ABSTRACT

Objectives Around 30% of patients with rheumatoid arthritis (RA) do not respond to tumour necrosis factor inhibitors (TNFi). We aimed to predict patient response to TNFi using machine learning on simple clinical and biological data.

Methods We used data from the RA ESPOIR cohort to train our models. The endpoints were the EULAR response and the change in Disease Activity Score (DAS28). We compared the performances of multiple models (linear regression, random forest, XGBoost and CatBoost) on the training set and cross-validated them using the area under the receiver operating characteristic curve (AUROC) or the mean squared error. The best model was then evaluated on a replication cohort (ABIRISK).

Results We included 164 patients from ESPOIR and 118 patients from ABIRISK. The key selected features selected were sex, DAS28, body mass index, smoking status, erythrocyte sedimentation rate, rheumatoid factor IgM, family history and past pregnancy. When predicting EULAR response, CatBoost achieved the best performances of the four tested models. It reached an AUROC of 0.74 (0.65–0.75) on ESPOIR and 0.70 (0.57–0.82) on ABIRISK. Better results were obtained when etanercept and monoclonal TNFi were tested separately. Two decision thresholds were tested. The first prioritised a high confidence in identifying responders and yielded a confidence up to 90% for predicting response. The second prioritised a high confidence in identifying inadequate responders and yielded a confidence up to 90% for predicting non-response. The change in DAS28 was predicted with an average error of 1.1 DAS28 points.

Conclusion The machine learning models developed allowed predicting patient response to TNFi exclusively using data available in clinical routine.

INTRODUCTION

Rheumatoid arthritis (RA) is a complex disease, heterogeneous in its clinical presentation, severity and response to therapies. Targeted disease-modifying antirheumatic drugs (tDMARDs) are recommended for patients who do not respond to first-line methotrexate therapy. Thirteen drugs with different mechanisms of action may be considered for treatment, and tailoring treatment for an individual patient can be challenging. Tumour necrosis factor inhibitors (TNFi) are frequently the first choice but unfortunately, around one-third of patients do not respond and would have benefited from another tDMARD. There is a lack of simple markers to identify TNFi responders which results in a trial-error process that is detrimental for the patient and costly for the healthcare system.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ There are no widely used clinical and/or biological factors that predict response to tumour necrosis factor inhibitors (TNFi) in patients with rheumatoid arthritis (RA).

WHAT THIS STUDY ADDS

⇒ We trained machine learning algorithms that use clinical and biological data to predict response to TNFi and validated them in a separate cohort.
⇒ We had a good overall prediction of TNFi response that was further improved when analysing etanercept and monoclonal TNFi separately.
⇒ We then set the decision thresholds of two different models to predict more accurately either response or non-response. We were thus able to accurately predict those two outcomes separately.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Accurately predicting non-response to TNFi could save time by directly using other targeted disease-modifying antirheumatic drugs.
⇒ Machine learning could improve management of patients with RA through predicting treatment response to TNFi.
Regarding RA management, predicting the therapeutic response or failure to a TNFi treatment prior to its initiation would be groundbreaking. Several studies have tried to identify biomarkers, but none of them have emerged as a reliable predictive factor of response.2

With the increasing amount of available data in medicine, new tools are required to extract information. Machine learning algorithms learn patterns from data and assume these will reproduce in the future. These algorithms identify patterns and rules without being explicitly programmed to do so, allowing unbiased discoveries. This is especially interesting in medicine to identify markers or combination of markers unknown so far by physicians. Machine learning is now widely used in healthcare, especially in radiology and oncology, whether it be for diagnosis, prognosis or treatment recommendation; and has

