BSR Guideline on the Management of Adults with Systemic Lupus Erythematosus (SLE) 2018: Baseline Multi-Centre Audit in the UK

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Conflicts of interest: CAS is supported by the National Institute for Health Research and INB is an NIHR Senior Investigator and is supported by the NIHR Manchester Biomedical Research Centre. The views expressed are those of the authors and not necessarily those of the NIHR, the NHS or the Department of Health and Social Care; INB has received honoraria and/or grant funding from GSK, Eli Lilly, Astra Zeneca, ILTOO, UCB and Merck Serono; BG is Chair of NHS England's Specialised Rheumatology Clinical Reference Group; EM is Chair of BSR Standards, Audit and Guidelines Working Group; CG has received honoraria from BMS, Centre for Disease Control, EMD Serono, UCB and grant funding from UCB to Sandwell and West Birmingham Hospitals NHS Trust unrelated to any drug used during the conduct of this study;.FAP, MR, RB, RG, HG, JL, NN, NE, JP, RS, SH, KO, AR and PCL have no disclosures.

Acknowledgements: We would like to acknowledge and thank all those who contributed to this audit by collecting data at the following sites (listed in alphabetical order): Belfast Health and Social Care Trust, Blackpool Teaching Hospitals NHS Foundation Trust, Bolton NHS Foundation Trust, Chelsea and Westminster Hospital NHS Foundation Trust, City Hospitals Sunderland NHS Foundation Trust, Cwm Taf University Health Board, Derby Hospitals NHS Foundation Trust, Doncaster and Bassetlaw Hospitals NHS Foundation Trust, Dudley Group NHS Foundation Trust, East Lancashire Hospitals NHS Trust, Gateshead Health NHS Foundation Trust, Great Western Hospital NHS Foundation Trust, Heart of England NHS Foundation Trust, Kettering NHS Foundation Trust, King's College Hospital NHS Foundation Trust, Kingston Hospital NHS Foundation Trust, Lancashire and South Cumbria NHS Foundation Trust, Lewisham and Greenwich NHS Trust, London North West University Healthcare NHS Trust, Manchester University NHS Foundation Trust - Manchester Royal Infirmary, Trafford General and Wythenshawe Hospital sites, NHS Greater Glasgow & Clyde, NHS Lanarkshire, Newcastle upon Tyne Hospitals Foundation Trust, North Bristol NHS Trust, Northampton General Hospital NHS Trust, Northumbria Healthcare NHS Foundation

Trust, Nottingham NHS Treatment Centre, Pennine Acute NHS Foundation Trust, Pennine Musculoskeletal Partnership, Robert Jones and Agnes Hunt Orthopaedic Hospital NHS Foundation Trust, Royal Bournemouth and Christchurch Hospitals NHS Foundation Trust, Royal Liverpool & Broadgreen University Hospitals NHS Trust, Royal United Hospitals Bath NHS Foundation Trust, Royal Wolverhampton Hospitals NHS Trust, Salford Royal NHS Foundation Trust, Sandwell and West Birmingham Hospitals NHS Trust, Sheffield Teaching Hospitals NHS Foundation Trust, Sherwood Forest Hospitals NHS Foundation Trust, South Tees Hospitals NHS Foundation Trust, South Warwickshire NHS Foundation Trust, Staffordshire and Stoke on Trent Partnership NHS Trust, Stockport NHS Foundation Trust, Tameside Hospital NHS Foundation Trust, University Hospitals Birmingham NHS Foundation Trust, University Hospitals Coventry and Warwickshire NHS Trust, University Hospitals of Leicester NHS Trust, University Hospitals of Morecambe Bay - Furness General and Royal Lancaster sites, Worcestershire Acute Hospitals NHS Trust

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 article. The audit department of the Dudley Group NHS Foundation Trust received payment for work in relation to this audit from the BSR.

Keywords:

Systemic lupus erythematosus

Audit

Standards of care

Health services research

Abstract

Objectives
To assess the baseline care provided to patients with SLE attending UK Rheumatology units, audited against standards derived from the recently published BSR guideline for the management of adults with SLE, the NICE Technology Appraisal for Belimumab, and NHS England's Clinical Commissioning Policy for Rituximab.

