A response of tumour necrosis factor α inhibitor treatment outcome in patients with rheumatoid arthritis

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Abstract

Introduction

The introduction of anti-tumour necrosis factor (TNF) agents has improved the outcomes for many patients with rheumatoid arthritis. To date, clinical response and disease activity after the induction of anti-TNF agents has been considered to discuss rheumatoid factor (RF) and anti-cyclic citrullinated protein (CCP) antibodies as serum markers. However, the mechanism of the reduction in autoantibody levels in response to anti-TNF agents remains unknown. In addition, many rheumatologists are still attempting to evaluate various difficult problems and to predict whether the effect of TNF inhibitors can be sustained over the clinical course. This critical review focuses on the serum autoantibodies of RF and anti-CCP as predictors of the effectiveness of TNF inhibitor in patients being treated for rheumatoid arthritis.

Conclusion

With such a high number of medications available for rheumatoid arthritis treatment, the problem faced is which medications to initiate and which to discontinue. Studies have supported early, aggressive treatment that is goal-directed.

Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease, which primarily causes symmetric polyarthritis, clinically manifesting as joint pain, stiffness and swelling. Untreated, most patients have a progressive course resulting in short- and long-term disability. Fortunately, the number of effective medications for the treatment of RA has rapidly expanded and includes synthetic disease-modifying antirheumatic drugs (DMARDs) and biological agents such as tumour necrosis factor α (TNFα) inhibitors1–2. The introduction of biological agents has dramatically improved the outcomes and expectations of RA for both patients and rheumatologists. There are currently four licensed TNFα-blocking therapies: infliximab (a chimeric monoclonal antibody), golimumab (a fully humanized monoclonal antibody), etanercept (a soluble fusion protein) and adalimumab (a fully humanized monoclonal antibody). All four bind to TNFα, both soluble and membrane bound, and etanercept is also capable of binding to lymphotoxin α (LTα), a cytokine that is known to be involved in lymphoid organ development but also plays a proinflammatory role3–5. The latter aspect has not been described as being relevant to the pathogenesis of RA. It is now clear that early diagnosis, referral and treatment of patients with RA result in improvement in the clinical signs and the prevention of joint destruction. Due to the increasing number of medications available for the treatment of RA, physicians and other healthcare providers involved in the care of RA patients must decide which medications to use, when to start them and when to change the therapeutic regimen. In recent years, research into the pathogenic mechanisms driving synovial inflammation and tissue damage in RA established a key role for proinflammatory cytokines such as TNFα and interleukin 1 (IL-1), leading to the development and clinical use of biological agents that bind to and inactivate these cytokines. Biological agents are effective in relieving the signs and symptoms of RA, slowing the progression of radiological joint damage, decreasing serum C-reactive protein levels and down-regulating inflammatory cytokines stimulated by TNFα3–5. However, despite the remarkable overall clinical effectiveness of TNFα inhibitors, more than one-quarter of patients have a poor clinical and radiological response6. Despite the impressive overall clinical impact of this treatment, more than a quarter of patients still have a poor response to these biological agents on the basis of both clinical and radiological evaluation7. Thus, many rheumatologists are being encouraged to evaluate whether the effects of TNFα inhibitors can be sustained over the clinical course. This critical review focuses on the serum autoantibodies of rheumatoid factor (RF) and anti-cyclic citrullinated protein (CCP) as useful tools for judging the response of TNFα inhibitors in patients being treated for RA.

Discussion

The authors have referenced some of their own studies in this review. The protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed.

RF

RF, an antibody against the Fc portion of IgG, was first described by Waaler and Rose in 19407. An increased level of RF is found in approx. 80%...
of patients with RA, and the suppression of RF production in RA has been variably attributed to the use of DMARDs. The existence of RF, especially IgM-RF, antibodies directed against the conserved region of IgG class immunoglobulin is one of the diagnostic criteria for RA. Classic IgM-RF is currently assessed in clinical practice; however, the combined detection of additional isotypes may improve this marker’s diagnostic and prognostic value. While some studies have demonstrated a decrease in IgM-RF titres during successful treatment with MTX, parenteral gold and TNFα inhibitor, some reports have described a decrease in IgA-RF titre during the treatment with TNFα inhibitor. Furthermore, there have been conflicting reports with regard to the influence of TNFα inhibitor and DMARDs on serum RF levels in RA. Below, we summarized the reports of whether IgM and IgA-RF could be associated with the effectiveness of TNFα inhibitor (Tables 1 and 2).

