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TESI DI LAUREA:

Belimumab efficacy on different subsets of musculoskeletal features in patients with systemic lupus erythematosus treated in real world setting. Results from a multicentric, nationwide cohort (BeRLiSS-Joint)

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ABSTRACT

Background. Belimumab is a monoclonal antibody that has long been used for the treatment of systemic lupus erythematosus (SLE) and has shown efficacy in managing the joint manifestations of the disease. Despite many studies on belimumab, none have so far analyzed in detail its efficacy in real-life on musculoskeletal manifestations in SLE.

Aims. To evaluate the efficacy of belimumab on different joint manifestations of the disease in a nationwide prospective multicenter cohort (BeRLISS-Joint) of patients with systemic lupus erythematosus (SLE).

Methods. In this retrospective observational study, we stratified adult SLE patients treated with belimumab (10 mg/kg/month IV or 200 mg/week SC) based on the joint phenotype (non-deforming non-erosive arthritis - NDNE, JA, and rhupus) at belimumab initiation. We analyzed the variation of DAS28 scores at baseline, 6, 12, 18, 24, 30 and 36 months of follow-up. The average daily dosage of glucocorticoids (prednisone equivalent) was analyzed at baseline and at 6, 12, 18, 24, 30, and 36 months of follow-up. Additionally, the glucocorticoid consumption stratified by daily dosage was analyzed at baseline and at 6, 12, 18, 24, 30, and 36 months of follow-up, but this analysis was limited to the cohort from Padua in this case. Parametric and nonparametric tests were used according to the data distribution.

Results. A total of 443 patients from 14 Italian centers were enrolled (F=394; 88.9%); the mean age at diagnosis was 29.9±13.2 years, and the mean treatment duration was 52.2±38.0 months. At the initiation of belimumab treatment, 272 patients had joint manifestations (61.4%), of which: 221 had non-deforming non-erosive arthritis (NDNE) (81.3%), 30 had Jaccoud's arthropathy (JA) (11%), and 21 had rhupus (7.7%). The median DAS28 value significantly decreased from baseline to 6 months ($p<0.001$) and from 6 to 12 months ($p=0.046$) for NDNE, while it significantly decreased from baseline to 6 months for JA ($p=0.005$) and rhupus ($p=0.011$). For all three phenotypes, the decrease was also significant from baseline to 36 months (NDNE $p<0.001$, JA $p<0.001$, rhupus $p=0.047$). Regarding remission rates based on DAS28 < 2.6, the difference between phenotypes was significant at 6 months

(p=0.002) and at 36 months (p=0.043). While the percentage of NDNE patients in remission increased over time, the percentage of JA and rhupus patients in remission showed irregular and less substantial improvement.

Considering all phenotypes the mean glucocorticoid daily dosage decreased, reaching mean values of ≤ 5 mg/day as recommended by 2023 EULAR recommendations. Regarding glucocorticoid consumption stratified by daily dosage and joint involvement subtype in the cohort of patients from Padua, at baseline 32,5% of NDNE patients, 25% of JA patients, and 20% of rhupus patients were on 0,1-5 mg/day of glucocorticoids, whereas 5% of NDNE patients, 8.33% of JA patients and 0% of rhupus patients did not use glucocorticoids.

At 36 months, more than 90% of patients of all three joint phenotypes had a dosage of ≤ 5 mg/day or did not use glucocorticoids. Specifically, 60,71% of NDNE patients, 40% of JA patients and 100% of rhupus patients were on 0,1-5 mg/day of glucocorticoids, whereas 32.14% of NDNE patients and 60% of JA patients did not use glucocorticoids. No rhupus patients completely discontinued the glucocorticoids.

Conclusions. Belimumab was effective in reducing GC use and joint involvement activity at 6, 12, 18, 24, 30 and 36 months, with a significant decrease in DAS28 observable as early as 6 months from treatment initiation across all joint phenotypes.

RIASSUNTO

Presupposti dello studio. Belimumab è un anticorpo monoclonale usato ormai da tempo per il trattamento del lupus eritematoso sistemico (LES) e ha dimostrato efficacia anche nella cura delle manifestazioni articolari della malattia, ma non sono mai state studiati nel real-life gli specifici livelli di efficacia per le diverse manifestazioni articolari.

Scopo dello studio. Valutare l'efficacia del belimumab su diverse manifestazioni articolari della malattia in una coorte prospettica multicentrica nazionale (BeRLISS-Joint) di pazienti con lupus eritematoso sistemico (LES).

Materiali e metodi. In questo studio osservazionale retrospettivo, abbiamo stratificato i pazienti adulti con LES trattati con belimumab (10 mg/kg/mese EV o 200 mg/settimana SC) in base al fenotipo articolare (artrite non deformante non erosiva - NDNE -, artropatia di Jaccoud e rhupus) all'inizio del trattamento con belimumab. Abbiamo analizzato la variazione dei punteggi DAS28 al basale, a 6, 12, 18, 24, 30 e 36 mesi di follow-up. È stato analizzato il consumo medio giornaliero di cortisone al basale, a 6, 12, 18, 24, 30 e 36 mesi di follow-up. È stato inoltre analizzato il consumo di cortisone stratificato per quantitativo giornaliero al basale, a 6, 12, 18, 24, 30 e 36 mesi di follow-up, ma limitatamente alla coorte di Padova in questo caso. Sono stati utilizzati test parametrici e non parametrici a seconda della distribuzione dei dati.

Risultati. Un totale di 443 pazienti provenienti da 14 centri italiani sono stati arruolati (F=394; 88,9%); l'età media alla diagnosi era di 29,9±13,2 anni e la durata media del trattamento era di 52,2±38,0 mesi. All'inizio del trattamento con belimumab, 272 pazienti presentavano manifestazioni articolari (61,4%), di cui: 221 con artrite non deformante non erosiva (NDNE) (81,3%), 30 con artropatia di Jaccoud (JA) (11%) e 21 con rhupus (7,7%). Il valore mediano del DAS28 è diminuito significativamente dal basale ai 6 mesi ($p<0,001$) e dai 6 ai 12 mesi ($p=0,046$) per NDNE, mentre è diminuito significativamente dal basale ai 6 mesi per JA ($p=0,005$) e rhupus ($p=0,011$). Per tutti e tre i fenotipi la diminuzione è stata inoltre significativa tra il basale e i 36 mesi (NDNE $p<0,001$, JA $p<0,001$, rhupus $p=0,047$). Nel caso delle percentuali di pazienti in remissione basate su DAS28 < 2,6, la differenza tra i fenotipi

è significativa a 6 mesi (p=0,002) e a 36 mesi (p=0,043). Mentre la percentuale di pazienti con NDNE in remissione è aumentata nel tempo, la percentuale di pazienti con JA e rhupus in remissione ha mostrato un miglioramento irregolare e meno consistente.

Il consumo medio di glucocorticoidi è diminuito in tutti e tre i fenotipi, raggiungendo valori medi di ≤ 5 mg/die come raccomandato dalle linee guida EULAR 2023. Per quanto riguarda il consumo di glucocorticoidi stratificato per dosaggio giornaliero e sottotipo di coinvolgimento articolare nella coorte di pazienti di Padova, al basale il 32,5% dei pazienti con NDNE, il 25% dei pazienti con JA e il 20% dei pazienti con rhupus assumevano tra 0,1 e 5 mg/die, mentre il 5% dei pazienti con NDNE, l'8,33% dei pazienti con JA e lo 0% dei pazienti con rhupus non utilizzavano glucocorticoidi.

A 36 mesi, più del 90% dei pazienti di tutti e tre i fenotipi articolari avevano un dosaggio di ≤ 5 mg/die o non utilizzavano il farmaco. Nello specifico, il 60,71% dei pazienti con NDNE, il 40% dei pazienti con JA e il 100% dei pazienti con rhupus assumevano tra 0,1 e 5 mg/die, mentre il 32,14% dei pazienti con NDNE e il 60% dei pazienti con JA non utilizzavano glucocorticoidi. Nessun paziente con rhupus ha sospeso completamente il farmaco.

Conclusioni. Il belimumab è stato efficace nel ridurre l’uso di glucocorticoidi e l'attività delle manifestazioni articolari a 6, 12, 18, 24, 30 e 36 mesi con una diminuzione significativa del DAS28 osservabile già a partire da 6 mesi dall'inizio del trattamento in tutti i fenotipi articolari.

INTRODUCTION

1. Introduction to the disease

1.1. Definition

Systemic lupus erythematosus (SLE) is an autoimmune disease with a wide spectrum of clinical manifestations varying from patient to patient, that can range from mild forms that may not heavily affect daily life, to organ failure and obstetric complications. SLE can potentially involve all organs (1). This condition mainly affects young patients, especially women, and it's more common in certain ethnic groups such as Black, Asian and Hispanic populations (1,2).

Global incidence and prevalence are highly variable between reports, due to inherent variations in population demographics, different environmental exposures and socio-economic factors. Furthermore, studies often differ in design and case definition, contributing to inconsistency between data (3). Unfortunately, mortality is still two to three times higher compared to general population, with infections and cardiovascular diseases being among the most frequent causes of death (4).

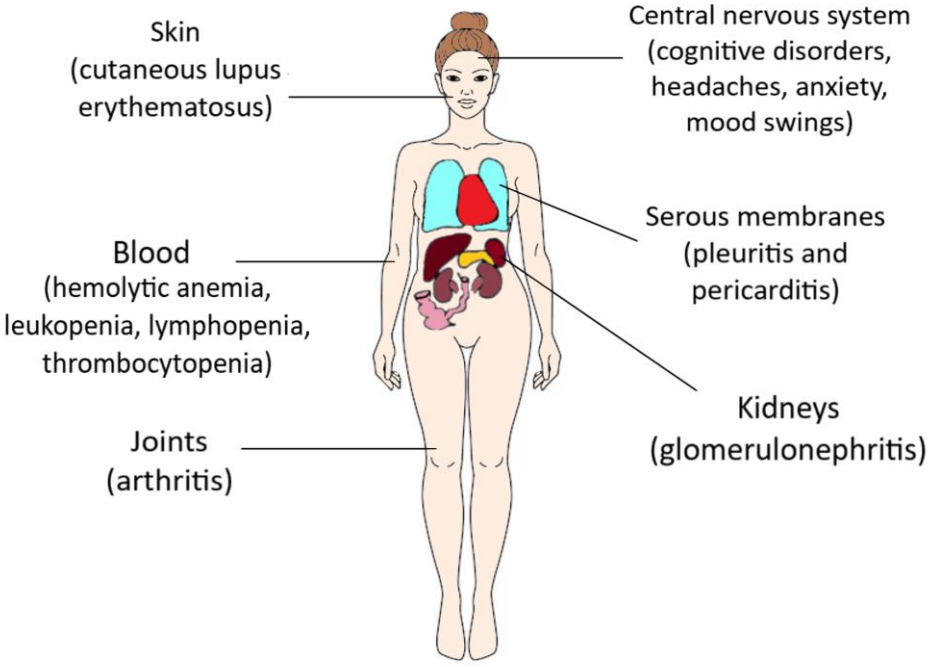

Fig.1 Some of the most common manifestations in SLE

1.2. Epidemiology

Recent global SLE incidence rates vary from country to country, ranging from:

- 3.7 per 100,000 people yearly to 49.0 per 100,000 in the US Medicare population in North America;
- 1.5 to 7.4 per 100,000 people yearly in Europe;
- 1.4 to 6.3 per 100,000 people yearly in South America;
- 2.5 to 8.6 per 100,000 people yearly in Asia.

No estimates of the current incidence of SLE in Australasia or Africa are available.

The prevalence of SLE varies between:

- 48 and 366.6 per 100,000 in North America;
- 29.3 and 210 per 100,000 in Europe;
- 24.3 and 126.3 per 100,000 in South America;
- 20.6 and 103 per 100,000 in Asia;
- 13 and 52 per 100,000 in Australasia

SLE mainly affects the female sex (2), with a F:M ratio of 9:1, although the forms affecting the male sex are more severe (5). The age group most affected is typically in the third and fourth decades of life, during childbearing age, suggesting the presence of a hormonal influence from estrogens (6).

Men with SLE diagnosed often have a more aggressive clinical course with rapid accrual of organ damage, resulting in a poorer prognosis compared with women with SLE. Men with SLE are reported to have more frequent serositis, cardiovascular diseases, cytopenias, hemolytic anemia, nephritis, antiphospholipid antibodies, thrombotic events and seizures (5).

SLE in pediatric age is quite uncommon, with an incidence of 0.3 to 0.9 per 100,000 children yearly and a prevalence of 3.3 to 8.8 per 100,000 children. In this case it is referred as pediatric-onset systemic lupus erythematosus (cSLE). A higher frequency of cSLE is reported among Asians, African Americans, Hispanics, and Native Americans (1,7).

1.3. Etiopathogenesis

1.3.1. Pathogenetic mechanism

The basic prerequisite for the development of SLE is the presence of a predisposing genetic background, which is compounded by exposure to an environmental trigger.
In literature different environmental trigger has been reported , including drugs or sunlight and viral infections, especially EBV. Most of these triggest ract as activator of the innate immunity leading to type I interferon synthesis (2), which stimulates the cells of the innate immune system, such as macrophages and dendritic cells, and the acquired immune system, B and T lymphocytes. Finally, cell death significantly contributes to the pathogenesis of SLE by leading to pathogenic alterations, abnormal processing and presentation of self-antigens (8), then leading to autoimmune processes.

B lymphocytes

B lymphocytes express on their membrane the B-cell receptor (BCR), which is responsible for both pathogen recognition and subsequent production of specific antibodies against the pathogen. During their development process, self-reactive B lymphocytes are typically eliminated by mechanisms of immunological tolerance. In the case of SLE, instead, these self-reactive clones proliferate and become activated, thus contributing to the development of the disease. After development, all B lymphocytes require the intervention of certain soluble factors to ensure their survival and proliferation, and the most important is the B-cell activating factor (BAFF) or B lymphocyte stimulator (BLys) (2).
BAFF/BLyS is a B cell survival factor that sustains autoreactive B cells and prevents their elimination. Its expression is also enhanced by both genetic alterations and viral infections. In addition, BAFF appears to be involved in several processes, such as in atherosclerosis, adipogenesis, neuroinflammatory processes, and ischemia-reperfusion injuries (9).

Self-reactive B lymphocytes produce antibodies primarily directed against nuclear antigens. An important source of antibody production will then be the long-lived

plasma cells (LLPC, which can also be produced in spontaneously formed germinal centers) as well as short-lived plasmablasts. The latter, in the germinal centers of the lymph nodes, interact with CD4+ T lymphocytes, become high-affinity plasma cells, migrate to specific niches in the bone marrow, and here, protected from external events, survive for a long time. B cells can also play the role of antigen-presenting cells (APC) to self-reactive T lymphocytes (2).

T lymphocytes

Self-reactive T cells are important in the development of SLE. Among them, T-helper 1 (Th1) cells play a central role in the pathogenesis (2,10) by fostering oxidative stress through IFNγ production. Conversely, there is a decrease in the number of IL-4-producing Th2 cells in the peripheral blood of SLE patients, indicating a potential protective function: moreover, SLE activity might be linked to an elevated IFNγ/IL-4 ratio.

T-helper 17 (Th17) cells also contribute to SLE pathogenesis as they are the primary producers of IL-17, a cytokine family with potent inflammatory effects, which can lead to tissue damage. IL-17 stimulates neutrophil recruitment, activates the innate immune system, and enhances B-lymphocyte functions. Studies have shown that IL-17 levels correlate with SLE Disease Activity Index (SLEDAI) in patients with lupus nephritis.

Regulatory T cells (T-regs) are crucial for maintaining peripheral tolerance to self-antigens. Although quantitative and qualitative differences in T-regs have been observed in SLE, research findings have been inconsistent, and their precise role in SLE remains unclear (2).

Type I interferon

The production of type I IFN is primarily triggered by the activation of nucleic acid-binding pattern recognition receptors. Among these are the endosomal TLRs 3, 4, 7, and 9, the cytosolic sensor cyclic GMP-AMP synthase, and the RIG-I-like receptors-MAVS for RNA. Under normal conditions, these nucleic acid sensing pathways are

tightly regulated and are necessary for forming appropriate antiviral responses. However, many SLE patients exhibit chronic hyperactivity in these pathways.

This chronic elevation of type I IFN levels in predisposed individuals is attributed to several factors: overproduction, heightened sensitivity, and impaired negative regulation. Genetic variations in genes like interferon regulatory factor (IRF)5 and IRF7 are associated with increased circulating type I IFN (11). Furthermore, downstream genes of the type I IFN receptor, such as Signal Transducer and Activator Of Transcription 4 (STAT4), are linked to SLE. Studies show that SLE patients with certain STAT4 risk alleles exhibit greater type I IFN-induced gene expression, indicating increased sensitivity to type I IFN (12). Additionally, deficiencies in negative regulators of type I IFN, such as immunoglobulin-like transcript 3 (ILT3) receptor expressed on dendritic cells (DCs), are associated with elevated circulating type I IFN levels in SLE patients.

Endogenous stimuli, such as immune complexes involving SLE-associated autoantibodies, interact with a susceptible genetic background to trigger type I IFN production. Neutrophils can also stimulate the endogenous type I IFN pathway through neutrophil extracellular traps (NETs), leading to increased IFN-α production by plasmacytoid dendritic cells (pDCs) in a TLR9-dependent pathway.

A feed-forward loop likely occurs, wherein type I IFN participates in the initial breakdown of tolerance. Both type I IFN and SLE-associated autoantibodies are elevated in the pre-disease state, supporting their roles in disease susceptibility and initiation. In the years preceding SLE diagnosis, there is an increase in the number of autoantibody specificities, indicating a diversification of the anti-self response in the pre-disease state. These autoantibodies can form nucleic acid immune complexes that stimulate type I IFN production.

Type I IFN levels rise in the pre-disease state, notably peaking approximately 2 years before the diagnosis of SLE. Pre-disease studies suggest that many key features of the dysregulated immune response in SLE begin years before patients exhibit clinical manifestations and seek medical attention (11).

Antibodies

The role of autoantibodies in the pathogenesis of SLE is still matter of debate. While their presence in serum years before clinical signs (2,11) suggest they may serve as biomarkers rather than direct pathogenic factors, considerable evidence points to their central role in SLE immunopathogenesis. For example, immune complexes containing various autoantibodies, including anti-dsDNA antibodies, are found in lupus nephritis at the glomerular level and their removal leads to disease amelioration (2). Furthermore, the levels of anti-DNA antibodies in serum vary with the activity of SLE in patients. Additionally, these autoantibodies have the potential to activate the complement cascade, infiltrate cells, influence gene expression, and even prompt profibrotic characteristics in renal cells (13).

Additionally, neonatal lupus erythematosus arises from the passive transfer of maternal autoantibodies across the placenta, underscoring their pathogenic potential. These observations suggest that autoantibodies may contribute, at least partially, to the clinical manifestations of SLE (2).

Types of antibodies that may be present, particularly in patients with thrombosis or obstetric complications are anti-phospholipid antibodies, which are the biomarker of antiphospholipid syndrome (APS). Their presence elevates the likelihood of neuropsychiatric SLE (especially cognitive impairment (14), thrombotic events, and obstetric complications.

Other antibodies present in SLE may be anti-Sm and anti-RNP antibodies, which can bind to the surface of human monocytes. More importantly, it has demonstrated that anti-Sm and anti-RNP work synergistically to enhance IL-6 production by human monocytes (15).

An example of an environmental trigger associated with antibodies is UV exposure, which increases the synthesis and expression of Ro antigen on the surface of epidermal keratinocytes. Anti-Ro/SSA antibodies from the circulation then bind to these surface antigens, and their Fc domains are recognized by lymphocytes, leading

to keratinocyte death. This hypothesis is supported by a study (16) showing a direct correlation between photosensitivity and the titer of circulating anti-Ro/anti-La antibodies with the expression of Ro and La antigens in skin specimens of patients with SLE.

Further evidence for the pathogenic role of anti-Ro and anti-La comes from studies of neonatal lupus erythematosus (NLE). Cardiac damage in NLE is related to the expression of Ro and La antigens in fetal cardiac tissue between the 18th and 24th weeks, particularly on the surface of cardiac myocytes (16).

1.3.2. Etiopatogenesis of musculoskeletal involvement

Although joint involvement is common in SLE, with a prevalence ranging from 69% to 95%, it is often overshadowed by other organ manifestations. However, it significantly impacts patients' quality of life and can lead to disability and impaired daily functioning (17).

The pathogenic mechanisms underlying joint involvement are not fully understood, but genetic variants and immunological factors play significant roles. Various studies have identified associations between specific genetic variants and SLE-related arthritis, suggesting potential links between certain genes and disease phenotype.

