ORIGINAL ARTICLE

Metformin for the treatment of hidradenitis suppurativa: a little help along the way

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Abstract

Background Despite recent insights into its aetiology, hidradenitis suppurativa (HS) remains an intractable and debilitating condition for its sufferers, affecting an estimated 2% of the population. It is characterized by chronic, relapsing abscesses, with accompanying fistula formation within the apocrine glandbearing skin, such as the axillae, ano-genital areas and breasts. Standard treatments remain ineffectual and the disease often runs a chronic relapsing course associated with significant psychosocial trauma for its sufferers.

Objective To evaluate the clinical efficacy of Metformin in treating cases of HS which have not responded to standard therapies.

Methods Twenty-five patients were treated with Metformin over a period of 24 weeks. Clinical severity of the disease was assessed at time 0, then after 12 weeks and finally after 24 weeks. Results were evaluated using Sartorius and DLQI scores.

Results Eighteen patients clinically improved with a significant average reduction in their Sartorius score of 12.7 and number of monthly work days lost reduced from 1.5 to 0.4. Dermatology life quality index (DLQI) also showed a significant improvement in 16 cases, with a drop in DLQI score of 7.6.

Conclusion Metformin helps control HS with minimal side effects and good patient compliance and can represent a further agent in the spectrum of treatments available in the treatment of this disease.

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Conflict of Interest

None declared.

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Introduction

Hidradenitis suppurativa (HS) is a stubborn inflammatory disorder affecting an estimated 2% of the population. Females are significantly more affected than males.

HS is insidious and develops typically in the second or third decade in otherwise healthy individuals. It should be strongly suspected in post pubertal adults presenting with recurrent, deep furuncular lesions in flexural sites, especially if such lesions respond poorly to antibiotic treatment.

It is characterized initially by the development of deep tender subcutaneous nodules primarily affecting the apocrine gland bearing areas, including the axillae, perineum, and sub and inframammary regions.

Over time these nodules may spontaneously rupture forming chronic, relapsing, deep-seated dermal abscesses. Eventually, these become complicated by fibrosis and formation of extensive sinus tracts, which can coalesce and potentially dissect into deep structures including muscle, lymph nodes, and even urethra and bowels. They extrude foul smelling purulent discharge. Subsequent repair with scarring, dermal contractures and in duration of the skin follows.

There is considerable physical pain from these disfiguring lesions as well as the immense social embarrassment. The enormity of its psychological impact on patients' social, personal, work and familial spheres of life has been well documented.[1,2]

Spontaneous resolution is unlikely, and progressive disability is commonly experienced by sufferers. It is primarily for this reason that this condition is associated with a high degree of morbidity.

Potential complications from HS include increased risk of squamous cell carcinoma developing in 2–4% of sufferers.[3,4] Other

long term sequelae are contractures, which can affect limb mobility, serious infections and anaemia.[5]

The aetiology of HS is still not completely understood.[6] It was long thought to have an infective aetiology, being a suppurative disorder, but bacterial colonization has now been shown to be a secondary event and even very potent antibiotic treatments remain unsuccessful, at least in the long term. Staphylococci eradicating combination therapy with Clindamycin and Rifampicin may sometimes be effective,[7,8] but improvement is temporary and recurrences common after discontinuation of the treatment.

The peculiarity of distribution within the apocrine glands led it to be considered a disease of the apocrine glands. However, histopathology studies have confirmed it to be mostly a disorder of the pilosebaceous unit with the central aspect of this pathological process being follicular structural abnormality and consequent inflammation with apocrine sweat gland involvement remaining a secondary aspect.[9–12] A genetic predisposition leading to a specific alteration of the terminal follicular epithelium with a possible dilatation and distortion of the upper infundibular tract seems to be the initial causative factor.[13] This would lead to the occlusion of the affected hair follicles with subsequent bacterial infection, pustula formation, fistulization and scarring.

