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Alimentary tract

Cost savings using a test-based de-escalation strategy for patients with Crohn's disease in remission on optimized infliximab: A discrete event model study

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ABSTRACT

Background: Drug de-escalation is considered in Crohn's disease patients in sustained remission on optimized infliximab treatment.
Aim: We built a model to evaluate the magnitude of cost savings in patients' disease course with or without drug de-escalation guided by infliximab trough levels.
Methods: We designed 4 virtual cohorts (P1–P4) of 10,000 patients in clinical remission on optimized infliximab treatment followed for 2 years. P1: no drug de-escalation — 10 mg/kg/8 weeks; P2: drug de-escalation from 10 mg/kg/8 weeks to 5 mg/kg/8 weeks according to trough levels; P3: no drug de-escalation — 10 mg/kg/6 weeks; and P4: drug de-escalation from 10 mg/kg/6 weeks to 10 mg/kg/8 weeks according to trough levels. For P2 and P4 cohorts, drug de-escalation was decided if trough levels were ≥7 μg/mL and no de-escalation if trough levels were <7 μg/mL. Only costs related to drug administration were considered.
Results: The cost differences when comparing P1 versus P2 and P3 versus P4 were 7.6% and 4.6%, respectively, corresponding to costs savings of €30.5 millions and €20.3 million for 10,000 patients.
Conclusion: Over a 2-year period, infliximab de-escalation according to trough levels led to cost saving of about 6%, corresponding to around €25.4 million.

1. Introduction

Biologics are increasingly used to treat refractory IBD. The monoclonal antibodies against tumor necrosis factor (TNF) – infliximab (IFX) and adalimumab (ADA) – induce and maintain remission in moderate to severe refractory inflammatory bowel diseases (IBD) [1,2]. Serum IFX trough levels (ITL) and antibodies against IFX (ATI) are associated with better outcomes compared to an empirical strategy in case of loss of response [3,4].

A Dutch study showed that healthcare costs are mainly driven by the cost of anti-TNF therapy in Crohn's disease (CD) [5]. In case of loss of response, IFX treatment optimization can be performed by doubling the dose and/or by shortening the interval between the infusions, which further increases the economic burden [6]. Therapeutic drug monitoring is cost-effective in IBD patients when compared to an empirical strategy in this model and according to the costs used in our study [7–10].

Following the optimization and maintenance of patients in remission, the treatment with of high doses of IFX raises both economic and safety concerns. In this context, drug dose de-escalation strategies are subject to intensive research [11]. Interestingly, the landmark TAXIT trial showed a significant reduction in IFX costs in this setting, using therapeutic drug monitoring [6,12,13]. Herein, we evaluated the cost savings of a drug de-escalation strategy based on the therapeutic drug monitoring of CD patients in remission on

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optimized IFX treatment using an original mathematical modeling approach.

2. Material and methods

2.1. Virtual populations

We designed 4 virtual cohorts of 10,000 patients in clinical remission on the usual optimized IFX treatment (10 mg/kg every 8 weeks or 10 mg/kg every 6 weeks [14]) followed for 2 years as P1: no drug de-escalation — 10 mg/kg every 8 weeks; P2: drug de-escalation from 10 mg/kg to 5 mg/kg every 8 weeks according to trough levels; P3: no drug de-escalation — 10 mg/kg every 6 weeks, and P4: drug de-escalation from 10 mg/kg every 6 weeks to 10 mg/kg every 8 weeks according to trough levels. For P2 and P4 cohorts, drug de-escalation was decided if trough levels were ≥7 μg/mL — defining P2a (ITL ≥7 μg/mL and drug de-escalation from 10 mg/kg to 5 mg/kg every 8 weeks) and P4a (ITL ≥7 μg/mL and drug de-escalation from 10 mg/kg every 6 weeks to 10 mg/kg every 8 weeks) sub-cohorts — and no de-escalation if trough levels were in the normal range or low (< 7 μg/mL) — defining P2b (ITL <7 μg/mL and no de-escalation from 10 mg/kg to 5 mg/kg every 8 weeks) and P4b (ITL <7 μg/mL and no de-escalation from 10 mg/kg every 6 weeks to 10 mg/kg every 8 weeks) sub-cohorts. P1 and P3 cohorts (not drug de-escalation and patients not tested for ITL) were used as control groups and corresponded to patients who continued their infliximab infusions during the two years of the simulation after exclusion of those stopping infliximab due to adverse events or loss of response.

