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Review

Patterns and clinical relevance of antibody responses during adalimumab therapy

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SUMMARY

All biologic therapies have the potential to induce immunogenicity. Homology reduces antigenicity, but 'humanization' does not equate with homology and human antibodies may be also immunogenic. Despite of its proved efficacy in Crohn's disease patients, adalimumab carries the potential of molecule-specific toxicities which may be expressed with several types of antibody responses, and which are usually divided as allergic, autoimmunity and immunogenicity phenomena.

Key words: adalimumab, antibodies, autoantibodies, immunogenicity, loss of response, Crohn's disease

1. INTRODUCTION

Adalimumab is a 148kDa recombinant human high-affinity IgG1 monoclonal antibody against TNFa preventing cytokine binding to its receptor and lysing cells that express TNFa on their surface.[1]

Despite its proved high efficacy in Crohn's disease (CD) patients, adalimumab carries the potential, as all other biologicals, of molecule-specific toxicities. These toxicities can sometimes be expressed with several types of antibody responses, and can be divided as allergic, autoimmunity and immunogenicity phenomena.[2]

2. SYSTEMIC AND INJECTION SITE ALLERGIC REACTIONS: THE ROLE OF IGE

Adalimumab has been rarely reported to be related with systemic or injection site allergic reactions. These reactions can be drug- or host- specific[2] and some of them seem to be IgE-mediated.

In clinical trials with adalimumab, approximately 1% of patients experienced allergic reactions such as allergic cutaneous eruptions, anaphylactic reaction, non-specified drug reaction and urticaria. In addition, anaphylaxis and angioneurotic edema have been reported rarely in post-marketing experience with adalimumab. An IgE-mediated immediate type I hypersensitivity reaction seems to play a role in the mediation of worsening injection site of diffuse skin reactions in some of these patients.[3] By contrast, in two patients who had an injection site reaction and positive adalimumab skin test, IgE levels were normal.[4]

Systemic allergic reactions clinically expressed as asthma have been also reported. In such a case, within 2 weeks of starting adalimumab a patient developed a diurnal bronchial wheeze with shortness of breath and was finally diagnosed with asthma. Authors hypothesized that in this patient a pre-existing subclinical asthma was precipitated by adalimumab. [5] In another case of adalimumab-induced bronchospasm the patient previously used infliximab and etanercept.[6]

Further studies are needed in these cases, also by means of functional tests, biopsies of lesions and skin test reactions and determination of serum-specific IgE and IgG to ascertain the precise mechanisms of these reactions.

3. AUTOIMMUNITY

In general, the anti-TNF-induced formation of autoantibodies does not seem to reduce the efficacy of TNF ther-

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Abbreviations:

ATA=antibodies to adalimumab
ATI=antibodies to infliximab
RA=rheumatoid arthritis
CD=Crohn's disease
DILE=drug-induced lupus erythematosus
TNFa=Tumor necrosis factor-alpha

apy and does not cause significant clinical consequences, although occasional lupus-like syndromes have been described. There is no indication for monitoring in patients who have no symptoms.[7]

Adalimumab in parallel to the other biologicals seems to enhance autoimmune phenomena. However, very rarely a laboratory-confirmed autoimmunity is reflecting a clinical syndrome needing special intervention.

It has to be stressed here that autoantibodies may also be related to immunomodulators, such as methotrexate. In a study with rheumatoid arthritis (RA) patients ANA was observed in 14.5% (8/55) of patients treated with methotrexate only.[8]

a. De novo increase in ANA and anti-dsDNA titers

A de novo increase in ANA and anti-dsDNA titers during adalimumab therapy is not infrequent but never needs specific intervention. ANA monitoring should not be routinely performed in adalimumab-treated patients with no clinically relevant symptoms.[9]

In patients with RA de novo increase in ANA titers has been reported to range from 5.3% to 44.8%.[10-12] Of interest, a significant concordance between anti-nucleosome antibodies and ANA positivity was observed.[12] The corresponding percentages for anti-dsDNA titers ranged from 3.4% to 12.9%.[10-12]

In the CLASSIC-II trial the incidence of ANA formation was estimated at 19% (33/172 patients). All these 33 CD patients were also positive for anti-dsDNA. Of interest, 4/13 patients who were ANA-positive at baseline visit were ANA-negative at their final visit.[13]

b. SLE, DILE and lupus-like syndromes

Adalimumab-induced lupus syndromes are rare. In cases of drug-induced lupus erythematosus (DILE), discontinuation of adalimumab remains the main therapeutic intervention and most patients experience a clinical improvement 6-12 weeks afterwards.[14]

Along these lines it is important to separate lupus-like syndromes and 'classic' DILE with the real systemic idiopathic lupus erythematosus (SLE). [15] To meet this classification each case has to satisfy 4 of 11 American College of Rheumatology criteria for idiopathic SLE.

