Metformin in conjunction with doxycycline is not superior to doxycycline monotherapy for hidradenitis suppurativa; results of a phase III double-blinded randomized placebo- controlled trial

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Dear Editor, Hidradenitis suppurativa (HS) is a chronic, immune-mediated skin disease which significantly impairs quality of life and is associated with several comorbidities.[1–4] Treatment options for HS remain limited overall, and no therapies are currently registered for patients with mild-to-moderate disease. Limited studies have shown that the oral antidiabetic metformin induces clinical improvement in HS, an effect attributed to its direct and indirect anti-inflammatory properties.[5–8] However, there is no unequivocal clarity about its clinical efficacy on inflammatory lesions in HS. To address the variable clinical efficacy data, we conducted a randomized placebo-controlled trial to evaluate the additional clinical efficacy of metformin in patients with mild-to-moderate HS.

This multicentre double-blind randomized placebo-controlled superiority trial (NCT04649502) was conducted at three university medical centres across the Netherlands from September 2021 to August 2023. Patients were randomized 1 : 1 to either metformin (uptitrated from 500 mg to 1500 mg daily) with doxycycline (100 mg daily) or placebo with doxycycline. Both groups received treatment for 6 months, with hospital visits every 6 weeks. The primary outcome measure was the change in the International Hidradenitis Suppurativa Severity Score System (Δ IHS4) between the groups after 24 weeks. Secondary outcomes assessed the IHS4-55 (55% reduction of the IHS4 score), Hidradenitis Suppurativa Clinical Response-50 (HiSCR50) [a ≥ 50% reduction in abscess and nodule (AN) count with no increase in abscesses and no increase in draining tunnels], change in AN count, patient-reported outcomes and metabolic parameters. Safety evaluations included adverse events, vital signs and laboratory assessments. The sample size calculation indicated 28 patients per treatment arm, based on the hypothesis that the metformin–doxycycline combination would be superior to doxycycline monotherapy. An intention-to-treat (ITT) analysis was performed with a conservative last observation carried forward to correct for missing data, for patients who had at least one visit after baseline. The protocol was reviewed and approved by the local institutional review board (MEC-2021-0024) and the study was conducted accordingly.

Sixty-two patients were randomized in two comparable groups with baseline characteristics, e.g. sex distribution, disease duration, family history, smoking status (data not shown), representative of the general HS population. Five patients discontinued before week 6. This resulted in 29 patients in the metformin–doxycycline group and 28 patients in the doxycycline monotherapy group for the ITT analysis (see Table 1). Both groups showed significant clinical improvement in median IHS4 after 24 weeks of –3 [interquartile range (IQR) –4.5 to –1.0; $P=0.002$] in the metformin–doxycycline group vs. –2 (IQR –4.8 to –1.0; $P=0.002$) in the doxycycline monotherapy group. However, between the groups no difference was observed ($P=0.596$). No differences between the groups were found in IHS4-55 ($P=0.900$), HiSCR50 ($P=0.131$), change in AN count ($P=0.234$), change in Dermatology Life Quality Index ($P=0.485$), change in flares ($P=0.110$) and change in pain scores ($P=0.234$). However, a significant difference between the two groups was found in the reduction of the body mass index ($P<0.001$), waist circumference ($P=0.006$) and fasting glucose ($P=0.049$) in favour of the metformin–doxycycline group compared with the doxycycline monotherapy group after 24 weeks.

The results of our powered multicentre, double-blind, randomized, placebo-controlled trial did not demonstrate an additional clinical effect of metformin, unlike previous publications. However, the evidence for metformin's clinical effect comes from limited nonrandomized, in part retrospective,

Table 1 Clinical and patient-reported outcome measures[a,b]

