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Dermatologists on the Medical Need for Therapeutic Drug Monitoring of Biologics in Psoriasis: Results of a Structured Survey

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Abstract

Background: Therapeutic drug monitoring (TDM) may lead to more rational use of biologics. Still, TDM is largely underexplored in psoriasis. Little is known about the dosing behavior of biologics by dermatologists, and their attitude towards TDM.

Objective: Exploration of the awareness and need for the concept of TDM in psoriasis amongst (inter)national dermatologists.

Method: A survey was distributed at the Belgian Dermatology Days 2019 and Skin Inflammation & Psoriasis International Network (SPIN) Congress 2019. Next, an online survey version was launched amongst the SPIN Scientific Committee members. We collected physician's characteristics, prescription behavior of biologics, data regarding clinical response to biologics and attitude towards TDM.

Results: A total of 107 surveys were included for analysis. Most dermatologists were Belgium-based (54.2%), others from European (23.4%) or non-European countries (19.6%). Seventy percent performed either dose increase (64.8%), time interval shortening (74.6%), dose lowering (16.9%) or time interval extension (33.8%). The majority who performed dose adaptations acknowledged the need for TDM.

Conclusion: This study showed most dermatologists perform dose adaptations empirically. The need for TDM was indicated by the majority, implying the need for effective communication regarding availability, utility and implementation of TDM assays in daily dermatology practice.

Keywords: biologics, drug concentration, psoriasis, questionnaire, therapeutic drug monitoring

Introduction

Biologics have revolutionized the treatment of chronic immune mediated inflammatory diseases (IMID), including inflammatory bowel disease (IBD), rheumatoid arthritis (RA), and psoriasis. They are prescribed when non-biological systemic treatments fail, and therefore mainly used as 'last resort' [1-4]. Though being the most effective treatment option for moderate-to-severe IMID cases, real world data has shown some issues. First, biologics are expensive and pose a heavy burden on the healthcare budget [5-7]. In addition, real life evidence demonstrates that drug survival is rather low, in most cases due to efficacy issues, i.e. primary and secondary non-response [8-16]. Primary non-response (PNR) is the inability to respond to therapy in the induction phase whereas secondary non-response (SNR) can be defined as loss of response after initial clinical benefit. Lastly, biologics are currently prescribed according to a fixed standard dosing regimen, also referred to as a 'one size fits all' regimen; with the exception of ustekinumab, which has a weight-based dosing scheme of 45 mg for less than 100 kg and 90 mg for 100 kg and more.

Previous research has demonstrated clinical response is related to (trough) drug concentration [17,18]. Given these exposure-response studies, we propose that good responders might be overtreated, putting them at higher risk for side effects while contributing to unnecessary costs [19,20]. Here, dose de-escalation might be suitable in order to achieve a minimal effective dose. On the other hand patients with PNR or SNR may be undertreated, and might benefit from dose intensification or switch to another biologic.

To counter these biologic-related issues, therapeutic drug monitoring (TDM) might be the key [17]. TDM is the clinical practice of measuring drug blood concentrations in order to optimize

clinical response and minimize drug related side effects. The TDM concept will introduce a first step towards evidence-based and personalized employment of biologics.

In psoriasis, evidence in favor of TDM is growing. Infliximab trough levels were positively correlated with clinical response and lower in presence of anti-infliximab antibodies in psoriasis patients [21-23]. For adalimumab, we defined a window-based on trough concentration (C_{trough}) from 3.51 to 7.00 µg/mL corresponding to optimal therapeutic effect [18]. This window has been confirmed by the Psoriasis Stratification to Optimize Relevant Therapy (PSORT) consortium [24]. Multiple studies showed a correlation between adalimumab (early) C_{trough} and (late) clinical response [24-26]. For secukinumab, our group found a minimal effective C_{trough} of 33.2 µm/mL in a pilot study [27]. With respect to ustekinumab, no consensus has been reached yet given the conflicting results [28-31]. Similar mixed observations are seen for etanercept [25,32,33]. Few data are available suggesting an exposure-response association of ixekizumab [34-36], guselkumab [37], risankizumab [38] and tildrakizumab [39] in psoriasis. For brodalumab and certolizumab pegol such data is, to our knowledge, lacking.

In IBD, TDM has evolved into the new standard of care as it emerged as a valuable tool to guide clinical decision making and individualizing dosing of biologics [40-49]. However, the development of a practical TDM-based algorithm for the optimization and tailoring of biologics is lagging behind in psoriasis. While TDM studies in psoriasis arose over the recent years, little is known about the current behavior of practicing dermatologists when encountering undesired clinical responses to biologics, and their attitude towards the use of TDM. The aim of this study is to explore the experiences of dermatologists with biologics related to TDM in order to underline the incentive for pharmaceutical industry and government instances to consider TDM in dermatology.

Materials and methods

Study design

To determine the fields of interest and content of the survey questions, we first collected literature on TDM in different disease areas. Based on this, we determined areas of interest for our survey that we consider as major obstacles that impact TDM implementation. We were interested in 3 specific areas: non-response experiences, willingness to adapt doses, and TDM accessibility. The first two areas were straightforward and questions were designed as such. TDM accessibility was more complex and was divided into 4 subcategories: familiarity, engagement, threshold to use (financially), and availability of assays. The questionnaire was first tested internally by completing it with random answers in order to detect flaws (i.e. incompatible answers). The resulting questionnaire included 14 questions. To distribute the survey, we selected one national and one international dermatology congress that cover scientific themes: the Belgian Dermatology Days (BDD) (February 2019, Brussels, Belgium), and the Skin Inflammation and Psoriasis International Network (SPIN) Congress (April 2019, Paris, France). The BDD is the annual Belgian dermatology congress hosted by the Royal Belgian Society of Dermatology. The SPIN is an international network of professionals and patients with specific interest in chronic inflammatory skin diseases. Next, the questionnaire was also emailed to the members of the SPIN Scientific Committee, a panel of international expert-dermatologists, to complete via an online application (SurveyMonkey) with a completion period from June until end of July 2019.

Next, the survey was distributed at the BDD 2019. Based on the response rate and first results, we expanded some response categories. This version was handed out at the SPIN Congress 2019, and throughout the SPIN Science Committee.

