RHEUMATOLOGY

Rheumatology 2018;57:1507–1509
doi:10.1093/rheumatology/kex337
Advance Access publication 11 September 2017

Editorial

Treatment adherence in systemic lupus erythematosus and rheumatoid arthritis: time to focus on this important issue

Treatment adherence in SLE and RA

RA and SLE are both chronic diseases, and non-adherence to treatment impairs their management. Generally, non-adherence rates in chronic diseases are surprisingly high. A Canadian study assessed primary non-adherence in various conditions and found that as many as 31% of the 37 506 first prescriptions were not filled in at all in the 9 months that followed [1]. Figures for the long-term take-up persistence are even worse; the non-adherence at 1 year ranged from 46 to 82% among 167 907 patients treated with drugs including statins and oral antidiabetics [2]. These numbers may be even higher in some countries without health insurance, too few specialists or other access issues. This non-adherence is referred to as unintentional and is strongly associated with social determinants of health (low literacy, inadequate or no health insurance, language discordance between provider and patient). In this editorial, we focus primarily on intentional, including forgetful, non-adherence by RA and SLE patients receiving care.

Consequences of non-adherence are well demonstrated [3]; there is a higher risk of emergency department visits and hospitalization in the subsequent year [4, 5], which confirms the idea that drugs do not work in patients who do not take them. To avoid persistent disease activity, flares and unnecessary treatment escalation, we must therefore recognize non-adherence as accurately as possible and do our best to overcome these issues with our patients. As we will see, both tasks are very challenging.

Adherence, usually reported as the percentage of the prescribed doses of the medication actually taken by the patient, and poor adherence, usually defined by rates $<80\%$, are both difficult to evaluate. None of the available assessment methods is perfect [3]. Self-administered questionnaires are limited by the fact that patients may underreport non-adherence to please their physicians or avoid embarrassment. Clinicians' assessments are highly subjective and inaccurate, partly because non-adherence is a task-specific behaviour rather than a personality trait. Attendance at scheduled visits does not correlate well with adherence to treatment. Pill counts, refilling data and electronic monitoring devices directly measure adherence by comparing the number of tablets brought back by the patients, collected in the pharmacy or taken from the device, against the number of tablets prescribed by the physician, which then makes it possible to calculate the mean proportion of days covered. These methods consistently report higher non-adherence rates than subjective methods but are not routinely applied, except for refill rates in some specific areas (e.g. Canada). Other methods use clinical or biological markers of non-adherence, such as the absence of Cushing-like appearance in patients treated with CSs. Furthermore, objective direct methods, such as unscheduled blood or urine measurement of drug concentrations, are interesting but often limited by their unavailability, cost and especially their inability, owing to short drug half-life, to identify poor adherence in patients whose adherence improves shortly before doctor appointments, which we can term as the white-coat compliance effect. Given that its half-life is at least 7 days, these limitations do not fully apply to blood HCQ assays; undetectable blood HCQ levels mean that the patients have not taken HCQ for a long time, and the white-coat compliance effect in patients with poor long-term non-adherence cannot usually increase HCQ blood levels to expected values [3]. Some centres therefore now use this assay routinely to diagnose non-adherence in SLE (and some RA) patients [6]. Finally, two separate and independent patterns of non-adherence have been described [3]: tablets missed relatively infrequently, and tablet intake completely stopped or frequently interrupted and erratic. In a recent international study on this aspect, it was shown that self-administered questionnaires best capture the first pattern, whereas very low blood drug concentrations identify the latter [6].