The infliximab threshold of 7 μg/mL was chosen because it is well established that it is required to minimize the risk of loss of response [15]. We considered in the model that a patient who had to be re-escaladed followed the same path as in de-escalation. Table 3 shows cohorts and sub-cohorts.

2.2. Modeling

Because of the difficulty in predicting of evolution of disease over time and the unstable nature of remission and relapse, choosing the suitable treatment for patients with CD may sometimes be challenging. For a given patient, events may occur, numerous or not, with potential changes in term of dosing medication, molecule change or surgery needed. The events may occur at random and vary from one individual to the next. Therefore, all-inclusive thinking taking into account the random nature of the disease is needed for modeling the evolution of patients with CD [16]. We decided to use the discrete event simulation, which describes and models by means of a life sequence chart, which is an extension of state chart. Conceptually, the modeler considers the patient as a reactive 'object' whose behavior is characterized by its response to random events and also by its past. The formalism of the state table was introduced by the team of Harel in 1985 [17]. After being used in the manufacturing industry, the application of event simulation has had increasing success in the life sciences since the early 2000s [18]. This model provides the entire medical path followed by the patient, including events that occurred in response to treatment, their potential adverse events and treatment changes during the whole simulation period. Based on the results of the simulation, the number and duration of the periods of treatment (a period of treatment corresponds to the use of a drug at a given dose for a specific duration) are calculated for each patient. The costs resulting from these periods of treatment can then be computed. By using Harel state chart, we are able to describe how a patient's state can change over time according to events that occur and treatment changes that are made.

2.3. Design of the model

The life sequence charts describing the flow of events for patients' cohorts P2 and P4 are represented in Fig. 1A and B, respectively. For every figure, path n°1 describes de-escalated sub-cohorts (P2a and P4a) and path n°2 describes sub-cohorts without drug de-escalation (P2b and P4b). The flow of events was elaborated via a consensus among the authors (AA, LPB and XR). The mathematic modeling was then developed to simulate the dynamics of each of the two paths (Fig. 2).

2.4. Data entered into the model

The model parameters, namely the different probabilities of events that may occur, were determined according to the literature. Table 1 shows the list of events considered and their associated probabilities of occurrence. These probabilities have been derived from annual probability estimations found in the literature and recalculated to take into account the different time units used in this work: the difference in the lengths of the periods of treatment between the two groups. Probabilities were obtained from an expert panel (AA, LPB and XR — Table 2) considering current knowledge when literature data were lacking, especially for de-escalation. These parameters were used to simulate the occurrence of various events, patient by patient, throughout the observation period. All probabilities were computed according to the efficacy, adverse events occurrence and of the switch to adalimumab (40 mg subcutaneous every 14 or 7 days).

2.5. Costs of anti-TNF treatment and therapeutic drug monitoring

The cost reimbursement of one patient having an infusion of IFX, paid to hospitals for this care by the French healthcare authorities (Caisse Nationale d'Assurance Maladie) was established at €361.75 in 2015; it includes costs relative to the day hospital needed for the infusion; only costs related to drug administration were considered (e.g. cost of infliximab, hospitalization and nurse). The cost of the drug for an average of 3 vials (€492.81/vial of 100 mg) per patient for a 5 mg/kg dose was €1478.43. This gives a total of €3318.61 for one infusion for a patient weighing 60 kg in average receiving a double dose of IFX. Because of the lower biosimilar IFX price in 2018 (€162.34/vial for biosimilar CT-P13) than the 2015 IFX princeps price, we also calculated the reduction in percentage and in absolute cost according to the use of the tests with the new price in P1 and P2 populations, including P2a and P2b sub-cohorts. For adalimumab, the direct cost of treatment was €417.05 for one dose of 40 mg (no hospitalization costs). The ITL was considered to be established using the Lisa-Tracker duo IFX ELISA kit® (Theradiag, Marne la Vallée, France) which cost €100/assay. Only one test per patient was performed in our model.

2.6. Model and statistical analysis

The software tool used (AnyLogic®, AnyLogic North America, Chicago, IL) generates the entire path of all patients in the cohort for the period considered based on events that occurred in the history of these patients. These paths are then analyzed using other software (R scripts), in order to calculate for each patient the number of periods of anti-TNF treatment a patient had during follow-up and their timing. This provides complete information on all changes of each patient over time and until the end of anti-TNF treatment. In order to perform our simulation and take into account the various probabilities, we randomly selected the treatment outcomes according to a prior uniform probability distribution given published data and the expert panel opinion. The probability of treatment failure (loss of response or drug intolerance) among

primary responders was estimated following a comprehensive literature search (Table 1).

