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ORIGINAL ARTICLE

Psychosocial burden of Hidradenitis Suppurativa patients' partners

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Abstract

Background Hidradenitis suppurativa is a debilitating disease related to a great psychosocial burden in affected patients and subsequently also people around them. Patients' partners as caregivers may indirectly experience wide range of devastating effects of the disease on their emotional and social life.

Objective The purpose of this study was to determine the QoL impairment in HS patients' partners and to identify its aspects that are affected the most. Correlation between QoL burden and disease severity, duration, sex, age and smoking was also assessed.

Methods A total of 50 HS sufferers were assessed according to disease severity and their partners' QoL was determined using the Family Dermatology Life Quality Index questionnaire.

Results The mean FDLQI for patients' partners was 8.7 ± 6.8 points, indicating generally a moderate effect of HS on their life. Quality of partners' life correlated significantly with disease severity but no correlation was found according to other factors.

Conclusion Hidradenitis suppurativa is a highly psychologically devastating disease not only for patients but also for their partners. It occurred to diminish partners' QoL mostly by increasing daily expenditure but also other problems were often reported. Clinicians should be aware of these psychosocial implications, in order to provide optimal therapy of HS affected families by a multidisciplinary specialized management addressing both, patients and their cohabitants simultaneously.

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Introduction

Hidradenitis suppurativa (HS) also known as acne inversa is an immune-mediated, relapsing, chronic dermatosis with a reported prevalence of about 1%.[1,2] The condition is manifested by deep-seated, inflammatory nodules, painful abscesses and secondary scarring affecting mainly the intertriginous body areas.[3,4] In a course of the disease also some subsequent malodorous draining sinus tracts and fistulas occur.[1–3] Patients find the symptoms of HS embarrassing what diminishes their self-esteem and results in a fact that the condition may have some profound negative psychological and social consequences, including patient's sense of stigmatization, social isolation and anxiety.[5–7] Nearly 43% coincidence with depression, as well as a twofold increased risk of suicide among HS patients was recently

reported.[7–9] HS is also associated with reduced patients' quality of life (QoL) and some serious sexual dysfunctions.[10–12] Sexual life impairment in HS patients has been reported to be significantly higher when comparing with both; healthy controls and psoriatic patients.[13] HS seems to be therefore profoundly debilitating and psychologically devastating chronic dermatosis.[14] Mean Dermatology Life Quality Index (DLQI) score in HS patients was reported to be impaired and assessed to be even greater than for other common dermatoses like psoriasis, atopic dermatitis (AD) or acne vulgaris.[14–21] Disease, particularly in its severe forms can negatively influence emotional and relational life of the patients and indirectly also people around them, including their partners and family members.[15,16] Because family members are involved in caregiving, they may experience a great impact of the disease on their own life, such as physical and mental exhaustion, but also social, marital and financial implications.[22,23] HS affects therefore not only the quality of patients' relationship but may also impair their partners QoL, what is still underestimated and poorly studied.

The objective of this study was to identify the QoL impairment in HS patients' partners and its different aspects that are most affected. We also assessed its correlation with disease severity as well as with other factors, including: sex, age, smoking and disease duration. To our best knowledge, this is the first work assessing and determining the devastating effects of HS on patients' partners QoL.

Material and methods

This study was approved by the Ethics Committee of Wroclaw Medical University and has been conducted in accordance with the guidelines for human studies and the World Medical Association Declaration of Helsinki. All subjects had written an informed consent form before joining the study. Patients were consecutively recruited from the Dermatology Department and outpatient clinic of Wroclaw Medical University.

A total of 84 adult patients with confirmed diagnosis of HS with a different disease severity and symptom duration were included in the study. All patients were examined and assessed according to disease severity using two scoring systems – The Hurley Staging System and The Hidradenitis Suppurativa Severity Index (HSSI). Afterwards, we asked patients if they were actually in any relationship, living or not in the same household with their partner. If they did, they were enrolled in the study group and their partners were asked to complete the Family Dermatology Life Quality Index (FDLQI) questionnaire (either in the office or as an online version sent by an e-mail). Additionally, socio-demographic and clinical characteristics of the subjects (both patients and their partners) were also recorded.

Family Dermatology Life Quality Index questionnaire is a popular and easy to use instrument for a routine clinical practice. It is a helpful tool, evaluating the dermatology-specific QoL of family members, relatives and partners of patients with skin diseases.[24,25] In our study, we used the Polish language version of FDLQI, which was created and validated by a group of prof. Szepietowski.[26] The FDLQI questionnaire comprises 10 questions, each scored 0-3 points with possible answers as follows: 'not at all'/'not relevant', 'a little', 'quite a lot' and 'very much'.

The items concern the relative's or partner's emotional distress experienced, impaired physical well-being, affected personal relationships and social life, problems with other peoples' reactions, disrupted leisure activities, burden of care, impact on job or study, extra housework and expenditure. The questionnaire refers to a situation over the last 1 month. Scoring range from 0 to 30 points, and the higher score indicates the greater QoL impairment. The interpretation of the questionnaire is that a total score of 0–1 indicates no effect, 2–5 small effect, 6–10 moderate effect, 11–20 very large effect and 21–30 extremely large effect of the disease on patients' partner's life.[24]

Statistical analysis was performed using Statistica 12.0 software for Windows software.

To assess if any significant association was present between the FDLQI score and different variables analysed in the study, a Pearson correlation was performed (it was used according to patients' and partners' age, disease duration and severity) and a Spearman's rank-order correlation was conducted to determine an association with sex and smoking. Quantitative variables were calculated and presented as mean ± standard deviation (SD), and statistical significance was achieved if $P < 0.05$.

Results

Of 84 patients invited for the study, 24 (28.6%) were not in any relationship and 10 partners declined to participate in the study and fill the questionnaire. The final analysis was eventually carried out on data obtained from 50 pairs of HS patients and their partners (response rate 83.3%). Of this group, 26 patients were men (52%). Therefore, males and females showed similar morbidity rates (male:female ratio, 1.08). Self-reported duration of patients' and their partners' relationship was less than 0.5 year for 1 pair of subjects, 0.5–2 years for 5 pairs, 2–5 years for 10 pairs, 5–10 years for 8 pairs, 10–20 years for 13 pairs and more than 20 years for 11 pairs (missing data: n = 2). Patients' characteristic is displayed in Table 1.

The mean score in FDLQI for all the subjects was 8.7 ± 6.8 points, indicating in general a moderate effect on patients' partners' life. FDLQI scores ranged from 0 to 23 points. The QoL burden was similar in both, male and female populations (8.66 ± 6.0 points vs 8.73 ± 7.5 points).

Table 1 Characteristic of the study group (patients)

Gender	24 women (48%), 26 men (52%)
Age (years)	38.6 (±11.8) (range: 21–66)
Smoking	Yes: 28 (56%), No: 22 (44%)
Mean disease duration (years)	8.2 (±6.6) (range: 1–30)

In overall, of 50 our patients' partners, 41 (82%) described some degree impairment in their QoL. Nine (18%) subjects reported that their partner's disease had no effect on their QoL and next 9 (18%) had a slightly higher score indicating small effect on QoL. Then, moderate, very large and extremely large effect was reported by 16 (32%), 12 (24%) and 4 (8%) individuals, respectively.

When comparing different aspects of FDLQI, it appeared that the most significantly affected item reported by the patients' partners was increased routine household expenditure (1.46 ± 1.1 points). Other high scoring items were as follows: emotional distress experienced (1.06 ± 1.0 points), additional housework (0.96 ± 1.0 points), disrupted recreation and leisure activities (0.96 ± 1.0 points) and affected physical well-being (0.94 ± 0.9 points). Using the percentage of subjects responding positively for a different question (answering 'a little', 'quite a lot' or 'very much'), the most frequently reported problems were as follows: increased routine household expenditure (indicated by 74% of subjects), emotional distress (64%) and affected physical well-being (64%). The results for different item of FDLQI are presented in Fig. 1 and 2.

The analysis revealed also a moderate statistically significant positive correlation between FDLQI scores and the severity of HS as measured by the Hurley Staging System and high positive correlation between FDLQI and disease severity in HSSI (r = 0.3314, 0.4653 and P = 0.0187, 0.0007, respectively).

Among our subjects, only a small QoL impairment was reported for the partners of patients in Hurley stage I with mean FDLQI 4.9 ± 5.4 points, however, it increased with the disease severity. Hurley stage II patients' partners scored mean 9.4 ± 6.9 points and Hurley stage III patients' partners scored 11.8 ± 6.5 points indicating moderate and very large effect of HS on partners' life, respectively. Partners of patients with more severe disease when assessed by HSSI also presented markedly greater burden in their QoL. And so, no effect, moderate and very large effect were reported for mild, moderate and severe

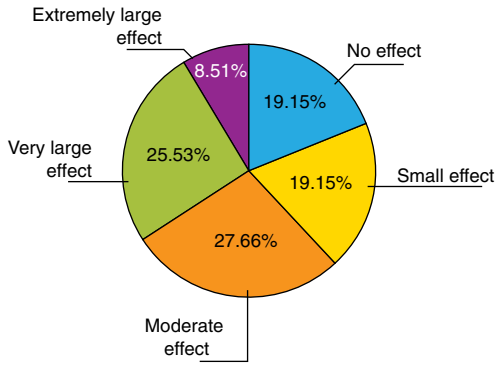

Figure 1 Mean scores obtained for different items of FDLQI.

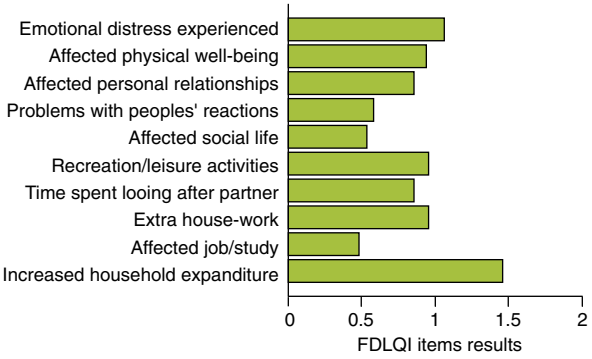

Figure 2 Effect of the disease on patients' partners' life.

Table 2 Mean FDLQI scores for partners of patients in each Hurley stage

Hurley stage	No. of subjects	Mean FDLQI score (SD)	Interpretation
1	12 (24%)	4.9 (5.4)	Small effect on patient's partner's life
2	30 (60%)	9.4 (6.9)	Moderate effect on patient's partner's life
3	8 (16%)	11.8 (6.5)	Very large effect on patient's partner's life

Table 3 Mean FDLQI scores for partners of patients in each HSSI score

HSSI	No. of subjects	Mean FDLQI score (SD)	Interpretation
Mild	4 (8%)	0.8 (1.5)	No effect on patient's partner's life
Moderate	20 (40%)	6.9 (5.7)	Moderate effect on patient's partner's life
Severe	26 (52%)	11.3 (6.7)	Very large effect on patient's partner's life

HSSI, Hidradenitis Suppurativa Severity Index.

Table 4 Pairwise correlations between the FDLQI score and the variables of interest.

Variable of interest	Pearson correlation coefficient	*P*-value
Patient's age	0.2749	0.0533
Partner's age	0.2775	0.051
Partner's gender	0.04033	0.781
Duration of the disease	0.1053	0.4669
Smoking	0.1875	0.1922
Hurley stage	**0.3314***	**0.0187**
HSSI	**0.4653***	**0.0007**

*Statistically significant.

HSSI forms, respectively. Average FDLQI scores according to disease severity are presented in Tables 2 and 3.

Quality of life of patients' partners did not significantly correlate with other factors, including sex, age, disease duration or smoking (Table 4).

Family Dermatology Life Quality Index scores were various in different age groups, and they were markedly higher for partners aged between 41 and 50 year old with the mean FDLQI score 12.4 ± 7.3 points.

