Received: 16 October 2023 | Accepted: 9 November 2023

DOI: 10.1111/jdv.19725

JEADV JOURNAL OF THE EUROPEAN ACADEMY OF DERMATOLOGY & VENEREOLOGY

ORIGINAL ARTICLE

Improved clinical effectiveness of adalimumab when initiated with clindamycin and rifampicin in hidradenitis suppurativa

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Abstract

Background: Adalimumab monotherapy for hidradenitis suppurativa (HS) is often insufficient with a maximum clinical efficacy of 60% in Hidradenitis Suppurativa Clinical Response (HiSCR) and limited effect on draining tunnels. Data suggest that adalimumab therapy could be improved by concomitant antibiotics.

Objective: To compare the clinical effectiveness of adalimumab with clindamycin and rifampicin versus adalimumab monotherapy after 12 weeks.

Methods: This retrospective study included patients who started adalimumab with additional clindamycin and rifampicin and patients treated with adalimumab monotherapy, matched on sex and refined Hurley score. The primary outcome measure was the difference in change in the International Hidradenitis Suppurativa Severity Score System (IHS4) at 12 weeks.

Results: In total, 62 patients were included in the combination therapy group ($n = 31$) and adalimumab monotherapy group ($n = 31$), showing comparable IHS4 scores; 32.5 versus 29, $p = 0.87$ at baseline respectively. The combination therapy demonstrated greater clinical effectiveness expressed in median IHS4 improvement (−20 vs. −9, $p < 0.001$), IHS4-55 (74% vs. 36%, $p = 0.002$), median draining tunnel reduction (−4 vs. −2, $p < 0.001$) and pain response (47% vs. 27%, $p = 0.02$).

Conclusion: Adalimumab initiated with clindamycin and rifampicin shows greater clinical effectiveness than adalimumab monotherapy. An important difference in effect was observed in the decrease of draining tunnels, addressing a serious limitation of adalimumab monotherapy.

INTRODUCTION

Hidradenitis suppurativa (HS) is a debilitating, chronic, inflammatory skin disease, that primarily manifests in the inverse body sites. Distinctive features are inflammatory nodules, abscesses and draining tunnels which can result in pain, pruritus, malodor and suppuration, causing a significant decrease in patient's quality of life.[1] The aetiology of HS is complex, with multiple interacting factors such as genetics, lifestyle factors, hormonal factors and microbiota being involved in both the onset and maintenance of the disease.[2] Furthermore, multiple pro-inflammatory cytokines, such as interleukins (ILs) and tumour necrosis factor (TNF), play a crucial role in the immune dysregulation in HS.[1,2]

Increased understanding of HS pathogenesis resulted in the first registered TNF inhibitor for HS, adalimumab.[3,4] However, adalimumab as monotherapy only shows efficacy in 41.8%–58.6% of patients as measured with the Hidradenitis Suppurativa Clinical Response (HiSCR) after 12 weeks of treatment.[4] Moreover, it has only a marginal effect on draining tunnels resulting and a possible delayed clinical response of up to 6 months.[4,5] This delay in the alleviation of symptoms could lead to unnecessary treatment discontinuation.

P. Aarts and J. C. van Huijstee contributed equally to this study.

Very limited data suggest an increased effectiveness of adalimumab when patients use concomitant antibiotics. However, no comparative studies with adalimumab monotherapy exist.[4,6–8] In the current guidelines, a 12-week course of clindamycin and rifampicin combination therapy is recommended as antibiotic therapy for patients with moderate to severe HS, with 48% of patients achieving HiSCR.[9,10] Rifampicin has antibacterial and anti-inflammatory effects, immunomodulatory properties on neutrophils and destructive activity on bacterial biofilms.[11,12] However, due to a high chance for bacterial resistance, rifampicin should not be prescribed as monotherapy. Therefore, clindamycin, a bacteriostatic and bactericidal antibiotic for gram-positive aerobe and anaerobe bacteria with TNF and IL-1β inhibitory properties, is added to rifampicin therapy.[13]

We hypothesized that initiation of adalimumab in conjunction with clindamycin and rifampicin would lead to an improved treatment response. Therefore, the aim of this study was to assess the effectiveness of adalimumab with clindamycin and rifampicin compared with adalimumab monotherapy in patients matched on sex and disease severity.

