Joint Involvement in Systemic Lupus Erythematosus

6

Daniela Rossi, Vittorio Modena, G. Bianchi, Raffaele Pellerito, and Dario Roccatello

Systemic lupus erythematosus (SLE) is a chronic immune-mediated disease affecting multiple organs including skin, brain, peripheral nervous system, heart, gastrointestinal tract, kidney, and, almost invariably, joints. Clinical features in individual patients are highly variable, and arthritis and arthralgias in SLE deserve to be specifically addressed.

D. Rossi • V. Modena (✉)
CMID – Center of Research of Immunopathology and Rare Diseases, Coordinating Center of the Network of Rare Diseases of Piedmont and Aosta Valley, Department of Rare, Immunologic, Hematologic and Immunohematologic Diseases, Giovanni Bosco Hospital, University of Turin, Turin 10154, Italy
e-mail: daniela.rossi@unito.it; modenavittorio@libero.it

G. Bianchi
Division of Rheumatology, Department of Locomotor System, ASL3 Genovese, Genoa, Italy

R. Pellerito
Department of Rheumatology, Mauriziano Hospital, Turin 10128, Italy

D. Roccatello
CMID – Center of Research of Immunopathology and Rare Diseases, Coordinating Center of the Network of Rare Diseases of Piedmont and Aosta Valley, Department of Rare, Immunologic, Hematologic and Immunohematologic Diseases, Giovanni Bosco Hospital, and University of Turin, Turin 10154, Italy

SCDU Nephrology and Dialysis, Giovanni Bosco Hospital, and University of Turin, Turin, Italy
e-mail: dario.roccatello@unito.it

D. Roccatello, L. Emmi (eds.), *Connective Tissue Disease: A Comprehensive Guide-Volume 1*, Rare Diseases of the Immune System 5,
DOI 10.1007/978-3-319-24535-5_6

6.1 Arthritis and Arthralgias in SLE

Articular involvement is very frequent in SLE. In 34–50 % of patients with SLE, joint involvement is the first manifestation of the disease, whereas during the course of SLE, it is almost always present [1–4]. Joint involvement occurs more frequently in women, both at onset and during the course of the disease [5–7]. It is polymorphous and shows varying degrees of clinical severity, with increasing frequency depending on age at SLE onset, and it is more frequent in patients with onset of illness in adulthood [8, 9]. It represents one of the most frequent causes of difficulties in daily activities, job reduction, and abandonment [10–12].

Articular signs, such as arthralgia or arthritis, may be observed in the course of SLE. Arthralgia, which is defined as the presence of joint pain in the absence of clear synovitis, erosion, or deformities, is very frequent both at the onset and during the course of the disease [13]. Arthralgia is persistent, migrant, transient, and frequently associated with myalgia. It is often extremely intense and disproportionate to the finding at the physical examination [14]. In patients with arthralgia alone, the most recent imaging techniques, such as magnetic resonance imaging (MRI) and ultrasonography (US), may frequently reveal inflammatory articular changes which is undetectable by clinical evaluation [15–17].

Arthritis in the course of SLE can be acute, subacute, and/or chronic and is often detected (in 67–87 % of cases) (Table 6.1) at disease onset. The differences in prevalence reported in various studies may depend on the racial backgrounds of the cohorts, on the different age of the patients, and on the level of expertise of the enrolling center (e.g., nephrology centers or rheumatology centers).

Acute arthritis may occur as polyarthritis or oligoarthritis; it may be symmetric or asymmetric, with preferential involvement of the joints of the hands, wrists, and knees [18–26]. It is sensitive to anti-inflammatory treatment and usually does not recur during therapy [14]. It is frequently associated with visceral involvement and systemic signs; thus it can be a warning symptom of an SLE flare.

Subacute arthritis has a more prolonged course with milder inflammatory signs and it is frequently accompanied by morning stiffness. In older patients, the clinical picture may resemble rheumatic polymyalgia [14]. Lastly, arthritis in the course of SLE can occur as chronic arthritis without deformities and erosions, or as deforming, non-erosive, reversible arthropathy, or in some patients as erosive arthritis.

Examination of the synovial fluid shows some inflammatory liquid with a predominance of mononuclear cells and a decrease in complement levels with hypergammaglobulinemia. Antinuclear antibodies (ANA), lupus erythematosus (LE) cells, hematoxylin bodies, and ragocytes may be observed [14]. In a recent study, LE cells were present in 5/31 patients suffering from SLE and in 9/27 patients with the overlap syndrome (rheumatoid arthritis (RA)/SLE). In the same study, LE cells were observed in 2.6 % of 331 patients with RA and in none of 4 subjects with Still's disease, in 9 with systemic scleroderma, in 132 with ankylosing spondylitis, in 57 with Reiter's syndrome, and in 34 with psoriatic arthritis [27].

Common findings at synovial biopsy include synoviocyte hyperplasia, scarce inflammatory infiltrate, vascular proliferation, edema and congestion, fibrinoid

Table 6.1 Prevalence (%) of arthritis in different series of adult patients of SLE

Arthralgia or arthritis														
	Europe	**Brazil**	**Spain**	**Puerto Rico**	**Latin America**			**LUMINA (Hispanics)**		**Portugal**	**Brazil**	**Brazil**	**North America**	**Italy**
References	[18]	[19]	[20]	[21]	[2]			[22]		[23]	[24]	[4]	[25]	[17]
Year	1993	1995	1995	1999	2004			2004		2007	2012	2012	2014	2015
					European	**Mestizo**	**African**	**Tex**	**Puerto Rican**					
Number of patients	1,000	685	307	124	507	537	152	105	81	544	305	888	2,139	102
Arthritis %	84	82	83	67.5	93.5a	92.5a	94.1a	79.1	69.1	72	77.36a	87.4	70.8	94.1a

By Borba et al. [4], modified

necrosis and intimal fibrous hyperplasia of blood vessels, presence of fibrin on the synovial surface, and fibrin-like deposits in the chorion [28]. Indeed, some synovial alterations, ranging from simple hyperemia to synovitis, may mimic those found in RA [14]. Some studies have found differences in the synovium of patients with SLE and those suffering from RA and osteoarthritis (OA) from a gene expression profile perspective [29]. The synovium of patients with SLE suffering from arthritis shows a very distinct molecular signature as compared to what is observed in patients with OA and RA. It is characterized by the upregulation of interferon-inducible genes, as observed in the peripheral blood and kidney glomeruli of SLE patients [30], and downregulation of genes involved in extracellular matrix homeostasis. This might suggest the presence of different pathogenic mechanisms in SLE and RA, which would explain the lack of bone erosion observed in SLE patients with arthritis [29, 31].

