

Preference for a prefilled syringe or an auto-injection device for delivering golimumab in patients with moderate-to-severe ulcerative colitis: a randomized crossover study

Séverine Vermeire,¹
François D'heygere,²
Antoine Nakad,³ Denis
Franchimont,⁴ Fernand
Fontaine,⁵ Edouard Louis,⁶
Philippe Van Hoetegem,⁷
Olivier Dewit,⁸ Guy
Lambrecht,⁹ Beatrijs
Strubbe,¹⁰ Filip Baert¹¹

¹Department of Gastroenterology, University Hospital Gasthuisberg, Leuven, Belgium; ²Department of Gastroenterology, AZ Groeninge, Kortrijk, Belgium; ³Department of Gastroenterology, CHWAPI, Tournai, Belgium; ⁴Department of Gastroenterology, Erasme Hospital, Brussels, Belgium; ⁵Department of Gastroenterology, CHC St Joseph, Liège, Belgium; ⁶Department of Gastroenterology, University Hospital CHU Sart Tilman, Liège, Belgium; ⁷Department of Gastroenterology, AZ St Lucas, Brugge, Belgium; ⁸Department of Gastroenterology, UCL St Luc, Brussels, Belgium; ⁹Department of Gastroenterology, AZ Damiaan, Oostende, Belgium; ¹⁰Department of Gastroenterology, OLV Hospital, Aalst, Belgium; ¹¹Department of Gastroenterology, AZ Delta, Roeselare-Menen, Belgium

Correspondence: Séverine Vermeire
Department of Gastroenterology,
University Hospitals Leuven,
Herestraat 49, 3000 Leuven, Belgium
Tel +32 16 344 218
Fax +32 16 344 419
Email severine.vermeire@uzleuven.be

Purpose: Simponi[®] (golimumab, MSD) is a fully human monoclonal antibody against tumor necrosis factor alpha administered subcutaneously using an autoinjector or a prefilled syringe. This study examined preference for administration of golimumab by autoinjector or prefilled syringe in patients with moderate-to-severe ulcerative colitis (UC).

Patients and methods: This was a multicenter, open-label, randomized crossover trial (EudraCT no 2014-000656-29). Patients with moderate-to-severe UC were randomized 1:1 to receive 2 subcutaneous injections of 50 mg golimumab with the autoinjector followed by 2 injections of 50 mg with the prefilled syringe or the same 4 injections administered in the opposite order. Patients assessed preference, ease of use, and discomfort immediately after the injections and 2 weeks later.

Results: Ninety-one patients were included (median age=42.7 years [range, 19.7–93.7]; 58% male). The autoinjector was preferred by 76.9% of patients immediately after injections and by 71.4% 2 weeks later. The autoinjector was more often considered extremely easy or easy to use (94.5%) than the prefilled syringe (73.6%). Moderate discomfort or worse was reported by more patients when using the prefilled syringe (20.9%) than when using the autoinjector (5.5%), and severe discomfort or discomfort preventing injection of future doses was reported by 8.8% for the prefilled syringe but not at all when using the autoinjector. A favorable or extremely favorable overall impression was reported by 89.0% for the autoinjector and 72.5% for the prefilled syringe.

Conclusion: Most patients with moderate-to-severe UC preferred to self-administer golimumab with the autoinjector over a prefilled syringe.

Keywords: autoinjector, adherence, anti-TNF, subcutaneous injection, treatment, self-injection

Introduction

Ulcerative colitis (UC) is a chronic and incurable autoimmune inflammatory bowel disorder characterized by continuous inflammation and ulceration of the mucosa of the rectum and, to a variable extent, the colon.^{1,2} The disease affects 2.5 million people worldwide and is usually diagnosed when individuals are in their 20s and peaks again in their 60s or 70s, but it can occur at any age. UC is generally characterized by flares that alternate with periods of remission, although some patients have continuous activity. The severity of flares and their response to treatment are difficult to predict, although the frequency of flares decreases with time. Between 25% and 40% of people living with UC will require surgery at some point in their life.¹

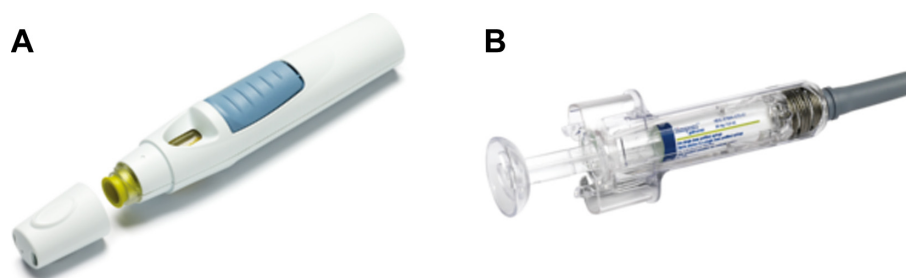


Figure 1 Golimumab injection devices.