MATERIALS AND METHODS

Study design

This retrospective comparative matched cohort study was conducted at the Department of Dermatology, Erasmus University Medical Center Rotterdam, the Netherlands. Clinical data and patient characteristics from patients with moderate to severe HS (refined Hurley)[14] who started adalimumab in combination with clindamycin and rifampicin therapy (hereafter referred to as combination therapy) between April 2020 and June 2023 were collected in our medical registry. Patients were randomly matched on sex and refined Hurley score with patients from a previously published pragmatic clinical trial who were treated with adalimumab monotherapy (hereafter referred to as monotherapy).[15] Collected data included age, sex, body mass index (BMI), family history of HS, smoking status, disease duration, refined Hurley stage, lesion count, dermatology life quality index (DLQI), Hidradenitis Suppurativa Physician's Global Assessment scale (HS-PGA) and numeric rating score (NRS) for pain. The NRS pain scale was converted into a 5-point rating scale, ranging from no pain to very severe pain, to ensure comparability with data from the pragmatic clinical trial (Table S2).[15]

Participants

All adult patients diagnosed with HS who started combination therapy were eligible for inclusion. Inclusion criteria were a lesion count at start of treatment and at the 12-week follow-up, start of adalimumab with concomitant clindamycin and rifampicin. Exclusion criteria were discontinuation of adalimumab, clindamycin or rifampicin prior to follow-up.

Assessments

The primary outcome was the difference in the change in International Hidradenitis Suppurativa Severity Score (IHS4)[16] after 12 weeks of treatment between patients treated with combination therapy and patients treated with monotherapy. Secondary outcome measures included the percentage of patients who achieved IHS4-55 (55% reduction in IHS4 score),[17] HiSCR50, HiSCR75 and HiSCR90 (respectively, ≥50%, 75% and 90% reduction in abscess and nodule (AN) count, no increase in abscesses, and no increase in draining tunnels),[18] a ≥2 point difference in the HS-PGA and a ≥2 point change on a 5-point pain rating scale after 12 weeks of treatment. Additionally, we analysed the change in AN count, draining tunnels and DLQI between groups after 12 weeks.

Statistical analysis

Patient characteristics are expressed as the number of patients and percentage (*n*, %) and mean ± standard deviation (SD) or median and [IQR] where appropriate. Normality was assessed using the Kolmogorov–Smirnov test. Continuous variables were analysed using unpaired *t*-tests or Mann–Whitney *U* tests. Categorical variables were analysed using chi-squared tests or Fisher's exact tests where applicable. Two-sided p-values ≤ 0.05 were considered statistically significant. Statistical analyses were performed using SPSS Statistics 26.0 (IBM Corporation, Armonk, NY, USA).

Ethics

This study was granted exemption from the Dutch Medical Research with Human subjects Law by the institutional medical ethics review board from the Erasmus MC (MEC-2022-0799). The study was conducted in accordance with the provisions of the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice guideline and applicable regulatory requirements. All patients provided written informed consent before data collection.

RESULTS

Study participants

Screening for combination therapy was performed in 36 patients. Of these, two patients had a positive quantiferon test and one patient withdrew consent for the treatment due to needle phobia. One patient was lost to follow-up, and one patient discontinued antibiotic treatment after 1 month due to a pharmacy error. No patients discontinued due to side effects. In total, 31 patients were included in the analysis and matched with 31 previously collected monotherapy controls. The groups had comparable IHS4 scores; 32.5 [IQR

17.5–38.8] versus 29.0 [IQR 24.0–43.0], $p = 0.87$ and DLQI scores; 19.0 [IQR 12.0–23.0] versus 15.0 [IQR 13.0–21.0], $p = 0.55$, at baseline for combination therapy and monotherapy, respectively. The combination group had significantly higher pain scores ($p = 0.04$) than the monotherapy group. Baseline characteristics are shown in Table 1.

Effectiveness

The patients treated with combination therapy showed a significantly greater decrease in IHS4 than patients treated with monotherapy, −20 [IQR −29 to −13] and −9 [IQR −16 to −4], $p < 0.001$ respectively (Figure 1). In addition, significantly more patients achieved IHS4-55 (74% (23/31) vs. 36% (11/31)), $p = 0.002$ and a ≥2 point change in HS-PGA (68%, (21/31) vs. 39% (12/31)), $p = 0.02$ in the combination therapy group compared with the monotherapy group. While HiSCR could not be calculated in 17 (55%) of the patients in the combination therapy group and 14 (45%) of the patients in monotherapy group, a significantly higher proportion of the combination therapy group achieved HiSCR50 (86%, 12/14) compared with the monotherapy group (41%, 7/17), $p = 0.02$ (Figure 2). Moreover, more patients from the combination therapy group achieved HiSCR75 (9/14 (64%) vs. 4/17 (24%), $p = 0.03$) and HiSCR90 (5/14 (36%) vs. 0/17 (0%), $p = 0.01$). Although there was no significant difference in the median change in AN count between the two groups (Table 2), patients in the combination therapy group demonstrated a significantly greater reduction in draining tunnels than the monotherapy group, with a median reduction of −4 [IQR −6 to −3] and −2 [IQR −3 to 0], $p < 0.001$, respectively (Figure 3).

