Review

Interleukin-7 in rheumatoid arthritis

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Recent data from several groups demonstrate high levels of IL-7 in the joints of RA patients, but much lower levels in OA. In contrast, circulating levels of IL-7 in RA remain a point of debate. IL-7 has many roles in T cell, dendritic cell and bone biology in humans. Reduced levels of circulating IL-7 probably underlie a number of the dysfunctions associated with circulating T cells in RA and may provide a mechanism for some of the unexplained systemic manifestations of the disease. However, IL-7 in the joint may have a more sinister role, contributing to a vicious cycle perpetuating inflammation. Typically, IL-1β and TNF-α increase the stromal production of IL-7 and in turn, IL-7 up-regulates the production of TNF-α by macrophages. Most importantly, IL-7 induces the production of osteoclastogenic cytokines by T cells, leading to the maturation of osteoclasts and therefore bone destruction. By linking the stroma with innate and adaptive immunity in RA, IL-7 may be directing the cellular network, leading to chronic inflammation and joint destruction. Blocking IL-7 may well therefore be of therapeutic value.

**Key words:** IL-7, RA, Inflammation, T cells.

**Interleukin-7**

IL-7 was identified in the late 1980s [1] and is also known as lymphopoietin (LP-1) or pre-B cell factor (in mice). It has recently come to the attention of the rheumatology community due to its high level of expression in the RA synovium and SF [2]. IL-7 was first identified for its essential role in maintaining the lymphoid progenitor population in the bone marrow (BM). Subsequently, many other functions have been associated with IL-7 and have been extensively reviewed [3–6]; we will therefore focus mainly on effects relevant to rheumatology. Recent data in RA are contradictory and the purpose of this review is to discuss the available information, as it is now accepted that IL-7 has potential as a target for therapeutic intervention in RA.

IL-7 is a well-characterized cytokine of the IL-2/IL-15 family. It is 152 amino acids long, and can be secreted or presented on the cell surface by heparan sulphate and fibronectin [7, 8]. A homologue of IL-7, thymic stromal lymphopoietin (TSLP), was identified in 2001, but its function remains to be elucidated [9, 10]. Notably, the TSLP knockout (KO) mice displayed a different phenotype from IL-7 KO and IL-7 receptor (IL-7R) KO. IL-7 is expressed by stromal cells (BM, thymus, soft tissue), epithelial cells (liver, gut), endothelial cells, fibroblasts, smooth muscle cells and keratinocytes and, following activation, by dendritic cells (DCs) [11–16]. The IL-7R uses a high affinity α-subunit (CD127) and the common γ-chain for signalling to JAK-1, STAT-5a and 5b, PI3 kinase and src kinases (for a review of IL-7R signalling, see [6]). IL-7R is expressed on all circulating CD4+ and CD8+ T-cells, NK-T-cells and monocytes, but not on human B cells.

**IL-7 and bone physiology**

A major role of IL-7 in modulating bone physiology has been identified using KO mice. The regulation of bone mass is a complex equilibrium between formation and resorption and the activation of osteoblasts and osteoclasts [5]. In IL-7 KO mice, a significant increase in bone mass has been observed [17], which was attributed to a lack of IL-7-driven expression of RANK ligand (RANKL) by T cells, leading to reduced bone resorption. The direct administration of IL-7 into the BM cavity reduced the size of the osteoclast population by re-directing lineage commitment of progenitors towards B cells [5, 18]. In contrast, the systemic administration of IL-7 to healthy mice resulted in bone loss [19, 20], by up-regulating osteoclast formation from blood precursors [21]. Thus, the net effect of IL-7 on bone is clearly negative.

