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Original Article

Introduction of Subcutaneous Infliximab CT-P13 and Vedolizumab in Clinical Practice: A Multi-Stakeholder Position Statement Highlighting the Need for Post-Marketing Studies

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Abstract

Background and Aims: Although subcutaneous formulations of infliximab CT-P13 and vedolizumab are registered for treating moderate-to-severe inflammatory bowel disease [IBD], many questions on their use remain unanswered. We set up a multi-stakeholder initiative resulting in a position statement.

Methods: Based on publicly available data, statements on subcutaneous infliximab and vedolizumab were developed and reviewed by 45 Belgian IBD physicians in a three-round modified Delphi process. During a consensus meeting, input from 16 IBD patients, nine IBD nurses and two clinical pharmacologists was provided and statements were further discussed, modified and scored. Statements achieving agreement by at least 70% of the IBD physicians were accepted.

Results: The Delphi process resulted in 79 agreed statements. In patients initiating intravenous therapy, IBD physicians would only consider switching to subcutaneous formulations in patients achieving both clinical and biological response [for Crohn's disease] or both clinical and endoscopic response [for ulcerative colitis]. For patients under maintenance therapy, switching to subcutaneous formulations was only considered in those achieving both clinical and endoscopic response while receiving standard dosing of infliximab or vedolizumab. While awaiting more scientific data, IBD physicians should consider weekly subcutaneous injections or switching back to an intravenous formulation in case of loss of response. Finally, switching to a subcutaneous formulation should always be a shared decision.

Conclusions: All stakeholders welcomed subcutaneous infliximab and vedolizumab. However, more scientific data are needed to select the right patients and timing for switching to these newer formulations, and to explore the optimal strategy in case of loss of response.

Key Words: Subcutaneous; biological; switching

1. Introduction

Both ulcerative colitis [UC] and Crohn's disease [CD] are chronic inflammatory conditions of the gastrointestinal tract that often require immunomodulatory therapy.[1,2] The introduction of biological therapies led to a revolution in the management of these inflammatory bowel diseases [IBD] and introduced new treatment targets such as steroid-free clinical remission and endoscopic remission.[3] In the long term, achieving endoscopic remission is associated with relapse-, hospitalization- and surgery-free survival as well as increased quality of life.[4] However, current medical therapies do not provide a definite cure of IBD, and long-term maintenance therapy is often indispensable.

As personalized medicine is not yet available in IBD, the choice between different treatment modalities is often the result of a shared decision-making process.[5] In such a process, not only are reimbursement criteria and data on safety and efficacy considered, but also the patient's preference. In a pivotal Swiss survey including 100 patients with CD naïve for anti-tumour necrosis factor [anti-TNF], patients preferred subcutaneous over intravenous therapy.[6] Furthermore, the patients' decision in selecting a specific anti-TNF drug was mainly influenced by the ease of use of the specific anti-TNF agent. Since patients are increasingly involved in treatment decisions, the information they receive

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should be understandable, transparent, individualized and supported by audio-visual material.[7]

When selecting a drug, patients should not only consider how the mode of administration—intravenous in a hospital setting, or [self-]injection or oral intake at home—will influence their quality of life during the induction period while having active disease, but also during long-term maintenance while being in full clinical remission. In the current IBD treatment armamentarium, both infliximab and vedolizumab were administered exclusively intravenously, creating a specific burden for the patient with an active lifestyle. However, new subcutaneous formulations of both infliximab CT-P13 and vedolizumab have recently become available.[8–11]

In a phase III study in patients with rheumatoid arthritis, subcutaneous infliximab CT-P13 was shown to be as efficacious as intravenous infliximab CT-P13.[12] Although data with subcutaneous infliximab CT-P13 in IBD are limited to exploratory phase I studies, they suggest a similar outcome in patients who switched to subcutaneous infliximab CT-P13 120 mg every other week from week 6 onwards.[13] Of note, infliximab trough concentrations were higher with subcutaneous than with intravenous infliximab CT-P13, but the overall drug exposure [mean area under the curve] was similar.[14] Safety was comparable between groups.

In VISIBLE 1, patients with moderate-to-severe UC who showed clinical response to intravenous vedolizumab 300 mg at weeks 0 and 2 were randomized to maintenance therapy with subcutaneous vedolizumab 108 mg every 2 weeks, intravenous vedolizumab 300 mg every 8 weeks or placebo.[15] At week 52, significantly more patients randomized to subcutaneous vedolizumab achieved clinical remission compared to patients randomized to placebo. Although this trial was not powered to compare subcutaneous with intravenous vedolizumab, clinical remission rates were similar. In VISIBLE 2, patients with moderate-to-severe CD showing clinical response to intravenous vedolizumab 300 mg at weeks 0 and 2 were randomly assigned to maintenance therapy with subcutaneous vedolizumab 108 mg every 2 weeks, or placebo.[16] However, in contrast to VISIBLE 1, no additional group with maintenance intravenous vedolizumab therapy was included. At week 52, more patients randomized to subcutaneous vedolizumab achieved clinical remission compared to patients randomized to placebo. In both VISIBLE 1 and VISIBLE 2, safety was comparable between subcutaneous vedolizumab and placebo.

Although the subcutaneous formulations of both infliximab CT-P13 and vedolizumab are registered by the European Medicines Agency, many questions on their use in daily clinical practice remain unanswered. Therefore, the Belgian IBD Research and Development [BIRD] group set up a three-round modified Delphi process involving IBD physician experts, IBD patients, IBD nurses, clinical pharmacologists and a methodologist in order to reach a Belgian position statement. This initiative was called DIAMOND, a birD posItion on the use of subcutAneous inflixiMab and vedOlizumab in patieNts with ibD.