Methods
SLE cases attending outpatient clinics during any 4-week period between February–June 2018 were retrospectively audited to assess care at the preceding visit. The effect of clinical environment (general vs. dedicated CTD/vasculitis clinic and specialised vs. non-specialised centre) were tested. Bonferroni's correction was applied to the significance level.

Results
51 units participated. We audited 1021 episodes of care in 1003 patients (median age 48 years, 74% diagnosed >5 years ago). Despite this disease duration, 286 (28.5%) patients had active disease. Overall 497 (49%) were receiving prednisolone, including 28.5% of patients who had inactive disease. Low documented compliance (<60% clinic visits) was identified for audit standards relating to formal disease-activity assessment, reduction of drug-related toxicity and protection against comorbidities and damage. Compared to general clinics, dedicated clinics had higher compliance with standards for appropriate urine protein quantification (85.1% vs 78.1%, p =< 0.001). Specialised centres had higher compliance with BILAG-BR recruitment (89.4% vs 44.4%, p =< 0.001) and blood pressure recording (95.3% vs 84.1%).

Conclusions
This audit highlights significant unmet need for better disease control, reduction in corticosteroid toxicity and is an opportunity to improve compliance with national guidelines. Higher performance with nephritis screening in dedicated clinics supports wider adoption of this service-delivery model.

Introduction

Clinical audit is an established way to measure standards, quality and variation in care through systematic review against explicit criteria(1). It empowers clinicians to implement change by identifying both best practice and failure to meet published standards(1). There is an increasing drive to identify and reduce unwarranted variations in care (2)(3)(4) in order to promote safety and quality standards, improve efficiency and cost-effectiveness, and improve the patient experience.

Whilst variation in some areas of medicine is relatively easy to record and interpret (e.g. length of stay following a routine planned surgical procedure), data on rare diseases are more difficult to capture due to the limited number and disperse nature of the patient group. The little data we have documenting variation in care in systemic lupus erythematosus (SLE) focuses on clinician self-reported variation(5) and until now no UK data have been available.

The importance of improving care for people living with SLE is clear; they die on average 25 years earlier than the mean for men and women in the UK(6). Multi-organ damage due to SLE occurs rapidly if the disease is not promptly and appropriately diagnosed, treated and monitored(6)(7)(8)(9). Increased disease activity is independently associated with increased mortality(10)(11).

Despite an increasing drive within the medical profession to develop and treat patients according to clinical guidelines, there is little evidence as to how these guidelines compare to pre-existing medical practice, and whether or not their implementation is achievable and/or will produce genuine changes in practice.

This audit was conducted in the four months following publication of the first British Society for Rheumatology (BSR) guideline on the management of SLE in adults(12), and used standards derived from this guideline, the NICE technology appraisal guidance [TA397] ‘Belimumab for treating active autoantibody-positive systemic lupus erythematosus’(13), and the NHS England interim commissioning policy statement on Rituximab in SLE (6).

By auditing care at the time of guideline publication, we aimed to identify the gap between the standards of care within the guideline and current clinical practice, providing a baseline to support subsequent quality improvement interventions.

Methods

Audit pro forma development

The audit was developed and piloted by a BSR project working group, including the guideline lead, the NHS England Specialised Rheumatology Clinical Reference Group chair, the BSR Standards, Audit and

Guidelines Working Group Chair, and other clinicians with experience of conducting multi-regional and national clinical audits. Data collection was hosted by the Audit department at the Dudley Group NHS Foundation Trust.

Guideline recommendations that were considered to be amenable to clinical audit were identified, and audit standards related to these determined by consensus opinion.

Involvement of units

All rheumatology units in the East and West Midlands, North East and North West of England were invited to participate. In addition, the BSR invited units to participate via eNewsletter to UK members. Participating units registered the audit with their local audit departments and completed a pro forma of unit-specific data, including staffing numbers and provision of dedicated clinics.

Audit data collection

The audit was conducted between 5 February and 12 June 2018, with each unit choosing any 4 week period within this timeframe in which to identify all SLE patients attending a rheumatology outpatient clinic.

In order to ensure that any care being audited was aligned with the guideline's intended patient group(12), to be eligible for inclusion patients needed to have *both*:

1. A consultant diagnosis of SLE (rather than, for example, undifferentiated connective tissue disease, or mixed connective tissue disease)

2. At least one immunological abnormality ever (relevant autoantibody or low complement).

This was a retrospective audit, meaning that data were collected by a clinician reviewing the case record of the previous clinic attendance (likely prior to guideline publication).

