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Research Article

The Interest of Therapeutic Drug Monitoring of Infliximab

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Abstract

The pharmaceutical industry develops an increasingly sophisticated biomedicines, which by their conception targets some specific pathological mechanisms, and have improved the management of various inflammatory diseases, for example chimeric anti-TNFα monoclonal antibodies such as Infliximab (IFX). However, the frequent occurrence of primary or secondary treatment failure, the high immunogenicity of this molecule, the problems of pharmacokinetic and pharmacodynamic variability as well as the strict conditions of interchangeability of its biosimilars make their use delicate. It is therefore recommended to determine for each patient the level of response to this treatment and to guide a therapeutic decision. So, we're talking about the Therapeutic Drug Monitoring (TDM).

The main objective of this work is to justify the interest of the TDM, to evaluate the effectiveness of the IFX, to analyze the predictive factors of treatment failure, to evaluate the tolerance by the detection of side effects and to estimate the cost of optimization strategies. For this purpose, a retrospective mono-centric prospective retrieval analysis was performed on the cohort of patients with IBD followed between 2012 and 2017 in the Hepato-gastroenterology department of the EHU Oran.

The cohort selected eight patients. Our correlation study of biological and clinical data, showed abnormally low values in remission or abnormally high thrust, suggesting that biological parameters are not strongly correlated with the effectiveness of IFX. In parallel, the study of the sensitivity confirmed these results. In our analysis, treatment failure occurred in 62.5% of cases after 3 to 16 months of treatment. Optimization was required in 37.5% of patients in our cohort. To avoid a failure, it was recommended to optimize 1 patient out of 3 under IFX. When applying this data to the additional cost of optimization strategies, the additional cost of the annual IFX treatment then ranges between 878970 and 5273820 Da per year. Thus, although these optimization strategies are identical to those of the literature, it is interesting to note that these strategies are taken at random and are the opposite of evidence-based medicine.

Our primary results justify the interest of the IFX's TDM to improve the management of patients on IFX. Further, prospective and randomized studies will be needed to demonstrate that the integration of this pharmacological parameter into the therapeutic strategy can modify the prognosis in the medium and long term of patients with IBD.

Keywords: Biomedicines; Infliximab; Failure; Optimisation; Therapeutic drug monitoring; Cost

Introduction

For more than 10 years, clinicians have had biomedicines that have revolutionized their practices. Today, 70% of new drugs are biomedicines.

Biomedicines, in particular TNFα antagonists, have improved the management of chronic rheumatic inflammatory diseases (rheumatoid arthritis, ankylosing spondylitis, juvenile idiopathic arthritis, psoriatic arthritis), cutaneous (psoriasis) and digestive (Crohn's disease, ulcerative colitis) as well as than the treatment of certain cancers.

Despite the initial response rates obtained in the range of 60 to 70% in the different pathologies, there remains a significant proportion of non-responder patients (primary inefficiency) [1] and among those who are, the level of response is variable from one individual to another, but also in the same individual over time (secondary inefficiency).

It is therefore crucial to accurately and objectively determine the response of patients to a treatment and to provide information allowing greater personalization of treatment: hence the interest of theranostics.

The main objective of this work was to Justify the interest of the IFX TDM in:

- Evaluating the effectiveness of IFX by indirect correlation with biological and clinical data.
- Analyzing predictors of IFX treatment failure.
- Evaluating tolerance by detecting side effects.
- Studying the cost of optimization strategies and the extra cost to avoid a failure.

Infliximab (IFX), chimeric monoclonal IgG1 directed against TNFα, is now a treatment of common use in the management of chronic inflammatory diseases, but delicate given the risk of high immunization. We chose to apply this monitoring to Infliximab, be-

cause it is the most used in EHUO to treat several pathologies and, because of its chimeric nature, it is highly immunogenic. This molecule alone has three biosimilars marketed worldwide and whose therapeutic ranges are defined.

Patients and Methods

A prospective mono-centric retrospective analysis was performed on the cohort of patients followed between 2012 and 2017 at the Hepato-gastroenterology department (day hospital service) of the EHU Oran. Inclusion criteria were adult patients with histologically objectified IBD in Infliximab. Patients with incomplete or missing medical records were not included.