2. Methods

To establish a consensus on the use of subcutaneous infliximab CT-P13 and vedolizumab, a modified Delphi process was established.[17] This three-round modified Delphi process included a scientific review of all publicly available information, two voting rounds in the format of an online survey and an online consensus meeting including a third live voting round. In parallel, focus groups were set up to allow a multi-stakeholder consensus and to identify areas of importance to IBD patients, IBD nurses, and clinical pharmacologists. The SurveyMonkey platform [SurveyMonkey Inc.] was used to send out all online surveys. The meeting platform Zoom [Zoom Video Communications Inc.] was used to organize the consensus meeting with integrated poll features.

2.1. Scientific review

After an open call to all members of BIRD [representing almost the whole Belgian IBD community], a Core Panel was established including four IBD physician experts, one IBD nurse, one clinical pharmacologist and one methodologist [Supplementary Table 1]. An electronic literature search was conducted on PubMed using the following combination of keywords: ['Crohn' or 'ulcerative colitis' or 'inflammatory bowel'] and ['infliximab' or 'vedolizumab'] and ['subcutaneous']. No start date limit was used and the search was performed until May 2021. A manual search was performed for abstracts presented in the past 5 years at the Digestive Disease Week, the United European Gastroenterology Week, and the congress of the European Crohn's and Colitis Organisation. The core panellists reviewed all publicly available data [full papers, congress abstracts and regulatory documents] on subcutaneous infliximab CT-P13 and vedolizumab. Where needed, additional information was requested from Celltrion and Takeda. Based on these data, four neutral informative videos were recorded to summarize the available scientific data: one for subcutaneous infliximab CT-P13 and one for subcutaneous vedolizumab, both in French and in Dutch [Supplementary Data]. Throughout the whole Delphi process, these videos were available to all participants. Based on the available data, the Core Panel formulated 41 preliminary statements on infliximab and 40 on vedolizumab.

A pilot group consisting of eight IBD physician experts [Supplementary Table 1] was established to review the informative videos, the SurveyMonkey platform and the preliminary statements that were formulated by the Core Panel. Based on their comments, the preliminary list of statements was revised and supplemented, resulting in 55 statements on infliximab and 54 on vedolizumab [Supplementary Table 2]. This revised list of statements was fed into the first Delphi round in the format of an online survey.

2.2. Delphi round 1, voting by the Physician Expert Panel

In total, 45 out of 112 invited IBD physician experts (42.2% working in an academic centre, median [interquartile range] years of practice as medical doctor 19 [11–26] years) agreed to participate as expert panellist in the three-round modified Delphi exercise [Supplementary Table 1]. After having viewed the informative videos, all 45 IBD experts were requested to anonymously score the 55 and 54 statements on infliximab and vedolizumab, respectively, and this on a Likert scale from 1 [completely disagree] to 10 [completely agree]. They were also requested to provide feedback on the available statements and to suggest missing items. Based on their input, the Core Panel composed an additional set of ten statements and nine multiple-choice questions on infliximab, and seven statements and nine multiple-choice questions on vedolizumab [Supplementary Table 2]. The multiple-choice questions were included as a basis to formulate proper state-

ments in the second Delphi round. These additional items were consequently sent out to the Expert Panel for their anonymous scoring.

2.3. Delphi round 2, voting by the Physician Expert Panel

Considering the results of and the comments to the first Delphi round, the Core Panel rephrased some of the statements to feed into the second Delphi round with the purpose of growing towards a consensus. This resulted in 49 statements on infliximab and 46 statements on vedolizumab [Supplementary Table 3]. This adapted list was again sent out to the Expert Panel to anonymously score on the same 10-point Likert scale in a second voting round. This second online survey was preceded by a report showing the anonymous results for each statement of the first voting round (median, mean [standard deviation] and percentage of agreement [score 7–10] or disagreement [score 1–4] by at least 70% of the IBD experts) and modifications that had been made to the statements.

2.4. Focus groups

The same updated set of 49 statements on infliximab and 46 statements on vedolizumab was shared with a Focus Group of nine IBD nurses [Supplementary Table 1]. Additionally, 12 statements related to pharmacokinetics and pharmacodynamics [PK/PD] were shared with a Focus Group of two clinical pharmacologists [Supplementary Table 1]. Both Focus Groups were asked to score all received statements anonymously on the same 10-point Likert scale in the form of an online survey.

A third Focus Group consisted of 16 IBD patients who were all [previously] exposed to biological therapy and were selected by the two existing Belgian IBD patient organizations [Supplementary Table 1]. Patients participated in an online group interview [either in French or in Dutch] after having reviewed the introduction videos and the set of statements rephrased for the second Delphi round. In the group interviews, an IBD physician expert and an IBD nurse clarified any remaining questions, and evaluated concerns and contemplations of the IBD patients on the use of these subcutaneous formulations. Furthermore, the participating IBD patients were given the possibility to suggest complementary statements. In addition, patients were asked to anonymously score five general statements about their potential fears and drivers for switching to subcutaneous formulations on a 10-point Likert scale in the form of an online survey, both before and after the group interview.