In RA synovial tissue, an important role of IL-7 is to drive the differentiation of CD14+ monocytes into multinucleated, giant, bone-resorbing, tartrate resistant acid phosphatase (TRAP)-positive cells. Following 3–4 weeks’ culture in the presence of synovial stromal cells, CD14+ monocytes developed into TRAP-positive cells. IL-7 was also the most potent factor (followed by IL-3, IL-5 and GM-CSF) to induce terminal differentiation into multinucleated cells from a panel of 16 cytokines and growth factors [22]. Interestingly, TNF-α, vitamin D3 and RANKL had no effect and combinations of IL-7 and IL-3 or GM-CSF were no more effective than IL-7 alone. Osteoclastogenesis was also shown to be specific to monocytes from RA as opposed to OA patients [23].

**IL-7 and T-cell development**

Both IL-7 and IL-7R KO mice show a striking paucity of both T- and B cells [24, 25] and a decrease in NK cell numbers [26]. In humans, however, IL-7 is not required for B cell development at any stage [27]. It is, therefore, difficult to extrapolate all mouse data to humans, particularly with regard to B cell biology. The IL-7-R is first expressed on the common lymphoid progenitor in the BM. During T-cell development in the thymus, IL-7 is involved at different stages of T-cell proliferation and positive/negative selection [4]. IL-7 signalling is also required for expression of the RAG1 gene and indirectly controls downstream VDJ recombination events in the T-lymphoid lineage [28, 29]. We have reported reduced IL-7 levels in serum and in BM stromal cell culture, as well as delayed thymic response to lymphodepletion in RA [30]. Defects in BM progenitor cell reserves and haematopoiesis supporting stromal function in RA were associated with TNF-α toxicity [31]. Progenitor survival in the BM may also be impaired in RA by lack of IL-7 production. In addition, independence from the inflammatory process appears to characterize this stromal IL-7 defect, as no consistent recovery
of IL-7 was observed post anti-TNF treatment [30]. Delayed thymic activity may reflect a lack of IL-7 thymic response to lymphopenia, as observed in the IL-7 systemic response [30]. These data provide evidence for an important role of stromal cells in RA. Several clinical trials use human recombinant IL-7 therapy to improve T-cell recovery in HIV, cancer and hepatitis [32, 33]. Supplementation with IL-7 in lymphopenic RA patients may prove beneficial; however, the fact that IL-7 has additional properties in autoimmunity (preferential expansion [34] and activation [35] of auto-reactive T-cells in multiple sclerosis (MS), genetic association with MS [36, 37] and association with lympho-proliferative disorders [38–40]) would probably postpone its use.

**IL-7 and T-cell homeostasis**

In the periphery, IL-7 is a major anti-apoptotic/survival factor through its up-regulation of Bcl-2 [41–43] and preserves the naı̈ve T-cell repertoire by increasing T-cell viability in the absence of antigen stimulation [44–46]. It also enhances memory T-cell survival and expansion [41, 47].

One of the most important functions of IL-7 is its role in the response to lymphopenia [30, 48–50] being a ‘major player in the regulation of peripheral T-cell homeostasis’ [51]. However, the mechanism of such a response remains elusive and it is unclear whether increased IL-7 results from active up-regulation or lack of scavenging by T-cells, as proposed by Fry and others [49, 51] and more recently by Mazzucchelli and Durum [52]. Our data in therapeutic lymphopenia induced in RA and cancer did not support the scavenging hypothesis; however, we observed a rise in IL-7 following depletion in cancer, but not in RA, despite more profound and more persistent lymphodepletion in RA [30].

Recent work has also implicated IL-7 in CD8+ memory T-cell survival [53–56]; however, no work has yet been done in RA regarding this observation. In our study of therapeutic lymphopenia in RA and cancer, factors other than IL-7 could effectively have driven CD8+ T-cell expansion [30] (potentially infections [57]).

**Circulating IL-7 in RA**

Four groups have reported IL-7 levels in the serum of RA patients with striking differences. In 2003, van Roon et al. [58] reported levels ranging from 1.5 to 3.8 pg/ml (Table 1). Stabler et al. [59] reported 20-fold higher levels of IL-7 (52 ± 58 pg/ml) using the newly developed Luminex technology. Another multi-cytokine profile study (also using Luminex) showed 100-fold higher serum IL-7 (~300 pg/ml) [60] while we reported low levels of circulating IL-7 in RA (6.9 ± 2.0 pg/ml) [30].

