Extra-articular rheumatoid arthritis

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Purpose of review
To discuss recent findings on the epidemiology and pathogenesis of extra-articular manifestations in rheumatoid arthritis (RA), and provide an update on the literature on treatment of patients with extra-articular RA (ExRA) manifestations.

Recent findings
ExRA is associated with increased comorbidity and mortality. Several surveys suggest that some ExRA manifestations, in particular vasculitis, occur less frequently than previously reported. This is probably due to improved overall control of disease activity. Active RA with high disease activity is associated with increased risk of severe ExRA manifestations. Studies on the impact of treatment with biologics on the occurrence of ExRA are inconclusive. Circulating immune complexes and T cells have been implicated in the pathogenesis of ExRA. The genetic background and related disease mechanisms may be somewhat different in manifestations such as vasculitis and interstitial lung disease. Limited data support a benefit from treatment with cyclophosphamide, TNF-inhibitors or rituximab in patients with severe ExRA.

Summary
ExRA remains a major diagnostic and therapeutic challenge in some patients. Further studies of the pathogenesis of systemic involvement and on the effect of treatment on such mechanisms may be helpful for further improvement of the management of RA.

Keywords
clinical features, epidemiology, interstitial lung disease, rheumatoid arthritis, vasculitis

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic disease. Vasculitis and other severe organ manifestations have a major impact on a subset of patients, with increased morbidity and mortality [1–3]. With more active management of RA, the outcome has improved in many patients, and extra-articular RA (ExRA) manifestations may occur less frequently. On the other hand, such manifestations present a major diagnostic and therapeutic challenge in some patients, and treatment recommendations have been based on a limited number of clinical trials and expert opinion [4,5]. The objective of this review is to discuss recent findings on the epidemiology and pathogenesis of ExRA, as well as the literature on treatment.

Epidemiology

Signs of systemic inflammation in patients with RA include constitutional features and localized extra-articular organ involvement. The most frequent of such manifestations, the subcutaneous rheumatoid nodule [6], has been reported to occur in 7% of patients with RA at the time of diagnosis [7], and about 30% have nodules at some time during the disease course [8]. Nodules occur mainly in rheumatoid factor positive RA and rarely in seronegative patients [7]. Severe ExRA manifestation, such as vasculitis, rheumatoid lung disease, pericarditis and pleuritis, are seen more frequently in RA patients with rheumatoid nodules [9], and patients who develop nodules within 2 years from RA diagnosis are at a particularly increased risk of severe ExRA [10]. Whereas some patients have signs of severe ExRA involvement such as interstitial lung disease (ILD), pleuritis or pericarditis at or even before the development of joint symptoms [11], severe ExRA is otherwise mostly seen in patients with long standing, severe disease.

There is a wide variation in the reported incidence of ExRA, partly due to methodological

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KEY POINTS

- The incidence of some ExRA manifestations, such as vasculitis, has decreased over time, whereas there may be less change in the occurrence of others, such as interstitial lung disease.
- Disease severity and smoking are risk factors for severe ExRA.
- The impact of TNF-inhibitors on the risk of ExRA is still unclear.
- Disease mechanisms in various ExRA manifestations may be partly different.
- Limited data support a benefit from treatment with cyclophosphamide, TNF-inhibitors or rituximab in patients with active, severe ExRA.

