Guselkumab for hidradenitis suppurativa: a phase II, open-label, mode-of-action study

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Abstract

Background The effectiveness of available biologics for the treatment of hidradenitis suppurativa (HS) is limited. Additional therapeutic options are needed.

Objectives To investigate the efficacy and mode of action of guselkumab [an anti-interleukin (IL)-23p19 monoclonal antibody] 200 mg subcutaneously every 4 weeks for 16 weeks in patients with HS.

Methods An open-label, multicentre, phase IIa trial in patients with moderate-to-severe HS was carried out (NCT04061395). The pharmacodynamic response in skin and blood was measured after 16 weeks of treatment. Clinical efficacy was assessed using the Hidradenitis Suppurativa Clinical Response (HiSCR), the International Hidradenitis Suppurativa Severity Score System (IHS4), and the abscess and inflammatory nodule (AN) count. The protocol was reviewed and approved by the local institutional review board (METC 2018/694), and the study was conducted in accordance with good clinical practice guidelines and applicable regulatory requirements.

Results Thirteen of 20 patients (65%) achieved HiSCR with a statistically significant decrease in median IHS4 score (from 8.5 to 5.0; $P=0.002$) and median AN count (from 6.5 to 4.0; $P=0.002$). The overall patient-reported outcomes did not show a similar trend. One serious adverse event, likely to be unrelated to guselkumab treatment, was observed. In lesional skin, transcriptomic analysis revealed the upregulation of various genes associated with inflammation, including immunoglobulins, S100, matrix metalloproteinases, keratin, B-cell and complement genes, which decreased in clinical responders after treatment. Immunohistochemistry revealed a marked decrease in inflammatory markers in clinical responders at week 16.

Conclusions Sixty-five per cent of patients with moderate-to-severe HS achieved HiSCR after 16 weeks of treatment with guselkumab. We could not demonstrate a consistent correlation between gene and protein expression and clinical responses. The main limitations of this study were the small sample size and absence of a placebo arm. The large placebo-controlled phase IIb NOVA trial for guselkumab in patients with HS reported a lower HiSCR response of 45.0–50.8% in the treatment group and 38.7% in the placebo group. Guselkumab seems only to be of benefit in a subgroup of patients with HS, indicating that the IL-23/T helper 17 axis is not central to the pathophysiology of HS.

What is already known about this topic?

- Hidradenitis suppurativa (HS) is a chronic recurrent inflammatory skin disease with a complex pathophysiology and limited treatment options.
- Currently, adalimumab is the only tumour necrosis factor inhibitor approved for the treatment of HS.

What does this study add?

- Guselkumab (200 mg via subcutaneous injection every 4 weeks for 16 weeks) induced a Hidradenitis Suppurativa Clinical Response (HiSCR) response in 65% of patients with moderate-to-severe HS.
- The double and more frequent dosing, relative to dosing of guselkumab in psoriasis, was well tolerated.
- In clinical responders, guselkumab modulated the gene expression of important HS-associated cytokines through inhibition of the interleukin-23/T helper 17 axis.

Hidradenitis suppurativa (HS) is a chronic, recurrent, inflammatory skin disease that presents with painful inflammatory nodules, abscesses and draining tunnels, typically in the axillae, inguinal and gluteal/perianal areas.[1] HS has a significant impact on patients' quality of life and occupational activity due to severe pain, itching, malodorous discharge and associated psychosocial burden.[2,3]

The aetiology of HS is multifactorial, with an established genetic basis, and associations with risk factors such as smoking, obesity, hormonal involvement and altered skin microbiota.[1,4] Primary pathological changes occur in hair follicles, resulting in follicular occlusion and rupture. The release of pathogen- and damage-associated molecular patterns, together with the highly inflammatory follicle content, activate resident immune cells to produce proinflammatory cytokines [i.e. interleukin (IL)-1, IL-8, IL-17, IL-12, IL-23 and tumour necrosis factor (TNF)], leading to the chemoattraction and activation of additional immune cells, initiating chronic inflammation.[1,4]

Adalimumab, which is the only US Food and Drugs Administration- and European Medicines Agency-approved biologic for HS, targets TNF and induces a 50% improvement in about half of treated patients.[5] However, in HS, the IL-23/T helper (Th)17 pathway has been consistently shown to be upregulated in lesional skin, making IL-23 a potential therapeutic target.[6,7] In an earlier open-label study, the IL-12/IL-23 inhibitor ustekinumab demonstrated clinical efficacy in 82% ($n = 14/17$) of patients with HS.[8] Here we report results from an open-label study to evaluate the safety, tolerability and efficacy of guselkumab, and, in particular, its mode of action, in patients with moderate-to-severe HS.

Patients and methods

Study design

This phase IIa, multicentre, open-label, mode-of-action study (NCT04061395), named the HiGUS study, was conducted at the Department of Dermatology of the University Medical Center Groningen and the Erasmus University Medical Center Rotterdam, the Netherlands.

