Biological treatment approach to inflammatory bowel disease is similar in academic and nonacademic centres – prime time for decentralisation of inflammatory bowel disease care?

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Background With the increasing number of inflammatory bowel disease (IBD) patients, it is difficult to manage them within specialised IBD teams in academic medical centres: many are therefore treated in nonacademic IBD centres. It is unclear whether the time to introducing biologics is the same in both settings.
Aim We aimed to compare treatment approach with biologics in academic vs. nonacademic centres.
Methods We analysed Slovenian national IBD registry data (UR-CARE Registry, supported by the European Crohn's and Colitis Organisation), which included 2 academic (2319 patients) and 4 nonacademic IBD (429 patients) centres.
Results The disease phenotype was similar in both settings. In total, 1687 patients received 2782 treatment episodes with biologics. We observed no differences in treatment episodes with TNF-alpha inhibitors (60% vs. 61%), vedolizumab (24% vs. 23%), or ustekinumab (17% vs. 16%) in academic compared to nonacademic centres ($P = 0.949$). However, TNF inhibitors were less often the first biologic in academic centres (TNF inhibitors: 67.5% vs. 74.0%, vedolizumab: 20.3% vs. 17.9%, ustekinumab: 12.1% vs. 8.1%; $P = 0.0096$). Consequently, more patients received ustekinumab (29.8% vs. 18.3%) and vedolizumab (17.4% vs. 13.5%) and fewer TNF inhibitors (52.7% vs. 68.2%) for Crohn's disease in academic compared to nonacademic centres, with no such differences for ulcerative colitis. The time to initiation of the first biologic from diagnosis was short and similar in both settings (11.3 vs. 10.4 months, $P = 0.2$).
Conclusion In this nationwide registry analysis, we observed that biological treatment choice was similar in academic and nonacademic settings. These findings support the decentralisation of IBD care. Eur J Gastroenterol Hepatol 36: 728–734

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Introduction

Inflammatory bowel disease (IBD), namely, Crohn's disease (CD) and ulcerative colitis (UC), is a chronic condition that continues to increase in incidence [1,2] worldwide. The management of the disease is complex, as it includes invasive diagnostics and imaging. Fortunately, several new treatments, including monoclonal antibodies against tumour necrosis factor-alpha, integrins, interleukins, and Janus kinase inhibitors [3], have become available in recent years. Nevertheless, the management of these patients typically involves multidisciplinary teams due to many aspects of the disease and treatments. Because of this, there is a tendency to centralise patients in a few specialised IBD centres with sufficient expertise and resources in many countries, with the argument that this will result in better care than if patients were treated locally in smaller nonacademic centres, where gastroenterologists are generally less subspecialized in specific conditions and thus could not provide equally good care as their IBD-subspecialized peers in academic centres who devote more time to IBD care.

The caveat here, however, is that academic centres are typically located only in larger cities, forcing patients to

travel long distances and consuming a great deal of time [4]. Additionally, many patients, especially when suffering from a flare, perceive this as a tremendous burden. Furthermore, patients with disease or treatment complications will typically seek help in local environments. Additionally, the rapidly increasing prevalence of patients burdens academic medical centres in many countries; therefore, it is challenging to provide sufficient resources for all IBD patients only in academic centres.

Because of the above-described issues, several years ago, the decision to decentralise IBD patient care was made in Slovenia. The two academic medical centres located in Ljubljana (University Medical Centre Ljubljana) and Maribor (University Medical Centre Maribor) offer support to four other nonacademic medical centres (general hospitals Celje, Jesenice, Izola, and diagnostic centre Bled), especially when step-up to/loss of response to advanced treatments or when complications of disease that need interventional radiology or surgical management are encountered.

However, it is not clear whether patients receive comparable treatments in nonacademic compared to academic centres. To our knowledge, a comparison of IBD patients' phenotypes and treatment approach with biologicals in academic vs. nonacademic settings has not yet been performed. Nevertheless, this knowledge would be important, as it could lead to the organisation of IBD units in different countries in light of the rapidly increasing number of patients.