The serum IL-7 values reported for healthy controls in these four studies also differed, which may explain the conflicting conclusions. IL-7 levels are highly dependent on the conditions of serum collection, in particular, the type of blood collection tubes used, as highlighted in ELISA manufacturers’ instructions. A survey of the literature found 17 papers with consistent control values for serum IL-7 (Table 2) reporting healthy control serum levels of average 13 ± 5 pg/ml. Different ELISAs (three commercial (R&D Systems, Abingdon, UK; Diaclone (IDS), Boldon, UK; Immunotec, Luton, UK) and an in-house ELISA) compared well with the Luminex technology and all produced similar results, with the exception of the study by van Roon et al. [58] (Table 2).

Thus, it appears that data will remain conflicting until comparable protocols are used. A number of comments can be made regarding this data. The main discrepancy in the data reported by the first IL-7 study in RA [58] stems from the levels of IL-7 measured in the control population which are not consistent with the rest of the literature (Table 2). Notably, most of the values reported in this work are below the detection threshold of the ELISA used (Table 1). The levels of IL-7 reported in the second Luminex study [60] have never been observed in any human disease (extensively reviewed in [51]). In both Luminex-based studies [59, 60], every cytokine/chemokine/growth factor analysed was increased compared with controls. Both these studies were performed before several reports highlighted the necessity of pre-absorbing auto-antibodies (such as RF) when

<p>| Table 1. IL-7 levels detected in blood, SF and synovial tissue |</p>
<table>
<thead>
<tr>
<th>n</th>
<th>Mean ± s.d. (range) pg/ml</th>
<th>ELISA manufacturer</th>
<th>Reference</th>
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<tr>
<td>RA patients</td>
<td></td>
<td></td>
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<tr>
<td>Serum</td>
<td>34</td>
<td>(1.5–3.8)</td>
<td>Diaclonene</td>
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<tr>
<td>22</td>
<td>50 (0–100)</td>
<td>Luminex</td>
<td>10–2000</td>
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<tr>
<td>41</td>
<td>~500</td>
<td>R&amp;D Systems</td>
<td>0.1–24</td>
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<tr>
<td>Synovial fluid</td>
<td>28</td>
<td>6.9 ± 2.0 (2.5–10.5)</td>
<td>Diaclonene</td>
</tr>
<tr>
<td>44</td>
<td>34 (0–600)</td>
<td>R&amp;D Systems</td>
<td>0.1–24</td>
</tr>
<tr>
<td>21</td>
<td>12.6 ± 6.8 (3.5 to 35)</td>
<td>R&amp;D Systems</td>
<td>0.1–24</td>
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<tr>
<td>Synovial tissue</td>
<td>17</td>
<td>(0–1.6)</td>
<td>R&amp;D Systems</td>
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<tr>
<td>OA patients</td>
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<td></td>
<td></td>
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<tr>
<td>Serum</td>
<td>12</td>
<td>12.2 ± 2.1 (8.8–14.8)</td>
<td>R&amp;D Systems</td>
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<tr>
<td>Synovial fluid</td>
<td>10</td>
<td>1 ± 2 (1–8)</td>
<td>Diaclonene</td>
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<td>17</td>
<td>6.9 ± 1.8 (3–10)</td>
<td>R&amp;D Systems</td>
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<tr>
<td>Synovial tissue</td>
<td>7</td>
<td>(0–0.1)</td>
<td>R&amp;D Systems</td>
</tr>
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*Estimated reading from figure in paper [60].
using this technology [61, 62]. Our data are consistent with the literature for healthy controls (Table 2) and correlate with a number of T-cell functions known to be associated with IL-7, such as thymic activity and homeostatic T-cell proliferation [30].