Patient-reported outcome measures

Significantly more patients in the combination therapy group (47%, 16/30) achieved ≥2 point change, on a 5-point scale, in pain scores than the monotherapy group (27%, 8/31), $p = 0.02$ (Table 2). Although the difference in DLQI

TABLE 1 Patient characteristics.

Patient characteristics	Combination therapy ($N = 31$)	Monotherapy ($N = 31$)	p-value
Age, median [IQR]	39.5 [32.5–49.0]	36 [29–48.0]	0.34
Sex[a], *n* (%)	15 (48)	15 (48)	
Body mass index, median [IQR]	31.4 [29.0–37.5]	29.1 [25.2–36.5]	0.16
Disease duration (years), median [IQR]	17 [11.0–23.8]	11 [7.0–24.0]	0.17
Positive family history, *n* (%)	8 (40)	15 (50)	0.49
Missing or unknown, *n*	11	1	
Current or ex-smoker, *n* (%)	20 (65)	25 (81)	0.16
IHS4-score, median [IQR]	32.5 [17.5–38.8]	29 [24.0–43.0]	0.87
Hurley stage			
Hurley stage I, *n* (%)	1 (3)	1 (3)	
Hurley stage II, *n* (%)	15 (48)	15 (48)	
Hurley stage III, *n* (%)	15 (48)	15 (48)	
Refined Hurley stage			
Moderate (1B, 2B), *n* (%)	4 (13)	4 (13)	
Severe (1C, 2C, 3), *n* (%)	27 (87)	27 (87)	
Lesion count			
Infl. nodules, median [IQR]	2.0 [0.3–4.0]	3.0 [0.0–6.0]	0.55
Abscesses, median [IQR]	0.0 [0.0–0.3]	0.0 [0.0–0.3]	0.80
Draining tunnels, median [IQR]	8.0 [4.0–9.0]	6.0 [4.0–10.0]	0.62
Pain			0.04
No pain, *n* (%)	2 (7)	3 (10)	
Little pain, *n* (%)	4 (13)	3 (10)	
Moderate pain, *n* (%)	3 (10)	13 (41)	
Severe pain, *n* (%)	12 (40)	9 (29)	
Very severe pain, *n* (%)	9 (30)	3 (10)	
Missing, *n*	1	0	

Note: Adalimumab in conjunction with clindamycin and rifampicin is referred to as combination therapy. Adalimumab monotherapy is referred to as monotherapy.
Abbreviations: IHS4, International Hidradenitis Suppurativa Severity Score System; IQR, interquartile range.
[a]Female.

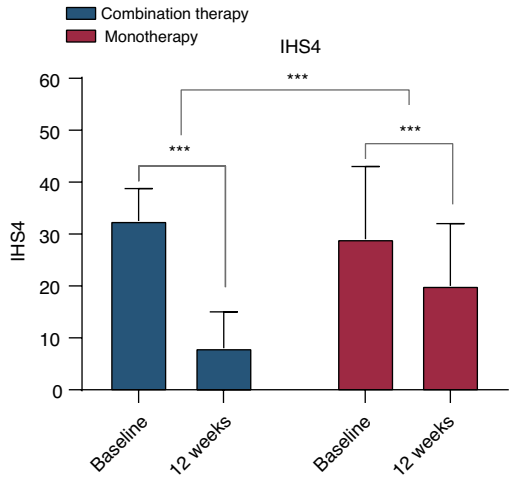

FIGURE 1 Median IHS4 scores at baseline and after 12 weeks of treatment. Both groups demonstrate a significant improvement. However, the decline is significantly greater in patients treated with adalimumab in conjunction with clindamycin and rifampicin (combination therapy) compared with adalimumab monotherapy. ***$p < 0.001$.