The aim of this study was thus to explore and compare the phenotypes of IBD patients and their treatment approach with biologicals in academic vs. nonacademic IBD centres in Slovenia. To do this, we used prospectively collected data in the Slovenian national IBD registry based on the European Crohn's and Colitis Organisation (ECCO)-powered platform UR-CARE.

Methods

Data source

We used data collected in the UR-CARE Registry for six Slovenian IBD centres, two high-volume academic IBD university tertiary referral centres (University Medical Centre Ljubljana and Maribor), and four nonacademic IBD centres (three general hospitals (two high-volume centres: General Hospital Izola and Celje; one low-volume centre: General Hospital Jesenice) and one independent government-funded low-volume outpatient unit (Diagnostics Centre Bled)). These six centres covered the great majority of patients treated with biological treatments in Slovenia at the time of data extraction. In Slovenia, there are no limitations on the choice of specific biological drug since 2019, therefore the availability of biological drugs is similar in academic and nonacademic IBD centres. However, before initiation of biological treatment, every patient is presented to the multidisciplinary IBD team in one of the two academic IBD centres. After the approval of the indication for initiation of biological treatment, this can be started by the treating physician. Importantly, the multidisciplinary IBD teams do not advise on the specific biological to be used for a particular patient. The choice of specific drug to be used as first-line treatment is thus left to the treating physician. This is because we believe that shared decision-making between the treating physician and the patient results in optimal selection of specific drug for each patient. However, in case of first-line biological failure or when treatment complications occur, the academic IBD teams give more specific instructions on the choice of the next drug and on the dosing (e.g. dose optimisation, combination with immunomodulators) to assist nonacademic centres.

The UR-CARE Registry is a validated platform for the prospective collection of clinical data developed and supported by the ECCO [5]. The UR-CARE Registry collects patient data, such as disease demographics, disease activity, disease complications, and treatment. In Slovenia, data collection started in September 2020.

Data extraction and analysis

Total data were extracted from the Slovenian UR-CARE Registry on 1 October 2022. In this first Slovenian national analysis, we focussed on describing the disease phenotypes (demographics, disease extension, extraintestinal manifestations) and treatment approach (utilisation of conventional vs. advanced treatments, distribution of different classes of biologicals).

We analysed utilisation of biologicals by comparing treatment episodes between academic and nonacademic centres. A treatment episode was defined as the use of one biological in a specific patient. However, one patient could have more than one treatment episode. For example, when a patient was exposed to two different biologicals during follow-up, we defined the first treatment episode as the time treated with the first biological and the second treatment episode as the time treated with the second biological.

Descriptive statistics are presented as the means ± standard deviations for parametric variables and percentages for categorical variables. To analyse potential differences between academic vs. nonacademic centres, we used the chi-square/Fisher's exact test or t-test when the data were normally distributed or the Mann–Whitney U test as appropriate when variables had abnormal distributions. Statistical significance for all tests was set at $P < 0.05$.

Data collection and analyses were performed using Microsoft Excel software (version 2301, build 16.0.16026.20196) and SPSS 21.0 (IBM Inc., Chicago, Illinois, USA). This study was approved by the National Medical Ethics Committee of Slovenia (ID 0120-576/2019/7).

Results

Patient characteristics and disease phenotypes

Overall characteristics of the cohort

At the time of data extraction, the Slovenian UR CARE Registry included 2748 patients with IBD. Demographic data are presented in Table 1 (row 1) and include patients from 6 different IBD centres in Slovenia. The majority of patients were diagnosed with CD (51.1%), followed by UC (45.0%), and only a small number of patients had unclassified IBD (3.5%). A minority of data regarding the diagnosis (0.4%) were missing from the registry and were

Table 1. Disease phenotype by academic vs. nonacademic inflammatory bowel disease centre in Slovenia

