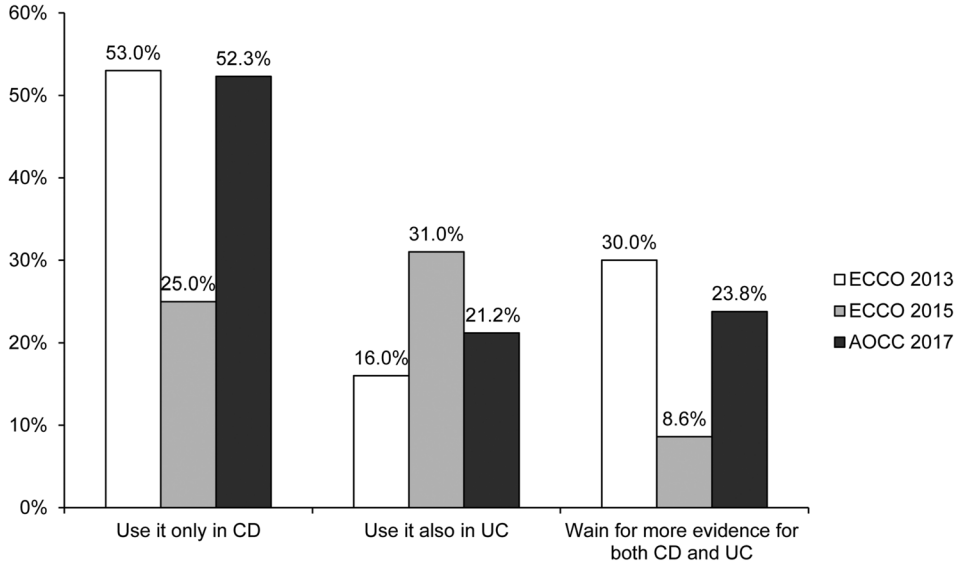

Fig. 3. Responses hypothesizing that a randomized controlled trial showed no difference between a biosimilar and the originator in CD. ECCO, European Crohn's and Colitis Organization; AOCC, Asian Organization of Crohn's and Colitis; CD, Crohn's disease; UC, ulcerative colitis.

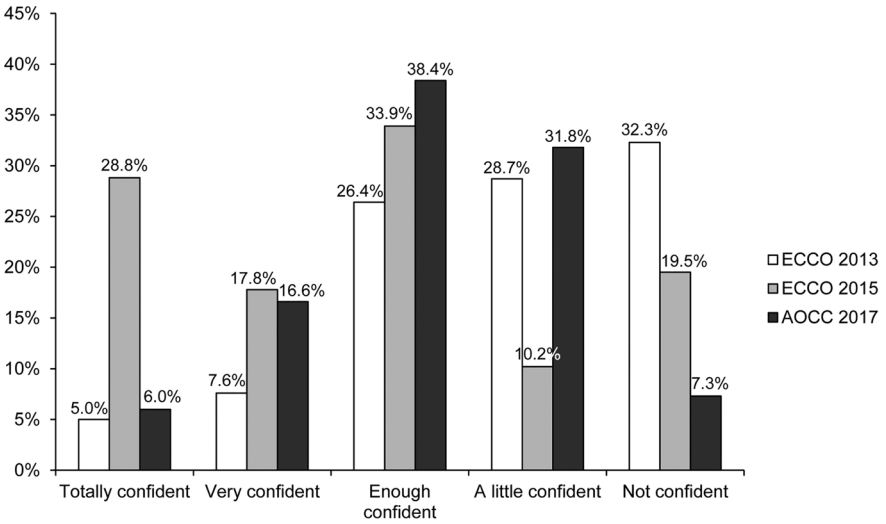

Fig. 4. Confidence in using biosimilars in clinical practice. ECCO, European Crohn's and Colitis Organization; AOCC, Asian Organization of Crohn's and Colitis.