Notes: (A) SmartJect autoinjector. (B) Prefilled syringe.

Simponi® (golimumab, MSD, Janssen Biotech, Inc., Horsham, PA, USA) is a fully human monoclonal antibody against tumor necrosis factor α (TNF- α) available in the European Union since 2013 for the treatment of moderate-to-severe active UC in adult patients who have had an inadequate response to conventional therapy or who are intolerant to or have medical contraindications for such therapies.³ Golimumab is also indicated for the treatment of moderate-to-severe active rheumatoid arthritis (RA) (in combination with methotrexate), active psoriatic arthritis (alone or in combination with methotrexate), and active ankylosing spondylitis.

Golimumab is administered with the SmartJect® autoinjector (MSD, Janssen Biotech, Inc.) or with a prefilled syringe (Figure 1). The SmartJect autoinjector was developed to simplify self-injection of golimumab for patients suffering from RA, psoriatic arthritis, and ankylosing spondylitis, with the objective of optimizing treatment adherence.⁴ Autoinjectors offer several advantages, including portability, convenience, and flexible scheduling, and they have been shown to improve treatment adherence.⁵⁻⁷ In the GO-MORE study, which examined the efficacy and safety of golimumab in biologic-naïve RA patients, two-thirds of those who self-injected chose to use the autoinjector over a prefilled syringe.⁴ In addition, most of the patients using the autoinjector had a favorable impression of it, considered it easy to use, and reported that it caused little pain or discomfort. Device preferences for UC patients, however, have not been reported and may be different from RA patients who often suffer from hand pain, swelling, and deformities. Here, we report the results of a study examining whether patients with moderate-to-severe UC prefer administration of golimumab using the SmartJect autoinjector or a prefilled syringe.

Patients and methods

Study design

This was a multicenter, open-label, randomized, crossover trial comparing preference for administration of golimumab

using the SmartJect autoinjector or a prefilled syringe in patients with moderate-to-severe UC (EudraCT no 2014-000656-29). The trial was conducted at 20 sites in Belgium (19 sites recruited patients) between July 2014 and October 2015. The primary objective was to determine whether UC patients prefer to administer golimumab using the autoinjector, using a prefilled syringe, or are undecided. Secondary objectives were to determine which of the 2 administration devices patients consider the easiest to use and result in the least discomfort, and how patient characteristics influence device preference.

The study included adults with an established diagnosis of UC and moderate-to-severe disease (Mayo score ≥ 6 , including an endoscopic subscore ≥ 2) and a previous conventional therapy of at least 3 months with aminosalicylates and at least 3 months with corticosteroids, 6-mercaptopurine, or azathioprine unless intolerant to or contraindicated for such therapies. Individuals who previously self-injected any agent or who were using other biological agents were excluded.

Patients completed a questionnaire to collect demographic data, and investigators collected information about the patient's medical history. Patients were then randomized 1:1 to receive 2 injections of golimumab 50 mg (Simponi®, MSD) with the autoinjector (SmartJect®, MSD) followed by 2 injections of 50 mg with the prefilled syringe or 2 injections of 50 mg golimumab with the prefilled syringe followed by 2 injections with the autoinjector (total 200 mg golimumab administered). All injections were subcutaneous, were in the same part of the body, and were performed on the same day (day 0). The first of the 2 injections with each device was performed by the physician, and the second by the patient under the physician's supervision.

Immediately after using each device, patients answered a questionnaire assessing the hand used to self-inject (left, right, both), ease of use for self-injection (extremely easy, easy, neither easy nor difficult, difficult, or extremely difficult), overall discomfort (none, mild, moderate, severe,

or such discomfort that I cannot inject future doses), and overall impression of the self-injection experience (extremely favorable, favorable, neither favorable nor unfavorable, unfavorable, or extremely unfavorable). After completing all 4 injections, patients completed a questionnaire on their preference for the devices (prefilled syringe, autoinjector, or undecided). After 2 weeks, the patient was contacted to complete the device preference questionnaire again to capture the effect of any delayed adverse events on the patient's responses.

