REPORT

Interleukin-7 induced immunopathology in arthritis

S A Y Hartgring, J W J Bijlsma, F P J G Lafeber, J A G van Roon

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Interleukin (IL)-7 is a potent immunoregulatory cytokine that is detected in joints of patients with rheumatoid and juvenile idiopathic arthritis and which correlates with parameters of disease. Several synovial cell types that play an important role in inflammation and immunopathology, such as macrophages, dendritic cells, and fibroblasts, produce IL-7. IL-7 induces cytokines produced by arthritogenic T cells (for example, interferon γ (IFNγ), IL-17), T cell differentiating factors (for example, IL-12), chemokines capable of attracting inflammatory cells (for example, macrophage induced gene (MIG), macrophage inflammatory protein (MIP)-1α) as well as molecules involved in cell adhesion, migration, and costimulation (for example, lymphocyte function associated antigen (LFA)-1, CD40, CD80). In addition, IL-7 can induce bone loss by stimulating osteoclastogenesis that is dependent on receptor activator of nuclear factor κB ligand (RANKL). IL-7 induces tumour necrosis factor α (TNFα) secretion by T cells and by monocytes after T cell dependent monocyte/macrophage activation. Importantly, induction of both IL-7 and IL-7 induced effects seems to be able to operate independent of TNFα. Together this suggests that IL-7 is an important cytokine in several rheumatic conditions, capable of inducing inflammation and immunopathology. Thus it may be an important target for immunotherapy.

Rheumatoid arthritis (RA) is characterised by persistent inflammation of the joints, which results in progressive destruction of cartilage and bone.[1] Several studies have revealed an important role for CD4+ T cells, B cells, and macrophages in the inflamed joints of patients with RA.[2–8] Large numbers of these cells have been demonstrated in the synovial fluid and tissue of RA patients and their numbers and/or activity have been shown to correlate with clinical symptoms.[3–5 7 9 10] Several ''anti-T cell'', anti-B cell and ''anti-macrophage'' therapies have resulted in good clinical responses[8 11 12] in a substantial proportion of patients with RA. Despite this success, a large number of patients still do not respond to therapy or respond partially, and effects of therapy are transient requiring repeated drug administration. This implies that it is still worthwhile to counteract other mediators and mechanisms that have been indicated to play an important role in the immunopathology of RA. Recent findings imply that interleukin (IL)-7, a potent immunoregulatory cytokine, could play a unique role in immunopathology of RA as well as other (rheumatic) inflammatory diseases.

ROLE OF IL-7 IN IMMUNITY AND INFLAMMATION

IL-7 is a member of the IL-2 family and signals through the IL-7 receptor-α chain (IL-7Rα), in conjunction with the common gamma chain (γc). A related cytokine, the stromal cell derived lymphopoietin-1 (TSLP-1), also interacts with IL-7Rα, but signals by formation of a heterodimer with a γc-like chain, called the TSLP receptor.[13–15]

Epithelial cells in lymphopoietic tissues such as bone marrow, thymus, spleen, and the gut produce IL-7. Apart from the sites of lymphopoiesis, many cell types throughout the body, such as keratinocytes, hepatocytes, endothelial cells as well as cells from the immune system including monocytes, and (follicular) dendritic cells, have the potential to produce IL-7.[16–18] Both IL-7 increased thymic output and expansion of peripheral T cells have been shown to contribute to expansion and maintenance of the peripheral T cell pool.[16 19] With progressing age and strong thymus atrophy[20] the expansion and maintenance of the T cell pool becomes largely dependent on thymic independent pathways.[16 21] IL-7 plays an important role in T cell homoeostasis in humans and in mice by provision of signals for proliferation, growth, and survival of both developing and mature T cells.[16 22 23]

Apart from the stimulating mechanisms that regulate T cell numbers, IL-7 has been shown to stimulate several effector functions of not only T cells but also other cells of both the acquired and innate immune systems. Although IL-7 can stimulate IL-4 production, human in vitro studies have shown that IL-7 primarily induces T helper (Th) 1 cytokine secretion (IFNγ production) by both human CD4+ and CD8+ T cells in the absence of IL-4 production.[24] In mixed mononuclear cell cultures from peripheral blood of healthy controls IL-7 induces IFNγ but no IL-4 secretion (van Roon, unpublished data). Besides cytokine secretion, IL-7 stimulates cytotoxic activity mediated by CD8+ T cells.[25 26] In addition to affecting function of CD4+ and CD8+ T cells, IL-7 also augments the function of natural killer (NK) cells.[27] In humans, this activity seems to be restricted to function of mature NK cells, since disruption of the IL-7 pathway in IL-7R deficient individuals does not lead to impaired development of NK cells.[28]