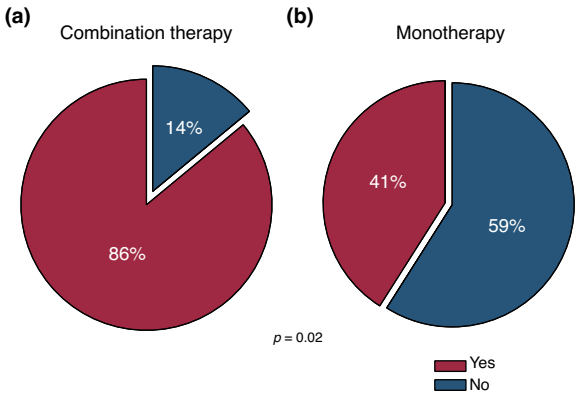

FIGURE 2 Hidradenitis Suppurativa Clinical Response (HiSCR50) achievers after 12 weeks of therapy with either adalimumab in conjunction with clindamycin and rifampicin (combination therapy (a)) or adalimumab monotherapy (monotherapy (b)). Significantly more patients achieve HiSCR in the combination therapy group (86%) compared with the monotherapy group (41%), $p = 0.02$.

improvement appeared to be striking, with a change from 18 [IQR 12.0–23.0] at baseline to 4 [IQR 1.5–12.5] after 3 months for the combination therapy group versus 15 [IQR 13.0–21.0] to 10 [IQR 5.0–15.0] for the monotherapy group, the difference was non-significant ($p = 0.12$).

Safety

In total, adverse events (AEs) were reported by 15 (48%) patients with combination therapy and 14 (45%) patients with monotherapy. Fourteen (45%) patients in the combination therapy group reported AEs possibly related to treatment compared with 10 (32%) patients in the monotherapy group The largest difference in adverse events was observed in gastrointestinal symptoms, with 11 patients (36%) in the combination therapy group versus one patient (3%) in the monotherapy group. Furthermore, the combination therapy group reported no HS flares, whereas the monotherapy group reported three HS flares. A full overview of the adverse events is shown in Table S1.

DISCUSSION

The initiation of HS treatment with the combination of adalimumab with clindamycin and rifampicin showed greater clinical effectiveness than adalimumab monotherapy as measured by IHS4 (–55), HS-PGA, pain, draining tunnels and HiSCR. With a HiSCR achievement rate of 41% and an IHS4-55 of 36%, the effectiveness of adalimumab monotherapy in our study was slightly lower than the efficacy rates of the PIONEER I trial, with 42% and 45%, respectively.[4] Moreover, it scores notably lower than the PIONEER II study with a HiSCR of 59% and an IHS4-55 of 61%.[4] This difference could be explained by the fact that the PIONEER studies were well controlled randomized trials in contrast to the patients in this study who were derived from our registry of a pragmatic RCT.[4,15,17] Pragmatic RCTs are designed to resemble real-world practice by allowing bias of daily practice to increase generalizability and therefore often results in lower treatment outcomes.

Both treatment groups achieved a minimal clinically important difference of 3.3 for the DLQI.[19] However, despite the stronger reduction in the combination therapy group, the difference was not statistically significant. This could be the explained by the retrospective design of the study, which increases the risk of missing data (total: $N = 9$, pairs: $N = 6$). Arguably, a significant difference might have been found with a larger paired sample size. Another outcome measure with a high missing data rate was the HiSCR ($N = 31$). However, this was as a result of the limitation of this score itself, as it cannot be used when a patient has an AN count lower than three.

Analysing the effects on individual lesions demonstrated no difference in AN count between the groups. However, a clear decrease was seen in draining tunnels (–4 vs. –2, $p < 0.001$) in the combination therapy group. This finding is particularly interesting, as adalimumab monotherapy has been shown to be less effective in reducing draining tunnels.[4,5] We hypothesize that the biofilm formed in dermal tunnels, is not targeted by adalimumab, potentially leaving a prominent source of inflammation during treatment. In contrast, rifampicin has shown to be effective in eradicating tunnel biofilm in HS skin cultures.[20] Therefore, we argue that the combination of adalimumab with clindamycin and rifampicin should be considered, especially in patients with draining tunnels.

In line with previously described side effects of clindamycin and rifampicin in HS patients receiving the combination therapy were more likely to experience gastrointestinal

TABLE 2 Clinical and patient reported outcomes after 12 weeks of treatment.

	Combination therapy ($N=31$)	Monotherapy ($N=31$)	p-value
Delta IHS4, median [IQR]	−20 [−29 to −13]	−9 [−16 to −4]	<0.001
IHS4-55, *n* (%)	23 (74)	11 (36)	0.002
HiSCR, *n* (%)			
50	12 (86)	7 (41)	0.02
75	9 (64)	4 (24)	0.03
90	5 (36)	0 (0)	0.01
Missing, *n*	17	14	
≥2 change in HS-PGA, *n* (%)	21 (68)	12 (39)	0.02
≥2 change in pain, *n* (%)	16 (47)	8 (27)	<0.01
Missing, *n*	1	0	
Delta AN count, median [IQR]	−1 [−4 to 0]	−1 [−4 to 0]	0.76
Delta draining tunnels	−4 [−6 to −3]	−2 [−3 to 0]	<0.001

Note: Adalimumab in conjunction with clindamycin and rifampicin is referred to as combination therapy. Adalimumab monotherapy is referred to as monotherapy.
Abbreviations: AN count, abscess and inflammatory nodule count; HiSCR, Hidradenitis Suppurativa Clinical Response; HS-PGA, Hidradenitis Suppurativa Physician's Global Assessment scale; IHS4, International Hidradenitis Suppurativa Severity Score System; IHS4-55, 55% reduction in IHS4 score.

