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Adalimumab and infliximab survival in patients with hidradenitis suppurativa: a daily practice cohort study*

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Summary

Background Biologics are often required for the treatment of hidradenitis suppurativa (HS). However, data on the drug survival of biologics in daily practice are currently lacking.

Objectives To assess the drug survival of antitumour necrosis factor biologics in a daily practice cohort of patients with HS and to identify predictors for drug survival.

Methods A retrospective multicentre study was performed in two academic dermatology centres in the Netherlands. Adult patients with HS using biologics between 2008 and 2020 were included. Drug survival was analysed with Kaplan–Meier survival curves and predictors of survival with univariate Cox regression analysis.

Results The overall drug survival of adalimumab (n = 104) at 12 and 24 months was 56·3% and 30·5%, respectively, which was predominantly determined by infectiveness. Older age (P = 0·02) and longer disease duration (P < 0·01) were associated with longer survival time. For infliximab (n = 44), overall drug survival was 58·3% and 48·6% at 12 and 24 months, respectively, and was predominantly determined by infectiveness and side-effects. Surgery during treatment was associated with a longer survival time (P = 0·01).

Conclusions Survival rates were comparable for adalimumab and infliximab at 12 months, and were mainly determined by ineffectiveness. Age, disease duration (adalimumab) and surgery (infliximab) are predictors for longer survival.

What is already known about this topic?

- Adalimumab is the only registered biological drug for the treatment of hidradenitis suppurativa (HS).
- Successful treatment with biologics is determined by drug survival.
- Data on drug survival in patients with HS in daily practice are lacking.

What does this study add?

- The survival rates of adalimumab (56·3%) and infliximab (58·3%) after 1 year are predominantly determined by ineffectiveness and side-effects.
- Age, disease duration (adalimumab) and surgery (infliximab) are predictors for longer survival.

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Hidradenitis suppurativa (HS) is a chronic autoinflammatory disease that has a substantial impact on patients' quality of life.[1–3] Currently, adalimumab – a tumour necrosis factor (TNF)-α inhibitor – is the only US Food and Drug Administration-approved biological treatment for HS, with Hidradenitis Suppurativa Clinical Response (HiSCR) achievement rates at week 12 of 41·8% (PIONEER I; n = 307) and 58·9% (PIONEER II; n = 326).[4] Long-term follow-up showed that this response was maintained in 52·3% of patients through to week 168 with weekly dosing.[5] However, a last observation carried forward (LOCF) approach was used for missing data, which could positively bias these long-term response rates. Moreover, long-term efficacy data from clinical trials cannot be extrapolated to daily practice owing to the highly controlled settings and strict eligibility criteria used in these trials.[6] For example, van den Reek *et al.* found higher drug survival rates for ustekinumab than for secukinumab in a daily practice psoriasis cohort, even though initial long-term results from the CLEAR study showed the superior efficacy of secukinumab.[7,8] Daily practice data on the long-term efficacy of biologics are important and provide the treating physician with valuable information on the probability of treatment success. Therefore, the aim of this study was to assess the drug survival of TNF-α inhibitors in the treatment of HS in a daily practice setting. In addition, we aimed to identify factors associated with drug survival.

Patients and methods

Data collection

Patients were identified via the electronic patient files of the departments of dermatology of University Medical Center Groningen (UMCG) and Erasmus University Medical Center, Rotterdam, the Netherlands. All adult patients with a diagnosis of HS who had received adalimumab or infliximab for HS between January 2008 and June 2020 were included. The minimum follow-up period was 6 months (but not in case of treatment discontinuation). Only the first treatment course of either infliximab or adalimumab was included in the analysis. Patient who had received previous treatment with anti-TNF-α, other than the biologic given at one of our centres, were also included. Primary analysis was performed to assess the influence of previous anti-TNF-α treatment on the primary outcome, which was not significant (data not shown). For the collection of retrospective anonymized data from regular care, written informed consent is not required. This study was granted exemption from ethical review by the Institutional Review Board of UMCG.

Patient characteristics

Age, sex, body mass index (BMI), age at onset of HS, disease severity, smoking status, treatment history, comorbidities and family history of HS were collected. Disease severity at the start of treatment was determined using both the International Hidradenitis Suppurativa Severity Score System (IHS4) and (refined) Hurley stage.