The total study duration was 24 weeks, comprising a 16-week treatment period and 8 weeks of follow-up. During the treatment period, patients received guselkumab 200 mg administered by subcutaneous (SC) injection at weeks 0 (baseline), 4, 8 and 12. Doubling of the psoriasis dose, similar to double adalimumab dosing in HS relative to psoriasis, was considered necessary, because of the well-known high inflammatory load in HS. The primary endpoints, Hidradenitis Suppurativa Clinical Response (HiSCR), treatment satisfaction and pharmacodynamic effects, were

assessed at week 16. All secondary endpoints were evaluated at weeks 0, 4, 12 and 16.

Patients

The inclusion and exclusion criteria are provided in Appendix S1, with the allowed concomitant medication and rescue therapy listed in Appendix S2 (see Supporting Information).

Primary and secondary endpoints

Changes in inflammatory pathways in skin and plasma induced by IL-23p19 blockade with guselkumab at week 16 relative to baseline, were assessed using transcriptomic (RNAseq) and proteomic methods.

Clinical efficacy was assessed using HiSCR with response thresholds of 50% and 75% improvement; reduction in abscess and inflammatory nodule (AN) count; and points improvement in the International Hidradenitis Suppurativa Severity Score System (IHS4). Patient-reported outcome measures (PROMs) included the patient global assessment, the Dermatology Life Quality Index (DLQI), numerical rating scales for pain and pruritus, and a 10-point treatment satisfaction score.

The safety and tolerability of guselkumab were evaluated based on the incidence of adverse events (AEs) from baseline throughout the safety follow-up period (week 24).

Biopsy collection and processing

At baseline, 4-mm punch biopsies were taken from an index HS lesion, perilesional skin and distant (> 10 cm) uninvolved (nonlesional) skin in the same anatomical area (Appendix S3 and Figure S1; see Supporting Information). At week 16, 4-mm punch biopsies were taken directly adjacent to the baseline lesional and the perilesional biopsy site. Biopsies were processed for bulk RNA sequencing, immunohistochemistry and proteomics of culture supernatants following an *ex vivo* cytokine release assay from 24 h cultured biopsies.[9] Blood was collected at baseline and at week 16 for plasma proteomic analysis.

Whole-tissue RNA sequencing

RNA was extracted from skin biopsies using the RNeasy Fibrous Tissue Mini Kit (Qiagen, Hilden, Germany). RNA was reverse transcribed and sequencing libraries were constructed using Universal RNA-Seq with NuQuant®+UDI (NuGen, San Carlos, CA, USA). The libraries were analysed using the LabChip® GX (Caliper Life Sciences, Hopkinton, MA, USA) and/or a Tapestation 4200 (Agilent Technologies, Santa Clara, CA, USA), and quantified using a Qubit 2.0

fluorometer (Life Technologies, Carlsbad, CA, UA). Libraries were sequenced on a NovaSeq 6000 instrument with NovaSeq 6000 S1 Reagent Kit (Illumina, San Diego, CA, USA) using 2×100-base pair paired-end reads. All were performed as per the manufacturers' protocols (Appendix S4; see Supporting Information).

Protein quantification

Quantification of protein levels in both plasma and biopsy supernatant was performed using the Meso Scale Discovery V-PLEX Human Cytokine 30-Plex Kit (Meso Scale Diagnostics, Rockville, MD, USA), the V-PLEX Human SAA Kit (Meso Scale Diagnostics) and a human beta defensin-2 assay developed by Janssen (Beerse, Belgium). Samples were diluted using the assay diluent according to the package insert. All samples were run in duplicate and processed according to the manufacturers' instructions (Appendix S4).

Immunohistochemistry

Immunohistochemical staining for S100A7, CD3, HLA-DR, CD79A and K16 was performed on cryosections as previously described.[10] Staining intensity was scored by two investigators blinded to treatment response, using a semi-quantitative grading scale from 0 to 5.

Statistical analysis

Patients who dropped out of the study before week 4 were replaced per protocol; however, all patients were included in the safety analyses. Patient characteristics were expressed as numbers of patients and percentages, and mean (standard deviation) or median [interquartile range (IQR)], where appropriate. Associations between patient characteristics and HiSCR response were assessed using univariable logistic regression analyses. Poisson mixed models on IHS4 and AN count, and linear mixed models on PROMs with Satterthwaite approximation were used to assess changes over time. Given the small sample size, no random effects were estimated. All models were corrected for sex and age, except for the AN count model, in which correction caused model misfit.