Respondents from the BDD 2019 and SPIN Congress 2019 were considered to have standard experience with the use of biologics, and are referred to as ‘Dermatologists’ (D). The

members of the Scientific Committee of SPIN were regarded as biologics experts, since most of them are involved in clinical trials of biologics and affiliated to academic dermatology practices, and hence referred to 'Expert Dermatologists' (ED). Ethical committee approval was not obtained as this study was of negligible risk since we did not collect any personal data. The study was conducted in accordance with the ethical principles of the Helsinki Declaration.

Statistical analysis

All collected responses were categorical variables, and expressed as frequencies and percentages. Descriptive statistics and where applicable crosstabs, Chi-square or Fisher's exact tests were performed, and odds ratio (OR) with confidence interval (CI) was calculated by IBM SPSS Statistics 26 (IBM Statistics, Costa Mesa, California) and GraphPad Prism version 8.4.3 for Windows (GraphPad Software, San Diego, California). GraphPad Prism was used for graphics design.

Results

Study cohort characteristics (Table 1)

The Dermatologists (D; being BDD 2019 and SPIN Congress 2019 attendees) filled in the written survey form, whereas the Expert Dermatologists (ED; SPIN Scientific Committee) completed the online form. At the BDD 2019, 775 attendees were present, among them 70 filled in the survey (completion rate = 9%). Three-hundred individuals attended the SPIN Congress 2019, and we received 27 survey responses resulting in a completion rate of 9%. There are 43 SPIN Scientific Committee members, of which 25 completed the survey (completion rate = 58%). A total of 122 respondents participated in the study. Only respondents who practiced dermatology, i.e. dermatologists (n=102) and residents in dermatology (n=14), were included for analysis. A small number of the respondents (7.8%)

had never prescribed a biologic, and therefore were also excluded from analysis. Response analysis was executed within the remaining 107 participants. Overall, the BDD attendees represented the biggest respondent group (53.3%), before SPIN attendees (24.3%) and SPIN Scientific Committee members (22.4%). Seventy-two (67.3%) of the 107 included surveys were fully completed. Question completion rate was lowest by the BDD attendees (**Supplementary tables 1 and 2**).

Most respondents were Belgium-based (54.2%), and from other European countries (23.4%). Additionally, non-European participants filled in the survey (9.3% North America, 4.7% South America, 1.9% Africa, 3.7% Asia). A few participants (2.8%) did not report their nationality. Half of all respondents had more than 20 years of clinical experience. The ED had at least 10 years of experience; approximately 80% had more than 20 years of experience. In contrast, the D group included less experienced clinicians (33.0% with at most 10 years of experience), and 41.5% had more than 20 years of experience. The survey results confirmed our respondent allocation to either the D or ED group based on our assumption that the SPIN Scientific Committee members were more experienced in the use of biologics, and therefore appointed as ED. ED had longer practice duration ($p = 0.001$), and prescribed biologics more frequently (83.3% of ED prescribed weekly to daily; 66.3% of D prescribed monthly to weekly) ($p < 0.001$). Moreover, all of the ED worked at least in an academic center, of which 41.7% in combination with a private practice or general hospital. Most D worked in an academic hospital (40.9%), of which one-fifth in combination with practicing privately or in a general hospital, or in a private practice exclusively (30.1%) ($p = 0.001$). The prescription behavior of biologics is displayed in **Figure 1**. The majority of the survey respondents (63.4%) prescribed biologics on a monthly to weekly basis.

Observation of unfavorable therapy outcomes and current management in daily practice

The vast majority (86.3%) of all clinicians confirmed loss of response or non-response to biologics in daily practice (**Fig. 2A**). These were mostly observed in one out of five to ten patients by the ED, and in one out of ten patients by the D group (**Fig. 2B**). A similar observation pattern is seen amongst clinicians with more than 20 years of clinical experience *versus* clinicians with at most 20 years of clinical experience (**Fig. 2C**).

Figure 3 illustrates the clinician's dose adaptation behavior. Up to 30% of all respondents had never changed the dose of a given biologic, 96.6% of these belonged to the D group (**Fig. 3A**). The remaining 71% of the respondents already performed either dose increase (64.8%), time interval shortening (74.6%), dose reduction (16.9%) or time interval extension (33.8%) (**Fig. 3B**). The D group was less likely to perform dose adaptations compared to ED (63.6% and 95.7% respectively) (p = 0.003; OR = 12.57 (95% CI: 1.95-134.70)) (**Fig. 3C**). When looking more in detail, both ED and D mainly changed dose in terms of time interval shortening, then dose increase, time interval lengthening, and lastly dose reduction (**Table 2, Fig. 3D**). In other terms, dose intensification was performed most by both ED and D (100% and 93.9% respectively), while dose de-escalation was used less frequently (36.4% and 34.7% respectively). Similar results are observed when comparing dose adaptation behavior of clinicians with more than and at most 20 years of clinical experience. Dose changes were more prevalent in the more experienced group (83.7%) compared to the less experienced group (60.0%) (p = 0.01; OR = 3.42 (95% CI: 1.31-8.78)) (**Fig. 3E)**. Upon closer look both groups mainly changed dose in terms of time interval shortening, then dose increase, time interval lengthening, and lastly dose reduction **(Table 3, Fig. 3F)**. Again, dose intensification was used most by both groups (95.1% and 96.7%; respectively) compared to dose de-escalation (41.5% and 26.7%; respectively). Almost 80% of the study respondents who

observed loss of response or non-response performed dose adaptations (p = 0.001) (**Supplementary fig. 1**).

Familiarity, engagement, costs and accessibility of TDM

Approximately 95% was familiar with the concept or knew what TDM entails, whereas about. 70% of the total study cohort acknowledged the need for TDM (**Fig. 4A-B**). More than 70% of the respondents who performed dose adaptations of biologics confirmed the need for TDM, though not significant (p = 0.37)(**Fig. 4C**). The majority was interested in a TDM workshop (84.0%) (**Fig. 4D**). Approximately one-quarter of the respondents assumed TDM costs between 21 EUR and 50 EUR per sample, and almost half anticipated more than 50 EUR per sample (**Fig. 5A**). Approximately half of the respondents believed personalized medicine will not be more expensive compared to usual care (**Fig. 5B**). Fifty percent of the ED indicated TDM-assays are available in laboratories within their practice environment (**Fig. 5C)**[1].