The data was retrospectively collected on patient records via a record card. The cost analysis was performed for Infliximab and the additional cost to avoid a treatment failure was then calculated by relating it to the effectiveness of the optimization of the molecule.

Results and Discussion

The retrospective study of patients with IBD in Infliximab, followed at the EHUO, selected eight patients.

Our first result of evaluating the efficacy of IFX therapy showed that included patients received a total of 54 IFX infusions with a range of 4 up to 11 infusions per patient, since the start of treatment. The average dose received from IFX is 5 mg/kg with a median number of 8 weeks between two infusions to treat in the majority of cases an active disease or corticosteroid. Similarly, patients with LAP or prevention of postoperative recurrence were most often put on IFX given its marketing authorization, as well as for its indications for severe relapses requiring close monitoring of patients

The evaluation criteria for IBD's grouped together clinical, biological, radiological and endoscopic evaluation to determine 54 states of thrust and remission.

Biological evaluation of the inflammatory component, which is an integral part of patient follow-up, is done by systemic CRP and VS assay to indirectly reflect the efficacy of infliximab (Figure 1, 2).

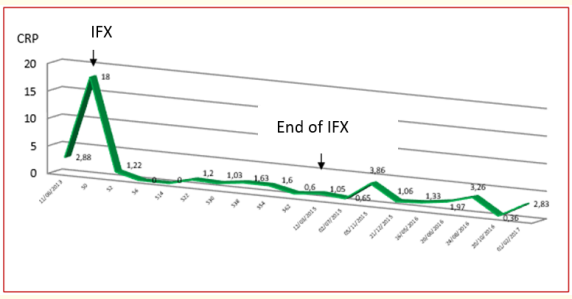

Figure 1: CRP before and after instauration of treatment with IFX. Patient M.H, 33years old, with Crohn disease.

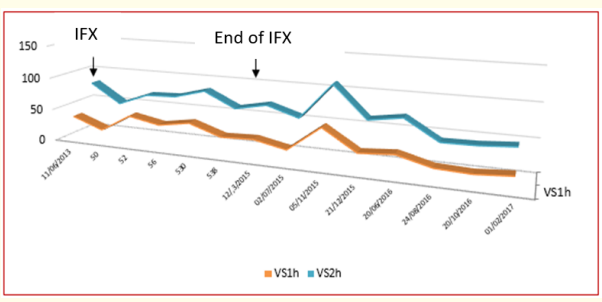

Figure 2: VS before and after instauration of treatment with IFX. In the same Patient.

Our study showed that 65.45% of CRP levels and 36.62% of VS levels were lower than the value taken to express biological remission: In 41.93% of cases the CRP was low or negative in active IBD and 4.16% was positive despite clinical remission. Similarly for VS, 28.15% of the values were abnormally low in relapses and 71.43% of the abnormally high values in remissions (Figure 3 and 4).

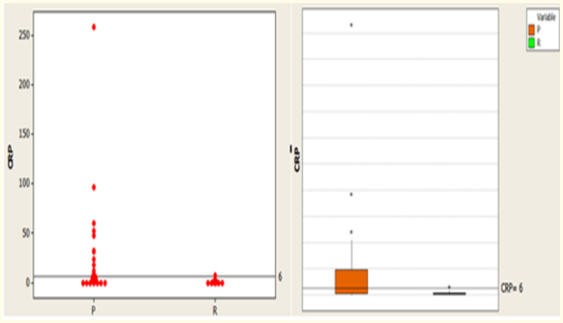

Figure 3: CRP value in Thrust (P) and Remission (R) group.

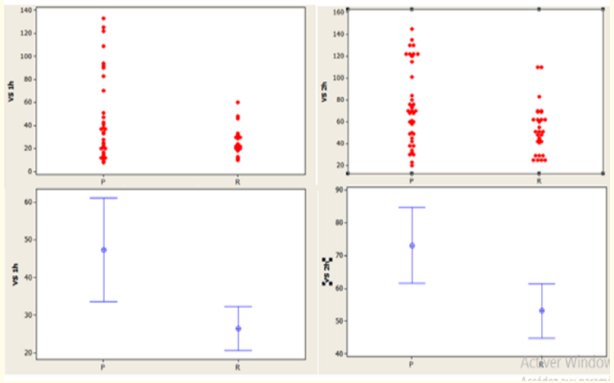

Figure 4: CRP value in Thrust (P) and Remission (R) group.