Investigators recorded adverse events according to the International Conference on Harmonization Guidelines for Good Clinical Practice including the following: adverse event/diagnosis; dates of onset and resolution; severity (mild, moderate, severe), whether the event was serious (yes/no) and, if so, why; potential relationship to the study drug (yes/no); and action taken. Adverse events were considered serious if they resulted in death, were life threatening, required hospitalization or prolongation of an existing inpatient hospitalization, resulted in a persistent or significant disability or incapacity, were a congenital abnormality or birth defect, were cancer, were associated with an overdose, or were any other important medical event.

Ethics

The study was approved by each site's independent ethics committee (Table S1) and was conducted in accordance with International Conference on Harmonization Guideline for Good Clinical Practice. All included patients provided written informed consent.

Study size estimate

A power calculation was not performed. Instead, a study size estimate of 100 subjects was planned based on sample sizes that yielded relevant results in similar studies.^{8–11} Assuming 10% dropout, approximately 110 subjects were to be screened.

Statistical analysis

The primary outcome measure (device preference) was analyzed in the per-protocol set, defined as all subjects who met the inclusion and exclusion criteria, received all 4 injections, and completed the device preference questionnaire. Statistical analyses of preference included frequency distribution overall immediately and 2 weeks after injection; by order of device administration; 2 weeks after injection by preference immediately after injection; and by age, sex, ethnicity, marital status, education level, employment status,

and total Mayo score category. Statistical analysis of secondary outcome measures (ease of use, discomfort, and overall impression) included frequency distribution overall and by order of injection. As stipulated in the study protocol, only descriptive statistics were calculated, although in a post hoc analysis, preferences were analyzed according to subject baseline characteristics by Cochran–Armitage trend test or Fisher's exact test, with *p*-values below 0.05 considered to indicate statistical significance. Missing data were not replaced. Calculations were made using SAS version 9.2 (SAS Institute, Cary, NC, USA).

Results

Patients

Between July 11, 2014, and September 17, 2015, 100 patients were included in the study, and the study was completed on October 5, 2015. Of the 100 recruited patients, 99 were treated. Another 8 patients did not fulfill the selection criteria. Thus, 91 patients were included in the analysis. Most of these patients were between 30 and 60 years of age, slightly more than half were male, and all but 2 were White/Caucasian (Table S2). On average, patients had been diagnosed with UC for 8.6 years. Disease severity was moderate in about two-thirds and severe in about one-third, although precise proportions depended slightly on the assessment (Mayo score, physician's global assessment, and sigmoidoscopic and endoscopic findings). Most were being treated with 5-aminosalicylic acid and corticosteroids, and most had not previously received anti-TNF therapy.

Device preference

Immediately after injections, approximately three-quarters of patients (76.9%) indicated that they preferred administering golimumab with the autoinjector (Figure 2). This was similar to the preference reported 2 weeks later, with 71.4% reporting that they preferred the autoinjector. This was also the case irrespective of the order of injection, although more patients who started with the autoinjector preferred it (84.4%) than patients who started with the prefilled syringe (69.6%). Also, most patients (92.3%) did not change their preference 2 weeks later: of those who preferred a prefilled syringe immediately after the injections, all still preferred it 2 weeks later, and of those that preferred the autoinjector immediately after the injections, 92.9% still preferred it 2 weeks later. Results were similar when analyzed for all 99 patients completing the questionnaire (data not shown). A post hoc analysis showed that preference for the autoinjector was not significantly affected by patient age, disease