6.2 Jaccoud's Arthropathy

The 1982 ACR classification criteria [32] modified the weight of joint involvement switching from "arthritis without deformity" of 1971 criteria [33] to "non-erosive arthritis." This change allowed to include patients with Jaccoud's arthropathy (JA) among those with SLE. In 2012, the SLICC criteria [34] proposed modifying the criterion to "synovitis ≥2 peripheral joints, characterized by pain, tenderness, swelling or morning stiffness ≥30 min," since new imaging techniques clearly show that some forms of SLE arthritis are in fact erosive [17].

In 1869, Jaccoud [35] first described deforming, non-erosive, reversible arthropathy associated with rheumatic fever. Later, this arthropathy was also observed in other rheumatic diseases and connective tissue diseases, as well as in sarcoidosis, infections, hypocomplementemic urticarial vasculitis, chronic pulmonary disease, inflammatory intestinal disease, pyrophosphate deposition disease, hypermobility syndrome, borreliosis, and neoplasia [36–41]. JA also occurs in an idiopathic form, in particular in the elderly, sometimes affecting several members of the same family [42, 43]. It was first described [44, 45] in patients suffering from SLE [24, 46–48] with a prevalence of up to 35 % [24, 26, 47–52].

The articular deformities of JA may be limited to the ulnar deviation at the metacarpal-phalangeal joint (MCP). Villaumey [53] and Alarcon-Segovia [46] considered this a diagnostic element for JA in the absence of erosions and rheumatoid factor (RF). JA may be widespread and can simulate evolved RA with lateral hyperlaxity of the distal interphalangeal articulations, swan neck deformities, boutonniere deformities, Z-shaped thumb, and carpal hyperlaxity. JA may also affect the feet [54, 55] and knees, sometimes in a disabling way, as well as the shoulders [14]. Deformities are usually reducible, even though some deformities may present elements of fixity [13].

In 1992, Spronk and coworkers [47] proposed a diagnostic index for JA (DIJA) based on the presence or absence of ulnar drift (>20′), swan neck deformities, boutonniere deformities, Z deformity, and limited MCP extension. Depending on the

number of affected fingers, the first four items of the diagnostic index are graded from 2 to 3, whereas the fifth item is graded from 1 to 2, with a maximum total score of 23. JA was considered as being present if the index exceeded five points. This scoring method was frequently cited but never validated in well-designed studies [13, 56]. In 1998, van Vugt [57] introduced the term "mild deforming arthropathy" for patients who present DIJA with a score equal to or below 5 in the presence of deforming arthropathy without erosion. New imaging techniques led to the detection of erosive signs not previously detected by conventional radiology, thus leading to a new step in the differentiation between JA, mild deforming arthropathy, and erosive arthritis [26]. Recently, new criteria to differentiate between "idiopathic" and "senescent" JA were proposed by Santiago et al. [56], including: (1) typical joint deformities which are correctable in a passive position, (2) presence or history of articular inflammation in the deformed joints, regardless of its intensity or etiology (RA, SLE, etc.), (3) absence of similar deformities in other healthy members of the same family, and (4) no erosions on conventional radiology, magnetic resonance, or high-performance ultrasound examination.

The presence of JA in patients with SLE has been associated with older age [58] and disease duration [47, 59, 60]. However, these findings were not in agreement with the observations by Alarcon-Segovia et al. [46]. Besides it has been shown that the main determinant for JA was high disease activity in the absence of synovitis [61].

JA is positively associated with Sjogren's syndrome [46, 58] and frequent tendon rupture [62] and negatively associated with renal involvement [24, 51].

Some authors have pointed out an association with the presence of RF [46, 47], but this finding was not confirmed by other studies [51, 59]. JA was associated with higher levels of C-reactive protein (CRP) [47, 60, 63], with the presence of lupus anticoagulant and anticardiolipin antibodies [57], and with the presence of antibodies against U1 RNP [64], and inconstantly with anti SS-A/Ro and -B/La [47, 51, 58, 65, 66]. A correlation with the presence of antibodies to type II collagen [67], with higher levels of interleukin-6 (IL-6) [60] and with anti-double-stranded DNA antibodies [46], was observed. Interestingly, JA has never been associated with antipeptide citrulline (anti-CCP) antibodies [68, 69].

In general, the development of JA is correlated with abnormalities of soft tissues, with ligament and capsular laxity, relaxation, and subsequent deviation of tendons from their axis with the association of muscular dysfunction. Some authors have speculated that the laxity of the articular capsules and ligaments may be secondary to inflammation with fibrosis of the articular capsule [70, 71]. A role of synovial vasculitis [57] has been proposed. Besides, it has been also hypothesized a role in JA development for a synovial vasculitis [57], persistent inflammatory process of the synovium with inflammatory cells infiltrate and IL-1 and IL-6 production [47, 72]. These observations are in line with the high levels of CRP observed in patients with JA [47, 60, 63], but not in other patients with SLE even during disease flare [26].

The detection of high levels of RF in patients with JA is inconsistent [46, 47, 51, 59]. Thus, the presence of RF may act as a local inductor of the inflammatory

process through the formation of immune complexes. However, it is worth noting that despite the documented presence of synovitis, this is not as aggressive as what is observed in RA [56]. JA can appear in other conditions as dermatomyositis, scleroderma, and chronic pulmonary disease without evidence of previous arthritis [40]. In 2006, Caznoch et al. [50] suggested a possible role of hyperparathyroidism linked to renal failure and the presence of an association between JA and the hypermobility syndrome, contrasting however with the previous observations by Klemp et al. [73]. A possible role for tenosynovitis has also been hypothesized [40], considering the reported association between JA and tendon ruptures [62]. As a matter of fact, 26 % of the 55 tendon ruptures in patients suffering from SLE were associated with the presence of JA [62]. Histological reports are very limited, though they led to the detection of mild synovitis without significant proliferation of the synovial membrane, light inflammatory infiltrates, microvascular alterations, fibrin precipitates, and hematoxylin corpuscles [47].

Based on a previous radiologic description, deforming chronic arthritis may present with swelling of the soft tissues; juxta-articular osteoporosis and joint space narrowing are rare, and exceptionally hook shaped erosions in the hands (and feet). All these features differ from what observed in RA (i.e., damage to the radial site of the metacarpal heads as well as a well-defined hook-shaped deformity with a sclerotic margin that is considered an adaptation to local stresses of persistent ulnar deviation) [74].