We estimated the cost of each treatment regimen (IFX every 8 or 6 weeks, IFX every 6 weeks with immunosuppressant, adalimumab every 1 or 2 weeks) and calculated the total cost of treatment for each patient, depending on the number of periods for each type of treatment regimen. We then calculated the treatment costs for each cohort P1–P4 as well as for all sub-cohorts. We compared the differences in costs for not de-escalated versus de-escalated cohorts (P1–P2; P3–P4) to evaluate our main outcome measure, which was the reduction in cost in tested populations versus non-tested populations. Our secondary endpoint was the calculation of the cost reduction within a tested cohort, whether patients were de-escalated or not (i.e. P2a–P2b and P4a–P4b). Chi2 test or ANOVA were done according to the number of classes of data (STATISTICA package version 10 (Quest Software, Aliso Viejo, CA) was used for all statistical analysis); $p < 0.05$ was considered significant.

3. Results

3.1. De-escalation within the P2 cohort (drug de-escalation according to infliximab trough levels in the 10 mg/kg every 8 weeks cohort)

Fig. 1A shows the flow chart of the P2 population. According to the probabilities of literature data shown in Table 1, the proportions of patients de-escalated (P2a) and non de-escalated (P2b) according to ITL were estimated by the model at 20.7% (n = 2067 supra-therapeutic ITL) and 79.3% (low and normal ITL; n = 7933), respectively. At 2 years – the duration of the virtual follow-up –,