This represents a sequence of events similar in certain aspects to acne vulgaris. It has therefore been strongly suggested that the name of 'acne inversa' is a more accurate representation of its pathology.[14]

Complementing the sequence of events described above is the recent observation of the alteration of sebaceous gland tissue mass in HS sufferers. Recent studies raised suspicion of the possibility of the primary involvement of sebaceous glands in the aetiology of HS, with a generalized reduction of Sebaceous gland tissue mass being demonstrated in perilesional tissue. Sebaceous glands contribute to the local homeostasis of the skin with their antibacterial, antifriction, endocrine and inflammation modulatory functions and it has been speculated that a reduction in their volume or possibly loss of one or more of their specific functions may represent one of the primary changes leading to the cascade of events that lead to HS.[15]

A further theory about HS having an immunological aetiology with an upregulation of toll-like receptors has also been suggested and immunological disregulation might represent another co-factor.[16,17] In particular an exaggerated expression of Toll-like receptor 2 has been found in the macrophages and dendritic cells infiltrating the dermis in HS affected areas. Toll-like receptor 2 is known to have a pivotal role in the innate immune response, and its overexpression had been suspected to represent a possible contributory factor in the pathogenesis of HS.[18] Also neutrophilic cells isolated from HS patients had been found to be responsible for an exaggerated release of free oxygen radicals, suggesting that dysfunctionality of neutrophils might play a role in the pathogenesis and progression of this disease.[17]The use of immunosuppressants, and biologic inhibitors of TNF-α, although promising in some cases,[19–22] have however given conflicting results in other cases,[23] leaving immunological disregulation as a theory of uncertain significance.

The notable female preponderance, the association with polycistic ovary syndrome (PCOS) and the observation that HS may decline significantly following menopause has suggested a possible hormonal influence.[24] Past studies, having observed the association of HS with irregular menstruation, hirsutism, premenstrual HS flares and acne vulgaris, suspected high total testosterone concentrations and higher free androgen index as possible factors.[25] Although some studies have argued against Hyperandrogenism as a possible cause, as androgen levels were found normal in a significant proportion of HS patients,[26,27] more recent studies seem to have definitely confirmed a hormonal influence, with a statistically significant association with obesity, hyper-androgenism, and PCOS (calculated as 38% of analyzed cases). Gene mapping of familial cases seem to have identified a genetic link[13] and further studies suggested a hormonal influence on gene expression.

In terms of treatment, an effective standalone therapy for HS has not yet been established. Traditional treatments have included retinoids, antibiotics (including eradication treatment with Clyndamycin and Rifampicin,[7,8]) and Dapsone, both systemic and topical.[28–30] Clinical and histological similarities of HS to acne vulgaris have led to treatment attempts with Isotretinoin. This medication, which is very effective for acne, is, however, almost redundant for HS. There is only anecdotal evidence substantiating any successful outcomes with its use. Acitretin has been more successful, however, its use is restricted to male patients (who are less commonly affected than females), and females of non-child bearing age (not frequently sufferers of this condition).[31,32]

As a result of the possible hormonal influence, there have been several trials conducted using anti-androgen therapies, such as cyproterone acetate[33]and finestride,[34] with some documented improvement in disease activity.

Anecdotal reports of improvements obtained with other various treatment options have also been published over the years: radiation therapy,[35,36] Botulinum toxin,[37] anti TNF-α antagonists[19] and PDT,[38,39] have been used with variable success.

Carbon dioxide laser therapy has been successfully used to ablate tissue, producing results similar to standard surgery at its endpoint.[40]

Early definitive surgical intervention has been regarded as one of the most effective treatments for intractable HS. Surgical removal of the entire follicular sweat gland apparatus with generous excision margins is currently being advocated as the gold standard.[4,41,42]

However poor surgical outcomes, often with results unacceptable to patients, have frequently been cited with surgery; the most commonplace complications being high recurrence rates, scarring, or skin graft failure.

This frustrating scenario led us to begin a systematic analysis of cases under our care and an analysis of the data collected

was begun in an attempt to improve and optimize outcomes or at least contribute to broadening the spectrum of treatment strategies.

As the vast majority of our patients were females with a relatively high BMI, it suggested that sex hormone balance could represent a possible treatment target, confirming the data found in specialized literature. Further findings from our analysis demonstrated that a number of subjects suffered from low glucose tolerance and that some cases were also affected by PCOS. These observations provided the rationale for considering Metforminas a novel potential treatment option.

Aim

To evaluate the clinical efficacy of Metformin in treating cases of HS, which have not responded to standard therapies.

Material and methods

Twenty-five patients with HS were identified and recruited from amongst a set of dermatology outpatientswith no past medical history of previous Metformin use. Twenty-four of them were already diagnosed with the condition and had already received numerous and protracted courses of antibiotics with poor or very minimal results. Twenty-two were females, three males (See Tables 1 and 4). In two cases the disease affected both mother and daughter.