**Tissue expression of IL-7**

In BM, the spontaneous release of IL-7 by stromal cells is reduced in RA compared with health [30]. SF IL-7 levels are reportedly higher in RA compared with OA (Table 1) [63]. We reproduced these data for OA (Table 1), but found lower IL-7 levels in RA compared with the previous study, although levels were still significantly higher than in OA (Table 1).

IL-7 message was detected in RA chondrocytes, but not in OA [64, 65]. In the synovial membrane, IL-7 expression was reported in nurse-like cells from RA patients in the late 1990s [2, 66]. IL-7 protein was detected in synovial fibroblasts freshly isolated from RA, but not OA patients [2]. In contrast, there was no detectable IL-7 expression in T-cells or macrophages isolated under similar conditions [2].

Immunohistochemistry (IHC) has shown IL-7-positive cells in RA synovial tissue biopsies [63]. IL-7 expression was co-localized with CD68 in RA; however, the antibody clone used to detect CD68 expression (EBM11) reacts with several cell types (macrophages and fibroblasts) [67]. In a recent study, IL-7 expression was also associated with fibroblasts, macrophages and endothelial cells but largely extracellularly and co-localized with deposits of extracellular matrix collagen IV [68]. More consistent IL-7 staining throughout the tissue was associated with samples containing lymphoid follicles (germinal centre-like structures) and gene expression patterns characteristic of IL-7 signalling were detected in this tissue using microarray analysis. A relationship between the number of IL-7-positive cells and staining with the EBM11 anti-CD68 antibody was also reported [63]. This antibody is a particularly good measure of disease activity [69], suggesting that inflammation and levels of IL-7 expression are closely related. The diffuse expression of IL-7 detected in a large area in active disease, in contrast to single isolated cells in clinical remission highlights this relationship (Fig. 1). We have observed a direct relationship between IL-7 mRNA levels in synovial fibroblast cultures and inflammation measured during arthroscopy (arthroscopic visual analogue score scales, \( n = 9, R = 0.965, P < 0.0001 \)). Levels of IL-7 were also related to levels of TNF-\( \alpha \) both in synovial tissue (measured by IHC) and SF (measured by ELISA) [70]. This observation is probably rooted in the feedback loop between TNF-\( \alpha \)/IL-1\( \beta \), which induce stromal cells to express IL-7 [2], and IL-7, which in return induces macrophages to produce TNF-\( \alpha \) and IFN-\( \gamma \) [58].

**IL-7 and T-cell response**

IL-7 has several effects on T-cells, including proliferation, co-stimulation and polarization. The direct proliferative effect of IL-7 on peripheral blood mononuclear cells (PBMCs) did not differ between RA patients and healthy controls [30, 71]. In contrast, IL-7 has a stronger co-stimulatory effect on phytohaemagglutination (PHA) activation in RA compared with healthy controls [71]. In a cohort of RA patients with varying levels of circulating IL-7 (active disease and clinical remission, levels ranging from low to normal [30]), T-cell responses to PHA were directly dependent on PBMCs having been exposed to IL-7 in vivo (Fig. 2). This effect was also seen for CD3/CD28 and PPD (data not shown). In contrast, co-stimulation of the PHA response by IL-7 restored proliferation to levels similar to healthy controls independently of previous exposure to IL-7 in vivo. There are several possible explanations for this observation. The lack of circulating IL-7 in RA [30] may have interfered with cell survival. Withdrawal of IL-7 reduces the expression of Bcl-2 [72] and Bel-X\(_L\) [73]. The expression of Bax, a pro-apoptotic factor, is up-regulated upon IL-7 withdrawal [72], and Bad (also pro-apoptotic) is inactivated in response to IL-7 [74]. However, we reported a lack of correlation between levels of Bcl-2, Bax or Bcl-X\(_L\) expression and circulating levels of IL-7 in RA patients [75]. IL-7 withdrawal also interferes with glucose metabolism through the PI3K and AKT pathway [76-78], but this has not been explored in RA. Finally, the lack of exposure to IL-7 may interfere directly with T-cell responsiveness. Several experiments of pre-incubating cells with cytokines have demonstrated effects beyond this stimulation. Notably, IL-7 pre-treatment of RA SF mononuclear cells (SFMCs) increased their production of IFN-\( \gamma \) and TNF-\( \alpha \) following reactivation in the absence of IL-7 [58]. The lack of such priming activity of IL-7, due to its low levels in RA [30], may be related to the general hypo-responsiveness of T-cells in RA [79-82].