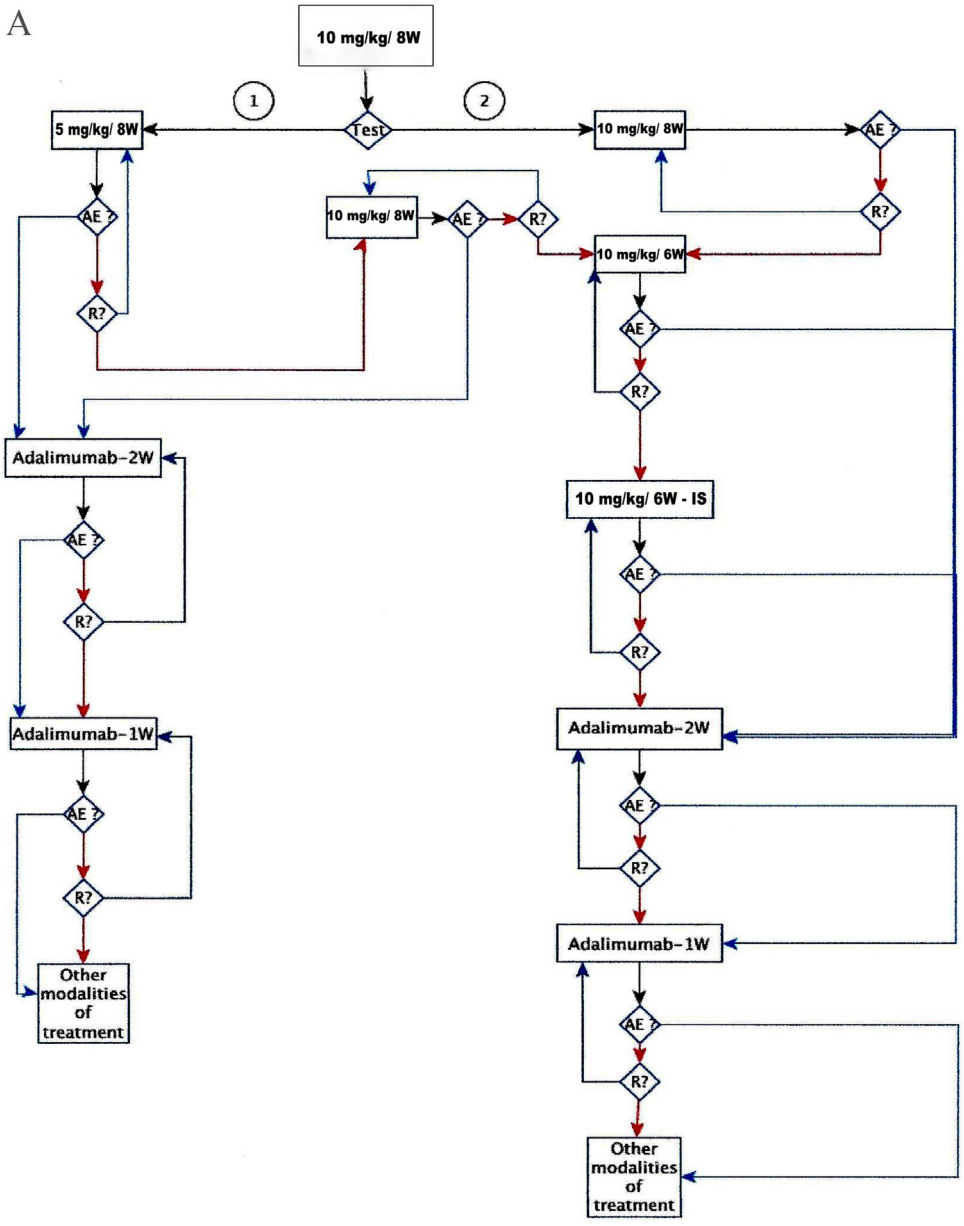

Fig. 1. Discrete event simulation of the flow of events used to compute life sequence charts distribution. (A) describes the flow of events for patients in the P2 cohort at 10 mg/kg of infliximab every 8 weeks de-escalated (path 1, sub-cohort P2a) or not (path 2, sub-cohort P2b). (B) represents the P4 cohort at 10 mg/kg every 6 weeks de-escalated (path 1, sub-cohort P4a) or not (path 2, sub-cohort P4b).
10 or 5 mg/kg/8W: IFX 10 or 5 mg/kg every 8 weeks. 10 mg/kg/6W: IFX 10 mg/kg every 6 weeks. 10 mg/kg/6W — IS: IFX 10 mg/kg every 6 weeks with immunosuppressor. R: clinical response; AE: adverse events; Adalimumab-2W: adalimumab every 2 weeks; Adalimumab-1W: adalimumab every 1 week; blue arrow = 'Yes', red arrow = 'No'. 1: supra-therapeutic (≥7 μg/mL), 2: normal or low range ITL (<7 μg/mL).