Discussion

HS has been extensively investigated according to its influence on patients' QoL and was proofed to be a debilitating disease, with different authors confirming its highly negative physical and mental consequences on affected individuals.[27] Most studies showed a moderate to very large QoL burden in HS patients.[15,18,27] Mean Dermatology Life Quality Index (DLQI) scores reported by different authors for HS sufferers were around 10–12.7 points.[10,15]

Hidradenitis suppurativa patients were proofed to experience some profound emotional and social consequences of their condition, including frustration, depression, helplessness and social rejection.[14,15,18] According to disease chronicity, visibility of the lesions, but also time-consuming and still often insufficient therapies, HS may affect major components of patients' everyday life. HS sufferers are unable to perform their everyday tasks, travel, enjoy sports and leisure activities. Personal relationships, family life, education and career can be influenced, social interaction becomes limited.[14,15,18] Owing to chronic pain and unpredictable course of the disease, some serious implications according to patients' ability to work like difficulties in performing their work duties occur.[18]

There is a great number of studies, confirming a significant decrease in QoL of dermatologic patients (including HS) but still a little is known about the influence of skin conditions on patients' relatives' and partners' life. Patients' partners may be influenced especially from a psycho-social aspect, but the impact may also be physical, or even economical.[22,23,28–30] The relatives living with and caring for a dermatological patient can experience a wide range of detrimental effects in aspects of education, career, social life, interpersonal relations and finances.[28,29]

Basra and Finlay[31] initiated a wider discussion in dermatology on the impact of chronic skin conditions on patients' relatives' and partners' life. They introduced the concept of 'Greater patient', to describe patient's close social network of people, involved in caregiving and affected by individual's skin condition.[31] This definition explains how the influence of chronic dermatosis extents to patient's environment and may affect the whole families' life. They underlined the significance of family QoL measurement, as an additional outcome, which healthcare providers should analyse additionally to the patient's QoL.[31] Therefore, an interest in family QoL of dermatological diseases has increased in recent years and FDLQI questionnaire has been used so far to estimate the family burden for a number of dermatoses, including epidermolysis bullosa (EB, 9.8 points),[32] psoriasis (10 points, no precise data was provided on mean FDLQI score in one of the studies),[33,34] vitiligo (10.3 points),[35] atopic dermatitis (AD, 11.8 and 13.6 points)[36,37] and leg ulcer (14.4 points).[38] When comparing these conditions, it occurred that highest rates of FDLQI were obtained in families of patients with leg ulcer and AD. It is important to emphasize that only a children patients' populations with AD were assessed. Children suffering from skin disease like AD usually need their parents to become deeply involved in caregiving, including helping with ointment application and attending doctor visits.[33,37] It is therefore quite difficult to compare this result with QoL impairment reported for partners, who can also be involved (less or more) in providing care to adult HS patients.

According to our findings, partners' QoL occurred to be affected in 82% of subjects but even 62% of individuals showed moderate to extremely large effect of HS on their life. This observation confirms HS as a highly debilitating disease both for patients and secondarily for their partners. No significant difference was found between male and female partners. In previous studies, comparable results of DLQI were obtained according to both male and female patients populations.[39] Therefore, mean QoL impairment obtained in our subjects (8.7 ± 6.8 points) occurred to be lower than the family burden reported for other dermatoses until now.[32–38] It can be explained with the specificity of our study group, which consisted only of patients' partners in contrary to previous researches. As was mentioned above, only a children AD patients' populations were assessed until now, so their parents were analysed as caregivers in these studies. In the study of Sampogna *et al.*[32] who analysed the family burden of EB sufferers, as well as in the work of Salman *et al.*[33] performed in psoriatic patients, above 84% of assessed caregivers were mothers. In other studies, the providing care subjects were various family members mixed, including parents, siblings and partners. Study group population is crucial for results of analysis. All the detrimental consequences resulting from providing care and so also the QoL burden are quite different, depending on the type of relationship between subjects and patients. What is obvious, the family impact of any skin disease would be more significant for parents, especially mothers of patients, because this is the group of relatives, who are involved in caregiving the most.

As expected, greater QoL impairment in our study was positively and significantly correlated with disease severity. Not surprisingly, our findings are comparable with results from studies performed on families of patients with plaque psoriasis and AD and confirm association between skin disease severity and increased family disruption.

When analysing components of partners' QoL, the factors differed between subjects. HS occurred to influence partners' QoL

mostly by increasing daily expenditure. Thus, financial costs related to living with HS affected partner seem to create a serious problem. Family financial burden in HS families includes healthcare costs (drugs, physician consultations) which were showed to be significantly higher than in patients without HS, but lower comparing with psoriatic patients.[40] Moreover, the symptoms of HS can result in patients' disability, including interference with ability to work full time, what results in repetitive work absence and sometimes even job loosing.[14,41] Significantly higher levels of work non-attendance in HS sufferers when compared with general population were reported.[14,41] It creates of course some serious consequences for a home budget and explains that HS is associated with a significant financial impact on both patients' but also their partners' economic status, especially if they are sharing a common home budget.[41]

It is not surprising, that because partners of HS patients are often involved in caregiving, their QoL may be indirectly impaired in multiple ways. As chronic disease that requires continuous skincare and causes a sequence of psychologically devastating complications, HS can have an extremely onerous impact on cohabitants as well. Similarly to the patients themselves, also their partners may experience several emotional reactions (worry, frustration and exhaustion) and physical effects but also a deteriorated social life, marital problems and sexual dysfunctions. It happens that caregivers need to change their plans, or adjust their daily activities and lifestyle to a course of the patient's disease. They have to do extra housework, spent a lot of time helping the patient with care duties and personal hygiene resulting in abandon of social life and leisure activities.

Of our initial study group, nearly one-third of patients declared not to be in a relationship and a great number of them indicated the disease as the major problem in getting into partnership.

Our study has some limitations, and the main is a relatively small sample size (n = 50). However, it resulted from a fact, that a great number of patients from an initial study group were not actually in any relationship, so there were correspondingly fewer partners to collect the data. Therefore, the results must be interpreted with caution and future studies with larger subjects' populations are required. Also the fact, that patients were recruited from a single academic centre in one European country, may affect our results in some matter. Finally, the study group consisted only of Caucasians so this uniform group may not be representative for general population. It would be beneficial to compare the results with an analysis of patients' partners in other ethnic groups and countries.

In conclusion, our research showed for the first time a great devastating influence of HS on patients' partners' QoL and indicated that this debilitating disease does not affect the individuals alone. These findings aid the dermatologists in better understanding the overall burden of HS from both the patient's and the partner's perspective and are helpful to establish new endpoints in daily clinical practice. Clinicians providing care to HS patients should be aware of their relatives' psychosocial implications, in order to adequately deal with both, personal and family burden, and improve holistic clinical outcomes. Optimal therapy of HS affected families cannot be only focused on patients' physical symptoms, but requires a multidisciplinary specialized management addressing the psychiatric health, psychosocial complications and QoL of patients and their cohabitants. HS patients' partners could benefit from healthcare educational programs, courses and backing groups focusing on consistent and coordinated psychosocial support. Further larger studies would also be instrumental for better understanding the critical area of the family psychosocial burden associated with HS in different settings and populations. Finally, the future efforts of dermatologists should focus on formulating new targeted strategies, treatment interventions and funding priorities when planning management of HS patients and their families, so all the disease-influenced family members may achieve an appropriate psychosocial support they need.

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Could Residents Adequately Assess the Severity of Hidradenitis Suppurativa? Interrater and Intrarater Reliability Assessment of Major Scoring Systems

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Keywords
Hidradenitis suppurativa · Acne inversa · Scoring systems · Disease severity · Assessment

Abstract
A wide variety of assessment tools have been proposed for hidradenitis suppurativa (HS) until now, but none of them meets the criteria for an ideal score. Because there is no gold standard scoring system, the choice of the measure instrument depends on the purpose of use and even on the physician's experience in the subject of HS. The aim of this study was to assess the intrarater and interrater reliability of 6 scoring systems commonly used for grading severity of HS: the Hurley Staging System, the Refined Hurley Staging, the Hidradenitis Suppurativa Severity Score System (IHS4), the Hidradenitis Suppurativa Severity Index (HSSI), the Sartorius Hidradenitis Suppurativa Score and the Hidradenitis Suppurativa Physician's Global Assessment Scale (HS-PGA). On the scoring day, 9 HS patients underwent a physical examination and disease severity assessment by a group of 16 dermatology residents using all evaluated instruments. Then, intrarater reliability was calculated using intraclass correlation coefficient (ICC), and interrater variability was evaluated using the coefficient of variation (CV). In all 6 scorings the ICCs were >0.75, indicating high intrarater reliability of all presented scales. The study has also demonstrated moderate agreement between raters in most of the evaluated measure instruments. The most reproducible methods, according to CVs, seem to be the Hurley staging, IHS4, and HSSI. None of the 6 evaluated scoring systems showed a significant advantage over the other when comparing ICCs, and all the instruments seem to be very reliable methods. The interrater reliability was usually good, but the most repeatable results between researchers were obtained for the easiest scales, including Hurley scoring, IHS4 and HSSI.

Introduction

Hidradenitis suppurativa (HS) is a chronic, relapsing, inflammatory dermatosis, affecting around 1% of the general population with a female predominance [1, 2]. It occurs as recurrent, deep-seated and painful lesions, including inflammatory nodules, abscesses, fistulas and scarring [1–4]. The disease involves body areas rich in apocrine glands, therefore it mainly affects the axilla, groin, and perianal area [3, 4]. HS etiology is multifactorial and still not fully understood, but hyperkeratosis and

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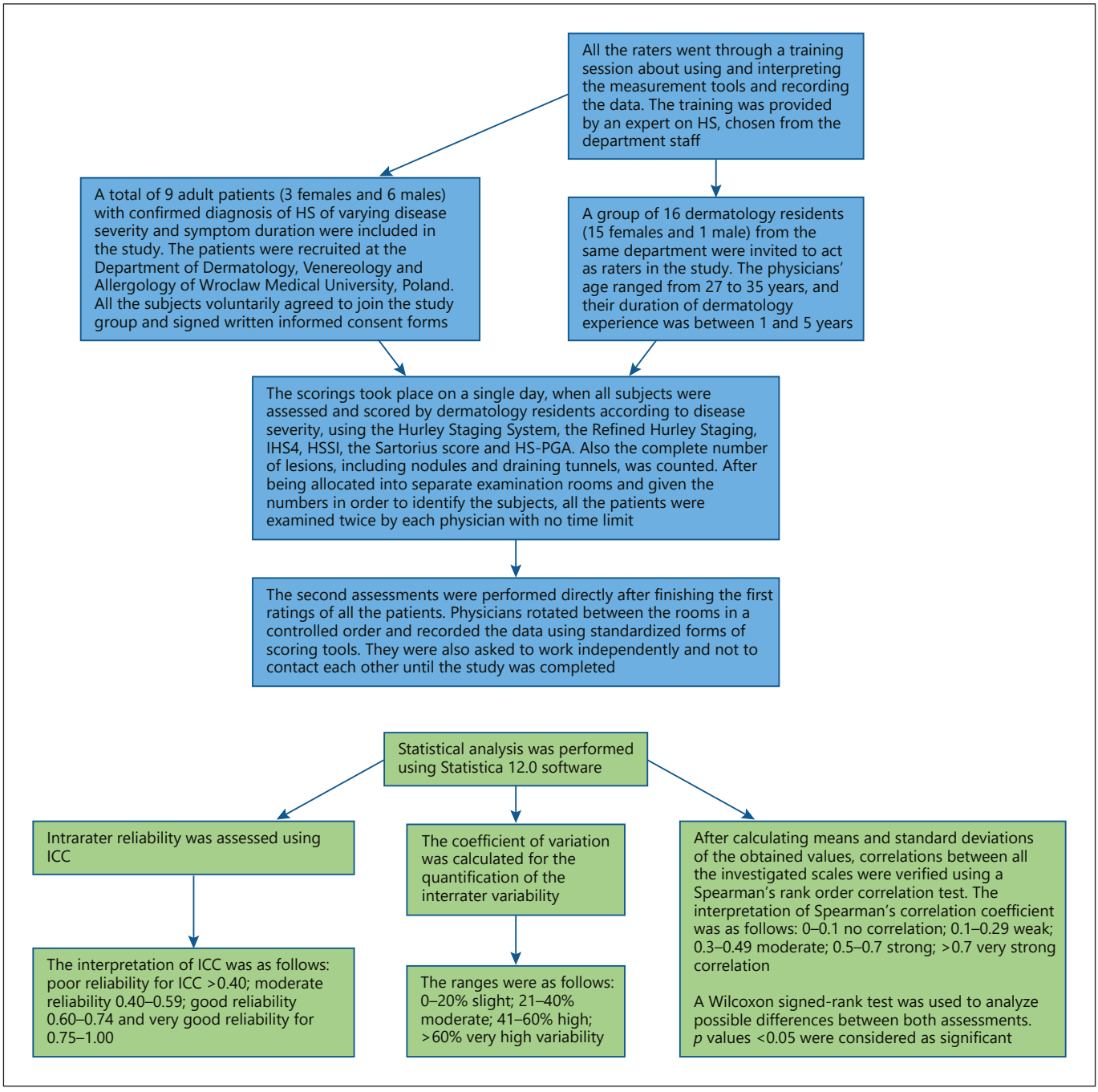

Fig. 1. Flowchart of Materials and Methods. HS, hidradenitis suppurativa; IHS4, Hidradenitis Suppurativa Severity Score System; HSSI, Hidradenitis Suppurativa Severity Index; HS-PGA, Hidradenitis Suppurativa Physician's Global Assessment Scale; ICC, intraclass correlation coefficient.

hair follicle occlusion with the secondary involvement of the apocrine glands and bacterial infection seem to play a crucial role [4]. HS is a debilitating condition, strongly influencing patients' quality of life [5–7].

No specific laboratory tests or parameters are available for HS, the diagnosis is therefore usually made by a clinical observation only [8, 9]. Also, a precise classification of disease severity is based on the subjective assessment of

the clinical manifestation by a physician, so the doctor's experience plays a significant role [9]. Sometimes subjective symptoms reported by the patient are also taken into account. The disease severity assessment is often confusing, especially for young, unexperienced dermatologists. The choice of the method depends on whether it is used for research purposes or in daily clinical practice. The proper classification of the patient according to disease severity is also substantial for choosing an appropriate treatment modality.