The diagnosis of HS was made on clinical grounds by two clinicians, and in two cases, biopsies were taken so as to rule out a possible cancerous transformation (Marjolin ulcer).

All the patients were extremely frustrated with their condition, and a few had even expressed suicidality as a direct consequence. Eleven patients had been sufficiently depressed to have been managed on anti-depressants.

All the patients had already received orthodox treatments, with both long term Augmentin, Erythromycin, Doxycycline or Rifampicin in combination with Clindamycin. Eleven had also received Isotretinoin and one man had received both Isotretinoin and Acitretin. Another seven had been hospitalized on several occasions to be treated surgically with excision of the affected areas, or drainage, with disappointing outcomes.

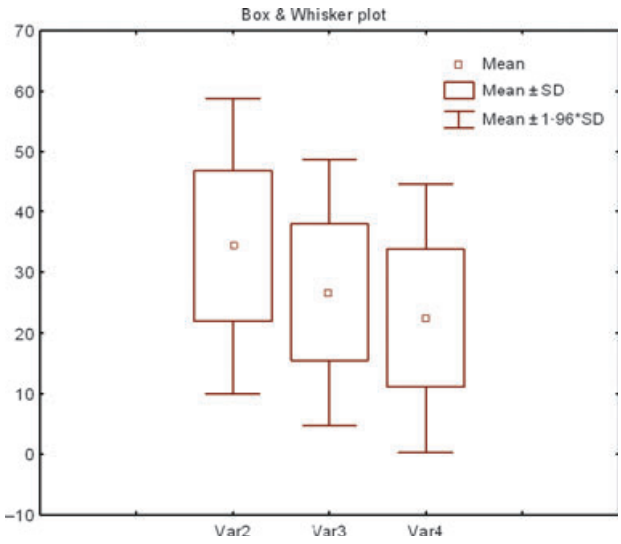
Table 1 Sartorious Score

Pt	Initials	Sex	Age	Location	Sartorius baseline	Sartorius 12 weeks	Sartorius 24 weeks
1	MM	F	25	Groins, vulva, perianal	58	41	36
2	NQ	F	30	Groins, vulva, perianal	40	23	26
3	MN	F	19	Groins, axillae	27	14	19
4	JT	F	45	Perianal, groins, vulva, breasts	55	40	21
5	SM	F	29	Axillae, groins	31	17	17
6	NNL	F	46	Armpits, groins, vulva	40	42	40
7	FA	F	24	Axillae	17	14	14
8	SA	F	51	Axillae, breasts, groins	51	20	17
9	SA	F	20	Axillae	18	18	11
10	MM	F	42	Axillae	35	35	36
11	JH	F	45	Breasts, axillae, groins	49	24	27
12	AT	F	22	Groins, perianal	26	22	13
13	IPDT	F	46	Axillae, breasts	36	33	13
14	ID	F	19	Axillae, groins	27	27	26
15	MH	M	49	Perianal, groins	54	51	55
16	BSA	M	19	Axillae	27	21	17
17	THY	M	17	Axillae	22	17	11
18	LSM	F	47	Breasts	32	38	22
19	CG	F	44	Axillae	34	36	33
20	HS	F	23	Axillae, breasts	29	24	16
21	GWM	F	19	Axillae, perianal, groins	53	43	29
22	MUM	F	45	Axillae, breasts	28	14	15
23	GBDI	F	23	Groins, breasts	26	18	12
24	BASA	F	17	Axillae	28	27	28
25	GSM	F	21	Axillae	17	10	8

Table 2 *T*-test for dependent samples (Sartorious score)

Variable	Mean	Minimum	Maximum	Standard deviation	Difference	Standard deviation difference	*P*
Time 0	34.40	17.00	58.00	12.46	0.0000	0.0000	1.0000
Time 12 Weeks	26.76	10.00	51.00	11.22	7.6400	8.84534	0.0055
Time 24 weeks	22.391	8.00	55.00	11.30	12.7826	10.0930	0.0001

Table 3 Sartorius Score's trend at 0, 12 and 24 weeks



Possible side effects were discussed and informed consent was obtained as per protocol.