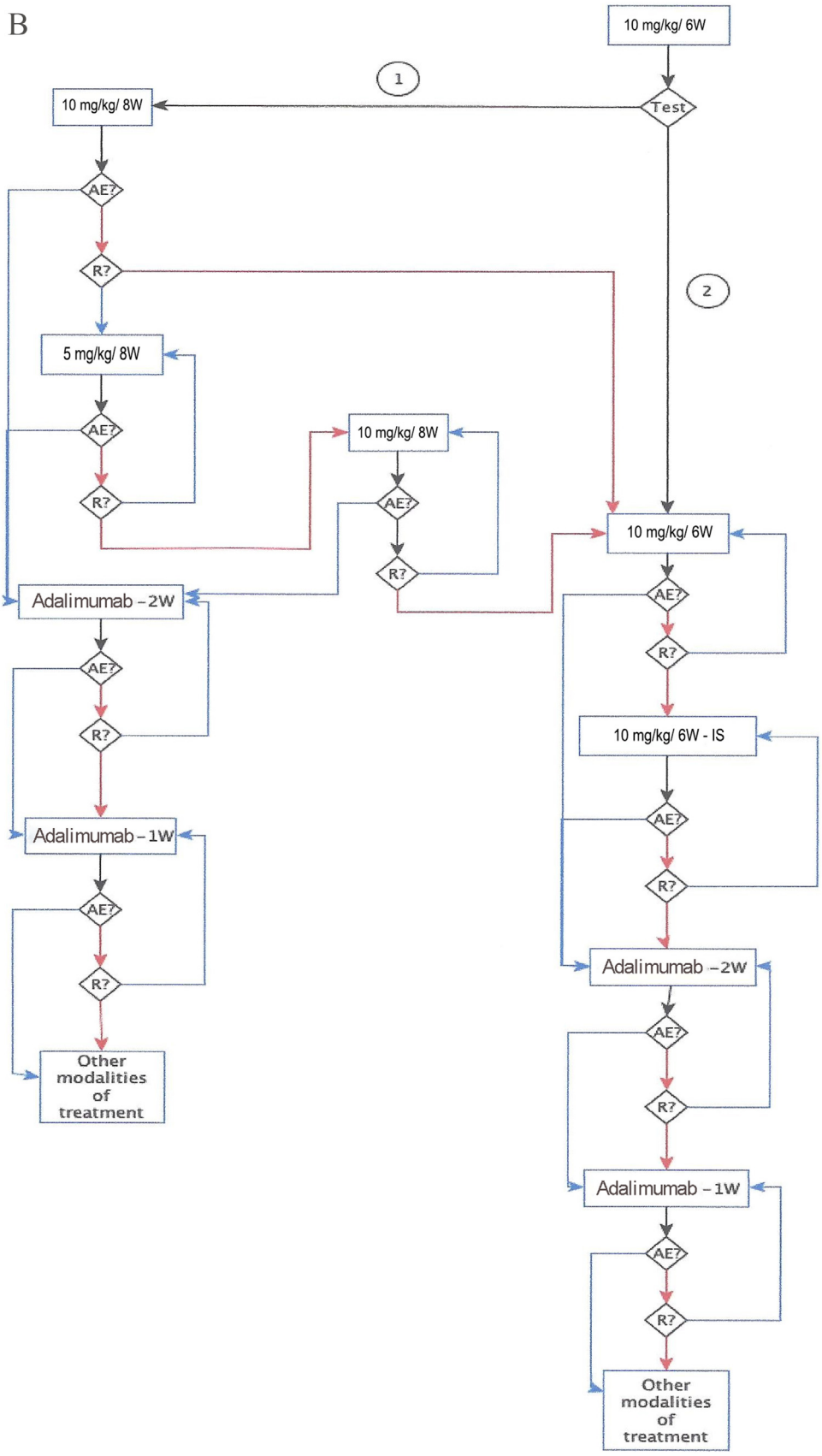

Fig. 1. (*Continued*)

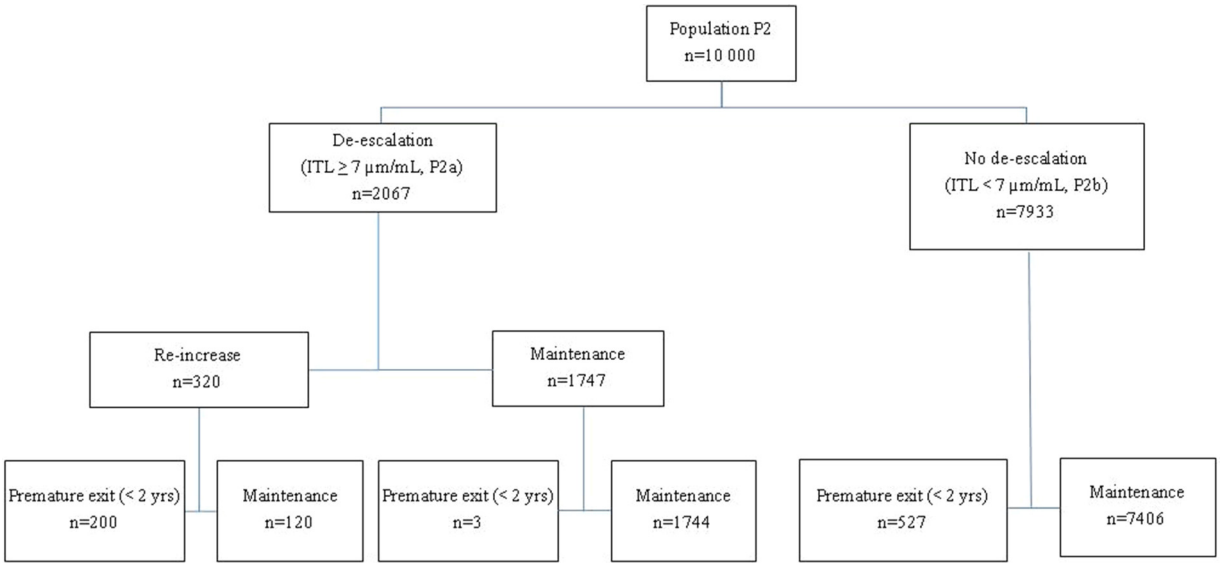

Fig. 2. Flow chart of the P2 virtual cohort of 10,000 patients having an optimized IFX therapy (10 mg/kg every 8 weeks) and de-escalated according to IFX' trough levels.

Table 1
Model inputs according to clinical events and litterature data.