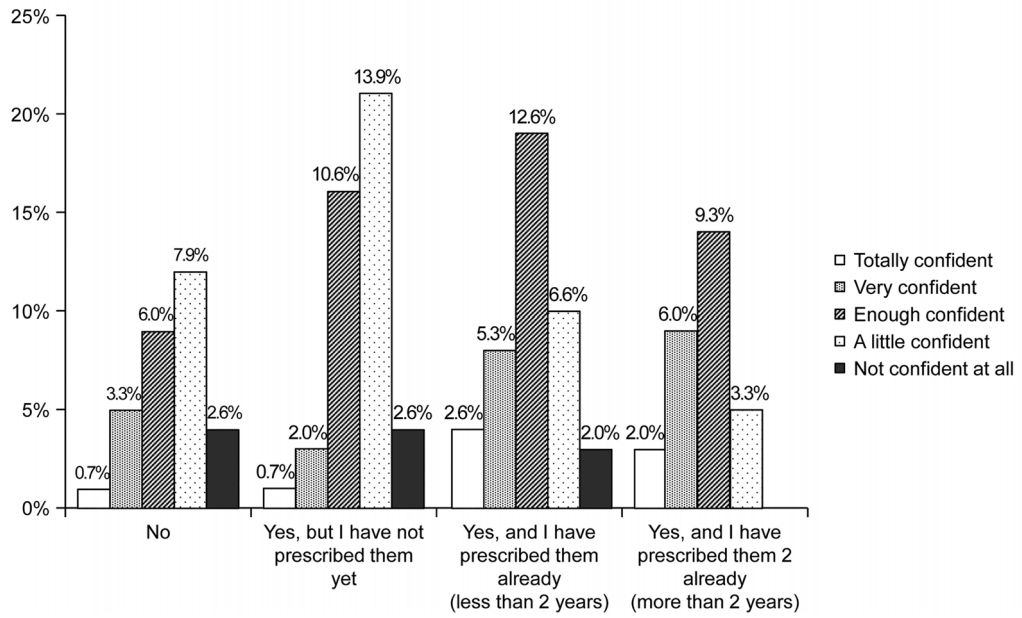

Fig. 5. Confidence according to access to biosimilars.

biosimilars (66% in ECCO 2013 and 75% in ECCO 2015), and 55.6% of respondents expressed a need for collaboration with health institutions to develop a consensus on the use of biosimilars (compared to 78% in ECCO 2013 and 47% in ECCO 2015); 58.3%, recommended the development of multispecialty practice guidelines (compared to 57% in ECCO 2013 and 26% in ECCO 2015), and 63.6% recommended the development of multispecialty safety registries (compared to 81% in ECCO 2013 and 52% in ECCO 2015).

5. Confidence regarding the use of biosimilars

Finally, when asked whether they would feel confident in prescribing biosimilars to their participants, only 6.0% felt confident in the use of biosimilars compared to 5% and 28.8% of ECCO members in 2013 and 2015, respectively (Fig. 4). When the association between the degree of confidence and access to biosimilars was analyzed, participants who had never prescribed these agents or participants from countries in which these agents were unavailable showed a higher proportion of little or no confidence (Spearman's r=-0.31, p<0.001) (Fig. 5).

DISCUSSION

The first infliximab biosimilar was introduced to the European market in 2013, and a survey investigating the opinions of European IBD physicians was undertaken with the logistic support of the ECCO in 2013 and subsequently in 2015.[3,4] The 2015 survey indicated that almost double the proportion of respondents were in favor of increasing the use of biosimilars, with limited concerns regarding their safety, compared to the 2013 survey.[4] The present survey showed that Asian gastroenterologists in 2017 were generally as well informed of the definitions of biosimilars, as were ECCO members in 2015, and the concerns about immunogenicity were not as high as ECCO members in 2015. On the other hand, there were more concerns regarding the concept of extrapolation across indications and less confidence about their use in clinical practice than those among ECCO members in 2015.

The first infliximab biosimilar, CT-P13 (Remsima®; Celltrion Inc.), was manufactured by a Korean biopharmaceutical company and was licensed for the market in Korea in 2012. Subsequently, CT-P13 (Remsima®; Celltrion Inc.) was introduced across Asia, first in Japan in 2014, then in Taiwan and Singapore in 2016, and recently in Hong Kong in 2017. Therefore, most of the participants (112/151, 74.2%) in the present study had biosimilars available for their clinical practice, and they were generally as well informed of the definitions of biosimilars as the ECCO members in 2015. On the other hand, there was a difference in the duration of biosimilar prescription among physicians within Asian countries.