### Table 1 Characteristics of the training set (ESPOIR) and validation set (ABIRISK) at last visit before treatment initiation

| Feature's name                                      | ESPOIR n=161 |          | ABIRISK n=118 |          |
|-----------------------------------------------------|---------------|----------|---------------|----------|
| Age, years                                          | 49 (13)       | 52 (13)  | 25.6 (5.5)    | 24.9 (4.6)|
| Female, n (%)                                       | 115 (71)      | 89 (76)  | 72 (61)       | 72 (45)  |
| Weight, kg                                          | 69 (15)       | 75 (19)  | 33 (28)       | 28 (17)  |
| Height, cm                                          | 166 (9)       | 167 (9)  | 28 (17)       | 28 (17)  |
| Body mass index                                     | 24.9 (4.6)    | 25.6 (5.5)| 70 (79)       | 72 (61)  |
| Autoimmunity family history, n (%)                 | 48 (30)       | 37 (32)  | 72 (61)       | 72 (45)  |
| Ever smokers, n (%)                                 | 72 (45)       | 72 (61)  | 72 (61)       | 72 (45)  |
| Current smokers, n (%)                              | 28 (17)       | 33 (28)  | 28 (17)       | 28 (17)  |
| Smoking cumulative dose, pack-year                  | 8 (13)        | 15 (14)  | 8 (13)        | 8 (13)   |
| Past pregnancy (among sex=female), n (%)           | 92 (74)       | 70 (79)  | 70 (79)       | 70 (79)  |
| DAS28                                               | 4.6 (1.6)     | 4.4 (1.1)| 4.4 (1.1)     | 4.6 (1.6)|
| CRP, mg/L                                           | 17 (27)       | 12 (16)  | 12 (16)       | 17 (27)  |
| Erythrocyte sedimentation rate, mm                  | 26 (23)       | 23 (19)  | 23 (19)       | 26 (23)  |
| Creatinine, µmol/L                                  | 74 (17)       | 66 (14)  | 66 (14)       | 74 (17)  |
| AST, UI/L                                           | 22 (8)        | 25 (13)  | 25 (13)       | 22 (8)   |
| ALT, UI/L                                           | 22 (13)       | 27 (20)  | 27 (20)       | 22 (13)  |
| White blood, cells/mm³                               | 7.9×10³ (2.6×10³) | 8.5×10³ (3.2×10³)| 113 (70)   | 81 (70)  |
| Neutrophils, cells/mm³                              | 5.4×10³ (2.4×10³) | 6.1×10³ (3.2×10³)| 119 (74%)  | 78 (68%) |
| Lymphocytes, cells/mm³                              | 1.7×10³ (6.8×10³) | 2.1×10³ (2.9×10³)| 22 (8)     | 25 (13)  |
| Presence of anti-citrullinated protein antibody, n (%) | 113 (70)      | 81 (70)  | 119 (74%)     | 78 (68%) |
| Presence of rheumatoid factor IgM                   | 119 (74%)     | 78 (68%) | 119 (74%)     | 78 (68%) |
| TNFi treatment sequences, N                        | N=208         | N=118    | N=208         | N=118    |
| Etanercept sequences, N (%)                         | 100 (48)      | 68 (58)  | 100 (48)      | 68 (58)  |
| Monoclonal anti-TNF antibodies sequences, N (%)    | 108 (52)      | 50 (42)  | 108 (52)      | 50 (42)  |
| Adalimumab sequences, N (%)                         | 80 (74)       | 39 (78)  | 80 (74)       | 39 (78)  |
| Infliximab sequences, N (%)                         | 17 (16)       | 11 (22)  | 17 (16)       | 11 (22)  |
| Certolizumab sequences, N (%)                       | 8 (7)         | 0 (0)    | 8 (7)         | 0 (0)    |
| Golimumab sequences, N (%)                          | 3 (3)         | 0 (0)    | 3 (3)         | 0 (0)    |
| First TNFi line, N (%)                              | 153 (74)      | 107 (91)| 153 (74)      | 107 (91)|
| Non-responder imputation, N (%)                     | 10 (4.8)      | 21 (18)  | 10 (4.8)      | 21 (18)  |
| Responder to sequences, N (%)                       | 122 (59)      | 72 (61)  | 122 (59)      | 72 (61)  |
| Etanercept, N (%)                                    | 64 (64)       | 42 (62)  | 64 (64)       | 42 (62)  |
| Monoclonal anti-TNF antibodies, N (%)               | 58 (54)       | 30 (60)  | 58 (54)       | 30 (60)  |
| Co-treated with corticosteroids, N (%)              | 94 (45)       | 51 (43)  | 94 (45)       | 51 (43)  |
| Co-treated with MTX, N (%)                          | 152 (73)      | 64 (54)  | 152 (73)      | 64 (54)  |

Results are presented as follows: mean (SD) for continuous variables and amount (percentage) for binary variables.