2.5. Delphi round 3, final vote by the Physician Expert Panel during an online consensus meeting

Prior to the online consensus meeting, a report was prepared by the Core Panel and shared with the physician experts. This report showed the anonymous results for each statement of the second voting round separately for the IBD experts, IBD nurses and clinical pharmacologists (median, mean [standard deviation] and percentage of agreement [score 7–10] by at least 70% of the respective group). Furthermore, statements were subdivided into three distinct categories. Category 1 consisted of statements that achieved an agreement [score 7–10] by 80% or more of the IBD experts, and did not have to be discussed during the consensus meeting. Category 2 consisted of statements that achieved an agreement [score 7–10] by 60–80% of the IBD experts and required additional discussion and voting during the consensus meeting. Category 3 consisted of statements that received an agreement [score 7–10] by less than 60% of the IBD experts, and did not have to be discussed during the consensus meeting. Prior to the consensus meeting, all Core and Expert panellists could indicate additional statements from categories 1 and 3 requiring further discussion during the consensus meeting. Eventually, two, 35 and four statements from, respectively, categories 1, 2 and 3 were selected for further discussion [Supplementary Table 4].

During the consensus meeting, the results of the selected statements were briefly presented by a moderator, and subsequently discussed by 41 participating IBD physician experts, one IBD nurse, one clinical pharmacologist and one methodologist. The clinical pharmacologist provided more data on the PK/PD profiles linked to switching from an intravenous to a subcutaneous formulation [Supplementary Figure 1]. When appropriate and only in case of general agreement, final modifications were made to some of the statements. Each discussion was immediately followed by a final and live anonymous voting round that was terminated when at least 85% of the IBD experts participating in the consensus meeting had submitted their score. Statements that achieved an agreement [score 7–10] by at least 70% of the IBD physician experts earlier or in the final voting during the consensus meeting were accepted.

2.6. Ethical considerations

The DIAMOND protocol was reviewed and approved by the Ethical Committee of the University Hospitals Leuven [S65467]. As all scores were submitted anonymously and patients participated as advisors, no informed consent was required. However, all participants [including the patients] received an informative letter prior to participation in this modified Delphi process.

3. Results

3.1. Results of Delphi rounds 1 and 2

Results of the first Delphi round are detailed in Supplementary Table 2. As shown in Figure 1, the majority of the IBD experts would wait longer than 6 weeks before considering a switch to subcutaneous therapy in patients initiating infliximab or vedolizumab, both for CD and for UC. In patients already on maintenance intravenous therapy, the suggested interval between the last intravenous and the first subcutaneous administration of both agents differed significantly from 2 to 8 weeks [Figure 2].

The results of the second Delphi round [including not only the 45 IBD physician experts, but also the nine IBD nurses and two clinical pharmacologists] are detailed in Supplementary Table 3.

During the group interviews with 16 IBD patients, several patients highlighted the influence of a potential switch to subcutaneous therapy on their quality of life. They also specified the need for a proper discussion of their fears and concerns with the IBD team, not only before but also [long] after switching. Based on the input gathered during these patient interviews, the Core Panel added two additional statements on infliximab and two additional statements on vedolizumab to be scored by the Expert Panel in the third Delphi round [Supplementary Table 4]. The results of the short patient survey on potential fears and drivers for switching to subcutaneous formulations are shown in Supplementary Table 5.

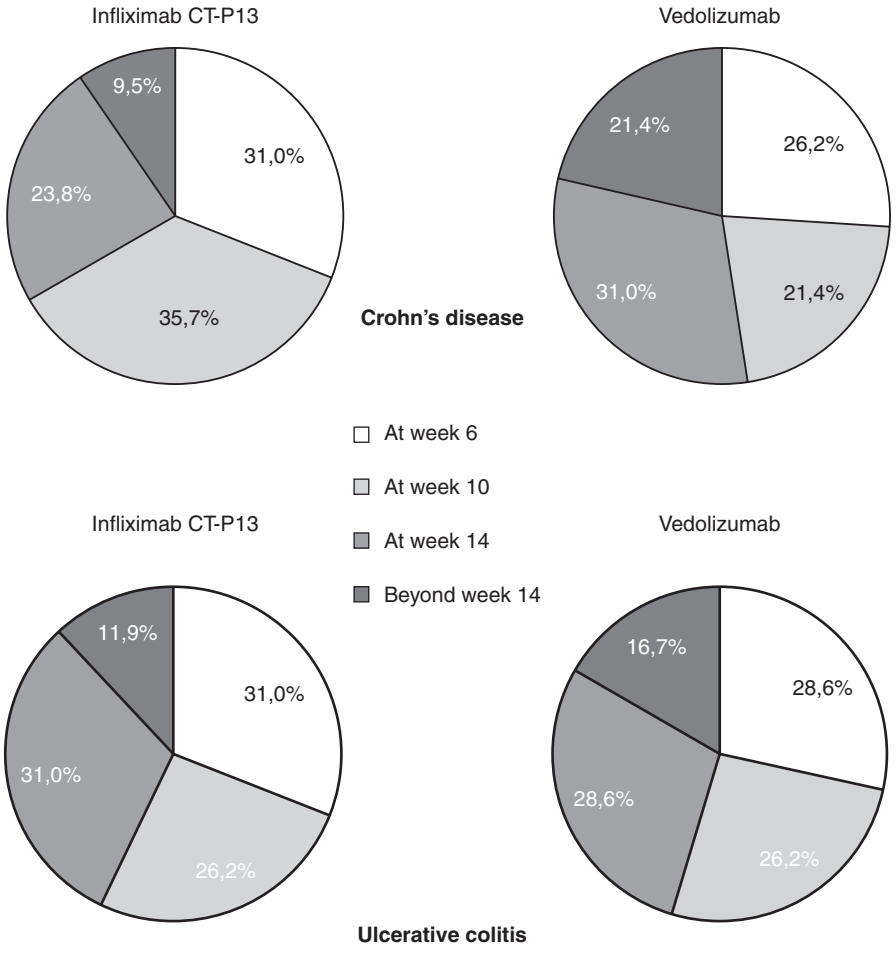

Figure 1. Time to consider first subcutaneous therapy after initiating infliximab or vedolizumab. The provided data are the result of four multiple-choice questions during the first Delphi round among 45 IBD physician experts.

