EXTRA-ARTICULAR MANIFESTATIONS OF RHEUMATOID ARTHRITIS, NOW

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Disclosure: The author has received honoraria for lectures from Abbvie, Pfizer, Roche, Bristol-Myers Squibb, MSD, Lilly and UCB, and honoraria for participation in advisory boards from Roche, UCB, and Pfizer.
Received: 23.03.14 **Accepted:** 15.05.14
Citation: EMJ Rheumatol. 2014;1:103-112.

ABSTRACT

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease, characterised by polyarthritis and extra-articular organ disease, including rheumatoid nodules, ophthalmologic manifestations, cardiopulmonary disease, vasculitis, neuropathy, glomerulonephritis, Felty's syndrome, and amyloidosis. Extra-articular manifestations of RA (ExRA) occur in 17.8–40.9% of RA patients, 1.5–21.5% of them presenting as severe forms and usually associated with increased morbidity and mortality. They can develop at any time during the course of the disease, even in the early stages, and are associated with certain predisposing factors, such as the presence of rheumatoid factor, smoking, and long-standing severe disease. Rheumatoid nodules, the most common ExRA, have been found to be associated with the development of severe features, such as vasculitis, rheumatoid lung disease, pericarditis, and pleuritis, especially in those patients who develop them within 2 years from RA diagnosis. There is no uniformity in the definition of the term ExRA, which limits comparability between different studies. Several recent surveys suggest a lower frequency, probably due to a better control of disease activity. Diagnosis of ExRA is a challenge for clinicians, given its variable and complex presentation, and the lack of specific diagnostic tests; it must be based on clinical recognition and exclusion of other causes of the signs and symptoms. Furthermore, management continues to be difficult with a bad prognosis in many conditions. This article reviews the clinical aspects of major ExRA, focusing on incidence, clinical features, and therapeutic approaches, and how modern immunosuppressive therapy can change the outcome.

Keywords: Rheumatoid arthritis, extra-articular manifestation, management, biologic treatment.

INTRODUCTION

Rheumatoid arthritis (RA) is an immune-mediated chronic inflammatory disease. Despite being characterised by inflammation of the synovial membrane and progressive destruction of the articular cartilage and bone, RA is a systemic disease often associated with other extra-articular manifestations, with a significant impact on mortality and morbidity.[1] A better control of disease activity in the last decades due to the availability of more efficacious drugs has resulted in a lower frequency of extra-articular manifestations of RA (ExRA), as well as better outcomes in many patients.

Epidemiology

ExRA can develop at any time during the course of the disease, even in the early stages.[2] They occur in 17.8–40.9% of RA patients, 1.5–21.5% of them presenting as severe forms and usually associated with greater comorbidity and premature death.[3] Higher frequencies are seen in Northern European countries, rather than Southern Europe, suggesting a role of environmental and genetic factors in their pathogenesis. Hospital-based studies also show more prevalence, probably due to inclusion of patients with more severe disease.[4] Until now there has been no uniformity in ExRA definition or classification, despite the fact that they have been

studied in numerous RA cohorts. This partly justifies the differences seen in descriptive reports and incidence studies.

Predisposing Factors

Prete et al.[4] recently reviewed all relevant articles related to ExRA published up to June 2011, and found smoking, early disability, antinuclear antibodies, and rheumatoid factor (RF) positivity as the principal predictor factors of severe ExRA. Gender was not found to have any effect, with the exception of one Italian study, which reported higher risk of developing any ExRA in men than in women (odds ratio, 1.68). Moreover, Turesson et al.[5] described the presence of rheumatoid nodules (RNs) as a predisposing factor for development of severe ExRA, such as vasculitis, rheumatoid lung disease, pericarditis, and pleuritis, especially in those patients who develop them within 2 years from RA diagnosis, and found a particularly high risk in those patients with long-standing, severe disease.