6.3 Rhupus

During the course of SLE, it is possible to observe, albeit rarely, an erosive arthritis similar to what is observed in RA. In 1971, Peter Schur [75] coined the term "rhupus" to describe patients with SLE who present arthritis and who also fulfill the classification criteria for RA [76]. Currently, the term rhupus is used by some to describe the coexistence of SLE and RA in the same patient [49, 57], while others use it to outline a subset of SLE patients with distinctive articular signs and typical clinical and radiological characteristics [3, 77]. However, the definition is still disputed since the immunopathological processes of SLE are considered to be exactly the opposite of the RA processes [78]. The real prevalence, the natural history and the clinical appearance are supported by few case series and small cohorts of patients, though with discrepancies in the definition of the cases and assessment methods [3, 77, 79–82]. It is however a very rare variant considering that until 2013, only 150 cases had been published [83]. Recently, the number of reports has been enriched by additional cohorts of patients [49, 84–86]. An epidemiological study showed a prevalence of about 0.09 % [79]. The prevalence of the more recent studies ranges from 1.30 to 5.8 % [49, 84, 85], which is surely higher than in previous reports [3, 79]. New imaging techniques for the study of the musculoskeletal system, like MRI and US [15–17, 70, 87, 88], have allowed to detect erosive alterations that would otherwise be undetectable by conventional radiology and to stress the higher prevalence of rhupus (9.7 %) [84].

Clinically, there are no statistically significant differences between the rhupus group and the control group regarding age and sex [49, 84, 85]. The signs of RA usually precede those of SLE [49, 84, 85] and these subjects have slower disease progression compared to patients with SLE without articular erosions [3, 49, 84, 89]. There were no significant differences in the prevalence of anti-double-stranded DNA, anti-Sm antibodies, anti- nuclear antibodies, and antiphospholipid antibodies between rhupus and SLE patients [49, 84]. On the other hand, patients suffering from rhupus present increased erythrocyte sediment rates and CRP levels [49, 84] and a greater presence of RF and antipeptide citrulline (anti-CCP) antibodies [49, 68, 84, 86, 90–94]. With regard to the presence of anti-CCP antibodies, a recent meta-analysis conducted on seven studies revealed 91.8 % and 47.8 % pooled specificity and sensitivity, respectively, in erosive arthropathy in SLE [92]. Comparatively in RA, a meta-analysis found the specificity and sensitivity of anti-CCP antibodies to be 95 % and 67 %, respectively [95]. The pooled specificity of anti-CCP antibodies in SLE patients with erosive disease is slightly lower than that of RA. It must be stressed that the studies by Qing et al. [93] and Zhao et al. [94] showed the highest sensitivity and lowest specificity, while Budhram et al. [92] hypothesized that these results can be explained by a threshold effect due to the low cutoff of anti-CCP antibody positivity that was used by the authors. Five studies reported anti-CCP antibody positivity in only 5 % or fewer patients with SLE and non-erosive arthritis [68, 91, 96–98]. The meta-analysis by Budhram suggests that the specificity of anti-CCP antibodies in SLE patients with erosive disease is comparable to that of RA when high cutoffs are used [92].

In rhupus, there is also a correlation between the severity of the articular involvement and positivity for anti-CCP antibodies [90–94]. A more recent study again confirms the association between anti-CCP antibodies and rhupus and highlights that the presence of these antibodies in patients suffering from SLE must make clinicians aware of the coexistence of RA [86], as confirmed by others Authors [69, 92].

Patients with rhupus have mild SLE activity and a lower incidence of visceral organ involvement compared to patients with SLE without RA and in particular with regard to renal and neurological involvement [49, 81, 84], although important clinical manifestations have also been reported [99, 100]. Patients with rhupus show a predominance of manifestations that are typical of RA, including clinical inflammation, deformities and erosions, and rheumatoid nodules, as well as a significantly high prevalence of RF and anti-CCP antibodies [3, 49, 69, 79, 81]. High titers of RF and anti-CCP antibodies are very often observed in patients meeting ACR criteria for RA and presenting articular erosions [69, 92]. Some authors believe that the appearance of rheumatoid nodules in patients with SLE represents a risk factor for rhupus [101].

A review of the medical literature on the correlation between anti-CCP antibodies and erosive arthritis in patients with SLE led Budhram et al. [92] to hypothesize the presence of two subgroups of patients with erosive arthritis. One subgroup presents a process that is pathologically different from that of RA, their anti-CCP antibodies are often negative, and these subjects likely do not meet the ACR criteria for RA. In the second subgroup, the pathogenesis of the erosions is the same as in RA, the anti-CCP antibodies are often positive, and these subjects likely meet the criteria for

RA. According to Budhram et al., patients in the two groups may present different erosive manifestations; in the former they may be similar to those described by Pastershank in JA [74], while the latter may show marginal erosions that are typical of RA. This theory should be investigated with specific imaging studies since the new imaging techniques, such as US and MRI, have shown an unexpectedly high prevalence of subclinical articular and periarticular involvement and, most importantly, a higher prevalence of bone erosions as compared to standard radiography, as well as an unexpectedly high prevalence of synovitis and tenosynovitis [15, 17, 102–104]. This hypothesis is supported by the observations that anti-CCP antibodies and RF show an additive effect on erosion and erosion size and number in RA [105].

Alongside the arthritic manifestations, tenosynovitis is frequently found in patients with SLE, mainly localized to the extensor tendons in the hands, with a prevalence ranging from 28 to 61 % [15, 17, 102–104].

6.4 Joint Involvment Management

There are some guidelines regarding the treatment of arthritis in the course of SLE [106]. An approach based on the type of arthritis has been proposed [107, 108]. First-line, short-term treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) is frequent in the presence of acute or subacute arthritis, given the episodic and limited nature of articular flares in many patients with SLE [107, 108]. Clearly, administration of these drugs must include rigorous renal and hepatic monitoring; cardiovascular and skin photosensitivity risks must also be taken into consideration, as should reports on rare cases of aseptic meningitis [108]. Many patients cannot tolerate NSAIDs or may present contraindications to their use, while others show more persistent arthritic episodes that are refractory to these drugs. In these cases, antimalarial drugs are recommended, in particular hydroxychloroquine, usually at a dosage of 6 mg/kg/die [109]; if necessary, corticosteroids should be associated [107–110]. Low-dose corticosteroids ($\leq$10 mg/day of prednisone equivalent) are usually administered, and if high doses are needed, corticoid-sparing agents should be used [108]. Direct injection of corticosteroids into joints can be useful, especially when involvement is limited to one or few joints or in tenosynovitis. In patients who do not respond to corticosteroids or antimalarial drugs, methotrexate or other immunosuppressants (azathioprine, leflunomide, mycophenolate mofetil) or non-conventional therapies must be taken into consideration [107, 111–113]. There is broad consensus on the use of methotrexate as a steroid-sparing agent [111] and its effectiveness in controlling articular manifestations [110, 111, 114–118]. Leflunomide proved to be effective in a controlled study of only 12 patients [119]; however, several cases of cutaneous lupus flare-up were reported [108]. Mycophenolate mofetil was also assumed to be effective [112, 120–122], even though evidence in the literature is limited [108]. Among the non-conventional drugs, some reports indicate the efficacy of rituximab [112, 122–124], even if there are no specific controlled studies on arthritic manifestations in SLE. With regard to belimumab, literature data [121, 126–128] suggest that it has potential for use in the