Treatment

Data regarding the type of biological agent, use of biosimilars, treatment regimens, start and stop dates, reasons for discontinuation, concomitant medication and side-effects were collected. Deviations from the per-label dosage and interval were recorded. Use of additional therapy for HS (either topical, systemic, surgical or combinations thereof) were recorded and patients were included in the analysis. Both primary and secondary nonresponses were judged by the treating physician.

Statistical analysis

Patient characteristics are presented as mean (SD) or median [interquartile range (IQR)], where appropriate, for continuous variables and as n (%) for categorical variables. Overall drug survival per biologic was analysed using Kaplan–Meier survival curves. Separate survival curves were calculated for discontinuation due to (i) ineffectiveness, (ii) side-effects and (iii) remission. Patients were censored at the date of their last visit, when they were lost to follow-up or when the biological agent was discontinued for reasons other than inefficacy, side-effects or remission. Subanalysis was performed stratifying the cohort based on previous biologic use, concomitant antibiotic use during biological treatment and surgery during treatment. The drug survival of each biologic was compared using Cox regression analysis. Possible predictors for overall drug survival and reason of discontinuation were assessed using univariate Cox regression analysis. All statistical tests were two-sided and a P-value $\leq 0{\cdot}05$ was considered to be statistically significant. Statistical analysis was performed using SPSS Statistics for Windows, Version 25 (IBM, Armonk, NY, USA).

Results

Patient characteristics

In total, 256 patient records were identified via searches in electronic patient files. Duplicates (n = 34) and cases with incomplete data (n = 54) were removed, and another 20 patients were excluded because they had a follow-up period of < 6 months. This left 148 patients for analysis. Fifty-six per cent of patients were female, with a median age of 38·0 years (IQR 28·5–49·0) at the start of treatment. Patient characteristics were comparable for both the adalimumab and infliximab groups (Table 1).

Treatment characteristics

The majority of patients received adalimumab (n = 104) and 44 patients received infliximab as a first treatment course

Table 1 Patient characteristics

	Total (n = 148)	Adalimumab (n = 104)	Infliximab (n = 44)	P-value[a]
Sex				0·59
Female	83 (56·1)	60 (57·7)	23 (52·3)	
Male	65 (43·9)	44 (42·3)	21 (47·7)	
Median (IQR) age at start treatment (years)	38·0 (28·5–49·0)	39·0 (29·0–49·0)	37·3 (28·0–45·8)	0·31
Median (IQR) age of onset (years)	20·5 (15·0–28·3)	19·8 (15·1–28·1)	21·0 (14·8–27·3)	0·93
Missing (n)	11	7	4	
Median (IQR) disease duration (years)	14·8 (8·1–22·9)	15·0 (7·9–23·7)	14·9 (10·1–22·5)	0·74
Missing (n)	11	7	4	
Mean (SD) BMI (kg m^{-2})	30·6 (7·6)	29·9 (7·3)	31·7 (7·6)	0·27
Missing (n)	61	41	14	
Smoking status				0·10
Current or ex-smoker	116 (80·5)	80 (76·9)	36 (90·0)	
Never smoked	28 (19·4)	24 (23·1)	4 (10·0)	
Missing (n)	4	0	4	
Positive family history	41 (27·7)	28 (26·9)	13 (29·5)	0·84
Hurley classification				0·71
Stage I	18 (13·4)	13 (13·3)	5 (13·9)	
Stage II	52 (38·8)	40 (40·8)	12 (33·3)	
Stage III	64 (47·8)	45 (45·9)	19 (52·8)	
Missing (n)	14	6	8	
Refined Hurley classification				0·82
Mild (IA, IIA)	8 (6·2)	6 (6·4)	2 (5·9)	
Moderate (IB, IIB)	21 (16·4)	17 (18·1)	4 (11·8)	
Severe (IC, IIC, III)	99 (77·3)	71 (75·5)	28 (82·4)	
Missing (n)	20	10	10	
IHS4				NP
Mild (≤ 3)	7 (6·4)	7 (8·1)	0 (0)	
Moderate (4–10)	28 (25·4)	23 (26·7)	5 (20·8)	
Severe (≥ 11)	75 (68·2)	56 (65·1)	19 (79·2)	
Missing (n)	38	18	20	
Prior biologics use				< 0·01
0 prior biologics	94 (63·5)	74 (71·2)	20 (45·5)	
≥ 1 prior biologics	54 (36·5)	30 (28·8)	24 (54·5)	
Prior antibiotic use				NP
0 prior antibiotics	9 (6·1)	7 (6·7)	2 (4·5)	
≥ 1 prior antibiotics	139 (93·9)	97 (93·3)	42 (95·5)	
Comorbidities				0·84
None	53 (35·8)	35 (33·6)	18 (40·9)	
Other skin disorders	37 (25·0)	23 (22·1)	14 (31·8)	
Inflammatory bowel diseases	20 (13·5)	17 (16·3)	3 (6·8)	
Inflammatory rheumatic diseases	8 (5·4)	7 (6·7)	1 (2·3)	
Cardiovascular disease	23 (15·5)	16 (15·4)	7 (15·9)	
Metabolic disorders	21 (14·2)	15 (14·4)	6 (13·6)	
Psychiatric disorders	27 (18·2)	20 (19·2)	7 (15·9)	
Other	46 (31·1)	33 (31·7)	13 (29·5)	