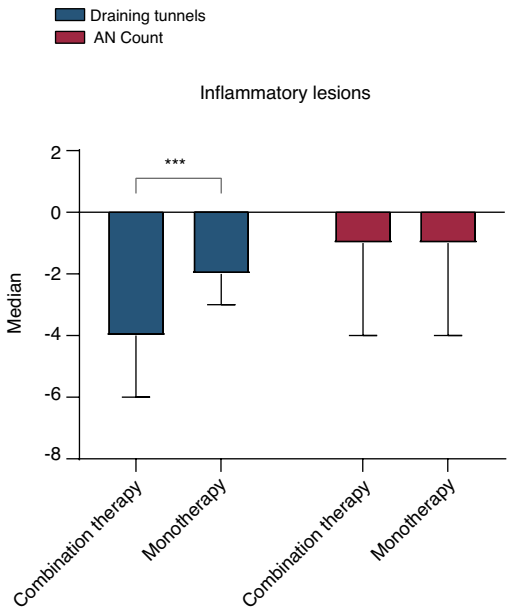

FIGURE 3 Median reduction of draining tunnels and AN count after 12 weeks of therapy with either adalimumab in conjunction with clindamycin and rifampicin (combination therapy) or adalimumab monotherapy (monotherapy). A greater reduction in draining tunnels was observed in the combination therapy group compared with the monotherapy group, while no difference was seen in AN count. ***$p<0.001$.

symptoms than the adalimumab monotherapy group ($n=11$ vs. 1).[21] Importantly, this did not lead to treatment discontinuation. In the monotherapy group two patients reported HS flaring, which required additional therapy with clindamycin and rifampicin which was started at the 12-week visit, and one patient reported an acute abscess that required incision and drainage at Week 12 for pain relief. No additional interventions were required in the combination therapy group.

The question remains whether the combination with other antibiotics used for the treatment of HS would also enhance the effectiveness of adalimumab. It has recently been demonstrated that the effectiveness of doxycycline is as effective as clindamycin and rifampicin combination therapy. Furthermore, increasing evidence reveals clindamycin monotherapy to be an effective therapy for HS.[12,22,23] Therefore, clinical studies investigating the effectiveness of tetracyclines or clindamycin with adalimumab should be initiated.

In accordance with current guidelines, clindamycin and rifampicin are not to be used for longer than 3 months, which limited follow-up time.[9] This could be considered as a limitation together with the retrospective design. The matching on disease severity and sex on the other hand, limits bias and could be considered as a strength of this study.

Evidently, our results are only applicable to adalimumab therapy. However, we believe that this beneficial effect with antibiotics could potentially also be applied to other antibiotics and biologics, such as infliximab and the European Medicines Agency-approved secukinumab. Further research will be needed to prove this hypothesis.

CONCLUSION

This retrospective matched cohort study shows significantly greater effectiveness when adalimumab is initiated with clindamycin and rifampicin compared with adalimumab monotherapy. Therefore, we would recommend the addition of clindamycin and rifampicin to adalimumab therapy during the first 12 weeks of treatment, particularly in patients with draining tunnels.

AUTHOR CONTRIBUTIONS

P. Aarts and J. C. van Huijstee conducted the research, wrote the initial manuscript and approved the final version. K. R. van Straalen, H. H. van der Zee and E. P. Prens participated in the conception and design of the study, revised the manuscript and approved the final version.

ACKNOWLEDGEMENTS
None.

FUNDING INFORMATION
No funding.

CONFLICT OF INTEREST STATEMENT
The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT
This study was granted exemption from the Dutch Medical Research with Human subjects Law by the institutional medical ethics review board from the Erasmus MC (MEC-2022-0799). The patients in this manuscript have given written informed consent to publication of their case details.

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SUPPORTING INFORMATION
Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Aarts P., van Huijstee JC, van der Zee HH, van Straalen KR, Prens EP. Improved clinical effectiveness of adalimumab when initiated with clindamycin and rifampicin in hidradenitis suppurativa. J Eur Acad Dermatol Venereol. 2023;00:1–6. https://doi.org/10.1111/jdv.19725