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ORIGINAL ARTICLE

Ixekizumab trough concentrations in psoriasis: Paving the way towards personalised therapy: A cohort study

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Abstract

Background: Biologics for psoriasis demonstrate varying clinical outcome in real-world practice, implying potential under- and overexposure.

Objectives: In this prospective cohort study we aimed to develop and validate an in-house sandwich-type enzyme-linked immunosorbent assay (ELISA) for ixekizumab (IXE), and to explore whether there is an exposure-response relationship in standard maintenance dose for IXE, and whether patient factors influence IXE exposure and clinical outcome.

Methods: This was a prospective, multicentric, cohort study in psoriasis patients treated with IXE according to standard dosing regimen (BIOLOPTIM-IXE). IXE trough concentrations (TCs) in sera collected at multiple timepoints were measured using an in-house immunoassay.

Results: Using MA-IXE117E12 and MA-IXE100F5-biotin as the capture and detection antibodies, respectively, an ELISA was developed with an exposure-response curve ranging from 10 to 0.16525 ng/mL. One hundred-fifteen steady-state serum samples from 48 patients (17 [35.4%] bio-experienced; median body weight, 81.5 kg) were measured. Optimal responders (Psoriasis Area and Severity Index [PASI] ≤ 2) had significantly higher TCs than suboptimal responders (PASI > 2) (median TCs, 4.4 and 3.0 μg/mL, respectively; $p = 0.026$). Median cohort IXE TC was 4.1 μg/mL [2.8−6.1]. An optimal steady-state IXE TC of 3.4 μg/mL was identified for clinical outcome defined by absolute PASI. Median TCs and absolute PASI were significantly lower and worse, respectively, in patients ≥ 90 kg ($p < 0.001$ and $p = 0.013$, respectively) and in bio-experienced subjects ($p < 0.001$ and $p = 0.029$, respectively).

Conclusions: This study identified an IXE exposure-response relationship and an optimal effective steady-state TC of 3.4 μg/mL in real-world psoriasis patients, revealing the potential of therapeutic drug monitoring in optimising IXE use.

KEYWORDS
Ixekizumab, psoriasis, therapeutic drug monitoring, trough concentrations

INTRODUCTION

Biologics have revolutionised the treatment landscape of moderate-to-severe psoriasis. Especially with the interleukin (IL)-17 and IL-23 inhibitors, the majority of patients achieve and maintain (almost) complete skin clearance. However, clinical response under standard dosing varies in real-world settings,[1–4] presumably due to either pharmacokinetics (under- and overexposure) and/or pharmacodynamic mechanisms.[5]

Dermatologists already attempt to step away from the *one-dose-fits-all* principle by modifying dosing regimens, predominantly through dose escalation in context of insufficient response. These modifications have mainly been performed empirically, leading to *trial-and-error* in clinical decision-making.[6] As biologics are expensive drugs, their use should be more rational and cost-effective.[7–9]

Therapeutic drug monitoring (TDM) may support treatment modifications in an evidence-based manner. Based on blood drug concentrations, dosing regimens are individualised to maximise clinical efficacy and minimise safety risk.[10] In psoriasis, evidence favoring TDM is rising.[11–15]

Ixekizumab (IXE) is associated with rapid and sustained high response in psoriasis, as reported by both randomised clinical trials (RCTs) and real-world studies.[16–23] So far, investigation of IXE exposure-response relationship is scarce and has been limited to RCT settings. First, a population pharmacokinetics–pharmacodynamics model built on data from a phase 2 dose-finding study suggested that non-responders assigned to lower IXE doses may potentially become responders if given doses with adequate exposures.[24] Next, *Reich* et al. reported that steady-state IXE serum TCs in both induction (Week 12) and maintenance (from Week 24 through 60) were associated with high response rates.[25] Pooled Week 12 data from three phase 3 studies (UNCOVER-1, -2, and -3) showed that higher IXE concentrations were obtained and associated with higher clinical outcome rates with the 80 mg every 2 weeks regimen compared to 80 mg every 4 weeks.[26] Further, in paediatric psoriasis patients weight category-based dosing led to comparable mean IXE serum TCs (3.20–3.33 μg/mL) as in adult psoriasis patients (mean [standard deviation (SD)], 3.48 [2.16] μg/mL), and similar or higher response rates compared to adult patients at Week 12.[27]

In this real-world study we developed and validated an in-house sandwich-type enzyme-linked immunosorbent assay (ELISA) for IXE quantification in serum, explored the IXE exposure–response relationship in psoriasis patients, and evaluated the influence of patient factors on IXE exposure and clinical response.