CLINICAL MANIFESTATIONS

Many different tissues and organs can be involved in RA patients in addition to the characteristic peripheral polyarthritis (Table 1). Several general symptoms can represent a major problem during the course of RA, many of them also being present before its diagnosis. Weight loss, fever, prolonged early morning stiffness, fatigue, generalised muscle weakness, low mood, and depression are often responsible for a significant loss in the quality of life of patients. Fatigue is reported in 40–80% of RA patients as their most disabling symptom.[6] The OMERACT (Outcome Measures in Rheumatology) network of international researchers highlighted fatigue as a main outcome, recommending its measure whenever possible.[7]

As a result of the inflammatory process, RA patients frequently developed normochromic-normocytic anaemia.[8] Other manifestations associated with chronic inflammation include injury of exocrine glands with the development of a secondary Sjögren's syndrome (SS), sarcopaenia, and osteoporosis.

RNs are the most frequent skin manifestation. They occur in about 30% of RA patients, mostly in RF-positive subjects, and are usually located subcutaneously on pressure areas, including the olecranon process and proximal ulna, finger joints, sacral prominences, occiput, and Achilles tendon. Usually painless, they have a variable consistency from a soft, mobile to a hard, rubbery mass attached firmly to the periosteum. Histologically they are characterised by a central necrotic area rimmed by a corona of palisading fibroblasts that is surrounded by a zone of tissue affected by perivascular cellular infiltration enriched with lymphocytes, plasma cells, and histiocytes.[9]

Regression of nodules may occur during treatment with disease modifying anti-rheumatic drugs (DMARD). Paradoxically, in 8–11% of methotrexate-treated RA patients an accelerated rheumatoid nodulosis can occur, with nodules usually located in the fingers or in the metacarpophalangeal and proximal interphalangeal joints. The condition regresses when methotrexate is reduced or withdrawn and if hydroxychloroquine or sulphasalazine treatment is started. Etanercept has also been related with the development of this type of nodulosis.[10] No effective treatment is available.

Ocular involvement occurs in 27% of RA patients.[11] Keratoconjunctivitis sicca (KCS), the most frequent and usually benign ophthalmologic manifestation, occurs in at least 10% of patients together with xerostomia, usually as a part of a secondary SS. Symptoms such as burning or a foreign body sensation can be warning signs. The diagnosis is supported by a positive Schirmer test and a reduced tear break-up time. On the other hand, a reduced salivary flow rate can confirm xerostomia. Some patients develop scleritis, episcleritis, peripheral ulcerative keratitis, or vasculitis involving retinal vessels. A clinical suspicion of such disorders in a patient with RA should lead to immediate referral to an ophthalmologist. Episcleritis, inflammation of the layer superficial to the sclera, usually correlates with the activity of RA. It presents in <1% of patients with RA and is generally a self-limiting condition. Symptoms are usually limited to focal redness and irritation of the eye without altering visual acuity. Scleritis is a more aggressive process, characterised by an intensely painful inflammation of the sclera itself. It is seen in patients with vasculitis and long-standing arthritis. There are three types of anterior scleritis: diffuse, nodular, and necrotising. The latter is also referred to as scleromalacia perforans, the most severe type. It is a degenerative thinning of the sclera that occurs in FR-positive female patients. It has been attributed to a vasculitic process with deposition of immune complexes.

Table 1: Extra-articular manifestations in rheumatoid arthritis.