**Infliximab**

Most studies coincided in finding that high levels of IgM-RF or the presence of IgM-RF were related to a decreased clinical response to TNFα inhibitor, whereas a few studies found a correlation between IgA, IgM and IgG-RF and response. In addition, Klaasen et al. also reported that a positive RF status does not correlate with clinical response, but that high IgA-RF levels may predict a poor response rate. Patients with low-positive IgA-RF and those with negative IgA-RF had a good response rate, whereas patients with high-positive IgA-RF were poor responders. IgA-RF has been reported to be more specific for RA than classic IgM-RF and to be more specifically associated with radiographic erosions in early disease. Previously, we reported that the clinical response to infliximab can be predicted by RF levels. In this study, our results show that the changes of RF levels were correlated with those of the CRP levels. At baseline and at 12 months after the initiation of treatment with infliximab, RF titres in the low-CRP and good-CRP response group were lower than those in the high-CRP and poor-CRP response group. In addition, low titres of RF at baseline seemed to be useful for predicting a good response to infliximab. The mechanism by which infliximab could lead to a decrease in the generation of autoantibody such as RF has not been well understood, and the explanation for this phenomenon remains speculative. Infliximab therapy has been proven to reduce the number of synovial infiltration cells, including plasma cells. RF-producing cells are present in the inflamed rheumatoid synovium, and because the local environment may favour synovial RF production, we can therefore speculate that the reduction in inflammatory lymphoplasmacytic infiltration into the rheumatoid synovium will lead to a reduced production of RF, although it is not known whether TNF blockers directly inhibit the production of antibodies.

**Etanercept**

Etanercept, a soluble TNFα receptor fusion protein, can bind and neutralize extracellular TNFα. There was a marked clinical efficacy with minimal toxicity in RA patients who have an inadequate response to conventional DMARD treatment. First, Chen et al. showed a significant decrease in the levels of RF in the sera of rheumatoid patients after 3 months of etanercept treatment. After their study, most reports coincided in finding that high levels of IgM- and IgA-RF were related to a decreased clinical response to etanercept. The pivotal role of TNFα in the inflammatory and proliferative processes of RA has been established. Except for the inhibition of TNFα activity, etanercept significantly reduces the number of peripheral blood mononuclear cells secreting IL1β, IL-6 and interferon-γ. High levels of IL-13 in rheumatoid sera have also been modulated by etanercept. Etanercept is able to induce cell-type-specific apoptosis in the synovial monocyte/macrophage population and to decrease the number of these cells secreting pro-inflammatory cytokines.

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**Table 1**: Reduction of IgM- or IgA-RF are correlated with disease activity upon treatment with TNFα inhibitor

<table>
<thead>
<tr>
<th>Biological agent</th>
<th>IgM-RF</th>
<th>IgA-RF</th>
</tr>
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<tbody>
<tr>
<td>Infliximab</td>
<td>9, 10, 11, 12, 13, 14</td>
<td>9, 11</td>
</tr>
<tr>
<td>Etanercept</td>
<td>11, 12, 15, 16</td>
<td>11</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>11, 12, 17</td>
<td>11</td>
</tr>
</tbody>
</table>

**Table 2**: Correlation of anti-CCP antibodies upon TNFα inhibitor treatment

<table>
<thead>
<tr>
<th>Biological agent</th>
<th>Clinical response</th>
<th>Anti-CCP antibody</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Infliximab</td>
<td>9, 12, 13, 15</td>
<td>11, 51</td>
</tr>
<tr>
<td>Etanercept</td>
<td>12, 15, 16</td>
<td>11, 18</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>12, 15, 48, 51</td>
<td>17, 18, 49</td>
</tr>
</tbody>
</table>

Positive; anti-CCP antibodies are correlated with disease activity upon TNFα inhibitor treatment. Negative; anti-CCP antibodies are not correlated with disease activity upon TNFα inhibitor treatment. CCP, anti-cyclic citrullinated peptide; TNF, tumour necrosis factor.
inflammatory cells in rheumatoid joints\textsuperscript{33}. These anti-inflammatory effects may account for the reduction in acute-phase reactants and autoantibody generation. However, more studies are needed to confirm and elucidate the role of etanercept in reducing these autoantibodies.

**Adalimumab**

Adalimumab, a fully human anti-TNF\(\alpha\) monoclonal antibody, was recently approved for the treatment of both moderate and severe RA\textsuperscript{34,35}. As with other TNF\(\alpha\) inhibitors, a few studies have reported that adalimumab induced a significant decrease in RF titre, and the reduction was correlated with RF and the clinical response to the therapy\textsuperscript{11,12,17}. So far, there has been no conflicting report about RF titres.