CRP, C reactive protein; DAS28, Disease Activity Score; MTX, methotrexate; TNFi, tumour necrosis factor inhibitors.
proven itself very useful in assisting physicians for certain precise tasks.\textsuperscript{3,4}

Recently, several studies have considered the increasing amount of available data and suggested that machine learning techniques could be clinically used to predict the TNFi therapeutic response.\textsuperscript{5–8} These suggestions are backed by recent initiatives implementing machine learning models on a variety of RA datasets. Two of these initiatives use genetic data to predict patient response to TNFi.\textsuperscript{9,10} Using this approach in clinical practice remains a challenge since genetic data are not widely available. Other initiatives\textsuperscript{11,12} apply machine learning on clinical and biological data for similar objectives. However, these approaches often fail to describe how such models could be useful in clinical practice. Specifically, they do not study the impact of the decision threshold that transposes the probability yielded by the model into a binary therapeutic response. Defining this threshold requires a deep understanding of the clinical context to assess the clinical impact of such a tool. Unfortunately, this process is often poorly described. Another key element is the explanation of the model’s predictions, as most studies do not show the impact of the variables in predicting the response to treatment. Underlining the key variables impacting the model predictions helps to build rheumatologists’ confidence in the technique and promote further clinical use. Ultimately, most of these existing models might be of limited clinical use due to the absence of replication cohorts to validate the results.

This study builds and compares different machine learning models to predict the therapeutic TNFi response for patients with RA based on routinely available clinical and biological data. It is based on data from the ESPOIR cohort to train our models, and the results were validated on the ABIRISK cohort.

### METHODS

#### Patients

We included patients from ESPOIR,\textsuperscript{13} a French multicentric, longitudinal and prospective early arthritis cohort that constituted the training dataset. ESPOIR is an observational study that followed patients for 11 years; and where patients were treated according to each centre’s clinical practice, without any modification for research. As validation cohort, we used ABIRISK,\textsuperscript{14} a prospective study investigating the predictive factors of development of anti-drug antibodies in patients with RA treated with a first TNFi. Patients were followed until the end of the treatment and up to 18 months after the treatment initiation. Patients were included if they fulfilled the 2010 American College of Rheumatology/EULAR criteria and received at least one injection of TNFi. No restriction on disease activity, disease duration, failure of previous DMARDs nor co-medication was applied so that the selected population reflects the diversity observed in clinical practice. The decision to introduce a TNFi was left to the choice of the treating physician according to local practice. Patients stopping the TNFi treatment within 6 months after initiation due to pregnancy, surgery, poor compliance to the protocol or unknown reasons were excluded from the study population. Patients stopping the TNFi treatment within 6 months after initiation due to inefficacy or adverse events were considered as inadequate responders (non-responder imputation). Patients stopping the TNFi treatment within 6 months after initiation due to remission were considered as responders.

In the ESPOIR cohort, a patient could switch from one TNFi drug to another during the follow-up. Each treatment sequence was considered as independent from each other. To account for these multiple treatments, we included a binary variable equal to 0 for TNFi-naïve patients at sequence initiation and 1 otherwise.

We performed the analysis in the population treated with any type of TNFi. We then divided the population into two sets: patients treated with etanercept and patients treated with monoclonal anti-TNFi antibodies, anticipating a potential difference in the response to these two types of TNFi.

#### Variables

We have included all the daily practice clinical and biological variables that were available in both cohorts. They include demographics, smoking status, Disease Activity Score (DAS28), C reactive protein, disease characteristics, complete blood count parameters, and liver and kidney parameters as shown in table 1.