There are multiple scoring systems and outcome measure instruments that have been proposed for HS classification until now. Some of these are recognized and commonly used evaluating methods but the others were reported to be used only in single clinical trials. Moreover, data confirming their validation and reliability are generally poor and incomplete [10]. Only three studies were found to investigate interrater reliability of the classification systems. It then appeared that 90% of the scoring instruments, previously used in randomized controlled trials of HS, have not any validation evidence supporting their usage [10]. Most of the scoring systems, especially the ones mainly related to a subjective physician's assessment, involve a measurement error. In order to avoid the misinterpretation of statistical analysis, it is essential to perform a proper reliability testing.

The aim of this study was to compare and assess the reliability and reproducibility of 6 scoring systems commonly used for grading severity of HS: the Hurley Staging System, the Refined Hurley Staging, the International Hidradenitis Suppurativa Severity Score System (IHS4), the Hidradenitis Suppurativa Severity Index (HSSI), the Sartorius Hidradenitis Suppurativa Score and the Hidradenitis Suppurativa Physician's Global Assessment Scale (HS-PGA) within a group of dermatology residents.

Materials and Methods

For further details, see the online supplementary material (see www.karger.com/doi/10.1159/000501771 for all online suppl. material) (Fig. 1).

Results

Intraclass correlation coefficients (ICCs) and the interpretation of intrarater reliability of all the scales for 16 raters are presented in Table 1. For all the scales ICCs were >0.75, indicating excellent intrarater reliability for all of the evaluated scoring systems. The highest ICC was observed for the Sartorius Score (0.97), the Hurley Staging (0.96) and the Refined Hurley Staging (0.95), and the lowest ICC was noted for IHS4 (0.87), but they all marginally differed between one another.

Table 1. Intraclass correlation coefficients for all of the scoring systems and their intrarater reliability interpretation

Scale	Intraclass correlation coefficient	Interpretation of intrarater reliability
IHS4 (points)	0.87	Excellent
Number of lesions	0.89	Excellent
IHS4	0.91	Excellent
HSSI (mild/moderate/severe)	0.92	Excellent
HSSI (points)	0.93	Excellent
PGA	0.94	Excellent
Refined Hurley	0.95	Excellent
Hurley Staging	0.96	Excellent
Sartorius	0.97	Excellent

Table 2. Coefficients of variation for all of the scoring systems and their interrater variability interpretation

Scale	Coefficient of variation, %	Interpretation of interrater variability
IHS4	6.5±10.1	Slight
HSSI	11.6±11.3	Slight
HSSI (points)	13.4±8.0	Slight
Hurley Staging	16.2±9.4	Slight
HS-PGA	16.6±8.2	Slight
Refined Hurley	19.3±9.6	Slight
Sartorius score	30.9±5.4	Moderate
IHS4 (points)	34.8±7.1	Moderate
Lesions, *n*	37.3±8.0	Moderate

Table 2 summarizes the coefficients of variation (CVs) and the interrater variability interpretation of all the measure instruments. The results demonstrated a good agreement between physicians in most of the evaluated scales. The lowest variability was found in assessing IHS4 and HSSI (the CVs were 6.5 ± 10.1 and 11.6 ± 11.3, respectively), so these methods seem to be the most reproducible. According to CVs, the highest interobserver variability was noticed for number of lesions (37.3 ± 8.0), IHS4 expressed in points (34.8 ± 7.1) and the Sartorius Score (30.9 ± 5.4); however, it was also only moderate.

The *p* values for differences between means of both assessments given to each subject by 16 physicians are pre-

Table 3. *p* values of the Wilcoxon signed-rank test used to compare 2 assessments and to evaluate whether their means obtained by 16 physicians differ

Patient	Hurley	Hurley Refined	IHS4 (points)	IHS4	HSSI (points)	HSSI	Sartorius	HS-PGA	Lesions, *n*
1	0.36	0.22	0.43	0.04	0.86	0.31	0.68	1.00	0.96
2	1.00	0.18	0.21	0.18	0.25	1.00	0.22	0.36	0.33
3	1.00	1.00	0.07	0.18	0.50	0.36	0.78	1.00	0.35
4	1.00	1.00	0.78	1.00	0.07	1.00	0.78	1.00	0.86
5	1.00	1.00	0.09	1.00	1.00	1.00	0.40	1.00	0.20
6	1.00	1.00	0.64	1.00	0.18	1.00	0.83	0.59	0.82
7	1.00	0.18	0.59	1.00	0.72	1.00	0.42	0.59	0.44
8	1.00	1.00	0.36	1.00	0.58	1.00	0.37	1.00	0.21
9	1.00	0.18	0.83	1.00	0.14	1.00	0.16	1.00	0.40

Table 4. Spearman's rank correlation coefficients (*r*) between all evaluated measure instruments obtained by all 16 physicians in 2 assessments ($p < 0.05$ for all *r* values)

Assessment 2	Assessment 1								
	Hurley	Hurley Refined	IHS4 (points)	IHS4	HSSI (points)	HSSI	Sartorius	HS-PGA	Lesions, *n*
Hurley	–	0.75	0.53	0.27	0.38	0.23	0.54	0.62	0.50
Refined Hurley	0.74	–	0.66	0.43	0.51	0.39	0.67	0.66	0.61
IHS4 (points)	0.52	0.65	–	0.67	0.60	0.57	0.90	0.73	0.88
IHS4	0.32	0.51	0.70	–	0.55	0.58	0.67	0.49	0.64
HSSI (points)	0.38	0.50	0.60	0.50	–	0.79	0.56	0.53	0.60
HSSI	0.27	0.41	0.57	0.55	0.82	–	0.57	0.47	0.56
Sartorius	0.56	0.66	0.88	0.60	0.58	0.56	–	0.73	0.88
HS-PGA	0.59	0.65	0.76	0.47	0.55	0.44	0.74	–	0.77
Lesions, *n*	0.51	0.61	0.87	0.59	0.62	0.58	0.89	0.74	–

sented in Table 3. When analyzing all scoring systems, no significant differences were observed between the first and second assessment for each score, with the only exception regarding IHS4 for patient 1 ($p = 0.04$). However, it is important to emphasize that the *p* value was in this case close to the borderline, so the result needs to be treated with caution.

Table 4 shows Spearman's rank correlation coefficients between two assessments of all the evaluated measure instruments obtained by all participating physicians. Significant positive correlations were noticed among all the scales in both ratings, and it was usually strong to very strong and even perfect between the first assessment of the Sartorius Score and the second assessment of IHS4 expressed in points ($r = 0.9$). However, only a weak correlation was observed comparing both assessments of the Hurley System and HSSI, as well as the first assessment of IHS4 and the second assessment of the Hurley System ($r = 0.23$; 0.27, 0.27, respectively).

Discussion

Already 30 different instruments and scoring systems have been proposed for HS classification, and this number continues to rise; however, no gold standard measurement tool has been identified until now [10]. On the other hand, the increasing heterogeneity of outcome measure instruments without its adequate testing makes it confusing to compare their reliability and to interpret the patient outcomes in a daily clinical practice.

In the present study a significant correlation was revealed between all the evaluated measure instruments, which confirms a good convergence of all the analyzed sys-

tems. However, results differed somehow between the scales, with the lowest correlation observed between the Hurley System and IHS4, as well as the Hurley System and HSSI. It can be explained by the fact that both (IHS4 and HSSI) do not consider a presence of cicatrization, which is a substantial element of the Hurley System classification.

When analyzing two assessments performed by each physician, we observed an excellent intrarater reliability for all the evaluated scales. Similarly, Zouboulis et al. [11] reported good intrarater agreement for all classification systems tested, including IHS4, HS-PGA, the Hurley System and the Refined Hurley System. In this study, IHS4 and the Hurley System showed the highest agreement between the first and the second assessment, what was explained by the fact that these scales are simple 3-degree scores.

According to CVs, our study has demonstrated a good agreement between physicians in most of the presented scales. The lowest variability was found for IHS4 and HSSI. On the other hand, even moderate interrater variability was reported for the number of lesions, IHS4 expressed in points, and the Sartorius Score.

Good agreement of IHS4 may also be confirmed by the result of the previously mentioned study by Zouboulis et al. [11], which revealed good interrater reliability of IHS4 as well as HS-PGA and only a moderate one for the Hurley System and the Refined Hurley System. However, in the second assessment of the study, an agreement between physicians improved and was reported as good for all of the scales [11].

In another recent study, performed by Thorlacius et al. [12], good interrater reliability was observed for the Hurley System when assessing axillary areas or gluteal region, and moderate reproducibility was reported for the Hurley System according to groins and for the PGA system. In the same study, much more variable results were noticed for the Hurley Staging Refined and IHS4, with only a fair reliability described for these scales [12].

It can be noticed that cited results of reliability assessment differ between authors. One explanation can be the fact that various raters' groups were chosen to evaluate the patients in each of the mentioned studies. Our assessors were only dermatology residents working in the same department with a variable time of dermatology practice. In the work of Zouboulis et al. [11], both residents gathered from different countries as well as experienced specialists in a field of dermatology were included, whereas, in the study of Thorlacius et al. [12] ratings performed by a group of HS experts from around the world were analyzed. It can therefore be assumed that young colleagues performed their assessments according to a knowledge acquired during their training on dermatology in the same department, additionally influenced by the training session provided just before the scorings. Their consistent results confirm the value and significance of initial training but also slightly hinder the interpretation of scoring system validation. In the real-life situation, the physicians are not reminded of assessment methods and need to rely on their own knowledge. On the other hand, specialists and especially experts in a subject of HS, due to their own experience and precise opinion about the disease, its manifestation, and severity assessment, are less susceptible to the rules presented during the training. Their scorings contain a great component of a subjective opinion and vary widely between each other. Therefore, the experts' results are much more difficult to compare.

We would also like to suggest that unexperienced dermatologists may experience some difficulties in HS lesion terminology, its distinguishing and identification (i.e., they sometimes had some serious problems in differentiation between small fistulas and large nodules or abscesses, which was important for the total result of the scoring). This could be a reason for relatively poor reliability we found in a group of dermatology residents for the composite methods, basing on the inflammatory and noninflammatory lesion counting, including IHS4, the Sartorius Score and number of lesions.

There are also other components of scoring systems, the evaluation of which can create some problems due to their subjective nature, e.g. the affected body area. In the Refined Hurley System and HSSI, it is calculated by the body surface area method and expressed as percentage of skin surface affected by the lesions [13]. Assessment of body surface area involvement is however unreliable when performed by unexperienced physicians [14]. Therefore, classification instruments concerning the extent of skin lesions as a substantial element of disease severity should be interpreted with caution. In contrast to BSA, the longest distance between two lesions within each anatomical region (which is used in the Sartorius Score and expressed as less than 5, 5–10 or more than 10 cm) seems to be much easier to interpret [15]. This method might therefore cause less variation between assessors.

The Sartorius score was the first validated scoring instrument for HS and is still very often used, both in daily practice and clinical trials. It includes not only the lesion's type and number in every body area affected, but also the distance between them and the presence of Hurley III lesions (cicatrization) [15]. The Sartorius score provides a very precise assessment of disease severity, not dividing

patients into simplified groups; however, it is a complicated and time-consuming method.

In contrast to the Sartorius score, IHS4 is a quick, simple, easy-to-perform and not very complicated scoring instrument for the assessment of HS [16]. Therefore, it would probably be a suitable tool to use in a busy daily practice, also by dermatologists with little experience in HS [16]. It also allows an early identification of moderate and severe cases of patients what has been used in the patient's classification to a biological therapy. Promising results were also reported for IHS4 according to interrater agreement in the study of Zouboulis et al. [11], and our observations confirm it as a reliable classification system. However, in contrast to that stands the study of Thorlacius et al. [12], with only a fair reliability of IHS4 reported. The biggest limitation of this scale is that it includes only some clinical manifestation (nodules, abscesses, draining fistulas) without taking into account the number of involved body areas or the patient's subjective symptoms.

Also, some divergent results were obtained in studies conducted for the Hurley Staging System, which seemed to be the most widely used scoring system for HS, especially in daily practice by unexperienced dermatologists. It shows that even such a simple instrument has some limitations and creates serious problems in a reliable disease classification.

Disadvantages are also that the Hurley System is not a dynamic score, evaluating only the extent of skin damage (sinus tracts, scarring), without taking into account the inflammatory component or current activity of the lesions [17, 18]. Finally, the subjective variables reported by the patients are not included in the total score either. The Hurley Staging System is therefore a useful instrument for a selection of appropriate treatment modalities in a clinical practice, especially when different physicians perform assessments [15, 19]. However, it is still an insufficient classification for clinical trials, because it contains a wide range of clinical findings within each stage group [19].