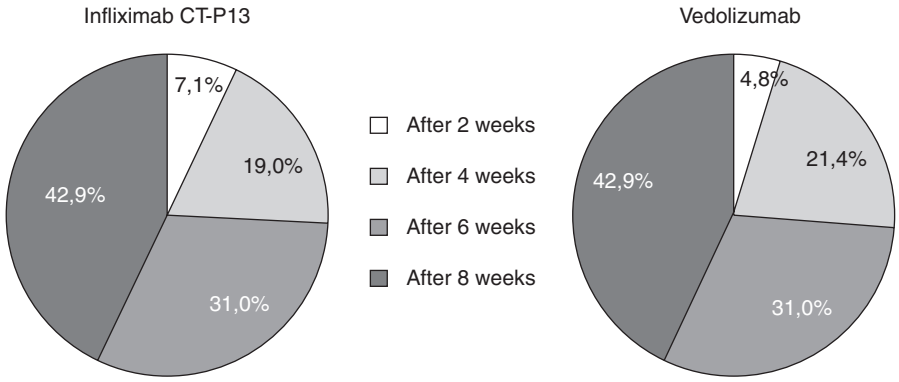

Figure 2. Interval between last intravenous and first subcutaneous administration of infliximab or vedolizumab. The provided data are the result of two multiple-choice questions during the first Delphi round among 45 IBD physician experts. After discussing the PK/PD profiles during the DIAMOND Consensus Meeting, 86.11% and 72.22% of the IBD physician experts would provide the first subcutaneous administration of, respectively, infliximab CT-P13 and vedolizumab earlier than 8 weeks after the last intravenous administration.

3.2. Results of the consensus meeting and the DIAMOND Platform

The consensus meeting was attended by 41 of the 45 IBD physician experts who participated in the first two Delphi rounds [91%]. The online discussion led to 15 modified and eight additional statements. The results of the Consensus Meeting are shown in Supplementary Table 4.

Based on the predefined criteria, the DIAMOND three-round modified Delphi process resulted in 42 agreed statements on subcutaneous infliximab CT-P13 and 37 agreed statements on subcutaneous vedolizumab [Table 1]. The main findings are as follows.

- In patients with CD, more scientific data are needed on switching to subcutaneous formulations when initiating infliximab or vedolizumab, as well as in patients under intravenous maintenance therapy with these agents.

Table 1. Final set of statements agreed by the DIAMOND Expert Panel

Statement	Round	Agree*	Statement	Round	Agree*
Initial considerations					
I01. Quality of life should be a main point of discussion with each individual patient when considering a switch from an intravenous formulation of infliximab to subcutaneous infliximab CT-P13.	3	97.22%	V01. Quality of life should be a main point of discussion with each individual patient when considering a switch from intravenous to subcutaneous vedolizumab.	3	94.44%
I02. When considering a switch from an intravenous formulation of infliximab to subcutaneous infliximab CT-P13, the local IBD team/specialist should be available to discuss potential patients' fears and concerns, and this not only before but also after switching.	3	100.00%	V02. When considering a switch from intravenous to subcutaneous vedolizumab, the local IBD team/specialist should be available to discuss potential patients' fears and concerns, and this not only before but also after switching.	3	100.00%
I03. The patient should only be offered the option to switch from an intravenous formulation of infliximab to subcutaneous infliximab CT-P13 if all reimbursement criteria are met and the treating gastroenterologist considers the patient to be a good candidate for such a switch.	2	100.00%	V03. The patient should only be offered the option to switch from intravenous to subcutaneous vedolizumab if all reimbursement criteria are met and the treating gastroenterologist considers the patient to be a good candidate for such a switch.	2	100.00%
I04. In the setting that an IBD nurse is available, this IBD nurse has a crucial role in explaining, guiding and following a potential switch to subcutaneous infliximab CT-P13.	2	100.00%	V04. In the setting that an IBD nurse is available, this IBD nurse has a crucial role in explaining, guiding and following a potential switch to subcutaneous vedolizumab.	2	100.00%
I05. Before considering a switch to subcutaneous infliximab CT-P13, the importance of compliance to medical therapy should be stressed with the patient.	2	100.00%	V05. Before considering a switch to subcutaneous vedolizumab, the importance of compliance to medical therapy should be stressed with the patient.	2	100.00%
I06. In patients not familiar with subcutaneous administrations, the first subcutaneous injection of infliximab CT-P13 should be administered under supervision of a physician or [IBD] nurse.	2	100.00%	V06. In patients not familiar with subcutaneous administrations, the first subcutaneous injection of vedolizumab should be administered under supervision of a physician or [IBD] nurse.	2	100.00%
I07. The introduction of subcutaneous infliximab CT-P13 will increase the workload for the IBD nurse.	2	93.18%	V07. The introduction of subcutaneous vedolizumab will increase the workload for the IBD nurse.	2	93.33%
I08. The introduction of subcutaneous infliximab CT-P13 will have an influence on the organization and the daily workload of the infusion unit.	2	97.73%	V08. The introduction of subcutaneous vedolizumab will have an influence on the organization and the daily workload of the infusion unit.	2	97.78%
I09. The introduction of subcutaneous infliximab CT-P13 will have a negative effect on hospital finances.	3	88.57%	V09. Not applicable		
General criteria for switching					
I10. Although data are only available for switching from intravenous infliximab CT-P13 to subcutaneous infliximab CT-P13 [Remsima®], these data can be extrapolated for switching from all intravenous formulations of infliximab [including Flixabi®, Inflectra®, Remicade®, and Zessly®] to subcutaneous infliximab CT-P13 [Remsima®].	2	93.18%	V10. Not applicable		
I11. Switching from maintenance therapy with an intravenous formulation of infliximab to subcutaneous infliximab CT-P13 can only be considered in patients who are receiving a dose of 5 mg/kg infliximab with an interval of at least 8 weeks.	2	90.91%	V11. Switching from maintenance therapy with intravenous to subcutaneous vedolizumab can only be considered in patients who are receiving a dose of 300 mg vedolizumab with an interval of at least 8 weeks.	2	91.11%
I12. In patients under 8-weekly maintenance therapy with an intravenous formulation of infliximab who are willing to switch to subcutaneous infliximab CT-P13, the first subcutaneous administration would best be foreseen earlier than 8 weeks after the last intravenous dose.	3	86.11%	V12. In patients under 8-weekly maintenance therapy with intravenous vedolizumab who are willing to switch to subcutaneous vedolizumab, the first subcutaneous administration would best be foreseen earlier than 8 weeks after the last intravenous dose.	3	72.22%

