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Abstract

Background. Severe Hurley stage 1 Hidradenitis suppurativa (HS1) is a difficult to treat form of the disease.

Objective. To assess the efficacy and tolerance of the oral combination of rifampin (10 mg/kg once daily) – moxifloxacin (400 mg once daily) – metronidazole (250 to 500 mg t.i.d) (RMoM) treatment strategy in severe HS1 patients.

Methods. Prospective, open-label, non-comparative cohort study in 28 consecutive patients. 19 patients were treated for 6 weeks by RMoM, followed by 4 weeks of RMo alone, then by cotrimoxazole after remission. Moxifloxacin was replaced by pristinamycin (1g t.i.d) in 9 cases because of contra-indications or intolerance. Primary endpoint was a Sartorius score of 0 (clinical remission, CR) at week 12.

Results. The median Sartorius score dropped from 14 to 0 ($p= 6 \times 10^{-6}$) at week 12, 75% of patients reaching CR. A low initial Sartorius score was a prognosis factor for CR ($p = 0.049$). Main side-effects were mild gastro-intestinal discomfort, mucosal candidiasis and asthenia. At one year of follow-up, the median [IQR] number of flares dropped from 21/year to 1 ($p = 10^{-5}$).

Limitations: small monocentric non-controlled study.

Conclusion: complete and prolonged remission can be obtained in severe HS1 using targeted antimicrobial treatments.

Key words: Hidradenitis Suppurativa, rifampin, moxifloxacin, metronidazole, Hurley, prospective cohort study, Sartorius score, clinical remission, prognosis

Capsule summary

- Prospective antibiotic therapy trials in Hurley Stage 1 Hidradenitis Suppurativa are lacking.
- An antibiotic combination targeted against bacterial pathogens associated with HS lesions can obtain a complete remission which can be prolonged with antibiotic monotherapy maintenance treatments. Controlled trials are needed to confirm these results.

INTRODUCTION

Hidradenitis Suppurativa (HS) is a chronic inflammatory hair follicle disease with a high prevalence (1%) [1]. In the absence of a validated medical treatment, the disease causes a severe handicap in daily life and accounts for one of the poorest quality of life among dermatological diseases [2]. In order to obtain some relief, continuous or repeated intermittent empirical antibiotic treatments are used to treat 54 to 88% HS patients [3-6] with various combinations, uncertain efficacy and a potential risk of antibiotic resistance emergence. Antibiotics are considered as first line treatment for HS [1, 7-9] but prospective data are limited.

In Hurley's clinical severity staging [10], 2/3 of patients have stage I HS, the mildest form of the disease [11]. However, these patients undergo recurrent or permanently active painful inflammatory nodules or abscesses [12].

Using prolonged bacterial cultures to grow fastidious anaerobes and 16S bacterial metagenomics, we previously identified 3 main microbiota associated with Hurley stage 1 HS lesions: *Staphylococcus lugdunensis* in 25% cases, a polymorphous anaerobic flora in 50% cases, or skin commensals [13-15]. Taking into account these results, we developed an oral targeted bactericidal antimicrobial treatment associating rifampin, moxifloxacin and metronidazole (RMoM) to treat patients with severe Hurley stage 1 HS, followed by a low dose of cotrimoxazole as secondary prophylaxis of flares. In our previous retrospective study, this treatment strategy obtained clinical remission in 6/6 Hurley stage 1 HS patients [16].

The primary aim of this study was to prospectively assess the efficacy of the RMoM treatment strategy at 12 weeks in adults consulting for severe Hurley stage 1 HS. The secondary objectives were to identify prognosis factors of clinical remission and to assess treatment tolerance and long-term efficacy during a one-year follow-up.

MATERIALS AND METHODS

Patients and collected data. Patients enrolled in this study had to fulfill the following characteristics: age ≥ 18 years, confirmed diagnosis of HS, Hurley stage 1 clinical severity defined as abscess formation (single or multiple), without sinus tracts and scarring. HS diagnosis was established according to consensus definition (1) by 2 HS specialized dermatologists at Institut Pasteur Medical Center, which is a reference center for HS in France. Only evere patients were enrolled, severity being defined as at least 3 years duration since disease onset, 2 inflammatory nodules at inclusion and 6 flares in the past 12 months. Main non-inclusion criteria were pregnancy, chronic liver or kidney disease, cancer or hematological disease, immunosuppression or immunosuppressive treatments, long term treatments with non-steroidal anti-inflammatory drugs.