On the other hand, the Hurley Staging Refined which is a more detailed version of the classic Hurley System and could be a more appropriate instrument for the evaluation of clinical trials, had only moderate or even fair reliability reported by different authors [11, 12, 20]. Assessment of the number of body areas affected, as well as presence of inflammation as a component of the Hurley Staging Refined, in contrast to the Hurley Staging System, is probably the factor responsible for the lower interobserver agreement of this 3-step algorithm.

The main limitation of our study is its relatively small number of participants (9 patients). However, a greater sample size would create a serious challenge in gathering so many assessments and fatigue the physicians, which could result in less precise ratings.

Another limitation is that our study was conducted in a group of dermatology residents selected from only one department. Probably a different result would be obtained by a multicenter cooperation, and interrater variability is then expected to be somewhat higher in conditions of routine clinical practice, without an initial training session.

In sum, an ideal scoring system for HS should be time effective, dynamic, valid, responsive, and reliable. Each of the available outcome measurements has advantages and disadvantages, and none can be highly recommended as being superior to the other. Thus, disease severity classification of HS still creates a serious challenge for the clinician, because of the lack of unequivocal consensus on the use of scoring systems and the wide variability in the clinical manifestations of the condition. Future efforts should therefore concentrate on an adequate evaluation of reliability, usability, and sensitivity of existing scoring systems, instead of developing the new ones. This is even more important, because an appropriate disease severity classification of HS patients results in choosing an optimal treatment modality [21, 22]. We hope this will also be the future task for authors in search of a consensus on core outcome domains such as the HISTORIC collaboration (PMID 29654696), which would lead to minimalizing the heterogeneity in outcome measure instruments [23].

We would also like to suggest that ultrasound examination performed simultaneously with physical examination of the patients could be beneficial for a better assessment of HS lesions and severity classification. However, this method is still not widely available, and not a lot of dermatologists can use and interpret ultrasound.

Data from our study have demonstrated that simple 3-degree scores, classifying patients as mild, moderate, and severe cases, including IHS4 and HSSI are the most reproducible methods. These scales are quick and easy to perform and should be chosen by inexperienced physicians in busy daily practice. It was also proven that interrater agreement can be improved by training provided by an expert in a field of HS. It confirms the importance of regular and systematic practice for a more reliable patient classification. However, we would also like to emphasize that full and reliable disease severity assessment, despite the clinical picture, should also consider some patient-reported items. Pain as a major feature of HS, as well as the patient's quality of life impairment which is a hallmark of this condition, are then suggested to be used to complement the reliable HS classification in future prospective

trials. Up to date, because of the lack of a gold standard scoring system available, relying on a single outcome measure instrument is usually insufficient for clinical trials. Therefore, precise classification of HS patients despite the reliable scoring instrument requires also a consideration of some subjective patient-reported outcomes.

Key Message

The article provides a reliability evidence for the most commonly used scoring systems of hidradenitis suppurativa in a group of dermatology residents.

Statement of Ethics

The study has been conducted according to the guidelines for human studies and to the World Medical Association Declaration of Helsinki. All the subjects have filled in an informed consent form before joining the study. The study protocol was also previously approved by the bioethical committee of Wroclaw Medical University.

Disclosure Statement

The authors have no conflicts of interest to declare.

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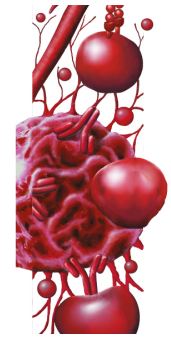

Biologics for hidradenitis suppurativa: an update

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Hidradenitis suppurativa (HS) is a chronic, inflammatory dermatosis characterized by an occurrence of nodules, abscesses, sinus tracks and scarring. Its pathogenesis is multifactorial and still not fully understood, therefore, current systemic therapies still remain a serious challenge. Increased levels of several proinflammatory cytokines have been reported in patients suffering from HS, therefore biologics appear as a new approach to therapy for this condition. Adalimumab is the only one internationally registered agent and should be considered first after the conventional therapies appear insufficient. The efficacy and safety profile of some preparations, like infliximab and etanercept was confirmed so far in randomized trials, but there are some new biologics which are still being evaluated and require more rigorous examination.

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Hidradenitis suppurativa (HS), also known as acne inversa, is a chronic, recurrent, inflammatory dermatosis characterized by an occurrence of deep, painful lesions like nodules, suppurative abscesses, sinus tracks and scarring [1]. The disease occurs in body areas rich in apocrine glands, including mainly axillae, groin and anogenital region [2]. The changes often spread to the buttocks, the anal area or the woman's interbreast area [1]. The pathogenesis of HS is still not fully understood. The condition is multifactorial and probably results from a combination of genetic, hormonal (mainly hyperandrogenism) and environmental factors. Pilosebaceous unit occlusion, hyperkeratinization and bacterial superinfection are now considered the main pathogenetic mechanisms [2]. Tobacco smoking, drugs and obesity are recognized as the major risk factors for HS development. Moreover, a direct relationship with smoking and the severity of the disease symptoms has been proven [3,4]. The incidence of the disease is around 1% with a female predominance (female to male ratio of 3:1), however, there is also a report suggesting even a 4% prevalence [5,6]. HS has been associated with several comorbid disorders known as immune-mediated inflammatory diseases (IMIDs), such as Crohn's disease, colitis ulcerosa, seronegative arthritis and pyoderma gangrenosum [7,8].

HS is a debilitating disease resulting in patient mutilation, it is also associated with chronic pain sensation. It was documented that HS patients have a poor quality of life (QOL) directly correlated to the severity of the disease. QOL impairment occurs also more frequently than those found in some other dermatoses such as psoriasis, atopic dermatitis and chronic urticarial [9–12].

Due to the multifactorial pathogenesis of the disease, the treatment of HS often occurs as a therapeutic challenge. European S1 guideline for HS has been developed by a group of experts, but an unambiguous treatment algorithm has not been established. Thus, the preparations most commonly used in HS therapy include 1% topical clindamycin, systemic antibiotics (including tetracycline or clindamycin and rifampicin combination), retinoids and hormone therapy [13]. It is important to emphasize that pharmacological therapies should be introduced while treating HS as early as possible, in order to avoid complications such as scars, sinus tracts or malignancies development (Marjolin's ulcer occuring in previously traumatized and chronically inflamed skin areas) [14].

Biologics that have been used for almost 20 years for the treatment of IMIDs, have also proven to be a promising therapeutic option for HS sufferers. They are successfully used in patients with moderate to severe HS when the conventional systemic therapies proved insufficient.

Future Medicine

TNF-α inhibitors

TNF-α is a cell signalling protein (cytokine) produced by many cell types such as activated macrophages, mast cells, $CD4^+$ lymphocytes, NK cells and neutrophils. It plays a key role in the inflammatory response in humans and is involved in various inflammatory responses, including acute phase reaction. TNF-α is generated as a precursor form called tmTNF (transmembrane). Its biological activity is associated with binding two receptors, TNFR1 (found in most tissues) and TNFR2 (expressed typically in cells of the immune system). The cytokine acts by promoting an expression of adhesion molecules, neutrophils migration and phagocytosis of macrophages. It also stimulates production of a number of mediators, including CRP, IL-1 oxidants and the inflammatory lipid PGE_2, as well as activates caspases, intracellular signaling NF-kB and MAPK. Currently, TNF-α is believed also to play an important role in the pathogenesis of HS lesions. This is indirectly confirmed by the fact that TNF-α inhibitors have been successfully used in HS therapy for several years.

The relationship between TNF-α blockade and HS improvement was first noticed in 2001, when Martinez *et al.* [15] observed an improvement in the condition of skin lesions in the course of HS among patients undergoing anti-TNF-α therapy due to co-morbid Crohn's disease. This observation subsequently prompted other researchers to do a deeper analysis of this issue to characterize the proinflammatory and anti-inflammatory cytokines profile in the body of patients suffering from HS.

Matusiak *et al.* [16] showed a significantly elevated level of TNF-α in the blood of HS patients compared with control, whereas the level of cytokine did not correlate with the disease severity, its duration or BMI. In another study, Van der Zee *et al.* [17]. reported increased expression of proinflammatory TNF-α and IL-1β as well as anti-inflammatory Il-10 in patients with HS compared with the healthy controls in both the diseased skin and perilesional area. It was also five-times higher than the values observed in psoriasis. Similar conclusions regarding the level of TNF-α in patients with HS have been reached by Mozeika *et al.* [18] showing elevated levels of cytokine in the skin, apocrine glands and hair follicles.

However, there are also opposite reports that have shown reduced levels of substances associated with innate immune response, including TNF-α in both the blood and tissues of patients suffering from HS. Van der Zee *et al.* [19] when assessing TNF-α levels in the skin of patients undergoing 16-week adalimumab therapy, did not observe any significant differences in cytokine concentration before and after treatment.

Despite contradictory reports, TNF-α seems to play a significant role in the pathogenesis of HS, the best confirmation of which are numerous positive reports on the use of TNF-α blockers in the therapy of this condition.

Adalimumab

Adalimumab (ADA) is a fully human monoclonal antibody against TNF-α. It binds with a high specificity and affinity to soluble and membrane-bound TNF-α and blocks its biological activity. ADA regulates the innate immune response by affecting the levels of proinflammatory cytokines such as Il-6, Il-8, Il-1β and sTNF-RI [20]. Treatment with ADA was also associated with decreased number of inflammatory leukocyte subsets including monocytes, macrophages, dendritic cells, T-helper and B lymphocytes [21].

ADA is administered by subcutaneous injections, and its highest effectiveness, according to European guidelines, is obtained with a dose regimen of 40 mg once weekly. There is no dose adjustment for patients with obesity [13]. The drug is contraindicated in NYHA class III–IV heart failure, history of tuberculosis or other severe infections, severe liver disease, demyelinating processes, malignancies, pregnancy or lactation. Women of childbearing age should therefore receive contraception up to 5 months after treatment [13].

The first reports of scientists about the efficacy of ADA on HS came from several case series. In the majority of studies, ADA was administered with the dosing regimen previously adopted for the treatment of psoriasis (80 mg at week 0, 40 mg at week 1 and then 40 mg every other week) [22]. The effects were satisfactory in accordance to both efficacy and safety of the treatment [21,23–33]. In subsequent years, prospective studies based on larger groups and longer observation of patients were published.

Blanco *et al.* [34] perform a retrospective analysis of a group of six patients treated with ADA for refractory HS. The initial dosage was 40 mg every other week and was increased to 40 mg weekly if the condition was inadequately controlled. All patients reported a marked reduction in the number of affected areas of the body, nodules, fistulas and laboratory parameters, as well as an improvement in the Dermatology Life Quality Index (DLQI). The mean follow-up period in this study was 21.5 months. Arenbergowa *et al.* [35] used ADA in a group of eight patients with severe, recalcitrant HS (Hurley grade III). Patients were treated for 1 year with a standard psoriasis dosing regimen and after that monitored for 1 year. Clinically significant improvement was observed in all patients within 4–6

weeks. Three of them remained stable with no relapse during the follow-up period. The average time to recurrence was 9.5 months.

In another open-label prospective study by Sotiriou *et al.* [36] 15 patients with moderate to severe HS were treated with ADA in a different from previously mentioned dose regimen: 80 mg was administered at week 0, and then 40 mg weekly for 24 weeks. After this time, a significant decrease in Sartorius score was reported. DLQI, as well as disease activity evaluated by visual analogue scale (VAS), also showed a marked reduction at week 24. There was however a significant worsening at week 48, and recurrences after discontinuation of treatment were noticed after mean time of 11 weeks.

In the study by Amano *et al.* [37] the results were not so promising. Ten patients were enrolled in this study and administered ADA for 12 weeks at doses of 160 mg at week 0, 80 mg at week 1 and 40 mg every other week. At week 12, none of the patients were classified as a responder compared with the baseline. There was also no statistically significant improvement in pain and QOL.

The first randomized, double-blind, prospective, placebo-controlled trial evaluating the efficacy and safety of ADA in the treatment of HS was carried out by Miller *et al.* [38] 21 patients suffering from moderate to severe HS (Hurley stage II or III) for at least 6 months were randomized 1:2 (placebo: active treatment). Thus, 15 patients received 80 mg ADA at week 0, followed by 40 mg every other week for 12 weeks, while six patients received placebo. A marked reduction in Sartorius score occurred after 6 weeks and in the ADA group when compared with placebo control. However, no significant change in the Hurley score, VAS or DLQI was seen after 12 weeks.

Kimball *et al.* [39] conducted another larger, randomized, placebo-controlled two-phased study. It included a group of 154 patients with moderate and severe HS (HS Physician Global Assessment [HS-PGA] score of moderate or worse) who had previously reported intolerance or lack of response to oral antibiotics. During period 1 (blinded phase) patients were randomized in a 1:1:1 ratio to ADA 40 mg every week, ADA 40 mg every other week (EOW) and placebo for 16 weeks. Period 2 was open-label and all patients were treated with ADA 40 mg EOW. At weeks 28 or 31 patients with a suboptimal response (HS-PGA score of moderate or worse) were switched to weekly dosing. At week 16, a significantly greater proportion of patients in the weekly group (17.6%) achieved a clinical response (HS-PGA score of clear, minimal or mild with at least a 2-grade improvement relative to baseline) compared with patients in EOW (9.6%) and placebo (3.9%) groups. This group also achieved a significantly greater reduction of pain (assessed by using VAS questionnaire). However, after the switch from weekly to EOW dosing in period 2, a decrease in response was reported. These observations suggest that the most effective dosing regimen for ADA is 40 mg every week. During the study, headaches and injection site reactions were the most frequently reported side effects. Serious adverse event rates in all three groups were: 7.8, 5.8 and 3.9%, respectively, and the worsening of HS, infectious complications and anemia were the most common.