SFMCs proliferate spontaneously when stimulated with IL-7 [58, 71] and show better response than matched PBMCs [71].

**Fig. 1.** IL-7 expression in RA synovial tissue. IL-7 expression in active disease (left) and in clinical remission (right) at magnification 400x. Cryostat serial sections of synovial tissue (4 \( \mu \)m) were cut and dried overnight at 37°C. Sections were fixed in 4% paraformaldehyde for 10 min. Endogenous peroxidase was quenched by treatment with 3% H\(_2\)O\(_2\) for 5 min, followed by pre-treatment with 3% normal serum for 20 min. Sections were incubated at room temperature for 1 h with specific monoclonal antibodies to IL-7 (R&D Systems, Abingdon, UK). An irrelevant isotype-matched monoclonal antibody acted as a negative control. A three-stage immunoperoxidase labelling technique incorporating avidin–biotin–immunoperoxidase complex was used (kit from Vector Laboratories, Burlingame, CA, USA). Slides were counterstained with haematoxylin and mounted.

**Fig. 2.** In vivo exposure to IL-7 conditions the T-cell response. Proliferation of 2 \( \times \) 10\(^5\) total CD4\(^+\) T cells (isolated by magnetic depletion) from 11 RA patients in clinical remission, in response to PHA (20ng/ml) or PHA+IL-7 (10ng/ml) in the presence of fixed APC. In vivo IL-7 levels were measured by ELISA (R&D Systems). A significant correlation was observed between serum IL-7 and the proliferative response of CD4\(^+\) T cells to PHA alone \((n=11, R=0.873, P<0.0001)\) but not to PHA+IL-7. Similar data were observed for anti-CD3\(^\text{a}\) anti-CD28 stimulation (data not shown, \( n=9, R=0.786, P=0.03 \)) and recall antigen PPD stimulation \((n=9, R=0.821, P=0.02)\) in the absence of IL-7 co-stimulation and both relationships were also abolished in the presence of IL-7.
In contrast to the periphery, where IL-7 is low, high levels are reported in the joint (Table 1). IL-7 co-stimulation of PHA-induced proliferation is observed in SFMCs, but to a lower extent than in PBMCs [71]. Priming of T-cell proliferation in the joint by IL-7 may, therefore, account for this hyper-responsiveness. The effect of IL-7 on PBMCs may be restricted to co-stimulation, whereas priming is more important in the joint. Most importantly, the proliferative effect of IL-7 is dependent on cell-cell contact between T-cells and monocytes/macrophages [63]. These cell-cell contact effects in the presence of IL-7 also induce changes in the phenotype of CD4+ T-cells increasing their expression of MHC class II and CD25, and increase the expression of CD80 and CD40 on monocytes/macrophages [63]. This is much less pronounced in PBMCs compared with SFMCs. In tissue, IL-7 is associated with the extracellular matrix [68] and presented on cell surfaces by heparan sulphate and fibronectin [7, 8] and this may have been reproduced in vitro by the presence of exogenous IL-7. Data are still too few to draw definite conclusions about the effect of IL-7 on peripheral T-cells in RA, but it appears that responses are not compromised and, therefore, the presence or absence of circulating IL-7 may be relevant.