Affected tissue or organ	Extra-articular manifestation
General symptoms	Weight loss Fever Prolonged early morning stiffness Fatigue Generalised muscle weakness Low mood and depression
Inflammatory-process associated features	NNA Secondary SS Sarcopenia Osteoporosis
Skin	RNs CuV RP
Eyes	KCS Scleritis Episcleritis PUK Vasculitis involving retinal vessels
PS	PNs PE ILD
CVS	PC MC CA CoV Arrhythmia VDs CHF IHD
NS	CD CM CNS vasculitis Rheumatoid nodules located within the CNS or meningitis Stroke MM SPN
Kidneys	GN IN Secondary amyloidosis
Haematological system	FS

NNA: normochromic-normocytic anaemia; SS: Sjögren's syndrome; RNs: rheumatoid nodules; CuV: cutaneous vasculitis; RP: Raynaud's phenomenon; KCS: keratoconjunctivitis sicca; PUK: peripheral ulcerative keratitis; PS: pulmonary system; PNs: pulmonary nodules; PE: pleural effusion; ILD: interstitial lung disease; CVS: cardiovascular system; PC: pericarditis; MC: myocarditis; CA: cardiac amyloidosis; CoV: coronary vasculitis; VDs: valve diseases; CHF: congestive heart failure; IDH: ischaemic heart disease; NS: nervous system; CD: cognitive dysfunction; CNS: central nervous system; CM: cervical myelopathy; MM: mononeuritis multiplex; SPN: sensory peripheral neuropathy; GN: glomerulonephritis; IN: interstitial nephritis; FS: Felty's syndrome.

This condition is often painless and can evolve to scleral perforation when it goes untreated.[12]

Pulmonary involvement in RA is frequent, although not always clinically recognised, and includes RNs, pleural effusion (PE), interstitial lung disease (ILD), small airway disease, and pulmonary vasculitis. It is responsible for 10-20% of overall mortality,[13,14] and can occur before the development of joint symptoms.[15,16] Parenchymal pulmonary nodules (PNs) are usually asymptomatic, but may cavitate and cause PEs (Figure 1); they also increase the risk of infections and pneumothorax. They are usually found in RF-positive patients with nodules elsewhere. Sometimes differentiation with neoplasms and infections can be difficult. PE, usually an exudate with mixed cell counts and high protein concentration, is common but frequently asymptomatic; autopsy studies reported pleural involvement in 50% of cases, with only 10% clinically detected.[17]

ILD is the most important pulmonary manifestation of RA, being the commonest pulmonary cause of death and a significant contributor to morbidity.[13,14,18,19] The most frequent histopathological patterns of ILD in RA are usual interstitial pneumonia (UIP) and nonspecific interstitial pneumonia (NSIP) (44–56% and 33–44%, respectively),[20] followed by mixed disease (0–12%). Other forms, such as obliterative bronchiolitis, are rare but associated with a high mortality.[21] Although it tends to occur more often in RF positive male patients with long-standing nodular disease,[22] studies in new onset RA have found lung abnormalities in a high percentage of patients.[23,24] Clinical presentation and course are similar to that of idiopathic pulmonary fibrosis, but the response to immunosuppressants is usually better. Diagnosis is based on clinical presentation, blood gases, pulmonary function tests, and high resolution computed tomography (HRCT).[25] As abnormalities can be detected by HRCT in about 50% of RA patients, but only 10% have clinically significant symptoms,[26] diagnosis should be supported not only on clinical signs and symptoms, but also in abnormal pulmonary function tests and either a compatible HRCT or lung biopsy. Physiological abnormalities include a reduction in lung volume, a low diffusing capacity for carbon monoxide (which is the measure best associated with the extent of disease in ILDs and a poorer prognosis in RA-ILD27), and oxygen desaturation during a 6-minute walk test.