The most recent and most significant Phase III trial for the evaluation of the efficacy and safety of ADA in HS therapy is the PIONEER I and II [40]. These multicenter studies, in which 307 and 326 patients participated, respectively, were similarly designed with two double-blind and placebo-controlled periods. In period 1 (12-weeks), patients were randomized in a 1:1 ratio into two groups – one receiving ADA (160 mg at week 0, 80 mg at week 2 and 40 mg weekly from week 4 through week 12), the second matching placebo. All patients who received ADA in period 1 and continued into period 2, were then re-randomized 1:1:1 to ADA 40 mg weekly, every other week or placebo. Patients who were in the placebo group in period 1 were reassigned to ADA 40 mg weekly (PIONEER I) or placebo (PIONEER II) for 24 weeks. Moreover, in PIONEER II an adjuvant therapy was also allowed (19% of patients received concomitant oral antibiotics).

The primary efficacy end point was HiSCR (Hidradenitis Suppurativa Clinical Response) defined as more than 50% reduction in total abscess and inflammatory nodule count, and no increase in abscess and draining fistula count at week 12 comparing to a baseline.

At week 12, HiSCR achievement rate was significantly higher for patients in the ADA group compared with the placebo group (41.8 vs 26% in PIONEER I and 58.9 vs 27.6% in PIONEER II). The marked improvement was observed in ADA group as early as 2 weeks into therapy.

Moreover, in the PIONEER II, although not in PIONEER I, ADA proved to be significantly more effective than placebo in secondary outcomes including: pain reduction (measured with Patient's Global Assessment of Skin Pain), disease severity (in Modified Sartorius score and Hurley Stage), as well as the number and morphology of skin lesions. This group also had statistically significant improvement in quality of life (DLQI). Also in this study, under ADA treatment tolerance was satisfactory. The most commonly reported adverse effects were headaches and infections (especially upper respiratory tract and the urinary tract infections). During period 1, serious adverse

events were observed in 1.3 ADA versus 1.3% patients in placebo group (PIONEER I) and 3.7 versus 1.8% respectively, in PIONEER II. By period 2, these rates were up to 4.6% with a similar frequency for both groups and studies.

ADA has therefore proved to be a drug with greater efficacy in HS treatment and a similar safety profile compared with a placebo.

In all of the studies, adverse side effects after administration of this preparation were usually mild to moderate. Relatively common adverse drug reactions were injection site reactions and infections, including serious infections such as pneumonia, arthritis, diverticulitis and pyelonephritis. Reactivations of latent tuberculosis or hepatitis B virus, as well as neurological and hematological complications were also reported during the course of a treatment [14]. Very rarely, malignancies (including lymphomas, squamous cell carcinoma or breast cancer) occurred [38,41]. A few cases of paradoxical reactions after ADA administration, due to other diseases therapy, were reported [42].

Therefore, ADA seems to give promising results both in effectiveness of HS therapy and safety of use. According to current evidence it also improves patients' QOL, reduces pain as well as depressive symptoms [43,44]. Three large prospective studies on ADA on a total estimated number of 914 patients are currently underway [45].

ADA is the only biologic drug approved by the US FDA and EMA for therapy of moderate to severe HS in adult patients after failure of classic treatment.

Infliximab

Infliximab (IFX) is a chimeric (mouse/human) monoclonal IgG1 class antibody that works against TNF-α. Similarly, to ADA, it binds to both soluble and transmembrane receptor-bound TNF-α and neutralizes its proinflammatory activity.

IFX is administered by intravenous infusion at a dose of 5 mg/kg body weight at weeks: 0, 2, 6 and then regularly in 8-week intervals for a long-term therapy [13]. Due to the possible infusion reactions, patients should remain under observation during the infusion and 1 hour after the drug administration [13].

A long-term prospective trial was carried out by Paradela *et al.* [46] on a group of ten patients suffering from moderate to severe refractory HS. IFX was administered intravenously in the previously mentioned dose regimen. Response, defined as more than 50% decrease in HSS (hidradenitis suppurativa score) comparing with baseline was achieved in eight patients. However, disease recurrence was noticed in 4 patients after the mean period of 37 weeks.

In another prospective, interventional study by Lesage *et al.* [47] ten patients were treated with IFX 5 mg/kg at weeks 0, 2, 6 and then every 4 weeks. A significant decrease in disease severity (assessed in Hurley score) as well as QOL improvement was noted in all subjects. Complete efficacy (defined as the absence of HS flares) was obtained for two patients and partial efficacy (moderate flares with no need for surgery) for eight.

The only one randomized, double-blind, placebo-controlled study on the efficacy and safety of IFX in HS therapy was performed by Grant *et al.* [48] on a group of 38 patients.

In the first phase of 8-weeks duration, patients with moderate to severe HS (HS Severity Index score greater than 8) were randomized to treatment with IFX 5 mg/kg at weeks 0, 2, 6 or matching placebo. The groups were then unblinded in the second phase of the study, and placebo patients had the opportunity to change therapy to the IFX for another 22 weeks. The last observational phase was followed until week 52. HSSI was used to assess the disease activity. At week 8 it was noted that significantly greater number of patients treated with the active drug achieved at least 50% improvement in skin lesions compared with placebo. Interestingly, a similar effect was achieved by subjects that switched from placebo to IFX in the second phase of the study. Also reduction of DLQI, VAS, PGA (Physician Global Assessment) score and laboratory inflammation markers was significantly greater in IFX-treated patients comparing with placebo. The mean DLQI change from baseline for patients treated with IFX was 10.0 and in placebo group it was 1.6, and the mean VAS change was 39.0 and 0.6, respectively.

Tolerance under IFX treatment was satisfactory, with, most commonly, mild adverse effects observed, including headaches, nausea and infections. Serious adverse events after IFX administration were similar to those reported during ADA therapy and mainly involved: reactivation of latent tuberculosis, Hepatitis B, hepatosplenic T cell lymphoma, hematological complications or neurologic events.

In the retrospective study conducted on two cohorts, each of ten patients, Van Rappard *et al.* [49] compared the effectiveness of IFX and ADA in HS therapy. Ten patients were treated with ADA 40 mg every other week, and the second group with IFX 5 mg/kg at weeks 0–2–6. A significant improvement in skin lesions, as well as reduction of the inflammatory laboratory parameters was obtained in both groups of subjects. The mean decrease

Table 1. Level of evidence and response rate for studies on TNF-α inhibitors.

Biologics	No. of papers	Level of evidence†			Responders (%)‡	Nonresponders (%)
		A	B	C		
Total	69§	4	25	40	55,3%	44,7%
Adalimumab	21	2	7	12	54%	46%
Infliximab	38	1	12	25	82%	18%
Etanercept	10	1	6	3	54%	46%

†The level of the study evidence was defined as: A (randomized controlled trials), B (lower-quality clinical trials), C (case reports and case series).
‡The patients were categorized as 'respoders' or 'non-responders' due to the criteria established for each study.
§References: 36,38,91,92 were not included, due to the lack of precized data about clinical response rate achieved by the patients in these studies.

in Sartorius score compared with baseline was 54% in the IFX group and 66% for the ADA group. However, only the improvement in the IFX group remained significant after one year of observation. Both preparations were beneficial, but IFX happened to be more effective in all aspects than ADA not only in decreasing disease severity, but also in improving QOL, normalizing of laboratory parameters and durability of achieved remission. No serious adverse effects were noticed in both groups.

Etanercept

Etanercept (ETA) is recombinant fusion protein that binds to transmembrane form of TNF-α and inhibits it. It is administrated by subcutaneous injections. It is approved by the US FDA for treatment of rheumatoid arthritis, plaque psoriasis, psoriatic arthritis, juvenile idiopathic arthritis and ankylosing spondylitis [50].

In a series of cases [51–53] as well as open cohort studies [54–59] conducted on groups of 4 to 15 patients who received ETA in doses of 25 mg twice weekly or 50 mg once/twice weekly, promising results regarding the efficacy of the drug in HS therapy were obtained.

Cusack *et al.* [56] reported a significant reduction in self-reported disease activity (mean reduction of 61%) as well as an improvement in the QOL (mean reduction in DLQI scores of 64%). In another study by Giamarellos-Bourboulis *et al.* [55] ETA was administered in a dose of 50 mg once weekly for 12 weeks. More than 50% decrease of disease activity (according to the Sartorius scale) was reported in 6/10 patients at week 12 and 7/10 patients at week 24. The reduction of VAS scores was noticed in 7/10 and 6/10 patients respectively.

Only one randomized, double-blind, placebo-controlled trial assessing the efficacy of ETA in moderate and severe HS has been published, but the results were unsatisfactory. It was carried out by Adams *et al.* [50] on a group of 20 patients. ETA (50 mg) or placebo was administered twice a week for 12 weeks. After that, all subjects received open-label ETA in the same dose regimen for 12 more weeks. At 12 or 24 weeks, there was no significant difference in patient global assessment, physician global assessment or QOL (assessed with DLQI) between ETA and placebo groups.

In most of the published studies, ETA was well tolerated and the most commonly reported adverse reactions were injection site reactions and infections. However, in one patients bilateral *Candida chorioretinitis* followed by septicemia was described [52].

Reports differ as to the ETA efficacy in HS, which, in the light of the more confirmed efficacy of ADA and IFX, argues for the greater utility of these preparations in HS therapy. The dominance of the other two TNF-α inhibitors over ETA can be explained by the fact that these drugs bind to both soluble and transmembrane TNF-α, whereas ETA inhibits only the transmembrane form [14].

Significantly increased expression of TNF-α found in HS sufferers supports the use of TNF-α inhibitors as a therapy of this condition. These preparations are also the most widely investigated biologic agents for the efficacy and safety of use. Both experimental and clinical trials have demonstrated the rationale behind using TNF-α inhibitors in HS treatment. The results of the published studies on ADA, IFX and ETA are summarized in the Table 1.

In total 69 papers were analysed, mostly including case reports and case series, but also randomized controlled trials for each preparation, which were mentioned above. The level of the study evidence was divided into three groups, which were respectively: A (randomized controlled trials), B (lower-quality clinical trials), C (case reports and case series). The patients were categorized as 'responders' or 'non-responders', according to the criteria established for each of the analyzed studies (e.g. decrease in HSSI, PGA score, achieving HiSCR). If no individual results were reported for each subject in a study, all patients were classified according to the mean achieved efficacy. Patients

receiving placebo in the cohort studies were not included. The highest response rate was observed with IFX and the percentage of responders to this preparation was 82% compared with 54% for ADA and ETA. However, it is important to emphasize that the highest quality of evidence was identified for ADA and many more patients were analyzed after its administration than after IFX and ETA, which makes the result of ADA efficacy the most reliable. Smaller studies of IFX and ETA, in which nonvalidated measurements were used to assess the effectiveness of the therapy also do not determine high quality of evidence. Overall, the quality of evidence was much lower for IFX and ETA than for ADA and differed between the preparations, making it difficult to compare these agents directly. Therefore, larger randomized controlled trials are needed to precisely estimate the effectiveness of these preparations in HS therapy.

Other biologics

Anakinra

Anakinra (ANA) is a recombinant IL-1 receptor antagonist. It competitively blocks the binding of naturally occurring IL-1 (IL-1α and IL-1β) to its receptor and inhibits its biological activity. IL-1 (similarly to TNF-α) is one of the major mediators of the inflammatory response that are also involved in the pathogenesis of HS [60].

Due to its immunomodulatory and anti-inflammatory properties, ANA may occur as a new, promising therapeutic approach in the management of HS and an alternative for patients who have failed to respond to other treatment regimens, including TNF-α blockers. ANA was originally registered for the treatment of moderate to severe rheumatoid arthritis. However, a successful off-label use of this drug was also reported in various conditions, often of autoimmune background, including psoriasis, atopic dermatitis, pyoderma gangrenosum, Schnitzler's syndrome, Sweet's syndrome or SAPHO syndrome [61]. In HS, ANA is typically administered by subcutaneous injections in a dose of 100 mg/day, which corresponds to the dosage regimen for rheumatoid arthritis.

