Rheumatoid arthritis

Anti-interleukin 1α autoantibodies

A natural treatment for rheumatoid arthritis

Prognostic markers are greatly needed to detect patients with rheumatoid arthritis (RA) at high risk of developing a destructive form of the disease as this may influence the choice of early treatment. Among the cytokines produced by the inflammatory synovium, interleukin 1 (IL1) appears to have a predominant role in joint destruction. Specific regulation of IL1 involves natural mechanisms, including soluble IL1 receptors, IL1 receptor antagonist (IL1ra), and anti-IL antibodies.[1 2] Autoantibodies directed against cytokines were first described in 1989 as being mostly of the IgG isotype and binding with high affinity mainly to IL1α.

It is easy to imagine that defects in this natural regulation may contribute to changes in disease incidence and severity. However, definite demonstration of this association needs confirmation from different studies. With reference to the new study published in this issue of the *Annals*,[3] we will focus on the effect of autoantibodies to IL1α on disease presentation.

METHODS OF DETECTION

The classical way of detecting antibodies to IL1α is by a precipitation method, in which antibodies bind the radiolabelled human [^{125}I]IL1α.[4] The antibody-cytokine complex is then precipitated with polyethylene glycol (PEG). After centrifugation, radioactivity is measured in the pellet. Levels of antibodies are calculated as the percentage of [^{125}I]IL1α precipitated.

Protein G immunoprecipitation is more specific than PEG precipitation, which allows precipitation of other than IgG complexes.[5] It is antibody specific, binding to all IgG subclasses. In addition, it prevents interactions with other IL1 regulatory molecules, such as soluble IL1 receptors, IL1, or IL1ra. Antibodies can also be detected by an enzyme linked immunosorbent assay (ELISA), in which the cytokine bound to the ELISA plate is incubated with serum or plasma.[6] After washes, the antibody bound to the cytokine is detected with an antihuman IgG enzyme labelled secondary antibody.

INCIDENCE OF ANTIBODIES TO IL1α IN CONTROLS AND IN PATIENTS WITH ARTHRITIS

Antibodies to IL1α are present in the sera of apparently healthy subjects, with an incidence ranging from 5 to 28%.[6–11] Such differences may be due to variation in the sensitivity and specificity between assays. The incidence appears to increase with aging.[12] They are also detected in polyclonal immunoglobulins used for treatment, as part of the human IgG repertoire.[13] In normal subjects where they are detected, their physiological role remains unclear. As least they do not appear to be associated with a higher incidence of infections or inflammatory conditions.

Autoantibodies to IL1α are also detected in sera of patients with various autoimmune disorders, including RA.[14] Incidence varies between studies with values often similar to those in controls,[14] but sometimes also higher levels.[15] Because they are present only in a small subset of patients, it was of interest to define that subset more precisely.

LINK WITH SEVERITY

To study the possible protective effects of these anti-proinflammatory cytokine antibodies, their incidence was compared in patients according to joint destruction. In a previous study we showed that neutralising anti-IL1α antibodies were found more commonly and at higher levels in patients with a non-destructive form of arthritis.[5] Furthermore, negative correlations were found between these levels and indices of disease activity and destruction. Similarly, these antibodies were also found in a subset of patients characterised by an increased proportion of primary Sjögren's syndrome or self limited inflammatory arthritis, with less joint inflammation and destruction.[14] In total, 62% of the patients with anti-ILα antibodies had a non-destructive form of arthritis (primary Sjögren's syndrome or self limiting inflammatory arthritis), diseases with a much better prognosis than RA.

Over a three year follow up, high levels of anti-ILα antibodies were associated with a better prognosis.[5] During this three year follow up, levels remained significantly different between patients with and those without destruction. During the same time, the erythrocyte sedimentation rate fell in those patients with antibodies who also used fewer steroids. About 90% of patients with high levels of anti-ILα antibodies had a non-destructive arthritis with a good prognosis. Moreover, indices of disease activity and severity were significantly lower in patients with high levels of anti-IL1α antibodies than in those with low levels.

The results presented in this issue of the *Annals* confirm and extend our results.[3] The authors of that study had the great advantage of access to serum samples from 685 patients with RA, which had been frozen from 1966 to 1978. Of these, 176 patients could be evaluated recently. This allowed a better demonstration of the prognostic value of these antibodies which had been present since the beginning of disease. On follow up it was found that patients who were first negative and then acquired antibodies had a more severe disease. The explanation is unclear but may be a consequence of prolonged exposition to, and stimulation by, IL1α.

"Are patients with anti-IL1α antibodies genetically different?"

HLA-DR4 alleles have been associated with RA severity. A possible genetic link was not evaluated in this new study. In our study 22.7% of patients with anti-IL1α antibodies were DR4 positive, compared with 59.2% of patients with RA without antibodies, and 21.3% of the control panel.[14] These results suggest a negative relationship between the presence of anti-IL1α antibodies and the DR4 allele, as well as the severity of the disease. Thus, patients with anti-IL1α antibodies seem to be genetically different from other patients with RA, but to have a similar HLA-DR4 distribution to that of a control group. Confirmation using DR4 subtypes is, however, needed.

The relative risk factor for developing RA rather than a non-destructive arthritis was 12 in the absence of high anti-ILα antibody levels. This risk factor increased to 18.2 when the presence of the HLA-DR4 antigen was combined with the absence of high anti-ILα antibody levels. A similar conclusion was reached in the new study with a much longer follow up.[3]

In keeping with this, HLA-DR4 positive subjects, either patients or controls, may be unable to produce anti-ILα antibodies.[14] Conversely, in patients unable to produce such protective antibodies, in part because of their genetic background, increased joint destruction was seen.