Data collected at inclusion included a standardized observation for demographic information (age, sex, body mass index, tobacco consumption, familial HS history) and disease history (age at onset, disease duration, number of flares per year before treatment, comorbidities, previous medical and surgical treatments including previous systemic antibiotics). All patients were treated using our routine protocols. This study was approved by Comité de Protection des Personnes Ile de France 2 (Ethical Committee, No IDRCB: 2011-A00536-35). Patients had to sign an informed consent and to have stopped antibiotics, systemic non-steroidal anti-inflammatory and steroid drugs for at least a month prior to enrollment. Patients' usual medications were continued.

Induction treatment, maintenance and relapse treatment strategy. The treatment strategy consisted of 6 weeks of rifampicin (10 mg/kg once daily, taken on an empty stomach at least 1 hour before or 2 hours after a meal), moxifloxacin (400 mg once daily) and metronidazole (500 mg t.i.d, half dosing regimen if weight < 60 kg [17]) followed by 4 weeks of rifampicin +

moxifloxacin [16]. If complete remission was obtained at week 10, a prophylaxis treatment with cotrimoxazole (400 mg/d or 800 mg/d if weight> 90kg) or doxycycline (200 mg once daily) was begun. In case of contra-indication, drug interaction or intolerance to rifampicin or moxifloxacin, these antibiotics could be replaced by pristinamycin (1g t.i.d).

Flares were defined as any painful inflammatory lesion occurring in a HS area, lasting more than 5 days and measuring more than 3 cm. Treatment of flares consisted in pristinamycin 1g t.i.d for 3 weeks. If inflammation did not regress after a week, metronidazole was added for 2 weeks. When a third flare after remission occurred in the same site, patients were advised to surgically remove the lesion by localized excision after a new treatment with pristinamycin and metronidazole.

Efficacy and safety assessment. Disease activity and treatment tolerance were assessed at inclusion and at scheduled follow-up visit: weeks 6 and 12, months 6 and 12, with additional visits in case of flare. In addition, patients' self-reported activity of the disease was recorded: number of flares between each follow-up visit, Visual Analogic Scale (VAS) for pain and quality of life with Skindex – France score [18]. Clinical remission of HS was defined as a Sartorius score of zero after 12 weeks of treatment, with absence of any inflammatory lesions. The Sartorius score, later modified [19, 20], describes and counts lesions and allows a dynamic evaluation of HS severity. The Sartorius score was counted by 2 physicians and, in case of difference, the mean score was calculated.

Treatment tolerance was assessed clinically at each follow-up visit and with laboratory tests (liver enzymes). Pre-therapeutic investigations included a hemogram, creatinine and liver enzymes blood level and an electrocardiogram.

Statistical analysis. Quantitative data were expressed by median and interquartile range (IQR), unpaired or paired comparisons of groups were performed by Wilcoxon rank sum tests. Qualitative data results were expressed by count (percentage) and comparison of groups were performed by Fisher's exact test. For efficacy data, p-values were adjusted for multiple comparisons using Holm's method. Statistical tests were considered as significant when p-value was <0.05. Efficacy of treatments was assessed by the intention-to-treat approach. For patients lost to follow-up, the "Last Observation Carried Forward" method was employed to impute missing endpoint values. No other missing data was imputed.

RESULTS

Patients. 28 consecutive severe Hurley stage 1 HS patients were enrolled in this study. The population was characterized by female predominance (21/28) and severe stage 1 HS aspects such as a median [IQR] disease duration of 14.5 years [3-33], a median number of areas involved of 5 [2-11] and a median number of flares per year of 21 [5-52] (Table 1). The median Sartorius score was 14 [12-19]. A majority had experienced ineffective previous antibiotic treatments (25/28) during the year before inclusion, and 24/28 underwent repeated surgery with a median of 5 [1-30] previous surgical procedures.

Treatments and follow-up. Among the 28 patients, 19 were treated by the rifampin-moxifloxacin-metronidazole treatment strategy. In 9 cases, moxifloxacin was replaced by pristinamycin due to a past history of tendonitis or joint pain or intolerance. Clinical severity of the disease as assessed by Sartorius and Skindex scores was similar in patients treated with RMoM or alternative treatment ($p = 0.55$ and $p = 0.24$, respectively). One patient receiving the RMoM combination, suffering from atopic dermatitis, developed generalized urticaria during the first week of treatment and stopped it after 10 days. One patient was lost to follow-up at the one-year visit.