Research has also focused on identifying molecular and cellular changes in the joints of SLE patients. Synovial fluid and membrane analysis have revealed distinct characteristics, including differences in cell composition and gene expression compared to rheumatoid arthritis (RA). Increased expression of interferon-induced genes (IFIs) and decreased expression of genes involved in extracellular matrix (ECM) homeostasis were found in the synovial tissue of patients with SLE, which could be due to increased inflammatory cells (18).

The presence of autoantibodies, including anti-citrullinated peptide antibodies (ACPA) and anti-Ro/SSA antibodies, has been linked to joint involvement in SLE patients. Citrullination, a post-translational modification implicated in RA

pathogenesis, may also play a role in SLE-related arthritis. Furthermore, associations between joint involvement and other clinical features, such as antiphospholipid syndrome, have been reported.
Inflammatory cytokines, particularly IL-6, have shown potential as biomarkers for SLE-related joint manifestations. Elevated IL-6 levels have been associated with ongoing arthritis and disease activity in SLE patients. However, the role of other cytokines, such as tumor necrosis factor, remains unclear in this context (19).

The role of type I interferons in arthritis might be intricate. IFN-α, predominantly synthesized by circulating plasmacytoid dendritic cells and monocytes, is commonly linked to more severe manifestations in SLE. Nonetheless, while blood interferon activity correlates with the overall disease activity and specific organ involvement like mucocutaneous disease, its association with arthritis remains unclear (20).

Overall, we can highlight the complex interplay of genetic, immunological, and environmental factors in the pathogenesis of joint involvement in SLE. Further research is needed to elucidate the underlying mechanisms and identify effective therapeutic strategies for managing this aspect of the disease (18,19).

2. Clinical manifestations

2.1. Overview

In the SLE patient, all the general symptoms that also occur in other connective tissue diseases, such as fever, asthenia, weight loss and anorexia, are present (21). The constitutional manifestations may be present at the onset as well as in the flare-up phases. SLE has both flare-up and remission phases, known as relapsing-remitting course (22). The clinical manifestations that occur in the course of the disease are manifold, as SLE can affect any organ or systems.
On the other hand, symptom attribution to SLE is a very delicate step in the clinical work-up of the patient: this is particularly important for neurological symptoms (23),

including headache, which may be caused by SLE, but also recognizes many other causes that may overlap with the diagnosis of SLE.

2.2. Musculoskeletal manifestations

Musculoskeletal manifestations, firstly described by Kaposi, in 1872, can affect joints, but also muscles, tendons, and bursae. They are the first presenting symptom in up to 50% of patients and can affect up to 95% during the clinical course (20).
The primary clinical symptom resulting from this involvement is joint pain, but, nevertheless, patients may also experience morning stiffness, joint swelling, myalgias, and muscular weakness.

2.2.1. Joints

SLE can affect both major and minor joints, encompassing proximal inter-phalangeal (PIP) joints, metacarpal-phalangeal (MCP) joints, wrists, ankles, elbows, and shoulders. Patients may experience joint pain with or without morning stiffness (inflammatory arthralgias) and joint swelling. Symmetrical polyarthritis involving PIP, MCP and wrists is commonly observed and, in addition, significant diffuse puffiness of the hands can also occur.

Joint involvement include:

- arthralgia;
- non-deforming non-erosive arthritis (NDNE);
- Jaccoud's syndrome.
- erosive arthritis and rhupus
- sacroileitis and entheseal involvement

Arthralgias

In joints the most common involvement are arthralgias, which affect most patients, about 90-100%. As previously mentioned, although they are not life-threatening for patients, they are still a source of disturbance in daily life, so much so that, along

with arthritis, they are among the manifestations that mostly worsen the patient's quality of life (24,25).

Non-deforming non-erosive arthritis (NDNE)

Another common joint manifestation is non-erosive arthritis, present in 40-80% of patients (26). The SLICC group has defined arthritis as either synovitis involving two or more joints characterized by swelling or effusion or tenderness in two or more joints and at least 30 min of morning stiffness (27). It presents as symmetrical polyarthritis affecting small joints, has a slow progression and a fluctuating (relapse-remitting) course, even in poorly treated disease. The diagnosis and precise evaluation of arthritis in SLE can be a challenge both in clinical practice and in clinical trials: some of the most used techniques are ultrasounds (US) and MRI, which can detect effusions as well as synovial and/or tenosynovial hypertrophy. Power and color Doppler US, including newer microvascular techniques and contrast-enhanced MRI, reveal active synovial inflammation. Compared with rheumatoid arthritis (RA), the swelling (from effusion, synovial hyperplasia and vascularity) in SLE arthritis is relatively mild. There is also widespread vasculitis affecting capillaries, arterioles, and venules, villous hypertrophy of the synovium covered by fibrin, along with low-grade lymphoplasmacytic inflammatory cell infiltrates in the subintima (28).

Other techniques are being developed to have precise framing, including the use of frequency domain optical imaging (FDOI), which has shown a significant difference in signal between patients with SLE and healthy volunteers. This technique shows potential to give an objective, nonuser-dependent assessment especially in proximal interphalangeal joints (29).

Jaccoud's syndrome (JA)

It’s characterized by joint misalignment that cannot be attributed, however, to joint erosion (unlike RA cases), but rather to periarticular tissue damage: for this reason, extension of the fingers leads to slight realignment of the joints.

This condition appears in the course of the disease and not at onset: it's the effect of persistence of fluctuating subclinical arthritis, which can progressively compromise the joint holding apparatus, causing joint deformities, even in the absence of erosion of the joint itself. Patients with JA usually have a long history of SLE, with more severe disease features than those with NDNE arthritis (30).

In the advanced stages of JA, 10 to 15 years after the onset of the disease process, adhesions develop within the joint apparatus, making joint realignment impossible and, consequently, making the deformity irreversible.

The appearance of this manifestation is reported in 3.5–43% of patients with SLE (30–33).

Generally involving hand's joints, Jaccoud-like arthropathy has been observed also in the neck, shoulders, knees, and feet. Neck involvement is characterized by atlantoaxial subluxation, which can be visualized via MRI. Reversible subluxation is also noted in knees and shoulders. Common foot deformities include hallux valgus, metatarsophalangeal subluxation, hammertoes, and forefoot widening, typically without erosions or bone cysts .

Erosive arthritis and rhupus

Erosive arthritis, on the other hand, is rarer but can still appear in some situations, about 7-8% of cases. It is characterized by deforming, irreversible and erosive arthritis. However, with the advent of sensitive imaging techniques, such as high-resolution ultrasound with power doppler or MRI, it has been shown that up to 40% of SLE patients with joint involvement can develop erosive damage. Therefore, the erosive phenotype can be found even in patients who have no overlap with rheumatoid arthritis (34).

Regarding rhupus, its exact definition is still debated (35). Most of the authors suggest that it is a clinical condition in which co-exist in the same patient signs and symptoms of SLE and rheumatoid arthritis (36,37). This hypothesis is supported by the presence in the same patient of different autoantibodies specific for SLE, such as anti-dsDNA and anti-Sm, and rheumatoid arthritis, such as ACPA (32,37). In this cases there is also a lower prevalence of SLE extra-articular manifestations compared

with patients with NDNE arthritis and JA (38). By contrast, other authors claim that this syndrome should be regarded as an erosive subset of lupus arthropathy (39). However, the coexistence of this condition with SLE is very unusual, estimated to be about 2% (35).

Sacroileitis and entheseal involvement

Sacroileitis, although rare, has been reported by some authors, in up to approximately 30% of patients (40). Similarly, entheseal involvement has also been recently reported in SLE patients using ultrasound, while it remains often unrecognized from a clinical point of view (41).

2.2.2. Muscles

Muscle involvement comprises mainly myositis, a manifestation that is however generally rare in SLE, as its incidence in these patients is about 1.05 cases per 1000 person-years.

Despite its low incidence, however, it is a potentially debilitating manifestation, and factors associated with the development of myositis in SLE are non-Caucasian ethnicity, arthritis, Raynaud's phenomenon, and anti-Sm antibodies (42).

African American descendent and patients with childhood-onset SLE have a significantly higher prevalence of inflammatory myositis. In most cases, inflammatory myositis presents at the onset of the disease (43).

Generalized myalgia and muscle tenderness, most prominent in proximal muscles such as deltoids and quadriceps, are common during disease onset or flares, observed in 40–80% of cases (44). Inflammatory myopathy, typically involving proximal muscles, is less frequently reported, occurring in 2.6–11% of patients and can develop at any point during the disease course (45,46). The overlap between SLE and idiopathic inflammatory myopathies, such as dermatomyositis or polymyositis, is rare (35). Diagnostic procedures including myositis-specific antibodies, electromyography, muscle MRI, and muscle biopsy should be considered when muscle inflammation is suspected.

Differential diagnosis of proximal muscle weakness can be challenging in clinical practice as it may not only stem from concurrent inflammatory myositis but also from drug-induced myopathy, mainly from glucocorticoids and antimalarials. Specific features of drug-induced myopathy are lacking. However, certain characteristics can aid in diagnosis. These include worsening of proximal muscle weakness, primarily in lower extremities, occurring when creatine-kinase levels are improving or normal, and no signs of active myositis on electromyography or MRI are evident. In cases of muscular toxicity due to glucocorticoids, additional muscular signs such as weight gain or even Cushing's features may support the diagnosis (47,48).

2.2.3. Tendons and bursae

Tendons and bursae, on the other hand, can be affected by tendinitis, tenosynovitis, bursitis, and, rarely, tendon ruptures. Recent studies have highlighted that many patients with SLE and musculoskeletal symptoms, despite not having clinically detectable synovitis, may exhibit detectable joint and tendon inflammation through ultrasound: in fact, in an ultrasound study, tenosynovitis of the hand was observed in 44% of patients (17). This inflammation, although not sufficient to qualify the patient for clinical trials or to score highly on disease activity assessment tools, can still significantly contribute to painful symptoms and disability (20).

Tendon synovitis can lead to carpal tunnel syndrome, which may be the initial presentation of SLE. Typically, it manifests bilaterally in such cases. Carpal tunnel syndrome is identified in about 11% of cases.

Tendon rupture in SLE predominantly affect weight-bearing areas, with commonly affected tendons including the Achilles, patellar, infrapatellar, and the hand's ones. They are associated with factors such as trauma, male gender, prolonged glucocorticoid use, intra-articular injections, diabetes, Jaccoud's deformities, and long disease duration (17). Interestingly, most patients were in clinical remission at the time of rupture. Diagnosis is typically confirmed via MRI, with tendon biopsy rarely deemed necessary.

2.2.4. Soft tissues

Soft tissue and periarticular calcinosis are commonly observed in systemic sclerosis, juvenile dermatomyositis, and overlap syndromes, but in some cases they have also been reported in patients with SLE (49). Calcinosis has been associated with factors such as trauma, pressure points, TNF-α-308A allele, and subcutaneous edema (50). Lesions typically contain calcium phosphate, cytokines (IL-6, IL-1, TNF-α), macrophages, osteocalcin, and bone matrix proteins. Calcifications can be easily identified through clinical examination and simple X-ray imaging.

2.2.5. Bones

Avascular bone necrosis (AVN) occurs in approximately 10% of SLE patients (51–53), with a higher prevalence of asymptomatic cases, about 29% (51). AVN can cause joint pain and disability, typically in larger joints, such as the hip and knee (17). The femoral head, tibial plateau, and humeral head are the most commonly affected areas by AVN, although multiple sites can be involved. Most instances are linked to glucocorticoid use, particularly at high dosages over the long term (54). Other potential factors include Raynaud's phenomenon, small-vessel vasculitis, fat emboli, and antiphospholipid syndrome (51). MRI is the preferred diagnostic modality due to its sensitivity, instead computed tomography and bone X-rays are less sensible as they may not detect early-stage AVN. In SLE, consideration of AVN diagnosis is warranted in patients experiencing joint pain in one or a few joints without evidence of joint inflammation and disease activity in other organs, particularly if they are receiving high-dose glucocorticoid therapy.

2.3. Other clinical manifestations

2.3.1. Hematological alterations

Anemia

Anemia is prevalent in SLE, affecting over 50% of patients throughout the disease course. It is defined as a hemoglobin level below 12 g/dl in women and 13.5 g/dl in men. In SLE, anemia can be either immune or non-immune mediated.

Anemia of chronic disease (ACD) is the most common type in SLE, accounting for approximately one-third of cases. It typically manifests as normocytic and normochromic anemia, often ranging from mild (hemoglobin 9–10 g/dl) to moderate (hemoglobin below 9 g/dl). In ACD, the reticulocyte count, serum iron concentration, and transferrin saturation are low. However, transferrin levels are normal, and ferritin levels may be elevated due to retention in the reticuloendothelial system.

Also iron deficiency anemia (IDA) is common among SLE patients, impacting approximately one-third of cases. It often arises from chronic gastrointestinal bleeding, often secondary to medication use, particularly NSAIDs and glucocorticoids.

Another type of anemia that may be present in SLE, but more rarely, is autoimmune hemolytic anemia (AIHA), that occurs when anti-red blood cell antibodies attack and damage erythrocytes, either through a complement-dependent or independent mechanism. AIHA can manifest as the initial symptom of SLE and may precede an SLE diagnosis by several years (55).

Leukopenia

In most cases this manifestation involves lymphocytes or neutrophils.

About 75% of SLE patients with active disease can present lymphopenia. Autoantibodies targeting lymphocytes appear to be involved in the pathogenesis, as titers of IgG antibodies against to lymphocytes (but not IgM) have been found to inversely correlate with lymphocyte and complement levels.

Another manifestation is neutropenia, that can be one of the contributing factors towards the infectious comorbidity in SLE (56). Neutropenia in autoimmune diseases can be classified as either primary or secondary. Anti-neutrophil antibodies can trigger neutropenia, but it may also arise from peripheral sequestration, bone marrow inhibition, or apoptosis. The exact target of these autoantibodies is unknown, and it's common for these cases to present with thrombocytopenia or hemolytic anemia concurrently (55).

Thrombocytopenia

Thrombocytopenia is a common manifestation in SLE patients, although it is often mild. Three main mechanisms are associated with thrombocytopenia: impaired production in the bone marrow, sequestration in the spleen, and accelerated destruction. The most prevalent mechanism involves immune-mediated platelet destruction in the peripheral circulation by antiplatelet antibodies (55).

2.3.2. Skin alterations

While about 20% of SLE patients have skin lesions as an initial presentation, 70-80% of patients will develop them during the course of disease (21). They are divided into specific and non-specific forms (57). Specific ones include:

- Acute cutaneous lupus: it can presents as a butterfly-shaped erythema (localized form) on the face, involving the bridge of the nose, the cheeks, and occasionally the eyelids, typically sparing the glabella and nasolabial folds. It may appear as more infiltrated erythema with scaling or simply as edema of the skin. Often, the butterfly erythema is accompanied by mucositis affecting the hard palate, which is also a sign of active disease;
- Subacute cutaneous lupus, divided in polycyclic annular and papulosquamous. This form primarily affects sun-exposed areas such as the face, the anterior, posterior, and upper regions of the chest, and the extensor surfaces of the limbs. It is often resistant to therapies and is frequently associated with smoking;
- Chronic cutaneous lupus, that can be discoid, verrucosum, profundus or tumidus. It is a highly infiltrative condition, with a significant scarring component, that often leaves behind significant and irreversible sequelae.

Non-specific forms, on the other hand, include non-scarring diffuse hair loss (unruly lupus hair), Raynaud's phenomenon, *livedo reticularis*, nailfold telangiectases, photosensitivity, bullous systemic lupus erythematosus, mouth ulcers and cheilitis, vasculitis, urticaria (21,57,58).

2.3.3. Kidney manifestations

Although deposits of immunoglobulin are commonly found in the glomeruli of SLE patients, only about half of them exhibit clinical nephritis. Asymptomatic patients often display hematuria and proteinuria in urine analysis. Renal failure and sepsis are some of the leading causes of mortality in SLE patients, with the kidney being the most commonly affected organ. While only around 50% of SLE patients develop clinically evident renal disease, biopsy studies indicate some degree of renal involvement in nearly all patients. Glomerular disease typically emerges within the first few years of SLE onset and is often asymptomatic. Acute or chronic renal failure may lead to symptoms associated with uremia and fluid overload. Acute nephritic disease may present with hypertension and hematuria, while nephrotic syndrome can cause edema, weight gain, or hyperlipidemia.

Lupus nephritis (LN), a common and potentially severe manifestation of SLE, occurs in more than half of SLE patients and is primarily characterized by the deposition of immune complexes.

The classification system of LN relies on renal biopsy, based on glomerular morphologic changes observed through microscopy, immune deposits detected via immunofluorescence, and electron microscopy. It should be performed in any patient suspected of renal involvement whenever feasible. However, renal biopsy is not routinely recommended for patients with normal creatinine values and normal urine analysis (21)

- Class 1: Minimal mesangial lupus nephritis. Glomeruli appear normal on light microscopy, with immune complex deposits seen in the mesangial space on immunofluorescence.
- Class 2: Proliferative mesangial lupus nephritis. Mesangial proliferation is evident on light microscopy, accompanied by immune complex deposits in the mesangial space on immunofluorescence.
- Class 3: Focal lupus nephritis. Immunofluorescence may reveal immune complex deposits in the mesangial, subendothelial, and/or subepithelial space.

- Class 4: Diffuse lupus nephritis. Immune complex deposits may occur in the mesangial, subendothelial, and/or subepithelial space. Lesions may be segmental, involving less than 50% of glomeruli, or global, involving more than 50%.
- Class 5: Membranous lupus nephritis. Immune complex deposits are found in the mesangial and subepithelial space. Thickening of capillary loops occurs due to subepithelial immune complex deposits. Nephrotic range proteinuria is characteristic. Class 5 may also include class 3 and 4 pathology.
- Class 6: Advanced sclerosing lupus nephritis. Most glomeruli are sclerosed, with more than 90% showing scarring. Immune complex deposits are not visualized on immunofluorescence.

Although lupus nephritis does entail associated morbidity and mortality, the prognosis of LN depends significantly on the specific WHO histopathology class it falls into. Class 1 and class 2 generally have a favorable long-term prognosis. By contrast, class 3 carries a poor prognosis, while class 4 has the poorest prognosis (59). Class 5 present also certain complications such as thromboembolism, and class 6 has a poor outcome as it is expression of irreversible injury (60). Additionally, the timing of therapy initiation influences the prognosis. Starting therapy early in the disease course typically leads to better disease outcomes (59).

2.3.4. **Neuropsychiatric manifestations**

Neuropsychiatric manifestations occur in the early stages of the disease, representing 39%-50% of SLE patients. NPSLE can present as either focal or diffuse, with clinical manifestations varying from subtle cognitive dysfunction to more severe conditions such as acute confusional states, seizure disorders, and psychosis. Headaches, anxiety, mood swings, and cognitive disorders are among the most common neuropsychiatric symptoms of SLE. Cerebrovascular disease, neuropathies, acute confusional states, and seizure disorders are the predominant serious manifestations associated with NPSLE (23).

Some symptoms, such as anxiety and depression, could be due to both the disease itself and possibly a consequence of the diagnosis of the disease, leading to greater difficulty in determining how many cases are actually manifestations of SLE.

Anxiety levels tend to increase over time in SLE patients, but these changes are not directly tied to disease activity. Also, the overall effectiveness of neuropsychiatric therapy in managing these symptoms is limited (61).

2.3.5. **Cardiac manifestations**

Although pericarditis is the most common heart manifestation in SLE, valvular disease and occasionally myocarditis may also be observed. In cases of myocarditis, prompt and aggressive treatment is crucial to prevent chronic complications such as congestive heart failure. As the disease progresses, accelerated atherosclerosis emerges as one of the most significant comorbidities of SLE, with cardiovascular events being a leading cause of death at relatively young ages. It is therefore essential to stratify patients at risk and manage traditional risk factors rigorously (62).

Another possible manifestation is Libman-Sacks (LS) endocarditis, also referred to as nonbacterial thrombotic endocarditis, that occurs in 6 to 11% of SLE patients. There is a notable correlation between the presence of LS endocarditis and both the duration and severity of SLE. This condition ranges from very small microscopic particles to large vegetations on previously normal heart valves, most commonly affecting the aortic and mitral valves. LS endocarditis is characterized by sterile vegetations on the cardiac valves, without any signs of infection. Its initial development is thought to result from endothelial injury in a hypercoagulable state (63).