treatment of severe joint symptoms in lupus that are resistant to corticosteroid treatment or refractory to conventional treatment [108, 113], whereas tocilizumab [129] is still being investigated.

Despite its reduced efficacy and frequently unfavorable effects [130], if all other therapies fail, abatacept may be taken into consideration (under strict control of a reference center or other experts) for patients in whom lupus manifests as a corticodependent joint disease [108], while the use of anti-TNF-alpha drugs is not recommended [108, 125].

Treatment of Jaccoud's arthropathy is the same as what is recommended for chronic arthritis in the course of SLE. However, despite their symptomatic effect, there are no guarantees that NSAIDs, low-dose steroids, antimalarial drugs, or methotrexate can inhibit the progression of deformities [56]. The benefits of physical therapy and the use of orthotic devices are yet to be demonstrated, and there are few reports on surgical procedures to correct JA [131–135] since the indications, the best modalities, and when to indicate them are still unknown [50].

There are several reports concerning the use of disease-modifying antirheumatic drugs (DMARDs), and in particular methotrexate, in rhupus [117, 136, 137], even in combination with other drugs [138]; however, many of them showed inadequate response [26]. There are small case series reporting the efficacy of mycophenolate mofetil [139] and cyclosporine [140]. Anti-TNF-alpha, which is effective in treating RA, seems to be less effective in treating rhupus and SLE. It can induce the production of autoantibodies, such as antinuclear antibodies and anti-DNA antibodies [141], and more rarely it may result in lupus manifestations in both RA [142, 143] and rhupus patients [144]. Thus, the use of anti-TNF-alpha is not recommended in SLE patients [125]. The use of rituximab shows more encouraging results, as demonstrated in small clinical series in open clinical studies [83, 145] as does abatacept [130, 146]. Finally, two of our patients benefited from the use of tocilizumab [147].

There is a need for further controlled studies and, consequently, specific guidelines for the various forms of arthritis during the course of SLE.

References

1. Cervera R, Kamasthta MA, Font J et al (1999) Morbidity and mortality in systemic lupus erythematosus during a 5 year period. A multicenter prospective study of 1000 patients. Medicine 78:167175
2. PonsEstel BA, Catoggio LJ, Cardiel MH et al (2004) The GLADEL multinational Latin American prospective inception cohort of 1,214 patients with systemic lupus erythematosus: ethnic and disease heterogeneity among "Hispanics". Medicine (Baltimore) 83:1–17
3. Fernandez A, Quintana G, Rondon F et al (2006) Lupus arthropathy: a case series of patients with rhupus. Clin Rheumatol 25:164–167
4. Borba EF, Araujo DB, Bonfa E, Shinjo SK (2013) Clinical and immunological features of 888 Brazilian systemic lupus patients from a monocentric cohort: comparison with other populations. Lupus 22:744–749
5. SchwartzmanMorris J, Putterman C (2012) Gender differences in the pathogenesis and outcome of lupus and of lupus nephritis. Clin Dev Immunol 1:9–18
6. Murphy G, Isenberg D (2013) Effect of gender on clinical presentation in systemic lupus erythematosus. Rheumatology 52:2108–2115

7. Faezi ST, Almodarresi MH, Akbarian M et al (2014) Clinical and immunological pattern of systemic lupus erythematosus in men in a cohort of 2355 patients. Int J Rheum Dis 17:394–399
8. Hoffman IEA, Lauwerys BR, De Keyser F et al (2009) Juvenile onset systemic lupus erythematosus: different clinical and serological pattern than adult onset systemic lupus erythematosus. Ann Rheum Dis 68:412–415
9. Feng X, Zou Y, Pan W, Wang X et al (2014) Associations of clinical features and prognosis with age at disease onset in patients with systemic lupus erythematosus. Lupus 23:327334
10. Malcus Johnsson P, Sandqvist G, Bengtsson A, Nived O (2008) Hand function and performance of daily activities in systemic lupus erythematosus. Arthritis Care Res 59:1432–1438
11. Yelin E et al (2012) A longitudinal study of the impact of incident organ manifestations and increased disease activity on work loss among persons with SLE. Arthritis Care Res (Hoboken) 64:169–175
12. Drenkard C, Bao G, Dennis G et al (2014) Burden of systemic lupus erythematosus on employment and work productivity: data from a large cohort in the southeastern United States. Arthritis Care Res 66:878–887
13. Ball EMA, Bell AL (2012) Lupus arthritis—do we have a clinically useful classification? Rheumatology 51:771779
14. Meyer, Kahn MF (2000) Lupus érithémateux Systémique. In: Kahn MF, Peltier AP, Meyer O, Piette JC (eds) Maladies et syndrome systemiques, vol 7. Médicines Sciences Flammarion, Paris, p 131396
15. Wright S, Filippucci E, Grassi W et al (2006) Hand arthritis in systemic lupus erythematosus: an ultrasound pictorial essay. Lupus 15:5016
16. Torrente Segarra V, Lisbona MP, RotésSala D et al (2013) Hand and wrist arthralgia in systemic lupus erythematosus is associated to ultrasonographic abnormalities. Joint Bone Spine 80:4026
17. Mosca M, Tani C, Carli L et al (2015) The role of imaging in the evaluation of joint involvement in 102 consecutive patients with systemic lupus erythematosus. Autoimmun Rev 14:10–15
18. Cervera R, Khamashta MA, Font J et al (1993) Systemic lupus erythematosus: clinical and immunologic patterns of disease expression in a cohort of 1000 patients. Medicine 72:113–124
19. Chahade WH, Sato EI, Moura JE Jr, Costallat LT, Andrade LE (1995) Systemic lupus erythematosus in Sa˜o Paulo/Brazil: a clinical and laboratory overview. Lupus 4:100–103
20. Blanco FJ, de la Mata J, Gòmez-Reino JJ et al (1995) Clinical and serological manifestations of 307 Spanish patients with systemic lupus erythematosus. Comparison with other ethnic groups [in Spanish]. Rev Clin Exp 195:534–540
21. Vilà LM, Mayor AM, Valentin AH, Garcia-Soberal M, Vilà S (1999) Clinical and immunological manifestations in 134 Puerto Rican patients with systemic lupus erythematosus. Lupus 8:279–286
22. Vilà LM, Alarcòn GS, McGwin G Jr et al (2004) LUMINA Study Group. Early clinical manifestations, disease activity and damage of systemic lupus erythematosus among two distinct US Hispanic subpopulations. Rheumatology (Oxford) 43:358–363
23. Santos MJ, Capela S, Figueira R et al (2007) Characterization of a Portuguese population with systemic lupus erythematosus. Acta Reumatol Port 32:153–161
24. Skare TL, Godoi Ade L, Ferreira VO (2012) Jaccoud arthropathy in systemic lupus erythematosus: clinical and serological findings. Rev Assoc Med Bras 58:48992
25. Somers EC, Marder W, Cagnoli P et al (2014) Population-based incidence and prevalence of systemic lupus erythematosus. The Michigan lupus epidemiology and surveillance program. Arthritis Rheumatol 66:369–378
26. Pipili C, Sfritzeri A, Cholongitas E (2008) Deforming arthropathy in systemic lupus erythematosus. Eur J Intern Med 19:4827
27. Puszczewicz M, Białkowska Puszczewicz G (2010) LE cells in synovial fluid: prevalence and diagnostic usefulness in rheumatic diseases. Ann Acad Med Stetin 56(Suppl 1):1058