Different reports regarding to the efficacy of ANA in the management of HS occurred. In a prospective open-label study, Leslie *et al.* [62] assessed the effectiveness, safety and tolerability of ANA in HS management. The group of six patients with moderate to severe HS were treated with daily ANA (100 mg/day) for 8 weeks, which was the active phase of the therapy, followed by 8-weeks observation phase. Inclusion criteria for this study included minimum modified Sartorius score of 25 or greater and presence of active skin lesions in at least two anatomic areas of the body. As a result, all of the five patients who completed the study (one subject was lost to follow-up because of socioeconomic factors) achieved a clinically meaningful improvement after 8 weeks of therapy. A mean decrease of modified Sartorius score was 34.8 points. Patients' QOL was also improved, and the average decrease in the DLQI was -8.4 points, which is comparable with that obtained under ADA therapy in a study conducted by Kimball *et al.* [39]. However, relapse occurred in HS disease activity as well as others assessed parameters after an 8-week follow-up. ANA was well tolerated – no adverse events were reported in any of the study participants during the entire treatment nor the follow-up period.

A larger randomized double-blind, placebo-controlled clinical trial in a group of 20 HS patients (Hurley stage II or III) was conducted by Tzanetakou *et al.* [63]. Patients were randomized in a 1:1 ratio, to receive placebo or ANA subcutaneously 100 mg once daily for 12 weeks (treatment phase), and then remained under observation for the next 12 weeks. At the baseline visit, the patients were evaluated among the disease activity, number of skin lesions, affected areas and QOL. In addition, peripheral blood samples were also taken from the subjects and mononuclear cells were stimulated to cytokine production. The study confirmed ANA as a potentially efficacious management in HS therapy.

A total of 78% of patients treated with ANA achieved a good clinical response (decrease of disease activity score) after 12 weeks of active therapy comparing to 30% of the placebo group.

After 24 weeks, these results were 67 and 20%, respectively, and the time to disease exacerbation was prolonged in patients treated with ANA. Moreover, there was also a decrease in the production of IFN-γ in ANA group, and the production of interleukin 22 was increased. No serious adverse effects of the therapy were noticed.

Zarchi *et al.* [64] reported the case of a 37-year-old obese patient (BMI = 40) who was successfully treated with ANA 200 mg daily, after the failure of other therapies, including IFX and ADA.

Despite promising reports confirming the efficacy of ANA in the treatment of moderate to severe HS, a few cases of 'nonresponse' to this treatment have also been reported [65–67].

Menis *et al.* [65] described even a worsening of skin lesions as well as DLQI and PGA in one of the two patients administered to with ANA. Due to contradictory reports in previously published studies, there is a need to assess the efficacy and safety of ANA in randomized trials with large groups of patients in the future.

Ustekinumab

Ustekinumab (UST) is a human IgG1 class monoclonal antibody directed against the p40 subunit of IL-12 and IL-23, which regulates specific components of the immune system.

Both IL-12 and IL-23 are involved in differentiation and activation of Th cells subsets (Th1 and Th17 respectively) which release other proinflammatory cytokines [68]. Due to their mechanism of action, IL-12 and IL-23 play a role in the pathogenesis of IMIDs by dysregulation of the immune system, thus UST has been successfully used in the treatment of disorders such as psoriasis, Crohn's disease or HS [69]. Furthermore, Schlapbach *et al.* [70] reported an increased expression of IL-12 and IL-23 in lesional skin of HS sufferers, which was related to infiltration of papillary and reticular dermis by macrophages. These data provide a rationale for UST as a new therapeutic approach for HS therapy.

In a study by Gulliver *et al.* [71] three cases of patients were reviewed to assess the efficacy of UST therapy. All subjects were administered with UST by subcutaneous injections in a previously mentioned dose. Different outcome was achieved in each subject. Complete disease remission in one of the patients was obtained at month 6, while 25-49% improvement was noticed in the second subject and no treatment effect in the third.

According to results of three other case reports, which were published by different authors [72–74], all patients reported a partial or complete response to UST therapy, however the effect of the treatment was not rapid and appeared within several months from the beginning of drug administration.

Blok and colleagues [75] conducted the only uncontrolled open-label clinical trial with prospective design to evaluate the efficacy of UST in HS therapy. 17 patients with moderate to severe HS (Hurley stage II–III) were included and treated with UST according to the further psoriasis dosing regimen: 45 mg s.c. (increased to 90 mg for patients weighing > 100 kg) at week 0, 4, 16 and 28. Results were promising – moderate to marked improvement of skin lesions (according to modified Sartorius score) was achieved in 82% of patients and the HiSCR in 47% at week 40. Moreover, 41% of subjects demonstrated clinically significant improvement in the DLQI. It was also noticed that the milder course of the disease and the lower leukotriene A4-hydrolase serum concentration were associated with a better response to UST therapy. The most commonly reported adverse events in this study were fatigue, headaches and upper respiratory tract infections.

Despite promising effects of UST in HS therapy, other preparations with better evidence for efficacy, such as ADA or IFX, should be considered first [76]. Regarding its unique mechanism of inhibiting IL-12/23, UST may provide a potential new therapeutic approach for HS in some patients after failure of other therapies.

Secukinumab

Secukinumab (SEC) is a fully human monoclonal antibody and is directed against IL-17A.

Recently published data confirmed that the level of IL-17A in the blood of HS patients is significantly elevated, compared with that found in healthy volunteers and directly correlates with the severity of the disease [77]. The expression of IL-17A was also enhanced in lesional as well as perilesional skin of HS sufferers [78]. IL-17A activates neutrophils and lymphocytes and induces the expression of proinflammatory cytokines including IL-1β, IL-6 and TNF-α. SEC binds with a high selectivity to IL-17A and inhibits the inflammatory cascade [77].

Only three cases have been published on SEC in HS treatment after failure of multiple pharmacologic therapies, including biologics. The drug was administered as a subcutaneous injection at a dose of 300 mg weekly (according to scheme 0-7-14-21-28) and then once a month as a maintenance therapy. In a study by Thorlacius *et al.* [79], the number of lesions reported by a patient was reduced from 23 to 7 and pain VAS from 5 to 3 at week 12 comparing to baseline. During the course of the treatment oral candidiasis occurred in the patient.

In the second case that was reported by Schuch *et al.* [80], a significant decrease in inflammatory nodules, as well as white blood cell count and CRP levels were observed. The patient did not experience any adverse effects related to the administered therapy. Jørgensen *et al.* [81] also reported a marked improvement in a patient treated with SEC, expressed by a remarkable reduction in VAS, DLQI, HSS and IHS4 (International Hidradenitis Suppurative Severity Score) after 6 months of therapy.

Currently, SEC is being tested in a randomized placebo-controlled trial in a group of 21 HS patients who receive 300 mg weekly for 4 weeks followed by 300 mg every 4 weeks. Treatment efficacy will be assessed after 24 weeks and the only outcome in this study is achievement of HiSCR. Its results may be helpful in evaluating the therapeutic approach of targeting Il-17 in HS [82].

Table 2. Ongoing trials on other biologic agents in hidradenitis suppurativa treatment (situation as at 20 June 2018).

Drug	Mechanism of action	Phase of study	US NCT number	Study sponsor
MABp1	IL-1α inhibitor	Phase II	NCT03512275	XBiotech, Inc.
CJM112	IL-17A inhibitor	Phase II	NCT02421172	Novartis Pharmaceuticals
Bimekizumab	IL-17 inhibitor	Phase II	NCT03248531	UCB Biopharma S.P.R.L.

IFX-1

IFX-1 is a first-in-class monoclonal antibody directed against complement factor C5a, which is one of the traditional activation products of the complement cascade. C5a is also involved in the activation of neutrophils and the production of proinflammatory cytokines, including TNF-α. Systemic complement activation occurs in HS. In a recent study it was shown that C5a level is significantly increased in the plasma of patients with HS comparing with healthy controls [83]. However, the negative correlation of circulating C5a concentration with HS severity was observed. Interestingly, C5a level in the plasma of HS sufferers was even greater than concentration reported for patients with severe sepsis or multiple organ failure [83]. IFX-1 by blocking C5a may be, therefore, helpful in regulating the inflammatory response in patients with HS.

In an open-label Phase II clinical trial the safety and efficacy of IFX-1 in HS patients were assessed [82,84]. 12 patients with Hurley Stage III HS were treated with IFX-1 at a dose regimen of 800 mg, administered intravenously on days 1, 4, 8, 15, 22, 29, 36, 43 and 50. As a result, HiSCR score was obtained in a rate of 75% in patients at the end of the treatment period (day 50) and 83% after a 12-week follow-up period (day 134). No adverse effects, allergic or anaphylactic reactions after drug infusion were reported during the course of the treatment.

In light of recent data, IFX-1 appears to be a new promising therapeutic approach for patients with HS who have failed to respond to previous conventional therapies or other biologicals. C5a blockade can become a new therapeutic option in diseases where increased systemic complement activation occurs, in particular HS.

A large randomized, double-blind, placebo-controlled, multicenter Phase II study on a group of 175 patients to estimate the efficacy and the safety of IFX-1 is currently under recruitment [45].

Ongoing trials & future perspective

Despite the large progress, HS therapy often remains a serious challenge. There is still an unmet need for a new treatment options which can be achieved by range of potential targets directed against specific mechanisms. A new Phase II trial for HS management has begun in recent years using a inhibition of the targetable inflammatory pathways which are IL-1α, IL-17 and C5a. These cytokines also seem to be involved in HS pathogenesis, therefore their blockade appears as a new approach to therapy of the condition [45]. Currently several new biological preparations are being investigated, including MABp1, CJM112 and bimekizumab. The results failed with the drug MEDI8968 and the trial has been terminated early because of the lack of efficacy [45]. The investigational drugs for HS which are currently in clinical trials are presented in Table 2 [45].

With one approved biologic available, several drugs under investigation and the ongoing development of novel therapeutic agents that act in different specified pathways in the inflammatory cascade, the future of HS management looks promising. The era of targeted treatment will allow for a more 'personalized' approach directed against predictive biomarkers which dysregulation underlies HS pathomechanism. Certain therapies (currently under active investigation), including agents targeting IL-1 or IL-17 may occur as potentially promising options for HS therapy in the future. The current landscape of biologics promises continuous development of these preparations in the next few years with more innovative methods appearing on the market and offering new therapeutic approaches. Therefore, in the coming years, the final goal should be to improve the currently known preparations as well as search for new drugs and finally to find a balance among efficacy, toxicity and cost of therapy. Comparative studies including different preparations and dosing regimens of biologics would be particularly helpful to enhance their therapeutic effect.

Conclusion

Summarizing, conventional treatment options for HS have largely been disappointing and current systemic therapies for this condition still remain a serious challenge, though great progress has been made in HS management within recent years. A substantial therapeutic need still exists in HS because of its high prevalence and the burden it places on affected patients.

Several cytokines have been found to drive inflammation in HS, including TNF-α, IL-1β, IL-17 and IL-23. Due to the role of immune dysregulation in HS pathogenesis, biologic therapy based on a targeted inhibition of these specific cytokines seems to create a promising option for patients with severe and moderate HS after conventional therapies proved insufficient.

According to current evidence, TNF-α inhibitors, especially ADA and IFX were found to be an effective and tolerable treatment modality for HS and appeared to significantly improve patients' QOL. Variable results have been seen with the use of other biologics in HS management, including ETA, ANA, UST, SEC and IFX-1. However, other agents still require more rigorous examination to be established as a therapeutic approach for this condition. Available data report usually good tolerance of biologics with mostly mild adverse events noticed. The results of the published studies on biologics in HS therapy are summarized in the Supplementary tables.

Up to date, ADA still remains as the only FDA/EMA-approved biologic drug in HS treatment and should be considered first, but other biologicals also play a increasing role in off-label therapy. Future large randomized controlled trials are needed to further establish the efficacy and safety profile of biologic agents in HS management.

Executive summary

Background

- Hidradenitis suppurativa (HS) is a chronic, debilitating dermatosis with occurrence of suppurative lesions, sinus tracks and scarring.
- Pathogenesis is multifactorial and a pilosebaceous unit occlusion, hyperkeratinization and bacterial superinfection play a key role.
- Several comorbid disorders (including immune-mediated inflammatory diseases), decreased quality of life and chronic pain appear in HS patients.
- Treatment of the condition is challenging- topical and systemic antibiotics, retinoids and hormone therapy are most commonly used, while biologics create a new promising option.

TNF-α inhibitors

- TNF-α seems to play a significant role in the pathogenesis of HS.
- Increased levels of TNF-α were found both in blood and skin lesions of patients suffering from HS.
- However, no significant difference was found in cytokine concentration before and after treatment with TNF-α inhibitors.

Adalimumab

- By blocking the biological activity of TNF-α, adalimumab (ADA) regulates the innate immune response and affects the levels of other proinflammatory cytokines, including Il-6, Il-8, Il-1β and sTNF-RI.
- The first reports about the efficacy of ADA on HS came from several case series and the effects were satisfactory but in a retrospective studies conducted by different authors, the results were contradictory due to ADA effectiveness.
- In randomized, double-blind, placebo-controlled trials, including one multicenter study, ADA appeared to be well tolerated and effective, especially when administered 40 mg every week.
- ADA is the only biologic agent approved by the and EMA for therapy of moderate to severe HS.