Metformin was up-titrated from a starting dose of 500 mg once/day (OD) in the first week, to 500 mg twice/day (BD) in the second week, with a maximum dose of 500 mg three times/day (TDS) introduced from the third week onwards.

The maximum Metformin dose that nine patients in the series could tolerate (due to gastrointestinal discomfort or lifestyle compromise) was 500 mg BD. The Metformin dose for another patient with a particularly high BMI was suitably adjusted to 850 mg BD.

Patients who suffered from both diabetes and HS, and had been started on Metformin in the past by other clinicians or GPs managing their care were not included in this study.

In one instance, a newly diagnosed patient asked to be started on Metformin immediately, as her mother was responding successfully to this treatment.

Prior to starting treatment, patients were assessed by both Dermatology life quality index (DLQI) and Sartorius score[43] and then again at 12 and 24 weeks (Tables 1 and 2).

Statistical analysis was then performed by using Student's *t*-test.

Results

Six patients remained unresponsive to treatment. However comparison of the results at time 0 and at subsequent follow up appointments (after 12 weeks from the first appointment, then after a further 12 weeks), showed a steady improvement in the majority of the patients (Figs 1–3).

Severity, calculated by Sartorious score, dropped from severe to mild/moderate in 48% of the cases (12 out of 25) with a reduction of the average score from 40.7 to 21. In another 7 cases there had been only marginal improvements which however were clearly notable when compared with previous photographs, with a drop from an average of 12.7 to 7.3. In general Sartorious score improved in 19 patients (76%) with a reduction of the Sartorious score from an average of 33.8 to 18.1. The inability to attend work or social events also fell: in particular the number of work days lost dropped from an average of 1.5 per month to almost zero (0.4). DLQI also dropped significantly (more than 50%) in 16 out of 25 cases (64%), with a reduction from an average of 14 to 4.1 and the patients seemed not to be as troubled by the disease as much as before. In three patients the DLQI only improved marginally (reduction from 13.3 to 8) and in six remained at the same level.

Depression, which had been a major issue for 11 patients, became a non severe issue for the whole group but four patients. Unfortunately, one of the patients in whom suicidality had been a persistent issue, failed to respond to treatment with Metformin, and severe depression and an inability to cope with life and work remained.

Sartorius score (See Tables 1–3)

Eighteen patients had clinically improved with an average reduction in Sartorius score of 12.7. In seven patients the improvement was significant, with reduction of the Sartorius Score of 50% or more.

Seven patients (28%) had no response.

DLQI (See Tables 4–6)

Nineteen patients improved, with an average reduction in DLQI = 7.6.

The improvement was quite significant in sixteen patients (64%).

Number of work days lost reduced from 1.5 to virtually zero (0.4).

Depression, previously ranked as 'severe' for 11 patients, became non-severe for all except four patients.

Table 4 DLQI Scores

Patient	Initials	Sex	Age	Location	DLQI – baseline	DLQI – 12 weeks	DLQI – 24 weeks
1	MM	F	25	Groins, vulva, perianal	24	13	11
2	NQ	F	30	Groins, vulva, perianal	16	5	7
3	MN	F	19	Groins, axillae	7	0	1
4	JT	F	45	Perianal, groins, vulva, breasts	17	8	2
5	SM	F	29	Axillae, groins	8	2	3
6	NNL	F	46	Armpits, groins, vulva	24	21	23
7	FA	F	24	Axillae	11	8	8
8	SA	F	51	Axillae, breasts, groins	14	4	1
9	SA	F	20	Axillae	9	10	4
10	MM	F	42	Axillae	20	18	20
11	JH	F	45	Breasts, axillae, groins	10	3	4
12	AT	F	22	Groins, perianal	13	10	4
13	IPDT	F	46	Axillae, breasts	19	12	7
14	ID	F	19	Axillae, groins	12	13	8
15	MH	M	49	Perianal, groins	25	22	25
16	BSA	M	19	Axillae	17	10	10
17	THY	M	17	Axillae	18	14	7
18	LSM	F	47	Breasts	11	14	6
19	CG	F	44	Axillae	13	14	12
20	HS	F	23	Axillae, breasts	12	6	2
21	GWM	F	19	Axillae, perianal, groins	14	7	2
22	MUM	F	45	Axillae, breasts	11	9	4
23	GBDI	F	23	Groins, breasts	14	10	5
24	BASA	F	17	Axillae	18	18	18
25	GSM	F	21	Axillae	18	1	2