Probability for one event at each consultation	Probabilities	References
Loss of response to infliximab therapy at maintenance dose without any adverse event if low ITL	0.021	Gisbert and Panés [14]
Serious adverse event on IFX therapy wathever the ITL	0.029	Hanauer et al. [2] Cummings et al. [23]
Loss of response after optimization of IFX therapy (double dose) without any serious adverse event if low ITL	0.101	Katz et al. [24]
Severe adverse event on IFX (10 mg/kg) wathever the ITL	0.029	Hanauer et al. [2] Cummings et al. [23]
Loss of response after optimization of IFX therapy (double dose) every 6 weeks without any serious adverse event if low ITL	0.077	Chapparo et al. [25]
Severe adverse event on IFX (10 mg/kg) every 6 weeks wathever the ITL	0.022	Hanauer et al. [2] Cummings et al. [23]
Loss of response after optimization of IFX therapy (double dose) every 6 weeks without any serious adverse event with addition of immunosuppressive therapy wathever the ITL	0.077	Chapparo et al. [25] Vande Casteele et al. [26] Roblin et al. [27]
Severe adverse event on IFX (10 mg/kg) every 6 weeks with addition of IS wathever the ITL	0.022	Roblin et al. [27] Billoud et al. [28]
Loss of response to ADA therapy at maintenance dose without any adverse event if low ITL	0.008	Colombel et al. [29] Baert et al. [13] Sandborn et al. [30,31]
Serious adverse event on ADA therapy wathever the ITL	0.007	Colombel et al. [29]
Loss of response on ADA therapy every week at maintenance dose without any adverse event wathever the ITL	0.004	Sandborn et al. [32] Roblin et al. [33]

ITL: infliximab trough level, IFX: infliximab, IS: immunosuppressor, ADA: adalimumab.

Table 2
Model inputs according to clinical events and expert opinion.

Event	Probability
Probability for a patient to be de-escalated according to the ITL	0.50
Probability for a patient to have a high ITL if de-escalated	0.40
Probability for a non-IFX responder patient without severe adverse events if de-escalated in a high ITL level	0.05
Probability for a non-IFX responder patient without severe adverse events if de-escalated in a normal range ITL level	0.60
Probability for a non-adalimumab-2w responder patient without severe adverse events if de-escalated in a high ITL level	0.05
Probability for a non-adalimumab-2w responder patient without severe adverse events if de-escalated in a normal range ITL level	0.60

ITL: infliximab trough level, IFX: infliximab.

17.4% (1744 out of 10,000) of patients remained de-escalated at the normal dose of 5 mg/kg every 8 weeks while 320 were re-escalated, of which 120 remained at the optimized dose.

The percentage of patients exiting prematurely, i.e. needed other modalities of treatment (non anti-TNF treatment or surgery) during the 2-year period of the study, was 9.8% (n = 203) and 6.6% (n = 527) (p = 0.0001) in the de-escalated sub-cohort (P2a) vs. the non de-escalated group (P2b), respectively. The mean number of weeks before patients entered these others modalities of treatment was 76.4 [95% confidence interval [CI]: 74.0–78.8] and 76.2 [95% CI: 74.8–77.6; p = 0.2] for non tested (P1) vs tested (P2) cohorts, respectively, as shown in Fig. 2.

3.2. Costs comparison between P1 and P2 cohorts at 2-years (Table 3)

The per-patient mean costs of treatment in the P2 and P1 cohorts were €37,327 (95% CI: 37,102–37,553) and €40,376 (95% CI:

Table 3
Costs according to cohorts at 2 years.

	P1: IFX 10 mg/kg every 8 weeks, no trough level testing	P2 : IFX 10 mg/kg every 8 weeks, trough levels testing for all patients				
		P2a (supra-therapeutic[a])	P2b (low though levels or normal though levels[a])	P2a–P2b	P2	P1–P2
	Not de-escalated patients	De-escalated patients	Not de-escalated patients		All patients	
n	10,000	2067	7933		10,000	
Total cost (€)	403,758,000				373,271,300	30,486,700
Mean cost per patient (€)	40,376	25,627	40,376	14,749	37,327	3049
	P3: IFX 10 mg/kg every 6 weeks, no trough level testing	P4 : IFX 10 mg/kg every 6 weeks, trough levels testing for all patients				
		P4a (supra-therapeutic[a])	P4b (low though levels or normal though levels[a])	P4a–P4b	P4	P3–P4
	Not de-escalated patients	De-escalated patients	Not de-escalated patients		All patients	
n	10,000	1995	8005		10,000	
Total cost (€)	443,538,100				423,266,905	20,271,195
Mean cost per patient (€)	44,354	34,193	44,354	10,161	42,326	2,027

IFX: infliximab, P1 to P4: 4 virtual cohorts of 10,000 patients in clinical remission on optimized IFX treatment.
[a] IFX supra-therapeutic (>7 μg/mL) or normal or low through levels (<7 μg/mL).

40,170–40,581), respectively; giving a total cost difference between P2 and P1 of €30.5 million for 10,000 patients, corresponding to a 7.6% cost reduction. The comparison of the corresponding costs between the P1 and P2 cohorts at 2 years, taking into account the price of the CT-P13 biosimilar instead of the originator, and modifying only the value of the variable "price of infliximab", made it possible to obtain a cost reduction of 7.4%, corresponding to a reduction of €13.8 million. In the P2 cohort, the costs per patient between de-escalated (P2a) and non de-escalated (P2b) ones were €25,627 (95% CI: 25,267–25,987) and €40,376 (95% CI: 40,145–40,606) respectively, which gives a difference for P2a and P2b of €267.3 million for 10,000 patients, corresponding to a 36.5% cost reduction.