These results resemble those found in the literature, according to Gross V., *et al.*, S Vermeire., *et al.* 2006 and Henriksen., *et al.* Gut-2008 [2], CRP is negative in 10% of active MCs and in 50 - 60% of active RCH's, as this rate is a function of the depth and extent of inflammation and its decrease is probably due to the polymorphism of CRP gene, to the expression of IL6 [2].

Indeed, the correlation study of biological data (CRP, VS) with the efficacy of IFX has shown in some patients a drop in the CRP and VS rate associated with a biological regression as soon as the drug is introduced. However, abnormally low values were found in remission or abnormally high thrust, which suggests that these two parameters are not strongly correlated with the effectiveness of the IFX (Figure 5 and 6).

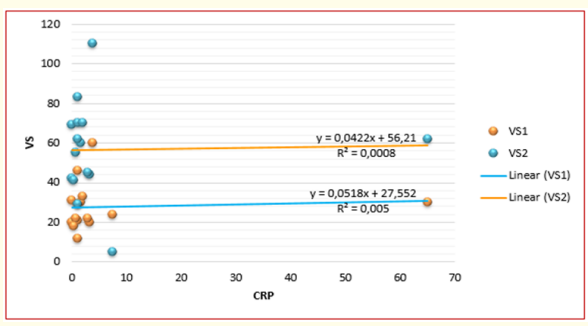

Figure 5: Correlation between VS and CRP in the same patient.

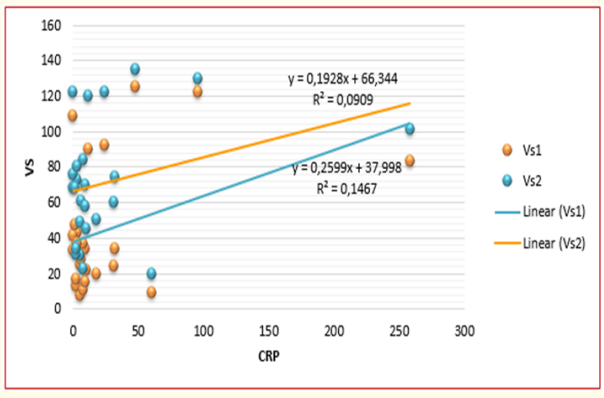

Figure 6: Correlation between VS and CRP in all patient.

In parallel, the study of the sensitivity confirmed these results; A sensitivity of only 58.06% was found for CRP. For this, and according to the latest recommendations, the CRP rate must be associated with the rate of TRI and ATI in the decision algorithms.

Therapeutic failure occurred in 62.5% of cases. These failures correspond strictly to the definitions of failure in the prospective studies existing in the literature [4].

In our analysis, predictors of treatment failure were clinical appearance, age, and treatment strategies. In fact, the fistulising form of Crohn's disease was associated with thrust states, whereas remission states are observed in patients with UC, because it is considered a disease with a good prognosis [5]. Failure following the indication of IFX as second-line therapy, especially in the presence of LAP, is a rather expected result, even though IFX is effective in the treatment of perianal fistulas with 55% complete closure. In Present study [5], the evolution is more often unfavorable and the patients are more difficult to treat.

Failure occurred after 3 to 16 months of treatment. This has led clinicians to either temporarily or permanently discontinue treatment or to therapeutic optimization. The results of the Schnitzler study [3] are comparable with our study: 33% of patients initially responding to IFX (versus 22% in the Schnitzler cohort) had to stop it despite attempts at optimization.

Another cause of failure was related to the occurrence of adverse effects. In evaluating treatment tolerance at IFX, we identified 29 side effects classified by severity as serious and non-serious adverse events.