	Overall	Academic centres	Nonacademic centres	*P*-value
Total number of patients with IBD	2748	2319 (84.4%)	429 (15.6%)	
CD, N (%)	1405 (51.1%)	1191 (51.4%)	214 (49.9%)	
UC, N (%)	1237 (45.0%)	1040 (44.8%)	197 (45.9%)	0.656
IBD-U, N (%)	95 (3.5%)	83 (3.6%)	12 (2.8%)	
Crohn's with isolated ileum disease, N (% of all CD)	326 (23.2%)	286 (24.0%)	40 (18.7%)	0.090
Crohn's with ileocolonic disease, N (% of all CD)	518 (36.9%)	431 (36.2%)	87 (40.7%)	0.212
Crohn's perianal, N (% of all CD)	264 (18.8%)	229 (19.2%)	35 (16.4%)	0.322
Age at diagnosis CD, years (mean ± SD)	33.1 ± 16.9	32.3 ± 16.8	37.5 ± 17.4	<0.001
Age at diagnosis UC, years (mean ± SD)	36.6 ± 16.8	36.4 ± 17.0	37.7 ± 15.9	0.292
Disease duration until biologic initiation (start of biological treatment from 2020–2022 (mean ± SD) [months]	4.68 ± 4.44	4.92 ± 4.68	3.72 ± 2.88	0.265
Disease duration until biologic initiation [months]	11.16 ± 10.08	11.28 ± 10.08	10.44 ± 10.08	0.236
Extraintestinal manifestations, N (% of all IBD patients)	338 (12.3%)	279 (12.0%)	59 (17.9%)	0.277

CD, Crohn's disease; IBD, inflammatory bowel disease; IBD-U, unclassified IBD; UC, ulcerative colitis.

classified as missing. The proportion between the sexes was similar. Patients with CD were on average younger than patients with UC at diagnosis. Perianal disease in CD cases was detected in 264 (18.8%) out of 1405 patients (Table 1). Disease extension is shown in Supplementary Figure 1, supplemental digital content 1, *http://links.lww.com/EJGH/B19* for CD, and Supplementary Figure 2, supplemental digital content 1, *http://links.lww.com/EJGH/B19* for UC patients. Seventy percent of patients with CD had ileal involvement, and approximately half had colonic disease. Approximately half of UC patients had disease extension beyond the splenic flexure. Most, but not all, patients with UC had an affected rectum (93.8%).

Comparison of academic vs. nonacademic centres

Demographic data classified by type of IBD centre (academic vs. nonacademic) are shown in Table 1 (rows 2 and 3). The overall characteristics of patients treated in academic IBD centres were similar to those of patients treated in nonacademic IBD centres. Data per respective IBD centre are shown in Supplementary Table 1, supplemental digital content 1, *http://links.lww.com/EJGH/B19*. The proportions of IBD patients with risk factors for disease complications (CD: ileal disease, perianal disease; UC: extensive colitis) were similar in academic compared to nonacademic centres. The only significant difference was age at diagnosis among patients with CD, with academic centres having patients that were approximately 5 years younger at diagnosis compared to nonacademic centres.

Biological treatment approach

Overall treatment approach in the cohort

In total, 1687 patients included in the registry at the time of data extraction underwent 2781 treatment episodes with biologicals (adalimumab N = 703 (originator N = 500, biosimilars N = 203), golimumab N = 79, infliximab 886 (originator N = 339, biosimilars N = 547), ustekinumab N = 456, vedolizumab N = 653, other off-label biologicals N = 4). Of these, 703/1687 (42%) discontinued first-line biologicals, 280/1687 (17%) discontinued second-line biologicals and 87/1687 (5%) discontinued third-line biologicals. A detailed sequence of the prescription of biological drugs is shown in Supplementary Table 2, supplemental digital content 1, *http://links.lww.com/EJGH/B19*.

Comparison of academic vs. nonacademic inflammatory bowel disease centres

The total utilisation of biologicals by drug class was similar in academic vs. nonacademic centres. Comparison of total treatment episodes by drug class in academic and nonacademic patients did not show differences ($P = 0.949$) (Table 2). However, statistical significance was observed for ongoing biological therapy by drug class in academic centres compared to nonacademic centres (Table 3). In academic centres, slightly fewer patients were receiving TNF-alpha inhibitors than in nonacademic IBD centres (48% vs. 57%). A reciprocal difference was observed for anti-integrin vedolizumab and anti-IL-12/23 drug ustekinumab, with slightly higher utilisation in academic IBD centres compared to nonacademic IBD centres.