28. Natour J, Montezzo LC, Moura LA, Atra E (1991) A study of synovial membrane of patients with systemic lupus erythematosus (SLE). Clin Exp Rheumatol 9:2215
29. Nzeusseu Toukap A, Galant C, Theate I, Maudoux AL et al (2007) Identification of distinct gene expression profiles in the synovium of patients with systemic lupus erythematosus. Arthritis Rheum 56:157988
30. Qing X, Putterman C (2004) Gene expression profiling in the study of the pathogenesis of systemic lupus erythematosus. Autoimmun Rev 3:5059
31. McInnes IB, Schett G (2011) The pathogenesis of rheumatoid arthritis. N Engl J Med 365:220519
32. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF et al (1982) The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 25:1271–1277
33. Cohen AS, Reynolds WE, Franklin EC et al (1971) Preliminary criteria for the classification of systemic lupus erythematosus. Bull Rheum Dis 21:643–648
34. Petri M, Orbai AM, Alarcon GS et al (2012) Derivation and validation of the systemic lupus international collaborating clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum 64:2677–2686
35. Jaccoud FS (1869) Sur une forme de rhumatisme chronique: lecions de clinique medicale faites a l'Hopital de la Charite. Paris, Delahaye, pp 598–616R
36. Bradley JD, Pinals RS (1984) Jaccoud's arthropathy in scleroderma. Clin Exp Rheumatol 2:337–340
37. Bradley JD (1986) Jaccoud's arthropathy in adult dermatomyositis. Clin Exp Rheumatol 4:273–276
38. Sturgess AS, Littlejohn GO (1988) Jaccoud's arthritis and panvasculitis in the hypocomplementemic urticarial vasculitis syndrome. J Rheumatol 15:858–861
39. Sukenik S, Hendler N, Yerushalmi B, Buskila D, Liberman N (1991) Jaccoud's type arthropathy: an association with sarcoidosis. Rheumatology 18:915–917
40. Santiago MB (2011) Miscellaneous noninflammatory musculoskeletal conditions. Jaccoud's arthropathy. Best Pract Res Clin Rheumatol 25:715725
41. Maher LV (2014) Jaccoud arthropathy. Am J Med Sci 348:81
42. Sivas F, Aydog S, Pekin Y, Ozoran K (2005) Idiopathic Jaccoud's arthropathy. APLAR J Rheumatol 8:60–62
43. Arlet JB, Pouchot J (2009) The senescent form of Jaccoud arthropathy. J Clin Rheumatol 15:151
44. Aptekar RG, Lawless OJ, Decker JL (1974) Deforming nonerosive arthritis of the hand in systemic lupus erythematosus. Clin Orthop Relat Res 100:120–124
45. Bywaters EGL (1975) Jaccoud's syndrome. A sequel to the joint involvement of systemic lupus erythematosus. Clin Rheum Dis 1:125148
46. AlarconSegovia D, AbudMendoza C, DiazJouanen E et al (1988) Deforming arthropathy of the hands in systemic lupus erythematosus. J Rheumatol 15:659
47. Spronk PE, ter Borg EJ, Kallenberg CG (1992) Patients with systemic lupus erythematosus and Jaccoud's arthropathy: a clinical subset with an increased C reactive protein response? Ann Rheum Dis 51:35861
48. Santiago MB, Galvão V (2008) Jaccoud arthropathy in systemic lupus erythematosus: analysis of clinical characteristics and review of the literature. Medicine (Baltimore) 87:3744
49. Li J, Honghua Wu H, Huang X et al (2014) Clinical analysis of 56 patients with rhupus syndrome: manifestations and comparisons with systemic lupus erythematosus a retrospective case–control study. Medicine 93:49–51
50. Caznoch CJ, Esmanhotto L, Silva MB et al (2006) Pattern of joint involvement in patients with systemic lupus erythematosus and its association with rheumatoid factor and hypermobility. Rev Bras Rheumatol 46:261–265
51. Molina JF, Molina J, Gutierrez S et al (1995) Deforming arthropathy of the hands (Jaccoud's) in systemic lupus erythematosus (SLE). An independent subset of SLE? Arthritis Rheum 38

