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PII: S1297-319X(20)30082-8

DOI: https://doi.org/doi:10.1016/j.jbspin.2020.04.017

Reference: BONSOI 5006

To appear in: *Joint Bone Spine*

Accepted Date: 24 April 2020

Please cite this article as: Hachulla E, Gouellec NL, Launay D, Balquet M-Hélène, Maillard H, Azar R, Boldron A, Bataille P, Lambert M, Buchdahl A-Laure, Allorge D, Hatron P-Yves, Sobanski V, Hennart B, Clerson P, Morell-Dubois S, Adherence to hydroxychloroquine in patients with systemic lupus: contrasting results and weak correlation between assessment tools, *Joint Bone Spine* (2020), doi: https://doi.org/10.1016/j.jbspin.2020.04.017

Adherence to hydroxychloroquine in patients with systemic lupus: contrasting results and weak correlation between assessment tools

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TITLE

Adherence to hydroxychloroquine in patients with systemic lupus: contrasting results and weak correlation between assessment tools.

Highlights:

- The adherence rate to HCQ treatment in SLE varied between 3.2% and 32.5%
- Correlations between blood HCQ-concentration and self-questionnaires are weak and agreement between methods was poor
- Combining blood HCQ concentration with MASRI and MMAS-8 may help to better identify non-adherence in SLE

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ABSTRACT

Objectives: Hydroxychloroquine (HCQ) is an anchor drug in the treatment of systemic lupus erythematosus (SLE). Adherence to HCQ is key for efficacy. Inaccurate evaluation of adherence could lead to non-justified switch to more expensive or less tolerated drugs.

Methods: Severe non-adherence rate to HCQ was estimated in a sample of SLE patients during a routine visit using blood HCQ concentration < 200 µg/L. Adherence was assessesd by the Medication Adherence Self-Report Inventory (MASRI) < 80/100, 8-item Morisky Medication Adherence Scale (MMAS-8) ≤ 6 /8, Health Care Provider (HCP) visual analog scale (VAS) < 80/100. Same procedures were to be repeated during a further routine visit 6 to 12 months later. We described agreement and correlations between tools and compared severely non-adherent patients and others on their characteristics.

Results: The study involved 158 patients (86.1% females) aged 42.2±12.6 years treated with HCQ for 9.6±6.9 years. Blood HCQ concentration (mean±standard deviation) was 1046±662 µg/L at visit 1 and 855±577 µg/L at visit 2. At visit 1, the non-adherence rate varied from 3.2% (blood HCQ level < 200 µg/L) to 7.7% (MASRI), 12.4% (HCP-VAS) or 32.5% (MMAS-8). 37.8% of patients met at least one of the definitions of non-adherence. Patients' characteristics including SLE activity, damage and quality of life were similar between severely non-adherent patients and others. Correlations between blood HCQ-concentration and self-questionnaires were weak (r <0.25) and agreement between methods was poor.

Conclusion: Blood HCQ concentration < 200 µg/L reveals severe non-adherence. Combining blood HCQ concentration with MASRI and MMAS-8 may help to better identify non-adherence in SLE. Agreement between methods was poor and correlations with HCQ level and SLE activity were weak.

Keywords : Systemic Lupus Hydroxychloroquine Adherence

1. Introduction

Systemic lupus erythematosus (SLE) is a chronic inflammatory condition, notably comprising joint, skin, kidney, and sometimes, nervous system damages, with an estimated prevalence of 4.7 per 10,000 inhabitants in France [1]. Hydroxychloroquine (HCQ), a 4-aminoquinolone antimalarial molecule, is the anchor drug of lupus treatment with a good safety profile and a favorable cost: effectiveness ratio. HCQ prevents flares [2], improves cutaneous manifestations [3] and arthritis [4], enhances survival [5,6], and decreases organ damages [7]. HCQ may be prescribed as a monotherapy or be combined with nonsteroidal anti-inflammatory drugs, corticosteroids, immunosuppressive drugs or biologics.

As observance to HCQ is key for efficacy, an accurate diagnosis of poor adherence may prevent inappropriate switch to more expensive or less tolerated drugs. Non-adherence to HCQ regimen increases health resource consumption [8] and the risk of subsequent acute care use [9]. The determination of blood HCQ concentration is an objective and direct measure of the patient's adherence. A cutoff of 200 µg/L has been proposed to define non-adherence [10]. Based on this threshold, the proportion of SLE patients who are poorly adherent appears to vary from 10% [11] to 22% [12]. Several other tools are available to assess patients' adherence. Indirect methods include medication event monitoring systems (MEMS), pharmacy records, health care provider assessment, and self-report.