Table 1 Baseline characteristics of 20 patients with hidradenitis suppurativa (HS) enrolled in the phase II, open-label, mode-of-action study of guselkumab for the treatment of HS

Age (years)	34.5 (28.5–38.5)
Female sex	13 (65)
Age of onset (years)	18.5 (17–20)
Family history of HS	5 (25)
Body mass index (kg m^{-2})	30.8 (25.8–40.7)
Current or ex-smoker	14 (70)
Refined Hurley stage	
IB	4 (20)
IC	5 (25)
IIB	7 (35)
IIC	3 (15)
III	1 (5)
IHS4 score	8.5 (4.3–16)
Mild	1 (5)
Moderate	11 (55)
Severe	8 (40)
AN count	6.5 (4–10.8)
HS PGA	
Mild	5 (25)
Moderate	12 (60)
Severe	2 (10)
Very severe	1 (5)
NRS pain score	7 (3.5–8)
NRS pruritus score	6 (5–8)
DLQI	15 (8–21)

Data are presented as *n* (%) or median (interquartile range). IHS4, International Hidradenitis Suppurativa Severity Score System; AN count, abscess and inflammatory nodule count; PGA, Physician's Global Assessment; NRS, numeric rating scale; DLQI, Dermatology Life Quality Index.

Statistical analyses of clinical outcome measures and PROMS were performed using SPSS Statistics 27.0 (IBM, Armonk, NY, USA). For additional methodology and statistical analyses of RNA sequencing and proteomics, see Appendix S4.

Results

Twenty-two patients were enrolled between July 2019 and December 2020. Thirteen of 20 patients included in the efficacy analyses were female (65%) with moderate disease severity based on the IHS4 (55%; Table 1). Two
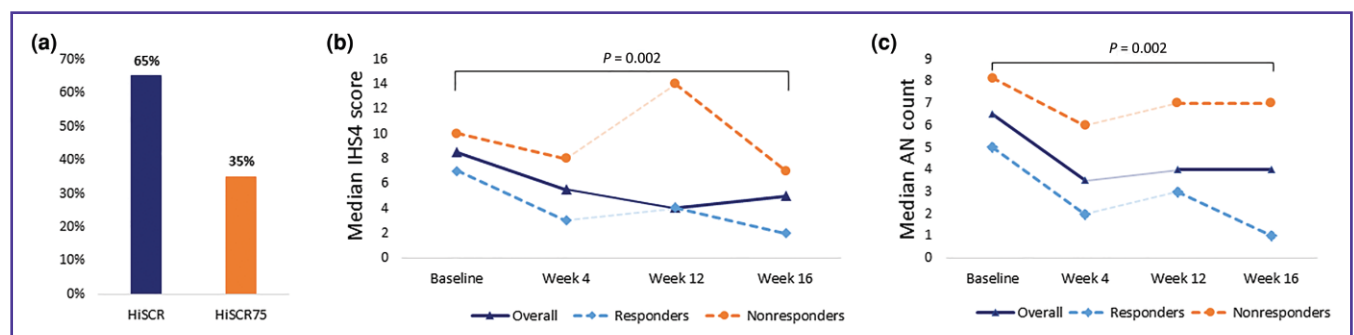

Figure 1 Overview of secondary outcome measures for clinical efficacy. (a) Achievement of Hidradenitis Suppurativa Clinical Response (HiSCR) and 75% improvement in HiSCR (HiSCR75). (b) International Hidradenitis Suppurativa Severity Score System (IHS4) score over time. Significance was achieved when comparing the overall group at week 16 with baseline. Analyses were performed with Poisson mixed models. (c) Abscess and inflammatory nodule (AN) count over time. Significance was achieved when comparing the overall group at week 16 with baseline. Analyses were performed with Poisson mixed models.

patients dropped out: one due to an AE after the baseline visit and the other was lost to follow-up after week 12. Both were included in the safety analysis but replaced for the efficacy analysis as per protocol (Figure S2; see Supporting Information).

Clinical outcome measures

After 16 weeks of treatment, 65% of patients ($n = 13/20$) achieved HiSCR and 35% ($n = 7/20$) reached a 75% improvement in HiSCR. When including the two patients who dropped out as nonresponders, HiSCR improvement was still achieved by 59% of patients ($n = 13/22$; Figure 1). Univariable logistic regression analyses indicated no significant associations between patient characteristics and HiSCR response. Both the median IHS4 and AN count decreased significantly between baseline and week 16, from 8.5 (IQR 4.3–16.0) to 5.0 [IQR 1.0–7.0; model estimate −4.42, 95% confidence interval (CI) −6.92 to −1.91 ($P = 0.002$)] and from 6.5 (IQR 4–10.8) to 4 [IQR 1–7; model estimate −3.48, 95% CI −5.46 to −1.50 ($P = 0.002$)], respectively (Figure 1). The first 4 weeks of treatment showed the fastest clinical improvement in patients, with a significant decrease of 2.23 in IHS4 (95% CI −4.26 to −0.20; $P = 0.033$) and 1.76 in AN count (95% CI −3.24 to −0.28; $P = 0.022$).