52. AgmonLevin N, Mosca M, Petri M, Shoenfeld Y (2012) Systemic lupus erythematosus one disease or many? Autoimmun Rev 11:5935
53. Villaumey J, Arlet J, Avouac B (1986) Diagnostic criteria and new etiologic events in the arthropathy of jaccoud: a report of 10 cases. Clin Rheum Press 4:156–175
54. Morley KD, Leung A, Rynes RI (1982) Lupus foot. BMJ 284:557–558
55. Ribeiro DS, Santiago M (2011) Imaging of Jaccoud's arthropathy in systemic lupus erythematosus: not only hands but also knees and feet. Rheumatol Int 3:34–38
56. Santiago MB (2013) Jaccoud's arthropathy: proper classification criteria and treatment are still needed. Rheumatol Int 33:2953–2954
57. van Vugt RM, Derksen RH, Kater L, Bijlsma JW (1998) Deforming arthropathy or lupus and rhupus hands in systemic lupus erythematosus. Ann Rheum Dis 57:540
58. Takeishi M, Mimori A, Suzuki T (2001) Clinical and immunological features of systemic lupus erythematosus complicated by Jaccoud's arthropathy. Mod Rheumatol 11:47–51
59. Esdaile JM, Danoff D, Rosenthall L et al (1981) Deforming arthritis in systemic lupus erythematosus. Ann Rheum Dis 40:124–126
60. Atta AM, Oliveira RC, Oliveira IS et al (2015) Higher level of IL6 in Jaccoud's arthropathy secondary to systemic lupus erythematosus: a perspective for its treatment? Reumatol Int 35:167–170
61. Bleifeld CJ, Inglis AE (1974) The hand in systemic lupus erythematosus. J Bone Joint Surg Am 56:1207–1215
62. Alves EM, Macieira JC, Borba E, Chiuchetta FA, Santiago MB (2010) Spontaneous tendon rupture in systemic lupus erythematosus: association with Jaccoud's arthropathy. Lupus 19:247–254
63. Manthorpe R, Bendixed G, Schioler H, Viderbal A (1980) Jaccoud's syndrome: a nasographic entity associated with SLE. J Rheumatol 7:169–177
64. Reilly PA, Evison G, McHugh NJ et al (1990) Arthropathy of hands and feet in systemic lupus erythematosus. J Rheumatol 17:777–784
65. Franchescini F, Cretti L, Quinzanini M, Rizzini FL, Cattaneo R (1994) Deforming arthropathy of the hands in systemic lupus erythematosus is associated with antibodies to SSA/Ro and to SSB/La. Lupus 3:419–422
66. Paredes JG, Lazaro MA, Citera G, Da Representacao S, Maldonado Cocco JA (1997) Jaccoud's arthropathy of the hands in overlap syndrome. Clin Rheumatol 16:65–69
67. Choi EK, Gatenby PA, Bateman JF, Cole WG (1990) Antibodies to type II collagen in SLE: a role in the pathogenesis of deforming arthritis? Immunol Cell Biol 68:27–31
68. DamiánAbrego GN, Cabiedes J, Cabral AR (2008) Anticitrullinated peptide antibodies in lupus patients with or without deforming arthropathy. Lupus 17:300–304
69. Kakumanu P, Sobel ES, Narain S et al (2009) Citrulline dependence of anti cyclic citrullinated peptide antibodies in systemic lupus erythematosus as a marker of deforming/erosive. Arthritis J Rheumatol 36:2682–2690
70. Ostendorf B, Scherer A, Specker C, Modder U, Schneider M (2003) Jaccoud's arthropathy in systemic lupus erythematosus: differentiation of deforming and erosive patterns by magnetic resonance imaging. Arthritis Rheum 48:157–165
71. Martini A, Ravelli A, Viola S, Burgio RG (1987) Systemic lupus erythematosus with Jaccoud's arthropathy mimicking juvenile rheumatoid arthritis. Arthritis Rheum 30:1062–1064
72. Eilertsen G, Nikolaisen C, BeckerMerok A, Nossent JC (2011) Interleukin6 promotes arthritis and joint deformation in patients with systemic lupus erythematosus. Lupus 20:60713
73. Klemp P, Majoos FL, Chalton D (1987) Articular mobility in systemic lupus erythematosus (SLE). Clin Rheumatol 6:202–207
74. Pastershank SP, Resnick D (1980) 'Hook' erosions in Jaccoud's arthropathy. J Can Assoc Radiol 31:1745
75. Schur PH (1971) Systemic lupus erythematosus. In: Beeson PB, McDermott W (eds) Cecilloeb textbook of medicine, 13th edn. WB Saunders, Philadelphia, p 821

76. Arnett F, Edworthy S, Bloch D et al (1988) The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 31:315–332
77. AmezcuaGuerra LM (2009) Overlap between systemic lupus erythematosus and rhematoid arthritis: is real or just an illusion? J Rheumatol 36:4–6
78. Hayakawa S, KomineAizawa S, Osaka S et al (2007) Rembrandt's Maria Bockenolle has a butterfly rash and digital deformities: overlapping syndrome of rheumatoid arthritis and systemic lupus erythematosus. Med Hypotheses 68:906–909
79. Panush RS, Edwards NL, Longley S, Webester E (1988) Rhupus syndrome. Arch Intern Med 148:1633–1636
80. Brand CA, Rowley MJ, Tait BD, Muirden KD, Whittingham SF (1992) Coexistent rheumatoid arthritis and systemic lupus erythematosus; clinical, serological, and phenotypic features. Ann Rheum Dis 51:17–36
81. Simon JA, Seeded J, Cabiedes J, Ruiz Morals J, Alcocer J (2002) Clinical and immunogenetic characterization of Mexican patients with 'rhupus'. Lupus 11:287–292
82. Satoh M, Ajmani AK, Akizuki M (1994) What is the definition for coexistent rheumatoid arthritis and systemic lupus erythematosus? Lupus 3:1378
83. Andrade-Ortega L, Irazoque-Palazuelos F, Mu˜nóz-López S, Rosales-Don Pablo VM (2013) Efficacy and tolerability of rituximab in patients with rhupus. Reumatol Clin 9:201–205
84. Tani C, D'Aniello D, Delle Sedie A et al (2013) Rhupus syndrome: assessment of its prevalence and its clinical and instrumental characteristics in a prospective cohort of 103 SLE patients. Autoimmun Rev 12:537–541
85. Liu T, Li G, Mu R, Ye H, Li W (2014) Clinical and laboratory profiles of rhupus syndrome in a Chinese population: a single centre study of 51 patients. Lupus 23:958963
86. Amaya A, MolanoGonzàlez N, Franco JS, RodrıguezJiménez M, RojasVillarraga A, Anaya JM (2015) AntiCCP antibodies as a marker of rhupus. Lupus 0:1–3
87. Delle Sedie A, Riente L, Scirè CA, Iagnocco A, Filippucci E, Meenagh G (2009) Ultrasound imaging for the rheumatologist XXIV. Sonographic evaluation of wrist and hand joint and tendon involvement in systemic lupus erythematosus. Clin Exp Rheumatol 27:897–901
88. Boutry N, Hachulla E, Flipo RM, Cortet B, Cotten A (2005) MR imaging findings in hands in early rheumatoid arthritis: comparison with those in systemic lupus erythematosus and primary Sjögren syndrome. Radiology 236:593–600
89. Prete M, Racanelli V, Digiglio L et al (2011) Extraarticular manifestations of rheumatoid arthritis: an update. Autoimmun Rev 11:123–131
90. Martinez JB, Valero AJ, Restrepo JF (2007) Erosive arthropathy: clinical variance in lupus erythematosus and association with anti-CCP case series an review of the literature. Clin Exp Rheumatol 25:47–51
91. Chan M, Owen P, Dumpy J, Cox B, Carmichael C, Korendowych E et al (2008) Associations of erosive arthritis with anticyclic citrullinated peptide antibodies and MHC class II alleles in systemic lupus erythematosus. J Rheumatol 35:77–83
92. Budhram A, Chu R, RustaSalleh S, Ioannidi G, Denbur JA, Adachi JD, Haaland DA (2014) Anti cyclic citrullinated peptide antibody as a marker of erosive arthritis in patients with systemic lupus erythematosus: a systematic review and meta-analysis. Lupus 23:1156–1163
93. Qing YF, Zhang QB, Zhou JG et al (2009) The detecting and clinical value of anticyclic citrullinated peptide antibodies in patients with systemic lupus erythematosus. Lupus 18:713–717
94. Zhao Y, Li J, Li XX, Li C, Li L, Li ZG (2009) What can we learn from the presence of anticyclic citrullinated peptide antibodies in systemic lupus erythematosus? Joint Bone Spine 76:501–507
95. Nishimura K, Sugiyama D, Kogata Y et al (2007) Metaanalysis: diagnostic accuracy of anticyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis. Ann Intern Med 146:797–808
96. Mediwake R, Isenberg DA, Schellekens GA, van Venrooij WJ (2001) Use of anticitrullinated peptide and antiRA33 antibodies in distinguishing erosive arthritis in patients with systemic lupus erythematosus and rheumatoid arthritis. Ann Rheum Dis 60:67–68