Efficacy of treatments at week 12. At Week 12, median Sartorius score dropped from 14 at inclusion to 0 ($p = 6 \times 10^{-6}$) and 75% of patients achieved clinical remission of all lesions (Table 2, Figure 1). Median pain VAS dropped from 4 to 0 ($p = 2 \times 10^{-4}$) and median Skindex France score from 93 to 69 ($p = 6 \times 10^{-4}$).

Clinical remission rate at week 12 was associated with a lower initial Sartorius score (median of 14 for responders and of 21 for non-responders, $p = 0.049$), but not with sex, age, HS type (familial/sporadic), duration of HS, number of affected sites, Skindex France score at

inclusion and pain VAS (data not shown). The improvement of Sartorius score, Skindex France score and pain (VAS) did not differ according to the received treatment (RMoM or alternative treatment, p = 0.58, p= 0.14, and p=0.07, respectively).

Three patients obtained clinical remission at week 6, but relapsed at week 12, after discontinuing metronidazole. These patients were back in remission after flare treatment respectively at month 3, 4, and 9.

Efficacy of the treatments at one year of follow-up. All patients in clinical remission except one received a low dosing regimen of cotrimoxazole as maintenance treatment. Median Sartorius score and pain VAS remained at 0 at 1 year (Table 2, Figure 1) and the rate of flares dropped from a median of 21/year before treatment to 1 at one year of follow-up ($p = 1.2 \times 10^{-5}$). The 19 patients treated with the RMoM strategy tended to be more frequently in clinical remission at all follow-up visits than the 9 patients treated with alternative treatment (12 weeks, 6 months and one year), but this difference did not reach statistical significance (63.2 vs 33.3%, p = 0.22). Skindex France score remained stable after week12. Remarkably, no new area was involved in any patient during the 1-year follow-up period under secondary prophylaxis.

Safety. Tolerance was acceptable, with mild digestive discomfort, mucosal candidiasis and asthenia in respectively 96, 64 and 79% of patients. None of these side-effects required treatment suspension. Before starting treatment, 2/28 patients were faecal carriers of extended spectrum betalactamase producing enterobacteriaceae (E-ESBL, Mendeley supplemental table 1, http://dx.doi.org/10.17632/pmsfcsf2fb.1). E-ESBL carriage persisted in one patient during all the study and disappeared in the other patient during follow-up. 3 patients acquired E-ESBLs during follow-up (3 *E. coli*, associated in one case with an ESBL *Klebsiella*

212 *pneumoniae* isolate), 2 as outpatients: one during a trip to Hong-Kong, one during a trip to
213 Morocco and one after a hospitalization for another reason than HS. During the study, no
214 patient was an initial faecal carrier or acquired vancomycin resistant enterococci or
215 carbapenemase producing enterobacteriaceae. There was no significant rise in liver enzymes.

DISCUSSION

HS treatment guidelines advise to use topical clindamycin or oral tetracycline in HS and, in case of failure, recommend the rifampicin-clindamycin association [1, 7-9]. However, only two small randomized trials assessed the efficacy of antibiotics (oral tetracycline and topical clindamycin) in HS and only demonstrated a slight and temporary improvement [21, 22]. The last recommendation relies on open label retrospective studies [23-27] and on two prospective studies [28, 29].

The aim of this study was to present the first prospective report on the efficacy of the rifampicin-moxifloxacin-metronidazole combination in real life conditions in our center. This combination is only given as first line therapy to patients with severe Hurley stage 1 HS as defined in the methods section. In this study, we observed a dramatic improvement of HS, 75% of patients achieving clinical remission after 12 weeks of treatment with a major improvement in pain and quality of life. In 9 patients, moxifloxacin was replaced by pristinamycin due to a past history of tendonitis or joint pain or intolerance, which did not seem to be associated with a different outcome at week 12. Pristinamycin is used in our center alone or in association with metronidazole in less severe Hurley stage 1 patients, or as an alternative to moxifloxacin in case of contra-indication or side effects because of its wide spectrum including staphylococci, streptococci and Gram-positive anaerobes. In countries where pristinamycin is not available, clindamycin alone, amoxicillin + clavulanic acid, tetracycline or minocycline could be used as alternative antibiotic treatments, taking into account previous patients' exposure which may lead to clinical failures due to antimicrobial resistance, in association with metronidazole [30, 31].