Table 1. Continued

Statement	Round	Agree*	Statement	Round	Agree*
Therapeutic drug monitoring					
I13. Therapeutic drug monitoring should be performed before switching from an intravenous formulation of infliximab to subcutaneous infliximab CT-P13.	2	84.09%	V13. Not applicable		
I14. There is a role for reactive therapeutic drug monitoring in patients losing response under maintenance therapy with subcutaneous infliximab CT-P13.	2	88.64%	V14. There is a role for reactive therapeutic drug monitoring in patients losing response under maintenance therapy with subcutaneous vedolizumab.	3	75.61%
I15. Not applicable			V15. There is NO role for proactive therapeutic drug monitoring in patients in clinical remission under maintenance therapy with subcutaneous vedolizumab.	3	81.58%
I16. The optimal infliximab trough concentration for patients under maintenance therapy with subcutaneous infliximab CT-P13 should still be determined.	3	87.50%	V16. The optimal vedolizumab trough concentration for patients under maintenance therapy with subcutaneous vedolizumab should still be determined.	2	95.56%
I17. It is not the trough concentration that drives the therapeutic response to subcutaneous infliximab CT-P13, but the overall exposure [area under the concentration-–time curve].	3	72.97%	V17. It is not the trough concentration that drives the therapeutic response to subcutaneous vedolizumab, but the overall exposure [area under the concentration–time curve].	3	80.00%
I18. Based on the scientific data currently available, one cannot conclude that subcutaneous infliximab CT-P13 is less immunogenic than an intravenous formulation of infliximab.	2	84.09%	V18. Based on the scientific data currently available, one cannot conclude that subcutaneous vedolizumab is less immunogenic than intravenous vedolizumab.	3	75.68%
Combination therapy					
I19. Combination therapy with a thiopurine or methotrexate is recommended during at least the first 6 months of infliximab therapy, even after a switch to subcutaneous infliximab CT-P13.	2	81.82%	V19. Combination therapy with a thiopurine or methotrexate is NOT recommended during the first 6 months of vedolizumab therapy, even after a switch to subcutaneous vedolizumab.	2	97.78%
Follow-up and optimization after switching					
I20. A first clinical evaluation after switching to subcutaneous infliximab CT-P13 [to check for efficacy, safety and compliance] is best foreseen within 8 weeks.	2	97.78%	V20. A first clinical evaluation after switching to subcutaneous vedolizumab [to check for efficacy, safety and compliance] is best foreseen within 8 weeks.	2	97.78%
I21. A clinical evaluation under maintenance therapy with subcutaneous infliximab CT-P13 [to check for efficacy, safety and compliance] is best foreseen every 4–6 months.	2	95.56%	V21. A clinical evaluation under maintenance therapy with subcutaneous vedolizumab [to check for efficacy, safety and compliance] is best foreseen every 4–6 months.	2	95.56%
I22. If a patient, who previously was in clinical remission under an intravenous formulation of infliximab, develops an objectified clinical relapse [with biological, endoscopic and/or radiological disease activity] under subcutaneous infliximab CT-P13, one could consider switching back to an intravenous formulation of infliximab.	3	97.30%	V22. If a patient, who previously was in clinical remission under intravenous vedolizumab, develops an objectified clinical relapse [with biological, endoscopic and/or radiological disease activity] under subcutaneous vedolizumab, one could consider switching back to intravenous vedolizumab.	3	97.30%
I23. If a patient, who previously was in clinical remission under an intravenous formulation of infliximab, develops an objectified clinical relapse [with biological, endoscopic and/or radiological disease activity] under subcutaneous infliximab CT-P13, one could consider to optimize to weekly injections of subcutaneous infliximab CT-P13.	2	84.44%	V23. If a patient, who previously was in clinical remission under intravenous vedolizumab, develops an objectified clinical relapse [with biological, endoscopic and/or radiological disease activity] under subcutaneous vedolizumab, one could consider to optimize to weekly injections of subcutaneous vedolizumab.	2	84.09%
I24. A patient in remission under maintenance therapy with subcutaneous infliximab CT-P13 should always be allowed to switch back to an intravenous formulation of infliximab at his/her own discretion.	3	94.59%	V24. A patient in remission under maintenance therapy with subcutaneous vedolizumab should always be allowed to switch back to intravenous vedolizumab at his/her own discretion.	3	94.59%

