Commentary
A follow-up to "Anti-cytokine therapy in chronic destructive arthritis" by Wim B van den Berg

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Abstract

In recent years, the effectiveness of anti-TNF therapy in treating rheumatoid arthritis (RA) has become apparent. While trials of IL-1 receptor antagonist in RA have been encouraging, it clearly is more difficult to target two molecules (IL-1 α and β) than one (TNF-α). In his review article, Professor Wim van den Berg argues that both TNF-α and IL-1 must be blocked in RA and that although TNF is clearly a potent inflammatory molecule, the dominant cytokine in the subsequent degradation of the joint tissue is IL-1. This commentary discusses his hypothesis in light of animal studies and the limitations of the conclusions that can be drawn from them. More broadly, it discusses the biology of TNF-α and IL-1 and suggests explanations of why TNF-α is a pivotal cytokine in this disease.

Keywords: anti-TNF, IL-1, IL-1ra, rheumatoid arthritis, TNF

In his review article [1], Professor van den Berg discusses anti-cytokine therapy of RA and hypothesises that, in order to prevent joint destruction, it is necessary to block IL-1 *in addition to* TNF. The rationale for this hypothesis stems largely from observations in experimental models of arthritis in rodents. However, as he points out in the abstract, the necessity arises "if elements of the models apply to the *arthritic process in RA patients*". This surely is the central point, and the critical question is whether animal models resemble the human disease process. This issue has been extensively debated and even in the best-defined models, such as collagen-induced arthritis in DBA/1 mice, the aggressive, acute nature of the disease makes it unlike human RA. The very lack of chronicity in experimental models is a major limitation. Although these models and cytokine transgenic mice, despite their drawbacks, have been an invaluable tool to test hypotheses *in vivo* and to further explore mechanisms in a real-life setting, they can never fully mimic human RA.

Perhaps one of the best-studied models illustrating the problem of extrapolation from animal models to human disease is one in the huTNF transgenic mouse developed by Kollias and colleagues a decade ago. Replacement with 3′UTR of β-globin of the normal regulatory untranslated region in the TNF gene resulted in chronic arthritis in the Tg 197 line; the development of this arthritis was specifically blocked by antihuman, but not antimouse, TNF-α antibodies [2]. However, what is clearly important (even central) to the development of arthritis in these mice is the fact that the *trans* gene is expressed as protein in the synovial fibroblasts [3]. Normal fibroblasts, while having the capability to make TNF mRNA, block the translation process [4,5]. This is expected as fibroblasts are found closely associated with extracellular matrix and the catabolic activity of this cytokine would be extremely detrimental in this environment. Thus, while the huTNF transgenic mouse has proved to be very useful in understanding TNF physiology and/or pathology, it is not a

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IL = interleukin; IL-1ra = interleukin-1 receptor antagonist; RA = rheumatoid arthritis; TNF = tumour necrosis factor.

model for the human disease, not least because of the aberrant nature of cells expressing TNF protein. However, limitations apart, it is of interest that in these huTNF transgenic mice, a neutralizing monoclonal antibody to the murine type I IL-1 receptor completely prevented the development of arthritis, suggesting that IL-1 acts downstream of TNF in the pathogenesis of chronic arthritis [6]. The efficacy of this treatment may well be influenced by the lytic nature of this antibody, as it is also effective in collagen-induced arthritis [7].

The potent chondrogenic effects of IL-1 are well recognised, and it is clear that IL-1 activates chondrocytes and fibroblasts more potently than TNF does, a difference that may reflect the relative abundance of IL-1 receptors on these cells. In contrast, on monocytes and, indeed, more-differentiated macrophages, TNF is a much more potent activator than IL-1. Clearly, this difference reflects receptor distribution, as monocytes have very few IL-1 receptors [8] but relatively abundant p55 and p75 TNF receptors. The pathogenicity of a molecule is thus determined by its ability to activate a wide range of cells and to induce several other proinflammatory molecules, which together orchestrate the pathological process. This hypothesis in relation to TNF has been demonstrated both in animal models [9] and, more importantly, in human patients with RA after anti-TNF antibody therapy (reviewed [10]). Thus the cytokine/chemokine cascade is downregulated [11,12], endothelium is deactivated [13,14], matrix metalloproteinases are reduced [15], and formation of new blood vessels (angiogenesis) is also affected [16].