Discussion

TDM has been a valuable tool in the use of anti-TNFα therapy among IBD patients and hence increasingly becoming part of standard care in IBD [43-50]. Multiple studies suggest the presence of a response-concentration association in psoriasis as well [18,24-27], though still more research needs to be executed to confirm the true value of TDM in the management of biologics. For example, we are currently conducting randomized controlled trials, where we aim to 1) define therapeutic windows based on C_{trough} levels of the newer biologics (BIOLOPTIM: NCT04080635, NCT04080648, NCT04083612, NCT04080661), and 2) attempt to lower the dose of biologics based on clinical assessment (BeNeBio, in collaboration with RadBoud University Medical Center Nijmegen: NCT04340076). However, little is known about the current behavior of practicing dermatologists when encountering

[1] The latter question was only incorporated in the survey completed by the ED.

unfavorable clinical responses to biologics in psoriasis, and their attitude towards the use of TDM.

According to our results, loss of response or non-response is frequently observed in dermatology practices, which corresponds with the reported previously efficacy issues and rather low drug survival data [8-11,16]. Improvement of treatment efficacy (biologics included) is an unmet need reported by dermatologists [51]. Our results suggest dermatologists already optimize treatment response to biologics by performing empirical off-label dose changes. The majority tries to overcome unfavorable outcomes by performing dose intensification by either time interval shortening or dose increase. Phung et al. provided the scientific value for this behavior by showing that the off-label dose escalation of secukinumab resulted in improved treatment efficacy in patients who failed to respond adequately to standard regimen [52,53]. However, some patients do not benefit clinically after dose escalation; here, TDM might act as a helpful tool to avoid dose escalation in patients who are unlikely to respond due to immunogenicity (development of anti-drug antibodies), or mechanistic failure [54].

Dose de-escalation on the other hand appears to be applied less frequently in our study cohort, despite its benefits such as reduced costs and decreased risk of side effects. This observation might be explained by the fact that physicians may be hesitant to lower dose, risking to lose efficacy, and subsequently having to deal with dissatisfied patients. The results of a systematic review in rheumatology propose that full withdrawal of biological therapy in early and established RA, PsA, and axial spondyloarthritis is risky in terms of disease flares. However, controlled dose tapering in patients with established disease might be valuable [55]. Next, Bouman et al. demonstrated that long-term disease outcome (and safety) in RA patients treated with TNFα-blockers maintained in both the dose reduction and usual care group [56]. In conclusion, dose tapering may be beneficial, but only if done rationally - not blindly or by

'trial-and-error' – to avoid disease flares. Therefore, TDM might be the right tool for controlled dose tapering through identifying the minimal effective dose for every individual.

Though TDM is yet to be implemented in dermatology, most of our respondents were familiar with the concept, demonstrating its popularity. Implementation barriers remain to be identified, though according to a survey among gastroenterologists, lack of general knowledge, and on how to interpret and employ TDM results are considered to be two major barriers regarding the use of TDM. Uncertainty about insurance coverage, high out-of-pocket patient costs, and time lag from serum sample to result are identified as important barriers as well [57]. Similar barriers are likely to be encountered in dermatology. Since these TDM-related barriers are already identified in IBD, we should consider these and tackle them in advance before we encourage to use TDM assays, in order to facilitate the implementation of TDM in common dermatology practice.

Next, we found that dermatologists generally acknowledge the need for TDM, though many assumed TDM to be rather costly. In accordance with the gastroenterology survey, we report general worries related to costs, which may represent a major barrier [57]. In addition, we report that opinions on the cost of personalized medicine varied: this in itself requires in-depth exploration since biologics already represent a costly drug category. Therefore, early negotiations about TDM reimbursement through a transparent dialogue between academics, healthcare professionals, pharmaceutical industry, and regulatory and health technology agencies is primordial in order to enable access to TDM, and eventually render biologics more cost-effective.

Limitations of this study include small sample size, including incomplete surveys. It needs to be pointed out that we used paper survey versions at the conferences during a limited time slot focused on psoriasis and biologics – reaching thus those dermatologists with a specific interest in psoriasis -, and therefore could not reach all attendees. Still, efforts have been made

in order to minimize data ascertainment: 1) the paper survey versions at the conferences were handed out at the entrances of the psoriasis and biologics specific sessions, and collected at the exits afterwards (i.e. consecutive sampling), and; 2) the online survey was distributed amongst the SPIN Scientific Committee members per e-mail, and all members were invited to complete the survey. Since the written survey was handed out during these biologics specific workshops, and participants of the SPIN 2019 and members of the SPIN Scientific Committee might also have preference for and are more experience in managing IMID such as psoriasis, there is a potential selection bias toward dermatologists with an interest in TDM. Therefore, reported results might be overestimated. Other limitations are lack of defining 'non-response' or 'loss of response' before survey completion, and not asking prior participation in order to prevent duplicate responses.

A strength of this study is the inclusion of dermatologists from different practice settings and varying clinical experience. In addition, to our knowledge this study is a first exploration of the use of biologics by practicing dermatologists, while gauging to the opinion towards TDM. We inquired about experiences in psoriasis, but extrapolation to other immune-mediated skin disorders such as atopic dermatitis is possible.

More research about the pharmacokinetics and pharmacodynamics of biologics in the context of treatment response is warranted to further explore the value of TDM of the newer biologics in psoriasis. Given all of our study results, we encourage clinical TDM experts and pharmaceutical industry to join forces in order to enhance accessibility in terms of training sessions, to increase availability of validated assays and skilled labs, and to facilitate the development of easier sampling techniques (eg. microsampling) and point of care assays [58]. Finally, decision algorithms on how to interpret tests results and how to act accordingly have to be developed to guide clinicians and patients to the most optimal dose.

In conclusion, this survey study shows that non-response and loss of response to biologics in psoriasis are real world issues, and already being counteracted by dermatologists through empirical dose adaptations. More importantly, dermatologists acknowledge the need for TDM, implying they are ready for a more rational and evidence-based, but also a personalized use of biologics.

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Disclosures of interest

The authors report no conflict of interest.

References

1. Kerdel F, Zaiac M. An evolution in switching therapy for psoriasis patients who fail to meet treatment goals. Dermatol Ther. 2015;28(6):390–403.
2. Alfonso-Cristancho R, Armstrong N, Arjunji R, et al. Comparative effectiveness of biologics for the management of rheumatoid arthritis: systematic review and network meta-analysis. Clin Rheumatol. 2017;36(1):25–34.
3. Lichtenstein GR, Loftus EV, Isaacs KL, et al. ACG Clinical Guideline: Management of Crohn's Disease in Adults. Am J Gastroenterol. 2018;113(4):481–517.
4. Kornbluth A, Sachar D. Ulcerative Colitis Practice Guidelines in Adults: American College of Gastroenterology, Practice Parameters Committee. Am J Gastroenterol. 2010;105(3):501–523.