Taking advantage of a regional network managing around 1500 SLE patients, we set up a study which aimed at estimating the prevalence of non-adherence using various tools including determination of HCQ blood concentration, use of well-validated questionnaires, and health care provider (HCP) assessment. We were thus able to

estimate various rates of non-adherence to HCQ, to describe the characteristics of SLE patients according to their adherence to HCQ and to correlate different tools routinely used for the assessment of adherence.

2. Material and methods

2.1 *Trial design, setting and ethics*

This was a prospective, longitudinal, observational study. The study protocol was approved by a locally appointed ethics committee (Comité de Protection des Personnes – Hauts de France). Each patient was informed of the aims and constraints of the study and gave an informed consent prior to any study procedure. The study complied with the Declaration of Helsinki. The study population was composed of adult patients with a diagnosis of SLE meeting the American College of Rheumatology (ACR) criteria [13], treated with HCQ for at least 3 months at a dose ≥ 200 mg/day. Pregnant and breast-feeding women were excluded from the study.

Data were collected during two routine visits at a planned interval of 6 to 12 months. SLE activity was measured using the Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) ranging from 0 to 105 [14]. Damages from the diagnosis of SLE onwards were evaluated by the Systemic Lupus International Collaborating Clinics (SLICC) damage index [15]. At both study visits, a blood sample was drawn from the patient, stored at ambient temperature and blood HCQ concentration was measured within 48 h (Toxicology Laboratory, Biology-Pathology Center, Lille) using liquid chromatography coupled to mass spectrometry detection (LC-MS). A blood HCQ concentration < 200 µg/L defined non-adherence [10]. The adherence was also evaluated by the Medication Adherence Self-Report Inventory (MASRI) questionnaire [16], a self-administered

questionnaire already used in SLE patients [17] with a cutoff of 80 according to the authors recommendations, and by the 8-item Morisky Medication Adherence Scale (MMAS-8) [18-21]. MASRI tries to quantify the number of missed pills and the overall adherence over the last 30 days. MMAS-8 explores the patient's behaviours regarding the treatment. Patients were considered to be poorly adherent if the MMAS-8 score was ≤ 6 [18]. MMAS-8 allows the intentional and unintentional non-adherence to be distinguished. Intentional non-adherence refers to non-adherence that is deliberate and largely associated with patient motivation whereas unintentional non-adherence is non-adherence that is largely driven by a lack of capacity or resources to take medications (for instance, when patient cannot have access to the treatment because of its cost). In addition, the reasons underlying intentional and unintentional non-adherence are not entirely independent in that certain types of unintentional non-adherence e.g. forgetting, are logically more likely when motivation for medication is low. Patients were asked to fill in a MMAS-8 scale regarding HCQ and another one regarding other treatments. The Health Care Provider (HCP) assessed the patient adherence on a 100-mm VAS. A convenient value < 80 was used to define poor adherence as patients with compliance of at least 80% are generally considered to be compliant [22] . In addition, patients were asked to self-rate their adherence to the HCQ regimen and the benefit brought by the treatment on two 100-mm VAS. Quality of life was assessed with the French version of the LupusQoL scale [23]. Anxiety and depression were explored by the HAD-Anxiety and HAD-depression scale, respectively.

2.2 Statistics

Results are expressed as mean±standard deviation or number (percentage). Percentages are calculated on observed data. The proportion of non-adherent patients was estimated with a two-sided 95% confidence interval (CI) at each visit assuming a binomial

distribution. Adherent and non-adherent patients according to blood HCQ concentration at visit 1 and/or visit 2 were compared using parametric (Student's t test) and non-parametric (Mann-Whitney's U test, chi squared test, Fisher's exact test) statistical tests depending on the nature and distribution of data. The type 1 error risk was set at 5% and the tests were two-sided. The comparative analysis was conducted on patients with documented blood HCQ concentrations at both visits. Correlations between assessment tools were quantified by the Pearson's method.