Table 1. Continued

Statement	Round	Agree*	Statement	Round	Agree*
I25. In patients switching back from subcutaneous infliximab CT-P13 [Remsima®] to an intravenous formulation, all intravenous formulations of infliximab could be considered [including Flixabi®, Inflectra®, Remicade® and Zessly®].	2	93.33%	V25. Not applicable		
I26. In patients who were in clinical remission under an intravenous formulation of infliximab, the optimal strategy in case of an objectified clinical relapse after switching to subcutaneous infliximab CT-P13 is currently unknown.	2	100.00%	V26. In patients who were in clinical remission under intravenous vedolizumab, the optimal strategy in case of an objectified clinical relapse after switching to subcutaneous vedolizumab is currently unknown.	2	93.33%
Crohn's disease					
I27. In a patient starting infliximab for Crohn's disease, the optimal timing of the first subcutaneous injection of infliximab CT-P13 should be decided case-by-case.	3	100.00%	V27. In a patient starting vedolizumab for Crohn's disease, the optimal timing of the first subcutaneous injection of vedolizumab should be decided case-by-case.	3	97.56%
I28. In a patient starting infliximab for Crohn's disease, switching from an intravenous formulation of infliximab to subcutaneous infliximab CT-P13 can only be considered in patients achieving clinical and biological response [based on C-reactive protein and/or faecal calprotectin].	3	97.44%	V28. In a patient starting vedolizumab for Crohn's disease, switching from intravenous to subcutaneous vedolizumab can only be considered in patients achieving clinical and biological response [based on C-reactive protein and/or faecal calprotectin].	3	94.87%
I29. In a patient under maintenance therapy with infliximab for Crohn's disease, switching from an intravenous formulation of infliximab to subcutaneous infliximab CT-P13 can only be considered in patients achieving clinical and endoscopic response.	3	91.67%	V29. In a patient under maintenance therapy with vedolizumab for Crohn's disease, switching from intravenous to subcutaneous vedolizumab can only be considered in patients achieving clinical and endoscopic response.	3	91.67%
I30. Patients with active perianal fistulizing Crohn's disease should NOT be offered a switch to subcutaneous infliximab CT-P13.	3	89.74%	V30. Patients with active perianal fistulizing Crohn's disease should NOT be offered a switch to subcutaneous vedolizumab.	2	88.89%
I31. Switching from an intravenous formulation of infliximab to subcutaneous infliximab CT-P13 can be considered in a patient with quiescent perianal fistulizing Crohn's disease.	3	86.11%	V31. Switching from intravenous to subcutaneous vedolizumab can be considered in a patient with quiescent perianal fistulizing Crohn's disease.	3	77.78%
I32. In my opinion, more data are needed on switching from an intravenous formulation of infliximab to subcutaneous infliximab CT-P13 in naïve patients with Crohn's disease initiating this therapy.	3	91.89%	V32. In my opinion, more data are needed on switching from intravenous to subcutaneous vedolizumab in naïve patients with Crohn's disease initiating this therapy.	3	94.59%
I33. In my opinion, more data are needed on switching from an intravenous formulation of infliximab to subcutaneous infliximab CT-P13 in patients with Crohn's disease under maintenance therapy.	3	89.74%	V33. In my opinion, more data are needed on switching from intravenous to subcutaneous vedolizumab in patients with Crohn's disease under maintenance therapy.	3	89.74%
I34. In general, the available scientific evidence is sufficient to consider switching to subcutaneous infliximab CT-P13 in at least a subset of my patients with Crohn's disease who achieved clinical response under an intravenous formulation of infliximab.	2	80.00%	V34. In general, the available scientific evidence is sufficient to consider switching to subcutaneous vedolizumab in at least a subset of my patients with Crohn's disease who achieved clinical response under intravenous vedolizumab.	2	86.67%
Ulcerative colitis					
I35. In a patient starting infliximab for ulcerative colitis, the optimal timing of the first subcutaneous injection of infliximab CT-P13 should be decided case-by-case.	3	97.56%	V35. In a patient starting vedolizumab for ulcerative colitis, the optimal timing of the first subcutaneous injection of vedolizumab should be decided case-by-case.	3	92.68%
I36. In a patient starting infliximab for ulcerative colitis, I would give the first subcutaneous injection from week 14 onwards [after at least three intravenous administrations at week 0, week 2 and week 6].	3	89.47%	V36. In a patient starting vedolizumab for ulcerative colitis, I would give the first subcutaneous injection from week 14 onwards [after at least three intravenous administrations at week 0, week 2 and week 6].	3	89.47%