5. Kuek A, Hazleman BL, Östör AJK. Immune- mediated inflammatory diseases (IMIDs) and biologic therapy: a medical revolution. Postgrad Med J. 2007;83(978):251–260.
6. Cheng J, Feldman SR. The cost of biologics for psoriasis is increasing. Drugs Context. 2014;3:212266.
7. Wu JJ, Feldman SR, Rastogi S, et al. Comparison of the cost-effectiveness of biologic drugs used for moderate-to-severe psoriasis treatment in the United States. J Dermatol Treat. 2018;29(8):769–774.
8. Lin PT, Wang H, Chi CC. Drug survival of biologics in treating psoriasis: a meta-analysis of real-world evidence. Sci Rep. 2018;30;8(1):1–7.
9. Menter A, Papp KA, Gooderham M, et al. Drug survival of biologic therapy in a large, disease-based registry of patients with psoriasis: results from the Psoriasis Longitudinal Assessment and Registry (PSOLAR). J Eur Acad Dermatol Venereol. 2016;30(7):1148–1158.
10. Arnold T, Schaarschmidt ML, Herr R, et al. Drug survival rates and reasons for drug discontinuation in psoriasis. J Dtsch Dermatol Ges J Ger Soc Dermatol. 2016;14(11):1089-1099.
11. Gniadecki R, Bang B, Bryld LE, et al. Comparison of long-term drug survival and safety of biologic agents in patients with psoriasis vulgaris. Br J Dermatol. 2015;172(1):244–252.
12. Lirhus SS, Lie Høivik M, Moum B, Melberg HO. P221 Drug survival of biologics in ulcerative colitis treatment in Norway. J Crohns Colitis 2019;13:S206.
13. Gisbert JP, Arredondo M, Chaparro M et al. P508 Drug survival and reasons for discontinuation of anti-TNF therapy in inflammatory bowel disease (IBD) in clinical practice. J Crohns Colitis 2014;8:S279.

14. Emery P, Vlahos B, Szczypa P, et al. Long-term drug survival of tumor necrosis factor inhibitors in patients with rheumatoid arthritis. J Rheumatol. 2019;181398.
15. Brodszky V, Bíró A, Szekanecz Z, et al. Determinants of biological drug survival in rheumatoid arthritis: evidence from a Hungarian rheumatology center over 8 years of retrospective data. Clin Outcomes Res. 2017;9:139–147.
16. Kishimoto M, Komine M, Kamiya K, et al. Drug survival of biologic agents for psoriatic patients in a real-world setting in Japan. J Dermatol. 2020;47:33–40.
17. Papamichael K, Vogelzang EH, Lambert J, et al. Therapeutic drug monitoring with biologic agents in immune mediated inflammatory diseases. Expert Rev Clin Immunol. 2019;15(8):837–848.
18. Menting SP, Coussens E, Pouw MF, et al. Developing a Therapeutic Range of Adalimumab Serum Concentrations in Management of Psoriasis: A Step Toward Personalized Treatment. JAMA Dermatol. 2015;151(6):616–622.
19. Perry M. SAT0194 Significant overtreatment with biological drugs is common in routine care for patients where serum drug levels are monitored. Scientific Abstracts, Ann Rheum Dis. 2018;77:958.
20. Waljee AK, Chaisidhivej N, Saini SD, et al. De-escalation of IBD Therapy: When, Who, and How? Crohns Colitis 360. 2019;1;1-5.
21. Takahashi H, Tsuji H, Ishida-Yamamoto A, et al. Plasma trough levels of adalimumab and infliximab in terms of clinical efficacy during the treatment of psoriasis. J Dermatol. 2013;40(1):39–42.
22. Gottlieb AB, Kalb RE, Blauvelt A, et al. The efficacy and safety of infliximab in patients with plaque psoriasis who had an inadequate response to etanercept: Results of a prospective, multicenter, open-label study. J Am Acad Dermatol. 2012;67(4):642–650.

23. Torii H, Nakagawa H. Infliximab monotherapy in Japanese patients with moderate-to-severe plaque psoriasis and psoriatic arthritis. A randomized, double-blind, placebo-controlled multicenter trial. J Dermatol Sci. 2010;59(1):40–49.
24. Wilkinson N, Tsakok T, Dand N, et al. Defining the Therapeutic Range for Adalimumab and Predicting Response in Psoriasis: A Multicenter Prospective Observational Cohort Study. J Invest Dermatol. 2019;139(1):115–123.
25. Mahil SK, Arkir Z, Richards G, et al. Predicting treatment response in psoriasis using serum levels of adalimumab and etanercept: a single-centre, cohort study. Br J Dermatol. 2013;169(2):306–313.
26. Carrascosa JM, Toro Montecinos M, Ballescá F, et al. Correlation between trough serum levels of adalimumab and absolute PASI score in a series of patients with psoriasis. J Dermatol Treat. 2018;29(2):140–144.
27. Soenen R, Meulewaeter E, Grine L, et al. Defining a Minimal Effective Serum Trough Concentration of Secukinumab in Psoriasis: A Step toward Personalized Therapy. J Invest Dermatol. 2019;139(10):2232-2235.
28. Menting SP, van den Reek JMPA, Baerveldt EM, et al. The correlation of clinical efficacy, serum trough levels and antidrug antibodies in ustekinumab-treated patients with psoriasis in a clinical-practice setting. Br J Dermatol. 2015;173(3):855–857.
29. Toro-Montecinos M, Ballescá F, Ferrandiz C, et al. Usefulness and correlation with clinical response of serum ustekinumab levels measured at 6 weeks versus 12 weeks. J Dermatol Treat. 2019;30(1):35–39.
30. Van den Berghe N, De Keyser E, Soenen R, et al. Clinical response correlates with 4-week postinjection ustekinumab concentrations in patients with moderate-to-severe psoriasis. Br J Dermatol. 2019;106:945-954.