3.3. De-escalation within the P4 cohort (drug de-escalation according to infliximab trough levels in the 10 mg/kg every 6 weeks cohort)

Fig. 1 B shows the flow chart of the P4 population. According to the probabilities of literature data shown in Table 1, the proportions of patients de-escalated (P4a) and non de-escalated (P4b) according to ITL were estimated by the model at 19.9% (1995 supra-therapeutic ITL) and 80,0% (normal or low ITL; n = 8005), respectively. At 2 years – the duration of the virtual follow up –, 8.7% (868 out of 10,000) of patients remained de-escalated at the dose of 10 mg/kg every 8 weeks while 1090 were re-escalated, of which 183 remained at the optimized dose.

The percentage of patients of patients who needed other modalities of treatment (non anti-TNF treatment or surgery) during the 2-year period of the study were 4.6% (n = 220) and 11.0% (n = 368; p = 0.0001) in the de-escalated sub-cohort (P4a) vs. the non de-escalated group (P4b), respectively. The mean number of weeks before patients entered these others modalities of treatment was 68.7 [95% confidence interval [CI]: 66.0–71.5] and 67.1 [95% CI: 65.2–70.0; p = 0.3] for non tested (P3) vs tested (P4) cohorts, respectively.

3.4. Costs comparison between P3 and P4 cohorts at 2-years (Table 3)

The per-patient mean costs of treatment in the P4 and P3 cohorts were €42,327 (95% CI: 42,004–42,649) and €44,354 (95% CI: 44,093–44,614); giving a total cost difference between P3 and P4 of €20.3 million for 10,000 patients, corresponding to a 4.6% cost reduction. In the P4 cohort, the costs per patient between de-escalated (P4a) and non de-escalated (P4b) ones were €34,193 (95% CI: 36,918–37,700) and €44,354 (95% CI 44,063–44,645), respectively, with a difference for P4a and P4b sub-cohorts of €286.8 million for 10,000 patients, corresponding to a 22.9% cost reduction.

3.5. Mean estimation of costs saving in both P2 and P4 cohorts

Making an average estimation of the P2 and P4 cohorts give a total cost difference around €25.4 million for 10,000 patients, corresponding to a 6% cost reduction.

3.6. Numbers of patients having others treatment modalities in P1–P4 cohorts

The number of patients who required other treatment modalities in the two IFX regimens and according to the realization of ITL was 646, 730, 485 and 588 in P1–P4 groups, respectively. There was a significant difference between P1 and P2 (difference 84 patients, p = 0.05) and between P3 and P4 (difference 103 patients, p = 0.05).

4. Discussion

Drug de-escalation is often considered in clinical practice in patients with IBD treated with optimized infliximab treatment and in sustained remission. In this discrete event modeling, two large cohorts of 10,000 patients optimized at 10 mg/kg every 8 or 6 weeks and in clinical remission with IFX were kept de-escalated for 2 years using ITL in 20.7% and 19.9% of cases. In a short series of 20 supra-therapeutic ITL patients, a strong proportion of them (18 out of 20) could be de-escalated 1 mg/kg less at each infusion to reach the normal range ITL at 8 months of follow up, without relapsing [12]. Using adalimumab, Baert et al. have shown that the de-escalation was successful in 63% at 55 months [13].

We calculated a cost saving per patient in the P2 cohort of around 7.6% or 36.5% in our model at 2 years (corresponding to 3.8% and 18.5% per year, respectively) when comparing the two cohorts (P2 vs P1; i.e. tested and a not tested) or, within the tested cohort (P2a vs P2b), respectively. Whatever the optimized treatment regimen, the costs saving in between tested or not tested cohorts were €30.5 and €20.3 million at 2 years and so, half this sum per year. The rate of cost reduction via the use of the ITL does not change according to whether one uses the infliximab princeps at the price of 2015 or the biosimilar at the price of 2018 but, on the other hand, there is logically a decrease in the absolute value of the cost saving at €13.8 million. We believe that this saving, linked to the use of the ITL and with the new price of IFX, remains substantial. Few studies have been published about the economic benefit of drug