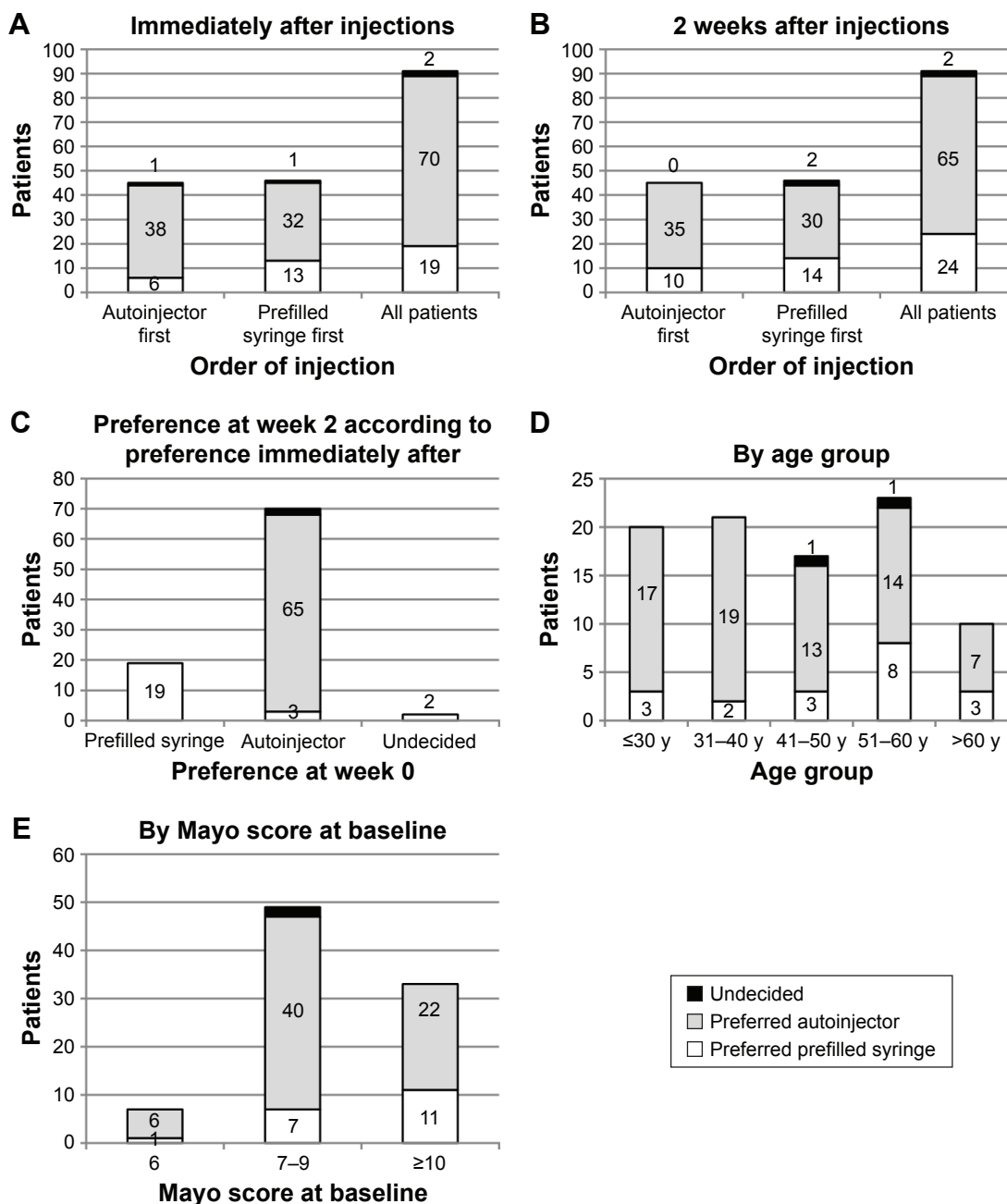


Figure 2 Device preference.

Notes: Patient preference for the different devices was assessed immediately after the injections and 2 weeks later. (A) Device preference according to order of presentation immediately after the injections. (B) Device preference according to order of presentation 2 weeks after the injections. (C) Device preference at week 2 according to preference immediately after the injections. (D) Device preference immediately after the injections according to age group. (E) Device preference immediately after the injections according to Mayo score at baseline.

severity as measured by the total Mayo score, sex, marital/cohabitation status, level of education, employment status, or time since UC diagnosis (data not shown).

Ease of use, discomfort, and overall impression of the devices

More patients considered the autoinjector extremely easy or easy to use (94.5%) than the prefilled syringe (73.6%) (Table 1). Moderate discomfort or worse was reported by

only 5 patients (5.5%) when using the autoinjector but by 19 patients (20.9%) when using the prefilled syringe. Severe discomfort or discomfort such that the patient could not inject future doses was reported by 8 patients (8.8%) when using the prefilled syringe but was not reported by any of the patients using the autoinjector.