Data are n (%) unless otherwise indicated. BMI, body mass index; IHS4, International Hidradenitis Suppurativa Severity Score System; IQR, interquartile range; NP, no P-value. [a]P-value calculated between the adalimumab group and infliximab group.

(Table S1; see Supporting Information). Most patients received adalimumab according to label and HS guidelines:[9] 40 mg weekly (73·3%) or 80 mg every 2 weeks (16·8%). Eight patients changed to weekly dosing and three patients switched from weekly dosing to every 2 weeks. For infliximab, 5 mg kg^{-1} per 6 weeks (52·3%) or per 8 weeks (29·5%) were the predominant dosing schedules. Dosage and/or interval was changed in eight patients: interval was shortened (n = 3); dosage was increased (n = 2); both shorter interval and increase in dosage (n = 1); and interval lengthened (n = 2). Concomitant medication for HS was used by 62·2% of patients, of which oral antibiotics (66·2%) were the most frequent. HS surgery, excluding incision and drainage, was performed in 56·8% of patients.

Adalimumab

Drug survival

Median overall drug survival for adalimumab was 18·1 months [95% confidence interval (CI) 11·4–24.8]. Overall drug survival at 12 and 24 months was 56·3% and 30·5%, respectively (Figure 1a). For discontinuation owing to ineffectiveness, the 12- and 24-month drug survival was 61·6% and 30·5% (Figure 1b); the 12- and 24-month drug survival related to side-effects was 84·9% and 66·7% (Figure 1c). For remission the 12- and 24-month drug survival was 100% and 81·8%, respectively (Figure S1; see Supporting Information). The overall drug survival curves stratified for biological treatment history, concomitant antibiotics and surgery during treatment are shown in Figure S2 (see Supporting Information). There was no significant difference between biologic-naïve and biologic-experienced patients in reaching 12 and at 24 months of treatment ($P = 0·623$ and $P = 0·77$, respectively). There was no difference in survival at 12 and 24 months for patients receiving concomitant antibiotics ($P = 0·82$ and $P = 1·00$, respectively). Regarding surgery during treatment, significantly more patients survived at 12 and 24 months ($P < 0·01$ and $P = 0·02$, respectively).

Reasons for discontinuation

Fifty-nine patients discontinued adalimumab treatment. The main reason for discontinuation was ineffectiveness ($n = 33$): 12 (36%) patients experienced a primary nonresponse and 21 (64%) were secondary nonresponders. Data on the presence of antibodies were only available for a small proportion of patients (39%). Twenty-four patients were tested for antibodies and in 10 patients (42%) antibodies were detected of which five patients were secondary nonresponders.