When we classified data by disease phenotype (CD vs. UC), we observed that this difference was driven by CD patients, as these patients were less often receiving TNF-alpha inhibitors in academic centres than in nonacademic centres. Conversely, ustekinumab was more often used in academic centres than in nonacademic centres (Table 4).

These differences were not observed for UC (Table 5). Similarly, we did not observe a difference in the proportion of patients with UC with ongoing vedolizumab treatment in academic compared to nonacademic centres.

Additionally, the time to initiation of biologicals decreased during recent years to a similar extent in both academic and nonacademic IBD centres (Table 1, rows 11–12).

Similarly, TNF-alpha inhibitors were prescribed slightly less often as first-line biologicals in academic centres than in nonacademic centres (TNF-alpha inhibitors: 67.5% vs. 74.0%). Conversely, vedolizumab (20.3% vs. 17.9%) and ustekinumab (12.1% vs. 8.1%) were slightly more often first-line biologicals in academic than in nonacademic centres ($P = 0.0096$). The choice of first-line treatment in academic vs. nonacademic centres, classified by specific disease phenotype, is shown in Fig. 1.

Intravenous TNF-alpha inhibitors were slightly less often started as first-line treatment than subcutaneous

Table 2. Number of prescriptions (treatment episodes) of biologicals by drug class in academic vs. nonacademic inflammatory bowel disease centres

	Overall	Academic	Nonacademic	*P*-value
All	2782	2499	283	0.949
Ustekinumab	459 (16%)	414 (17%)	45 (16%)	
Vedolizumab	654 (24%)	588 (24%)	66 (23%)	
TNF-alpha inhibitors	1669 (60%)	1497 (60%)	172 (61%)	

Table 3. Number of patients with ongoing biological treatment by drug class in academic vs. nonacademic inflammatory bowel disease centres

	Overall	Academic	Nonacademic	*P*-value
All	1515	1307	208	0.041
Ustekinumab	360 (24%)	322 (25%)	38 (18%)	
Vedolizumab	412 (27%)	360 (28%)	52 (25%)	
TNF-alpha inhibitors	743 (49%)	625 (48%)	118 (57%)	

Table 4. Number of patients with ongoing biological treatment by drug class in academic vs. nonacademic inflammatory bowel disease centres (Crohn's disease)

	Overall	Academic	Nonacademic	*P*-value
All	942	816	126	0.004
Ustekinumab	266 (28.2%)	243 (29.8%)	23 (18.3%)	
Vedolizumab	160 (17.0%)	143 (17.4%)	17 (13.5%)	
TNF-alpha inhibitors	516 (54.8%)	430 (52.7%)	86 (68.2%)	

Table 5. Number of patients with ongoing biological treatment by drug class in academic vs. nonacademic inflammatory bowel disease centres (ulcerative colitis)

	Overall	Academic	Nonacademic	*P*-value
All	531	455	76	0.759
Ustekinumab	83 (15.6%)	69 (15.2%)	14 (18.4%)	
Vedolizumab	234 (44.1%)	201 (44.2%)	33 (43.4%)	
TNF-alpha inhibitors	214 (45.4%)	185 (40.6%)	29 (38.2%)	