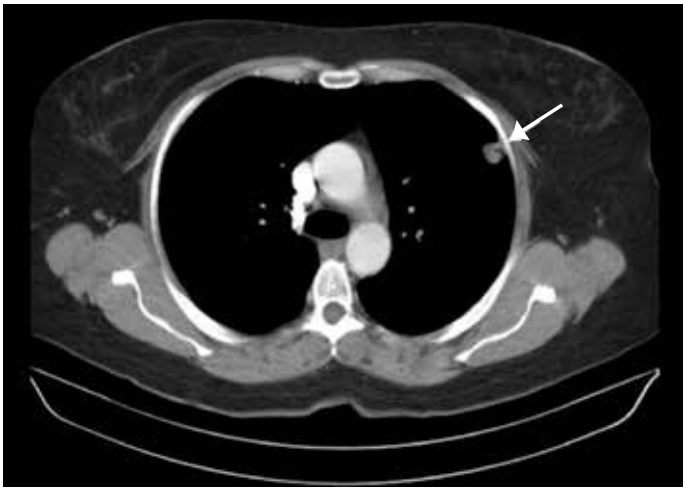

Figure 1: Pulmonary nodule with a central cavity (arrow).

Cardiovascular (CV) features in RA are common,[28] including pericarditis, myocarditis, cardiac amyloidosis, coronary vasculitis (CoV), arrhythmia, valve diseases, and, most importantly, congestive heart failure[29] and ischaemic heart disease (IHD). The last two have been associated with an increased morbidity and mortality in RA patients compared with the general population due to an accelerated atherogenesis process that cannot be fully explained by the classic atherosclerosis risk factors;[30,31] the presence of chronic inflammation and a possible genetic component are important contributing agents.[32,33]

Within the classical cardiac manifestations, pericarditis is the most common; both echocardiography and autopsy studies reveal evidence of pericardial inflammation in 50% of patients, although symptoms are relatively uncommon, occurring in about 1–4% of patients. It usually occurs in RF-positive nodular RA, and pericardial fluid analysis reveals features similar to those found in rheumatoid PEs. Conversely, symptomatic myocarditis, endocarditis, and CoV rarely occur, and are almost exclusively demonstrated by autopsy.[34] Cognitive dysfunction is frequently found in RA patients, with prevalence rates ranging from 38-71%.[35,36] Education, income, glucocorticoid use, and cardiovascular disease (CVD) risk factors are independent predictors of its development.[37]

On the contrary, neurological involvement in RA is rare, present in only 1% of patients. Disorders of the central nervous system (CNS) include cervical myelopathy, vasculitis, RNs located within the CNS,

or meningitis. Stroke also occurs with increased frequency.[38] CNS vasculitis is extremely rare. The diagnosis is supported by magnetic resonance imaging (MRI), alone or with magnetic resonance angiography (MRA), showing the segmental vascular stenosis characteristic of vasculitis.[39] Peripheral neuropathy is usually manifested as sensorimotor neuropathy or mononeuritis multiplex. The underlying mechanism is small vessel vasculitis of the vasa vasorum of the nerves with ischaemic neuropathy and demyelinisation as part of the rheumatoid vasculitis (RV) syndrome.

RA and kidney disease (KD) often coincide. There are several potential causes of nephropathy such as drug-related renal disease, secondary renal amyloidosis, and various types of glomerulonephritis (GN). Mesangial proliferative GN is the most frequent histological lesion followed by membranous GN,[40,41] the latter usually being related to gold or D-penicillamine, with both therapies not currently in use. Other infrequent causes of KD can be interstitial nephritis, minimal change glomerulopathy, IgA nephritis, focal proliferative GN, or rapidly progressive GN due to microscopic polyangiitis.[42] Prevalence has been recently established; the MATRIX study[43] found KD in 46.3% of RA patients according to the National Kidney Foundation (NKF) classification[44] with a stage distribution of 11.3% in Stage 1 (normal kidney function with kidney damage), 20.0% in Stage 2 (mild renal insufficiency with kidney damage), 15.0% in Stage 3 (moderate renal insufficiency), and no patients in Stages 4 or 5. The study was not designed to identify the potential causes of KD. A recent retrospective review[45] has shown that RA patients are more likely to develop reduced kidney function over time, with CVD at baseline and elevated erythrocyte sedimentation rate as predisposing factors, and found a relationship between renal impairment and increased morbidity from CVD development.