For each audited patient, data were collected on demographics (age, gender, ethnicity, smoking status), drug treatment and lupus disease activity state. The latter was ascertained by the auditing clinician from their assessment of the audited clinic record and according to definitions in the BSR guideline; mild was defined as clinically stable lupus with no life-threatening organ involvement, moderate as more serious manifestations, and severe as organ- or life-threatening(12). Data were collected on items related to compliance with guideline recommendations including screening for modifiable risk factors, treatments, comorbidities, and hospital admissions in the previous year.

Data were entered onto web-based survey software, conforming to the best available security and accessibility and compliant with ISO 27001, the internationally recognised gold standard for information security systems.

Data analysis

Data were cleaned to remove test, duplicate and impossible entries (e.g. age >110 years). Most data items were recorded as yes or no, and few required further categorisation as described below. The individual patient audit form did not allow submission without complete data. Therefore, statistical techniques to impute missing data were not necessary. One department did not submit unit data and was excluded from the centre analysis.

Dichotomous variables are described using proportions; continuous values are presented as means with standard deviations, or medians with interquartile range, as appropriate.

Urine quantification was defined as "appropriate" if the patient either had a urine dip whose result was recorded as negative or a trace of protein only, or recorded as ≥1+ protein and it was sent for urine protein quantification, or it was documented that the patient was unable to provide a urine sample at that clinic visit. It was defined as "not appropriate" if the patient had no urine dip with no reason for this documented, or they had a urine dip showing ≥1+ protein and it was not sent for urine protein quantification (figure 1).

Levels of proteinuria were categorized into normal/mild, moderate/severe and nephrotic, based on the BILAG score glossary(14) (appendix 1).

We defined a 'specialised' centre as one that is permitted by NHS England to prescribe belimumab, as provided by the NHS England Specialised Rheumatology Clinical Reference Group chair. Hospitals outside England were excluded from this specific analysis (4 hospitals, n=98 visits). Within England, 'specialised' centres contributed 558 (60.5%) of the patient visits included in this comparison, and non-specialised centres 365 (39.5%).

Audit standards for comparison between specialised centres compared to non-specialised centres, and between patients seen in a dedicated clinic compared to a general rheumatology clinic were decided a priori to prevent selective reporting of significant results. Members of the project working group ranked potential comparators in order of perceived importance. Scores were combined and the highest scoring nine standards were selected. Comparisons were made using Chi-squared testing or Fisher's exact test. To counteract problems with multiple comparisons increasing the risk of finding significant associations solely by chance, we used Bonferroni's correction to the significance level for each comparison.

Results

51 units within England, Scotland, Wales and Northern Ireland participated in the audit (appendix 2). A total of 1,021 clinic visits, made by 1,003 patients, were audited (13 patients made an additional 18 clinic visits during the audit period). Each unit contributed data on be-tween 1 and 127 clinic visits. The majority of units (35/50, 70%) reported having a dedicated SLE, connective tissue disease (CTD) or vasculitis clinic. 745 patients (73%) attended this clinic type, 256 (25%) attended a general rheumatology clinic and 20 (2%) attended another type of clinic in the rheumatology department.

Demographics and clinical characteristics of the 1003 patients are shown in table 1. Patients had a median age of 48 (interquartile range 36-58) years, and 935 (93%) were female. 586 (58.4%) were White, 157 (15.7%) Asian or Asian British and 147 (14.7%) Black or Black British; other ethnic groups each contributed less than 5%. The majority (74%) had been diagnosed with SLE more than 5 years ago. At the audited visit, 286 (28.5%) patients had active disease. The majority of those with active disease were not newly diagnosed; 183 of these (64.0%) had a disease duration of more than 5 years.