Our primary endpoint, i.e. clinical remission, was ambitious, since most published studies have only an improvement objective. Moreover, studies on antibiotics on HS rarely include a long-term assessment of efficacy and tolerance. A dramatic decrease in the number of flares

and therefore of the use of new courses of antibiotics was observed at one year of follow-up. Clinical adverse events were frequent, but mild and easy to handle. One patient was a faecal carrier of ESBL producing *E. coli*. This frequency (1/28) is consistent with the 5-10% carriage prevalence of ESBL producing enterobacteriaceae described in the French community [32]. 3 patients acquired resistant bacteria during treatment, but only one persisted. All our patients were treated at home, thus limiting the risk of acquiring or transmitting multi-resistant bacteria in the hospital.

In our previous retrospective study on the RMoM treatment strategy which included, in severe (Hurley stage 2 and 3) patients, a 3 week-course of i.v. ceftriaxone and oral metronidazole as induction treatment, 6/6 (100%), 8/10 (80%) and 2/12 (17%) of Hurley stage 1, 2 and 3 patients, achieved clinical remission respectively [16]. In the present study, only one clinical factor was associated with a higher clinical remission rate in Hurley stage 1 patients: a lower Sartorius score at enrollment. Together, these data suggest that the clinical severity of disease is a prognostic factor for clinical remission in HS using antibiotic treatments.

The RMoM combination has a wide antimicrobial spectrum including anaerobes and targeting the different flora isolated from HS lesions [13-15, 33]. Compared to the rifampin-clindamycin combination, which also has an appropriate antibacterial spectrum in HS, the pharmacokinetics of the RMoM association are more favorable, with mild interactions between rifampin and moxifloxacin [34]. This may account for the high clinical remission rate of this antibiotic association that we observed in severe Hurley stage 1 patients and not only improvement as reported with the rifampicin-clindamycin combination [23-29]. We started using this treatment strategy when we noticed that the use of the oral rifampicin-clindamycin combination resulted in a dramatic decrease of clindamycin plasma levels leading to a quasi-rifampicin-monotherapy after 10 days of treatment. Indeed, rifampicin is a potent inducer of the P450 cytochrome that mediates the metabolism of clindamycin [35-37] and this

pharmacokinetic interaction recently led to propose clindamycin monotherapy in HS [27, 30]. Metronidazole was added to the rifampicin-moxifloxacin combination to optimize anaerobes coverage, but it needs to be stopped after 6 weeks because of potential neurotoxicity.

The limits of this study are that it is a monocentric open label study with a relatively small sample of patients. These results should be validated by a large controlled trial, as well as the interest of using a low dosing regiment of cotrimoxazole as secondary prophylaxis of flares in pre-existing lesions, or to prevent new lesions. Because of potential side effects, including tendonitis and tendon rupture for fluoroquinolones and metronidazole disulfiram-like reaction with alcohol, this oral treatment strategy should be given to selected (severe) Hurley stage 1 patients, and physicians should be aware of potential drug interactions with rifampin. Finally, the efficacy and safety of cotrimoxazole which is associated severe cutaneous drug reactions should be assessed vs. alternative maintenance treatments such as tetracycline.

In conclusion, the rifampin-moxifloxacin-metronidazole treatment combination followed by a a low dose regimen of cotrimoxazole appears to be a well-tolerated and successful treatment option for severe Hurley stage 1 HS patients. This strategy could be a major step forward in severe stage 1 HS patient management and could lower the burden of this disease for patients and society.

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Figure 1. Hurley stage 1 Hidradenitis Suppurativa. Treatment results at week 12 and at one year of follow-up.

Figure 1 legend. Hurley stage 1 HS. Left panel (violin plots): presented data are median (dashed line) and IQR. Right panel: the same variables are presented in classes. NA: not available data (one patient was lost to follow-up at month 12).

Table 1. Hurley stage 1 HS patients' characteristics

No. of patients	28
Sex ratio (male/female)	0.33 (7/21)
Age of patients (years), median [IQR]	31.5 [25 – 41]
Body mass index ($kg.m^{-2}$), median [IQR]	26 [21 – 29]
Tobacco, n (%)	26 (93)
Familial HS, n (%)	8 (29)
Age at onset of HS (years), median [IQR]	17.5 [15-19]
Duration of HS (years), median [IQR]	14.5 [9.5 - 23]
N° of flares per year, median [IQR]	21 [12-52]
Patients with ≥ 1 flare/month, n (%)	23 (82)
N° of HS active lesions, n [IQR]	5 [4-7]
Sartorius score, median [IQR]	14 [12 - 19]
Skindex France score, median [IQR]	93 [78 - 115]
Pain VAS, median [IQR]	4.0 [3.0-6.5]
Previous medical treatments during the last year	
Antibiotics, n (%)	25 (89)
Rifampicin-clindamycin, n (%)	8 (29)
Pristinamycin, n (%)	14 (50)
Tetracycline, n (%)	11 (39)
Reported use of non-steroidal anti-inflammatory drugs, n (%)	23 (82)
Previous surgical acts	
Drainage, n (%)	18 (64)
Local surgery, n (%)	27 (96)
Wide surgery, n (%)	10 (36)