MATERIAL AND METHODS

Study design and data collection

The BIOLOPTIM-IXE (NCT04083612) is a prospective, multicentric cohort study. Clinical data and blood samples were collected between May 2019 and July 2022 at the Departments of Dermatology of Ghent University Hospital and AZ Delta Torhout, Belgium. This study was approved by the ethics committees of the participating sites and conducted in accordance with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from each patient for participation (B670201940656). The study data were retrieved and managed using the Research Electronic Data Capture (REDCap) system, hosted at the Ghent University Hospital.[28]

Participants and clinical data

Patients ≥ 18 years receiving IXE in standard maintenance dosing regimen (80 mg every 4 weeks) following induction dose (initial dose of 160 mg followed by 80 mg every 2 weeks until Week 12) for the treatment of moderate-to-severe psoriasis were eligible for inclusion. Exclusion criteria were a predominance of a psoriasis type other than psoriasis vulgaris, or treatment with IXE for a disease other than psoriasis.[29] All demographic and clinical data were obtained from the patients' medical record and discussed with the patients during study visits. Blood sampling was planned at fixed timepoints (Week 12, 24, 36, 48, and/or 52), and/or cross-sectionally anytime during maintenance therapy (max. 3 cross-sectional samples). Treatment adherence was actively questioned during study visits. If the IXE injection was administered > ±1 week from the planned injection date, this timepoint was excluded from statistical analysis. Disease activity was assessed at the same day as the blood sampling using absolute Psoriasis Area and Severity Index (PASI) and the percentage of PASI reduction from baseline PASI (ΔPASI). Optimal and suboptimal clinical response were defined as an absolute PASI ≤ 2 or ΔPASI ≥ 90, and absolute PASI > 2 or ΔPASI < 90, respectively.

Blood sampling

Blood samples were retrieved right before the next scheduled drug administration (i.e., at trough) for TC measurement. After an incubation time at room

temperature of maximum 24 h, all blood samples were centrifuged for 15 min at 252*g* at room temperature (Model 5804; Eppendorf). Serum was prepared and stored at −20°C or −80°C until analysis at the Laboratory of Diagnostic and Therapeutic Antibodies, KU Leuven.

Development of IXE ELISA, assay validation and measurement of patient serum samples

A panel of 25 monoclonal antibodies towards IXE was generated, purified, and conjugated to biotin with Sulfo-NHS-LC-biotin (Fisher Scientific) according to the manufacturer's instructions at KU Leuven, as previously described for guselkumab.[30] The monoclonal antibodies were pairwise tested for their suitability as capture and detecting antibody in an ELISA for IXE concentration measurement. After development of the IXE ELISA, the assay limit of detection (LOD) was determined by measuring a panel of 25 IXE-naive patient serum samples, obtained from psoriasis patients just before they initiated IXE treatment. The LOD was based on the mean optical density of a 1/200 dilution of the 25 IXE-naive serum samples plus three times the SD. The limit of quantification (LOQ) was defined as the lowest concentration that could be accurately measured in serum with a coefficient of variation (CV) of ≤20%. The accuracy and imprecision of the assay was determined by preparing five quality control samples in normal human serum (1, 2, 5, 10, and 20 μg/mL IXE) and measuring four repeats on one plate for the intra-assay variability, and one repeat on four different plates for the interassay variability. Acceptance criteria were defined as an accuracy of 80–120% and a CV ≤ 20% for the intra-assay and interassay imprecision.

For measurement of IXE concentrations in quality control and patient serum samples, 96-well plates were coated overnight at 4°C with 100 μL of 4 μg/μL MA-IXE117E12 in a sodium carbonate buffer (pH 9.6). After coating, the plates were blocked with 200 μL PBS containing 1% bovine serum albumin (BSA) for 2 h at room temperature. Four serial dilutions, starting either at a 1/200 or 1/2000, of the patient serum samples were prepared in PTAE buffer (phosphate buffered saline [PBS] with 0.1% BSA, 0.002% Tween 80 and EDTA). One hundred μL of the samples was applied to the blocked plate and incubated for 2 h at room temperature on a plate shaker (300 rpm). Afterwards, the plates were thoroughly washed with wash buffer (PBS with 0.008% Tween 80), and incubated with 100 μL of the biotinylated detecting antibody (MA-IXE100F5-biotin) in PTA buffer (PBS with 0.1% BSA and 0.002% Tween 80) for 2 h at room temperature. After incubation, the plates were again thoroughly washed with wash buffer and incubated with streptavidin poly-horseradish peroxidase (HRP; Sanquin Reagents), followed by developing the plates using 0.4 g/L o-phenylenediamine and 0.003% H_2O_2 in citrate buffer (pH 5.0). After 30 min, the reaction was stopped by adding 50 μL of 4 mol/L H_2SO_4, and the absorbance was measured at 490 nm with an absorbance microplate reader (Model ELx808, BioTek Instruments Inc.) and the IXE concentration-response curve was analysed by nonlinear regression (one-site specific binding, GraphPad Prism).