Eight of 59 patients discontinued adalimumab owing to side-effects, which included fatigue ($n = 3$), shortness of breath ($n = 3$), dizziness and/or palpitations ($n = 3$), oedema ($n = 2$) and itch ($n = 3$). One patient stopped owing to secondary nonresponse and side-effects. Eight patients who discontinued treatment owing to remission all did so after surgery. In addition, nine discontinued adalimumab therapy for other reasons, such as uncontrolled disease other than HS or a wish to become pregnant. Twenty-two switched to another biologic (either infliximab or ustekinumab).

Associated factors

Univariate Cox regression analysis showed that sex, smoking status, previous treatment with biologics, the presence of comorbidities and the use of co-medication were not significantly associated with overall adalimumab survival (Table 2). Older age at the start of treatment was significantly associated with a longer survival time [hazard ratio (HR) 0·97, 95% CI 0·952–0·996]. Longer disease duration (HR 0·95, 95% CI 0·92–0·98) and a higher BMI (HR 0·93, 95% CI 0·870–0·998) were also associated with prolonged survival time. More severe disease was significantly associated with longer survival time: Hurley stage II (HR 0·42, 95% CI 0·19–0·95) compared with Hurley stage I, and the IHS4 category of severe (HR 0·33, 95% CI 0·13–0·89) compared with the category of mild. The HR of undergoing surgery during adalimumab treatment was 0·63 (95% CI 0·36–1·11), suggesting an association with longer survival time, but this was not significant ($P = 0·11$).

For discontinuation owing to ineffectiveness, older age, longer disease duration, moderate-to-severe disease and undergoing surgery were significantly associated with longer drug survival. For side-effects, moderate and severe disease and surgery were significantly associated with longer drug survival. For remission, BMI, disease duration and the presence of at least one comorbidity were significantly associated with longer drug survival (Tables S2–S4; see Supporting Information).

Infliximab

Drug survival

The median overall drug survival was 19·5 months (95% CI 0·0–52·1). The 12- and 24-month overall drug survival rates were 58·3% and 48·6%, respectively (Figure 1a). The 12- and 24-month drug survival related to ineffectiveness was 67·7% and 48·6%, respectively (Figure 1b); and the 12- and 24-month drug survival related to side-effects was 72·4% and 65·4%, respectively (Figure 1c). For remission, the 12- and 24-month survival rates were 91·3% and 85·0% (Figure S1; see Supporting Information). Figure S2 shows the overall drug survival curves stratified for biologic treatment history, concomitant antibiotics and surgery during treatment (see Supporting Information). No significant differences were found between biologic-naïve and biologic-experienced patients ($P = 0·50$ for both timepoints) or between patients with concomitant antibiotics during treatment in reaching 12 and 24 months of treatment ($P = 0·46$ and $P = 0·26$, respectively). Significantly more patients who had surgery during treatment reached 12 and 24 months of treatment ($P < 0·01$ and $P = 0·01$, respectively).

Reasons for discontinuation

Thirty patients discontinued infliximab, for which ineffectiveness ($n = 12$) was the predominant reason. Two patients were primary nonresponders and 10 were secondary nonresponders. Of these 10 patients, seven (70%) were positive for neutralizing antibodies. For all patients receiving infliximab, 20 were tested and 11 (55%) were positive for antibodies. Seven patients stopped infliximab owing to side-effects, which were identified as infusion reactions: itch and erythema of the skin ($n = 3$), and angio-oedema of the face and/or throat and shortness of breath ($n = 2$). Two patients experienced both secondary nonresponse and side-effects. Six patients discontinued treatment owing to remission after surgery, and three for other unknown reasons. Eight patients switched to adalimumab, etanercept or ustekinumab.

