Place of the dosage of Anti-TNFα and anti-biological antibodies in the monitoring of the patients treated by these medicines in the long term.

Symposium
November 30th 2010
We are meeting this morning for a symposium organized by Biomedical Diagnostics, to speak about a subject which is going to become essential in the management of the biological treatments of certain inflammatory diseases that is to say the place of the dosage of anti-TNFα in the monitoring of the patients treated by these long-term medicines.

Over the last years, these biological treatments took a fundamental importance in the treatment of inflammatory diseases. It is rather surprising that even if we modulate the dose, there is at present no efficient tool for the dosage of these medicines that helps to specify at best the efficiency and the tolerance.

Probably, in the coming years, with the availability of numerous biological treatments, it will become essential to follow up patients in a more accurate way.

It is the fundamental interest of this new research objective: measure medicines and search an immunization against these medicines in order to get an individualized treatment, more adapted for every patient.

The first conference concerns exactly this concept of biological medicines’ clearance, and emphasizes the existence of an individual adaptation which is absolutely necessary to figure out in order to identify the best therapeutic strategy. The four following presentations show the first encouraging results on the use of the dosage of these biological treatments and the anti-biological antibodies.

This technique, already available today, should be implemented in large-scale within the next months to allow a monitoring of a wider proportion of our patients.
At the moment, we identified at least 3 mechanisms that contribute to the half-life of proteins for therapeutic usage (essentially monoclonals), with at all levels, the possibilities of heterogeneity between individuals.

The first mechanism is linked to the function of the neonatal receptor. This receptor, expressed on the surface of numerous cells (endothelial, epithelial, macrophages), allows the preservation of the level of Immunoglobulins (Ig) in the blood. To certain species, it also transports maternal Ig through membranes (placenta, intestinal barrier), as its name indicates. It can also influence the half-life of circulating Ig, their binding in acid environment with the receptor protecting them from the degradation by lysosomes, allowing so a permanent recycling. The neonatal receptor is saturable and present in limited quantity. Consequently the degree of protection is connected to the quantity of circulating IgG.

If the blood concentration of the IgG is very high, the time of half-life is very brief due to the saturation of the neonatal receptor. The existing relation between the affinity with the neonatal receptor and the half-life of monoclonals is of linear type: the higher affinity the longer monoclonal’s half-life will be. However, there are some exceptions following the example of chimeric antibodies. Based on this statement, derivatives of therapeutic monoclonal antibodies having an increased affinity for the neonatal receptor are currently under development. In animal models, we succeeded in bringing to light that the therapeutic efficiency of these monoclonals so mutated, was increased in a proportional way in their time of plasma half-life.

Another important mechanism contributes in the half-life time of therapeutic monoclonal: it is the formation of immune complexes. In case of immunization, the monoclonal antibody will be covered by antibodies directed against itself and is thus eliminated in the form of immune complexes. With the decline of the concentration of circulating monoclonal antibodies, an activation of the immune system is associated.

Finally, the last involved mechanism is a «consumption» of the monoclonal antibody by the target cell. If the antibody recognizes a membrane protein and activates the complement, it will be destroyed at the same time as the target cell, otherwise it can lead the apoptosis of this target cell as it is the case of rituximab and anti-CD20 monoclonals. It was demonstrated that there was a consumption of the therapeutic monoclonal according to the mass of cell targets in a murin model and that the equivalent was possible with human beings as in the case of treatments by infliximab. In case of important inflammation, the «inflammatory cellular mass» is going to consume the infliximab explaining that in residual, we have a concentration lower than that of the less inflammatory patients.

3 parameters necessarily are to be taken into account if we want to understand the individual differences: a possibility of genetic heterogeneity, the characteristics of the disease or another phenomenon of immunization.
The objective of this retrospective study is to estimate the dosage of the TNF, the medicine and antibodies anti-medicine in serums of patients treated by anti-TNF. It includes 2 types of patients: those who respond to verify that we succeed in measuring the medicine and those who become refractory or who are relapsing.

All in all, the study gathered 104 serums of 21 patients treated by Infliximab, 52 serums of 17 patients treated by Adalimumab and 26 serums of 10 patients treated by Etanercept. The patients included are treated for the greater part by Infliximab for an indication of Rheumatoid Arthritis (RA) but the other patients are affected by uveitis, by Ankylosing Spondylitis (AS) or Still disease.

We observe a relapse to 14/21 of the patients treated by Infliximab, 12/17 of the patients treated by Adalimumab and 7/10 of the patients treated by Etanercept. For the patients treated successively by Infliximab and Adalimumab, the dosage in parallel of these two medicines brings to light a crossed reactivity as the ELISA technique recognizes the fraction Fc which is common to all the medicines. In practice, in case of request of dosages LISA TRACKER, it will thus be necessary to specify the molecule prescribed to the patient.