The effects of IL-7 on B cell activity differ significantly between mice and humans. Although clear effects on B cell development have been shown in IL-7 knockout mice, and immature human B cells can respond to IL-7,[29] IL-7Rα deficiency in humans does not affect B cell development.[28 30] IL-7Rα deficient individuals only have abnormalities in T cell development as measured by diminished CD3+ T cell numbers and reduced lymphocyte proliferation to mitogen and allogenic cells, whereas B cell numbers are normal.[28 30] Despite the lack of direct effect of IL-7 on B cell numbers, IL-7Rα deficiency does influence B cell activity since Ig levels in IL-7Rα deficient humans can be reduced.[28] As the IL-7Rα expression levels of mature human B cells are low to absent this observation might be largely related to T cell dependent effects on B cell activity.

Abbreviations: IFN, interferon; IL, interleukin; IL-7Rα, IL-7 receptor-α chain; JIA, juvenile idiopathic arthritis; MIG, macrophage induced gene; MIP, macrophage inflammatory protein; NK, natural killer; RA, rheumatoid arthritis; RANKL, receptor activator of nuclear factor κB ligand; Th, T helper; TNF, tumour necrosis factor

In addition to the acquired immune system, IL-7 has also been shown to activate cells from the innate immune system. IL-7 induces secretion of IL-1α, IL-1β, IL-6, IL-8, macrophage inflammatory protein (MIP)-1β and tumour necrosis factor α (TNFα) by human monocytes.[25 31 32] However, it should be noticed that high, possibly supraphysiological, levels of IL-7 (50–100 ng/ml) are required to induce this cytokine secretion, approximately 100–1000-fold higher than observed for activation of T cells.[25 33 34] This may be related to the much lower to absent expression of the IL-7Rα protein levels on monocytes compared with T cell surfaces.[35] In contrast with T cells and monocytes, IL-7 does not have any direct effect on granulocyte activity, related to the absence of IL-7Rα expression on these cells.[36]

In vivo administration of IL-7 in *mice* has also shown strong effects on cells from the acquired and innate immune systems. Administration of IL-7 resulted in increases in T cells, NK cells, and macrophages, and stimulation of B lymphocyte production.[37] T cells from IL-7-treated mice have been shown to have enhanced proliferative responses to various stimuli in vitro, and these cells were able to potentiate cytotoxic T lymphocyte responses in vivo.[37] In bone marrow transplant studies, in which mice were treated with IL-7 after transplantation, lymphocyte regeneration was accelerated and T and B cell function improved.[38] An in vivo mouse model of IL-7 transfected glioma cells showed reduction of tumorigenicity that was reversed by injecting an anti-IL-7 antibody at the tumour site. In addition IL-7 can promote delayed-type hypersensitivity reactions in mice.[39]

Effects of IL-7 in rodents and *primates* differ markedly in some aspects, as demonstrated by studies of IL-7Rα deficient humans and mice.[16 28 30] Thus analysis of IL-7 induced effects in primates is also important. In baboons, IL-7 increased virus specific IFNγ producing CD4+ T cell numbers.[40] After treatment of baboons (after TBI and CD34 cell transplantation) and Indian rhesus macaques with IL-7, CD4+ and CD8+ lymphocytes populations were increased and lymph nodes were enlarged compared with untreated animals.[41 42] Furthermore, IL-7 increased the ability of CD4+ and CD8+ T central memory and T effector memory cells to produce the proinflammatory cytokines TNFα and IFNγ.[41] In contrast with IL-7 stimulated T cell reconstitution on TBI followed by CD34 cell transplantation, IL-7 did not increase B cell, monocyte, and NK cell counts in baboons.[42]

The above data indicate that IL-7 is an important immunoregulatory cytokine, which stimulates immunity that could contribute to inflammation and inflammation induced immunopathology in RA as well as other chronic inflammatory (rheumatic) diseases.

ROLE OF IL-7 IN INFLAMMATION IN (RHEUMATOID) ARTHRITIS

Recent studies indicate IL-7 to be a factor with many activities which could contribute to inflammation and tissue destruction in RA in a unique manner.