differences in epidemiologic studies and lack of consensus on the case definition. In 2004, in order to enable a more consistent assessment of the extent of extra-articular disease, criteria for severe ExRA were proposed [8]. These criteria were based on previous studies [12,13] with retrospective assessment of ExRA through a structured review of medical records. In such a study, severe ExRA manifestations (including vasculitis, vasculitis-related neuropathy, Felty's syndrome, glomerulonephritis, pericarditis, pleuritis or scleritis) were found to develop in about 15% of patients with RA during long-term follow-up of a community-based cohort of incident cases of RA in Olmsted County, Minnesota, United States, corresponding to an estimated incidence of 1/100 person-years [13]. In an extended study [14] of this cohort, including patients diagnosed with RA between 1955 and 1995, there was no evidence for a decline in vasculitis or other severe ExRA manifestations over time. This is in contrast to a survey of the Norwich Health Authority area in the United Kingdom between 1988 and 2002, in which hospitalization for systemic rheumatoid vasculitis was reduced from 11.6 to 3.6 per million inhabitants [15]. However, in the most recent investigation of the Olmsted county RA population, there was a decline in the 10-year cumulative incidence of RA associated vasculitis from 3.6% in patients diagnosed with RA between 1985 and 1994 to 0.6% among those diagnosed 1995–2007, whereas there was no major change in the incidence of other severe ExRA manifestations (Fig. 1) or in rheumatoid nodules [16▪▪]. In addition, a recent survey of a large sample of US veterans indicated a decline in severe ExRA manifestations around 2000, with the exception of RA-associated lung disease [17]. Secondary amyloidosis with clinically apparent organ manifestations, which may occur in patients who have active disease with high levels of serum amyloid A for extended periods of time, was not observed in patients with RA diagnosed after 1985 in the Olmsted County cohort [16▪▪]. On the contrary, milder ExRA manifestations, such as keratoconjunctivitis sicca, were diagnosed more frequently among patients with a more recent onset of RA, possibly because of improved clinical surveillance [16▪▪].

These patterns are compatible with the concept that management of RA according to modern evidence-based recommendations [18–20] should

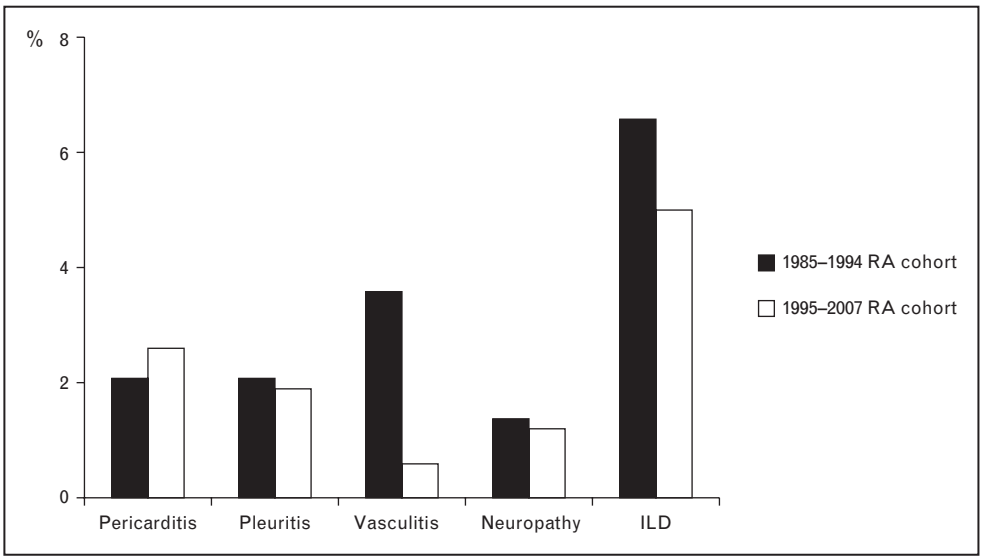

FIGURE 1. Ten-year cumulative incidence of severe extra-articular manifestations in incident patients with rheumatoid arthritis (RA) in Olmsted County, Minnesota, diagnosed in 1985–1994, compared with those diagnosed in 1995–2007. ILD, Interstitial lung disease. Based on data from [16▪▪].

reduce the risk of poor outcomes, such as severe ExRA manifestations. Indeed, high disease activity and extensive disability during the first 2 years after diagnosis have been shown to predict subsequent development of severe ExRA in an inception cohort of patients with early RA [11]. A double gene dose of the RA-associated shared epitope of human leukocyte antigen (HLA)-DRB1 [21], which is also a predictor of progressive joint damage in RA [22], is associated with increased risk of severe ExRA [23,24]. Patients with RA who smoke are more likely to develop rheumatoid nodules [7], but also severe ExRA manifestations, in particular vasculitis [25]. A reduced rate of smoking over time in the general population may also contribute to a reduced incidence of severe ExRA and possibly also reduce adverse outcomes due to comorbidities in such patients.