**CCP**

The presence or absence of anti-CCP antibodies has been shown to be a useful diagnostic tool, particularly in the early stages of the disease, and to be predictive of disease progression and radiological damage\textsuperscript{16–20}. In particular, anti-CCP antibodies seem to possess a strong specificity for RA, though this was accompanied by a relatively poor sensitivity according to the first-generation anti-CCP test (anti-CCP1)\textsuperscript{36,40}. However, the currently available so-called second-generation anti-CCP test (anti-CCP2) has been shown to retain a high specificity for RA accompanied by a reasonable sensitivity\textsuperscript{40–42}. Anti-CCP antibodies have also been found in the early phases of RA\textsuperscript{37,41}, with a significantly greater prevalence in the sera of patients who subsequently develop more severe radiological damage\textsuperscript{36–39}. RA is currently thought to be a clinical syndrome comprising different pathogenic subsets\textsuperscript{31}. Growing evidence suggests that the presence of anti-CCP antibodies defines a specific RA subset. Indeed, specific gene-environment interactions involving the HLA-DR\(4\) shared epitope are mainly found in anti-CCP antibodies+ RA, at least in north-western Europe\textsuperscript{44,45}, and clonal alterations of synovial T cells are elevated in anti-CCP antibodies+ vs. anti-CCP antibodies– patients\textsuperscript{46}. The role of anti-CCP antibodies as an early predictor for identifying patients at risk of more aggressive and erosive disease might be of great importance, as it has been suggested that early and aggressive treatment, even with the use of biological agents, can prevent the progression of joint damage\textsuperscript{47}.

Some studies have demonstrated a decrease in anti-CCP antibodies during successful treatment with TNF\(\alpha\) inhibitor\textsuperscript{9,12,11,15,16,48,51}; however, several reports demonstrated that there is no correlation between the clinical response to TNF\(\alpha\) inhibitor and CCP antibodies in RA\textsuperscript{11,17,18,49–51}. Below, we summarized the current findings as to whether anti-CCP antibodies could be useful tools in the treatment with TNF\(\alpha\) inhibitor.

**Infliximab**

Alessandri et al. reported that the titres of anti-CCP and RF in the sera of patients were decreased significantly after 24 weeks of anti-TNF\(\alpha\) treatment with infliximab\textsuperscript{13}. While a reduction in RF after infliximab treatment has already been described, although in a small subgroup of patients\textsuperscript{34}, this is the first evidence of down-regulation of anti-CCP antibodies following anti-TNF\(\alpha\) treatment. The relatively high prevalence of patients who were positive for anti-CCP antibodies and RF at baseline reflects the probable selection of patients with more aggressive disease, who were resistant to previous DMARD treatment and were eligible for anti-TNF\(\alpha\). This provides indirect confirmation of the association between anti-CCP antibodies and a more severe disease course. However, small studies have investigated the utility of anti-CCP antibodies for predicting response to treatment with biological agents, but results have been inconsistent\textsuperscript{13} after the first report. Bobbio et al.\textsuperscript{11} reported that anti-CCP antibody levels were not correlated with the response to infliximab. Thus, no established data are currently available on the prognostic importance of a quantitative evaluation of anti-CCP levels in patients with RA. The mechanisms whereby the blocking of infliximab could lead to a decrease in the generation of anti-CCP antibody are not understood, and the explanation of this phenomenon remains speculative. However, it has been shown that infliximab can down-regulate the production of several inflammatory cytokines and mediators\textsuperscript{22,23}, and these anti-inflammatory effects may account for the reduction in autoantibody generation, particularly in the synovial compartment. It has also been shown that ctitrullination represents a post-translational modification of proteins in the apoptotic process\textsuperscript{54} and that ctitrullinated fibrin is one of the major CCPs in rheumatoid synovium, and so represents an important antigenic target of anti-filaggrin antibodies\textsuperscript{35}. It has been found that anti-TNF\(\alpha\) treatment can modulate apoptotic processes, as recently shown in inflammatory bowel disease\textsuperscript{56}; so it is possible that the regulation of apoptosis following TNF\(\alpha\) inhibitor administration could partially explain our observation. However, further studies involving large populations are needed to determine whether changes in the serum levels of anti-CCP antibodies occur during infliximab treatment. Many authors have found a drop in RF levels during treatment with infliximab, whereas the changes induced in anti-CCP levels remain a controversial issue\textsuperscript{11,51}.

**Etanercept**

Mikuls et al. reported that anti-CCP antibodies have been reported to be reduced by treatment only early in the disease course\textsuperscript{37}. Data regarding etanercept are also conflicting; Canhão et al. have reported the reduction of both anti-CCP and
Abbreviations list

CCP, cyclic citrullinated protein; DMARD, disease-modifying anti-rheumatic drug; IL, interleukin; LT, lymphotoxin; RA, rheumatoid arthritis; RF, rheumatoid factor; TNF, tumour necrosis factor

References

Critical review

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