IL-7/IL-7 receptor expression in RA

Serum levels of IL-7 in patients with RA have been shown to be higher than in healthy controls and correlate positively with markers of inflammation. Although a number of groups have reported increased serum levels of IL-7 in patients with RA and juvenile idiopathic arthritis (JIA),[33 43 44] there are conflicting data on serum levels.[45] Such differences in IL-7 levels may be due to heterogeneity in drug use between the studies as explained below. In support of a role of IL-7 in RA synovitis is the observation that in RA synovial fluid levels of IL-7 (up to 480 pg/ml) were strongly elevated compared with the levels in synovial fluid of patients with osteoarthritis (a joint disease with mild or no inflammation).[34] Furthermore, in synovial tissue (biopsies) from RA patients high IL-7 levels are expressed by macrophages, fibroblasts, and endothelial cells throughout the tissue. Numbers of IL-7+ cells have been shown to strongly correlate with the presence of CD68+ macrophages in the lining and sub-lining. Double staining has demonstrated that CD68+ macrophages are major producers of IL-7.[34] In addition, dendritic-like cells in the lymphoid follicles have been found.[34] Recently, we supported the latter observation by showing that in vitro GM-CSF/IL-4 generated dendritic cells from RA patients were indeed significant producers of IL-7 (van Roon *et al*, unpublished data). In addition, IL-7 production by dendritic cells from healthy controls has been previously shown by other groups.[18 46]

Both in RA peripheral blood and synovial fluid the receptor that is essential for IL-7 signalling (IL-7Rα) is primarily expressed on T cells, with the highest expression on CD4+ T cells. In addition NK T cells express considerable IL-7Rα on their cell surface although at a lower level than on CD4+ T cells. In contrast, CD19+ B cells and monocytes in the circulation of patients with RA express no to very little IL-7Rα on their surface. However, subpopulations of macrophages and CD19+ B cells from synovial fluid display increased surface IL-7Rα levels (Hartgring *et al*, unpublished data). This might be due to the local inflammatory milieu because treatment of monocytes with cytokines and toll-like receptor agonists has been shown to induce IL-7Rα expression on these cells (van Roon *et al*, unpublished data). The IL-7Rα distribution suggests that in RA patients T cells may be a primary target of IL-7 and that initial IL-7 driven effects may be primarily mediated by T cells. In vitro studies support this suggestion.

IL-7 activity on human CD4+ T cells and monocytes in vitro

RA is characterised by a diverse autoreactive T cell response against numerous self-antigens expressed in the inflamed joints (for example, collagen type II, heat-shock proteins, aggrecan).[47] However, although detectable, such T cells are present in a low frequency and are part of an oligo/polyclonal intra-articular T cell response.[48] Several groups have tried to explain this widespread T cell response, but a causal linkage has not been found. In fact, the contribution of T cells in RA may have been underestimated because, based on the use of T cell receptor (TCR) mediated mitogenic stimuli, hyporesponsiveness of intra-articular T cells from RA patients to TCR driven activation has been suggested.[49] This contrasts with the observation that in RA joints a large activated T cell pool is found. Until now, there is a limited number of factors that explain these (hyper)activated T cells.[50 51]

Our data have demonstrated that intra-articular CD4+ T cells are hyperresponsive to IL-7.[34] In co-cultures of monocytes/macrophages and CD4+ T cells, T cell activation was shown to require cell contact and was related to the IL-7 induced expression of costimulatory molecules on macrophages from the synovial fluid, such as CD40, CD86, and, in particular, CD80.[34] In addition, upregulation of costimulatory molecules such as lymphocyte function associated antigen (LFA)-1 and CD69 has been observed and could play an important role in (CD4+) T cell activation. Recently we have shown that this IL-7 induced contact dependent activation, which is associated with monocyte activation (measured by upregulation of CD80 and CD40), is also associated with TNFα production.[35] IL-7 (at similar concentrations) fails to induce TNFα secretion by isolated T cells or monocytes cultured separately. These data support our previous data that IL-7 induces TNFα secretion by mononuclear cells from the synovial fluid of RA patients.[33]

