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. 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, 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 [125I]IL1α. 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 [125I]IL1α precipitated.

Protein G immunoprecipitation is more specific than PEG precipitation, which allows precipitation of other than IgG complexes. 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. After washes, the antibody bound to the cytokine is detected with an anti-human 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%. Such differences may be due to variation in the sensitivity and specificity between assays. The incidence appears to increase with aging. They are also detected in polyclonal immunoglobulins used for treatment, as part of the human IgG repertoire. 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. Incidence varies between studies with values often similar to those in controls, but sometimes also higher levels. 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. 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. In total, 62% of the patients with anti-IL1α 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. 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. 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. 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.

In keeping with this, HLA-DR4 positive subjects, either patients or controls, may be unable to produce anti-ILα antibodies. 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.13 Indeed, using in vitro sys-
tems, purified anti-IL1α antibodies block
the fixation of IL1α to its receptors and its biological activity on IL6 secretion by
synoviocytes.23 They can interact directly
with specific domains recognised on IL6
by its receptors. Thus these autoantibod-
ies 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-IL1α autoanti-
bodies protects from, or delays, erosions
and joint destruction.24

This proposal was further extended when a human monoclonal antibody was
isolated.22 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 pro-
duced after repeated exposition to the
same antigen. However, in autoimmune
diseases, it is still questionable whether
such autoantibodies result from an ab-
normal 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 associ-
ated with autoantibodies, such as lupus,
anti-IL1α antibodies were not seen.

In contrast with the common deleteri-
ous contribution of autoantibodies in
lupus, the presence of anti-IL1α antibod-
ies appears to be beneficial in arthritis.
Direct demonstration of the protective
effect of these natural autoantibodies
could come from a new therapeutic interven-
tion in RA—namely, treatment with an anti-tumour necrosis factor α
(anti-TNFα) monoclonal antibody. This
could include the use of anti-IL1α anti-
bodies obtained either from affinity puri-
fication of polyclonal gammaglobulins25
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 proin-
flammatory cytokines, a combined strat-
egy 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 prop-
erties with specificities for each
cytokine.18,25

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 inflamma-
tory 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,26 the latter being predominant in
blood. Anti-IL1α antibodies may act
upstream of the cascade of proinflam-
matory cytokines where IL1 induces the
production of IL6, IL8, and granulocyte-
monocyte colony stimulating factor, its
blockade leading to an anti-
inflammatory effect. Finally, administra-
tion of anti-IL1 antibodies prevented
both early and late stages of arthritis in
mouse models.27 Recent studies with
knockout mice for IL1α and IL1β have
indicated that both forms contribute to
arthritis.27

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.28 Increased inflammation leads
to an increased production of IL1ra.
Accordingly, levels of IL1ra are posi-
tively 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 polymor-
phism have a more active and destructive
disease associated with levels of circulat-
ing IL1ra lower than expected from the
degree of inflammation.29

Cell response to IL1 is controlled by
two types of receptors. Interaction with
membrane type 1 receptors leads to
signal transduction and biological
effects.30 Conversely, type II receptors do
not transduce any signal but are rather
secreted, acting as an inhibitory decoy
receptor.31 Levels of soluble type II IL1
receptors correlated positively with indi-
cates of activity and severity.32 This was
not seen with type I soluble receptors.
Accordingly, as for anti-IL1α antibodies,
administration of type II soluble recep-
tors may represent a therapeutic ap-
proach 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 indica-
tion, clinical trials could evaluate the
potential benefits associated with anti-
IL1α antibodies. One is thus surprised to
see that such an antibody has not yet
been used in this way. It seems that an
unread patent issue has been inter-
ferring with the clinical development of
antibodies as inhibitors of IL1. New con-
firmatory evidence may push the deci-
dion forward.

Another method might be the induc-
tion of these protective antibodies. The
antibodies 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 justifica-
tion for, treatment.

Ann Rheum Dis 2002;61:577–579

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Ann Rheum Dis: first published as 10.1136/ard.61.7.577 on 1 July 2002. Downloaded from http://ard.bmj.com/ on September 21, 2023 by guest. Protected by copyright.