3. Results

3.1 Population

The study included 158 patients. Blood HCQ concentration was determined in 156 patients at visit 1, in 146 patients at visit 2 and in 145 patients at both visits, spaced by 12.0±4.2 months (blood HCQ measurements were not performed in 2 patients at visit 1 and in 12 patients at visit 2 for technical reasons). Mean age was 42.2±12.6 years and 136 patients (86.1%) were females. Almost all documented patients were positive for antinuclear antibodies (152/153), and 26 (16.5%) patients had an associated antiphospholipid syndrome. Twenty-one patients (13.3%) had an associated Sjögren syndrome and 6 (3.8%) patients had a diagnosis of fibromyalgia. The SLICC damage index was 0 for 126 (81.3%) patients, 1 for 20 patients (12.9%), 2 for 8 (5.2%) patients, and 5 for one patient (0.7%). SLICC damage index was missing in 3 patients. At entry in the study, the mean SELENA-SLEDAI score was 2.7±3.7.

Patients were treated with HCQ for 9.6±6.9 years at a daily dose of 297.1±97.9 mg and 304.9±93.6 mg at visit 1 and 2, respectively. Concomitant treatments included corticosteroids (N = 86; 54.4%), immunosuppressive drugs (N = 42; 26.6%) and biologics

(N = 3; 1.9%). Patients rated the benefit brought by the therapy at 70.7±22.8 and estimated their adherence to HCQ to be 88.9±17.5 on 100 mm VAS. 123 (77.9%) patients had undergone at least one blood HCQ determination in the past.

3.2 Non-adherence rates

Blood HCQ concentration (m±SD) was 1046±662 µg/L and 855±577 µg/L at visit 1 and 2, respectively (Figure 1). Two patients had undetectable blood HCQ concentration at visit 1. There were no patients with undetectable HCQ concentration at visit 2. Based on blood HCQ concentration < 200 µg/L, non-adherence rate varied over time and poor adherence was more frequent at visit 2. Five (3.2%) patients were poorly adherent at visit 1 and 14 (9.6%) at visit 2. Only one patient was poorly adherent at both visits and 18 (12.4%) patients were poorly adherent on at least one visit (Table 1). The blood HCQ concentration was not significantly different between patients who have had at least one dosage in the past (1060±654 µg/L) and those who had none (994±697 µg/L) (p=0.61). The blood HCQ concentration was higher in patients taking more than one HCQ pill daily (1119±617 µg/L *versus* 917±718 µg/L) (p=0.08) and 3 out the 5 non-adherent patients identified at visit 1 were taking one pill per day.

At visit 1, the mean MMAS-8 score was 6.6±1.7 and 50 (32.5%) patients had a MMAS-8 ≤ 6. MMAS-8 score was 3.4±1.0 for intentional non-adherence and 3.3±0.9 for unintentional non-adherence. Among the 50 patients non-adherent according to the MMAS, poor adherence was intentional in 16 (10.8%) patients, unintentional in 27 (18.2%) and undetermined in 7 patients. Among the 45 patients with MAAS-8 documented for HCQ and other treatments and who were not adherent to HCQ, 34 were also poorly adherent to other medications. The mean scores for intentional and

unintentional non-adherence were similar for HCQ and for other medications. Forty-seven (33.6%) patients were not adherent at visit 2 and 66 (45.5%) patients were considered as non-adherent on at least one visit. The MASRI score was 92.7±11.8 at visit 1 and 12 patients (7.7%) had a MASRI < 80. Poor adherence rate was 10.7% at visit 2 and 20 (13.8%) patients had a MASRI <80 on at least one visit. HCP-VAS was used only at visit 1 and the mean score was 87.8±12.0. Nineteen (12.4%) patients were rated less than 80. Depending on the assessment tools and on their combinations, non-adherence rates varied from 3.2% to 37.8% at visit 1, from 9.6% to 33.4% at visit 2 and from 12.4% to 49.0% when considering both visits (table 1).

3.3 Characteristics of patients according to adherence defined by various methods

Non-adherent patients at visit 1 and/or visit 2 according to blood HCQ concentration were compared to adherent patients (Table 2). The analysis involved the 145 patients documented for blood HCQ concentration at both visits. Non-adherent patients (N=18) had no specific characteristics when compared to adherent patients. They presented more frequently an associated antiphospholipid syndrome (33.3% *versus* 11.8%; p=0.03) and their MASRI and MMAS-8 scores were significantly lower (p=0.01 and p=0.02, respectively). In contrast, physicians did not differentiate poor and good compliers (p=0.37). Adherence had no impact on the patients' quality of life (figure 2).