2.3.6. **Pulmonary manifestations**

Pulmonary involvement is common in SLE, affecting 50 to 70% of patients, and may be the initial presenting feature in 4 to 5% of cases. Within 10 years of diagnosis, 12% of patients will have some form of permanent lung damage. SLE can affect all anatomical structures of the lungs, pleura, and pulmonary vasculature. Pulmonary complications are diverse and include pleural disease, interstitial lung disease (ILD), vasculitis, pulmonary embolism, pulmonary hypertension, large airway disease, shrinking lung syndrome, and infections. These conditions can range from mostly

asymptomatic, such as mild pleural effusion or obstructive airway disease, to life-threatening, such as acute lupus pneumonitis or diffuse alveolar hemorrhage.

While ILD and pulmonary hypertension are also common in other autoimmune rheumatic diseases like systemic sclerosis, they tend to be milder in SLE and have a comparatively favorable prognosis (64). Pleuritis is a frequent feature, seen in about 30% of patients, whereas interstitial lung disease and pulmonary embolism are less common. Other complications, such as lupus pneumonitis, diffuse alveolar hemorrhage, shrinking lung syndrome, and pulmonary arterial hypertension, are rare (62).

2.3.7. Seroimmunologic alterations

SLE is characterized by a wide range of immunological alterations, detected through laboratory methods that identify the production of autoantibodies targeting various cellular structures of the body. Over 100 autoantibodies have been described in the context of SLE. The most well known and best characterized are:

- anti-nuclear antibodies (ANA): directed against antigens present in cell nuclei, ANAs are present in almost all patients with SLE, although they can also occur in other conditions, making them nonspecific for SLE;
- anti-double-stranded DNA antibodies (anti-dsDNA): specific to SLE, they target double-stranded DNA and may correlate with renal involvement and disease activity;
- anti-Smith antibodies (anti-Sm): targeting the Smith nuclear antigen, they are specific to SLE but do not appear to correlate with disease activity;
- anti-ribonucleoprotein antibodies (anti-RNP): directed against ribonucleoproteins, they are not specific to SLE and can be found in other autoimmune diseases such as systemic sclerosis and mixed connective tissue disease;
- anti-Ro/SSA and anti-La/SSB antibodies: their positivity is associated with an increased risk of symptoms such as photosensitivity, cutaneous lesions, and mucosal dryness, but they are not specific to SLE;

- antiphospholipid antibodies: this heterogeneous group of autoantibodies can cause arterial and venous thrombotic complications and may be positive in 30-40% of patients with SLE, not necessarily associated with APS.
- antibodies against ribosomal proteins (anti-RibP) are a serological marker present in 13-20% of cases (65) and are associated with NPSLE and lupus nephritis.
- autoantibodies directed against blood cell components: these antibodies can cause hemolytic anemia and thrombocytopenia in SLE, manifesting positivity in the direct Coombs test and being associated with various forms of thrombocytopenia (66);

In addition to autoantibodies, other characteristic laboratory parameters of SLE are:

- decrease in complement fractions C3 and C4, which plays a fundamental role both in the diagnosis of the disease and in the clinical monitoring of its activity (66,67). Complement levels, along with anti-dsDNA antibodies positivity, is included in most indices used to assess disease activity;
- hypergammaglobulinemia, which manifests as an increase in total circulating antibodies in the blood, due to stimulation of the immune response mediated by B cells;
- increase in erythrocyte sedimentation rate (ESR), due to hypergammaglobulinemia. Although it does not necessarily indicate disease activity, as it can be persistently elevated over time (66).

3. Diagnosis

The wide heterogeneity of disease manifestations, combined with the variability in presentation and fluctuating symptoms, makes diagnosis challenging. This is primarily based on a combination of clinical assessment and serological analysis and exclusion of conditions that mimic SLE. Early diagnosis of SLE is crucial for timely therapeutic intervention, which can increase the likelihood of disease remission and improve patient prognosis (68). In fact, there is typically a delay in diagnosis up to 5 years, during which patients mainly consult their primary care physician, with

unspecific symptoms like arthritis, rashes, fatigue, serositis, and fever (69). Medical figures frequently involved in SLE diagnosis are internist and rheumatologist, the latter being the ones who in the majority of cases make the diagnosis (80% of cases) (70).

The most common presenting symptoms at onset are joint-related (68% of patients), particularly arthritis and arthralgia, and skin-related, with rashes (in 23-40% of patients) (69,70). Regarding manifestations that most frequently lead to a first hospital admission, neuropsychiatric symptoms are prominent (25% of admissions), especially secondary to cerebrovascular events (70).

3.1. Laboratory abnormalities

Antinuclear antibodies (ANA)

ANAs are a group of autoantibodies that bind to different nuclear and cytoplasmic antigens. They are sensitive but unspecific biomarkers for the evaluation of SLE, but also for other ANA-associated rheumatic diseases.

For ANA assay, there are three tests mainly: enzyme immunoanalysis, multiplex immunoanalysis, and indirect immunofluorescence on HEp-2 cells. The latter is the gold standard.

As a screening test, however, ANAs have limited specificity (2), as up to 25% of healthy patients may test positive. ANA positivity is more frequent in female sex and in certain ethnic and racial groups, such as African Americans. There are differences then between healthy ANA-positive and diseased individuals: healthy ANA-positive individuals often have antibodies directed toward the DFS70 antigen, whereas anti-DFS70 antibodies are really very rare in patients with suspected ANA-associated rheumatic disease (69).

ANA, detected by indirect immunofluorescence on HEp-2 cells, is a key immunologic biomarker in serum to classify a patient with SLE and assess eligibility for this disease. An ANA IIF titer of 1:80 or higher is a mandatory entry criterion

according to the EULAR/ACR-2019 criteria. If positive, additional testing for antigen-specific ANA such as dsDNA, SSA, SSB, Sm, and RNP should be performed. While not unique to SLE, ANA is highly characteristic and can be used for classification, diagnosis, prognosis, and staging. It has high sensitivity (90%-95%) but low specificity (5%-20%), being able to occur even in healthy controls, especially the elderly ones.

Variability in ANA IIF testing, effects of nuclear antigens on HEp-2 cells and variations in laboratory procedures can cause inconsistency in results. Although immunofluorescence on HEp-2 cells is widely used, ELISA is another option, with different sensitivity and specificity. Both methods have advantages and disadvantages, so anyone conducting ANA testing should know the specific assay used, including its sensitivity and specificity (71).

Anti-Nucleosome Antibodies (ANuA)

The presence of antinucleosome antibodies (ANuA) in SLE varies significantly, with a prevalence of 50% to 100%. These ANuA, when combined with clinical findings and other laboratory tests, can be crucial for the diagnosis of both SLE and drug-induced lupus. Their presence is closely related to glomerulonephritis and disease activity in SLE patients. The test for ANuAs shows a sensitivity of 61% and a specificity of 94%. ANuAs carry an overall positive likelihood ratio of 13.81, while the negative likelihood ratio is 0.38: in practice, this means that an individual with positive ANuAs is 41 times more likely to have SLE than an individual with negative ANuAs (71).

Anti-dsDNA antibodies

Anti-dsDNA antibodies are an important laboratory parameter for diagnosis, monitoring disease activity and classification of SLE (72). They also may predict the development of LN. Their presence over time may vary with SLE activity: they may disappear during treatment and reappear during a relapse, especially when there is active nephritis. However, despite their high specificity (96%), they have low diagnostic sensitivity (52-70%) because of their transient appearance. The most

common tests to detect these antibodies are indirect immunofluorescence using Crithidia luciliae as substrate and ELISA (71), but there are other methods such as fluoroenzyme immunoassay (FEIA), chemiluminisence immunoassay (CIA) and multiplexed bead-based assays and Farr-RIA (72).

Anti-Sm antibodies

Anti-Sm antibodies, more commonly found in individuals of African descent (73), are included in the classification criteria for SLE and are a distinctive biomarker of the disease. Their presence is highly specific for the disease and is not found in other rheumatic diseases or in healthy individuals. However, they have a low diagnostic sensitivity, around 5-30% (71,73). Anti-Sm antibodies are associated with LN, and some author fount that they are associated with early adverse outcomes in LN (71). Assays used to identify anti-Sm antibodies include counterimmunoelectrophoresis (CIE), immunoblotting, and ELISA. These assays utilize purified or recombinant proteins, as well as synthetic peptides (73).

Anti-C1q antibodies

Hereditary C1q deficiency, although rare, is closely related to SLE, being one of its strongest monogenic causal factors. In contrast, an acquired deficiency of C1q by autoantibodies is frequent among patients with SLE (74). Anti-C1q antibodies cause a decrease in C1q, which could contribute to the pathogenetic process of LN by inhibiting the removal of immune and apoptotic complexes or by depositing them in the glomerular basement membrane. High levels of anti-C1q antibodies are associated with the prediction of renal relapse in LN, with a sensitivity of 81% to 97% and specificity of 71% to 95%. However, despite their potential as noninvasive biomarkers, anti-C1q antibodies are not included in the classification criteria or clinical management of SLE because of the lack of a standardized laboratory test. Importantly, these antibodies can also be present in other autoimmune diseases and even in healthy individuals (71).

Complement levels

Immune complexes can activate complements. Serum levels of C3 and C4 are used to assess the presence of biologically active immune complexes and monitor disease activity (67). Low levels of C3 or C4 are considered immune biomarkers in the SLICC-2012 SLE classification criteria (75). In the EULAR/ACR-2019 classification criteria, low levels of both C3 and C4 are weighted higher than low levels of both C3 and C4 individually (76). The presence of low levels of both C3 and C4 facilitates the diagnosis of SLE, with a specificity of 94.3% when combined with a positive ANA test and 97.6% when both levels are low together with a positive ANA. Decreased levels of C3 and C4 may precede clinically evident flare-ups and correlate positively with disease activity, especially in cases complicated by renal or hematologic flare-ups. However, the low specificity of C3 and C4 in the diagnosis of SLE may limit their reliability as biomarkers, especially when used individually (71).

Erythrocyte sedimentation rate and C-reactive protein

In clinical practice, elevation of erythrocyte sedimentation rate (ESR) values, along with low C-reactive protein (CRP) levels, are a relevant sign of inflammation in SLE, proving useful in monitoring disease activity. Specifically, ESR and CRP levels are observed to increase proportionally and simultaneously in a subgroup of SLE patients with manifestations such as serositis and/or arthritis. ESR values above 25 mm/h are particularly significant and are strongly associated with disease activity in the context of SLE (71). C-reactive protein (CRP), although is a good marker for inflammation in SLE, is a better marker for infections than for SLE activity, where there is only a limited association (77).

Biomarkers in Lupus Nephritis (LN)

Renal biopsy is critical for diagnosing, classifying, and prognosticating lupus nephritis (LN), but its wide application is limited by significant disadvantages. It is inherently invasive, carries bleeding risks, and has the potential for sampling errors. In addition, percutaneous fine-needle biopsy may have a risk of up to 10-20%

misclassification due to the possibility of not reaching the pathologic site of the kidney or errors in analysis (78). Serial biopsies are difficult because of the invasive nature and potential complications. These factors have led to controversy about the absolute necessity of routine renal biopsy for the diagnosis of LN (71).

Urinary biomarkers

Urine represents an easily obtainable and noninvasive biological sample that directly reflects pathological changes in the kidneys. Consequently, urinary biomarkers seem to be more promising than serum biomarkers. Proteinuria, protein/creatinine ratio in spot urine, and the amount of protein in urine collected over 24 hours are conventional urinary biomarkers for LN. However, the protein/creatinine ratio in spot urine is not always a reliable indicator of 24-hour proteinuria. Therefore, new urinary biomarkers have been explored. Several candidate protein biomarkers in urine, including chemokines, cytokines, growth factors, and adhesion molecules, have been evaluated as potential biomarkers for SLE, although only some of them have been independently validated (71). Some important issues regarding urinary biomarkers include their daily variability, potential interference of urinary infections, and lack of specificity for a specific disease.

Biomarkers for skin lesions

Skin lesions are common manifestations of SLE, and only a few biomarkers are associated with them. The ratio of aromatic hydrocarbon receptor in Th17 cells to those in T-reg cells correlates with SLE activity, suggesting a possible role as an independent risk factor for skin lesions in SLE. In addition, anti-SSA antibodies have been identified as related to subacute cutaneous lupus. Increased expression of vestigial protein family 3 in the skin is associated with a pro-inflammatory gene expression program that may contribute to cutaneous lupus (71).

Biomarkers in neuropsychiatric SLE

NPSLE represents a serious complication of SLE involving both the central and peripheral nervous systems. Biomarkers for NPSLE are obtained from serum or cerebrospinal fluid (CSF). Antiphospholipid antibodies, such as lupus anticoagulant, anticardiolipin, and anti-β2-glycoprotein I antibodies, detected in serum and/or CSF, are associated with the manifestations of NPSLE and are used to make therapeutic decisions.

Antibodies against ribosomal proteins (anti-RibP), described in the 1980s, are a serological marker present in 13-20% of cases (65) and are highly specific for the diagnosis of SLE and are associated with NPSLE, although the variability of anti-RibP test results is a challenge for their clinical use. In addition, elevated levels of immunological biomarkers in CSF, such as interleukin-6, interleukin-8, interleukin-10, TNF-α, IFN-γ, monocyte chemotactic protein-1 and IP-10, have been associated with NPSLE (71).

Biomarkers for cardiovascular involvement

Cardiovascular disease (CVD) is a major complication of SLE and a significant factor in morbidity and mortality. Biomarkers such as monocyte/high-density lipoprotein cholesterol ratio and low-density granulocyte/high-density lipoprotein cholesterol ratio are elevated in SLE patients with atherosclerosis, but not in patients without CVD, and thus can be used to identify the risk of CVD in patients with SLE, even in the early stages of the disease. In addition, elevated levels of dysfunctional high-density lipoprotein cholesterol are indicative of accelerated atherosclerosis in SLE and may represent potential therapeutic biomarkers for SLE patients with CVD. High-sensitivity serum cardiac troponin T was the first independently identified biomarker associated with incident cardiovascular events in patients with SLE. Antibodies to paraoxonase 1 and high-density lipoprotein in serum are potential early biomarkers of endothelial damage and early atherosclerosis in SLE, and thus may represent useful therapeutic targets to prevent CVD in patients with SLE. In addition, serum levels of IgG-anticardiolipin and E-selectin antibodies are associated with CVD in SLE and correlated with disease activity (71).

3.2. Differential diagnosis

Differential diagnosis is a crucial aspect in SLE, as many other autoimmune diseases have both clinical similarities and autoantibody-like positivities. There are "lupus mimickers," similar to SLE from both a laboratory and clinical perspective, who may present as a lupus-like condition (79).

3.2.1. Infections

Among the main conditions that enter into differential diagnosis with SLE there are viral infections. The most frequent pathogen is Parvovirus B19, which strikes mainly at a young age. Skin involvement is prevalent, typically manifesting as a butterfly rash on the face, often accompanied by photosensitivity. Arthralgia and arthritis are also common, present in 75% of cases. Constitutional, flu-like symptoms such as fever, fatigue, and myalgia may be present. Regarding laboratory tests cytopenia is frequent, with leukopenia and non-hemolytic anemia, but hypocomplementemia may also occur, while active urinary sediment may be present in one third of cases. Regarding the autoantibody profile, ANA positivity has been detected in up to 70% of cases, along with anti-dsDNA, ENA, aCL and RF.

Parasites, on the other hand, may enter the differential diagnosis because of frequent constitutional involvement, arthralgias with arthritis and hepatomegaly.
Fungi, instead, may be associated with cutaneous involvement, mainly maculopapular rash. Discoid lupus-like lesions have also been found.
Bacteria are associated with constitutional symptoms and arthralgias, indices of acute inflammation and possible autoantibody positivity, especially ANA (79).

3.2.2. Neoplasms

Malignant neoplasms can enter differential diagnosis as they may present with constitutional symptoms in about half of the cases, as well as anemia, almost always, and leukopenia, in 50% of patients. Some are also ANA positive.

For benign neoplasms, instead, we consider Kikuchi disease and Castleman's disease. Kikuchi-Fujimoto disease is a benign condition that tends to resolve on its own, characterized by subacute necrotizing cervical lymphadenopathy, typically accompanied by mild fever and night sweats (80). Less common symptoms include weight loss, nausea, vomiting, and sore throat. Extra-nodal manifestations include mucocutaneous and articular involvement, which could be mistaken also for SLE. It is frequently associated with ANAs, but less commonly also anti-dsDNA and ENAs.

Castleman's disease is a rare condition characterized by non-cancerous growth of lymph nodes and related tissues. In affected patients, cells in the lymphatic tissue start to proliferate, leading to the development of enlarged lymph nodes. Other manifestations include renal involvement, arthralgia, serositis, and cutaneous manifestations. From a laboratory perspective, leukopenia and thrombocytopenia are commonly found, but also ANAs and ENAs (79).

3.3. Classification criteria

SLE classification criteria, despite their high specificity, have a low sensitivity, making them poorly suited for the diagnosis of the disease, which may be at risk of not being detected in the early stages.

According to the EULAR/ACR classification (81), there is an entry criterion, which is that ANAs must be present at a titer higher than or equal to 1:80. Below this titer, the principal diagnostic hypothesis is an infection and the hypothesis of SLE can be directly ruled out. Accordingly, 7 clinical criteria and 3 serologic criteria are considered, which include several variables, each with different weights. For a person to be classified as SLE patient in a study, he or she must achieve a score greater than or equal to 10, with least one clinical and one laboratory criterion (81).

Tab. I: EULAR/ACR Clinical Domains and Criteria for SLE (81)

Domain	**Criteria considered**	**Points**
Constitutional	Fever	2
Hematologic	Leukopenia	3
	Thrombocytopenia	4
	Autoimmune hemolysis	4
Neuropsychiatric	Delirium	2
	Psychosis	3
	Seizure	5
Mucocutaneous	Non-scarring alopecia	2
	Oral ulcers	2
	Subacute cutaneous **or** discoid lupus	4
	Acute cutaneous lupus	6
Serosal	Pleural or pericardial effusion	5
	Acute pericarditis	6
Musculoskeletal	Joint involvement	6
Renal	Proteinuria > 0.5 g/24 h	4
	Renal biopsy class II or V lupus nephritis	8
	Renal biopsy class III or IV lupus nephritis	10

Tab. II: EULAR/ACR Immunologic Domains and Criteria for SLE (81)

Domain	**Criteria considered**	**Points**
Antiphospholipid antibodies	Anticardiolipin antibodies *or* Anti-β2GP1 antibodies *or* Lupus anticoagulant	2
Complement proteins	Low C3 *or* low C4 Low C3 *and* low C4	3 4
SLE-specific antibodies	Anti-dsDNA antibody *or* Anti-Smith antibody	6

4. Prognosis

SLE mortality depends on several factors, both epidemiological, sociodemographic, genetic, and clinical. Lupus nephritis and NPSLE are the main typical manifestations of the disease associated with mortality, while bacterial infections and cardiovascular pathology are other important causes of death in these patients, so much so that, with regard to cardiovascular pathology in particular, mortality is almost twice as high as in comparisons among people of the same age and sex.

Some other features may then worsen the prognosis, such as time from onset to diagnosis greater than one year, renal involvement, high SLEDAI, severe organ involvement In contrast, steroids, immunosuppressants, plasmapheresis, some biologic drugs and vaccinations have shown efficacy in reducing mortality rates (82).

There is increased risk (2.6-fold) in the all-cause mortality rate among patients with SLE compared with the general population: in particular, the risk of all-cause mortality is higher among younger patients, with a 5.5-fold increased risk of death among patients younger than 44 years old. Among the most frequent causes of death

in this age group there are cardiovascular disease and cancer, while infectious diseases are less prevalent (15).

Mortality in SLE exhibits a bimodal pattern. Patients who die early in the course of the disease often have active lupus, receive high doses of steroids, and have a significant incidence of infections. Conversely, those who die later typically have inactive lupus, have been on long-term steroid therapy, and face a notable incidence of myocardial infarction due to atherosclerotic heart disease (83).

Also, damage accrual is associated with mortality rates: a study found that over half of the patients accrued organ damage linearly within the first decade, then stabilized. Severe damage was in a quarter of the patients.
Musculoskeletal damage was most common, followed by cardiovascular, neuropsychiatric, and peripheral vascular damage. Persistent disease activity (measured by WAS scores, Weighted average SLEDAI scores) was the main risk factor for damage accrual. Case fatalities increased in the second and third decades of the disease, with risk factors for death including high WAS scores and age over 40 at disease onset.

Baseline SLEDAI scores > 10, CNS involvement, and leukocytopenia were associated with damage development, while no association was found with renal disease or anti-dsDNA antibody. Over time, the overall disease activity was the overriding predictor of severe damage accrual, highlighting the importance of achieving early clinical quiescence.