Secondary (reactive AA) amyloidosis can be seen in long-standing disease and poor response to therapy, and markedly influences these patients' outcomes.[46] Prevalence is around 7%,[47] with clinically symptomatic amyloidosis much lower.[48] Common clinical signs of reactive AA amyloidosis in patients with RA can be found by careful observation for the onset of proteinuria, kidney insufficiency, or gastrointestinal tract symptoms. Biopsy is often necessary to make an accurate diagnosis.

RV is a rare but potentially serious necrotising vasculitis, which can develop in patients with RA sometimes in the absence of active joint disease. RV typically occurs in male patients with long-standing RF-positive erosive nodular RA,[49] in association with a severe disease course and other ExRA features including episcleritis, pleural, and pericardial effusions or pulmonary fibrosis.[50] Smoking is associated with an increased risk of vasculitis among patients with RA[51] and there also appears to be a genetic predisposition, with major histocompatibility complex, Class 2, DR beta 1 (HLA-DRB1)-shared epitope genotypes strongly associated.[52] Any size of blood vessel may be involved, but capillaries, small venules, veins, arterioles, and medium-sized arteries are the most frequently affected. Histopathologically, it is characterised by a necrotising panarteritis showing fibrinoid necrosis of the vessel wall, with an inflammatory cell infiltrate in early lesions. Later on, arterial wall fibrosis with occlusion can appear. It may present with palpable purpura, distal vasculitis (ranging from splinter haemorrhages and fingertips infarction to gangrene), cutaneous ulceration, mononeuritis multiplex, or arteritis of viscera, including heart, lungs, bowel, kidney, liver, spleen, pancreas, lymph nodes, and testis. Sometimes vasculitis is limited to the nail folds, and this has a better prognosis and does not usually herald the onset of systemic disease.[53]

FS is an uncommon ExRA, occurring in <1% of RA patients. It is defined as a combination of RA with neutropaenia and splenomegaly, and occurs mostly among women around the age of 60 with a long history of severe articular disease, RF-positive in association with antibodies to cyclic citrullinated peptides, and who have the HLA-DR4*0401 antigen.[54] Almost 75% of patients with FS will present cutaneous nodules. Other features that are usually present include lymphadenopathy, hepatopathy, vasculitis, leg ulcers, and skin pigmentation. Its poor prognosis is due to a higher incidence of severe infection related to the neutropaenia that normally accompanies it, whose cause lies in both decreased granulopoiesis and increased peripheral destruction of granulocytes.[55] It is important to exclude haematopoietic malignancy when making the diagnosis of FS. The clinical significance of FS resides in the fact that often inactive joint disease distracts the clinician's attention from the severe extra-articular disease and neutropaenia, causing recurrent - sometimes fatal - infections. Furthermore, FS has been

associated with an increased risk of malignant lymphoproliferative disease compared to other patients with RA. This highlights the importance of careful evaluation of these cases.

MANAGEMENT

The first step in management of RA with or without extra-articular manifestations must be early treatment with DMARD, both to control inflammation with subsequent articular progression and to reduce the risk of further extra-articular complications (Table 2). Progression of scleromalacia perforans can be prevented with this approach, although refractory cases may benefit from the use of biological agents; several papers have shown good results in controlling ocular complications, but clinical trials have not yet been reported.[56]

Table 2: Management of extra-articular manifestations in rheumatoid arthritis.