IL-7 and polarization

DC development, maturation and antigen presentation are partly controlled by IL-7 [83, 84]. Peripheral blood-derived DCs have been shown to produce IL-7, but only upon activation [15, 16]. The ability of DCs to produce IL-7 is quite remarkable, considering that no other cell type from the haematopoietic lineage can do so, including monocytes. IL-7 therapy in mice has also been shown to significantly increase DC functions in vivo [43]. Crucially, IL-7 preferentially induces DC1 and T helper (Th1) polarization [16, 85–87] and increases IL-2 and IFN-γ production [85]. The role of IL-7 in Th1 polarization is mediated by its direct effect on the expression of the IL-12R on T-cells [86].

Th1 polarization is affected in RA, notably at the level of IL-2 production and differentiation of cells double positive for IL-7 and IFN-γ [88, 89]. A defect in T-bet expression (an essential transcription factor for Th1 polarization [90]) was reported in RA, but not in control samples, correlating positively with IFN-γ mRNA levels and negatively with CRP levels [91]. We replicated this data at the protein level, correlating circulating IFN-γ with T-bet expression in RA [92]. Furthermore, we showed that circulating IL-7 in RA is directly associated with T-bet mRNA levels [92].

Differentiation of peripheral naïve T cells towards Th2 cells is not impaired in RA patients [88, 93]. Th2 polarization from CD45RA+ T cells in RA patients is, however, improved by the presence of IL-7 [93]. IL-7 stimulation of SFMCs under Th2 polarization conditions produces a Th1 response associated with high secretion of TNF-α [93]. In the presence of IL-7, the release of IFN-γ and TNF-α is further increased [58]. Most importantly, IL-7 increases the spontaneous release of TNF-α from SFMCs in the absence of any other stimuli [58]. The mechanisms by which IL-7 increases TNF-α and IFN-γ production are also different, the latter being IL-12 dependent [58]. However, T-cells in RA comprise a large proportion of cells with an inflammatory cytokine-activated phenotype, independently of an antigen [94, 95]. The differential effects of IL-7 between controls and RA patients may, therefore, reflect different responses due to previous activation by circulating pro-inflammatory cytokines (such as IL-6, TNF-α and IL-15 [96, 97]).

IL-7 as a lymphoid tissue inducer

Recent work has unravelled the role of IL-7 as a lymphoid tissue organizer [98]. Using transgenic mice IL-7 has been shown to be essential for the development of Peyer’s patches and lymph nodes (LNs). Increased expression of IL-7 promotes the survival of lymphoid tissue-inducer cells, resulting in increased numbers of Peyer’s patches and the formation of ectopic LN. T-cell-dependent B cell responses and germinal centres develop normally in these ectopic LN, demonstrating that IL-7 can regulate the formation of both normal and ectopic lymphoid organs.

Activation of the IL-7 pathway may play an important role in lymphoid neogenesis in the RA synovium, similar to its role in the development of normal lymphoid tissue. This was recently confirmed by findings from Timmer et al. [68], demonstrating preferential IL-7 signalling in synovial tissues containing ectopic lymphoid structures associated with JAK/STAT signalling and T-cell-B cell interactions. Protein expression of IL-7 in these tissues is co-localized with extracellular matrix structures around the B cell follicles [68].

IL-7 and disease activity

Tissue levels of IL-7 are quite closely associated with local measures of disease activity; however, as discussed, circulating levels of IL-7 are subject to controversy. Surprisingly, correlations between SF levels of IL-7 and CRP, ESR and disease duration were not found [63]. Correlations have been found between elevated plasma IL-7 and disease activity in children [99]. CRP and IL-6 levels were positively correlated with plasma IL-7; however, this was not translated into other measures of disease activity or severity such as ESR, disease duration, joint swelling or the number of joints involved. A correlation between elevated circulating IL-7 levels and CRP has also been reported in adult RA patients [58], but only 5/21 patients studied had raised CRP (>10 mg/l). In a similar analysis, we failed to confirm any relationship with disease activity measurements (CRP, disease duration, RF positivity, extra-articular features, number of failed DMARDs), as IL-7 levels were low in all samples [30]. Comparing active disease and remission (disease activity score-28 < 2.6), we observed recovery of IL-7 levels comparable with health in 50% of remission patients [30]. This was, again, independent of any other parameter, but correlated with functional thymic output of new T-cells [30]. We did find that a younger age at onset of RA and smoking at that time were significantly associated with a lack of recovery to normal IL-7 levels in remission [100].