Patient-reported outcome measures

Overall, across all PROMs, no significant changes over time were found (Figure S3; see Supporting Information). However, HiSCR responders showed a statistically significantly greater reduction in DLQI scores after 16 weeks of treatment compared with nonresponders [$P = 0.046$ (Table S1; see Supporting Information)]. Moreover, median patient treatment satisfaction at week 16 was rated 7/10 (IQR 5–9), with a higher score representing higher treatment satisfaction.

Safety and tolerability

Fourteen of 22 (64%) patients reported one or more AE. Overall, 63% ($n = 26/41$) of reported AEs were considered to be mild and 34% ($n = 14/41$) moderate (Table S2; see Supporting Information). The most common AEs were headache (after injection), infection (most frequently upper respiratory tract infections) and nausea. One serious AE [SAE; myocardial infarction (MI)] occurred after 16 weeks of treatment and was judged as unlikely to be related to guselkumab treatment (see 'Discussion').

Translational outcome measures

Transcriptomics in hidradenitis suppurativa
In comparison with nonlesional skin, lesional skin showed 376 upregulated and 66 downregulated differentially expressed genes (DEGs) at baseline. Among the upregulated DEGs were genes coding for multiple immunoglobulin heavy and light chains, S100 proteins, collagens, matrix metalloproteinases (MMPs), keratins, B-cell-associated proteins (CD79A and CXCL13), and complement components and receptors (Figure 2). Downregulated DEGs included LL37, CXCL14 and dermcidin. The top 15 enriched Gene

Ontology (GO) biologic processes included phagocytosis, humoral immune response, B-cell-mediated immunity, complement activation and lymphocyte-mediated immunity (Figure 2). Gene set variation analysis (GSVA) of selected gene sets (after correction for multiple testing) identified significant upregulation of the IL-17 and IL-23 pathways, neutrophil pathway, T- and B-cell receptor signalling, and Toll-like receptor signalling genes in lesional skin (Figure 2). Additional analyses were performed to identify whether the expression of genes associated with the IL-17 and IL-23 pathways at baseline could serve as predictors for HiSCR response, but no significant correlation was demonstrated.

Comparison between perilesional and nonlesional skin at baseline identified no DEGs. DEGs between lesional and perilesional skin showed similar patterns to those found between lesional and nonlesional skin described above (data not shown).

HiSCR nonresponders showed no significant differences in gene expression patterns in lesional skin between week 16 and baseline (data not shown). HiSCR responders showed 168 downregulated and 62 upregulated DEGs at week 16 vs. baseline at the index lesion site. Downregulated genes included those encoding fibrosis-associated proteins, MMPs, keratins, S100 proteins, and multiple immunoglobulin and B-cell-associated proteins, indicating a trend towards normalization of these genes after treatment (Figure 3). Upregulated genes were mainly genes encoding keratin and keratin-associated proteins. The top 15 downregulated GO biological processes included those associated with extracellular matrix organization, as well as humoral immune response (Figure 3).

Proteomics analysis in hidradenitis suppurativa biopsy culture supernatant and plasma
Overall, 31 proteins were measured in biopsy culture supernatant and plasma samples from study participants (Tables S3 and S6; see Supporting Information). After statistical analysis and corrections, no statistically significant changes were found for any proteins in the samples when comparing week 16 with baseline in the overall population (Tables S3 and S6). However, HiSCR achievers showed a nonsignificant trend toward lower expression of IL-12/IL-23p40, IL-17A, TNF-α, IL-1β and human beta-defensin 2 after 16 weeks of treatment (Tables S4 and S5, and Figure S4; see Supporting Information).

Immunohistochemistry of hidradenitis suppurativa index skin lesions
Immunohistochemical staining for S100A7, CD3, HLA-DR, CD79A and K16 of biopsies taken at week 16 showed a consistent trend of improvement in HiSCR achievers and no improvement in nonresponders (Table S7; see Supporting Information). HiSCR achievers showed a marked decrease relative to baseline in all markers, particularly in S100A7, CD3 and HLA-DR, indicative of decreased inflammation (Figure 4 and Table S7).