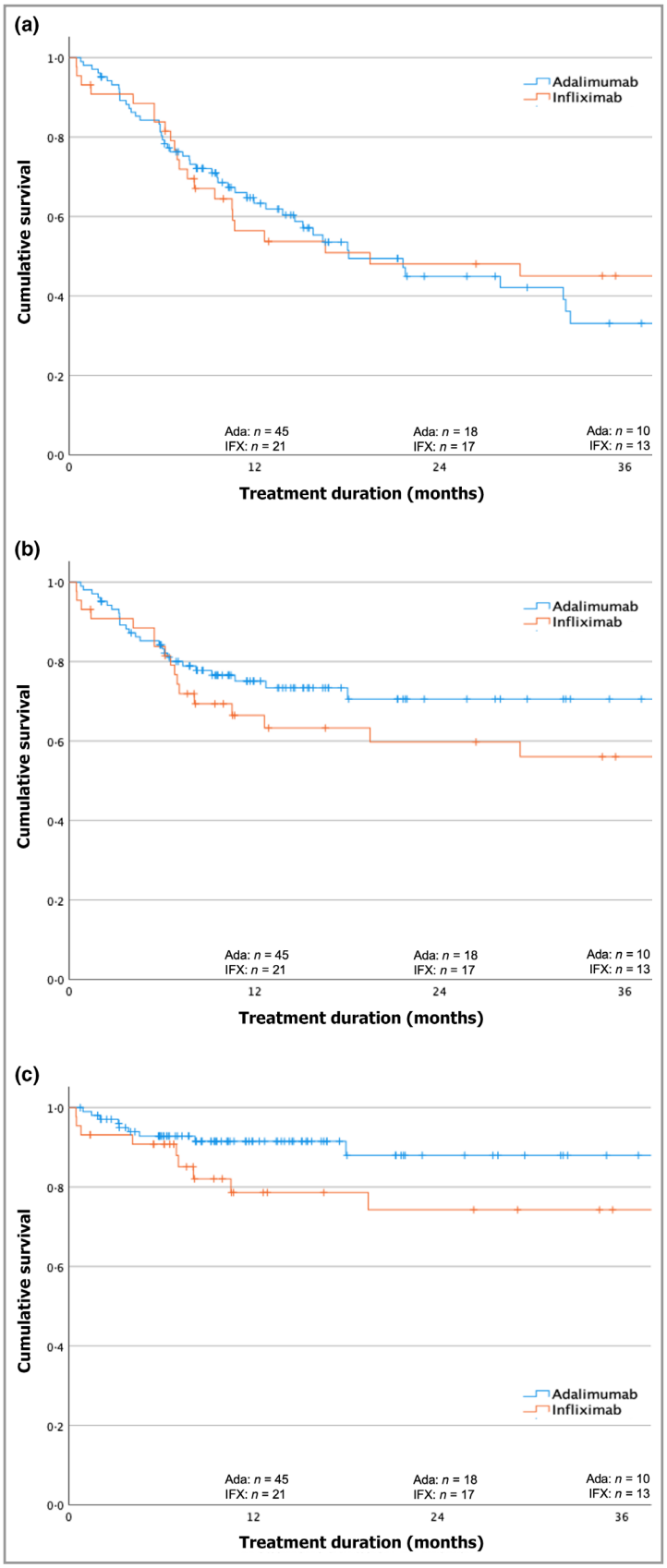

Figure 1 Kaplan–Meier curves showing (a) the overall cumulative survival per biological agent, and survival related to (b) drug ineffectiveness and (c) to side-effects. Ada, adalimumab; IFX, infliximab.

Table 2 Univariate Cox regression analysis per biological agent

	Adalimumab			Infliximab		
	n	HR (95% CI)	P-value	n	HR (95% CI)	P-value
Sex	104	1·22 (0·70–2·13)	0·49	44	0·89 (0·41–1·92)	0·76
Age	104	0·97 (0·95–0·996)	0·02	44	1·01 (0·98–1·04)	0·58
BMI	63	0·93 (0·87–0·998)	0·04	30	1·01 (0·95–1·07)	0·82
Disease duration	97	0·95 (0·92–0·98)	< 0·01	40	0·99 (0·95–1·04)	0·76
Smoking	104	0·96 (0·49–1·89)	0·91	40	3·31 (0·44–24·79)	0·25
Biologic naïve	104	0·90 (0·49–1·66)	0·75	44	1·15 (0·53–2·51)	0·72
Comorbidities	104	0·91 (0·50–1·68)	0·77	44	1·02 (0·44–2·35)	0·96
Hurley classification	98			36		
Stage I		Ref.			Ref.	
Stage II		0·42 (0·19–0·95)	0·04		0·59 (0·16–2·16)	0·43
Stage III		0·46 (0·21–1·00)	0·05		0·55 (0·17–1·82)	0·33
IHS4 categories	86			24		
Mild		Ref.				NP
Moderate		0·55 (0·19–1·58)	0·27			
Severe		0·33 (0·13–0·89)	0·03			
Refined Hurley classification	94			34		
Mild (IA, IIA)		Ref.			Ref.	
Moderate (IB, IIB)		0·32 (0·09–1·11)	0·07		1·01 (0·18–5·76)	0·99
Severe (IC, IIC, III)		0·50 (0·20–1·29)	0·15		0·16 (0·03–0·82)	0·03
Co-medication – all	104	0·60 (0·34–1·02)	0·07	44	0·96 (0·43–2·17)	0·93
Co-medication – antibiotics	104	0·76 (0·42–1·38)	0·36	44	0·63 (0·25–1·58)	0·33
Surgery	104	0·63 (0·36–1·11)	0·11	43	0·32 (0·14–0·78)	0·01