#### Endpoints

Two endpoints were considered, resulting in two distinct predictive tasks:

1. The primary endpoint was the prediction of the therapeutic response, defined as good or moderate EULAR response\textsuperscript{15} assessed 12 months (±6 months due to yearly visits in the ESPOIR cohort) after treatment initiation. This endpoint is binary (response vs inadequate response) and is analysed using the area under the receiver operating characteristic (ROC) curve.

| Table 2 | Result of the variable selection process for the prediction of the EULAR response |
| --- | --- |
| TNFi | Etanercept | Monoclonal antibodies TNFi |
| DAS28 | DAS28 | DAS28 |
| Age | Sex | Sex |
| Ever smoked | Ever smoked | Ever smoked |
| Weight | BMI | Weight |
| Lymphocytes | ESR | |
| Neutrophils | |
| ALT | |

The feature selection was run on the training set (ESPOIR). BMI, body mass index; DAS28, Disease Activity Score; ESR, erythrocyte sedimentation rate; TNFi, tumour necrosis factor inhibitors.
(AUROC). A higher AUROC corresponds to a better model.

2. The secondary endpoint was the prediction of change in the erythrocyte sedimentation rate DAS28. It is defined as the difference between DAS28 12 months after treatment initiation and DAS28 at treatment initiation. This difference is noted $\Delta$DAS28 in the following. This endpoint is continuous and analysed using the mean squared error (MSE). A lower MSE corresponds to a better model.

Models

For both endpoints, the prediction pipeline is composed of consecutive blocks (online supplemental figure 1):

► A missing data imputation method.
► A variable selection process to select the predictive variables.
► A machine learning model predicting the outcome based on the predictive variables.

Four machine learning models were assessed: a linear regression model (logistic regression for the therapeutic response prediction and ridge regression for the $\Delta$DAS28 prediction), a random forest model and two gradient boosted trees models (XGBoost and CatBoost). Advantages and limits of these models are detailed in online supplemental methods.

Each model uses the variables available at the last visit before treatment initiation to predict the outcome. For the primary endpoint, the models output a score (between 0 and 100) which is interpreted as a probability for the patient to respond to TNFi. Ultimately, this score is compared with a decision threshold to obtain a binary prediction (response vs inadequate response). For the secondary endpoint, the models directly predict the DAS28 12 months after initiation.

The variables available in both cohorts are presented in table 1. Variable selection process and missing data imputation methods are presented in online supplemental methods.

Evaluation

The whole process (automated feature selection and model training) was evaluated using leave-one-out cross-validation on the training dataset. Only the best trained model was evaluated on the validation dataset to ensure the replication of the results. The metrics used to compare the models were the AUROC for the response classification (the higher, the better) and the MSE for the $\Delta$DAS28 prediction (the lower, the better).

The prediction of the therapeutic response is a binary classification task and in such a case, classic epidemiological metrics exist. Specifically, for this task, we computed, to provide clinical perspective, the positive predictive value (PPV), the negative predictive value (NPV), the sensitivity and the specificity.

The models predict a probability for a patient to respond to TNFi. This probability is compared with a decision threshold to obtain the final binary outcome. The choice of this decision threshold requires to determine the best use case for the clinician. Two scenarios can be considered:

1. A high decision threshold guaranteeing the highest possible confidence when predicting a patient as responder to the treatment.
2. A low decision threshold guaranteeing the highest possible confidence when predicting a patient as inadequate responder to the treatment.

| Table 3 Performances of the best models for the EULAR response prediction |
|-------------------------------|-----------------|-----------------|-----------------|-----------------|
| Drug                          | Best model      | Best missing value imputer | AUROC (train)   | AUROC (validation) |
| Overall TNFi                  | CatBoost        | MICE             | 0.72 (0.68 to 0.73) | Not evaluated since worse than drug-class-specific models on the training set |
| Etanercept                    | Random forest   | Median           | 0.74 (0.68 to 0.75) | 0.70 (0.57 to 0.82) |
| Monoclonal anti-TNF antibodies | CatBoost        | MICE             | 0.74 (0.69 to 0.77) | 0.71 (0.55 to 0.86) |

The best model and best missing value imputer were selected on the training set (ESPOIR) using AUROC. The replication of the results was assessed on the validation set (ABIRISK). Numbers in brackets refer to 95% CIs. AUROC, area under the receiver operating characteristic curve; TNFi, tumour necrosis factor inhibitors.
To choose the high threshold, we fixed a minimum PPV of 80% and selected the threshold that maximised the sensitivity on the cross-validated training set given this minimum PPV. To select the low threshold, we set a minimum value of 80% for the NPV. Given this minimum NPV, we selected the threshold that resulted in the best specificity on the cross-validated training set.