Discussion

This phase IIa, open-label study aimed to evaluate the mode of action, efficacy, safety and tolerability of guselkumab
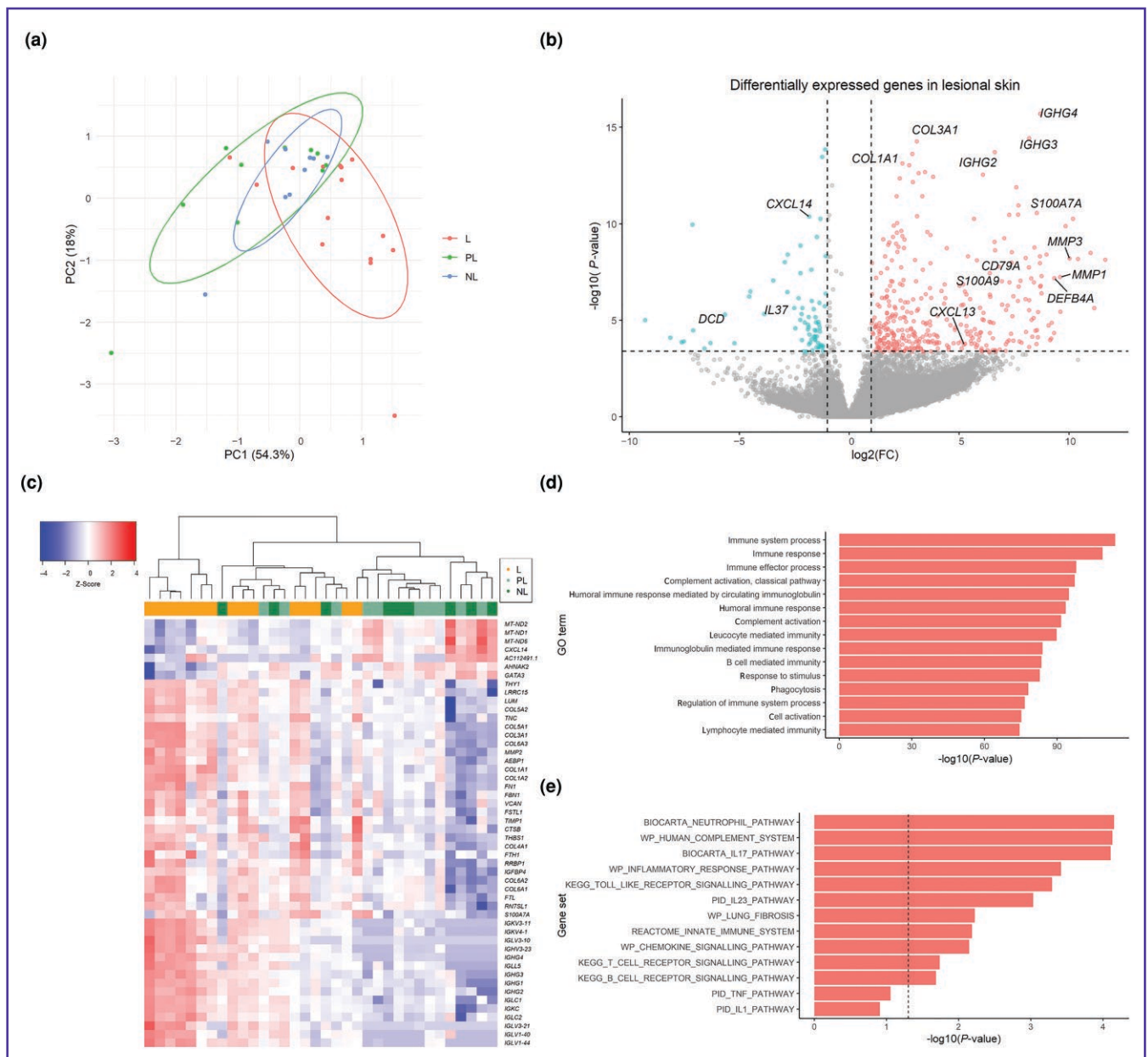
Figure 2 Differentially expressed genes (DEGs) in lesional hidradenitis suppurativa (HS) skin at baseline. (a) Principal component (PC) analysis plot of HS skin samples at baseline. (b) Volcano plot showing upregulated (right upper section) and downregulated (left upper section) DEGs in lesional HS skin vs. nonlesional skin. Graph shows log fold change (FC) in the gene expression of lesional HS skin over nonlesional HS skin samples plotted against the negative log *P*-value of the differences. (c) Heatmap of the top 50 DEGs. (d) Top 15 Gene Ontology (GO) biological processes enriched in lesional skin. (e) Gene set variation analysis (GSVA) analysis of selected pathways. L, lesional skin; PL, perilesional skin; NL, nonlesional skin.

200 mg SC injections once every 4 weeks over a 16-week treatment period.

In a previous small open-label study with ustekinumab in HS, 47% of patients achieved HiSCR.[8] This suggests that guselkumab might be more efficacious than ustekinumab in the treatment of HS. However, a multicentre, placebo-controlled, double-blind phase IIb study of two dosing strategies (NOVA trial; ClincalTrials.gov identifier NCT03628924) with 181 treated patients reported 45.0% and 50.8% HiSCR achievers vs. 38.7% in the placebo arm. These results indicate that guselkumab is not effective in all patients with HS. Owing to the small sample size of our study and the limited data, we could not define the patients who were

responsive to guselkumab treatment. Further research is needed to characterize this subset of patients with HS who benefit from guselkumab therapy.

