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Journal Pre-proof

Rifampin-moxifloxacin-metronidazole combination therapy for severe Hurley Stage 1 Hidradenitis Suppurativa: prospective short-term trial and one-year follow-up in 28 consecutive patients

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2
3 **Rifampin-moxifloxacin-metronidazole combination therapy for severe Hurley Stage 1**
4 **Hidradenitis Suppurativa: prospective short-term trial and one-year follow-up in 28**
5 **consecutive patients**

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45

46 **Abstract**

47

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

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

53 **Methods.** Prospective, open-label, non-comparative cohort study in 28 consecutive patients.
54 19 patients were treated for 6 weeks by RMoM, followed by 4 weeks of RMo alone, then by
55 cotrimoxazole after remission. Moxifloxacin was replaced by pristinamycin (1g t.i.d) in 9
56 cases because of contra-indications or intolerance. Primary endpoint was a Sartorius score of 0
57 (clinical remission, CR) at week 12.

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

62 **Limitations:** small monocentric non-controlled study.

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

65

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

68

69

70

71

72 **Capsule summary**

73 • Prospective antibiotic therapy trials in Hurley Stage 1 Hidradenitis Suppurativa are
74 lacking.

75 • An antibiotic combination targeted against bacterial pathogens associated with HS
76 lesions can obtain a complete remission which can be prolonged with antibiotic
77 monotherapy maintenance treatments. Controlled trials are needed to confirm these
78 results.

79

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80 **INTRODUCTION**

81 Hidradenitis Suppurativa (HS) is a chronic inflammatory hair follicle disease with a high
82 prevalence (1%)¹. In the absence of a validated medical treatment, the disease causes a severe
83 handicap in daily life and accounts for one of the poorest quality of life among dermatological
84 diseases². In order to obtain some relief, continuous or repeated intermittent empirical
85 antibiotic treatments are used to treat 54 to 88% HS patients³⁻⁶ with various combinations,
86 uncertain efficacy and a potential risk of antibiotic resistance emergence. Antibiotics are
87 considered as first line treatment for HS^{1,7-9} but prospective data are limited.

88 In Hurley's clinical severity staging¹⁰, 2/3 of patients have stage I HS, the mildest form of the
89 disease¹¹. However, these patients undergo recurrent or permanently active painful
90 inflammatory nodules or abscesses¹².

91 Using prolonged bacterial cultures to grow fastidious anaerobes and 16S bacterial
92 metagenomics, we previously identified 3 main microbiota associated with Hurley stage 1 HS
93 lesions: *Staphylococcus lugdunensis* in 25% cases, a polymorphous anaerobic flora in 50%
94 cases, or skin commensals¹³⁻¹⁵. Taking into account these results, we developed an oral
95 targeted bactericidal antimicrobial treatment associating rifampin, moxifloxacin and
96 metronidazole (RMoM) to treat patients with severe Hurley stage 1 HS, followed by a low
97 dose of cotrimoxazole as secondary prophylaxis of flares. In our previous retrospective study,
98 this treatment strategy obtained clinical remission in 6/6 Hurley stage 1 HS patients¹⁶.

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

103 **MATERIALS AND METHODS**

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

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

123

124 **Induction treatment, maintenance and relapse treatment strategy.** The treatment strategy
125 consisted of 6 weeks of rifampicin (10 mg/kg once daily, taken on an empty stomach at least
126 1 hour before or 2 hours after a meal), moxifloxacin (400 mg once daily) and metronidazole
127 (500 mg t.i.d, half dosing regimen if weight $<$ 60 kg¹⁷) followed by 4 weeks of rifampicin +

128 moxifloxacin¹⁶. If complete remission was obtained at week 10, a prophylaxis treatment with
129 cotrimoxazole (400 mg/d or 800 mg/d if weight > 90kg) or doxycycline (200 mg once daily)
130 was begun. In case of contra-indication, drug interaction or intolerance to rifampicin or
131 moxifloxacin, these antibiotics could be replaced by pristinamycin (1g t.i.d).

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

138

139 **Efficacy and safety assessment.** Disease activity and treatment tolerance were assessed at
140 inclusion and at scheduled follow-up visit: weeks 6 and 12, months 6 and 12, with additional
141 visits in case of flare. In addition, patients' self-reported activity of the disease was recorded:
142 number of flares between each follow-up visit, Visual Analogic Scale (VAS) for pain and
143 quality of life with Skindex – France score¹⁸. Clinical remission of HS was defined as a
144 Sartorius score of zero after 12 weeks of treatment, with absence of any inflammatory lesions.
145 The Sartorius score, later modified^{19, 20}, describes and counts lesions and allows a dynamic
146 evaluation of HS severity. The Sartorius score was counted by 2 physicians and, in case of
147 difference, the mean score was calculated.