Details of the statistical methods for model comparison and CIs are detailed in online supplemental methods.

**Explainability of the prediction of response to TNFi**

Ultimately, we studied how the models yielded their decisions. One of the most popular packages to date to explain machine learning predictions is SHAP.\(^9\) SHAP is based on the concept of Shapley value. A Shapley value is specific to a patient and to a characteristic. This value measures the weight of a patient characteristic on the patient outcome. A positive (resp. negative) Shapley value indicates a positive (resp. negative) influence on patient response to treatment. Higher Shapley values indicate stronger influences on patient response and vice versa.

We performed Shapley explanation on the ESPOIR and ABIRISK sets to obtain several visualisations for each model. We displayed explanation diagrams at the dataset level, plotting for each patient and each feature the contribution of this feature to the prediction.

**RESULTS**

**Screening process**

Among the patients from the ESPOIR cohort, 161 were included, of whom 95 initiated a treatment by etanercept and 96 initiated a treatment with an anti-TNF monoclonal antibody (in the ESPOIR cohort, 30 patients switched from one TNFi to another during the follow-up, resulting in more treatment sequences than the number of patients). In the ABIRISK cohort, 118 patients were included, of whom 68 initiated a treatment by etanercept and 50 initiated a treatment with adalimumab or infliximab.

The percentage of response to TNFi is 59% in the training set (ESPOIR) and 61% in the validation set (ABIRISK). The baseline characteristics of treatment sequences are displayed in table 1.

**Results of the variable selection process**

A backward feature selection process was applied to the variables presented in table 1 for each of the drug classes. The result of the feature selection process is presented in table 2 for the EULAR response and online supplemental table 2 for the ΔDAS28 prediction. Only these variables were used to train the models for the prediction of the therapeutic response and the prediction of the ΔDAS28.

**Evaluation of the models**

The four machine learning models were assessed for the prediction of the EULAR therapeutic response. First, all TNFi were considered. Then, the models were assessed on the etanercept and on the anti-TNF monoclonal antibodies groups. Results and comparison of the models are displayed in figure 1. Overall, CatBoost and random
Results were better on the training set when splitting all TNFi in etanercept and monoclonal TNFi antibodies, we then only evaluated the drug-class-specific models on the validation set. For each drug class, the model that performed the best on the training dataset was then assessed on the validation dataset (table 3).

ROC curves for the best models for each drug on both ESPOIR and ABIRISK are presented in figure 2. They showed that models had a good generalisability with overlapping curves between the training and validation datasets. Calibration curves are presented in online supplemental figures 5–7.

For the two decision strategies detailed in the evaluation section, we computed for each group of drugs the specificity, the sensitivity, the PPV and the NPV of the best model on the validation dataset (table 3). When the strategy maximising the confidence in the detection of the responders was used, we looked in particular at the specificity and the PPV of the model. We obtained a higher PPV in the monoclonal antibody group (92%) than in the etanercept group (78%). On the other hand, we focused on the sensitivity and the NPV for the strategy identifying inadequate responders confidently. Sensitivity replicated very well on the validation set and reached 90% whatever be the drug class.

Evaluation of the ∆DAS28 prediction models is detailed in online supplemental figure 3. Overall, the ridge regression model had the best performances suggesting limited non-linear interaction effects between the variables.

For each drug, the model that performed the best on the training set was then evaluated on the validation database (ABIRISK); the results are presented in online supplemental table 3 with their 95% CIs. The mean average error was computed on the validation set as it is easier to interpret. Overall, our models predicted the ∆DAS28 after treatment initiation with an error around 1.1 points of DAS28. This error should be compared with the 0.6 threshold, which is the minimum clinically relevant variation of the DAS28.

### DISCUSSION

This study establishes that machine learning models are efficient to assess the therapeutic TNFi response using exclusive data available in clinical routine. We obtained a good AUROC on the replication cohort. By underlining how each variable impacted the model’s predictions, this study provides insight on how these predictions are made.