Non-adherent patients defined according to MMAS-8 differed from adherent patients on some points. They were younger (p=0.0002), had a lower number of pills to take daily (p=0.03), a lower MASRI score (p<0.0001), as well as a lower score on HCP-VAS (p=0.004). Using MASRI < 80 for the definition of poor adherence, non-adherent patients were younger (p=0.04), had a lower self-assessed adherence (p=0.0006), a lower MMAS-

8 score (p<0.0001) and a lower HCP-VAS (p=0.01). Poor compliers defined by HCP-VAS < 80 had also, albeit not significant, lower MASRI and MMAS-8 scores.

3.4 Correlations and agreement between tools

Correlations between the different adherence assessment tools were weak to moderate (Table 3). MMAS-8 and MASRI were well-correlated (r=0.81 at visit 1, r=0.56 at visit 2). Correlations between low blood HCQ concentration and other assessment tools at visit 1 did not exceed 0.20. There was no agreement between tools on the definition of non-adherent patients. Taking blood HCQ concentration< 200 µg/L as gold standard, sensitivity and specificity were 80.0% and 94.7% for MASRI < 80 at visit 1, and 38.5% and 92.1% at visit 2. Sensitivity and specificity for MMAS-8 ≤ 6 were 100.0% and 69.8% at visit 1, 42.9% and 67.5% at visit 2. MMAS-8 < 6 had a high sensitivity to predict MASRI < 80 (100.0% at visit 1 and 92.9% at visit 2) and a moderate specificity (73.0% at visit 1 and 74.8% at visit 2). Conversely, MASRI < 80 had a low sensitivity to predict MMAS-8 < 6 (24.0% at visit 1 and 29.5% at visit 2), but a high specificity (100.0% and 98.9% at visit 1 and visit 2). Blood HCQ < 200 µg/L displayed high sensitivity, but poor sensitivity, to predict MASRI < 80 or MMAS-8 < 6 independently of the visit (Table 4).

3.5 Analysis of an alternative cutoff for blood HCQ concentration

A HCQ blood cutoff of 500 µg/L has also been proposed [24]. Using this threshold increased the proportion of non-adherent patients at visit 1 (N=28; 19.3%), but did not improve the agreement between assessment methods: sensitivity was 14.3% for MASRI < 80 and 39.3% for MMAS-8 < 6; specificity was 93.7% and 69.0%, respectively.

4. Discussion

Inaccurate assessment of adherence to HCQ of SLE patients may lead to the inappropriate prescription of more expensive or less tolerated drugs. There is a need for reliable assessment tools that can be used in practice to assess adherence. Subjective and objective measures have been proposed but are poorly correlated with each other.

Using blood HCQ determination and a cutoff of 200 μg/L, we found that the non-adherence rate was around 10%. In a study involving SLE flaring patients, Costedoat-Chalumeau [12] reported that HCQ levels were < 200 μg/L in 14.5% of patients, and undetectable in 7.2%. In our study including a majority of non-flaring patients, the proportion of poor adherence was similar than those (7%) previously reported in a non-flaring SLE population [10]. In contrast, and despite the use of a less stringent HCQ cutoff at 100 μg/L, some authors [25,26] reported a poor adherence rate of 29%. In a population of 70 patients with childhood-onset SLE, Ting *et al* found that only 29% were adherent to HCQ treatment when adherence was based on undetectable HCQ levels (< 0.1 μg/L) [25]. The educational program set up in our department for more than 10 years, individual and collective information delivered to the patients, free access to internet website of French sector on Auto-immune and Auto-inflammatory diseases (https://www.fai2r.org) may explain our apparent good results. Nevertheless, this deserves further studies.

On the 18 patients who were diagnosed as being non-adherent based on blood HCQ concentration, only one was poorly adherent at both visits. In a group-based trajectory model, among 10,406 HCQ initiators with SLE in the US Medicaid database, 17% were persistent compliers, 36% persistent non-compliers, and 47% formed two dynamic patterns of partial adherence [27]. In our study, the rate of non-adherence to HCQ varied between visit 1 and visit 2, 12 months apart, and the rate of non-adherent patients was

higher at visit 2 than at visit 1. We cannot easily explain this counter-intuitive finding since visits 1 and 2 were routine visits and neither the HCQ daily dose nor the SELENA-SLEDAI score varied between visits. Moreover, patients were aware that a new determination of blood HCQ concentration would be performed at visit 2 and it could be expected that a history of recent HCQ determination would increase adherence. We did not find a better adherence in patients who have had a previous measure of HCQ blood concentration as has been reported by Durcan et al [24]. However a large part of our patients has had such a measure before entering in the study and comparisons may have suffered from a lack of power.