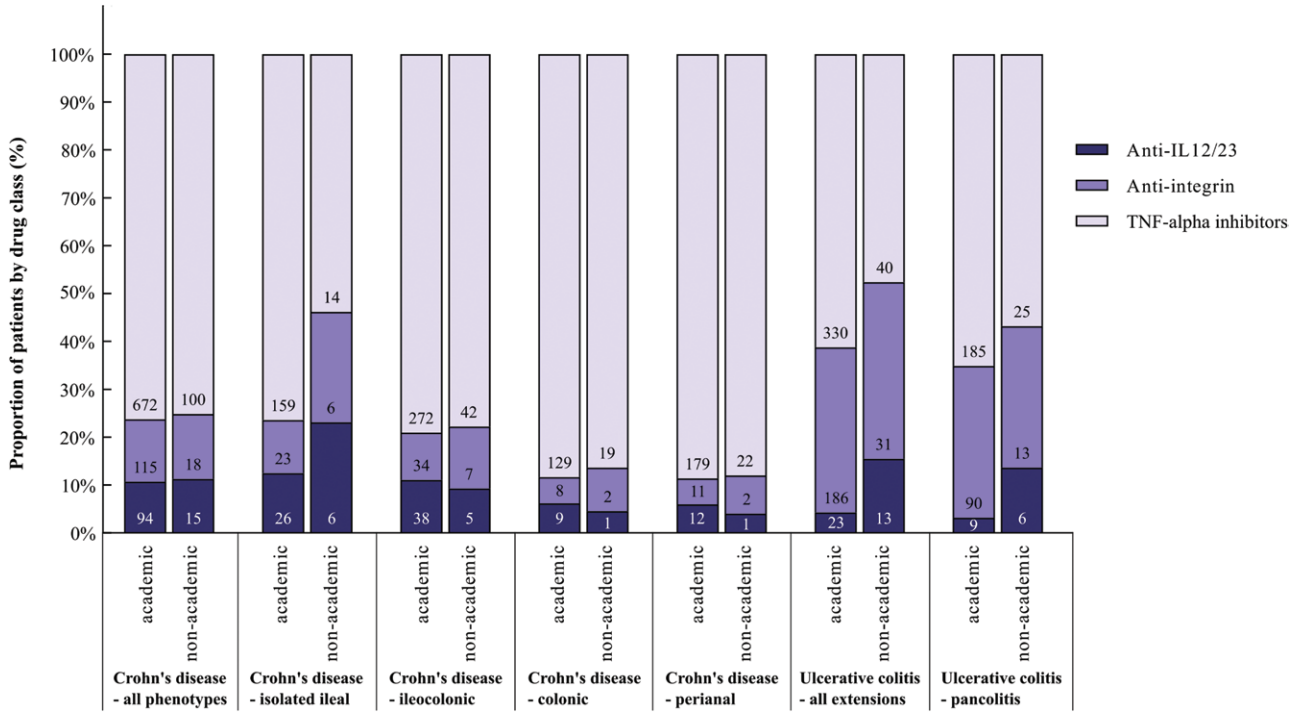

Fig. 1. Choice of first-line biological treatment in academic vs. nonacademic centres for specific phenotypes of inflammatory bowel disease.

TNF-alpha inhibitors in academic compared to nonacademic centres (534/1025 (52.1%) vs. 91/143 (63.6%), P = 0.01). This difference was driven mainly by CD as intravenous TNF-alpha inhibitors were chosen in 311/672 (46.3%) patients in academic centres compared to 60/100 (60.0%) patients in nonacademic centres (P = 0.01). In UC this difference was not observed as intravenous TNF-alpha inhibitors were chosen in 213/330 (64.5%) patients in academic compared to 29/40 (72.5%) patients in nonacademic centres (P = 0.318).

Discussion

The burden of IBD has increased during the last decade to the extent that precludes the management of these patients only in highly specialised IBD academic centres. Many patients therefore have to be treated outside specialised academic settings. However, it is reassuring that our analysis of the nationwide Slovenian IBD registry confirmed that IBD patients received similar biological treatments in academic and nonacademic medical centres. We observed only slight differences in the choice of first-line biologicals with less use of TNF-alpha inhibitors for CD in academic settings but not for UC. In the last 2 years, we have witnessed a decrease in time from diagnosis to the introduction of biologics both in academic and nonacademic IBD centres. Our data thus suggest that IBD can also be effectively managed outside academic settings, provided that continuous support is offered by academic teams. This is an important clinical message that could guide national

strategies for many countries with a rapidly increasing burden of IBD.