The effect of treatment on the risk of extra-articular rheumatoid arthritis

Based on the association between ExRA involvement and general disease severity (see above), a reduced incidence of severe ExRA in patients treated with tumour necrosis factor (TNF)-inhibitors and other biologics may be expected. On the contrary, there have been a number of case reports on patients developing severe ExRA [26,27] or worsening of preexistent ExRA manifestations [28] during anti-TNF treatment. In a large US sample of patients with RA, there was no association between current treatment with TNF-inhibitors and hospitalization for RA-associated ILD [29]. In a recent community-based study [30▪] from southern Sweden, the estimated incidence of severe ExRA was lower among those treated with TNF-inhibitors compared with those not treated (0.49/100 person-years vs. 1.16/100 person-years). However, due to the small sample size, the study had limited statistical power for this comparison (incidence rate ratio for those with vs. without TNF-inhibitor treatment 0.42; 95% confidence interval 0.10–1.73). Channeling bias may also be an issue in such observational studies, as patients with severe RA who start anti-TNF treatment may have a higher baseline risk of developing severe ExRA than patients who are not considered eligible for such treatment. In the Olmsted County RA cohort, treatment with biologic response modifiers was actually associated with a three-fold increase in the occurrence of severe ExRA, adjusted for the presence of erosive/destructive changes of radiographs, RF positivity and a history of at least three recorded erythrocyte sedimentation rates of at least 60 mm/h [16▪▪]. It should be noted, however, that this analysis was based on a rather limited sample size of 99 patients treated with biologics. Furthermore, the adjusted model probably did not completely reflect differences in baseline disease severity between those treated and those not treated with biologics. Additional studies of larger samples, with longer follow-up, are necessary. The challenge with larger studies is to ensure a consistent and valid assessment of both ExRA and treatment exposure. In my opinion, it is unlikely that treatment with biologics causes severe ExRA manifestations in a large number of patients, although further studies may be helpful for assessment of the risk/benefit ratio in individual patients.

Impact on morbidity and mortality

Severe ExRA has been associated with an increased mortality compared with patients with RA in general [6,12,31,32]. Patients with severe ExRA manifestations are at an increased risk of developing cardiovascular disease [33,34] or severe infections [35]. This may reflect an underlying association between RA-related immune and inflammatory abnormalities and comorbidities.

An association between severe ExRA and serious infections was also seen in a recent observational study [36] of patients with treated with rituximab, suggesting that this pattern with increased infection risk in patients with severe ExRA manifestations is also relevant in the era of extensive biologic treatment for RA. The risk of comorbidities should be taken into account in treatment decisions for patients with severe rheumatic disease, including those with severe ExRA.

RA severity in general may also affect survival in patients with RA. In line with this, other ExRA manifestations, such as rheumatoid nodules, have also been associated with an increased overall mortality [13]. In patients with established ExRA, the occurrence of a second ExRA manifestation, in particular rheumatoid nodules or rheumatoid lung disease, further increased the risk of death [37]. By contrast, no impaired survival compared with other RA patients was noted in patients with secondary Sjögren's syndrome [13,38].

The impact of ExRA on overall mortality may be decreasing due to better management. In the most recent study [16▪▪] of the Olmsted County RA cohort, there was a trend towards a reduced mortality risk among those diagnosed with ExRA in 1995–2007 cohort compared with the 1985–1994 cohort, although the difference did not reach significance. In patients diagnosed with RA in 1995–2007, the occurrence of a second ExRA manifestation was not associated with impaired survival

[16▪▪], suggesting that the impact of the burden of systemic disease on morbidity and mortality may have decreased over time.