IL-7 and response to treatment

Two studies report variable levels of IL-7 according to treatment. In systemic juvenile RA, IL-7 levels were higher in patients on NSAIDs in combination with MTX and/or prednisolone compared with NSAIDs alone [99]. In contrast, both MTX and HCQ were associated with lower IL-7 levels in adult RA [63] and TNF blockade with higher levels [63]). This study, however, compared groups on therapy. Matched pre- and post-treatment samples would be required to establish whether therapies are truly affecting circulating levels of IL-7, or whether the reported differences reflect choice of treatment according to disease severity. Recently, TNF blockade was shown to have no effect on IL-7-induced SFMC proliferation responses in vitro, but TNF blockade in patients responding to therapy was associated with a specific reduction in circulating levels of IL-7 [70]. We failed to associate high or low levels of IL-7 with any patient group [30] and our data on TNF blockade in vivo (Ponchel, manuscript in preparation) contradict this study [70]. It is quite clear that until similar protocols are used to measure circulating IL-7, conflicting data will prevent definite conclusions.

Genetics of IL-7 and IL-7R

In the last 12 months, several groups have reported associations between the IL-7R gene and human diseases [37, 101–104]. No functional work has been done to define whether these
particular allelic variants have specific biochemical properties. We analysed two polymorphisms in the promoter and enhancer of the IL-7 gene and found no allele frequency difference between RA patients and healthy controls, or remission patients (with or without family history), or in relation to IL-7 levels. Despite these associations, levels of IL-7 in the circulation are apparently not driven by the genetic alterations studied so far. A polymorphism generating a 3bp deletion in the first exon of the IL-7 gene has recently been associated with different expression levels of IL-7 [105]. We are currently investigating this polymorphism as well as the MS-associated IL-7R polymorphism [100].

Blocking IL-7 may be of therapeutic value in RA

Supplementation with recombinant IL-7 has been explored as a means to improve immune reconstitution in lymphopenic HIV, hepatitis or cancer patients [32, 33] (http://bethesdatrials.cancer.gov/solid_tumor/nci03c0152/trial.html, and http://www.clinicaltrials.gov/ct/show/NCT00099671). To date no clinical trial has used anti-IL-7 in humans, however, a vaccination strategy has been developed to enhance patients’ anti-tumour activity against melanoma [106].

Animal models using IL-7 blockade have mostly investigated bone resorption. However, a recent transgenic model for a dominant mutant of the gp130 IL-7 receptor subunit spontaneously developed a lymphocyte-mediated RA-like joint disease, dependent on both MHC-II restricted T cells and the IL-6 family cytokines [107]. However, the gp130 mutation was only required in non-haematopoietic cells for the disease to develop and resulted in the specific increased production of IL-7. Anti-IL-7 antibody treatment inhibited the development of this spontaneous disease.

Testing whether IL-7 blockade could have therapeutic potential for RA is now under serious consideration [108] and several options are available. Human and mouse cytokines cross-react and, therefore, a strategy using a humanized anti-IL-7 antibody is possible. A soluble form of the IL-7R, gene therapy with a decoy IL-7R using adeno-associated virus, or active anti-IL-7 vaccination, are also possible. However, these therapies may have both systemic and local effects. As IL-7 is also a co-stimulatory factor for T-cells, blocking it may have additional beneficial effects on the expansion of auto-reactive T cells, but a negative effect on already immunosuppressed patients. Immune surveillance of these patients should be strict, but no more so than in patients receiving anti-TNF or other biologic agents.

**Rheumatology key messages**

- IL-7 is involved in chronic inflammation linking stroma and adaptive immunity.
- Blocking IL-7 may be of therapeutic value.

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