Dosing of biologics in HS is critical and often higher than in other immune-mediated inflammatory diseases. Consequently, compared with the approved psoriasis dose, a higher dose of guselkumab (200 mg) and a more frequent dosing regimen (every 4 weeks) were implemented in this trial. Despite this, the rates of AEs (70%) and SAEs (4.5%) were marginally above those observed in the VOYAGE 1 (AEs: 51.7%; SAEs: 2.4%), VOYAGE II (AEs: 58.3%; SAEs: 3.6%) and NAVIGATE trials (AEs: 64.4%; SAEs: 6.7%).[11–13] One SAE occurred in this study: a MI during the safety
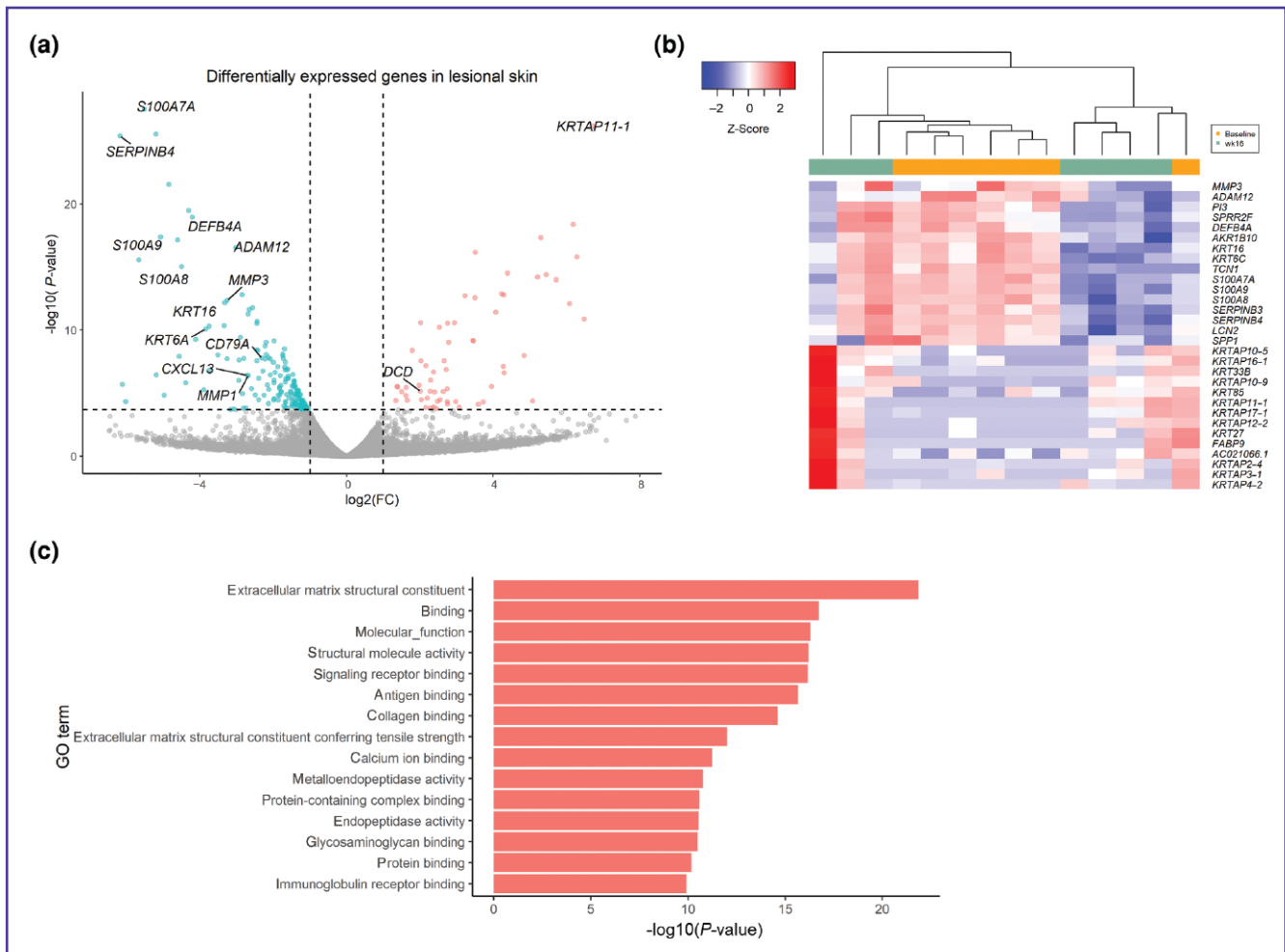
Figure 3 Differentially expressed genes (DEGs) between baseline and week 16 at the index lesion site in Hidradenitis Suppurativa Clinical Response (HiSCR) responders. (a) Volcano plot showing upregulated (right upper section) and downregulated (left upper section) DEG in after 16 weeks of guselkumab treatment compared to baseline. Graph shows log fold change (FC) in gene expression of lesional hidradenitis suppurativa (HS) skin at week 16 over baseline lesional HS skin samples plotted against the negative log *P*-value of the differences. (b) Heatmap of the top 30 DEGs at week 16 of guselkumab-treated HiSCR responders. (c) Top 15 downregulated Gene Ontology (GO) biologic processes.