Non-adherence rates range from 3 to 76% in SLE patients [3] and from 14 to 80% in RA patients [7], varying with the assessment method and the drug. Electronic monitoring of oral therapies in two 2-year prospective cohort studies found that 74% of 78 SLE patients and 79% of 107 RA patients [8] had average adherence rates $<80\%$. In a recent study using US pharmacy refill information, 79% of 9600 new SLE users of HCQ and 83% of 3829 new SLE users of oral immunosuppressive drugs had adherence rates $<80\%$ [5]. Interestingly, in RA, adherence to biologic agents may be higher [7]. In a multicentre study of pharmacy refill information, only 14% of 363 RA patients were non-adherent to s.c. biologicals, and patients using the most convenient monthly administration period had better adherence rates than those on weekly administration, whereby non-adherence was 6.4 and 17.4%, respectively; $P = 0.034$) [9]. In another study

© The Author 2017. Published by Oxford University Press on behalf of the British Society for Rheumatology. All rights reserved. For Permissions, please email: journals.permissions@oup.com

EDITORIAL

Downloaded from https://academic.oup.com/rheumatology/article-abstract/57/9/1507/4111200 by universite catholique de louvain user on 28 November 2019

using pharmacy refill information 1 year after treatment initiation, 73% of the 3724 patients treated with etanercept plus MTX were non-adherent to at least one agent compared with 82% of the 818 patients using the triple therapy (MTX, HCQ and SSZ; $P < 0.0001$) [10].

Once the difficulty in diagnosing non-adherence has been overcome, the next major challenge is trying to improve it, especially over the long term. As non-adherence is multifactorial and no single intervention has been effective in improving it, interventions should use combined strategies. When non-adherence is unintentional and attributable, as it often is, to poor health access, providers or their staff can potentially aid patients with, for example, contacting patient assistance programmes, making social-work referrals and using interpreter services. When non-adherence is intentional, evidence suggests that simply providing patients with information, education and advice, or using dominant or persuasive communication, does not result in permanent improvement in adherence [7]. The use of musculoskeletal ultrasound to image the inflamed joint encouraged RA patients to understand the necessity of medication, but this did not improve adherence [11]. Long-term results of interventions using self-management and cognitive behavioural programmes have often been disappointing, including those in RA. Novel interventions involving smart e-technologies and the use of social support might be more effective, especially among younger patients, but require evaluation. Nevertheless, simple things should not be forgotten; reducing dosing (HCQ can be given once a day, biologics once a month) or choosing i.v. infusions may be useful. Good patient-tailored communication can be beneficial, especially for patients from ethnic minorities and lower education levels [7], as well as more consideration of the patient's personal beliefs about medication, as demonstrated in RA [12]. The observed limited patient contact time in current clinical daily practice may be partly overcome with the participation of other health providers, such as nurses, psychologists and physical therapists.

In our experience, one of the most difficult tasks is to recognize severe non-adherence. Its diagnosis by testing blood HCQ levels can lead to non-judgmental and positive discussions with the patients and help us to respond to their specific concerns. This can lead to better explanations of the benefit–risk ratio of some drugs, such as HCQ, or even to *post hoc* recognition that their own treatment modifications, such as quicker CS dose reduction when disease remains particularly well controlled, are smart.

In conclusion, non-adherence is, unfortunately, a regular occurrence and has important clinical implications. Adherence behaviour should therefore be systematically and routinely considered within our clinical practice. This assessment should be repeated from visit to visit because patient attitudes towards treatment and behaviour may vary over time.

Funding: No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this manuscript.

Disclosure statement: The authors have declared no conflicts of interest.

Nathalie Costedoat-Chalumeau[1,2], Farah Tamirou[3] and Jean-Charles Piette[4]