As the gene for TNF is transcribed and translated rapidly (faster than that for IL-1), it probably occupies a higher hierarchical position under conditions of cellular stress. The development of sepsis in baboons given a bolus of LPS is characterised by the sequential appearance of TNF, IL-1, and IL-6 in the blood [17,18]. Moreover the development of sepsis in these animals is blocked with anti-TNF antibody, which also abrogates the serum rise in IL-1 and IL-6. These findings are consistent with the pivotal role of TNF in RA that our group proposed in 1989 [19]. More recently, a paper published by Ulfgren and colleagues, using a modified immunohistochemical method, showed that, after TNF-blocking, synovial synthesis of both IL-1 and TNF was diminished [20]. Clearly, immunohistology is a limited technique, and in that study the number of patients was small and the cytokine profile heterogeneous, but the finding does further indicate the importance of TNF in the cytokine cascade in RA.

Are arguments about TNF versus IL-1 relevant? While IL-1 is a very potent proinflammatory cytokine, the real therapeutic problem rests with the requirement to neutralise both IL-1α and IL-1β in arthritic disease. In the setting of diseased tissue, the normally cell-bound form of IL-1 (IL-1α) is found in abundance as a soluble molecule [21]. Interleukin-1 receptor antagonist (IL-1ra) is a very efficient antagonist, but virtually all of the IL-1 receptors on a cell must be blocked to abrogate signalling [22]. Secondly, it is not clear why a substantial amount of IL-1ra remains intracellular. Thus, although the trials of recombinant IL-1ra in human RA look encouraging, the lack of a dose–response effect is of concern [23]. The efficacy of the anti-TNF modalities, particularly those with an IgG_1 backbone, may contribute to the better pharmokinetics of these drugs than of IL-1ra. Alternatively, a different approach using IL-1ra, such as gene therapy, may prove to be more effective [24].

Does anti-TNF therapy prevent damage to cartilage and bone? In his article, van den Berg hinted that it does not. However, the publication of two full-length papers about two anti-TNF agents, infliximab and etanercept, has now made it very clear that anti-TNF treatment does indeed slow down or prevent joint damage in human RA [25,26]. What is particularly remarkable about the infliximab study was the observation that infliximab not only protected intact cartilage but also halted/reversed ongoing erosions. Furthermore, the group that did not respond clinically (as assessed by the criteria of the American College of Rheumatology) showed as much joint protection as the responders. In the case of infliximab trials, further investigation is needed to clarify how concomitant administration of weekly doses of methotrexate contributes to these clinical endpoints. However, these observations raise the real possibility that the proportion of RA patients that respond to anti-TNF therapy, at least as regards joint destruction, is actually much higher than expected from the observed reduction of symptoms and signs.

From the clinical trials described above, it is now clear that proinflammatory cytokines are good targets in RA disease. Furthermore, the mechanism of anti-TNF therapy has been extensively studied in the infliximab studies and it its effectiveness is clearly due to its ability to deactivate endothelium, reduce the cytokine cascade, reduce the production of matrix metalloproteinase, and prevent erosion. If blocking IL-1 results in a chondroprotective/ bone protective modality alone, this may not be enough. A good therapy in chronic inflammatory disease must achieve several objectives, including the amelioration of signs and symptoms of disease and the abrogation of joint destruction, and must also be safe. However, because RA is a chronic disease, a good therapy would also be one in which the cycle of chronicity was broken. It is unclear at present whether the anti-TNF or IL-1 antagonism therapies modulate the chronicity of the disease. Therefore, there is still ample room for modulation and improvement of these therapies, and in particular it is important to targeting the mechanism(s) leading to the disregulated production of these proinflammatory mediators in inflamed tissue.

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