Statistical analysis

Descriptive statistics were reported as frequencies for categorical and medians with interquartile range (IQR) for continuous variables. Scatterplots, Spearman rank correlations, boxplots, and Mann–Whitney *U* tests were used for exploratory analysis. Receiver operator characteristic analysis and index of union were used to determine an optimal threshold IXE TC at steady-state (i.e., ≥22 weeks of IXE treatment).[31,32] Next, concentration-effect curves were created. All TCs were ranked in ascending order with corresponding absolute PASI and ΔPASI score, and quantile analyses were performed. Per quantile, median TC and median (Δ)PASI were calculated and visualised. All statistical analyses were performed with a 95% confidence interval [CI] and a p Value of 0.05 as threshold for statistical significance. IBM SPSS Statistics version 26 for Windows (IBM) and GraphPad Prism version 9.2.0 for Windows (GraphPad Software) were used for statistics and graph plotting.

RESULTS

Study cohort

As one nonadherent patient was excluded, data of 48 adult psoriasis patients were used for statistical analysis. Briefly, 60% were male subjects and median cohort body weight was 81.5 kg [IQR: 70.0–92.8]. Median disease duration was 20.0 years [11.0–28.0]. Thirty-five percent of the patients had prior biologic experience. Median cohort baseline PASI was 8.1 [4.9–12.1] with no significant difference observed between biologic experienced and biologic naive patients (median 9.1 [6.3–15.6] vs. 8.0 [4.4–11.8]; $p = 0.347$). Demographic and clinical characteristics are summarised in Table 1.

TABLE 1 Baseline demographic and clinical cohort characteristics.

Parameter	Value
Number of patients, n	48
Demographics	
Sex, women, *n* (%)	19 (39.6)
Age, years, median [IQR]	46.5 [36.5–60.0]
Ethnicity, *n* (%)	
Caucasian	47 (97.9)
North-African	1 (2.1)
Weight, kg, median [IQR]; *n*	81.5 [70.0-92.8]; 38
BMI, kg/m^2, median [IQR]; *n*	27.1 [24.3-30.6]; 38
Medical history	
Smoking status, *n* (%)	
Active smoking	16 (33.3)
Past smoking	10 (20.8)
Never smoking	20 (41.7)
Age of onset psoriasis, years, median [IQR]; *n*	24.0 [16.0–33.0]; 47
Psoriasis disease duration, median [IQR]; *n*	20.0 [11.0–28.0]; 47
Baseline PASI, median [IQR]; *n*	8.1 [4.9–12.1]; 43
Drug history	
Number of prior nonbiological therapy, median [IQR]; *n*	2.0 [2.0–3.0]; 48
Prior nonbiological therapy, *n* (%)	
Yes	46 (95.9)
Methotrexate	43 (89.6)
Cyclosporin	38 (79.2)
Retinoids	15 (31.3)
Fumarates	1 (2.1)
Apremilast	5 (10.4)
No	2 (4.2)
Biological experience, *n* (%)	
Naive	31 (64.6)
Experienced	17 (35.4)
Prior biological therapy, *n* (%)	
Adalimumab	10 (20.8)
Etanercept	6 (12.5)
Infliximab	3 (6.3)
Ustekinumab	6 (12.5)
Guselkumab	1 (2.1)
Risankizumab	0 (0.0)
Tildrakizumab	0 (0.0)
Ixekizumab	1 (2.1)
Secukinumab	4 (8.3)
Brodalumab	0 (0.0)
Number of prior biologicals, median [IQR]; *n*	0.0 [0.0–1.0]; 48

Abbreviations: BMI, body mass index; IQR, interquartile range; IMID, immune-mediated inflammatory disorder; PASI, Psoriasis Area and Severity Index; PsA, psoriatic arthritis.