[IQR]: interquartile range

Table 2. Hurley stage 1 HS patients. Efficacy of treatments at week 12 and at one year of follow-up

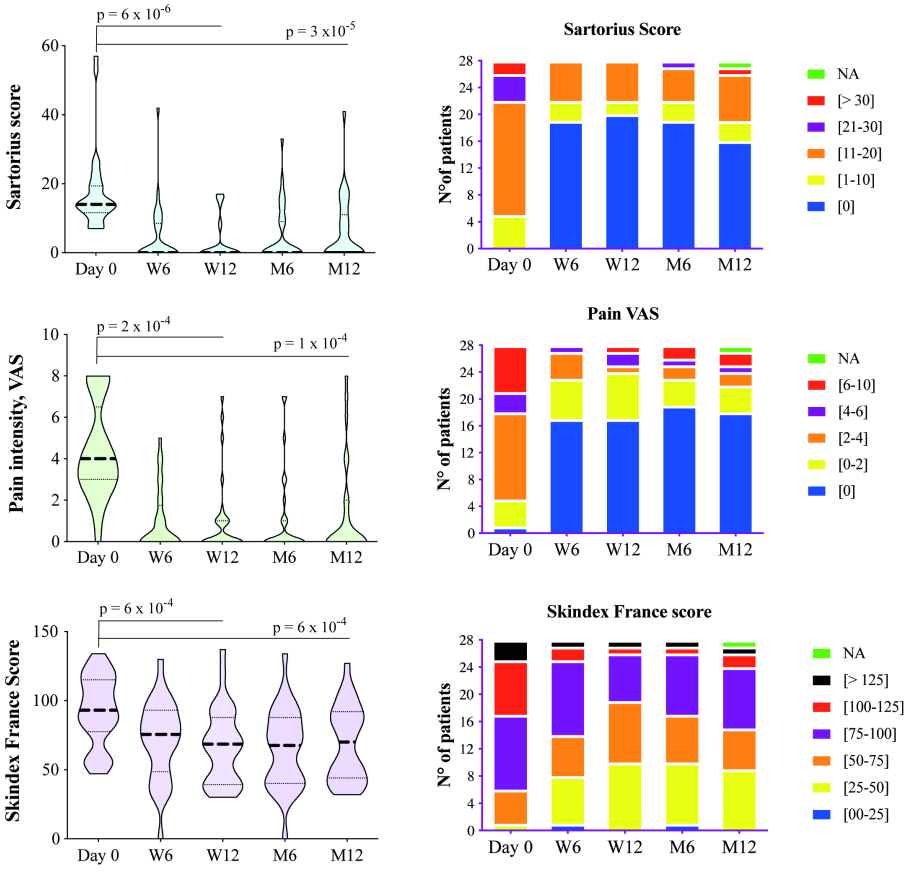
	Day 0	week 12	1 year[2]	p[3]
Sartorius score[1]	14 [12 - 19]	0 [0- 2]	0 [0-9]	6×10^{-6}; 3×10^{-5}
Pain VAS[1]	4.0 [3.0-6.5]	0 [0- 1]	0 [0- 2]	2×10^{-4}; 10^{-4}
Skindex France[1]	93 [78 - 115]	69 [40-88]	70 [44-88]	6×10^{-4}; 6×10^{-4}
N° of flares/year	21 [12-52]	na	1 [0, 16]	na; 10^{-5}

[1] median [IQR, interquartile range]

[2] 1 patient was lost to follow-up at 1 year.

[3] week 12 vs Day 0; 1 year vs Day 0

Na: non-assessable


p = 6 x 10-6
p = 3 x10-5
Sartorius score
Day 0
W6
W12
M6
M12
Sartorius Score
N°of patients
NA
[> 30]
[21-30]
[11-20]
[1-10]
[0]
p = 2 x 10-4
p = 1 x 10-4
Pain intensity, VAS
Pain VAS
N° of patients
NA
[6-10]
[4-6]
[2-4]
[0-2]
[0]
p = 6 x 10-4
p = 6 x 10-4
Skindex France Score
Skindex France score
N° of patients
NA
[> 125]
[100-125]
[75-100]
[50-75]
[25-50]
[00-25]