Medications for SLE that were being prescribed (both existing and new prescriptions) at the end of the visit being audited are shown in table 2. 297 (29.1%) were on no specific SLE drug treatment. Overall, 497 (48.7%) of patients were on prednisolone, 732 (71.7%) on hydroxychloroquine, 238 (23.3%) on mycophenolate mofetil, 137 (13.4%) on azathioprine, 105 (10.3%) on methotrexate, 94 (9.2%) on rituximab (in the last 12 months), and 8 (0.8%) on belimumab. Other medications were used rarely (in less than 1%). 252 (24.7%) were on an ACE-inhibitor, and 158 (15.5%) were on a statin. Of 301 visits with active disease, only 162 (53.8%) resulted in a change in management, with a drug for SLE either initiated or an established drug escalated in dose (excluding topical treatments). Of these, 70/103 (68.0%) visits with moderate disease and 12/16 (75.0%) with severe disease resulted in a change of management, with the rest being of mild or unknown severity.

243 (24.2%) of the group had ever had lupus nephritis. Of the 827 patients who provided a urine sample, moderate/severe proteinuria was present in 84 (10.2%), with nephrotic range proteinuria in an additional 13 (1.6 %). Of the 84 patients with moderate/severe proteinuria, 46 (54.8%) were on an ACE inhibitor (ACEi) or Angiotensin Receptor Blocker (ARB) and of note, 5/13 (38.5%) patients with nephrotic range proteinuria were on an ACEi/ARB.

The most common co-morbidity was hypertension, which affected 233 (23.3%), whilst diabetes, ischaemic heart disease, and stroke/transient ischaemic attack affected approximately 5% each (55, 53 and 49 patients respectively). 185 (18.4%) had been admitted to hospital in the previous 12 months. 70 (7.0%) had had an admission with infection.

Compliance of the combined performance of all units against the audit standards is shown in table 3. The standards were met for blood pressure and eGFR measurement. Compliance was within 10% of our proposed audit standard for appropriate urine protein quantification (82.6%), enrolment in BILAG-BR for patients on rituximab (81.9%) and for a prednisolone dose of ≤7.5mg daily if patients have inactive SLE and are on prednisolone (84.0%).

Results were below the audit standards in assessment of disease activity using BILAG or SLEDAI (21.3%), documentation of monitoring for hydroxychloroquine retinopathy (52.8%), enrolment of patients on belimumab in BILAG-BR (75.0%) and documentation within the last 12 months of lipid profile (39.0%), vaccination advice (32.7%), UV protection (30.3%), smoking status (61.8%), and pregnancy counselling (48.3%).

Comparison of key audit standards between specialised and non-specialised centres, and between patients seen in dedicated SLE/CTD/Vasculitis clinics compared to general rheumatology or other clinics, are shown in table 4. Specialised centres performed significantly better at compliance with recruitment to BILAG-BR for all patients treated with biologics (89.4% vs 44.4%), and at recording a measurement of blood pressure at the audited clinic visit (95.3% vs 84.1%). Dedicated SLE/CTD/Vasculitis clinics performed significantly better than general rheumatology clinics or other clinics at recording a measurement of blood pressure (94.5% vs 82.0%), and, although both were below the audit standard for appropriate urine protein quantification, dedicated clinics performed better (85.1% vs 75.8%). Other comparisons did not show significant differences, including in the proportion of patients with a formal disease activity score, record of a lipid profile in the last 12 months, maintenance prednisolone dose of <7.5mg, total proportion of eligible patients on hydroxychloroquine, and proportion of patients on hydroxychloroquine whose dose did not exceed 6.5mg/kg.

Discussion

Strengths and limitations

This audit is the largest ever multi-centre clinical audit of any rare rheumatic disease, making it a rich resource for improving the quality of care of SLE patients both in the UK and internationally. As described later, through identifying existing practice and opportunities to improve care, the audit has enabled the development of quality improvement tools.

The audit included patients treated in large specialised centres and small district general hospitals, representing a range of healthcare settings across all 4 nations of the UK. The identification of all patients within the same timeframe has enabled a contemporary “real-life” sample of patient care.

Our cohort was similar to those of previously published studies on SLE incidence and prevalence in the UK, with a notable female preponderance(6) and over-representation of Black and Asian ethnic groups (6)(15)(16)(17)(18) although there were slightly fewer Black patients and more Asian patients than in some other studies(18)(19), reflecting the patient demographics of the participating units.

Limitations include that the diagnoses were reliant on clinician reporting and we were unable to confirm the autoantibody status of the patients said to have lupus, nor the histological type of nephritis.