The proportion of physicians in Korea who prescribed biosimilars for more than 2 years was 41.5% in Korea, 20.6% in China, and less than 5% in other Asian countries (Supplementary Table 2). In addition, a proportion of Asian gastroenterologists still had misconceptions regarding biosimilars, viewing them as generic copies of the original biologic agents. Compared to ECCO members, a lower percentage of respondents considered lower prices as the main advantage of biosimilars in this study. An explanation may be that because Asian governments are using pharmaceutical pricing strategies to contain rising healthcare costs, there is a relatively small price difference between the originators and biosimilars.[9] In particular, the single price system is applied in Korea so that the prices of the innovator drug and its alternative have become similar.[10] In Asia, although the concerns of immunogenicity were not serious, they were higher than ECCO 2015, and the proportion of respondents who thought that each biosimilar should carry a distinct INN was higher than ECCO 2015.

In the present survey, there were more concerns regarding the extrapolation of biosimilars across indications and less confidence about their use in clinical practice than for the ECCO members in 2015. The reason might be that there have been few studies supporting the safety and effectiveness of infliximab biosimilars in the Asian IBD population, as all published studies were conducted in Korea.[11,12] A retrospective multicenter study evaluated the clinical efficacy and safety of CT-P13 (Remsima®; Celltrion Inc.) in 32 anti-TNF-naïve CD patients and 42 anti-TNF-naïve UC patients.[11] In anti-TNF-naïve CD patients, the remission rates were 68.8%, 84.4%, 77.3%, and 75.0% at 2, 8, 30, and 54 weeks. In anti-TNF-naïve UC patients, remission rates were 19.0%, 38.1%, 47.8% and 50.0% at 2, 8, 30, and 54 weeks. In another post-marketing study, which included patients with active moderate-to-severe CD, fistulizing CD, or moderate-to-severe UC treated with CT-P13 (Remsima®; Celltrion Inc.),[12] treatment-related adverse events occurred in 10% of patients and were mostly mild-moderate in severity. Positive outcomes for response/remission were reported regardless of whether the patients had received prior infliximab or not.

Currently, prospective randomized non-inferiority trials evaluating the clinical efficacy and safety, as well as the interchangeability of biosimilars in Korean IBD patients are ongoing.[13] In Western countries, clinical evidence regarding biosimilars is derived from cohort studies on IBD patients, both in CD and UC.[14-24] Although the extrapolation for use in other indications is essential to keep the cost of biosimilars competitive, well-designed, prospective randomized non-inferiority trials for efficacy and safety, as well as immunogenicity and interchangeability will be needed before clinicians confidently integrate biosimilars into IBD treatment. In addition, as the physician's accessibility and experience derived from the follow-up time to the prescription were associated with increased confidence in using biosimilars in clinical practice in this survey, both clinical evidence and individual experience might be needed. This study had limitations in that because most of the responders were from three Asian countries (Korea, Japan, and China), it will be difficult for the survey result to represent other Asian physicians' knowledge and viewpoints. Therefore, this survey should be conducted on other Asian physicians' in the future.

In conclusion, Asian gastroenterologists are generally well informed about biosimilars. On the other hand, compared to ECCO members in 2015, Asian gastroenterologists had more concerns and less confidence about the use of biosimilars in clinical practice. Thus, IBD-specific data on a comparison of the efficacy, safety, and immunogenicity in Asian patients will be needed.

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Supplementary Table 1. Multinational Survey of the 4th AOCC Meeting in Seoul

<Basic characteristics of respondents>

1. Sex
   1) Male
   2) Female
2. What is your country?
   1) Korea
   2) Japan
   3) China
   4) Other (please specify,)
3. What is your type of practice?
   1) Private clinic
   2) Academic teaching hospital
   3) Other (please specify,)
4. What is your specialty?
   1) Gastroenterologist specializing in inflammatory bowel disease (IBD)
   2) General gastroenterologist
   3) Surgeon
   4) Pediatrician
   5) Other (please specify,)
5. How long have you been caring for patients with IBD?
   1) Less than 5 years
   2) More than 5 years; less than 10 years
   3) More than 10 years
6. How many patients with IBD are registered in your unit?
   1) Less than 100
   2) 100-500
   3) More than 500
   4) NA
7. How many patients with ulcerative colitis (UC) per week do you care for in your practice?
   1) Less than 10
   2) 10-30
   3) More than 30
   4) NA
8. How many patients with Crohn's disease (CD) do you care for in your practice?
   1) Less than 10
   2) 10-30
   3) More than 30
   4) NA
9. What is your e-mail address?