31. Tsakok T, Wilson N, Dand N, et al. Association of Serum Ustekinumab Levels With Clinical Response in Psoriasis. JAMA Dermatol. 2019;155(11):1235–1243.
32. Elberdín L, Outeda M, Salvador P, et al. Positive correlation between etanercept concentration and the decrease in Psoriasis Area and Severity Index scale value. Int J Clin Pharm. 2016;38(5):1142–1148.
33. Detrez I, Van Steen K, Segaert S, et al. The association between etanercept serum concentration and psoriasis severity is highly age-dependent. Clin Sci Lond Engl 1979. 2017;131(11):1179–1189.
34. Chigutsa E, Velez de Mendizabal N, Chua L, et al. Exposure-Response Modeling to Characterize the Relationship Between Ixekizumab Serum Drug Concentrations and Efficacy Responses at Week 12 in Patients With Moderate to Severe Plaque Psoriasis. J Clin Pharmacol. 2018;58(11):1489–1500.
35. Reich K, Jackson K, Ball S, et al. Ixekizumab Pharmacokinetics, Anti-Drug Antibodies, and Efficacy through 60 Weeks of Treatment of Moderate to Severe Plaque Psoriasis. J Invest Dermatol. 2018;138(10):2168–2173.
36. Tham LS, Tang CC, Choi SL, et al. Population exposure–response model to support dosing evaluation of ixekizumab in patients with chronic plaque psoriasis. J Clin Pharmacol. 2014;54(10):1117–1124.
37. Hu C, Yao Z, Chen Y, et al. A comprehensive evaluation of exposure–response relationships in clinical trials: application to support guselkumab dose selection for patients with psoriasis. J Pharmacokinet Pharmacodyn. 2018;45(4):523–535.
38. Pang Y, Khatri A, Suleiman AA, et al. Clinical Pharmacokinetics and Pharmacodynamics of Risankizumab in Psoriasis Patients. Clin Pharmacokinet. 2019; 59:311–326.

39. Papp K, Thaçi D, Reich K, et al. Tildrakizumab (MK-3222), an anti-interleukin-23p19 monoclonal antibody, improves psoriasis in a phase IIb randomized placebo-controlled trial. Br J Dermatol. 2015;173(4):930–939.
40. Yanai H, Hanauer SB. Assessing response and loss of response to biological therapies in IBD. Am J Gastroenterol. 2011;106(4):685–698.
41. Restellini S, Chao CY, Lakatos PL, et al. Therapeutic Drug Monitoring Guides the Management of Crohn's Patients with Secondary Loss of Response to Adalimumab. Inflamm Bowel Dis. 2018;24(7):1531–1538.
42. Roblin X, Rinaudo M, Del Tedesco E, et al. Development of an algorithm incorporating pharmacokinetics of adalimumab in inflammatory bowel diseases. Am J Gastroenterol. 2014;109(8):1250–1256.
43. Guidi L, Pugliese D, Panici Tonucci T, et al. Therapeutic drug monitoring is more cost-effective than a clinically-based approach in the management of loss of response to infliximab in inflammatory bowel disease: an observational multi-centre study. J Crohns Colitis. 2018;12:1079–1088.
44. Papamichael K, Vajravelu RK, Vaughn BP, et al. Proactive Infliximab Monitoring Following Reactive Testing is Associated With Better Clinical Outcomes Than Reactive Testing Alone in Patients With Inflammatory Bowel Disease. J Crohns Colitis. 2018;12(7):804–810.
45. Papamichael K, Juncadella A, Wong D, et al. Proactive Therapeutic Drug Monitoring of Adalimumab Is Associated With Better Long-term Outcomes Compared With Standard of Care in Patients With Inflammatory Bowel Disease. J Crohns Colitis. 2019;13(8):976–981.
46. Papamichael K, Chachu KA, Vajravelu RK, et al. Improved Long-term Outcomes of Patients With Inflammatory Bowel Disease Receiving Proactive Compared With

Reactive Monitoring of Serum Concentrations of Infliximab. Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc. 2017;15(10):1580-1588.

47. Papamichael K, Vande Casteele N, Gils A, et al. Long-term outcome of patients with Crohn's disease who discontinued infliximab therapy upon clinical remission. Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc. 2015;13(6):1103–1110.
48. Lucidarme C, Petitcollin A, Brochard C, et al. Predictors of relapse following infliximab de-escalation in patients with inflammatory bowel disease: the value of a strategy based on therapeutic drug monitoring. Aliment Pharmacol Ther. 2019;49(2):147–154.
49. Papamichael K, Cheifetz AS. Therapeutic drug monitoring in patients on biologics: lessons from gastroenterology. Curr Opin Rheumatol. 2020;32(4):371-379.
50. Detrez I, Van Stappen T, Martín Arranz MD, et al. Current Practice for Therapeutic Drug Monitoring of Biopharmaceuticals in Inflammatory Bowel Disease. Ther Drug Monit. 2017;39(4):344–349.
51. van de Kerkhof PCM, Reich K, Kavanaugh A, et al. Physician perspectives in the management of psoriasis and psoriatic arthritis: results from the population- based Multinational Assessment of Psoriasis and Psoriatic Arthritis survey. J Eur Acad Dermatol Venereol. 2015;29(10):2002–2010.
52. Phung M, Georgakopoulos JR, Ighani A, et al. Secukinumab dose optimization in adult psoriasis patients: A retrospective, multicenter case series. JAAD Case Rep. 2018;4(4):310–313.
53. Phung M, Ighani A, Georgakopoulos JR, et al. Off-Label High-Dose Secukinumab for the Treatment of Moderate-to-Severe Psoriasis. J Cutan Med Surg. 2019;23(4):391–393.

54. Hermans C, Herranz P, Segaert S, et al. Current Practice of Therapeutic Drug Monitoring of Biopharmaceuticals in Psoriasis Patients. Ther Drug Monit. 2017;39(4):356–359.

55. Edwards CJ, Fautrel B, Schulze-Koops H, et al. Dosing down with biologic therapies: a systematic review and clinicians' perspective. Rheumatol Oxf Engl. 2017;56(11):1847–1856.

56. Bouman CA, van Herwaarden N, van den Hoogen FH, et al. Long-term outcomes after disease activity-guided dose reduction of TNF inhibition in rheumatoid arthritis: 3-year data of the DRESS study - a randomised controlled pragmatic non-inferiority strategy trial. Ann Rheum Dis. 2017;76(10):1716–1722.

57. Grossberg LB, Papamichael K, Feuerstein JD, et al. A Survey Study of Gastroenterologists' Attitudes and Barriers Toward Therapeutic Drug Monitoring of Anti-TNF Therapy in Inflammatory Bowel Disease. Inflamm Bowel Dis. 2017;24(1):191–197.