There is the possibility of selection bias. For example, patients with higher disease activity are more likely to have been included due to their frequent clinic attendance. Conversely, patients receiving intravenous cyclophosphamide may have been missed because they attend day-case units rather than clinics. There is also survivor bias when assessing past events and comorbidities. The audit is therefore representative of patients attending rheumatology outpatient clinics, which might differ from the overall population of people with lupus in the UK.

Hospital admissions and infections may have been underestimated as any patients admitted during the audited timeframe may not have been captured.

As data were collected retrospectively, the audit captured what was recorded by clinicians at the audited clinic visit, meaning that any undocumented aspects of care were not reflected in the findings. Certain advice, for example regarding immunisations, may be given intermittently and may not have been reflected by auditing a single clinic visit.

A large number of rheumatology units and patients were included. However, SLE remains a rare disease and the audit numbers are too small for a well-powered comparison of rare outcomes. For example, it is difficult to compare specialised vs non-specialised centres on outcomes such as hydroxychloroquine doses in excess of 6.5mg/kg due to the small numbers of patients involved.

Main findings

Almost a third of patients had on-going disease activity, notably independent of disease duration. Whilst this was predominately categorised by the auditing clinician as mild, this highlights an unmet need both for optimising available treatment strategies and for novel therapies in SLE. In particular, nearly half of those audited, and more than a quarter of those who had inactive SLE, were being prescribed maintenance prednisolone. Of the patients with inactive disease, 16.0% were on maintenance prednisolone doses of >7.5mg/day. Of 480 women of reproductive age, 45% were on drugs not considered compatible with pregnancy and 44% of these patients had no record of pregnancy discussions. Whilst this could have occurred previously without documentation, unplanned pregnancy in this situation would be a concern.

In addition, there is a need for improvement in documented compliance with guideline recommendations to measure lipids for cardiovascular disease risk factor assessment; communication to patients about vaccinations and UV protection; monitoring for hydroxychloroquine retinopathy; and for formally measuring disease activity with a validated score. There is also a need to improve enrolment of patients starting biologics to BILAG-BR, as per the NHS England Clinical Commissioning Policy for Rituximab(20) and the Nice Technology Appraisal for Belimumab(13). Infection remains an important cause of morbidity, with one third of hospital admissions in the past year related to infection.

Comparison to other literature

Specialised vs general clinics

The quality of the care we provide is influenced by the structure of services. The published literature suggests that specialised clinics perform better than general clinics on key measures of care quality(21), with cardiovascular risk assessment, sunscreen counselling and vaccination advice highlighted as being performed more frequently in dedicated clinics in the USA(21). Our audit also demonstrated that patients seen in a specialised SLE/CTD/Vasculitis clinic were more likely to receive appropriate urine quantification and blood pressure measurement. Whilst there was no significant difference in the other key audit standards, these calculations were relatively underpowered. This suggests that patients should be seen in dedicated clinics to improve assessment and outcomes.

Additionally, specialised clinics were significantly more likely to have recruited patients receiving biologics to the BILAG BR registry, which is a requirement of the clinical commissioning policies for both Rituximab and Belimumab (13)(20). Engagement with registries is important in order to contribute to outcome research and to secure our continued access to high cost drugs in the future.

Renal disease

Overall, the care demonstrated in this audit related to appropriate urinalysis screening for nephritis were below recommended standards. This introduces the risk of delayed recognition and treatment of flares of renal disease. A previous study by Hui et al. (22) found that 25% of people diagnosed with lupus nephritis had no record of urine protein quantification at the previous clinic visit. Moreover, up to 35% of patients with lupus nephritis develop it after their SLE diagnosis(23). As urinalysis is a sensitive screening tool for renal disease and forms part of the diagnostic criteria for lupus nephritis(24), ongoing monitoring is required. In

this audit, the prevalence of lupus nephritis was relatively low at 24.2% (a prospective study of an international multiethnic cohort found an incidence of 38.3%(25)), possibly because many patients with significant renal disease are managed in nephrology clinics which were not captured by this audit.13/50 (26.0%) units reported that they had a combined Renal/Rheumatology clinic.

Only around half of patients with moderate, severe or nephrotic range proteinuria were on an ACEi/ARB, although data on contraindications or adverse events precluding treatment were not sought. Whilst a proportion of these patients may have had new, active disease and treatment may not have yet been initiated, this is unlikely to account for all 97 patients recorded. ACEi/ARB are well-established treatments and have been shown to reduce proteinuria by 30%, as well as delay progression to end stage renal disease(24). They are recommended for patients in whom UPCR>50mg/mmol (moderate proteinuria or above)(12)(24) unless contraindicated.