In agreement with these findings, 89.0% of patients had an overall extremely favorable or favorable impression of the autoinjector, while 72.5% had an extremely favorable or

Table 1 Ease of use, discomfort, and overall impression of the devices

Assessment	Category	Autoinjector			Prefilled syringe		
		Autoinjector first	Prefilled syringe first	Overall	Autoinjector first	Prefilled syringe first	Overall
Ease of use of self-injection	Extremely easy	27 (60.0)	26 (56.5)	53 (58.2)	9 (20.0)	15 (32.6)	24 (26.4)
	Easy	17 (37.8)	16 (34.8)	33 (36.3)	20 (44.4)	23 (50.0)	43 (47.3)
	Neither easy nor difficult	1 (2.2)	1 (2.2)	2 (2.2)	11 (24.4)	5 (10.9)	16 (17.6)
	Difficult	0 (0.0)	1 (2.2)	1 (1.1)	2 (4.4)	1 (2.2)	3 (3.3)
	Extremely difficult	0 (0.0)	2 (4.3)	2 (2.2)	3 (6.7)	2 (4.3)	5 (5.5)
Discomfort during self-injection	No discomfort	27 (60.0)	29 (63.0)	56 (61.5)	11 (24.4)	24 (52.2)	35 (38.5)
	Mild discomfort	17 (37.8)	13 (28.3)	30 (33.0)	20 (44.4)	17 (37.0)	37 (40.7)
	Moderate discomfort	1 (2.2)	4 (8.7)	5 (5.5)	9 (20.0)	2 (4.3)	11 (12.1)
	Severe discomfort	0 (0.0)	0 (0.0)	0 (0.0)	3 (6.7)	0 (0.0)	3 (3.3)
	Such discomfort that I cannot inject future doses	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.4)	3 (6.5)	5 (5.5)
Overall impression of the self-injection experience	Extremely favorable	17 (37.8)	26 (56.5)	43 (47.3)	8 (17.8)	18 (39.1)	26 (28.6)
	Favorable	25 (55.6)	13 (28.3)	38 (41.8)	19 (42.2)	21 (45.7)	40 (44.0)
	Neither favorable nor unfavorable	3 (6.7)	5 (10.9)	8 (8.8)	13 (28.9)	4 (8.7)	17 (18.7)
	Unfavorable	0 (0.0)	2 (4.3)	2 (2.2)	3 (6.7)	1 (2.2)	4 (4.4)
	Extremely unfavorable	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.4)	2 (4.3)	4 (4.4)

Note: Data presented as n (%).

favorable impression of the prefilled syringe. An unfavorable impression of the device or worse was reported by only 2 patients (2.2%) when using the autoinjector but by 8 patients (8.8%) when using the prefilled syringe.

The order of use of the 2 different devices appeared to slightly bias the subjects toward the device they used first. For example, the proportion of patients with an extremely favorable or favorable impression of the autoinjector was 93.3% when it was used first vs 84.8% when it was used second. Likewise, the proportion of patients with an extremely favorable or favorable impression of the prefilled syringe was 84.8% when it was used first vs 60.0% when it was used second.

Safety

None of the patients experienced a serious adverse event. Treatment-emergent adverse events, all mild or moderate in severity, were reported by 10 patients (10.1%) (Table S3). These events included injection-site hematoma (n=2), injection-site pain (n=1), palpitations (n=1), UC flare (n=1), dyspepsia (n=1), flatulence (n=1), hemorrhoidal hemorrhage (n=1), tooth sensitivity (n=1), parotid gland enlargement (n=1), viral upper respiratory tract infection (n=1), headache (n=1), and hot flush (n=1).

Discussion

This study showed that most patients with moderate-to-severe UC preferred to self-administer golimumab with the autoinjector over a prefilled syringe. More patients found the autoinjector easier to use and to less often cause

discomfort than the prefilled syringe. This preference for the autoinjector did not change when measured again 2 weeks later, during which time most delayed reactions would have appeared. Demographic characteristics did not significantly affect preference. Order of presentation did not affect the overall preference for the autoinjector, although it biased the preference somewhat toward the device first presented. The results of this study are strengthened by the fact that data were collected in a real-life clinical setting at multiple sites. In addition, although the absolute sample size was small, this study included a relatively large population for UC and was enough to observe meaningful differences in preference.