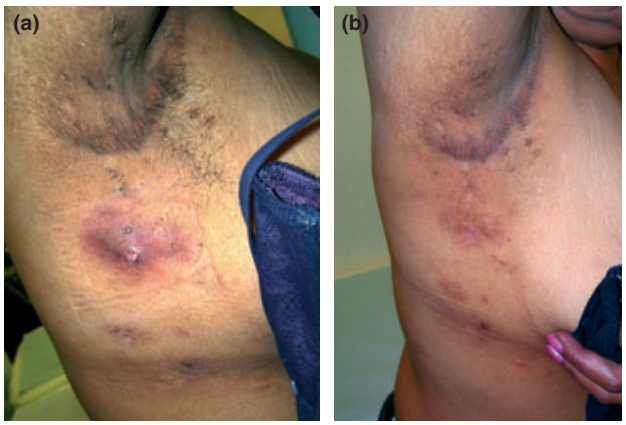


Figure 1. This lady suffered with recurrent boils under the armpit for over 20 years. The use of Metformin determined a consistent improvement (Fig. 1b).

Discussion

HS is a chronic disease which impacts on patients both physically and psychologically. Current treatment options, both medical and surgical, do not assure complete recovery, and relapse is common. In early 2004 we began analyzing cases under our care in order to improve treatment. The patients were almost entirely female with the majority of them being overweight, which suggested to us that the sex hormone balance could have been a possible treatment target.

Further observations from this series indicated that there were a disproportionate number of patients suffering from low glucose tolerance, frank diabetes and PCOS.

The link between HS and PCOS has been well established, with some authors even supporting the view that all female patients presenting with HS should be evaluated for underlying PCOS and insulin resistance. Recent literature also advocates that hormonal manipulation should be attempted in all women presenting with PCOS. After it was demonstrated that hyperinsulinaemia is a fundamental disturbance in PCOS, the use of insulin-sensitizing drugs such as Metformin was introduced, and is now considered the first choice of drug for patients affected with this condition, either alone or as an adjunct to other treatments.[44–46]

A literature search also showed that antiandrogen therapy was superior to oral antibiotic therapy (55% vs. 26%)[8,47] in treating HS. Cyproterone acetate has had a degree of success in some cases but in our experience however, even with some notable successes, the results of Cyproterone acetate therapy were invariably below expectations.

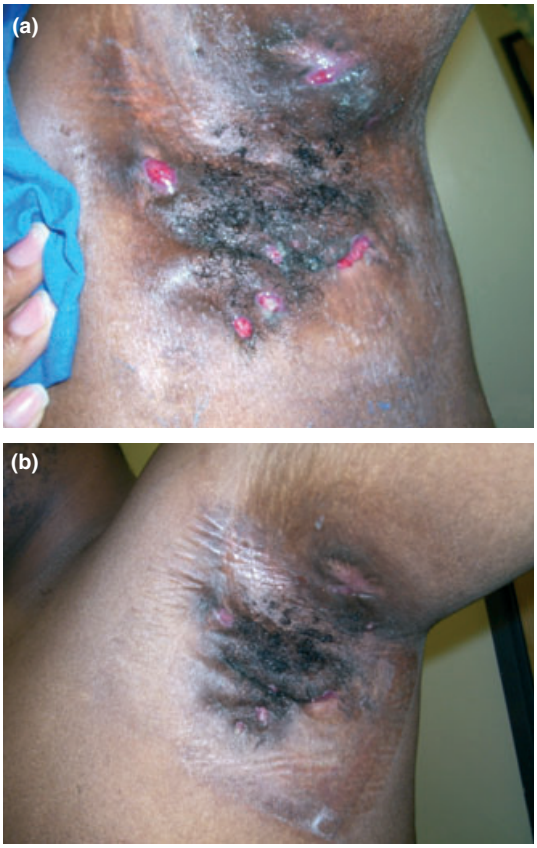


Figure 2. This young man was refractory to any type of antibiotic treatment. After Metformin was initiated, the condition subsided and after 24 weeks no inflamed spots were present (Fig. 2b).