97. Amezcua-Guerra LM, Márquez-Velasco R, Bojalil R (2008) Erosive arthritis in systemic lupus erythematosus is associated with high serum C-reactive protein and anti-cyclic citrullinated peptide antibodies. Inflamm Res 57:555–557
98. Taraborelli M, Inverardi F, Fredi M et al (2012) Anticyclic citrullinated peptide antibodies in systemic lupus erythematosus patients with articular involvement: a predictive marker for erosive disease? Reumatismo 64:321–325
99. Wang JG, Tang HH, Tan CY, Liu Y, Lin H, Chen YT (2010) Diffuse lupus encephalopathy in a case of rhupus syndrome. Rheumatology 30:9613
100. Sciascia S, Roccatello D, Rossi D, Russo A, Mereuta MO, Cavallo R (2012) High-titer anti-aquaporin4 IgG-associated myelitis in rhupus syndrome. J Rheumatol 39:8713
101. Richter Cohen M, Steiner G, Smolen JS et al (1998) Erosive arthritis in systemic lupus erythematosus: analysis of a distinct clinical and serological subset. Br J Rheumatol 37:421–424
102. Gabba A, Piga M, Vacca A, Porru G, Garau P, Cauli A et al (2012) Joint and tendon involvement in systemic lupus erythematosus: an ultrasound study of hands and wrists in 108 patients. Rheumatology 51:2278–2285
103. Iagnocco A, Ossandon A, Coari G, Conti F, Priori R, Alessandri C et al (2004) Wrist joint involvement in systemic lupus erythematosus. An ultrasonographic study. Clin Exp Rheumatol 22:621–624
104. Iagnocco A, Ceccarelli F, Rizzo C, Truglia S, Massaro L, Spinelli FR et al (2013) Ultrasound evaluation of hand, wrist and foot joint synovitis in systemic lupus erythematosus. Rheumatology 2:34–41
105. Hecht C, Englbrecht M, Rech J et al (2014) Additive effect of anti-citrullinated protein antibodies and rheumatoid factor on bone erosions in patients with RA. Ann Rheum Dis 2:34–55
106. Tunnicliffe DJ, Singh-Grewal D, Kim S, Craig JC, Tong A (2015) Diagnosis, monitoring and treatment of systemic lupus erythematosus: a systematic review of clinical practice guidelines. Arthritis Care Res (Hoboken). doi:10.1002/acr.22591 [Epub ahead of print]
107. Grossman JM (2009) Lupus arthritis. Best Pract Res Clin Rheumatol 23:495–506
108. Artifoni M, Puéchala X (2012) How to treat refractory arthritis in lupus? Joint Bone Spine 79:347–350
109. Nikpour M, Bridge JA, Richter S (2014) A systematic review of prevalence, disease characteristics and management of systemic lupus erythematosus in Australia: identifying areas of unmet need. Intern Med J 44:1170–1179
110. Islam MN, Hossain M, Haq SA et al (2012) Efficacy and safety of methotrexate in articular and cutaneous manifestations of systemic lupus erythematosus. Int J Rheum Dis 15:62–68
111. Sakthiswary R, Suresh E (2014) Methotrexate in systemic lupus erythematosus: a systematic review of its efficacy. Lupus 23:225–235
112. Calvo-Alen J, Silva-Fernandez L, Ucar-Angulo E, Pego-Reigosa JM, Olive A, Martinez-Fernandez C et al (2013) SER consensus statement on the use of biologic therapy for systemic lupus erythematosus. Reumatol Clin 09:281–296
113. Muangchan C, van Vollenhoven RF, Bernatsky SR et al (2015) Treatment algorithms in systemic lupus erythematosus. Arthritis Care Res (Hoboken). doi:10.1002/acr.22589 [Epub ahead of print]
114. Miescher P, Riethmueller D (1965) Diagnosis and treatment of systemic lupus erythematosus. Semin Hematol 2:1–28
115. Gansauge S, Breitbart A, Rinaldi N, Schwarz-Eywill M (1997) Methotrexate in patients with moderate systemic lupus erythematosus (exclusion of renal and central nervous system disease). Ann Rheum Dis 56:382–385
116. Rahman P, Humphrey-Murto S, Gladman DD, Urowitz MB (1998) Efficacy and tolerability of methotrexate in antimalarial resistant lupus arthritis. J Rheumatol 25:243–246
117. Carneiro JR, Sato EI (1999) Double blind, randomized, placebo controlled clinical trial of methotrexate in systemic lupus erythematosus. J Rheumatol 26:1275–1279