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

151

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

160

161

162 **RESULTS**

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

170

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

179

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

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

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

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

193
194 **Efficacy of the treatments at one year of follow-up.** All patients in clinical remission except
195 one received a low dosing regimen of cotrimoxazole as maintenance treatment. Median
196 Sartorius score and pain VAS remained at 0 at 1 year (Table 2, Figure 1) and the rate of flares
197 dropped from a median of 21/year before treatment to 1 at one year of follow-up ($p = 1.2 \times 10^{-5}$).
198 The 19 patients treated with the RMoM strategy tended to be more frequently in clinical
199 remission at all follow-up visits than the 9 patients treated with alternative treatment (12
200 weeks, 6 months and one year), but this difference did not reach statistical significance (63.2
201 vs 33.3%, $p = 0.22$). Skindex France score remained stable after week 12. Remarkably, no new
202 area was involved in any patient during the 1-year follow-up period under secondary
203 prophylaxis.

204
205 **Safety.** Tolerance was acceptable, with mild digestive discomfort, mucosal candidiasis and
206 asthenia in respectively 96, 64 and 79% of patients. None of these side-effects required
207 treatment suspension. Before starting treatment, 2/28 patients were faecal carriers of extended
208 spectrum betalactamase producing enterobacteriaceae (E-ESBL, Mendeley supplemental table
209 1, <http://dx.doi.org/10.17632/pmsfcsf2fb.1>). E-ESBL carriage persisted in one patient during
210 all the study and disappeared in the other patient during follow-up. 3 patients acquired E-
211 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.

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216 **DISCUSSION**

217 HS treatment guidelines advise to use topical clindamycin or oral tetracycline in HS and, in
218 case of failure, recommend the rifampicin-clindamycin association ^{1, 7-9}. However, only two
219 small randomized trials assessed the efficacy of antibiotics (oral tetracycline and topical
220 clindamycin) in HS and only demonstrated a slight and temporary improvement ^{21, 22}. The last
221 recommendation relies on open label retrospective studies ²³⁻²⁷ and on two prospective studies
222 ^{28, 29}.

223 The aim of this study was to present the first prospective report on the efficacy of the
224 rifampicin-moxifloxacin-metronidazole combination in real life conditions in our center. This
225 combination is only given as first line therapy to patients with severe Hurley stage 1 HS as
226 defined in the methods section. In this study, we observed a dramatic improvement of HS,
227 75% of patients achieving clinical remission after 12 weeks of treatment with a major
228 improvement in pain and quality of life. In 9 patients, moxifloxacin was replaced by
229 pristinamycin due to a past history of tendonitis or joint pain or intolerance, which did not
230 seem to be associated with a different outcome at week 12. Pristinamycin is used in our center
231 alone or in association with metronidazole in less severe Hurley stage 1 patients, or as an
232 alternative to moxifloxacin in case of contra-indication or side effects because of its wide
233 spectrum including staphylococci, streptococci and Gram-positive anaerobes. In countries
234 where pristinamycin is not available, clindamycin alone, amoxicillin + clavulanic acid,
235 tetracycline or minocycline could be used as alternative antibiotic treatments, taking into
236 account previous patients' exposure which may lead to clinical failures due to antimicrobial
237 resistance, in association with metronidazole ^{30, 31}.

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

241 and therefore of the use of new courses of antibiotics was observed at one year of follow-up.
242 Clinical adverse events were frequent, but mild and easy to handle. One patient was a faecal
243 carrier of ESBL producing *E. coli*. This frequency (1/28) is consistent with the 5-10%
244 carriage prevalence of ESBL producing enterobacteriaceae described in the French
245 community³². 3 patients acquired resistant bacteria during treatment, but only one persisted.
246 All our patients were treated at home, thus limiting the risk of acquiring or transmitting multi-
247 resistant bacteria in the hospital.

248 In our previous retrospective study on the RMoM treatment strategy which included, in severe
249 (Hurley stage 2 and 3) patients, a 3 week-course of i.v. ceftriaxone and oral metronidazole as
250 induction treatment, 6/6 (100%), 8/10 (80%) and 2/12 (17%) of Hurley stage 1, 2 and 3
251 patients, achieved clinical remission respectively¹⁶. In the present study, only one clinical
252 factor was associated with a higher clinical remission rate in Hurley stage 1 patients: a lower
253 Sartorius score at enrollment. Together, these data suggest that the clinical severity of disease
254 is a prognostic factor for clinical remission in HS using antibiotic treatments.