Consequently, the detection of anti-ILα autoantibodies may be a marker of prognosis. The development of a quantitative assay could help to discriminate more readily patients with a good prognosis from those prone to develop an erosive form. Such information could be used to select the intensity and duration of treatment at an early stage of the disease before destruction occurs.

FUNCTION OF ANTI-IL1α AUTOANTIBODIES

The demonstration of free antibodies and the lack of circulating IL1α/anti-IL1α immune complexes indicate the availability of these autoantibodies for biological neutralisation. It argues against a possible role as an IL1α transporter.[16] Indeed, using in vitro systems, purified anti-IL1α antibodies block the fixation of IL1α to its receptors and its biological activity on IL6 secretion by synoviocytes.[14] They can interact directly with specific domains recognised on ILα by its receptors. Thus these autoantibodies can play a part in vivo, and contribute to the clinical presentation. Long term studies as reported here further indicate that the presence of anti-ILα autoantibodies protects from, or delays, erosions and joint destruction.[3]

This proposal was further extended when a human monoclonal antibody was isolated.[17] This was carried out with activated peripheral blood B cells using a CD40 activating system. Isolation of B cell clones by limiting dilution analysis allowed the identification of B cell clones producing anti-IL1α antibody. Cloning of isolated IgG genes led to the production of a fully monoclonal recombinant anti-IL1α antibody. Its inhibitory activity against IL1α but not IL1β was demonstrated in relation to a high affinity with a Kd of 1.2×10^{-10} M.

> "Detection of anti-IL1α antibodies might aid prognosis"

IgG are high affinity molecules produced after repeated exposition to the same antigen. However, in autoimmune diseases, it is still questionable whether such autoantibodies result from an abnormal immune response and are partly responsible for disease presentation or whether they represent a secondary response aiming at controlling such a process. These autoantibodies are not merely a reflection of B cell polyclonal activation because in conditions associated with autoantibodies, such as lupus, anti-IL1α antibodies were not seen.

In contrast with the common deleterious contribution of autoantibodies in lupus, the presence of anti-IL1α antibodies appears to be beneficial in arthritis. Direct demonstration of the protective effect of these natural autoantibodies could come from a new therapeutic intervention in RA—namely, treatment with an anti-tumour necrosis factor α (anti-TNFα) monoclonal antibody. This could include the use of anti-ILα antibodies obtained either from affinity purification of polyclonal gammaglobulins[13] or from monoclonal antibodies. The high affinity human monoclonal antibody to IL1α might provide a new means of treating patients with RA, in which the production of such protective antibodies appears to be defective.[17] Its human origin would allow repeated cycles of treatment.

In view of the key role of both IL1 and TNFα in the activation cascade of proinflammatory cytokines, a combined strategy with such monoclonal antibodies or soluble receptors might prove even more potent. Such effect has already been demonstrated with other combinations in animal in vivo and human ex vivo models where TNFα and IL1 share properties with specificities for each cytokine.[18 19]

WHY ARE ANTIBODIES DIRECTED AGAINST IL1α AND NOT IL1β?

In chronic inflammation, in vivo studies have shown that peripheral monocytes secrete IL1β, migrate into the inflammatory site, and then differentiate into macrophages that express membrane bound IL1α. As membrane expression of an antigen increases its antigenicity, this might contribute to the higher incidence and levels of anti-IL1α but not of anti-IL1β antibodies. Furthermore, in RA synovium, cells at the cartilage-pannus junction highly express IL1α but not IL1β,[20] the latter being predominant in blood. Anti-IL1α antibodies may act upstream of the cascade of proinflammatory cytokines where IL1 induces the production of IL6, IL8, and granulocyte-monocyte colony stimulating factor, its blockade leading to an anti-inflammatory effect. Finally, administration of anti-IL1 antibodies prevented both early and late stages of arthritis in mouse models.[21] Recent studies with knockout mice for IL1α and IL1β have indicated that both forms contribute to arthritis.[22]

INTERACTIONS WITH OTHER REGULATORS OF IL1 ACTION

The other regulators of IL1 are IL1ra and soluble IL1 receptors. IL1ra circulating levels are regulated like an acute phase protein.[23] Increased inflammation leads to an increased production of IL1ra. Accordingly, levels of IL1ra are positively correlated with indices of severity. Part of this effect is genetically controlled at the level of IL1. Indeed, patients with the rare allele for one IL1β gene polymorphism have a more active and destructive disease associated with levels of circulating IL1ra lower than expected from the degree of inflammation.[24]

Cell response to IL1 is controlled by two types of receptors. Interaction with membrane type I receptors leads to signal transduction and biological effect.[25] Conversely, type II receptors do not transduce any signal but are rather secreted, acting as an inhibitory decoy receptor.[26] Levels of soluble type II IL1 receptors correlated positively with indices of activity and severity.[27] This was not seen with type I soluble receptors. Accordingly, as for anti-IL1α antibodies, administration of type II soluble receptors may represent a therapeutic approach for RA.

WAITING FOR A DRUG

The concepts developed above in clinical studies, combined with the availability of a human antibody, are strong arguments for the use of this tool for treatment. As described for an anti-TNFα monoclonal antibody now approved for this indication, clinical trials could evaluate the potential benefits associated with anti-ILα antibodies. One is thus surprised to see that such an antibody has not yet been used in this way. It seems that an unresolved patent issue has been interfering with the clinical development of antibodies as inhibitors of IL1. New confirmatory evidence may push the decision forward.

Another method might be the induction of these protective antibodies. The antigen might be inactivated IL1α itself or derived peptides. It remains to be seen if the genetic control described above represents a limitation of, or a justification for, treatment.

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