Infliximab

- Infliximab (IFX) is another monoclonal antibody that works against TNF- α and was found to decrease disease severity and improve patients' quality of life.
- In only one randomized, double-blind, placebo-controlled study conducted on a group of 38 patients, a significantly greater number of patients treated with IFX achieved at least 50% improvement in skin lesions compared with placebo.
- In the comparative study, IFX occurred to be more effective in all aspects than ADA with a mean 54% decrease in Sartorius score compared with baseline.

Etanercept

- Promising results regarding the efficacy of etanercept (ETA) (which is another TNF- α inhibitor) in HS therapy were obtained in several case series, as well as, in open cohort studies.
- However, the results were unsatisfactory in only one RCT trial and there was no significant difference in patient global assessment, physician global assessment or quality of life between ETA and placebo groups.

Anakinra

- Anakinra (ANA) is an IL-1 receptor antagonist which was originally registered for the treatment of moderate to severe rheumatoid arthritis.
- One author when assessing the efficacy of ANA in HS therapy in a group of 6 patients reported a clinically significant improvement of disease severity and a mean decrease of modified Sartorius Score in this study was 34.8 points.

- In a larger randomized double-blind, placebo-controlled clinical trial 78% of patients treated with ANA achieved a good clinical response which confirmed ANA as a potentially efficacious management of HS.

Ustekinumab

- Ustekinumab (UST) regulates specific components of the immune system by inhibiting (IL)-12 and IL-23, which were found to be increased in lesional skin of HS sufferers.
- According to results of several case reports including, in total, six patients, different outcomes were achieved from no treatment effect to complete response to UST therapy.
- In the only open-label clinical trial on UST efficacy, moderate to marked improvement of skin lesions (according to mSs) was achieved in 82% and the Hidradenitis Suppurativa Clinical Response in 47% of patients.

Secukinumab

- Secukinumab (SEC) inhibits the inflammatory cascade by working against IL-17A, of which, expression was found to be significantly enhanced both in the blood and the skin of patients with HS.
- Three cases have been published on SEC in HS treatment – the effects were satisfactory and all patients experienced a marked improvement in the course of the disease within a few months.
- Currently, SEC is being tested in a randomized placebo-controlled trial in a group of 21 patients.

IFX-1

- IFX-1 is an antibody directed against complement factor C5a, which is one of the activation products of the complement cascade and is notably increased in the plasma of HS patients.
- In an open-label Phase II clinical trial the efficacy of IFX-1 in HS patients was assessed and as a result Hidradenitis Suppurativa Clinical Response score was achieved in a rate of 75% in patients at day 50 and 83% at day 134.

Ongoing trials & future perspective

- Currently several new biological agents are being investigated in HS therapy, including MABp1, CJM112, bimekizumab and secukinumab.
- Novel biological agents targeted against specific elements of proinflammatory cascade, including IL-1α, IL-17 and C5a may occur as potentially promising options for HS therapy in the future.

Conclusion

- Several cytokines have been found to drive inflammation in HS, including TNF-α, IL-1β, IL-17 and IL-23 and their targeted inhibition appears to create a promising option for patients with severe and moderate HS after a failure of conventional therapies.
- TNF-α inhibitors, especially ADA and IFX were found to be effective and in general well tolerated therapy for HS and still more rigorous evaluation is needed for other agents

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Supplementary data

To view the supplementary data that accompany this article please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/imt-2018-0090. References 85–121 refer to the supplementary tables.

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Streszczenie

Wstęp

Hidradenitis suppurativa (HS), zwany również trądzikiem odwróconym to przewlekła, nawrotowa, zapalna dermatoza o nie do końca poznanej, wieloczynnikowej etiologii. U jej podłoża leży hiperkeratoza i okluzja mieszka włosowego, z wtórnym zajęciem gruczołów apokrynowych i infekcją bakteryjną. Choroba manifestuje się występowaniem głęboko umiejscowionych zmian zapalnych (guzków, ropni oraz przetok), najczęściej zajmujących okolice anogenitalne, pośladki, pachy i pachwiny. Leczenie trądziku odwróconego często okazuje się dużym wyzwaniem terapeutycznym, a w zależności od stopnia nasilenia choroby zastosowanie znajdują zarówno preparaty miejscowe, substancje działające systemowo, jak i metody chirurgiczne, a w przypadku braku skuteczności konwencjonalnych metod leczenia, alternatywę mogą stanowić również preparaty biologiczne.

Ze względu na obraz kliniczny oraz charakterystyczną lokalizację zmian, trądzik odwrócony zwykle wiąże się ze znacznym poziomem bólu, stygmatyzacji, depresji i lęku u dotkniętych nią pacjentów. Badania ostatnich lat wskazują na znacznie obniżoną jakość życia pacjentów z HS, również w porównaniu z innymi przewlekłymi dermatozami. Kolejny problem stanowi fakt, że obraz kliniczny trądziku odwróconego może znacznie różnić się między poszczególnymi pacjentami. O ile postawienie diagnozy zwykle nie stwarza problemów, to zakwalifikowanie pacjenta do odpowiedniego stopnia zaawansowania choroby zwykle nie jest już tak oczywiste. Klasyfikacja nasilenia HS opiera się bowiem zwykle wyłącznie na subiektywnej ocenie obrazu klinicznego przez lekarza. Czasami brane są również pod uwagę objawy podawane przez pacjenta, co dodatkowo komplikuje obiektywną ocenę przypadku. W literaturze zostało zaproponowanych dotychczas wiele systemów służących ocenie stopnia zaawansowania HS, jednak dane dotyczące ich walidacji i wiarygodności są na ogół niedostępne lub niekompletne.

Cele pracy

1. Ocena wpływu choroby na zaburzenie jakości życia partnerów pacjentów z HS. Identyfikacja poszczególnych składowych jakości życia partnerów, na które trądzik odwrócony obecny u osoby chorej ma największy wpływ. Zbadanie zależności pomiędzy stopniem obniżenia

jakości życia u partnerki/a, a nasileniem choroby u pacjenta, jak i pozostałymi czynnikami socjo-demograficznymi.

2. Przeprowadzenie walidacji i oceny wiarygodności najczęściej używanych skal zaawansowania klinicznego choroby w grupie rezydentów dermatologii. Identyfikacja najbardziej powtarzalnych i wiarygodnych skal nasilenia trądziku odwróconego wśród lekarzy z niewielkim doświadczeniem klinicznym w tej jednostce chorobowej.
3. Dokonanie przeglądu piśmiennictwa dotyczącego dotychczas dostępnych form terapii biologicznej trądziku odwróconego i ich skuteczności.

Materiał i metody

Badaniem dotyczącym rodzinnej jakości życia objętych zostało 50 par pacjentów z hidradenitis suppurativa pozostających pod opieką Katedry i Kliniki Dermatologii, Wenerologii i Alergologii Uniwersytetu Medycznego we Wrocławiu, oraz ich partnerów.
U wszystkich pacjentów wykonana została szczegółowa ocena kliniczna, wraz z oceną nasilenia choroby przy wykorzystaniu skali Hurley oraz HSSI, a także zebrany został wywiad dotyczący dotychczasowego leczenia, danych demograficznych oraz czynników środowiskowych.
W grupie 50 partnerów pacjentów wykonana została ocena jakość życia partnerów według kwestionariusza oceniającego wpływ choroby dermatologicznej na jakość życia rodziny (FDLQI, The Family Dermatology Life Quality Index), oraz zebrany został wywiad socjo-demograficzny wśród partnerów celem określenia charakterystyki badanej grupy.

Do badania dotyczącego walidacji skal nasilenia choroby zaproszono grupę 16 rezydentów dermatologii będących na różnym etapie kształcenia specjalizacyjnego. Młodzi lekarze zostali poproszeni o ocenę 9 pacjentów z HS pod względem stopnia zaawansowania choroby z użyciem 6 skal nasilenia trądziku odwróconego (The Hurley Staging, Modified Hurley Staging, Hidradenitis Suppurativa Severity Score System, Hidradenitis Suppurativa Severity Index, Sartorius Hidradenitis Suppurativa Score oraz Hidradenitis Suppurativa Physician's Global Assessment Scale). Każdy pacjent został oceniony dwukrotnie przez wszystkich lekarzy.
Powtarzalność wyników pomiędzy obiema ocenami przeprowadzonymi przez jednego badacza oceniono na podstawie współczynnika korelacji (ICC, intra-class correlation coefficient).

Zmienność wyników uzyskanych w trakcie badania tego samego pacjenta przy użyciu tej samej skali przez wszystkich lekarzy obliczono natomiast z wykorzystaniem współczynnika zmienności (CV, coefficient of variation).

W trzeciej pracy przeprowadzono analizę 85 publikacji na temat wykorzystania i skuteczności różnych preparatów biologicznych w terapii trądziku odwróconego. Większą część prac stanowiły opisy pojedynczych przypadków i serie przypadków, ale znaleziono również kilka dużych randomizowanych badań klinicznych. Najwięcej doniesień dotyczyło inhibitorów TNF-α, które stanowią grupę najszerzej dotychczas stosowaną i najlepiej przebadaną w tej jednostce chorobowej.

Wyniki

A. W całej grupie partnerów badanych pacjentów obserwowano umiarkowanie obniżoną jakość życia, ze średnim indeksem FDLQI równym 8.7±6.8 punktów. Wykazano ponadto istotną statystycznie pozytywną korelację między stopniem zaawansowania choroby u pacjenta, zarówno w skali Hurley jak i HSSI, a nasileniem zaburzenia jakości życia u jego partnera. Średni wynik FDLQI dla partnerów pacjentów w stopniu nasilenia choroby Hurley I, II i III wyniósł odpowiednio 4.9±5.4, 9.4±6.9 i 11.8±6.5 punktów, natomiast w przypadku oceny zaawansowania trądziku odwróconego przeprowadzonej w skali HSSI średni wskaźnik FDLQI wyniósł 0.8±1.5, 6.9±5.7 i 11.3±6.7 punktów. Wyniki te pokazały więc bardzo duży wpływ HS na obniżenie jakości życia partnerów pacjentów z ciężkim przebiegiem choroby. Najczęściej podawanymi przez badanych elementami jakości życia, które podlegały wpływowi pozostawania w związku z osobą chorą na trądzik odwrócony były: udręka emocjonalna, gorsze samopoczucie fizyczne, wpływ na rozrywkę i czas wolny, dodatkowe obowiązki domowe oraz zwiększone wydatki. W badaniu nie wykazano korelacji między FDLQI a pozostałymi analizowanym parametrami, takimi jak wiek pacjentów i ich partnerów, płeć, czas trwania choroby czy palenie papierosów.

B. Dane uzyskane w trakcie analizy porównawczej poszczególnych systemów zaawansowania trądziku odwróconego wykazały istotną korelację między wszystkimi analizowanymi skalami. Porównując współczynniki korelacji pomiędzy kolejnymi ocenami przeprowadzonymi przez

jednego badacza, zaobserwowano podobną powtarzalność wyników i była ona bardzo dobra dla wszystkich skal. Żaden z 6 ocenianych instrumentów nie wykazał w tym względzie znaczącej przewagi nad innymi i żaden nie może być zalecany jako metoda nadrzędna w stosunku do pozostałych. W badaniu wykazano również w większości umiarkowane i niskie współczynniki zmienności między wynikami uzyskanymi przez poszczególnych oceniających lekarzy. Najwyższą zmienność wśród analizowanych instrumentów klasyfikacji obserwowano dla skali Sartorius, skali IHS4 (wyrażonej w punktach) oraz całkowitej liczby zmian, natomiast najbardziej powtarzalne wyniki między badaczami (najniższe współczynniki zmienności) uzyskano dla najprostszych 3-stopniowych klasyfikacji, w tym skali Hurley, IHS4 oraz HSSI.

C. Analizując dane z dotychczas opublikowanych doniesień na temat terapii biologicznej HS najwyższą skuteczność obserwowano dla infliximabu. Odsetek pozytywnych odpowiedzi na leczenie dla tego leku wyniósł we wszystkich badaniach 82%, natomiast dla dwóch pozostałych blokerów TNF-α (adalimumabu i etanerceptu) był na poziomie 54%. Warto jednak podkreślić, iż badania dotyczące zastosowania adalimumabu zostały przeprowadzone na znacznie większych grupach pacjentów niż w przypadku dwóch pozostałych preparatów, co czyni dane dotyczące skuteczności tego leku najbardziej wiarygodnymi.

Podsumowanie

Trądzik odwrócony jest wyniszczającą dermatozą wywierającą znaczny wpływ na codzienne życie i funkcjonowanie dotkniętych nią pacjentów, ale także pośrednio osób z ich otoczenia, w tym przede wszystkim partnerów osób chorych. Choroba powoduje znaczące obniżenie jakości życia partnerów pacjentów, a wpływ ten jest istotnie związany z nasileniem objawów chorobowych.

W odpowiedniej kwalifikacji klinicznej pacjentów z HS, a co za tym idzie wyborze najlepszej metody leczenia, pomocne są systemy oceny stopnia zaawansowania choroby. Mnogość jednak klasyfikacji, subiektywizm oceny, brak odpowiednich walidacji i wytycznych odnośnie stosowania skal nasilenia choroby sprawiają często problemy w codziennej praktyce, szczególnie mniej doświadczonych klinicznie dermatologów.

