

# TREATMENT ADHERENCE AND CLINICAL OUTCOME IN SYSTEMIC LUPUS ERYTHEMATOSUS

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## Abstract

*The adherence to the treatment, that is the tenacity and the consistency with which the patient respects his personal doctor's indications, are decisive factors for the evolution of chronic diseases, especially of those with low prognosis. Authors review the paper works dedicated to this subject and consider the elements that are of great importance for the adherence of patients with systemic lupus erythematosus at therapeutic indications.*

## Rezumat

### **Aderența la tratament și evoluția lupusului eritematos systemic**

*Aderența la tratament, definită ca tenacitatea și consecvența cu care bolnavul respectă indicații medicului, sunt factori hotărâtori pentru evoluția bolilor cronice, îndeosebi a celor cu prognostic rezervat. Autorii trec în revistă lucrările dedicate acestui subiect și discută elementele de care depinde aderența bolnavilor cu lupus eritematos systemic la indicațiile terapeutice.*

## INTRODUCTION

Times are changing. Gone are the days when patients would meekly accept prescriptions and instructions from doctors whom they perceived as omniscient. With the advent of the Internet, and with the increasing media coverage of developments in science and medicine, patients can now gain access to a wide range of information about diseases and treatment options, though the quality of this information is very variable (1, 2).

Increasingly, consultations require the physician to answer questions about information gleaned from such sources, to convince patients that not all such information may be accurate or relevant to their illness and to explain treatment decisions and recommendations more fully. An example from our clinic was a patient with chronic back pain who when an MRI scan of the lumbar spine was proposed, countered with the suggestion that "might not a spiral CT be better?" A more worrying case was that of a patient who attended carrying samples of expensive herbs, supplements and magnetic gadgets, which she had purchased to substitute for her regular medications.

Doctors and patients are becoming aware that the successful management of chronic diseases, like lupus, involves a partnership based on a mutual

understanding of specific treatment goals, which is the best way to minimize morbidity and improve clinical outcomes. Ward et al. (3) used audiotapes of routine physician-patient consultations involving 78 patients with systemic lupus erythematosus (SLE) to assess the degree of active participation by patients in these consultations. They showed that patients who participated more actively accrued less organ damage over a median follow-up period of 4.7 years. Although not measured specifically in the study of Ward et al. (3), the concept of adherence may play an important role in linking the participation of patients in clinical decisions about their care with the long-term outcome in these patients. Indeed, the most basic question that determines efficacy of treatment for patients with SLE is: will the patient actually take the medication prescribed?

Treharne and colleagues (4) recently discussed the concepts of compliance, adherence and concordance with reference to a number of different rheumatic diseases. Their editorial provided a comprehensive review of literature on the measurement of adherence and concordance, and focused particularly on rheumatoid arthritis (RA). In this editorial, we concentrate on the issue of adherence in patients with SLE and focus specifically on why this is likely to play a critical role in determining clinical outcome in these patients.

## WHAT IS ADHERENCE TO MEDICATIONS?

Adherence is defined as the extent to which a person's behaviour – taking medication, following a diet and/or executing lifestyle changes – corresponds with agreed recommendations from the health care provider. This term has now largely replaced the use of the term “compliance” (the extent to which a patient follows medical instructions). This growing acceptance of the term “adherence” reflects changing perspectives within society and the medical community which indicated a need for patients to be more involved in making decisions about prescribed treatments (5, 6).

## THE CLINICAL IMPORTANCE OF POOR ADHERENCE IN PATIENTS WITH SLE

Several studies suggest that there are problems with treatment adherence, which may directly influence clinical outcomes in patients with SLE. In one such study, Petri and colleagues (7) determined patient compliance with treatment and percentage of protocol visits kept in a cohort of 198 patients, 115 of whom were black and 73 white. There were 179 females and 19 males. The authors concluded that non-compliance was a significant factor in determining renal morbidity (important renal disease being defined as creatinine level 1.5 mg/dl or greater, renal failure, or the nephrotic syndrome). Black patients were twice as likely as white patients to have important renal disease and were also more commonly classified as non-compliant (56%) than white patients (34%) using physician global assessment. However, in multiple regression analysis, important renal disease was only significantly associated with physician global assessment of compliance and hypertension, and not with black race. This suggests that, in this cohort, the apparent relationship between ethnicity and renal disease may be mediated through differences in adherence.