Other tools aiming to objectively measure the patient adherence have been proposed and have reported very high rates of poor adherence. The Medication Event Monitoring System (MEMS) records all openings of the jar containing the HCQ pills. Seventy-six percent of patients were shown to have taken less than 80% of the prescribed pills over a 2-year follow-up [28]. A similar rate was reported when analyzing pharmacy refill information of the US Medicaid data [9]. Also based on pharmacy refill information, 51% of patients had an adherence to HCQ < 80% in a random sample of 63 SLE patients attending rheumatology clinics associated with University Medical Centers [29].

The poor agreement between methods of assessment has already been highlighted by others, raising interesting questions. This could be due to differences in the recall periods. The recall period is 30 days for MASRI. One MMAS-8 item refers to the day before and another one to the previous two weeks; there is no recall period for the remaining 6 items. Blood HCQ concentration over 200 µg/L is reached after only few days of treatment [30]. Therefore the 200 µg/L threshold may be reached even in case of global poor adherence

provided the patient had thoroughly taken the treatment for a few days before the visit, the so-called “white coat” compliance effect. In addition, the different tools may capture different elements of non-adherence which might explain the lack of overlap between tools. Self-questionnaires refer to perception whereas blood HCQ concentration refers to pharmacokinetics. Moreover, low blood HCQ concentration and questionnaires assess to different patterns of non-compliance. Blood HCQ concentration < 200 μg/L reflects severe poor adherence but blood HCQ concentration above this threshold does not define good adherence. Episodic omissions will not translate in low blood HCQ concentration. Conversely MASRI and MMAS-8 may detect such behaviors. Finally, it cannot be excluded that some patients had low blood HCQ concentration for pharmacokinetic reasons despite a correct adherence to HCQ regimen (due to digestive malabsorption for example). This has been discussed for a cut-off of 500 μg/L, but seems unlikely or at least very infrequent for a lower threshold like 200 μg/L.

We found no specific characteristics in poorly adherent patients compared to adherent patients. This could be due to the small number of poor adherent patients and the subsequent lack of power of statistical analyses. In contrast, Costedoat-Chalumeau [12] found that younger age at diagnosis, non-use of steroids, higher body mass index, and unemployment were independent predictors of non-adherence. These differences may be explained by the inclusion criteria. Costedoat- Chalumeau included only SLE flaring patients whereas in our study there were mostly non-flaring patients. In a cohort of SLE patients in USA, patients with sub-therapeutic blood HCQ concentration (< 500 μg/L) were preferably females, less than 30 or over 60 years old, and had a lower blood concentration in vitamin D [24]. Using pharmacy refill information, Koneru *et al* [29] showed that significant risk factors of insufficient adherence included being single,

having low educational level, presence of other comorbidities, limited comprehension of physician explanations and instructions, and having to take the medication more than once daily. Using MMAS-4, the Lupus Erythematosus Long-Term Study (LuLa-study), a nationwide longitudinal study among German Caucasian patients with SLE, reported that the use of azathioprine, prednisone < 7.5 mg, being older and having an external health locus of control were predictors for high adherence. On the contrary, the general perception of medication being harmful, or addictive was detrimental [31]. Using Medication possession ratio, Lee *et al* found that low disease activity was a predictor of poor adherence in Korean SLE patients initiating HCQ [32]. We also found no clinical consequences of severe poor adherence to HCQ with similar SLEDAI score, SLIC damage index and quality of life, which contrasts with previous results. This could be explained by the fact that our patients were recruited during a routine visit, and/or by the low proportion of non-adherent patients and patients with active SLE whatever the adherence assessment method.

Should the blood HCQ threshold be questioned? A higher threshold such as 500 μg/L has been advocated. Durcan *et al* reported that in a cohort of US SLE patients, 44% had sub-therapeutic level (< 500 μg/L) [24]. In our study, using a 500 μg/L threshold obviously increased the rate of non-adherent patients, but did not improve the agreement between assessment methods.