58. Vermeire S, Dreesen E, Papamichael K, et al. How, When, and For Whom Should We Perform Therapeutic Drug Monitoring? Clin Gastroenterol Hepatol. 2019;18(6):1291-1299

Tables

Table 1. Baseline characteristics of survey respondents (n = 107)

Participant type % (n)			
Belgian Dermatology Days 2019			53.3 (57)
SPIN Congress 2019			24.3 (26)
Scientific Committee SPIN			22.4 (24)
Clinical experience % (n)			
Expert dermatologists			22.4 (24)
Dermatologists			77.6 (83)
	Total respondent group	**ED**	**D**
Clinical experience, years % (n)	**100 (106)**	**100 (24)**	**100 (82)**
0-5	17.0 (18)	0 (0)	22.0 (18)
5.1-10	8.5 (9)	0 (0)	11.0 (9)
10.1-15	8.5 (9)	8.3 (2)	8.5 (7)
15.1-20	16.0 (17)	12.5 (3)	17.1 (14)
>20	50.0 (53)	79.2 (19)	41.5 (34)
Practice location % (n)	**100 (107)**	**100 (24)**	**100 (83)**
PP	23.4 (25)	0 (0)	30.1 (25)
GH	10.3 (11)	0 (0)	13.3 (11)
AH	37.4 (40)	58.3 (14)	31.3 (26)
PP + GH	12.1 (13)	0 (0)	15.7 (13)
PP + AH	14.0 (15)	33.3 (8)	8.4 (7)
GH + AH	1.9 (2)	4.2 (1)	1.2 (1)
PP + GH + AH	0.9 (1)	4.2 (1)	0 (0)

Abbreviations: *ED*, expert dermatologists; *D*, dermatologists; *PP*, private practice; *GH*, general hospital; *AH*, academic hospital.

Table 2. Details kinds of dose changes: ED *versus* D

	ED (%)	**D (%)**	**OR**	**CI**	***P*-value**
Dose increase	81.8	57.1	3.38	1.08-10.13	0.06
Time interval shortening	86.4	69.4	2.79	0.74-9.89	0.15
Dose reduction	22.7	14.3	1.77	0.53-6.35	0.50
Time interval lengthening	36.4	32.7	1.18	0.38-3.15	0.79

Abbreviations: *ED*, expert dermatologists; *D*, dermatologists; *OR*, odds ratio; *CI*, confidence interval

Table 3. Details kinds of dose changes: more than *versus* at most 20 years of clinical experience

	> 20 years experience (%)	**≤ 20 years experience (%)**	**OR**	**CI**	***P*-value**
Dose increase	55.1	38.0	1.12	0.43-3.07	>0.99
Time interval shortening	61.2	46.0	0.83	0.30-2.38	0.79
Dose reduction	16.3	8.0	1.58	0.46-5.09	0.54
Time interval lengthening	34.7	14.0	2.33	0.80-6.09	0.13

Abbreviations: *OR*, odds ratio; *CI*, confidence interval

Figure captions

Figure 1. Prescription behavior of biologics among the total study cohort (n=104).

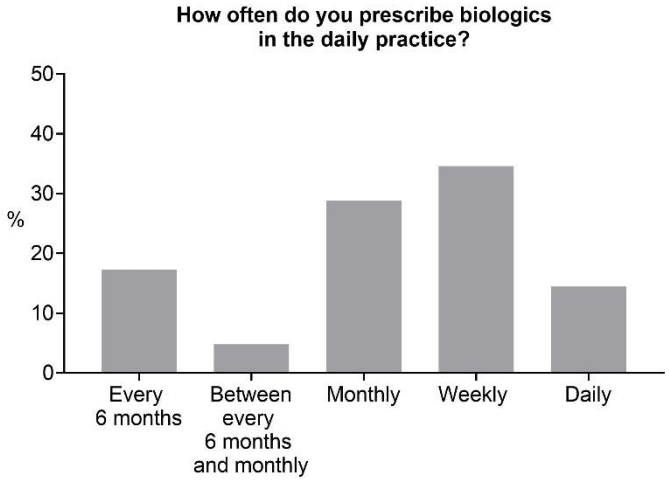
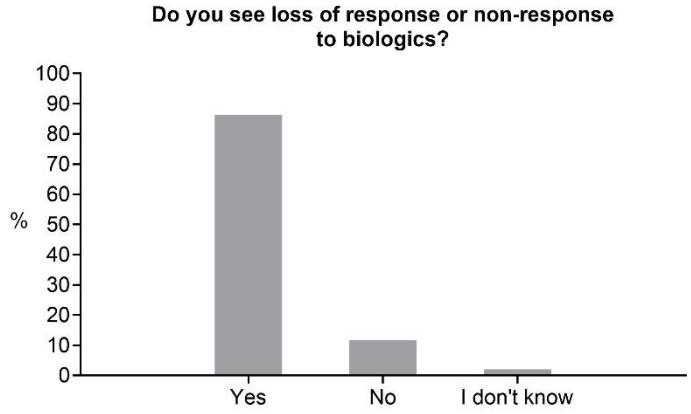


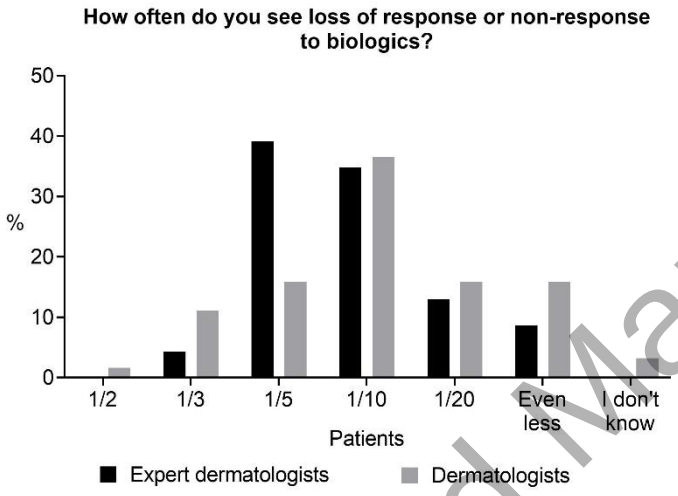
Figure 2. Loss of response and non-response to biologics in daily practice: (a) observation of LoR/NR amongst all respondents (n=102); (b) estimated observation of LoR/NR by ED and D (respectively n=23; n=63); (c) estimated observation of LoR/NR by clinicians with more than and at most 20 years of clinical experience (respectively n=48; n=37).