Pathogenesis

Factors such as circulating immune complexes (CIC) [39]) and an abnormal T-cell repertoire [40] have been implicated in the pathogenesis of ExRA. Increased levels of CIC compared with patients with nonextraarticular RA have been found in RA patients with vasculitis [39], Felty's syndrome [41] and other severe ExRA manifestations [42]. Complement activation has also been demonstrated in such patients [43], and patients who subsequently develop ExRA have lower levels of complement factor C4 at RA diagnosis [44]. Low C4 has also been shown to predict mortality in patients with RA-associated vasculitis [45]. Vasculitis and other severe ExRA manifestations occur mainly in patients with rheumatoid factor positive RA [25,46], and at the time of active ExRA, rheumatoid factor levels are higher in such patients compared with RA controls [47]. This suggests a role for rheumatoid factor in the formation of complement activating CIC, which are involved in the pathogenesis of ExRA.

Additional observations support the involvement of the adaptive immune system in the development of RA-associated ILD. Quantification of lymphocytes in biopsies from RA-associated ILD demonstrated significantly higher counts for $CD4^+$ T-cells and B-cells compared with idiopathic ILD [48,49].

Interestingly, the genetic background and related pathogenesis may be different for ILD and other ExRA manifestations. A recent survey from Japan demonstrated a negative association between the shared epitope of HLA-DRB1 and ILD in patients with RA [50▪]. This is in contrast to studies of other ExRA manifestations, in particular vasculitis and Felty's syndrome [24]. Ethnicity could partly explain these discrepancies, but in a multicentre study [24] of mainly Caucasians from Sweden and Minnesota, United States, the proportion of carriers of the shared epitope also tended to be lower in patients with RA-associated ILD. On the contrary, in the same study, both vasculitis and ILD were associated with HLA-C3 [25], and there is a significantly increased cooccurrence of ILD and vasculitis in patients with RA [9]. Taken together, these results suggest that there are common as well as differential pathomechanisms underlying these manifestations. An improved understanding of these mechanisms may be the basis for further improvement of management of such patients.

Treatment

In severe ExRA manifestations like systemic vasculitis with or without serious ocular complications (scleritis or retinal vasculitis) or vasculitis-associated peripheral neuropathy, treatment with cyclophosphamide and high-dose corticosteroids is recommended according to the same principles as for primary systemic small-vessel vasculitis. This is based on open clinical trials and long-term experience [51–55,56▪] (Table 1). Such treatment should also be considered for ILD with rapid worsening [57]. Limited data suggest that treatment with chlorambucil [58], cyclophosphamide [58] and TNF-inhibitors [59] each may improve outcome in patients with systemic amyloidosis and serious organ involvement.

There is no consensus on the role of TNF-inhibitors in the treatment of RA-associated lung disease. Although there have been reports on excellent response in refractory patients [60], worsening of interstitial lung disease after treatment with TNF-inhibitors has also been reported [27]. Some experimental models suggest that TNF may play a role in preventing pulmonary fibrosis [61], although there are conflicting results [62]. In a study [63] from the British Society for Rheumatology database for biologic treatment of RA, there was no difference in mortality between patients with physician reported RA-associated ILD who had been treated with TNF-blockers and those treated with traditional disease modifying anti-rheumatic drugs (DMARDs). In my opinion, a TNF-inhibitor is not the treatment of choice for a patient with severe, progressive RA-associated ILD, but a history of stable ILD in a patient with severe RA should not be considered a contraindication for anti-TNF treatment, given the potential long-term benefits of controlling the disease.

Case reports demonstrating efficacy of cyclosporine in treatment refractory patients with RA associated ILD are consistent with an importance of T cell abnormalities in this context [64]. Clinical experience and case series [65] suggest that treatment with methotrexate is effective in some patients, although the risk of methotrexate induced toxic pneumonitis is a concern, in particular among patients with severely impaired respiratory function. Like for TNF-inhibitors, the overall benefits of successful treatment with methotrexate in RA must be taken into account when making treatment decisions in individual patients with a complicated disease.