This study brought to the light the existence of profiles. So we can identify subgroups of patients according to the profile of the modifications of detection of antibody or cytokines. The expected situation in case of relapse is the detection of TNF. The TNF which is rather unstable can indeed be difficult to detect if it is not preserved in optimal conditions (fast freezing). On the other hand, the patients where TNF is detected are patients with extremely high rates of TNF.

Besides, the patients having TNF and very high rates of medicines in residual without antibodies anti-medicines correspond probably to another mechanism of resistance. Finally, these dosages could be an interesting monitoring tool of observance for medicines prescribed by subcutaneous administration and thus potentially administered at home as Etanercept and Adalimumab because we know that in spite of the vital stake in these severe chronic diseases, the compliance to treatment is not optimal.

The quality of preservation of serums is an essential factor of the good use of LISA TRACKER kits, as well as the correlation of clinical data with the presence of antibodies and the monitoring after a therapeutic adjustment.

Lisa tracker: Practical experience through the evaluation of 3 clinical teams

These kits are definitely of importance in the immune monitoring of patients treated with biotherapeutics even if it remains important to determine their position in the global management of these patients. In case of relapse in the treatment, it is necessary to estimate the impact on the cost of biotherapics, what could be made in the future by a standardized decision-making algorithm.
This multicenter prospective study performed between 2003 and 2010 by the hospitals of Kremlin Bicêtre, St-Antoine and Rouen deals with the dosage of antibodies anti-medicines directed against anti-TNFα (Etanercept, Adalimumab and Infliximab) and aims at identifying a possible predictive factor of response after a rotation of anti-TNFα.

Indeed, 30 to 40 % of the RA and SA patients treated with anti-TNFα are in therapeutic failure and half of these failures is improved either after therapeutic intensification or after a rotation (change of anti-TNFα). Regarding monoclonal antibodies, it was demonstrated that the decrease of the therapeutic response was associated with a low blood rate of anti-TNFα and with the presence of antibodies directed against the anti-TNFα (Adab). Furthermore, there is a correlation between the use of Methotrexate (MTX) and the decrease of Adab.

The main objective of this study thus is to determine if the patients responding to the rotation of anti-TNFα have a lower concentration of the initial anti-TNFα than the non responder patients after 3 months. The secondary objectives are to compare the concentrations of the anti-TNFα according to Adab, to estimate the effect of the MTX on the presence of ADAb and finally to identify a possible link between the dosage of Etanercept on one hand and Adalimumab on the other hand with the weight of the patient.

The patients included are affected by RA (40) or by SA (29) and in primary therapeutic failure (absence of an initial response to the treatment) or secondary (decrease of the therapeutic response in spite of a validated initial efficiency) or intolerant in treatments by anti-TNFα. Was excluded every patient in failure with a therapeutic decision of intensification (and not of rotation) as well as those presenting time limits overtaking respectively 1 week for ETN, 2 weeks for ADA and 8 weeks for IFX.

The working hypothesis consists in distinguishing 2 types of non responder patients: on one hand true non responders, the pathologies of which are little mediated by TNF, for whom a rotation of anti-TNF would lead to a failure and thus possibly eligible in other treatments than anti-TNFα, and on the other hand false non responders which would present antibodies directed against the anti-TNFα, a defect of compliance, a pathology with a lot of TNF, or a poorly adapted medicine which would better respond to a change of anti-TNFα.

In 3 months, the response rate is close to 65 % in RA and of 40 % in SA consistent with data of the literature for patients in failure after a first anti-TNFα treatment.

The results do not bring to light a predictive factor and, more exactly, the dosage of anti-TNFα and ADAb during a failure with a first treatment with an anti-TNFα, does not allow planning the response to a new anti-TNFα after a rotation. However, it appears a trend close to a significativity (P=0,09) in the sense where good responders to a rotation have all the same rate of the previous anti-TNFα lower than non-responders.

If this trend is confirmed, it would be necessary to consider the hypothesis of a failure of molecular class and these patients would be rather eligible in a change of molecular class rather than in a rotation.

Certain clinical trials compare both possible strategies for a patient in failure of an anti-TNFα treatment: the rotation of anti-TNFα and the change of molecular class. But in clinical practice we could perfectly measure the medicine, measure antibodies anti-medicine and use these dosages to choose the most appropriate strategy.
This study was realized between January and September, 2010 at the outpatient Hospital of Bordeaux (France). Its main objective is the evaluation of the LISA TRACKER kit allowing the simultaneous dosage of the circulating TNFα, the medicines anti-TNFα administered and antibodies anti-medicines. We try in particular to know if the drug concentration is lower for the patients in failure, if the presence of ADAb leads to a failure, if the prescription of MTX prevents the appearance of ADAb or still if the previous administration of another anti-TNFα favors the appearance of ADAb.