Mnogość problemów klinicznych związanych z diagnostyką i leczeniem HS, oceną zaawansowania choroby, a także powikłaniami psychospołecznymi u dotkniętych nim pacjentów i ich najbliższych wymaga wciąż wielu badań i dalszej analizy.

Summary

Introduction

Hidradenitis suppurativa (HS), also known as acne inversa, is a chronic, recurrent, inflammatory dermatosis, which pathogenesis is multifactorial and still not fully understood. It results from the hyperkeratosis and occlusion of hair follicle, with secondary involvement of apocrine glands and bacterial superinfection. The disease manifests itself in the presence of deeply located inflammatory lesions (nodules, abscesses and fistulas), most often affecting the anogenital area, buttocks, armpits and groin. The treatment of HS often occurs as a great therapeutic challenge. Depending on disease severity, both, topical preparations and systemic medications, but also some surgical methods are used. When conventional therapies occur insufficient, the biologics may also be an alternative option.

Due to the clinical picture and the typical localization of the lesions, HS is usually associated with a great pain sensation, stigmatization, depression and anxiety in the affected patients. The recent studies showed a significantly reduced quality of life of HS patients, also when comparing with other chronic dermatoses. Another problem is that the clinical picture of HS can vary greatly between patients. While diagnosis is usually not problematic, it is often not so obvious to qualify the patient into the appropriate stage of disease. The classification of disease severity in HS is usually based solely on the subjective assessment of the clinical picture made by a physician. Sometimes the symptoms reported by the patient are also taken into account, what further complicates the objective staging. So far, many systems for HS classification have been proposed in the literature, but the data on their validation and reliability are generally poor and incomplete.

Objectives

1. Assessment of the impact of the disease on the quality-of-life impairment in HS patients' partners. Identification of the components of the partners' quality of life, that are mostly affected by HS present in the patient. Evaluation of the relationship between the partner's quality of life impairment and the patient's disease severity, as well as other socio-demographic factors.

2. Conducting a validation and reliability assessment of the most frequently used HS classification systems, in a group of dermatology residents. Identification of the most reproducible and reliable HS staging systems, among doctors with a poor clinical experience in this condition.

3. Carrying out a review of the literature on the currently available biological therapy options for HS and their effectiveness.

Material and methods

The study on family quality of life included 50 pairs of hidradenitis suppurativa patients remaining under the care of the Department of Dermatology, Venereology and Allergology of the Medical University of Wroclaw, and their partners.

Detailed clinical evaluation was performed in all patients. At the same time the disease severity assessment with the Hurley system and HSSI was conducted, and a medical interview regarding previous treatment methods, demographic data and environmental factors was carried out.

In a group of 50 patients' partners, the partners' quality of life was assessed using The Family Dermatology Life Quality Index (FDLQI), and some socio-demographic data was collected to determine the characteristics of the study group.

A group of 16 dermatology residents at various stages of their residency program was invited to the study on the validation of the disease severity scales. Young doctors were asked to evaluate 9 HS patients according to disease severity using 6 HS classification systems (The Hurley Staging, Modified Hurley Staging, Hidradenitis Suppurativa Severity Score System, Hidradenitis Suppurativa Severity Index, Sartorius Hidradenitis Physician's Score Suppurativa Physician's Score and Hidradenitis Suppurativa Physician's Global Assessment Scale). Each patient was assessed twice by all doctors.

Results repeatability between both assessments conducted by one investigator was analyzed using the intra-class correlation coefficient (ICC). The variability of results obtained during the patient's examination with the use of the same scale performed by all physicians was calculated with the coefficient of variation (CV).

In the third study, 85 publications on the use and effectiveness of various biological preparations for HS were analyzed. The majority of the studies were case reports and case series, but some large

randomized controlled clinical trials were also found. The greatest number of reports concerned TNF-α inhibitors, which have been most widely used and best studied in this condition.

Results

A. In the entire group of the patients' partners, a moderately reduced quality of life was observed, with an average FDLQI index 8.7 ± 6.8 points. Moreover, a statistically significant positive correlation was found between the disease severity measured with both, the Hurley and HSSI scale, and the partner's quality of life impairment. The mean FDLQI score for Hurley I, II and III patients' partners was 4.9 ± 5.4, 9.4 ± 6.9 and 11.8 ± 6.5 points, respectively, and when assessing the severity of HS with HSSI scale, mean FDLQI score was 0.8 ± 1.5. 6.9 ± 5.7 and 11.3 ± 6.7 points, respectively. These results showed a very large impact of HS on the quality-of-life reduction in partners of patients with severe disease course. The most frequently reported quality of life components influenced by being in a relationship with a person suffering from HS were: emotional distress experienced, disturbed physical well-being, influenced recreation and free time, some extra housework and increased expenses. The study showed no correlation between FDLQI and other analyzed parameters, such as patients' and their partners' age, gender, disease duration and smoking.

B. The data obtained during comparative analysis of different HS severity score systems showed a significant correlation between all the analyzed scales. When comparing the correlation coefficients between both assessments carried out by one researcher, a similar repeatability of the results was observed for each scale and it was very good for all the systems. None of the 6 evaluated instruments showed a significant advantage over the others in this aspect and none can be recommended as a superior to the others. The study also showed mostly moderate and low coefficients of variation for the results obtained by different evaluators. The highest variability among the analyzed classification systems was observed for the Sartorius Score, the IHS4 scale (expressed in points) and the total number of lesions, while the most repeatable results between investigators (the lowest coefficients of variation) were obtained for the simplest 3-grade classifications, including the Hurley, IHS4 and HSSI scores.

C. When analyzing the data from the previously published reports on the biological HS therapies, the highest efficacy was observed for infliximab. The positive response rate for this drug was 82% in all studies, while for the other two TNF-α blockers (adalimumab and etanercept) it was 54%. However, it is worth to emphasize, that studies on the use of adalimumab were carried out on much larger groups of patients than it was in the case of the other two preparations, what makes the data on its effectiveness the most reliable.

Conclusions

Hidradenitis suppurativa is a debilitating dermatosis that has a significant impact on the daily life and functioning of the affected patients, but indirectly also people around them, including their partners. The disease significantly reduces the quality of life of patients' partners, and this impact is significantly related to the severity of disease symptoms.

Systems for assessing the severity of the disease are helpful in the appropriate clinical qualification of patients with HS, and thus in the selection of the best treatment option. However, the multiplicity of classifications, subjective assessment, lack of appropriate validation and guidelines for the use of disease severity scales often cause some problems in everyday practice, especially among less clinically experienced dermatologists.

The multitude of clinical problems related to the diagnosis and treatment of HS, assessment of the disease severity, as well as psychosocial complications in the affected patients and their relatives still requires further research and analysis.

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- Polskie Towarzystwo Dermatologiczne
- European Hidradenitis Suppurativa Foundation

ZNAJOMOŚĆ JĘZYKÓW OBCYCH:
Język angielski - biegle w mowie i piśmie

DOROBEK NAUKOWY

Pełne prace:

1. **Włodarek K.,** Szepietowski J.C.: Rola podłoża w lecznictwie dermatologicznym. *Med. Faktów* 2018; 11:151-155.

2. Zouboulis C.C., Matusiak Ł., Jemec G.B.E., Szepietowski J.C., Alvarez-Chinchilla P.J., Asoskova A., Bonnekoh H., Brattoli G., Cetinarslan T.S., Dawicka J., Dente V., Gallyamova Y., Giovanardi G., Glasenhardt K., Ionescu A.M., Janushaj E., Lakhssassi M.K., Lorincz K.K., Ludew D., Makmatov-Rys M., Malickova M., Mengesha S.W., Mintoff D., Otlewska A., Papakou M., Pirvan A.M., Provvidenziale L., Quadrana F., Savickaja N., Tamulyte G., Trifu A., Vigante A., **Włodarek K.**, Zouboulis V.A. Inter-rater and intrarater agreement and reliability in clinical staging of hidradenitis suppurativa/acne inversa. *Br. J. Dermatol.* 2019; 181:852-854.

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1. **Włodarek K.**, Szepietowski J.: Świąd. [w:] Terapia w Dermatologii. Szepietowski J., Baran W. (red.). Wydawnictwo Lekarskie PZWL 2019; 176-196.

Streszczenia:

1. **Włodarek K.**, Głowaczewska A., Matusiak Ł, Szepietowski J.: Quality of life impairment in hidradenitis suppurativa patients' partners.
   Acta Dermatovenereol. 2019; 99:743.
   18th Congress of the European Society for Dermatology and Psychiatry. Giessen, Germany, June 20-22, 2019.

2. **Włodarek K.**, Stefaniak A., Reich A., Matusiak Ł., Szepietowski J.C.: Assessment of reliability of six commonly used scoring systems for hidradenitis suppurativa in a group of dermatology residents.
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3. **Włodarek K.**, Ponikowska M., Matusiak Ł., Szepietowski J.C.: Biologics in HS: where are we now?
   Exp. Dermatol. 2019; 28:45-46.
   8th European Hidradenitis Suppurativa Foundation (EHSF) Conference. Wrocław, Poland, February 6-8, 2019.

4. **Włodarek K.**, Głowaczewska A., Matusiak Ł, Szepietowski J.C: Quality of life in hidradenitis suppurativa patients' partners: preliminary results.
   Exp. Dermatol. 2019; 28:17.
   8th European Hidradenitis Suppurativa Foundation (EHSF) Conference. Wrocław, Poland, February 6-8, 2019.

KOMISJA BIOETYCZNA
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OPINIA KOMISJI BIOETYCZNEJ Nr KB – 131/2019

Komisja Bioetyczna przy Uniwersytecie Medycznym we Wrocławiu, powołana zarządzeniem Rektora Uniwersytetu Medycznego we Wrocławiu nr 133/XV R/2017 z dnia 21 grudnia 2017 r. oraz działająca w trybie przewidzianym rozporządzeniem Ministra Zdrowia i Opieki Społecznej z dnia 11 maja 1999 r. (Dz.U. nr 47, poz. 480) na podstawie ustawy o zawodzie lekarza z dnia 5 grudnia 1996 r. (Dz.U. nr 28 z 1997 r. poz. 152 z późniejszymi zmianami) w składzie:

dr hab. Jacek Daroszewski, prof. nadzw. (endokrynologia, diabetologia)
prof. dr hab. Krzysztof Grabowski (chirurgia)
dr Henryk Kaczkowski (chirurgia szczękowa, chirurgia stomatologiczna)
mgr Irena Knabel-Krzyszowska (farmacja)
prof. dr hab. Jerzy Liebhart (choroby wewnętrzne, alergologia)
ks. dr hab. Piotr Mrzygłód, prof. nadzw. (duchowny)
mgr Luiza Műller (prawo)
dr hab. Sławomir Sidorowicz (psychiatria)
dr hab. Leszek Szenborn, prof. nadzw (pediatria, choroby zakaźne)
Danuta Tarkowska (pielęgniarstwo)
prof. dr hab. Anna Wiela-Hojeńska (farmakologia kliniczna)
dr hab. Andrzej Wojnar, prof. nadzw. (histopatologia, dermatologia) przedstawiciel Dolnośląskiej Izby Lekarskiej)
dr hab. Jacek Zieliński (filozofia)

pod przewodnictwem
prof. dr hab. Jana Kornafela (ginekologia i położnictwo, onkologia)

Przestrzegając w działalności zasad Good Clinical Practice oraz zasad Deklaracji Helsińskiej, po zapoznaniu się z projektem badawczym pt.

„Aspekty kliniczne i psychospołeczne trądziku odwróconego (hidradenitis suppurativa)"

zgłoszonym przez **lek. Katarzynę Włodarek** uczestniczkę studiów doktoranckich w Katedrze i Klinice Dermatologii, Wenerologii i Alergologii Uniwersytetu Medycznego we Wrocławiu oraz złożonymi wraz z wnioskiem dokumentami, w tajnym głosowaniu postanowiła wyrazić zgodę na przeprowadzenie badania w Klinice Dermatologii, Wenerologii i Alergologii Uniwersyteckiego Szpitala Klinicznego we Wrocławiu pod nadzorem prof. dr hab. Jacek Szepietowski **pod warunkiem zachowania anonimowości uzyskanych danych**.

Uwaga: Badanie to zostało objęte ubezpieczeniem odpowiedzialności cywilnej Uniwersytetu Medycznego we Wrocławiu z tytułu prowadzonej działalności:

Pouczenie: W ciągu 14 dni od otrzymania decyzji wnioskodawcy przysługuje prawo odwołania do Komisji Odwoławczej za pośrednictwem Komisji Bioetycznej UM we Wrocławiu

Opinia powyższa dotyczy: projektu badawczego będącego podstawą rozprawy doktorskiej

Wrocław, dnia 22 lutego 2019 r.

BW

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przewodniczący
prof. dr hab. Jan Kornafel

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Za zgodność z oryginałem

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Wrocław, 2020-09-28

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Niniejszym oświadczam, że w pracy:

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mój udział polegał na zbieraniu materiału do badań.

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