IXE ELISA development and validation

MA-IXE117E12 and MA-IXE100F5-biotin were selected as capture and detecting antibodies, respectively. Using this combination, a nonlinear IXE calibration curve, ranging from 0.15625 to 10 ng/mL, was obtained. Based on the measurement of 25 IXE-naive serum samples, a LOD of 0.07 μg/mL and LOQ of 0.2 μg/mL IXE were determined. The assay complied with the requirements for accuracy, with a mean accuracy of 98% (range 84–116%) and imprecision, with an intra-assay CV of 5% (range 4–8%), and an interassay CV of 10% (range 7–15%) for all quality control samples tested.

IXE trough concentrations (TCs), treatment duration, and clinical response

Of the 48 patients, 115 IXE serum TC samples were collected between Week 22 and 154 of treatment. The median number of samples collected per patient was 3.0 [2.0–3.0; min.–max.: 1.0–6.0]. Median cohort steady-state IXE TC was 4.1 μg/mL [2.8–6.1].

The IXE TCs and clinical response remained stable throughout follow-up ($\rho = -0.074$, $p = 0.432$, Figure 1a; $\rho = 0.185$, $p = 0.651$, Figure 1b, respectively). Next, IXE TC was significantly correlated with absolute PASI ($\rho = -0.232$, $p = 0.013$, Figure 1c), but not with ΔPASI ($\rho = 0.163$, $p = 0.093$, data not shown). Noteworthy, Figure 1c could elucidate two extreme subgroup of patients: optimal responders with low IXE TCs (dots within blue rectangle), and suboptimal responders with high IXE TCs (dots within red oval).

Additionally, a significant difference in IXE TCs between optimal and suboptimal response (absolute PASI) was observed, with a median TC of 4.4 μg/mL [2.9–6.3] and 3.0 μg/mL [2.4–4.4], respectively