Previously we have shown that IL-7 promotes arthritogenic Th 1 cell activity in cultures of mononuclear cells from RA patients. IL-7 primes T cells for IFNγ and TNFα production in contrast to IL-4 production.[33] IFNγ induction by IL-7 is dependent on IL-12 since blockade of IL-12 markedly reduced IFNγ production. Interestingly, IL-7 induced production of TNFα is not inhibited by IL-12 blockade.[33] This may be related to the induction of other regulatory cytokines. Using cytokine arrays we found that IL-7 can not only stimulate Th 1 activity (IFNγ production) but possibly also Th 17 activity because IL-17 production by RA mononuclear cells was increased by IL-7. This was in the absence of induction of Th 2 activity (no IL-4, IL-5). Th 1 activity was associated with induction of Th 1 cell differentiating factors such as IL-12 and small amounts of IL-18. Interestingly, IL-7 also induced chemokines (macrophage induced gene (MIG) and MIP-1α) that can lead to chemotaxis of—in particular—Th 1 cells.

Persistence of IL-7 activity and levels on anti-TNFα treatment

Anti-TNFα treatment is presently the treatment of choice in refractory RA. Although this treatment is effective in a significant number of patients, considerable numbers of patients do not respond.[12] From a utilisation perspective (possible use of anti-IL-7 treatment) it has been of major importance to study IL-7 in relation to TNFα and under anti-TNFα conditions.

IL-7 significantly enhances TNFα production by isolated naive and memory CD4+ T cells from RA patients that were costimulated with CD3/28.[33 52] However, recently we have found that IL-7 can also induce T cell dependent production of TNFα by monocytes.[35 53] In addition, the levels of expression of TNFα and IL-7 in the synovial fluid and synovial tissue correlated significantly. This relation indicates that in the synovial compartment IL-7 could contribute to increased TNFα levels. Alternatively, TNFα inducing IL-7 production could contribute to increased IL-7 levels. TNFα has been shown to induce IL-7 production by RA fibroblasts and bone marrow stromal cells.[54 55] To test the latter possibility we measured the effect of TNFα blockade on circulating IL-7 levels in RA patients. It was observed that in non-responding patients serum levels of IL-7 were not reduced but in fact slightly increased, whereas in anti-TNFα responders IL-7 levels were significantly decreased.[35] After two weeks of therapy changes in disease activity scores correlated with changes in IL-7 levels. The persistence of IL-7 levels after TNFα blockade in a non-responding subpopulation of patients suggests that, in particular in these patients, IL-7 could persist to promote inflammatory responses (not regulated by TNFα). In addition, as IL-7 in vitro has been shown to induce TNFα production, IL-7 blockade could at least partially prevent TNFα induced inflammation. Furthermore, in vitro studies have shown that to a considerable extent IL-7 induced proinflammatory responses cannot be abolished by TNFα blockade.[35] Potentially, because of their mutual inductive capacities, synergistic immunosuppression may be achieved by blockade of TNFα together with blockade of IL-7.

ROLE OF IL-7 IN IMMUNOPATHOLOGY IN (RHEUMATOID) ARTHRITIS

IL-7 is an inducer of TNFα, which has been shown to be a pivotal inducer of inflammation and joint destruction in a large proportion of RA patients. This implies that IL-7 may also contribute besides IL-7 induced TNFα dependent inflammation to TNFα dependent joint destruction. However, independent of TNFα IL-7 could also promote joint destruction by the induction of other mediators—for example, IL-17. In addition, by induction of many proinflammatory cytokines IL-7 can promote inflammation and consequently inflammation induced destruction of joint tissues such as cartilage and bone.

Another mechanism contributing to joint destruction that IL-7 might induce in particular is the activation of fibroblasts. Th 1 cells, either by cell contact or cytokine secretion (for example, IFNγ), have been shown to activate fibroblasts.[56] Because IL-7 induces Th 1 activation it is anticipated that IL-7 might also induce fibroblast activation and possibly fibroblast induced destruction of cartilage and bone matrices. However, direct proof is needed. In this respect, the independence of IL-7 from TNFα in this context remains to be demonstrated. The notion that TNFα, in contrast with IL-7, does not induce but inhibits Th 1 development, points towards IL-7 induced, TNFα independent, effects that could occur.[57]

Apart from fibroblast activation IL-7 recently has been shown to play a pivotal role in osteoclastogenesis and bone loss. In mice IL-7 induces bone loss through increased osteoclastogenesis, whereas it has been found that IL-7Rα deficient mice show greatly increased femoral trabecular bone volume compared with wild-type and heterozygous littermates.[58] The IL-7-induced bone loss in mice is mediated by induction of receptor activator of nuclear factor κB ligand (RANKL) and TNFα production by T cells.[59] These cytokines were found to induce osteoclasts from monocytes and bone marrow B cell precursors.[59] Similarly, IL-7 induced osteoclast formation from human monocytes in a T cell dependent way that was strongly (approximately 50%) dependent on RANKL.[55] Together, this suggests that IL-7 could contribute to bone destruction in RA by induction of T cell dependent osteoclastogenesis.