Overall opinions were also favorable in the GO-MORE trial, in which patients with active RA self-injected or had someone else administer subcutaneous golimumab with the same device.⁴ Although individuals with RA often suffer from hand pain, swelling, and deformities, in GO-MORE, two-thirds of patients who chose to self-inject selected the autoinjector over a prefilled syringe. Most of the patients in the GO-MORE study who used the autoinjector had a favorable impression of it, considered it easy to use, and reported that it caused little pain or discomfort. However, the study did not directly assess preference or compare patient experiences between the autoinjector and injection with the prefilled syringe. A preference for the golimumab autoinjector over previous injection devices was also reported by 70.6% of patients in the GO-SAVE trial, which included patients with active RA who were switched from adalimumab or etanercept to golimumab.¹²

Prefilled pens or other autoinjectors are also preferred over and considered easier to use and less painful than syringes for self-administration of darbepoetin by chronic kidney disease patients,¹¹ methotrexate¹³ and adalimumab¹⁴ for RA patients, and insulin for diabetes patients.^{15–18} Similarly, a study in healthy volunteers found that subcutaneous injection by autoinjector was preferred over syringe injection by a nurse.¹⁹

A systematic review in 2013 found that treatment adherence to anti-TNF biologics in UC patients was only 52.7%.²⁰ It also found that administration with a syringe vs a pen was a predictor of nonadherence. Although the SmartJect autoinjector might therefore be expected to improve adherence to golimumab, we did not assess adherence in this study.

Conclusion

This study showed that patients with UC generally prefer to administer golimumab with an autoinjector. Although this should help inform prescribers about what their patients may expect, they should be aware that some patients might still prefer using a prefilled syringe.

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Author contributions

S Vermeire participated in developing a first draft of the manuscript together with the medical writer. All authors contributed to patient recruitment, analysis and interpretation of the results, critical revision of the manuscript, and approval of the final version.

Disclosure

S Vermeire has received consulting fees from AbbVie, MSD, Takeda, Ferring, Genentech/Roche, Shire, Pfizer Inc, Galapagos, Mundipharma, Hospira, Celgene, Second Genome, and Janssen; research grants from AbbVie, MSD, and Takeda; and speaker fees from AbbVie, MSD, Takeda, Ferring, Dr Falk Pharma, Hospira, and Tillots. F Baert received research grants from AbbVie, Chiesi, MSD, and Ipsen, Roche; and speaker and consultancy fees from AbbVie, Hospira, Janssen (Johnson & Johnson), MSD, Mundipharma, Falk, Ferring, and Takeda. O Dewit received

research grants from AbbVie and MSD; consulting fees from Ferring, Mundipharma, Hospira, Takeda, and Janssen; and speaker fees from MSD, Ferring, Mundipharma, Hospira, and Takeda. P Van Hootegeem received consultancy fees from Janssen (Johnson & Johnson) and Takeda; and speaker fees from Falk and Ferring. D Franchimont received honorarium fee for lectures; consulting fees and/or educational grants from Amgen, Pfizer, Mundipharma, AbbVie, MSD, Takeda, Ferring, Falk, Merck Serono, Roche and Janssen. E Louis has received grants from MSD and AbbVie; speaker fees from AbbVie, Ferring, MSD, Chiesi, Mitsubishi Pharma, Hospira, Janssen, and Takeda; and is on the advisory board of AbbVie, Ferring, MSD, Takeda, Mitsubishi Pharma, Celltrion, and Prometheus. The authors report no other conflicts of interest in this work.

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Supplementary materials

Table S1 List of participating ethics committees

UZ Leuven

Commissie Medische Ethiek

Professor Minne Casteels
Herestraat 49
B-3000 Leuven
Tel: 016 34 86 00 Fax 016 34 86 01
Email ec-submission@uzleuven.be

UZ Gent

Commissie Medische Ethiek

Professor Dirk Matthys
De Pintelaan 185
B-9000 Gent
Tel: 09 332 33 36 Fax 09 332 49 62
Email ethisch.comite@ugent.be

AZ Groeninge, Campus Loofstraat

Commissie Medische Ethiek

Dokter Peter Doubel
Loofstraat 43
8500 Kortrijk
Tel: 056 63 50 72 Fax 056 63 50 57
Email ethisch.comite@azgroeninge.be

UZ Antwerpen

Commissie Medische Ethiek

Patrick Cras
Wilrijkstraat 10
2650 Edegem
Tel: 03 821 35 44 Fax 03 821 42 54
Email ethisch.comite@uza.be

CHU Sart Tilman

Comité d'Ethique Hospitalo-Facultaire Universitaire de Liège

Professeur V. Seutin
Centre Hospitalier Universitaire du Sart Tilman, B35
4000 Liège
Tel: 04 366 83 10 Fax 04 366 74 41
Email ethique@chu.ulg.ac.be