follow-up after week 16. Based on predisposing risk factors and the short treatment window, the treating cardiologist deemed it unlikely that guselkumab was the causal factor. However, while rare cases of major adverse cardiovascular events have been described in long-term guselkumab treatment for psoriasis, the VOYAGE studies indicated no elevated rates for AEs (including MI) compared to placebo or adalimumab.[14]

Our transcriptomic data identified similar profiles of upregulated and downregulated genes in baseline HS lesional skin vs. nonlesional skin, as previously described.[15,16] Upregulation of genes related to both the IL-23 and IL-17 pathways in lesional HS skin was found through GSVA, supporting the rationale for guselkumab treatment in HS. The high number of extracellular matrix-associated genes found among the significantly decreased number of DEGs could be directly related to the effect of anti-IL-23 treatment. Downstream effects of IL-23 include the induction of IL-17, which is known to promote the activation of several cell types, including keratinocytes and fibroblasts, thereby aiding extracellular matrix degradation, remodelling and fibrosis.[17] The failure

of guselkumab to induce improvement in the majority of patients with HS, suggests that other, IL-23-independent cells are involved in the pathophysiology of HS. Besides IL-23–IL-17 pathway-driven IL-17 production, several other – mostly innate – cell types are capable of IL-23-independent IL-17 production.[18,19] Considering the consistently demonstrated IL-17 upregulation in HS lesions and the promising clinical phase II results of anti-IL-17 biologics in HS, IL-17 remains a druggable target in HS.

Immunohistochemistry of biopsies from HiSCR responders showed a significant decrease in total T cells (CD3) and B cells (CD79A), as well as S100A7 and HLA-DR expression at week 16, indicating a decrease in overall inflammation. However, proteomic analysis of lesional biopsy supernatant samples cultured *ex vivo* showed only a nonsignificant trend toward decreased levels of IL-17A, IL-23, IL-1β and TNF-α after 16 weeks of treatment.

Similarly to three previous small studies, we could not show a consistent association between translational data and the overall clinical response.[8,20,21] This might be explained by the high degree of heterogeneity among biopsy samples with regard to differences in the level of
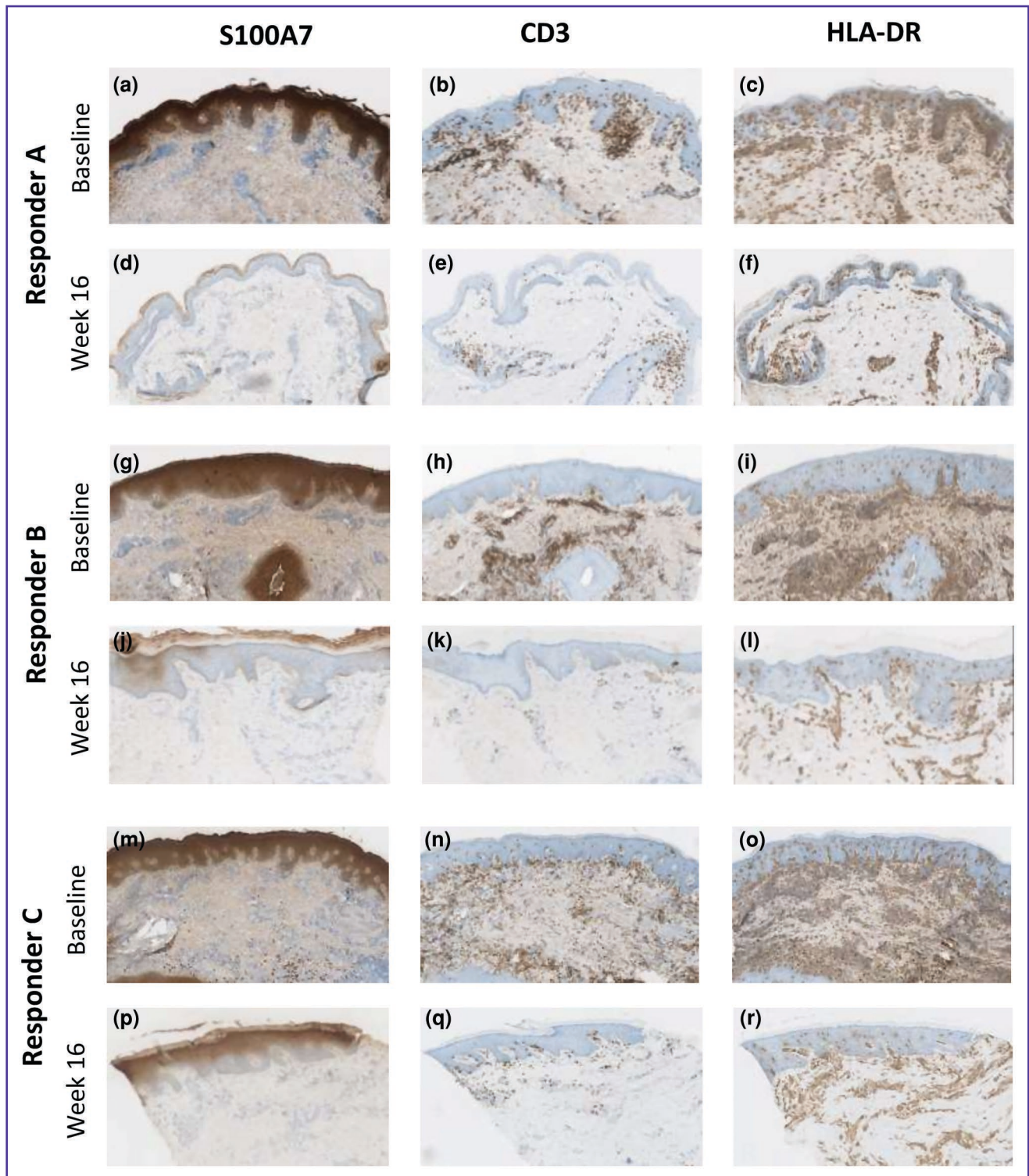
Figure 4 Expression of markers of skin inflammation in lesional biopsies at baseline and week 16 in responders. Created with NanoZoom (× 40). (a–r) Effect of four doses of subcutaneous guselkumab 200 mg on the expression of (a, d, g, j, m, p) S100A7, (b, e, h, k, n, q) CD3 and (c, f, i, l, o, r) HLA-DR at week 16 vs. baseline for three responders.