BMI, body mass index; CI, confidence interval; HR, hazard ratio; IHS4, International Hidradenitis Suppurativa Severity Score System; NP, no P-value; Ref., reference.

Associated factors

Undergoing surgery during treatment was significantly associated with a longer survival time (HR 0·32, 95% CI 0·14–0·78), as was having severe HS (based on refined Hurley stage), compared with mild HS (HR 0·16; 95% CI 0·03–0·82). No HR was calculated for the IHS4 variable owing to the low numbers per category. Other variables, such as sex, smoking status, previous treatment with biologics, the presence of comorbidities and co-medication, were not significantly associated with infliximab survival.

For discontinuation owing to drug ineffectiveness, more severe disease and undergoing surgery during treatment were significantly associated with longer drug survival [HR 0·18 (95% CI 0·04–0·89) and HR 0·25 (95% CI 0·10–0·65), respectively]. For side-effects and remission, no factors were significantly associated with drug survival.

No significant differences between overall drug survival of adalimumab and infliximab (Figure 1a) were found using both the log-rank test ($P = 0·85$) and the Breslow test ($P = 0·83$). The latter was performed as the log-rank test is less suitable when survival curves cross.

Discussion

To our knowledge, this is the first study to assess the drug survival of anti-TNF-α biologics in patients with HS in a daily practice setting. For adalimumab, the overall drug survival rate was 56% at 12 months and 31% at 24 months; for infliximab, the survival rates were 58% after 12 and 49% after 24 months. The main reasons for discontinuing either adalimumab or infliximab were ineffectiveness, side-effects and remission following surgical interventions.

The long-term efficacy data for adalimumab from the PIONEER trials showed a sustained HiSCR response in 52·3% of patients through to week 168 (42 months).[5] However, only 88 of 508 patients initially included in the PIONEER studies were included in this open-label extension (OLE) study. A post-hoc analysis by Frew *et al.* reported a dropout rate of 51 of 88 patients in the OLE study.[10] A LOCF approach was used to handle the missing data of the patients who dropped out, which could have positively biased the efficacy rates. Nonetheless, drug survival and drug efficacy are two different entities that cannot be directly compared. Drug survival concerns the time a patient is on a certain therapy, whereas for efficacy the change in severity is assessed at a predefined timepoint.

Based on the results from trials in patients with psoriasis, where a higher BMI was associated with poorer drug survival of systemic treatment, it has been proposed that BMI may negatively influence the efficacy and survival of adalimumab in patients with HS.[11] One study aimed to assess the influence of patient characteristics on HiSCR achievement in patients with HS. However, the authors did not specifically assess how BMI influences HiSCR in patients on adalimumab. This post-hoc multivariate regression analysis of the clinical trial data from the PIONEER I and PIONEER II trials was performed on

all PIONEER participants as a whole (including those using adalimumab and those on placebo) with both adalimumab use and BMI as covariates.[12] The resulting significance of the influence of BMI on HiSCR achievement should therefore be interpreted as being independent of adalimumab use. However, in a subsequent article, analysis of HiSCR achievement stratified by sex, smoking status, BMI category, Hurley stage and family history did not show significant differences in the cumulative incidence curves for HiSCR achievement or loss of HiSCR achievement.[10] Similar to these results, our data suggest that BMI does not negatively influence the drug survival of adalimumab in patients with HS. Instead, a higher BMI was associated with longer drug survival. However, from our survival study no conclusions can be drawn regarding the influence of BMI on the efficacy of adalimumab.