Higher SDI scores (SLICC/ACR Damage Index) were reported in non-surviving patients, but SDI was not a significant predictor of death after adjusting for WAS scores and age. The deleterious effect of damage is mediated through aging and disease activity affecting organ function reserve capacity (80) .

Musculoskeletal involvement

This manifestations, although not life-threatening for the patient, can still be a source of severe pain and motor difficulties (24,25), which also impact daily life, from increased sedentary living to decreased autonomy and even decreased social life.

In addition, another aspect that the disease involves is the impact on employment: a Canadian study conducted across several centers found significant associations between work disability and socio-demographic factors, co-morbidities such as fibromyalgia and fatigue, and disease-related factors. The employment rate among patients was only 47%, while 34% had work disability due to the disease. Among patients with musculoskeletal manifestations, 34% stopped working after a median of 4 years. The risk of losing work is higher among patients aged 55-64 years and those with increased disease activity (31).

With the exception of rhupus syndrome, arthritis-related disability in SLE patients tends to be less severe compared to rheumatoid arthritis. In many cases, the response to glucocorticoids and antimalarials is both rapid and complete. Similarly positive responses to glucocorticoids are observed in patients with myositis. However, individuals with rhupus syndrome often experience a more persistent and refractory form of arthritis, leading to poorer prognoses in terms of health status and quality of life (25).

5. Clinimetry

Clinimetry is a discipline which measure and value clinical symptoms and signs in medical and health care settings. It’s used to provide tools and methodologies to objectively quantify and assess the clinical conditions of patients. This assessment can be used to monitor disease evolution, evaluate the effectiveness of treatments, compare the effect of different therapies, and facilitate communication among health professionals. Essentially, it helps to transform clinical observations in a scientific and quantitative way, thus helping to improve the quality of health care.

5.1. PGA

The Physician Global Assessment (PGA) is designed to evaluate the overall disease activity by considering the severity of active manifestations, while excluding organ damage, serology, and subjective findings unrelated to disease activity. The PGA scale ranges from “no disease activity” (0) to the “most severe disease activity” (3) and includes the values 1 and 2 as intermediate markers to categorize disease activity as mild (≥0·5 to 1), moderate (>1 and ≤2), and severe (>2 to 3). Only experienced physicians are qualified to assess the PGA, and it is preferable for the same rater to score it consistently at each visit (84).

5.2. SLEDAI and SLEDAI-2K

The SLEDAI (Systemic Lupus Erythematosus Disease Activity Index) is an instrument used to assess disease activity in SLE. It’s an index consisting of a series of questions and clinical observations that measure the severity of symptoms and signs of SLE. The results of the SLEDAI are used by clinicians to monitor disease progress over time and to evaluate the effectiveness of treatments. SLEDAI-2K was introduced and validated in 2002 (85) and it’s a modification of the SLEDAI, designed to capture persistent, active disease by including descriptors that had previously only assessed new or recurrent occurrences. The SLEDAI-2K has a strong correlation ($r = 0.97$) with the original SLEDAI. Both scoring methods for SLEDAI equally predicted mortality ($p = 0.0001$) and provided similar descriptions of disease activity as perceived by clinicians. The SLEDAI-2K, which accounts for persistent activity in rash, mucous membranes, alopecia, and proteinuria, is suitable for use in clinical trials and studies investigating the prognosis of SLE (86).

5.3. BILAG

The British Isles Lupus Assessment Group (BILAG) index is a computerized tool designed to assess clinical disease activity in SLE, based on the principle of the physician's 'intention to treat'. The index assigns individual alphabetical scores to eight organ-based systems, without calculating a total score. Researches have

illustrated strong reliability among raters when using the BILAG index for each organ-based system (87).

5.4. DAS28

The Disease Activity Score is an index for assessing disease activity primarily from an articular perspective. It is used and validated for rheumatoid arthritis and also utilized in many studies on SLE (88,89). It is based on the count of the number of tender and/or swollen joints, the measurement of ESR or CRP, and patient's assessment of their own health status. DAS28 value indicates:

- below 2.6 remission;
- between 2.6 and 3.2 low disease activity;
- between 3.2 and 5.1 moderate disease activity;
- above 5.1 high disease activity.

In the hands, joints that are evaluated include the first and fifth metacarpophalangeal joints, the thumb interphalangeal joint, and the second and fifth proximal interphalangeal joints. Knees, shoulders, elbows and wrists are then evaluated. GH, the global health parameter, represents the patient's self-assessment of disease activity on a scale of 0 to 100, where 100 means maximum activity. A reduction in DAS28 score of 0.6 represents a moderate improvement, while a reduction greater than 1.2 represents a significant improvement. (90–93)

5.5. CLASI

Cutaneous LE Disease Area and Severity Index (CLASI) comprises two scores: the first summarizes disease activity, while the second measures disease-related damage. Disease activity is assessed based on erythema, scale/hyperkeratosis, mucous membrane involvement, acute hair loss, and non-scarring alopecia. Damage is evaluated in terms of dyspigmentation and scarring, including scarring alopecia. Patients are queried if dyspigmentation due to CLE lesions typically persists for more than 12 months, indicating permanence. If so, the dyspigmentation score is doubled. Scores are calculated by simple addition based on symptom severity. The

CLASI is structured as a table where rows represent anatomical areas and columns assess major clinical symptoms. The extent of involvement for each skin symptom is documented based on specific anatomical regions, with scoring determined by the most severe lesion within each area for each symptom (94).

5.6. SRI-4

The SLE Responder Index (SRI) serves as a composite measure to evaluate treatment response in SLE clinical trials. It has become a standard primary efficacy endpoint in both phase II and III randomized controlled trials (RCTs) over the past decade. A SRI-4 response is defined by a reduction in the SLEDAI of at least 4 points, without worsening of the BILAG index or a significant increase in PGA from baseline.

Analysis indicates that SRI responder classification is mainly determined by meeting the SLEDAI reduction criteria. However, the inclusion of BILAG and PGA criteria aims to identify substantial worsening not captured by SLEDAI alone. Yet, data from trials suggest that BILAG and PGA criteria rarely disagree with SLEDAI criteria when analyzed individually (95).

5.7. SLICC-DI

The Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SLICC/ACR DI) was created to quantify the cumulative damage that occurs in patients with lupus from the time of disease onset. This index is a validated tool that correlates well with patient mortality.

In the SLICC/ACR DI, damage is defined as an irreversible change that is not due to active inflammation, arising since the onset of lupus. This damage must be confirmed through clinical assessment and persist for at least 6 months. If damage recurs, it must do so at least 6 months apart to be scored as a separate event and thus score 2 points. Importantly, the same lesion cannot be counted more than once (96).

6. Therapy

SLE requires lifelong therapy, which can sometimes impact the patient's daily quality of life. Therefore, it is crucial to find the appropriate treatment for each individual patient, in order to achieve the greatest number of benefits minimizing side effects. Treatment of SLE can be subdivided in pharmacological and non-pharmacological.

6.1. Non pharmacological therapies

6.1.1. Lifestyle habits

SLE patients should, as far as possible, avoid certain behaviors that can put their health at risk. These include cigarette smoking and sun exposure. In particular, these patients are advised, to avoid more damage from the disease, to not expose themselves directly to the sun, least of all in the warmer months and, in case, to always use a 50+ sunscreen (97). Cigarette smoking, instead, exacerbates the disease and is associated with increased disease risk and worsened outcomes. Studies reveal a higher prevalence of smoking among SLE patients compared to the general population. Smoking significantly diminishes the effectiveness of medications like hydroxychloroquine for cutaneous lesions and belimumab for systemic manifestations. Despite these risks, SLE patients often lack awareness of smoking's detrimental effects on disease progression and treatment efficacy (98).

6.1.2. Physical exercise

Regarding gentler activities such as some types of yoga, there seems to be a possible benefit, especially for patients with joint manifestations (99). Also, the prevalence of fibromyalgia, characterized by fatigue, heightened symptoms, and widespread pain in response to illness and psychosocial stress, is elevated in individuals with SLE. Engaging in regular light exercise and incorporating stretching routines can contribute to alleviating fatigue, cognitive dysfunction, and pain associated with fibromyalgia (97).

6.2. Pharmacological therapies

Treatment for SLE over the years was always evolving, with new periodic updates on what treatments were best. Different drugs are used depending on the different organs involved. Specifically for the control of systemic symptoms, such as fever and inflammation, first-line therapy is used:

- NSAIDs: especially in the early stages when fever is present;
- Cortisone: cornerstone of SLE therapy;
- Antimalarials: hydroxychloroquine is particularly used.

Second-line therapy, undertaken in cases of severe or recurrent manifestations, or refractory to first-line therapy, involves the administration of immunosuppressants:

- Cyclophosphamide;
- Azathioprine;
- Mycophenolate mofetil;
- Cyclosporin A and Tacrolimus;
- Methotrexate.

Finally, some monoclonal antibodies can be used, such as:

- Anti-BlyS (Belimumab);
- Anti-IFN receptor (Anifrolumab);
- Anti-CD20 (Rituximab) (100).

6.3. New EULAR recommendations 2023

6.3.1. Principles

The general principles for the management of SLE provide basic guidelines that reflect common sense, although they are not accompanied by specific scientific evidence. They are essential for creating a general framework in the approach to the patient with SLE and emphasize the importance of physician-patient interaction. These principles have been unanimously agreed upon and provide a solid foundation for the overall management of the disease. In particular, they concern:

- the need for a multidisciplinary approach;
- the evaluation of disease activity scores at each visit;
- the use of non-pharmacological treatments, such as smoking cessation and sun protection;
- given the heterogeneity of the disease from patient to patient, an individualized approach is necessary;
- early diagnosis and frequent monitoring are essential (100).

6.3.2. Statements

Hydroxychloroquine

This drug is recommended for all patients with SLE, unless contraindicated, at a target dose of 5 mg/kg of actual body weight per day, but individualized based on the risk of flare and retinal toxicity. Furthermore, in some countries where HCQ might not be readily available, alternatives such as chloroquine have been considered, although its higher toxicity compared to HCQ should be taken into account. It is indicated as first-line therapy in patients with active skin disease.

Glucocorticoids

Glucocorticoids, starting with a dose based on the severity of organ involvement, should be reduced to a maintenance dose of $\leq$ 5 mg/day and ideally discontinued for avoiding its adverse outcomes. In patients with moderate or severe disease, pulses of intravenous methylprednisolone can be considered. It is indicated in patients with active neuropsychiatric involvement, for the acute management of severe autoimmune thrombocytopenia and, like HCQ, as first-line therapy in active skin disease. For individuals with SLE who have achieved sustained remission, a gradual reduction of treatment should be contemplated, beginning with the withdrawal of glucocorticoids.

Immunomodulatory and immunosuppressive drugs

Traditional immunosuppressant, such as methotrexate, azathioprine, or mycophenolate, and biological treatments like belimumab or anifrolumab (the latter

with a higher level of evidence in this situations) are good options for patients who don't show improvement with hydroxychloroquine alone or with glucocorticoids (or for those who cannot lower their glucocorticoid dosage to levels suitable for long-term use). They can also be used in second-line therapy for active skin disease.
In case of organ-threatening or life-threatening conditions, intravenous cyclophosphamide is a suggested option. In cases where patients do not respond to conventional treatments, rituximab could be an alternative option to explore.

Antiplatelet agents, anticoagulants and vitamin K antagonists

Antiplatelet agents and anticoagulants are recommended to manage manifestations associated with atherothrombotic or antiphospholipid antibodies.
In case of SLE linked with thrombotic antiphospholipid syndrome (APS), vitamin K antagonists are used for an extended duration following the initial arterial or unprovoked venous thrombotic episode. Also low-dose aspirin may be contemplated for individuals with SLE but without APS who exhibit a high-risk antiphospholipid profile.

Lupus nephritis

In case of active proliferative lupus nephritis, the treatment typically involves a combination of low-dose intravenous cyclophosphamide or mycophenolate, along with glucocorticoids. Additionally, therapy may include belimumab in combination with either cyclophosphamide or mycophenolate, or calcineurin inhibitors.
After achieving a renal response, treatment for lupus nephritis should be continued for a minimum of three years. For those who were initially treated with cyclophosphamide (alone or in combination with belimumab), mycophenolate or azathioprine should replace cyclophosphamide.
For patients deemed at high risk of kidney failure, characterized by reduced glomerular filtration rate, histological evidence of cellular crescents or fibrinoid necrosis, or severe interstitial inflammation, the consideration of high-dose intravenous cyclophosphamide in conjunction with pulse methylprednisolone may be appropriate.

Vaccinations

Vaccinations to prevent infections, maintenance of bone health, kidney protection, cardiovascular risk management, and screening for malignancies should be undertaken (100).

6.4. Treatment of musculoskeletal manifestations

In this section, the medications used to treat musculoskeletal manifestations will be discussed, both from a pain and an inflammatory perspective. Biological drugs will be excluded, as they will be addressed in the subsequent section.

According to EULAR recommendations, glucocorticoids and hydroxychloroquine are used among the main first-line drugs, while, for patients who don't show improvement with this drugs alone, second-line therapy (including immunosuppressant, such as methotrexate, and biological treatments) should be used (100).

6.4.1. Glucocorticoids and NSAIDs

Musculoskeletal manifestations are usually managed using glucocorticoids and nonsteroidal anti-inflammatory drugs (NSAIDs), which are used to decrease inflammation and pain. The maintenance dose of GCs should, as mentioned above, be less than 5 mg/day (100), while NSAIDs are taken in case of need. These drugs, however, may contribute to an increased risk of long-term cardiovascular complications, such that cardiovascular disease is the leading cause of mortality in SLE patients (101). Long-term complications of GCs include cataracts, as well as skin atrophy, striae, acne, and obesity, which can also give cosmetic problems. Also higher risks of osteoporosis, osteonecrosis, infection, and cancer are associated with previous GC therapy (102). NSAIDs, on the other hand, are associated with long-term gastrointestinal complications and, particularly in older patients, increased risk of cardiovascular, renal and hepatic complications (103).

6.4.2. Hydroxychloroquine

This drug is an antimalarial and immunomodulant, that can act in different ways. It can accumulates in lysosomes by entering along a pH gradient. In lysosomes, it inhibits the degradation of cargo proteins, which can come from external sources (via endocytosis or phagocytosis) or internal pathways (via the autophagy pathway), by increasing the pH. This prevents the activity of lysosomal enzymes. The inhibition of lysosomal activity can subsequently prevent MHC class II-mediated autoantigen presentation.

Another mechanism of action of hydroxychloroquine is to accumulate in endosomes and bind to the minor groove of double-stranded DNA, but also this drug can interfere with immune activation by inhibiting various innate and adaptive immune processes (104).

The target dose is 5 mg/kg of actual body weight per day, but it has to be individualized, based on the risk of complications like flares and retinal toxicity (100).

The drug is available in 200 mg tablets. In SLE, the average starting dose is 2 tablets once or twice daily, with a possible reduction to 1 tablet daily for maintenance therapy.

In general, the drug is well tolerated, but gastric disorders, skin and allergic reactions may occur. It may worsen conditions such as psoriasis and porphyria, and increase the risk of hypoglycemia in diabetic patients. In patients with heart disease or rhythm abnormalities, it should be used with caution. Other rare side effects include eye, muscle and liver problems. Retinal toxicity is possible especially when the drug is taken for long period of time (more than 10-15 years), so an eye examination before initiation of therapy and regular monitoring during treatment is recommended (105).

6.4.3. Methotrexate

Methotrexate (MTX), an analog and antagonist of folic acid, is widely used in treating various malignant and non-malignant conditions. Originally developed as an anticancer drug, MTX is now the first-line treatment for rheumatoid arthritis (RA),

juvenile idiopathic arthritis, and psoriasis. It is also beneficial in inflammatory bowel diseases, multiple sclerosis, vasculitis, SLE, and other connective tissue diseases, as well as in transplantation, due to its anti-inflammatory and immunomodulatory effects.

The drug acts on numerous points of the immune and inflammatory systems, among them for example:

- it reduces production of proinflammatory cytokines such as IL1β, IL6, and TNF-α by monocytic/macrophagic cells, while increasing expression of Th2 anti-inflammatory cytokines like IL4 and IL10. It also decreases expression of Th1 proinflammatory cytokines such as IL2 and IFNγ;
- MTX downregulates expression levels of IgG Fc receptors FcγRI and IIa on monocytes, reducing their activation;
- it disrupts signals between synovial fibroblasts and T cells;
- it increases reactive oxygen species synthesis in T cells, monocytes, and neutrophils, leading to reduced growth and increased apoptosis of these cells;
- MTX inhibits prostaglandin E2 production and expression of its synthesizing enzymes, microsomal prostaglandin E2 synthase 1 and cyclooxygenase 2;
- it reduces production of synovial metalloproteinases while stimulating their inhibitors (106).

It's used in combination with glucocorticoid therapy at low to medium doses. It represents one of the drugs used for maintenance of remission (107).

6.4.4. Leflunomide

Leflunomide is an isoxazole derivative developed for the treatment of RA, now widely used both as a monotherapy and in combination with other drugs. Upon administration, it is metabolized into its active form, teriflunomide, which significantly inhibits the lymphocyte enzyme dihydroorotate dehydrogenase in the pyrimidine biosynthetic pathway. This inhibition results in a decrease in T-cell proliferation and other modifications in the immune response. Clinical trials have demonstrated that leflunomide's efficacy in managing the signs and symptoms of RA

is comparable to that of methotrexate. Additionally, leflunomide has been associated with the slowing of joint damage progression (108).

This drug is used as a first-line treatment for rheumatoid arthritis in cases where there are contraindications to MTX (109), so it can be an option also for rhupus.

6.5. Biological drugs and small molecules for musculoskeletal manifestations

6.5.1. Rituximab

This antibody is a chimeric antibody targeting CD20, a transmembrane protein expressed on all B-lineage cells except for pro-B cells and plasma cells. By binding to CD20, it triggers both cell-mediated and antibody-mediated cytotoxicity, leading to the depletion of CD20+ B cells (110). Two studies about the use of this drug for SLE have failed, but despite this, it is used as an off-label because observational studies affirm its validity. The drug, according to 2023 EULAR guidelines, in SLE is used in patients with organ-threatening or life-threatening disease, in cases that prove refractory to cyclophosphamide. It can also be used for acute treatment of severe autoimmune thrombocytopenia, together with high doses of glucocorticoids, with or without intravenous immunoglobulin G, and/or high-dose intravenous cyclophosphamide. For maintenance therapy, rituximab, azathioprine, mycophenolate, or cyclosporine may then be used (100). In joint manifestations of SLE, it's an important drug for the treatment of rhupus, the combination of SLE and rheumatoid arthritis. In the latter, rituximab is used as a second-line therapy when synthetic DMARDs fail and poor prognostic factors are present (109).

6.5.2. JAK inhibitors

The JAK family consists of intracellular tyrosine kinases that bind directly beneath cell surface receptors and serve as crucial signal mediators for numerous cytokines and hormones. Comprising four members (JAK1, JAK2, JAK3, TYK2), these tyrosine kinases facilitate the signal transduction of over 50 cytokines (111). JAK inhibitors are small-molecules enzyme inhibitors, which consist in proteins that

interact with specific enzyme receptors, JAKs, located inside the cell, blocking a series of chemical reactions responsible for activating the inflammatory response. Drugs in this category include:

- tofacitinib, relatively selective for JAK1/3, for RA and ulcerative colitis;
- baricitinib, selective for JAK1/2, for RA, atopic dermatitis, alopecia areata, and SARS-CoV-2 pneumonia;
- peficitinib, pan-JAK inhibitor for treating RA;
- upadacitinib for treating RA, psoriatic arthritis, axial spondyloarthritis, atopic dermatitis, and ulcerative colitis;
- filgotinib, which is selective for JAK1, for treating RA and ulcerative colitis (111).

Clinical trials of JAK inhibitors and biologics are ongoing for SLE and lupus nephritis as an adjunct to standard therapies, such as hydroxychloroquine, immunosuppressive agents, and glucocorticoids.

Regarding possible adverse effects, herpes zoster is a common adverse event caused by JAK inhibitors, but the risk may be even higher in patients with SLE, for whom the incidence of shingles is already high. Another adverse effect, although rare, is the increased risk of thromboembolic events (109,111), such that it has been reported that thrombosis is more common in patients with SLE than in those with other immunologic diseases: consequently, increased surveillance for these kinds of risks is necessary, especially in patients with increased cardiovascular risk (109).

6.5.3. Anifrolumab

Anifrolumab is a fully human IgG1 kappa-type monoclonal antibody that inhibits type I interferon receptor signaling, thereby counteracting the activity of all type I interferons, which play an important pathogenic role in this disease. It's indicated as an adjunctive treatment for active disease when it's of moderate to severe grade.