97 of the patients included are affected by RA (20) or by SA (77), and in the course of treatment by Infliximab (IFX), 18 of them begin their treatment. Serums are collected before infusion and frozen within 3 hours.

From the 79 patients in follow-up, 22 have a disease which we consider “active” and 57 others have a pathology qualified as “inactive”.

Dosage of the medicine

The posology of anti-TNFα being different from one patient to another, the mathematicians realized a POSMOY variable to compare the dose of medicine administered with the measured concentration. This analysis allows concluding that the concentration in IFX is significantly superior for patients presenting an inactive pathology.

Another parametric approach eliminating the possible bias related to the 9 patients with Adab by excluding them from the analysis leads to identical results: the patients having an inactive pathology have a concentration in IFX superior to those of active group whatever is the administered posology.

Dosage of antibodies anti-medicine

The presence of ADAb is a predictive factor of the response to IFX: a low rate is associated with a less good response. At our patients, the presence of ADAb is really linked to ineffectiveness.

Factors favoring the appearance of ADAb

Concerning the link between the appearance of the ADAb and the administration of MTX or the preliminary administration of Adalimumab, we did not observe significant difference. But it can result from the small size of our sample and it would thus be interesting to increase the size of the population to confirm or contradict these results.

In conclusion, the dosage of the medicine seems interesting for the monitoring of the patients under IFX and seems particularly useful for their long-term management. Investigations on a more important population are necessary to determine its interest in the detection of early failures and possibly the early adjustment of the posology.
Pr. Mariette: Do we know regions on the Fc part of IgG which govern this affinity for the FcRn? Is it the same that those who govern the affinity on the other Fc gamma receptors?

- Pr. Émilie: Yes, we know the part of the IgG molecule which binds on neonatal receptors because it is exactly the mutation of these regions that allows to derivate new generations of monoclonals having a bigger affinity for FcRn and thus a prolonged half-life. This region is independent from the one allowing the binding on the conventional Fc gamma receptors.

Pr. Mariette: There is today a 4th anti-TNFα, Certolizumab, which is pegylated and deprived of Fc fragment. How should we do because it is not detectable at present by available kits?

- Ermis Parussini, Biomedical Diagnostics: bmd will soon provide a kit for the dosage of Certolizumab based on the same antigen-antibody principle but from which the revelation will be different and will take into account the peculiarity of this molecule (binding with polyethylene glycol to increase the half-life time).

Pr. Mariette: I was surprised to see that you had found twice antibodies anti-Etanercept on 7 of 10 relapses while in the literature they never find it, was this rate really significant?

- Dr. Miyara: yes, nevertheless this result would deserve to be validated on bigger series.

- Pr. Mariette: the absence of antibodies anti-Etanercept could be explained by the fact that antibodies directed against biotherapies are mostly anti-idiotypics and that Etanercept has no idiotype as it is a soluble receptor coupled with a Fc fragment.

Ermis Parussini: within the framework of the determination of a cut-off value of ADAb, what would be the meaning?

Do the available data allow having a more precise idea of this cut off value?

Dr. Richez: the possible identification of such a cutoff value would allow discriminating between the patients’ response and thus can direct the patient whose response is insufficient towards another type of treatment. In practice, this criterion would be particularly useful to adapt the therapeutic strategy, therefore avoiding pursuing the administration of an expensive treatment and potentially responsible for side effects for patients who are not going to respond to it. A study with a larger cohort would be needed nevertheless to specify this notion

Pr. Mariette: Is it critical to know this cut off value or finally the presence (or the absence) of ADAb would it be enough to provide expected information?

Pr. Émilie: this notion of cut off is doubtless very relevant and was moreover demonstrated in the Crohn Disease.

Dr. Marotte: in the placebo group of the ARMADA study, there was a patient with ADAb. What is finally the real meaning of the ADAb?

Pr. Émilie: we recommend to perform a pre-therapeutic blood sample to be certain that what we measure is good in connection with the treatment and is not linked to a natural crossed relation. The cases of positive dosages reported before initiation of the treatment are the real crossed reactions.

Pr Mariette: is there also a cut-off for anti-TNFα compounds?

Pr. Émilie: on the scale of an important population the cut-off is situated near 1 microgram by ml. This said there are individual situations of non-controlled patients having 10 micrograms by ml and controlled patients having less than 1 microgram by ml. There is thus a cut-off on the scale of population but not in the individual level.