255 The RMoM combination has a wide antimicrobial spectrum including anaerobes and targeting
256 the different flora isolated from HS lesions^{13-15, 33}. Compared to the rifampin-clindamycin
257 combination, which also has an appropriate antibacterial spectrum in HS, the
258 pharmacokinetics of the RMoM association are more favorable, with mild interactions
259 between rifampin and moxifloxacin³⁴. This may account for the high clinical remission rate
260 of this antibiotic association that we observed in severe Hurley stage 1 patients and not only
261 improvement as reported with the rifampicin-clindamycin combination²³⁻²⁹. We started using
262 this treatment strategy when we noticed that the use of the oral rifampicin-clindamycin
263 combination resulted in a dramatic decrease of clindamycin plasma levels leading to a quasi-
264 rifampicin-monotherapy after 10 days of treatment. Indeed, rifampicin is a potent inducer of
265 the P450 cytochrome that mediates the metabolism of clindamycin³⁵⁻³⁷ and this

266 pharmacokinetic interaction recently led to propose clindamycin monotherapy in HS ^{27, 30}.

267 Metronidazole was added to the rifampicin-moxifloxacin combination to optimize anaerobes

268 coverage, but it needs to be stopped after 6 weeks because of potential neurotoxicity.

269 The limits of this study are that it is a monocentric open label study with a relatively small

270 sample of patients. These results should be validated by a large controlled trial, as well as the

271 interest of using a low dosing regiment of cotrimoxazole as secondary prophylaxis of flares in

272 pre-existing lesions, or to prevent new lesions. Because of potential side effects, including

273 tendonitis and tendon rupture for fluoroquinolones and metronidazole disulfiram-like reaction

274 with alcohol, this oral treatment strategy should be given to selected (severe) Hurley stage 1

275 patients, and physicians should be aware of potential drug interactions with rifampin. Finally,

276 the efficacy and safety of cotrimoxazole which is associated severe cutaneous drug reactions

277 should be assessed vs. alternative maintenance treatments such as tetracycline.

278

279 In conclusion, the rifampin-moxifloxacin-metronidazole treatment combination followed by a

280 a low dose regimen of cotrimoxazole appears to be a well-tolerated and successful treatment

281 option for severe Hurley stage 1 HS patients. This strategy could be a major step forward in

282 severe stage 1 HS patient management and could lower the burden of this disease for patients

283 and society.

284

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287

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

394

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

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398 **Table 1. Hurley stage 1 HS patients' characteristics**

399		
400	No. of patients	28
401	Sex ratio (male/female)	0.33 (7/21)
402	Age of patients (years), median [IQR]	31.5 [25 – 41]
403	Body mass index (kg.m ⁻²), median [IQR]	26 [21 – 29]
404	Tobacco, n (%)	26 (93)
405	Familial HS, n (%)	8 (29)
406	Age at onset of HS (years), median [IQR]	17.5 [15-19]
407	Duration of HS (years), median [IQR]	14.5 [9.5 - 23]
408	N° of flares per year, median [IQR]	21 [12-52]
409	Patients with ≥ 1 flare/month, n (%)	23 (82)
410	N° of HS active lesions, n [IQR]	5 [4-7]
411	Sartorius score, median [IQR]	14 [12 - 19]
412	Skindex France score, median [IQR]	93 [78 - 115]
413	Pain VAS, median [IQR]	4.0 [3.0-6.5]
414		
415	Previous medical treatments during the last year	
416	Antibiotics, n (%)	25 (89)
417	Rifampicin-clindamycin, n (%)	8 (29)
418	Pristinamycin, n (%)	14 (50)
419	Tetracycline, n (%)	11 (39)
420	Reported use of non-steroidal anti-inflammatory drugs, n (%)	23 (82)
421		
422	Previous surgical acts	
423	Drainage, n (%)	18 (64)
424	Local surgery, n (%)	27 (96)
425	<u>Wide surgery, n (%)</u>	<u>10 (36)</u>

426 [IQR]: interquartile range

427

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

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

435 ¹ median [IQR, interquartile range]

436 ² 1 patient was lost to follow-up at 1 year.

437 ³ week 12 vs Day 0; 1 year vs Day 0

438 Na: non-assessable

439

440