<Knowledge of biosimilars in IBD>

1. Do you have access to biosimilars in your country?
   1) No
   2) Yes, but I have not prescribed them yet
   3) Yes, and I have prescribed them already (less than 2 years)
   4) Yes, and I have prescribed them already (more than 2 years)

Supplementary Table 1. Continued

2. How would you best define a monoclonal antibodies (mAb) biosimilar?
   1) A biosimilar is similar, but not equal to the originator
   2) A biosimilar is a copy of a biological agent, identical to the originator (like a generic)
   3) A biosimilar is a different anti-TNF agent, like adalimumab and infliximab
3. What could be issues or advantages of a mAb biosimilar? (more than one answer possible)
   1) They can work differently from the originator
   2) They can have a different immunogenicity pattern than the originator
   3) Switching from originator to one or more of its biosimilars may boost immunogenicity
   4) The patients' rights to know which drug is given to them may be challenged
   5) They will be less expensive than the originator
   6) There will be more extensive indications than for the originator
   7) The effectiveness of biosimilars in all indications may not have been derived from clinical trials
   8) There is no additional issue
4. Regarding the impact of biosimilars on healthcare costs
   1) Biosimilars can significantly reduce healthcare costs
   2) Biosimilars can have only a marginal impact on healthcare costs
   3) Additional costs of introduction, regulation and pharmacovigilance can develop to offset any potential savings
   4) I don't know
5. Do you think mAb biosimilars have different feature(s) compared to the other available biosimilars (erythropoietin, growth factors, etc.)? (more than one answer possible)
   1) Monoclonal antibodies are more complex than other biosimilars, thus there are higher risks of being not similar enough
   2) They require more accurate postmarketing pharmacovigilance
   3) They require well-designed clinical trials in each indication for which the originator is approved
   4) There are no differences with other biosimilars
6. Do you think that a biosimilar mAb should have a different International Nonproprietary Names (INN) than its originator?
   1) Yes
   2) No
   3) I do not know
7. Pharmacists can autonomously replace original medications with generics. Do you think that the same should apply for biosimilars?
   1) Yes
   2) No
   3) I do not know
8. If the substitution is no longer in the hands of the physicians for biosimilars, do you think that it should be automatic?
   1) Yes, in all cases
   2) Yes, but only for new prescriptions
   3) Yes, but only in patients responding well to the originator
   4) No
   5) I do not know
9. Which of the following actions do you think medical societies should undertake about biosimilars? (more than one answer possible)
   1) Promote information and culture on biosimilars mAb
   2) Collaborate with health institutions and regulators to develop rules in this sector
   3) Endorse the extrapolation of indications for a biosimilar not tested in the specialty
   4) Develop multispecialty practice guidelines
   5) Create multispecialty international registries to monitor switching practices, effectiveness, safety, and immunogenicity of biosimilars
10. Which of the following actions do you think patient organizations should undertake regarding biosimilars?
   1) Patient organizations should be involved in these processes (see answers in question 8)
   2) There should be joint position statements by physicians and patients' associations to regulators
   3) This is a matter for expert physicians and regulatory agencies only