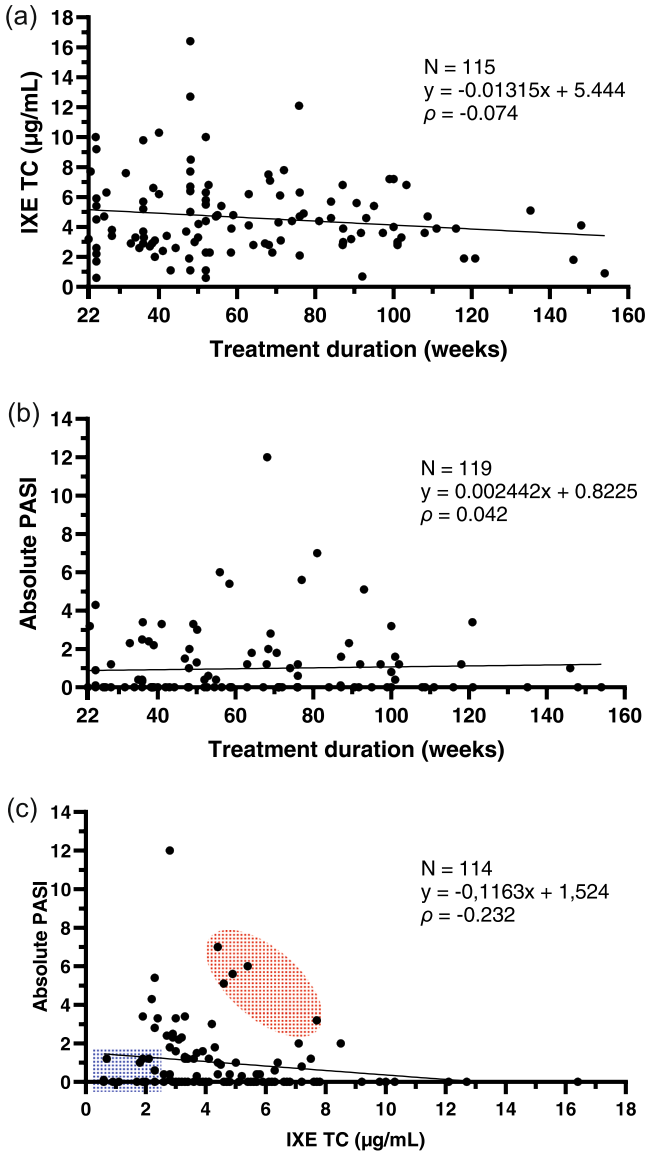

FIGURE 1 Treatment duration, IXE TCs, and clinical response at steady-state. (a) Treatment duration (weeks) and IXE TCs (µg/mL): IXE TCs remained stable at steady-state treatment ($\rho = -0.074$, $p = 0.432$); (b) Treatment duration and clinical response (absolute PASI): clinical response remained stable at steady-state phase ($\rho = 0.042$, $p = 0.651$); (c) IXE TCs and clinical response (absolute PASI): higher IXE TC was associated with lower absolute PASI ($\rho = -0.232$, $p = 0.013$). The dots within the blue rectangle represent patients with optimal response and low IXE TCs; the dots within the red oval represent patients with suboptimal response and high TCs. No correction for multiple testing was performed. ρ, Spearman rank correlation; IXE, ixekizumab; *N*, number of data pairs; PASI, Psoriasis Area and Severity Index; TC, trough concentration; y, linear regression equation.

($p = 0.026$, Figure 2). Despite higher TCs in patients demonstrating ΔPASI ≥ 90, no significant difference was found between optimal ($n = 74$, median TC = 4.7 µg/mL [3.0–6.2]) and suboptimal ($n = 33$, median TC = 3.7 µg/mL [2.8–5.2]) response in terms of ΔPASI ($p = 0.185$).

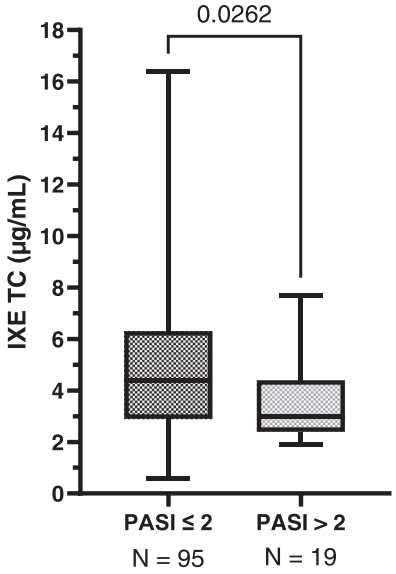

FIGURE 2 IXE steady-state TCs between optimal and suboptimal response. TCs were compared between patients showing optimal (PASI ≤ 2) and suboptimal (PASI > 2,) response ($p = 0.026$). Median TCs of optimal and suboptimal response were 4.4 µg/mL [2.9-6.3] and 3.0 µg/mL [2.4-4.4], respectively. No correction for multiple testing was performed. IXE, ixekizumab; N, number of data pairs; PASI, Psoriasis Area and Severity Index; TC, trough concentration.

Defining an IXE TC associated with optimal response

We found an optimal steady-state IXE TC of 3.4 µg/mL with an area under the curve (AUC) of 0.66 (95% CI = 0.55–0.78, $p = 0.027$), sensitivity of 68.4% (95% CI 46.0–84.6), specificity of 67.4% (95% CI 57.4–76.0), positive and negative predictive value of 91.3% (95% CI 81.6–96.4) and 30.0% (95% CI 17.4–46.0) for clinical response defined by absolute PASI (Figure 3).[31] For clinical outcome defined by ΔPASI, we were not able to identify a statistically significant optimal steady-state TC (AUC = 0.58, 95% CI = 0.47–0.69, $p = 0.184$). The quantile concentration-effect curves for both absolute and ΔPASI depicted horizontal curves without any significant trend (Supporting Information S1: Figure 1a-b).

Patient factors and IXE TCs

Steady-state TCs did not differ between women (3.9 µg/mL [2.8–6.2]) and men (4.5 µg/mL [2.9–6.0]) ($p = 0.788$). Also, age was not correlated with IXE TC ($\rho = -0.014$, $p = 0.884$). On the other hand, baseline PASI was negatively correlated with IXE TCs ($\rho = -0.301$; $p = 0.002$). Next, weight and body mass index (BMI) were also negatively correlated with IXE

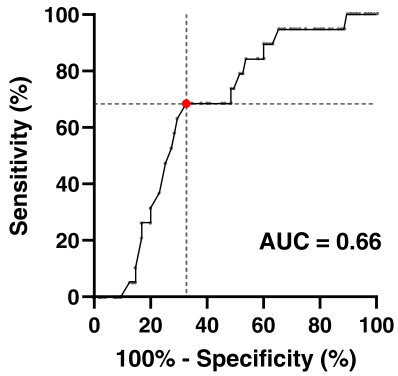

FIGURE 3 ROC analysis of IXE TC to differentiate optimal (PASI ≤ 2) from suboptimal response (PASI > 2). An optimal cut-off point was selected by using the index of union. The minimal effective TC was set at 3.4 μg/mL (red dot). The area under the ROC curve was 0.66 (95% CI 0.55–0.78). No correction for multiple testing was performed. AUC, area under the curve; CI, confidence interval; IXE, ixekizumab; PASI, Psoriasis Area and Severity Index; ROC, receiver operator characteristic; TC, trough concentration.