For treatment, the recommended dose is 300 mg by intravenous infusion over 30 minutes every four weeks, but it can be discontinued if there is no improvement in disease control after six months (112). Anifrolumab can be used as first-line therapy

when severe skin and joint involvement is present in extrarenal SLE, and without major organ involvement, after failiure glucocorticois and antimalarials (EULAR reccomandations). Use of the drug as adjunctive therapy, however, is mainly in forms with severe skin involvement. In severe neuropsychiatric manifestations, the drug is not recommended (100).

6.5.4. Belimumab

Mechanisms of action

Belimumab is an antagonist of BAFF or BlyS, a cytokine with survival function for B lymphocytes, which intervenes in some checkpoints of immune tolerance, particularly in the transactivation stage from the marrow before the follicular stage.

As a survival factor for B lymphocytes, it is also important for the survival of B lymphocytes that produce SLE antibodies: the drug, therefore, allows the elimination of these pathological B lymphocytes, which can't survive without BlyS. Belimumab primarily targets the soluble cytokine (110,113).

Treatments for SLE

It is approved in the treatment of both renal and non-renal SLE. Some of the manifestations for which it is most used are renal, musculoskeletal and mucocutaneous. Usually it can be administered e.v. 10 mg pro kg monthly or subcutaneously 200 mg weekly (114).

First studies

Belimumab has been used for several years in patients with SLE, with studies dating back to early 2000s.

The phase I investigation of belimumab (LymphoStat-B), in a 2003 study (115), assessed its safety, tolerability, immunogenicity, and pharmacology across four doses (1, 4, 10, and 20 mg/kg) in patients with stable SLE of mild-to-moderate disease activity. The study followed patients for 84–105 days.

All LymphoStat-B cohorts exhibited significant reductions in CD20+ cells compared to placebo and, overall, the drug was well tolerated, with no withdrawals due to adverse events. Incidence of adverse events and infections was similar between LymphoStat-B and placebo groups. Serious adverse events occurred at similar frequencies in both groups, none of which were attributed to the study agent. Infrequent severe laboratory abnormalities or adverse events were observed. Some patients experienced decrease in anti-dsDNA or immunoglobulin levels, but no change in SLE disease activity was noted. The study concluded that LymphoStat-B led to significant reductions in peripheral B cells, consistent with its mechanism of action in inhibiting BLyS activity (115).

Phase II studies

In 2009 was carried out a randomized, double-blind, placebo-controlled, dose-ranging study of belimumab in patients with active SLE (116): patients were randomized to receive 1, 4, or 10 mg/kg of belimumab or placebo by intravenous infusion 52 weeks. In this studies the main findings were:

- significant differences were not observed between the treatment and placebo groups for either primary endpoint, and no dose-response relationship was noted;
- the reduction in SELENA-SLEDAI score from baseline was 19.5% in the combined belimumab group compared to 17.2% in the placebo group;
- the median time to first SLE flare was shorter in the placebo group overall, but during weeks 24-52, it was significantly longer with belimumab treatment;
- in serologically active patients (71.5% of the subgroup), belimumab treatment resulted in significantly better responses at week 52 compared to placebo for SELENA-SLEDAI, PGA, and SF-36 PCS scores;
- treatment with belimumab also led to notable decrease in various B cell populations and anti-dsDNA titers by week 52;
- rates of adverse events (AEs) and serious AEs were similar between the belimumab and placebo groups.

Phase III studies

BLISS-52 is a randomized, placebo-controlled phase III trial which results were published in 2011. A total of 867 patients were randomly assigned in a 1:1:1 ratio to belimumab, 1 mg/kg or 10 mg/kg, or placebo by intravenous infusion.

At week 52, belimumab 1 mg/kg and 10 mg/kg, compared to placebo, demonstrated:

- significantly higher SRI rates;
- more patients with at least a 4-point reduction in the SELENA-SLEDAI score;
- no new BILAG A or no more than one new B flare;
- no worsening in the PGA score;
- the rates of adverse events were similar in the groups treated with belimumab and placebo, both in terms of serious infections (an average of 6% of patients) and serious or severe hypersensitivity reactions on the infusion day (>1% of patients with belimumab and no cases in the placebo group). Finally, no malignant diseases were reported (117).

BLISS-76, published in December 2011, is a multicenter, randomized, double-blind, placebo-controlled trial. 826 patients with SLE were assigned to receive placebo, or belimumab 1 or 10 mg/kg by intravenous infusion.

The main findings were:

- at week 52, there were more SRI responders in the belimumab 10 mg/kg group and belimumab 1 mg/kg group than in the placebo group;
- at week 76, the SRI response rates were still greater with belimumab 10 mg/kg and 1 mg/kg versus placebo;
- significantly more patients receiving belimumab 10 mg/kg had a ≥ 4 point reduction in SELENA-SLEDAI score at week 52 versus placebo. Specifically, SELENA-SLEDAI improved significantly between weeks 44 and 76 with belimumab 10 mg/kg, and between weeks 52 and 76 with belimumab 1 mg/kg;
- there were no significant differences in mean change in PGA score at week 24 between the placebo and belimumab groups;
- in the subgroup of patients receiving prednisone (or equivalent) > 7.5 mg/d at baseline, a greater proportions of patients receiving belimumab were able to

reduce corticosteroids by ≥ 25% and to ≤ 7.5 mg/d between weeks 40 and 52 compared with placebo, but these differences were not statistically significant. The next weeks there was a similar proportional prednisone reduction;

- there were sustained improvements in serologic activity, with significant reductions in anti-dsDNA antibody titers and increases in C3 and C4 concentrations (118).

Approval

Based on the efficacy results of the BLISS-52 and BLISS-76 trials (117,118), belimumab received Food and Drug Administration (FDA) approval in 2011, in patients older than 18 years, for the treatment of moderate to severe SLE (2). Even European Medicine Agency (EMA) approved the drug in 2011, under additional monitoring, which aims to improve the reporting of suspected adverse drug reactions for medicines with a less established clinical evidence base. The primary objectives are to gather information as early as possible to better inform the safe and effective use of these medicines and to understand their benefit-risk profile in routine medical practice (119).

6.5.5. BLISS-NEA

The objective of this study was to evaluate the efficacy of belimumab in patients from North East Asia (NEA) with SLE, analyzing subgroups based on baseline demographics and disease characteristics.

An analysis of patient subgroups from the BLISS-NEA study was conducted, which included adults with SLE who were randomized to receive either belimumab (10 mg/kg intravenously) or a placebo. The primary endpoint was the SRI-4 response rate at week 52. Subgroup analyses were conducted based on gender, country, prednisone-equivalent dose, concomitant medications, SELENA-SLEDAI score, complement levels, anti-dsDNA positivity, and SLICC/ACR DI.

The study included 677 patients in total, with 451 receiving belimumab and 226 receiving a placebo. The majority of participants were from China (76.4%), followed

by Korea (14.8%) and Japan (8.9%). The mean age of participants was 32.1 years, and 92.9% were female. In the overall population:

- 53.8% of patients treated with belimumab were SRI-4 responders at week 52, compared to 40.1% in the placebo group. SRI-4 response rates in various subgroups were generally consistent with the overall population;
- a greater response to belimumab was observed in patients with a baseline SELENA-SLEDAI score of ≥10 compared to those with a score of ≤9, as well as in patients with low C3/C4 levels and those who were anti-dsDNA positive at baseline.

In conclusion, these results support the efficacy of belimumab in treating SLE patients from North East Asia, demonstrating consistent benefits across different demographic and disease characteristic subgroups (120).

6.5.6. BeRLiSS

The BeRLiSS (Belimumab in Real Life Setting Study) represents the largest nationwide multicenter cohort focused on evaluating the effects of belimumab on disease activity, damage progression, and the achievement of remission and low disease activity (LDA) in patients with SLE. This study also seeks to identify predictors of treatment response across several Italian lupus treatment centers.

Patients were followed prospectively according to EULAR recommendations. Anonymized data were collected in a database from the start of belimumab treatment and updated regularly. Variables collected at baseline and every 6 months included SLEDAI-2K score, fatigue levels, daily prednisone intake, blood cell count, 24-hour proteinuria, anti-dsDNA antibody levels, C3 and C4 levels, and concomitant medications. Data were systematically evaluated, and inconsistencies were corrected by the centers.

The BeRLiSS project included a total of 466 SLE patients from 24 Italian centers, with a median follow-up period of 18 months (range 1–60 months).

Results were:

- Among SLE patients treated with belimumab, there were significant decreases in SLEDAI-2K scores, fatigue levels, anti-dsDNA antibody levels, DAS28 scores, CLASI activity, 24-hour proteinuria, and daily prednisone intake. Conversely, serum levels of C3 and C4 showed an increase during the treatment period;
- In patients with positive anti-dsDNA levels at baseline, 261 had available data at 12 months, and 138 at 24 months. Of these, 54.4% were seronegative at 12 months, and 33.3% were seronegative at 24 months;
- SRI-4 response, once achieved, was mostly maintained over time. Notably, 38.2% of the 157 patients who were non-responders at 6 months became responders at 12 months, indicating that 6 months may be insufficient to fully evaluate the response to belimumab;
- Over 90% of patients who achieved low disease activity at any time point received ≤7.5 mg of prednisone daily after 6 months of belimumab therapy. Additionally, 66.1% of patients maintained low disease activity for at least half of the follow-up period, and 44.3% achieved disease remission for at least a quarter of the time. One-third of patients who achieved remission for at least 25% of the follow-up period stopped glucocorticoid treatment entirely;
- Univariate analysis showed that concomitant antimalarial treatment was associated with lower damage accrual at the end of follow-up. Conversely, age, disease duration of ≥10 years, and a baseline SDI score of > 0 were associated with a higher risk of damage accrual;
- Among 10.104 IV belimumab infusions, there were no deaths or severe infusion reactions. Some adverse events were infections, noninfectious reactions, hypersensitivity reactions and infusion reactions.

The study demonstrated that early initiation of belimumab treatment leads to significant and lasting remission or low disease activity in SLE patients. It confirmed previous findings on the benefits of belimumab, including reduced disease activity, lower prednisone doses, fewer flares, and slowed damage progression. These data suggest that earlier use of belimumab in active SLE could improve patient outcomes

by enhancing response rates, achieving remission or low disease activity, and reducing damage accrual (121).

6.5.7. BeRLiSS LN: belimumab for lupus nephritis

Limited data exists on the efficacy of belimumab in patients with lupus nephritis (LN) treated in routine clinical practice, and clear prognostic factors for renal response have not yet been identified. This study conducted a subanalysis on patients with renal involvement who were enrolled in the BeRLiSS (Belimumab in Real Life Setting Study) cohort. The aim of BeRLiSS-LN is to assess the efficacy and safety of belimumab in LN patients and to identify predictive factors of renal response in a real-world clinical setting.

The primary endpoint was the attainment of Primary Efficacy Renal Response (PERR), assessed at 6, 12, and 24 months. PERR was defined as proteinuria ≤0.7 g/24 h, eGFR ≥60 ml/min/1.73 m2, and no rescue therapy.
The secondary endpoint was Complete Renal Response (CRR) at the same time points, defined as proteinuria <0.5 g/24 h, eGFR ≥90 ml/min/1.73 m2, and no rescue therapy. Additionally, the study assessed the frequency of renal flares, defined based on the SELENA-SLEDAI Flare Index (SFI). This involved considering all episodes of proteinuria increase >0.5 g/24 h from the previous assessment or an increase in creatinine as potential LN flares.

At 24 months, of the 91 patients involved, PERR was achieved by 66.1% of them and CRR by 37.3%. Additionally the mean time to reach PERR was less than 12 months, a timeframe often considered indicative of a favorable response. At multivariable analysis, hypertension, high baseline serum creatinine, and high baseline proteinuria negatively predicted PERR, while baseline anti-Sm positivity and having achieved PERR at 6 months were positive predictors of PERR at 12 and 24 months.
These findings suggest that belimumab could be efficacious as an adjunctive therapy for patients with lupus nephritis, even in real-world clinical settings. (122).

6.5.8. BeRLiSS J-S: belimumab for joint and skin

Clinical experience of over ten years has confirmed the efficacy and safety of belimumab in the treatment of SLE. Data from the BeRLiSS cohort indicate that many patients experienced clinical improvement with belimumab, especially those treated early. Even if some patients do not respond within 6 months, they may respond later. Analyses suggest that belimumab is effective in musculoskeletal and cutaneous involvement, but further clinical evidence is needed. BeRLiSS-JS evaluated the efficacy of belimumab in patients with joint and skin involvement. (88).

Joints

Taking into account specific inclusion criteria, 328 patients were considered for joint co-induction, but some were not included in the final study for various reasons, including discontinuation of the drug before 6 months (due to inefficacy, adverse events or loss of follow-up) or incomplete data that did not allow further analysis to be conducted. Therefore, the final cohort to evaluate drug efficacy at 6 months was 277 patients. The mean follow-up period for patients with joint involvement was 23.7 ± 14.3 months.

Among patients with joint involvement, SRI-4 response was achieved by:

- 143 (51.6%) at 6 months;
- 147 (58.5%) at 12 months;
- 86 (62.3%) at 24 months;
- 46 (64.8%) at 36 months.

In contrast, remission was achieved by:

- 62 (22.3%) at 6 months;
- 84 (33.4%) at 12 months;
- 41 (29.7%) at 24 months;
- 25 (35.2%) at 36 months.

Low disease activity (LDA) was achieved by:

- 103 (37.1%) at 6 months;
- 121 (48.2%) at 12 months;

- 77 (55.8%) at 24 months;
- 61 (60.5%) at 36 months.

It is also important to note that 57.4% of patients were on prednisone in amounts less than 5 mg per day and 8.5% were without prednisone at 6 months. These proportions then increased to 72.7% and 16.3% at 12 months, 85.1% and 28.9% at 24 months, and 87.7% and 38.5% at 36 months, respectively.

Among the 243 patients with DAS28 ≥ 2.6 at baseline, remission was achieved by:

- 109 (44.8%) at 6 months;
- 116 (50%) at 12 months;
- 81 (61.4%) at 24 months;
- 45 (64.3%) at 36 months.

In addition, patients with Boolean-type remission, that includes non-swollen joints, non-painful joints, VAS 1/10, PCR ≤ 1 mg/L, were respectively:

- 12 (4.9%) at 6 months;
- 26 (11.2%) at 12 months;
- 24 (18.2%) at 24 months;
- 23 (32.8%) at 36 months (88).

Skin

According to the inclusion criteria, 172 patients with skin manifestations were considered, but the final cohort included 151 patients at baseline, again due to loss of some patients to follow-up or ineffectiveness. The mean follow-up period in patients with skin involvement was 25.9 ± 15.7 months.

Among patients with skin manifestations at time baseline:

- 17 patients (11.2%) had CLASI > 10;
- 59 (38.8%) had CLASI ≤ 10 and >5;
- 68 (45.4%) had CLASI ≤ 5 and >1;
- 7 (4.6%) had CLASI = 1.

Among patients with skin manifestations, remission was achieved by

- 25 (16.5%) at 6 months;
- 36 (26.1%) at 12 months;

- 27 (33.7%) at 24 months;
- 18 (36.7%) at 36 months.

Low disease activity (LDA) was also observed in:

- 49 (32.4%) at 6 months;
- 57 (41.3%) at 12 months;
- 45 (56.2%) at 24 months;
- 34 (69%) at 36 months.

In addition, 54% of patients were taking less than 5 mg per day of prednisone, and 7.8% were prednisone free at 6 months. These percentages then increased to 85.7% and 26.5% at 36 months.

Patients who achieved CLASI equal to 1 decreased over time as remission was progressively achieved, while the proportion of patients with CLASI > 10 decreased significantly from baseline, from 14.5% to 4.8% at 6 months, 0% at 12 months, 1.4% at 24 months, and 0% at 36 months.

In addition, a large proportion of patients with high disease activity, i.e., CLASI > 10, who did not reach remission, still experienced clinically significant improvement in skin involvement during follow-up (88).

Tab III. Number of SLE patients with joint or skin involvement considered in the analyses at different timepoints, including those in follow-up and those who discontinued the drug due to inefficacy in the 6 months before achieving the timepoint (88).

	Joint Involvement		Skin Involvement	
Months	**Number of patients in follow-up***	**Patients discontinuing belimumab in the 6 months before the timepoint****	**Number of patients in follow-up***	**Patients discontinuing belimumab in the 6 months before the timepoint****
6	**272**	**5**	**147**	**4**
12	**215**	**36**	**118**	**20**
24	**114**	**24**	**69**	**11**
36	**59**	**15**	**42**	**7**
48	**28**	**4**	**23**	**3**
(* Number of patients achieving the 6, 12, 24, 36 and 48 months of follow-up; ** Due to inefficacy)				

AIMS OF THE STUDY

Clinical experience spanning over a decade has validated the efficacy and safety of belimumab in treating SLE. BeRLiSS-JS assessed the efficacy of belimumab in patients with joint and skin involvement, demonstrating clinical improvement in a substantial number of patients with joint or skin involvement in a real-world setting and was linked to a glucocorticoid-sparing effect. A notable proportion of patients with a partial response at 6 months achieved remission later during follow-up.

Despite BeRLiSS-JS demonstrating an improvement in both musculoskeletal and cutaneous manifestations (88), it did not individually consider the different phenotypes of these manifestations. The BeRLiSS newJS aims to individually evaluate the joint and cutaneous phenotypes of SLE to identify any differences in the efficacy of belimumab on them, in a nationwide prospective multicenter cohort (BeRLISS-Joint) of patients with SLE.

MATERIALS AND METHODS

Patients

Inclusion criteria were:

1) fulfillment of the ACR 1982 revised criteria for SLE or the SLICC/ACR classification criteria for SLE or the EULAR/ACR 2019 classification criteria for SLE;
2) active joint manifestations, according to SLEDAI-2K score of > 0, that is refractory to a standard of care regimen according to EULAR recommendations 2019;
3) IV belimumab (10 mg/kg on days 1, 14, and 28, and then every 28 days) or SC belimumab (200 mg/week) as adjunct or mono-therapy;
4) available follow-up every 6 months

Exclusion criteria were:

1) age < 16 years;
2) insufficient data.

Standard of care was defined, according to the 2023 EULAR recommendations for the management of SLE, as glucocorticoids and antimalarials (if not absolutely contraindicated), with or without immunosuppressive agents. SLE patients who were treated between May 2013 and May 2024 were included. Inclusion and follow-up of patients in this study did not interfere with clinical practice.

Data collection and management

In this retrospective observational study, adult SLE patients treated with belimumab (10 mg/kg/month EV or 200 mg/week SC) were stratified based on the joint phenotype at belimumab initiation:

- non-deforming non-erosive arthritis (NDNE);
- Jaccoud's arthropathy;
- rhupus.

Anonymized patient data were collected in an ad hoc database since belimumab initiation and were regularly updated. Clinical and laboratory variables collected at baseline and every 6 months were:

- daily prednisone intake;
- dsDNA;
- C3;
- C4;
- White cells
- Lymhpocytes;
- Hemoglobin;
- 24 hour proteinuria;
- Creatinine;
- Hypertension;
- Vitamin D;
- SLICC;
- PGA;
- SRI;

All collected data were systematically and regularly evaluated. Patient data that did not fulfill inclusion and qualitative control criteria were excluded.
Informed consent was obtained from each patient regarding personal data treatment.

We analyzed the variation of DAS28 score at baseline, 6, 12, 18, 24, 30, 36 months of follow-up. In particular, the number of patients in remission (DAS28 < 2.6) was evaluated over various periods. We even analyzed the daily use of GC at baseline, 6, 12, 18, 24, 30, 36 months of follow-up, but in this case limited to the Padova cohort. Parametric and nonparametric tests were used according to the data distribution displayed by each variable.
In this study, a univariate analysis was conducted. DAS28 median scores were reported as median and interquartile range.

To perform comparisons between groups, χ^2-test was employed for categorical dicotomic data. Continuous data with non-parametric distribution were analyzed using Wilcoxon's rank sum test and Wilcoxon's test for paired data. To assess the variation over time of different variables, ANOVA test and Friedman's test with Bonferroni's correction were used for parametric and non-parametric data respectively. For comparisons between three or more groups, ANOVA for repeated measures was utilized for parametric data and one-way repeated measures analysis of variance by ranks through Friedman's test was utilized for non-parametric data. p-values less than 0.05 were considered significant.

The study was approved by the University of Padova ethics committee (380/AO/16) and carried out according to Helsinki declaration.