Lupus-like syndromes

In a published overview of the safety of adalimumab in the treatment of RA, which analyzed 10,050 patients representing 12,506 patient years, 13 cases of 'lupus-like' syndrome were reported.[16]

Adalimumab safety in CD clinical trials including induction trials (CLASSIC-I, GAIN, open-label period of CHARM, double blind maintenance (CLASSIC-II, CHARM) and all CD clinical trials including open-label extension), in total 1459 patients representing 1506 patient years only 3 lupus-like cases were recorded. Of note is the fact that not all the above patients met the strict diagnostic criteria for DILE.[17]

DILE

The relative rarity of cases with systemic DILE due to adalimumab compared to those receiving infliximab or etanercept is still debatable.[18-19]

According to recent experience from a Spanish IBD group DILE seems more prevalent in adalimumab-treated patients compared to the infliximab-treated ones.[18] By contrast, in the CLASSIC-II trial no cases of DILE were noted.[19]

The Spanish study suggested that previous exposure to infliximab, may represent a potential risk factor for developing DILE when adalimumab is prescribed.[18] Of interest, until 2007 none such DILE case had been reported to the Netherlands Pharmacovigilance Centre.[20] In the same study, it has been hypothesized that adalimumab may boost the infliximab-induced mechanisms for anti-dsDNA development.[20] In fact, increased cytokine and anti-dsDNA levels accompany SLE development upon infliximab-adalimumab conversion.[20] By contrast, a patient with a history of infliximab-associated DILE was treated with adalimumab and achieved successful control of CD without any worsening of lupus or changes in ANA or anti-dsDNA titers.[21]

To conclude, a logical clinically relevant approach is that in cases of ANA positive patients who are switched from one anti-TNFa agent to another no specific caution or follow up is necessary except in those rare cases in which the patient was previously diagnosed with DILE or 'lupus-like' syndrome while receiving the initial anti-TNFa therapy.

c. Clinically irrelevant other organ or tissue-specific antibodies

In a study clinical and serological data from 20 patients with rheumatoid arthritis treated with adalimumab and 50 healthy controls were analyzed.[22] All individuals were tested at baseline and after 6 months of therapy for thyroperoxidase (TPOAb), thyroglobulin (TgAb),

anti-tissue transglutaminase (anti-tTG), anti-smooth muscle (SMA), anti-liver kidney microsome (LKM), anti-parietal cells (APCA), anti-mitochondrial (AMA), anti-liver cytosolic protein type 1 (LC1), anti-adrenal gland (ACA), anti-pancreatic islet (ICA) and anti-steroid producing cell (stCA) antibodies. The prevalence of organ-specific antibodies did not seem to change during adalimumab treatment in these patients. Only a slight and probably irrelevant increase of IgG anti-tTG antibody levels was observed. [22] In another study from the same center anti-cardiolipin (aCL) and anti-β2 glycoprotein I (anti-β2GPI) autoantibodies were not detected in significant quantities.[8]

d. Clinically relevant other organ or tissue-specific antibodies

The incidence of organ or tissue-specific antibodies does not seem to be affected during adalimumab treatment in RA patients but a similar study for CD patients is lacking.

In general, organ or tissue-specific antibodies seem not to be influenced in their great majority during adalimumab therapy. However, some disease-specific markers for RA such as rheumatoid factor (RF) and anti-cyclic citrullinated peptide (CCP) seem to be influenced (decreased) in adalimumab responders. Finally, rare cases of antibody-related clinical syndromes in patients with RA have been reported.

In a study with 57 RA patients not responsive to methotrexate and treated with adalimumab[8], treatment with adalimumab induced a significant decrease in RF and anti-CCP serum levels, and the decrease in antibody titers correlated with the clinical response to therapy and this was confirmed by another study.[23] In another cohort of 188 patients with RA treated with adalimumab, IgM-RF and anti-CCP serum levels decreased, but only in patients responsive to treatment. Of interest, the reduction in IgM-RF levels was greater than for anti-CCP and correlated to measures of the acute-phase response.[24]

e. Other antibody-related rare clinical cases

A case of a patient with RA treated with adalimumab who developed myositis as part of a complex overlap syndrome with positive anti-polymyositis-scleroderma (anti-PM-Scl) antibodies has been reported.[25] In safety analyses of adalimumab a RA patient was diagnosed with anti-phospholipid antibody syndrome and an additional patient was diagnosed with deep vein thrombosis associated with positive anti-cardiolipin antibodies.[16] Two other rare cases in RA patients, one with cytoplasmic ANCA associated necrotizing glomerulonephritis[26] and one with anti-histone antibodies and lupus tumidus after eight months of adalimumab therapy[27] have been also reported.