TC ($\rho = -0.369$, $p < 0.001$ and $\rho = -0.358$, $p = 0.001$, respectively; Figure 4a,b). Correspondingly, IXE TC was significantly lower in patients weighing ≥ 90 kg (3.0 μg/mL [2.3–4.4]) than in those weighing < 90 kg (4.8 μg/mL [3.3–6.3]) ($p < 0.001$, Figure 4c). Active smokers showed significantly lower TCs (3.1 [2.3–4.7] μg/mL) than nonsmokers (4.3 μg/mL [3.1–6.6]) ($p = 0.006$, Figure 4d). Lastly, significantly lower TCs were observed in biologic-experienced patients (3.0 μg/mL [2.1–4.6]) versus biologic-naive patients (4.7 μg/mL [3.4–6.3]) ($p < 0.001$, Figure 4e).

Patient factors and clinical response

Weight ≥ 90 kg and prior biological treatment were also associated with worse clinical response (absolute PASI) ($p = 0.013$ and $p = 0.029$, respectively, Supporting Information S1: Figure 2a-b). Clinical response did not differ between active and nonsmoking patients

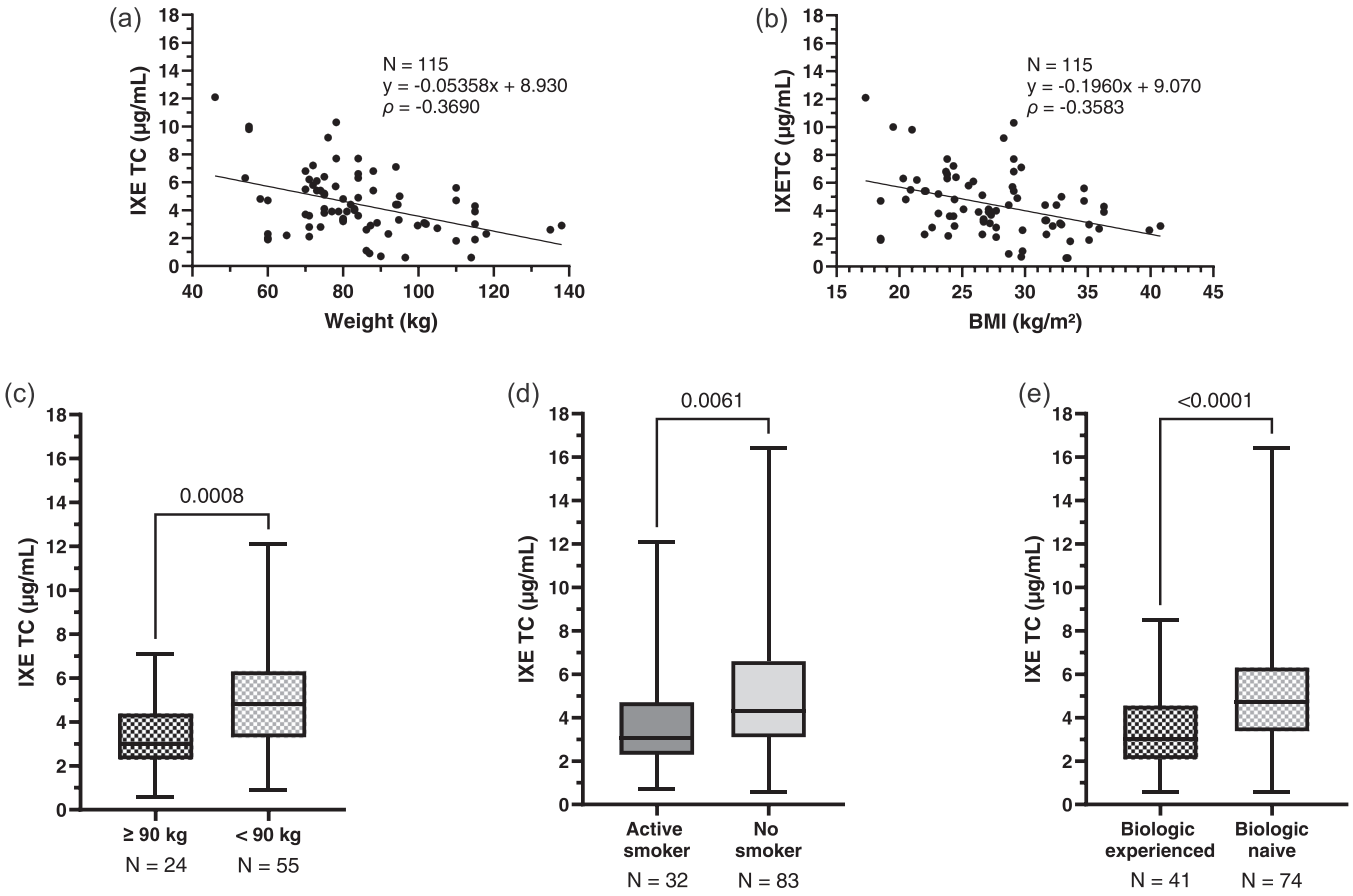

FIGURE 4 IXE steady-state serum TCs and patient characteristics. (a) Weight (kg) and TCs (μg/mL) ($\rho = -0.369$, $p < 0.001$); (b) BMI (kg/m²) and TCs ($\rho = -0.358$, $p = 0.001$); TCs were compared between (c) patients weighing ≥ 90 kg versus < 90 kg ($p < 0.001$); (d) active smokers versus nonsmokers ($p = 0.006$); and (e) biologic experienced versus biologic naive patients ($p < 0.001$). No correction for multiple testing was performed. ρ, Spearman rank correlation; BMI, body mass index; IXE, ixekizumab; *N*, number of data pairs; TC, trough concentration; y, linear regression equation.

($p = 0.259$) and was not correlated with baseline PASI ($\rho = 0.010$; $p = 0.922$).

DISCUSSION

This is the first study reporting on the exposure-response relationship of IXE in psoriasis in a real-world setting. The observed median IXE TC of 4.1 μg/mL is higher compared to the TC medians in clinical trial context reported by *Reich* et al., which were ranging 3.03−3.31 μg/mL at different timepoints.[25] The use of other ELISA methods (in-house assay, Leuven, Belgium, vs. Intertek Pharmaceutical Science) might have contributed to this difference in median TCs.

Here, optimal response (PASI ≤ 2) was obtained with standard IXE dosing in 83.3% of patients, exhibiting high effectiveness of IXE. Nonetheless, we were able to define an optimal IXE TC target of 3.4 μg/mL with a positive and negative predictive value of 91.3% and 30.0%, respectively. Accordingly, 70.0% of the patients with TCs < 3.4 μg/mL already showed an optimal response. Still, if a target of 3.4 μg/mL would be used (e.g., by means of TDM), the chance of having optimal response to IXE could be raised to more than 90%. On the one hand, dose escalation of suboptimal responders with subtherapeutic levels is a valuable strategy. On the other hand, patients with optimal response and supratherapeutic IXE TCs (in our cohort 57% of the samples) could be eligible candidates for controlled dose tapering.