RESULTS

Of the 443 patients enrolled in the BeRLiSS-neJS study, from 14 different italian centers, 394 (88,9%) were females. Mean age at diagnosis was 29.9 ± 13.2 years, while mean treatment duration was 31.6 ± 20.8 months.

Regarding musculoskeletal involvement, at belimumab initiation 272 (61,4%) patients had active joint manifestations, of which:

- 221 had NDNE (81,3%);
- 30 had JA (11,0%);
- 21 had rhupus (7,7%).

Tab. IV:. DAS28, current age, age at diagnosis, duration of disease pre-belimumab and current therapy in patients with articular active manifestations at the beginning of the study

	Mean	Standard deviation	Median	75th percentile	25th percentile
DAS28	4,01	3,44	3,76	4,61	2,89
Current age	48,02	12,31	48,72	56,55	39,40
Age at diagnosis	30,35	12,04	28,53	38,03	21,31
Disease duration before Benlysta (years)	11,82	9,59	10,15	18,05	3,88
MMF (grams)	1,70	0,84	2,00	2,00	1,00
MTX (mg/week)	11,20	5,70	11,30	15,00	7,50
AZA (mg)	80,00	45,00	100,00	100,00	50,00
CsA	77,00	61,00	100,00	125,00	1,00
HCQ (mg)	301,00	81,00	300,00	400,00	200,00
Fatigue (VAS 0-10)	5,00	2,70	5,00	7,00	3,00

Tab. V: Gender, antibodies and previous involvement in patients at the beginning of the study only in patients with active articular involvement

	Number of patients	% of patients
Females	246	90,50%
Males	26	9,50%
relapsing remitting	168	61,60%
chronic active	104	38,70%
ANA	271	99,70%
ANTI-DNA	246	90,50%
ANTI-SM	76	28,00%
ANTI-SSA	123	45,70%
ANTI-SSB	43	16,00%
ANTI-URNP	90	33,10%
ANTI-P RIB	20	7,50%
ANTI-PHOSPHOLIPIDS	85	31,80%
APS	33	12,20%
OVERLAP	40	16,00%
Pregr MTX	38	14,6%
Pregr AZA	37	14,2%
Pregr CsA	14	5,4%
Pregr CYF	66	24,40%
Pregr MMF	66	25,4%
Pregr RTX	29	10,80%
Pregr HCQ	175	67,3%
previous IMMUNOSUPPRESSOR	229	88,10%
IS_in progress	223	81,90%
CQ (mg)	7	2,70%

Tab VI:. Laboratory and clinimetric values at the beginning of the study including only patients with active articular manifestations

	Mean	Standard deviation	Median	25th percentile	75th percentile
PDN mg/day	10,09	8,10	8,00	5,00	12,50
SLEDAI-2K	9,00	4,00	8,00	8,00	10,00
PGA	2,17	1,51	2,00	1,30	2,00
C3 (mg/dl)	74,14	23,21	72,00	60,00	86,00
C4 (mg/dl)	11,45	6,80	10,00	7,00	15,00
Fatigue (VAS 0-10)	5,00	2,70	5,00	3,00	7,00
SLICC_DI	1,00	1,00	1,00	0,00	1,00

1. Non deforming-non erosive arthritis (NDNE)

At baseline 221 patients with NDNE were analyzed, during follow-up we analyzed 199 patients at 6 months, 181 at 12 months, 151 at 18 months, 137 at 24 months, 126 at 30 months, and 102 at 36 months.

Median DAS28

Tab. VII: DAS28 median values for NDNE

DAS28 median values for NDNE	
DAS28 at baseline (n=221)	**3.7 (2.7 - 4.5)**
Baseline vs 6 months	*p<0.001*
DAS28 at 6 months (n=199)	**2.2 (1.6-2.9)**
6 vs 12 months	*p=0.046*
DAS28 at 12 months (n=181)	**2.0 (1.5 - 2.8)**
12 vs 18 months	*p=0.224*
DAS28 at 18 months (n=151)	**1.9 (1.2-2.5)**
18 vs 24 months	*p=0.094*
DAS28 at 24 months (n=137)	**1.6 (1.1-2.4)**
24 vs 30 months	*p=0.554*
DAS28 at 30 months (n=126)	**1.6 (0.1-2.4)**
30 vs 36 months	*p=0.738*
DAS28 at 36 months (n=102)	**1.6 (1.2-2.5)**
Baseline vs 36 months	*p<0.001*

In the case of NDNE, the initial median value of DAS28 was 3.7 (moderate disease activity). The reduction of DAS28 to remission median values occurred within 6 months and then remained not only below this threshold but continued to decrease progressively, reaching a stable value of 1.6 at 24 months, which was maintained at

30 and 36 months. The significant improvement was between baseline and 6 months (p<0,001), and between 6 months and 12 months (p=0,046). No significant differences were observed at 18, 24, 30, 36 months.

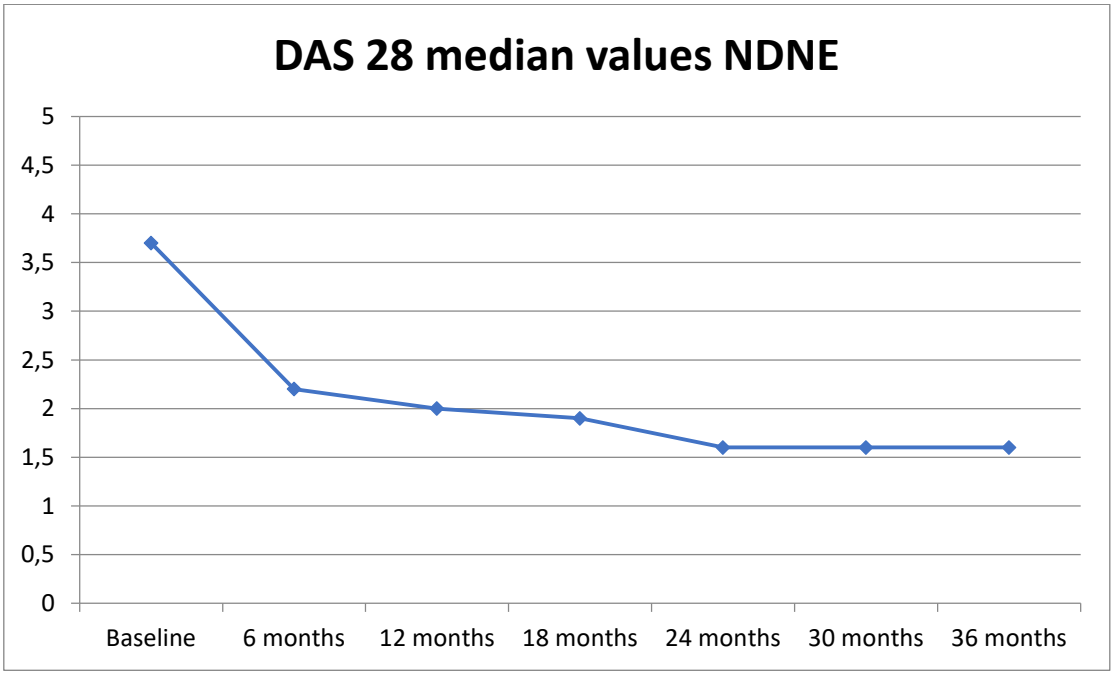

Fig. 2: DAS28 median values for NDNE

Remission rate

Tab. VII:. DAS28 remission in patients with NDNE arthritis

% NDNE patients with DAS28 <2,6	
DAS28 <2,6 at 6 months	59,6%
DAS28 <2,6 at 12 months	59,5%
DAS28 <2,6 at 18 months	72,4%
DAS28 <2,6 at 24 months	77,9%
DAS28 <2,6 at 30 months	75,3%
DAS28 <2,6 at 36 months	77,8%

Regarding the percentage of patients who achieved a DAS28 remission value, there was a progressive increase in the value over time, with an 18.2% increase in patients in remission: at 6 months 59,6% of patients, at 36 months 77,8%.

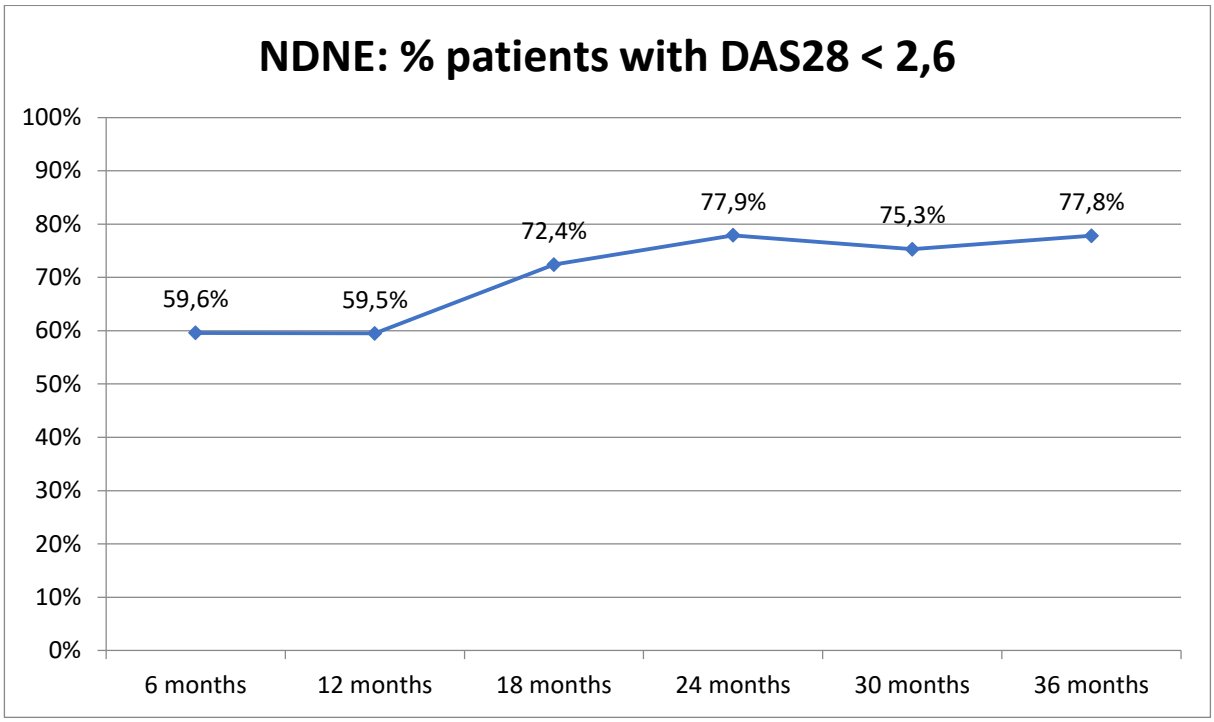

Fig. 3: DAS28 remission percentages for NDNE

Mean glucocorticoid (prednisone equivalent) reduction

186 NDNE patients presented a valid value of GC intake at the beginning of the study. At baseline, the mean GC use was 10,2 mg/day, during the follow-up it was 6,06 at 6 months, 5,53 at 12 months, 4,31 at 18 months, 3,98 at 24 months, 3,78 at 30 months, 3,43 at 36 months.

Tab. VIII: Daily mean use of GC of NDNE patients

	N° of patients	Mean (mg/day)	Standard deviation
Baseline	186	10,20	7,82
6 months	165	6,06	5,64
12 months	148	5,35	6,50
18 months	126	4,31	4,00
24 months	115	3,98	4,01
30 months	103	3,78	2,87
36 months	83	3,43	3,00

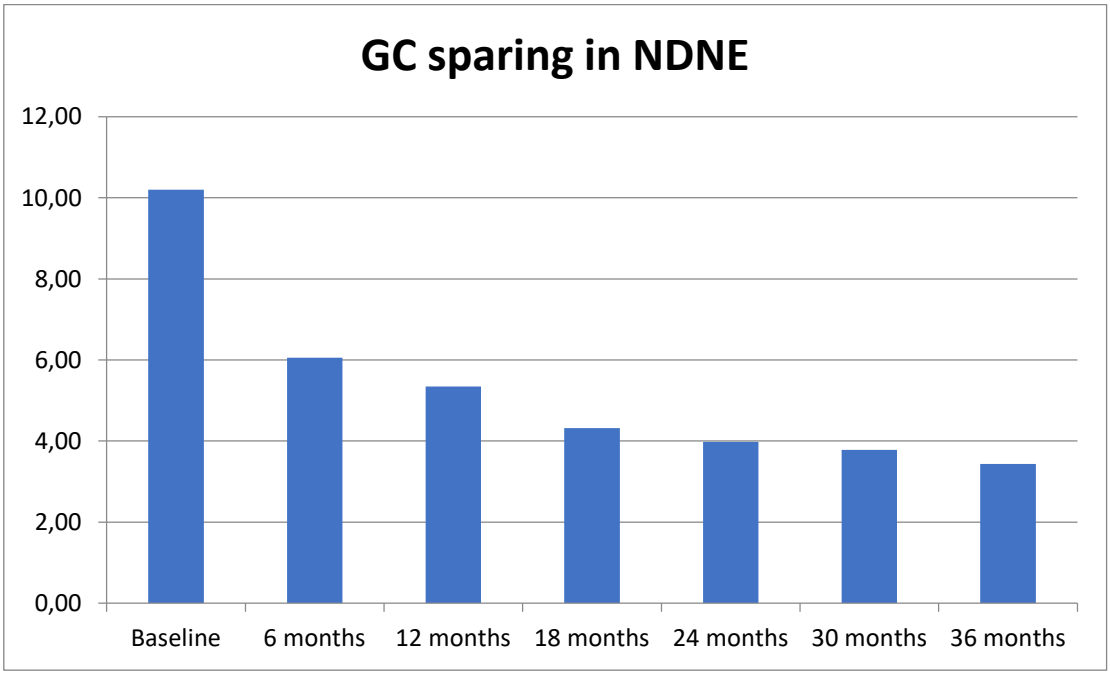

Fig.4: Daily mean use of GC of NDNE patients

Glucocorticoid (prednisone equivalent) reduction stratified

Padova cohort had 80 NDNE patients At baseline 51,25% of patients of the Padova cohort were on >7,5 mg/day of GC, at 12 months 4,69%, at 36 months only 7,14%. At 36 months, over 90% of patients were on ≤ 5 mg/day: 60,71% between 0,1 and 5 mg/day, and 32,14% even stopped the drug.

Tab. IX: Daily use of GC of NDNE patients

Number of patients							
Daily use of GC	**T0**	**T6**	**T12**	**T18**	**T24**	**T30**	**T36**
0 mg/day	4	5	12	12	14	15	9
0,1-5 mg/day	26	38	38	32	22	21	17
5,1-7,5 mg/day	9	11	11	4	4	4	0
>7,5 mg/day	41	17	3	3	3	1	2

Percentage of patients							
Daily use of GC	**T0**	**T6**	**T12**	**T18**	**T24**	**T30**	**T36**
0 mg/day	5,00%	7,04%	18,75%	23,53%	32,56%	36,59%	32,14%
0,1-5 mg/day	32,50%	53,52%	59,38%	62,75%	51,16%	51,22%	60,71%
5,1-7,5 mg/day	11,25%	15,49%	17,19%	7,84%	9,30%	9,76%	0,00%
>7,5 mg/day	51,25%	23,94%	4,69%	5,88%	6,98%	2,44%	7,14%

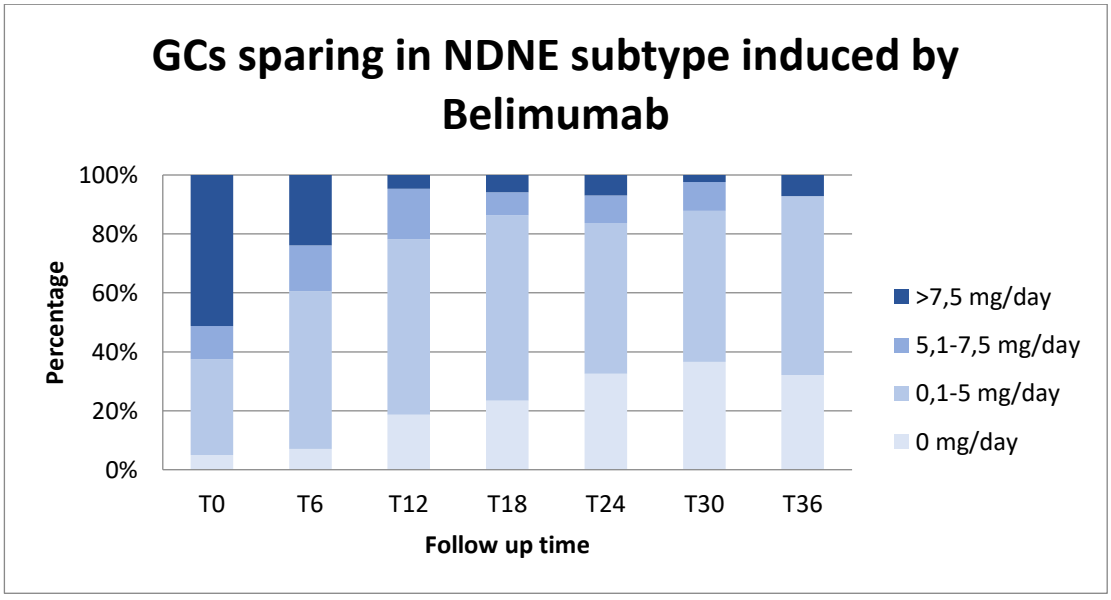

Fig.5: Daily use of GC of NDNE patients

2. Jaccoud's arthropathy

At baseline 30 patients with JA were analyzed, during follow-up we analyzed 27 patients at 6 months, 22 at 12 months, 17 at 18 months, 17 at 24 months, 15 at 30 months, and 12 at 36 months.

Median DAS28

In JA, the initial median value of DAS28 was 4.1 (moderate disease activity). Here too, there was a decrease in median DAS28, but it was smaller and more irregular compared to NDNE.

Tab. X: DAS28 median values for JA

DAS28 median values for JA	
DAS28 at baseline (n=30)	**4.1 (3.1-5.1)**
Baseline vs 6 months	*p=0.005*
DAS28 at 6 months (n=27)	**2.8 (1.5-3.6)**
6 vs 12 months	*p=0.595*
DAS28 at 12 months (n=22)	**2.1 (1.7-3.3)**
12 vs 18 months	*p=0.197*
DAS28 at 18 months (n=17)	**2.2 (1.7-3.8)**
18 vs 24 months	*p=0.563*
DAS28 at 24 months (n=17)	**1.8 (1.6-3.4)**
24 vs 30 months	*p=0.954*
DAS28 at 30 months (n=15)	**2.5 (1.6-3.6)**
30 vs 36 months	*p=0.563*
DAS28 at 36 months (n=12)	**2.1 (1.4-2.7)**
Baseline vs 36 months	*p<0.001*

Specifically, despite a significant reduction in DAS28 already seen at 6 months (2,8), a remission value (2.1) was achieved only at 12 months. Furthermore, the value did not progressively decrease but increased again at 30 months (2.5, still a remission value but close to low disease activity), then decreased again at 36 months (2.1). The significant improvement was between baseline and 6 months (p=0,005). No significant differences were observed at 12, 18, 24, 30, 36 months.

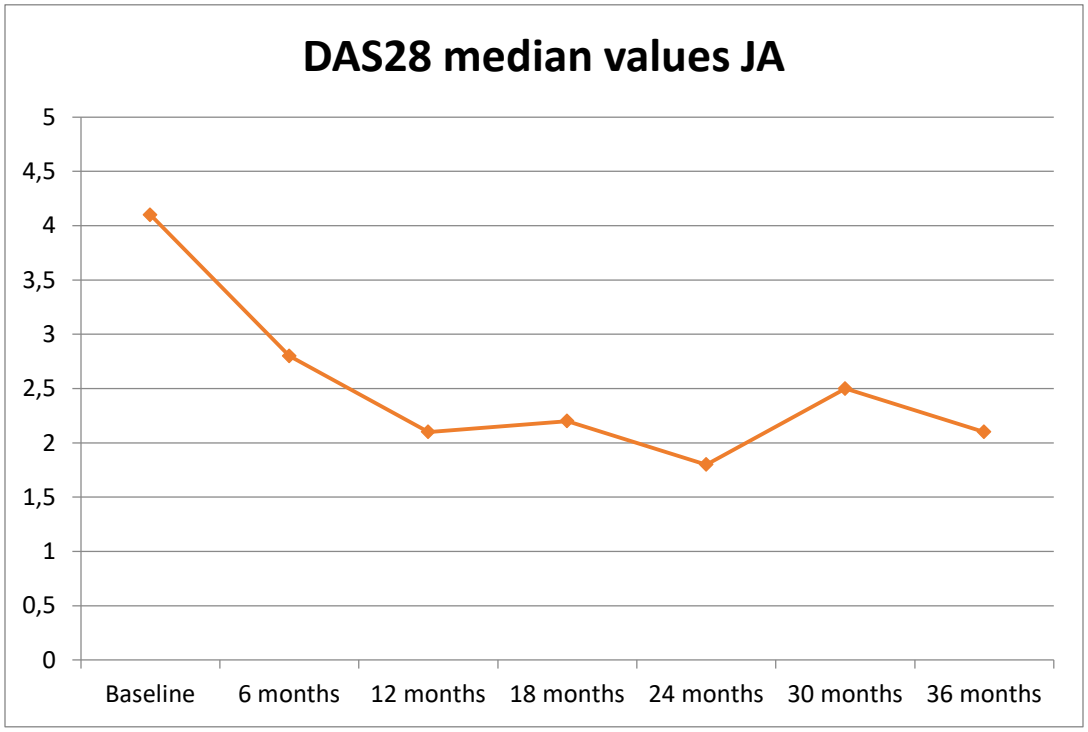

Fig. 6: DAS28 median values for JA

Remission rate

Regarding the percentage of patients who achieved a DAS28 remission value, the number initially increased significantly, rising from 18.8% to 55.6% at 24 months. However, it subsequently declined, reaching 37.5% at 30 months, followed by a slight increase to 42.9% at 36 months.