LoR, loss of response; *NR*, non-response; *ED*, expert dermatologists; *D*, dermatologists.

(a)



(b)



(c)

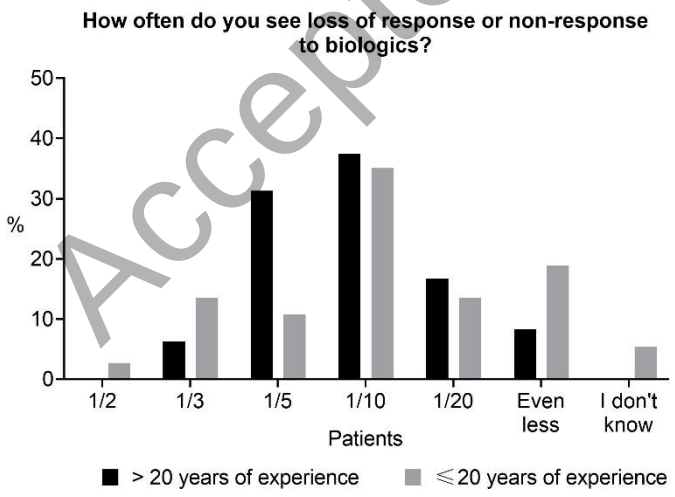
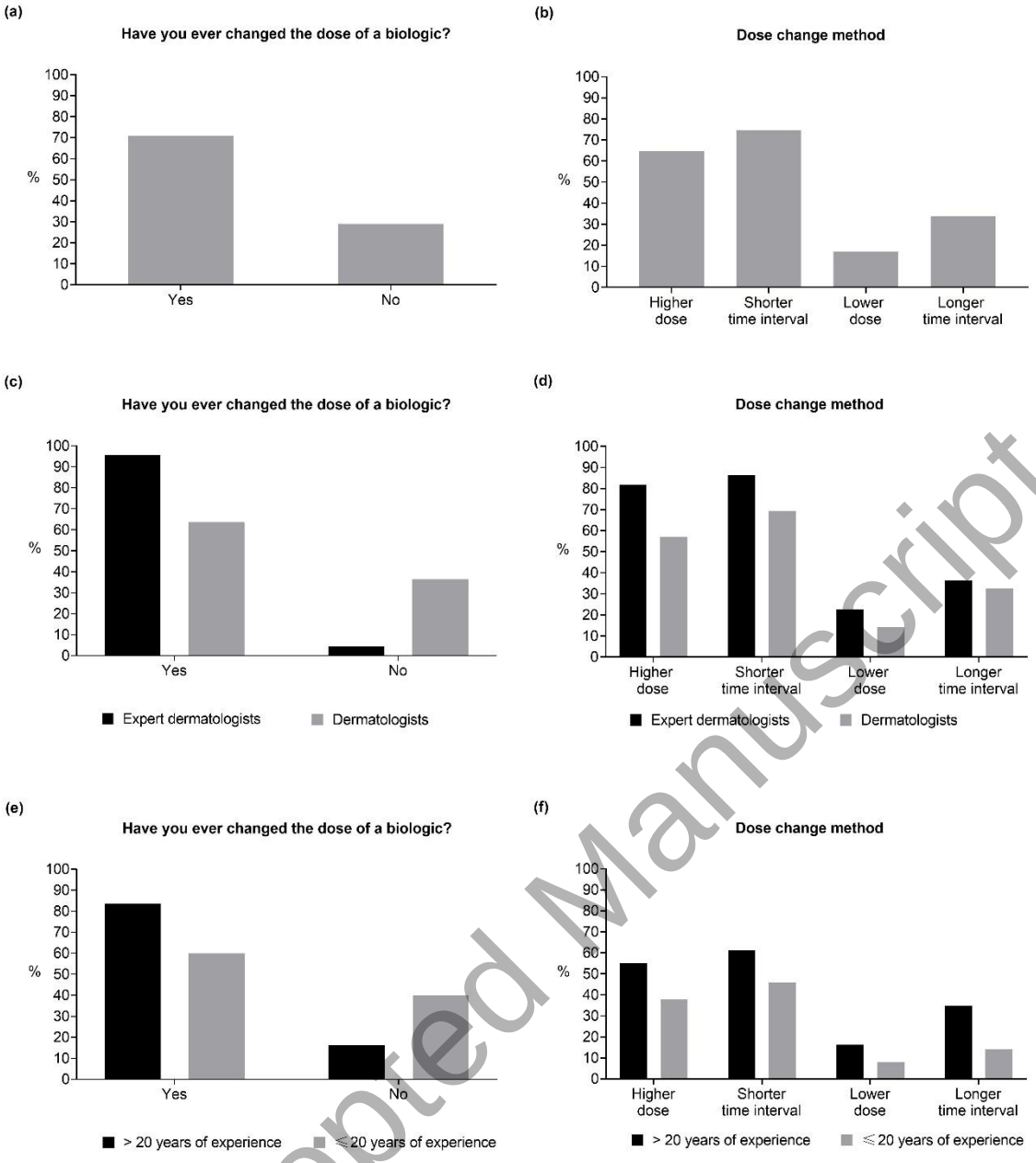
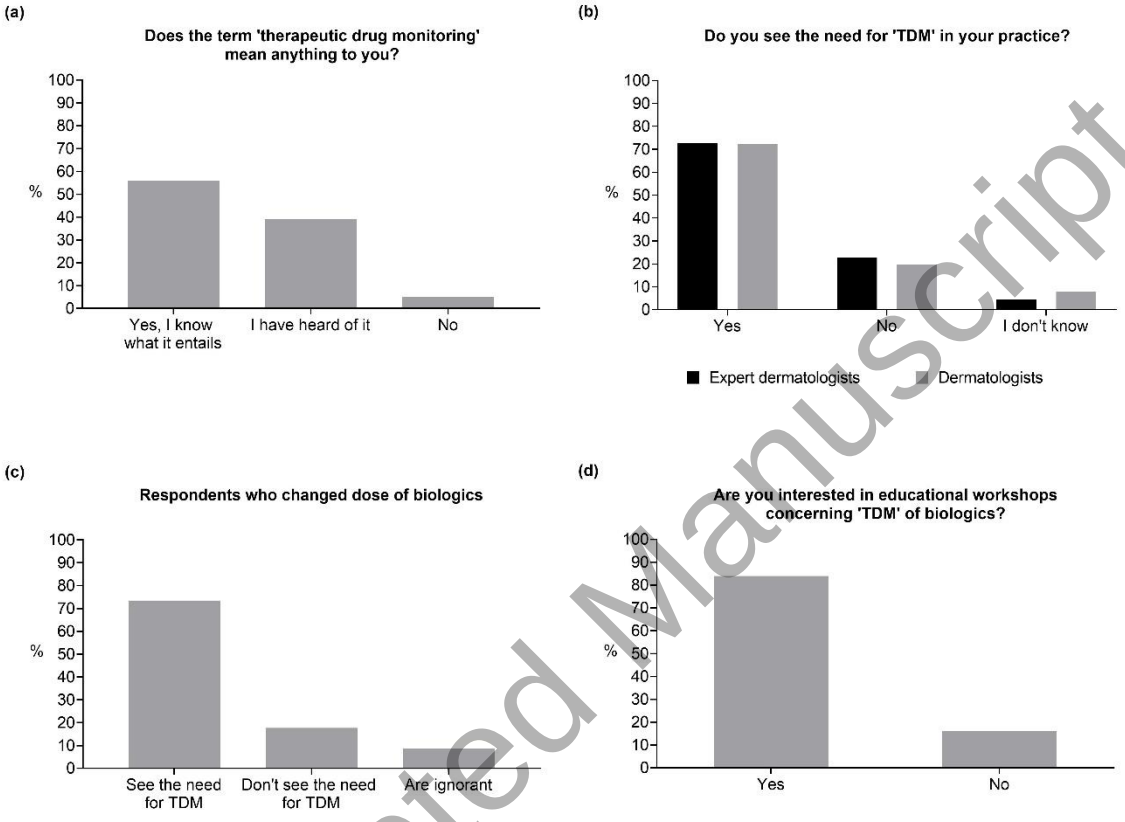