Despite the great variability among the observed IXE TCs, our cohort demonstrated a significant—still rather weak—exposure-response relation, which is comparable with the exposure-response relationships found for adalimumab and secukinumab.[11,33] Therefore, IXE's pharmacodynamic mechanisms might play a significant role in clinical response as well. As illustrated in Figure 1c, the cohort withheld two subgroups: few patients showed an excellent response regardless of low TCs, and others demonstrated worse response despite high TCs. Consequently, IXE's pharmacokinetic and pharmacodynamic contribution to clinical outcome might be individually dependent, the latter potentially determined by the patient's underlying molecular signature. Regardless, IXE dose escalation would presumably not lead to better clinical outcome in the supratherapeutic patients.

Weight ≥ 90 kg was significantly associated with lower TCs and worse—still excellent—treatment outcome. Though, these results suggest that a weight-based dosing regimen for IXE could be debated, especially since overweight is very common in psoriasis and is known to be associated with worse treatment response.[34–37] Coherently, weight-based prescription of biologics is not novel in Pso. First, ustekinumab and tildrakizumab are prescribed according to a standard weight-based dosing regimen (45 mg and 90 mg for ustekinumab and 100 and 200 mg for tildrakizumab for patients < 90 kg and ≥90 kg, respectively). Additionally, psoriasis patients weighing ≥ 90 kg showed higher and sustained efficacy with 300 mg of secukinumab every 2 weeks compared with 300 mg every 4 weeks.[38] Lastly, exposure–efficacy modelling in the IXORA-PEDS trial also supported weight category-based IXE dosing regimens in paediatric patients.[27]

Also biologic experience was significantly associated with lower TCs and higher absolute PASI. Since other real-world studies suggest that prior biologic experience impacts both biologic survival and effectiveness,[2,3,39–42] prescribing the right biologic at first and using it as long as possible at its maximal capacity should be encouraged. Hasty switch to another biologic is tempting but potentially unnecessary, and could be avoided by means of TDM in those responding to dose escalation.