	Metformin + doxycycline $n=29$	Compared with baseline *P*-value	Doxycycline monotherapy $n=28$	Compared with baseline *P*-value	Between-group comparison *P*-value
Baseline					
IHS4	5 (3.0–7.5)		5 (2.3–7.8)		0.702
DLQI	11 (6.0–16.0)		12 (8.8–16.5)		0.186
Flares	5 (3.0–8.0)		4 (2.0–5.0)		0.143
Pain	3 (2.0–5.3)		3.5 (2.0–6.0)		0.406
AN count	4 (2.8–6.0)		3 (2.0–6.0)		0.234
24 weeks					
IHS4	1 (0.0–3.5)	0.002	2 (1.0–5.0)	0.002	0.347
Δ IHS4	–3 (–4.5 to –1.0)		–2 (–4.8 to –1.0)		0.596
AN count	1 (0.0–2.5)	< 0.001	1.5 (0.3–3.0)	< 0.001	0.555
Δ AN count	–3 (–4.0 to –1.0)		–1.5 (–3.8 to –1.0)		0.234
IHS4-55, *n* (%)	16 (55)		15 (54)		0.900
HiSCR50, *n* (%)	15 (65)		7 (41)		0.131
Missing	6		11		
DLQI	5 (2.0–10.0)	< 0.001	7 (4.0–16.5)	0.011	0.395
Δ DLQI	–5 (–10.0 to 0.0)		–5 (–7.0 to 0.3)		0.485
Missing	3		2		
Flares	3 (1.0–6.5)	0.015	4 (2.0–7.8)	0.394	0.573
Δ flares	–2 (–4.0 to 0.0)		–1 (–3.0 to 2.0)		0.110
Pain	1 (0.0–3.0)	< 0.001	2.5 (1.0–4.8)	0.015	0.947
Δ pain	–2 (–3.0 to 0.5)		–1 (–3.0 to –1.0)		0.234
Missing	0		1		

Δ, change from baseline to week 24; AN count, abscess and nodule count; DLQI, Dermatology Life Quality Index; HiSCR, Hidradenitis Suppurativa Clinical Response; HiSCR50, ≥50% clinical response; IHS4, International Hidradenitis Suppurativa Severity Score System; IQR, interquartile range.
[a]Sample size explanation: The sample size was calculated based on an expected mean IHS4 of 3.0 (SD 2.0) in the doxycycline group and 1.5 (SD 2.0) in the combination group after 24 weeks. A total of 28 patients per arm was required to achieve 80% power at a significance level of 0.05. Allowing for a 10% drop-out rate, the final sample size for randomization was set at 62 participants. [b]All data are depicted as median (IQR) unless specified otherwise.

case series. Our results indicate that the significant clinical improvements in both groups were driven by doxycycline. This could be due to overlapping anti-inflammatory mechanisms or a clinical ceiling effect in mild-to-moderate HS, leaving little room for metformin to provide additional benefits. We observed a significant reduction in flare count within the metformin–doxycycline group, while no such improvement was seen in the doxycycline monotherapy group, although the between-group difference did not reach statistical significance. In line with metformin's main mode of action, we observed significant improvements in metabolic parameters in patients in the metformin–doxycycline group, whereas the doxycycline monotherapy group showed no such effect. Arguably, the improvement in weight loss and metabolic parameters could indirectly lead to improvement of inflammatory activity over a longer time, especially in patients with metabolic risk factors. Furthermore, these improvements in metabolic parameters demonstrate good medication adherence in our metformin study population. Even though metformin therapy did not improve the clinical outcome, we still consider it an addition to the HS treatment armamentarium for the improvement of HS comorbidities. Improvement of metabolic risk factors should be a treatment goal which, if successful, could lead to clinical improvement over time. While metformin did not demonstrate additional short-term clinical benefit over doxycycline, it is important to note that doxycycline is not a viable long-term treatment option for HS based on concerns about antimicrobial resistance. In contrast, metformin is suitable for longer-term use.

In conclusion, this multicentre double-blind randomized placebo-controlled trial shows that the clinical efficacy of metformin combined with doxycycline is not superior to doxycycline monotherapy in patients with mild-to-moderate HS. The observed improvements in metabolic parameters could be a reason to prescribe metformin alongside other anti-inflammatory therapy for HS, especially in patients with known metabolic risk factors such as obesity, insulin resistance and metabolic syndrome.

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