In addition to the production of IL-7 by cells from the synovial tissue, increased expression of IL-7 mRNA by articular cartilage chondrocytes from RA patients compared with chondrocytes from patients with osteoarthritis has been detected.[60] We have recently demonstrated by immunohistochemistry IL-7 protein expression in chondrocytes in the cartilage tissue from a patient with RA. The role of this IL-7 remains to be elucidated, however, it does not seem to play a role in the metabolism of cartilage matrix components as cartilage proteoglycan turnover is not affected directly by IL-7 (van Roon *et al*, unpublished observations).

Based on data from our work and other groups we propose a concept in which IL-7 is suggested to induce cell contact dependent spreading of the autoimmunity and immunopathology in RA via an alternative, primarily cytokine driven route (fig 1). This unique route could operate, at least in a subpopulation of patients or in certain stages of the disease, largely independent of TNFα induced immunopathology. This pathway may not only play a role in RA but also in other chronic inflammatory rheumatic diseases.

IL-7 IN OTHER CHRONIC INFLAMMATORY (AUTOIMMUNE) DISEASES

In patients with JIA, with active systemic disease, plasma levels of IL-7 have been shown to be higher than in healthy children.[44] Patients with JIA in remission had levels comparable with controls. Recently, increased IL-7 levels have been detected in the synovial fluid of JIA patients, and these were related to clinical activity in that IL-7 levels were higher in polyarthritis compared with the milder oligoarthritic forms.[63] IL-7 was found to abrogate the suppressive activity of regulatory T cells, altering the balance between proinflammatory effector and suppressor T cells, a balance that was related to clinical activity in these patients.[63]

A proinflammatory role of IL-7 has also been suggested in another rheumatic autoimmune disorder—primary Sjögren's syndrome (pSS), which is characterised by lymphocyte