H Hart Ziekenhuis Roeselare – Menen vzw

Commissie Medische Ethiek

Dr. L. Harlet
Wilgenstraat 2
8800 Roeselare
Tel: 056 52 22 30 Fax 056 522 520
Email sdeneve@hhr.be October 2014 Page 2

Sint Augustinus (GZA Ziekenhuizen)

Commissie Medische Ethiek

Professor Bart Van den Eynden
Sint-Vincentiusstraat 20
2018 Antwerpen
Tel: 03 443 45 58 Fax 03 239 23 23
Email hilde.poullissen@gza.be

Table S1 (Continued)

Zol Genk, Campus St Jan

Comité Medische Ethiek

Doctor Patrick Noyens
Schiepse Bos 6
3600 Genk
Tel: 089 32 16 02 Fax 089 32 79 00
Email ec.submission@zol.be

AZ ST Jan Brugge

Commissie Medische Ethiek

Doctor Ludo Vanopdenbossch
Ruddershove 10
8000 Brugge
Tel: 050 45 99 42 Fax 050 45 30 57
Email ethisch.comite@azsintjan.be

UCL St Luc

Commission d'Ethique Biomédicale Hospitalo-Facultaire de l'UCL

Professor J.M. Maloteaux
Avenue Hippocrate 55.14, Tour Harvey, niveau 0
1200 Bruxelles
Tel: 02 764 55 14 Fax 02 764 55 13
Email commission.ethique@md.ucl.ac.be

CHC St Joseph Liège

Comité d'ethique médicale des cliniques St Joseph

Doctor René Stevens
Rue de Hesbaye 75
4000 Liège
Tel: 04 224 89 90 Fax 04 229 89 92
Email rene.stevens@chc.be

La citadelle de Liège

Comité d'ethique médicale

Professeur François DAMAS
Boulevard du 12ème de Ligne, 1
4000 Liège
Tel: 04 225 69 35 Fax 04 225 76 41
Email marie.louise.frenay@chrcitadelle.be

OLV ziekenhuis Aalst

Ethisch Comité OLV Ziekenhuis

Doctor Antoon Leloup
Moorselbaan 164
9300 Aalst
Tel: 053 72 46 60 Fax 053 72 46 89
Email antoon.leloup@olvz-aalst.be

Hôpital Erasme

Comité d'Ethique

Prof. Dr. André Herchuelz
Route de Lennik 808
1070 Bruxelles
Tel: 02-555 37 07 Fax 02-555 46 20
Email comite.ethique@erasme.ulb.ac.be

(Continued)

(Continued)

Table S1 (Continued)**GHDC, Saint-Joseph, Charleroi**
Comité d'Ethique Hospitalier, Grand Hopital de Charleroi

Mrs Laurence Gillard

Grand Rue 3

6000 Charleroi

Tel: 071 10 43 30 Fax 071 10 85 96

Email duthoy.audrey@ghdc.be**ZNA Jan Palfijn Antwerpen**

Dr. P.P. De Deyn

Commissie voor Medische Ethiek ZNA

ZNA Koningin Paola Kinderziekenhuis (P6- lokaal 617)

Lindendreef 1,

2020 Antwerpen

Tel: 03/280.34.29 of 03/280.34.28 Fax 03/280.30.60

Email ethische.commissie@zna.be**Centre Hospitalier de Wallonie picarde – CHwapi A.S.B.L.****Site Union**

Dr. Luc Desplanque

Comité d'Ethique

39, Boulevard Lalaing

7500 Tournai

Tel: 069 33 17 56 Fax 069 25 86 54

Email luc.desplanque@chwapi.be / nathalie.mat@chwapi.be

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Virga Jesse ziekenhuis, Hasselt

Dr. Koen Magerman

Ethische Toetsingscommissie Virga Jesse

Stadsomvaart 11

3500 Hasselt

Tel: 011/30.91.11 Fax 011/30.91.18

Email ethische.toetsingscommissie@virgajesse.be

CHR Peltzer La Tourelle

Dr. Hassan Kalantari

Comité d'Ethique

Rue du Parc 29

4800 Verviers

Tel: 087/21 21 71 Fax 087/21.21.39

Email comite.ethique@chplt.be

AZ Sint Maarten

Dr. J. Vander Sande

Ethisch comité van vzw Emmaüs

Edgard Tinellaan 1c

2800 Mechelen

Tel: 015/44 67 21 Fax 015 44 67 10

Email brigitte.van.looy@emmaus.be

AZ Damiaan

Dr. Guy Fonteyn

Ethisch Comité

Gouweloestraat 100

8400 Oostende

Tel: 050 41 40 67 Fax 050 41 40 78

Email mbrusselle@azdamiaan.be

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Table S1 (Continued)