4. IMMUNOGENICITY AND ANTIBODIES TO ADALIMUMAB (ATAS)

Adalimumab appears to be less immunogenic than Infliximab, confirming that in general chimeric antibodies are more immunogenic than human antibodies.[28-29] The formation of human anti-human antibodies has been already reported long ago[30-32] however, it still remains unclear which part of adalimumab induces anti-human antibody response.[33] Nowadays It is clear that in clinical practice immunogenicity plays a role in adalimumab treatment because of the development of ATAs.

a. Prevalence of ATAs in clinical studies

In patients with RA the rate of ATA formation ranges from 1% to 17%.[34-36] Of interest the rate was 1% for patients receiving concomitant therapy with methotrexate and 12% for patients not receiving methotrexate.[37-38]

In the clinical trials with adalimumab in CD, 0.4% (1/225) of patients in CLASSIC I study[39] and 2.8% (6/215) of patients in CLASSIC II study[13] developed ATAs. Of note, none of the 159 patients in the GAIN 4-week study[40] developed ATAs while immunogenicity was not evaluated in the CHARM trial.[41]

b. Predictors and determinants of ATAs

Previous Infliximab exposure and antibodies to Infliximab (ATIs)

Previous infliximab treatment might be an important immunizing factor increasing the rate of adalimumab immunogenicity. In a study of 30 CD patients receiving adalimumab after infliximab discontinuation, ATIs were positive in 57% of patients while ATAs were detected in 5/30 (17%) patients and 4 out of these five patients were adalimumab non-responders.[42] According to this study, patients previously treated with infliximab with high levels of ATIs have a lower response rate to adalimumab than patients with low levels of ATIs. [42]

Adalimumab dose escalation

In a study with RA patients it has been shown that the incidence of ATAs was dose related[28] and in another study ATAs were no longer detectable in patients with ATAs in whom the dosing frequency was increased.[36] Increasing the dosing frequency might overload the capacity of the immune system to produce ATAs, or alternatively induce immunotolerance. It can be speculated that continuation of treatment with an increased dosing frequency of adali-

mumab can be effective in some patients with ATAs; however, dose escalation is not effective in all patients.[38, 43] It is currently unknown how ATA are influenced in patients requiring decrease of adalimumab dosing intervals.

Adalimumab discontinuation

In a study with RA patients it has been suggested that continuous high levels of adalimumab induced immunotolerance, and when adalimumab treatment was discontinued, serum levels dropped and ATAs developed.[36] Probably the same phenomenon occurs during adalimumab episodic use.

Concomitant immunomodulators

According to data from RA patients methotrexate use lowered the incidence of ATAs. [11,36,43] The CHARM[41] and the CLASSIC-II[13] studies have shown ATA formation in 2.8% of CD patients and this did not differ between patients on or not on concomitant immunomodulators. However, CLASSIC II study claims lack of power for safe results on the protective role of azathioprine, or methotrexate in the occurrence of ATAs between the adalimumab and the placebo group.[13] Anyway, attempts to modulate the development of antibodies to anti-TNFa therapies through concomitant immunosupression do not necessarily prevent the need for dose escalation and/or reduced dosing interval.[7]

5. ATAS AND CLINICAL EFFICACY OF ADALIMUMAB

a. ATAs and loss of response to adalimumab

Response failure due to induction of antibodies against biopharmaceuticals is increasingly appreciated as one of the mechanisms of drug failure. In studies with RA patients a clear association was found between the presence of ATAs and a diminished clinical response, indicating that the formation of ATAs may be an explanation for non-response to adalimumab treatment.[36,43-44]

In one of these studies, ATAs were present in 34% of the RA patients not having a response whereas only 5% of the good responders had ATAs.[36] Patients with ATAs showed less improvement in disease activity and had lower serum adalimumab concentrations than patients without ATAs. An interesting observation in another among these studies was that moderate responders still had circulating levels of adalimumab and not detectable levels of antibodies. Very small amounts of antibodies may be not detectable by assays available or patients are not responding to therapy per se.[44]

In the CLASSIC II trial, three of the seven patients (43%) developing ATAs were in remission at week 24 and only two of seven (29%) were in remission at week 56.[13] In addition, ATAs were associated with non-response to adalimumab in a study with 30 CD patients previously exposed to infliximab.[42]

b. ATAs and adalimumab serum and trough levels

Measurement of drug concentrations is a preferred measure of a biologic response and directly correlates with drug efficacy. In addition, high titers of ATAs have been shown to interfere with the pharmacokinetics of the drug and diminished adalimumab concentrations.[36,42]