High-dose corticosteroid treatment can be effective in severe ExRA manifestations, with or without other kinds of immunosuppression [4,5]. In general, active DMARD treatment is recommended for patients with severe ExRA manifestations, both to

Table 1. Evidence-based induction therapy in patients with rheumatoid arthritis and systemic rheumatoid vasculitis

Treatment	Study	Patient population	Outcome	Reference(s)
Cyclophosphamide				
Intravenous	Open, nonrandomized trial: Intermittent cyclophosphamide + methylprednisolone vs. other immunosuppressive drugs	Definite or classic RA [53] systemic rheumatoid vasculitis (SRV) – Mononeuritis multiplex/peripheral gangrene/biopsy verified vasculitis + systemic illness or other ExRA manifestations, $N=45$	At 4 months: greater improvement in all measures with cyclophosphamide At 48 months: lower relapse rate with cyclophosphamide: 24% vs. 54%	Scott 1984 [51]
Oral	Open, nonrandomized trial: cytotoxic therapy (oral cyclophosphamide or methotrexate) vs. high-dose corticosteroids ± other DMARDs	Definite or classic RA [53] + necrotizing scleritis and/or peripheral ulcerative keratitis, $N=34$	Less progression of ocular lesions, less extra-ocular vasculitis and lower mortality in the group receiving cytotoxic therapy faster healing of ocular lesions in subset treated with cyclophopshamide	Foster 1984 [52]
TNF-inhibitors	Case series, based on a national retrospective survey in France	RA (1987 ACR criteria [54]) SRV according to predefined critiera 51 Active SRV with failure of cyclophsophamide and corticosteroids Second line treatment with TNF inhibitors ($N=9$; infliximab: 7, etanercept: 2)	At 6 months: 6/9 patients in remission (5 complete, 1 partial) 2 patients relapsed within 13 months, 3 patients had serious infections	Puéchal 2008 [55]
Rituximab	Observational study, based on the autoimmunity and Rituximab register in France	RA (1987 ACR criteria) (54) SRV according to predefined critiera [51] Treatment with rituximab [$N=17$; first-line ($n=7$) or second line induction therapy ($n=6$); or salvage therapy ($n=4$)]	At 6 months: 16/17 patients responded (12 complete remission, 4 partial response) 6–12 months: 6 patients received subsequent rituximab doses: no relapse, 6 received methotrexate alone and 3 no maintenance therapy: 3 relapses, 3 patients had serious infections	Puéchal 2012 [56▪]

ACR, American College of Rheumatology; DMARD, disease modifying anti-rheumatic drugs; RA, rheumatoid arthritis; TNF, tumour necrosis factor.

reduce the risk of further extra-articular complications and to prevent comorbidities related to inflammation and severe progression of RA [4,5].

There are a number of reports in the literature of cases with systemic rheumatoid vasculitis in which treatment with TNF-inhibitors has been found to be helpful. The largest sample of these is a retrospective study [55] from France of nine patients with RA and vasculitis that had been refractory to cyclophosphamide and high-dose corticosteroids. Substantial improvement was seen in the majority of these patients, but there were also high rates of relapses and severe side effects (Table 1).

B-cell depleting therapy with rituximab has also been used as successful treatment of RA-associated vasculitis. In a recent observational study [56▪], also from France, 16/17 patients who received rituximab as either first-line, second-line or salvage therapy were responders after 6 months (Table 1). Limited follow-up in this study suggests that relapses may be prevented by retreatment with rituximab (Table 1).

There are no direct or indirect comparisons between different treatment strategies in RA-associated vasculitis. In my opinion, treatment with intravenous cyclophosphamide is still the treatment of choice for this subset, but rituximab should be considered when such treatment is unsuccessful or contraindicated, in particular in cases with high levels of rheumatoid factor. TNF-inhibitors may be an alternative, in particular for patients who also have severe joint inflammation with progressive structural damage.

CONCLUSION

ExRA remains a major diagnostic and therapeutic challenge in some patients. Better overall control of disease activity may be associated with a reduced risk of some manifestations, in particular vasculitis. The effect of TNF inhibitors and other biologics on the occurrence of ExRA, and their role in the management of severe, active ExRA, require further investigation. Together with studies of the underlying disease mechanisms, this may facilitate further improvement of the management of RA.

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Conflicts of interest

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- ▪ of special interest
- ▪▪ of outstanding interest

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