AZ St Lucas

Dr. Rob Schildermans

Ethische Commissie

AZ St Lucas Brugge

Sint-Lucaslaan 29

8310 Brugge

Tel: +32 50 36 56 91 Fax +32 50 36 56 95

Email nancy.vanavermaete@stlucas.be**Table S2** Patient demographic characteristics

Characteristic	Value
Number included in the per-protocol analysis	91
Age (years)	
Mean (SD)	42.7 (14.4)
Range	19.7–93.7
Sex, n (%)	
Male	54 (59.3)
Female	37 (40.7)
Ethnicity, n (%)	
White/Caucasian	89 (97.8)
Other	2 (2.2)
Marital status, n (%)	
Single	23 (25.3)
Married/living together	67 (73.6)
Widow	1 (1.1)
Highest education level, n (%)	
Primary education	6 (6.6)
Vocational secondary education	13 (14.3)
Technical secondary education	13 (14.3)
General secondary education – humanities	12 (13.2)
Higher education (graduate/nonuniversity)	30 (33.0)
Higher education (university)	17 (18.7)
Professional status, n (%)	
Student	9 (9.9)
Working full time	48 (52.7)
Working part time	11 (12.1)
Not working	23 (25.3)
Time since UC diagnosis (y)	
Mean (SD)	8.6 (8.8)
Range	0.0–38.1
Most frequent concomitant conditions ($\geq 3\%$), n (%)	
Arthritis	4 (4.4)
Arthralgia	4 (4.4)
Psoriasis	3 (3.3)
Primary sclerosing cholangitis	3 (3.3)
Other	6 (6.6)
Previous exposure to anti-TNF, n (%)	
Naive	76 (83.5)
Experienced	15 (16.5)
Concomitant medications, n (%)	
5-Aminosalicylic acid	68 (74.7)
Corticosteroids	59 (64.8)
Azathioprine	37 (40.7)
Other	2 (2.2)

(Continued)

Table S2 (Continued)

Characteristic	Value
Total Mayo score	
Mean (SD)	8.8 (1.6)
Min, max	6, 12
Total Mayo score categories, n (%)	
6	7 (7.9)
7–9	49 (55.1)
≥ 10	33 (37.1)
Stool frequency, n (%)	
Normal	0 (0.0)
1–2 stools more than normal	6 (6.7)
3–4 stools more than normal	41 (45.6)
5 or more stools more than normal	43 (47.8)
Rectal bleeding, n (%)	
No blood seen	6 (6.7)
Streaks of blood with stools less than half the time	27 (30.0)
Obvious blood with stool most of the time	37 (41.1)
Blood alone passed	20 (22.2)
Physician's global assessment, n (%)	
Normal	0 (0.0)
Mild disease	4 (4.4)
Moderate disease	65 (72.2)
Severe disease	21 (23.3)
Sigmoidoscopic/endoscopic findings, n (%)	
Normal or inactive disease	0 (0.0)
Mild disease	1 (1.1)
Moderate disease	54 (60.7)
Severe disease	34 (38.2)

Abbreviations: UC, ulcerative colitis; TNF, tumor necrosis factor.

Table S3 Treatment-emergent adverse events

Adverse event	Severity	Patients	Onset (time after injections)	Potentially related	Action taken	Resolution (time after onset)
Injection-site hematoma	Mild	1	1 day	Yes	None	6 days
	Mild	1	2 days	No	None	12 days
Injection-site pain	Mild	1	6 days	Yes	None	Ongoing
Palpitations	Mild	1	3 days	No	None	1 day
Flatulence	Moderate	1	6 days	No	None	3 months
Dyspepsia	Mild	1	10 days	No	Medication	3 months
UC flare	Moderate	1	1 day	Yes	Medication	2 months
Viral upper respiratory tract infection	Mild	1	1 day	Yes	None	
Headache	Mild	1	3 days	Yes	Medication	Ongoing
Hot flushes	Mild	1	1 day	Yes	None	Ongoing
Hemorrhoidal hemorrhage	Mild	1	9 days	No	None	Ongoing
Tooth sensitivity	Mild	1	6 days	Yes	None	Ongoing
Parotid gland enlargement	Mild	1	12 days	No	Echography	1 month

Abbreviation: UC, ulcerative colitis.

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