Supplementary Table 1. Continued

11. Are you aware of any action or education initiated by a patient organization in your country about biosimilars?
    1) Yes, activities have started in IBD
    2) Yes, activities have started in another specialty
    3) Not aware of any action or education by a patient organization
12. A randomized clinical trial on rheumatoid arthritis showed no differences in efficacy and safety between the originator and a biosimilar mAb. You conclude:
    1) The tested biosimilar mAb can be approved for all rheumatologic indications
    2) All biosimilar mAb of the same originator can be approved for rheumatoid arthritis
    3) The tested biosimilar mAb can be approved for all indications for which the originator is approved
    4) All biosimilars of the same originator can be approved for all indications of the originator
    5) None of the above
13. One randomized clinical trial on rheumatoid arthritis and one on ankylosing spondylitis showed no differences in efficacy and safety between the originator and a biosimilar mAb, with a 30% saving in costs. You conclude:
    1) The tested biosimilar mAb should be the first choice for rheumatoid arthritis and ankylosing spondylitis
    2) The tested biosimilar mAb should be the first choice for all indications as the originator
    3) The originator and the tested biosimilar mAb should be first choices for the two indications
    4) The originator and the tested biosimilar mAb should be first choices for the all indications of the originator
    5) None of the above
14. Assume that there is a randomized clinical trial showing similarity between a biosimilar and the originator mAb in CD for the induction and maintenance of remission. Would you:
    1) Use it only in CD
    2) Use it also in ulcerative colitis for the induction and maintenance
    3) Use it in ulcerative colitis also, but just for induction
    4) I would wait for more evidence of biosimilarity for both diseases
15. An IBD patient of yours is in prolonged remission under an original mAb. You are asked to continue the scheduled therapy with a biosimilar mAb. Do you agree? (more than one answer possible)
    1) Yes, the two molecules are interchangeable
    2) No, because the SWITCH study between infliximab and adalimumab gave poor results
    3) No, because there are limited data about the impact of switching on immunogenicity (against either originator or biosimilar)
    4) Yes, but I would inform my patient in detail, because of the limited data on the safety of biosimilars
    5) No, there is no disease specific evidence about their interchangeability
16. How would you qualify the education on biosimilars that you followed during the last 18 months?
    1) Fair, balanced, and very useful as the issue is of importance to my practice
    2) Too optimistic on biosimilars safety and efficacy
    3) Confusing and leading to more uncertainty in your mind
    4) Unneeded as biosimilars will be introduced into the system by regulators and payors anyway
    5) Unneeded because biosimilars are at least as similar to their originator than separate batches of the originator have been during the last decade
17. Do you (or would you) feel confident in using biosimilars in your everyday clinical practice today?
    1) Totally confident
    2) Very confident
    3) Sufficiently confident
    4) A little confident
    5) Not confident at all

AOCC, Asian Organization of Crohn's and Colitis; NA, not available; TNF, tumor necrosis factor.

Supplementary Table 2. Results of the 17-question Multiple Choice Anonymous Web Survey of AOCC Members

