Arguments for interleukin 1 as a target in chronic arthritis

Wim B van den Berg

Abstract
Tumour necrosis factor (TNF) and interleukin 1 (IL1) are considered as master cytokines in chronic, destructive arthritis. Therapeutic approaches in rheumatic arthritis (RA) patients so far mainly focused on TNF. Although TNF is a major inflammatory mediator in RA and a potent inducer of IL1, anti-TNF treatment is not effective in all patients, nor does it fully control the arthritic process in affected joints of good responders. Analysis of cytokine patterns in early synovial biopsy specimens of RA patients reveals prominent TNF staining in 50% of the patients, whereas IL1b staining was evident in 100%. This argues that TNF independent IL1 production occurs in some of the patients. Studies in a range of experimental arthritis models in mice make it clear that TNF is involved in early joint swelling. However, TNF alone is not arthritogenic nor destructive and exerts its arthritogenic potential through IL1 induction. Intriguingly, TNF independent IL1 production is found in many models. Its relevance is further underlined by the greater efficacy of anti-IL1 treatment as compared with anti-TNF treatment and the total lack of chronic, erosive arthritis in IL1b deficient mice. IL1b is not necessarily involved in early joint swelling, but is a crucial mediator in chronic arthritis and cartilage erosion in all models studied so far. This makes IL1 an attractive target in chronic, destructive arthritis.

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Arthritogenic potency of tumour necrosis factor and interleukin 1
It is now generally accepted that arthritis can be induced in mice by tumour necrosis factor (TNF) as well as interleukin 1 (IL1). This is first demonstrated by local injection of recombinant cytokines in the knee joint, and substantiated by studies in transgenic mice and induction of arthritis by local cytokine overexpression in joint tissues with viral vectors. Intriguingly, IL1 is much more potent as compared with TNF, to induce cartilage destruction in vivo. Tiny amounts of IL1 are already sufficient to cause chondrocyte proteoglycan synthesis inhibition, whereas roughly a 100-fold to 1000-fold higher dose of TNF is needed to obtain the same effect.1 Of importance, synergy between IL1 and TNF has been seen. Apart from potency differences, it is clear that it is hard to measure significant TNF levels in inflamed synovial tissue or synovial fluid and the levels are certainly not higher as compared with IL1. It should be noted that most effects might be related to membrane bound forms of cytokines, which are hard to measure. On the other hand, impact on articular cartilage from synovium derived mediators probably needs traffic of soluble forms.

A further argument for the limited, direct role of TNF in arthritis emerged from elegant studies in TNF transgenic mice. Joint inflammation was completely arrested when these mice were treated with anti-IL1 receptor antibodies.2 This argues that the pathology runs through the induction of IL1, which is the real arthritogenic trigger, either alone or in synergy with TNF. TNF levels were still high after anti-IL1R treatment, which implies that TNF alone is hardly arthritogenic.

Final support for the crucial role of IL1 emerged from the recent demonstration of spontaneous arthritis in Balb/c mice, deficient in IL1 receptor antagonist (IL1Ra) (table 1).3 Earlier work already identified higher susceptibility of IL1Ra deficient DBA mice for collagen induced arthritis.4 The occurrence of spontaneous arthritis, when the IL1Ra deficiency was backcrossed to a Balb/c genetic background, illustrates the continued arthritogenic pressure of environmental IL1, which is normally controlled by the endogenous IL1Ra.

Table 1 Arguments for a dominant role of IL1 in destructive arthritis

| Higher arthritogenic potency of IL1 compared with TNF |
| TNF induced arthritis can be fully blocked with IL1R antibodies |
| TNF independent IL1 production occurs in many arthritis models |
| Greater net efficacy of anti-IL1 as compared with anti-TNF treatment in many models |
| Erosive arthritis can still be induced in TNF deficient mice |
| No erosive experimental arthritis in IL1b deficient mice |
| Spontaneous destructive arthritis occurs in IL1Ra deficient mice |

TNF independent IL1 production in models, when?
The above reasoning does not exclude TNF as a major therapeutic target. There is an old claim that spontaneous IL1 production in RA synovial tissue is TNF dependent.5 However, these findings have not been confirmed so far. Moreover, in experimental model situations there is now ample evidence of direct IL1 generation.

To further our understanding of relative TNF dependency of IL1 production under various arthritic conditions, we compared the efficacy of TNF and IL1 in a range of experimental arthritis models, including immune and non-immune triggering. Moreover, similar analysis of models was done in TNF and IL1b deficient mice.

Major findings are summarised in table 2 and can be found in several studies.6-20 IL1 is not necessarily a dominant cytokine in the acute, inflammatory stages of most arthritis...
models, but plays a crucial part in propagation of joint inflammation and concomitant cartilage and bone erosion in all models. The fact that the chronic, destructive stage is IL1 and not TNF dependent indirectly proves that TNF independent IL1 production occurs under all experimental model conditions listed. Most abundant TNF dependence of acute inflammation is found when arthritis is induced with a phogistic trigger such as streptococcal cell walls or Zymosan (yeast particle). However, erosions still develop in these models after treatment with anti-TNF antibodies and this observation has been strengthened by the high degree of erosions when such models were induced in TNF deficient mice. Not surprisingly, IL1 levels were still high under these conditions, identifying considerable TNF independent IL1 triggering (fig 1). When repeat injections with SCW fragments were given, the inflammation became partly IL1 dependent, erosions still developed in TNF deficient mice and were fully absent in IL1b deficient mice. It is expected that repeat SCW injection will generate specific T cell immunity and that the repeated flare model becomes more T cell dependent. Studies are in progress to elucidate the relative role of TNF and lymphotixin, using double knockout mice. First data suggest that synovial cell density in chronic SCW arthritis is even more pronounced in TNF deficient as compared with normal mice, suggesting a homeostatic role of TNF in control of synovial cell survival. This implies that full TNF blockade should be avoided in therapeutic approaches. Arthritis appeared clearly reduced in lymphotixin deficient mice. 