inflammation, differences in lesion types and size, and changes within lesions over time.[1] Moreover, inherent to this study's design, week-16 biopsies were always obtained from the same index lesion, regardless of whether it had improved or persisted. Therefore, translational data based on samples from the index lesion may not necessarily correlate with overall clinical responses. Additionally, in some cases, the biopsy procedure itself might impact the lesion in a manner leading to reduced inflammation (e.g. removing inflammatory cells and/or immunogenic keratin

fragments). These issues highlight the complexities associated with collecting and analysing samples for biomarker analysis in HS studies.

The limitations of this study include its open-label design, the small number of patients and the lack of a placebo control arm. Nonetheless, the lack of a placebo group does not detract from the primary objective of this study, which was to evaluate the mode of action of guselkumab in HS. Moreover, pain and pruritus were measured as the 'most intense pain/pruritus during the past 7 days'. Even patients who achieve HiSCR may develop one new acute, painful lesion, thereby interfering with the clinical efficacy results relative to patient-reported pain outcomes. Pain and pruritus measurement are likely to be more representative of overall disease severity when measured as an average over the previous 7 days.

Overall, in this phase IIa, open-label, mode-of-action study, 65% of patients achieved HiSCR. PROMs other than those for patient satisfaction and DLQI in responders did not correlate with clinical improvement. Transcriptomic data supported the rationale for IL-23 inhibition with guselkumab in HS but did not consistently correlate with protein expression and clinical responses. Guselkumab seems of benefit only in a subgroup of patients with HS, indicating that the IL-23/Th17 axis is not central to the pathophysiology of HS.

Funding sources

Conflicts of interest

K.D., K.B., P.A., R.S., E.F., B.v.H., L.M.P. and K.R.v.S. report no conflicts of interest. H.H.v.d.Z. has received honoraria from AbbVie, Galderma, Novartis and InflaRX for participation as a speaker and for serving on advisory boards. E.P.P. has received honoraria from AbbVie, Amgen, Celgene, Janssen, Galderma, Novartis and Pfizer for participation as a speaker and for serving on advisory boards, and has also received investigator-initiated grants (paid to Erasmus University Medical Center) from AbbVie, AstraZeneca, Janssen and Pfizer. B.H. reports receiving fees from Janssen-Cilag (advisory boards, educational grants, consultations, investigator initiative studies), AbbVie (advisory boards, educational grants, consultations, investigator initiative studies), Novartis Pharma (advisory boards, consultations, investigator initiative studies), UCB Pharma (advisory boards, consultations), LEO Pharma (consultations), Solenne B.V. (investigator initiative studies), Celgene (consultations, investigator initiative studies), Akari Therapeutics (consultations, investigator initiative studies), Philips (consultation), Roche (consultation), Regeneron (consultation) and Sanofi (consultation), which were paid to the institution. Y.C., S.E.D. and E.J.M.-E. were employees of Janssen Pharmaceuticals at the time the study was conducted.

Data availability

The data underlying this article will be shared upon reasonable request to the corresponding author.

Ethics statement

This study was approved by the institutional review board of the University Medical Center Groningen and Erasmus University Medical Center (METC 2018/694), and the study was conducted in accordance with good clinical practice guidelines and applicable regulatory requirements. All patients provided written informed consent before enrolment.

Supporting Information

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

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