In support of this, Adler and colleagues (8) in the UK reported outcomes in 127 patients with lupus nephritis, and noted that a disproportionate number of black patients progressed to end stage renal failure (ESRF), requiring dialysis and/or renal transplant, compared with whites and Asians. The possibility of a genetic influence on the poor renal outcomes in blacks was considered by the authors, but they noted that adherence to treatment (as assessed independently by two physicians) was poor in 11 of the 21 ESRF patients, nine of whom were black (8).

In these two studies, physician assessment was used to quantify adherence, which appeared to differ

in different ethnic groups. Physician assessment of adherence in chronic diseases may, however, show poor correlation with more objective assessments of adherence (9). Mosley-Williams and colleagues (10) compared treatment adherence, as assessed by patients themselves, in 68 African American and 54 white women with lupus using questionnaires and interviews. In contrast to Petri et al. (7) and Adler et al. (8), these authors found that both ethnic groups were comparable on self-reported medication nonadherence. Population characteristics differed between these studies (7, 8, 10). However, these contrasting findings on treatment adherence in different ethnic groups highlight the need for more objective assessments of patient adherence. A study involving both quantitative and qualitative assessment of treatment adherence in 400 lupus patients of three ethnic groups (Blacks, Asians and Whites), incorporating comparisons of patient self-reports with physician assessment is currently underway at the University College London Hospital, UK.

Bruce and colleagues (11) in Toronto determined the prevalence and underlying reasons for the development of chronic renal insufficiency (CRI) in 462 patients with SLE followed up between 1995 and 1998. Seventeen patients developed CRI with patient-related factors being the major reason in five of these patients (three non-white and two who were white immigrants). These five patients had been reluctant to take high-dose corticosteroids because of potential adverse effects. Two patients refused to continue treatment with steroids and immunosuppressives and chose “alternative medications” as sole therapy. At the time of study publication in 2000, the authors reported that one patient had died, three required long-term renal replacement, and one patient had a serum creatinine of 250 mmol/l.

Rojas-Serrano and colleagues (12) noted that poor compliance was one of the important variables associated with hospitalization in lupus patients in an emergency unit in Mexico.

## WHY SHOULD WE AIM TO IMPROVE ADHERENCE TO MEDICATIONS IN PATIENTS WITH SLE?

The studies described above suggest that poor adherence may be a marker for poor clinical outcome in patients with SLE, but this does not prove that failure to take medications is the direct cause of poor outcome in those patients. In achieving concordance (4) between the health professional and the patient, it is clearly important that both should believe that taking medications will have a discernible effect on clinical

outcome. This belief is supported by direct evidence for efficacy of medications in the treatment of patients with SLE. Although there are no specific data showing that poor adherence to medications is associated with increased mortality in SLE, it is very clear that mortality in this disease has fallen as a result of drug treatment. In the 1950s, 50% of patients with SLE died within four years whereas now around 80% are alive at 15 years (13). This improvement in mortality is at least partly due to the development of renal dialysis and kidney transplantation (and these procedures are themselves very demanding of adherence for optimal outcome).

Other reasons include earlier diagnosis and treatment of the disease, more judicious use of corticosteroids and better supportive care for organ failure and infective complications (14). Use of high-dose immunosuppression with steroids and cyclophosphamide has contributed to the improvement in outcome in lupus nephritis and cerebral disease, as shown by several published studies (15–17), though side effects of cyclophosphamide are troublesome (18).

In less severe forms of lupus, the balance between efficacy and adverse effects is finer. Short-term use of moderate-dose corticosteroids is effective in preventing flares in patients with serologically active, but clinically stable SLE (19). Hydroxychloroquine is effective in reducing treatment flares if taken regularly, and lower use of antimalarials is one variable that has been shown to be associated with mortality in the LUMINA study (20). Azathioprine (21) and hydroxychloroquine (22) have been used successfully to treat various lupus manifestations in pregnant women.

Overall, the evidence is that these drugs are beneficial in patients with SLE so that one would predict that non-adherence to treatment would be detrimental in the majority of these patients.

### **WHY MIGHT PATIENTS WITH SLE BE POORLY ADHERENT TO TREATMENT?**

Garcia Popa-Lisseanu and colleagues (23) in TX, USA, conducted focus groups to explore the determinants of adherence to medical recommendations, including drug therapy and appointment-keeping, among 40 ethnically diverse and economically disadvantaged patients with RA (n = 18) and SLE (n = 22). The patients reported financial problems, fear of side effects, difficulty navigating the public health system and perceived treatment inefficacy as important barriers to adherence.