Questions	Korea	Japan	China	Others	p-value
1. Access to biosimilars					<0.001
Prescribed for more than 2 years	22 (41.5)	2 (4.3)	7 (20.6)	0 (0.0)	
Prescribed for less than 2 years	17 (32.1)	20 (42.6)	2 (5.9)	5 (29.4)	
Have not prescribed them yet	14 (26.4)	23 (48.9)	4 (11.8)	4 (23.5)	
Not available in this country	0 (0.0)	2 (4.3)	21 (61.8)	8 (47.1)	
2. Define a monoclonal antibodies					<0.001
A biosimilar is a similar, but not equal to the originator	28 (52.8)	37 (78.7)	23 (67.6)	12 (70.6)	
A biosimilar is a copy of a biological agent, identical to the originator (like a generic)	25 (47.2)	8 (17.0)	5 (14.7)	4 (23.5)	
A biosimilar is a different anti-TNF agent, like adalimumab to infliximab	0 (0.0)	2 (4.3)	6 (17.6)	1 (59)	
3. Issues or advantages of a mAb biosimilar					
Different mechanism of action than the originator	9 (17.0)	8 (17.0)	10 (29.4)	3 (17.6)	0.04
Different immunogenicity pattern than the originator	23 (43.4)	9 (19.1)	16 (47.1)	10 (58.8)	0.007
Switching from originator to one or more of its biosimilars may boost immunogenicity	10 (18.9)	7 (14.9)	11 (32.4)	4 (23.5)	0.27
Patients' right to know which drug is given to them may be challenged	26 (49.1)	9 (19.1)	12 (35.3)	7 (41.2)	0.02
Less expensive than the originator	40 (75.5)	38 (80.9)	23 (67.6)	16 (94.1)	0.17
More extensive indications than for the originator	0 (0.0)	2 (4.3)	3 (8.8)	0 (0.0)	0.12
The reported effectiveness of biosimilars in different indications may not have been derived from clinical trials	25 (47.2)	16 (34.0)	18 (52.9)	12 (70.6)	0.05
4. Regarding the impact of biosimilars on healthcare costs					0.002
Biosimilars can significantly reduce healthcare costs	24 (45.3)	29 (61.7)	23 (67.6)	13 (76.5)	
Biosimilars have only a marginal impact on healthcare costs	25 (47.2)	13 (27.7)	2 (5.9)	2 (11.8)	
Additional costs of introduction, regulation and pharmacovigilance can develop to offset any potential savings	2 (3.8)	1 (2.1)	4 (11.8)	0 (0.0)	
5. mAb biosimilars have different feature(s) compared to the other available biosimilars (erythropoietin, growth factors, etc.)					
Monoclonal antibodies are more complex than other biosimilars thus have higher risks of not being sufficiently similar	22 (41.5)	14 (29.8)	14 (29.8)	11 (64.7)	0.07
They require more accurate postmarketing pharmacovigilance	25 (47.2)	23 (48.9)	23 (48.9)	11 (64.7)	0.28
They require well-designed clinical trials in each indication for which the originator is approved	24 (45.3)	15 (31.9)	15 (31.9)	6 (35.3)	0.01
There are no differences with other biosimilars	6 (11.3)	6 (12.8)	3 (8.8)	1 (5.9)	0.85
6. Biosimilar mAb should have a different INN than its originator	29 (54.7)	14 (29.8)	25 (73.5)	10 (58.5)	0.006
7. Autonomously replace original medications with biosimilars	3 (5.7)	5 (10.6)	12 (35.3)	0 (0.0)	<0.001
8. Substitution automatically					<0.001
In all cases	0 (0.0)	7 (14.9)	4 (11.8)	0 (0.0)	
Only for new prescriptions	9 (17.0)	7 (14.9)	8 (23.5)	2 (11.8)	
Only in patients responding well to the originator	8 (15.1)	4 (8.5)	15 (44.1)	1 (5.9)	
Never	33 (62.3)	18 (38.3)	4 (11.8)	12 (12.6)	
9. Actions, medical societies should undertake with regards to biosimilars					
Promote information and culture on biosimilar mAb	20 (37.7)	17 (36.2)	20 (58.8)	12 (70.6)	0.02
Collaborate with health institutions and regulators to develop rules in this sector	32 (60.4)	16 (34.0)	22 (64.7)	14 (82.4)	0.001
Endorse the extrapolation of indications for a biosimilars not tested in the specialty	8 (15.1)	2 (4.3)	11 (32.4)	4 (23.5)	0.007
Develop multispecialty practice guidelines	30 (56.6)	5 (53.2)	21 (61.8)	12 (70.6)	0.61
Create multispecialty international registries to monitor switching practices, effectiveness, safety, and immunogenicity of biosimilars	34 (64.2)	222 (46.8)	23 (67.6)	17 (100)	0.001