The first objective of the study was to assess the performances of a machine learning model based exclusively on clinical and biological data. It is worth noting that the results replicate properly between the training set (ESPOIR) and the validation set (ABIRISK). For the EULAR response prediction, the AUROC dropped by less than 0.05 points (etanercept and monoclonal anti-TNF antibodies). Interestingly, even though dividing by molecule groups leads to smaller study groups, which should decrease the prediction efficacy, the ∆DAS28 and the EULAR response prediction were more efficient when treatments were analysed separately (ie, etanercept and monoclonal anti-TNF antibodies) than together. This improvement in the results suggests differential

### Table 4  Metrics of interest regarding the prediction of the EULAR response

| Drug                      | Strategy 1 (high confidence in response) | Strategy 2 (high confidence in non-response) |
|---------------------------|----------------------------------------|--------------------------------------------|
|                           | Sensitivity | Specificity | PPV | NPV | Sensitivity | Specificity | PPV | NPV |
| Etanercept                | 60% (44% to 74%) | 73% (55% to 89%) | 78% (63% to 92%) | 53% (36% to 69%) | 95% (88% to 100%) | 15% (4% to 30%) | 64% (52% to 76%) | 67% (20% to 100%) |
| Monoclonal anti-TNF       | 37% (20% to 55%) | 95% (83% to 100%) | 92% (73% to 100%) | 50% (35% to 66%) | 90% (78% to 100%) | 40% (19% to 62%) | 69% (54% to 84%) | 73% (44% to 100%) |

For the two strategies presented in methods, we display the metrics on the validation set (ABIRISK). Numbers in brackets refer to 95% CIs.

NPV, negative predictive value; PPV, positive predictive value; TNF, tumour necrosis factor.

### Explanation of the models

For the prediction of the therapeutic response, the models with the best performances on the validation dataset were the CatBoost and random forest models. To interpret these models, we computed the SHAP values on the concatenation of the training and validation datasets for each class of drug (online supplemental figure 2). As an example, high DAS28 was obviously associated with response to treatment, whereas a low value contributed to inadequate response for all TNFi. When plotted individually (figure 4), non-linear interactions arise, especially for values above 5 for which the effect of DAS28 on response was limited. Biological variables such as ALT and lymphocytes had a U shape relationship with prediction of response. Thus, high and low values were associated with response and mid-range with inadequate response (figure 3).

Explanation of the ∆DAS28 prediction models is detailed in online supplemental results.
mechanisms of action between the two classes of drug. This suggestion is strengthened by the observation that the variables used to predict response to etanercept or monoclonal anti-TNF antibodies are partially different or have different weight in the prediction (table 2 and online supplemental table 2).

The results of this study can be compared with similar initiatives using machine learning to predict treatment response to TNFi. The prediction of the therapeutic response is the most frequent task; however, the only study providing a replication dataset and using the EULAR response as the primary endpoint is the publication of the winners of the DREAM RA Challenge. Their model was developed using genomic data and reached an AUROC of 0.62. Numerically, our models seem to outperform theirs, especially when separating TNFi in groups of drugs. Nevertheless, large CIs do not allow us to conclude definitively. This comparison tends to confirm the potential of simple clinical and biological data for the identification of TNFi inadequate responders while extensive genetic data are not available in routine clinical practice. This remark is aligned with the conclusions of the DREAM RA challenge, which noted that genetic data had limited effect on the final performance of the models.

The second objective of the study was to assess the potential of artificial intelligence-derived tools in clinical practice. Two different perspectives are offered to a clinician using these models: having the highest possible confidence of response when prescribing an anti-TNF or having the highest possible confidence when deciding to skip the anti-TNF drugs and directly prefer another tDMARD. The first scenario prioritises the PPV and the specificity of the algorithm, whereas the second prioritises the NPV and the sensitivity of the algorithm. We thus defined two decision thresholds to adapt the model to those two perspectives.

The first model brings the highest possible confidence in the detection of responders. It enables clinicians to prescribe TNFi with a 80% (etanercept) to 90% (monoclonal anti-TNF antibodies) confidence of response (PPV), which is much higher than the 60%–65% response rate observed in our cohorts and in the literature. Using this algorithm and reaching this confidence would result in 50% (etanercept) to 75% (monoclonal anti-TNF antibodies) fewer patients treated with TNFi. Among these untreated patients, we would have missed 50% (etanercept and monoclonal anti-TNF antibodies) of responders (complementary of the NPV). These figures can be balanced given the large therapeutic arsenal of targeted treatments available in RA. Patients predicted as inadequate responders could easily be given another tDMARD.