Should an assessment tool be emphasized to measure HCQ adherence? Recognizing poor adherence is of paramount importance for its deleterious consequences. All assessment tools have their own limitations. The physician opinion is probably one of the worst tools to differentiate poor and good adherent patients highlighting the need for other tools. Questionnaires offer an insight in patients' perceptions about medication intake

behavior, but cannot reflect the real behavior [33]. MEMS would certainly be a good tool, since jar openings reflect the daily adherence over the whole period between visits and offer the advantage of assessing adherence over a continuum. Episodic omissions, as well as prolonged treatment discontinuations, may be detected and distinguished calling for specific interventions. Jar openings may not be synonymous of medication intake, but this method has proven to be superior to patient self-reports and pill counting for measuring adherence [34]. Considering MEMS as a gold standard, Pasma *et al* found no or weak correlation with adherence questionnaire or methotrexate polyglutamate concentration in a population of patients with rheumatoid arthritis [33]. However, this cannot be routine practice for economic and practical considerations. Self-questionnaires are easy to use, but some of them are licensed; blood HCQ dosage is not expensive but is not performed in all centers.

Even if the combination of objective and subjective definitions might result in an overestimation of the non-adherence rate, over-diagnosing poor adherence would only lead to uselessly remind the importance of good adherence to patients already convinced. Since both MEMS-based and pharmacy refill-based studies have reported very high rates of non-adherence, most patients would take advantage of regular reminders. This position has also been advocated by Costedoat-Chalumeau *et al* [12] in SLE flaring patients before questioning treatment efficacy and escalating the therapy.

Our study has strengths and limitations. The major strength was that patients entered the study during a routine visit. Indeed, previously informed patients could have adhered to the prescribed regimen only for a few days before the visit and been wrongly considered to be adherent, as a few days on HCQ are usually enough to increase the HCQ

concentration over 200 μg/L. Moreover, no patients refused to participate when informed on the aims of the study. Therefore, we are confident that our population was representative of the SLE patients routinely taken in charge by our regional network. The study also had some limitations. Blood HCQ concentration was measured on the day of the visit and measurement was untimed relative to the last dose of HCQ. However, regarding the long half-life of HCQ and the relative stability of blood HCQ concentration at steady state, a very limited impact can be expected on our results [35]. Since there is no gold standard for the measurement of adherence to HCQ, we were unable to question the cutoff of 200 μg/L for blood HCQ concentration. A further study combining MEMS as the gold standard, self-questionnaires, the calculation of the dispensed boxes by the pharmacist and blood HCQ would be of great interest to determine optimal thresholds.

5. Conclusion

Depending on the assessment method, the adherence rate to HCQ treatment varied between 3.2% and 32.5% with poor correlation and agreement between blood HCQ concentration, self-questionnaires on adherence and health care provider opinion. This could be explained by the different dimensions explored by each of these tools: from blood drug concentration to self-report of behaviour. Blood HCQ concentration < 200 μg/L reveals severe non-adherence. Combining blood HCQ concentration with MASRI and MMAS-8 may help to better identify non-adherence in SLE, thus guiding educational therapy.

Disclosure of interest

EH, MMF, NLG, DL, HM, MHB, RA, TQ, AB, PB, ML, AL, ALB, VS, PYH, SD, GW and SMD have no conflict of interest. PC works as an independent statistician and has no conflict of interest to declare.

Grant

This work was supported by the “Conseil Régional Hauts de France”, Direction de la Recherche, Enseignement Supérieur, Santé et Technologies de l’Information et de la Communication, 151 Boulevard Hoover, 59555 LILLE cedex.

Acknowledgements

The authors acknowledge the other members of the ESSTIM investigators group: Thomas Quemeneur, Valenciennes; Pierre Savinel, Lens; Eric Auxenfants, Roubaix, Aurélia Lanteri, Lille.

Sarahe Dehimat is acknowledged for her technical research assistance during all the protocol, Quentin Ducrocq for his MMAS-8 training and Géraldine Wojtasik for her implication in patient education.

Licensing

A Morisky Widget MMAS-8 License Agreement was made between the CHU de Lille – Hôpital HURIEZ (HURIEZ) 1 PLACE DE VERDUN Service de médecine interne 59037 Lille cedex ("Licensee") and MMAS Research LLC, 14725 NE 20th St. Bellevue Washington 98007.

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