Thirteen immediate side effects were noted during infusions in 6 patients; namely: headache (n = 2), vomiting (n = 1), hypo / hypertension (n = 5) and fatigue (n = 1). These were considered benign and allowed to continue the infusion. While the onset of fever (n = 1) required slowing down and then continuing the infusion after initiating symptomatic treatment with injectable paracetamol.

The other sixteen side effects were delayed onset; Only a therapeutic stop occurred following the appearance of cutaneous manifestations. It is therefore necessary to monitor TRI and the ATI's since several studies have clearly and accurately shown the relationship between these two parameters and the occurrence of adverse effects.

The use of Immunosuppressor (IS) was associated with 81.81% in remission states while a poorly reinforced protocol favored the development of IBD outbreaks, sometimes with a shift to more severe forms. As in the SONIC study, the advantages of IS-anti-TNFα combotherapy are then well demonstrated (better remission rate) [6].

The IFX seems more effective if we optimize the treatment for our results, which are however to be taken with care given the retrospective nature of the study. Optimization was required in 37.5% of patients in our cohort, while the change in dosage was preferred over other optimization strategies. These results are close to those of the literature. Indeed, in the Schnitzler study, 50% of the patients with an IFX MC were optimized, 39.6% of which consisted of an approximation of the injections. Like the Chaparro study [7] where 41% of IFX-mediated MCs benefited from a dose escalation and the study by Oussalah [8] where 45% of the RCH under IFX required optimization. The switch has been shown to be the solution in case of loss of response to the IFX.

According to our results, to avoid a failure it is recommended to optimize 1 patient out of 3 under IFX. When applying this data to the additional cost of optimization strategies, the additional cost of the annual IFX treatment then ranges between 878970 and 5273820 Da per year.

In our cost analysis, we did not consider expenses related to the administrative arrangements. Similarly, we have estimated the additional costs associated with IFX for a typical fixed-weight patient, without taking into account the losses associated with unused bottle remains.

The maximum optimization strategy of IFX at 10 mg/kg/ 4 weeks costs 3177000 Da per failure avoided. However, the clinician uses this optimization only exceptionally.

This estimated cost is not negligible, but it avoids a certain cost in terms of hospitalization for states of thrust or surgical interventions, not to mention the additional cost for the population related to work stoppages for example.

Finally, although these optimization strategies are identical to those of the literature, it is interesting to note that these strategies are taken at random and are the opposite of evidence-based medicine.

Many recent studies have shown the interest of pharmacological dosage of IFX in optimization strategies: a low Infliximabemia seems predictive of a loss of response during the follow-up, while the interest of the ATI seems interesting in timing of immunization against IFX

In economic terms, a therapeutic strategy based on optimization based on pharmacological levels was significantly less expensive than a conventional clinical strategy based on the Markov model, Velayos., *et al.* [4] The use of serum levels has significantly reduced health costs with an estimated saving of more than 1,000,000 euros [9].

For this purpose, a protocol has been proposed for the determination of residual serum concentrations of IFX and its antibodies.

Conclusion

Our primary results justify the interest of pharmacological therapeutic monitoring of IFX in improving the management of patients on IFX.

Further, prospective and randomized studies will be needed to demonstrate that the integration of this pharmacological parameter into the therapeutic strategy can modify the prognosis in the medium and long term of patients with IBD.

Limits of the Study

- The retrospective nature of the study posed limitations in the interpretation of the results.
- Implementation and implementation of ATI and Infliximabemia assays are ongoing in our department. However, not having studied and included them in our therapeutic strategy could be perceived/seen as a disadvantage, but it is due to the delay and the difficulties of the supply of reagents!

Future Perspectives

As for our future perspectives, we are looking to:

- Perform a similar cohort taking into account the IFX assay results;
- Observe the appearance of immunization against IFX with the appearance of the ATI and study their association with possible side effects;
- Launch a correlation study between the different biological parameters (TRI, ATI, CRP, VS...);
- Compare the medico-economic profile of relapses by standardized optimization versus the personalized strategy.
- Propose models of pharmacokinetic prediction represented by algorithms taking into account the clinical and biological evaluation as well as the TRI and the ATI assay results and the associated failure factors.

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