The second model prioritises the confidence in the detection of inadequate responders. It enables clinicians to skip the TNFi and switch to another tDMARD with around 70% confidence of inadequate response (NPV). Reaching this level of confidence using our algorithm would result in 50% (etanercept) to 75% (monoclonal anti-TNF antibodies) fewer patients treated with TNFi. Among these untreated patients, we would have missed 50% (etanercept and monoclonal anti-TNF antibodies) of responders (complementary of the NPV). These figures can be balanced given the large therapeutic arsenal of targeted treatments available in RA. Patients predicted as inadequate responders could easily be given another tDMARD.

The second model prioritises the confidence in the detection of inadequate responders. It enables clinicians to skip the TNFi and switch to another tDMARD with around 70% confidence of inadequate response (NPV). Reaching this level of confidence using our algorithm would result in 50%–35% less patients treated with TNFi. Among these untreated patients, we would have missed 50%–35% of responders (complementary of the NPV). The NPV of this strategy is quite satisfactory compared with the current clinical practice in which no clear markers are available.
The third objective of the study was to emphasise
the explainability of the machine learning models. To
provide a medical perspective, this study thoroughly
details the explainability of the algorithm using the
SHAP values. Our method was inspired by the successful
application of SHAP values in oncology. Several clinical
studies assessed the influence of classic clinical variables
on the response to TNFi. Even if the conclusions on
the influence of several variables are contradictory, a lot
of consensus stands out and can be compared with the
SHAP values of the models. In general, male sex, younger
age and low body mass index (BMI) were associated with
response, whereas smoking was associated with inade-
quate response. They are also consistent with the results
of the EULAR response prediction presented (online supple-
mental figure 4). As for the three classes of drugs (overall
TNFi, etanercept and monoclonal anti-TNF antibodies),
male sex, younger age and low BMI were associated with
response, whereas smoking was associated with inade-
quate response. The impact of the smoking status is unclear however, and the
sex variable was not selected.

The SHAP values demonstrate that the models capture
complex non-linear interactions between the features
and the output. These non-linearities are partially clear when plotting the Shapley values against DAS28 (figure 3). They also highlight turning points of influ-
ence between EULAR response and inadequate response;
DAS28=4 appears as a clear frontier, for instance.

This study faces several limitations. The main limita-
tion is the sample size which is rather small compared
with data amount usually used in machine learning. The
number of patients limits the accuracy of the algorithms
and prevents from drawing very strong conclusions, given
the spread of the CIs. Then, the use of data from two very
different prospective cohorts results in a varying time
between follow-ups. However, this variance highlights our
model strengths since their performances are similar on
those two very different cohorts. Modelling limitations
can also be pointed out. In particular, for the predic-
tion of the DAS28, we only selected patients for which
the DAS28 6 months after treatment initiation was avail-
able, which resulted in immortal time bias. This bias is
not present in the prediction of the EULAR therapeutic
response however, for which we used an inadequate
response imputation rule. To improve the modelling of
longitudinal data, Recurrent Neural Networks have been explored.

Although this modelling would complicate the
insertion of this algorithm into a clinical environ-
ment, it could also result in a significant improvement.

To envision the use of this algorithm in clinical prac-
tice, we aim to design treatment strategy clinical trials.
They would compare usual care with a decision based on
the prediction of response by the algorithm.

CONCLUSION
In this study, we have demonstrated the ability of
machine learning algorithms to predict response to TNFi
using simple clinical and biological variables. Focusing
on clinical use, we developed a model and assessed its
performances in two scenarios, having a high confidence
in either identifying TNFi responders or identifying TNFi
inadequate responders. Both demonstrated interesting
results compared with the current clinical practice and
these algorithms pave the way to a personalised treat-
ment strategy in RA.

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Contributors SH and PB collected and cleaned the ABIRISK database. VB, JD,
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built the prediction models, analysed the data and prepared all figures. SB and XM
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