Extra-articular manifestation	Management
General symptoms Inflammatory-process associated features	Early treatment with DMARD, and when necessary with biologics, both to control inflammation and to reduce the risk of further extra-articular complications
Skin	Hydroxychloroquine or sulphasalazine Avoid methotrexate if accelerated RN occurs
Eyes	DMARD and/or biologics to control inflammation Rituximab[56]
PS	Cyclophosphamide and high-dose corticosteroids[67] Cyclosporine[68,69]
CVS	
PC MC CoV CHF IHD	Non-steroidal anti-inflammatory drugs or steroids Immunosuppressive treatment Strict control of CVD risk factors[57,58]
NS	Cyclophosphamide and high-dose corticosteroids
Kidney	Cyclophosphamide and high-dose corticosteroids
FS[61]	Methotrexate Granulocyte colony-stimulating factor Rituximab in refractory cases[62] Splenectomy
SV	Cyclophosphamide and high-dose corticosteroids[63] TNF-inhibitors[64] Rituximab[65,66]
Amyloidosis	Chlorambucil[76] Cyclophosphamide[77] TNF-inhibitors[78,79] Tocilizumab[80,81]

DMARD: disease modifying anti-rheumatic drugs; RN: rheumatoid nodulosis; PS: pulmonary system; CVS: cardiovascular system; PC: pericarditis; MC: myocarditis; CoV: coronary vasculitis; CHF: congestive heart failure; IHD: ischaemic heart disease; CVD: cardiovascular disease; NS: nervous system; FS: Felty's syndrome; SV: systemic vasculitis; TNF: tumour necrosis factor.

Although there is some evidence that CV risk in RA is reduced by successful suppression of inflammation, it remains important to identify and target traditional CVD risk factors as well. Guidelines emphasising the need for regular screening of patients with RA for CV risks have been recently published.[57,58] Congestive heart failure requires special consideration, since it does not appear to be fully related to traditional CVD risk factors or clinical IHD. Findings from a number of studies have shown that inflammatory cytokines are related to the echocardiographic indices of both systolic and diastolic left ventricular function.[59] In addition, the inhibition of interleukin-1 (IL-1) showed an ability to improve myocardial deformation in these patients.[60]

The majority of traditional cardiac complications in RA are silent and do not require treatment. Symptomatic pericardial disease without haemodynamic compromise can be resolved with non-steroidal anti-inflammatory drugs or steroids, but recurrent forms may need immunosuppressive treatment. Constrictive pericarditis, and rapidly progressive pericarditis, require emergency intervention and can worsen the outcome of patients.

In patients with FS, neutropaenia can be effectively managed with DMARDs, the widest experience being with methotrexate. Splenectomy results in immediate improvement of neutropaenia in 80% of patients, but the rate of infection decreases to a lesser degree. Granulocyte colony-stimulating factor can be useful too. It seems to be logical to suppose that early aggressive treatment of RA may prevent the development of FS, but there are no epidemiological data to support this hypothesis.[61] Some investigators reported a response of FS to rituximab, while others found this treatment questionable. A systematic review evaluating biological treatment in FS concludes that the use of RTX can only be recommended as a second-line therapy in patients with refractory FS; experience with anti-tumour necrosis factor (TNF) agents is very limited with no improvement in neutrophil count.[62] Spontaneous remission of the syndrome can also occur.

For severe ExRA, such as systemic vasculitis, treatment with cyclophosphamide and high-dose corticosteroids has been considered as the recommended approach.[63] According to other reports,[64] we have observed a dramatic response of severe cutaneous vasculitic ulcers after anti-TNF treatment in a RF-positive RA patient with long-standing severe disease (data unpublished, Figure 2). On the other hand, rituximab has proved beneficial in RV, being an alternative to cyclophosphamide in selected patients.[65,66]