Despite the cohort's small size and predominance of optimal responders, we could identify an exposure-response relationship for IXE and elucidate an optimal TC to discriminate optimal from suboptimal response. Still, validation of our findings in larger cohorts is awaited. Further, we focused on steady-state TCs. Still, prediction of clinical outcome based on TCs earlier during treatment (<22 weeks) would be relevant as well for evaluation. Next, an in-house assay was developed and used for this study as no commercial assay was available at time of the study, which now might hamper clinical utility and transfer from and to other facilities. However, as more research has approved the value of blood concentrations of biologics, interest for the development of commercial assays has followed during the past years. Pre-implementation planning including validation of TCs and proposed targets needs to be carried out if other (local) assays are employed. This strategy has already been carried out successfully by *Raharja* et al. in a real-world TDM study with adalimumab.[43]

Nevertheless, the proposed optimal effective IXE TC may already be useful in clinical practice to guide IXE treatment alterations (no change, dose changes, and drug switch), and corroborates the potential utility of a TDM algorithm—as already proposed by our group.[39] Suboptimal responders with IXE TCs < 3.4 μg/mL may be undertreated and benefit from dose escalation. Next, in patients with suboptimal response and high IXE TCs, dose escalation should not be attempted whilst switch to another biologic

would be the most rational action. Importantly, besides improving clinical response to biologics, overtreatment with biologics should also be tackled as well to reduce its high burden on healthcare expenditures. Therefore, controlled dose de-escalation in optimal responders with high IXE TCs should be of consideration. Such TDM algorithm needs to be confirmed in a prospective patient cohort. Noteworthy, as psoriasis' nature is complex, clinical response is presumably influenced by more factors than biologics' pharmacokinetics alone, including pharmacodynamics, patient and clinical factors, genomics and so forth. predicting an subsequent evolution from TDM to model informed precision dosing (MIPD). With MIPD, timely dose (or treatment) adjustment could be carried out in each individual based on his/her multifactorial profile.[44]

AUTHOR CONTRIBUTIONS

Study visits and blood sampling were carried out by Lisa Schots, Rani Soenen, Eylenbosch Anke, and Annelies Stockman. Assay development and validation and blood sample analysis were performed by Debby Thomas. Statistical analysis was carried out by Lisa Schots with guidance of Erwin Dreesen and Rani Soenen. The manuscript was drafted by Lisa Schots, with critical revision of Jo Lambert, Rani Soenen, Erwin Dreesen, Debby Thomas, and Annelies Stockman.

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CONFLICTS OF INTEREST STATEMENT

J. L. received unrestricted grants from AbbVie, Almirall, Celgene, Eli Lilly, Janssen-Cilag, LEO Pharma, Novartis, UCB; served as a speaker for AbbVie, Almirall, Bristol-Myers Squibb, Janssen-Cilag, Pfizer, UCB; served as a consultant for AbbVie, argenx, Bristol-Myers Squibb, Celgene, Celltrion, Eli Lilly, Janssen-Cilag, LEO Pharma, Novartis, UCB. All fees and grants are paid to Ghent University (Hospital) scientific accounts, and not to any personal account of J. L. L. S. has received paid speaker fees by AbbVie, Novartis and Janssen. All fees were paid to the Ghent University (Hospital) scientific accounts. A. S. has received speaker fees by Abbvie, Eli Lilly and UCB and served as a consultant for Novartis, Abbvie, LEO Pharma, UCB and Bristol-Myers Squibb. E. D. received consultancy fees from Alimentiv and argenx, lecture fees from Galapagos, and financial support from Janssen, R-Biopharm, and Prometheus [all honoraria/fees are paid to KU Leuven]. K. U. Leuven holds a license agreement with apDia and R-Biopharm. The remainig authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

All patients in this manuscript have given written informed consent for participation in the study and the use of their deidentified, anonymized, aggregated data and their case details for publication. This study was approved by the ethics committees of the participating sites (B670201940656).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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