Kennedy and Erb (24) analysed the contribution of financial constraints to poor compliance amongst people with chronic illnesses and disabilities in the USA. Their study population comprised 25 805 adults who had reported impairments, chronic conditions, functional limitation or receipt of disability benefits in the National Health Interview Survey and who were sent a further survey (the Disability Follow-Back Survey) 6–18 months later. Although the respondents in this survey were older, poorer and in worse health than the general population, the authors weighted all data such that results would be generalizable to the overall US population.

The results of the survey allowed the authors to estimate that about 70% of the disabled adult population were prescribed medications and about 13% of those people were non-compliant. About one-third of non-compliant respondents cited cost-related factors as reasons for non-compliance. Non-compliance led to adverse health consequences such as exacerbation of symptoms, pain and discomfort in more than half of those respondents who had cited cost as a problem in maintaining compliance.

In the USA, the Medicare scheme helps defray the healthcare costs of the poorest members of society, but there remain many millions of people who are neither poor enough to qualify for Medicare, or work in jobs not covered by health insurance. Furthermore, caps on Medicare drug benefits have contributed to low treatment adherence and unfavourable clinical outcomes (25).

In the UK, financial causes of poor adherence may initially be less evident. Health care is “free at the point of entry” to the National Health Service. However, patients do pay for their medications, and even with pre-payment certificates, the annual cost to each patient may exceed  $\leq 100.00$ . As in the USA, ethnic minorities are at greater socio-economic disadvantage than their white counterparts in the UK and this may have an impact on adherence and hence clinical outcomes. There are also cultural differences between ethnic groups, which may influence patients’ perceptions of the need to take their medicines, as has been demonstrated in studies of ethnicity and the use of anti-hypertensives and oral hypoglycaemic agents in the UK (26, 27).

Patients understandably have concerns about the efficacy and safety of their medications in the long term and this may influence treatment adherence (10). Side effects of medications are a recognized deterrent to adherence in lupus (23). Several non-steroidal anti-

inflammatory drugs, often co-prescribed with immunosuppressants, have various side effects such as gastro-intestinal toxicity and an increased risk of myocardial events (28). Corticosteroids are widely used in lupus, but are well known to cause distortion in facial appearance, striae, easy bruising, hypertension and osteoporosis (29, 30).

The older immunosuppressive drugs, azathioprine and cyclosporin, may predispose to an increased risk of infection and a wide variety of other problems including bone marrow dysfunction, nausea, liver test abnormalities and lung disease (29). Cyclophosphamide presents additional challenges, with amenorrhoea and bone marrow dysfunction being particularly prominent among its complications (29).

Newer immunosuppressive drugs, leflunomide and mycophenolate (the latter is increasingly used in the treatment of lupus nephritis), may cause troublesome gastrointestinal side effects, and although on the whole they demonstrate more favourable safety profiles than cyclophosphamide, long-term follow up data are lacking (29). Some of the new biological agents used in lupus including infliximab (31) and rituximab (32), show good tolerability, but adverse events, particularly opportunistic infections have been reported with these drugs and the risks of longer-term complications have yet to be established. Since different drugs have different side-effect profiles, patients have been noted to display varying levels of adherence depending on the medications prescribed.

McElhone and colleagues (33) reported on treatment adherence in 50 out-patients with SLE using an anonymous self-report questionnaire. Sixty-eight percent of the patients considered themselves adherent for NSAIDs in contrast to 83% for hydroxychloroquine, 94% for oral steroids and 100% for azathioprine. Interestingly, the lower adherence rate for NSAIDs seems more likely to have been related to the patients' views about importance of medications than to experience of side effects. The percentages of patients who found NSAIDs, steroids and azathioprine very troublesome were 5, 6 and 13%, respectively, whereas the percentages who believed that these medications were very important were 48% for NSAIDs, 66% for oral steroids and 50% for azathioprine. Nevertheless, some patients do present a challenge in terms of managing side effects as well as clinical symptoms. Other potential barriers to adherence may include depression, short-term memory problems, disease symptoms, comorbid conditions and a lack of trust in physicians (10).

## HOW CAN WE IMPROVE ADHERENCE IN PATIENTS WITH SLE?

Adherence is a spectrum that ranges from high through to the various 'shades' of poor adherence. No studies have yet defined a target level for treatment adherence in patients with lupus. An adherence level of 85% (i.e. the correct medication is taken 85% of the time) has been defined in some studies as the bar that distinguishes good from poor adherence in RA (34), but even above this 85% level, there may be medication-taking patterns and behaviours that require exploration. The same applies to patients with lupus.