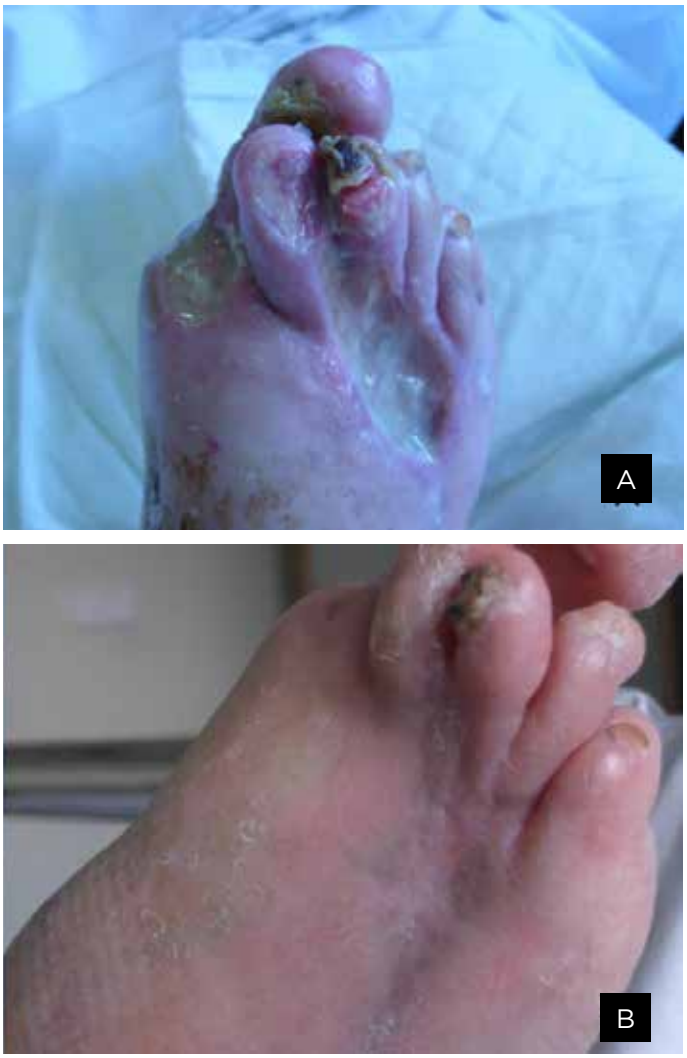

Figure 2: Complete healing of severe cutaneous vasculitic ulcers after anti-tumour necrosis factor treatment (A: pre-treatment; B: post-treatment).

RA-associated lung disease treatment is controversial. It is mainly based on systemic steroids and cyclophosphamide,[67] existing also positive data with cyclosporine.[68,69] Although a beneficial effect of anti-CD20 therapy has been described in several case reports, physicians should be aware that this drug could trigger or worsen RA-related pulmonary fibrosis.[70] Conflicting results have been published with TNF-inhibitors, with reports on excellent response in refractory patients,[71] as well as worsening of ILD in others.[72-74] Regression of parenchymal PNs after tocilizumab treatment has been observed.[75]

Standard treatment for AA amyloidosis has been based for a long time on colchicine, chlorambucil,[76] or cyclophosphamide,[77] but TNF inhibitors have proved effective in controlling the progression of renal amyloidosis in patients with RA.[78,79] Since the activation of the serum amyloid A gene depends more on the presence of IL-6 than on the presence of TNF alpha, tocilizumab will probably be a first-line treatment in the future.[80,81]

EXTRA-ARTICULAR MANIFESTATIONS OF RA, NOW

A better control of disease activity during the last decades has improved the outcome of RA.[82] ExRA incidence seems to be reduced too, although it is not equal for all manifestations: a decline in RV incidence has been found in several studies,[83,84] even though clinical manifestations remain similar and its prognosis remains poor despite modern immunosuppressive therapy.[85] Secondary amyloidosis with clinically apparent organ manifestations is not present in the most recent series of RA patients. On the contrary, it has not been a significant change in the incidence of other severe ExRA manifestations, like RA-associated lung disease. Moreover, milder ExRA manifestations, such as KCS, has been diagnosed more frequently among patients with a more recent onset of RA, possibly because of improved clinical surveillance.[86] The clinician must be familiar with ExRA diagnosis, which is often complicated and difficult, and its management. New immunosuppressive drugs may offer interesting possibilities, although until now quality studies are lacking and there is a need to act with care. Undoubtedly, the future for RA patients is encouraging.

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