118. Pego-Reigosa JM, Cobo-Ibáñez T, Calvo-Alén J et al (2013) Efficacy and safety of nonbiologic immunosuppressants in the treatment of nonrenal systemic lupus erythematosus: a systematic review. Arthritis Care Res (Hoboken) 65:1775–1785
119. Tam LS, Li EK, Wong CK et al (2004) Double-blind, randomized, placebo controlled pilot study of leflunomide in systemic lupus erythematosus. Lupus 13:601–604
120. Karim MY, Alba P, Cuadrado MJ et al (2002) Mycophenolate mofetil for systemic lupus erythematosus refractory to other immunosuppressive agents. Rheumatology (Oxford) 41:876–882
121. Ginzler EM, Wofsy D, Isenberg D et al (2010) Nonrenal disease activity following mycophenolate mofetil or intravenous cyclophosphamide as induction treatment for lupus nephritis: findings in a multicenter, prospective, randomized, open-label, parallel-group clinical trial. Arthritis Rheum 62:211–221
122. Aringer M, Burkhardt H, Burmester GR et al (2011) Current state of evidence on "off label" therapeutic options for systemic lupus erythematosus, including biological immunosuppressive agents, in Germany, Austria, and Switzerland – a consensus report. Lupus 3:34–41
123. Terrier B, Amoura Z, Ravaud P et al (2010) Safety and efficacy of rituximab in systemic lupus erythematosus: results from 136 patients from the French autoimmunity and rituximab registry. Arthritis Rheum 62:2458–2466
124. Bang SY, Lee CK, Kang YM et al (2012) Multicenter retrospective analysis of the effectiveness and safety of rituximab in Korean patients with refractory systemic lupus erythematosus. Autoimmune Dis 5:65039
125. Aringer M, Smolen JS (2015) Safety of off-label biologicals in systemic lupus erythematosus. Expert Opin Drug Saf 14:243–251
126. Manzi S, Sanchez-Guerrero J, Merrill JT et al (2010) Belimumab, a BLyS-specific inhibitor, reduced disease activity across multiple organ domains: combined efficacy results from the phase 3 BLISS-52 and -76 studies (abstract). Arthritis Rheum 62:S607–S608
127. Navarra SV, Guzmán RM, Gallacher AE et al (2011) Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. Lancet 377:721–731
128. Furie R, Petri M, Zamani O, for the BLISS-76 Study Group et al (2011) A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus. Arthritis Rheum 63:3918–3930
129. Illei GG, Shirota Y, Yarboro CH et al (2010) Tocilizumab in systemic lupus erythematosus: data on safety, preliminary efficacy, and impact on circulating plasma cells from an open-label phase I dosage-escalation study. Arthritis Rheum 62:542–552
130. Merrill JT, Burgos-Vargas R, Westhovens R et al (2010) The efficacy and safety of abatacept in patients with non-life-threatening manifestations of systemic lupus erythematosus: results of a twelve-month, multicenter, exploratory, phase IIb, randomized, double-blind, placebo-controlled trial. Arthritis Rheum 62:3077–3087
131. Evans JA, Hastings DE, Urowitz MB (1977) The fixed lupus hand deformity and its surgical correction. J Rheumatol 4:170–175
132. Schumacher HR, Zweiman B, Bora FW Jr (1976) Corrective surgery for the deforming hand arthropathy of systemic lupus erythematosus. Clin Orthop Relat Res 17:292–295
133. Dray GJ, Millender LH, Nalebuff EA, Philips C (1981) The surgical treatment of hand deformities in systemic lupus erythematosus. J Hand Surg [Am] 6:339–345
134. Alnot JY, Liverneaux P, Welby F (2004) Jaccoud's arthropathy. Surgical results of 41 hands. Chir Main 23:229–236
135. Oda R, Fujiwara H, Tokunaga D et al (2014) Spontaneous flexor tendon rupture in systemic lupus erythematosus: a case report. Mod Rheumatol 20:1–4
136. Fortin PR, Abrahamowicz M, Ferland D et al (2008) Steroid-sparing effects of methotrexate in systemic lupus erythematosus: a double-blind, randomized, placebo-controlled trial. Arthritis Rheum 59:1796–1804

137. Winzer M, Aringer M (2010) Use of methotrexate in patients with systemic lupus erythematosus and primary Sjogren's syndrome. Clin Exp Rheumatol 28(5 Suppl 61):S156–S159
138. Li J, Wu H, Huang X et al (2014) Clinical analysis of 56 patients with rhupus syndrome: manifestations and comparisons with systemic lupus erythematosus a retrospective case–control study. Medicine (Baltimore) 93:e49
139. Benavente EP, Paira SO (2011) Rhupus: report of 4 cases. Reumatol Clin 7:333–335
140. Seo SR, Lee SJ, Park DJ et al (2011) Successful treatment using cyclosporine in a patient with rhupus complicated by aplastic anemia: a case report and review of the literature. Clin Exp Rheumatol 29:708–711
141. Eriksson C, Engstrand S, Sundqvist K-G et al (2005) Autoantibody formation in patients with rheumatoid arthritis treated with anti-TNF α . Ann Rheum Dis 3:403–407
142. Charles PJ, Smeenk RJ, De Jong J et al (2000) Assessment of antibodies to double-stranded DNA induced in rheumatoid arthritis patients following treatment with infliximab, a monoclonal antibody to tumor necrosis factor alpha: findings in open-label and randomized placebo-controlled trials. Arthritis Rheumatol 43:2383–2390
143. De Bandt M, Sibilia J, Le Loet X et al (2005) Systemic lupus erythematosus induced by anti-tumour necrosis factor alpha therapy: a French national survey. Arthritis Res Ther 3:R545–R551
144. Chogle AR, Shah CV, Murthy AK et al (2011) Role of anti-tumor necrosis factor-α blockers in inducing lupus erythematosus tumidus in 'rhupus syndrome'. J Rheumatol 38:1218–1219
145. Piga M, Gabba A, Cauli A, Garau P, Vacca A, Mathieu A (2013) Rituximab treatment for 'rhupus syndrome': clinical and power-Doppler ultrasonographic monitoring of response. A longitudinal pilot study. Lupus 22:624–628
146. Ikeda K, Sanayama Y, Makita S et al (2013) Efficacy of abatacept for arthritis in patients with an overlap syndrome between rheumatoid arthritis and systemic lupus erythematosus. Clin Dev Immunol 2013:697525
147. Rossi D, Sciascia S, Manna E, Binello G, Modena V, Roccatello D (2013) Tocilizumab as a therapeutic option for Rhupus patients who do not respond to conventional therapy. Ann Rheum Dis 72(Suppl3):1004