Figure 3. Dose adaption behavior: (a) whether dose adaptations were performed among the total respondent group (n=100); (b) performance of the different kinds of dose changes in the total study cohort (n=71); (c) whether dose changes were performed by ED and D (respectively n=23; n=77); (d) performance of different kinds of dose changes: ED *versus* D (respectively n=22; n=77); (e) whether dose changes were performed by clinicians with more than and at most 20 years of clinical experience (respectively n=49; n=50); (f) performance of different kinds of dose changes by clinicians with more than and at most 20 years of clinical experience (respectively n=49; n=50).



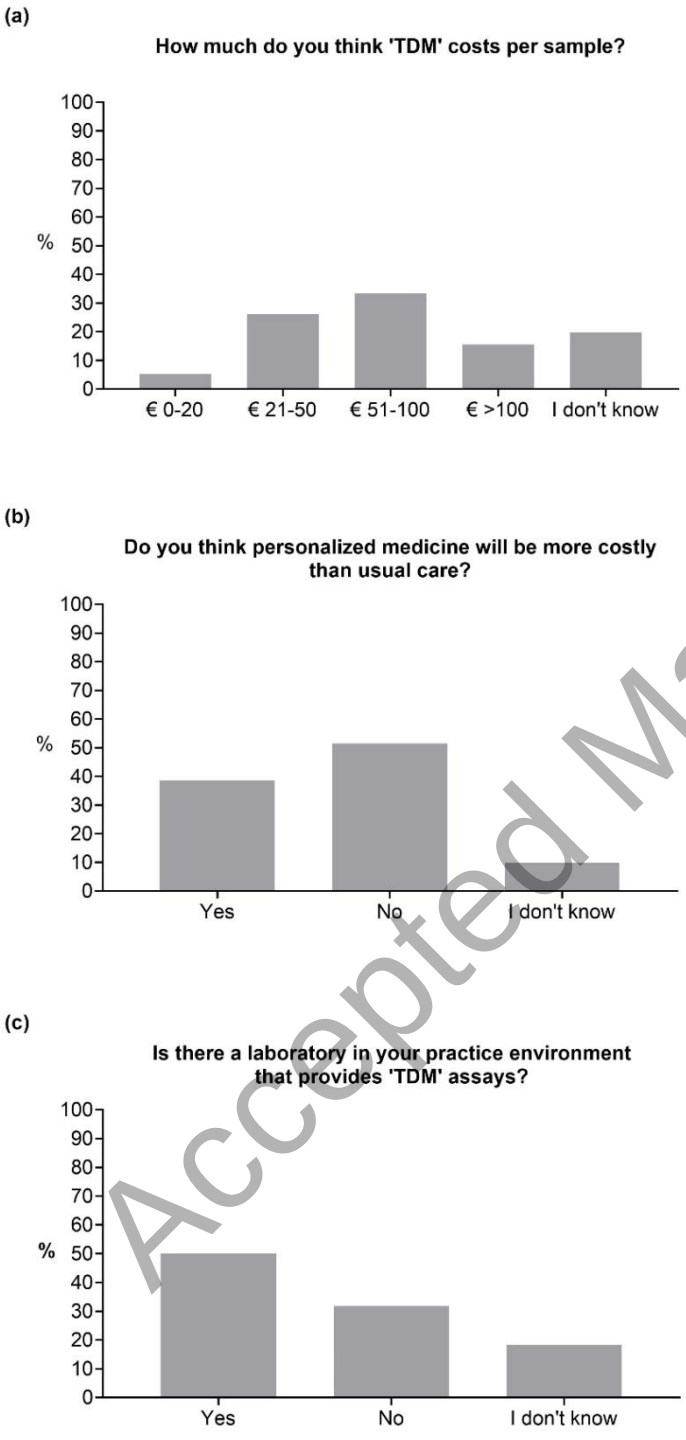
LoR, loss of response; *NR*, non-response; *ED*, expert dermatologists; *D*, dermatologists.

Figure 4. The concept of therapeutic drug monitoring: (a) familiarity with the term 'TDM' (n=102); (b) need for TDM according to ED and D (respectively n=22; n=76); (c) whether respondents who performed dose adaptations of biologics see the need for TDM (n=68); (d) engagement for TDM: whether the respondents are interested in educational workshops (n=75).



TDM, therapeutic drug monitoring.

Figure 5. Costs and accessibility of therapeutic drug monitoring: (a) expected costs per sample (n=96); (b) whether the respondents presume personalized medicine will be more costly than usual care (n=101); (c) TDM assay accessibility (n=22; ED only).



TDM, therapeutic drug monitoring; *ED*, expert dermatologists.