Table 1. Continued

Statement	Round	Agree*	Statement	Round	Agree*
I37. In a patient starting infliximab for ulcerative colitis, switching from an intravenous formulation of infliximab to subcutaneous infliximab CT-P13 can only be considered in patients achieving clinical and endoscopic response.	3	97.44%	V37. In a patient starting vedolizumab for ulcerative colitis, switching from intravenous to subcutaneous vedolizumab can only be considered in patients achieving clinical and endoscopic response.	3	97.44%
I38. In a patient under maintenance therapy with infliximab for ulcerative colitis, switching from an intravenous formulation of infliximab to subcutaneous infliximab CT-P13 can only be considered in patients achieving clinical and endoscopic response.	3	97.14%	V38. In a patient under maintenance therapy with vedolizumab for ulcerative colitis, switching from intravenous to subcutaneous vedolizumab can only be considered in patients achieving clinical and endoscopic response.	3	97.14%
I39. Patients who initiated infliximab for acute severe [steroid-refractory] ulcerative colitis but are currently in sustained clinical remission with endoscopic improvement [Mayo 0 or 1] under an intravenous formulation of infliximab 5 mg/kg every 8 weeks could be offered a switch to subcutaneous infliximab CT-P13.	3	94.74%	V39. Not applicable		
I40. In my opinion, more data are needed on switching from an intravenous formulation of infliximab to subcutaneous infliximab CT-P13 in naïve patients with ulcerative colitis initiating this therapy.	3	89.47%	V40. Not applicable		
I41. In my opinion, more data are needed on switching from an intravenous formulation of infliximab to subcutaneous infliximab CT-P13 in patients with ulcerative colitis under maintenance therapy.	3	94.74%	V41. In my opinion, more data are needed on switching from intravenous to subcutaneous vedolizumab in patients with ulcerative colitis under maintenance therapy.	3	86.84%
I42. In general, the available scientific evidence is sufficient to consider switching to subcutaneous infliximab CT-P13 in at least a subset of my patients with ulcerative colitis who achieved clinical response under an intravenous formulation of infliximab.	2	88.64%	V42. In general, the available scientific evidence is sufficient to consider switching to subcutaneous vedolizumab in at least a subset of my patients with ulcerative colitis who achieved clinical response under intravenous vedolizumab.	2	93.33%

*The 'agree' percentage represents the percentage of the expert panellists scoring the statement 7–10 on a 10-point Likert scale in the corresponding round. Statements that received an agreement [score 7–10] by 80% or more of the IBD experts in the second Delphi round did not have to be discussed during the Consensus Meeting [third Delphi round].

- In patients with UC, more scientific data are needed on switching to subcutaneous therapy in patients initiating infliximab, as well as in patients under maintenance therapy with intravenous infliximab or vedolizumab.
- Switching to subcutaneous infliximab CT-P13 or vedolizumab should be a shared decision, with a crucial role for both the patient and the IBD nurse.
- In a patient starting biological therapy, the optimal timing of the first subcutaneous injection of infliximab CT-P13 or vedolizumab should be decided case-by-case. In a patient with CD, switching can only be considered in patients who achieved both clinical and biological response [based on C-reactive protein and/or faecal calprotectin]. In contrast, in a patient with UC, such a switch can only be considered in patients achieving both clinical and endoscopic response.
- In patients under maintenance intravenous biological therapy, switching to subcutaneous infliximab CT-P13 or vedolizumab can only be considered in patients who are receiving a dose of 5 mg/kg infliximab or a dose of 300 mg vedolizumab with an interval of at least 8 weeks. Furthermore, both for patients with CD and UC, switching to subcutaneous formulations can only be considered in patients who have achieved both clinical and endoscopic response. Based on the PK/PD profile, the first subcutaneous administration of infliximab CT-P13 or vedolizumab would best be foreseen earlier than 8 weeks after the last intravenous dose.
- In patients who were in clinical remission under intravenous therapy, the optimal strategy in case of an objectified clinical relapse after switching to a subcutaneous formulation is currently unknown. Both switching back to an intravenous formulation or optimization to weekly subcutaneous injections could be considered.
- Patients with active perianal fistulising CD should not be offered a switch to subcutaneous infliximab CT-P13 or subcutaneous vedolizumab.

4. Discussion

With the DIAMOND initiative, the BIRD group aimed to develop a position statement on the practical use of subcutaneous formulations of infliximab CT-P13 and vedolizumab in patients with IBD. As scientific data were often lacking,

the IBD experts identified some open research questions highlighting a need for further post-marketing research. As a consequence, the provided statements are based on expert opinion rather than scientific evidence, and this even more so for data on infliximab CT-P13 as data in IBD only come from two small phase I studies. However, to achieve a broad consensus, the DIAMOND three-round modified Delphi process not only involved 45 IBD physician experts, but also 16 IBD patients, nine IBD nurses, two clinical pharmacologists and a methodologist.

Although IBD experts considered switching to subcutaneous infliximab CT-P13 and vedolizumab in at least a subset of their patients with CD and UC, they all stressed the need for more supportive data. While data from VISIBLE 1 were regarded as adequate to indicate using a subcutaneous formulation in patients with UC initiating vedolizumab, IBD experts requested more data in patients with UC initiating infliximab, and patients with CD initiating infliximab or vedolizumab.[15]

Although in the pivotal trials the switch to subcutaneous therapy was already performed at week 6 after two intravenous administrations, less than one-third of the IBD physician experts would follow this strategy in their daily clinical practice, and expressed the need for a case-by-case decision.[14–16] In a patient with CD initiating therapy, they would only consider switching to subcutaneous infliximab CT-P13 or vedolizumab in patients when both clinical and biological response [based on C-reactive protein and/or faecal calprotectin] were achieved. Similarly, in a patient with UC, they would only consider switching to a subcutaneous formulation in case of both clinical and endoscopic response. These positions statements reflect the most recent STRIDE 2.0 guidelines.[18] However, they are also influenced by Belgian reimbursement criteria, which impose an endoscopic evaluation after induction therapy in patients with UC but not in CD. In CD, many experts would only perform an endoscopic evaluation 6–12 months after initiation of a biological. Furthermore, in Belgium faecal calprotectin is only reimbursed for patients with CD.