The disease phenotype of IBD was similar in academic and nonacademic centres, with roughly equal proportions of CD and UC patients. Similar results were also observed for disease location, as the proportions of ileocolonic CD, isolated ileum CD and perianal CD were similar in both academic and nonacademic centres and comparable with those reported by others [6,7–10]. Additionally, the proportion of UC patients with pancolitis in our study was in line with other reports [6,9,10]. The same was observed for the proportion of patients with perianal fistulizing disease (18.8%) in our study, as this was similar to that reported by others [11–14]. The added value of our study is that we observed that the proportion of perianal fistulizing disease patients was similar in academic and nonacademic centres, suggesting that these patients are also successfully managed outside highly specialised teams. However, we did not have data on combined immunosuppression or the rate of dose optimisation for these patients. Nevertheless, we believe that continuous support offered by the two types of academic centres allows efficient treatment of these patients by community gastroenterologists outside academic medical centres in Slovenia.

The demographics of patients treated at academic and nonacademic medical centres were similar. The only difference was that patients were 5 years younger at diagnosis of CD in academic centres. Our explanation for this is that perhaps younger patients move more easily to larger cities than older patients, perhaps due to enrolment in schools and employment opportunities. However, we did not specifically investigate this, and there are no published data on similar comparisons in the literature.

Treatment approaches with biological drugs were generally in line with those reported elsewhere [15]. Approximately half of the patients were treated with TNF-alpha inhibitors, and the others were treated with ustekinumab or vedolizumab. Similarly, as reported by others, ustekinumab was more often used in CD and vedolizumab in UC [16,17]. Our main observation here was that in academic centres, TNF-alpha inhibitors were slightly less often a first-line biological for CD than in nonacademic centres. Consequently, the proportion of patients with ongoing ustekinumab treatment was slightly higher (approximately 10%) in academic centres than in nonacademic centres. Interestingly, in line with this is a recent report in which adoption of ustekinumab was higher in high-volume urban facilities than in rural facilities and in facilities with greater teamwork [18]. Despite this difference being small, it could still be relevant due to the more favourable safety profiles of ustekinumab compared to TNF-alpha inhibitors with comparable efficacy demonstrated recently [19]. However, time to initiation of biologicals from diagnosis of IBD was similar in both academic and nonacademic medical centres, further indicating that patients are approached similarly in both settings. An interesting observation was also that first-line TNF-inhibitor was more often subcutaneous in academic centres, but intravenous in nonacademic centres in CD. This might be due to higher local availability for infusions in lower volume nonacademic centres.

In general, the proportion of vedolizumab-treated patients with CD was low in both academic and nonacademic centres, despite the documented efficacy for healing different bowel segments, including the ileum [20]. Tools such as a clinical decision support tool (CDST) could perhaps assist in decision-making in such cases in the future [21]. Such scoring systems perhaps would be of more value for nonacademic centres where the proportion of CD patients treated with vedolizumab is particularly low. The proportion of UC patients treated with vedolizumab was similar and high in both academic and nonacademic settings. Nevertheless, the use of TNF inhibitors was high among patients with UC. This can be at least partly explained by the fact that before 2019 in Slovenia, vedolizumab and ustekinumab were reserved for second-line treatment after TNF-alpha inhibitors had failed.

We acknowledge some important limitations of our report. Not all patients with IBD in Slovenia were entered into the UR-CARE Registry at the time of data extraction. Additionally, most centres contributed to the registry by first entering patients treated with biologicals at this early stage; thus, we were not able to compare the proportion of patients treated with biologicals vs. conventional drugs in different centres. However, since the disease phenotypes of biologically treated patients were similar in academic and nonacademic centres, we believe that patient selection for biologicals was similar in both settings. In line with this is also the similar time from diagnosis to initiation of first biologicals in both settings. We also failed to analyse treatment outcomes in academic vs. nonacademic centres, but for IBD, this difference might only be evident after prolonged periods [22]. Because of this, we will be able to assess potential differences in outcomes only a few years after launch of the registry in Slovenia. We also did not have data on the dose optimisation of biologicals and thus were unable to compare this aspect of treatment in both settings. Although the incidence of extraintestinal manifestations in our cohort was in line with those reported by others [23,24], we cannot exclude that at this early stage for the UR-CARE Registry in Slovenia, data capture was insufficient for extraintestinal manifestations; thus, we might have underestimated its true incidence. Additionally, due to the low number of specific extraintestinal manifestations, we were unable to perform more focussed analyses. It should also be acknowledged that in our country two multidisciplinary IBD teams in both academic centres support local hospitals. Thus, our findings cannot be generalised if such support is not provided.