de-escalation. Importantly, in the 1-year randomized controlled TAXIT trial including 263 IBD adults with stable disease on IFX maintenance therapy, among 72 supra-therapeutic ITL patients, 67 patients (93%) achieved a normal range of ITL of 3–7 μg/mL after IFX dose reduction to the normal dose, leading to a 28% drug cost reduction calculated on the basis of the mean IFX cost per patient over 4 weeks [6]. They also showed a €2415 cost difference between concentration-based and clinically based dosing per patient and per year. Using our model, we found a €1524 cost reduction at one year. This difference may be explained by some differences in methodology and study design as well as the cost of the drug and the test. Indeed, only costs related to drug administration were considered. It is also interesting to note that among exiting patients to other treatment modalities, they are significantly more in the tested (P2 and P4) than in untested cohorts (P1 and P3). These few patients benefit from the test, whatever the result, and move on to other treatment modalities without loss of additional time.

Regarding the increasing use of ITLs measurement in drug escalation, the few follow up or model studies that have been published showed a cost savings per patient between $ 5 396 and € 13,130 from 12 to 52 weeks [7,10,19]. Interestingly, and contrary to popular belief, patients are inclined to continue optimized IFX if necessary and ITL can help them better understand the usefulness of dose changes in their treatment. Indeed, in a retrospective study of 100 patients, less than 10% of patients receiving IFX wished to interrupt it, although a fifth could consider it in the future [20].

The main strength of our study is the use of discrete event modeling. In IBD, the patient's journey leads to a large number of possible pathways and options. This variety of outcomes can generate a complex design methodology that is, difficult to describe with a decision tree. Data analysis becomes unreadable and unmanageable. Indeed, the number of branches on the decision tree quickly becomes too large to be able to be represented and analyzed. Other methods based on models of differential equations usually used to describe the evolution of epidemics are also unusable. Moreover, the chain of a Markov model cannot be applied because it does not take into account changes in the temporal state that varies from one patient to another. The pathway variation of a patient must be taken into account in the model at each step; a procedure incompatible with the modeling of a Markov chain.

This work has weaknesses. Our results are a reflection of what is being done in France in 2015 and can be difficult to extrapolate to other health care systems. Also, we did not evaluate all costs associated with infusions by considering that these charges existed in all cases of the selected de-escalation options and that they canceled each other out without our having to quantify them. Also recently, the cost of treatment has decreased with the increasing use of IFX biosimilars. In a budget impact study a 10–30% price reduction with one of the biosimilars of IFX, CT-P13, used in autoimmune diseases, the cumulative cost saving at one year was evaluated to range from €25.8 million (10% reduction) to €77.4 million (30% reduction) [21]. Using a Markov model, the biosimilar versus originator IFX therapy resulted in the most favourable incremental cost-utility ratios ranging from €34,580 to €77,062/QALY [22]. Even if the price of the product decreases, the drug monitoring reduces the amount of infliximab administered. One question that we did not answer in our study is that of variation of cost if P2 and P4 cohorts become subtherapeutic. We could not predict in our model how many patients would be below 3 μg/mL after drug de-escalation as no studies addressed this issue in this patient population in the literature. Hence, this will require further investigation. Also, we did not include the presence of anti-IFX antibodies and their title in the model because of the complexity generated. However, the positive effect of adding an immunosuppressant is at least partially mediated by the decrease or disappearance of the antibodies. It is therefore an indirect consideration of the presence of the antibodies. Finally, expert evaluation of patient outcomes in the absence of data in the literature is also a weakness of the study. However, it was necessary to estimate the outcome of patients even in the absence of data; otherwise the estimate of the cost reduction would not have been possible.

In conclusion, over a 2-year period, IFX de-escalation yielded a cost savings of around 6% when comparing tested versus not-tested patients. Taken together, these findings confirm that de-escalation is cost effective when using therapeutic drug monitoring and may be considered in selected patients.

Conflict of interest

A.A. lecture and consulting fees from Takeda, Nukleus, Abbvie, Aptalis, Bouchara-Recordati; L.P.B., lecture and consulting fees from Merck, Abbvie, Janssen, Genentech, Mitsubishi, Ferring, Norgine, Tillots, Vifor, Therakos, Pharmacosmos, Pilège, BMS, UCB-pharma, Hospira, Celltrion, Takeda, Biogaran, Boerhinger-Ingelheim, Lilly, Pfizer, Index Pharmaceuticals, Amgen, Sandoz, Forward Pharma GmbH, Celgene, Biogen, Lycera, Samsung Bioepis, HAC-pharma; X.R., lecture and consulting fees from Merck, Abbvie and Theradiag. The other authors declare no conflicts of interest.

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