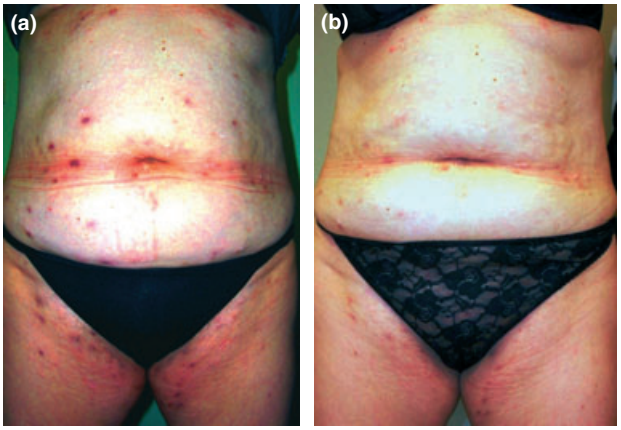


Figure 3. This patient suffered with Hidradenitis Suppurativa for 22 years. Fig. 3b Shows the clinical picture at week 12.

In light of these considerations, we thought it very likely that Metformin could have a role to play in the treatment of HS: Metformin improves glucose utilization, both in lowering its level and by increasing receptor sensitivity. The anti-androgenic properties of Metformin have long been established, and androgens imbalance have been found to be a contributory factor to HS (see ante).

Metformin is now the first line treatment for restoring cyclicity and ovulation in women with polycystic ovarian syndrome,[48,49] the accompanying improvement in glucose utilization may also play a part in ameliorating the symptoms in HS.

In our view Metformin provides a new option for the treatment of HS that may represent a new approach. The mechanism as to how Metformin operates in the treatment of HS is not entirely clear and studies are still needed, but it may be that it works through two pathways. The first is through its anti-androgenic effect, thus influencing expression of the genes possibly involved in this condition and the second might be through lowering the insulin resistance that is usually present in some patients with HS.

Metformin induced a remission of the disease in the sense that if pustules were still present, they were less numerous, less severe and less debilitating. The disease was also not as painful with improvement to quality of life and the majority of patients continued on the treatment well past the time of the trial. The majority of the patients reported that, although the condition was still present, it was more tolerable, and not as debilitating as before.

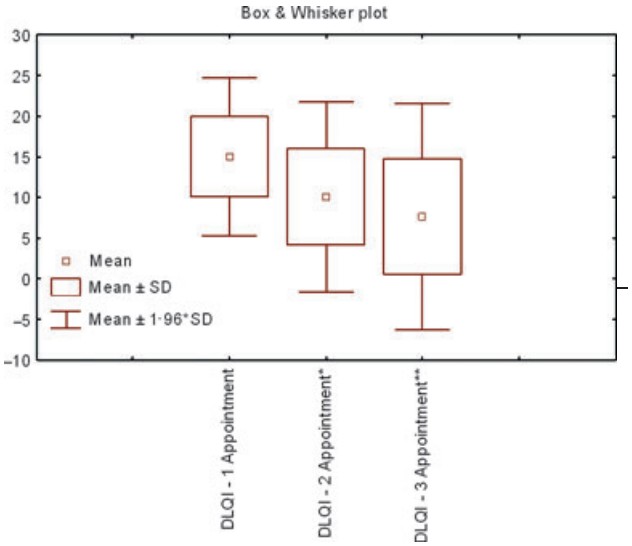
Very importantly no significant adverse effects were recorded and blood tests regularly taken during the trial period have remained within the normal range for all patients. Only minor gastrointestinal disturbances at the beginning of treatment were recorded. Even patients who did not enroll in the study because of their difficulties in attending appointments (and who remained

Table 5 *T*-test for dependent samples (DLQI)

Variable	Mean	Minimum	Maximum	Standard deviation	Difference	Standard deviation difference	*P*
Time 0	15.0000	7.000	25.000	4.9581	0.00000	0.000000	1.000000
Time 12 Weeks	10.0800	0.000	22.000	5.9576	4.92000	4.618080	0.0017
Time 24 Weeks	7.65217	1.000	25.000	7.1198	7.60870	4.774355	0.000009

Marked differences are significant at $P < 0.05000$.

Table 6 DLQI trend at time 0, week 12 and week 24.



inconsistent with their follow-up attendances) continued using Metformin which was prescribed by their GPs.

Conclusion

Metformin helps control HS with minimal or null side effects and good patient compliance. Based on our results we think that this treatment is a good alternative to current treatments such as high dose, long term antibiotics. Larger trials to further evaluate the benefits are indicated.

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