In the CLASSIC-I trial concomitant therapy with azathioprine and 6-mercaptopurine did not produce a significant change in serum concentrations of adalimumab.[39] By contrast, data from RA trials showed higher serum concentrations of adalimumab when administered concomitantly with methotrexate.[36,43-44]

It has been suggested that low adalimumab serum levels should be an indication to look for ATA formation. Levels of ATAs could then be a guide in deciding whether to increase the dose or to switch to another therapeutic monoclonal antibody.[28]

Response to infliximab or adalimumab closely follows the trough levels of the drugs and the presence of antibodies against the drugs in RA patients.[44] This has been confirmed also in CD patients were the presence of ATAs was associated with low serum trough adalimumab levels. Authors suggested that the reduced adalimumab concentration was because of the increased clearance of adalimumab via the formation of immune complexes between ATAs and adalimumab.[42]

6. ATAS AND SAFETY

The real impact of ATAs in the mechanisms of the early and late allergic reactions to adalimumab is currently unknown. In addition, the impact-if any- of ATAs on cancer, lymphomas, infections or other co-morbidities is also undetermined. As far as vaccination efficacy and safety is concerned patients with RA treated with adalimumab can generally be effectively and safely immunized with pneumococcal and influenza vaccines.[45-46] The ongoing adalimumab Crohn's safety registry study (PYRAMID), which is anticipated to enroll 5000 patients or more over five years should help provide additional insight into this and other important clinical safety questions.[19]

7. EFFICACY AND SAFETY OF ADALIMUMAB IN NORTHWEST GREECE IBD PATIENT COHORT

A total number of 17 patients (12 men / 5 women, aged 23-65 years) with inflammatory bowel disease have so far been offered Adalimumab therapy in our IBD referral center in northwest Greece. Of these patients, 12 were diagnosed with Crohn's disease and 5 with ulcerative colitis. Adalimumab was offered to UC patients as rescue protocol therapy in case of non-response to Infliximab or other conventional immunosuppressive therapy with azathioprine or methotrexate. Observation period ranged from 12-76 weeks. Four patients have not responded to previous Infliximab administration, two patients lost response to Infliximab and one patient was Infliximab allergic. In our center our policy for Infliximab non-responders is to decrease Infliximab intervals (from 8 to 6 or 4 weeks) and then increase dose (from 5 to 10mg/Kg). All patients received adalimumab induction therapy (160 and then 80 mg) and were then scheduled for adalimumab maintenance scheme (40mg every other week).

In Crohn's disease patients adalimumab induced disease remission [CDAI<150 points] in 8 of them (8/12 or 66.7%). Two patients achieved disease remission with concomitant corticosteroids (up to 16mg/day of methylprednisolone). Two male patients (2/12 or 16%) discontinued adalimumab therapy. In detail, one patient was operated for bowel obstruction (had stenotic disease phenotype) and one patient developed reversible proteinuria, which subsided after adalimumab discontinuation.

During follow up of these 12 Crohn's disease patients on adalimumab we successfully treated three episodes of microbial infections and one panic disorder relapse. Two patients needed adalimumab 40mg every week to maintain sustained disease remission.

In patients diagnosed with ulcerative colitis adalimumab induced disease remission in 4 of them (4/5 or 80%). Of these four patients, one young female patient after achieving disease remission for 1 year interrupted adalimumab in order to become pregnant. One young male patient was diagnosed with herpes zoster and discontinued therapy (1/5 or 20%).

Overall, according to our referral center experience, adalimumab proved efficient in 12/17 patients (70%) and partially efficient in another 2 patients (2/17 or 12%) exhibiting a very good tolerance and patient acceptability profile. Three patients (3/17 or 18%) had to discontinue adalimumab because of side effects, all of them reversible.

8. FUTURE DIRECTIONS AND OPEN QUESTIONS

Reducing immunogenicity and predicting loss of response

All biologic therapies have the potential to induce immunogenicity. Homology reduces antigenicity, but 'humanization' does not equate with homology and human antibodies may also be immunogenic. When comparing the relative immunogenicity, we have to take into account not only the extent of humanization but also the differences in dosing schedules and route of administration of monoclonal antibodies. We have also to appreciate loss of response to adalimumab is only partly explained by antibody formation and immunogenicity; other factors including individual differences in pharmacokinetics are likely to play a role and need further study. [42,47]

Individualized therapy tailored by antibodies, serum and trough levels

The question still remains unanswered regarding what causes ATA formation in some patients, but not in others, and what could explain the differences between patients with high and low ATA concentrations. Probably serum level of the therapeutic monoclonal (and its rate of decay) is the best indication of how much clinically relevant anti-antibody is formed. In addition, quantification of serum adalimumab and anti-adalimumab antibody and learning more about the underlying factors that affect these concentrations should lead to more individualized and optimized treatment in the future.

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