Data on switching from an intravenous to a subcutaneous formulation in patients under long-term maintenance intravenous therapy are scarce. This is remarkable, as this will be the most common scenario to consider the use of these subcutaneous formulations. Therefore, IBD experts expressed the need for more scientific data on switching to subcutaneous formulations of infliximab CT-P13 and vedolizumab in patients under maintenance intravenous therapy. At the start of the COVID-19 pandemic, some British hospitals switched all their IBD patients from intravenous to subcutaneous infliximab CT-P13. Real-world experience in Kettering and Liverpool, including 163 IBD patients, suggested that this switch was well tolerated, with only one patient discontinuing subcutaneous therapy due to antibody formation, and two patients switching back to intravenous therapy because of complicated perianal disease.[19] However, long-term efficacy data are missing. At this stage, Belgian IBD experts would only consider switching to subcutaneous infliximab CT-P13 or vedolizumab in patients receiving a dose of 5 mg/kg infliximab or a dose of 300 mg vedolizumab with an interval of at least 8 weeks. Furthermore, they would only consider such a switch in patients having demonstrated both clinical and endoscopic response, again reflecting the STRIDE 2.0 guidelines.[18] In addition, most IBD experts would be very cautious in switching to subcutaneous infliximab CT-P13 in patients who initiated infliximab for acute severe [steroid-refractory] UC. Belgian IBD experts do consider switching to subcutaneous formulations in patients with quiescent perianal fistulizing CD, as this was demonstrated to be efficacious in a recent cohort of 18 patients from Liverpool.[20] However, Belgian IBD experts would not consider such a switch in patients with active perianal fistulizing CD. This is probably driven by previous observations suggesting the need for higher serum levels [often requiring dose intensification] in order to achieve fistula healing.[21] Finally, studies should be conducted to come to any recommendation in children and adolescents.

Remarkably, the optimal interval between the last intravenous and first subcutaneous administration has not yet been explored. Based on the simulated PK profile of both agents, most IBD experts would actually foresee a first subcutaneous administration of infliximab CT-P13 or vedolizumab earlier than 8 weeks after the last intravenous dose. An interval of 8 weeks—as suggested in the phase I study with infliximab CT-P13—could indeed lead to subtherapeutic serum concentrations for several weeks [when taking subcutaneous serum levels as a reference], theoretically increasing the risk of a disease flare.[14] In addition, the optimal trough concentration for patients under maintenance therapy with subcutaneous infliximab CT-P13 or vedolizumab should still be determined. Although it is generally believed that drug exposure with trough concentration as a surrogate marker is the driver for efficacy, the proposed posology of subcutaneous infliximab CT-P13 was selected based on PK/PD modelling, aiming to exceed the 5 mg/L trough threshold for optimal efficacy and generating a steady-state area under the concentration–time curve over 8 weeks that aligned closely to that achieved following 5 mg/kg infusions.[8] Similarly, the posology of subcutaneous vedolizumab was chosen to provide similar average serum concentrations at steady state as compared to intravenous infusions.[15] Consequently, targeting similar overall drug exposure results in higher trough concentrations with subcutaneous formulation compared to intravenous formulations. Nevertheless, it was shown that these higher concentrations were required to achieve the same efficacy.[15] The IBD experts highlighted the need for more data to conclude on a lower immunogenicity of subcutaneous infliximab CT-P13 and the need for combination therapy with a thiopurine or methotrexate after switching to this subcutaneous formulation.

As for all biological therapies, one can expect a loss of response under maintenance subcutaneous infliximab CT-P13 or vedolizumab. Unfortunately, the pivotal trials did not [adequately] evaluate this and the best strategy in case of an objectified clinical relapse after switching to subcutaneous infliximab CT-P13 or vedolizumab is currently unknown. IBD experts would consider both switching back to an intravenous formulation or optimization to weekly subcutaneous injections, although both strategies are currently not foreseen in the European label. Of note, in the UK, weekly administration of infliximab CT-P13 had to be implemented in several patients, sometimes even from the start.[19]

In general, IBD experts agreed that a potential switch could only be the result of a shared decision. A thorough discussion with the IBD patients is therefore paramount, and the IBD team should not only stress the importance of therapeutic compliance, but should also listen to the impact on quality of life, as well as potential fears and concerns. These items encompass also the main remarks raised by the IBD patients

during the group interviews. Furthermore, it was felt that a first clinical evaluation should be foreseen within 8 weeks after switching to a subcutaneous formulation. The role of the IBD nurse is regarded as crucial in explaining, guiding and following a potential switch, and teaching the mode of administration. In this context, education of the complete multidisciplinary IBD team with accurate data on switching from intravenous to subcutaneous formulations is crucial, in order to provide the most appropriate information to the patient. Therefore, the introduction of subcutaneous infliximab CT-P13 and vedolizumab is expected to increase the workload for the IBD nurse.

In conclusion, IBD physician experts, IBD patients and IBD nurses participating in the DIAMOND platform recognized the added value of subcutaneous formulations of infliximab CT-P13 and vedolizumab. However, they all expressed the need for further scientific data in order to select the right patients and the right timing to consider a switch to these newer formulations. Furthermore, post-marketing studies will be required to explore the best strategy in case of loss of response under subcutaneous infliximab CT-P13 or vedolizumab every other week.

Supplementary Data

Supplementary data are available online at *ECCO-JCC* online.

Conference Presentation

Part of this work was presented as a poster presentation during the digital ECCO congress in July 2021.

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Author Contributions

L.F. and M.F. wrote the manuscript. L.F., C.F., E.H., T.L., E.D., J.S. and M.F. were members of the DIAMOND Core Panel and designed the study. All authors and collaborators participated in the three-round modified Delphi process, critically reviewed the manuscript and accepted its submission for publication.

Data Availability Statement

The data underlying this article are available in the article and in its online supplementary material.

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