<table>
<thead>
<tr>
<th>Arthritis model</th>
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<th>Erosive arthritis cytokine involvement</th>
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<tr>
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<td>+</td>
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<tr>
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<td>+</td>
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Cytokine involvement, based on experiments with neutralising antibodies, started at the onset of arthritis. It does not reflect potential involvement during preimmunisation (CIA and AIA).

Cartilage erosion

Destruction of articular cartilage is caused by the combination of inhibited synthetic activity of the articular chondrocytes and enzymatic breakdown of the matrix. The latter can be elicited by enzymes released from chondrocytes and/or the inflamed synovial tissue, in particular at sites of so called pannus overgrowth of the cartilage. Early changes are characterised by loss of proteoglycans, which in principle is a reversible process. A major step in erosive tissue loss is the destruction of collagen bundles. Intriguingly, IL1 is very potent in inducing suppression of matrix synthesis by the chondrocytes. It also induces release of active aggrecanase, which is the dominant enzyme responsible for proteoglycan loss. In contrast, IL1 induces the release of latent forms of metalloproteinases, including stromelysin (MMP-3) and collagenase (MMP-13). The latter is crucial in collagen breakdown and stromelysin seems pivotal in collagenase activation. IL1 alone gives limited cartilage erosions, linked to moderate MMP autoactivation. In the presence of immune complexes in the joint, IL1 induced, latent MMPs become broadly activated and cause major tissue erosion. Fc receptor binding on leucocytes and/or chondrocytes and release of activating mediators are a crucial element in this immune complex mediated activation step. Cartilage erosion is absent in antigen induced arthritis elicited in Fc receptor deficient mice despite florid joint inflammation. In addition, IL1Ra treatment prevents erosions and MMP activity in this model, with limited suppression of acute joint inflammation. These findings identify IL1 as a pivotal initiating step in erosive processes and underline the role of immune complexes in exaggeration of destruction. Rheumatoid factor positivity is correlated to

Figure 1: IL1b levels in tissue washouts six hours after injection of SCW fragments into the knee joint of mice. The first set depicts IL1 levels in control and anti-TNFα treated mice (see also van den Berg). The second set depicts values in control and TNF-/- mice. Although some reduction is consistently noted in TNF-/- mice, it does not reach statistical significance, implying that most of the IL1 is produced in a TNF independent fashion.

Table 2: Cytokine dependence of various murine arthritis models

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Cytokine involvement, based on experiments with neutralising antibodies, started at the onset of arthritis. It does not reflect potential involvement during preimmunisation (CIA and AIA).

SCW = streptococcal cell wall fragments.

SCW-A flares reflect the situation after three consecutive SCW flares with seven days interval.

AIA = antigen induced arthritis.

SCW-A flares reflect the situation after three consecutive SCW flares with seven days interval.

ICA = passive immune complex (IC) arthritis.

*Efficacy of anti-TNF treatment only when started at onset of first signs of arthritis.

**Van den Berg 2002**

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more severe and destructive forms of RA, which may fit with the above concept.

Bone erosion
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Although TNF was abundantly present in some RA patients, TNF was undetectable in half of the patients. In contrast, IL1b was found in all RA synovial biopsy specimens studied so far (table 3). Remarkably, distinct IL17 staining was also clearly present in 70% of the RA patients, arguing a reconsideration of T cell involvement.

Repeat biopsy specimens taken and three sections of at least three suitable (suitable from control staining with irrelevant antibodies.

The heterogeneity in cytokine patterns argues for different disease pathways in various RA patients or depicts various stages of the disease. It is clear from the experimental arthritis model studies that many pathogenic pathways cause TNF dependent IL1 production, with a particular skewing to IL1 dominance in immune complex mediated events (fig 4). It seems obvious that future treatment will consist of combination treatment, at least touching both TNF and IL1. It is tempting to consider treatment did not identify significant suppression of IL1 staining in the synovial tissue in our hands. This may be interpreted as suggestive evidence of a lack of a TNF-IL1 cascade in many patients, but it may also suggest that the beneficial clinical effect is mainly attributable to systemic cytokine blocking,29 without a rapid, consistent impact on local events. Studies are in progress to evaluate repeat biopsy specimens after more prolonged anti-TNF treatment.

Table 3: Immunostaining of cytokines in early synovial biopsy specimens of RA patients

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<th>Cytokine</th>
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<tr>
<td>TNF</td>
<td>n=28</td>
<td>50</td>
</tr>
<tr>
<td>IL1b</td>
<td>n=28</td>
<td>100</td>
</tr>
<tr>
<td>IL17</td>
<td>n=28</td>
<td>70</td>
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Five blind synovial needle biopsy specimens per RA patient were taken and three sections of at least three suitable (suitable from control staining with irrelevant antibodies.


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