Disease activity

More than a quarter of patients had active disease. Active disease predicts damage, and damage predicts damage accumulation and increased mortality(9)(10). Many patients with SLE have ongoing disease activity despite standard treatment(13)(26)(27) and very few patients enter sustained remission, even with treatment(28)(29). This highlights an unmet need for effective therapies in refractory SLE(8).

Formal disease activity scoring with BILAG disease activity index or SLEDAI only occurred in 21.3% of clinic visits captured in the audit, despite evidence that such clinical measures are more sensitive to small changes in disease activity than laboratory tests(30) and that active disease as measured by BILAG scoring predicts organ damage and mortality(10). BILAG/SLEDAI scoring was absent even in patients judged to have active, including moderately/severely active, disease (26.3% and 33.6% respectively), even though formal recording of disease activity scores is a prerequisite for funding of biologic therapies (13)(20), if required for treatment escalation.

Active disease, current corticosteroid exposure and current or previous cyclophosphamide exposure are independently associated with the development of damage (6)(9). Cumulative glucocorticoid dose is also associated with damage accrual(31)(32), as well as an increased risk of bacterial infection(32). 48.7% of patients were on prednisolone, including 28.5% of those with inactive disease. Whilst we do not have data on the specific reasons for continued steroid use in this inactive group, these might include physician or patient concern (e.g.previous flare on steroid withdrawal), physiological non-lupus related dependence on steroids, serological disease activity despite clinical quiescence and also potentially a failure to focus on optimising steroid reduction at each clinic appointment(33). Whatever the reason, our data highlights the continuing need to actively review prednisolone therapy in stable patients and to consider dose reduction or corticosteroid discontinuation or replacement with other agents where appropriate, to mitigate steroid side effects.

Disease sequelae

There is a three-fold risk of death in patients with SLE, particularly from cardiovascular disease and infection(34). SLE is an independent risk factor for cardiovascular disease(35) and cardiovascular events contribute significantly to morbidity and mortality. Our data demonstrate the need for improvement in screening for cardiovascular risk factors, with low rates of documented screening for smoking status and lipid profile in particular.

The high hospitalisation rate of patients with lupus is well-recognised, with common reasons including active disease and infection (36)(37)(38), although admissions with stroke, acute coronary syndrome and chronic renal failure are increasingly seen(39).

Hydroxychloroquine

Of the patients prescribed medication for SLE, the vast majority (71.7%) were on hydroxychloroquine. With regards to hydroxychloroquine dosing, the Royal College of Ophthalmology guideline(40) released in February 2018 recommended a dose of <5mg/kg/day. Previous guidelines in 2002 had recommended a dose of <6.5mg/kg/day(24). As the guidance changed after the audited visits, we have reported compliance with the <6.5mg/kg/day dosing schedule.

Wider implications and quality improvement

Clinical practice guidelines have increased exponentially over the last few decades and their development is well documented. However, data on the adaptation, adoption and impact of such guidelines is lacking (41)(42)(43) and the effect on patient outcomes is unknown. Implementation of a guideline requires behavioural change, as well as potential alterations in the structure of service provision, workforce, resources and training(41)(44).

Through the identification of gaps between the published guideline and current clinical practice(43)(44), this audit offers a unique opportunity to explore the value of guidelines - can they be implemented and what is their impact on patient outcomes?

Each contributing unit received a summary of the data they submitted, compared to the national data. Along with this, quality improvement tools such as example driver diagrams were developed and distributed and are available open access on the BSR website(45). A clinic prompt (appendix 3 - also available through the BSR website(45)) was produced to support decision making, training and education. The aim is to provide practical resources that can be used by clinicians to implement the guideline recommendations.

This audit should be viewed as a catalyst for every rheumatology unit to evaluate and undertake any local quality improvements that are needed to enable implementation of the BSR guideline, to improve the care of people living with lupus.

Key messages:

1. There is evidence that dedicated SLE clinics provide better patient care

2. Significant numbers of patients have active disease despite therapy, highlighting the need for new treatments

3. Over a quarter of patients with inactive disease remain on corticosteroids which risks potential sequelae

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