[1]*Université René Descartes Paris, V; Centre de Référence des Maladies Auto-immunes Systémiques Rares d'Ile de France, Service de médecine interne Pôle médecine, Hôpital Cochin, AP-HP, 27 rue du Faubourg Saint Jacques, 75679 Paris cedex 14,* [2]*INSERM U 1153, Center for Epidemiology and Statistics Sorbonne Paris Cité (CRESS), Paris,* [3]*Service de Rhumatologie, Cliniques Universitaires Saint-Luc, 10 avenue Hippocrate, 1200 Bruxelles, Belgique; Pôle de pathologies rhumatismales inflammatoires et systémiques, Institut de Recherche Expérimentale et clinique, Université catholique de Louvain and* [4]*AP-HP, Service de Médecine Interne, Centre de Référence des Maladies Auto-immunes Systémiques Rares d'Ile de France, Centre Hospitalier Universitaire Pitié-Salpêtrière, Paris, France*
Revised version accepted 08 August 2017
Correspondence to: Nathalie Costedoat-Chalumeau, Centre de Référence des Maladies Auto-immunes Systémiques Rares d'Ile de France, Service de médecine interne, Hôpital Cochin, AP-HP, 27 rue du Faubourg Saint Jacques, 75679 Paris cedex 14, France.
E-mail: nathalie.costedoat@gmail.com

References

1 Tamblyn R, Eguale T, Huang A, Winslade N, Doran P. The incidence and determinants of primary nonadherence with prescribed medication in primary care. A cohort study. Ann Intern Med 2014;160:441–50.

2 Yeaw J, Benner JS, Walt JG, Sian S, Smith DB. Comparing adherence and persistence across 6 chronic medication classes. J Manag Care Pharm 2009;15:728–40.

3 Costedoat-Chalumeau N, Pouchot J, Guettrot-Imbert G *et al*. Adherence to treatment in systemic lupus erythematosus patients. Best Pract Res Clin Rheumatol 2013;27:329–40.

4 Wabe N, Lee A, Wechalekar M *et al*. Adherence to combination DMARD therapy and treatment outcomes in rheumatoid arthritis: a longitudinal study of new and existing DMARD users. Rheumatol Int 2017;37:897–904.

5 Feldman CH, Yazdany J, Guan H, Solomon DH, Costenbader KH. Medication nonadherence is associated with increased subsequent acute care utilization among Medicaid beneficiaries with systemic lupus erythematosus. Arthritis Care Res 2015;67:1712–21.

6 Costedoat-Chalumeau N, Houssiau F, Izmirly P *et al*. A prospective international study on adherence to treatment in 305 patients with flaring SLE: assessment by drug levels and by self-questionnaires. Clin Pharmacol Ther 2018;103:1074–82.

7 Marengo MF, Suarez-Almazor ME. Improving treatment adherence in patients with rheumatoid arthritis: what are the options? Int J Clin Rheumtol 2015;10:345–56.

Downloaded from https://academic.oup.com/rheumatology/article-abstract/57/9/1507/4111200 by universite catholique de louvain user on 28 November 2019

8 Waimann CA, Marengo MF, de Achaval S *et al*. Electronic monitoring of oral therapies in ethnically diverse and economically disadvantaged patients with rheumatoid arthritis: consequences of low adherence. Arthritis Rheum 2013;65:1421–9.

9 Calvo-Alen J, Monteagudo I, Salvador G *et al*. Non-adherence to subcutaneous biological medication in patients with rheumatoid arthritis: a multicentre, non-interventional study. Clin Exp Rhuematol 2017;35:423–30.

10 Bonafede M, Johnson BH, Tang DH *et al*. Etanercept-methotrexate combination therapy initiators have greater adherence and persistence than triple therapy initiators with rheumatoid arthritis. Arthritis Care Res 2015;67:1656–63.

11 Joplin SK, van der Zwan R, Bagga H, Joshua F, Wong PK. Pilot study assessing the novel use of musculoskeletal ultrasound in patients with rheumatoid arthritis to improve patient attitudes and adherence to medication. Int J Rheum Dis 2016;19:658–64.

12 van den Bemt BJ, Zwikker HE, van den Ende CH. Medication adherence in patients with rheumatoid arthritis: a critical appraisal of the existing literature. Expert Rev Clin Immunol 2012;8:337–51.

Downloaded from https://academic.oup.com/rheumatology/article-abstract/57/9/1507/4111200 by universite catholique de louvain user on 28 November 2019