In conclusion, this analysis of nationwide data indicated that IBD patients receive similar biological treatments early in the course of the disease in academic and nonacademic IBD centres. This is a reassuring message for patients and physicians, as it indicates that IBD can be successfully managed outside highly specialised high-volume academic settings. This finding has important implications for stakeholders, as it suggests that decentralisation of IBD care is a valid approach to cope with the increasing prevalence of IBD.

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KT, DŠ, and DD conceptualised the study, collected the data, performed the analysis and wrote the manuscript. All authors contributed to data collection. All authors critically reviewed and revised the manuscript, and all authors approved the final manuscript as submitted. Guarantor of the article: David Drobne.

The authors confirm that the data supporting the findings of this study are available within the article [and/or] its supplementary materials.

Conflicts of interest

KT has served as a speaker, consultant, and/or advisory board member for Pfizer, Abbvie, and Krka. JH has served as a consultant for Abbvie, Alimentiv Inc., Janssen, and Takeda. UK has served as a speaker, consultant, and/or advisory board member for MSD, Takeda, Medtronic, Zaloker & Zaloker, Abbot, and Abbvie. GN has served as a speaker, consultant, and/or advisory board member for Takeda in Ethicon. RŠ has served as a speaker, consultant, and/or advisory board member for Takeda, Abbvie, Lek, Pfizer, and Janssen. MŽ has served as a speaker, consultant, and/or advisory board member for Abbvie. JB has served as a speaker, consultant, and/or advisory board member for Abbvie, Takeda, Pfizer, Janssen, Viatris, Lek, and Krka. AO has served as a speaker, consultant, and/or advisory board member for MSD, Abbvie, Takeda, Pfizer, Janssen, Krka, Oktal Pharma, Novartis, Amgen, Biogen, Lek, Abbott, Mediasi, Sobi, dr Falk Pharma, and Carso Pharm. CPD has served as a speaker, consultant, and/or advisory board member for MSD, Abbvie, Takeda, Pfizer, and Janssen. TM has served as a speaker, consultant, and/or advisory board member for MSD, Abbvie, Takeda, Krka, Janssen, Amgen, and Pfizer. NK has served as a speaker, consultant, and/or advisory board member for Lek, Krka, Abbvie, Sobi, dr Falk Pharma, Janssen, and Ferring. AZ has served as a speaker, consultant, and/or advisory board member for Abbvie, Takeda, Pfizer, Ferring, Janssen, Krka, Amgen, Biogen, Lek, Sobi, and dr Falk Pharma. NJB has served as a speaker, consultant, and/or advisory board member for Amgen, Pfizer, Janssen, Abbvie, and Lek. NS has served as a speaker, consultant, and/or advisory board member for AbbVie, Takeda, Janssen, Pfizer, Oktal Pharma, Novartis, Sobi, Amgen, Biogen, and MSD. GN has served as a speaker, consultant, and/or advisory board member for Abbvie, Takeda, Pfizer, Janssen, Oktal Pharma, Sobi, Krka, Sandoz, and Biogen. TK has served as a speaker, consultant, and/or advisory board member for Takeda, MSD, Abbvie, Janssen, Ferring, and Abbvie. BŠ has served as a speaker, consultant, and/or advisory board member for MSD, Abbvie, Takeda, Pfizer, and Janssen. DD has served as a speaker, consultant, and/or advisory board member for MSD, Abbvie, Takeda, Pfizer, Janssen, Krka, Eli Lilly, Oktal Pharma, Roche, Novartis, Amgen, and Lek. For the remaining authors, there are no conflicts of interest.

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