How can we measure adherence in clinical practice? In the absence of direct observation of pill-taking, there is no highly accurate way of assessing treatment adherence in lupus. Surveys and questionnaires such as the rheumatology compliance questionnaire (35) may give an indication of medication-taking behaviours and their relation to demographic details. Measures of adherence were discussed extensively by Treharne et al. (4) in a recent editorial. Qualitative studies can also provide a wealth of additional information regarding cultural, psychosocial and lifestyle barriers to adherence (36).

Pill counts and pharmacy records may give information regarding compliance. However, even if patients regularly fill their prescriptions or open-metered pill bottles, there is no guarantee that they have taken the medications.

Adherence in lupus is also difficult to monitor using biochemical or serological indices, as some patients may fall into the category of clinically active yet serologically quiescent lupus (37), hence their DNA binding and complement levels would be difficult to interpret in the context of treatment adherence. In some patients, favourable changes in ESR or renal function may indicate that the patient is taking some of the tablets, but not necessarily in the correct dose or at the recommended times. In clinical practice, a combination of methods may provide more reliable information about patient adherence.

Each lupus patient presents a unique set of challenges with respect to what constitutes the most appropriate medication, including the dose and duration of therapy required, as well as the overall acceptability of that treatment. Bruce and colleagues (11) recommended an educational programme based on the patient's cultural background to enhance patient understanding of the aims, risks and benefits of therapy in SLE. The age of the patient must also be taken into account.

Approximately 15% of patients will develop their disease in childhood or adolescence (38), and although the mortality from SLE has improved over the years, the disease and its treatments are associated with significant morbidity in both children and adults and the psychosocial implications of such a long-term illness are not to be underestimated. Addressing these issues in an honest and compassionate manner is an essential step in achieving adherence (39, 40).

Where poor adherence has been identified, steps must first be taken to determine why patients may not take their medications. Theoretically, each medical consultation presents an ideal opportunity to enquire about obstacles that patients might be experiencing with their medication regimen and to educate the patient about their disease and medications. Patient education may incorporate the services of nurse specialists and pharmacists and has been shown to be an important tool in overcoming poor adherence in some rheumatic diseases such as RA (41, 42).

An important factor in determining adherence, outside the control of the physician, is the nature of the healthcare system in which drugs are being prescribed. This may have important financial implications which control whether patients can actually afford to adhere to treatment.

In the UK, patients with some diseases, e.g. diabetes, are entitled to free prescribed medications, but lupus is not one of these diseases. As a consequence, even with „pre-payment card“ options, the yearly „drugs bill“ for any patient can be very high and this is an important barrier to obtaining medications in the National Health Service (43).

The mean annual cost to the UK health sector was estimated in 2001 to be ≤7913.00 per patient with SLE. Greater disease activity and greater damage are associated with higher direct costs (44). If patients cannot afford to purchase the drugs to control their disease, then it is conceivable that this will translate to poor clinical outcome and greater costs to the health sector.

Mortality and morbidity in SLE are improving, but remain far from ideal. Newer medications that utilize convenient routes of drug delivery, less frequent dosing and more tolerable side effects remain significantly in the remit of the drug companies. There is much governments can do to improve the availability and affordability of the drugs, and as clinicians, our role is to ensure that we are following the best prescribing practice and that we are attuned to the concerns of patients so that we can give them appropriate support and advice.

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## În actualitate

### Gabapentin în tratamentul fibromialgiei

Pentru evaluarea eficacității și siguranței gabapentinului la bolnavi cu fibromialgie a fost inițiat un studiu dublu-orb, randomizat, controlat, în care 75 de subiecți suferind de această afecțiune au fost comparați cu un grup egal de martori. Utilizând *Brief Pain Inventory* cu o scară de intensitate a durerii de la 1

la 10 s-a considerat ca răspuns favorabil reducerea cu = 30% a acestui simptom. Pacienții tratați cu gabapentin au înregistrat beneficii semnificativ mai însemnate decât martorii ( $p < 0,015$ ), iar la capătul perioadei de observație, care a fost de 12 săptămâni, au fost considerați ca responsivi 51% față de 31% dintre

martori. Beneficii similare au fost obținute și după evaluări pe alte sisteme utilizate în evaluarea fibromialgiei. Medicamentul a fost bine tolerat. Concluzia studiului este că 1.200-2.400 mg/24h gabapentin este eficace în tratarea durerii și simptomelor asociate cauzate de fibromialgie.

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