Tab. XI: DAS28 remission stratified for JA

% JA patients with DAS28 <2,6	
DAS28 <2,6 at 6 months	18,8%
DAS28 <2,6 at 12 months	36,4%
DAS28 <2,6 at 18 months	50,0%
DAS28 <2,6 at 24 months	55,6%
DAS28 <2,6 at 30 months	37,5%
DAS28 <2,6 at 36 months	42,9%

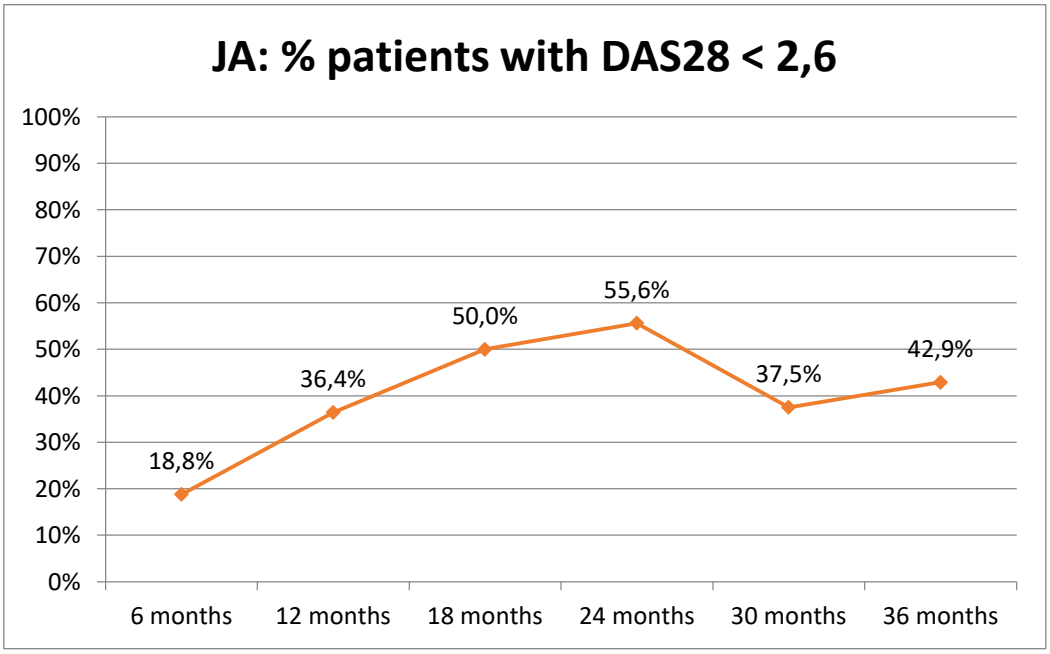

Fig. 7: DAS28 remission percentages for JA

Mean glucocorticoid (prednisone equivalent) reduction

19 JA patients presented a valid value of GC intake at the beginning of the study At baseline, the mean GC use was 8,95 mg/day, during the follow-up it was 5,91 at 6 months, 5,46 at 12 months, 8,98 at 18 months, 4,81 at 24 months, 4,25 at 30 months, 3,88 at 36 months.

Tab. XII: Daily mean use of GC of JA patients

	N° of patients	Mean (mg/day)	Standard deviation
Baseline	19	8,95	4,86
6 months	16	5,91	4,37
12 months	13	5,46	3,79
18 months	11	8,98	13,91
24 months	11	4,81	4,27
30 months	11	4,25	3,14
36 months	8	3,88	3,59

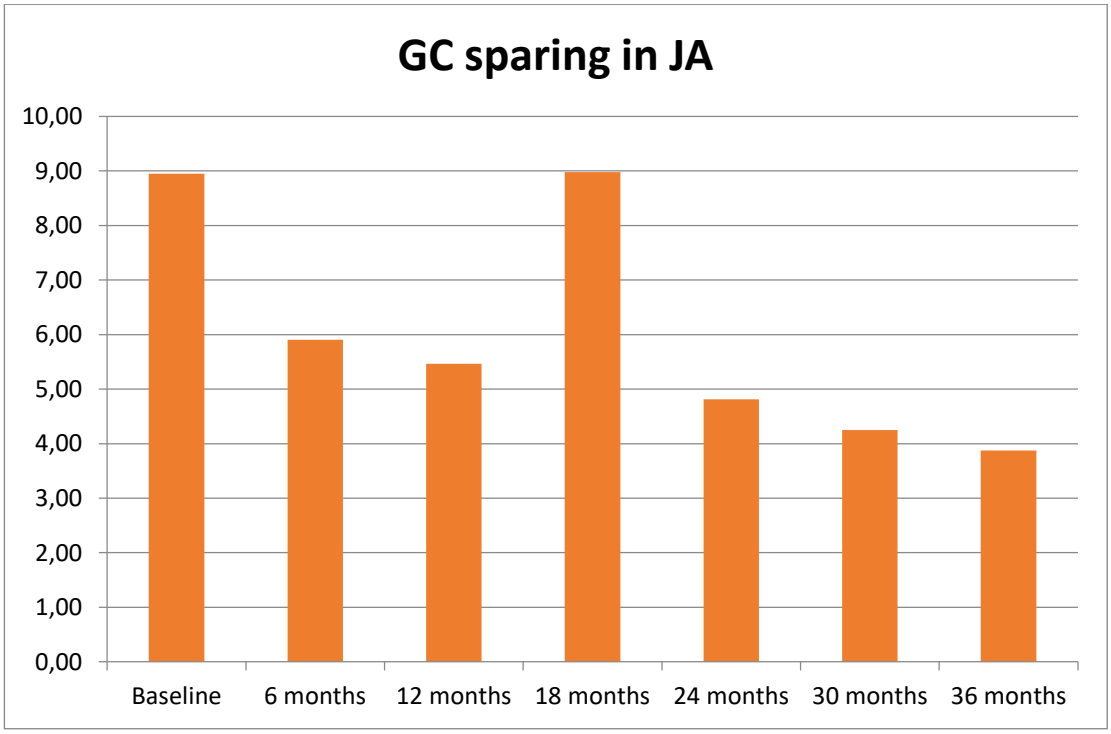

Fig. 9: Daily mean use of GC of JA patients

Glucocorticoid (prednisone equivalent) reduction stratified

Padova cohort had 12 JA patients At baseline, 50% of patients of the Padova cohort were taking >7.5 mg/day of GC. At 12 months, this percentage decreased to 12.5% and at 30 months none were taking >7.5 mg/day of GC. By 36 months, 40% of patients were not using GC, and the remaining 60% were using ≤ 5 mg/day.

Tab. XIII: Daily use of GC of JA patients

Number of patients							
Daily use of GC	**T0**	**T6**	**T12**	**T18**	**T24**	**T30**	**T36**
0 mg/day	1	1	1	3	4	3	3
0,1-5 mg/day	3	6	5	4	2	1	2
5,1-7,5 mg/day	2	2	1	0	1	1	0
>7,5 mg/day	6	2	1	0	0	0	0

Percentage of patients							
Daily use of GC	**T0**	**T6**	**T12**	**T18**	**T24**	**T30**	**T36**
0 mg/day	8,33%	9,09%	12,50%	42,86%	57,14%	60,00%	60,00%
0,1-5 mg/day	25,00%	54,55%	62,50%	57,14%	28,57%	20,00%	40,00%
5,1-7,5 mg/day	16,67%	18,18%	12,50%	0,00%	14,29%	20,00%	0,00%
>7,5 mg/day	50,00%	18,18%	12,50%	0,00%	0,00%	0,00%	0,00%

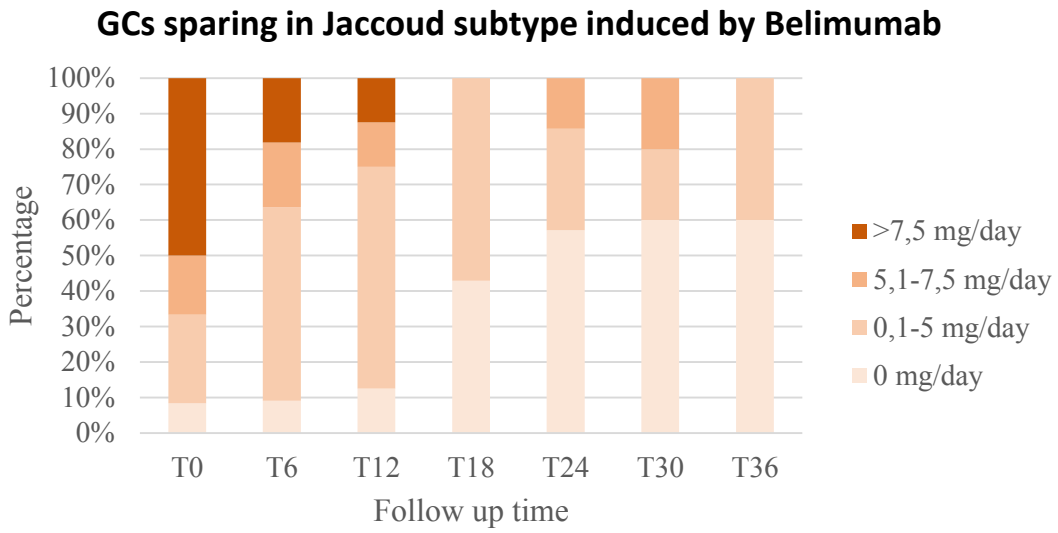

Fig. 10: Daily use of GC of JA patients

3. Rhupus

At baseline 21 patients with rhupus were analyzed, during follow-up we analyzed 18 patients at 6 months, 17 at 12 months, 12 at 18 months, 11 at 24 months, 10 at 30 months, and 8 at 36 months.

Median DAS28

In rhupus, the initial median DAS28 value was 4.3 (moderate disease activity). In this case, the DAS28 values decreased even more irregularly, without achieving a definite and sustained remission at 36 months.

Tab. XIV: DAS28 median values for rhupus

DAS28 median values for rhupus	
DAS28 at baseline (n=21)	**4.3 (3.2-5.2)**
Baseline vs 6 months	*p=0.011*
DAS28 at 6 months (n=18)	**2.8 (2.0-4.6)**
6 vs 12 months	*p=0.522*
DAS28 at 12 months (n=17)	**3.2 (2.3-4.0)**
12 vs 18 months	*p=0.841*
DAS28 at 18 months (n=12)	**3.3 (2.1-5.3)**
18 vs 24 months	*p=0.162*
DAS28 at 24 months (n=11)	**2.5 (2.0-3.2)**
24 vs 30 months	*p=0.705*
DAS28 at 30 months (n=10)	**2.4 (1.9-4.4)**
30 vs 36 months	*p=0.925*
DAS28 at 36 months (n=8)	**2.7 (2.1-3.7)**
Baseline vs 36 months	*p=0.047*

Despite a reduction in the median value already seen at 6 months, the level remained in the low-moderate disease activity range, reaching remission values only at 24 and 30 months. However, these remission values were not maintained, resulting in an increase back to disease activity levels, albeit low, at 36 months. The significant improvement was between baseline and 6 months (p=0,011). No significant differences were observed at 12, 18, 24, 30, 36 months.

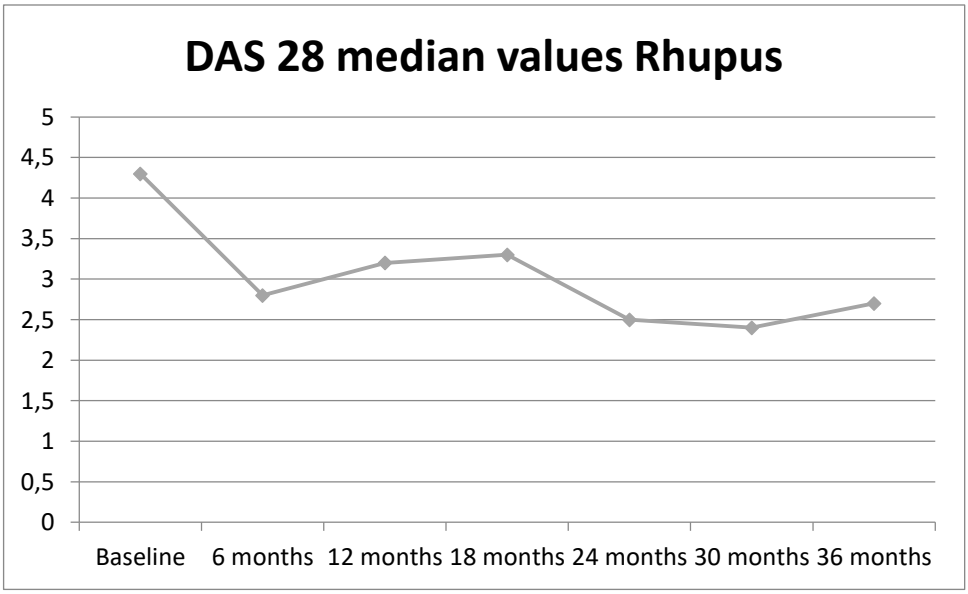

Fig. 11: DAS28 median values for rhupus

Remission rate

Tab. XV: DAS28 remission stratified for rhupus

% rhupus patients with DAS28 <2,6	
DAS28 <2,6 at 6 months	30,0%
DAS28 <2,6 at 12 months	33,3%
DAS28 <2,6 at 18 months	40,0%
DAS28 <2,6 at 24 months	75,0%
DAS28 <2,6 at 30 months	66,7%
DAS28 <2,6 at 36 months	33,3%

Regarding the percentage of patients who achieved a DAS28 remission value, initially there was only a slight improvement, followed by a significant increase at 24 months, with patients in remission rising from 30% to 75%. However, subsequently, the value dropped again, returning close to the initial level at 33.3%.

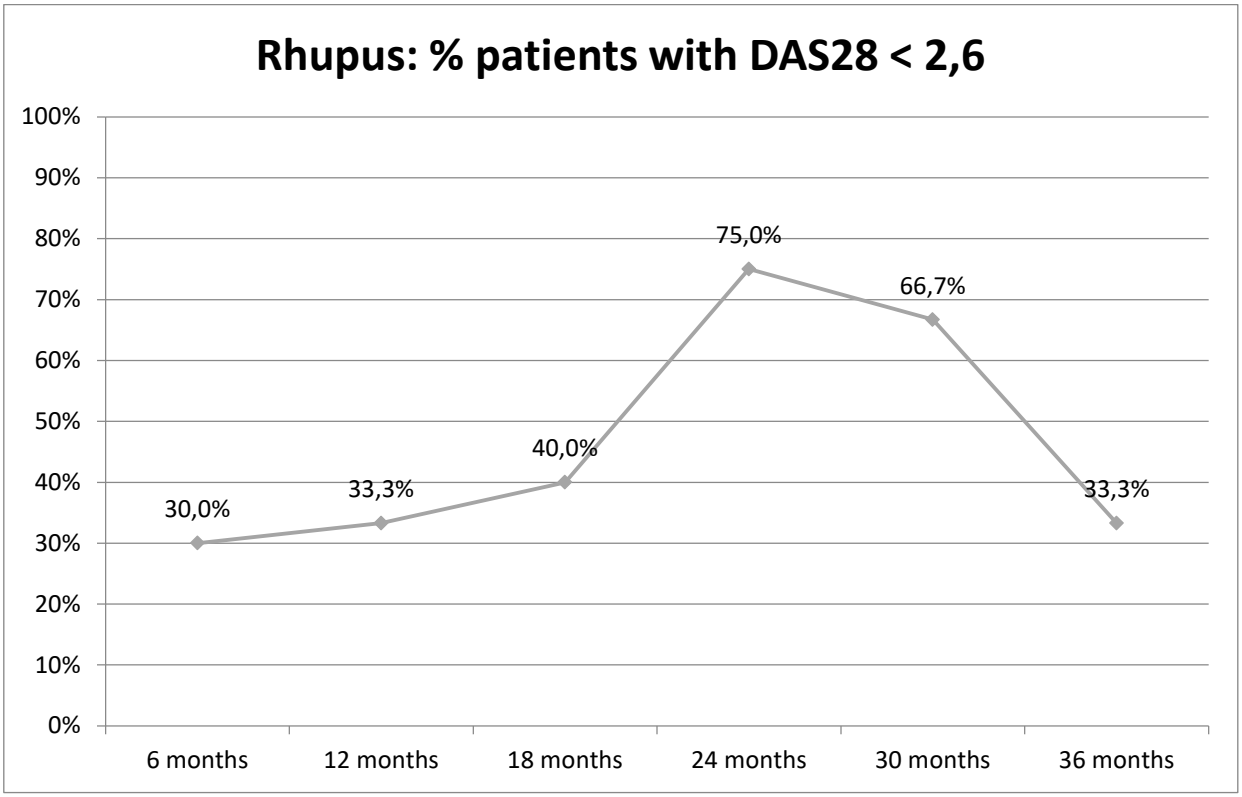

Fig. 12: DAS28 remission percentages for rhupus

Mean glucocorticoid (prednisone equivalent) reduction

13 rhupus patients presented a valid value of GC intake at the beginning of the study At baseline, the mean GC use was 8,17 mg/day, during the follow-up it was 5,81 at 6 months, 5,59 at 12 months, 4,69 at 18 months, 3,63 at 24 months, 3,31 at 30 months, 2,1 at 36 months.

Tab. XVI: Daily mean use of GC of rhupus patients

	N° of patients	Mean (mg/day)	Standard deviation
Baseline	13	8,17	6,59
6 months	12	5,81	3,85
12 months	11	5,59	4,11
18 months	9	4,69	3,84
24 months	8	3,63	4,32
30 months	6	3,31	3,69
36 months	6	2,10	3,66

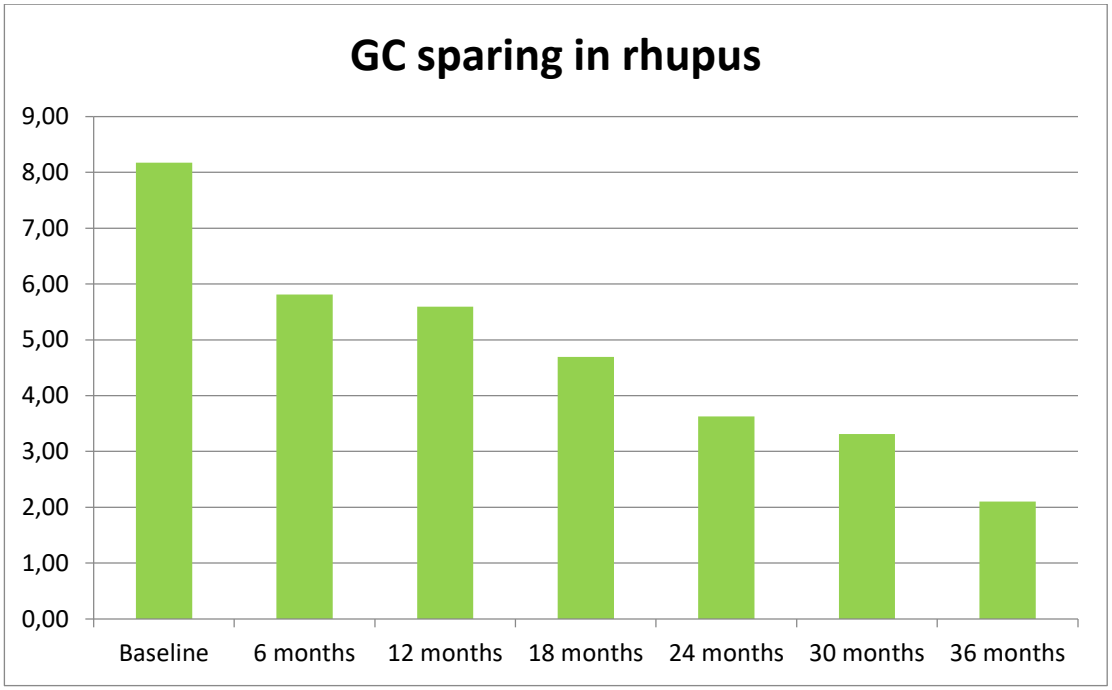

Fig. 13: Daily mean use of GC of rhupus patients

Glucocorticoid (prednisone equivalent) reduction stratified

Padova cohort had 5 rhupus patients. At baseline, 80% of patients of the Padova cohort were on more than 7.5 mg/day, but within 12 months, this percentage dropped to 25%, and then to 0% in the subsequent months. By 36 months, all patients were on less than 5 mg/day of GC, but none had completely eliminated the drug.