Supplementary Table 2. Continued

Questions	Korea	Japan	China	Others	p-value
10. Actions of patient organizations					<0.001
Actions patient organizations should undertake about biosimilars should be involved in these processes	6 (11.3)	16 (34.0)	7 (20.6)	5 (29.4)	
There should be joint position statements by physicians and patients' associations to regulators	24 (45.3)	25 (53.2)	21 (61.8)	2 (11.8)	
This is a matter for expert physicians and regulatory agencies only	23 (43.4)	6 (12.8)	6 (17.6)	10 (58.8)	
11. Aware of any action or education initiated by a patient organization about biosimilars					0.004
Yes, activities have started in IBD	6 (11.3)	10 (21.3)	14 (41.2)	0 (0.0)	
Yes, activities have started in another specialty	3 (5.7)	1 (2.1)	3 (8.8)	1 (5.9)	
Not aware of any action or education	44 (83.0)	36 (76.6)	17 (50.0)	16 (94.1)	
12. A RCT on RA showed no differences in efficacy and safety between the originator and a biosimilar mAb. You conclude:					0.18
The tested biosimilar mAb can be approved for all rheumatologic indications	17 (32.1)	23 (48.9)	10 (29.4)	2 (11.8)	
All biosimilar mAb of the same originator can be approved for RA	5 (9.4)	3 (6.4)	3 (8.8)	3 (17.6)	
The tested biosimilar mAb can be approved for all indications for which the originator is approved	25 (47.2)	13 (27.7)	13 (38.2)	8 (47.1)	
All biosimilars of the same originator can be approved for all indications of the originator	1 (1.9)	2 (4.3)	0 (0.0)	0 (0.0)	
13. One RCT on RA and one on AS showed no differences in efficacy and safety between the originator and a biosimilar mAb, with a 30% saving in costs. You conclude:					0.24
The tested biosimilar mAb should be the first choice for RA and AS	4 (7.5)	10 (21.3)	10 (29.4)	3 (17.6)	
Should be the first choice for all indications as the originator	5 (9.4)	2 (4.3)	4 (11.8)	2 (11.8)	
The originator and the tested biosimilar mAb should be first choices for the two indications	29 (54.7)	24 (51.1)	10 (29.4)	9 (52.9)	
The originator and the tested biosimilar mAb should be first choices for the all indications of the originator	11 (20.8)	6 (12.8)	4 (11.8)	2 (11.8)	
14. Let us assume that there is a RCT showing similarity between a biosimilar and the originator mAb in CD for the induction and maintenance of remission. Would you:					0.06
Use it only in CD	28 (52.8)	21 (44.7)	17 (50.0)	13 (76.5)	
Use it also in UC for the induction and maintenance	15 (28.3)	11 (23.4)	4 (11.8)	2 (11.8)	
Use it in UC also, but just for induction	1 (1.9)	0 (0.0)	3 (8.8)	0 (0.0)	
I would wait for more evidence of biosimilarity for both diseases	9 (17.0)	15 (31.9)	10 (29.4)	2 (11.8)	
15. Your IBD patient of yours is in prolonged remission under an original mAb. You are asked to continue the scheduled therapy with a biosimilar mAb. Do you agree?					
Yes, the two molecules are interchangeable	12 (22.6)	10 (21.3)	7 (20.6)	0 (0.0)	0.20
No, because the SWITCH study between infliximab and adalimumab gave poor results	3 (5.7)	2 (4.3)	2 (5.9)	1 (5.9)	0.98
No, because there are limited data about the impact of switching on immunogenicity (against either originator or biosimilar)	27 (50.9)	10 (21.3)	13 (38.2)	5 (29.4)	0.02
Yes, but I would inform my patient in detail because of the limited data on the safety of biosimilars	17 (32.1)	26 (55.3)	20 (58.8)	12 (70.6)	0.01
No, there is no disease specific evidence about their interchangeability	11 (20.8)	4 (8.5)	5 (14.7)	4 (23.5)	0.30
16. Qualify the education on biosimilars that you followed during the last 18 months					0.52
Fair, balanced and very useful as the issue is of importance to your practice	28 (52.8)	16 (34.0)	17 (50.0)	8 (47.1)	
Too optimistic on biosimilars safety and efficacy	10 (18.9)	17 (36.2)	9 (26.5)	4 (23.5)	
Confusing and leading to more uncertainty in your mind	11 (20.8)	9 (19.1)	5 (14.7)	4 (23.5)	

Supplementary Table 2. Continued

Questions	Korea	Japan	China	Others	p-value
Unneeded as biosimilars will be introduced into the system by regulators and payors anyway	0 (0.0)	1 (2.1)	0 (0.0)	1 (5.9)	
Unneeded because biosimilars are at least as similar to their originator than separate batches of the originator have been during the last decade	4 (7.5)	4 (8.5)	3 (8.8)	0 (0.0)	
17. Feel confident in using biosimilars in your everyday clinical practice today?					0.02
Totally confident	5 (9.4)	2 (4.3)	1 (2.9)	1 (5.9)	
Very confident	13 (24.5)	4 (8.5)	7 (20.6)	1 (5.9)	
Sufficiently confident	23 (43.4)	15 (31.9)	9 (26.5)	11 (64.7)	
A little confident	12 (22.6)	19 (40.4)	14 (41.2)	3 (17.6)	
Not confident at all	0 (0.0)	7 (14.9)	3 (8.8)	1 (5.9)	

Values are presented as n (%).

AOCC, Asian Organization of Crohn's and Colitis; TNF, tumor necrosis factor; mAb, monoclonal antibodies; INN, International Nonproprietary Names; IBD, inflammatory bowel diseases; RCT, randomized controlled trial; RA, rheumatoid arthritis; AS, ankylosing spondilitis; CD, Crohn's disease; UC, ulcerative colitis.