Drug survival in this study seems to be considerably lower than in other HS-associated immune-mediated diseases. For psoriasis, the 12-month drug survival of adalimumab and infliximab ranges from 75% to 84% and from 65% to 75%, respectively.[13–15] For inflammatory bowel disease, a higher survival rate at 12 months was also demonstrated for both adalimumab (estimated 65%) and infliximab (estimated 75%).[16] In addition, Flouri *et al.* showed a 1-year estimated survival rate in spondyloarthritis of 85% for adalimumab and 90% for infliximab.[17] The TNF-α–inteleukin-23–T helper cell 17 inflammatory pathways play a role in ankylosing spondylitis, Crohn disease and psoriasis, as well as in HS. However, in HS other cells and inflammatory pathways, such as neutrophil-mediated neutrophil extracellular trap activation and release (NETosis), and B- and plasma cell activation, as well as complement activity, are involved in the pathogenesis and influence disease activity, and make treatment dosages different from psoriasis. In particular, the involvement of B and plasma cells may influence neutralizing antibody formation. Furthermore, in spondyloarthritis and Crohn disease, concomitant therapy with an additional immunosuppressant is more common than in HS. This could influence the drug survival of TNF-α inhibitors in patients with these diseases, for example, as concomitant methotrexate can lower the chance of antibody formation when given adjuvant to adalimumab.

Interestingly, when looking at predictors of drug survival, older age and longer disease duration were found to be significant predictors of increased survival for adalimumab, as well as moderate HS (Hurley classification) or severe HS (IHS4 score > 11). We hypothesized that patients carrying the burden of this disease for years are fully aware of the limited treatment options, and, for this reason, they would be more eager to continue treatment. Furthermore, older patients might be more responsible than younger patients regarding their health and therefore perhaps be more compliant with medication.

Surprisingly, our analysis also showed a significantly longer survival for patients with a higher BMI in the adalimumab group but not in the infliximab group. However, this statistically significant finding of longer survival in patients with a higher BMI, in a modest-sized cohort (n = 104), might lack relevance in daily practice. Comparing predictors for adalimumab or infliximab was challenging, as other published studies did not analyse predictors separately for each biological agent.

In the infliximab group, only two predictors were found for longer drug survival. More severe disease was associated with longer infliximab survival vs. mild disease. Surgery significantly improved infliximab drug survival; this trend was also noticed in the adalimumab group. Major surgery is often combined with continued biological treatment – without interruption – to prevent relapse.[9] The preliminary results of a randomized controlled study investigating the combination of adalimumab and surgery showed no increased risk of postoperative adverse events.[18] This finding further supports the importance of integrating different treatment modalities in the management of HS.

Our study was limited by its retrospective design. However, in a previous evaluation of drug survival in patients with psoriasis, prospective and retrospective data on drug survival were compared, and no differences were found.[7] As our study is the first to quantify the drug survival of biologics in patients with HS, comparisons with other studies were not possible. Further studies are required to corroborate our findings and to find predictors of drug survival, in order to improve the performance of anti-TNF-α biological therapy in patients with HS.

In this daily-practice study, adalimumab and infliximab showed comparable survival rates at 12 months in patients with HS. Drug survival for both TNF-α inhibitors was predominantly determined by ineffectiveness. For adalimumab, older age, longer disease duration and more severe disease were associated with longer drug survival. In the infliximab group, the survival rate was higher for patients undergoing surgery during treatment. Combining biological and surgical therapies could optimize the use of the limited available biological treatments for patients with HS.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Figure S1 Kaplan–Meier curves showing the cumulative survival per biological agent due to remission.

Figure S2 Kaplan–Meier curves showing the cumulative survival per biological agent, stratified for biological-naïve vs. previous biological treatment for concomitant use of antibiotics during treatment and for surgery during treatment.

Table S1 Treatment characteristics.

Table S2 Univariate Cox regression analysis for ineffectiveness per biological agent.

Table S3 Univariate Cox regression analysis for side-effects per biological agent.

Table S4 Univariate Cox regression analysis for remission per biological agent.