Tab. XVII: Daily use of GC of rhupus patients

Number of patients							
Daily use of GC	**T0**	**T6**	**T12**	**T18**	**T24**	**T30**	**T36**
0 mg/day	0	0	0	0	0	0	0
0,1-5 mg/day	1	1	1	0	1	2	2
5,1-7,5 mg/day	0	1	2	2	1	0	0
>7,5 mg/day	4	2	1	0	0	0	0

Percentage of patients							
Daily use of GC	**T0**	**T6**	**T12**	**T18**	**T24**	**T30**	**T36**
0 mg/day	0,00%	0,00%	0,00%	0,00%	0,00%	0,00%	0,00%
0,1-5 mg/day	20,00%	25,00%	25,00%	0,00%	50,00%	100,00%	100,00%
5,1-7,5 mg/day	0,00%	25,00%	50,00%	100,00%	50,00%	0,00%	0,00%
>7,5 mg/day	80,00%	50,00%	25,00%	0,00%	0,00%	0,00%	0,00%

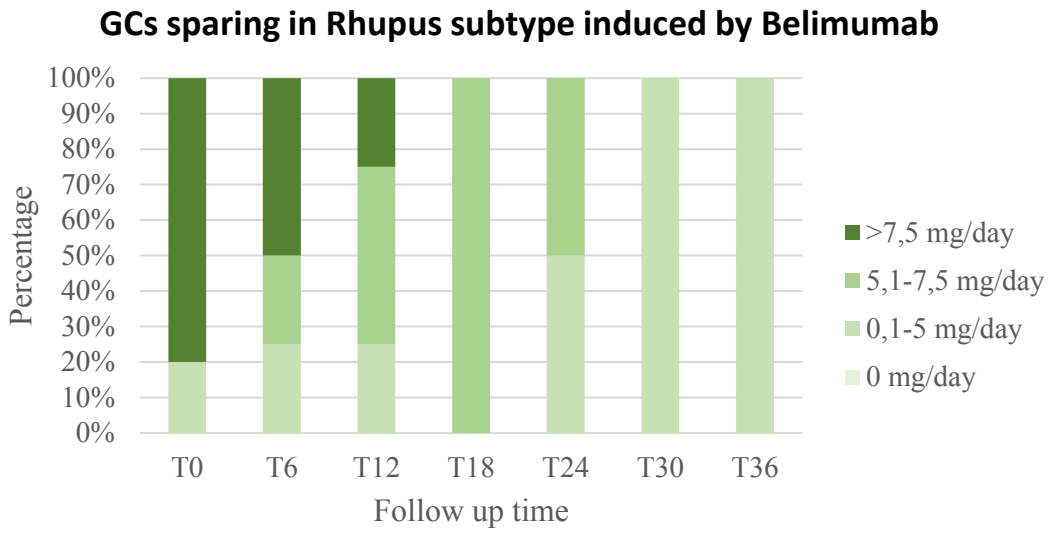

Fig. 14: Daily use of GC of rhupus patients

4. Comparison between different phenotypes of joint involvement

Median DAS28

Tab. XVIII: DAS28 median values for different joint phenotypes. DAS28 scores are reported as median and interquartile range. P values were assessed by Friedman's test.

Joint phenotype	NDNE	JA	Rhupus
DAS28 at baseline (n=260)	**3.7 (2.7 - 4.5)**	**4.1 (3.1-5.1)**	**4.3 (3.2-5.2)**
Baseline vs 6 months	*p<0.001*	*p=0.005*	*p=0.011*
DAS28 at 6 months (n=224)	**2.2 (1.6-2.9)**	**2.8 (1.5-3.6)**	**2.8 (2.0-4.6)**
6 vs 12 months	*p=0.046*	*p=0.595*	*p=0.522*
DAS28 at 12 months (n=220)	**2.0 (1.5 - 2.8)**	**2.1 (1.7-3.3)**	**3.2 (2.3-4.0)**
12 vs 18 months	*p=0.224*	*p=0.197*	*p=0.841*
DAS28 at 18 months (n=180)	**1.9 (1.2-2.5)**	**2.2 (1.7-3.8)**	**3.3 (2.1-5.3)**
18 vs 24 months	*p=0.094*	*p=0.563*	*p=0.162*
DAS28 at 24 months (n=165)	1.6 (1.1-2.4)	1.8 (1.6-3.4)	2.5 (2.0-3.2)
24 vs 30 months	*p=0.554*	*p=0.954*	*p=0.705*
DAS28 at 30 months (n=151)	**1.6 (0.1-2.4)**	**2.5 (1.6-3.6)**	**2.4 (1.9-4.4)**
30 vs 36 months	*p=0.738*	*p=0.563*	*p=0.925*
DAS28 at 36 months (n=122)	**1.6 (1.2-2.5)**	**2.1 (1.4-2.7)**	**2.7 (2.1-3.7)**
Baseline vs 36 months	*p<0.001*	*p<0.001*	*p=0.047*

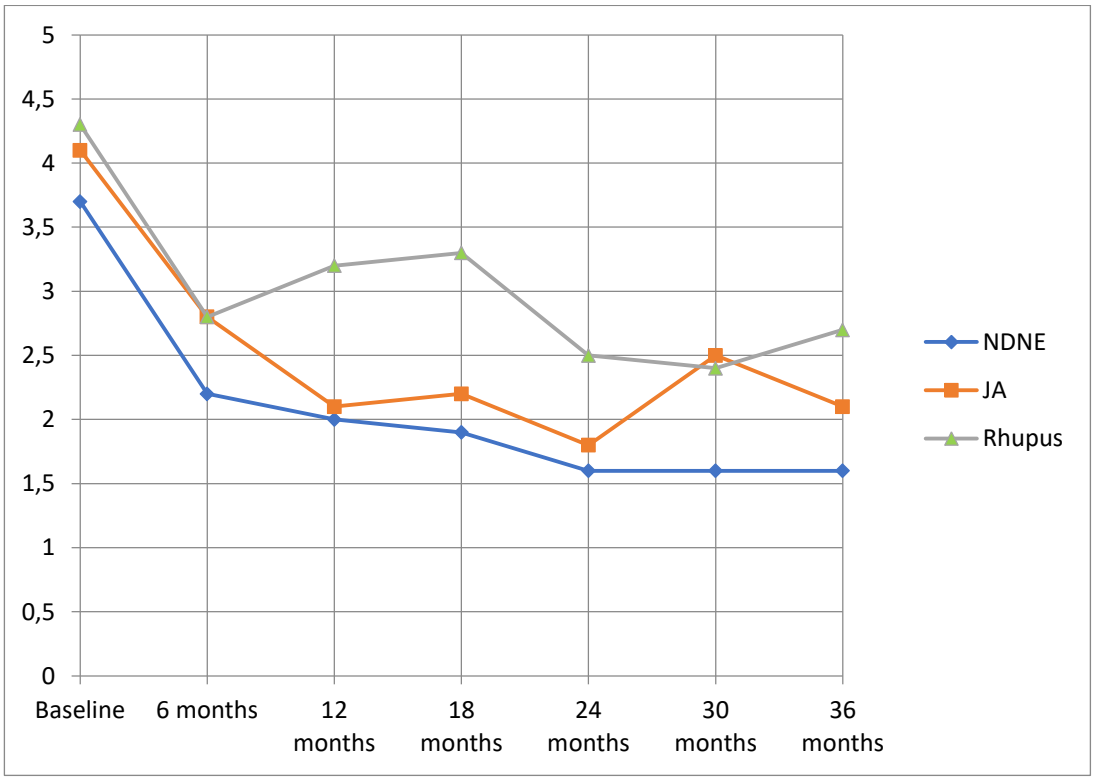

Fig. 15: DAS28 median values

A statistically significant decrease in DAS28 compared with baseline was observable at 6 and 12 months for NDNE ($p<0.001$), JA ($p=0.005$) and rhupus ($p=0.011$). Significant further improvement of DAS28 in patients with NDNE was also observable when comparing DAS28 at 6 vs 12 months ($p=0.046$).

Remission rate

Tab. XIX: DAS28 remission stratified for different joint phenotypes. p-values were assessed by Chi-squared test with Bonferroni correction

	NDNE		JA		Rhupus		
Time	number of patients with DAS28 < 2,6	% of patients with DAS28 < 2,6	number of patients with DAS28 < 2,6	% of patients with DAS28 < 2,6	number of patients with DAS28 < 2,6	% of patients with DAS28 < 2,6	p-value
6 months	90	59,6%	3	18,8%	3	30,0%	0,002
12 months	78	59,5%	4	36,4%	3	33,3%	0,118
18 months	76	72,4%	4	50,0%	2	40,0%	0,142
24 months	67	77,9%	5	55,6%	3	75,0%	0,330
30 months	58	75,3%	3	37,5%	2	76,7%	0,077
36 months	49	77,8%	3	42,9%	1	33,3%	0,043

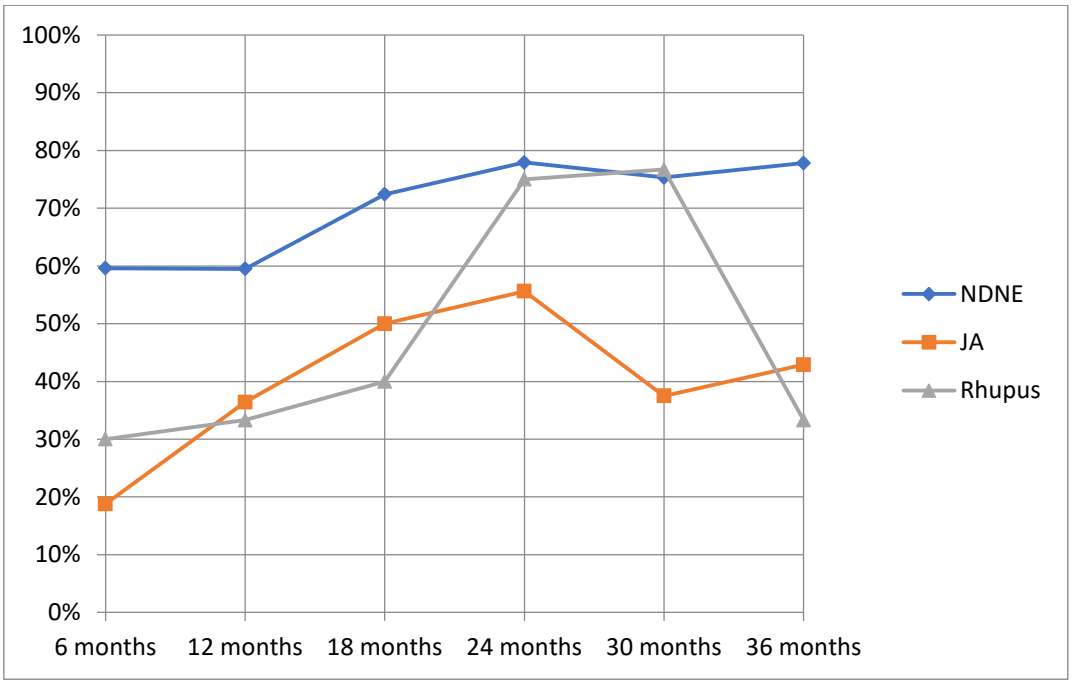

Fig. 15: DAS28 remission stratified for different joint phenotypes

In the case of remission rates, the difference is significant only at 6 months (p=0,002) and at 36 months (p=0,043). While the percentage of NDNE patients with remission increased over time, percentage of JA and rhupus patients in remission faced an irregular and less substantial improvement.

Mean glucocorticoid (prednisone equivalent) reduction

Tab. XX: mean use of GC for the three phenotypes

	NDNE N° of patients	Mean (mg/day)	Standard deviation	JA N° of patients	Mean (mg/day)	Standard deviation
Baseline	186	10,20	7,82	19	8,94737	4,863825
6 months	165	6,06	5,64	16	5,91	4,37
12 months	148	5,35	6,50	13	5,46	3,79
18 months	126	4,31	4,00	11	8,98	13,91
24 months	115	3,98	4,01	11	4,81	4,27
30 months	103	3,78	2,87	11	4,25	3,14
36 months	83	3,43	3,00	8	3,88	3,59

	Rhupus N° of patients	Mean (mg/day)	Standard deviation	Total N° of patients	Mean (mg/day)	Standard deviation	p-value
Baseline	13	8,17	6,59	218	9,97	7,54	0,536
6 months	12	5,81	3,85	193	6,03	5,44	0,984
12 months	11	5,59	4,11	172	5,37	6,19	0,991
18 months	9	4,69	3,84	146	4,69	5,43	0,023
24 months	8	3,63	4,32	133	4,03	4,03	0,777
30 months	6	3,31	3,69	120	3,80	2,92	0,808
36 months	6	2,10	3,66	97	3,39	3,07	0,535

A decrease in the mean value of GC is present in all joint phenotypes, reaching average values below 5 mg/day.

With Bonferroni correction, the only significant p-value is at 18 months, between NDNE and JA.

Glucocorticoid (prednisone equivalent) reduction stratified

Tab. XXI: use of GC stratified of all articular patients of the Padova cohort

Number of patients	T0	T6	T12	T18	T24	T30	T36
0 mg/day	7	7	13	14	20	21	17
0,1-5 mg/day	44	57	59	53	36	34	26
5,1-7,5 mg/day	14	21	19	8	7	6	1
>7,5 mg/day	61	26	6	4	3	1	2

Percentage of patients	T0	T6	T12	T18	T24	T30	T36
0 mg/day	5,56%	6,31%	13,40%	17,72%	30,30%	33,87%	36,96%
0,1-5 mg/day	34,92%	51,35%	60,82%	67,09%	54,55%	54,84%	56,52%
5,1-7,5 mg/day	11,11%	18,92%	19,59%	10,13%	10,61%	9,68%	2,17%
>7,5 mg/day	48,41%	23,42%	6,19%	5,06%	4,55%	1,61%	4,35%

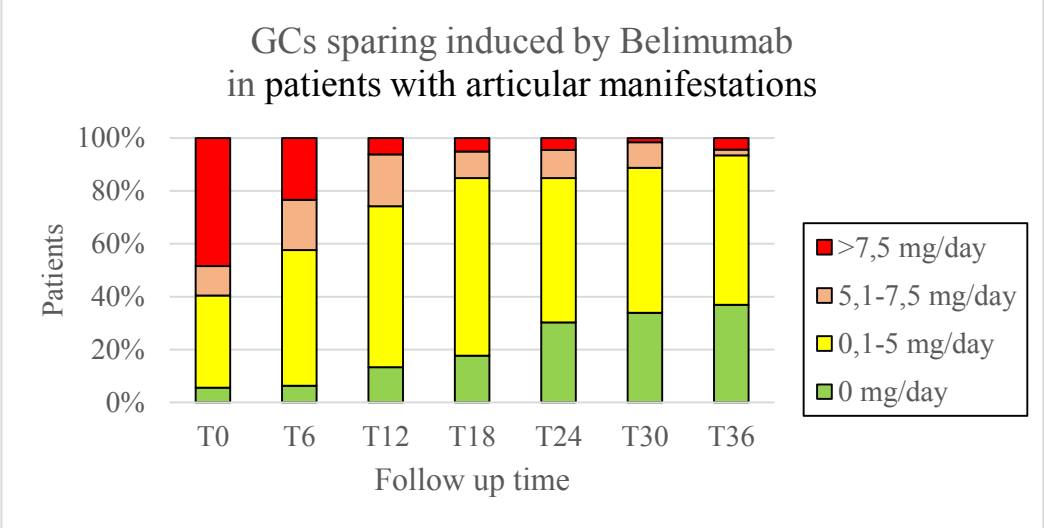

Fig.16: use of GC stratified of all articular patients of the Padova cohort

At baseline, 59.52% of patients were taking a cortisone dose greater than 5 mg/day. This percentage decreased to 42.34% at 6 months and continued to decrease progressively, reaching 6.52% at 36 months.

DISCUSSION

In our study, we assessed the effectiveness and safety of belimumab, as well as the achievement rate of new therapeutic targets (i.e., remission in musculoskeletal manifestations) in a very large nationwide cohort of SLE patients, prospectively followed up in a real-life setting. A statistically significant decrease in DAS28 compared to baseline was observed at 6 months for NDNE ($p< 0.001$), Jaccoud's arthropathy ($p=0.005$), and rhupus ($p=0.011$). Further significant improvement in DAS28 for patients with NDNE was also noted when comparing DAS28 at 6 versus 12 months ($p=0.046$). DAS28 remission was more common in patients with NDNE than in those with Jaccoud's arthropathy and rhupus subtypes at 6 and 36 months.

Overall, the musculoskeletal manifestation with the best results, both in terms of reduction in DAS28 and percentage of patients in remission, was NDNE. This result could be due to the fact that this involvement is due to the expression of systemic disease activity and does not lead to permanent damage, unlike JA and rhupus.

In the case of JA the improvements were less significant, probably because Jaccoud’s arthropathy is an expression of periarticular alteration resulting from a long-standing and chronic subclinical disease activity, which might be a condition more difficult to improve compared to NDNE, in addition joint deformities observable in patients with Jaccoud’s arthropathy is by themselves expression of joint damage. On the other hand, in our cohort only a few patients presented JA, and being statistically and epidemiologically less frequent, its response is more difficult to analyze.

In rhupus, the results were the worst, which could be due to the fact that it is an overlap with rheumatoid arthritis, where additional damage mechanisms may be present, not only deformities, but also bone erosions.
There may also be a more significant inflammatory process, making it more difficult to improve compared to the other phenotypes.

As for Jaccoud's arthropathy, there were only a few patients with rhupus, which led to large variations in the data even for small changes. This is indeed a manifestation that is statistically and epidemiologically even less frequent than JA, and therefore more difficult to interpret. Additionally, rhupus tends to flare up more frequently, which is also reflected in our data.

Nonetheless, in JA and rhupus, there was clinical improvement, although it was less evident compared to NDNE arthritis.

This study, however, has some limitations: the absence of a control group, which would have allowed for a comparison with patients not treated with belimumab and thus demonstrated a clear cause-effect relationship; the need to also consider patients who, for various reasons, discontinued the drug. Strengths of this study are that this is a large multicenter study; all patients were homogeneity treated according to EULAR guidelines finally, all were treated in specialized outpatient clinics dedicated exclusively to the treatment of SLE (lupus clinics).

Regarding GC use, BeRLiSS-newJoint confirmed what had already been observed in BeRLiSS-JS (88), namely that belimumab allows for its reduction. Specifically, most patients achieved the target dose of ≤ 5 mg/day within 12 months, as recommended by the EULAR 2023 recommendations (100). In the case of JA and rhupus, due to the small number of patients, despite the decrease in GC consumption, results should be further analyzed in larger and more significant samples.

CONCLUSIONS

Belimumab was effective at reducing joint involvement activity at 6, 12, 24 and 36 months with significant decrease in DAS28 being observable as early as 6 months from treatment start across all joint phenotypes. Remission rates were statistically significant only at 6 and 36 months. The phenotype with the best results regarding efficacy was NDNE, although JA and rhupus also showed clinical improvement, albeit less evident and consistent.

Regarding GC use, it is confirmed that belimumab is effective in reducing the daily dose. However, more precise percentages would benefit from a larger study, especially among JA and rhupus patients.

In conclusion, we can highlight the effectiveness of belimumab on the three joint phenotypes. However, further analyses on larger cohorts are necessary to determine its actual level of efficacy, especially in less common manifestations such as rhupus and JA. Additionally, it is important to note how the intrinsic behavior of the individual phenotypes also impacts the overall effectiveness.

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