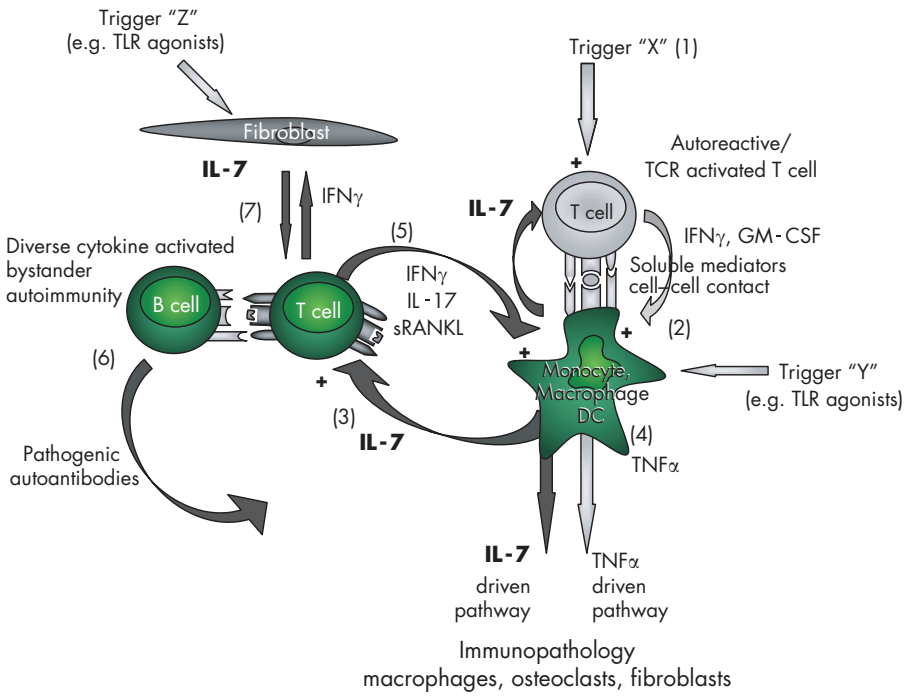

Figure 1 On the basis of our published data and preliminary work, and recent data from other groups, we propose the following concept: in autoimmune diseases such as rheumatoid arthritis (RA) an unknown trigger ''X'' (1) may cause (self)-antigen specific T cell activation, resulting in cytokine production (for example, by interferon γ (IFNγ) and granulocyte macrophage-colony stimulating factor (GM-CSF)) and cell contact that lead to activation of cells such as monocytes, macrophages, and dendritic cells (2) which is associated with interleukin (IL)-7 and tumour necrosis factor α (TNFα) production.[18] Increased IL-7 (*not* TNFα[34 57]) induces cell contact dependent,[34 61] cytokine activated T cells (3) causing a spreading of T cell activation associated with autoantigenic recognition (possibly intermediate affinity self-antigens).[62] This can operate independent of TNFα (4). Such cytokine activated, bystander T cells in turn stimulate monocytic cells and possibly B cells (5).[28 34] As a consequence, monocytes differentiate into macrophages and osteoclasts that mediate inflammation and joint destruction.[34 55 59] Activated B cells in their turn are potent antigen presenting cells and can develop into plasma cells that secrete pathogenic autoantibodies (6).[8] Finally, activated T cells could interact (via cell contact and cytokine production) with and activate synovial fibroblasts, which can be associated with further IL-7 production (7).[56] Stimulated IL-7 production by both fibroblasts and macrophages (which could also be induced by alternative routes, triggers ''Y'' and ''Z''—for example, via toll-like receptor agonists) can further enhance IL-7-driven immunopathology. RANKL, receptor activator of nuclear factor κB ligand; TLR, toll-like receptor.

infiltration in salivary and lachrymal glands. Levels of IL-7 in saliva and salivary glands of patients with pSS were significantly higher compared with those of controls (van Woerkom *et al*, manuscript submitted for publication). Expression of IL-7 correlated with the presence of local and peripheral disease activity parameters (lymphocyte focus score/IgA producing plasma cells and erythrocyte sedimentation rate/serum IgG levels, respectively). IL-7 induced production of cytokines that can contribute to activation of proinflammatory Th 1 cells (IL-12 and IL-15), and induced cytokines produced by Th 1 cells (IFNγ) as well as chemokines that facilitate migration of such cells (MIG and IP-10). This was in contrast to IL-4, the major defining Th 2 cytokine, which was not significantly induced. These findings corroborate previous findings demonstrating a predominance of Th 1 cell activity in patients with pSS.[64]

IL-7 is also increased in relapsing polychondritis, a systemic disorder in which there is recurrent, widespread chondritis of the auricular, nasal, and tracheal cartilages. The pathology is suspected to be autoimmune, on the basis of association with human leucocyte antigen (HLA)-DR4 and evidence of humoral and cellular responses against cartilage components.[43] IL-7 levels are also significantly higher in the lesional regions of the skin of patients with psoriasis, compared with controls as well as non-lesional skin of patients[65]; this has been found in skin biopsies as well as samples from the stratum cornea. Serum levels in patients were significant higher than those of controls. As circulating cells did not show an increased production compared with healthy controls, it was suggested that the increased skin and serum concentrations of IL-7 were skin derived, most likely produced by keratinocytes.

CONCLUSION

IL-7 is a potent immunoregulatory cytokine that is produced by cells of the immune system and tissue cells at the inflammatory site of several rheumatic disorders, correlating with parameters of disease. IL-7 activates T cells and seems to cause primarily T cell dependent B cell and macrophage activation. In addition, IL-7 can induce bone loss by stimulating RANKL dependent osteoclastogenesis. It is suggested that IL-7 induces both TNFα dependent and independent inflammatory responses and immunopathology. Considering the lack of response or partial response to anti-TNFα therapy in a considerable number of patients the elucidation of the role IL-7 in immunopathology will be of major value. In this respect, study of the capacity of IL-7 blockade to reduce arthritis and joint pathology in experimental animal models for arthritis is a necessity.

Authors' affiliations
S A Y Hartgring, J W J Bijlsma, F P J G Lafeber, J A G van Roon, Rheumatology and Clinical Immunology, University Medical Center Utrecht, Utrecht, the Netherlands

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Correspondence to: J A G van Roon, Rheumatology and Clinical Immunology (F02.127), University Medical Center Utrecht, P.O. Box 85500, 3508 GA Utrecht, the Netherlands; J.vanRoon@umcutrecht.nl

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